



Nutritional risk in major abdominal surgery: NURIMAS Liver (DRKS00010923) – protocol of a prospective observational trial to evaluate the prognostic value of different nutritional scores in hepatic surgery



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ABSTRACT

Background: Malnutrition is commonly known as a risk factor in surgical procedures. The nutritional status seems particularly relevant to the clinical outcome of patients undergoing hepatic resection. Thus, identifying affected individuals and taking preventive therapeutic actions before surgery is an important task. However, there are only very few studies, that investigate which existing nutritional assessment score (NAS) is suited best to predict the postoperative outcome in liver surgery.

Objective: Nutritional Risk in Major Abdominal Surgery (NURIMAS) Liver is a prospective observational trial that analyses the predictive value of 12 different NAS for postoperative morbidity and mortality after liver resection.

Methods: After admission to the surgical department of the University Hospital in Heidelberg or the municipal hospital of Karlsruhe, all patients scheduled for elective liver resection will be screened for eligibility. Participants will fill in a questionnaire and undergo a physical examination in order to evaluate nutritional status according to Nutritional Risk Index, Nutritional Risk Screening Score, Subjective Global Assessment, Malnutrition Universal Screening Tool, Mini Nutritional Assessment, Short Nutritional Assessment Questionnaire, Imperial Nutritional Screening System, Imperial Nutritional Screening System II, Nutritional Risk Classification and the ESPEN malnutrition criteria. Postoperative morbidity and mortality will be tracked prospectively throughout the postoperative course. The association of malnutrition according to each score and occurrence of at least one major complication will be analysed using both chi-squared tests and a multivariable logistic regression analysis. Already established risk factors in liver surgery will be added as covariates.

Discussion: NURIMAS Liver is a bicentric, prospective observational trial. The aim of this study is to investigate the predictive value of clinical nutritional assessment scores on postoperative morbidity and mortality after hepatic resection. This is necessary, as only a validated identification of malnourished patients at high risk for postoperative complications, enables targeted preventive action.

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Abbreviations: NAS, nutritional assessment score; POD, postoperative day; PLF, postresectional liver failure.

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1. Introduction

Malnutrition is frequently observed among surgical patients. Between 16 and 67 per cent of surgical patients are malnourished before their operation [1–7]. The estimates vary depending on the population examined and the diagnostic instruments used. Patients scheduled for liver resection are a particularly affected group: in a study at the National Cancer Centre in Korea patients with cancerous diseases of the liver had the highest prevalence

of malnutrition with a rate of 86.6%. In the total sample of 8895 patients 61% were malnourished [8].

Several studies have identified poor nutritional status as an independent risk factor for postoperative morbidity and mortality in certain patient populations [6,9–11]. However, different instruments for diagnosing malnutrition often show varying and sometimes even contradicting results [12]. In a meta-analysis van Bokhorst-de van der Schueren et al. [12] compared construct/criterion validity and predictive value on clinical outcome of 32 NAS. The authors come to the conclusion that only a few scores are suited to assess nutritional status and accurate in predicting the clinical outcome. Nevertheless, they argue that the development of new scores would be redundant and not likely to achieve higher sensitivity and specificity. Instead, the authors call for trials that analyse different NAS in specific patient populations. This would allow for a better comparison of the diagnostic instruments and could further validate the scores with regard to their predictive value on the clinical outcome.

For patients undergoing hepatic resection, the nutritional status is particularly relevant [13,14]. One of the predictive variables for successful outcome after liver resection, is the remnant liver's ability to regenerate and hence its capacity to sustain metabolic, synthesizing and detoxifying functions [13,15]. Nutritional status before surgery is regarded as one of the key factors that influence this process [2,16]. Yet, there are only few studies that investigate which nutritional markers and screening instruments for malnutrition are suited to predict postoperative liver failure (PLF) and other complications after hepatic resection. Bo et al. investigated the predictive value of the Nutritional Risk Index (NRI) on postoperative survival time after liver resection in patients with primary liver cancer [2]. They showed that patients suffering from malnutrition according to the NRI (values ≤ 100) had a significantly shorter postoperative survival time compared to patients with NRI values > 100 . Huang et al. identified low preoperative prealbumin values as an independent risk factor for PLF after resection for primary liver cancer [17]. In a database analysis of 2313 hepatectomies, Aloia et al. identified low preoperative serum albumin levels as major risk factor for poor outcome [18]. They defined albumin levels as a marker for nutritional status.

