Measurements of nutritional status and impact of malnutrition in polytrauma patients

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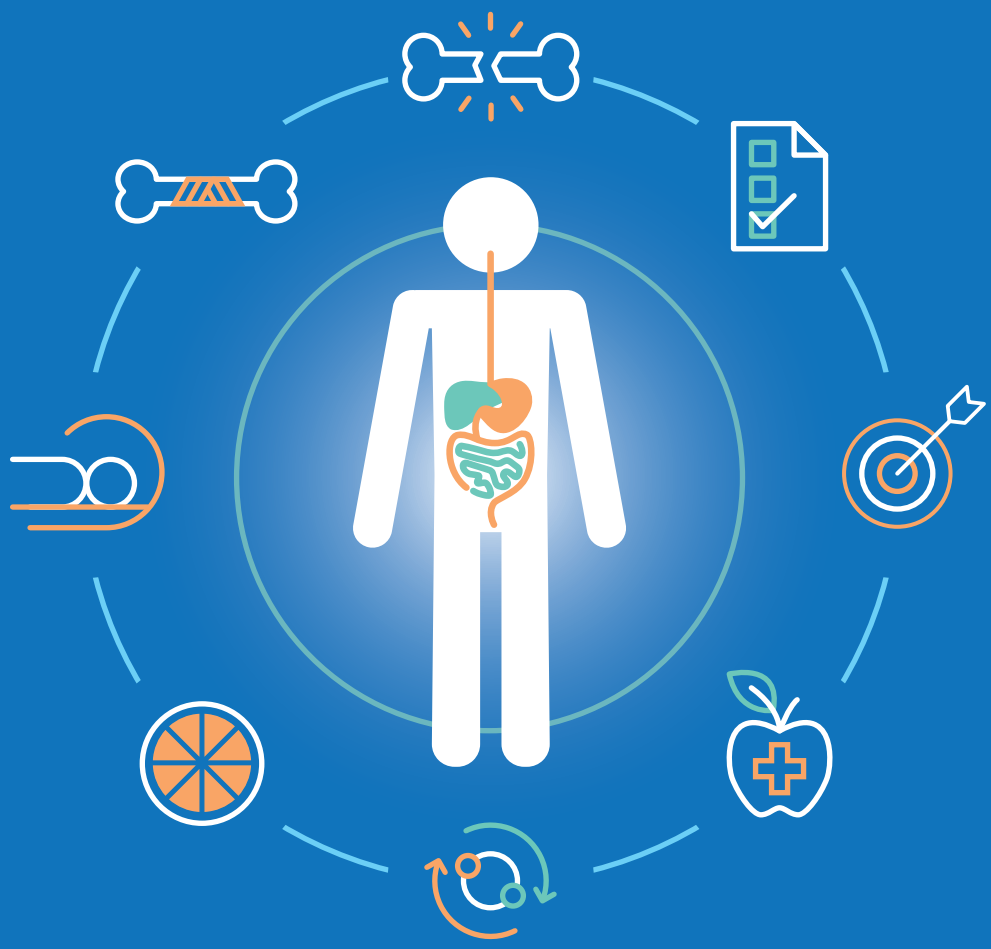

Esmee Verheul

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Printed by Proefschriftspecialist | proefschriftspecialist.nl
Layout and design: Erwin Timmerman, persoonlijkproefschrift.nl

Financial support for the publication of this thesis was kindly provided by Netwerk Acute Zorg West, Nutricia, Universiteit Leiden, and VoedingOnline.

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Proefschrift

ter verkrijging van
de graad van doctor aan de Universiteit Leiden,
op gezag van rector magnificus prof.dr.ir. H. Bijl,
volgens besluit van het college voor promoties
te verdedigen op dinsdag 28 oktober 2025
klokke 11:30 uur

door

Esmee Agnes Hendrika Verheul
geboren te Woerden
in 1999

Promotor
Prof. dr. I.B. Schipper

Copromotoren
Dr. S. Dijkink
Dr. P. Krijnen

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Dr. J.M. Hoogendoorn, Haaglanden Medisch Centrum

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Chapter 1

General introduction, aim, and outline of the thesis

Malnutrition is the leading cause of death and disease worldwide.[1] Malnutrition refers to deficiencies, excesses, or imbalances in a person's intake of energy and/or nutrients. Therefore, the spectrum of malnutrition includes both undernutrition and overnutrition. Globally in 2022, 2.5 billion adults were overweight, while 390 million were underweight.[1] With a world population of 8 billion people, this means that around one-third of the population is considered to be overweight and five percent is underweight.

For the purposes of this thesis, 'malnutrition' is limited to and used interchangeably with 'undernutrition'.

Pathophysiology of malnutrition

Although malnutrition is commonly perceived as an issue in developing countries, it can also pose significant problems in developed countries. Reasons for developing malnutrition can be multifactorial and are not just limited to not having enough dietary intake. The Determinants of Malnutrition in Aged Persons (DoMAP model), which was developed in elderly patients and agreed upon by consensus, gives an insight into the different factors playing a role in developing malnutrition (**Figure 1**).[2]

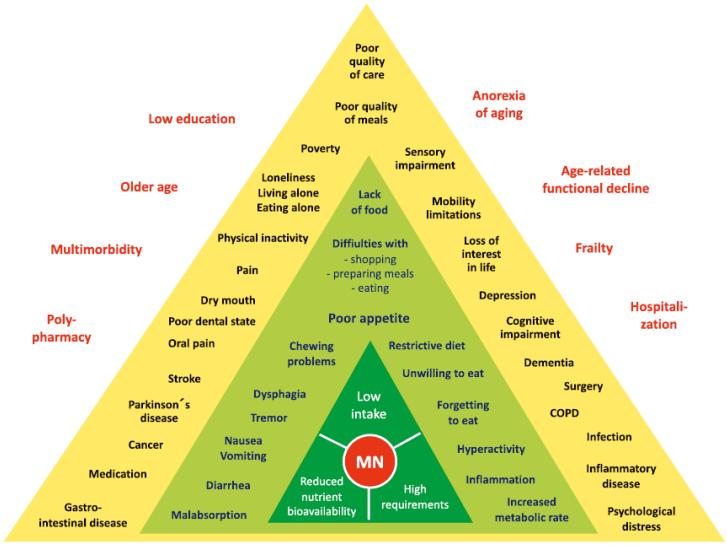

Figure 1: Determinants of malnutrition in aged persons [2]

MN: Malnutrition

The three central etiologic mechanisms causing malnutrition, including low intake, reduced nutrient bioavailability, and high requirements, are shown in the center of the graph (dark green). The factors in light green can directly lead to one of the three mechanisms in dark green. Furthermore, factors in yellow may contribute to factors in light green. For example, infection may lead to inflammation and increased metabolic rate, which then causes increased requirements. The factors in red surrounding the triangle may contribute to the factors in a more indirect way.

According to the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines, three types of adult malnutrition can be identified (**Figure 2**).[3] Firstly, malnutrition without disease can be caused by socioeconomic or psychological factors, such as poverty and hunger strikes, or hunger-related factors, such as deprivation of food.[3] A second type of malnourishment is disease-related malnutrition without inflammation. This could include dysphagia resulting from neurologic disorders such as stroke or psychiatric conditions like anorexia nervosa.[3] Lastly, disease-related malnutrition with inflammation is a condition characterized by an inflammatory response, elicited by an underlying disease. This can be divided into either the acute or chronic form. Acute disease- or injury-related malnutrition is caused by acute and severe inflammation, for example in case of major infection, burns, and trauma.[4] Furthermore, in case of chronic disease-related malnutrition with inflammation, with or without infection, chronic inflammation of mild to moderate degree is present. Examples of these diseases include organ failure, malignancies, or rheumatoid arthritis.[4] Especially critically ill patients and severely injured patients are more susceptible to developing malnutrition because of their critical illness.

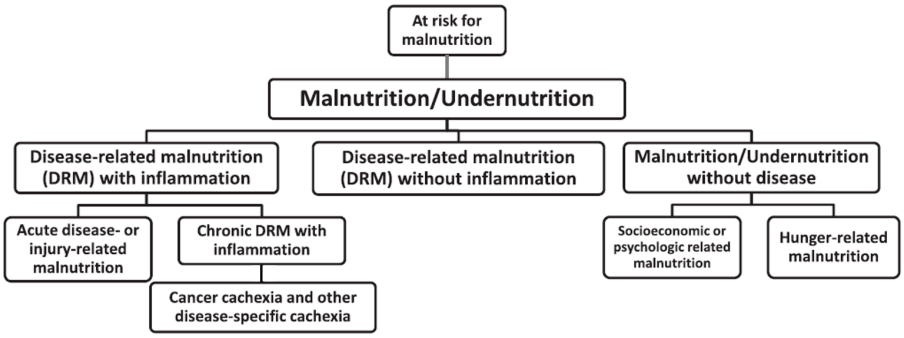

Figure 2: Types of malnutrition [3]

The focus of this thesis is on the development of disease (i.e. trauma)-related malnutrition with inflammation, which may have several causes, as shown in **Figure 3**.[5] During illness, patients often experience a decrease in dietary intake. This is believed to occur due to a decline in appetite sensation triggered by alterations in cytokines, glucocorticoids, insulin, and insulin-like growth factors.[6] Furthermore, in patients with gastro-intestinal failure or in those undergoing abdominal surgery, malnutrition is caused by malabsorption of important nutrients.[5] In case of enterocutaneous fistulae or severe burns, patients may experience excessive or specific nutrient losses, with altered nutritional requirements.[5] In patients with major trauma, head injury, or burns, energy expenditure may be considerably higher, for a shorter or longer period of time.[7,8]

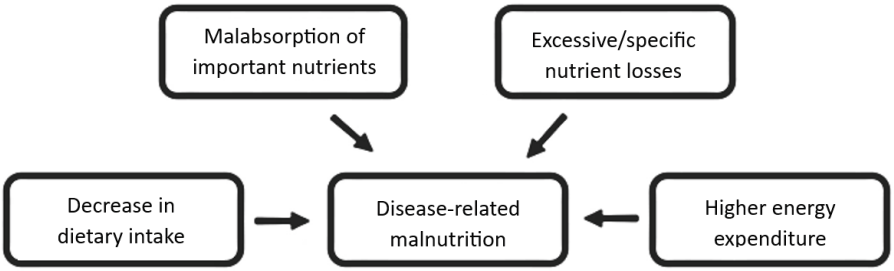

Figure 3: Factors contributing to disease-related malnutrition

Adverse outcomes of malnutrition

The detrimental effects of malnutrition on the function and recovery of various organ systems may potentially result in adverse in-hospital outcomes (**Figure 4**). If dietary intake is insufficient over an extended period, the body utilizes functional reserves in tissues such as muscle, adipose tissue, and bone, leading to changes in body composition.[6] This can lead to weight loss, characterized by the depletion of both fat and muscle mass. Muscle function declines even before changes in muscle mass are present.[8] A decrease in muscle function can lead to significant respiratory issues, including a higher risk of respiratory infections and compromised lung function.[9] In addition, malnutrition affects immune function as it impairs cell-mediated immunity and cytokine, complement, and phagocyte function. It can therefore lead to an increased risk of developing infections.[5] Delayed wound and fracture healing is also described in malnourished surgical patients. These factors contribute to a longer hospital stay, a poorer response to medical treatment, and an increased use of medication, which leads to an increase in healthcare costs.[8] In the Search Engine Optimization (SEO) report 'Malnutrition underestimated', the total costs of malnutrition due to illness in the Netherlands are estimated at 1.8 billion euros a year.[10]

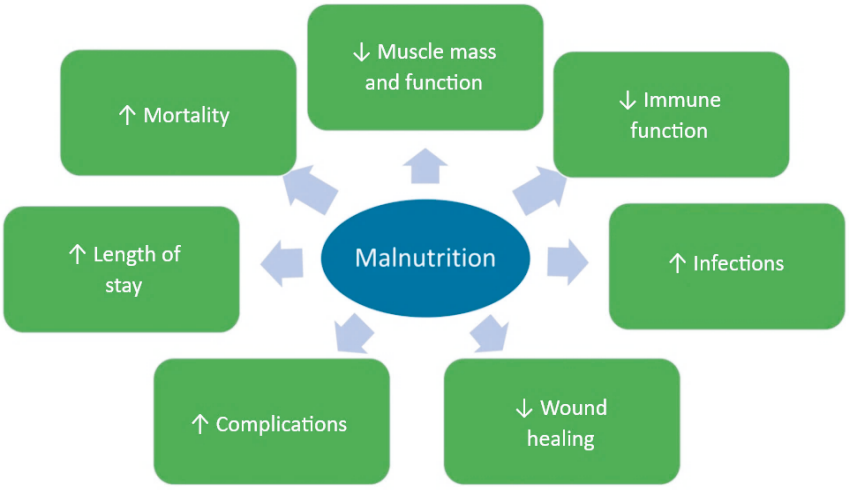

Figure 4: Adverse outcomes of malnutrition

Malnutrition in trauma patients and its consequences

Worldwide, traumatic injuries are still the leading cause of death in people under 45 years of age.[11] Despite substantial improvement in the care for the severely injured over the past decades, many challenges for further improvement of outcomes remain, not only at an organizational level but also at the level of patient care. One of the areas in which progress is lacking relates to the nutrition therapy of hospitalized trauma patients, particularly during admission to the Intensive Care Unit (ICU). As stated above, severely injured patients are susceptible to developing 'Disease-related malnutrition' because of their increased energy expenditure (**Figure 3**). The pathophysiological processes and metabolic effects of malnutrition in severely injured ('polytrauma') patients are illustrated in **Figure 5**.

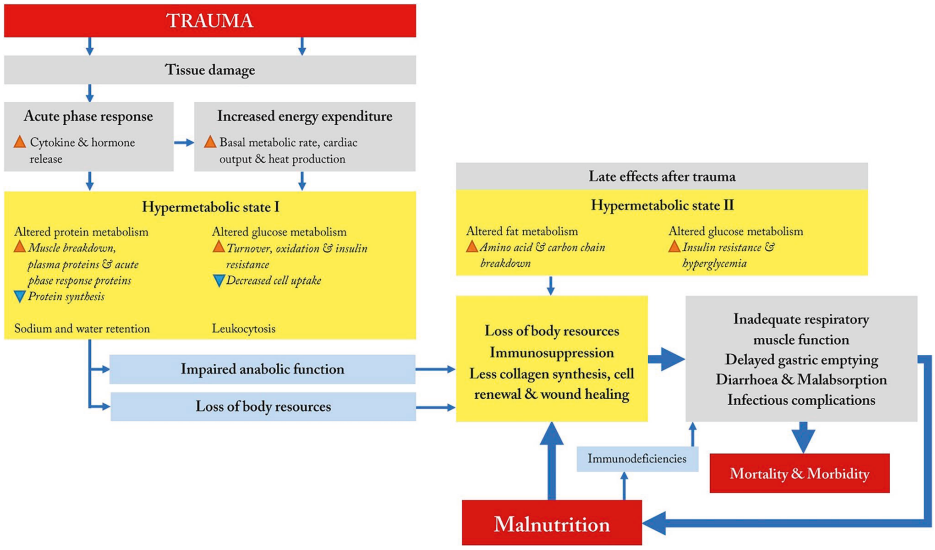

Figure 5: Model of effects of the hypermetabolic state and malnutrition in severely injured patients [19]

After severe trauma, the body reacts to tissue damage with an acute phase response. Several cytokines and hormones are released that act as catabolic stimulants.[12-15] This acute phase response is essential for recovery, but a maladaptive prolonged and/or disturbed metabolic response is related to complications, morbidity, and mortality.[16] Energy expenditure can increase up to 50% in trauma patients compared to patients after elective surgery. The combination of the acute phase response and increased energy expenditure causes the body to be in a hypermetabolic catabolic state ('Hypermetabolic state I'; **Figure 5**) with altered protein and

glucose metabolism, sodium and water retention, and leukocytosis.[14,17,18] The hypermetabolic state is characterized by impaired anabolic function and a loss of body resources.[14,15] In addition, between 3-7 days after trauma, patients experience the late effects of trauma ('Hypermetabolic state II'; **Figure 5**).[15] This includes altered fat metabolism with breakdown of amino acids and body stores, and altered glucose metabolism with increased insulin resistance and hyperglycemia.[13-16,18] These processes all contribute to a loss of body resources, immunosuppression, and less collagen synthesis, cell renewal, and wound healing.[16] Muscle breakdown in the respiratory muscles can lead to inadequate respiratory function, resulting in prolonged ventilator dependency, pneumonia, and an increased risk of mortality.[13,18] The cytokine cascade and immunosuppression can cause delayed gastric emptying, diarrhea, and malabsorption, which can also increase the risk of developing malnutrition.[13,16,18] Malnutrition negatively influences the metabolic response and can lead to relative immunodeficiency. This renders trauma patients even more susceptible to infectious complications and further loss of body resources, and thus may induce a vicious circle of further deterioration of the nutritional and health status.[14,16,18]

Nutritional assessment and screening tools

The prevalence of malnutrition depends on the study population and the definition and criteria used to diagnose malnutrition. It is thought that in the hospitalized population, the prevalence of malnutrition ranges between 20 and 50%.[20] In ICU patients, this percentage is probably even higher, since they experience 'acute disease- or injury-related malnutrition' with acute and severe inflammation (**Figure 2**).[4] In severely injured trauma patients, additionally to these malnutrition-causing factors, the energy expenditure will be increased due to severe injuries, which causes these patients to be even more susceptible to malnutrition (**Figure 3**).[7,8]

As malnutrition is associated with adverse outcomes, its recognition and early management potentially result in better outcomes. There are several nutritional assessment tools and nutritional screening tools available to assess the nutritional status of critically ill patients.[21] The large number of available screening tools immediately points out the main problem, namely that there is no "gold standard" to diagnose malnutrition.

Nutritional assessment tools assess the current nutritional status and can be used to diagnose malnutrition. The Subjective Global Assessment (SGA) and Mini Nutritional Assessment (MNA) are two examples of assessment tools used in ICU patients.[21] Both tools include diet history, gastrointestinal symptoms, severity of illness, and physical assessment of patients.[22,23] The MNA score is designed for and validated in elderly patients in outpatient clinics, hospitals, and nursing homes.[23] The MNA has not been validated in the ICU population.[24]

On the other hand, the SGA was developed in a patient group admitted for elective surgery, and was validated for the acute hospital setting, surgical patients, and ICU patients requiring mechanical ventilation.[22,25,26] Although, neither of these tools is considered to be the "gold standard" to diagnose malnutrition in severely injured patients, the SGA is currently considered the most appropriate nutritional assessment tool as it is validated in the critically ill setting. The six items of the SGA score are shown in **Figure 6**.

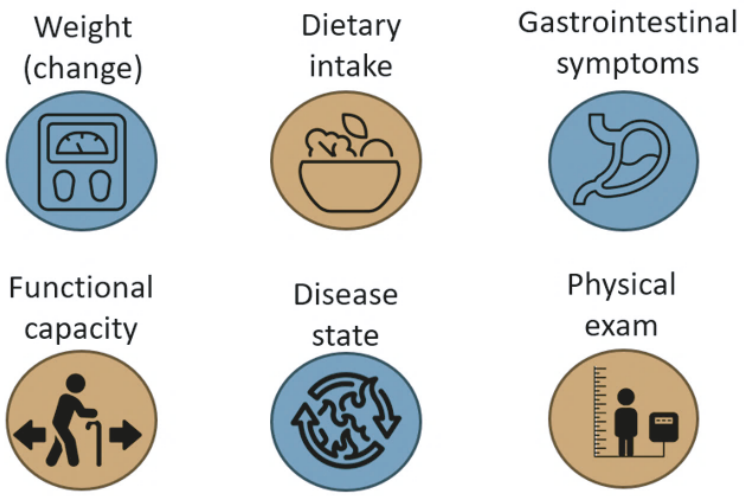

Figure 6: Items of the Subjective Global Assessment scale

Nutritional screening tools focus on assessing the risk of developing malnutrition.[21] The mostly used nutritional screening tools include the Nutritional Risk Screening-2002 (NRS-2002), Malnutrition Universal Screening Tool (MUST), and Short Nutritional Assessment Questionnaire (SNAQ).[21] In addition, a relatively

new nutritional screening tool was developed specifically for ICU patients, the Nutrition Risk in the Critically Ill (NUTRIC) Score. This score comprises of two severity of disease scores, age, number of comorbidities, duration of hospitalization before admission to the ICU, and levels of Interleukin-6 (IL-6).[27] This score can also be used without including the IL-6 assessment, as IL-6 is not commonly analyzed. In such cases, it is referred to as the modified NUTRIC (mNUTRIC) score.[28]

Objective assessment of the nutritional status

Currently, there is no 'gold standard' for determining malnutrition in severely injured patients. Therefore, there is a need for simple, objective, and routinely available assessment tools. Biomarkers, short for 'biological markers', refer to a category of objective markers of medical state, that can be measured accurately and reproducibly.[29] Biomarkers can be analyzed in the blood, but also in saliva, urine, or tissues such as muscle or tumors.[30-32] Important blood biomarkers include C-reactive protein (CRP) as a biomarker for inflection and inflammation, and hemoglobin A1c (HbA1c) as a biomarker for the presence and severity of hyperglycemia, and over time as a biomarker for diabetic complications.[33,34]

Nutritional biomarkers are biomarkers that can be used as an indicator of nutritional status and/or dietary intake.[35,36] Visceral proteins, such as albumin and pre-albumin, are considered the conventional nutritional biomarkers. Poor protein and energy intake can result in low circulating levels of these visceral proteins. However, impaired liver synthetic function, as well as inflammatory status, may also cause a decrease in visceral protein levels.[36] Since the body reacts to severe trauma with an acute phase response, visceral proteins might be severely influenced by the inflammatory state in polytrauma patients, which makes them unreliable for nutritional assessment in polytrauma patients.[37] New nutritional biomarker analyses are emerging, such as the study of lipoproteins, small metabolites, and vitamins to assess the nutritional status.[38] These biomarkers offer the potential to analyze the nutritional status on a nutrient level.

In addition, computerized tomography (CT) scans can provide more knowledge on body composition. CT scans are routinely obtained of polytrauma patients at admission, and can potentially serve as a new way of assessing body composition and therefore provide potential information about the nutritional status.[39] In abdominal CT images, the quality and quantity of skeletal muscle and abdominal fat

can be analyzed and therefore provide more accurate assessments of frailty and cachexia in specific patient groups.[40] CT-derived body composition parameters have been proven indicative of nutritional status in several patient populations, such as those with Crohn's disease, and malignancies,[41-44] but have not yet been studied in relation to the nutritional status of polytrauma patients.

The Malnutrition in Polytrauma Patients (MaPP)-study

The above introduction illustrates that much is known about nutritional status in general and ways of measuring related parameters. However, much of this knowledge does not apply to or has not been studied in polytrauma patients. The overall intention of this thesis is to contribute to the optimal treatment of polytrauma patients by acknowledging the burden of malnutrition in these patients and determining reliable parameters for assessing the nutritional status in a controlled manner.

Although the hypermetabolic state after severe trauma and the resulting increased risk of developing malnutrition in polytrauma patients are known, the occurrence of malnutrition and its related complications in these patients is not yet clearly described in the current literature. Therefore, the Department of Trauma Surgery of the Leiden University Medical Center initiated, in collaboration with their American research partners, a multi-center prospective observational study to investigate the incidence and prevalence of malnutrition, and its relation with complications, in polytrauma patients admitted to the ICU. Polytrauma patients are defined as trauma patients with a blunt mechanism of injury with an injury severity score (ISS) ≥16 points. The three participating centers in the United States are the Massachusetts General Hospital in Boston, Brigham and Women's Hospital in Boston, Massachusetts, and Ryder Trauma Center in Miami, Florida. The two participating Dutch centers are the Leiden University Medical Center in Leiden and Haaglanden Medical Center Westeinde in The Hague. All centers are Level-1 trauma centers according to national standards. The protocol of this so-called prospective Malnutrition in Polytrauma Patients (MaPP) study was published earlier.[45] In this study the SGA score is chosen for assessment of malnutrition and the mNUTRIC score is used to assess nutritional risk.

Aim and outline of this thesis

The primary aim of this thesis is to analyze the prevalence and incidence of malnutrition and nutritional risk and its relation with adverse in-hospital outcomes in polytrauma patients. The second aim is to study potentially new biomarkers and body composition parameters for the assessment of the nutritional status and nutritional risk in polytrauma patients.

The first two studies of this thesis address the primary research aim by evaluating the impact of malnutrition and high nutritional risk in severely injured patients. **Chapter 2** describes the prevalence and incidence of malnutrition, assessed using the SGA score, in polytrauma patients admitted to the ICU. In addition, the relationship between malnutrition and adverse in-hospital outcomes, including complications, mortality, and length of stay parameters, is analyzed. **Chapter 3** describes the prevalence of high nutritional risk at ICU admission, assessed with the mNUTRIC score, and its relation with the development of malnutrition in polytrauma patients. Other adverse in-hospital outcomes, such as complications and mortality, are also studied in relation to the mNUTRIC score.

The second part of this thesis focuses on the analysis of new objective measurements of nutritional status. **Chapter 4** provides an overview of the current knowledge about the value of metabolites and vitamins for the assessment of nutritional status in hospitalized patients. In the following three chapters, data from the MaPP study are used to assess the relevance of metabolites and vitamins for assessing the nutritional status of severely injured patients. Firstly, **Chapter 5** aims to analyze the relevance of plasma lipoproteins and small metabolites for the assessment of nutritional status in polytrauma patients. Lipoproteins and small metabolites are involved in multiple important processes in the body, such as energy storage, the immune response, and oxidative stress response. Since malnutrition is related to oxidative stress and muscle catabolism, the value of lipoproteins and small metabolites in the assessment of nutritional status warrants investigation. Secondly, **Chapter 6** discusses the relationship between fat-soluble vitamins and the nutritional status as well as complications in polytrauma patients. Although all ICU patients receive protocolized multivitamin supplementation to prevent decreases in vitamin concentrations and complications potentially related to vitamin deficiency, the relation between vitamin levels and the nutritional status and complications has not been studied in polytrauma patients. Lastly,

Chapter 7 aims to evaluate the relationship between CT-derived body composition parameters (CT-BCPs) and the nutritional status in polytrauma patients. These CT-BCPs include muscle density, skeletal muscle index, and visceral adipose tissue and they could potentially give new insights into a patient's nutritional status. Given that the majority of polytrauma patients undergo CT scans for initial trauma assessment, nutritional assessment through body composition analysis could be easily integrated into clinical practice. **Chapter 8** presents a general discussion on the studies described above.

REFERENCES

1. World Health Organisation. Fact sheets - Malnutrition. https://www.who.int/news-room/fact-sheets/detail/malnutrition
2. Volkert D, Kiesswetter E, Cederholm T, Donini LM, Eglseer D, Norman K, et al. *Development of a Model on Determinants of Malnutrition in Aged Persons: A MaNuEL Project.* Gerontol Geriatr Med. 2019;5:2333721419858438.
3. Cederholm T, Barazzoni R, Austin P, Ballmer P, Biolo G, Bischoff SC, et al. *ESPEN guidelines on definitions and terminology of clinical nutrition.* Clin Nutr. 2017;36(1):49-64.
4. Jensen GL, Mirtallo J, Compher C, Dhaliwal R, Forbes A, Grijalba RF, et al. *Adult starvation and disease-related malnutrition: A proposal for etiology-based diagnosis in the clinical practice setting from the International Consensus Guideline Committee.* JPEN J Parenter Enteral Nutr. 2010;34(2):156-9.
5. Saunders J, Smith T. *Malnutrition: causes and consequences*. Clin Med (Lond). 2010;10(6):624-7.
6. Jackson AA. *Severe malnutrition*. vol 1. Oxford textbook of medicine. Oxford: Oxford University Press; 2003.
7. Elia M. *Changing concepts of nutrient requirements in disease: implications for artificial nutrition support*. Lancet. 1995;345:1279-84.
8. Green CJ. *Existence, causes and consequences of disease-related malnutrition in the hospital and the community, and clinical and financial benefits of nutrition intervention*. Clin Nutr. 1999;18(2):3-28.
9. Tharumakunarajah R, Lee A, Hawcutt D, Harman N, Sinha I. *The Impact of Malnutrition on the Developing Lung and Long-Term Lung Health: A Narrative Review of Global Literature*. Pulm Ther. 2024 Jun;10(2):155-70
10. Koopmans C, Kok L, Scholte R. *Malnutrition Underestimated*. SEO Economic Research. 2014;11
11. *10 Leading Causes of Death by Age Group, United States – 2016.* National Vital Statistics System, National Center for Health Statistics, CDC.
12. Rogobete AF, Sandesc D, Papurica M, Stoicescu ER, Popovici SE, Bratu LM, et al. *The influence of metabolic imbalances and oxidative stress on the outcome of critically ill polytrauma patients: a review*. Burns Trauma. 2017;5:8.
13. Burns HJ. *The metabolic and nutritional effects of injury and sepsis*. Bailliere's Clin Gastroenterol. 1988;2(4):849-67.
14. Chiolero R, Revelly JP, Tappy L. *Energy metabolism in sepsis and injury*. Nutrition. 1997;13(9):45s-51s.
15. Ryan NT. *Metabolic adaptations for energy production during trauma and sepsis*. Surg Clin North Am. 1976;56(5):1073-90.
16. Soeters PB, Grimble RF. *Dangers, and benefits of the cytokine mediated response to injury and infection*. Clin Nutr. 2009;28(6):583-96.
17. Cuthbertson DP, Tilstone WJ. *Nutrition of the Injured*. Am J Clin Nutr. 1968;21(9):911-22.
18. Kinney JM, Elwyn DH. *Protein metabolism and injury*. Annu Rev Nutr. 1983;3:433-66.
19. Dijkink S, Meier K, Krijnen P, Yeh DD, Velmahos GC, Schipper IB. *Malnutrition and its effects in severely injured trauma patients*. Eur J Trauma Emerg Surg. 2020;46(5):993-1004.
20. Barker LA, Gout BS, Crowe TC. *Hospital malnutrition: prevalence, identification and impact on patients and the healthcare system*. Int J Environ Res Public Health. 2011;8(2):514-27.

21. Lew CCH, Yandell R, Fraser RJL, Chua AP, Chong MFF, Miller M. *Association between malnutrition and clinical outcomes in the intensive care unit: A systematic review.* JPEN J Parenter Enteral Nutr. 2017;41(5):744-58.

22. Detsky AS, McLaughlin JR, Baker JP, Johnston N, Whittaker S, Mendelson RA, et al. *What is subjective global assessment of nutritional status?* JPEN J Parenter Enteral Nutr. 1987;11(1):8-13.

23. Vellas B, Guigoz Y, Garry PJ, Nourhashemi F, Bennahum D, Lauque S, et al. *The Mini Nutritional Assessment (MNA) and its use in grading the nutritional state of elderly patients*. Nutrition. 1999;15(2):116-22.

24. Moradi Moghaddam O, Niakan Lahiji M, Yazdan Panah L, Talebi-Taher M, Rajabi A, Mirhosseini SF. *Relationship between Mini Nutritional Assessment Score and Infection in Critical Care Patients*. Med J Islam Repub Iran. 2022;36:91.

25. Sheean PM, Peterson SJ, Gurka DP, Braunschweig CA. *Nutrition assessment: the reproducibility of Subjective Global Assessment in patients requiring mechanical ventilation*. Eur J Clin Nutr. 2010;64(11):1358-64.

26. Bector S, Vagianos K, Suh M, Duerksen DR. *Does the subjective global assessment predict outcome in critically ill medical patients?* J Intensive Care Med. Aug 2016;31(7):485-9.

27. Heyland DK, Dhaliwal R, Jiang X, Day AG. *Identifying critically ill patients who benefit the most from nutrition therapy: the development and initial validation of a novel risk assessment tool*. Crit Care. 2011;15(6):R268.

28. Rahman A, Hasan RM, Agarwala R, Martin C, Day AG, Heyland DK. *Identifying critically-ill patients who will benefit most from nutritional therapy: Further validation of the "modified NUTRIC" nutritional risk assessment tool*. Clin Nutr. 2016;35(1):158-62.

29. Strimbu K, Tavel JA. *What are biomarkers?* Curr Opin HIV AIDS. 2010;5(6):463-6.

30. Sequeira-Antunes B, Ferreira HA. *Urinary Biomarkers and Point-of-Care Urinalysis Devices for Early Diagnosis and Management of Disease: A Review*. Biomedicines. 2023;11(4):1051.

31. Melguizo-Rodríguez L, Costela-Ruiz VJ, Manzano-Moreno FJ, Ruiz C, Illescas-Montes R. *Salivary Biomarkers and Their Application in the Diagnosis and Monitoring of the Most Common Oral Pathologies*. Int J Mol Sci. 2020;21(14):5173.

32. Lancellotti C, Cancian P, Savevski V, Kotha SRR, Fraggetta F, Graziano P, et al. *Artificial Intelligence & Tissue Biomarkers: Advantages, Risks and Perspectives for Pathology.* Cells. 2021;10(4):787.

33. Gabay C, Kushner I. *Acute-phase proteins and other systemic responses to inflammation*. N Engl J Med. 1999;340(6):448-54.

34. Lyons TJ, Basu A. *Biomarkers in diabetes: hemoglobin A1c, vascular and tissue markers*. Transl Res. 2012;159(4):303-12.

35. Picó C, Serra F, Rodríguez AM, Keijer J, Palou A. *Biomarkers of Nutrition and Health: New Tools for New Approaches.* Nutrients. 2019;11(5):1092.

36. Keller U. *Nutritional laboratory markers in malnutrition*. J Clin Med. 2019;8(6):775.

37. Yeh DD, Johnson E, Harrison T, Kaafarani HMA, Lee J, Fagenholz P, et al. *Serum levels of albumin and prealbumin do not correlate with nutrient delivery in surgical intensive care unit patients.* Nutrition in Clinical Practice. 2018;33(3):419-25.

38. Mogensen KM, Lasky-Su J, Rogers AJ, Baron RM, Fredenburgh LE, Rawn J, et al. *Metabolites associated with malnutrition in the intensive care unit are also associated with 28-day mortality*. JPEN J Parenter Enteral Nutr. 2017;41(2):188-97.

39. Treskes K, Saltzherr TP, Luitse JS, Beenen LF, Goslings JC. *Indications for total-body computed tomography in blunt trauma patients: a systematic review*. Eur J Trauma Emerg Surg. 2017;43(1):35-42.

40. Bates DDB, Pickhardt PJ. *CT-Derived Body Composition Assessment as a Prognostic Tool in Oncologic Patients: From Opportunistic Research to Artificial Intelligence-Based Clinical Implementation*. AJR Am J Roentgenol. 2022;219(4):671-80.

41. Almasaudi AS, McSorley ST, Dolan RD, Edwards CA, McMillan DC. *The relation between Malnutrition Universal Screening Tool (MUST), computed tomography-derived body composition, systemic inflammation, and clinical outcomes in patients undergoing surgery for colorectal cancer.* Am J Clin Nutr. 2019;110(6):1327-34.

42. Huang DD, Yu DY, Song HN, Wang WB, Luo X, Wu GF, et al. *The relationship between the GLIM-defined malnutrition, body composition and functional parameters, and clinical outcomes in elderly patients undergoing radical gastrectomy for gastric cancer*. Eur J Surg Oncol. 2021;47(9):2323-31.

43. Sánchez M, Castro-Eguiluz D, Luvián-Morales J, Jiménez-Lima R, Aguilar-Ponce JL, Isla-Ortiz D, et al. *Deterioration of nutritional status of patients with locally advanced cervical cancer during treatment with concomitant chemoradiotherapy*. J Hum Nutr Diet. 2019;32(4):480-91.

44. Lidoriki I, Schizas D, Mpaili E, Vailas M, Sotiropoulou M, Papalampros A, et al. *Associations between skeletal muscle mass index, nutritional and functional status of patients with oesophago-gastric cancer.* Clin Nutr ESPEN. 2019;34:61-7.

45. Dijkink S, Meier K, Krijnen P, Yeh DD, Velmahos GC, Arbous MS, et al. *The malnutrition in polytrauma patients (MaPP) study: Research protocol*. Nutr Health. 2019;25(4):291-301.








Chapter 2

Prevalence, incidence, and complications of malnutrition in severely injured patients

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ABSTRACT

Introduction

Severely injured patients may suffer from acute disease-related or injury-related malnutrition involving a marked inflammatory response. This study investigated the prevalence and incidence of malnutrition and its relation with complications in severely injured patients admitted to the intensive care unit (ICU).

Methods

This observational prospective cohort study included severely injured patients (Injury Severity Score ≥16), admitted to the ICU of five level-1 trauma centers in the Netherlands and United States. Malnutrition was defined as a Subjective Global Assessment score ≤5. Complications included systemic-, surgery-, and fracture-related complications, pneumonia, urinary tract infection, deep venous thrombosis, and pulmonary embolism. In-ICU and in-hospital mortality were recorded separately. The complication rate was compared between patients who had or developed malnutrition and patients who remained well-nourished, using multivariable logistic regression analysis.

Results

Of 100 included patients, twelve (12%) were malnourished at admission. Of the 88 well-nourished patients, 44 developed malnutrition during ICU admission, (ICU incidence 50%, 95% confidence interval [CI] 40-60%). Another 18 patients developed malnutrition at the ward (overall in-hospital incidence 70%, 95% CI 61-80%). The 62 patients who developed malnutrition and 12 patients who were malnourished upon admission had more complications than the 26 patients who remained well-nourished (58% vs 50% vs 27% respectively; p=0.03; Odds Ratio 3.4, 95% CI 1.2-9.6).

Conclusion

50% of severely injured patients developed malnutrition during ICU admission, increasing to 70% during hospital admission. Malnutrition was related to an increased risk of complications. Recognition of sub-optimally nourished severely injured patients and assessment of nutritional needs could be valuable in optimizing their clinical outcomes.

INTRODUCTION

Malnutrition is a common but frequently unrecognized problem in hospitalized patients, despite its association with adverse outcomes, such as infections, prolonged hospital stay, impaired wound healing, and mortality.[1-4] According to the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) three types of malnutrition are defined based on etiology, including social and environmental circumstances, chronic illness, and acute illness.[4] Severely injured patients may suffer from acute disease-related or injury-related malnutrition involving a marked inflammatory response.[4] Because of the stress response following traumatic injuries, severely injured patients often endure an altered metabolic state in order to preserve energy for vital tissues. This can cause a deterioration of the nutritional status, which again negatively influences the stress and metabolic response after trauma.[5] Due to this vicious circle of deterioration of the nutritional- and health status, severely injured patients are at risk for considerable additional harm from malnutrition. Current estimates of the in-hospital prevalence of malnutrition at admission in severely injured patients range from 7 to 76%, depending upon the setting, population, and nutritional assessment tool used.[5]

Recognition of sub-optimally nourished severely injured patients and assessment of their nutritional needs is crucial in order to improve their clinical outcomes. Despite the increasing number of studies on malnutrition in hospitalized patients, little is known about the risk of developing malnutrition during hospital admission and its consequences in the severely injured patient population. The goal of this study was to determine the prevalence and incidence of malnutrition, and the relation with complications in severely injured patients who are admitted to the intensive care unit (ICU).

METHODS

The Malnutrition in Polytrauma Patients (MaPP) study is an observational prospective cohort study that was performed at five Level-1 trauma centers, three in the United States and two in the Netherlands. All consecutive adult (≥18 years) patients with severe injuries (Injury Severity Score, ISS ≥16), caused by blunt trauma, who were admitted to the ICU of one of the participating centers were eligible for in-

clusion. Patients must be admitted to the ICU for more than 48 hours and should not be primarily managed in another hospital. Patients with burn wounds and penetrating injuries were excluded because the factors influencing prognosis and treatment differ significantly from those in blunt trauma patients, and it was anticipated that there would not be sufficient cases to conduct subanalyses. Written informed consent was obtained from the patients or their legal representative on the day of ICU admission or as soon as possible after that day. The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the local Institutional Review Boards (protocol number: NL64016.058.17). The study is described in detail in the published study protocol.[6] Patient inclusion in the Netherlands began in July 2018 and concluded in April 2022, while in the United States, it started in May 2018 and ended in February 2020. This study has been reported in line with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement.[7]

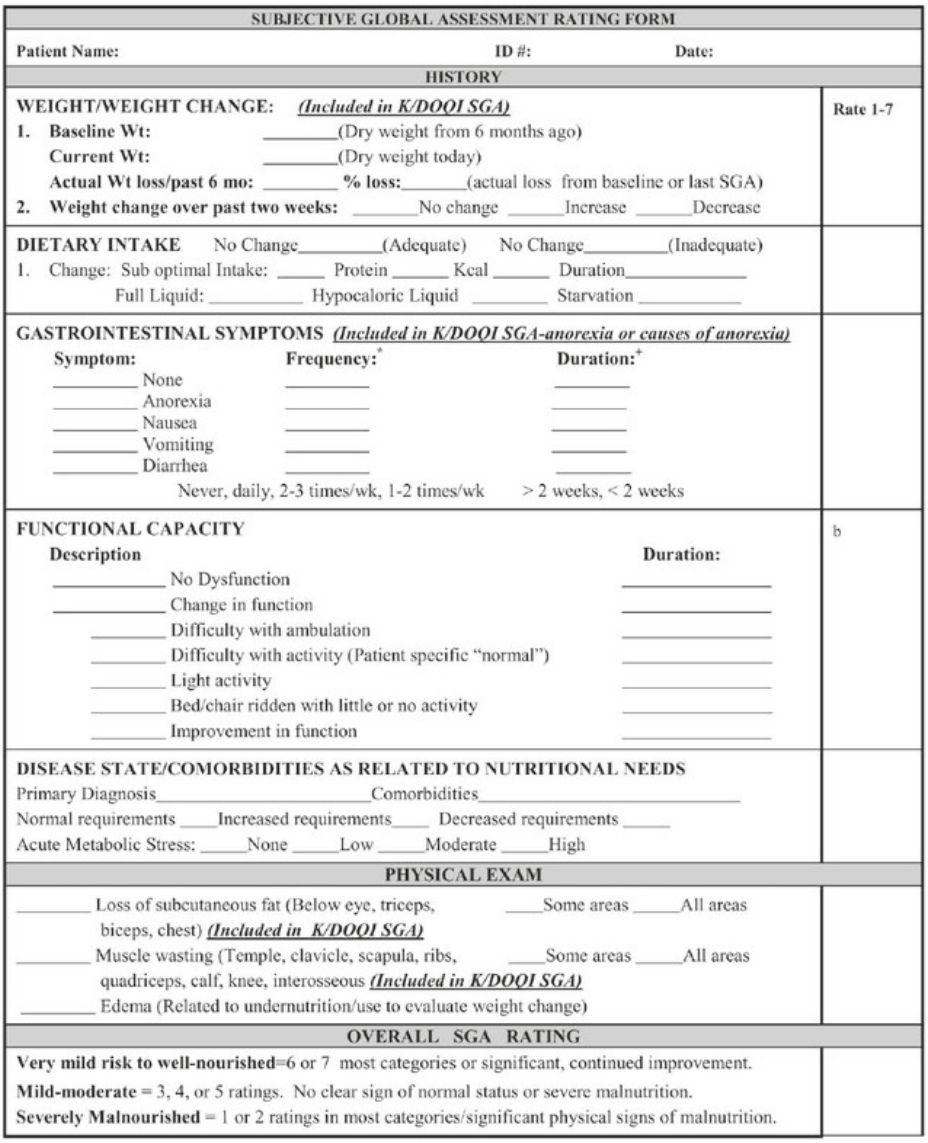
Sample size

As described in the study protocol, the a priori sample size calculation showed that 195 patients were needed to show a difference in complication rate between the groups with and without malnutrition.[6] However, due to the low inclusion rate during the COVID-19 pandemic, it was decided to prematurely end the inclusion at 100 patients.

Study parameters

Nutritional status

The Subjective Global Assessment scale (**Figure 1**) was used to assess the nutritional status and determine pre-existent and in-hospital developed malnutrition.[8] The SGA scale is a nutritional assessment tool that has been validated for the acute hospital setting, for surgical patients and for patients admitted to the ICU requiring mechanical ventilation.[8-10] The SGA evaluates weight change (over the past 2 weeks and 6 months), in-/ adequate dietary intake change, gastrointestinal symptoms (less appetite, nausea, vomiting, diarrhea), and functional capacity (dysfunction, bedridden, difficulty with normal activities). Determining the SGA score also includes a physical examination of subcutaneous fat loss (eyes, triceps, biceps) and muscle wasting (e.g., clavicle, knee, shoulder, and quadriceps). The SGA is scored on a scale ranging from 1 to 7.



SUBJECTIVE GLOBAL ASSESSMENT RATING FORM

Patient Name: ID #: Date:

HISTORY

WEIGHT/WEIGHT CHANGE: *(Included in K/DOQI SGA)* — Rate 1-7

1. **Baseline Wt:** _____(Dry weight from 6 months ago)
   Current Wt: _____(Dry weight today)
   Actual Wt loss/past 6 mo: _____ **% loss:**_____(actual loss from baseline or last SGA)
2. **Weight change over past two weeks:** _____No change _____Increase _____Decrease

DIETARY INTAKE No Change_____(Adequate) No Change_____(Inadequate)

1. Change: Sub optimal Intake: _____ Protein _____ Kcal _____ Duration_____
   Full Liquid: _____ Hypocaloric Liquid _____ Starvation _____

GASTROINTESTINAL SYMPTOMS *(Included in K/DOQI SGA-anorexia or causes of anorexia)*

Symptom:	Frequency:*	Duration:+
_____ None	_____	_____
_____ Anorexia	_____	_____
_____ Nausea	_____	_____
_____ Vomiting	_____	_____
_____ Diarrhea	_____	_____

Never, daily, 2-3 times/wk, 1-2 times/wk > 2 weeks, < 2 weeks

FUNCTIONAL CAPACITY — b

Description	Duration:
_____ No Dysfunction	_____
_____ Change in function	_____
_____ Difficulty with ambulation	_____
_____ Difficulty with activity (Patient specific "normal")	_____
_____ Light activity	_____
_____ Bed/chair ridden with little or no activity	_____
_____ Improvement in function	_____

DISEASE STATE/COMORBIDITIES AS RELATED TO NUTRITIONAL NEEDS

Primary Diagnosis_____Comorbidities_____
Normal requirements ____Increased requirements____ Decreased requirements _____
Acute Metabolic Stress: _____None _____Low _____Moderate _____High

PHYSICAL EXAM

_____ Loss of subcutaneous fat (Below eye, triceps, biceps, chest) *(Included in K/DOQI SGA)* ____Some areas _____All areas

_____ Muscle wasting (Temple, clavicle, scapula, ribs, quadriceps, calf, knee, interosseous *(Included in K/DOQI SGA)* ____Some areas _____All areas

_____ Edema (Related to undernutrition/use to evaluate weight change)

OVERALL SGA RATING

Very mild risk to well-nourished=6 or 7 most categories or significant, continued improvement.
Mild-moderate = 3, 4, or 5 ratings. No clear sign of normal status or severe malnutrition.
Severely Malnourished = 1 or 2 ratings in most categories/significant physical signs of malnutrition.

Figure 1: Subjective Global Assessment rating form [8]

Patients are classified as A (well-nourished; scores 6-7), B (mild to moderately malnourished; scores 3-5) or C (severely malnourished; scores 1-2).[11] In this study, B and C were combined in one category (malnourished, defined by an SGA score ≤5).[6] The SGA was scored by trained personnel at ICU admission, every five days during ICU admission, at ICU discharge, every week on the ward, and at hospital

discharge. A recent systematic review indicated that the SGA score can be used to assess in-hospital acquired malnutrition.[12]

Other parameters and in-hospital outcomes

Information on nutritional support was collected, and patients were categorized based on whether they received oral feeding or (par)enteral feeding. In the patients who received (par)enteral nutrition, it was documented whether nutrition was initiated within 48 hours or after 48 hours of admission. Target energy goals were calculated through a weight-based predictive equation (25 kcal/kg/day). In overweight patients (BMI >25 kg/m2), the ideal body weight was used, which is calculated by the following equation: 0.9 x height in cm - 100 (male) (or - 106 (female)).[13] According to the ESPEN guidelines, target energy goals should be met after 3-7 days of admission. It was documented whether goals were met after <48 hours, 3-7 days, and after >7 days of admission. Albumin and pre-albumin levels were measured within 24 hours of admission. Surgical procedures that required patients to go to the operating room were documented. The following complications were included in the analysis: systemic complications (sepsis, Acute Respiratory Distress Syndrome (ARDS), Systemic Inflammatory Response Syndrome (SIRS), multiple-organ failure), surgery-related complications (anastomotic leak, stoma surgical site infection deep and superficial, abscess, (re)bleeding, wound infection), pneumonia, urinary tract infection (UTI), deep venous thrombosis (DVT), pulmonary embolism (PE), and fracture-related complications (compartment syndrome, thromboembolic disease, fat embolism syndrome, reoperation due to non-union or mal-union). Pneumonia was defined as lung inflammation caused by a bacterial or viral infection. Consequently, COVID-19 pneumonia was also classified as pneumonia. Furthermore, in-ICU and in-hospital mortality were included in the analysis. Other in-hospital outcomes included hospital length of stay (LOS), ICU LOS, and ventilator days.

Statistical analysis

Statistical analyses were performed with IBM SPSS Statistics for Windows, version 25. P-values <0.05 were considered statistically significant. The baseline characteristics and outcomes of the patients who remained well-nourished throughout hospital admission (Group 1; **Figure 2**), patients who became malnourished during hospital admission (Group 2), and patients who had malnutrition at hospital admission (Group 3) were compared using the Chi-

Square test for categorical variables and the one way ANOVA test for continuous variables. Furthermore, the baseline characteristics and outcomes of the patients who became malnourished during ICU admission (Group 2A; **Figure 2**) were compared to those of the patients who became malnourished during admission to the ward (Group 2B) using the Fisher's exact test for categorical variables and the independent samples T-test for continuous variables.

The *prevalence of pre-existing malnutrition* was calculated as the proportion (with 95% confidence interval [CI]) of patients who were malnourished at ICU admission. The *incidence of in-ICU malnutrition* was calculated as the proportion (with 95% CI) of patients who became malnourished during ICU stay. The *incidence of in-hospital malnutrition* was calculated as the proportion (with 95% CI) of patients that became malnourished during total hospital stay.

The complication rate was calculated as the proportion of patients with any of the included complications during hospital admission. The complication rate was compared between patient groups using the Chi-square test. The odds ratio (OR) (with 95% CI) of complications during hospital stay for patients with malnutrition (Groups 1 and 2; **Figure 2**) compared to well-nourished patients (Group 3) was calculated. To correct for potential confounders a multivariate logistic regression analysis was performed including the baseline characteristics that differed between the well-nourished and malnourished groups with univariate $p<0.10$.

RESULTS

Prevalence and incidence of malnutrition

The mean age of the 100 included patients was 50 (± 21) years, 70 patients were male (**Table 1**). Seven patients died during their stay at the Intensive care unit (ICU), and four more patients died while being admitted to the ward. Twelve patients were considered malnourished at ICU admission (SGA score ≤5; Group 1; **Figure 2**), the prevalence of pre-existing malnutrition being 12% (95% CI 5.6 – 18.4%). These patients scored insufficient (i.e. ≤5 points in SGA item) on weight (loss) (n=8), dietary intake (n=12), gastrointestinal symptoms (n=3), functional capacity (n=1), disease state (n=12), and/or physical exam (n=5). All 12 malnourished patients

remained malnourished throughout hospital admission. Of the 88 patients that were well-nourished at admission, 44 became malnourished during ICU stay (Group 2A; **Figure 2**) (incidence of in-ICU malnutrition 50.0%, 95% CI 39.6-60.4%). These 44 patients scored insufficient on weight (loss) (n=32), dietary intake (n=42), gastrointestinal symptoms (n=2), functional capacity (n=14), disease state (n=44), and/or physical exam (n=26). Additionally, 18 patients became malnourished during admission to the ward (Group 2B; **Figure 2**). These 18 patients scored insufficient on weight (loss) (n=16), dietary intake (n=14), gastrointestinal symptoms (n=5), functional capacity (n=18), disease state (n=18), and/or physical exam (n=15). In total, 62 patients became malnourished during hospital stay (Group 2; **Figure 2**), with an incidence of in-hospital malnutrition of 70.5% (95% CI 60.9-80.0%).

