The malnutrition in polytrauma patients (MaPP) study: Research protocol

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Abstract

Background: Polytrauma patients are at risk of considerable harm from malnutrition due to the metabolic response to trauma. However, there is little knowledge of (the risk of) malnutrition and its consequences in these patients. Recognition of sub-optimally nourished polytrauma patients and their nutritional needs is crucial to prevent complications and optimize their clinical outcomes. Aim: The primary objective is to investigate whether polytrauma patients admitted to the Intensive Care Unit (ICU) who have or develop malnutrition have a higher complication rate than patients who are and remain well nourished. Secondary objectives are to determine the prevalence of pre-existent and in-hospital acquired malnutrition in these patients, to assess the association between malnutrition and long-term outcomes, and to determine the association between serum biomarkers (albumin and pre-albumin) and malnutrition. Methods: This international observational prospective cohort study will be performed at three Level-1 trauma centers in the United States and two Level-1 centers in the Netherlands. Adult polytrauma patients (Injury Severity Score ≥ 16) admitted to the ICU of one of the participating centers directly from the Emergency Department are eligible for inclusion. Nutritional status and risk of malnutrition will be assessed using the Subjective Global Assessment (SGA) scale and Nutritional Risk in Critically Ill (NUTRIC) score, respectively. Nutritional intake, biomarkers and complications will be collected daily. Patients will be followed up to one year after discharge for long-term outcomes. Conclusions: This international prospective cohort study aims to gain more insight into the effect and consequences of malnutrition in polytrauma patients admitted to the ICU.

Keywords
Trauma, nutrition, multicenter, critical care, nutritional status, outcomes

Introduction

Malnutrition is widespread among hospitalized patients, with 20%–40% of patients affected by malnutrition, depending on the population, setting and criteria used. This percentage is estimated to be even higher in the critically ill population (Barker et al., 2011; Edington et al., 2000; Mogensen et al., 2015; Pirlich et al., 2006). Although there is still debate about the exact definition, malnutrition is currently defined as an imbalance in nutrition due to inadequate nutrient intake, or the inability to use or absorb ingested nutrients, resulting in an altered body composition (decreased fat-free mass and a decreased body cell mass) and diminished body function (e.g. muscular performance, organ function, body composition and functional capacity) (Hoffer, 2001; Jeejeebhoy, 2000; Lochs et al., 2006).

Malnutrition in hospitalized patients is a risk factor for increased morbidity and mortality (Correia and Waitzberg, 2003; Keel and Trentz, 2005; Kruijzena et al., 2016; ¹ Department of Surgery, Leiden University Medical Center, The Netherlands ² Ryder Trauma Center, DeWitt Daughtry Family Department of Surgery, University of Miami Miller School of Medicine, Florida, USA ³ Division of Trauma, Emergency Surgery, and Surgical Critical Care, Department of Surgery, Massachusetts General Hospital, Boston, Massachusetts, USA ⁴ Department of Intensive Care, Leiden University Medical Center Leiden, The Netherlands ⁵ Department of Clinical Epidemiology, Leiden University Medical Center Leiden, The Netherlands ⁶ Department of Surgery, Division of Trauma, Burn and Surgical Critical Care, Brigham and Women’s Hospital, Harvard Medical School, Boston, Massachusetts, USA ⁷ Department of General Surgery, Haaglanden Medical Center Westeinde, The Hague, The Netherlands ⁸ Contributed equally to this manuscript and therefore share first authorship.

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Mogensen et al., 2015). Patients with malnutrition suffer from decreased functional capabilities and impaired quality of life during their hospital stay (Norman et al., 2006). Because of its negative effect on patient recovery and outcome, malnutrition is also associated with increased hospital costs; the annual cost of disease-associated malnutrition in the United States was estimated to be $156.7 billion in 2014 (Snider et al., 2014).