The disparity of markers and definitions used in the mentioned studies mirrors the lack of validated instruments for identifying malnourished patients that have a higher risk for complications and need additional treatment. There are no studies that compare different nutritional screening tools in terms of their predictive value on postoperative complications in liver surgery.

This trial is part of a series of studies on nutritional risk in major abdominal surgery (NURIMAS), that aims at testing different NAS for their predictive value on postoperative complications in certain patient populations. Trials with patients undergoing upper gastrointestinal and colorectal surgery are planned for the future. Recently published results of the first study, "NURIMAS Pancreas", suggest that none of the tested nutritional scores adequately predicts the clinical outcome for patients undergoing pancreatic surgery [19].

2. Aim of the trial

With the NURIMAS Liver trial we want to investigate whether commonly used NAS are suited to predict postoperative complications after hepatic resection.

Validation of these tools is necessary, since a screening for malnutrition and possible preventive therapeutic actions are only beneficial, if those individuals can be identified, who have a higher operative risk due to their poor nutritional status. Based on a validated screening method in a certain population, measures like

peri-operative parenteral nutrition or immunonutrition could be taken effectively.

3. Methods

Study design, measures and statistical analyses of NURIMAS Liver are based on the structure of NURIMAS Pancreas (DRKS00006340) [20].

3.1. Study population

All patients that are scheduled for elective liver resections at the surgical department of the University Hospital Heidelberg and of the municipal hospital in Karlsruhe, will be included. The following criteria will be applied for eligibility (Table 1):

The study population comprises patients with all diseases that result in a hepatic resection. This includes malign oncologic diseases (HCC, CCC, metastasis), as well as benign ones, for example symptomatic cysts, echinococcosis or haemangiomas. Thus, collected data will allow analyses of a representative population, with patients at different ages and health status.

3.2. Diagnostic intervention (Nutritional assessment scores)

Before surgery, information for a total of 12 NAS will be gathered. 11 scores were chosen based on the systematic review by Van Bokhorst-de van der Schueren et al. [12]. In a meta-analysis, they looked at construct and predictive validity of 32 NAS. 11 scores were chosen, that seemed most suitable or promising in a surgical context. In addition, the malnutrition criteria defined by the European Society of clinical nutrition and metabolism (ESPEN) [21] is included. Table 2 gives an overview of the 12 NAS that will be analysed.

3.3. Outcome measures

The association between nutritional risk, as evaluated by the NAS, and complications after liver resection, will be analysed. Thus, postoperative morbidity and mortality is the primary endpoint in this study. Secondary endpoints are comprehensive complication index [32], length of stay in hospital, length of stay in intensive care unit, administration of postoperative enteral or parenteral nutrition and place of discharge (to home, rehabilitation or care facility).

3.4. Trial site and sample size calculation

The trial will be conducted at the department of general, visceral and transplantation surgery of the University Hospital Heidelberg and the department of general and visceral surgery of the municipal hospital of Karlsruhe.

The sample size calculation is based on nomograms for diagnostic studies [33]. Prevalence of malnutrition in liver surgery patients is known to be about 56% [34]. For the sample size a prevalence of 60% was assumed. With a specificity and sensitivity of 95% and a confidence interval of 0.05, according to the nomograms a total of 180 patients will be needed. Taken into account a drop-out of

Table 1
Eligibility criteria.

Inclusion criteria	Exclusion criteria
Age ≥ 18 and ≤ 90 years	Language problems
Elective liver resection	Inability to understand the trial
Written informed consent	

Table 2
Nutritional assessment scores.

Name	Classification for nutritional risk
Nutritional Risk Index [22]	Normal/Mild/Moderate/ Severe
Nutritional Risk Screening Score and revised version [23,24]	Low/Moderate/ High
Subjective Global Assessment [25]	No/Moderate/ Severe
Malnutrition Universal Screening Tool [26]	Low/Medium/ High
Mini Nutritional Assessment and revised version [27,28]	Normal/At risk/ Malnourished
Short Nutritional Assessment Questionnaire [29]	Low/Moderate/ Severe
Imperial Nutritional Screening System I [30]	Not at risk/ At risk
Imperial Nutritional Screening System II [30]	Green/Amber/ Red
Nutritional Risk Classification [31]	Low/ At risk
ESPEN malnutrition criteria [21]	Normal/ Malnourished

10% patients will be consecutively recruited until the study population will consist of 200 patients undergoing liver resections of any kind. Based on the departments' data (about 150 liver resections per year in Heidelberg and 80 in Karlsruhe), recruitment will be completed within 12 months after inclusion of the first patient.