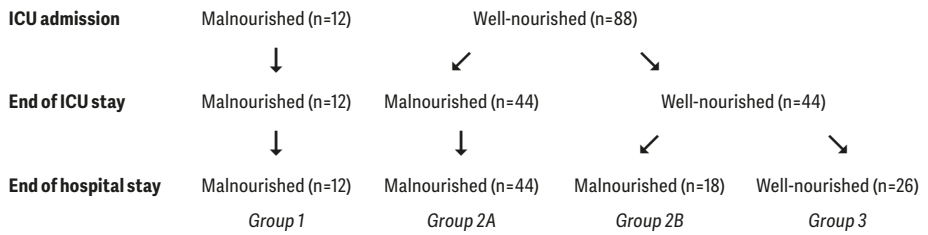


Figure 2: Distribution of severely injured patients according to their nutritional status based on the Subjective Global Assessment (SGA)

Patient characteristics

Patients who became malnourished during their hospital stay (Group 2; **Figure 2**) were significantly more likely to have very severe injuries (ISS ≥25), than the patients who were malnourished at admission (Group 1) or the patients who remained well-nourished throughout hospital stay (Group 3) (77% vs 42% vs 54% respectively; p<0.01; **Table 1**). Furthermore, a higher percentage of these patients underwent surgery (89%) compared to the patients who were already malnourished (58%) or those who remained well-nourished (77%; p=0.03; **Table 1**). Comparison between the 44 patients who became malnourished during ICU admission (Group 2A; **Figure 2**) and the 18 patients who became malnourished during admission to the ward (Group 2B) revealed no statistically significant differences (**Table 2**).

Table 1: Patient characteristics according to their nutritional status

	Total (n=100)	Malnourished at admission (n=12; Group 1)	Become malnourished during hospital stay (n=62; Group 2)	Well-nourished throughout hospital stay (n=26; Group 3)	P value
Age in years, mean ± SD	50 ± 21	61 ± 25	47 ± 20	52 ± 21	0.09
Male sex, n (%)	70 (70)	10 (83)	40 (65)	20 (77)	0.29
BMI in kg/m², mean ± SD	26 ± 5	26 ± 4	26 ± 5	27 ± 6	0.57
Obesity (BMI ≥ 30 kg/m²), n (%)	19 (19)	3 (25)	11 (18)	5 (19)	0.84
Severe injury (AIS ≥ 4), n (%)					
Head	44 (44)	3 (25)	32 (52)	9 (35)	0.13
Chest	29 (29)	2 (17)	19 (31)	8 (31)	0.60
Abdomen	9 (9)	1 (8)	6 (10)	2 (8)	0.95
Extremity	14 (14)	1 (8)	10 (16)	3 (12)	0.71
ISS ≥ 25, n (%)	67 (67)	5 (42)	48 (77)	14 (54)	**0.01**
GCS score ≤ 8, n (%)	42 (42)	3 (25)	29 (47)	10 (38)	0.34
Alcohol abuse, n (%)	15 (15)	2 (17)	10 (16)	3 (12)	0.85
Malignancy, n (%)	8 (8)	2 (17)	3 (5)	3 (12)	0.29
Nutrition, n (%)					0.19
Oral	29 (29)	5 (42)	14 (23)	10 (39)	
(Par)enteral	71 (71)	7 (58)	48 (77)	16 (62)	
Initiation of (par)enteral nutrition, n (%)					0.94
< 48 hours	63 (89)	6 (86)	43 (90)	14 (88)	
≥ 48 hours	8 (11)	1 (14)	5 (10)	2 (13)	
Time until target energy goals were met, n (%)					0.33
< 48 hours	19 (19)	0 (0)	14 (23)	5 (19)	
3-7 days	67 (67)	10 (83)	38 (61)	19 (73)	
> 7 days	14 (14)	2 (17)	10 (16)	2 (8)	
Albumin level at admission in g/L, mean ± SD	34 ± 7	35 ± 7	33 ± 7	34 ± 8	0.69
	(n=91)	(n=11)	(n=57)	(n=23)	
Pre-albumin level at admission in g/L, mean ± SD	0.17 ± 0.06	0.15 ± 0.05	0.18 ± 0.06	0.17 ± 0.06	0.29
	(n=64)	(n=6)	(n=41)	(n=17)	
Surgery, n (%)	82 (82)	7 (58)	55 (89)	20 (77)	**0.03**

AIS, Abbreviated Injury Scale severity (last digit of the AIS code); BMI, Body Mass Index; GCS, Glasgow Coma Scale; ISS, Injury Severity Score: SD, Standard deviation

Table 2: Patient characteristics of the 62 patients who developed malnutrition during hospital admission

	Total (n=62)	Become malnourished during ICU stay (n=44; Group 2A)	Become malnourished during admission to the ward (n=18; Group 2B)	P value
Age in years, mean ± SD	47 ± 20	47 ± 20	46 ± 19	0.85
Male sex, n (%)	40 (65)	26 (59)	14 (78)	0.24
BMI in kg/m², mean ± SD	26 ± 5	25 ± 4	27 ± 5	0.32
Obesity (BMI ≥ 30 kg/m²), n (%)	11 (18)	7 (16)	4 (22)	0.72
Severe injury (AIS ≥ 4), n (%)				
Head	32 (52)	25 (57)	7 (39)	0.27
Chest	19 (31)	11 (25)	8 (44)	0.14
Abdomen	6 (10)	3 (7)	3 (17)	0.34
Extremity	10 (16)	7 (16)	3 (17)	1.00
ISS ≥ 25, n (%)	48 (77)	32 (73)	16 (89)	0.20
GCS score ≤ 8, n (%)	29 (47)	24 (55)	5 (28)	0.09
Alcohol abuse, n (%)	10 (16)	8 (18)	2 (11)	0.71
Malignancy, n (%)	3 (5)	2 (5)	1 (6)	1.00
Nutrition, n (%)				0.32
Oral	14 (23)	8 (18)	6 (33)	
(Par)enteral	48 (77)	36 (82)	12 (67)	
Initiation of (par)enteral nutrition, n (%)				0.31
< 48 hours	43 (90)	31 (86)	12 (100)	
≥ 48 hours	5 (10)	5 (14)	0 (0)	
Time until target energy goals were met, n (%)				0.71
< 48 hours	14 (23)	9 (21)	5 (28)	
3-7 days	38 (61)	27 (61)	11 (61)	
> 7 days	10 (16)	8 (18)	2 (11)	
Albumin level at ICU discharge in g/L, mean ± SD	33 ± 7	32 ± 7	36 ± 5	0.05
	(n=57)	(n=41)	(n=16)	
Pre-albumin level at ICU discharge in g/L, mean ± SD	0.18 ± 0.06	0.18 ± 0.06	0.19 ± 0.05	0.38
	(n=41)	(n=27)	(n=14)	
Surgery, n (%)	55 (89)	39 (89)	16 (89)	1.00

AIS, Abbreviated Injury Scale severity (last digit of the AIS code); BMI, Body Mass Index; GCS, Glasgow Coma Scale; ICU, Intensive Care Unit; ISS, Injury Severity Score: SD, Standard deviation

Complications and other in-hospital outcomes

The complication rate during hospital admission was significantly higher in the 62 patients who developed malnutrition (Group 2; **Figure 2**) and the 12 patients who were malnourished upon admission (Group 1) compared to the 26 patients who remained well-nourished throughout their hospital stay (Group 3) (58% vs 50% vs 27% resp.; p=0.03; **Table 3**). ICU LOS, number of ventilator days, and hospital LOS were not statistically different between the three groups. No significant difference in ICU-mortality and in-hospital mortality was seen between the patients who became malnourished, those who were already malnourished, and those who remained well-nourished.

Table 3: Patient outcomes according to their nutritional status

	Total (n=100)	Malnourished at admission (n=12; Group 1)	Become malnourished during hospital stay (n=62; Group 2)	Well-nourished throughout hospital stay (n=26; Group 3)	P value
Complication, n (%)	49 (49)	6 (50)	36 (58)	7 (27)	**0.03**
ICU-mortality, n (%)	7 (7)	0 (0)	3 (5)	4 (15)	0.13
In-hospital mortality, n (%)	11 (11)	1 (8)	5 (8)	5 (19)	0.30
Systemic complications, n (%)	10 (10)	2 (17)	7 (11)	1 (4)	0.41
Surgical complications, n (%)	9 (9)	1 (8)	6 (10)	2 (8)	0.95
Fracture-related complications, n (%)	2 (2)	1 (8)	1 (2)	0 (0)	0.22
Pneumonia, n (%)	40 (40)	4 (33)	30 (48)	6 (23)	0.08
Urinary tract infection, n (%)	11 (11)	1 (8)	8 (13)	2 (8)	0.74
Venous thromboembolism, n (%)	7 (7)	0 (0)	7 (11)	0 (0)	0.10
ICU LOS in days *, mean ± SD	13 ± 18	11 ± 8	14 ± 18	11 ± 23	0.73
Ventilator days *, mean ± SD	8 ± 14	7 ± 8	9 ± 10	9 ± 24	0.91
Hospital LOS in days **, mean ± SD	29 ± 24	25 ± 17	33 ± 26	19 ± 22	0.05

ICU, Intensive care unit; LOS, Length of stay; n, number; SD, standard deviation;

* Patients who died during ICU admission were excluded (n=7)

** Patients who died during hospital admission (n=11) or were transferred to another hospital (n=2) were excluded

Concerning the 62 patients who developed malnutrition during hospital admission, the 44 patients who became malnourished during ICU stay (Group 2A; **Figure 2**) suffered significantly more from pneumonia than the 18 patients who developed malnutrition during admission to the ward (Group 2B; **Figure 2**) (59% vs 22%; p=0.01; **Table 4**). Furthermore, ICU LOS and ventilator days were significantly

higher in the patients who became malnourished during ICU stay than the patients who developed malnutrition during admission to the ward.

The crude odds ratio (OR) for complications in malnourished compared to well-nourished patients was 3.3 (95% CI 1.3 – 8.4). After correction for age, injury severity, and surgery, the increased risk of complications in malnourished patients remained statistically significant (OR 3.4, 95% CI 1.2 – 9.6).

Table 4: Patient outcomes of the 62 patients who developed malnutrition during hospital admission

	Total (n=62)	Become malnourished during ICU stay (n=44; Group 2A)	Become malnourished during admission to the ward (n=18; Group 2B)	P value
Complication, n (%)	36 (58)	28 (64)	8 (44)	0.26
ICU-mortality, n (%)	3 (5)	3 (7)	0 (0)	0.55
In-hospital mortality, n (%)	5 (8)	5 (11)	0 (0)	0.31
Systemic complications, n (%)	7 (11)	5 (11)	2 (11)	1.00
Surgery-related complications, n (%)	6 (10)	5 (11)	1 (6)	0.66
Fracture-related complications, n (%)	1 (2)	1 (2)	0 (0)	1.00
Pneumonia, n (%)	30 (48)	26 (59)	4 (22)	**0.01**
Urinary tract infection, n (%)	8 (13)	6 (14)	2 (11)	1.00
Venous thromboembolism, n (%)	7 (11)	5 (11)	2 (11)	1.00
ICU LOS in days *, mean ± SD	14 ± 18	17 ± 20	8 ± 5	**0.01**
Ventilator days *, mean ± SD	9 ± 10	10 ± 11	5 ± 5	**0.01**
Hospital LOS in days **, mean ± SD	33 ± 26	35 ± 29	31 ± 18	0.67

ICU, Intensive care unit; LOS, Length of stay; n, number; SD, standard deviation;

* Patients who died during ICU admission were excluded (n=3)

** Patients who died during hospital admission (n=5) or were transferred to another hospital (n=2) were excluded

DISCUSSION

To our knowledge, this is the first study that analyzed the relationship between in-hospital developed malnutrition and complications in severely injured patients. Twelve percent of all severely injured patients admitted to the ICU were already malnourished at admission. The incidence of in-ICU malnutrition was 50.0% and the incidence of in-hospital malnutrition was 70.5%. Complications occurred significantly more often in malnourished patients than in well-nourished patients.

Several studies have been published concerning the prevalence of malnutrition in trauma patients, as assessed by the SGA at hospital admission. In two studies including trauma patients admitted to the ICU, the prevalence of malnutrition at admission was 11 and 12%.[14,15] In patients with a moderate-to-severe traumatic brain injury (TBI) admitted to the ICU, 14% were found to be malnourished.[16] These results are comparable to our results. When looking at all trauma patients, both ICU and non-ICU patients, this prevalence ranged up to 48% at admission.[17-19] In studies including geriatric trauma patients, 30-66% were malnourished at hospital admission.[20-22] Since malnutrition is more common in the elderly population, this probably explains the higher prevalence of malnutrition in these study groups.[23]

Studies reporting the changes in the nutritional status of trauma patients also found a significant increase in malnutrition during hospital admission. In acute care surgery patients, 27% were malnourished at admission and 41% was malnourished after one week of admission.[24] In a study by Chapple et al. concerning ICU patients with moderate TBI (GCS 9-12) or severe TBI (GCS 3-8), malnutrition increased from 14% at admission to 44% at hospital discharge.[16] We found that the incidence of in-hospital malnutrition was 70.5%, with a prevalence of malnutrition of 74% at hospital discharge. A higher Injury Severity Score (ISS) is found to be related to higher levels of proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6).[25] These proinflammatory cytokines can cause the body to be in a hypermetabolic state and therefore lead to a loss of body resources.[5] In addition, severely injured patients might suffer more from gastro intestinal-problems such as an ileus, or have to undergo surgery more frequently than TBI patients, which could cause a deterioration in the nutritional status. This might explain the higher incidence of in-hospital malnutrition in our severely injured patient study group compared to the isolated TBI population of Chapple et al.[16]

The high incidence of malnutrition is not simply a matter of insufficient emphasis on nutritional support in the five included hospitals, as the ICU protocols of the five included hospitals align with the ESPEN recommendations.[13] According to these guidelines, (par)enteral nutrition ((P)EN) should be initiated within 48 hours if oral intake is not possible. In our patient group, 89% of the (P)EN was initiated within 48 hours. Reasons for not starting P(EN) within 48 hours were: septic shock (n=1), gastric retention (n=2), or fasting before multiple sur-

geries (n=5). In these 8 patients, (P)EN was initiated between 48-96 hours after admission. Furthermore, ESPEN recommends that full (P)EN (i.e. meeting 100% of caloric needs) shall be prescribed within three to seven days to prevent overfeeding. However, 19 patients (19%) received full (P)EN within 48 hours and 14 patients (14%) did not meet caloric needs within 7 days. This was not statistically significant between the patients who were malnourished or developed malnutrition and the patients who remained well-nourished. Possibly, the hypermetabolic catabolic state following severe trauma cannot be sufficiently compensated so that a deterioration in nutritional status can be prevented in all cases, even with adequate nutritional therapy. Additionally, the unavoidable fasting period before surgery and the resulting acute phase response after surgery make polytrauma patients exceptionally susceptible to malnutrition. Studies on developments related to peri-operative management are regularly published, such as the Enhanced Recovery After Surgery (ERAS) protocol.[26] One component of the ERAS protocol is early oral feeding after surgery (starting 4 hours post-surgery). This approach can lead to faster intestinal recovery, shorter postoperative hospital stays, and fewer complications for patients undergoing gastrointestinal surgery.[27] Since polytrauma patients frequently have multiple surgeries within the initial days of ICU admission, careful monitoring of enteral nutrition and close collaboration with a dietitian is essential for managing both the timing and quantity of enteral feeding.

However, providing more nutrition is not always beneficial, as overfeeding is known to pose risks for ICU patients.[28] Overfeeding can lead to complications such as hyperglycemia, increased carbon dioxide production (leading to respiratory complications), and fat accumulation in the liver, especially in critically ill patients.[29] The endogenous glucose production is elevated in the early phases of critical illness due to stress-induced metabolic changes, which makes patients particularly vulnerable to overfeeding during this time.[30] Indirect calorimetry is a tool that measures oxygen consumption (VO_2) and carbon dioxide production (VCO_2) to calculate a patient's actual energy expenditure.[31] This allows healthcare providers to tailor nutritional interventions more precisely, avoiding the potential risks of both underfeeding and overfeeding, especially during ICU admission. On the other hand, following ICU admission, calorie and protein requirements typically rise as patients become more physically active and mobilized during their transition to the ward.[32] However, nutritional intake during this phase may fall short of meeting the increased demands, leaving severely injured patients

vulnerable to malnutrition, even while admitted to the ward. Personalized nutrition plans, based on each patient's metabolic needs, can improve recovery outcomes and reduce complications associated with improper feeding strategies.

In earlier publications, malnutrition, defined as SGA ≤5, was found to be related to increased mortality, complications, and prolonged hospital LOS in trauma patients.[17,18,24] In critically ill patients, a significant association was demonstrated between SGA and mortality, pressure injuries, length of stay, and ICU readmission rates.[10,33,34] Our study found a relationship between malnutrition and complications (**Table 3**). Surprisingly, ICU mortality and in-hospital mortality seemed higher in the well-nourished patients compared to the patients who were malnourished or developed malnutrition (15% vs 0% vs 5%, p=0.13; 19% vs 8% vs 8%, p=0.30, resp.), although both differences were not statistically significant (**Table 3**). This apparent contradictory result may be due to the fact that deterioration in nutritional status occurs gradually and can take several days. Of the 11 patients who died during hospital admission, 6 died within the first week of admission. It seems unlikely that their nutritional status could have deteriorated that much during the short period until their passing, resulting in a higher percentage of patients who were still well-nourished at the time of death. Concerning other in-hospital outcomes among patients who survived their admission, such as ICU LOS, ventilator days, and hospital LOS, no difference was found in the patients that were malnourished or developed malnutrition during admission and the patients who were well-nourished (**Table 3**). Although the hospital LOS seemed longer for the patients who became malnourished (**Table 3**), this difference was not statistically significant (p=0.05), possibly due to a lack of statistical power. Lastly, patients who developed malnutrition during their ICU stay experienced significantly higher rates of pneumonia, had a longer ICU length of stay, and required more ventilator days compared to those who became malnourished during ward admission (**Table 4**). Thus, malnutrition seems to be evidently correlated with complications and in-hospital outcomes. However, the causal relationship between malnutrition and these outcomes remains ambiguous, as both have the potential to influence the other. For example, malnutrition can make a person more susceptible to infection, and infection also contributes to a deterioration of the nutritional status.[35] In addition, malnutrition at admission is known to be associated with prolonged hospital LOS.[36] Furthermore, the longer a patient stays in a hospital, the higher the probability of acquiring an infection.[37] In conclusion, malnutrition seems to be evidently corre-

lated with complications and in-hospital outcomes, but the causal correlation cannot be established.

Limitations

Since not much nutritional research has been done on severely injured patients, this study can be considered one of the largest studies on the subject. The sample size was limited to 100 patients for pragmatic reasons. Not all patients who were considered eligible for the study were included. The primary reasons for this were organizational challenges as the study demanded significant time from ICU staff, and difficulties in obtaining informed consent (which can be considered burdensome for families of critically ill patients). However, we do not believe that this has led to selection bias in the included patient group. Although the difference in the overall complication rate between the patient groups was statistically significant, the statistical power was too low to detect clinically relevant differences for specific complications, for instance for in-hospital mortality, pneumonia, and venous thromboembolism. Another limitation is presented by the fact that there is no 'gold standard' for assessing nutritional status. We used the SGA, as it has been validated for ICU patients and is proven to be the most predictive for outcomes. The SGA score itself, however, is not very discriminative, since the difference between an SGA score of 5 (malnourished) or 6 (well-nourished) can be very minimal. To increase reliability and reduce interobserver variability, the SGA scores were verified by one investigator at the end of data collection. Unfortunately, not enough patients with severe malnutrition (SGA ≤2) were included to perform a separate analysis for SGA groups. Therefore, no distinction was made in the severity of malnutrition; SGA scores of 1 to 5 all reflected a malnourished status. Lastly, as already stated in the discussion section, the causal correlation between malnutrition and both complications and in-hospital outcomes cannot be established, since these components are interdependent.

CONCLUSION

Over 50% of all well-nourished severely injured patients develop malnutrition during ICU admission, increasing to 70% during their total hospital stay. Malnutrition in severely injured patients developed during ICU and hospital admission is found to be related to an increased risk of complications. There-

fore, awareness of the importance of nutritional strategies needs to become a common ground for all clinicians treating severely injured patients. Recognition of sub-optimally nourished severely injured patients and assessment of their nutritional needs is crucial in order to improve their clinical outcome.

REFERENCES

1. Osooli F, Abbas S, Farsaei S, Adibi P. *Identifying critically ill patients at risk of malnutrition and underfeeding: A prospective study at an academic hospital*. Adv Pharm Bull. 2019;9(2):314-20.
2. Norman K, Pichard C, Lochs H, Pirlich M. *Prognostic impact of disease-related malnutrition*. Clin Nutr. 2008;27(1):5-15.
3. Barker LA, Gout BS, Crowe TC. *Hospital malnutrition: prevalence, identification and impact on patients and the healthcare system*. Int J Environ Res Public Health. 2011;8(2):514-27.
4. White JV, Guenter P, Jensen G, Malone A, Schofield M, Academy Malnutrition Work Group, et al. *Consensus statement: Academy of Nutrition and Dietetics and American Society for Parenteral and Enteral Nutrition: characteristics recommended for the identification and documentation of adult malnutrition (undernutrition).* J Parenter Enteral Nutr. 2012;36(3):275-83.
5. Dijkink S, Meier K, Krijnen P, Yeh DD, Velmahos GC, Schipper IB. *Malnutrition and its effects in severely injured trauma patients.* Eur J Trauma Emerg Surg. Oct 2020;46(5):993-1004.
6. Dijkink S, Meier K, Krijnen P, Yeh DD, Velmahos GC, Arbous MS, et al. *The malnutrition in polytrauma patients (MaPP) study: Research protocol*. Nutr Health. 2019;25(4):291-301.
7. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. *STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies*. BMJ. 2007;335(7624):806-8.
8. Detsky AS, McLaughlin JR, Baker JP, Johnston N, Whittaker S, Mendelson RA, et al. *What is subjective global assessment of nutritional status?* JPEN J Parenter Enteral Nutr. 1987;11(1):8-13.
9. Sheean PM, Peterson SJ, Gurka DP, Braunschweig CA. *Nutrition assessment: the reproducibility of Subjective Global Assessment in patients requiring mechanical ventilation*. Eur J Clin Nutr. 2010;64(11):1358-64.
10. Bector S, Vagianos K, Suh M, Duerksen DR. *Does the subjective global assessment predict outcome in critically ill medical patients?* J Intensive Care Med. Aug 2016;31(7):485-9.
11. Baker JP, Detsky AS, Wesson DE, Wolman SL, Stewart S, Whitewell J, et al. *Nutritional assessment: a comparison of clinical judgement and objective measurements*. N Engl J Med. 1982;306(16):969-72.
12. Cass AR, Charlton KE. *Prevalence of hospital-acquired malnutrition and modifiable determinants of nutritional deterioration during inpatient admissions: A systematic review of the evidence*. J Hum Nutr Diet. 2022;35(6):1043-58.
13. Singer P, Blaser AR, Berger MM, Calder PC, Casaer M, Hiesmayr M, et al. *ESPEN practical and partially revised guideline: Clinical nutrition in the intensive care unit*. Clin Nutr. 2023;42(9):1671-89.
14. Chakravarty C, Hazarika B, Goswami L, Ramasubban S. *Prevalence of malnutrition in a tertiary care hospital in India*. Indian J Crit Care Med. 2013;17(3):170-3.
15. Javid Mishamandani Z, Norouzy A, Hashemian SM, Khoundabi B, Rezaeisadrabadi M, Safarian M, et al. *Nutritional status of patients hospitalized in the intensive care unit: A comprehensive report from Iranian hospitals, 2018.* J Crit Care. 2019;54:151-8.
16. Chapple LS, Deane AM, Williams LT, Strickland R, Schultz C, Lange K, et al. *Longitudinal changes in anthropometrics and impact on self-reported physical function after traumatic brain injury.* Crit Care Resusc. 2017;19(1):29-36.

17. Goiburu ME, Goiburu MM, Bianco H, Díaz JR, Alderete F, Palacios MC, et al. *The impact of malnutrition on morbidity, mortality and length of hospital stay in trauma patients*. Nutr Hosp. 2006;21(5):604-10.

18. Kushwaha NS, Rana DB, Singh A, Saxena S, Srivastava S, Sharma V. *Assessment of Nutrition Status and Its Effect on Outcomes in Patients With Limb Injuries Using the Subjective Global Assessment as a Screening Tool*. Cureus. 2023;15(9):e44953.

19. Subwongcharoen S, Areesawangvong P, Chompoosaeng T. *Impact of nutritional status on surgical patients*. Clin Nutr ESPEN. 2019;32:135-9.

20. Sánchez-Torralvo FJ, Pérez-Del-Río V, García-Olivares M, Porras N, Abuín-Fernández J, Bravo-Bardají MF, et al. *Global Subjective Assessment and Mini Nutritional Assessment Short Form Better Predict Mortality Than GLIM Malnutrition Criteria in Elderly Patients with Hip Fracture*. Nutrients. 2023;15(8):1828.

21. Wong AM, Xu BY, Low LL, Allen JC, SG. L. *Impact of malnutrition in surgically repaired hip fracture patients admitted for rehabilitation in a community hospital: A cohort prospective study*. Clin Nutr ESPEN. 2023;44:188-93.

22. Goost H, Vidakovic E, Deborre C, Randau T, Wirtz DC, Burger C, et al. *Malnutrition in geriatric trauma patients: Screening methods in comparison.* Technol Health Care. 2016;24(2):225-39.

23. Norman K, Haß U, Pirlich M. *Malnutrition in Older Adults-Recent Advances and Remaining Challenges*. Nutrients. 2021;13(8):2764.

24. Abahuje E, Niyongombwa I, Karenzi D, Bisimwa JA, Tuyishime E, Ntirenganya F, et al. *Malnutrition in Acute Care Surgery Patients in Rwanda*. World J Surg. 2020;44(5):1361-7.

25. Cai J, McKinley T, Billiar I, Zenati MS, Gaski G, Vodovotz Y, et al. *Protective/reparative cytokines are suppressed at high injury severity in human trauma*. Trauma Surg Acute Care Open. 2021;6(1):e000619.

26. Melnyk M, Casey RG, Black P, Koupparis AJ. *Enhanced recovery after surgery (ERAS) protocols: Time to change practice?* Can Urol Assoc J. 2011;5(5):342-8.

27. Canzan F, Longhini J, Caliaro A, Cavada ML, Mezzalira E, Paiella S, et al. *The effect of early oral postoperative feeding on the recovery of intestinal motility after gastrointestinal surgery: a systematic review and meta-analysis of randomized clinical trials*. Front Nutr. 2024;11:1369141.

28. Hermans A, Laarhuis B, Kouw I, van Zanten A. *Current insights in ICU nutrition: tailored nutrition*. Current Opinion in Critical Care. 2023;29(2):101-7.

29. Cade JF, Jones DA, Bellomo R. *Nutrition in the intensive care unit - you must breathe what you eat*. Crit Care Resusc. 2016;18(4):224-7.

30. Wischmeyer PE, Bear DE, Berger MM, De Waele E, Gunst J, McClave SA, et al. *Personalized nutrition therapy in critical care: 10 expert recommendations*. Crit Care. 2023;27(1):261.

31. Haugen HA, Chan LN, Li F. *Indirect calorimetry: a practical guide for clinicians*. Nutr Clin Pract. 2007;22(4):377-88.

32. De Waele E, Jonckheer J, Wischmeyer PE. *Indirect calorimetry in critical illness: a new standard of care?* Curr Opin Crit Care. 2021;27(4):334-43.

33. Ferrie S, Weiss NB, Chau HY, Torkel S, Stepniewski ME. *Association of Subjective Global Assessment with outcomes in the intensive care unit: A retrospective cohort study*. Nutr Diet. 2022;79(5):572-81.

34. Fontes D, de Vasconcelos Generoso S, Toulson Davisson Correia MI. *Subjective global assessment: a reliable nutritional assessment tool to predict outcomes in critically ill patients*. Clin Nutr. 2014;33(2):291-5.

35. Katona P, Katona-Apte J. *The interaction between nutrition and infection*. Clin Infect Dis. 2008;46(10):1582-8.

36. Nigatu YD, Gebreyesus SH, Allard JP, Endris BS. *The effect of malnutrition at admission on length of hospital stay among adult patients in developing country: A prospective cohort study.* Clin Nutr ESPEN. 2021;41:217-24.

37. Hassan M, Tuckman HP, Patrick RH, Kountz D, Kohn J. *Hospital Length of Stay and Probability of Acquiring Infection*. Int J Pharm Healthc Mark. 2010;4(4):324-38.








CHAPTER 3

Association of modified NUTRIC score for nutritional risk and in-hospital developed malnutrition in adults with severe injuries: a prospective observational cohort study

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ABSTRACT

Introduction

This study investigated the prevalence of high nutritional risk (modified Nutrition Risk in Critically Ill (mNUTRIC) score ≥5) and its relation with malnutrition and other adverse in-hospital outcomes in severely injured patients (Injury Severity Score ≥16), admitted to the ICU. We hypothesized that high nutritional risk is associated with an increased risk of developing malnutrition (primary hypothesis) and of complications and mortality (secondary hypotheses) in adults with severe injuries compared to those with low nutrition risk.

Methods

In this observational prospective study, 100 severely injured patients admitted to the ICU of five Level-1 trauma centers in the US and the Netherlands between 2018-2022 were included. During ICU and hospital stay, malnutrition rates (Subjective Global Assessment score ≤5), complication rates (systemic complications, pneumonia, urinary tract infection, venous thromboembolism), and mortality of severely injured patients with high versus low nutritional risk were compared. A cause-specific Cox regression model was fitted to analyze whether high nutritional risk was related to developing malnutrition.

Results

Eighteen percent of patients had high nutritional risk (95% confidence interval [CI] 10.5-25.5%) at admission. High nutritional risk was not related to in-ICU or in-hospital developed malnutrition. In patients with high nutritional risk, the hazard ratio for developing malnutrition was 1.3 (95% CI 0.7-2.6, p=0.45). Severely injured patients with high nutritional risk had more complications during ICU (78% vs 29%, p<0.001; OR 8.5, 95% CI 2.5-28.3) and hospital stay (83% vs 41%, p<0.01; OR 6.0, 95% CI 1.5-24.9). ICU mortality (22% vs 4%, p=0.02; OR 7.5, 95% CI 1.5-37.3) and hospital mortality (33% vs 6%, p<0.01; OR 5.9, 95% CI 1.3-26.4) were also higher in patients with high nutritional risk.

Conclusion

About one-fifth of severely injured patients admitted to the ICU had high nutritional risk. High nutritional risk in severely injured patients is not associated with malnutrition. It is potentially associated with adverse in-hospital outcomes.

INTRODUCTION

Malnutrition is reported to be independently associated with higher mortality risk, longer hospital length of stay (LOS), and increased cost of hospitalization.[1,2] A variety of tools are available to assess the nutritional status, including nutritional screening tools to assess the risk of developing malnutrition and nutritional assessment tools to evaluate current nutritional status and diagnose malnutrition.[3] Assessing malnutrition using a nutritional assessment tool remains a significant challenge in severely injured patients, as obtaining their dietary history is often complicated by decreased consciousness and/or the need for mechanical ventilation. Evaluation of muscle wasting can be misleading due to swelling and edema, and serum levels of visceral proteins (albumin and pre-albumin) concentrations are affected by the acute-phase response after inflammation or trauma.[4-6]

Alternatively, nutritional screening tools can assess the risk of developing malnutrition and enable timely initiation of appropriate nutritional interventions. This proactive approach helps prevent the onset and progression of malnutrition, along with its associated complications. Among the nutritional screening tools, the modified Nutrition Risk in the Critically Ill (mNUTRIC) score is a validated tool used to quantify the risk of malnutrition and adverse outcomes that may be modified by nutrition therapy in the critical care setting.[7] The mNUTRIC score is based on age, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, Sequential Organ Failure Assessment (SOFA) score, number of comorbidities, and days in-hospital prior to ICU admission.[8] The prevalence of high nutritional risk, defined as mNUTRIC score ≥5, ranges from 22 to 91% in critically ill patients.[9]

Little is known about the nutritional risk of severely injured patients. Timely identification of patients at risk for malnutrition is essential as severely injured patients experience a hypermetabolic state after severe trauma, leading to increased muscle protein mobilization for energy, and decreased protein synthesis leading to catabolism.[10] This hypermetabolic state makes them more vulnerable to acute disease-related or injury-related malnutrition involving a marked inflammatory response.[11] Consequently, an objective measure for assessing nutritional risk, such as the mNUTRIC score, can demonstrate its value if patients identified as having high nutritional risk are more likely to develop malnutrition during their admission. Then, nutritional interventions might be initiated to prevent the onset of malnutrition.

The primary goal of this observational prospective cohort study is to test the hypothesis that high nutritional risk is associated with an increased risk of developing malnutrition in adults with severely injured compared to those with low nutritional risk. Furthermore, the relation between high nutritional risk and other adverse in-hospital outcomes, including complications and mortality, in severely injured patients admitted to the ICU was assessed.

METHODS

Design and setting

The Malnutrition in Polytrauma Patients (MaPP) study is an observational prospective cohort study that was performed on 100 adult severely injured patients at five Level-1 trauma centers, three in the United States (Massachusetts General Hospital and Brigham and Women's Hospital at Boston, and Ryder Trauma Center in Miami) and two in the Netherlands (Leiden University Medical Center at Leiden and Haaglanden Medical Center Westeinde at The Hague). The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the local Institutional Review Boards (protocol number Netherlands: NL64016.058.17, approved on February 21, 2018; protocol number USA: 2018P000202/PHS, approved on April 3, 2018). This study is reported in line with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement.[12] The study methods are described in detail in the published study protocol.[13]

Inclusion and exclusion criteria

All consecutive adult (≥18 years) patients with severe injuries (defined as Injury Severity Score, ISS ≥16) caused by blunt trauma, admitted to the ICU of one of the participating centres, were eligible for inclusion. Patients needed to be admitted to the ICU for more than 48 hours and were not primarily managed in another hospital. Patients with burn wounds and penetrating injuries were excluded.

Patient enrolment

Trauma patients newly admitted to the ICU were screened for inclusion criteria upon admission by the investigators at the participating hospitals between July 2018 and April 2022. Eligible patients were asked to provide written informed consent for participation in the study. If the patient was unable to provide consent (e.g., due to unconsciousness), a legal representative was asked to provide in-

formed consent. If a legal representative gave consent, and the patient became able to provide consent later in the study, they were asked to confirm it themselves. In cases where the patient did not have a legal representative, data was collected prospectively, and the patient was asked for consent once they could do so. If the patient declined to participate in the study, their data was removed from the electronic database. The patient and/or their legal representative could withdraw consent and exit the study at any time.

Sample size

As described in the study protocol, the a priori sample size calculation showed that 195 patients were needed to answer the primary question of the MaPP study.[13] Due to the low inclusion rate during the COVID-19 pandemic, it was decided to prematurely end the inclusion at 100 patients.

Study parameters

Nutritional risk

Our exposure of interest was high nutritional risk defined by modified Nutrition Risk in the Critically Ill (mNUTRIC) ≥5.[8] Our comparator was low nutritional risk defined by mNUTRIC <5. The mNUTRIC score was determined by trained personnel within 24 hours after ICU admission. This score is based on five items: age, Acute Physiology and Chronic Health Evaluation II (APACHE II) score,[14] Sequential Organ Failure Assessment (SOFA) score,[15] the number of comorbidities, and number of days in-hospital prior to ICU admission. The APACHE II score measures ICU mortality based on a number of laboratory values and patient signs. The SOFA score uses measurements of major organ function to determine the degree of organ failure. The mNUTRIC, APACHE II, and SOFA scores are listed in the **Appendix**.

In-hospital outcomes

The primary outcome was malnutrition, defined as a Subjective Global Assessment (SGA) score ≤5. The SGA score was assessed at ICU admission, every five days during ICU stay, at ICU discharge, weekly during admission to the ward, and at hospital discharge.[16] The SGA is a nutritional assessment tool that has been validated for the acute hospital setting, surgical patients, and patients admitted to the ICU requiring mechanical ventilation.[17-19] The SGA score is shown in the **Appendix**.

Secondary outcomes were complications, including systemic complications (sepsis, Acute Respiratory Distress Syndrome (ARDS), Systemic Inflammatory Response Syndrome (SIRS), multiple-organ failure), pneumonia, urinary tract infection (UTI), deep venous thrombosis (DVT), and pulmonary embolism (PE). Mortality was analysed as a separate outcome parameter. This was also described in the study protocol.[13]

Patient demographics, including age, sex, and body mass index (BMI), were recorded, along with trauma characteristics such as the Abbreviated Injury Scale (AIS) for all body regions and the ISS. Information on nutritional support was collected, and patients were categorized based on whether they received oral feeding or (par) enteral feeding. For the patients who received (par)enteral nutrition, the timing of its administration was documented, and whether it was initiated within 48 hours or after 48 hours of admission. Target energy goals were calculated through a weight-based predictive equation (25 kcal/kg/day). In overweight patients (BMI >25 kg/m2), the adjusted body weight was used, which is calculated through the ideal body weight. The ideal body weight is calculated by the following equation: 0.9 x height in cm - 100 (male) (or - 106 (female)). To account for the metabolic demand of adipose tissue and muscle, an additional 25% of the excess weight (actual body weight minus ideal body weight) is added to the ideal body weight to calculate the adjusted weight.[20] According to the ESPEN guidelines, target energy goals should be met after 3-7 days of admission. It was documented whether goals were met after <48 hours, 3-7 days, and after >7 days of admission. Surgical procedures that required patients to go to the operating room were documented. Other in-hospital outcomes included hospital length of stay (LOS), ICU LOS, and ventilator days.

Statistical analysis

All analyses were performed using IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, N.Y., USA) and R version 4.2.2. P-values <0.05 were considered statistically significant. The baseline characteristics of the patients with low and high nutritional risk were compared using the Chi-square test or Fisher's exact test (in case of expected cell counts <5) for categorical variables, the independent samples T-test for normally distributed continuous variables, and the Mann-Whitney U test for skewed continuous variables.

The prevalence of high nutritional risk was calculated as the proportion with a 95% confidence interval (CI) of patients with a mNUTRIC score ≥5. The malnutrition

rate was calculated as the proportion of patients well-nourished at admission who developed malnutrition during admission as diagnosed with the SGA. The patients who were already malnourished at admission were excluded from this analysis. The incidences of malnutrition, complications, and mortality during ICU and total hospital stay were compared between the patients with high and low nutritional risk using the Chi-square test. Furthermore, a cause-specific Cox regression model was fitted to analyse whether high nutritional risk was related to developing malnutrition during hospital admission. In this model, receiving (par)enteral feeding was added as a binary time-dependent covariate.

RESULTS

Patient and trauma characteristics

The median age of the 100 included severely injured patients was 51 (interquartile range (IQR) 32-64) years, and 70 patients were male (**Table 1**). 59 patients were involved in motor vehicle accidents, 37 fell from a height, and 4 sustained injuries from other causes. Severe head trauma (AIS ≥4) was the most common, and 67% were considered to be very severely injured (ISS ≥25). 4 patients underwent abdominal surgery, 1 in the high nutritional risk and 3 in the low nutritional risk group. 52 patients had a healthy weight (BMI 18.5-25 kg/m^2), 30 were overweight (BMI 25-30 kg/m^2), and 19 were classified as obese (BMI ≥30 kg/m^2). Eighteen patients were considered to have high nutritional risk (mNUTRIC ≥5) at admission (18%, 95% CI 10.5-25.5%). As expected, patients with a high and low nutritional risk differed with respect to the five mNUTRIC score items (**Table 1**). Patients with high nutritional risk were more frequently obese (44% vs 13%; p=0.02). Twelve patients were malnourished at admission, 17% in the high nutritional risk group vs 11% in the low nutritional risk group (p=0.45).

Nutritional support

In patients with high nutritional risk, (par)enteral feeding was initiated more frequently than in patients with low nutritional risk (94% vs 66%; p=0.02, **Table 1**). Furthermore, in the patients who received (par)enteral feeding, this was not initiated within the recommended 48 hours in 29% of the patients with high nutritional risk, compared to 6% of the patients with low nutritional risk (p=0.02). The timing until target energy goals were met did not differ statistically significant between the two groups. Additionally, among patients with high nutritional risk who did receive

(par)enteral feeding, initiation within the recommended 48 hours was less common compared to the patients with low nutritional risk (71% vs 94%, p=0.02, **Table 1**).

High nutritional risk and incidence of malnutrition

Of the 73 patients with low nutritional risk who were well-nourished at admission, 49% developed malnutrition during ICU stay and 71% during total hospital stay, compared to 53% and 67% respectively of the 15 patients with high nutritional risk who were well-nourished at admission (p=1.00 and p=0.76; **Tables 2 and 3**). No statistically significant difference was seen between the time to development of malnutrition during ICU and hospital stay in the patients with low and high nutritional risk (**Tables 2 and 3**). **Figure 1** shows the cumulative incidence of malnutrition and mortality during hospital stay for the patients with high and low nutritional risk in the cause-specific Cox regression analysis. High nutritional risk did not pose a statistically significant risk of developing malnutrition when correcting for receiving (par)enteral feeding (hazard ratio 1.31, 95% confidence interval 0.65–2.64; p=0.45).

High nutritional risk and other complications

Patients with high nutritional risk developed more other complications during ICU and total hospital stay than patients with low nutritional risk: 78% (n=14/18) vs 29% (n=24/82) during ICU stay (p<0.001; **Table 2**) and 83% (n=15/18) vs 41% (n=34/82) during total hospital stay (p<0.01, **Table 3**). In particular, pneumonia and systemic complications occurred more frequently in the patients with high nutritional risk (**Tables 2 and 3**).

Seven patients died during their stay at the ICU, and four more patients died while being admitted to the ward (**Table 1**). Twenty-two percent (n=4/18) of the patients with high nutritional risk died during ICU admission compared to 4% (n=3/82) of the patients with low nutritional risk (p=0.02; **Table 2**). The in-hospital mortality was 33% (n=6/18) in the patients with high nutritional risk and 6% (n=5/82) in the patients with low nutritional risk (p<0.01; **Table 3**).

Patients with high nutritional risk had a statistically significant longer hospital stay compared to those with low nutritional risk (44 ± 23 vs 27 ± 24, p=0.03, **Table 3**).

Table 1: Patient characteristics according to nutritional risk at admission

	Total (n=100)	Low nutritional risk (mNUTRIC <5) (n=82)	High nutritional risk (mNUTRIC ≥5) (n=18)	P value
mNUTRIC score items				
Age in years, median (IQR)	51 (32-64)	45 (28-62)	66 (60-77)	**<0.001**
APACHE II, median (IQR)	16 (11-20)	14 (10-18)	22 (20-27)	**<0.001**
SOFA, median (IQR)	6 (4-8)	6 (4-8)	10 (7-11)	**<0.001**
>1 comorbidity *	45 (45%)	28 (34%)	17 (94%)	**<0.001**
≥1 day in hospital prior to ICU admission	0 (0%)	0 (0%)	0 (0%)	**-**
Other parameters				
Male sex	70 (70%)	55 (67%)	15 (83%)	0.28
BMI category				**<0.01**
Healthy weight (<25.0)	52 (52%)	47 (57%)	5 (28%)	
Overweight (≥25.0 - <30.0)	30 (30%)	24 (29%)	5 (28%)	
Obese (≥30.0)	19 (19%)	11 (13%)	8 (44%)	
Severe injury (AIS ≥4)				
Head	44 (44%)	34 (42%)	10 (56%)	0.41
Chest	29 (29%)	24 (29%)	5 (28%)	1.00
Abdomen	9 (9%)	8 (10%)	1 (6%)	0.91
Extremity	14 (14%)	11 (13%)	3 (17%)	1.00
ISS ≥25	67 (67%)	54 (66%)	13 (72%)	0.81
Malnourished at admission (SGA ≤5)	12 (12%)	9 (11%)	3 (17%)	0.45
Type of nutrition				**0.02**
Oral	29 (29%)	28 (34%)	1 (6%)	
(Par)enteral	71 (71%)	54 (66%)	17 (94%)	
Initiation of (par)enteral nutrition				**0.02**
<48 hours	63 (89%)	51 (94%)	12 (71%)	
≥48 hours	8 (11%)	3 (6%)	5 (29%)	
Time until target energy goals were met				0.46
<48 hours	19 (19%)	16 (20%)	3 (17%)	
3-7 days	67 (67%)	53 (65%)	14 (78%)	
>7 days	14 (14%)	13 (16%)	1 (6%)	
Surgery	82 (82%)	65 (79%)	17 (94%)	0.18

n(%) unless stated otherwise

AIS, Abbreviated Injury Scale severity (last digit of the AIS code); BMI, Body Mass Index; ICU, Intensive care unit; IQR, Interquartile range; ISS, Injury Severity Score; n, number; SGA, Subjective Global Assessment;

* According to the mNUTRIC comorbidity list

Table 2: Patient outcomes during ICU stay per nutritional risk group

	Total (n=100)	Low nutritional risk (mNUTRIC <5) (n=82)	High nutritional risk (mNUTRIC ≥5) (n=18)	P value
Malnutrition developed during ICU admission*	44 (50%)	36 (49%)	8 (53%)	1.00
Time to develop malnutrition (days), mean ± SD	6.0 ± 4.6	5.8 ± 4.8	7.2 ± 3.0	0.41
Complication	38 (38%)	24 (29%)	14 (78%)	**<0.001**
Systemic complications	10 (10%)	5 (6%)	5 (28%)	**0.02**
Pneumonia	32 (32%)	20 (24%)	12 (67%)	**<0.01**
Urinary tract infection	4 (4%)	2 (2%)	2 (11%)	0.30
Venous thromboembolism	4 (4%)	4 (5%)	0 (0%)	0.77
ICU mortality	7 (7%)	3 (4%)	4 (22%)	**0.02**
ICU LOS, mean ± SD **	13 ± 18	12 ± 16	22 ± 26	0.16
Ventilator days, mean ± SD **	8 ± 14	6 ± 9	19 ± 27	0.12

n(%) unless stated otherwise

ICU, Intensive care unit; LOS, Length of stay; n, number; SD, Standard deviation;

* Patients that were malnourished at ICU admission were excluded (n=12), comprising 9 patients in the low nutritional risk group and 3 patients in the high nutritional risk group.

** Patients that died during ICU admission were excluded (n=7)

Table 3: Patient outcomes during hospital stay per nutritional risk group

	Total (n=100)	Low nutritional risk (mNUTRIC <5) (n=82)	High nutritional risk (mNUTRIC ≥5) (n=18)	P value
Malnutrition developed during hospital admission*	62 (70%)	52 (71%)	10 (67%)	0.76
Time to develop malnutrition (days), mean ± SD	7.8 ± 5.3	7.8 ± 5.5	7.9 ± 4.6	0.97
Complication	49 (49%)	34 (41%)	15 (83%)	**<0.01**
Systemic complications	10 (10%)	5 (6%)	5 (28%)	**0.02**
Pneumonia	40 (40%)	27 (33%)	13 (72%)	**<0.01**
Urinary tract infection	11 (11%)	8 (10%)	3 (17%)	0.67
Venous thromboembolism	7 (7%)	6 (7%)	1 (6%)	1.00
In-hospital mortality	11 (11%)	5 (6%)	6 (33%)	**<0.01**
Hospital LOS, mean ± SD **	29 ± 24	27 ± 24	44 ± 23	**0.03**

n(%) unless stated otherwise

LOS, Length of stay; n, number; SD, Standard deviation;

* Patients that were malnourished at ICU admission were excluded (n=12)

** Patients that died during hospital admission (n=11) or were transferred to another hospital (n=2) were excluded

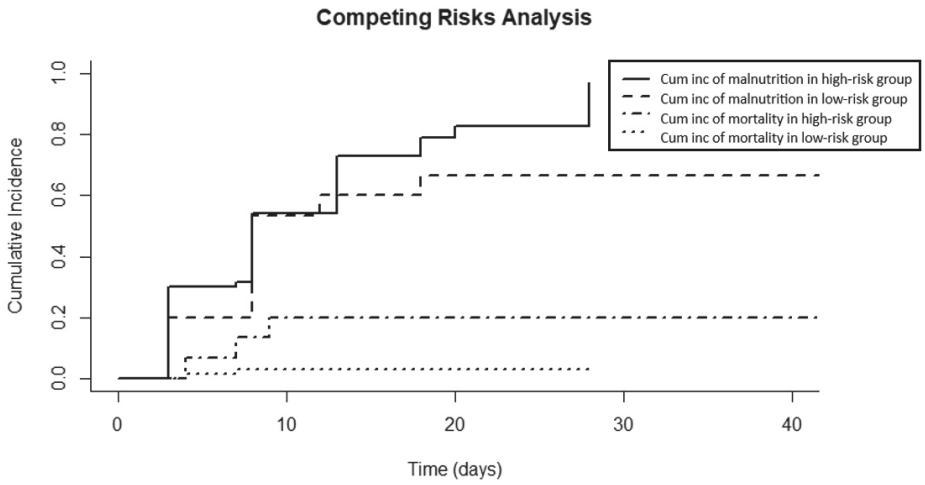

Figure 1: Cumulative incidence functions for malnutrition and mortality during hospital admission, stratified by nutritional risk

Cum inc, Cumulative incidence; High risk, High nutritional risk (mNUTRIC ≥5); Low risk, Low nutritional risk (mNUTRIC <5); Malnutrition, Malnutrition developed during hospital admission (SGA ≤5); Mortality, In-hospital mortality

DISCUSSION

The aim of this study was to investigate the prevalence of high nutritional risk and its relation with malnutrition and other adverse in-hospital outcomes in severely injured patients admitted to the ICU. Eighteen percent of these patients were considered to have high nutritional risk at admission. Nutritional risk was not related to the development of malnutrition during ICU and hospital stay. Complications, especially pneumonia and systemic complications, and mortality, occurred more often in the severely injured patients with high nutritional risk compared to the severely injured patients with low nutritional risk.

To our knowledge, no previous study has been performed on the relation between high nutritional risk and in-hospital developed malnutrition, as defined as SGA score ≤5. We hypothesized that patients identified as having high nutritional risk would demonstrate a correspondingly increased risk of developing malnutrition during admission. However, no relation was found between high nutritional risk and in-ICU (**Table 2**) and in-hospital (**Table 3**) developed malnutrition. In the survival

analysis, patients with high nutritional risk appeared to have a higher risk of developing malnutrition (**Figure 1**), but this difference was not statistically significant when the receipt of (par)enteral feeding was included in the proportional cause-specific hazard regression model.