In a Dutch study, roughly 6% of admitted trauma patients were at risk for malnutrition (Kruizenga et al., 2016). Severely injured patients (‘polytrauma patients’) are at even greater risk for harm from malnutrition due to a trauma-related inflammatory (‘stress’) response. Because of the stress response following traumatic injuries, polytrauma patients often endure an altered metabolic state in order to preserve energy for vital tissues (Cuesta and Singer, 2012; Dijkink et al., 2019; Preiser et al., 2014; Rogobete et al., 2017). This state is associated with catabolic processes, tissue breakdown, muscle wasting and anorexia (Cederholm et al., 2017). The more severe the injuries, the more severe the stress response. This renders polytrauma patients susceptible to complications such as infections, gastrointestinal dysfunction, acute kidney injury and multiple organ dysfunction syndrome (Keel and Trentz, 2005). However, there is little factual up-to-date knowledge about the consequences of malnutrition in the polytrauma patient population.

Currently, the diagnosis of malnutrition is often based on clinical questionnaires and measurement of body parameters (‘anthropomorphic measurements’); however, both methods have proven to be challenging in polytrauma patients. The use of anthropomorphic measurements is limited due to edema and/or history taking is not possible in sedated or mechanically ventilated patients. There is increasing interest in the use of biomarkers to assess nutrition status, but their predictive value in polytrauma patients remains questionable (Yeh et al., 2018).

The overall aim of this study is to obtain insight into the prevalence, incidence and impact of malnutrition in polytrauma patients in the Intensive Care Unit (ICU). The primary objective is to investigate whether polytrauma patients (Injury Severity Score (ISS) ≥16) admitted to the ICU, who have or develop malnutrition during hospital admission, have a higher complication rate than polytrauma patients who are and remain well nourished during hospital admission. Our primary hypothesis is that polytrauma patients who are and remain well nourished have fewer complications compared with patients who are malnourished and those who have a decline in nutritional status.

Secondary objectives are to determine the prevalence of patients with (a risk of) malnutrition on admission, and the incidence of patients that develop malnutrition on the ICU or during their stay in the hospital. Furthermore, we aim to assess whether calorie/protein deficiencies during ICU and hospital stay are associated with malnutrition and subsequently with worse clinical outcomes, and to assess the predictive value of biomarkers in the development of malnutrition during ICU admission and hospital admission. Also, we intend to determine the relationship between malnutrition and long-term outcomes, if any.

**Methods**

For this prospective study a template for clinical research provided by the Dutch Central Committee on Research Involving Human Subjects Committee (CCMO) was used. This template incorporates all the checkpoints provided by the SPIRIT guidelines (Chan et al., 2013).

**Design and setting**

This observational prospective cohort study will be performed at three Level-1 trauma centers in the United States (Massachusetts General Hospital and Brigham and Women’s Hospital in Boston, and Ryder Trauma Center in Miami) and two Level-1 trauma centers in the Netherlands (Leiden University Medical Center and Haaglanden Medical Center Westeinde, The Hague).

**Study Population**

**Inclusion criteria.** Adult (≥18 years) polytrauma patients (ISS ≥16), with a blunt trauma mechanism, admitted to the ICU of one of the enrolling Level-1 trauma centers within six hours after trauma and for a period longer than 48 hours, are eligible for inclusion. Patients will be excluded if they are transferred from another hospital to the participating center. Patients with burn wounds or penetrating traumatic injuries will be excluded.

**Sample size calculation.** In the study by Goiburu et al. (2006), 40% of the ICU trauma patient population was found to have malnutrition according to the Subjective Global Assessment (SGA) tool. The complication rate for the ‘malnutrition’ group was 71%, compared with 50% in the well-nourished group. To determine such a difference in complication rate in our study with alpha of 0.05 and power of 0.80 (beta = 0.20), 195 patients are needed (117 in the well-nourished group and 78 in the malnutrition group). Our goal is to include 140 patients in both countries, thereby meeting our threshold to answer our primary aim.

**Recruitment**

Trauma patients newly admitted to the ICU will be screened on the inclusion criteria upon admission by the investigators in the participating hospitals. In case of uncertainty about presence of polytrauma (ISS ≥16), the attending trauma surgeon will be consulted.

Eligible patients will be asked to provide written informed consent (IC) to participation in the study. If the patient is unable to do so (e.g. due to unconsciousness), a legal representative will be asked for IC. When a legal
representative has provided IC and the patient is able to give the IC him- or herself later during the study, the patient will be asked to confirm the consent. If the patient does not have a legal representative, data will be collected prospectively and the patient will be asked for IC when he or she is able to do so. If the patient does not want to participate in the study his or her data will be deleted from the electronic database. The patient and his/her legal representative can withdraw consent and leave the study at any time.

