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The Netherlands

Measurements of nutritional status and impact of malnutrition in polytrauma patients

Verheul, E.A.H.

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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

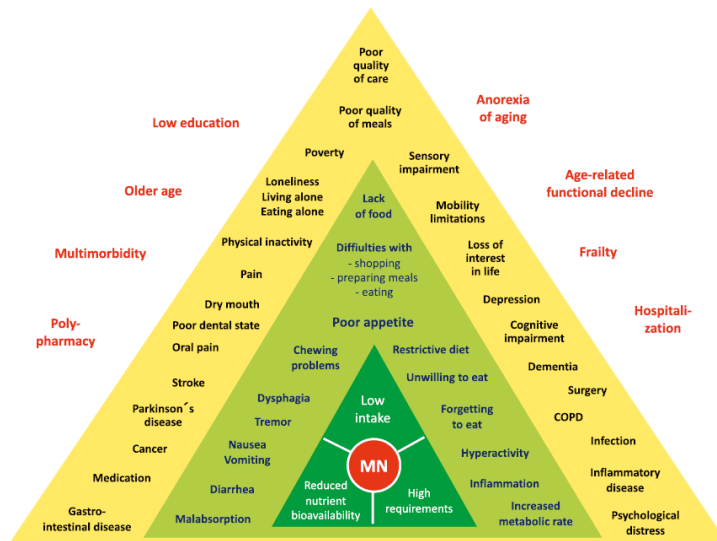


Figure 1: Determinants of malnutrition in aged persons ²

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.