We attempted to provide an explanation for the lack of correlation observed between the mNUTRIC and SGA score. Heyland et al. chose to select the NUTRIC variables based on comparative analyses of ICU survivors and non-survivors.[7] BMI, oral intake in the week prior to enrolment, and weight loss in the last three months were not significantly different in the survivors vs non-survivors groups, and thus not included in the mNUTRIC score. However, weight change and dietary intake are two out of six SGA items.[16] In addition, evaluating malnutrition in patients with obesity presents challenges as muscle and fat wasting are less readily apparent. Therefore, SGA-diagnosed malnutrition might be missed in patients with obesity. In our study population, the patients with high nutritional risk suffered also more frequently from obesity (**Table 1**). To our knowledge, the relation between the mNUTRIC score and obesity has not been stated before. However, a large meta-analysis showed that severe obesity was found to be related to increased mortality among patients experiencing blunt and/or penetrating trauma.[21] Since the mNUTRIC score is also related to mortality, this could explain the relation between obesity and the mNUTRIC score. Lastly, the goal of the mNUTRIC score is to identify patients who would benefit from aggressive nutrition intervention and the SGA score diagnoses malnutrition. Apparently, not all patients who develop SGA-diagnosed malnutrition were assumed to benefit from aggressive nutrition intervention at ICU admission according to the mNUTRIC score.

The relationship between the mNUTRIC score and malnutrition at ICU admission, as diagnosed by the SGA, has been examined in two studies involving critically ill patients.[22,23] This finding was not confirmed in our study. Both studies concluded that high nutritional risk is not related to SGA-diagnosed malnutrition at ICU admission since these tools do not uniformly identify patients as malnourished or at high nutritional risk.[22,23] Their explanation for not finding a correlation was that the SGA score is based on a combination of nutritional parameters prior to admission and physical status at admission, but the mNUTRIC score is largely a prospective assessment based on the expected effect of hospitalization on future nutritional status.[23] Thus, both the mNUTRIC at ICU admission and the

SGA during hospital admission serve as valuable indicators for nutritional risk and nutritional status, respectively. However, attempting to find a correlation between these two tools appears to lack clinical significance.

A systematic review by Cattani et al. summarized the results of 26 studies on the prevalence of high nutritional risk using the mNUTRIC score in critically ill patients.[9] The lowest prevalence of high nutritional risk was found in a surgical ICU population by Özbilgin et al., who found a prevalence of 22.4%.[24] In a retrospective study of 771 trauma patients admitted to the ICU, the prevalence of high nutritional risk was 24.1%.[25] These percentages are comparable to our polytrauma population. In other patient groups admitted to the ICU, the prevalence of high nutritional risk ranged up to 91.1% in elderly (≥65 years) patients on mechanical ventilation and 88.7% in sepsis patients.[26,27]

The mNUTRIC score has extensively been researched in relation to mortality.[9] In the majority of studies, the mNUTRIC score was predictive for 28-day-, ICU-, and in-hospital mortality in critically ill patients. The association of the mNUTRIC score with adverse clinical outcomes is to be expected based on the fact that it includes disease severity–related variables such as APACHE II and SOFA, which are recognized predictors of these outcomes.[14,15] Our study also showed a significantly higher in-hospital mortality rate in severely injured patients with high nutritional risk. In addition, we found that high nutritional risk in severely injured patients coincides with other in-hospital developed complications, such as pneumonia and sepsis. A true association cannot be established, since this analysis did not account for confounders.

LIMITATIONS

This study is the first study to assess the relation between high nutritional risk and in-hospital developed malnutrition in severely injured patients. The sample size was limited to 100 patients for pragmatic reasons. Subsequently, the number of patients with high mNUTRIC scores was even smaller, <20%. The small sample size may have introduced a type II error. This, and the analyses done on a high risk patient group of only 18, require careful interpretation of the results.

Not all patients who were considered eligible for the study were included. The primary reasons for this were organizational challenges as the study demanded significant time from ICU staff, and difficulties in obtaining informed consent (which can be considered burdensome for families of critically ill patients). However, we do not believe that this has led to selection bias in the included patient group, as the non-inclusion of eligible patients was at random.

We used the SGA for the assessment of the nutritional status. The SGA has been validated for ICU patients and is proven to be the most predictive for outcomes. However, the SGA is not very discriminative, since the difference between an SGA score of 5 (malnourished) or 6 (well-nourished) can be very minimal. The SGA was assessed by either a research nurse or a member of the research team, all of whom had received training in physical examination as part of their medical education and could accurately evaluate muscle mass. To enhance reliability and minimize interobserver variability, one investigator reviewed and verified all SGA scores at the conclusion of data collection. The results of the study suggest that the use of the mNUTRIC score might be valuable to identify severely injured patients at high risk of adverse in-hospital outcomes. Although the potential of mNUTRIC as an indicator for mortality and morbidity in severely injured patients seems promising, future studies with larger sample sizes and sub-analyses based on nutritional intake are needed to confirm its reliability in both trauma and non-trauma related clinical settings.

CONCLUSION

About one-fifth of severely injured patients admitted to the ICU are at high nutritional risk, as assessed by the mNUTRIC score. High nutritional risk in severely injured patients does not seem to be related to malnutrition during hospital stay. It does coincide with other in-hospital developed complications and mortality in severely injured patients. In this light, the mNUTRIC score impresses as a potential indicator of morbidity and mortality in severely injured patients. Larger studies are needed to confirm these preliminary results.

REFERENCES

1. Lim SL, Ong KC, Chan YH, Loke WC, Ferguson M, Daniels L. *Malnutrition and its impact on cost of hospitalization, length of stay, readmission and 3-year mortality*. Clin Nutr. 2012;31(3):345-50.
2. Correia MI, Waitzberg DL. *The impact of malnutrition on morbidity, mortality, length of hospital stay and costs evaluated through a multivariate model analysis*. Clin Nutr. 2003;22(3):235-9.
3. Lew CCH, Yandell R, Fraser RJL, Chua AP, Chong MFF, Miller M. *Association between malnutrition and clinical outcomes in the intensive care unit: A systematic review.* JPEN J Parenter Enteral Nutr. 2017;41(5):744-58.
4. Kalaiselvan MS, Renuka MK, Arunkumar AS. *Use of nutrition risk in critically ill (NUTRIC) score to assess nutritional risk in mechanically ventilated patients: A prospective observational study.* Indian J Crit Care Med. 2017;21(5):253-6.
5. Yeh DD, Johnson E, Harrison T, Kaafarani HMA, Lee J, Fagenholz P, et al. *Serum levels of albumin and prealbumin do not correlate with nutrient delivery in surgical intensive care unit patients*. Nutr Clin Pract. 2018;33(3):419-25.
6. Van Bokhorst-de van der Schueren MA, Guaitoli PR, Jansma EP, de Vet HC. *Nutrition screening tools: does one size fit all? A systematic review of screening tools for the hospital setting.* Clin Nutr. 2014;33(1):39-58.
7. Heyland DK, Dhaliwal R, Jiang X, Day AG. *Identifying critically ill patients who benefit the most from nutrition therapy: the development and initial validation of a novel risk assessment tool.* Crit Care. 2011;15(6):R268.
8. Rahman A, Hasan RM, Agarwala R, Martin C, Day AG, Heyland DK. *Identifying critically-ill patients who will benefit most from nutritional therapy: Further validation of the "modified NUTRIC" nutritional risk assessment tool.* Clin Nutr. 2016;35(1):158-62.
9. Cattani A, Eckert IC, Brito JE, Tartari RF, Silva FM. *Nutritional risk in critically ill patients: how it is assessed, its prevalence and prognostic value: a systematic review*. Nutr Rev. 2020;78(12):1052-68.
10. Dijkink S, Meier K, Krijnen P, Yeh DD, Velmahos GC, Schipper IB. *Malnutrition and its effects in severely injured trauma patients.* Eur J Trauma Emerg Surg. Oct 2020;46(5):993-1004.
11. Jensen GL, Mirtallo J, Compher C, Dhaliwal R, Forbes A, Grijalba RF, et al. *Adult starvation and disease-related malnutrition: A proposal for etiology-based diagnosis in the clinical practice setting from the International Consensus Guideline Committee*. JPEN J Parenter Enteral Nutr. 2010;34(2):156-9.
12. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. *STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies*. BMJ. 2007;335(7624):806-8.
13. Dijkink S, Meier K, Krijnen P, Yeh DD, Velmahos GC, Arbous MS, et al. *The malnutrition in polytrauma patients (MaPP) study: Research protocol*. Nutr Health. 2019;25(4):291-301.
14. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. *APACHE II: a severity of disease classification system.* Crit Care Med. 1985;13(10):818-29.
15. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H, et al. *The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine.* Intensive care med. 1996;22(7):707-10.

16. Baker JP, Detsky AS, Wesson DE, Wolman SL, Stewart S, Whitewell J, et al. *Nutritional assessment: a comparison of clinical judgement and objective measurements.* N Engl J Med. 1982;306(16):969-72.

17. Detsky AS, McLaughlin JR, Baker JP, Johnston N, Whittaker S, Mendelson RA, et al. *What is subjective global assessment of nutritional status?* JPEN J Parenter Enteral Nutr. 1987;11(1):8-13.

18. Sheean PM, Peterson SJ, Gurka DP, Braunschweig CA. *Nutrition assessment: the reproducibility of Subjective Global Assessment in patients requiring mechanical ventilation.* Eur J Clin Nutr. 2010;64(11):1358-64.

19. Bector S, Vagianos K, Suh M, Duerksen DR. *Does the subjective global assessment predict outcome in critically ill medical patients?* J Intensive Care Med. Aug 2016;31(7):485-9.

20. Singer P, Blaser AR, Berger MM, Calder PC, Casaer M, Hiesmayr M, et al. *ESPEN practical and partially revised guideline: Clinical nutrition in the intensive care unit*. Clin Nutr. 2023;42(9):1671-89.

21. Cromwell PM, Reynolds IS, Heneghan HM, Glasgow SM. *Obesity and outcomes in trauma - a systematic review and meta-analysis.* Injury. 2023;54(2):469-80.

22. Coltman A, Peterson S, Roehl K, Roosevelt H, Sowa D. *Use of 3 tools to assess nutrition risk in the intensive care unit*. J Parenter Enteral Nutr 2015;39:28e33.

23. Rattanachaiwong S, Zribi B, Kagan I, Theilla M, Heching M, Singer P. *Comparison of nutritional screening and diagnostic tools in diagnosis of severe malnutrition in critically ill patients.* Clin Nutr. Nov 2020;39(11):3419-25.

24. Özbilgin Ş, Hancı V, Ömür D, Özbilgin M, Tosun M, Yurtlu S, et al. *Morbidity and mortality predictivity of nutritional assessment tools in the postoperative care unit*. Medicine (Baltimore). 2016;95(40):e5038.

25. Iwuchukwu C, O'Keefe GE, Day AG, Jiang X, Heyland DK. *Application of the modified Nutrition Risk in Critically Ill score to nutritional risk stratification of trauma victims: A multicenter observational study.* J Trauma Acute Care Surg. 2020;89(6):1143-8.

26. Hsu PH, Lee CH, Kuo LK, Kung YC, Chen WJ, Tzeng MS. *Higher Energy and Protein Intake from Enteral Nutrition May Reduce Hospital Mortality in Mechanically Ventilated Critically Ill Elderly Patients*. Int J Gerontol. 2018;12(4)

27. Jeong DH, Hong SB, Lim CM, Koh Y, Seo J, Kim Y, et al. *Relationship between Nutrition Intake and 28-Day Mortality Using Modified NUTRIC Score in Patients with Sepsis*. Nutrients. 2019;11(8):1906.

APPENDIX

Table 1: modified Nutrition Risk in Critically ill (mNUTRIC) score [8]

Variable	Range	Points
Age	<50 50-74 ≥75	0 1 2
APACHE II score	<15 15-19 ≥20	0 1 2
SOFA score	<6 6-9 ≥10	0 1 2
Number of comorbidities	0-1 ≥2	0 1
Days from hospital to ICU admission	0 ≥1	0 1

Table 2: APACHE II score [14]

Variables	Range	Points
Age	<45	0
	45-54	2
	55-64	3
	65-74	5
	≥75	6
History of severe organ insufficiency or immunocompromised	Yes, and nonoperative or emergency postoperative patient	5
	Yes, and elective postoperative patient	2
	No	0
Rectal temperature (°C)	<30	4
	30-32	3
	32-34	2
	34-36	1
	36-38.5	0
	38.5-39	1
	39-41	3
	≥41	4

Table 2: APACHE II score [14] *(continued)*

Variables	Range	Points
MAP (mmHg)	<50	4
	50-70	2
	70-110	0
	110-130	2
	130-160	3
	≥160	4
Heart rate (beats per minute)	<40	4
	40-54	3
	55-69	2
	70-109	0
	110-139	2
	140-179	3
	≥180	4
Respiratory rate (breaths per minute)	<6	4
	6-9	2
	10-11	1
	12-24	0
	25-34	1
	35-49	3
	≥50	4
Oxygenation (use PaO_2 if FiO_2 <50%, otherwise use A-a gradient)	PaO_2 <55	4
	PaO_2 55-61	3
	PaO_2 61-71	1
	A-a gradient <200 (if FiO_2 over 49%) or pO_2 >70 (if FiO_2 less than 50%)	0
	A-a gradient 200-350	
	A-a gradient 350-500	2
	A-a gradient ≥500	3
		4
Arterial pH	<7.15	4
	7.15-7.25	3
	7.25-7.33	2
	7.33-7.50	0
	7.50-7.60	1
	7.60-7.70	3
	≥7.70	4

Table 2: APACHE II score [14] *(continued)*

Variables	Range	Points
Serum sodium (mmol/L)	<111	4
	111-119	3
	120-129	2
	130-149	0
	150-154	1
	155-159	2
	160-179	3
	≥180	4
Serum potassium (mmol/L)	<2.5	4
	2.5-2.9	2
	3.0-3.4	1
	3.5-5.4	0
	5.5-5.9	1
	6.0-6.9	3
	≥7.0	4
Serum creatinine (mg/dL)	<0.6	2
	0.6-1.5	0
	1.5-2.0 and chronic renal failure	2
	2.0-3.5 and chronic renal failure	3
	1.5-2.0 and acute renal failure	4
	≥3.5 and chronic renal failure	4
	2.0-3.5 and acute renal failure	6
	≥3.5 and acute renal failure	8
Haematocrit (%)	<20	4
	20-29	2
	30-45	0
	46-49	1
	50-59	2
	≥60	4
White blood count (total/mm^3)	<1	4
	1-3	2
	3-15	0
	15-20	1
	20-40	2
	≥40	4
Glasgow Coma Scale	1-15	15 – Glasgow Coma Scale score

MAP, Mean arterial pressure;

Table 3: Sequential Organ Failure Assessment (SOFA) score [15]

Variable	Range	Points
PaO_2/FiO_2 (mmHg)	≥400	0
	<400	1
	<300	2
	<200 and not MV	2
	<200 and MV	3
	<100 and MV	4
Platelets ($x10^3/\mu L$)	≥150	0
	100-149	1
	50-99	2
	20-49	3
	<20	4
Glasgow Coma Scale	15	0
	13-14	1
	10-12	2
	6-9	3
	<6	4
Bilirubin (mg/dL)	<1.2	0
	1.2-1.9	1
	2.0-5.9	2
	6.0-11.9	3
	≥12.0	4
MAP (mmHg) or administration of vasoactive agents (µg/kg/min)	MAP ≥70	0
	MAP <70	1
	Dopamine ≤5 or Dobutamine (any dose)	2
	Dopamine >5, Epinephrine ≤0.1, or Norepinephrine ≤0.1	3
	Dopamine >15, Epinephrine >0.1, or Norepinephrine >0.1	4
Creatinine (mg/dL) or urine output	<1.2	0
	1.2-1.9	1
	2.0-3.4	2
	3.5-4.9 or urine output <500 mL/day	3
	≥5.0 or urine output <200 mL/day	4

MAP, Mean arterial pressure; MV, mechanically ventilated;

Table 4: Subjective Global Assessment rating form [16]

SUBJECTIVE GLOBAL ASSESSMENT RATING FORM	
Patient Name: **ID #:** **Date:**	
HISTORY	
WEIGHT/WEIGHT CHANGE: ***(Included in K/DOQI SGA)***	**Rate 1-7**
1. **Baseline Wt:** _____(Dry weight from 6 months ago) **Current Wt:** _____(Dry weight today) **Actual Wt loss/past 6 mo:** _____ **% loss:**_____(actual loss from baseline or last SGA)	
2. **Weight change over past two weeks:** _____No change _____Increase _____Decrease	
DIETARY INTAKE No Change_____(Adequate) No Change_____(Inadequate)	
1. Change: Sub optimal Intake: _____ Protein _____ Kcal _____ Duration_____ Full Liquid: _____ Hypocaloric Liquid _____ Starvation _____	
GASTROINTESTINAL SYMPTOMS ***(Included in K/DOQI SGA-anorexia or causes of anorexia)***	
Symptom: **Frequency:*** **Duration:***	
_____ None _____ _____ _____ Anorexia _____ _____ _____ Nausea _____ _____ _____ Vomiting _____ _____ _____ Diarrhea _____ _____	
Never, daily, 2-3 times/wk, 1-2 times/wk > 2 weeks, < 2 weeks	
FUNCTIONAL CAPACITY	b
Description **Duration:**	
_____ No Dysfunction _____ _____ Change in function _____ _____ Difficulty with ambulation _____ _____ Difficulty with activity (Patient specific "normal") _____ _____ Light activity _____ _____ Bed/chair ridden with little or no activity _____ _____ Improvement in function _____	
DISEASE STATE/COMORBIDITIES AS RELATED TO NUTRITIONAL NEEDS	
Primary Diagnosis_____Comorbidities_____ Normal requirements ____Increased requirements____ Decreased requirements _____ Acute Metabolic Stress: _____None _____Low _____Moderate _____High	
PHYSICAL EXAM	
_____ Loss of subcutaneous fat (Below eye, triceps, biceps, chest) ***(Included in K/DOQI SGA)*** ____Some areas _____All areas _____ Muscle wasting (Temple, clavicle, scapula, ribs, quadriceps, calf, knee, interosseous ***(Included in K/DOQI SGA)*** ____Some areas _____All areas _____ Edema (Related to undernutrition/use to evaluate weight change)	
OVERALL SGA RATING	
Very mild risk to well-nourished=6 or 7 most categories or significant, continued improvement. **Mild-moderate** = 3, 4, or 5 ratings. No clear sign of normal status or severe malnutrition. **Severely Malnourished** = 1 or 2 ratings in most categories/significant physical signs of malnutrition.	








Chapter 4

The value of metabolites and vitamins for the assessment of nutritional status in hospitalized patients. A systematic review

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Top Clin Nutr. 2024;39(3):198-212

ABSTRACT

This systematic review aims to summarize the currently available literature regarding the association of plasma metabolites and vitamins with the nutritional status in adult hospitalized patients.

A systematic literature search was performed in PubMed and EMBASE, and all studies comparing metabolite or vitamin levels in malnourished versus well-nourished hospitalized patients were included. Twenty-three studies were eligible for inclusion, representing 3803 hospitalized patients.

Several metabolites involved in the metabolism of methionine, purine, glutathione, carnitine, phenylalanine, and tryptophan, as well as some vitamins, seem to be associated with malnutrition in hospitalized patients. These compounds can potentially be used to assess nutritional status.

INTRODUCTION

Malnutrition is the result of an imbalance between intake, uptake, and the required amount of macro- and micronutrients. This imbalance leads to an altered body composition and body cell mass which diminishes physical and mental function and impairs recovery from disease.[1] Together with the stress-related catabolism caused by inflammation, malnutrition increases the risk for impaired wound healing, infections, and organ dysfunction.[2] These complications can cause an increase in the inflammatory response and therefore result in further aggravation of malnutrition.[2,3] To break this vicious circle, it is essential to adequately diagnose malnutrition and prevent deterioration.

Research has shown that up to 50% of hospitalized patients are malnourished, depending on the definition used and population included.[2] Several tools to assess nutritional status have been developed, including nutritional screening tools, such as the Subjective Global Assessment (SGA), Patient-Generated Subjective Global Assessment (PG-SGA), Mini Nutritional Assessment (MNA), Nutritional Risk Screening (NRS-2002), and Malnutrition Universal Screening Tool (MUST), as well as visceral proteins, and anthropometric measures (height, weight, and body composition). Some of these screening tools were developed for specific populations; for example the MNA is designed to diagnose malnutrition in elderly patients, and the MUST and PG-SGA are validated for oncology patients.[4,5] However, there is still no gold standard for measuring nutritional status in all hospitalized patients.[6] The currently available nutritional screening tools include information on the history of a patient's weight and diet, which is not always available in clinical settings. The Academy of Nutrition and Dietetics and the American Society for Parenteral and Enteral Nutrition described a standardized approach to identify adult malnutrition in routine clinical practice.[7] The criteria that a registered dietitian can obtain and document to support a diagnosis of malnutrition include energy intake, weight loss, and physical exam. Moreover, fluid resuscitation and edema influence weight, body circumferences, and other anthropometric measurements.[8] Additionally, visceral proteins (e.g. albumin, and pre-albumin) lack sensitivity as they are influenced by inflammation. During inflammatory states, the production of acute-phase proteins in the liver is increased and therefore the synthesis of visceral proteins is decreased regardless of nutritional status.[9]

A relatively new but promising method is the use of plasma metabolites and vitamins to assess nutritional status. Metabolites are intermediate- or end-products of biochemical pathways, such as glycolysis and citric acid cycle. Examples include sugars, amino acids, and nucleotides. Metabolites are considered to be biomarkers of several phenotypic states, and research suggests that metabolites can even act as controllers of the phenotype.[10] The metabolome is the global collection of all low-molecular-weight metabolites that are produced by cells during metabolism.[11] The human metabolome comprises over 100,000 metabolites and new metabolites continue to be added to the Human Metabolome Database (HMDB).[12] Because the metabolite composition is influenced by many processes in the body, changes in plasma metabolite levels may occur much earlier than any clinical symptoms. Metabolites have been considered as biomarkers for many diseases, such as pancreatic cancer, non-insulin dependent diabetes mellitus, and memory impairment.[13-15] Additionally, vitamins are related to a healthy diet and several vitamins are known to function as antioxidants. Since malnutrition is related to oxidative stress, the question arises whether vitamins might also be useful in diagnosing malnutrition.[16] The purpose of this study is to systematically review the body of published scientific evidence and summarize the value of plasma metabolites and vitamins as potential biomarkers for monitoring nutritional status in hospitalized patients.

METHODS

Search Strategy

This systematic review was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.[17] A literature search was performed in PubMed and EMBASE in collaboration with an experienced medical librarian in December 2021. The search strategy included synonyms and related terms for hospitalized patients, biomarkers, metabolites, vitamins, antioxidants, and nutritional status (**Appendix 1**).

Eligibility Criteria and Article Selection

Article selection was performed independently by two researchers (EAHV and JJJO). The titles and abstracts of identified studies were screened, using the following selection criteria: (1) the study included adult hospitalized patients, (2)

one or more plasma metabolites or vitamins were researched, (3) the nutritional status was assessed using a nutritional assessment/screening tool (e.g. SGA, MUST, or MNA), the Body Mass Index (BMI), or a combination of laboratory results and anthropometric measurements, and (4) the relationship between plasma metabolite/vitamin levels and nutritional status was evaluated. Articles that researched the nutritional status of patients after bariatric surgery were excluded. Publications in English, German, and Dutch were selected, between 1952 and 2021. The full-text of potentially eligible articles were read, and included when all the inclusion criteria were met. The reference lists of the included articles were screened for additional literature.

Data Extraction and Risk of Bias Assessment

Data extraction and risk of bias assessment were performed independently by the same two researchers (EAHV and JJJO). Data on study characteristics (study design, country, participants (number, mean age, sex), applied nutritional assessment tool, researched biomarker(s)), and study results (percentage of malnourished patients, metabolite levels, and their association) were extracted from the articles.

The risk of bias in the selected studies was assessed according to the Methodological Index for Non-Randomized Studies (MINORS) criteria, which includes 12 items for comparative studies and 8 items for non-comparative studies that are scored as 0 (not reported), 1 (reported but inadequate), or 2 (adequately reported). The maximum score is 16 for non-comparative studies and 24 for comparative studies.[18]

RESULTS

Selection of Articles

The literature search identified 936 studies in PubMed and 126 studies in Embase. 1006 records were screened after duplicate removal. 851 articles were excluded based on title and abstract. Three articles were added after hand search of the reference lists. After reading the full-text articles of the remaining 158 studies, 135 studies were excluded for various reasons (**Figure 1**). Relevant data from the twenty-three included studies are summarized in **Table 1**.

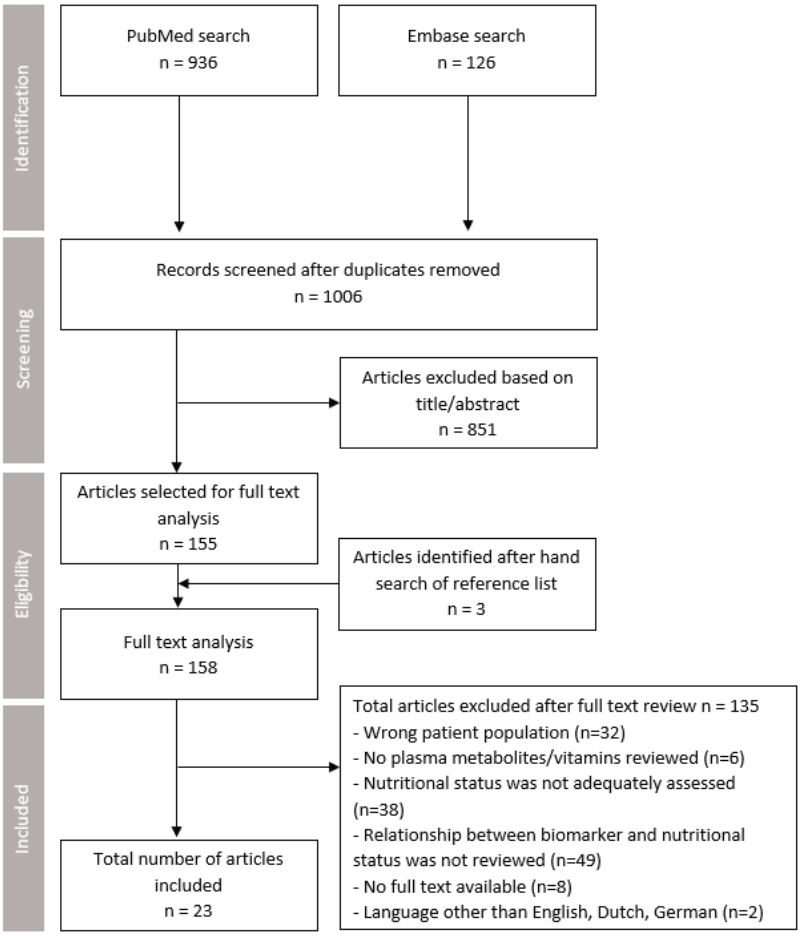

Figure 1: Studies resulting from literature search with reason for exclusion

Risk of Bias

Risk of bias of the included studies was assessed, using the MINORS-criteria, as low (total score ≥20 out of 24) for the studies by Chou et al,[19] Katić et al,[20] Tas Kilic et al,[21] Ramel et al,[22] and Vosoughi et al,[23] and moderate (total score 15-19 out of 24) for the other studies (**Table 2**). In all studies, the assessment of study endpoints was potentially biased, as no study evaluated the study endpoints blindly. Additionally, only Chou et al[19] and Vosoughi et al[23] performed a sample size calculation or noted why the sample size calculation could not be performed. Two studies collected the data retrospectively, and therefore did not score the maximum of 2 points for prospective collection of data.[24,25]

Table 1: Study characteristics and outcomes

Reference	Country	Design	n	Hospitalized population	Male (%)	Age (yrs)*	Nutritional assessment	Prevalence MN	Biomarker(s)	Relation between biomarker(s) and nutritional status*
Avelino et al [39]	Brazil	Prospective cohort	150	Patients admitted to the clinical and surgical wards	51	SGA A: 50 (±15); SGA B: 48 (±16); SGA C: 52 (±18)	No MN: SGA A Mild MN: SGA B Severe MN: SGA C	No MN: 50.7% (n=76) Mild MN: 25.3% (n=38) Severe MN: 24.0% (n=36)	VitC (mg/dL) and Creat (mg/dL) VitC deficiency: <0.4	No MN vs mild MN vs severe MN: VitC: 0.7 (0.1-1.5) vs 0.5 (0.2-1.3) vs 0.3 (0.0-0.9) (p<0.05) Creat: 0.9 (0.1-3.3) vs 0.9 (0.5-1.7) vs 0.9 (0.5-2.5) (p>0.05) Vitamin C deficiency (%) in No MN vs mild MN vs severe MN: 21.1 vs 34.2 vs 63.9 (p<0.05)
Christopher et al [32]	USA	Cross-sectional	210	Patients with newly diagnosed solid malignant tumor	62	<50 yrs: 19% (n=39) 50-69 yrs: 63% (n=133) ≥70 yrs: 18% (n=38)	No MN: PG-SGA A Mild MN: PG-SGA B Severe MN: PG-SGA C	No MN: 39.7% (n=83) Mild MN: 36.4% (n=76) Severe MN: 23.9% (n=50)	25(OH)D (ng/mL): Suboptimal: <30 (n=131) Optimal: 30-80 (n=79)	Suboptimal vs optimal 25(OH)D levels: No MN: 36.9% (n=48) vs 44.3% (n=35); Mild MN: 36.9% (n=48) vs 35.4% (n=28); Severe MN: 26.2% (n=34) vs 20.3% (n=16) Suboptimal 25(OH)D: No MN: OR=1**; Mild MN: OR=0.97** (95% CI 0.48-1.95); Severe MN: OR=1.28** (95% CI 0.53-3.07)
Chou et al [19]	Taiwan	Prospective cohort	95	Mechanically ventilated patients with sepsis admitted to the medical ICU	61	70 (60-78)	No MN: NRS-2002 0-2 MN: NRS-2002 ≥ 3	-	TMAO (µmol/L) Low TMAO: <0.4 (n=32) Median TMAO: 0.4-2.5 (n=32) High TMAO: ≥ 2.5 (n=31)	NRS-2002 score in low TMAO vs median TMAO vs high TMAO: 5.0 (5.0-6.0) vs 4.0 (4.0-5.8) vs 4.0 (3.0-4.0) (p<0.001) Spearman correlation coefficient: r=-0.51 (p<0.001) Univariate linear regression: β=-0.453 (p<0.001)

Table 1 *(Continued)*

Reference	Country	Design	n	Hospitalized population	Male (%)	Age (yrs)*	Nutritional assessment	Prevalence MN	Biomarker(s)	Relation between biomarker(s) and nutritional status*
Cunha et al [26]	Brazil	Cross-sectional	127	Elderly patients (≥65 yrs)	63	No MN: 72 (±6) MN: 74 (±7)	No MN: BMI ≥18.5 MN: BMI <18.5	No MN: 83.5% (n=106) MN: 16.5% (n=21)	VitA (µg/dL), VitC (mg/dL), VitE (µg/dL), Ct (µg/dL), and EGRAC Deficiencies: VitA ≤19; VitC <0.3; VitE <0.7; Ct <39; EGRAC >1.29	No MN vs MN: VitA: 41.9 (9.3-132.2) vs 39.6 (16.5-78.4); VitC: 0.3 (0.0-1.0) vs 0.2 (0.1-1.2); VitE: 1.0 (0.3-11.0) vs 1.0 (0.5-2.2); Ct: 106 (27.2-416.2) vs 121 (35.3-298.3); EGRAC: 1.3 (1.0-3.3) vs 1.4 (1.0-2.6) Deficiencies (%) in No MN vs MN: VitA: 29.6 vs 28.6 (p>0.05); VitC: 56.7 vs 80.9 (p<0.01); VitE: 25.0 vs 18.7 (p>0.05); Ct: 3.0 vs 14.3 (p<0.01); EGRAC: 56.2 vs 58.8 (p>0.05)
Djurasinovic et al [33]	Belgrade	Prospective cohort	133	Patients with lympho-proliferative malignancies	54	58 (18–84)	No MN: NRS-2002 0-2 MN: NRS-2002 ≥ 3	No MN: 54.9% (n=73) MN: 45.1% (n=60)	25(OH)D (nmol/L): SevDef: ≤25 (n=37); Def: 25-50 (n=80); Ins: 50-75 (n=12)	SevDef vs Def vs Ins: No MN: 37.8% (n=14) vs 60.0% (n=48) vs 68.8% (n=11); MN: 62.2% (n=23) vs 40.0% (n=32) vs 31.2% (n=5); (p=0.04)
Førli et al [36]	Norway	Cross-sectional	71	Patients with advanced pulmonary disease considered for lung transplantation	45	No MN: 52 (26-60) MN: 47 (25-60)	No MN: BMI 20-25 MN: BMI < 20	No MN: 40.8% (n=29) MN: 59.2% (n=42)	25(OH)D (nmol/L) and 1,25di(OH)D (pmol/L) 25(OH)D: Def: <37.5 Ins: 37.5-75	No MN vs MN: 25(OH)D: 37.2 (±15.7) vs 38.0 (±16.5) (p>0.05) 1,25di(OH)D: 82.4 (±30.6) vs 76.2 (±35.4) (p>0.05) Def: 55% (n=16) vs 52% (n=22) (p>0.05); Ins: 45% (n=13) vs 45% (n=19) (p>0.05)

Table 1 *(Continued)*

Reference	Country	Design	n	Hospitalized population	Male (%)	Age (yrs)*	Nutritional assessment	Prevalence MN	Biomarker(s)	Relation between biomarker(s) and nutritional status*
Holden et al [37]	Canada	Cross-sectional	172	Patients with stage 3-5 chronic kidney disease	61	61 (±14)	No MN: SGA A Mild MN: SGA B Severe MN: SGA C	No MN: 79.3% (n=138) Mild MN: 20.7% (n=36) Severe MN: 0% (n=0)	VitK1 (nmol/L), %ucOC, PIVKA-II, 25(OH)D (nmol/L)	Spearman correlation coefficients for SGA: VitK1: r=0.11 (p=0.17) %ucOC: r=0.02 (p=0.79) PIVKA-II: r=0.08 (p=0.41) 25(OH)D: -0.08 (p=0.31)
Hosseini et al [27]	Iran	Cross-sectional	225	Patients >65 years with CHF and NYHA class III-IV	68	71 (±1)	No MN: MNA >23.5 Risk of MN: MNA 17-23.5 MN: MNA <17	No MN: 9.3% (n=21) Risk of MN: 80.9% (n=182) MN: 9.8% (n=22)	BUN (mmol/L)	No MN vs risk of MN vs MN: 24.9 (±8.1) vs 25.9 (±14.5) vs 24.9 (±9.2) (p=0.9)
Jatoi et al [40]	USA	Cross-sectional	27	Patients admitted to the Adult Gastro-enterology and General Internal Medicine services	41	46 (±16)	No MN: SA >3.5, ALC >1.5, BW ≥80% of ideal, and uWL <4.5 kg or <15% of BW in 3 months MN: At least one of SA, ALC, BW, uWL in abnormal range	No MN: 25.9% (n=7) MN: 74.1% (n=20)	VitK1 (nmol/L)	No MN vs MN: 0.25 (0.02-0.52) vs 0.19 (0.07-3.93) (p=0.73)
Katić et al [20]	Croatia	Cross-sectional	310 (298 are included in NA)	Patients with chronic graft-vs-host disease after allo-HSCT	55	48 (36-57)	No MN: PG-SGA A Mild MN: PG-SGA B Severe MN: PG-SGA C	No MN: 65.8% (n=196) Mild MN: 28.2% (n=84) Severe MN: 6.0% (n=18)	25(OH)D (ng/mL) Low: ≤20 (n=68) High: >20 (n=230)	No MN vs mild MN vs severe MN: Low: 19.4% (n=38) vs 23.8% (n=20) vs 55.6% (n=10); High: 80.6% (n=158) vs 76.2% (n=64) vs 44.4% (n=8); (p=0.004) No MN vs mild/severe MN: Low: 19.4% (n=38) vs 29.4% (n=30); High: 80.6% (n=158) vs 70.6% (n=72); (p=0.06)

Table 1 *(Continued)*

Reference	Country	Design	n	Hospitalized population	Male (%)	Age (yrs)*	Nutritional assessment	Prevalence MN	Biomarker(s)	Relation between biomarker(s) and nutritional status*
Li et al[35]	China	Cross-sectional	82	Patients with fractures who had surgical treatment	27	70 (54–85)	No MN: NRS-2002 0-2 MN: NRS-2002 ≥ 3	No MN: 63.4% (n=52) MN: 36.6% (n=30)	25(OH)D (ng/mL), Ca (mmol/L), OC (ng/mL), PTH (pg/mL)	No MN vs MN: 25(OH)D: 26.5 (±1.2) vs 17.2 (±2.1) (p=0.00) OC: 3.7 (±0.5) vs 1.3 (±0.2) (p=0.00) Ca: 2.2 (±0.0) vs 2.2 (±0.1) (p=0.21) PTH: 21.0 (±2.1) vs 13.0 (±5.6) (p=0.12)
Mogensen et al[34]	USA	Prospective cohort	85	Patients with SIRS or sepsis admitted to the ICU	57	55 (±14)	No MN: WN or at risk for MN; MN: Diagnosis of (non)specific protein-calorie MN; Diagnosis was made by a registered dietician based on a combination of laboratory results and anthropometric measurements	No MN: 62% (n=53) MN: 38% (n=32)	281 metabolites	15 most predictive metabolites for MN: OH-PA VIP=2.61 Hx VIP=2.54 TML VIP=2.52 OH-PL VIP=2.45 NAM VIP=2.29 PyrGln VIP=2.29 Andros-S VIP=2.21 Kyn VIP=2.20 NAPhe VIP=2.12 MTA VIP=2.09 Urea VIP=2.05 P-GPA VIP=2.05 VitB3 VIP=2.02 S-GPA VIP=2.00 Cl VIP=1.98
										Linear regression coefficient

Table 1 *(Continued)*

Reference	Country	Design	n	Hospitalized population	Male (%)	Age (yrs)*	Nutritional assessment	Prevalence MN	Biomarker(s)	Relation between biomarker(s) and nutritional status*
										MTA β=0.71 (p=0.01) P-GPA β=−0.63 (p=0.02) TML β=0.60 (p=0.02) VitB3 β=−0.70 (p=0.03) NAM β=0.51 (p=0.03) PyrGln β=0.49 (p=0.03) Val β=−0.60 (p=0.03) Hx β=0.46 (p=0.04) Kyn β=0.53 (p=0.04) PL β=0.32 (p=0.049) TrpB β=−0.33 (p=0.05) γ-GPA β=0.47 (p=0.06) OH-PL β=0.32 (p=0.07) 3-UPA β=0.37 (p=0.07) Urea β=0.42 (p=0.07)
Olvera-Soto et al[38]	Mexico	Cross-sectional	70	Patients aged 18-65 years with stage 4 Chronic Kidney Disease	46	47 (34-53)	No MN: SGA A Mild MN: SGA B Severe MN: SGA C	No MN: 67.1% (n=47) Mild MN: 25.7% (n=18) Severe MN: 7.1% (n=5)	25(OH)D (ng/mL) Suf: ≥30 (n=0) Ins: 20-30 (n=18) Def: 10-20 (n=36) SevDef: <10 (n=16)	Ins vs Def vs SevDef: No MN: 23.4% (n=11) vs 51.1% (n=24) vs 25.5% (n=12); (p=0.69) Mild MN: 33.3% (n=6) vs 50.0% (n=9) vs 16.7% (n=3); (p=0.68) Severe MN: 20% (n=1) vs 60% (n=3) vs 20% (n=1); (p=1.00)
Pourhassan et al[25]	Germany	Cross-sectional	233	Patients ≥ 60 years admitted to geriatric acute care ward	37	82 (±7)	No MN: MNA-SF 12-14 Risk of MN: MNA-SF 8-11 MN: MNA-SF 0-7	No MN: 14% (n=32) Risk of MN: 47% (n=106) MN: 39% (n=89)	VitB1 (ng/mL)	No MN vs risk of MN vs MN: 67.0 (±21.8) vs 64.5 (±18.8) vs 65.5 (±28.1) (p=0.45)

Table 1 *(Continued)*

Reference	Country	Design	n	Hospitalized population	Male (%)	Age (yrs)*	Nutritional assessment	Prevalence MN	Biomarker(s)	Relation between biomarker(s) and nutritional status*
Ramel et al [28]	Iceland	Cross-sectional	60	Elderly patients >65 years	37	83 (±8)	No MN: less than 3/7 of parameters abnormal MN: at least 3/7 of parameters abnormal TSF <5th P; MAMC <5th P, BMI <20; TLC <1.82; SA <31; SPA <180; uWL >5%	No MN: 41.7% (n=25) MN: 58.3% (n=35)	VitB12 (pmol/L), FA (nmol/L), CysC (mg/L), HC (µmol/L)	No MN vs MN: VitB12: 597 (±367) vs 659 (±412) (p=0.56) FA: 19.7 (±12.1) vs 22.6 (±11.8) (p=0.36) CysC: 1.51 (±0.88) vs 1.62 (±0.55) (p=0.046) HC: 12.9 (±5.8) vs 14.1 (±6.7) (p=0.50)
Ramel et al [22]	Iceland	Cross-sectional	60	Elderly patients >65 years	37	83 (±8)	According to Ramel et al [28]	No MN: 41.7% (n=25) MN: 58.3% (n=35)	25(OH)D (nmol/L) Def: <25 (n=7) Ins: 25-75 (n=43) Suf: ≥75 (n=10)	No MN vs MN: 46.4 (± 21.5) vs 53.9 (±23.0) (p=0.22)

Table 1 *(Continued)*

Reference	Country	Design	n	Hospitalized population	Male (%)	Age (yrs)*	Nutritional assessment	Prevalence MN	Biomarker(s)	Relation between biomarker(s) and nutritional status*
Soysal et al [29]	Turkey	Cross-sectional	615	Elderly patients ≥60 years	39	73 (±9)	No MN: MNA-SF 12-14 Risk of MN: MNA-SF 8-11 MN: MNA-SF 0-7	No MN: 33.7% (n=207) Risk of MN: 43.7% (n=269) MN: 22.6% (n=139)	Glu (mg/dL), TSH (uIU/mL), fT3 (nmol/L), fT4 (nmol/L), Creat (mg/dL), VitB12 (pmol/L), FA (ng/mL)	No MN vs risk of MN vs MN: Glu: 132.9 (±70.9) vs 145.7 (±80.2) vs 139.0 (±73.2) TSH: 3.6 (±15.6) vs 1.9 (±2.1) vs 2.2 (±3.7) fT3[a,d]: 3.6 (±0.9) vs 3.3 (±0.9) vs 2.9 (±1.0) fT4[c]: 14.5 (±3.6) vs 15.3 (±3.3) vs 15.4 (±4.0) Creat[d]: 1.1 (±0.8) vs 1.3 (±1.5) vs 1.7 (±1.6) VitB12: 374.3 (±235.7) vs 348.1 (±184.2) vs 382.6 (±212.1) FA: 8.4 (±3.9) vs 8.2 (±4.2) vs 7.7 (±3.7) [a] Risk of MN vs MN: p<0.002 [b] Risk of MN vs MN: p<0.05 [c] No MN vs MN: p<0.05 [d] No MN vs MN: p<0.001 Pearson correlation with MNA-SF: VitB12: r=0.01 (p>0.05); FA: r=0.16 (p>0.05)
Tas Kilic et al [21]	Turkey	Cross-sectional	62	Patients with systemic sclerosis	10	50 (±13)	No MN: MUST 0 Medium risk of MN: MUST 1 High risk of MN: MUST ≥2	No MN: 74.2% (n=46) MN: 25.8% (n=16)	VitB12 (pg/mL) Suf: >300 (n=18) Def: ≤300 (n=44)	No MN vs MN: Suf: 77.8% (n=14) vs 22.2% (n=4); Def: 72.7% (n=32) vs 27.3% (n=12) (p>0.05)

Table 1 *(Continued)*

Reference	Country	Design	n	Hospitalized population	Male (%)	Age (yrs)*	Nutritional assessment	Prevalence MN	Biomarker(s)	Relation between biomarker(s) and nutritional status*
Terlikowska et al[24]	Poland	Cross-sectional	136	Caucasian women surgically treated for ovarian cancer	0	53 (±21)	No MN: PG-SGA A Mild MN: PG-SGA B Severe MN: PG-SGA >8	No MN: 44.9% (n=61) Mild MN: 36.0% (n=49) Severe MN: 19.1% (n=26)	ATRa, 25(OH)D, ATR, Ax, Lu, Zx, βTCP, γTCP, βCx, αTCP, Ly, αCt, βCt, Q_{10} (μmol/L)	No MN vs mild MN vs severe MN: ATRa: 0.004 (±0.002) vs 0.005 (±0.001) vs 0.005 (±0.001) (p=0.93) 25(OH)D: 0.08 (±0.03) vs 0.06 (±0.03) vs 0.03 (±0.01) (p=0.01) ATR: 5.6 (±1.8) vs 3.2 (±1.0) vs 2.0 (±0.9) (p=0.02) Ax: 0.003 (±0.001) vs 0.003 (±0.001) vs 0.002 (±0.001) (p=0.96) Lu: 0.55 (0.22) vs 0.51 (±0.22) vs 0.47 (±0.25) (p=0.29) Zx: 0.05 (±0.02) vs 0.03 (±0.01) vs 0.04 (±0.02) (p=0.98) β+γTCP: 1.4 (±0.7) vs 1.4 (0.7) vs 1.3 (0.2) (p=0.93) βCx: 0.007 (±0.004) vs 0.006 (±0.003) vs 0.005 (±0.002) (p=0.97) αTCP: 21.9 (±7.1) vs 19.0 (±5.2) vs 17.6 (±4.5) (p=0.09) Ly: 0.13 (±0.09) vs 0.12 (±0.05) vs 0.11 (±0.09) (p=0.25) αCt: 0.06 (±0.05) vs 0.06 (±0.05) vs 0.05 (±0.05) (p=0.08) βCt: 0.25 (±0.08) vs 0.23 (±0.14) vs 0.23 (±0.18) (p=0.90) Q_{10}: 0.03 (±0.04) vs 0.03 (±0.03) vs 0.03 (±0.02) (p=0.82)

Table 1 *(Continued)*

Reference	Country	Design	n	Hospitalized population	Male (%)	Age (yrs)*	Nutritional assessment	Prevalence MN	Biomarker(s)	Relation between biomarker(s) and nutritional status*
Tsagari et al [30]	Greece	Prospective cohort	101	Elderly patients ≥65 years with a hip fracture	19	Females: 81 (75-86) Males: 80 (75-89)	No MN: MNA >23.5 Risk of MN: MNA 17-23.5 MN: MNA <17	Mean (±SD) MNA score: Females: 20 (18-22) Males: 21 (15-24)	25(OH)D (ng/mL) Ins: <20 Suf: ≥20	Pearson correlation with MNA: Total: r=0.41 (p<0.001), females: r=0.33 (p<0.001), males: r=0.56 (p=0.007) Discriminatory performance of MNA to predict Ins 25(OH)D: *Total population:* AUC 0.84 [SE 0.06, 95% CI 0.72-0.96] (p=0.01). MNA <25.75: Sensitivity 90.7% and specificity 77.8% *Only females:* AUC 0.85 [SE 0.08, 95% CI 0.70-1.00] (p=0.009) MNA <24: Sensitivity 92.1% and specificity 60%
Venzin et al [41]	Switzerland	Prospective cohort	430 (423 are included in NA)	Patients admitted to the internal medicine department, without patients directly admitted to the ICU	52	63 (±19)	No MN: MNA >23.5 Risk of MN: MNA 17-23.5 MN: MNA <17	No MN: 69.5% (n=294) Risk of MN: 20.1% (n=85) MN: 10.4% (n=44)	BUN (mmol/L), Creat (μmol/L)	No MN vs risk of MN vs MN: BUN: 7.4 (±5.2) vs 8.0 (±6.9) vs 9.5 (±9.6) (p>0.05) Creat: 89.2 (±79.6) vs 102.8 (±111.9) vs 94.5 (±72.8) (p>0.05)
Vischer et al [31]	Switzerland	Cross-sectional	164 (163 are included in NA)	Patients receiving geriatric inpatient care	30	85 (±6)	No MN: MNA-SF 12-14 Risk of MN: MNA-SF 8-11 MN: MNA-SF 0-7	No MN: 31.9% (n=52) Risk of MN: 50.3% (n=82) MN: 17.8% (n=29)	Iron (μmol/L), 25(OH)D (nmol/L)	No MN vs risk of MN vs MN: Iron: 10.8 (±4.9) vs 11.3 (±7.3) vs 9.7 (±5.1) (p>0.05) 25(OH)D: 40.4 (±22.4) vs 43.7 (±23.3) vs 46.6 (±39.3) (p>0.05)

Table 1 *(Continued)*

Reference	Country	Design	n	Hospitalized population	Male (%)	Age (yrs)*	Nutritional assessment	Prevalence MN	Biomarker(s)	Relation between biomarker(s) and nutritional status*
Vosoughi et al [23]	Iran	Prospective cohort	185	Patients admitted to the ICU	51	56 (±1)	No MN: MAMC >90; Mild MN: MAMC 81-90; Moderate MN: MAMC 70-80; Severe MN: MAMC <70	No MN: 61% (n=113); Mild MN: 29% (n=54); Moderate-severe MN: 10% (n=18)	25(OH)D (ng/mL) Ins: < 30 Suf: 30-100	No MN vs mild MN vs moderate-severe MN: Ins: 61% (n=105) vs 29% (n=50) vs 10% (n=18); Suf: 67% (n=8) vs 33% (n=4) vs 0% (n=0); (p=0.5) Ins: no MN: OR=1***; mild MN: OR=0.99 (95% CI 0.96-1.04; p=0.89)***; moderate-severe MN: OR=0.89 (95% CI 0.77-1.04; p=0.14)***

5th P, 5th percentile of the National Health and Nutrition Examination Survey standardized for age and sex; ALC, Absolute lymphocyte count (x109 cells/L); Allo-HSCT, allogeneic hematopoietic stem cell transplantation; AUC, Area under the curve; BMI, Body Mass Index (kg/m2); BW, Body weight (kg); CHF, Congestive heart failure; CI, Confidence interval; Def, Deficiency; ICU, Intensive care unit; Ins, Insufficiency; MAC, Mid-arm circumference (cm); MAMC, Mid-arm muscle circumference, calculated through Mid-arm circumference (cm) – 3/14 x TSF (%); MN, Malnutrition/Malnourished; MNA-SF, Mini Nutritional Assessment-Short Form; MUST, Malnutrition Universal Screening Tool; NA, Nutritional assessment; NRS-2002, Nutritional Risk Screening 2002; NYHA, New York heart association; OR, Odds Ratio; PG-SGA, Patient-Generated Subjective Global Assessment; SA, Serum albumin (g/dL); SE, Standard error; SevDef, Severe deficiency; SGA, Subjective Global Assessment; SIRS, Systemic inflammatory response syndrome; SPA, Serum prealbumin (mg/dL); Suf, sufficiency; TSF, Skin-fold thickness at triceps (cm); uWL, Unintentional weight loss; WN, Well-nourished; Yrs, Years %ucOC, Percentage of osteocalcin that is not carboxylated; 1,25di(OH)D, 1,25-dihydroxycholecalciferol (pmol/L); 25(OH)D, 25-hydroxycholecalciferol (ng/mL, nmol/L or µmol/L); 3-UPA, 3-Ureidopropionate; Andros-S, Andro steroid monosulfate 2; ATR, All-trans-retinol (µmol/L); ATRa, All-trans-retinoic acid (µmol/L); Ax, Astaxanthin (µmol/L); BUN, Blood urea nitrogen (mmol/L); Ca, Calcium (mmol/L); CI, Chiro-inositol; Creat, Creatinine (mg/dL); Ct, Carotenoids (µg/dL); CysC, Cystatin C (mg/L); EGRAC, erythrocyte glutathione reductase activation coefficient; FA, Folic acid (ng/mL or nmol/L); fT3, Free T3 (nmol/L); fT4, Free T4 (nmol/L); γ-GPA, γ-Glutamylphenylalanine; Glu, Glucose (mg/dL); HC, Homocysteine (µmol/L); Hx, Hypoxanthine; Iron, Serum iron (µmol/L); Kyn, Kynurenine; Lu, Luthein (µmol/L); Ly, Lycopene (µmol/L); MTA, 5-Methylthioadenosine; NAM, N-acetylmethionine; NAPhe, N-acetylphenylalanine; OC, Osteocalcin (ng/mL); OH-PA, 4-hydroxyphenylacetate; OH-PL, 3-(4-hydroxyphenyl)lactate; P-GPA, 1-Palmitoylglycerophosphoethanolamine; PIVKA-II, Protein Induced Vitamin K Absence or Antagonist-II; PL, Phenyllactate; PTH, Parathyroid hormone (pg/mL); PyrGln, Pyroglutamine; Q10, Coenzyme Q10 (µmol/L); S-GPA, 1-stearoylglycerophosphoethanoamine; TMAO, Trimethylamine-N-oxide (µmol/L); TML, N-6-trimethyllysine; TrpB, Tryptophan betaine; TSH, thyroid stimulating hormone (uIU/mL); Val, Valerate; VitA, Vitamin A (µg/dL); VitB1, Vitamin B1 (thiamin) (ng/mL); VitB3, Vitamin B3 (nicotinamide); VitB12, Vitamin B12 (pg/mL or pmol/L); VitC, Vitamin C/Ascorbic acid (mg/dL); VitE, Vitamin E (µg/dL); VitK1, Vitamin K1/Phylloquinone (nmol/L); Zx, Zeaxanthin (µmol/L); αCt, α-carotene (µmol/L); αTCP, α-Tocopherol (µmol/L); βCt, β-Carotene (µmol/L); βCx, β-cryptoxanthin (µmol/L); βTCP, β-Tocopherol (µmol/L); γTCP, γ-Tocopherol (µmol/L)

