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Body composition and muscle strength at the end of ICU stay are associated with 1-year mortality, a prospective multicenter observational study

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Abstract

Background & Aims: After a prolonged intensive care unit (ICU) stay patients experience increased mortality and morbidity. The primary aim of this study was to assess the prognostic value of nutritional status, body mass composition and muscle strength, as assessed by body mass index (BMI), bioelectrical impedance analysis (BIA), handgrip (HG) test, and that of the biological features to predict one-year survival at the end of a prolonged ICU stay.

Methods: This was a multicenter prospective observational study. Survivor patients older than 18 years with ICU length of stay > 72 h were eligible for inclusion. BIA and HG were performed at the end of the ICU stay. Malnutrition was defined by BMI and fat-free mass index (FFMI). The primary endpoint was one-year mortality. Multivariable logistic regression was performed to determine parameters associated with mortality.

Results: 572 patients were included with a median age of 63 years [53.5;71.1], BMI of 26.6 kg/m² [22.8;31.3], SAPS II score of 43[31;58], and ICU length of stay of 9 days [6;15]. Malnutrition was observed in 142 (24.9%) patients. During the 1-year follow-up after discharge, 96 (18.5%) patients died. After adjustment, a low HG test score (aOR=1.44 [1.11;1.89], $p=0.01$) was associated with 1-year mortality. Patients with low HG score, malnutrition, and Albuminemia < 30 g/L had a one-year death rate of 41.4%. Conversely, patients with none of these parameters had a 1-year death rate of 4.1%.

Conclusion: BIA to assess FFMI, HG and albuminemia at the end of ICU stay could be used to predict 1-year mortality. Their ability to identify patients eligible for a structured recovery program could be studied.

Keywords: hand grip test, bioelectrical impedance analysis, long-term outcomes, malnutrition, ICU-acquired weakness.

Introduction

Increasing numbers of patients are surviving critical illness but their death rate is higher than in the general population, reaching almost 25% at one year [1–3]. At the end of a prolonged ICU stay, despite the different nutritional strategies adopted [4], malnutrition and ICU-acquired weakness (ICU-AW) [5], characterized by critical illness, neuropathy and/or myopathy, and muscle atrophy, are often observed [4]. For instance, it has been reported that in patients suffering from acute respiratory distress syndrome (ARDS), the incidence of ICU-AW on awakening is 60 % [6]. Possible pre-existing malnutrition, insufficient nutritional intake, and hypercatabolism due to aggression are the main causes of malnutrition in ICU, and could explain part of the muscle mass loss and associated ICU-AW [7]. Malnutrition and weakness can persist after ICU discharge and be associated with long-term outcomes including deterioration of functional outcomes [1,8,9] such as quality of life impairment [10] and loss of social status [11]. Some studies have shown that weakness independently contributed to 1-year mortality [12] while others have reported an association between ICU-AW and the post-intensive care syndrome (PICS) [13], including long-term functional outcomes. However, these studies focused mainly on weight loss to define malnutrition, and almost none made an overall assessment of malnutrition and functional status at ICU discharge to characterize long-term outcomes of ICU survivors. In addition, most of the studies involved only specific subgroups of ICU patients, such as septic patients or patients with ARDS [14–16] while others dealt only with the effect of muscle mass loss during the early stage of critical illness on mortality but not on muscle mass at ICU discharge [17]. Nutritional status can be assessed by the usual recommended parameters such as body mass index (BMI), which has been approved as a nutritional risk screening tool, but also by serum albumin and transthyretin levels. Unfortunately, during ICU stay these indicators are influenced by fluid overload and inflammation, which limits their prognostic values at

discharge [18]. The Global Leadership Initiative on Malnutrition (GLIM) consensus group for malnutrition assessment, and the European Society for Clinical Nutrition and Metabolism (ESPEN) proposed to include muscle mass as a key phenotypic criterion in the definition of malnutrition [4,19]. Bioelectrical impedance analysis (BIA) [20,21] could therefore be helpful. BIA assesses fat-free mass, cell membrane integrity, body cell mass, phase angle and extracellular water (ECW)/ total body water (TBW), an indicator of fluid overload. When these parameters were assessed at ICU admission most [22] were associated with worse outcomes [23]. However, they were never used to assess body composition at the end of ICU stay to predict long-term outcomes. Muscle strength, which is associated with malnutrition and poor outcomes, can be assessed in the ICU by the handgrip (HG) test [24].