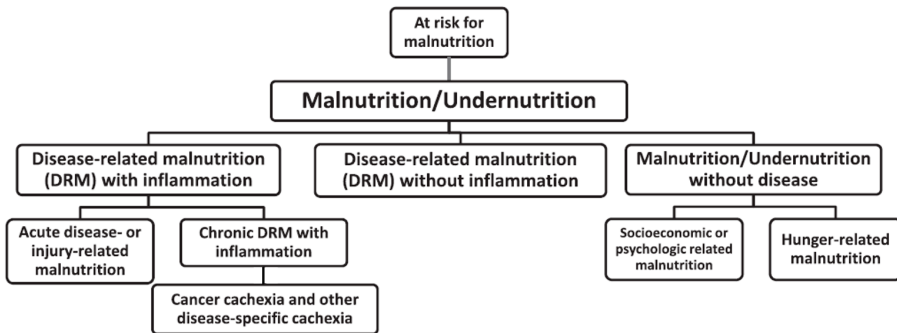


Figure 2: Types of malnutrition³

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}

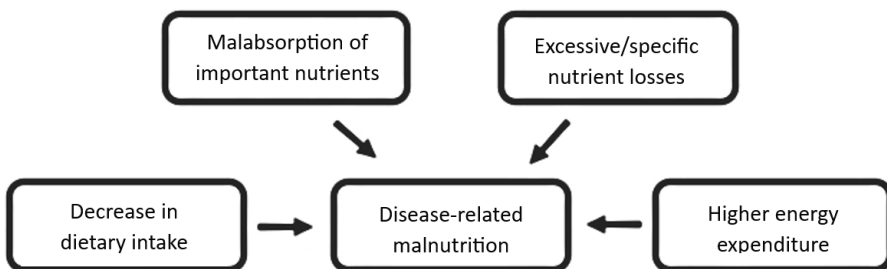


Figure 3: Factors contributing to disease-related malnutrition

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

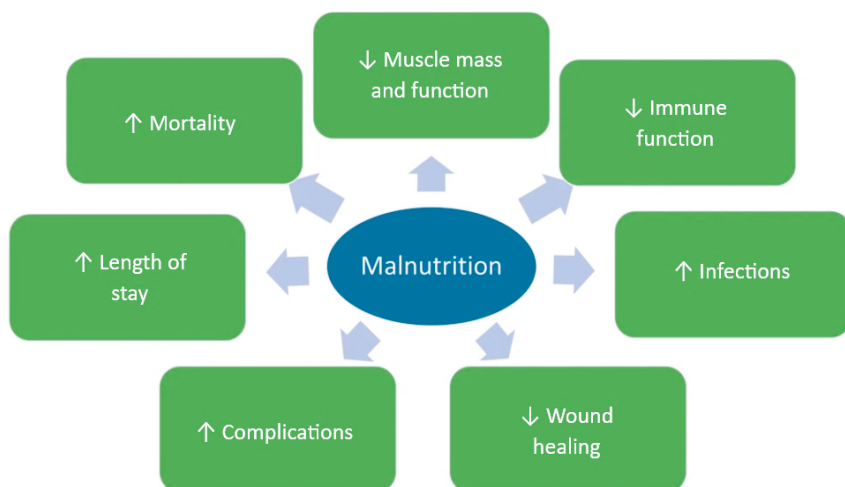


Figure 4: Adverse outcomes of malnutrition

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.

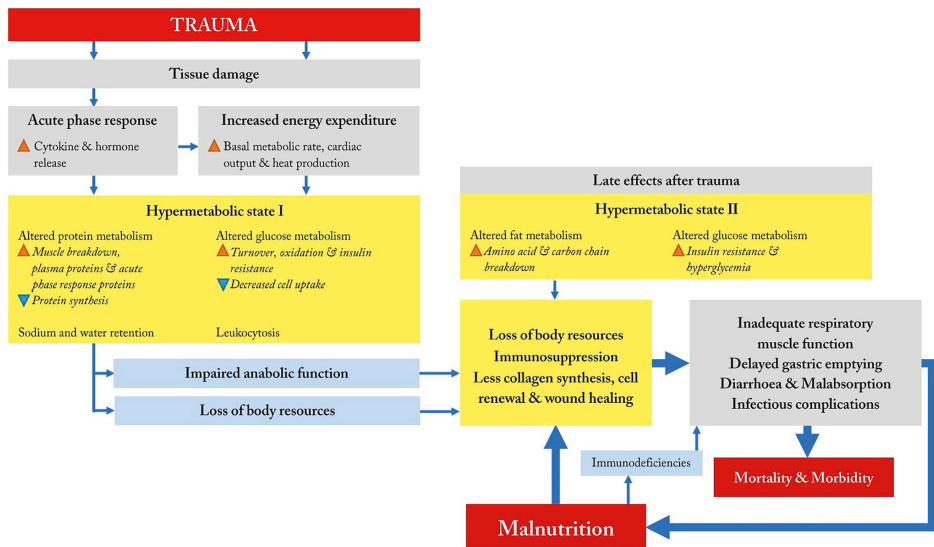


Figure 5: Model of effects of the hypermetabolic state and malnutrition in severely injured patients¹⁹

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**.

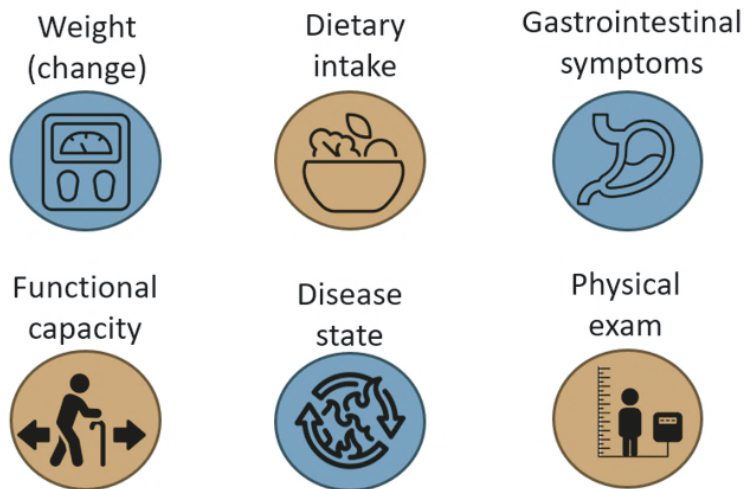


Figure 6: Items of the Subjective Global Assessment scale

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 infection 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.

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