*Data presented as Mean (±SD), Median [IQR], Median (range), or Percentage (number)

** Adjusted for tumor type, BMI category, race, and gender

*** Adjusted for age, sex, length of hospital stay, infection, C-reactive protein

Table 2: Risk of Bias in the included cohort studies according to MINORS criteria

	Avelino et al [39]	Christopher et al [32]	Chou et al [19]	Cunha et al [26]	Djurasinovic et al [33]	Førli et al [36]
1. Clearly stated aim	2	2	2	2	2	2
2. Inclusion of consecutive patients	2	2	2	1	2	2
3. Prospective collection of data	2	2	2	2	2	2
4. Endpoints appropriate to aim of study	2	2	2	2	2	2
5. Unbiased assessment of study endpoints	0	0	0	0	0	0
6. Follow-up period appropriate to aim of study	2	2	2	2	2	2
7. <5% lost to follow-up	2	2	2	2	2	2
8. Prospective calculation of study size	0	0	2	0	0	0
9. An adequate control group	2	2	2	1	2	1
10. Contemporary groups	2	2	2	2	2	2
11. Baseline equivalence of groups	1	1	2	1	1	1
12. Adequate statistical analyses	2	2	2	2	2	2
Total	19	19	22	17	19	18
	Holden et al [37]	Hosseini et al [27]	Jatoi et al [40]	Katić et al [20]	Li et al [35]	Mogensen et al [34]
1. Clearly stated aim	2	2	2	2	2	2
2. Inclusion of consecutive patients	2	2	2	2	2	2
3. Prospective collection of data	2	2	2	2	2	2
4. Endpoints appropriate to aim of study	2	2	2	2	2	2
5. Unbiased assessment of study endpoints	0	0	0	0	0	0
6. Follow-up period appropriate to aim of study	2	2	2	2	2	2
7. <5% lost to follow-up	2	2	2	2	2	2
8. Prospective calculation of study size	0	0	0	0	0	0
9. An adequate control group	2	2	1	2	2	2
10. Contemporary groups	2	2	2	2	2	2
11. Baseline equivalence of groups	0	1	0	2	1	1
12. Adequate statistical analyses	2	2	1	2	2	2
Total	18	19	16	20	19	19
	Olivera-Soto et al [38]	Pourhassan et al [25]	Ramel et al [28]	Ramel et al [22]	Soysal et al [29]	Tas Kilic et al [21]
1. Clearly stated aim	2	2	2	2	2	2
2. Inclusion of consecutive patients	2	2	2	2	2	2
3. Prospective collection of data	2	0	2	2	2	2
4. Endpoints appropriate to aim of study	2	2	2	2	2	2
5. Unbiased assessment of study endpoints	0	0	0	0	0	0
6. Follow-up period appropriate to aim of study	2	2	2	2	2	2
7. <5% lost to follow-up	2	2	2	2	2	2
8. Prospective calculation of study size	0	0	0	2	0	0
9. An adequate control group	2	2	2	2	2	2
10. Contemporary groups	2	2	2	2	2	2
11. Baseline equivalence of groups	1	1	0	0	1	2

Table 2 *(Continued)*

	Olivera-Soto et al [38]	Pourhassan et al [25]	Ramel et al [28]	Ramel et al [22]	Soysal et al [29]	Tas Kilic et al [21]
12. Adequate statistical analyses	2	2	2	2	2	2
Total	19	17	18	20	19	20
	Terlikowska et al [24]	Tsagari et al [30]	Venzin et al [41]	Vischer et al [31]	Vosoughi et al [23]	
1. Clearly stated aim	2	2	1	2	2	
2. Inclusion of consecutive patients	2	2	2	2	2	
3. Prospective collection of data	0	2	2	2	2	
4. Endpoints appropriate to aim of study	2	2	2	2	2	
5. Unbiased assessment of study endpoints	0	0	0	0	0	
6. Follow-up period appropriate to aim of study	2	2	2	2	2	
7. <5% lost to follow-up	2	2	2	2	2	
8. Prospective calculation of study size	0	0	0	0	2	
9. An adequate control group	2	2	2	2	2	
10. Contemporary groups	2	2	2	2	2	
11. Baseline equivalence of groups	0	1	1	1	2	
12. Adequate statistical analyses	2	2	2	2	2	
Total	16	19	18	19	22	

Criteria were scored 2 (reported and adequate), 1 (reported but inadequate) or 0 (not reported), with a maximum total score of 24

Patient Population

The selected studies included 3,803 hospitalized patients, both ICU patients (n=365) and non-ICU patients (n=3,438) (**Table 1**). Eight studies focused on elderly patients older than 60 or 65 years old,[22,25-31] and the other studies included all adult patients. Regarding the reason for hospital admission, three studies focused on patients with malignancies,[24,32,33] one on patients with chronic graft-vs-host disease after allogeneic hematopoietic stem cell transplantation,[20] two studies included patients with SIRS or sepsis[19,34] and two studies included patients with fractures.[30,35] Other studied patient groups included patients with pulmonary disease considered for lung transplantation,[36] chronic kidney disease,[37,38] chronic heart failure,[27] and systemic sclerosis.[21] The other articles included all patients admitted to the hospital ward or ICU.[22,23,25,26,28,29,31,39-41]

Prevalence of Malnutrition

In five studies including only elderly patients, 44-81% were at risk of malnutrition and 10-39% were diagnosed with malnutrition based on the MNA or MNA Short-Form (MNA-SF).[25,27,29-31] In three other studies, 16.5% of the elderly patients had a BMI below 18.5 kg/m^2 and 58% were diagnosed with malnutrition based on a

combination of anthropometric measurements and laboratory values.[22,26,28] In three studies with patients with (hematologic) malignancies, 28-36% were diagnosed with mild malnutrition, and 6-24% had severe malnutrition based on the PG-SGA.[20,24,32] Djurasinovic et al[33] used the Nutritional Risk Screening (NRS-2002) and found that 45% of the patients with lymphoproliferative malignancies were malnourished. In the other patient groups, 20-26% of the patients were mildly malnourished and 0-24% were severely malnourished based on the SGA.[37-39] In the study by Venzin et al,[41] 20% were at risk of malnutrition and 10% were malnourished according to the MNA. Vosoughi et al[23] found that 29% of the patients admitted to the ICU were mildly malnourished and 10% were severely malnourished based on the mid-arm muscle circumference (MAMC). Other nutritional assessment tools found a prevalence of malnutrition between 26% and 74%.[19,21,34-36,40]

Metabolites and Malnutrition

Many different plasma metabolites were studied in their relation with malnutrition. No association was found between creatinine levels and the SGA or MNA score,[39,41] but creatinine levels were significantly higher in the patients with malnutrition diagnosed with the MNA-SF (1.7 (±1.6) mg/dL vs 1.1 (±0.8) mg/dL ($p<0.001$)).[29] The NRS-2002 score was found to be significantly lower in the group with high Trimethylamine N-oxide (TMAO) levels, compared to the groups with median or low TMAO levels (NRS-2002 score 4.0 (3.0-4.0) vs 4.0 (4.0-5.8) vs 5.0 (5.0-6.0) ($p<0.001$)).[19] The percentage of osteocalcin that is not carboxylated (%ucOC) was not found to be related to the SGA score ($r=0.02$; $p=0.79$).[37] Osteocalcin levels were significantly higher in the well-nourished patients compared to the patients with malnutrition based on the NRS-2002 score (3.7 (±0.5) vs 1.3 (±0.2) ng/mL; $p=0.00$).[35] Hosseini et al[27] and Venzin et al[41] did not find a relation between blood urea nitrogen (BUN) levels and malnutrition diagnosed with the MNA score ($p=0.9$ and $p>0.05$ resp.), but Mogensen et al[34] found that high urea levels might be predictive for malnutrition when diagnosed through a combination of anthropometric measurements and laboratory results (VIP=2.05). The other metabolites that were the best predictors of malnutrition in a partial least squares discriminant analysis, are described in **Table 1**. Mogensen et al[34] also found that the levels of 5-methylthioadenosine, N-6-trimethyllysine, N-acetylmethionine, pyroglutamine, hypoxanthine, kynurenine, and phenyllactate were significantly higher, and the levels of 1-palmitoylglycerophosphoethanolamine, and valerate were significantly lower in patients with malnutrition compared to the well-nourished patients ($p<0.05$). Ramel et al[28]

concluded that cystatine C levels were significantly higher in the patients with malnutrition diagnosed through a combination of anthropometric measurements and laboratory results. Free T3 levels were significantly lower (2.9 (±1.0) nmol/L vs 3.6 (±0.9) nmol/L) and free T4 levels were significantly higher (15.4 (±4.0) nmol/L vs 14.5 (±3.6) nmol/L) in the patients with malnutrition based on the MNA-SF compared to the patients without malnutrition.[29,31]

Vitamins and Malnutrition

25(OH)D levels seemed to be lower in patients with malnutrition diagnosed with the PG-SGA score compared to the well-nourished patients.[20,24] However, when adjusted for tumor type, BMI category, race, and gender, 25(OH)D levels were not related to the PG-SGA score.[32] Additionally, malnutrition diagnosed with the NRS-2002 was associated with a higher prevalence of severe 25(OH)D deficiency and with lower 25(OH)D levels.[33,35] Malnutrition based on the MNA score was also found to be related with lower 25(OH)D levels ($p<0.001$).[30] On the other hand, the MNA-SF, SGA, BMI, MAMC, and a combination of anthropometric measurements and laboratory results were not related to 25(OH)D levels ($p>0.05$).[31,36-38] 1,25-dihydroxycholecalciferol (1,25di(OH)D) was not related to a BMI <20 kg/m^2.[36]

Vitamin C levels were significantly lower in the severely and mildly malnourished group compared to the well-nourished group based on the SGA score (0.3 (0.0-0.9) mg/dL vs 0.5 (0.2-1.3) mg/dL vs 0.7 (0.1-1.5) mg/dL ($p<0.05$)).[39] Vitamin C deficiency was also more common in the group with malnutrition based on the SGA score and a BMI <18.5 kg/m^2.[26,39] A BMI <18.5 kg/m^2 was also related to a higher rate of carotenoids deficiency, but not related to a vitamin A, vitamin E, or vitamin B2 deficiency (diagnosed with the erythrocyte glutathione reductase activation coefficient (EGRAC)).[26] Vitamin K1 and the related Protein Induced Vitamin K Absence or Antagonist-II (PIVKA-II) were not related to malnutrition diagnosed with the SGA or a combination of anthropometric measurements and laboratory results.[37,40] The presence of vitamin B12 deficiency was not significantly different in the malnourished group based on the MUST score and vitamin B12 levels were not significantly different in the groups based on the MNA-SF or a combination of anthropometric measurements and laboratory results.[21,28,29] Vitamin B1 (thiamin) was not related to malnutrition measured using the MNA-SF, and vitamin B9 (folic acid) was not related to a combination of anthropometric measurements and laboratory results or the MNA-SF.[25,28,29] Nicotinamide (vitamin

B3) levels were significantly lower in patients with malnutrition compared to the well-nourished patients ($p<0.05$).[34] Terlikowska et al[24] studied many carotenoids and tocopherols in the relation with the PG-SGA score. Only all-trans-retinol levels were significantly lower in the severely malnourished group compared to the mildly malnourished and the well-nourished group (2.0 (±0.9) µmol/L vs 3.2 (±1.0) µmol/L vs 5.6 (±1.8) µmol/L ($p=0.02$)).

DISCUSSION

To our knowledge, this is the first systematic review that summarizes the evidence about the value of plasma metabolites and vitamins for assessing nutritional status of hospitalized patients. Our review demonstrates that several metabolites and vitamins are related to malnutrition and may offer a promising method for assessment of nutritional status in hospitalized patients.

Most of the metabolites that showed significant difference between the malnourished and well-nourished hospitalized patients are shown in **Figure 2**.[19,26,29,34,35,39,42-55] This figure depicts the relationship between these metabolites (striped and black boxes) and other metabolic pathways in the body. The essential amino acids lysine, methionine, phenylalanine, and tryptophan play an important role within the pathways in **Figure 2**. N-6-trimethyllysine, 5-methylthioadenosine, hypoxanthine, and N-acetylmethionine are all related to the methionine cycle,[12,56-59] and the levels of these metabolites were all found to be increased in patients with malnutrition.[34] Phenyllactate, 4-hydroxyphenylacetate, 3-(4-hydroxyphenyl)lactate, N-acetylphenylalanine, and pyroglutamine are all related to the phenylalanine and/or glutamate metabolism.[12,60-62] All 5 metabolite levels were increased in patients with malnutrition.[34] Andro steroid monosulfate 2, 1-palmitoylglycerophosphoethanolamine, and 1-stearoylglycerophosphoethanolamine are involved in the lipid metabolism, and these levels were all decreased in patients with malnutrition. Chiro-inositol is also related to the lipid metabolism, but the level of this metabolite was increased in patients with malnutrition.[12,34]

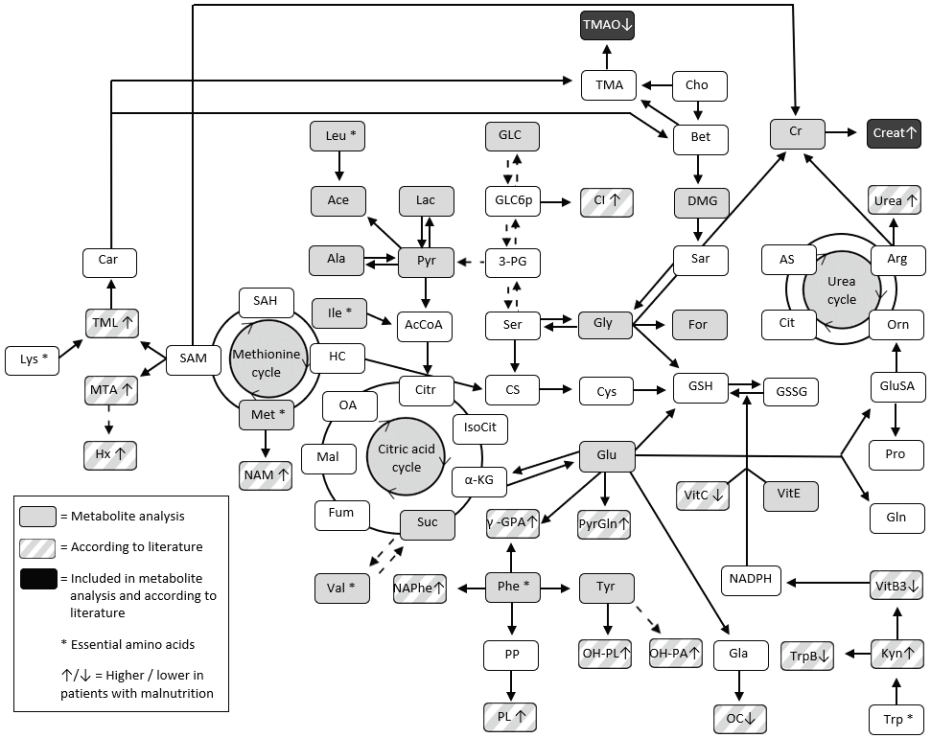

Figure 2: Metabolites analyzed in this study within their metabolic cycles and their association with malnutrition according to available literature

3-PG, 3-phosphoglycerate; AcCoA, Acetyl-CoA; Ace, Acetic acid; Ala, Alanine; Arg, Arginine; AS, Argininosuccinate; α-KG, α-ketoglutarate; Bet, Betaine; Car, Carnitine; Cho, Choline; CI, Chiro-inositol; Cit, Citrulline; Citr, Citrate; Cr, Creatine; Creat, Creatinine; CS, Cystathionine; Cys, Cysteine; DMG, N,N-Dimethylglycine; For, Formic acid; Fum, Fumarate; Gla, γ-carboxyglutamic acid; GLC, glucose; GLC6p, Glucose-6-phosphate; Gln, Glutamine; Glu, Glutamic acid; GluSA, Glutamate-1-semialdehyde; Gly, Glycine; GSH, Reduced glutathione; GSSG, Glutathione disulfide; γ-GPA, γ-Glutamyl phenylalanine; HC, Homocysteine; Hx, Hypoxanthine; Ile, Isoleucine; IsoCit, Isocitrate; Kyn, Kynurenine; Lac, Lactic acid; Leu, Leucine; Lys, Lysine; Mal, Malate; Met, Methionine; MTA, 5-Methylthioadenosine; NADPH, Nicotinamide-adenine-dinucleotidephosphate; NAM, N-acetylmethionine; NAPhe, N-acetylphenylalanine; OA, Oxaloacetate; OC, Osteocalcin; OH-PA, 4-hydroxyphenylacetate; OH-PL, 3-(4-hydroxyphenyl)lactate; Orn, Ornithine; Phe, Phenylalanine; PL, Phenyllactate; PP, Phenylpyruvate; Pro, Proline; Pyr, Pyruvic acid; PyrGlu, Pyroglutamate; SAH, S-adenosylhomocysteine; SAM, S-adenosylmethionine; Sar, Sarcosine; Ser, Serine; Suc, Succinic acid; TMA, Trimethylamine; TMAO, Trimethylamine-N-oxide; TML, N-6-trimethyllysine; Trp, Tryptophan; TrpB, Tryptophan Betaine; Tyr, Tyrosine; Val, Valine; VitB3, Vitamin B3 (nicotinamide); VitC, Vitamin C; VitE, Vitamin E;

Kynurenine is responsible for 95% of the catabolic route of tryptophan and results in the production of tryptophan betaine and nicotinamide (vitamin B3).[63-65] Nicotinamide is the precursor of nicotinamide-adenine-dinucleotidephosphate (NADPH),[66] which is, together with vitamin E and vitamin C, responsible for the conversion of glutathione disulfide to reduced glutathione.[67-70] According to Mogensen et al[34] kynurenine levels were higher in patients with malnutrition, and tryptophan betaine and nicotinamide levels were lower in patients with malnutrition. The percentage of vitamin C deficiency was significantly higher in the group with malnutrition according to Avelino et al[39] and Cunha et al.[26] Clinical studies have shown a correlation between elevated TMAO levels and an increased risk for cardiovascular events.[71] Interestingly, Chou et al[19] stated that decreased TMAO levels might be indicative of malnutrition.

Vitamins can be classified as fat-soluble or water-soluble. Vitamin A, D, E, and K are considered to be fat-soluble vitamins and are absorbed and transported similarly. Fat-soluble vitamins are packed into newly formed micelles in the small intestine and absorbed into the enterocytes. The vitamins are then repackaged into chylomicrons and secreted into the lymphatic system and the bloodstream.[72] After release of the fat-soluble vitamins, retinol-binding proteins, vitamin D binding proteins, and α-tocopherol transporting proteins transport vitamin A, D, and E, respectively, through the body.[73,74] Fat and protein are thus necessary for absorption of fat-soluble vitamins into the body and transport through the body. Several studies have found a relationship between low albumin levels and vitamin A, D, and E deficiencies in hospitalized patients.[73,75-77] Malnourished patients might therefore not only have a lower vitamin intake but the absorption and transport of vitamins might also be diminished, which can cause a further decrease in vitamin levels. On the other hand, most of the vitamins D and E in the body are stored in fat tissue.[78,79] When patients become acutely malnourished, stored vitamins might be released into the bloodstream when fat is metabolized to produce adenosine triphosphate. Differentiating between chronic malnutrition (concerning patients who are already malnourished upon admission) and acute malnutrition (concerning patients who become malnourished during hospital admission) might therefore be important when using vitamins for nutritional assessment.

Metabolites may also be used as prognostic biomarkers to assess the risk of developing complications during admission.[80] Mogensen et al[34] and Rogers et

al[81] studied the relationship between several metabolites and 28-day mortality. 3-(4-hydroxyphenyl)lactate, gamma-glutamylphenylalanine, and kynurenine were studied by both researchers and they found a significant relation between these metabolites and mortality in critically ill patients (P<0.05). In total, Rogers et al[81] found 57 metabolites to be related to the 28-day mortality.

Limitations

The most important limitation of this systematic review is that the researchers of the included studies used different nutritional assessment tools. This illustrates the fact that a criterion standard for the assessment of nutritional status is lacking, which poses a major challenge in nutritional research. Another limitation is that hospitalized patients with very diverse underlying conditions were included. Despite these limitations, our study is important because it points out the possibilities for future research.

Recommendations for further research

Based upon the findings of this systematic review, metabolites and vitamins offer a promising method for assessing the nutritional status in hospitalized patients. However, many challenges and questions need to be addressed. Further studies involving nutrition-related research in hospitalized patients should incorporate the following recommendations. First, the metabolite and vitamin levels should be assessed in large patient groups to obtain statistical power and identify clinically relevant metabolites. Second, standardized data collection, preferably by registered dietitians, on clinically relevant time points and universal assessment tools should be used to make international research comparable. Third, metabolite and vitamin levels should be measured at different time points during admission to analyze fluctuations over time. Our study group has initiated a multicenter prospective cohort study to gain greater insight in the value of lipoproteins and small metabolites for the assessment of nutritional status in severely injured patients.[82] There is a need for an objective marker to assess nutritional status in this patient group, as nutritional assessment in these patients is even more difficult than in the standard hospitalized patients. The goal of our study is to analyze the metabolite profiles of severely injured patients (Injury Severity Score ≥16) during their ICU stay, including several of the biomarker candidates described in this review.

CONCLUSION

The evidence for metabolites and vitamins as predictors of nutritional status is scarce; however, according to this literature review several metabolites partaking in the methionine, purine, glutathione, carnitine, phenylalanine, and tryptophan pathways, as well as a number of vitamins seem to be associated with malnutrition in hospitalized patients. More research is needed to further evaluate the value of metabolites and vitamins to diagnose malnutrition and assess the risk of developing malnutrition in hospitalized patients. The clinical usability and effectiveness of the metabolite analysis should be investigated for use in clinical practice.

REFERENCES

1. Cederholm T, Barazzoni R, Austin P, Ballmer P, Biolo G, Bischoff SC, et al. *ESPEN guidelines on definitions and terminology of clinical nutrition.* Clin Nutr. 2017;36(1):49-64.
2. Norman K, Pichard C, Lochs H, Pirlich M. *Prognostic impact of disease-related malnutrition.* Clin Nutr. 2008;27(1):5-15.
3. Barker LA, Gout BS, Crowe TC. *Hospital malnutrition: prevalence, identification and impact on patients and the healthcare system*. Int J Environ Res Public Health. 2011;8(2):514-527.
4. Vellas B, Guigoz Y, Garry PJ, Nourhashemi F, Bennahum D, Lauque S, Albarede JL. *The Mini Nutritional Assessment (MNA) and its use in grading the nutritional state of elderly patients*. Nutrition. 1999;15(2):116-122.
5. Chao PC, Chuang HJ, Tsao LY, Chen PY, Hsu CF, Lin HC, et al. *The Malnutrition Universal Screening Tool (MUST) and a nutrition education program for high risk cancer patients: strategies to improve dietary intake in cancer patients*. Biomedicine. 2015;5(3):17.
6. van Bokhorst-de van der Schueren MA, Guaitoli PR, Jansma EP, de Vet HC. *Nutrition screening tools: does one size fit all? A systematic review of screening tools for the hospital setting.* Clin Nutr. 2014;33(1):39-58.
7. White JV, Guenter P, Jensen G, Malone A, Schofield M. *Consensus statement: Academy of Nutrition and Dietetics and American Society for Parenteral and Enteral Nutrition: characteristics recommended for the identification and documentation of adult malnutrition (undernutrition).* JPEN J Parenter Enteral Nutr. 2012;36(3):275-83.
8. Jensen GL, Wheeler D. *A new approach to defining and diagnosing malnutrition in adult critical illness*. Curr Opin Crit Care. 2012;18(2):206-11.
9. Keller U. *Nutritional laboratory markers in malnutrition*. J Clin Med. 2019;8(6):775.
10. Rinschen MM, Ivanisevic J, Giera M, Siuzdak G. *Identification of bioactive metabolites using activity metabolomics.* Nat Rev Mol Cell Biol. 2019;20(6):353-67.
11. Sun YV, Hu YJ. *Integrative Analysis of Multi-omics Data for Discovery and Functional Studies of Complex Human Diseases*. Adv Genet. 2016;93:147-90.
12. Wishart DS, Feunang YD, Marcu A, Guo AC, Liang K, Vázquez-Fresno R, et al. *HMDB 4.0: the human metabolome database for 2018.* Nucleic Acids Res. 2018;46(D1):D608-D617.
13. Clish CB. *Metabolomics: an emerging but powerful tool for precision medicine*. Cold Spring Harb Mol Case Stud. 2015;1(1):a000588.
14. Bujak R, Struck-Lewicka W, Markuszewski MJ, Kaliszan R. *Metabolomics for laboratory diagnostics*. J Pharm Biomed Anal. 2015;113:108-20.
15. Zhang Z, Pereira SL, Luo M, Matheson EM. *Evaluation of blood biomarkers associated with risk of malnutrition in older adults: A systematic review and meta-analysis*. Nutrients. 2017;9(8)
16. Margaritelis NV, Paschalis V, Theodorou AA, Vassiliou V, Kyparos A, Nikolaidis MG. *Rapid decreases of key antioxidant molecules in critically ill patients: A personalized approach.* Clin Nutr. 2020;39(4):1146-54.
17. Moher D, Liberati A, Tetzlaff J, Altman DG. *Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement*. PLoS Med. 2009;6(7):e1000097.

18. Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. *Methodological index for non-randomized studies (minors): development and validation of a new instrument.* ANZ J Surg. 2003;73(9):712-6.

19. Chou RH, Wu PS, Wang SC, Wu CH, Lu SF, Lien RY, et al. *Paradox of trimethylamine-N-oxide, the impact of malnutrition on microbiota-derived metabolites and septic patients*. J Intensive Care. 2021;9(1):65.

20. Katić M, Pirsl F, Steinberg SM, Dobbin M, Curtis LM, Pulanić D, et al. *Vitamin D levels and their associations with survival and major disease outcomes in a large cohort of patients with chronic graft-vs-host disease*. Croat Med J. 2016;57(3):276-86.

21. Tas Kilic D, Akdogan A, Kilic L, Sari A, Erden A, Armagan B, et al. *Evaluation of Vitamin B12 Deficiency and Associated Factors in Patients With Systemic Sclerosis*. J Clin Rheumatol. 2018;24(5):250-4.

22. Ramel A, Jonsson PV, Bjornsson S, Thorsdottir I. *Vitamin D deficiency and nutritional status in elderly hospitalized subjects in Iceland.* Public Health Nutr. 2009;12(7):1001-5.

23. Vosoughi N, Kashefi P, Abbasi B, Feizi A, Askari G, Azadbakht L. *The relationship between Vitamin D, clinical outcomes and mortality rate in ICU patients: A prospective observational study*. J Res Med Sci. 2016;21:75.

24. Terlikowska KM, Dobrzycka B, Kinalski M, Terlikowski SJ. *Serum Concentrations of Carotenoids and Fat-Soluble Vitamins in Relation to Nutritional Status of Patients with Ovarian Cancer.* Nutr Cancer. 2021;73(8):1480-8.

25. Pourhassan M, Angersbach B, Lueg G, Klimek CN, Wirth R. *Blood Thiamine Level and Cognitive Function in Older Hospitalized Patients.* J Geriatr Psychiatry Neurol. 2019;32(2):90-6.

26. Cunha DF, Cunha SF, Unamuno MR, Vannucchi H. *Serum levels assessment of vitamin A, E, C, B2 and carotenoids in malnourished and non-malnourished hospitalized elderly patients*. Clin Nutr. 2001;20(2):167-70.

27. Hosseini S, Keshavarz SA, Amin A, Bakshandeh H, Maleki M, Shahinfard A, et al. *Nutritional status assessment of the elderly patients with congestive heart failure by mini nutritional assessment test*. Res Cardiovasc Med. 2017;6(1)(1):e31898.

28. Ramel A, Jonsson PV, Bjornsson S, Thorsdottir I. *Total plasma homocysteine in hospitalized elderly: associations with vitamin status and renal function*. Ann Nutr Metab. 2007;51(6):527-32.

29. Soysal P, Isik AT, Uğur A, et al. *Vitamin B12 and folic acid levels are not related to length of stay in elderly inpatients*. Nutrition. 2013;29(5):757-9.

30. Tsagari A, Toulis KA, Makras P, Skagias K, Galanos A, Lyritis G. *Performance of the mini nutritional assessment score in the detection of vitamin D status in an elderly Greek population*. Horm Metab Res. 2012;44(12):896-9.

31. Vischer UM, Frangos E, Graf C, Gold G, Weiss L, Herrmann FR, Zekry D. *The prognostic significance of malnutrition as assessed by the Mini Nutritional Assessment (MNA) in older hospitalized patients with a heavy disease burden.* Clin Nutr. 2012;31(1):113-7.

32. Christopher KL, Wiggins AT, Van Meter EM, Means RT Jr, Hayslip JW, Roach JP. *Differences in vitamin D nutritional status between newly diagnosed cancer patients from rural or urban settings in Kentucky*. Nutr Cancer. 2013;65(5):653-8.

33. Djurasinović VT, Mihaljević BS, Šipetić Grujičić SB, Ignjatović SD, Trajković G, Todorović-Balint MR, et al. *25(OH) vitamin D deficiency in lymphoid malignancies, its prevalence and significance. Are we fully aware of it?* Support Care Cancer. 2018;26(8):2825-32.

34. Mogensen KM, Lasky-Su J, Rogers AJ, Baron RM, Fredenburgh LE, Rawn J, et al. *Metabolites associated with malnutrition in the intensive care unit are also associated with 28-day mortality*. J Parenter Enteral Nutr. 2017;41(2):188-97.

35. Li Y, Hui M, Chang X, Li M, Wang Y, Zhang B, Yu J. *BMI reduction and vitamin D insufficiency mediated osteoporosis and fragility fractures in patients at nutritional risk: a cross-sectional study*. Eur J Clin Nutr. 2018;72(3):455-9.

36. Førli L, Bjortuft O, Boe J. *Vitamin D status in relation to nutritional depletion and muscle function in patients with advanced pulmonary disease*. Exp Lung Res. 2009;35(6):524-38.

37. Holden RM, Morton AR, Garland JS, Pavlov A, Day AG, Booth SL. *Vitamins K and D status in stages 3-5 chronic kidney disease.* Clin J Am Soc Nephrol. 2010;5(4):590-7.

38. Olvera-Soto MG, Melquiades-Castillo D, Castillo-Martínez L, Clark P, Medeiros M, Monroy A, Valdez-Ortiz R. *25 hydroxyvitamin D and nutritional parameters correlation in adults with stage 4 chronic kidney disease*. Clin Nutr ESPEN. 2018;28:80-7.

39. Avelino DD, Maltos AL, Portari GV, Gonçalves ÁC, da Cunha DF. *Vitamin C Status in Hospitalized Adults According to Subjective Global Assessment Method*. JPEN J Parenter Enteral Nutr. 2019;43(6):789-93.

40. Jatoi A, Lennon C, O'Brien M, Booth SL, Sadowski J, Mason JB. *Protein-calorie malnutrition does not predict subtle vitamin K depletion in hospitalized patients*. Eur J Clin Nutr. 1998;52(12):934-7.

41. Venzin RM, Kamber N, Keller WCF, Suter PM, Reinhart WH. *How important is malnutrition? A prospective study in internal medicine*. Eur J Clin Nutr. 2009;63(3):430-6.

42. Shen W, Gao C, Cueto R, Liu L, Fu H, Shao Y, et al. *Homocysteine-methionine cycle is a metabolic sensor system controlling methylation-regulated pathological signaling*. Redox Biol. 2020;28:101322.

43. Czibik G, Steeples V, Yavari A, Ashrafian H. *Citric acid cycle intermediates in cardioprotection*. Circ Cardiovasc Genet. 2014;7(5):711-9.

44. Adeva-Andany M, López-Ojén M, Funcasta-Calderón R, Ameneiros-Rodríguez E, Donapetry-García C, Vila-Altesor M, Rodríguez-Seijas J. *Comprehensive review on lactate metabolism in human health.* Mitochondrion. 2014;17:76-100.

45. Liu X, Cooper DE, Cluntun AA, Warmoes MO, Zhao S, Reid MA, et al. *Acetate Production from Glucose and Coupling to Mitochondrial Metabolism in Mammals*. Cell. 2018;175(2):502-13.

46. Dessi A, Fanos V. *Myoinositol: a new marker of intrauterine growth restriction?* J Obstet Gynaecol. 2013;33(8):776-80.

47. Robergs RA, Griffin SE. *Glycerol. Biochemistry, pharmacokinetics and clinical and practical applications*. Sports Med. 1998;26(3):145-67.

48. Lever M, George PM, Dellow WJ, Scott RS, Chambers ST. *Homocysteine, glycine betaine, and N,N-dimethylglycine in patients attending a lipid clinic*. Metabolism. 2005;54(1):1-14.

49. Taegtmeyer H, Ingwall JS. *Creatine--a dispensable metabolite?* Circ Res. 2013;112(6):878-80.

50. Burton BK. *Urea cycle disorders.* Clin Liver Dis. 2000;4(4):815-30.

51. Maas MN, Hintzen JCJ, Porzberg MRB, Mecinovic J. *Trimethyllysine: From Carnitine Biosynthesis to Epigenetics.* Int J Mol Sci. 2020;21(24)

52. Lu SC. Glutathione synthesis. Biochim Biophys Acta. 2013;1830(5):3143-53.

53. Deponte M. *Glutathione catalysis and the reaction mechanisms of glutathione-dependent enzymes*. Biochim Biophys Acta. 2013;1830(5):3217-66.

54. Kaufman S. *A model of human phenylalanine metabolism in normal subjects and in phenylketonuric patients*. Proc Natl Acad Sci. 1999;96(6):3160-4.

55. Arazi H, Taati B, Suzuki K. *A review of the effects of leucine metabolite (beta-Hydroxy-beta-methylbutyrate) supplementation and resistance training on inflammatory markers: A new approach to oxidative stress and cardiovascular risk factors*. Antioxidants (Basel). 2018;7(10):148.

56. Sanderson SM, Gao X, Dai Z, Locasale JW. *Methionine metabolism in health and cancer: a nexus of diet and precision medicine*. Nat Rev Cancer. 2019;19(11):625-37.

57. Jinnah HA, Sabina RL, Van Den Berghe G. *Metabolic disorders of purine metabolism affecting the nervous system.* Handb Clin Neurol. 2013;113:1827-36.

58. Strijbis K, Vaz FM, Distel B. *Enzymology of the carnitine biosynthesis pathway*. IUBMB Life. 2010;62(5):357-62.

59. Smith T, Ghandour MS, Wood PL. *Detection of N-acetyl methionine in human and murine brain and neuronal and glial derived cell lines*. J Neurochem. 2011;118(2):187-94.

60. Schuck PF, Malgarin F, Cararo JH, Cardoso F, Streck EL, Ferreira GC. *Phenylketonuria Pathophysiology: on the Role of Metabolic Alterations.* Aging Dis. 2015;6(5):390-9.

61. *PubChem Compound Summary for CID 111299, gamma-Glutamylphenylalanine*. National Center for Biotechnology Information. Accessed March 1, 2022, https://pubchem.ncbi.nlm.nih.gov/compound/gamma-Glutamylphenylalanine

62. Liu YD, Goetze AM, Bass RB, Flynn GC. *N-terminal glutamate to pyroglutamate conversion in vivo for human IgG2 antibodies*. J Biol Chem. 2011;286(13):11211-7.

63. Yang Y, Sauve AA. *NAD(+) metabolism: Bioenergetics, signaling and manipulation for therapy*. Biochim Biophys Acta. 2016;1864(12):1787-800.

64. Mayneris-Perxachs J, Lima AA, Guerrant RL, Leite ÁM, Moura AF, Lima NL, et al. *Urinary N-methylnicotinamide and beta-aminoisobutyric acid predict catch-up growth in undernourished Brazilian children*. Sci Rep. 2016;6:19780.

65. Keller BO, Wu BT, Li SS, Monga V, Innis SM. *Hypaphorine is present in human milk in association with consumption of legumes*. J Agric Food Chem. 2013;61(31):7654-60.

66. Makarov MV, Trammell SAJ, Migaud ME. *The chemistry of the vitamin B3 metabolome*. Biochem Soc Trans. 2019;47(1):131-47.

67. Lu SC. *Regulation of glutathione synthesis*. Mol Aspects Med. 2009;30(1-2):42-59.

68. Park S, Ahn S, Shin Y, Yang Y, Yeom CH. *Vitamin C in Cancer: A Metabolomics Perspective*. Front Physiol. 2018;9:762.

69. Packer L, Weber SU, Rimbach G. *Molecular aspects of alpha-tocotrienol antioxidant action and cell signalling.* J Nutr. 2001;131(2):369S-373S.

70. Schmolz L, Birringer M, Lorkowski S, Wallert M. *Complexity of vitamin E metabolism.* World J Biol Chem. 2016;7(1):14-43.

71. Janeiro MH, Ramírez MJ, Milagro FI, Martínez JA, Solas M. *Implication of Trimethylamine N-Oxide (TMAO) in Disease: Potential Biomarker or New Therapeutic Target*. Nutrients. 2018;10(10):1398.

72. Reddy P, Jialal I. *Biochemistry, Fat Soluble Vitamins*. Treasure Island(FL): StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK534869/

73. Abbott-Johnson W, Kerlin P, Clague A, Johnson H, Cuneo R. *Relationships between blood levels of fat soluble vitamins and disease etiology and severity in adults awaiting liver transplantation.* J Gastroenterol Hepatol. 2011;26(9):1402-10.

74. Bouillon R, Schuit F, Antonio L, Rastinejad F. *Vitamin D Binding Protein: A Historic Overview*. Front Endocrinol. 2020;10:910.

75. El-Eshmawy MM, Arafa MM, Elzehery RR, Elhelaly RM, Elrakhawy MM, El-Baiomy AA. *Relationship between vitamin A deficiency and the thyroid axis in clinically stable patients with liver cirrhosis related to hepatitis C virus*. Appl Physiol Nutr Metab. 2016;41(9):985-91.

76. Ghashut RA, Talwar D, Kinsella J, Duncan A, McMillan DC. *The effect of the systemic inflammatory response on plasma vitamin 25 (OH) D concentrations adjusted for albumin.* PLoS One. 2014;9(3):e92614.

77. Teriaky A, Mosli M, Chandok N, Al-Judaibi B, Marotta P, Qumosani K. *Prevalence of fat-soluble vitamin (A, D, and E) and zinc deficiency in patients with cirrhosis being assessed for liver transplantation.* Acta Gastroenterol Belg. 2017;80(2):237-41.

78. Landrier JF, Marcotorchino J, Tourniaire F. *Lipophilic micronutrients and adipose tissue biology*. Nutrients. 2012;4(11):1622-49.

79. Blum M, Dolnikowski G, Seyoum E, Harris SS, Booth SL, Peterson J, et al. *Vitamin D(3) in fat tissue*. Endocrine. 2008;33(1):90-4.

80. Stoppe C, Wendt S, Mehta NM, Compher C, Preiser JC, Heyland DK, Kristof AS. *Biomarkers in critical care nutrition*. Crit Care. 2020;24(1):499.

81. Rogers AJ, McGeachie M, Baron RM, Gazourian L, Haspel JA, Nakahira K, et al. *Metabolomic derangements are associated with mortality in critically ill adult patients*. PLoS One. 2014;9(1):e87538.

82. Dijkink S, Meier K, Krijnen P, Yeh DD, Velmahos GC, Arbous MS, et al. *The malnutrition in polytrauma patients (MaPP) study: Research protocol.* Nutr Health. 2019;25(4):291-301.

APPENDIX 1

PubMed search

((("Metabolomics"[majr] OR "Metabolomics"[ti] OR "metabolites"[ti] OR "metabolite"[ti] OR "Metabolomic"[ti] OR "Metabolome"[majr] OR "Metabolome"[ti] OR "Metabolom*"[ti] OR "Metabolic Profile"[ti] OR "Metabolic Profiles"[ti] OR "Metabolic changes"[ti] OR "Metabolic change"[ti] OR ("Malnutrition/metabolism"[majr] AND "metabolism"[Subheading:NoExp] AND "analysis"[Subheading:noexp])) AND ("Nutritional status"[majr] OR "Nutritional status"[ti] OR "Nutrition status"[ti] OR "Malnutrition"[majr] OR "Malnutrition"[ti] OR "Nutritional Deficiency"[ti] OR "Nutritional Deficiencies"[ti] OR "Undernutrition"[ti] OR "Malnourishment"[ti] OR "Malnourish*"[ti] OR "Ascorbic Acid Deficiency"[ti] OR "Ascorbic Acid Deficient"[ti] OR "Avitaminosis"[ti] OR "Beri beri"[ti] OR "Beriberi"[ti] OR "Choline Deficiency"[ti] OR "Choline Deficient"[ti] OR "Chronic Kidney Disease-Mineral and Bone Disorder"[ti] OR "Deficiency Disease"[ti] OR "Deficiency Diseases"[ti] OR "Folic Acid Deficiency"[ti] OR "Folic Acid Deficient"[ti] OR "Hyperhomocysteinaemia"[ti] OR "Hyperhomocysteinemia"[ti] OR "Hyperhomocysteinemia"[ti] OR "Kwashiorkor"[ti] OR "Magnesium Deficiency"[ti] OR "Magnesium Deficient"[ti] OR "Osteomalacia"[ti] OR "Pellagra"[ti] OR "Pernicious Anaemia "[ti] OR "Pernicious Anemia "[ti] OR "Potassium Deficiency"[ti] OR "Potassium Deficient"[ti] OR "Protein Deficiency"[ti] OR "Protein Deficient"[ti] OR "Refeeding Syndrome"[ti] OR "Riboflavin Deficiency"[ti] OR "Riboflavin Deficient"[ti] OR "Rickets"[ti] OR "Scurvy"[ti] OR "Severe Acute Malnutrition"[ti] OR "Starvation"[ti] OR "Steatitis"[ti] OR "Subacute Combined Degeneration"[ti] OR "Swayback"[ti] OR "Thiamine Deficiency"[ti] OR "Thiamine Deficient"[ti] OR "Vitamin A Deficiency"[ti] OR "Vitamin A Deficient"[ti] OR "Vitamin B 12 Deficiency"[ti] OR "Vitamin B 12 Deficient"[ti] OR "Vitamin B 6 Deficiency"[ti] OR "Vitamin B 6 Deficient"[ti] OR "Vitamin B Deficiency"[ti] OR "Vitamin B Deficient"[ti] OR "Vitamin D Deficiency"[ti] OR "Vitamin D Deficient"[ti] OR "Vitamin E Deficiency"[ti] OR "Vitamin E Deficient"[ti] OR "Vitamin K Deficiency"[ti] OR "Vitamin K Deficiency Bleeding"[ti] OR "Vitamin K Deficient"[ti] OR "Wernicke Encephalopathy"[ti]) NOT (("Animals"[mesh] OR "veterinary"[ti] OR "rabbit"[ti] OR "rabbits"[ti] OR "animal"[ti] OR "animals"[ti] OR "mouse"[ti] OR "mice"[ti] OR "rodent"[ti] OR "rodents"[ti] OR "rat"[ti] OR "rats"[ti] OR "pig"[ti] OR "pigs"[ti] OR "porcine"[ti] OR "horse"[ti] OR "horses"[ti] OR "equine"[ti] OR "cow"[ti] OR "cows"[ti] OR "bovine"[ti] OR "goat"[ti] OR "goats"[ti] OR "sheep"[ti] OR "ovine"[ti] OR "canine"[ti] OR "dog"[ti] OR "dogs"[ti] OR "feline"[ti] OR "cat"[ti] OR "cats"[ti]) NOT

"Humans"[mesh]) AND ("Patients"[mesh] OR "hospitalized"[tw] OR "hospitalised"[tw] OR "patients"[tw] OR "patient"[tw] OR "Patient Care"[mesh] OR "Hospital Units"[mesh] OR "Hospitals"[mesh])) **OR** (("Malnutrition"[mesh] OR "Malnutrition"[tw] OR "Nutritional Deficiency"[tw] OR "Nutritional Deficiencies"[tw] OR "Undernutrition"[tw] OR "Malnourishment"[tw] OR "Malnourish*"[tw] OR "Ascorbic Acid Deficiency"[tw] OR "Ascorbic Acid Deficient"[tw] OR "Avitaminosis"[tw] OR "Beri beri"[tw] OR "Beriberi"[tw] OR "Choline Deficiency"[tw] OR "Choline Deficient"[tw] OR "Chronic Kidney Disease-Mineral and Bone Disorder"[tw] OR "Deficiency Disease"[tw] OR "Deficiency Diseases"[tw] OR "Fetal Nutrition Disorders"[tw] OR "Folic Acid Deficiency"[tw] OR "Folic Acid Deficient"[tw] OR "Hyperhomocysteinaemia"[tw] OR "Hyperhomocysteinemia"[tw] OR "Hyperhomocysteinemia"[tw] OR "Kwashiorkor"[tw] OR "Magnesium Deficiency"[tw] OR "Magnesium Deficient"[tw] OR "Osteomalacia"[tw] OR "Pellagra"[tw] OR "Pernicious Anaemia "[tw] OR "Pernicious Anemia "[tw] OR "Potassium Deficiency"[tw] OR "Potassium Deficient"[tw] OR "Protein Deficiency"[tw] OR "Protein Deficient"[tw] OR "Refeeding Syndrome"[tw] OR "Riboflavin Deficiency"[tw] OR "Riboflavin Deficient"[tw] OR "Rickets"[tw] OR "Scurvy"[tw] OR "Severe Acute Malnutrition"[tw] OR "Starvation"[tw] OR "Steatitis"[tw] OR "Subacute Combined Degeneration"[tw] OR "Swayback"[tw] OR "Thiamine Deficiency"[tw] OR "Thiamine Deficient"[tw] OR "Vitamin A Deficiency"[tw] OR "Vitamin A Deficient"[tw] OR "Vitamin B 12 Deficiency"[tw] OR "Vitamin B 12 Deficient"[tw] OR "Vitamin B 6 Deficiency"[tw] OR "Vitamin B 6 Deficient"[tw] OR "Vitamin B Deficiency"[tw] OR "Vitamin B Deficient"[tw] OR "Vitamin D Deficiency"[tw] OR "Vitamin D Deficient"[tw] OR "Vitamin E Deficiency"[tw] OR "Vitamin E Deficient"[tw] OR "Vitamin K Deficiency"[tw] OR "Vitamin K Deficiency Bleeding"[tw] OR "Vitamin K Deficient"[tw] OR "Wernicke Encephalopathy"[tw]) AND ("Nutritional status"[mesh] OR "Nutritional status"[tw] OR "Nutrition status"[tw] OR "Nutrition Assessment"[mesh] OR "Nutrition Assessment"[tw] OR "Nutritional Assessment"[tw]) AND ("Vitamins"[majr] OR "Vitamins"[ti] OR "Vitamin"[ti] OR "Vitamin A"[ti] OR "Vitamin B 12"[ti] OR "Vitamin B 6"[ti] OR "Vitamin D"[ti] OR "Vitamin E"[ti] OR "Vitamin K"[ti] OR "Vitamin K 1"[ti] OR "Vitamin K 2"[ti] OR "Vitamin K 3"[ti] OR "Vitamin U"[ti] OR "1 alpha-hydroxyergocalciferol"[Supplementary Concept] OR "24,25-Dihydroxyvitamin D 3"[majr] OR "25-Hydroxyvitamin D 2"[majr] OR "7-dehydrocholesterol"[Supplementary Concept] OR "Acetylcarnitine"[majr] OR "alpha-cryptoxanthin"[Supplementary Concept] OR "alpha-Tocopherol"[majr] OR "aminopyrine, dexamethasone, phenylbutazone, thiamine, vitamin B12 drug combination"[Supplementary Concept] OR

"Ascorbic Acid"[majr] OR "beta Carotene"[majr] OR "Beta-Cryptoxanthin"[majr] OR "beta-Tocopherol"[majr] OR "Biotin"[majr] OR "Calcifediol"[majr] OR "Calcitriol"[majr] OR "calcium ascorbate"[Supplementary Concept] OR "Cholecalciferol"[majr] OR "choline, dehydrocholic acid, magnesium orotate, orotic acid, Vitamin B12 drug combination"[Supplementary Concept] OR "Cobamides"[majr] OR "Cod Liver Oil"[majr] OR "coenzyme Q10"[Supplementary Concept] OR "Dehydroascorbic Acid"[majr] OR "Dehydrocholesterols"[majr] OR "Dihydrotachysterol"[majr] OR "Dihydroxycholecalciferols"[majr] OR "Ergocalciferols"[majr] OR "Ergosterol"[majr] OR "Flavin Mononucleotide"[majr] OR "Folic Acid"[majr] OR "Formyltetrahydrofolates"[majr] OR "Fursultiamin"[majr] OR "gamma-Tocopherol"[majr] OR "Hydroxocobalamin"[majr] OR "Hydroxycholecalciferols"[majr] OR "Inositol"[majr] OR "Leucovorin"[majr] OR "Niacin"[majr] OR "Niacinamide"[majr] OR "Nicorandil"[majr] OR "Nicotinic Acids"[majr] OR "Palmitoylcarnitine"[majr] OR "Pantothenic Acid"[majr] OR "provitamin C"[Supplementary Concept] OR "Pteroylpolyglutamic Acids"[majr] OR "Pyridoxal"[majr] OR "Pyridoxal Phosphate"[majr] OR "Pyridoxamine"[majr] OR "Pyridoxine"[majr] OR "Riboflavin"[majr] OR "sapotexanthin"[Supplementary Concept] OR "Tetrahydrofolates"[majr] OR "Thiamine"[majr] OR "Thiamine Monophosphate"[majr] OR "Thiamine Pyrophosphate"[majr] OR "Thiamine Triphosphate"[majr] OR "Thioctic Acid"[majr] OR "Tocopherols"[majr] OR "Tocotrienols"[majr] OR "Tocovid"[Supplementary Concept] OR "Vitamin A"[majr] OR "vitamin A, pentifyllin, nicotinic acid, and vitamin E combination"[Supplementary Concept] OR "Vitamin B 12"[majr] OR "Vitamin B 6"[majr] OR "Vitamin D"[majr] OR "Vitamin E"[majr] OR "Vitamin K"[majr] OR "Vitamin K 1"[majr] OR "Vitamin K 2"[majr] OR "Vitamin K 3"[majr] OR "Vitamin U"[majr] OR "Antioxidants"[majr] OR "Antioxidant"[ti] OR "Antioxidants"[ti]) NOT (("Animals"[mesh] OR "veterinary"[ti] OR "rabbit"[ti] OR "rabbits"[ti] OR "animal"[ti] OR "animals"[ti] OR "mouse"[ti] OR "mice"[ti] OR "rodent"[ti] OR "rodents"[ti] OR "rat"[ti] OR "rats"[ti] OR "pig"[ti] OR "pigs"[ti] OR "porcine"[ti] OR "horse"[ti] OR "horses"[ti] OR "equine"[ti] OR "cow"[ti] OR "cows"[ti] OR "bovine"[ti] OR "goat"[ti] OR "goats"[ti] OR "sheep"[ti] OR "ovine"[ti] OR "canine"[ti] OR "dog"[ti] OR "dogs"[ti] OR "feline"[ti] OR "cat"[ti] OR "cats"[ti]) NOT "Humans"[mesh]) AND ("Patients"[mesh] OR "hospitalized"[tw] OR "hospitalised"[tw] OR "patients"[tw] OR "patient"[tw] OR "Patient Care"[mesh] OR "Hospital Units"[mesh] OR "Hospitals"[mesh]))**)**

EMBASE search

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OR "Beriberi".ti OR "Choline Deficiency".ti OR "Choline Deficient".ti OR "Chronic Kidney Disease-Mineral and Bone Disorder".ti OR "Deficiency Disease".ti OR "Deficiency Diseases".ti OR "Fetal Nutrition Disorders".ti OR "Folic Acid Deficiency".ti OR "Folic Acid Deficient".ti OR "Hyperhomocysteinaemia".ti OR "Hyperhomocysteinemia".ti OR "Hyperhomocysteinemia".ti OR "Kwashiorkor".ti OR "Magnesium Deficiency".ti OR "Magnesium Deficient".ti OR "Osteomalacia".ti OR "Pellagra".ti OR "Pernicious Anaemia ".ti OR "Pernicious Anemia ".ti OR "Potassium Deficiency".ti OR "Potassium Deficient".ti OR "Protein Deficiency".ti OR "Protein Deficient".ti OR "Refeeding Syndrome".ti OR "Riboflavin Deficiency".ti OR "Riboflavin Deficient".ti OR "Rickets".ti OR "Scurvy".ti OR "Severe Acute Malnutrition".ti OR "Starvation".ti OR "Steatitis".ti OR "Subacute Combined Degeneration".ti OR "Swayback".ti OR "Thiamine Deficiency".ti OR "Thiamine Deficient".ti OR "Vitamin A Deficiency".ti OR "Vitamin A Deficient".ti OR "Vitamin B 12 Deficiency".ti OR "Vitamin B 12 Deficient".ti OR "Vitamin B 6 Deficiency".ti OR "Vitamin B 6 Deficient".ti OR "Vitamin B Deficiency".ti OR "Vitamin B Deficient".ti OR "Vitamin D Deficiency".ti OR "Vitamin D Deficient".ti OR "Vitamin E Deficiency".ti OR "Vitamin E Deficient".ti OR "Vitamin K Deficiency".ti OR "Vitamin K Deficiency Bleeding".ti OR "Vitamin K Deficient".ti OR "Wernicke Encephalopathy".ti) AND (exp *"Nutritional status"/ OR "Nutritional status".ti OR "Nutrition status".ti OR exp *"Nutritional Assessment"/ OR "Nutrition Assessment".ti OR "Nutritional Assessment".ti) AND (exp *"Vitamin"/ OR "Vitamins".ti OR "Vitamin".ti OR "Vitamin A".ti OR "Vitamin B 12".ti OR "Vitamin B 6".ti OR "Vitamin D".ti OR "Vitamin E".ti OR "Vitamin K".ti OR "Vitamin K 1".ti OR "Vitamin K 2".ti OR "Vitamin K 3".ti OR "Vitamin U".ti OR *"1 alpha-hydroxyergocalciferol"/ OR *"24,25-Dihydroxyvitamin D 3"/ OR *"25-Hydroxyvitamin D 2"/ OR *"7-dehydrocholesterol"/ OR *"Acetylcarnitine"/ OR *"alpha-cryptoxanthin"/ OR *"alpha-Tocopherol"/ OR *"aminopyrine, dexamethasone, phenylbutazone, thiamine, vitamin B12 drug combination"/ OR *"Ascorbic Acid"/ OR *"beta Carotene"/ OR *"Beta-Cryptoxanthin"/ OR *"beta-Tocopherol"/ OR *"Biotin"/ OR *"Calcifediol"/ OR *"Calcitriol"/ OR *"calcium ascorbate"/ OR *"Cholecalciferol"/ OR *"choline, dehydrocholic acid, magnesium orotate, orotic acid, Vitamin B12 drug combination"/ OR *"Cobamides"/ OR *"Cod Liver Oil"/ OR *"coenzyme Q10"/ OR *"Dehydroascorbic Acid"/ OR *"Dehydrocholesterols"/ OR *"Dihydrotachysterol"/ OR *"Dihydroxycholecalciferols"/ OR *"Ergocalciferols"/ OR *"Ergosterol"/ OR *"Flavin Mononucleotide"/ OR *"Folic Acid"/ OR *"Formyltetrahydrofolates"/ OR *"Fursultiamin"/ OR *"gamma-Tocopherol"/ OR *"Hydroxocobalamin"/ OR *"Hydroxycholecalciferols"/ OR *"Inositol"/ OR *"Leucovorin"/ OR *"Niacin"/ OR *"Niacinamide"/ OR

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Chapter 5

Relevance of plasma lipoproteins and small metabolites in assessment of nutritional status among patients with severe injuries

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J Intensive Med. 2024;4(4):496-507

ABSTRACT

Introduction

This study aimed to identify plasma lipoproteins and small metabolites associated with high risk of malnutrition during intensive care unit (ICU) stay in patients with severe injuries.