In this context, the main aim of our study was to assess the prognostic value of nutritional status, body composition and muscle strength at the end of a prolonged ICU stay for 1-year survival. The secondary objective was to assess their relationships with functional outcomes.

Material & Methods

This project was a French multicenter prospective observational study (ClinicalTrial.gov; n=NCT01750671) involving the intensive care departments of three tertiary academic hospitals (Clermont-Ferrand, Lyon Sud and Strasbourg) with a total number of 100 beds.

The research protocol was approved by the Clermont Ferrand University Hospital Ethics Committee (CPP Sud Est I, 04/16/2012 [ref:2011-35]), and then by the ethics committee of each participating hospital.

Patients

All patients admitted to the ICU were eligible. The enrollment period ran from April 2013 to June 2016. Inclusion criteria were age >18 years, length of stay >72 h, organ failure requiring at least one organ support, affiliation to health insurance and written informed consent from

the patient. Exclusion criteria were limitation of care, pregnancy, and being under supervision or legal guardianship.

Study endpoints

The primary endpoint was 1-year mortality, i.e. during the year following discharge from the ICU. This information was collected via medical records and phone calls to the relevant hospital department or the patient's general physician.

The secondary endpoints were functional outcomes assessed, at one year, by: 1) the post-traumatic stress symptoms checklist-10 (PTSS-10) and the hospital anxiety and depression scale (HAD) [27, 28] for symptoms of post-traumatic stress disorder (PTSD), anxiety and depression at assessments; 2) the medical outcomes study short form 36 (SF-36) for quality of life [27]; 3) the Karnofsky Performance Scale Index [28] for the level of activity and autonomy (see supplementary file); 4) the HG test for muscle strength; and 5) BMI, laboratory features and body composition using BIA for the evolution of nutritional status (Fig. S1).

The number of hospital stays following ICU discharge was also recorded.

Data collection

Several variables were collected.

1. *at baseline*, i.e. on ICU admission, general characteristics such as age, gender, comorbidities, Karnofsky performance score and two ICU-validated severity scores, the Simplified Acute Physiology Score II (SAPS II) and sequential organ failure assessment (SOFA) score
2. *during the ICU stay*, the number of days under organ supports, i.e. invasive or non-invasive mechanical ventilation, vasopressors, renal replacement therapy, and administration of sedatives, neuromuscular blocking agents, corticosteroids or chemotherapy, and enteral or parenteral feeding

3. *at inclusion, i.e. on ICU discharge*, data on nutritional assessment, body composition and muscle strength.

Nutritional assessment was based on BMI(kg/m²), biological features, including serum albumin, transthyretin, orosomucoid and C reactive protein, and body composition using BIA. Body composition was measured with a portable BIA device (InBody S10®, InBody Corp., Cerritos, California, USA) at an alternating current of 50-kHz [29,30]. The procedure is described in the supplementary file. Resistance, reactance and a phase angle (PhA) were determined. Segmental measurements were used to calculate TBW and ECW. Thereafter, the software used validated methods to calculate fat mass (FM) and fat-free mass (FFM).

Appendicular skeletal muscle mass (aSM) was estimated by Kyle's equation [29]. Fat-free mass index (FFMI) and appendicular skeletal muscle mass index (aSMi) were then calculated by dividing FFM and aSM by height squared (m²). The ECW/TBW ratio was used to characterize fluid overload.

Functional assessment was made with the HG test, which was performed three times on each hand [31]. The best performance was considered for analysis. If patients were unable to carry out the test performance was set at 0 kg.

