Measurements of nutritional status and impact of malnutrition in polytrauma patients

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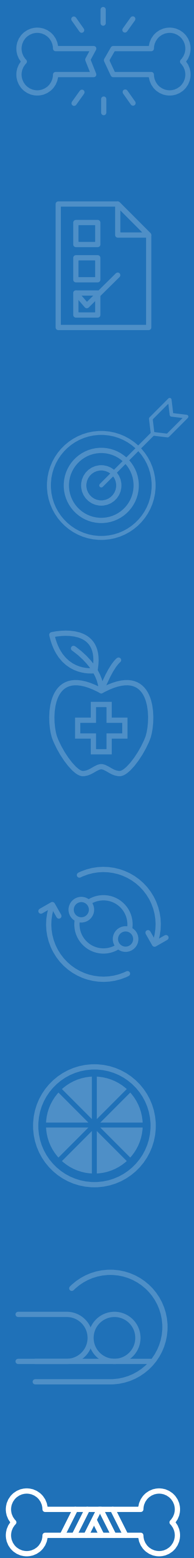

Chapter 8

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), supplemental 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), disease 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.

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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.

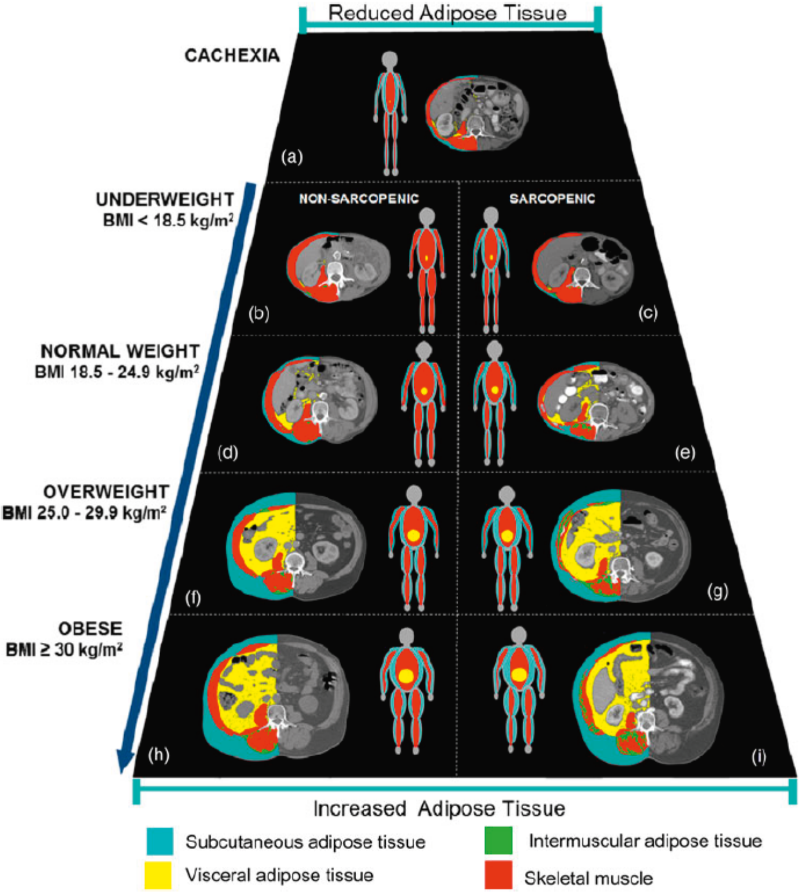

Figure 1: Trapezium model of body composition in cancer illustrating the variability in body composition in patients with identical BMI [27]

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.

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