Study parameters

Demographic data and vital signs. The following study parameters will be acquired from the electronic patient files: age, sex, medical history, usual body weight (kg), height, actual body weight (ABW), body mass index (BMI), recent weight loss and the mechanism of injury on admission. Vital signs that are collected on admission are systolic blood pressure (SBP), heart rate and respiratory rate.

Classification of severity of disease

Abbreviated Injury Scale (AIS) and ISS. The AIS (update 2008) score is a consensus-derived scoring system that classifies injury severity on a six-point scale and according to the anatomical body regions (Gennarelli et al., 2008). The overall severity of (multiple) injuries is expressed by the ISS (Baker et al., 1982) which is calculated as the sum of squares of the highest AIS codes in the three most severely injured body regions. ISS is an internationally recognized scoring system in trauma patients and correlates with mortality and morbidity (Baker et al., 1982).

Acute Physiology and Chronic Health Evaluation II (APACHE II) score. The APACHE II score estimates ICU mortality based on the worst laboratory values and clinical parameters in the first 24 hours of ICU admission. The higher the APACHE II score the higher the mortality risk (Zimmerman et al., 1998). The APACHE II score has been validated in different patient populations including critically injured patients in whom it has shown accurate predictive value with a specificity and sensitivity of 94.6% and 79.2% respectively (Aslar et al., 2004; Rutledge et al., 1993). The APACHE II score will be calculated within 24 hours of ICU admission. The full APACHE II score is shown in Appendix I (Knaus et al., 1985).

Sequential Organ Failure Assessment (SOFA) score. The SOFA score is a tool used to track a patient’s clinical status during ICU admission. It is calculated based on the score for each of the six variables: respiratory, hepatic, coagulation, renal, cardiovascular and neurological. Both the mean SOFA score and the total maximum SOFA score while on the ICU are predictors of outcome (Vincent et al., 1996). The SOFA score has been validated for the critically ill injured patient and a higher score is associated with a longer length of stay (LOS) in the ICU (Antonelli et al., 1999). The SOFA score will be calculated daily during ICU admission (Appendix II) (Ferreira et al., 2001).

Nutritional status parameters

The SGA and patient-generated SGA (PG-SGA) will be used to detect and measure malnutrition. The SGA score is recommended as a tool for assessment of nutritional status in the critically ill (Benbow, 2017; Charney, 2008; Correia, 2017; Lochs et al., 2006; van Bokhorst-de van der Schueren et al., 2014). The SGA is validated for the acute hospital setting, surgical patients and patients admitted to the ICU requiring mechanical ventilation (Bector et al., 2016; Detsky et al., 1987; Sheean et al., 2010). The PG-SGA was originally developed to assess the nutritional status of oncology patients, however it has been validated for diverse groups of patients, including surgical patients, since then and it has been translated into many languages (Bauer et al., 2002; Ottery, 1996; Sealy et al., 2017).

The SGA and PG-SGA scores are based on weight change (past six months and two weeks), (inadequate) dietary intake change, gastrointestinal symptoms (less appetite, nausea, vomiting, diarrhea) and functional capacity (dysfunction, bedridden, difficulty with normal activities). Both scales include a physical examination on subcutaneous fat loss (eyes, triceps, biceps) and muscle wasting (e.g. clavicle, knee, shoulder and quadriceps) (Detsky et al., 1987).

The SGA and PG-SGA scale ranges from 1 to 7. 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 general consensus, in this study patients will be divided into two categories: well-nourished (A, scores 6–7) and malnutrition (B and C, scores 1–5). After inclusion in the study, the patient’s SGA scale will be scored within 24 hours after ICU admission by a trained dietician, nurse or member of the research team to determine pre-existing malnutrition. The SGA will be assessed every five days at the ICU and on the day of discharge from the ICU to detect malnutrition developed within the ICU. At the hospital ward the patient’s nutritional status will be assessed every seven days to detect malnutrition developed while in hospital. The patient’s nutritional status will be assessed using the PG-SGA on the day of discharge from hospital, and three, six, nine and 12 months after discharge. The full SGA questionnaire is displayed in Appendix III (Steiber et al., 2004). The PG-SGA can be found on the website of the PG-SGA/Pt-Global Platform (Platform, 2015).