Definitions

Malnutrition was defined according to ESPEN recommendations [32] and GLIM criteria [4] with BMI cut-off values set at < 20 kg/m² for subjects < 70 years of age, and < 22 kg/m² for subjects aged 70 years and older, and/or FFMI at < 15 and < 17 kg/m² in women and men, respectively. Low muscle mass was characterized by aSMI < 5.75(F) or < 8.50(M) kg/m²[33]. The performance of laboratory markers of malnutrition was assessed using the cut-offs for albuminemia, transthyretin, orosomucoid and C reactive protein of 30 g/L, 0.2 mg/L, 1.8 mg/L and 40 mg/L respectively.

Because most of the cut-offs suggested in the medical scientific literature for BIA and HG parameters have not been assessed in critically ill populations, we evaluated the performance of BIA and HG parameters after dichotomization, according to their median and taking into account patient gender.

Statistical analysis

Sample size calculation

The calculation of sample size was based on the estimated prevalence of malnutrition and 1-year mortality, the recruitment capacity of each center and the estimation of statistical power. On the basis of reports in the medical scientific literature, we anticipated a death rate at one year of 25% and expected that malnutrition was related to an increased risk of death of 10% one year after ICU discharge (30% in case of malnutrition and 20% in case of non-malnutrition).

We used PASS 2008 software (NCSS, LLC. Kaysville, Utah, USA) to estimate the number of patients needed to be included. Estimating the proportion of patients with malnutrition at ICU discharge to be 40% and anticipating a 10% risk of loss to follow-up in group and given bilateral α of 5% and a power of 80%, 249 patients needed to be included in the group with malnutrition and 371 in the non-malnutrition group. As a precaution, given the uncertainty regarding the percentage, we planned to recruit 680 patients, including 280 with malnutrition at ICU discharge.

Statistical analysis

Continuous data are presented as median with interquartile range (IQR) or range and were compared by the Wilcoxon rank sum test. Categorical data were compared by Chi 2 or Fisher's test as appropriate. ROC curves were used to analyze the association of each variable with 1-year mortality. ROC curves were analyzed with their AUCs and 95 % confidence intervals (CIs).

Because parameters obtained from BIA and the HG test depend on the age and gender of patients, they were adjusted for these two dimensions.

Multivariable logistic regression adjusted for the factors with a p -value of < 0.2 in the univariate analysis were performed with a backward stepwise elimination process eliminating all variables that did not contribute (p -value ≥ 0.05). For continuous variables, the adjusted odds ratio was expressed for a 1-point increase. From this model we computed a risk-score of 1-year mortality. After exploration of the nature of the missing data, multiple imputations were performed. A two-sided p -value of < 0.05 was statistically significant. To assess the robustness of our finding, we performed internal validation using a bootstrapping procedure, which was done by taking a large number of samples of the original one finding. This technique provides nearly unbiased estimates of the confidence intervals (CI) of the odds ratio (OR) of the independent covariates.

Statistical analysis was performed with SAS version 9.4(SAS Institute Inc., Cary, North Carolina, USA) and R software (version 3.6.3).

Results

Main characteristics of the patients (Table 1)

Overall, 572 patients were included, of whom 193 (33.7%) were female (Fig. S2). Their median age was 63 years [53.5;71.1] and median BMI 26.6 kg/m² [22.8;31.3]. The main comorbidities were diabetes (151 [26.8%]), cancer (106 [18.8%]) and COPD (100 [17.7%]). More than half of the patients had a Karnofsky Performance Scale Index of less than 50% (231/405 [57%]).

The median SAPS II and SOFA scores were respectively 43 [31;58] and 6 [4;9]. The main treatments related to muscle loss during ICU stay were steroids (188 [33%]) and neuromuscular blocking agents (151 [26.5%]). The main organ supports during ICU stay were vasopressors (363 [63.7%]), invasive mechanical ventilation (428 [75.1%]) and renal replacement therapy (98 [17.3%]). The median ICU length of stay was 9 days [6;15].