3.5. Planned study conduct and trial rounds

All patients admitted for elective surgery at the department of general surgery at the University Hospital will be screened. If they are eligible, patients will be informed about background, purpose and procedures of the study on the day before their operation. They have to give a written informed consent in order to participate in the trial. Afterwards, participants will undergo a physical examination and fill in a questionnaire. The information gathered contains the data for the 12 NAS plus already established risk factors for postoperative complication in liver surgery [35–38].

After surgery, a series of rounds will be performed in pre-set time intervals to follow the clinical course. Table 3 shows the outline for the conduct.

Depending on the length of hospital stay, between one and three rounds will be conducted. A third round will be conducted on POD 30, if a patient stays at the hospital for more than 30 days, an additional round on the day of discharge will be implemented. On these occasions, complications will be recorded using the scheme as depicted in Table 4. Moreover, relevant data for all secondary endpoints will be collected during the rounds.

Table 3
Flowchart of the NURIMAS trial – course of examinations.

Rounds	0 Preoperative Screening	1 POD 3–7	2 POD 10–14	3 Discharge or POD 30
Eligibility	x			
Informed consent	x			
Baseline data	x			
Nutritional scores	x			
Laboratory analyses	x			
Assessment of surgical procedure		x	x	x
Assessment of complications/SAE		x	x	x
Secondary endpoints		x	x	x

3.6. Data management and monitoring

All required data will be recorded on a paper based case report form. After a participant's discharge, data will be entered in a password-protected and validated relational database (SQL Server 2008 Express). After finishing the last participant's entry, the database will be soft locked. 100% of the data relevant for evaluation of the primary endpoint will be monitored; randomly selected 20% of the remaining data will also be monitored. Finally, the database will be hard locked and made ready for statistical analyses.

3.7. Statistical analysis

Main interest of this study is to investigate the association between nutritional risk, as evaluated by the NAS, and complications after liver resection. The 12 tested NAS use different classifications for grading the severity of malnutrition, distinguishing between two, three or four degrees of nutritional risk, respectively. Thus, a simplification of the NAS-results is necessary in order to make the patient's scores comparable. Only patients in the highest nutritional risk group of each NAS (see Table 2) will be assigned the label "at risk for malnutrition"; patients in all other risk categories will be assigned to the "not at risk for malnutrition" group. Furthermore, patients will be separated into two groups for assessing the outcome variable (postoperative morbidity). That is, whether they had one or more major complications (i.e. Clavien-Dindo III–IV) or not. This allows for compilation of a contingency table for each of the 12 NAS (Fig. 1). Sensitivity, positive predictive value and c-index will be calculated. The association of the label "at risk for malnutrition" with the occurrence of at least one major complication will be given as odds ratio with 95% confidence interval for each of the NAS.

Two statistical test will be applied to assess the significance of the association. First, association between nutritional risk and major complications will be tested by using a chi-squared test at a level of significance of 5% (without Yate's-correction). Second, a multivariable logistic regression analysis will be performed (level of significance 5%). As covariates age [years] and operation time [minutes] will be included. Factors will be malignancy, gender, use of laparoscopy, intraoperative radiotherapy, resection of vessels (portal vein, hepatic vein or artery), inclusion in an interventional trial, ASA classification, upper gastrointestinal surgery in patient's history, preoperative serum albumin level < 35 mg/dl and liver surgery associated risks (intraoperative blood loss, number of segments resected [35–37]). For different resection types, subgroup analyses will be performed separately, as well as for the predictive value of all others than the highest risk category of the NAS.

Analyses of the secondary endpoints will be performed descriptively. Measures of the empirical distributions will be noted in tabular form, i.e. depending on the level of variables, means, standard variations, medians, 1st and 3rd quartiles, minima and maxima or

Table 4
Assessed postoperative complications.