Nutrition Risk in the Critically Ill (NUTRIC) score will be used to measure the risk of malnutrition on admission. NUTRIC is designed and recommended for the assessment of nutritional risk in critically ill adult patients (Heyland et al., 2011; Taylor et al., 2016). The NUTRIC score consists of six items collected from the electronic patient file: age, APACHE II score, number of comorbidities, SOFA score, days in hospital prior to ICU admission and interleukin-6 (IL-6). The APACHE II score (Knaus et al.,
1985) is an item of the NUTRIC score, and is computed based on the following parameters: age, temperature, acute renal failure, history of severe organ failure (or immune-compromised), mean arterial pressure, pH, heart rate, respiratory rate, creatinine, hematocrit, potassium, sodium and white blood cell count. The SOFA score (Vincent et al., 1996) is computed based on the parameters PaO₂, FiO₂, bilirubin, creatinine, platelet count, hypotension level and Glasgow Coma Scale (GCS). The NUTRIC scale ranges from 1 to 10, and a score ≥6 (if IL-6 is available) is regarded as high risk for malnutrition. The items of the NUTRIC score are all strongly correlated with mortality rate, mechanical ventilation duration and LOS (Heyland et al., 2011; Mendes et al., 2017). In this study, the NUTRIC score will be determined without IL-6. The NUTRIC scale without IL-6 available is reliable (≥5 indicates high risk) (Heyland et al., 2011).

After inclusion in the study, the patient’s NUTRIC score will be assessed within 24 hours after ICU admission by a dietitian trained to administer the questionnaire. The NUTRIC score questionnaire is displayed in Appendix IV (Heyland et al., 2011), the criteria for the SOFA score in Appendix II, and the criteria for the APACHE II score in Appendix I.

**Nutritional needs and support.** Energy expenditure is the amount of energy used for the basal metabolic processes: the thermic effect of food, for example, the energy required to digest and absorb food, and the energy used for physical activity. Indirect calorimetry, which is considered the clinical gold standard to measure resting energy expenditure (Oshima et al., 2017), is not available in all participating hospitals. Therefore, the Harris-Benedict equation will be used to measure resting energy expenditure, which is a well-validated alternative, although it is known that it overestimates resting energy expenditure (Harris and Benedict, 1918; Roza and Shizgal, 1984; Tignanelli et al., 2017). The following equation is used for women: 447,593 + (9,247 X weight) – (4,33 X age). The equation for men is: 88,362 + (13,397 X weight) + (4,799 X height) – (5,677 X age). The resting energy expenditure will be assessed daily during the patient’s hospital stay.

Nutritional support will be measured by a careful record of caloric and protein prescription and intake to be kept in the electronic patient files of the participant patients while in the ICU. In addition, the amount of propofol given is collected daily in the electronic patient file in the ICU. Propofol is a lipid-soluble emulsion often used in the ICU to provide sedation for patients on mechanical ventilation. This propofol lipid emulsion contains 1.1 kcal/ml. Although on average the total contribution of propofol to the total calories received will not be clinically significant, if the continuous infusion rate is above 20ml/h it has significant caloric value and can even contribute to overfeeding (DeChicco et al., 1995). Calorie and protein deficiency will be computed as the calories and proteins delivered minus the calories and proteins prescribed. Both deficiencies are calculated daily from admission to ICU to discharge from ICU. During hospital admission, the type of nutritional support will also be registered as enteral nutrition, parenteral nutrition or oral diet.

**Biomarkers of nutritional status.** Albumin is the most abundant plasma protein and is vital for maintaining the colloid oncotic pressure within the vasculature. In clinical practice albumin is often considered an important factor in the assessment of nutritional status (Smith, 2017). However, its long half-life of roughly 20 days, and the influence of systemic inflammation and acute phase proteins on albumin levels, may render the use of albumin as a nutritional status marker in polytrauma patients inaccurate (Parent et al., 2016; Yeh et al., 2018). Our goal is to assess the relationship between albumin and nutritional status in polytrauma patients, therefore it will be assessed daily in the ICU and weekly on the ward.