Nutritional status and muscle strength at the end of ICU stay

The median albuminemia, transthyretin, orosomuroid and C-reactive protein were 27.4 g/L [23.6 ; 31.7], 0.2 mg/L [0.1 ; 0.3], 1.8 mg/L [1.4 ; 2.1] and 44.1 mg/L [17.2 ; 86.2]. The main results of the HG tests and BIA according to patient gender are given in table S1. Malnutrition was observed in 142 (24.9%) patients. In male patients, the HG test value, FFMi and PhA were respectively 27 kg [18;36], 20.3 [17.9;22.7], and 5.3 [4.2;6.6], and in females 14 kg [8;20], 16.6 [14.7;18.9], and 4.9 [4;6.5]. Of note, 19 patients were unable to perform handgrip and were attributed a 0 kg score, 5 had a maximum of 1 kg, 12 a maximum of 2 kg, 1 of 3 kg, and 8 of 4 kg: all the other patients had a hand grip test strength of at least 5 kg with both their left and right hands.

Association between parameters assessing nutritional status, body composition and physical strength and mortality at one year.

At one year, 96 (18.5%) patients had died. Comparisons of vital status at one year are given in table 1. After adjustment for age and sex, a low HG test score (aOR=1.54 [1.19;2.00], $p<0.01$) and malnutrition (OR=1.37[1.07;1.76], $p=0.01$) were associated with an increased risk of death. The HG test was the most reliable means to predict death at one year (AUC=0.7[0.64;0.75])(Table 2).

After uni-and multivariate analyses, age, chronic kidney disease, cancer, Karnofsky Performance Scale Index, low HG test score and malnutrition were the variables associated with one-year outcome (model 1, Tables 2-S2-S3). Prediction of one-year mortality was improved using these variables (AUC=0.74[0.69;0.8]). Prediction of death using only nutritional and functional assessment at the end of the ICU stay (Albuminemia, HG test, malnutrition, and age) could also predict death fairly accurately at one year (AUC=0.71[0.66;0.76])(Model 2). Models 1 and 2 were better able to predict death at one year than the HG test and malnutrition alone (Figure 1).

All these results were confirmed using bootstrap sensitivity analysis (Table S4).

Using model 2, we built a score based on age, HG test, albuminemia and malnutrition called the NUtritional and Functional status at ICU Discharge Score (NUFID score, Figure 2). Death rates, according to a NUFID score of 0-1, >1, and < 4 or ≥ 4 were, respectively, < 5%, between 15 and 20%, and $\geq 40\%$.

Association between parameters assessing nutritional status, body composition and physical strength and function outcomes at one year

Characteristics depending on NUFID score are presented in Tables S5 and S6. Among the 133 patients who underwent functional assessment at one year, malnutrition, a low HG test score and a low SF-36 PCS score were more prevalent in those with a score ≥ 3 . All the patients had similar proportions of PTSD and HADS A and D alteration. Finally, classification of the

patients according to their albuminemia, HG test, malnutrition and associated characteristics are given in Figure 3 and Tables S7 and S8.

Patients with a low HG test score, malnutrition and albuminemia < 30 g/L had a 1-year death rate of 41.4%. In contrast, patients without any of these parameters had a 1-year death rate of 4.1% (Table S7).

Mental disorders at one year did not seem to be affected by functional status at the end of the ICU stay (Table S8).

Discussion

Main findings

At the end of the ICU stay, 25% of the patients in our cohort had malnutrition, and at one year their death rate was 18.5%. Among the parameters of functional and nutritional status at the end of ICU stay, only malnutrition and a low HG test score were independently associated with 1-year mortality. Patients with hypoalbuminemia, a low HG test score, and malnutrition had 1-year mortality of 41.4% as against 4.1% in patients with none of those parameters. Patients with a NUFID score ≥ 4 had a death rate of 45.9% or a worse functional assessment at one year. The NUFID score was not useful to predict mental disorders at one year.

These results warrant several comments.

First, the prevalence of malnutrition at the end of ICU stay was 25% in our cohort. Ours is one of the first studies to report such a result since malnutrition is generally assessed at ICU admission [38, 39]. Most previous studies reported weight loss at the end of ICU stay. For instance, in historical studies, Herridge et al. [15] observed that patients with ARDS lost around 18% of their body weight at the end of ICU stay, and Kvåle et al. that 40% of patients lost more than 10 kg during ICU stay [13, 40]. Muscle loss has also been documented during ICU stay and has been found in up to one-third of ICU survivors [6], sometimes reaching up to 1.5 to 3 kg per week [41, 42]. Other studies have focused on ICU-AW [12,39], whose

reported incidence varies from 25 to 65% depending on the patient population studied and the timing of the evaluation. For instance, ICU-AW was found in about 25% of patients requiring prolonged mechanical ventilation [43, 44].