Methods

This observational prospective exploratory study was conducted at two level-1 trauma centers in the Netherlands. Adult patients (aged ≥18 years) who were admitted to the ICU for more than 48 h between July 2018 and April 2022 owing to severe injuries (polytrauma, as defined by Injury Severity Scores of ≥16) caused by blunt trauma were eligible for inclusion. Overall, 51 patients were included. Partial least squares discriminant analysis was used to analyze the relationship of 112 lipoprotein-related components and 23 small metabolites with the risk of malnutrition (modified Nutrition Risk in Critically Ill score). Malnutrition was diagnosed based on Subjective Global Assessment scores. The relationship of lipoprotein properties and small metabolite concentrations with malnutrition (during ICU admission) was evaluated using mixed effects logistic regression.

Results

Lower (very) low-density lipoprotein ([V]LDL) (free) cholesterol and phospholipid levels, low particle number, and higher levels of LDL triglycerides were associated with a higher risk of malnutrition (variable importance in projection [VIP] value > 1.5). Low levels of most (V)LDL and intermediate-density lipoprotein subfractions and high levels of high-density lipoprotein Apo-A1 were associated with the diagnosis of malnutrition (VIP value >1.5). Increased levels of dimethyl sulfone, trimethylamine N-oxide, creatinine, N N-dimethylglycine, and pyruvic acid and decreased levels of creatine, methionine, and acetoacetic acid were also indicative of malnutrition (VIP value >1.5). Overall, 14 lipoproteins and 1 small metabolite were significantly associated with a high risk of malnutrition during ICU admission ($p<0.05$); however, the association did not persist after correcting the false discovery rate ($p=0.35$ for all).

Conclusion

Increased triglyceride in several lipoprotein subfractions and decreased levels of other lipoprotein subfraction lipids and several small metabolites (involved in the homocysteine cycle, ketone body formation, and muscle metabolism) may be indicative of malnutrition risk. Following validation in larger cohorts, these indicators may guide institution of preventive nutritional measures in patients admitted to the ICU with severe injuries.

INTRODUCTION

Malnutrition is a serious concern in hospitalized patients, as it is known to be associated with adverse events such as infections, prolonged hospital stay, impaired wound healing, and mortality.[1-3] In this context, the American Society for Parenteral and Enteral Nutrition defines three types of malnutrition: (1) pure chronic starvation without inflammation, (2) malnutrition resulting from chronic disease or conditions that lead to sustained inflammation of a mild to moderate degree, and (3) malnutrition caused by acute disease or injury states with a marked inflammatory response.[4] Patients with severe injuries predominantly experience acute malnutrition (type 3), as the body is in a hypermetabolic state after severe trauma.[4,5] The incidence of in-hospital malnutrition ranges from 7% to 76% in these cases, depending upon the setting, population, and nutritional assessment tool used.[5] Several tools are available for nutritional assessment; some help diagnose current malnutrition, while others screen for the risk of future malnutrition.[6] Nevertheless, the objective in-hospital measurement of nutritional status in critically ill and severely injured patients remains a challenge owing to various factors. Mechanical ventilation often makes it difficult to obtain a dietary history, swelling and edema may hinder the accurate evaluation of muscle wasting, and the acute-phase response after inflammation or trauma may affect visceral protein (albumin and pre-albumin) concentrations.[7-9] As most patients are healthy individuals prior to trauma, nutritional biomarkers may serve as better indicators of malnutrition in these patients than in those with other critical illnesses (as they may have more comorbidities).

Plasma lipoproteins and small metabolites (low-molecular-weight metabolites) are potentially useful laboratory parameters for the assessment of nutritional

status and risk of malnutrition.[10,11] Lipoproteins are involved in multiple processes such as cell membrane formation, energy storage, and fat-soluble vitamin transportation; they also serve as chemical messengers.[12] High-density lipoproteins (HDLs) have been found to play an important role in the immune system, and are involved in the modulation of complement system activation, regulation of antigen-presenting functions in macrophages, and activation of B and T cells.[13] Notably, HDL levels and function are altered in several auto-immune diseases including rheumatoid arthritis and multiple sclerosis, and during inflammatory responses.[13] In addition, high levels of total and low-density lipoprotein (LDL) cholesterol have been found to be associated with increased cardiovascular mortality.[14] In this context, small metabolites represent intermediate- or end-products of biochemical pathways, and are related to oxidative stress, muscle catabolism, and nucleotide synthesis.[15] As malnutrition is also related to oxidative stress and muscle catabolism, the relation between plasma lipoprotein and small metabolite levels and malnutrition, and their potential value in the assessment of nutritional status, warrant investigation.[16,17] Several small metabolites and vitamins appear to be associated with malnutrition in hospitalized patients. However, research pertaining to the value of lipoproteins and small metabolites in the assessment of nutritional status in severely injured patients is scarce.[18] The available literature is limited by the paucity of potential biomarkers and measurement (of lipoproteins and small metabolites) at only one time point during hospital admission.

This exploratory study aimed to identify the plasma lipoproteins and small metabolites that may be used to assess nutritional status in patients admitted to the intensive care unit (ICU) with severe injuries. We evaluated whether specific lipoproteins and small metabolites are associated with a high risk of malnutrition at admission in patients with severe injuries. We also assessed the relationship between plasma levels of these lipoproteins and small metabolites and the incidence and prevalence of malnutrition during ICU admission.

METHODS

This observational prospective exploratory study was conducted at two level-1 trauma centers in the Netherlands (Leiden University Medical Center and

Haaglanden Medical Center Westeinde). The study was incorporated in the Malnutrition in Polytrauma Patients (MaPP) study, which was initiated in July 2018.[19] The MaPP study and the present metabolomics substudy were approved by the local institutional review boards (protocol number: NL64016.058.17). Adult patients (aged ≥18 years) with severe injuries (having polytrauma, defined by Injury Severity Scores [ISS] of ≥16) caused by blunt trauma, who were admitted to the ICU of the two centers between July 2018 and April 2022, were eligible for inclusion. Only patients who were admitted to the ICU for more than 48 h and were not primarily managed in another hospital were included. Those with burn wounds and penetrating injuries were excluded. Informed consent was obtained from the patients or their legal representative on the day of ICU admission or as soon as possible. In cases where a legal representative had initially provided written informed consent, the patient was asked to confirm consent (if able to provide written informed consent later during the course of the study).

Data collection

Patient data including those pertaining to the medical history, ISS, height and weight, and other clinical data recorded during hospital admission were obtained from the patient files and stored on the Castor EDC system.[19,20] The type of nutritional support received (enteral nutrition, parenteral nutrition, or oral diet) was recorded daily. Data pertaining to the values of albumin and pre-albumin, as observed within 48 h of admission, were also collected.

Study parameters

The Subjective Global Assessment (SGA) and modified Nutrition Risk in Critically Ill (mNUTRIC) scores were the main study parameters. We evaluated the association between these parameters and alterations in plasma lipoprotein and small metabolite levels in patients with severe injuries. In this context, the SGA and mNUTRIC scores represent the current nutritional status and future malnutrition risk, respectively.

SGA

The SGA score is a nutrition assessment tool, which can be used to diagnose malnutrition.[6] The tool was developed to assess the nutritional status and predict clinical outcomes in surgical patients. It is therefore expected to offer better prediction outcomes in ICU patients than the Mini Nutritional Assessment (MNA), which

was developed to assess nutritional status in an elderly population.[6,21-23] The SGA score is based on weight change (past 2 weeks and past 6 months), changes in adequacy of dietary intake, gastrointestinal symptoms (less appetite, nausea, vomiting, and diarrhea), and functional capacity (dysfunction, bedridden, and difficulty with normal activities). The score also includes physical examination components including subcutaneous fat loss (around the eyes, triceps, and biceps) and muscle wasting (including those around the clavicle, knee, shoulder, and quadriceps). The total scores range from 1 to 7, and are classified as follows: (A) well-nourished (scores 6–7), (B) mildly/moderately malnourished (scores 3–5), and (C) severely malnourished (scores 1–2). Groups B and C are often combined under one category (malnourished) in general practice.[19] During this study, the SGA score was assessed at ICU admission, every 5 days during ICU admission, and at ICU discharge.

mNUTRIC

The mNUTRIC score is a nutrition screening tool, which is used to determine the risk of malnutrition.[6] The tool identifies critically ill patients who are most likely to benefit from aggressive nutritional treatment and is the first risk assessment tool developed and validated specifically for critically ill patients.[24,25] The score is calculated based on the Acute Physiology and Chronic Health Evaluation (APACHE) II score, Sequential Organ Failure Assessment (SOFA) score, age, burden of comorbidities, and number of days of hospital stay prior to ICU admission.[24,26] Notably, the APACHE II score is used as a general measure of disease severity and the SOFA score provides information regarding the prognosis of critically ill patients.[27,28] For this study, data pertaining to all parameters needed to calculate the mNUTRIC score were obtained on the day of admission. An mNUTRIC score of <5 and ≥5 was considered to indicate a low and high risk of malnutrition, respectively.

Lipoproteins and small metabolites

In all cases, an additional tube of blood was drawn solely for the purpose of this research project. This was clearly explained in the study information that was provided to the patient and/or their relatives before obtaining informed consent and study inclusion. The plasma concentrations of a standard panel of lipoproteins and small metabolites were measured at the Center for Proteomics and Metabolomics of the Leiden University Medical Center using nuclear magnetic resonance (NMR).[29] The NMR spectra of the plasma samples were acquired according to the

protocols required by the Bruker In Vitro Diagnostics research platform (B.I. Methods); however, heparinized plasma samples were used instead of ethylenediaminetetraacetic acid plasma or serum samples (which are usually used). The lipoprotein and small metabolites were quantified automatically using the B.I.LISA and B.I.QUANT-PS web services.[30] The full list of the 112 lipoproteins and 23 small metabolites that were analyzed, and the procedure of sample preparation for analysis, have been presented in the supplementary material. An overview of the small metabolites and related metabolic cycles evaluated in this study, and the relation between small metabolites associated with malnutrition (according to available literature), is shown in **Figure 1**.

Statistical analysis

The sample size was not calculated, as this was an exploratory study. The collection of multiple samples per patient increased the study power.[31] Statistical analyses were performed using IBM SPSS Statistics version 25 (IBM, Armonk, NY, USA),[32] R version 4.2.2 (R Core Team, Vienna, Austria),[33] and MetaboAnalyst 3.0 (Wishart Research Group, Alberta, Canada), a web-based metabolic data processing tool.[34] P-values <0.05 were considered statistically significant. The baseline characteristics were compared between patients with low (mNUTRIC score <5) and high (mNUTRIC score ≥5) risk of malnutrition on admission.[25] The Fisher's exact, independent samples T, and Mann–Whitney U tests were used for categorical variables, continuous variables with normal distribution, and continuous variables with non-normal distribution, respectively (using IBM SPSS Statistics). Outlier analysis was performed to detect the samples with extreme values; 4 samples with extremely high values (considered to reflect laboratory errors) were removed, as the values for lipoproteins and small metabolites differed considerably from those of other samples (>3 lipoprotein/small metabolite values with >6 standard deviation differences from the mean concentration). The samples were then divided into seven time periods (TPs), as shown in **Figure 2**. The average concentrations of the daily measurements within each TP were then calculated to assess the relationship with the corresponding SGA score. Lipoprotein and metabolic profiles were analyzed via three approaches, as described below.

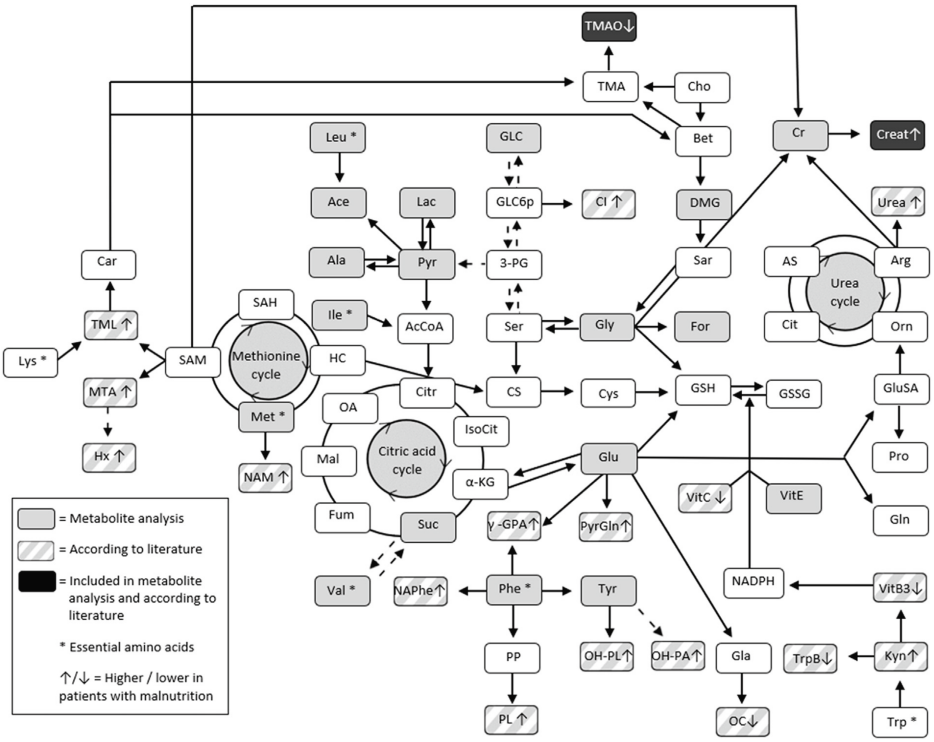

Figure 1: Small metabolites analyzed in this study. Associated metabolic cycles and relation with malnutrition (according to available literature)[18]

Solid arrows signify single-step reactions and dotted arrows signify multiple steps.

γ-GPA: *γ*-Glutamyl phenylalanine; *α*-KG: *α*-ketoglutarate; 3-PG: 3-phosphoglycerate; AcCoA: Acetyl-CoA; Ace: Acetic acid; Ala: Alanine; Arg: Arginine; AS: Argininosuccinate; Bet: Betaine; Car: Carnitine; Cho: Choline; CI: Chiro-inositol; Cit: Citrulline; Citr: Citrate; Cr: Creatine; Creat: Creatinine; CS: Cystathionine; Cys: Cysteine; DMG: N,N-Dimethylglycine; For: Formic acid; Fum: Fumarate; Gla: *γ*-carboxyglutamic acid; GLC: Glucose; GLC6p: Glucose-6-phosphate; Gln: Glutamine; Glu: Glutamic acid; GluSA: Glutamate-1-semialdehyde; Gly: Glycine; GSH: Reduced glutathione; GSSG: Glutathione disulfide; HC: Homocysteine; Hx: Hypoxanthine; Ile: Isoleucine; IsoCit: Isocitrate; Kyn: Kynurenine; Lac: Lactic acid; Leu: Leucine; Lys: Lysine; Mal: Malate; Met: Methionine; MTA: 5-Methylthioadenosine; NADPH: Nicotinamide adenine-dinucleotide-phosphate; NAM: N-acetylmethionine; NAPhe: N-acetylphenylalanine; OA: Oxaloacetate; OC: Osteocalcin; OH-PA: 4-hydroxyphenylacetate; OH-PL: 3-(4-hydroxyphenyl)lactate; Orn: Ornithine; Phe: Phenylalanine; PL: Phenyllactate; PP: Phenylpyruvate; Pro: Proline; Pyr: Pyruvic acid; PyrGln: Pyroglutamate; SAH: S-adenosylhomocysteine; SAM: S-adenosylmethionine; Sar: Sarcosine; Ser: Serine; Suc: Succinic acid; TMA: Trimethylamine; TMAO: Trimethylamine N-oxide; TML: N-6-trimethyllysine; Trp: Tryptophan; TrpB: Tryptophan Betaine; Tyr: Tyrosine; Val: Valine; VitB3: Vitamin B3 (nicotinamide); VitC: Vitamin C; VitE: Vitamin E.

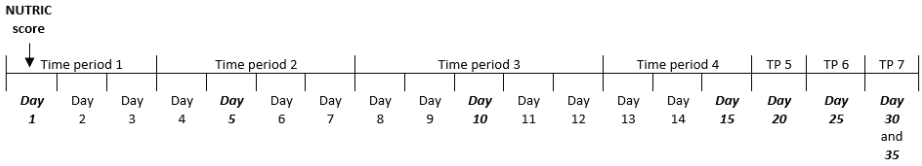

Figure 2: Clustering of daily metabolite analyses during the time periods

Bold and italicized = Day of nutritional assessment using the SGA tool

mNUTRIC: Modified Nutrition Risk in Critically Ill; SGA: Subjective Global Assessment; TP: Time period.

Multivariate analysis was used to construct a lipoprotein and small metabolite-based model that could classify future malnutrition risk

The MetaboAnalyst tool was used to analyze the log-transformed lipoprotein and small metabolite levels during period 1 (days 1–3 of ICU admission; **Figure 2**). Partial least squares discriminant analysis (PLS-DA) was used to compare lipoproteins and small metabolites between patients with high and low risk of malnutrition, based on the mNUTRIC score on the day of ICU admission.[35-37] In this context, PLS-DA is a multivariate dimensionality-reduction tool that has been recommended for use in metabolomics data analyses, in which the data sets often have considerably fewer samples than features.[38] Cross-validation of the model resulted in a Q2 value, which provides an estimate of the predictive ability of the model. This value is determined by comparing the predictive and original data and calculating the sum of squared errors. The prediction error is then summed over all samples (predicted residual sum of squares). Good predictions have low predicted residual sum of squares or high Q2 values.[34,39] A model with Q2 = 1 has perfect predictive accuracy, while that with Q2 <0 has no predictive power. Variable importance in projection (VIP) scores were calculated to assess the importance of each lipoprotein/small metabolite in the PLS model projection.[40] VIP values of >1.5 were considered to be influential for discrimination between the groups with high and low risk of malnutrition.[35] Multivariate receiver operating characteristic curve analysis was also performed based on PLS-DA, and an area under the receiver operating characteristic (AUROC) value was calculated for the model.[36] A lipoprotein and small metabolite-based model was constructed using multivariate analysis to classify concomitant malnutrition. The log-transformed lipoprotein and small metabolite levels during period 2 (days 4–7 of ICU admission) were analyzed using MetaboAnalyst. PLS-DA was used to compare lipoproteins and small metabolites between malnourished patients, based on the SGA score on Day 5 of

ICU admission. Notably, the majority of patients were well-nourished at the time of ICU admission (as this represented the pre-hospitalization nutritional status). However, many of the previously well-nourished patients were expected to have developed malnutrition during the second TP. The second TP was therefore selected to compare the malnourished and well-nourished groups.

Univariate analysis was performed to evaluate the association of lipoproteins and small metabolites with nutritional status

For the third analysis, a mixed effects logistic regression analysis (with repeated measures for each lipoprotein and small metabolite) was performed in R. The log-transformed concentrations of the mean lipoprotein and small metabolite levels were tested for their ability to indicate malnutrition (SGA score category B or C) during each TP (**Figure 2**). Baseline mixed effects logistic regression was performed for each lipoprotein and small metabolite, considering malnutrition as a binary outcome variable, TP as a fixed effect, and patient number as a random effect. A second mixed effects logistic regression was then fitted by adding the lipoprotein/small metabolite level (as the main effect) and an interaction term of the lipoprotein/small metabolite level with TP (as fixed effect) to the baseline model. The interaction term was added to allow for changes in the association between lipoprotein/small metabolite levels and malnutrition over time. The likelihood ratio test (LRT) was used to identify any association between malnutrition and each of the lipoprotein parameters and small metabolites over time.[41] False discovery rate (FDR) correction was applied to the LRT P -values to correct for multiple testing, with a threshold of 0.05.[42] The main effect of the lipoprotein/small metabolite and the interaction term have been presented for the models (of the lipoproteins/small metabolites) with significant P -values (at 5%), in addition to the β-coefficients for every unit increase and P -values for the TP. As the lipoprotein and small metabolite concentrations were log-transformed, the β-coefficients were multiplied by log10 (1.10) and exponentiated to calculate the odds ratio (OR) for malnutrition (for a 10% increase in the lipoprotein/small metabolite concentration during each TP).

RESULTS

Study population

Data from 51 patients in the MaPP study were included for analysis. Of these patients, 364 samples were collected in the seven time points according to **Figure 2** (TP 1: 103 samples, TP 2: 129 samples, TP 3: 89 samples, TP 4: 28 samples, TP 5: 8 samples, TP 6: 5 samples, and TP 7: 2 samples). The median age of the cohort was 53.0 (interquartile range [IQR]: 32.0–64.0) years and 67% of patients were male (**Table 1**). Overall, 12 and 39 patients had a high (mNUTRIC score ≥5) and low (mNUTRIC score <5) risk of malnutrition on the day of ICU admission, respectively. These groups did not differ in terms of the body mass index, ISS, and Glasgow Coma Scale score at admission. Compared to one patient in the low risk group, those with a high risk of malnutrition were significantly older (65.5 [IQR: 60.0–79.8] years] vs. 44.0 [IQR: 28.0–57.0] years; p<0.001), had a higher body weight (87.5 [IQR: 78.5–111.5] kg vs. 76.0 [IQR: 68.0–85.0] kg; p=0.030); three patients had a history of malignancy (p=0.036). The SOFA and APACHE II scores were significantly higher in the group with high mNUTRIC scores (p<.001). The 30-day mortality rate was found to be 16% and no significant differences were found between the groups. The SGA scores at ICU admission did not differ between the groups. One patient in each group was found to be malnourished at admission, based on the SGA scores. All patients with severe injuries developed malnutrition after 20 days of ICU stay. The group with a high mNUTRIC score demonstrated significantly lower pre-albumin values than that with a low mNUTRIC score ([0.13 ± 0.03] g/L vs. [0.17 ± 0.06] g/L; p=0.015) (**Table 1**). Overall, 45 and 6 patients received enteral tube feeding and an oral diet, respectively. Tube feeding was started as soon as possible after ICU admission (between Day 1 and Day 3), depending on the need for preoperative fasting.

Table 1: Patient characteristics according to risk of malnutrition

Characteristic		Low risk of malnutrition (mNUTRIC score <5) (n=39)	High risk of malnutrition (mNUTRIC score ≥5) (n=12)	P value	Total (n=51)
Age, mean ± SD, y		43.4 ± 17.5	69.5 ± 9.9	**<0.001**	49.5 ± 19.5
Male sex, n (%)		25 (64)	9 (75)	0.73	34 (67)
Weight at admission, mean ± SD, kg		77.8 ± 12.5	91.3 ± 19.7	**0.04**	81.0 ± 15.5
BMI at admission, mean ± SD, kg/m2		25.2 ± 3.7	29.0 ± 6.4	0.07	26.1 ± 4.7
Obesity at admission (BMI ≥30 kg/m2), n (%)		4 (10)	5 (42)	**0.02**	9 (18)
SOFA score at admission, mean ± SD		6.0 ± 2.7	9.3 ± 2.2	**<0.001**	6.8 ± 2.9
APACHE II score at admission, mean ± SD		14.4 ± 5.6	23.1 ± 4.3	**<0.001**	16.4 ± 6.5
ISS, mean ± SD		32.6 ± 10.3	31.1 ± 8.1	0.62	32.3 ± 9.8
GCS score at admission, mean ± SD		8.5 ± 4.7	6.6 ± 4.1	0.19	8.0 ± 4.6
ICU admission days, mean ± SD, days *		10.4 ± 8.9	13.1 ± 8.7	0.42	10.9 ± 8.7
Ventilator days, mean ± SD, days *		7.2 ± 8.0	9.7 ± 7.8	0.42	7.7 ± 7.9
Malignancy, n (%)		1 (3)	3 (25)	**0.04**	4 (8)
30-Day mortality, n (%)		4 (10)	4 (33)	0.08	8 (16)
Malnourished according to SGA score, n (%)	*D0*	1/39 (3)	1/12 (8)	0.42	2/51 (4)
	D5	11/32 (34)	4/12 (33)	1.00	15/44 (34)
	D10	13/17 (76)	6/9 (67)	0.66	19/26 (73)
	D15	8/10 (80)	2/2 (100)	1.00	10/12 (83)
	D20	7/7 (100)	1/1 (100)	-	8/8 (100)
Albumin, mean ± SD, g/L		33.3 ± 5.9	30.7 ± 4.8	0.17	32.7 ± 5.7
Pre-albumin, mean ± SD, g/L		0.17 ± 0.06	0.13 ± 0.03	**0.02**	0.16 ± 0.06

Data are expressed as n (%), mean ± standard deviation or median (interquartile range).

APACHE II: Acute Physiology and Chronic Health Evaluation; BMI: Body Mass Index; D0: Day of admission; D5: Day 5 of ICU admission; D10: Day 10 of ICU admission; D15: Day 15 of ICU admission; D20: Day 20 of ICU admission; GCS: Glasgow Coma Scale; ICU: Intensive Care Unit; ISS: Injury Severity Score; mNUTRIC: Modified Nutrition Risk in Critically Ill; ; SGA: Subjective Global Assessment; SOFA: Sequential Organ Failure Assessment; .

* Patients who died during ICU admission were excluded.

Predominant lipoproteins and small metabolites for the "risk of malnutrition "classifier

Lipoprotein and small metabolite values of two patients were not available for the first period of ICU admission. The data from the remaining 49 patients were therefore included for the PLS-DA; 10 and 39 of these patients had a high and low risk of malnutrition, respectively, as determined by the mNUTRIC scores. The mean levels of total triglycerides, total cholesterol, LDL cholesterol (LDL-C), and HDL cholesterol (HDL-C) were 159(±153) mg/dL, 132 (± 37) mg/dL, 59(± 26) mg/dL, and

45(±14) mg/dL, respectively. The PLS-DA model was based on two partial least-squares components and had a Q2 value of 0.04, indicating marginal predictive ability; the AUROC value of the model was 0.72. The 15 lipoprotein parameters and small metabolites with the highest VIP values are shown in **Figure 3**. Specific subfractions of (V)LDL with low levels of (free) cholesterol and phospholipids, low particle number (Cholesterol Subfraction of LDL-1 [L1CH], Free Cholesterol Subfraction of LDL-1 [L1FC], Phospholipids Subfraction of LDL-1 [L1PL], Apo-B Subfraction of LDL-1 [L1AB], LDL-1 Particle Number [L1PN], Free Cholesterol Subfraction of LDL-4 [L4FC], and Free Cholesterol Subfraction of VLDL-5 [V5FC]), and high triglyceride levels of one of the LDL subfractions (L5TG), were indicative of a high risk of malnutrition. Increased levels of dimethyl sulfone, trimethylamine N-oxide (TMAO), creatinine, and N,N-dimethylglycine (DMG), and decreased levels of creatine, methionine, and acetoacetic acid, were also indicative of a high risk of malnutrition.

Predominant lipoproteins and small metabolites for the "malnutrition on day 5 "classifier

Data pertaining to lipoprotein and small metabolite levels were not available for eight patients during the second period of ICU admission. Therefore, 44 patients were included in the PLS-DA malnutrition model; 15 and 29 of these patients were malnourished and well-nourished, respectively, based on Day 5 SGA scores. The PLS-DA model was based on two partial least-squares components with a Q2 value of 0.09, indicating marginal predictive accuracy; the AUROC value of the model was 0.56. The 15 lipoproteins and small metabolites with the highest VIP values are shown in **Figure 4**. Subfractions of (V)LDL and intermediate-density lipoprotein (IDL) with low levels of (free) cholesterol, particle number, triglyceride, and phospholipids (Cholesterol Subfraction of VLDL-1 [V1CH], Cholesterol Subfraction of VLDL-4 [V4CH], L1FC, L4TG, VLDL Particle Number [VLPN], V5FC, Triglycerides Subfraction of LDL-2 [L2TG], and Phospholipids Subfraction of VLDL-5 [V5PL]); (V)LDL subfractions with high levels of (free) cholesterol; and triglyceride subfractions (Free Cholesterol Subfraction of VLDL-3 [V3FC], L5TG, and Cholesterol Subfraction of LDL-3 [L3CH]) were indicative of malnutrition. High levels of Apo-A1 subfractions of HDL-2 (H2A1) and pyruvic acid were indicative of malnutrition.

Lipoproteins and small metabolites associated with a change in nutritional status

Data from all 51 patients were included in the mixed effects logistic regression analysis. Among all 135 biomarkers, 14 lipoproteins and 1 small metabolite were found to significantly predict the risk of malnutrition during ICU admission (**Table 2**). However, the LRT P-value was no longer statistically significant after FDR correction (p=0.35 for all). Only the main effects of Apo-A2 Subfraction of HDL-4 (H4A2) and Triglycerides Subfraction of VLDL-1 (V1TG) were found to be significant (p=0.04 and p=0.03 respectively, **Table 2**). These lipoprotein subfractions had ORs of 0.77 and 0.89, respectively in period 1 (**Table 3**).

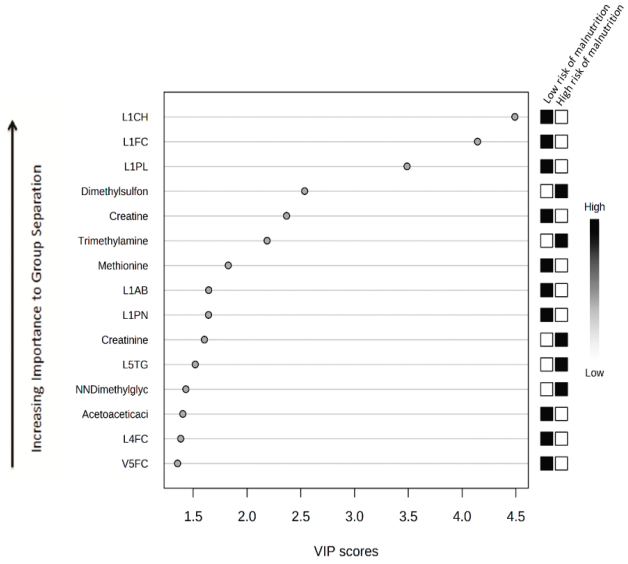

Figure 3: Risk of malnutrition biomarker identification using PLS-DA

PLS-DA was used to determine any relation between the risk of malnutrition (as defined by the mNUTRIC score) and the lipoprotein and small metabolite data. A VIP value was calculated to rank the top 15 lipoproteins and small metabolites according to their prognostic importance for the risk of malnutrition. The boxes on the right indicate the relative concentrations of the lipoprotein/small metabolite in the risk for malnutrition groups. For this analysis, the Q2 value is 0.04.

L1AB: Apo-B Subfraction of LDL-1; L1CH: Cholesterol Subfraction of LDL-1; L1FC: Free Cholesterol Subfraction of LDL-1; L1PL: Phospholipids Subfraction of LDL-1; L1PN: LDL-1 Particle Number; L4FC: Free Cholesterol Subfraction of LDL-4; L5TG: Triglycerides Subfraction of LDL-5; mNUTRIC: Modified Nutrition Risk in Critically Ill; PLS-DA: Partial Least Squares Discriminant Analysis; V5FC: Free Cholesterol Subfraction of VLDL-5; VIP: Variable Importance in Projection.

Table 2: Lipoproteins/small metabolites that were significant predictors of malnutrition according to the LRT

Lipoprotein/small metabolite	Time period		Main effect		Interaction effect		P-value LRT	P-value LRT after FDR correction
	P-value	β-coefficient	P-value	β-coefficient	P-value	β-coefficient		
L5TG (mg/dL)	0.11	2.5 ± 1.6	0.14	7.2 ± 4.9	0.96	0.1 ± 2.5	<0.01	0.35
L3FC (mg/dL)	0.39	1.0 ± 1.2	0.70	-1.4 ± 3.8	0.07	4.1 ± 2.3	0.02	0.35
L3AB (mg/dL)	0.79	-0.5 ± 1.9	0.73	-1.2 ± 3.6	0.06	4.2 ± 2.3	0.02	0.35
L3PN (nmol/L)	0.21	-5.8 ± 4.6	0.73	-1.2 ± 3.6	0.06	4.2 ± 2.3	0.02	0.35
L4TG (mg/dL)	0.06	3.0 ± 1.6	0.16	6.6 ± 4.7	0.82	-0.5 ± 2.2	0.02	0.35
L2FC (mg/dL)	0.93	-0.1 ± 1.6	0.52	-1.9 ± 3.0	0.07	4.5 ± 2.5	0.03	0.35
L3PL (mg/dL)	0.66	0.7 ± 1.6	0.77	-1.0 ± 3.5	0.10	3.4 ± 2.0	0.03	0.35
L6TG (mg/dL)	0.12	5.5 ± 3.5	0.11	11.7 ± 7.4	0.37	-3.6 ± 4.0	0.03	0.35
L2PL (mg/dL)	0.82	-0.6 ± 2.4	0.93	-0.3 ± 3.6	0.16	3.8 ± 2.7	0.03	0.35
Creatinine (mmol/L)	0.01	8.6 ± 3.5	0.06	-11.8 ± 6.2	0.06	4.2 ± 2.2	0.04	0.35
L2CH (mg/dL)	0.94	-0.2 ± 2.1	0.85	-0.5 ± 2.9	0.16	2.9 ± 2.0	0.04	0.35
L3TG (mg/dL)	0.11	3.4 ± 2.2	0.13	9.7 ± 6.4	0.65	-1.5 ± 3.3	0.0463	0.35
H3A2 (mg/dL)	0.22	-1.8 ± 1.5	0.12	-6.4 ± 4.1	0.01	6.7 ± 2.6	0.0469	0.35
H4A2 (mg/dL)	0.25	1.1 ± 1.0	0.04	-6.2 ± 3.0	0.10	1.9 ± 1.1	0.0479	0.35
V1TG (mg/dL)	0.11	1.7 ± 1.0	0.03	-2.7 ± 1.3	0.13	1.1 ± 0.7	0.0496	0.35

Mixed effects logistic regression analysis with repeated measures was used to evaluate the relationship between the nutritional status (defined by the SGA score) and the lipoprotein and small metabolite data. Overall, 14 lipoproteins and 1 small metabolite were found to be significant predictors according to the LRT, and therefore, appear to be associated with malnutrition over time. The P-value in the last column is after FDR correction. The β-coefficients for every unit increase and P -values of time period, the main effect of the lipoprotein/small metabolite, and the interaction term are shown (log10 transformed data).

FDR: False Discovery Rate; H3A2: Apo-A2 Subfraction of HDL-3; H4A2: Apo-A2 Subfraction of HDL-4; L2CH: Cholesterol Subfraction of LDL-2; L2FC:Free Cholesterol Subfraction of LDL-2; L2PL: Phospholipids Subfraction of LDL-2; L3AB: LDL Subfractions, Apo-B, LDL-3; L3FC: LDL Subfractions, Free Cholesterol, LDL-3; L3PL: Phospholipids Subfraction of LDL-3; L3PN: LDL-3 Particle Number, LDL-3 Particle Number; L3TG:Triglycerides Subfraction of LDL-3; L4TG: Triglycerides Subfraction of LDL-4; L5TG: LDL Subfractions, Triglycerides, LDL-5; L6TG: Triglycerides Subfraction of LDL-6; LRT: Likelihood Ratio Test; SGA: Subjective Global Assessment; V1TG: Triglycerides Subfraction of VLDL-1.

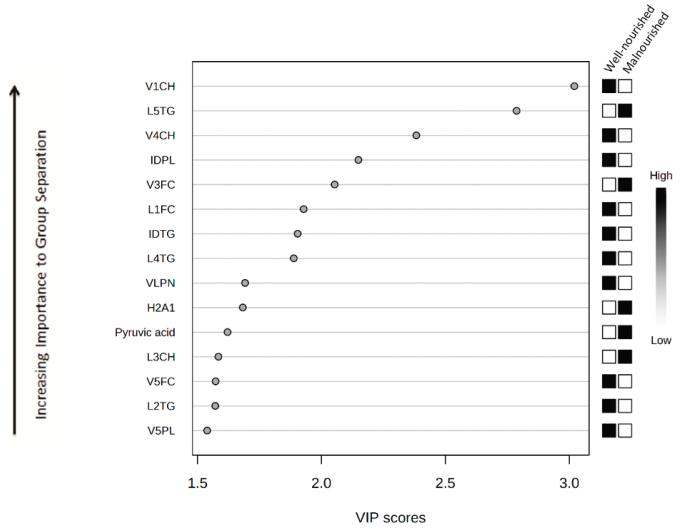

Figure 4: Malnutrition based on ICU day 5 biomarkers using PLS-DA

PLS-DA was used to relate the diagnosis of malnutrition on day 5 of ICU admission (defined by the SGA score) to the lipoprotein and small metabolite data. A VIP value was calculated to rank the top 15 lipoproteins and small metabolites according to their prognostic importance for the diagnosis of malnutrition. The boxes on the right indicate the relative concentrations of the lipoprotein/small metabolite in the nutritional status groups. For this analysis, the Q2 value was 0.09.

H2A1: Apo-A1 Subfraction of HDL-2; ICU: Intensive Care Unit; IDPL: Lipoprotein Main Fractions, Phospholipids, IDL; IDTG: Lipoprotein Main Fractions, Triglycerides, IDL; L1FC: Free Cholesterol Subfraction of LDL-1; L2TG: Triglycerides Subfraction of LDL-2; L3CH: Cholesterol Subfraction of LDL-3; L4TG: Triglycerides Subfraction of LDL-4; L5TG: Triglycerides Subfractions of LDL-5; PLS-DA: Partial Least Squares Discriminant Analysis; SGA: Subjective Global Assessment; V1CH: Cholesterol Subfractions of VLDL-1; V3FC: Free Cholesterol Subfraction of VLDL-3; V4CH: Cholesterol Subfraction of VLDL-4; V5FC: Free Cholesterol Subfraction of VLDL-5; V5PL: Phospholipids Subfraction of VLDL-5; VIP, Variable Importance in Projection; VLPN: VLDL Particle Number.

Table 3: ORs for malnutrition with a 10 % increase in the lipoprotein/small metabolite levels for every time period

Lipoprotein/small metabolite	TP 1	TP 2	TP 3	TP 4	TP 5	TP 6	TP 7
L5TG	1.35	1.36	1.36	1.37	1.38	1.39	1.39
L3FC	0.94	1.12	1.33	1.57	1.87	2.21	2.62
L3AB	0.95	1.13	1.35	1.61	1.92	2.29	2.73
L3PN	0.95	1.13	1.35	1.61	1.92	2.29	2.73
L4TG	1.31	1.29	1.26	1.23	1.21	1.19	1.16
L2FC	0.92	1.11	1.34	1.62	1.95	2.35	2.83
L3PL	0.96	1.10	1.27	1.46	1.67	1.92	2.21
L6TG	1.63	1.40	1.21	1.04	0.89	0.77	0.66
L2PL	0.99	1.15	1.35	1.57	1.84	2.15	2.51
Creatinine	0.61	0.73	0.87	1.03	1.22	1.46	1.73
L2CH	0.98	1.10	1.24	1.40	1.58	1.78	2.01
L3TG	1.49	1.40	1.32	1.24	1.17	1.10	1.03
H3A2	0.77	1.01	1.34	1.77	2.34	3.09	4.08
H4A2	0.77	0.83	0.90	0.97	1.05	1.14	1.23
V1TG	0.89	0.93	0.98	1.02	1.07	1.12	1.18

The ORs were calculated for the models of lipoproteins and small metabolites with a significant LRT P -value. As the lipoprotein and small metabolite concentrations were log-transformed, the β-coefficients were multiplied by log10(1.10) and exponentiated to calculate the ORs for malnutrition with a 10 % increase in the lipoprotein/small metabolite levels for every TP.

H3A2: Apo-A2 Subfraction of HDL-3; H4A2: Apo-A2 Subfraction of HDL-4; L2CH: Cholesterol Subfraction of LDL-2; L2FC:Free Cholesterol Subfraction of LDL-2; L2PL: Phospholipids Subfraction of LDL-2; L3AB: LDL Subfractions, Apo-B, LDL-3; L3FC: LDL Subfractions, Free Cholesterol, LDL-3; L3PL: Phospholipids Subfraction of LDL-3; L3PN: LDL-3 Particle Number, LDL-3 Particle Number; L3TG:Triglycerides Subfraction of LDL-3; L4TG: Triglycerides Subfraction of LDL-4; L5TG: LDL Subfractions, Triglycerides, LDL-5; L6TG: Triglycerides Subfraction of LDL-6; LRT: Likelihood Ratio Test; OR, Odds ratio; SGA: Subjective Global Assessment; TP: Time period,V1TG, Triglycerides Subfraction of VLDL-1.

DISCUSSION

The findings from this study imply that at ICU admission, LDL subfractions with increased levels of triglycerides and (V)LDL subfractions with decreased levels of (free) cholesterol, phospholipids, and decreased particle numbers were associated with a high risk of malnutrition. Subfractions of (V)LDL and IDL with decreased levels of (free) cholesterol, triglyceride, and phospholipids, lower particle number, and increased levels of (V)LDL (free) cholesterol, (V)LDL triglyceride subfractions, and HDL Apo-A1 were indicative of malnutrition on Day 5. HDL Apo-A2 and (V)LDL-free cholesterol may have been associated with malnutrition during ICU admission.

Additionally, increased levels of dimethyl sulfone, TMAO, creatinine, and DMG, and decreased levels of creatine, methionine, and acetoacetic acid were found to be related to a high risk of malnutrition at ICU admission. Increased levels of pyruvic acid were indicative of malnutrition on Day 5 of ICU admission.