Pre-albumin (PAB) is more suitable as a malnutrition marker due to its shorter half-life of two days and its small total body pool (Bharadwaj et al., 2016; Raguso et al., 2003). Research suggests that PAB levels increase during the course of adequate nutritional support (Erstad et al., 1994; Nataloni et al., 1999; Raguso et al., 2003; Sergi et al., 2005; Tuten et al., 1985). In postoperative patients, PAB has been shown to be a better indicator of nutrition status than albumin (Erstad et al., 1994). Serial PAB measurements of the participant patients to evaluate the nutritional status, will be taken daily in the ICU and weekly on the ward (Raguso et al., 2003). An additional 5 ml blood sample will be collected during standard blood draws (to minimize risks and additional discomfort) in a separate blood collection container to measure PAB.

C-reactive protein (CRP) is a typical inflammation marker and is inversely related to PAB (Ingenbleek and Young, 1994; Raguso et al., 2003). In traumatic brain injury patients, a shorter hospital LOS and a more aggressive enteral nutrition therapy are both associated with low CRP (in proportion to albumin) (Taylor et al., 1999). This inflammation marker can be used to determine if the changes in malnutrition (albumin and PAB) are caused by a change in inflammation response or by a change in nutritional status (Bharadwaj et al., 2016). CRP will be measured daily in the ICU and weekly on the ward.

White blood cells (WBC) are a heterogeneous group of cells that play an important role in phagocytosis and immunity. The WBC count and differential count are used to assess the body’s reaction to certain conditions such as inflammation and infection, but also to traumatic injuries (Hershkovitz et al., 2015). In addition to CRP, the WBC and differential count can be used to assess if changes in PAB and albumin are due to changes in nutritional status or inflammatory status. This marker will be measured daily.

**Primary outcome.** Data will be collected prospectively from the electronic patient files and with questionnaires (see Table 1 and Table 2 for measurement moments). The
### Table 1. Overview of study measurements during stay in the ICU.

| Metric                        | <24 h from ICU admission | Daily in ICU | Every five days in ICU | ICU discharge day |
|-------------------------------|--------------------------|--------------|-------------------------|------------------|
| **Baseline characteristics**  | X                        | X            |                         |                  |
| *Vital signs on admission*    | X                        |              |                         |                  |
| SBP                           |                          |              |                         |                  |
| HR                            |                          |              |                         |                  |
| RR                            |                          |              |                         |                  |
| **Weight**                    |                          | X            |                         |                  |
| **NUTRIC score**              | X                        |              |                         |                  |
| APACHE II                     |                          |              |                         |                  |
| SOFA                          |                          |              |                         |                  |
| **APACHE II score**           |                          | X            |                         |                  |
| *A-a Gradient or PaO₂*        |                          |              |                         |                  |
| *Potassium*                   |                          |              |                         |                  |
| *Sodium*                      |                          |              |                         |                  |
| Creatinine                    |                          |              |                         |                  |
| Hematocrit                    |                          |              |                         |                  |
| WBC count                     |                          |              |                         |                  |
| GCS                           |                          |              |                         |                  |
| *Heart rate*                  |                          |              |                         |                  |
| *Mean arterial pressure*      |                          |              |                         |                  |
| Temperature                   |                          |              |                         |                  |
| Respiratory rate              |                          |              |                         |                  |
| **SOFA score**                |                          | X            | X                       | X                |
| *PaO₂*                        |                          |              |                         |                  |
| *FiO₂*                        |                          |              |                         |                  |
| Bilirubin                     |                          |              |                         |                  |
| Coagulation platelets         |                          |              |                         |                  |
| Creatinine                    |                          |              |                         |                  |
| GCS                           |                          |              |                         |                  |
| **SGA scale**                 | X                        | X            | X                       | X                |
| Weight (change)               |                          |              |                         |                  |
| Dietary intake                |                          |              |                         |                  |
| Gastrointestinal symptoms     |                          |              |                         |                  |
| Functional capacity           |                          |              |                         |                  |
| Comorbidities                 |                          |              |                         |                  |
| Subcutaneous fat loss         |                          |              |                         |                  |
| Muscle wasting                |                          |              |                         |                  |
| Edema                         |                          |              |                         |                  |
| **Biomarkers**                | X                        | X            |                         |                  |
| Albumin                       |                          |              |                         |                  |
| *PAB* (Protein for Albumin)   |                          |              |                         |                  |
| CRP                           |                          |              |                         |                  |
| WBC count                     |                          |              |                         |                  |
| Differential count            |                          |              |                         |                  |
| **Resting energy expenditure**| X                        | X            |                         |                  |
| Harris-Benedict calculation   |                          |              |                         |                  |
| **Energy intake and deficiency**| X                        | X            |                         |                  |
| Calories prescribed (kcal/kg) |                          |              |                         |                  |
| Calories received (kcal/kg)   |                          |              |                         |                  |
| Protein prescribed (g/kg)     |                          |              |                         |                  |
| Protein received (g/kg)       |                          |              |                         |                  |
| Dose propofol received (ml)   |                          |              |                         |                  |