Second, in the present study, malnutrition and a low HG test were the most reliable parameters to predict long-term mortality. The two parameters are complementary, with the first directly measuring muscle mass, and the second measuring muscle strength.

As a general rule, malnutrition is assessed at ICU admission, and is usually associated with unfavorable outcomes including reduction in overall muscle strength, longer mechanical ventilation duration, increased risk of nosocomial infections, longer ICU and hospital length of stay, and increased risk of death [41]. For instance, it was reported that critically ill patients with a high mNUTRIC score admitted to a general ICU [34] or for COVID-19 pneumonia were more at risk of 90-day mortality [42].

Interestingly, other studies found that BMI with different parameters predicted worse outcomes. For instance, it was reported that low skeletal muscle area, as assessed by CT scan at ICU admission, was independently associated with higher mortality but not BMI in a cohort of 240 ventilated patients [17]. More recently, Tsai et al. assessed the combination of a mNUTRIC score and BMI to predict 90-day mortality and showed that prognosis was modified by a mNUTRIC score (+/-5) in underweight and overweight patients but not in those of normal weight [43].

Surprisingly, PhA in our study was not associated with long-term outcome [21]. For instance, low PhA at ICU admission in a general cohort of critically ill patients was associated with an increased risk of 90-day mortality [22], and likewise in a more recent study of critically ill COVID-19 patients [21, 47–49]. Our result could be due to a lack of power, or to the timing of the measurement since PhA was measured only in survivors and at the end of the ICU stay. Our patients might have had less overhydration or dehydration and less cell damage, which

would have made the observed differences less significant. In addition, malnutrition in our study, and therefore FFMi, were more often associated with long-term mortality. The timing of measurements could also have played a role. In our study, BIA was performed at the end of the ICU stay. Low muscle mass and thus differences in FFMi could have been more pronounced than in previous studies assessing the performance of BIA parameters measured at ICU admission or on day 5.

Third, the HG test was useful to assess overall muscle strength and thus to detect ICU-AW, which is already known to be associated with hospital mortality [47]. Indeed, the notion that ICU-AW could have an impact on long-term outcome is not new and has been debated before. For instance, Hermans et al. reported an increased risk of 1-year mortality for patients with an ICU-AW as defined by a Medical Research Council (MRC) sum score of less than 48 [40], but also for long ICU stay patients with muscle weakness defined by electrophysiology [48]. Muscle strength per se and not only low muscle mass seemed therefore to be more predictive of 1-year mortality.

Fourth, hypoalbuminemia was predictive of 1-year mortality, but not C reactive protein, nor transthyretin. However, in our cohort, those three biomarkers were correlated (table S2), and transthyretin and C reactive protein levels were significantly different between survivors and no survivors (table 1), but low C reactive protein and low transthyretin levels, defined by usual cut-offs were not associated with 1-year mortality in univariate analyses (table 2).

Briefly, albumin and isolated transthyretin levels are not good markers of nutritional status. Albumin is a marker of severity of the condition and reflects the inflammatory status and is usually correlated with C reactive protein [51]. Because turnover of albumin is low, low albumin in critically ill patients, is mainly caused by redistribution to the extracellular space from the intravascular compartment or losses due to major bleeding. Transthyretin in ICU is most of all used to assess the response to nutrition therapy[52]. In addition, lower

hypoalbuminemia was recently reported to be associated with hospital mortality after hospitalization for acute heart failure in an internal medicine department[49]. Similarly, hypoalbuminemia was also associated with long term mortality of chronic dialyzed patients admitted to the ICU[50].

In our study, the best predictor of 1-year mortality came from the combination of malnutrition, hypoalbuminemia and the HG test. We are the first to propose such a score.