Numerous lipoprotein subfraction parameters were investigated in terms of their relation with the nutritional status and risk of malnutrition; these included (V)LDL particles which transport cholesterol to the peripheral tissues and HDL particles which take excess cholesterol and return it to the liver for excretion.[43,44] In their meta-analysis, Zhang et al.[11] evaluated the association between blood biomarkers (including LDL and HDL) and the nutritional status (assessed using the MNA) in elderly patients. They found no significant difference in HDL between the three groups (based on the MNA score); they also found the LDL levels to be significantly lower in the malnourished patients. In this context, the relationship between lipoprotein levels and malnutrition may be partly explained by the production of cytokines. Malnutrition is found to be related to an increase in several cytokines including interferon-*γ*, interleukins 2 and 4, and tumour necrosis factor-*α* (TNF-α).[45] Notably, TNF-*α* is known to increase fatty acid levels by increasing both fatty acid synthesis and adipose tissue lipolysis. The fatty acids are re-esterified into triglycerides and released into the circulation as (V)LDL.[46] Cytokines decrease both LDL-C and HDL-C levels by inhibiting cholesterol synthesis and decreasing cholesterol secretion.[46] These findings are in concordance with ours. In our study, decreased levels of (free) cholesterol and phospholipids in subfractions of (V)LDL and decreased particle numbers during the first 3 days of admission (period 1) were associated with a high risk of malnutrition. Increased levels of LDL triglycerides during this period were also related to a high risk of malnutrition (**Figure 3**). In addition, several (V)LDL related parameters were found to be indicative of malnutrition on Day 5. Among the 14 lipoprotein subfraction variables with the highest VIP value, the majority included (V)LDL and IDL particles; these were indicative of malnutrition when decreased during period 2 (**Figure 4**). Interestingly, a study that compared lipid profiles between patients with sepsis and trauma found no significant difference in terms of LDL-C and triglyceride levels. Although HDL-C levels were markedly low during sepsis, no change was observed in the early phase of trauma (relative to standard HDL concentrations).[47] In this context, several studies found LDL-C, HDL-C, and total cholesterol levels to be significantly lower and triglyceride levels to be significantly higher in patients suffering from severe

acute respiratory syndrome coronavirus 2 (compared to control subjects).[48-50] This dyslipidaemia may have been caused by the production of cytokines; however, it may also be attributed to liver damage and increased degradation by free radicals consequent to the infection.[48] In another study on patients with sepsis, the levels of LDL-C, HDL-C, and total cholesterol were decreased and those of triglyceride were increased at admission.[51] In our univariate generalized linear mixed models, 14 lipoprotein parameters and 1 small metabolite were found to be significantly related to the nutritional status during ICU admission. However, this association did not remain significant after FDR correction (**Table 2**). The identified lipoprotein parameters and metabolites may have therefore demonstrated significance due to the large number of parameters (135 in total) analyzed, and may represent false positives. This factor needs to be considered when interpreting the results. **Table 2** shows the β-coefficients and P-values of the TPs, individual factors (main effect) of the 14 lipoproteins and small metabolites, and interaction terms. Only the main effects of HDL Apo-A2 and (V)LDL triglycerides were found to be significantly related to the nutritional status (H4A2, V1TG), with a β-coefficient of −6.23 and −2.75, respectively. This indicates that a 1-unit increase in the log-transformed values of these lipoprotein subfractions during period 1 reduced the log-odds of malnutrition by 6.23 or 2.75-fold, respectively. **Table 3** shows the ORs for malnutrition for a 10 % increase in the levels of these 14 lipoproteins and 1 small metabolite for each TP. The odds of malnutrition during period 1 was lowered by 23% and 11% for every 10% increase in H4A2 and V1TG, respectively (OR=0.77 and 0.89, respectively). An increase in H4A2 and V1TG during the first four or three TPs, respectively, indicated a decrease in the risk of malnutrition. After these periods, an increase in levels was more likely to be related to a decrease in the risk of malnutrition. Notably, a decrease in Apo-A2 is also seen in cases of inflammation and infection.[46] The main effects of the other lipoproteins were not significantly related to malnutrition; this may be attributed to the lack of power. Interestingly, the ORs for LDL (free) cholesterol, Apo-B, particle number, and phospholipid levels (Free Cholesterol Subfraction OF LDL-3 [L3FC], Apo-B Subfraction of LDL-3 [L3AB], LDL-3 Particle Number [L3PN], Free Cholesterol Subfraction of LDL-2 [L2FC], Phospholipids Subfraction of LDL-3 [L3PL], Phospholipids Subfraction of LDL-2 [L2PL], and Cholesterol Subfraction of LDL-2 [L2CH]) included all negative values during period 1. This indicated that an increase in these LDL subfractions may be related to a decreased risk of malnutrition; however, all values were not significant (**Table 3**). An increase in the levels of these LDL subfractions from period 2 may

be attributed to malnutrition. Interestingly, a similar trend has been seen in septic patients. In a study, the LDL-C and HDL-C levels were found to have decreased during the first 3 days of ICU admission. Although the levels were higher at ICU discharge than at Day 3, the levels measured prior to hospitalization were not attained.[51] These changes in lipoprotein levels appeared to be restored after 7 days of admission.[52] In our cohort, increased levels of L5TG were found to be related to a high risk of malnutrition (**Figure 3**). Increasing levels of LDL triglyceride may have also been related to malnutrition during ICU admission; however, the association was not significant (**Table 2**). As mentioned before, this may be explained by the increased production of TNF-*α*, which causes an increase in triglyceride levels.[46]

In patients with severe injuries or illness, large quantities of muscle proteins are broken down, owing to the release of stress-hormones and cytokines. Alanine is transported to the liver and converted into pyruvate, and amino-acids are transformed into glucose and positive acute-phase proteins (such as fibrinogen and C-reactive protein) via gluconeogenesis.[53] In our study, decreased levels of the amino acid methionine were found to be related to a high risk of malnutrition (**Figure 3**). In this context, methionine is a precursor of homocysteine (HC), and hyperhomocysteinemia is known to be a risk factor for cardiovascular disease, cognitive impairment, and Alzheimer's disease. Deficiencies in micronutrients, such as vitamin B12 and folate, are known to influence HC concentrations. HC can be remethylated by either the methionine synthase or betaine-HC S-methyltransferase pathways. DMG is a product of the latter; an increase in its levels was found to be related to an increased risk of malnutrition (**Figure 3**).[54,55] N-acetylmethionine is also related to the HC cycle, and increased levels have already been found to be associated with malnutrition in critically ill patients.[10] Notably, the liver begins to transform fatty acids into ketone bodies during continued fasting; the latter can be used by the brain as the main energy source.[56,57] Increased levels of acetoacetic acid, one of the ketone bodies, have been found to be related to an increased risk of malnutrition (**Figure 3**). Increased levels of TMAO have also been found to be related to a high risk of malnutrition during the first few days of ICU admission (**Figure 3**). TMAO is a pro-inflammatory metabolite that originates from the bacterial metabolism of choline-rich foods. Elevated TMAO levels have been found to be associated with coronary artery disease, chronic kidney disease, and chronic obstructive pulmonary disease. In their study, Chou et al.[58] found that decreased levels of TMAO were associated with acute and chronic

malnutrition in septic patients. They, however, observed that antibiotic treatment and liver dysfunction were also significantly associated with a decrease in TMAO levels; this may explain the difference in our results. Increased levels of creatinine, an endogenous product of muscle metabolism, have been found to be related to malnutrition.[59] In our study, increased creatinine levels were found to be associated with a high risk of malnutrition (**Figure 3**). An increase in creatinine concentrations may therefore be related to malnutrition; however, the association was not significant (**Table 2**). Creatine is the precursor to serum creatinine and is synthesized in the liver. Decreased serum creatine levels on ICU admission were found to be related to a high risk of malnutrition (**Figure 3**). This may be attributed to decreased liver function or muscle mass.[59,60]

Limitations

As this was an exploratory pilot study, the time available for patient recruitment was limited; this led to a relatively small sample size. Therefore, it was not possible to perform subanalyses based on certain variables (for example, gender, age, or trauma site). This issue was addressed to a certain extent by obtaining multiple samples per patient; this provided the added opportunity to track the course of malnutrition over time. Additionally, this exploratory study was conducted as part of a larger observational prospective study and according to the routines in daily practice. Blood samples were therefore not obtained on the exact day of assessment of nutritional status; average values of the plasma levels obtained around the day of assessment were used instead. Subtle fluctuations over time may have therefore been overlooked. However, the fluctuations were expected to be minimal and probably had negligible influence. In this context, changes in lipoprotein and small metabolite levels are not the only factors related to the deterioration of nutritional status. Inflammation, oxidative stress, medication, and comorbidities also play a role in many metabolic processes within the body and influence the nutritional parameters. The lack of a gold standard for assessment of (the risk of) malnutrition represents a major limitation for all studies pertaining to the condition. We used the SGA and mNUTRIC scores, as those are validated for ICU patients and have been proven to have the highest predictive value for outcomes. The SGA score by itself is known to be an approximate measure, as the difference between an SGA score of 5 (malnourished) or 6 (well-nourished) can be considerably minimal. The models were therefore trained using imperfect data, which limited model performance. The SGA scores were

verified by one investigator at the end of data collection to increase reliability and reduce interobserver variability. Additionally, no difference was made in terms of the severity of malnutrition, as SGA scores of 1 to 5 are all considered to indicate malnutrition. Unfortunately, the number of included patients with severe malnutrition (SGA ≤2) was inadequate for performing subanalyses. The lipid intake (including enteral and oral feeding) and propofol infusion were not considered during the analyses; this represents another limitation. In addition, VIP values were used to identify the lipoproteins and small metabolites that could influence discrimination between groups in the PLS-DA regression model; however, the model itself demonstrated marginal predictive ability for malnutrition. More patients need to be included in the analysis in order to increase the predictive power of the model. Additionally, NMR is considered a considerably expensive method for analysis; this represents a challenge to the incorporation of metabolite and lipoprotein analyses into everyday clinical practice. An alternative includes Lipoprint®(Mayo Clinic and Foundation, MN, USA), which is a relatively rapid system compared with most gel electrophoresis methods and is less expensive.[61] Lastly, the VIP values only reflect the importance of each variable in the projection used in this specific PLS model. Therefore, these results need to be validated using larger sample sizes; this will allow the calculation of cut-off values for normal ranges of lipoproteins and small metabolites prior to their use in clinical practice. The incorporation of lipoprotein and small metabolite analysis in routine care will represent a major step forward in providing personalized medicine, which considers individual differences in metabolism.

CONCLUSION

The findings from this study suggest that increased triglyceride levels in several plasma lipoprotein (sub)fractions and decreased levels of other lipoprotein subfractions may be associated with a high risk of malnutrition in patients with severe injuries; they may also be associated with a decrease in nutritional status during ICU admission. Additionally, small metabolites involved in the HC cycle, ketone body formation, and muscle metabolism may be indicative of (the risk of) malnutrition. Following validation of our findings in studies with larger sample sizes, the identified biomarkers may be used as indicators for an institution of preventive nutritional measures in patients admitted to the ICU with severe injuries.

As malnutrition is not the only process that influences metabolic patterns, further research is needed to investigate the value of lipoproteins and small metabolites in diagnosing malnutrition and assessing the risk of developing the condition.

REFERENCES

1. Osooli F, Abbas S, Farsaei S, Adibi P. *Identifying critically ill patients at risk of malnutrition and underfeeding: a prospective study at an academic hospital*. Adv Pharm Bull 2019;9(2):314–20.
2. Norman K, Pichard C, Lochs H, Pirlich M. *Prognostic impact of disease-related malnutrition*. Clin Nutr 2008;27(1):5–15.
3. Barker LA, Gout BS, Crowe TC. *Hospital malnutrition: prevalence, identification and impact on patients and the healthcare system*. Int J Environ Res Public Health 2011;8(2):514–27.
4. Jensen GL, Mirtallo J, Compher C, Dhaliwal R, Forbes A, Grijalba RF, et al. *Adult starvation and disease-related malnutrition: a proposal for etiology-based diagnosis in the clinical practice setting from the International Consensus Guideline Committee*. JPEN J Parenter Enteral Nutr 2010;34(2):156–9.
5. Dijkink S, Meier K, Krijnen P, Yeh DD, Velmahos GC, Schipper IB. *Malnutrition and its effects in severely injured trauma patients.* Eur J Trauma Emerg Surg 2020;46(5):993–1004.
6. Lew CCH, Yandell R, Fraser RJL, Chua AP, Chong MFF, Miller M. *Association between malnutrition and clinical outcomes in the intensive care unit: a systematic review*. JPEN J Parenter Enteral Nutr 2017;41(5):744–58.
7. Kalaiselvan MS, Renuka MK, Arunkumar AS. *Use of nutrition risk in critically ill (NUTRIC) score to assess nutritional risk in mechanically ventilated patients: a prospective observational study*. Indian J Crit Care Med 2017;21(5):253–6.
8. Yeh DD, Johnson E, Harrison T, Kaafarani HMA, Lee J, Fagenholz P, et al. *Serum levels of albumin and prealbumin do not correlate with nutrient delivery in surgical intensive care unit patients*. Nutr Clin Pract 2018;33(3):419–25.
9. van Bokhorst-de van der Schueren MA, Guaitoli PR, Jansma EP, de Vet HC. *Nutrition screening tools: does one size fit all? A systematic review of screening tools for the hospital setting*. Clin Nutr 2014;33(1):39–58.
10. Mogensen KM, Lasky-Su J, Rogers AJ, Baron RM, Fredenburgh LE, Rawn J, et al. *Metabolites associated with malnutrition in the intensive care unit are also associated with 28-day mortality*. JPEN J Parenter Enteral Nutr 2017;41(2):188–97.
11. Zhang Z, Pereira SL, Luo M, Matheson EM. *Evaluation of blood biomarkers associated with risk of malnutrition in older adults: a systematic review and meta-analysis.* Nutrients 2017;9(8):829.
12. Lent-Schochet D, Jialal I. *Biochemistry, lipoprotein metabolism*. Treasure Island (FL): StatPearls Publishing; 2022.
13. Norata GD, Pirillo A, Ammirati E, Catapano AL. *Emerging role of high density lipoproteins as a player in the immune system.* Atherosclerosis 2012;220(1):11–21.
14. Jung E, Kong SY, Ro YS, Ryu HH, Shin SD. *Serum cholesterol levels and risk of cardiovascular death: a systematic review and a dose-response meta-analysis of prospective cohort studies*. Int J Environ Res Public Health 2022;19(14):8272.
15. Christopher KB. *Nutritional metabolomics in critical illness*. Curr Opin Clin Nutr Metab Care 2018;21(2):121–5.
16. Margaritelis NV, Paschalis V, Theodorou AA, Vassiliou V, Kyparos A, Nikolaidis MG. *Rapid decreases of key antioxidant molecules in critically ill patients: a personalized approach*. Clin Nutr 2020;39(4):1146–54.

17. Fischer M, JeVenn A, Hipskind P. *Evaluation of muscle and fat loss as diagnostic criteria for malnutrition*. Nutr Clin Pract 2015;30(2):239–48.

18. Verheul EAH, Ouwerkerk JJJ, Dijkink S, Krijnen P, Verhoeven A, Giera M, et al. *The value of metabolites and vitamins for the assessment of nutritional status in hospitalized patients. A systematic review*. Top Clin Nutr 2024;39(3):198–212.

19. Dijkink S, Meier K, Krijnen P, Yeh DD, Velmahos GC, Arbous MS, et al. *The malnutrition in polytrauma patients (MaPP) study: research protocol*. Nutr Health 2019;25(4):291–301.

20. *Castor EDC - Medical Research - For researchers by researchers*. Available from: https://www.castoredc.com/. [Accessed 1 April 2018].

21. Bector S, Vagianos K, Suh M, Duerksen DR. *Does the subjective global assessment predict outcome in critically ill medical patients?* J Intensive Care Med 2016;31(7):485–9.

22. Detsky AS, McLaughlin JR, Baker JP, Johnston N, Whittaker S, Mendelson RA, et al. *What is subjective global assessment of nutritional status?* JPEN J Parenter Enteral Nutr 1987;11(1):8–13.

23. Gattermann Pereira T, da Silva Fink J, Tosatti JAG, Silva FM. *Subjective global assessment can be performed in critically ill surgical patients as predictor of poor clinical outcomes*. Nutr Clin Pract 2019;34(1):131–6.

24. Heyland DK, Dhaliwal R, Jiang X, Day AG. *Identifying critically ill patients who benefit the most from nutrition therapy: the development and initial validation of a novel risk assessment tool*. Crit Care 2011;15(6):R268.

25. Rahman A, Hasan RM, Agarwala R, Martin C, Day AG, Heyland DK. *Identifying critically-ill patients who will benefit most from nutritional therapy: further validation of the "modified NUTRIC" nutritional risk assessment tool*. Clin Nutr 2016;35(1):158–62.

26. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. *APACHE II: a severity of disease classification system*. Crit Care Med 1985;13(10):818–29.

27. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H, et al. *The SOFA (sepsis-related organ failure assessment) score to describe organ dysfunction/failure. On behalf of the working group on sepsis-related problems of the European Society of Intensive Care Medicine*. Intensive Care Med 1996;22(7):707–10.

28. Rattanachaiwong S, Zribi B, Kagan I, Theilla M, Heching M, Singer P. *Comparison of nutritional screening and diagnostic tools in diagnosis of severe malnutrition in critically ill patients*. Clin Nutr 2020;39(11):3419–25.

29. Sumner LW, Amberg A, Barrett D, Beale MH, Beger R, Daykin CA, et al. *Proposed minimum reporting standards for chemical analysis Chemical Analysis Working Group (CAWG) metabolomics standards initiative (MSI)*. Metabolomics 2007;3(3):211–21.

30. *NMR Clinical Research Solutions*. Bruker corporation. Billerica (MA), USA. Available from: https://www.bruker.com/en/products-and-solutions/mr/nmr-clinicalresearch-solutions.html. [Accessed 6 May 2022].

31. FitzMaurice GM, Laird NM, Ware JH. *Applied longitudinal analysis*. 2nd ed. New Jersey: John Wiley & Sons, Inc.; 2011.

32. *IBM Corp. Released IBM SPSS statistics for windows, version 25.0*. Armonk, NY: IBM Corp; 2017.

33. *R Core Team R: a language and environment for statistical computing*, Vienna, Austria: R Foundation for Statistical Computing; 2022. Available from: https://www.R-project.org/ [Accessed 13 August 2022] .

34. Xia J, Wishart DS. *Using MetaboAnalyst 3.0 for comprehensive metabolomics data analysis*. Curr Protoc Bioinform 2016;55:1–14.

35. Xia J, Psychogios N, Young N, Wishart DS. *MetaboAnalyst: a web server for metabolomic data analysis and interpretation*. Nucleic Acids Res 2009;37 (Web Server issue):W652–60.

36. Xia J, Sinelnikov IV, Han B, Wishart DS. *MetaboAnalyst 3.0 – making metabolomics more meaningful*. Nucleic Acids Res 2015;43(W1):W251–7.

37. Barker M, Rayens W. *Partial least squares for discrimination*. J Chemom 2003;17(3):166–73.

38. Ruiz-Perez D, Guan H, Madhivanan P, Mathee K, Narasimhan G. *So you think you can PLS-DA?* BMC Bioinform 2020;21(1):2.

39. Szyma ń ska E, Saccenti E, Smilde AK, Westerhuis JA. *Double-check: validation of diagnostic statistics for PLS-DA models in metabolomics studies*. Metabolomics 2012;8(1):3–16.

40. Hair J, Alamer A. *Partial least squares structural equation modeling (PLS-SEM) in second language and education research: guidelines using an applied example.* J Res Appl Linguist 2022;1(3):100027.

41. National Centre for Research Methods Using statistical regression methods in education research. *Module 4 - Binary Logistic Regression*; 2011. Available from: https://www.restore.ac.uk/srme/www/fac/soc/wie/research-new/srme/modules/mod4/12/index.html [Accessed 3 January 2023].

42. Glickman ME, Rao SR, Schultz MR. *False discovery rate control is a recommended alternative to bonferroni-type adjustments in health studies*. J Clin Epidemiol 2014;67(8):850–7.

43. Tsoupras A, Lordan R, Zabetakis I. *Inflammation, not cholesterol, is a cause of chronic disease*. Nutrients 2018;10(5):604.

44. Craig M, Yarrarapu SNS, Dimri M. *Biochemistry, cholesterol.* StatPearls Treasure Island (FL): StatPearls Publishing; 2020.

45. Takele Y, Adem E, Getahun M, Tajebe F, Kiflie A, Hailu A, et al. *Malnutrition in healthy individuals results in increased mixed cytokine profiles, altered neutrophil subsets and function*. PLoS ONE 2016;11(8):e0157919.

46. Khovidhunkit W, Kim MS, Memon RA, Shigenaga JK, Moser AH, Feingold KR, et al. *Effects of infection and inflammation on lipid and lipoprotein metabolism: mechanisms and consequences to the host*. J Lipid Res 2004;45(7):1169–96.

47. Tanaka S, Labreuche J, Drumez E, Harrois A, Hamada S, Vigué B, et al. *Low HDL levels in sepsis versus trauma patients in intensive care unit.* Ann Intensive Care 2017;7(1):60.

48. Wei X, Zeng W, Su J, Wan H, Yu X, Cao X, et al. *Hypolipidemia is associated with the severity of COVID-19.* J Clin Lipidol 2020;14(3):297–304.

49. Begue F, Chemello K, Veeren B, Lortat-Jacob B, Tran-Dinh A, Zappella N, et al. *Plasma Apolipoprotein concentrations are highly altered in severe intensive care unit COVID-19 patients: preliminary results from the LIPICOR cohort study*. Int J Mol Sci 2023;24(5):4605.

50. Ballout RA, Kong H, Sampson M, Otvos JD, Cox AL, Agbor-Enoh S, et al. *The NIH Lipo-COVID study: a pilot NMR investigation of lipoprotein subfractions and other metabolites in patients with severe COVID-19*. Biomedicines 2021;9(9):1090.

51. Tanaka S, Stern J, Bouzid D, Robert T, Dehoux M, Snauwaert A, et al. *Relationship between lipoprotein concentrations and short-term and 1-year mortality in intensive care unit septic patients: results from the HIGHSEPS study.* Ann Intensive Care 2021;11(1):11.

52. Tanaka S, Diallo D, Delbosc S, Genève C, Zappella N, Yong-Sang J, et al. *High-density lipoprotein (HDL) particle size and concentration changes in septic shock patients*. Ann Intensive Care 2019;9(1):68.

53. Chourpiliadis C, Mohiuddin SS. *Biochemistry, gluconeogenesis*, StatPearls Treasure Island (FL): StatPearls Publishing; 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK544346/ [Accessed 28 June 2022].

54. Lever M, George PM, Dellow WJ, Scott RS, Chambers ST. *Homocysteine, glycine betaine, and N,N-dimethylglycine in patients attending a lipid clinic.* Metabolism 2005;54(1):1–14.

55. Liu YQ, Huang LH, Liu PP, Xing QB, Han F, Wang Q, et al. *Effect of N,Ndimethylglycine on homocysteine metabolism in rats fed folate-sufficient and folate-deficient diets*. Biomed Environ Sci 2021;34(5):356–63.

56. Emery PW. *Metabolic changes in malnutrition*. Eye (Lond) 2005;19(10):1029–34.

57. Hall JE, Hall ME. *Lipid metabolism*. Guyton and Hall textbook of medical physiology. London, England: W B Saunders; 2021. p. 853–64.

58. Chou RH, Wu PS, Wang SC, Wu CH, Lu SF, Lien RY, et al. *Paradox of trimethylamine-N-oxide, the impact of malnutrition on microbiota-derived metabolites and septic patients*. J Intensive Care 2021;9(1):65.

59. Wyss M, Kaddurah-Daouk R. *Creatine and creatinine metabolism*. Physiol Rev 2000;80(3):1107–213.

60. Loria A, Glance LG, Melucci AD, Boodry C, Justiniano CF, Dunne RF, et al. *Low preoperative serum creatinine is common and associated with poor outcomes following non-emergent inpatient surgery.* Ann Surg 2022;277(2):246–51.

61. Hoefner DM, Hodel SD, O'Brien JF, Branum EL, Sun D, Meissner I, et al. *Development of a rapid, quantitative method for LDL subfractionation with use of the quantimetrix lipoprint LDL system*. Clin Chem 2001;47(2):266–74.

APPENDIX 1

Analysed biomarkers

Small metabolites
- Ethanol
- Trimethylamine-N-oxide (TMAO)
- Alanine
- Creatine
- Creatinine
- Glutamic acid
- Glycine
- Histidine
- Isoleucine
- Leucine
- Methionine
- N,N-Dimethylglycine
- Phenylalanine
- Tyrosine
- Valine
- Acetic acid
- Formic acid
- Lactic acid
- Succinic acid
- Acetoacetic acid
- Pyruvic acid
- Glucose
- Dimethyl sulfone

Lipoproteins
- Apolipoproteins -A1 (total and HDL (total & 1-4))
- Apolipoproteins -A2 (total and HDL (total & 1-4))
- Apolipoproteins -B (total, VLDL, IDL (total & 1-6), LDL)
- Particle number (total, VLDL, IDL, LDL, LDL 1-6)
- Triglycerides (total, VLDL (total & 1-6), IDL, LDL (total & 1-6), HDL (total & 1-4))
- Cholesterol (total, VLDL (total & 1-6), IDL, LDL (total & 1-6), HDL (total & 1-4))

- Free cholesterol (VLDL (total & 1-6), IDL, LDL (total & 1-6), HDL (total & 1-4))
- Phospholipids (VLDL (total & 1-6), IDL, LDL (total & 1-6), HDL (total & 1-4))

Sample preparation Nuclear Magnetic Resonance (NMR) serum measurements

The sample preparation was performed according to the requirements of the Bruker B.I.LISA lipoprotein analysis protocol, except for the use of heparin plasma instead of EDTA plasma or serum. The plasma samples were thawed at room temperature. Immediately after thawing the samples were homogenized by inverting the tubes 10 times. Next, 500 µl of serum was manually transferred to a Ritter 96 deepwell plate. A Gilson 215 liquid handler robot was used to mix 300 µL of plasma with 300 µLof 75 mM disodium phosphate buffer in H2O/D2O (80/20) with a pH of 7.4 containing 6.15 mM NaN3 and 4.64 mM sodium 3-[trimethylsilyl] d4-propionate (Cambridge Isotope Laboratories). Using a modified second Gilson 215 liquid handler, 565 µl of each sample was transferred into 5 mm Bruker SampleJet NMR tubes. Subsequently, the tubes were closed by POM ball insertion and transferred to the SampleJet autosampler where they were kept at 6°C while queued for acquisition.

NMR experiments and processing

All proton nuclear magnetic resonance (1H-NMR) experiments were acquired on a 600 MHz Bruker Avance Neo spectrometer (Bruker Corporation, Billerica, USA) equipped with a 5 mm triple resonance inverse (TCI) cryogenic probe head with Z-gradient system and automatic tuning and matching.

The NMR spectra were acquired following the Bruker B.I.Methods protocol. A standard 5 mm sample of 99.8% methanol-d4 (Bruker) was used for temperature calibration (Findeisen, M., Brand, T. & Berger, S. A. Magnetic Resonance in Chemistry 45, 175–178, 2007) before the measurements. A standard 5 mm QuantRefC sample (Bruker) was measured as the quantification reference and for quality control. All experiments were recorded at 310 K. The duration of the π/2 pulses were automatically calibrated for each individual sample using a homonuclear-gated nutation experiment (Wu, P. S. C. & Otting, G. Journal of Magnetic Resonance 176, 115–119, 2005) on the locked and shimmed samples after automatic tuning and matching of the probe head. For water suppression, presaturation of the water resonance with an effective field of γB1 = 25 Hz was applied during the relaxation

delay and the mixing time of the NOESY1D experiment (Price, W. S. Annual Reports on NMR Spectroscopy 38, 289–354, 1999).

The NOESY1D experiment was recorded using the first increment of a NOESY pulse sequence (Kumar, A., Ernst, R. R. & Wüthrich, K. Biochemical and Biophysical Research Communications 95, 1–6, 1980) with a relaxation delay of 4 s and a mixing time of 10 ms. 32 scans of 98,304 points covering a sweepwidth of 17,857 Hz were recorded after applying 4 dummy scans.

The lipoprotein values were extracted from the NOESY1D serum spectra by submitting the data to the commercial Bruker IVDr Lipoprotein Subclass Analysis (B.I.-LISA) platform.








Chapter 6

Fat-soluble vitamins as biomarkers of nutritional status and their relation with complications in polytrauma patients

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Nutr Health. 2024:2601060241273640

ABSTRACT

Introduction

This exploratory observational prospective study aimed to evaluate fat-soluble vitamin plasma levels during hospital admission and its relation with the development of malnutrition and complications in polytrauma patients, considering the protocolized multivitamin supplementation during ICU admission.

Methods

In 49 well-nourished polytrauma (Injury Severity Score≥16) patients admitted to the intensive care unit of two Level-1 trauma centres, vitamin A, D, and E levels were assessed weekly during hospital stay. All patients received multivitamin supplementation during ICU stay. Linear mixed-effect models were used to assess a trend in vitamin levels over time during hospital stay. Mixed effects logistic regression analysis was performed to relate vitamin concentrations with malnutrition, defined as a Subjective Global Assessment score ≤5, and complications.

Results

Vitamin A levels increased 0.17 µmol/L per week (95% confidence interval 0.12-0.22, $p<0.001$), vitamin D levels increased 1.49 nmol/L per week (95% confidence interval 0.64-2.33, $p<0.01$), vitamin E levels increased 1.17 µmol/L per week (95% confidence interval 0.61-1.73, $p<0.001$) during hospital stay (29 ± 17 days). Vitamin levels were not related to malnutrition or complications during hospital stay.

Conclusion

Vitamin A, D, and E levels increased due to supplementation during hospital admission. Plasma levels of vitamins A, D, and E do not seem to be useful as biomarkers for the nutritional status of polytrauma patients during hospital stay. No correlation with complications could be demonstrated.

INTRODUCTION

Malnutrition is a serious problem during hospital admission, as it is known to be associated with adverse events, such as increased risk of mortality, infections, and increased hospital stay.[1,2] Research has shown that up to 50% of hospitalized patients were malnourished, depending on the patient population and definition used for diagnosis.[3] Severely injured patients are even more susceptible for malnutrition, because of their hypermetabolic state after severe trauma, with an estimated prevalence range from 7 to 76%.[4-6] Nevertheless, objective assessment of the nutritional status of severely injured patients remains a major challenge.[7-9]

Potential new biomarkers for the assessment of nutritional status in severely injured patients are vitamins A, D, and E. These fat-soluble vitamins play a substantial role in a multitude of physiological processes.[10] For example, vitamin A aids in vision, vitamin D is important for bone mineralization, and vitamin E is known for its antioxidant properties.[10] A deficiency in these vitamins may have a significant impact on recovery after trauma and could increase the risk of several complications during hospital admission.[11] Vitamin A deficiency can impair the humoral defense mechanism during the inflammatory phase in the wound healing process, as vitamin A plays a key role in the differentiation, migration, and development of T cells, modulates the balance between Th1 and Th2 immunity, and induces transcriptional and functional changes in natural killer cells leading to altered metabolism.[12-14] This may reduce (re)epithelialization, collagen synthesis, and granulation tissue development in the proliferative and remodeling phases.[15,16] Vitamin D is specifically involved in bone metabolism and immune response modulation.[17,18] A vitamin D deficiency may lead to decreased bone mineral density, fragile bones, and a higher risk of fractures.[19] Furthermore, vitamin D has protective effects on the innate immune system and inhibitory effects on adaptive immunity.[14] Concerning in-hospital outcomes, vitamin D deficiency increases susceptibility for severe infections and mortality, and low vitamin D receptor levels were found to be associated with high mortality in critically ill patients.[20,21] Vitamin E is best known for its antioxidant qualities, by inhibiting the generation of reactive oxygen species during the fat oxidation and the propagation of free radical reactions.[10,22] Furthermore, it regulates gene expression and transcription of, for example, connective tissue growth factor. As a result, immunity against soft tissue infections is enhanced by vitamin E.[23,24]

Although several studies concluded that fat-soluble vitamin deficiencies might be related to malnutrition in hospitalized patients, no studies regarding this topic in the polytrauma patient population were found.[25] The goal of this exploratory study was to evaluate the trend in plasma vitamins A, D, and E levels during hospital admission and its relation with the development of malnutrition and complications in polytrauma patients, considering the protocolized multivitamin supplementation during ICU admission.

METHODS

This study was conducted at two Level-1 trauma centres as part of the Malnutrition in Polytrauma Patients (MaPP) study.[26] The MaPP study is an observational cohort study, that prospectively included adult (≥18 years) patients with severe injuries ('polytrauma', defined as Severity Injury Score ≥16), who were admitted to the Intensive Care Unit (ICU). Included patients had to be primarily managed in one of the participating hospitals and needed to be admitted to the ICU for ≥48 hours. Additionally, only patients that were well-nourished at admission, based on the Subjective Global Assessment (SGA), were included. Patients with penetrating injuries or burn wounds were excluded. The study was conducted according to the Declaration of Helsinki guidelines and approved by the local Institutional Review Boards (protocol number: NL64016.058.17). Informed consent was obtained from the patients or their legal representative at the day of ICU admission or as soon as possible after that day. Patient inclusion started in July 2018 and ended in April 2022. This study has been reported in line with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement.[27]

As described in the study protocol, the a priori sample size calculation showed that 195 patients were needed to show a difference in complication rate between the groups with and without malnutrition.[26] Due to the slow inclusion rate during the COVID-19 pandemic, however, it was decided to prematurely end the inclusion at 100 patients. For this study, all patients admitted to two of five participating centers and of whom blood samples were available for vitamin analysis were included.

A weekly plasma sample was drawn at the ICU or ward for the determination of plasma levels of vitamins A (retinol), D (25-hydroxy-vitamin D), and E (tocopherol). The samples were stored at the Clinical Chemistry and Laboratory Medicine (CCLM) department of the corresponding hospital at -80°C, transported on dry ice if necessary, and analyzed by the CCLM. The vitamin concentrations were matched with the corresponding SGA score assessed within 24 hours and clustered into time periods (**Figure 1**). The first week was divided into the first 48 hours (baseline period, the hyperacute early phase) and days 3-7 (week 1, subsequent period of metabolic instability and catabolism). After that, every week was a new time period (period of anabolism).[28]

All ICU patients received daily oral multivitamin supplementation (Supradyn, containing 800µg vitamin A, 5µg vitamin D, and 12mg vitamin E per tablet) for a minimum of five days upon admission. The multivitamin supplementation was continued as long as the patient received tube feeding. One patient received additional vitamin D supplementation other than the multivitamin supplementation. For this patient, the vitamin determinations after this supplementation were excluded from analyses.

Nutritional status, the primary outcome measure, was assessed using the Subjective Global Assessment (SGA). The SGA is recommended as assessment tool for the nutritional status in the critically ill, since it is validated as a screening tool for predicting outcomes in the ICU and in the severely injured population.[29] Patients are classified as A: well-nourished (scores 6-7), B: mild/moderate malnutrition (scores 3-5), and C: severe malnutrition (scores 1-2). Following the general consensus, patient scores were divided into two categories: well-nourished (SGA category A, scores 6-7) and malnourished (SGA categories B and C, scores 1-5). The SGA was scored within 24 hours after ICU admission to determine pre-existing malnutrition, and exclude the patients that were already malnourished upon admission. After that, the SGA was scored every 5 days at the ICU during ICU stay, on the day of discharge from the ICU, every week on the ward, and on hospital discharge day to determine in-hospital developed malnutrition. All SGA scores were determined by trained personnel, including a dietician, nurse, and a member of the research team.

Complications included systemic complications (sepsis, Acute Respiratory Distress Syndrome (ARDS), Systemic Inflammatory Response Syndrome (SIRS), multiple-organ failure), surgery-related complications (such as wound infection), pneumonia, urinary tract infection (UTI), deep venous thrombosis (DVT), pulmonary embolism (PE), fracture-related complications (such as compartment syndrome and fat embolism syndrome), and in-hospital mortality.[26] The patients' clinical files were checked for the presence of a complication on the day of vitamin analysis.

Statistical analysis

The data was analyzed using IBM SPSS Statistics and R version 4.2.2.

P-values <0.05 were regarded as statistically significant. The characteristics of the patients who developed malnutrition during hospital admission were compared with those of patients who remained well-nourished. Continuous variables were presented as mean with standard deviation (SD) and categorical variables were presented as frequency with percentage.

In the linear mixed-effects model analyses, the trends of the vitamin A, D, and E concentrations over time during hospital admission were analyzed. Vitamin concentration was the dependent variable, time period (according to **Figure 1**) was the fixed effect, and patient was included as random effect.

Mixed-effects logistic regression analysis with repeated measures was performed to test the ability of each vitamin to determine malnutrition in each time period (**Figure 1**). For each vitamin, a baseline mixed effects logistic regression model was fitted with malnutrition as binary outcome variable, time period as fixed effect, and patient as random effect. Then, a second mixed effects logistic regression model was fitted by adding vitamin levels and an interaction term of vitamin level with time period as fixed effects (full model). The interaction term was added to allow for changes in the association between vitamin levels and malnutrition over time. The likelihood ratio (LR) test was used to test the association between each of the vitamins and malnutrition over time.

Similar mixed-effects logistic regression analyses were performed to assess whether there was an association between each of the vitamins and complications over time.

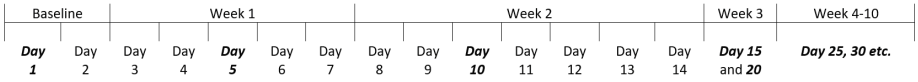


Figure 1: Combining the weekly vitamin concentration measurements with the Subjective Global Assessment

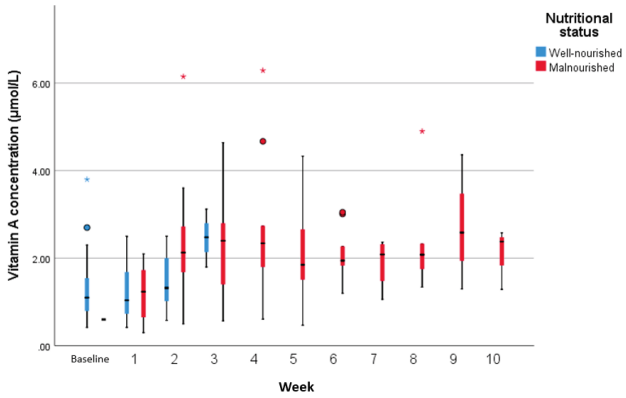
Bold and italic = Day of nutritional assessment using the Subjective Global Assessment

RESULTS

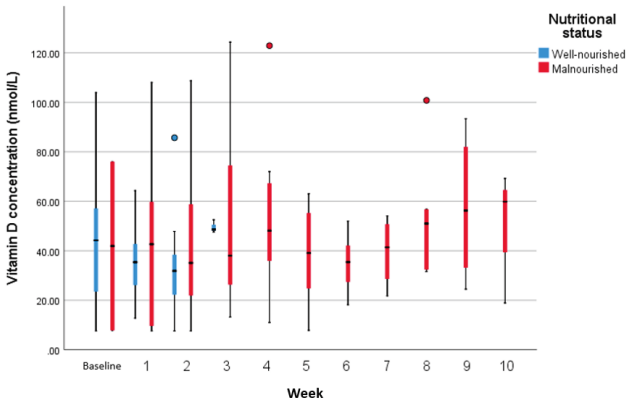
Of the 100 patients included in the MaPP study, 51 patients were included in the two centers participating in this study. Two patients were malnourished at admission, and therefore data was collected from 49 patients that were well-nourished at admission. The mean age of the included patients was 50 years (range 18 to 85 years). Eight patients died during hospital admission (16%). **Table 1** shows the baseline characteristics for the patients who remained well-nourished (SGA >5; n=12) and patients who became malnourished (SGA ≤5; n=37) during their hospital stay. 40 patients (82%) received mechanical ventilation during ICU admission, which did not differ between the two groups. In addition, 43 patients (88%) received enteral feeding. This percentage seemed higher in the patients who developed malnutrition compared to the patients who remained well-nourished (92% vs 75%), but this difference was not statistically significant (p=0.15). Patients who became malnourished during hospital stay had a significantly longer ICU length of stay (LOS) (12 ± 10 vs 5 ± 2 days, p<0.001) and hospital LOS (32 ± 17 vs 17 ± 5 days, p<0.001), and more ventilator days (9 ± 8 vs 2 ± 1, p<0.001) than the patients who remained well-nourished during admission. In-hospital mortality in the patients that became malnourished seemed higher (33% vs 11%), but this difference was not statistically significant (p=0.09).

Vitamin A levels increased with 0.17 µmol/L per week (95% confidence interval [CI] 0.12-0.22, p<0.001), vitamin D levels increased 1.49 nmol/L per week (95% CI 0.64-2.33, p<0.01), and vitamin E levels increased 1.17 µmol/L per week (95% CI 0.61-1.73, p<0.001) during hospital stay.

A



B



C

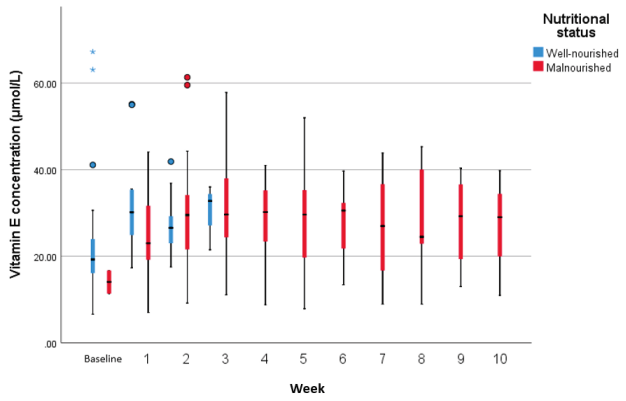


Figure 2: Boxplots of vitamin A (A), vitamin D (B) and vitamin E (C) levels by time and nutritional status during hospital stay

From week 7 onwards, each period included <6 patients. The boxes represent the median vitamin concentrations with the first and third quartile. The whiskers show the minimum and maximum vitamin levels.

The boxplots in **Figure 2** show the vitamin concentration distributions for the well-nourished and malnourished patients in each time period during hospital admission. After 3 weeks of admission, all the patients that were still admitted (n=25) had become malnourished and remained malnourished until discharge. Vitamin A, D, and E levels did not predict malnutrition (**Table 2**). For all vitamins, the likelihood ratio test between the base model (time only) and the full model (with time and malnutrition) was not statistically significant (p=0.45, 0.62 and 0.34 respectively).

No association was found between vitamin A, D, and E levels and complications over time (**Table 3**). For all vitamins, the likelihood ratio test between the base model (time only) and the full model (with time and complications) was not statistically significant (p=0.60, 0.76 and 0.78 resp).

Table 3: Patient characteristics according to their nutritional status during hospital admission

Characteristic	Total (n=49)	Developed malnutrition during admission (n=37)	Remained well-nourished during admission (n=12)	P value
Age in years, mean ± SD	50 ± 20	49 ± 20	53 ± 18	0.52
Female sex, n (%)	16 (33)	14 (38)	2 (17)	0.29
BMI in kg/m², mean ± SD	26 ± 5	26 ± 5	27 ± 5	0.32
Obesity (BMI >30 kg/m²), n (%)	9 (18)	6 (15)	3 (25)	0.67
Injury Severity Score ≥25, n (%)	40 (82)	31 (84)	9 (75)	0.67
Glasgow Coma Scale <8, n (%)	24 (49)	19 (51)	5 (42)	0.74
Mechanical ventilation, n (%)	40 (82)	31 (84)	9 (75)	0.67
Type of feeding, n (%)				0.15
Only oral	6 (12)	3 (8)	3 (25)	
Enteral	43 (88)	34 (92)	9 (75)	
Parenteral	0 (0)	0 (0)	0 (0)	
Alcohol abuse, n (%)	8 (16)	6 (16)	2 (17)	1.00
Malignancy, n (%)	3 (6)	2 (5)	1 (8)	1.00
In-hospital mortality, n (%)	8 (16)	4 (11)	4 (33)	0.09
ICU LOS in days *, mean ± SD	11 ± 9	12 ± 10	**5 ± 2**	**<0.001**
Ventilator days *, mean ± SD	7 ± 8	9 ± 8	2 ± 1	**<0.001**
Hospital LOS in days **, mean ± SD	29 ± 17	32 ± 17	17 ± 5	**<0.001**

BMI, Body Mass Index; ICU, Intensive care unit; kg, kilograms; LOS, Length of stay; n, number; SD, Standard deviation;

* Patients that died during ICU admission were excluded (n=6)

** Patients that died during hospital admission (n=8) or were transferred to another hospital (n=2) were excluded

Table 2: Mixed-effects logistic regression analysis predicting malnutrition during hospital admission based on vitamin concentration and time

Vitamin		Odds ratio (95% CI)	P value	P value LR test
Vitamin A	Time period	**81 (1.28 - 5087)**	**0.04**	0.45
	Main effect VitA	2.64 (0.22 - 32)	0.45	
	Interaction effect	0.93 (0.24 - 3.56)	0.91	
Vitamin D	Time period	**64 (1.23 - 3276)**	**0.04**	0.62
	Main effect VitD	1.01 (0.92 - 1.10)	0.86	
	Interaction effect	1.01 (0.96 - 1.07)	0.61	
Vitamin E	Time period	**366 (1.54 - 86759)**	**0.03**	0.34
	Main effect VitE	1.17 (0.91 - 1.51)	0.22	
	Interaction effect	0.95 (0.85 - 1.07)	0.43	

LR test, Likelihood Ratio test comparing base model (including only Time period) and full model

Table 3: Mixed-effects logistic regression analysis predicting complications during hospital admission based on vitamin concentration and time

Vitamin		Odds ratio (95% CI)	P value	P value LR test
Vitamin A	Time period	1.12 (0.80 - 1.56)	0.53	0.60
	Main effect VitA	0.92 (0.50 - 1.70)	0.79	
	Interaction effect	0.97 (0.82 - 1.14)	0.70	
Vitamin D	Time period	1.14 (0.83 - 1.56)	0.42	0.76
	Main effect VitD	1.00 (0.98 - 1.03)	0.68	
	Interaction effect	1.00 (0.99 - 1.00)	0.48	
Vitamin E	Time period	1.14 (0.82 - 1.60)	0.44	0.78
	Main effect VitE	1.01 (0.97 - 1.06)	0.56	
	Interaction effect	1.00 (0.98 - 1.01)	0.49	

LR test, Likelihood Ratio test comparing base model (including only Time period) and full model

DISCUSSION

In this exploratory study, an increase in vitamin A, D, and E levels was observed during hospital admission, but no association was found between vitamin A, D, and E levels and nutritional status or complications in polytrauma patients.

This is the first study to evaluate the trend in fat-soluble vitamin levels during hospital admission in polytrauma patients. Polytrauma patients suffer from an

acute phase response after severe trauma, with a hypermetabolic state.[4] Previous research in hospitalized patients has shown that a systemic inflammatory response, defined by increased C-reactive protein (CRP) levels, influences plasma vitamin levels.[30] Inflammation causes an increase of capillary permeability, leading to a redistribution of retinol binding protein and vitamin D binding protein into the interstitial fluid. Since retinol binding protein and vitamin D binding protein are also considered to be negative acute phase proteins, inflammation causes a decrease in vitamin A (retinol) and vitamin D levels, respectively.[11,30-32] Vitamin E levels are less affected by inflammation, because of the large size of the lipoprotein in which vitamin E is incorporated, which limits its transfer across capillaries into the extravascular space.[11,30] In a small study including patients undergoing limb surgery, a decrease in serum vitamin A, D, and E levels was demonstrated around 24-48 hours after surgery, alongside with a peak in CRP levels. Subsequently, the vitamin levels increased and CRP levels decreased substantially in the days that followed.[33] In our study, an increase in vitamin A, D, and E levels is demonstrated during hospital admission. Our study population received multivitamin supplementation according to a standardized hospital protocol for a minimum of five days during ICU admission, which explains the significant increase in vitamin levels. It can be hypothesized that all polytrauma patients, without vitamin supplementation, might have become deficient for all three vitamins. This suggest that the standardized supplementation protocols used, sufficiently elevated the plasma vitamin levels in ICU admitted polytrauma patients.

Concerning the relation between plasma vitamin levels and malnutrition, several studies have been performed involving other types of hospitalized patients.[25] Terlikowska et al. found no relation between vitamin E levels and moderate or severe malnourishment in women who were surgically treated for ovarian cancer patients, but did find that the malnourished patients had significantly lower levels of vitamin A than the well-nourished patients.[34] A study by Cunha et al., found no association between vitamin A and E levels and malnutrition in hospitalized patients aged older than 65 years.[35] In addition, several other studies found no relation between vitamin D levels and malnutrition in hospitalized patients.[36-42] On the other hand, previous studies on patients with fractures found that the risk of malnutrition was correlated with decreased vitamin D levels.[43,44] In our study, no relation was found between plasma vitamin A, D, and E levels and in-hospital de-

veloped malnutrition. However, comparing our findings to those of the referenced studies poses challenges due to the difference in type of malnutrition. Our study population developed malnutrition caused by 'acute injury states with marked inflammatory response', while the cited studies included patients enduring 'malnutrition as a result of chronic disease', such as malignancies.[45] As stated earlier, our patients suffer from inflammation, which might also influence the results. In addition, the supplementation obscures the potential vitamin deficiencies, that might correlate with malnutrition.

Several nutritional assessment tools are available to diagnose malnutrition, although no "gold standard" has been established. We used the SGA score to diagnose malnutrition in the polytrauma patients in our study, as it is validated in the critically ill population. In 2019, after the start of our study, a consensus report was published by the Global Leadership Initiative on Malnutrition (GLIM),[46], pointing out that the nutritional status of hospitalized patients should be assessed according to the GLIM diagnostic criteria for malnutrition. These criteria include: 1) Non-volitional weight loss, 2) Low body mass index (BMI), 3) Reduced food intake or assimilation, 4) Disease burden/inflammation, and 5) Reduced muscle mass. The SGA score entails weight (change) (point 1), dietary intake and gastrointestinal symptoms (point 3), disease state (point 4), and physical examination (point 5).[47,48] The SGA criteria match those of the GLIM to a large degree, since only low BMI is not included in the SGA. However, according to the GLIM consensus statement, the BMI is seldom used as a clinical malnutrition marker in North America, since the American population is often overweight or obese.[47] The SGA score thus largely fulfills the GLIM diagnostic criteria for malnutrition. In line with the literature, we found that all polytrauma patients who were admitted for at least three weeks, became malnourished.[49-51]

The ESPEN Micronutrient guideline describes that patients with vitamin A deficiency are more susceptible for respiratory tract infections and that low vitamin E levels could make a patient more susceptible for infections.[11] Several studies suggest that adequate vitamin A, D, and E levels play an important protective role in septic patients due to its role in the regulation of inflammatory responses against infection.[11,52,53] Moreover, the study of Takeuti et al. recommended vitamin D supplementation against sepsis prevention and sepsis treatment.[54] The inflammatory response triggered by sepsis can disrupt the normal metabolism of vitamin A,

D, and E.[55] This is in line with other studies, that show that vitamin A, D, and, E are commonly lower in septic patients.[56-60] We did not find a relation between vitamin levels and complications. One of the reasons for not finding a relation might be the heterogeneity of this patient population. The age of the included patients ranged from 18 to 85 years old, including previously healthy patients and patients with several comorbidities. For example, kidney failure causes an increase in vitamin A levels as it impairs the degradation of retinol binding protein. Vitamin D levels on the other hand, tend to decrease with progressive loss of kidney function.[61] In addition, vitamin A and D levels tend to influence each other, as vitamin A and D act through a similar type of receptor. In case of hypervitaminosis A, vitamin D supplementation is less effective.[14] Since multi-organ failure in polytrauma patients may also induce progressive kidney failure, this should be taken into account when supplementing vitamins in polytrauma patients.

Due to daily vitamin supplementation during ICU stay, vitamin A, D, and E levels increased during hospital admission. The vitamin levels were not related to malnutrition or complications during hospital stay nor could a correlation with complications be demonstrated. Thus, these fat-soluble vitamins do not seem to be useful as biomarkers for the nutritional status or complications of polytrauma patients in clinical practice. More research could help establish the detailed relation between fat-soluble vitamins and nutritional status and whether additional supplementation of these vitamins plays a role in reducing the risk of developing hospital complications.

Limitations

This study has several limitations. A gold standard to determine malnutrition does not exist worldwide. In this study, the SGA was used to determine the nutritional status of the polytrauma patients, which is a reliable assessment tool and recommended by the European Society for Clinical Nutrition and Metabolism (ESPEN).[1,62] However, a limitation of the SGA is its accuracy in relation to the experiences of the person conducting the SGA, due to the minimal difference between an SGA score of 5 (malnourished) and an SGA score of 6 (well-nourished).[63] On account of this limitation, the measured SGA was verified by another person in order to minimize the risk of bias. Additionally, with only 49 participants the statistical power of this study is low, potentially causing clinically relevant differences between patient groups to remain statistically not significant. As stated earli-

er, the heterogeneity of the study population is a limitation. Intubation is known to result in significant tracheal inflammation and sepsis can disrupt the normal metabolism of fat-soluble vitamins.[55,64] We were not able to correct for these confounders because of the low sample size. Future studies with larger patient cohorts could take several confounders into account, such as comorbidities, mechanical ventilation, type of feeding, and CRP level. The ESPEN micronutrient guideline states that vitamin A, D, and E levels become less interpretable with high CRP values.[11]

CONCLUSION

This exploratory prospective study showed that plasma levels of vitamins A, D, and E do not seem to be useful as biomarkers for the nutritional status of polytrauma patients during hospital stay.

REFERENCES

1. Lochs H, Allison SP, Meier R, Pirlich M, Kondrup J, Schneider S, et al. *Introductory to the ESPEN Guidelines on Enteral Nutrition: Terminology, definitions and general topics*. Clin Nutr. 2006;25(2):180-6.
2. Ruiz AJ, Buitrago G, Rodríguez N, Gómez G, Sulo S, Gómez C, et al. *Clinical and economic outcomes associated with malnutrition in hospitalized patients*. Clin Nutr. 2019;38(3):1310-16.
3. Barker LA, Gout BS, Crowe TC. *Hospital malnutrition: prevalence, identification and impact on patients and the healthcare system*. Int J Environ Res Public Health. 2011;8(2):514-27.
4. Dijkink S, Meier K, Krijnen P, Yeh DD, Velmahos GC, Schipper IB. *Malnutrition and its effects in severely injured trauma patients.* Eur J Trauma Emerg Surg. Oct 2020;46(5):993-1004.
5. Mogensen KM, Robinson MK, Casey JD, Gunasekera NS, Moromizato T, Rawn JD, et al. *Nutritional Status and Mortality in the Critically Ill*. Crit Care Med. 2015;12:2605-15.
6. Thomas JM, Isenring E, Kellett E. *Nutritional status and length of stay in patients admitted to an Acute Assessment Unit*. J Hum Nutr Diet. 2007;20(4):320-8.
7. Kalaiselvan MS, Renuka MK, Arunkumar AS. *Use of nutrition risk in critically ill (NUTRIC) score to assess nutritional risk in mechanically ventilated patients: A prospective observational study.* Indian J Crit Care Med. 2017;21(5):253-6.
8. Yeh DD, Johnson E, Harrison T, Kaafarani HMA, Lee J, Fagenholz P, et al. *Serum levels of albumin and prealbumin do not correlate with nutrient delivery in surgical intensive care unit patients*. Nutr Clin Pract. 2018;33(3):419-25.
9. Van Bokhorst-de van der Schueren MA, Guaitoli PR, Jansma EP, de Vet HC. *Nutrition screening tools: does one size fit all? A systematic review of screening tools for the hospital setting*. Clin Nutr. 2014;33(1):39-58.
10. Reddy P, Jialal I. *Biochemistry, Fat Soluble Vitamins*. Treasure Island(FL): StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK534869/
11. Berger MM, Shenkin A, Schweinlin A, Amrein K, Augsburger M, Biesalski HK, et al. *ESPEN micronutrient guideline*. Clin Nutr. 2022;41(6):1357-424.
12. Ross AC. *Vitamin A and retinoic acid in T cell-related immunity*. Am J Clin Nutr. 2012;96(5):1166S–72S.
13. Jeong M, Cortopassi F, See JX, De La Torre C, Cerwenka A, Stojanovic A. *Vitamin A-treated natural killer cells reduce interferon-gamma production and support regulatory T-cell differentiation*. Eur J Immunol. 2024:e2250342.
14. Džopalić T, Božić-Nedeljković B, Jurišić V. *The role of vitamin A and vitamin D in modulation of the immune response with a focus on innate lymphoid cells*. Cent Eur J Immunol. 2021;46(2):264-9.
15. Zhang J, Sun RR, Yan ZX, Yi WX, Yue B. *Correlation of serum vitamin A, D, and E with recurrent respiratory infection in children*. Eur Rev Med Pharmacol Sci. 2019;23(18):8133-8.
16. Polcz ME, Barbul A. *The Role of Vitamin A in Wound Healing. Nutrition in Clinical Practice.* 2019;34(5):695-700.
17. Muresan GC, Hedesiu M, Lucaciu O, Boca S, Petrescu N. *Effect of Vitamin D on Bone Regeneration: A Review*. Medicina (Kaunas). 2022;58(10):1337.
18. Gorter EA, Hamdy NA, Appelman-Dijkstra NM, Schipper IB. *The role of vitamin D in human fracture healing: a systematic review of the literature*. Bone. 2014;64:288-97.