(continued)
primary outcome is the complication rate, calculated as the proportion of patients with one or more of the following complications, which will be recorded from the electronic patient files during hospital stay and through surveys during one year after hospital discharge:

- Systemic complications, such as sepsis (i.e. life-threatening organ dysfunction induced by a dysregulated response to infection (Singer et al., 2016)), multiple organ failure (MOF) (i.e. potentially reversible and progressive physiologic dysfunction involving two or more organ systems, induced by various acute insults (Bone, 1992)), and acute respiratory distress syndrome (ARDS) (acute, diffuse, bilateral inflammatory lung injury, not fully explained by fluid overload or cardiac failure (Ranieri et al., 2012))
- Surgery-related complications, such as anastomotic leak, abscess, (re)bleeding and wound infection (i.e. deep, superficial, or organ/space surgical site infection within 30 days post-operation (Horan et al., 1992))
- Acute kidney injury for which continuous renal replacement therapy is needed (AKI-CRRT) (Alvarez et al., 2019)
- Pneumonia
- Urinary tract infection
- Venous thromboembolisms, such as deep venous thrombosis and pulmonary embolism
- Fracture-related complications, such as compartment syndrome, thromboembolic disease, fat embolism syndrome and reoperation (other than due to non-union or mal-union)
- In-hospital mortality

Secondary outcomes. Secondary outcome parameters include LOS in ICU until ready for discharge (i.e. judged clinically ready for discharge, but remains on the ward beyond the ready-for-ICU-discharge date), hospital LOS, ventilator-free days, surgery, reoperation rates due to reasons other than non-union or mal-union, discharge disposition, readmission rates, 30-day mortality
Statistical analyses are carried out using IBM SPSS Statistics. Before analysis, data will be checked for sphericity and homogeneity of variance. P-values <0.05 are considered statistically significant. Normally distributed variables will be displayed as mean (± standard deviation) and compared using independent sample t-test. Non-normally distributed variables are displayed as medians (± interquartile range) and compared with Wilcoxon-ranksum test. Categorical variables will be presented as percentage (%) and compared using Chi-squared test or Fisher’s exact test. The proportion of patients with pre-existing malnutrition (according to SGA score within 24 hours of ICU admission), patients that developed malnutrition (decline in SGA score from category well-nourished to malnutrition between admission to ICU and hospital discharge), and patients at risk for malnutrition (according to NUTRIC score ≥6 at ICU admission) will be calculated. A chi-square test will be used to compare complication rate (yes/no) and long-term outcomes between the group that has or develops malnutrition and the

Table 2. Overview of study measurements after discharge from ICU.