Fifth, among the survivors at one year who underwent functional and mental assessment those who had malnutrition, a low HG test score, and hypoalbuminemia tended also to have worse functional outcomes at one year. This result reinforces previous findings which showed that quality of life including physical functioning is severely affected even months after hospital discharge in patients with ICU-AW [6, 14, 52].

Against this background, the NUFID score and therefore the assessment of malnutrition, albuminemia, and muscle strength by the HG test could be proposed to identify patients who would benefit the most from a structured recovery program including personalized nutritional therapy and rehabilitation [39]. This new tool could be used in addition to other screening tools such as the CPAX score [54], and the PICUPS score [55], which are measures already used or in development of weakness and specific rehabilitation needs assessed during ICU stay or at ICU discharge.

Surprisingly, ICU LOS was not associated with 1-year mortality. This could be explained first because we only took into account ICU survivors and only the most severe patients admitted to the ICU. It would be interesting, however, to test our results in patients with persistent critical illness, i.e. those with an ICU LOS of more than 10 days[56].

Finally, our parameters were not useful to predict mental disorders, which is not surprising since the usual predictive factors are sepsis or direct central nervous system injury with delirium during ICU stay [57].

The main strengths of this study are the large size of its patient population and its multicenter nature with prospective data collection in a good quality database allowing an accurate assessment of nutritional and functional status at the end of ICU stay.

The main limitations are related to missing data, mostly for nutritional and functional assessment at one year. A part of biological features such as C reactive protein and transthyretin were also missing, that could have attenuated their effects on outcomes and therefore might have prevented the selection of these covariates into the final models. Also, our main objective (mortality at one year) is questionable, and functional assessment could have been more appropriate. However, the study was designed initially for mortality and once again, because of missing data, the association with long-term functional outcomes could not be properly explored. Hence, no definitive causal conclusions should be drawn from our results. BIA data were not adjusted for fluid overload, which is difficult to estimate in the ICU. The patients being assessed were at the end of their ICU stay and so fluid overload may have been minimized by depletion. We however acknowledge that FFMi could have been overestimated in some patients. Other parameters could have been used to assess body composition at the end of the ICU stay, such as measurement of skeletal muscle area and FM by CT scan, or measurement of quadriceps muscle by ultrasonography [58,59]. We could also have assessed ICU AW with the Medical Research Council (MRC) sum score and compare its performance with that of the NUFID score. The GLIM malnutrition criteria could also have been tested [58, 59] but taking into consideration only the phenotypic criterion based exclusively on BMI and FFMi. Weight loss could not be considered because it was not prospectively recorded at ICU admission. For the same reason, we did not use the Nutrition Risk Screening Score, which is more commonly used in current practice for ICU patients than the GLIM[62,63]. The patients recruited, by the fact of ICU admission, possessed all the etiologic criteria. Of note, recently, experts proposed a panel of outcomes, including survival,

that could be measured in clinical trials of nutritional and metabolic interventions in critical illness, and also function outcomes using the activities of daily living, or measurements of physical function by SF-36, nutritional status based on GLIM criteria , or muscle function using the hand grip test[64]. Such criteria should be considered for ongoing studies dealing with long term functional outcomes.

We also acknowledge that if certain data, such as calory and protein intake and physical activity during ICU stay, had been recorded we would have had a better interpretation of our results. However, we wanted to focus solely on nutritional and functional status at the end of ICU stay. Part of the functional status observed at the end of ICU stay could have been related to pre-existing weakness. For that purpose, to assess the association with long-term mortality, we adjusted on the Karnofsky performance scale in one of our analyses. This score could have been replaced by the frailty score, but unfortunately was not collected prospectively during the study. We did not use reference methods to assess ICU AW but chose cut-off values from our cohort, as most of the cut-offs proposed in the literature were obtained from healthy patients or non-ICU subgroups of patients. This study was devised and performed almost 10 years ago. Since then, new papers have been published on nutritional management including studies on calorie and protein restrictions (permissive or trophic feeding) [65–69] that have changed the concept of malnutrition in ICU. However, the largest studies evidenced no effect of macronutrient intake in the ICU on long-term outcomes, including quality of life [59, 63]. Then, the 1-year mortality rate was 18.5%, and only 25% of our survivors had malnutrition. Both of these results could be considered to be low. The external validity of our results could be discussed in light of these findings.