19. Han A, Park Y, Lee YK, Park SY, Park CY. *Position Statement: Vitamin D Intake to Prevent Osteoporosis and Fracture in Adults*. J Bone Metab. 2022;29(4):205-15.

20. De Haan K, Groeneveld AB, de Geus HR, Egal M, Struijs A. *Vitamin D deficiency as a risk factor for infection, sepsis and mortality in the critically ill: systematic review and meta-analysis*. Crit Care. 2014;18(6):660.

21. Erdoğan M, Fındıklı HA. *Novel biomarker for predicting sepsis mortality: vitamin D receptor.* J Int Med Res. 2021;49(8):03000605211034733.

22. Rizvi S, Raza ST, Ahmed F, Ahmad A, Abbas S, Mahdi F. *The role of vitamin E in human health and some diseases*. Sultan Qaboos Univ Med J. 2014;14(2):e157-e165.

23. Hobson R. *Vitamin E and wound healing: an evidence-based review*. Int Wound J. 2016;13(3):331-5.

24. Pierpaoli E, Cirioni O, Barucca A, Orlando F, Silvestri C, Giacometti A, et al. *Vitamin E supplementation in old mice induces antimicrobial activity and improves the efficacy of daptomycin in an animal model of wounds infected with methicillin-resistant Staphylococcus aureus*. J Antimicrob Chemother. 2011;66(9):2184-5.

25. Verheul EAH, Ouwerkerk JJJ, Dijkink S, Krijnen P, Verhoeven A, Giera M, et al. *The value of metabolites and vitamins for the assessment of nutritional status in hospitalized patients. A systematic review*. Top Clin Nutr. 2024;39(3):198-212.

26. Dijkink S, Meier K, Krijnen P, Yeh DD, Velmahos GC, Arbous MS, et al. *The malnutrition in polytrauma patients (MaPP) study: Research protocol*. Nutr Health. 2019;25(4):291-301.

27. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. *STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies*. BMJ. 2007;335(7624):806-8.

28. Singer P, Blaser AR, Berger MM, Alhazzani W, Calder PC, Casaer MP, et al. *ESPEN guideline on clinical nutrition in the intensive care unit.* Clin Nutr. 2019;38(1):48-79.

29. Fontes D, de Vasconcelos Generoso S, Toulson Davisson Correia MI. *Subjective global assessment: a reliable nutritional assessment tool to predict outcomes in critically ill patients*. Clin Nutr. 2014;33(2):291-5.

30. Duncan A, Talwar D, McMillan DC, Stefanowicz F, O'Reilly DS. *Quantitative data on the magnitude of the systemic inflammatory response and its effect on micronutrient status based on plasma measurements.* Am J Clin Nutr. 2012;95(1):64-71.

31. Hernández-Álvarez E, Pérez-Barrios C, Blanco-Navarro I, Pérez-Sacristán B, Donoso-Navarro E, Silvestre RA, et al. *Association between 25-OH-vitamin D and C-reactive protein as a marker of inflammation and cardiovascular risk in clinical practice*. Ann Clin Biochem. 2019;56(4):502-7.

32. Waldron JL, Ashby HL, Cornes MP, Bechervaise J, Razavi C, Thomas OL, et al. *Vitamin D: a negative acute phase reactant. Journal of Clinical Pathology*. 2013;66(7):620-2.

33. Louw JA, Werbeck A, Louw ME, Kotze TJ, Cooper R, Labadarios D. *Blood vitamin concentrations during the acute-phase response. Critical Care Medicine*. 1992;20(7):934-41.

34. Terlikowska KM, Dobrzycka B, Kinalski M, Terlikowski SJ. *Serum Concentrations of Carotenoids and Fat-Soluble Vitamins in Relation to Nutritional Status of Patients with Ovarian Cancer*. Nutr Cancer. 2021;73(8):1480-8.

35. Cunha DF, Cunha SF, Unamuno MR, Vannucchi H. *Serum levels assessment of vitamin A, E, C, B2 and carotenoids in malnourished and non-malnourished hospitalized elderly patients*. Clin Nutr. 2001;20(2):167-70.

36. Christopher KL, Wiggins AT, Van Meter EM, Means RT Jr, Hayslip JW, Roach JP. *Differences in vitamin D nutritional status between newly diagnosed cancer patients from rural or urban settings in Kentucky*. Nutr Cancer. 2013;65(5):653-8.

37. Førli L, Bjortuft O, Boe J. *Vitamin D status in relation to nutritional depletion and muscle function in patients with advanced pulmonary disease*. Exp Lung Res. 2009;35(6):524-38.

38. Holden RM, Morton AR, Garland JS, Pavlov A, Day AG, Booth SL. *Vitamins K and D status in stages 3-5 chronic kidney disease.* Clin J Am Soc Nephrol. 2010;5(4):590-7.

39. Olvera-Soto MG, Melquiades-Castillo D, Castillo-Martínez L, Clark P, Medeiros M, Monroy A, et al. *25 hydroxyvitamin D and nutritional parameters correlation in adults with stage 4 chronic kidney disease*. Clin Nutr ESPEN. 2018;28:80-7.

40. Ramel A, Jonsson PV, Bjornsson S, Thorsdottir I. *Vitamin D deficiency and nutritional status in elderly hospitalized subjects in Iceland*. Public Health Nutr. 2009;12(7):1001-5.

41. Vischer UM, Frangos E, Graf C, Gold G, Weiss L, Herrmann FR, et al. *The prognostic significance of malnutrition as assessed by the Mini Nutritional Assessment (MNA) in older hospitalized patients with a heavy disease burden*. Clin Nutr. 2012;31(1):113-7.

42. Vosoughi N, Kashefi P, Abbasi B, Feizi A, Askari G, Azadbakht L. *The relationship between Vitamin D, clinical outcomes and mortality rate in ICU patients: A prospective observational study.* J Res Med Sci. 2016;21:75.

43. Li Y, Hui M, Chang X, Li M, Wang Y, Zhang B, et al. *BMI reduction and vitamin D insufficiency mediated osteoporosis and fragility fractures in patients at nutritional risk: a cross-sectional study*. Eur J Clin Nutr. 2018;72(3):455-9.

44. Tsagari A, Toulis KA, Makras P, Skagias K, Galanos A, Lyritis G. *Performance of the mini nutritional assessment score in the detection of vitamin D status in an elderly Greek population*. Horm Metab Res. 2012;44(12):896-9.

45. Jensen GL, Mirtallo J, Compher C, Dhaliwal R, Forbes A, Grijalba RF, et al. *Adult starvation and disease-related malnutrition: A proposal for etiology-based diagnosis in the clinical practice setting from the International Consensus Guideline Committee*. JPEN J Parenter Enteral Nutr. 2010;34(2):156-9.

46. Cederholm T, Jensen GL, Correia MITD, Gonzalez MC, Fukushima R, Higashiguchi T, et al. *GLIM criteria for the diagnosis of malnutrition - A consensus report from the global clinical nutrition community*. Clin Nutr. 2019;38(1):1-9.

47. Cederholm T, Barazzoni R, Austin P, Ballmer P, Biolo G, Bischoff SC, et al. *ESPEN guidelines on definitions and terminology of clinical nutrition.* Clin Nutr. 2017;36(1):49-64.

48. Detsky AS, McLaughlin JR, Baker JP, Johnston N, Whittaker S, Mendelson RA, et al. *What is subjective global assessment of nutritional status?* JPEN J Parenter Enteral Nutr. 1987;11(1):8-13.

49. Volkert D, Kiesswetter E, Cederholm T, Donini LM, Eglseer D, Norman K, et al. *Development of a Model on Determinants of Malnutrition in Aged Persons: A MaNuEL Project*. Gerontol Geriatr Med. 2019;5:2333721419858438.

50. Fávaro-Moreira NC, Krausch-Hofmann S, Matthys C, Vereecken C, Vanhauwaert E, Declercq A, et al. *Risk Factors for Malnutrition in Older Adults: A Systematic Review of the Literature Based on Longitudinal Data*. Adv Nutr (Bethesda, Md). 2016;7(3):507-22.

51. Amarya S, Singh K, Sabharwal M. *Changes during aging and their association with malnutrition*. J Clin Gerontol Geriatr. 2015;6(3):78-84.

52. Herr C, Greulich T, Koczulla RA, Meyer S, Zakharkina T, Branscheidt M, et al. *The role of vitamin D in pulmonary disease: COPD, asthma, infection, and cancer*. Respir Res. 2011;12(1):31.

53. Izadpanah M, Khalili H. *Potential benefits of vitamin D supplementation in critically ill patients*. Immunotherapy. 2013;5(8):843-53.

54. Takeuti FAC, Guimaraes FSF, Guimaraes PSF. *Applications of vitamin D in sepsis prevention*. Discovery Medicine. 2018;25(140):291-7.

55. Wald EL, Badke CM, Hintz LK, Spewak M, Sanchez-Pinto LN. *Vitamin therapy in sepsis*. Pediatr Res. 2022;91(2):328-36.

56. Delrue C, Speeckaert R, Delanghe JR, Speeckaert MM. *Vitamin D Deficiency: An Underestimated Factor in Sepsis?* Int J Mol Sci. 2023;24(3):2924.

57. Chae B, Kim YJ, Kim SM, Hong SI, Shin YS, Kim JS, et al. *Vitamin D deficiency on admission to the emergency department is a mortality predictor for patients with septic shock treated with early protocol-driven resuscitation bundle therapy*. Am J Med Sci. 2023;365(4):361-7.

58. Li CH, Tang X, Wasnik S, Wang X, Zhang J, Xu Y, et al. *Mechanistic study of the cause of decreased blood 1,25-Dihydroxyvitamin D in sepsis*. BMC Infect Dis. 2019;19(1):1020.

59. Zhang X, Yang K, Chen L, Liao X, Deng L, Chen S, et al. *Vitamin A deficiency in critically ill children with sepsis*. Crit care. 2019;23(1):267.

60. Corcoran TB, O'Neill MA, Webb SA, Ho KM. *Prevalence of vitamin deficiencies on admission: relationship to hospital mortality in critically ill patients.* Anaesth Intensive Care. 2009;37(2):254-60.

61. Juszczak AB, Kupczak M, Konecki T. *Does Vitamin Supplementation Play a Role in Chronic Kidney Disease?* Nutrients. 2023;15(13):2847.

62. Norman K, Schütz T, Kemps M, Josef Lübke H, Lochs H, Pirlich M. *The Subjective Global Assessment reliably identifies malnutrition-related muscle dysfunction.* Clin Nutr. 2005;24(1):143-50.

63. Xu YC, Vincent JI. *Clinical measurement properties of malnutrition assessment tools for use with patients in hospitals: a systematic review*. Nutr J. 2020;19(1):106.

64. Puyo CA, Dahms TE. *Innate immunity mediating inflammation secondary to endotracheal intubation.* Arch Otolaryngol Head Neck Surg. 2012;138(9):854-8.








Chapter 7

The correlation of CT-derived muscle density, skeletal muscle index, and visceral adipose tissue with nutritional status in severely injured patients

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Eur J Trauma Emerg Surg. 2024;50(6):3209-3215

ABSTRACT

Introduction

This study explored if computerized tomography-derived body composition parameters (CT-BCPs) are related to malnutrition in severely injured patients admitted to the Intensive Care Unit (ICU).

Methods

This prospective cohort study included severely injured (Injury Severity Score ≥16) patients, admitted to the ICU of three level-1 trauma centers between 2018-2022. Abdominal CT scans were retrospectively analyzed to assess the CT-BCPs: muscle density (MD), skeletal muscle index (SMI), and visceral adipose tissue (VAT). The Subjective Global Assessment was used to diagnose malnutrition at ICU admission and on day 5 of admission, and the modified Nutrition Risk in Critically ill at admission was used to assess the nutritional risk.

Results

Seven (11%) of the 65 analyzed patients had malnutrition at ICU admission, increasing to 23 patients (35%) on day 5. Thirteen (20%) patients had high nutritional risk. CT-BCPs were not related to malnutrition at ICU admission and on day 5. Patients with high nutritional risk at admission had lower MD (median (IQR) 32.1 HU (25.8–43.3) vs 46.9 HU (37.7–53.3); $p<0.01$) and higher VAT (median 166.5 cm^2 (80.6–342.6) vs 92.0 cm^2 (40.6–148.2); $p=0.01$) than patients with low nutritional risk.

Conclusion

CT-BCPs do not seem related to malnutrition, but low MD and high VAT may be associated with high nutritional risk. These findings may prove beneficial for clinical practice, as they suggest that CT-derived parameters may provide valuable information on nutritional risk in severely injured patients, in addition to conventional nutritional assessment and screening tools.

INTRODUCTION

Malnutrition is associated with an increased risk of complications, mortality, prolonged hospital length of stay, and reduced quality of life in severely injured patients.[1] The prevalence of malnutrition in this patient group ranges from 7 to 76%, depending upon the setting, population, and nutritional assessment tool used.[1] However, objective in-hospital measurement of the nutritional status of severely injured patients remains a challenge, since obtaining their dietary history is often hampered by a decreased level of consciousness or mechanical ventilation. Evaluation of muscle wasting can be misleading due to swelling and oedema, and serum concentrations of visceral proteins are affected by the acute-phase response after inflammation or trauma.[2-4]

Computerized tomography derived body composition parameters (CT-BCPs) may be helpful for the assessment of nutritional status of severely injured patients.[5] CT scans are routinely obtained of severely injured patients at admission, and can potentially serve as a new way of assessing body composition.[6] The CT-BCPs include muscle density (MD), skeletal muscle index (SMI), and visceral adipose tissue (VAT), and are assessed through abdominal CT scan analysis. MD reflects the density of muscles to indicate intramuscular fat accumulation and therefore muscle quality: a higher MD correlates with better muscle quality.[7,8] The SMI is the skeletal muscle mass normalized for the patient's height.[9] In oncology patients, a low SMI is found to be associated with malnutrition.[9] VAT defines the visceral adipose tissue surrounding the intra-abdominal organs.[7] A lower VAT is related to malnutrition in patients with gastric cancer.[10] These CT-BCPs have been proven indicative of nutritional status in several patient populations, such as those with Crohn's disease, and malignancies,[9-12] but have not yet been studied in relation to nutritional status of severely injured patients.

This study aimed to examine the value of CT-BCPs (MD, SMI, and VAT) as assessment tools for malnutrition and nutritional risk in severely injured patients admitted to the ICU.

METHODS

Study design and population

This exploratory cohort study is based on both prospectively and retrospectively collected data at one level-1 trauma center in the United States, and two Level-1 trauma centers in the Netherlands. The study is part of the prospective Malnutrition in Polytrauma Patients (MaPP) study, which was initiated in July 2018.[13] In the MaPP study, patients were included if they: (i) were aged ≥18 years; (ii) had an Injury Severity Score (ISS) ≥16, due to blunt trauma; and (iii) were admitted to the Intensive Care Unit (ICU) at a participating hospital within six hours after trauma and for a period longer than 48 hours between July 2018 and April 2022. Patients were excluded if they: (i) were transferred from another hospital to a participating center; or (ii) had burn wounds or penetrating injuries. Informed consent was obtained from the patients or their legal representative on the day of ICU admission or as soon as possible thereafter. In total, 100 patients were included in the MaPP study.

For the present exploratory substudy, no sample size was calculated. The substudy included all 65 MaPP study patients with an abdominal CT scan made for trauma assessment at admission to the emergency department of three of the five MaPP-centers. The abdominal CT scan data was analyzed retrospectively. Since 91 of 100 MaPP patients were admitted to three of the five centers, it was decided to restrict this substudy to these three centers for practical reasons. Both the MaPP study and the present CT-BCPs substudy were approved by the local Institutional Review Boards of the participating hospitals.

Study parameters and definitions

Baseline data, such as medical history, Injury Severity Score (ISS), height and weight, and clinical data during the hospital stay, were gathered prospectively in Castor Electronic Data Capture (EDC).[14]

CT derived Body Composition Parameters

Abdominal CT scans with intravenous contrast, 120 kV, and coupe thickness of 5 mm on the day of ICU admission were retrospectively analyzed using Quantib-U.[15,16] This software program automatically marks and quantifies different tissues, such as muscle and visceral adipose fat.[15,16] CT-BCPs included MD (in Hounsfield Units

(HU)), SMI (in cm^2/m^2), and VAT (in cm^2). MD and VAT were determined by analysis of single-slice axial abdominal CT scans at the top of the third lumbar vertebra (L3 level).[15,17]

The mean radiation attenuation of the complete muscle area at the top L3 level was calculated from contrast-enhanced CT scans to assess the skeletal muscle density.[18] MD was calculated as the mean density of the skeletal muscle area (SMA) of the following muscle groups; musculus rectus abdominis, musculus transverses, musculus obliquus internus, musculus obliquus externus, musculus psoas major and minor, musculus erector spinae and musculus quadratus lumborum, and was expressed in HU.[17] To adjust for height, SMI was calculated by dividing the SMA (in cm^2) by the square of the height of the patient (in m^2), and was therefore expressed in cm^2/m^2.[19] VAT was determined by staining the visceral adipose tissue at the L3 level with the use of Quantib-U (in cm^2). Corresponding HU were -29 to +150 for SMA and -50 to -150 for VAT.[7,20] In **Figure 1**, an example of area measurement at the L3 level is presented.

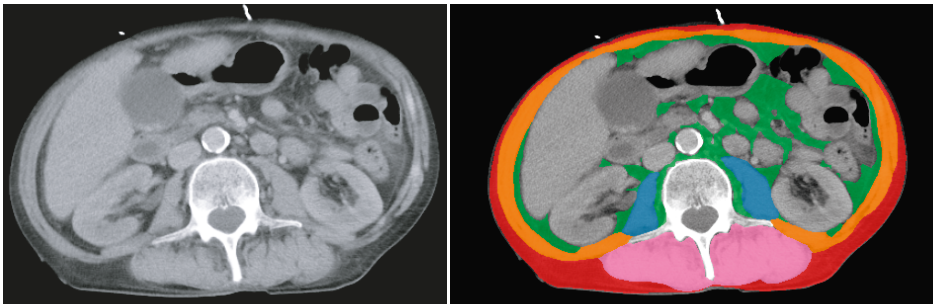

Figure 1: Example of an area analysis of CT-BCPs on the L3 level of a CT scan
Measurement of visceral adipose tissue area: 59.1 cm^2 (green), subcutaneous adipose tissue area: 52.9 cm^2 (red), psoas muscle area: 17.7 cm^2 (blue), abdominal muscle area: 61.6 cm^2 (orange), long spine muscle area: 51.5 cm^2 (pink).

Malnutrition

Malnutrition was assessed with the Subjective Global Assessment (SGA) score. The SGA score can be used to diagnose malnutrition, and was developed in surgical patients.[21,22] It includes weight change (over the past 2 weeks and past 6 months), dietary intake change, gastrointestinal symptoms (less appetite, nausea, vomiting, diarrhea), and functional capacity (difficulty with normal activities, dys-

function, bedridden). In addition, the SGA score includes a physical examination of muscle wasting (e.g. clavicle, knee, shoulder, and quadriceps), and subcutaneous fat loss (eyes, biceps, triceps). The SGA score ranges from 1-7, with 1-5 indicating malnutrition, and score 6-7 indicating no malnutrition.[22] SGA was scored by a trained nurse or member of the research group by using information provided by the patient him/herself, or, if this was not possible, by using information provided by family or the partner.

For this study, the nutritional status at ICU admission and day 5 of ICU admission were determined.

Nutritional risk

The modified Nutrition Risk in the Critically Ill (mNUTRIC) scale was assessed by trained personnel within 24 hours after ICU admission.[21] It identifies critically ill patients who are most likely to benefit from aggressive nutritional treatment and is the first nutritional risk assessment tool developed and validated specifically for critically ill patients.[23,24] The mNUTRIC score is based on age, the Acute Physiology And Chronic Health Evaluation (APACHE II) score, the Sequential Organ Failure Assessment (SOFA) score, the number of comorbidities, and the number of days in the hospital before ICU admission.[23,25] The APACHE II score is used as a general measure of the severity of the disease, and the SOFA score provides information about the prognosis of critically ill patients.[26,27] The mNUTRIC score ranges from 1 to 9 is, and a score ≥5 is regarded as high nutritional risk.[24]

Statistical Analysis

Baseline characteristics of patients with and without malnutrition on day 5 and of patients with high and low nutritional risk were compared using the Chi-square test or Fisher's exact test for categorical variables, the independent samples T-test for normally distributed continuous variables, and the Mann-Whitney U test for skewed continuous variables. The Mann-Whitney U test was also used for all CT-BCP analyses.

First, to assess the value of CT-BCPs in diagnosing malnutrition, the CT-BCP levels in patients with and without SGA-diagnosed malnutrition at ICU admission were compared. Second, to evaluate whether CT-BCPs are predictive for developing malnutrition, the CT-BCPs were compared in the groups with and without malnutrition at day 5 of ICU admission. Third, the CT-BCP levels in patients with high and low nutritional risk (according to mNUTRIC score) were compared.

P-values of <0.05 were considered statistically significant. All analyses were performed using IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, N.Y., USA).

RESULTS

Study population

Seven of the 65 analyzed patients (11%) were malnourished at ICU admission, which increased to 23 patients (35%) on day 5 of admission. Characteristics of the 65 patients grouped according to their nutritional status on day 5 are presented in **Table 1**. The malnourished and well-nourished patients were comparable regarding baseline characteristics. The mean age was 48.9 (±19.0) years, and 66% were male. Eight (12%) patients died during hospital admission, of which five died during ICU admission, and three after being admitted to the ward.

Thirteen (20%) patients were considered to have high nutritional risk (mNUTRIC ≥5) at admission. The patients with high nutritional risk were significantly older (66.2 ± 10.5 vs 44.6 ± 18.3 years; p<0.001), suffered more often from a Glasgow Coma Scale (GCS) ≤8 (77% vs 39%; p=0.03), and had more often more than one comorbidity (92% vs 27%; p<0.001).

Table 1: Patient characteristics grouped according to their nutritional status on day 5 of admission

	Total (n=65)	Well-nourished (SGA ≤5) (n=42)	Malnourished (SGA >5) (n=23)	P value
Age in years, mean ± SD	48.9 ± 19.0	46.2 ± 17.0	54.0 ± 21.8	0.12
Male sex	43 (66)	29 (69)	14 (61)	0.59
APACHE II score, median (IQR)	17.0 (11.0-20.0)	16.0 (10.0-19.3)	18.0 (12.0-21.0)	0.19
SOFA score at admission, median (IQR)	7.0 (4.0-9.0)	7.0 (4.0-10.0)	6.0 (4.0-8.0)	0.32
BMI category				0.58
Healthy weight (18.5-25.0)	29 (45)	17 (40)	12 (52)	
Overweight (25.0-30.0)	22 (34)	16 (38)	6 (26)	
Obese (≥30.0)	14 (22)	9 (21)	5 (22)	
Severe injury (AIS ≥ 4)				
Head	27 (42)	15 (36)	12 (52)	0.29
Chest	20 (31)	16 (38)	4 (17)	0.10
Abdomen	6 (9)	3 (7)	3 (13)	0.66
Extremity	12 (19)	10 (24)	2 (9)	0.19
ISS ≥ 25	46 (71)	32 (76)	14 (61)	0.26
GCS score ≤ 8	30 (46)	20 (48)	10 (43)	0.80
>1 Comorbidity *	26 (40)	14 (33)	12 (52)	0.19

n(%) unless stated otherwise

AIS, Abbreviated Injury Scale; APACHE II, Acute Physiology and Chronic Health Evaluation; BMI, Body Mass Index; GCS, Glasgow Coma Scale; IQR, Interquartile range; ISS, Injury Severity Score; kg, kilograms; n, number; SD, standard deviation; SGA, Subjective Global Assessment; SOFA, Sequential Organ Failure Assessment;

* According to mNUTRIC comorbidity list

Body composition parameters

The CT-BCP levels did not differ between the malnourished and the well-nourished patients at ICU admission (**Table 2a**), nor did CT-BCP levels differ between the malnourished and the well-nourished patients at day 5 of ICU admission (**Table 2b**).

In the patients with high nutritional risk, the median MD was significantly lower than in the patients with low nutritional risk (32.1 HU, interquartile range (IQR) 25.8 – 43.3 vs 46.9 HU, IQR 37.7 – 53.3; p<0.01), and the median VAT was significantly higher (166.5 cm^2, IQR 80.6 – 342.6 vs 92.0 cm^2, IQR 40.6 – 148.2; p=0.01) (**Table 3**).

Table 2: Median CT-BCPs levels (interquartile range) in patient groups according to their nutritional status (a) at admission and (b) on day 5

Nutritional status (SGA score)			
	Well-nourished	Malnourished	P value
(a) At admission	n=58	n=7	
MD	43.6 (35.7 – 51.9)	45.4 (29.6 – 53.0)	0.82
SMI	50.1 (41.5 – 58.5)	40.3 (35.9 – 59.6)	0.43
VAT	101.5 (52.7 – 155.7)	179.7 (39.0 – 235.7)	0.37
(b) On day 5	n=42	n=23	
MD	44.3 (36.6 – 52.0)	41.9 (26.9 – 50.5)	0.27
SMI	50.1 (41.5 – 59.1)	48.1 (38.6 – 58.3)	0.38
VAT	99.5 (51.7 – 157.4)	105.0 (54.1 – 185.5)	0.61

CT-BCPs, Computerized Tomography derived Body Composition Parameters; MD, Muscle Density (Hounsfield Units); SGA, Subjective Global Assessment; SMI, Skeletal Muscle Index (cm^2/m^2); VAT, Visceral Adipose Tissue (cm^2).

Table 3: Median CT-BCPs levels (interquartile range) in patient groups according to nutritional risk at admission

Nutritional risk (mNUTRIC score)			
	Low risk (n=52)	High risk (n=13)	P value
MD	46.9 (37.7 – 53.3)	32.1 (25.8 – 43.3)	**<0.01**
SMI	48.4 (40.3 – 58.2)	51.5 (40.1 – 60.1)	0.67
VAT	92.0 (40.6 – 148.2)	166.5 (80.6 – 342.6)	**0.01**

CT-BCPs, Computerized Tomography derived Body Composition Parameters; MD, Muscle Density (Hounsfield Units); mNUTRIC, modified Nutrition Risk in Critically ill; SMI, Skeletal Muscle Index (cm^2/m^2); VAT, Visceral Adipose Tissue (cm^2).

DISCUSSION

This study aimed to examine the value of CT scan-derived body composition parameters (MD, SMI, and VAT) as assessment tools for malnutrition and nutritional risk in severely injured patients admitted to the ICU. No correlation was found between the CT-BCPs and malnutrition as measured by the SGA on admission and at day 5 after admission. Low MD and high VAT were found to be related to high nutritional risk for severely injured patients who were admitted to the ICU.

Several studies have evaluated the relation between CT-BCPs and malnutrition in cancer patient populations. Malnourished patients undergoing radical gastrectomy for gastric cancer had lower SMI, MD, and VAT than the well-nourished patients.[10]

In patients suffering from esophageal and gastric cancer, malnourished patients had a lower SMI than well-nourished patients.[9] However, this relation was less evident in patients admitted to the ICU. In critically ill patients that require mechanical ventilation, MD and SMI seemed to be slightly lower in SGA-diagnosed malnourished patients, however not statistically significant.[28] This is comparable to our results, as we found that SMI tended to be lower in the malnourished patients compared to the well-nourished patients at ICU admission (40.3 (IQR 35.9 – 59.6) vs 50.1 (41.5 – 58.5) cm^2/m^2; **Table 2a**), however not statistically significant (p=0.43). In addition, the median VAT seemed higher in the malnourished patients at ICU admission compared to the well-nourished patients, but also not statistically significant (179.7 (39.0 – 235.7) vs 101.5 (52.7 – 155.7) cm^2, p=0.37; **Table 2a**). A possible explanation for not finding a relation between SGA-diagnosed malnutrition and CT-BCPs could be the increasing prevalence of obesity.[28] When the SGA was developed in 1982, nutritional assessment primarily entailed the detection of obvious signs of muscle and fat wasting.[22,29] However, when a person is overweight or obese, malnutrition may not immediately be recognized by the conventional nutritional assessment tools.[28]

Previous studies have shown that the risk of malnutrition was related to high VAT values and low SMI values in patients undergoing surgery for colorectal cancer.[11] Our study did not find a relation between CT-BCPs and malnutrition on day 5 of admission (**Table 2b**). On the other hand, we did find that the severely injured patients with high nutritional risk had significantly lower MD and higher VAT values (**Table 3**). High levels of MD and SMI are desirable, while high levels of VAT are associated with impaired survival in critically ill patients.[7,30] In addition, two large systematic reviews pointed out that sarcopenia, defined by the presence of both low muscle mass and low muscle function, and visceral adiposity were related to mortality.[31,32] Since the mNUTRIC is also related to mortality, this could indirectly explain why our study found low MD and high VAT in patients with high nutritional risk.[33] Furthermore, in contrast to the SGA, the mNUTRIC does not require a physical examination and is thus not influenced by the increasing prevalence of obesity.[23]

To conclude, body composition analysis can provide objective information about muscle and adiposity status, and that can enhance nutritional assessment in addition to the conventional nutritional assessment and screening tools. CT scans

are routinely conducted on severely injured patients, which allows for easy integration of determination of CT-BCPs into clinical practice.[6] Efficient analysis of these parameters on body composition can be performed using artificial intelligence segmentation algorithms, such as the Quantib-U deep learning algorithm.[15,16,34] Calculating MD and VAT in severely injured patients can be a routine assessment that does not require additional diagnostic actions by healthcare professionals.

Limitations

Several limitations of this study should be taken into consideration when interpreting its results. There is no gold standard or solid measure for the determination of the nutritional status of a patient. We used the SGA score, as it is validated for ICU patients and proven to be the most predictive for in-hospital outcomes. The difference between an SGA score of 6 (well-nourished) or 5 (malnourished) can, however, be minimal. To increase the reliability of this study, the SGA scores were verified by a second investigator after the completion of data collection. Furthermore, this study covered a prospective cohort with retrospectively analyzed CT scans. Several MaPP-study patients could not be included, due to missing or incorrectly produced CT scans. Standardizing trauma-CT scans will ensure their reliability and comparability across the entire study population and minimize the risk of errors or inconsistencies. Finally, the study's sample size was small with a low number of patients that had an SGA of 5 or less. The low number may pose challenges in extrapolating the results. Due to the limited sample size, it was not feasible to incorporate other variables into the analysis and perform sub-analyses.

Future research could focus on collecting multiple CT scans at different time points in more extensive patient cohorts, enabling to study the changes in body composition within individuals more precisely. Including higher numbers of patients would allow for more in-depth analyses. It would probably also allow for the composition of prediction models on hospital parameters and functional outcomes related to CT-BCPs.

CONCLUSION

This study did not find a correlation between CT-derived body composition parameters and malnutrition itself. It did show an increased nutritional risk for

severely injured patients with low CT-measured muscle density or high visceral adipose tissue parameters. Given that CT scans are routinely conducted on severely injured patients, it allows for easy integration of these parameters in clinical practice as a routine assessment. In this way CT scans can provide valuable information on body composition in severely injured patients in addition to conventional nutritional assessment and screening tools, identifying those severely injured patients with increased risk of malnutrition at the moment of hospital admission.

REFERENCES

1. Dijkink S, Meier K, Krijnen P, Yeh DD, Velmahos GC, Schipper IB. *Malnutrition and its effects in severely injured trauma patients.* Eur J Trauma Emerg Surg. 2020 Oct;46(5):993-1004.
2. Kalaiselvan MS, Renuka MK, Arunkumar AS. *Use of nutrition risk in critically ill (NUTRIC) score to assess nutritional risk in mechanically ventilated patients: A prospective observational study.* Indian J Crit Care Med. 2017;21(5):253-6
3. Yeh DD, Johnson E, Harrison T, Kaafarani HMA, Lee J, Fagenholz P, et al. *Serum Levels of Albumin and Prealbumin Do Not Correlate With Nutrient Delivery in Surgical Intensive Care Unit Patients.* Nutr Clin Pract. 2018;33(3):419-25.
4. Van Bokhorst-de van der Schueren MA, Guaitoli PR, Jansma EP, de Vet HC. *Nutrition screening tools: does one size fit all? A systematic review of screening tools for the hospital setting.* Clin Nutr. 2014;33(1):39-58
5. Smith LO, Olieman JF, Berk KA, Ligthart-Melis GC, Earthman CP. *Clinical applications of body composition and functional status tools for nutrition assessment of hospitalized adults: A systematic review*. JPEN J Parenter Enteral Nutr. 2023;47(1):11-29
6. Treskes K, Saltzherr TP, Luitse JS, Beenen LF, Goslings JC. *Indications for total-body computed tomography in blunt trauma patients: a systematic review*. Eur J Trauma Emerg Surg. 2017;43(1):35-42
7. Lucassen CJ, Groen JV, Aziz MH, Bastiaannet E, Bonsing BA, Leistra E, et al. *Visceral adipose tissue is a better predictor than BMI in the alternative Fistula Risk Score in patients undergoing pancreatoduodenectomy.* HPB. 2022;24(10):1679-87
8. Taaffe DR, Henwood TR, Nalls MA, Walker DG, Lang TF, Harris TB. *Alterations in muscle attenuation following detraining and retraining in resistance-trained older adults*. Gerontology. 2009;55(2):217-23
9. Lidoriki I, Schizas D, Mpaili E, Vailas M, Sotiropoulou M, Papalampros A, et al. *Associations between skeletal muscle mass index, nutritional and functional status of patients with oesophago-gastric cancer*. Clin Nutr ESPEN. 2019;34:61-7
10. Huang DD, Yu DY, Song HN, Wang WB, Luo X, Wu GF, et al. *The relationship between the GLIM-defined malnutrition, body composition and functional parameters, and clinical outcomes in elderly patients undergoing radical gastrectomy for gastric cancer*. Eur J Surg Oncol. 2021;47(9):2323-31
11. Almasaudi AS, McSorley ST, Dolan RD, Edwards CA, McMillan DC. *The relation between Malnutrition Universal Screening Tool (MUST), computed tomography-derived body composition, systemic inflammation, and clinical outcomes in patients undergoing surgery for colorectal cancer*. Am J Clin Nutr. 2019;110(6):1327-34
12. Sánchez M, Castro-Eguiluz D, Luvián-Morales J, Jiménez-Lima R, Aguilar-Ponce JL, Isla-Ortiz D, Cetina L. *Deterioration of nutritional status of patients with locally advanced cervical cancer during treatment with concomitant chemoradiotherapy*. J Hum Nutr Diet. 2019;32(4):480-91
13. Dijkink S, Meier K, Krijnen P, Yeh DD, Velmahos GC, Arbous MS, et al. *The malnutrition in polytrauma patients (MaPP) study: Research protocol*. Nutr Health. 2019;25(4):291-301
14. *Castor EDC - Medical Research - For researchers by researchers*. https://www.castoredc.com/
15. Pieters TT, Veldhuis WB, Moeskops P, de Vos BD, Verhaar MC, Haitjema S, et al. *Deep learning body-composition analysis of clinically acquired CT-scans estimates creatinine excretion with high accuracy in patients and healthy individuals.* Sci Rep. 2022;12(1):9013

16. *Quantib AI Node Research*. research.quantib.com. Accessed April 7, 2023.

17. Mourtzakis M, Prado CM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. *A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care*. Appl Physiol Nutr Metab. 2008;33(5):997-1006

18. Ní Bhuachalla ÉB, Daly LE, Power DG, Cushen SJ, MacEneaney P, Ryan AM. *Computed tomography diagnosed cachexia and sarcopenia in 725 oncology patients: is nutritional screening capturing hidden malnutrition*. J Cachexia Sarcopenia Muscle. 2018;9(2):295-305

19. Liu X, Ji W, Zheng K, Lu J, Li L, Cui J, Li W. *The correlation between skeletal muscle index of the L3 vertebral body and malnutrition in patients with advanced lung cancer*. BMC Cancer. 2021;21(1):1148

20. Aubrey J, Esfandiari N, Baracos VE, Buteau FA, Frenette J, Putman CT, Mazurak VC. *Measurement of skeletal muscle radiation attenuation and basis of its biological variation*. Acta Physiologica. 2014;210(3):489-97

21. Lew CCH, Yandell R, Fraser RJL, Chua AP, Chong MFF, Miller M. *Association between malnutrition and clinical outcomes in the intensive care unit: A systematic review.* JPEN J Parenter Enteral Nutr. 2017;41(5):744-58

22. Baker JP, Detsky AS, Wesson DE, Wolman SL, Stewart S, Whitewell J, et al. *Nutritional assessment: a comparison of clinical judgement and objective measurements*. N Engl J Med. 1982;306(16):969-72

23. Heyland DK, Dhaliwal R, Jiang X, Day AG. *Identifying critically ill patients who benefit the most from nutrition therapy: the development and initial validation of a novel risk assessment tool.* Crit Care. 2011;15(6):R268

24. Rahman A, Hasan RM, Agarwala R, Martin C, Day AG, Heyland DK. *Identifying critically-ill patients who will benefit most from nutritional therapy: Further validation of the "modified NUTRIC" nutritional risk assessment tool*. Clin Nutr. 2016;35(1):158-62

25. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. *APACHE II: a severity of disease classification system.* Crit Care Med. 1985;13(10):818-29

26. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, et al. *The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine*. Intensive Care Med. 1996;22(7):707-10

27. Rattanachaiwong S, Zribi B, Kagan I, Theilla M, Heching M, Singer P. *Comparison of nutritional screening and diagnostic tools in diagnosis of severe malnutrition in critically ill patients*. Clin Nutr. 2020;39(11):3419-25

28. Sheean PM, Peterson SJ, Gomez Perez S, Troy KL, Patel A, Sclamberg JS, et al. *The prevalence of sarcopenia in patients with respiratory failure classified as normally nourished using computed tomography and subjective global assessment*. JPEN J Parenter Enteral Nutr. 2014;38(7):873-9

29. Flegal KM, Carroll MD, Kuczmarski RJ, Johnson CL. *Overweight and obesity in the United States: prevalence and trends, 1960-1994*. Int J Obes Relat Metab Disord. 1998;22(1):39-47

30. Kong M, Xu M, Zhou Y, Geng N, Lin N, Song W, et al. *Assessing Visceral Obesity and Abdominal Adipose Tissue Distribution in Healthy Populations Based on Computed Tomography: A Large Multicenter Cross-Sectional Study*. Front Nutr. 2022;9:871697

31. Xu J, Wan CS, Ktoris K, Reijnierse EM, Maier AB. *Sarcopenia Is Associated with Mortality in Adults: A Systematic Review and Meta-Analysis.* Gerontology. 2022;68:361-76

32. Saad RK, Ghezzawi M, Horanieh R, Khamis AM, Saunders KH, Batsis JA, Chakhtoura M. *Abdominal Visceral Adipose Tissue and All-Cause Mortality: A Systematic Review.* Front Endocrinol (Lausanne). 2022;13:922931

33. de Vries MC, Koekkoek WK, Opdam MH, van Blokland D, van Zanten AR. *Nutritional assessment of critically ill patients: validation of the modified NUTRIC score.* Eur J Clin Nutr. 2018;72(3):428-35

34. Bates DDB, Pickhardt PJ. *CT-Derived Body Composition Assessment as a Prognostic Tool in Oncologic Patients: From Opportunistic Research to Artificial Intelligence-Based Clinical Implementation.* AJR Am J Roentgenol. 2022;219:671-80








Chapter 8

General discussion

When Alice met the crossroads in Wonderland, she asked the Cheshire Cat *"Would you tell me, please, which way I ought to go from here?"* The Cheshire Cat answered: *"That depends a good deal on where you want to get to."*

This quote appeared in a recently published review article that emphasized the need for a consensus on defining nutritional risk and the importance of setting clear goals for nutritional risk screening.[1] The same applies to nutritional assessment tools, as there is no 'gold standard' for diagnosing malnutrition. Given the multitude of available nutritional risk screening and nutritional assessment tools, it is crucial to identify the most suitable tools for specific populations, such as polytrauma patients. In this thesis, the mNUTRIC score was utilized to identify polytrauma patients at high nutritional risk upon admission, while the SGA score was employed to diagnose malnutrition during admission. These tools were used to evaluate the impact of high nutritional risk and malnutrition in polytrauma patients and to identify new objective methods for defining nutritional risk and diagnosing malnutrition. The primary goal of this thesis was to analyze the prevalence and incidence of high nutritional risk and malnutrition and their relation with adverse in-hospital outcomes in polytrauma patients. Additionally, this discussion details the nutritional interventions that can be initiated based on the results of both the nutritional risk screening and assessment tools. The second aim was to study new biomarkers and body composition parameters for nutritional risk screening and nutritional assessment in polytrauma patients.

Nutritional risk screening

According to the Global Leadership Initiative on Malnutrition (GLIM) criteria for the diagnosis of malnutrition, nutritional risk screening should be performed systematically in all hospitalized adult patients at hospital admission.[2] The screening should be performed with a validated nutritional screening tool, such as the Malnutrition Universal Screening Tool (MUST), Nutrition Risk Screening 2002 (NRS-2002), and the Nutrition Risk in Critically ill (NUTRIC) score. The NUTRIC score, developed by Heyland et al., is designed specifically for critically ill patients to assess their nutritional risk at the time of ICU admission.[3] It includes parameters commonly assessed in ICU patients, though IL-6 levels are not typically measured.[3] To address this, the modified NUTRIC (mNUTRIC) score was created without IL-6, making it more practical for integration into standard care for critically ill patients.[4] In patients with high nutritional risk (mNUTRIC ≥5), sup-

plemental parenteral nutrition or strategies to improve enteral nutrition delivery could be initiated to prevent nutrition-related adverse in-hospital outcomes, such as mortality.[3] In contrast, patients with low nutritional risk may even be harmed by such an approach.[3] In the MaPP study, 18% of the polytrauma patients were considered to be at high nutritional risk (**Chapter 3**). A clear correlation was found between a high mNUTRIC score and adverse in-hospital outcomes, such as complications, mortality, and increased hospital length of stay (**Chapter 3**). Possibly, aggressive nutritional therapy could have been beneficial in these high-risk patients, a topic that will be explored further in this chapter.

In conclusion, based on the GLIM criteria for diagnosing malnutrition, nutritional screening should be conducted for all hospitalized patients, including polytrauma patients admitted to the ICU. This approach helps identify patients with high nutritional risk who are more susceptible to adverse in-hospital outcomes.

Nutritional status assessment

The GLIM consensus statement recommends that diagnosing malnutrition should involve a two-step procedure using a nutritional risk screening tool followed by a nutritional assessment tool.[2] In the patients with a high risk for malnutrition, the nutritional status should be assessed using the GLIM diagnostic criteria for malnutrition:

1. Non-volitional weight loss
2. Low body mass index (BMI)
3. Reduced food intake or assimilation
4. Disease burden/inflammation
5. Reduced muscle mass

These criteria were retrieved from existing approaches for nutritional assessment. The GLIM criteria were not used in the MaPP study because this statement was published while the MaPP study was already ongoing. Instead, the SGA score was employed, because at that time it was the most appropriate tool that was validated in the critically ill population. Although the GLIM criteria nowadays are considered the preferable tool for nutrition assessment, the SGA score largely fulfills the GLIM diagnostic criteria for malnutrition. The SGA score entails weight (change) (point 1), dietary intake and gastrointestinal symptoms (point 3), dis-

ease state (point 4), and physical examination (including muscle mass; point 5).[5,6] Thus only the GLIM criterion "low BMI" is not included in the SGA. However, according to the GLIM consensus statement, the BMI is seldom used as a clinical malnutrition marker in North America, since the American population is often overweight or obese.[5]

Surprisingly, no relation was found between high nutritional risk, as assessed with the mNUTRIC score, and SGA-diagnosed malnutrition in polytrauma patients (**Chapter 3**). A possible explanation is that high nutritional risk may be more closely associated with the development of malnutrition during admission according to the GLIM criteria, rather than SGA-diagnosed malnutrition, despite the close similarity between the GLIM criteria and SGA score. The patients with high nutritional risk were more frequently obese, which could impede nutritional assessment, as malnutrition is more difficult to diagnose in the severely overweight population. Therefore, since the GLIM criteria include BMI in their assessment, unlike the SGA score, it is possible that fewer patients would be classified as malnourished when using the GLIM criteria. It would be interesting to investigate whether polytrauma patients with high nutritional risk are more prone to developing malnutrition according to the GLIM diagnostic criteria. Another reason no relationship was observed between the mNUTRIC score and the SGA score could be the variation in nutritional support provided to patients with high versus low nutritional risk. Among those with high nutritional risk, 94% received (par)enteral nutrition, compared to only 66% in the low nutritional risk group (**Chapter 3**). It is possible that patients with high nutritional risk received adequate preventive medical nutrition, preventing them from becoming malnourished. However, in 29% of high-risk patients, the recommendation to initiate (par)enteral feeding within 48 hours of admission was not followed, compared to only 6% in the low-risk group.[7]

It is recommended that nutritional risk screening and nutritional status assessment be conducted separately in polytrauma patients, rather than as a sequential two-step process for diagnosing malnutrition. Otherwise, patients deemed to have a low nutritional risk based on the mNUTRIC score may not undergo further nutritional assessment using the SGA score. As a result, patients with low nutritional risk who develop malnutrition during their hospital stay could be overlooked. This view is also supported by the revised guidelines of the European Society for Clinical Nutrition and Metabolism (ESPEN) on clinical nutrition in the

ICU.[7] They state that every critically ill patient staying for more than 48 hours in the ICU should be considered at risk for malnutrition, regardless of the nutritional risk screening results. Therefore, nutritional assessment should be performed on every polytrauma patient admitted to the ICU for more than 48 hours, not only for those deemed to be at high nutritional risk at ICU admission.

In the MaPP study population, the nutritional status was assessed at ICU admission, every five days during ICU admission, at ICU discharge, every week at admission to the ward, and at hospital discharge. Twelve percent of all polytrauma patients admitted to the ICU were malnourished at admission according to the SGA (**Chapter 2**). Of all well-nourished polytrauma patients, 50% developed malnutrition during ICU admission, increasing to 70% during their total hospital stay. This high incidence may be the consequence of gastrointestinal problems such as an ileus, which might be more common in polytrauma patients than in other critically ill patients due to abdominal trauma, or of superimposed local or systemic infectious problems. Another important cause of development of malnutrition may be due to the fact that polytrauma patients on average undergo surgery more frequently than 'monotrauma' patients. These surgical 'second' hits may result in superimposed deterioration of the nutritional status after every consecutive surgical intervention. In addition, polytrauma patients are more susceptible to malnutrition as they enter into a hypermetabolic state after severe trauma.[8] The importance of adequate nutritional therapy to treat malnutrition is also supported by the other results of **Chapter 2**. SGA-diagnosed malnutrition in polytrauma patients was found to be related to an increased risk of complications. However, the causal relationship between malnutrition and these outcomes remains ambiguous, as both have the potential to influence each other. For example, malnutrition may render a person more susceptible to infection, but infection in its turn contributes to deterioration of the nutritional status.[9] In addition, malnutrition at admission is known to be associated with prolonged hospital length of stay (LOS).[10] But so are complications such as local or systemic infections. Furthermore, the longer a patient stays in a hospital, the higher the probability of acquiring an infection, which again may prolong the hospital stay.[11] In conclusion, malnutrition is correlated with complications and prolonged hospital stay, but a causal relation cannot be established.

Objective markers for nutritional status

Small metabolites and lipoproteins

In polytrauma patients included in the MaPP study, several small metabolites involved in the methionine cycle, ketone body formation, and muscle metabolism were found to be associated with high nutritional risk and malnutrition (**Chapter 5**). Furthermore, decreased levels of several (very) low-density lipoprotein ((V)LDL) particles and increased levels of (V)LDL triglycerides were related to high nutritional risk. Similar changes in lipid metabolism are seen in patients with severe COVID-19 infections.[12-14] Moreover, it was found that an increase in the majority of LDL subfractions in the first three days of ICU admission was related to a decreased risk of malnutrition, and after those days a positive correlation was found. Only in the case of LDL triglycerides, high levels might also indicate an increase in the risk of being malnourished. In a study concerning septic patients, LDL cholesterol levels decreased and triglyceride levels increased during the first days of ICU admission, with partial restoration observed by the time of ICU discharge.[15] Thus, the lipid changes in malnutrition might resemble dyslipidemia in sepsis. Although these results are promising, several steps must be completed before small metabolite and lipoprotein levels can be utilized in clinical practice. In the analyses in **Chapter 5**, a Partial Least Squares Discriminant Analysis (PLS-DA) was used, as this multivariate dimensionality-reduction tool has been recommended for use in metabolomics data analyses in which the data sets often have lot fewer samples than features.[16] With PLS-DA, small metabolites and lipoproteins can be found that are indicative of malnutrition. However, there were no cut-off points determined for these small metabolites to assess the nutritional risk and nutritional status. Moreover, several patient characteristics, such as gender, age, body composition, inflammation, or medication use were not taken into account, although those factors could also significantly influence metabolite and lipoprotein levels. Future large studies on the topic should evaluate different cut-off values and take the patient specific characteristics into account when determining which small metabolites and lipoproteins might be used as objective measures for the assessment of nutritional risk and nutritional status.

Vitamins

Vitamins play a substantial role in a multitude of physiological processes.[17] For example, vitamin A aids in vision and immune function, vitamin C is needed

for tissue repair and growth, and acts as an antioxidant, vitamin D is important for bone mineralization, muscle function, and immunity, and vitamin E is known for its antioxidant properties.[17] A deficiency in these vitamins may have a significant impact on recovery after trauma and could increase the risk of several complications during hospital admission.[18] The systematic review in **Chapter 4** found that malnourished patients had lower levels of water-soluble vitamin C, with deficiencies being more common in this group. Other water-soluble vitamins, such as riboflavin, folic acid, and vitamin B12 did not demonstrate a consistent association with malnutrition. Additionally, while several studies identified a relation between low albumin levels and deficiencies in fat-soluble vitamins A, D, and E among hospitalized patients, other studies found no relationship between these vitamins and malnutrition. These conflicting results may be explained by the complex relationship between vitamin levels and adiposity. Fat-soluble vitamins (A, D, E, and K) are closely associated with adiposity, as fats are necessary for their absorption and transport through the bloodstream.[17,19] In hospitalized patients with malnutrition, lower vitamin intake may be compounded by impaired absorption and transport, further reducing vitamin levels. However, excessive adipose tissue can negatively impact vitamin levels, resulting in vitamin insufficiency.[20] Other factors, such as patient characteristics, can also influence vitamin levels. For instance, alcoholic patients tend to have lower vitamin levels due to inadequate nutrient intake, reduced absorption, impaired utilization, increased nutrient requirements, and a genetic predisposition to nutrient deficiencies. Alcohol directly interferes with nutrient effectiveness, even when nutrients are present.[21] These factors may contribute to the heterogeneous findings regarding the relationship between vitamin levels and malnutrition in hospitalized patients.