|                                | Daily after ICU discharge during hospital stay | Weekly after ICU discharge during hospital stay | Hospital discharge | Every three months after hospital discharge for up to one year after hospital admission (Survey) |
|--------------------------------|-----------------------------------------------|-----------------------------------------------|-------------------|------------------------------------------------------------------------------------------|
| SGA                           |                                                |                                               |                   |                                                                                          |
| Weight (change)               | X                                              |                                               |                   |                                                                                          |
| Dietary intake                |                                               |                                               |                   |                                                                                          |
| Gastrointestinal symptoms     |                                               |                                               |                   |                                                                                          |
| Functional capacity           |                                               |                                               |                   |                                                                                          |
| Comorbidities                 |                                               |                                               |                   |                                                                                          |
| Subcutaneous fat loss         |                                               |                                               |                   |                                                                                          |
| Muscle wasting                |                                               |                                               |                   |                                                                                          |
| Fluid status                  |                                               |                                               |                   |                                                                                          |
| PG-SGA                        |                                               |                                               |                   |                                                                                          |
| See SGA items                 |                                               |                                               |                   |                                                                                          |
| Weight                        | X                                              |                                               |                   |                                                                                          |
| Biomarkers                    |                                               |                                               |                   |                                                                                          |
| Albumin                       |                                               |                                               |                   |                                                                                          |
| PAB                           |                                               |                                               |                   |                                                                                          |
| CRP                           |                                               |                                               |                   |                                                                                          |
| WBC count                     |                                               |                                               |                   |                                                                                          |
| Differential count            |                                               |                                               |                   |                                                                                          |
| Resting energy expenditure    | X                                              |                                               |                   |                                                                                          |
| Harris-benedict calculation   |                                               |                                               |                   |                                                                                          |
| Protein/caloric deficiency    | X                                              |                                               |                   |                                                                                          |
| Calories prescribed (kcal/kg) |                                               |                                               |                   |                                                                                          |
| Calories received (kcal/kg)   |                                               |                                               |                   |                                                                                          |
| Protein prescribed (g/kg)     |                                               |                                               |                   |                                                                                          |
| Protein received (g/kg)       |                                               |                                               |                   |                                                                                          |
| Type nutritional support      |                                               |                                               |                   |                                                                                          |
| Parenteral nutrition          |                                               |                                               |                   |                                                                                          |
| Enteral nutrition             |                                               |                                               |                   |                                                                                          |
| Oral diet                     |                                               |                                               |                   |                                                                                          |
| Complications*                | X                                              |                                               |                   |                                                                                          |
| Other study parameters**      | X                                              |                                               |                   |                                                                                          |
| Functional outcome and health-related quality of life | X              |                                               |                   |                                                                                          |
| GOSE                          |                                               |                                               |                   |                                                                                          |
| EQ-5D                         |                                               |                                               |                   |                                                                                          |

* Parameters collected not part of standard clinical practice.
** ICU LOS, readiness for ICU discharger, hospital LOS, readiness for hospital discharge, ventilator-free days, surgery, reoperation rates due to other reasons than non-union or mal-union, discharge disposition, readmission rates, 30-day mortality.

a file cabinet. Data and blood samples will be stored for 15 years with permission of the patient.

Statistical analyses are carried out using IBM SPSS Statistics. Before analysis, data will be checked for sphericity and homogeneity of variance. P-values <0.05 are considered statistically significant. Normally distributed variables will be displayed as mean (± standard deviation) and compared using independent sample t-test. Non-normally distributed variables are displayed as medians (± interquartile range) and compared with Wilcoxon-ranksum test. Categorical variables will be presented as percentage (%) and compared using Chi-squared test or Fisher’s exact test. The proportion of patients with pre-existing malnutrition (according to SGA score within 24 hours of ICU admission), patients that developed malnutrition (decline in SGA score from category well-nourished to malnutrition between admission to ICU and hospital discharge), and patients at risk for malnutrition (according to NUTRIC score ≥6 at ICU admission) will be calculated. A chi-square test will be used to compare complication rate (yes/no) and long-term outcomes between the group that has or develops malnutrition and the
group that remains well nourished. Multivariate logistic regression analysis will be performed with complication rate (yes/no) as outcome, including potential confounders (e.g. age, gender, APACHE II scores and ISS). The difference between resting energy expenditure and calories and proteins prescribed by the clinicians will be calculated. An independent sample t-test is performed to test this difference between patients who develop malnutrition within the ICU or during their hospital stay and those who do not. The association between caloric and protein deficiencies (i.e. calories and proteins delivered minus the calories and proteins prescribed) and malnutrition developed in the ICU or in hospital is unknown. This will be explored graphically by visually inspecting the course of the deficiencies during ICU admission between patients with and without in-ICU developed malnutrition, and during hospital stay between patients with and without in-hospital developed malnutrition. Multiple regression analysis or mixed models including potential confounders (e.g. age, gender, APACHE II scores and ISS) will be used if there seems to be a trend over time. The added value of the NUTRIC score for the identification of developing malnutrition in the ICU will be evaluated by constructing a receiver operating characteristic (ROC) curve, and by calculating the area under the ROC curve (area under the curve (AUC)). The added value of the change in biomarkers over time (CRP, albumin, PAB and WBC count) to the SGA score will be assessed using a multivariable logistic regression model. ROC analysis will be performed and a c-statistic (AUC) will be calculated for the SGA model and the SGA with the change in biomarkers model. Lastly, sensitivity and specificity for different cut-off points in the change of biomarkers will be calculated.