Post-hepatectomy liver failure [39]
Bile leakage [40]
Post-hepatectomy haemorrhage [41]
Surgical Site Infection [42]
Other Infections and Sepsis [43]
Chylous ascites (Triglycerides in drainage) [44]
Serious adverse event [45]

	Major Complication			
	+	-		
“At risk“ for malnutrition	+	True positive (A)	False positive (B)	Positive predictive value $A/(A+B)$
	-	False negative (C)	True negative (D)	Odds ratio $A*D/B*C$
		Sensitivity $A/(A+C)$	Specificity $D/(B+D)$	C-index $((A*D)+(0.5*(A*B+C*D)))/(A+B+C+D)$

Fig. 1. Contingency table for calculation of primary study endpoint for the prognostic value of every nutritional assessment score [20].

absolute and relative frequencies will be given. Descriptive p-values of the corresponding statistical test and the associated 95% confidence intervals will be entered.

For all analyses, statistical computing software R will be used.

3.8. Methods for minimising bias

Minimising selection bias: All patients admitted to the trial site will be screened for eligibility. Everyone who meets inclusion criteria and gives an informed consent to the study, will participate in this single-arm trial.

Minimising performance and detection bias: No analyses of neither pre- nor postoperative data will be performed before ending the trial. Since data for the different NAS is collected in an aggregated form, it is not possible to see whether a patient is rated as being at risk for malnutrition by any of the scores, before entering the data into the database. Thus, the postoperative course will be followed unbiased, without knowing a patient's nutritional status as assessed by the NAS.

Minimising attrition bias: to minimise bias due to incomplete outcome data, statistical techniques like imputation will be employed [46]. Furthermore, the trial will be reported in accordance with the STARD statement [47].

Minimising reporting bias: The trial was prospectively registered in the German Clinical Trials Register (DRKS00010923). Selective reporting will be avoided by publishing this trial protocol with complete information about endpoints and outline of statistical analyses using the SPIRIT statement as guideline [48]. Report on association of survival in cancer patients and malnutrition is planned separately.

Minimising other bias: Any financial relationship or any conflict of interest that could inappropriately influence this project will be stated explicitly [49].

Confounding will be minimised by inclusion of covariates and factors in the statistical analysis of the primary endpoint as mentioned in the statistical analysis section.

4. Ethics, informed consent and data protection

The NURIMAS Liver trial is conducted in accordance with the Declaration of Helsinki in its actual version [50]. As provided in the professional code for physicians in Germany (§15 BOÄ), the trial protocol has been reviewed and approved by the Ethics Committee of the medical faculty of the University of Heidelberg (S-336/2016).

Before inclusion in the NURIMAS Liver study, patients will be informed both verbally and in writing about all relevant aspects of the trial, i.e. aims, methods, possible benefits, risks and discomfort the study may entail. The patients' free decision to participate will be documented by signature on the informed consent form. All patient related information comes within medical confidentiality and the German Federal Data Protection Act. Data transfer will be performed pseudonymised, third parties will not have any insight into original data.

5. Discussion

NURIMAS Liver is a bicentric, prospective observational trial. It is part of a series of studies, which aim at investigating whether commonly used NAS are suited to predict postoperative complications after major abdominal surgery. Only if patients who have a higher risk for complications due to their poor nutritional status can be detected properly, preventive therapeutic actions can be taken. Recently published results of the first study in the series, NURIMAS Pancreas, suggest that none of the tested nutritional scores adequately predicts the clinical outcome for patients undergoing pancreatic surgery. This calls into question the validity of those scores in other patient populations, in particular patients undergoing liver resections.

Conflict of interest

All authors declare to have no competing interests that could possibly compromise the outcome of the trial.

Funding

This is an investigator initiated study. For this study, no additional funding source is available. However, the resources and the facilities available at the University of Heidelberg are availed for conducting the trial.

Ethical Approval

The trial protocol has been reviewed and approved by the Ethics Committee of the medical faculty of the University of Heidelberg (S-336/2016).

Consent

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Author contribution

Pascal Probst, Juri Fuchs, Philipp Knebel and Katrin Hoffmann developed the study concept and wrote the manuscript. Michael R. Schoen, Georgios Polychronidis, Tobias Forster, Arianeb Mehrabi and Alexis Ulrich helped to develop the study concept and revised the manuscript. All authors read and approved the final manuscript. Furthermore, all authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Research Studies

Deutsches Register Klinischer Studien (www.germanctr.de): DRKS00010923.

Guarantor

Pascal Probst.

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