Chapter 6 examines the relationship between acute in-hospital malnutrition and levels of fat-soluble vitamins during hospital admission. The patient conditions in this study differ from those in the systematic review because, in the review, vitamin levels and nutritional status were assessed at admission (**Chapter 4**). Malnutrition at hospital admission can also be considered pre-existent malnutrition, and therefore most probably chronic malnutrition. The polytrauma patients in **Chapter 6** were all well-nourished at admission, with some developing malnutrition during their hospital stay. This type of malnutrition can therefore be classified as acute malnutrition. Furthermore, the polytrauma patients received daily multivitamin supplementation, unlike those in the systematic review, who

were newly admitted and had not yet started any vitamin supplementation (except for some who might have used vitamin supplements before hospital admission). No relationship was found between levels of vitamins A, D, and E and either nutritional status or complications in polytrauma patients. Therefore, fat-soluble vitamins do not appear to be effective biomarkers for these conditions.

Body composition parameters

The GLIM consensus statement points out that reduced muscle mass (point 5) might be assessed with dual-energy absorptiometry or corresponding standards using other body composition methods like bioelectrical impedance analysis, CT, or Magnetic Resonance Imaging (MRI). When not available, physical examination or standard anthropometric measures like mid-arm muscle or calf circumferences may be used.[5] Thus, computerized tomography-derived body composition parameters (CT-BCPs; **Chapter 7**), including muscle density (MD), skeletal muscle index (SMI), and visceral adipose tissue (VAT), might provide more information on body composition than the physical examination included in the SGA score. Given that CT scans are routinely obtained in polytrauma patients during admittance at emergency department of many hospitals, it allows for easy integration of these parameters in clinical practice as a routine assessment of nutritional risk at admission. Efficient analysis of these parameters on body composition can be performed using artificial intelligence segmentation algorithms, such as the Quantib-U deep learning algorithm.[22-24] CT-BCPs might be particularly valuable in patients with sarcopenic obesity, characterized by the combination of obesity, defined by high body fat percentage, and sarcopenia, defined as low skeletal muscle mass accompanied by low muscle function.[25] The incidence of sarcopenic obesity is rising rapidly, primarily due to the aging global population and the ongoing obesity epidemic.[26] Sarcopenic obesity is linked to numerous clinical complications, including frailty, fractures, cardiovascular diseases, cancer, and an increased risk of hospitalization and mortality.[26] As shown in **Figure 1**, patients with the same BMI can have a completely different body composition.[27] In our patient group, the SMI ranged from 23.8 cm^2/m^2 (indicative of sarcopenia) to 79.4 cm^2/m^2 (indicative of high muscularity) among those with a normal BMI (18.5 – 25 kg/m^2). Additionally, VAT ranged from 16.7 to 235.7 cm^2 in these patients, with levels above 163 cm^2 being associated with an increased risk of coronary heart disease.[28] Therefore, CT-BCPs may prove valuable for assessing body composition, making them a useful tool in the nutritional assessment of polytrauma patients.

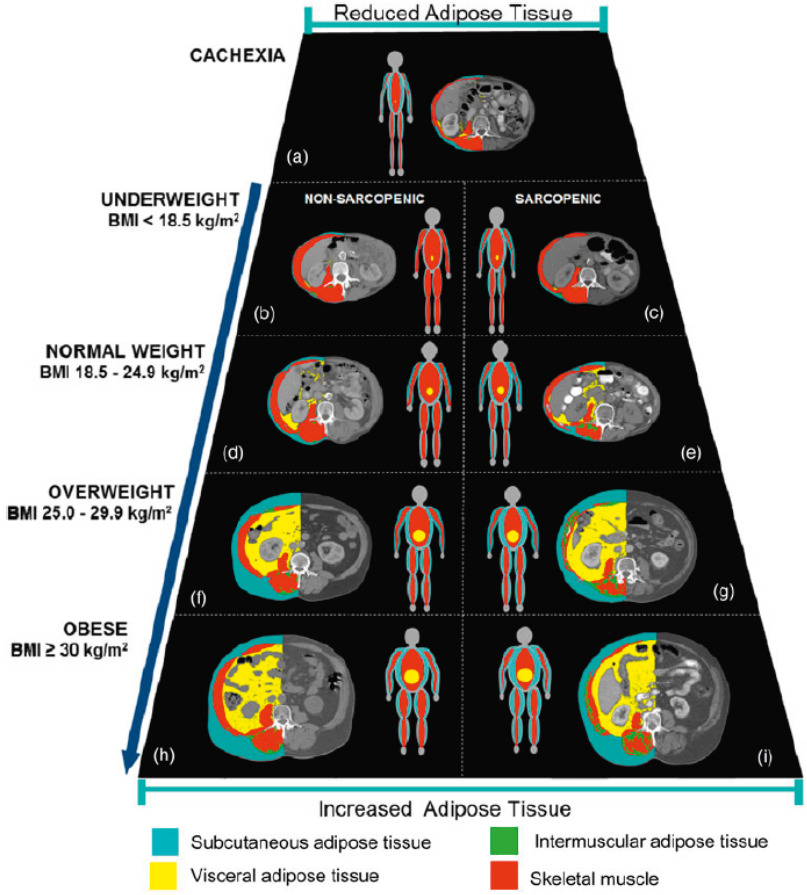

Figure 1: Trapezium model of body composition in cancer illustrating the variability in body composition in patients with identical BMI [27]

Supplementation of macronutrients

Nutrients are vital compounds necessary for sustaining physiological processes and are divided into two main categories: macronutrients and micronutrients. Macronutrients, including carbohydrates, proteins, and lipids, are substances needed in larger quantities that are crucial for energy production, the synthesis of structural molecules, and the regulation of metabolic pathways.[29]

The high incidence of malnutrition is not simply a matter of insufficient emphasis on nutritional support in the five included hospitals, as the ICU protocols of the five included hospitals align with the ESPEN[7] and American Society for Parenteral

and Enteral Nutrition (ASPEN)[30] recommendations. According to these guidelines, (par)enteral nutrition ((P)EN) should be initiated within 48 hours if oral intake is not possible. In our patient group, 89% of the (P)EN was initiated within 48 hours. Reasons for not starting P(EN) within 48 hours were: septic shock (n=1), gastric retention (n=2), or fasting before multiple surgeries (n=5). In these 8 patients, (P)EN was initiated between 48-96 hours after admission. Furthermore, ESPEN recommends that full (P)EN (i.e. meeting 100% of caloric needs) shall be prescribed within three to seven days to prevent overfeeding. In our patient group, 19% of patients received full (P)EN within 48 hours. Fourteen percent of patients did not meet caloric needs within 7 days. There was no statistically significant difference in the time of initiation of (par)enteral feeding or the time taken to achieve target energy goals between malnourished and well-nourished patients (**Chapter 2**). Possibly, the hypermetabolic catabolic state following severe trauma cannot be sufficiently compensated so that a deterioration in nutritional status can be prevented in all cases, even with adequate nutritional therapy. Additionally, the unavoidable fasting period before surgery and the resulting acute phase response after surgery make polytrauma patients exceptionally susceptible to malnutrition. Simply substituting enteral nutrition with parenteral nutrition during the fasting period before surgery may not be beneficial. Parenteral nutrition is associated with several complications, such as infections, and could potentially be harmful to well-nourished patients.[31] Studies on developments related to peri-operative management are regularly published, such as the Enhanced Recovery After Surgery (ERAS) protocol.[32] One component of the ERAS protocol is early oral feeding after surgery (starting 4 hours post-surgery). This approach can lead to faster intestinal recovery, shorter postoperative hospital stays, and fewer complications for patients undergoing gastrointestinal surgery.[33] Since polytrauma patients frequently have multiple surgeries within the initial days of ICU admission, careful monitoring of enteral nutrition and close collaboration with a dietitian are essential for managing both the timing and quantity of enteral feeding.

Assessing the nutritional needs of polytrauma patients and providing personalized nutritional support is crucial to prevent deterioration of the nutritional status. One approach to achieve this is by estimating the basal metabolic rate using the Harris-Benedict formula.[34] However, predictive equations like this can be highly inaccurate, with errors of up to 60%, potentially leading to over- or underestimation of nutritional needs and resulting in overfeeding or underfeeding.[7]

Indirect calorimetry, which measures oxygen consumption (VO_2) and carbon dioxide production (VCO_2), is considered the gold standard for assessing resting energy expenditure (REE).[7,35] Ideally, indirect calorimetry should be conducted two to three times per week, or whenever there is a significant change in the patient's clinical status, such as the onset of a new infection, a sepsis episode, or increased physical activity or rehabilitation.[36] In conclusion, indirect calorimetry offers a more accurate assessment of nutritional needs, helping to prevent both overfeeding and underfeeding, as well as reducing the risk of nutrition-related complications.

Furthermore, the mNUTRIC score can be used to identify patients that would benefit from aggressive nutritional therapy.[3] An example of aggressive nutritional therapy, also described by the research group that developed the NUTRIC score, is the Enhanced Protein-Energy Provision via the Enteral Route Feeding Protocol (PEP uP) protocol.[37] In this protocol, daily volume-based goals of enteral nutrition (EN) were set instead of hourly rate targets. For example, if EN was paused during a radiological procedure, the hourly rate could be increased for the remaining hours of the day to ensure daily volume goals were still met. They chose a semi-elemental, concentrated feeding solution that would be useful in both full-volume and trophic-fed (minimal volume of EN designed to maintain gastrointestinal structure and function, not designed to meet the patients' caloric or protein needs) patients. In addition, on day 1 of ICU admission, metoclopramide was initiated in the absence of contraindications, and a protein supplement (24 g protein per day) was added to tube feeding. The implementation of this protocol caused a significant increase in received protein-energy. The PEP uP protocol has also been studied in surgical ICU patients who were expected to need mechanical ventilation for more than 24 hours and an ICU stay exceeding 72 hours.[38] In this patient group, the PEP uP protocol appeared to enhance protein intake, but it was challenging to implement effectively and led to higher rates of vomiting. However, it has not yet been demonstrated that initiating the PEP uP protocol in patients with high nutritional risk reduces complications in ICU patients. A prospective cohort study examining whether integrating the mNUTRIC score into standard care, along with using the PEP uP protocol in response to its findings, could reduce complications in ICU-admitted polytrauma patients would be of great value.

Concerning protein supplementation, personalized nutritional supplementation is also thought to be beneficial. A daily intake of 2.0 g/kg of protein in critically ill patients resulted in worse health-related quality of life compared to 1.2 g/kg.[39] While this calculation is typically based on total body weight, protein requirements would be more accurately determined using total muscle mass.[7] Ongoing research is focused on calculating total muscle mass using the muscle mass at the L3 vertebra. Although still under investigation, this approach could enhance the clinical utility of CT-BCPs.

In conclusion, increasing the intake of macronutrients may help prevent malnutrition and nutrition-related complications. On the other hand, increasing carbohydrate and protein intake does not always result in improved outcomes. Therefore, individualized macronutrient supplementation is necessary to prevent deterioration of the nutritional status and nutrition-related adverse events in polytrauma patients.

Immunonutrition and supplementation of micronutrients

The information gathered from **Chapter 5** serves as a starting point for intervention trials to supplement small metabolites in the critically ill setting, also called 'immunonutrition'. This concept entails the supplementation of several different nutrients thought to boost the immune response.[40] For example, several studies suggested that the supplementation of glutamine could decrease mortality and infections.[40] On the other hand, a large intervention trial showed a dramatic increase in mortality rates with high doses of enteral and parenteral glutamine.[41] Furthermore, in a large randomized controlled trial, it was found that a high-protein formula enriched with arginine, glutamine, antioxidants, and omega-3 fatty acids had no significant effect on in-hospital outcomes in ICU patients.[42] It is obvious that further research is needed in order to state whether immunonutrition would be beneficial or harmful to polytrauma patients admitted to the ICU.

Micronutrients, including vitamins, minerals, and trace-elements, are vital compounds required in smaller quantities for biochemical processes such as regulating gene transcription, catalyzing enzymatic reactions, and providing protection against oxidative stress.[29] For several decades, the supplementation of exogenous micronutrients to restore antioxidant levels in critically ill patients has been considered.[43] For example, ESPEN recommends a daily intake of 1500 µg of vitamin

A, 30 µg of vitamin D, and 40 mg of vitamin E in critically ill patients, along with other vitamins and trace elements.[18] The patients in the MaPP study also receive a multivitamin supplement for at least five days, containing 800 µg of vitamin A, 5 µg of vitamin D, and 12 mg of vitamin E per supplement, along with other vitamins and micronutrients. Together with vitamin-rich enteral feeding, patients received an adequate amount of vitamins according to the ESPEN recommendations. **Chapter 6** showed that vitamin levels tended to increase during hospital admission in the MaPP-study patients. This suggests that standardized vitamin supplementation at least prevents vitamin levels from decreasing during the hospital stay of polytrauma patients. However, the question remains whether vitamin supplementation to prevent a decline in vitamin levels is sufficient, or if patients should receive additional supplementation. In this study, 13% of patients had a vitamin A deficiency (<0.7 µmol/L), 64% had a vitamin D deficiency (<50 nmol/L), and 23% had a vitamin E deficiency (<16 µmol/L) upon ICU admission. Most patients with a vitamin deficiency at admission continued to have deficiencies at hospital discharge. This suggests that standard multivitamin supplementation may be insufficient, and targeted supplementation could help raise vitamin levels to sufficient or even optimal ranges (>1 µmol/L for vitamin A, 75 nmol/L for vitamin D, and 30 µmol/L for vitamin E[44-46]). Therefore, while measuring vitamin levels is not routinely practiced in the ICU, it may offer significant benefits and help prevent complications.

FINAL CONSIDERATIONS

This thesis demonstrates that 18% of polytrauma patients are classified as high nutritional risk, based on the mNUTRIC score at hospital admission, and these patients face a greater likelihood of developing complications during their hospital stay. In addition, 50% of severely injured patients developed SGA-diagnosed malnutrition during ICU admission, increasing to 70% during hospital admission. Furthermore, the SGA score is found to be related to complications in polytrauma patients. For future research, the GLIM diagnostic criteria may provide a more appropriate method for assessing nutritional status in this patient population. Several interventions have been suggested to address the findings from mNUTRIC and SGA assessments in polytrauma patients admitted to the ICU. The second part of this thesis explored the search for objective markers of nutritional

status in polytrauma patients. While certain small metabolites and lipoproteins show potential for nutritional screening and assessment, further research is necessary before they can be integrated into clinical practice. Fat-soluble vitamins do not appear to be valuable for evaluating nutritional status, and although multivitamin supplementation during ICU admission seems appropriate for polytrauma patients, this study did not demonstrate its effectiveness in preventing complications. Nutritional assessment can be enhanced using CT-BCPs, especially given the rising prevalence of (sarcopenic) obesity, which necessitates new approaches for assessing body composition. Understanding the impact of malnutrition on polytrauma patients, conducting objective nutritional assessments, and implementing proactive nutritional strategies are crucial for optimizing clinical outcomes in this population.

REFERENCES

1. Jager-Wittenaar H, Sealy M, Naumann E, de van der Schueren M. *Nutritional risk screening: a need to guide Alice in Nutritionland*. Curr Opin Clin Nutr Metab Care. 2024;27(5):381-386.
2. Cederholm T, Jensen GL, Correia MITD, Gonzalez MC, Fukushima R, Higashiguchi T, et al. *GLIM criteria for the diagnosis of malnutrition - A consensus report from the global clinical nutrition community*. Clin Nutr. 2019;38(1):1-9.
3. Heyland DK, Dhaliwal R, Jiang X, Day AG. *Identifying critically ill patients who benefit the most from nutrition therapy: the development and initial validation of a novel risk assessment tool.* Crit Care. 2011;15(6):R268.
4. Rahman A, Hasan RM, Agarwala R, Martin C, Day AG, Heyland DK. *Identifying critically-ill patients who will benefit most from nutritional therapy: Further validation of the "modified NUTRIC" nutritional risk assessment tool.* Clin Nutr. 2016;35(1):158-62.
5. Cederholm T, Barazzoni R, Austin P, Ballmer P, Biolo G, Bischoff SC, et al. *ESPEN guidelines on definitions and terminology of clinical nutrition.* Clin Nutr. 2017;36(1):49-64.
6. Detsky AS, McLaughlin JR, Baker JP, Johnston N, Whittaker S, Mendelson RA, et al. *What is subjective global assessment of nutritional status?* JPEN J Parenter Enteral Nutr. 1987;11(1):8-13.
7. Singer P, Blaser AR, Berger MM, Calder PC, Casaer M, Hiesmayr M, et al. *ESPEN practical and partially revised guideline: Clinical nutrition in the intensive care unit*. Clin Nutr. 2023;42(9):1671-89.
8. Dijkink S, Meier K, Krijnen P, Yeh DD, Velmahos GC, Schipper IB. *Malnutrition and its effects in severely injured trauma patients.* Eur J Trauma Emerg Surg. Oct 2020;46(5):993-1004.
9. Katona P, Katona-Apte J. *The interaction between nutrition and infection*. Clin Infect Dis. 2008;46(10):1582-8.
10. Nigatu YD, Gebreyesus SH, Allard JP, Endris BS. *The effect of malnutrition at admission on length of hospital stay among adult patients in developing country: A prospective cohort study.* Clin Nutr ESPEN. 2021;41:217-24.
11. Hassan M, Tuckman HP, Patrick RH, Kountz D, Kohn J. *Hospital Length of Stay and Probability of Acquiring Infection.* Int J Pharm Healthc Mark. 2010;4(4):324-38.
12. Wei X, Zeng W, Su J, Wan H, Yu X, Cao X, et al. *Hypolipidemia is associated with the severity of COVID-19*. Clin Lipidol. 2020;14(3):297-304.
13. Begue F, Chemello K, Veeren B, Lortat-Jacob B, Tran-Dinh A, Zappella N, et al. *Plasma Apolipoprotein Concentrations Are Highly Altered in Severe Intensive Care Unit COVID-19 Patients: Preliminary Results from the LIPICOR Cohort Study*. Int J Mol Sci. 2023;24(5):4605.
14. Ballout RA, Kong H, Sampson M, Otvos JD, Cox AL, Agbor-Enoh S, et al. *The NIH Lipo-COVID Study: A Pilot NMR Investigation of Lipoprotein Subfractions and Other Metabolites in Patients with Severe COVID-19*. Biomedicines. 2021;9(9):1090.
15. Tanaka S, Stern J, Bouzid D, Robert T, Dehoux M, Snauwaert A, et al. *Relationship between lipoprotein concentrations and short-term and 1-year mortality in intensive care unit septic patients: results from the HIGHSEPS study.* Ann Intensive Care. 2021;11(1):11.
16. Ruiz-Perez D, Guan H, Madhivanan P, Mathee K, Narasimhan G. *So you think you can PLS-DA?* BMC Bioinformatics. 2020;21(1):2.
17. Reddy P, Jialal I. *Biochemistry, Fat Soluble Vitamins.* Treasure Island(FL): StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK534869/

18. Berger MM, Shenkin A, Schweinlin A, Amrein K, Augsburger M, Biesalski HK, et al. *ESPEN micronutrient guideline.* Clin Nutr. 2022;41(6):1357-424.

19. Abbott-Johnson W, Kerlin P, Clague A, Johnson H, Cuneo R. *Relationships between blood levels of fat soluble vitamins and disease etiology and severity in adults awaiting liver transplantation*. J Gastroenterol Hepatol. 2011;26(9):1402-10.

20. Tang W, Zhan W, Wei M, Chen Q. *Associations Between Different Dietary Vitamins and the Risk of Obesity in Children and Adolescents: A Machine Learning Approach*. Front Endocrinol (Lausanne). 2022;12:816975.

21. Ham BJ, Choi I. *Psychiatric Implications of Nutritional Deficiencies in Alcoholism*. Psychiatry Investig. 2005;2(2):44-59.

22. Pieters TT, Veldhuis WB, Moeskops P, de Vos BD, Verhaar MC, Haitjema S, et al. *Deep learning body-composition analysis of clinically acquired CT-scans estimates creatinine excretion with high accuracy in patients and healthy individuals*. Sci Rep. 2022;12(1):9013.

23. *Quantib AI Node Research*. research.quantib.com. Accessed April 7, 2023.

24. Bates DDB, Pickhardt PJ. *CT-Derived Body Composition Assessment as a Prognostic Tool in Oncologic Patients: From Opportunistic Research to Artificial Intelligence-Based Clinical Implementation*. AJR Am J Roentgenol. 2022;219(4):671-80.

25. Donini LM, Busetto L, Bischoff SC, Cederholm T, Ballesteros-Pomar MD, Batsis JA, et al. *Definition and Diagnostic Criteria for Sarcopenic Obesity: ESPEN and EASO Consensus Statement*. Obes Facts. 2022;15(3):321-35.

26. Wei S, Nguyen TT, Zhang Y, Ryu D, Gariani K. *Sarcopenic obesity: epidemiology, pathophysiology, cardiovascular disease, mortality, and management*. Front Endocrinol (Lausanne). 2023;14:1185221.

27. Prado CM, Cushen SJ, Orsso CE, Ryan AM. *Sarcopenia and cachexia in the era of obesity: clinical and nutritional impact*. Proc Nutr Soc. 2016;75(2):188-98.

28. Nicklas BJ, Penninx BW, Ryan AS, Berman DM, Lynch NA, Dennis KE. *Visceral adipose tissue cutoffs associated with metabolic risk factors for coronary heart disease in women*. Diabetes Care. 2003;26(5):1413-20.

29. Espinosa-Salas S, Gonzalez-Arias M. *Nutrition: Macronutrient Intake, Imbalances, and Interventions.* StatPearls [Internet] Treasure Island (FL): StatPearls Publishing. 2024;

30. McClave SA, Taylor BE, Martindale RG, Warren MM, Johnson DR, Braunschweig C, et al. *Society of Critical Care Medicine; American Society for Parenteral and Enteral Nutrition. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.).* JPEN J Parenter Enteral Nutr. 2016;40(2):159-211.

31. Veterans Affairs Total Parenteral Nutrition Cooperative Study Group. *Perioperative total parenteral nutrition in surgical patients.* N Engl J Med. 1991;325(8):525-32.

32. Melnyk M, Casey RG, Black P, Koupparis AJ. *Enhanced recovery after surgery (ERAS) protocols: Time to change practice?* Can Urol Assoc J. 2011;5(5):342-8.

33. Canzan F, Longhini J, Caliaro A, Cavada ML, Mezzalira E, Paiella S, et al. *The effect of early oral postoperative feeding on the recovery of intestinal motility after gastrointestinal surgery: a systematic review and meta-analysis of randomized clinical trials*. Front Nutr. 2024;11:1369141.

34. Harris JA, Benedict FG. *A Biometric Study of Human Basal Metabolism.* Proc Natl Acad Sci USA. 1918;4(12):370-3.

35. Delsoglio M, Achamrah N, Berger MM, Pichard C. *Indirect Calorimetry in Clinical Practice*. J Clin Med. 2019;8(9):1387.

36. De Waele E, Jonckheer J, Wischmeyer PE. *Indirect calorimetry in critical illness: a new standard of care?* Curr Opin Crit Care. 2021;27(4):334-43.

37. Heyland DK, Cahill NE, Dhaliwal R, Wang M, Day AG, Alenzi A, et al. *Enhanced protein-energy provision via the enteral route in critically ill patients: a single center feasibility trial of the PEP uP protocol*. Crit Care. 2010;14(2):R78.

38. Yeh DD, Ortiz LA, Lee JM, Chan J, McKenzie K, Young B, et al. *PEP uP (Enhanced Protein-Energy Provision via the Enteral Route Feeding Protocol) in Surgical Patients-A Multicenter Pilot Randomized Controlled Trial.* JPEN J Parenter Enteral Nutr. 2020;44(2):197-204.

39. Bels JLM, Thiessen S, van Gassel RJJ, Beishuizen A, De Bie Dekker A, Fraipont V, et al. *Effect of high versus standard protein provision on functional recovery in people with critical illness (PRECISe): an investigator-initiated, double-blinded, multicentre, parallel-group, randomised controlled trial in Belgium and the Netherlands*. Lancet. 2024;404(10453):659-69.

40. Preiser JC, van Zanten AR, Berger MM, Biolo G, Casaer MP, Doig GS, et al. *Metabolic and nutritional support of critically ill patients: consensus and controversies.* Crit Care. 2015;19(1):35.

41. Heyland D, Muscedere J, Wischmeyer PE, Cook D, Jones G, Albert M, et al. *A randomized trial of glutamine and antioxidants in critically ill patients.* N Engl J Med. 2013;368(16):1489-97.

42. Kieft H, Roos AN, van Drunen JD, Bindels AJ, Bindels JG, Hofman Z. *Clinical outcome of immunonutrition in a heterogeneous intensive care population*. Intensive Care Med. 2005;31(4):524-32.

43. Chudow M, Adams B. *ABC's of Vitamin Supplementation in Critical Illness*. J Pharm Pract. 2021;34(6):934-42.

44. Souverijn JHM, Goswami PR, Schreurs MWJ, Tax GHM, Wielders J. *Handboek Medische Laboratoriumdiagnostiek (Handbook Medical Laboratory Diagnostics).* Prelum; 2020.

45. Aloia JF, Patel M, Dimaano R, Li-Ng M, Talwar SA, Mikhail M, et al. *Vitamin D intake to attain a desired serum 25-hydroxyvitamin D concentration.* Am J Clin Nutr. 2008;87(6):1952-7.

46. Péter S, Friedel A, Roos FF, Wyss A, Eggersdorfer M, Hoffmann K, et al. *Systematic Review of Global Alpha-Tocopherol Status as Assessed by Nutritional Intake Levels and Blood Serum Concentrations.* Int J Vitam Nutr Res. 2015;85(5-6):261-81.








Chapter 9

Summary

The primary aim of this thesis was to analyze the prevalence and incidence of malnutrition and nutritional risk, and its relation with adverse in-hospital outcomes in polytrauma patients. The second aim was to study new biomarkers and body composition parameters for the assessment of the nutritional status in polytrauma patients.

In **Chapter 1** the different types of malnutrition, the pathophysiology of malnutrition specifically in polytrauma patients, and the adverse outcomes of malnutrition were discussed. In addition, the existing nutritional screening and assessment tools, the lack of a 'gold standard' in polytrauma patients, and the need for new objective measurements of the nutritional status were stated.

In order to analyze the prevalence and incidence of malnutrition and nutritional risk, and its relation with adverse in-hospital outcomes, our study group initiated a multicenter international observational prospective cohort study in the Netherlands and the United States. In this study, called the Malnutrition in Polytrauma Patients (MaPP) study, adult polytrauma patients (Injury Severity Score ≥16) suffering from blunt trauma were included. In **Chapter 2** and **Chapter 3**, we focused on the first aim of this thesis. **Chapter 2** states the prevalence and incidence of malnutrition and the relation with complications in polytrauma patients. Malnutrition was assessed using the Subjective Global Assessment (SGA) score, which is developed in surgical patients and validated in critically ill patients. In this study, the prevalence of pre-existing malnutrition was 12%. This study showed that 50% of the severely injured patients developed malnutrition during their ICU stay, and an additional 20% developed malnutrition during admission to the ward. Malnutrition was found to be related to an increased risk of complications. **Chapter 3** showed the prevalence of high nutritional risk at ICU admission and the relation with adverse in-hospital outcomes in polytrauma patients. The nutritional risk at ICU admission is assessed with the modified Nutrition Risk in Critically Ill (mNUTRIC score). 18% of the polytrauma patients admitted to the ICU had high nutritional risk. The mNUTRIC was not found to be related to developing malnutrition during hospital admission, as assessed with the SGA score. On the other hand, high nutritional risk was found to be related to complications, especially pneumonia and systemic complications, and mortality.

In conclusion, these studies together showed that both SGA-diagnosed malnutrition and high nutritional risk as assessed with the mNUTRIC score, were found to be related to an increased risk of developing complications in polytrauma patients. Recognition of sub-optimally nourished polytrauma patients, assessment of their nutritional needs, and preemptive nutritional strategies are crucial to optimize their clinical outcomes.

In the second part of this thesis, we aimed to analyze several biomarkers and body composition parameters for the assessment of the nutritional status. **Chapter 4** gives an overview of the current knowledge about the value of metabolites and vitamins for the assessment of nutritional status in hospitalized patients. Several metabolites involved in the metabolism of methionine, purine, glutathione, carnitine, phenylalanine, and tryptophan, as well as some vitamins seem to be associated with malnutrition in hospitalized patients. This systematic review was the foundation for our prospective study of polytrauma patients. As part of the MaPP study, our study group initiated a study on the relevance of plasma lipoproteins and small metabolites in the assessment of nutritional status in polytrauma patients, which was discussed in **Chapter 5**. In this study, the MaPP patients who were admitted to a Dutch hospital and of whom plasma samples were available for biomarker analysis, were included. In these 51 patients, increased triglyceride in several lipoprotein subfractions and decreased levels of other lipoprotein subfraction lipids were found to be related to malnutrition risk. Furthermore, several small metabolites involved in the homocysteine cycle, ketone body formation, and muscle metabolism may be indicative of malnutrition risk. Following validation in larger cohorts, these indicators may guide institution of preventive nutritional measures in patients admitted to the ICU with severe injuries. The second study on the analysis of nutritional biomarkers is discussed in **Chapter 6**. In this study, the patients from **Chapter 5** who were well-nourished at ICU admission were included. In these 49 polytrauma patients, the trends of plasma vitamin A, D, and E levels during hospital admission were analyzed, and their relation to the development of malnutrition and complications, taking into account the protocolized multivitamin supplementation during ICU admission. We demonstrated that these fat-soluble vitamin levels increased during hospital admission, despite the critical illness following severe trauma. This could be potentially related to the fact that all patients received the protocolized multivitamin supplementation during ICU admission. Vitamins A, D, and E did not seem to be valuable biomarkers for the assessment

of nutritional status. Subsequently, no correlation with complications could be demonstrated in polytrauma patients.

In **Chapter 7**, computerized tomography-derived body composition parameters (CT-BCPs) were investigated in relation to the nutritional status of polytrauma patients. Patients who were admitted to a Dutch hospital or one of the three participating trauma centers in the US, and had an abdominal CT scan made for trauma assessment at admission to the emergency department, were included. In these 65 patients, three CT-BCPs were examined, namely, muscle density (MD), skeletal muscle index (SMI), and visceral adipose tissue (VAT). A higher MD and SMI correlate with better muscle quality, and a higher VAT indicates more visceral adipose tissue surrounding the intra-abdominal organs. To assess the nutritional status, the SGA score was used to diagnose malnutrition at ICU admission and on day 5 of admission, and the mNUTRIC at admission was used to assess the nutritional risk. We found that CT-BCPs were not related to malnutrition at ICU admission and on day 5. Low MD and high VAT were found to be related to high nutritional risk for polytrauma patients that were admitted to the ICU. Given that CT scans are routinely conducted on polytrauma patients, it allows for easy integration of these parameters in clinical practice as a routine assessment. In this way CT scans can provide valuable information on body composition in polytrauma patients in addition to conventional nutritional assessment and screening tools, identifying those polytrauma patients with increased risk of malnutrition at the moment of hospital admission.

Chapter 8 presents a discussion on the prevalence and incidence of malnutrition in polytrauma patients, the pathophysiological process of the development of malnutrition, and the related increased risk of developing complications in this patient group. It is suggested that both the mNUTRIC and the SGA are useful tools to assess nutritional risk and malnutrition, respectively, in polytrauma patients. Furthermore, these tools can prove their value in indicating which polytrauma patients might be more prone to developing complications during admission. This information can be used to start nutritional therapy earlier during admission or to intensify nutritional therapy in specific polytrauma patients. Additionally, several small metabolites and lipoproteins seem to be related to the nutritional status of polytrauma patients, but more research is needed to investigate the clinical relevance and to provide guidelines for its use in determining nutritional

status. Fat-soluble vitamin supplementation appears to be adequate in polytrauma patients, potentially obscuring the relationship between vitamin levels, nutritional status, and complications. Body composition parameters might prove their value in assessing the nutritional status in addition to the conventional nutritional assessment tools. This chapter further discusses the future perspectives and potential implications of the findings in this thesis.








Chapter 10

Samenvatting

Het primaire doel van dit proefschrift was het analyseren van de prevalentie en incidentie van ondervoeding en het bijbehorende risico, evenals de relatie met ongunstige ziekenhuisuitkomsten bij polytraumapatiënten. Het tweede doel was het onderzoeken van nieuwe biomarkers en lichaamssamenstellingsparameters voor een betere beoordeling van de voedingsstatus bij polytraumapatiënten.

In **Hoofdstuk 1** worden de verschillende vormen van ondervoeding, de negatieve gevolgen ervan, bestaande meet- en screeningsinstrumenten en mogelijke nieuwe objectieve methoden om ondervoeding te bepalen besproken.

Om de prevalentie en incidentie van ondervoeding en het voedingsrisico vast te stellen en de relatie met ongunstige uitkomsten in het ziekenhuis te analyseren, heeft onze onderzoeksgroep een internationale, multicenter, observationele, prospectieve cohortstudie opgezet. Deze studie, genaamd de Malnutrition in Polytrauma Patients (MaPP) studie, includeerde volwassen polytraumapatiënten (Injury Severity Score ≥16) met stomp trauma. Patiënten moesten langer dan 48 uur op de intensive care (IC) verblijven en mochten niet primair in een ander ziekenhuis behandeld zijn. In totaal werden 100 patiënten in deze studie geïncludeerd.

Het eerste deel van deze thesis richt zich op de eerste onderzoeksvraag**. Hoofdstuk 2** beschrijft de prevalentie en incidentie van ondervoeding en de relatie met complicaties bij polytraumapatiënten. Ondervoeding werd gemeten met de Subjective Global Assessment (SGA)-score, die oorspronkelijk is ontwikkeld voor chirurgische patiënten en gevalideerd in IC-patiënten. In deze studie was de prevalentie van reeds bestaande ondervoeding bij IC-opname 12%. Van de 88 patiënten die bij IC-opname goed gevoed waren, ontwikkelde 50% ondervoeding tijdens het IC-verblijf en nog eens 20% tijdens het verblijf op de afdeling. Ondervoeding bleek geassocieerd te zijn met een verhoogd risico op complicaties. **Hoofdstuk 3** belicht de prevalentie van een hoog voedingsrisico bij IC-opname en de relatie met ongunstige ziekenhuisuitkomsten bij polytraumapatiënten. Het voedingsrisico bij IC-opname werd beoordeeld met de modified Nutrition Risk in Critically Ill (mNUTRIC)-score. Ongeveer een vijfde van de polytraumapatiënten die op de IC werden opgenomen had een hoog voedingsrisico. De mNUTRIC-score bleek niet gerelateerd te zijn aan de ontwikkeling van ondervoeding tijdens de ziekenhuisopname, zoals vastgesteld met de SGA-score. Wel was een hoog voedingsrisico geassocieerd met complicaties, met name longontsteking, systemische compli-

caties en mortaliteit. Concluderend bleken zowel SGA-gediagnosticeerde ondervoeding als een hoog voedingsrisico volgens de mNUTRIC-score gerelateerd te zijn aan een verhoogd risico op complicaties bij polytraumapatiënten. Het vroegtijdig herkennen van suboptimaal gevoede polytraumapatiënten, het inschatten van hun voedingsbehoeften en het starten van preventieve voedingsstrategiën zijn cruciaal om klinische uitkomsten te verbeteren.

In het tweede deel van deze thesis hebben we verschillende biomarkers en parameters van lichaamssamenstelling geanalyseerd voor de beoordeling van de voedingsstatus. **Hoofdstuk 4** biedt een overzicht van de huidige kennis over de waarde van metabolieten en vitamines voor de beoordeling van de voedingsstatus bij gehospitaliseerde patiënten. Verschillende metabolieten, betrokken bij het metabolisme van methionine, purine, glutathion, carnitine, fenylalanine en tryptofaan, evenals enkele vitamines, lijken geassocieerd te zijn met ondervoeding in deze populatie. Deze systematic review diende als basis voor toekomstig onderzoek. Als onderdeel van de MaPP-studie heeft onze onderzoeksgroep een studie opgezet naar de relevantie van plasma lipoproteïnen en kleine metabolieten bij de beoordeling van de voedingsstatus van polytraumapatiënten, zoals besproken in **Hoofdstuk 5**. Patiënten uit een Nederlands ziekenhuis, van wie bloedplasma beschikbaar was voor biomarkeranalyse, werden geïncludeerd. Hieruit bleek dat verhoogde triglyceriden van verschillende lipoproteïnesubfracties en verlaagde concentraties van andere lipoproteïnesubfracties geassocieerd waren met een hoog voedingsrisico. Daarnaast bleken kleine metabolieten, betrokken bij de homocysteïnecyclus, ketonlichaamvorming en spiermetabolisme, indicatief voor een hoog voedingsrisico. Na validatie in grotere cohorten kunnen deze biomarkers bijdragen aan vroegtijdige preventieve voedingsmaatregelen voor IC-patiënten met ernstige verwondingen. De tweede studie over de analyse van biomarkers, besproken in **Hoofdstuk 6**, richtte zich op de 49 polytraumapatiënten die bij IC-opname als goed gevoed werden geclassificeerd. Hierbij werden de trends in vitamine A-, D- en E-concentraties tijdens de ziekenhuisopname geanalyseerd en de relatie met het ontwikkelen van ondervoeding en complicaties onderzocht. Ondanks kritieke ziekte na ernstig trauma stegen de vet oplosbare vitamineconcentraties gedurende de opname, waarschijnlijk door geprotocolleerde suppletie. Vitamines A, D en E bleken niet geschikt als biomarkers voor de voedingsstatus en er werd geen correlatie aangetoond met complicaties.

In **Hoofdstuk 7** werden met computertomografie (CT) afgeleide lichaamssamenstellingsparameters (CT-BCP's) geanalyseerd in relatie tot de voedingsstatus bij polytraumapatiënten. Patiënten uit een Nederlands ziekenhuis en drie Amerikaanse traumacentra, bij wie een abdominale CT-scan was gemaakt bij opname, werden geïncludeerd. Bij deze 65 patiënten werden drie CT-BCP's onderzocht: spierdichtheid (MD), skeletspierindex (SMI) en visceraal vetweefsel (VAT). Een hogere MD en SMI correleerden met een betere spierkwaliteit, terwijl een hogere VAT duidde op meer visceraal vetweefsel rond de intra-abdominale organen. De SGA-score werd gebruikt om ondervoeding te diagnosticeren en de mNUTRIC-score om het voedingsrisico te bepalen. De studie toonde aan dat CT-BCP's niet direct gerelateerd waren aan ondervoeding bij IC-opname en op dag 5. Echter, een lage MD en hoge VAT waren wel geassocieerd met een hoog voedingsrisico. Aangezien CT-scans routinematig worden uitgevoerd bij polytraumapatiënten, kunnen deze parameters eenvoudig in de klinische praktijk worden geïntegreerd.

Hoofdstuk 8 bespreekt de prevalentie en incidentie van ondervoeding bij polytraumapatiënten, het pathofysiologische proces van ondervoeding en het daarmee samenhangende verhoogde risico op complicaties. Zowel de mNUTRIC- als de SGA-score blijken waardevolle hulpmiddelen te zijn voor respectievelijk het inschatten van het voedingsrisico en het diagnosticeren van ondervoeding. Deze instrumenten kunnen helpen te identificeren welke patiënten tijdens opname een verhoogd risico lopen op complicaties en baat kunnen hebben bij vroegtijdige of intensievere voedingsinterventies. Daarnaast lijken kleine metabolieten en lipoproteïnen relevante indicatoren voor de voedingsstatus, maar verder onderzoek is nodig om de klinische toepasbaarheid te bevestigen. Tot slot suggereren de bevindingen dat lichaamssamenstellingsparameters aanvullende waarde kunnen bieden bij het beoordelen van de voedingsstatus, naast conventionele screeningsmethoden. **Hoofdstuk 8** reflecteert op de toekomstperspectieven en de mogelijke implicaties van deze bevindingen voor de klinische praktijk.








Chapter 11

Curriculum Vitae

Esmee Agnes Hendrika Verheul was born on January 5, 1999 in Woerden and grew up in Zegveld. After graduating cum laude from her secondary school "Kalsbeek College" in Woerden, she started her medical studies at Leiden University in 2017. Esmee completed her Bachelor's degree in Medicine in three years. In addition to her studies, Esmee completed the "Bachelor's Honors College Medicine" and worked at the Organ Center of the Dutch Transplant Foundation as well as the dissection room of the LUMC. She was also an active member of the student association L.M.D. Forestus.

Before starting her clinical rotations, Esmee completed her LUMC scientific internship at the Department of Trauma Surgery at the Leiden University Medical Center. After completing her Master's thesis, she started her medical internships in September 2021.

She continued her research during her clinical rotations under the supervision of Prof. dr. I.B. Schipper. During her clinical rotations, she coordinated the metabolite, lipoprotein, and vitamin analyses. Additionally, she supervised two students during their research internships, which resulted in two of the publications included in this thesis.

After her graduation in March 2024, Esmee started as a full-time PhD student at the LUMC with Prof. dr. I.B. Schipper as her primary thesis advisor. In September 2024 she started as a resident not in training (ANIOS) at the Antonius Ziekenhuis in Utrecht.








Chapter 12

List of publications, co-authors, and presentations

ARTICLES

1. **Verheul EAH**, Dijkink S, Krijnen P, Hoogendoorn JM, Arbous MS, Peters R, Velmahos GC, Salim A, Yeh DD, Schipper IB. Prevalence, incidence, and complications of malnutrition in severely injured patients. *Eur J Trauma Emerg Surg*. 2025;51(1):72. doi: 10.1007/s00068-024-02711-8.

2. **Verheul EAH**, Koole D, Dijkink S, Krijnen P, Hoogendoorn JM, Arbous MS, Peters R, Velmahos GC, Salim A, Yeh DD, Schipper IB. Association of modified NUTRIC score for nutritional risk and in-hospital developed malnutrition in adults with severe injuries: a prospective observational cohort study. *Eur J Trauma Emerg Surg.* 2025;51(1):214. doi: 10.1007/s00068-025-02887-7.

3. **Verheul EAH**, Ouwerkerk JJJ, Dijkink S, Krijnen P, Verhoeven A, Giera M, Yeh DD, Schipper IB. The value of metabolites and vitamins for the assessment of nutritional status in hospitalized patients. A systematic review. *Top Clin Nutr.* 2024;39(3):198-212. doi: 10.1097/TIN.0000000000000350.

4. **Verheul EAH,** Dijkink S, Krijnen P, Verhoeven A, Giera M, Tsonaka R, Hoogendoorn JM, Arbous MS, Peters R, Schipper IB. Relevance of plasma lipoproteins and small metabolites in assessment of nutritional status among patients with severe injuries. *J Intensive Med*. 2024;4(4):496-507. doi: 10.1016/j.jointm.2024.02.004.

5. **Verheul EAH** & Horzum E, Dijkink S, Krijnen P, Hoogendoorn JM, Arbous MS, Peters R, Schipper IB. Fat-soluble vitamins as biomarkers of nutritional status and their relation with complications in polytrauma patients. *Nutr Health*. 2024:2601060241273640. doi: 10.1177/02601060241273640.

6. van Ee EPX & **Verheul EAH**, Dijkink S, Krijnen P, Veldhuis W, Feshtali SS, Avery L, Lucassen CJ, Mieog SD, Hwabejire JO, Schipper IB. The correlation of CT-derived muscle density, skeletal muscle index, and visceral adipose tissue with nutritional status in severely injured patients. *Eur J Trauma Emerg Surg*. 2024;50(6):3209-3215. doi: 10.1007/s00068-024-02624-6.

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Verheul EAH, Dijkink S, Krijnen P, Verhoeven A, Giera M, Tsonaka R, Hoogendoorn JM, Arbous MS, Peters R, Schipper IB. Relevance of plasma lipoproteins and small metabolites in assessment of nutritional status among patients with severe injuries. *Oral presentation. 21st European Congress of Trauma and Emergency Surgery, April 24-26, 2022 in Oslo, Norway.*

Verheul EAH, Dijkink S, Krijnen P, Hoogendoorn JM, Arbous MS, Peters R, Velmahos GC, Salim A, Yeh DD, Schipper IB. Prevalence, incidence, and complications of malnutrition in polytrauma patients. *Oral presentation. Resident symposium of the Dutch Association of Trauma Surgery, January 26, 2024 in Breukelen, the Netherlands.*

Verheul EAH, Dijkink S, Krijnen P, Hoogendoorn JM, Arbous MS, Peters R, Velmahos GC, Salim A, Yeh DD, Schipper IB. Prevalence, incidence, and complications of malnutrition in polytrauma patients. *Poster presentation. 23rd European Congress of Trauma and Emergency Surgery, April 28-30, 2024 in Lisbon, Portugal.*

Verheul EAH & van Ee EPX, Dijkink S, Krijnen P, Veldhuis W, Feshtali SS, Avery L, Lucassen CJ, Mieog SD, Hwabejire JO, Schipper IB. The correlation of CT-derived muscle density, skeletal muscle index, and visceral adipose tissue with nutritional status in polytrauma patients. *Poster presentation. 23rd European Congress of Trauma and Emergency Surgery, April 28-30, 2024 in Lisbon, Portugal.*

Verheul EAH, Dijkink S, Krijnen P, Hoogendoorn JM, Arbous MS, Peters R, Velmahos GC, Salim A, Yeh DD, Schipper IB. Prevalence, incidence, and complications of malnutrition in polytrauma patients. *Oral presentation. Annual Meeting of the Dutch Surgical Society, May 30-31, 2024 in Veldhoven, The Netherlands.*

Verheul EAH, Dijkink S, Krijnen P, Hoogendoorn JM, Arbous MS, Peters R, Velmahos GC, Salim A, Yeh DD, Schipper IB. Prevalence, incidence, and complications of malnutrition in polytrauma patients. *Oral presentation. Annual Meeting of the Orthopedic Trauma Association, October 23-26, 2024 in Montréal, Canada.*








Chapter 13

Acknowledgements

Dit proefschrift had nooit tot stand kunnen komen zonder de hulp en steun van veel mensen in mijn omgeving.

Allereerst wil ik alle patiënten en hun naasten bedanken voor hun bereidheid om deel te nemen aan de MaPP-studie. Juist in een periode van onzekerheid hebben jullie bijgedragen aan het verbeteren van de zorg voor ernstig gewonde patiënten.

Beste Prof. dr. Schipper, Beste Inger, Hartelijk dank voor het vertrouwen dat je in mij hebt gesteld na mijn wetenschapsstage. Ik heb ontzettend veel van je mogen leren, niet alleen over onderzoek doen, maar ook op persoonlijk vlak.

Beste Dr. Dijkink, Beste Suzan, Na jouw promotie kreeg ik het voorrecht om de MaPP-studie van jou over te nemen. Je hebt me altijd met enthousiasme begeleid en het was een eer om met jou samen te mogen werken.

Beste Dr. Krijnen, Beste Pieta, Jouw kennis op het gebied van statistiek en onderzoek doen is van grote waarde. Zonder jouw scherpe blik en waardevolle bijdragen was dit proefschrift niet geworden wat het nu is.

Beste Prof. dr. Giera en Dr. Verhoeven, Beste Martin en Aswin, Jullie expertise maakte het mogelijk om de lipoproteïne- en metabolietenanalyses uit te voeren en te interpreteren. Bedankt voor jullie tijd, inzet en het meedenken bij onze onderzoeken!

Beste Drs. Peters, Beste Ron, Zowel tijdens het includeren van patiënten voor de MaPP-studie als gedurende mijn keuzecoschap aan het einde van mijn studie, heb ik de kans gehad om rond te lopen op de IC van het HMC. Dank voor de ondersteuning bij de uitvoering van de studie én voor je persoonlijke begeleiding tijdens mijn coschap. Daarnaast wil ik ook de andere intensivisten, A(N)IOS'en en verpleegkundigen, in het bijzonder Femke van der Horst, bedanken voor hun onmisbare hulp bij de studie.

Beste Prof. dr. Arbous, Beste Sesmu, En natuurlijk alle andere intensivisten, A(N)IOS'en en verpleegkundigen op de IC van het LUMC, met een speciale dank aan Ingeborg Henkes, Jullie enthousiasme en bereidheid om patiënten te includeren waren essentieel voor het succes van de MaPP-studie. Bedankt voor jullie inzet!

Dear Dr. Velmahos, Dr. Yeh, and Drs. Salim, Thank you for your invaluable support in conducting the MaPP study at Massachusetts General Hospital, Brigham and Women's Hospital, and Ryder Trauma Center. I would also like to extend my gratitude to all the ICU physicians, nurses, and staff members for their assistance in including patients and assessing their nutritional status.

Beste Dr. Hoogendoorn, Beste Jochem, En alle collega's van de afdeling traumachirurgie in het HMC, Bedankt voor jullie inzet en ondersteuning bij de MaPP-studie. Dankzij jullie bijdragen hebben we dit kunnen realiseren. Mijn dank is groot!

Beste Ebru en Elaine, Dank jullie wel voor de fijne samenwerking tijdens jullie wetenschapsstages. Jullie hulp was heel waardevol bij het schrijven van dit proefschrift.

Lieve Lisa en Mare, Vanaf dag één van de geneeskundeopleiding zijn jullie al hele goede vriendinnen. Het is prachtig om te zien hoe jullie je de afgelopen jaren hebben ontwikkeld tot de sterke vrouwen die jullie nu zijn. Bedankt dat jullie mijn paranimfen wilden zijn en ik kijk uit naar nog vele jaren van vriendschap!

Lieve Jolanda, Van huisgenootje tot een van mijn beste vriendinnen. Bedankt voor alle gezamenlijke studiesessies, maar ook voor de gezellige studiepauzes en de talloze andere fijne momenten. Zonder jou was het onderzoek doen een stuk minder leuk geweest! En natuurlijk wil ik ook al mijn andere oud-huisgenoten bedanken voor de vele gezellige momenten!

Lieve andere mensen die ik tijdens de studie geneeskunde heb mogen leren kennen, Dank jullie wel voor alle gezelligheid en de bijzondere momenten samen. Naast het onderzoek en studeren was er altijd ruimte voor ontspanning en plezier. Jullie hebben mijn studietijd onvergetelijk gemaakt!

Lieve Tessa, Jessica, Femke, Vera en Renske, Al sinds de middelbare school zijn we een hechte groep en ondanks dat iedereen haar eigen pad is gaan bewandelen, hebben we altijd onze vriendschap behouden. Bedankt voor al die jaren samen en ik hoop op nog veel meer mooie jaren met jullie!

Lieve papa, mama en Robert, Tijdens het schrijven van dit proefschrift hebben jullie mij altijd gesteund. Op momenten dat ik vastliep, stonden jullie klaar om mee te denken en waardevolle inzichten te delen, waardoor ik weer vooruit kon. Jullie hebben mij altijd geleerd dat ik met doorzettingsvermogen en hard werken veel kan bereiken, maar zonder jullie steun en vertrouwen was dit niet mogelijk geweest. Dank jullie wel voor alles!