Summary
Severely injured patients (polytrauma patients) are at risk of considerable harm from malnutrition, due to disease-related malnutrition with inflammation. Even though this is acknowledged, there is little knowledge of the risk of malnutrition and its consequences in the polytrauma patient population. The primary objective is to investigate whether polytrauma patients (ISS ≥16) admitted to the ICU who have or develop malnutrition have a higher complication rate than patients who are and remain well nourished. Secondary objectives of the study are to investigate the prevalence of both pre-existent and in-hospital developed malnutrition in polytrauma patients admitted to the ICU, to assess the association between malnutrition and complications, to determine the association between caloric and protein deficiencies and malnutrition and to assess the relationship between malnutrition and long-term outcomes. Lastly, we aim to assess the predictive value of biomarkers in malnutrition.

This international multicenter observational prospective cohort study will be performed at three Level-1 trauma centers in the United States and two Level-1 trauma centers in the Netherlands, including adult (age ≥18 years) polytrauma patients (ISS ≥16) admitted to the ICU within six hours after trauma for one year, from January 2018 to January 2019. Patients will be excluded if they are transferred from other hospitals to one of the participating trauma centers and if they stay on the ICU for less than 48 hours.

The results of this study may help to identify patients at risk and thus help to optimize care for the vulnerable polytrauma patient. Trials like these, with standardized data dictionaries and clinically relevant outcomes, are essential to further improve the nutritional status of polytrauma patients.

Author contributions
S. Dijkink and K. Meier contributed equally to this research protocol.

| Component of the research                                           | Author’s number |
|---------------------------------------------------------------------|-----------------|
| Substantial contribution to conception and design                   | 1,2,3,4,5,6,7,8,9 |
| Substantial contribution to acquisition of data                     | 1,2             |
| Substantial contribution to data analysis and interpretation of data| 1,2,3,4,5,6,7,8,9 |
| Drafting the article for intellectual content                      | 1,2             |
| Final approval of the version to be published                       | 1,2,3,4,5,6,7,8,9 |

Availability of data and materials
Anonymized data generated during the study will be made available by the corresponding author on motivated request.

Declaration of conflicting interests
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Ethical approval
The protocol was approved by the local and regional Institutional Review Boards. The responsible investigator will ensure that this study is conducted in agreement with both the Declaration of Helsinki and laws and regulations of the
country. Participants’ informed consent will be obtained according to the ICH Guidelines of Good Clinical Practice.

**List of abbreviations and relevant definitions**

- **AIS**: Abbreviated Injury Score
- **APACHE**: Acute Physiology and Chronic Health Evaluation score
- **ARDS**: Acute respiratory distress syndrome
- **BMI**: Body mass index
- **CCI**: Charlson Comorbidity Index
- **CRP**: C-reactive protein
- **GCS**: Glasgow Coma Scale
- **GOSE**: Extend Glasgow Outcome Scale
- **IC**: Informed consent
- **ICU**: Intensive Care Unit
- **ISS**: Injury Severity Score
- **LOS**: Length of stay
- **MOF**: Multiple organ failure
- **NUTRIC**: Nutrition Risk in the Critically Ill
- **PG-SGA**: Patient-Generated Subjective Global Assessment
- **RTS**: Revised Trauma Score
- **SBP**: Systolic blood pressure
- **SGA**: Subjective Global Assessment
- **SIRS**: Systemic inflammatory response syndrome
- **SOFA**: Sequential Organ Failure Assessment Score
- **WBC**: White blood cells

**Supplemental material**

Supplemental material for this article is available online.

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