Conclusion

After a prolonged ICU stay, malnutrition and low muscle strength are independently associated with 1-year mortality. BIA, HG tests and a nutritional biological assessment to

calculate the NUFID score before ICU discharge could be used to identify patients who might benefit the most from a structured recovery program with personalized nutritional therapy and rehabilitation. These findings also suggest that weak patients should be closely monitored after ICU and hospital discharge to prevent complications that lead to late death.

List of abbreviations

aOR: adjusted odds ratio
ARDS: acute respiratory distress syndrome
aSM: appendicular skeletal muscle mass
AUC: area under the curve
BIA: bioelectrical impedance analysis
BMI: body mass index
CI: confidence intervals
CPP: comité protection de la personne
ECM: extracellular water
ESPEN: European society of parenteral and enteral nutrition
F: female
FFM(I): fat-free mass (index)
FM: fat mass
GLIM: global consensus group for malnutrition
h: hours
HAD: hospital and depression scale
HG: handgrip test
ICU: intensive care unit
ICU-AW: ICU acquired weakness
IQR: interquartile range
M: male
NUFID: nutritional and functional status at ICU discharge
p: p-value
PhA: phase angle
PICS: post-intensive care syndrome
PINI: prognostic inflammatory and nutritional index
PTSD: post-traumatic stress disorder
PTSS: post-traumatic stress symptoms checklist
ROC curves: receiver operator characteristic
SAPS II: simplified acute physiology score
SF-36: short form 36
SOFA: sequential organ failure assessment
TBW: total body water

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Conflict of interest

"The authors declare that they have no conflict of interest"

Author contribution

AA, NF, BS, NC, YB, CD assisted in data collection and analysis, drafted and edited the manuscript. CD and BP assisted in data analysis and edited the manuscript. FM, DG, JB, SC, DB, RC, JMC, RT, NA, HR, VS, MH assisted in data collection and edited the manuscript.

Figure legends

Figure 1: Prediction of 1-year mortality according to main characteristics during ICU stay and nutritional and physical assessment at the end of ICU stay.

Model 1: Age, chronic kidney disease, cancer, Karnovsky Performance Scale Index, low handgrip score with cut-off values of 14 (F) or 27 (M), and malnutrition

Model 2: Characteristics of the patients depending on PINI, handgrip score and malnutrition at the end of ICU stay

Figure 2: Nutritional and functional status at ICU discharge (NUFID) score for prediction of death at one year depending on nutritional and physical assessment at the end of ICU stay

PINI: prognostic inflammatory and nutritional index

Figure 3: Distribution of the patients at the end of ICU stay and associated death rate at one year depending on their hand grip test and PINI scores, and presence of malnutrition.

PINI: prognostic inflammatory and nutritional index

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Table 1: Main characteristics of the population, comparison, and prediction of vital status at one year

Variable	All Patients (N=572)	Alive at one year (n = 476)	Dead at one year (n = 96)	p-value
Age – years	63 [53.5 ; 71.1]	61.9 [51.3 ; 70.1]	68.3 [60.9 ; 75.6]	<0.01
Sex (female/male)	193 (33.7)	167 (35.1)	26 (27.1)	0.13
BMI (kg/m ²) (missing=1)	26.6 [22.8 ; 31.3]	26.8 [23.2 ; 31.4]	24.7 [22.3 ; 30.1]	0.03
Chronic cardiac disease (missing =8)	52 (9.2)	38 (8.1)	14 (14.7)	0.04
Chronic respiratory failure (missing =8)	56 (9.9)	42 (9)	14 (14.7)	0.09
Chronic kidney disease (missing =9)	76 (13.5)	55 (11.7)	21 (22.3)	<0.01
Diabetes (missing =8)	151 (26.8)	121 (25.8)	30 (31.6)	0.25
Cancer (missing =9)	106 (18.8)	73 (15.6)	33 (34.7)	<0.01
Karnofsky Performance Scale Index < 50% (miss=167)	231 (57)	183 (52.9)	48 (81.4)	<0.01
Karnofsky Performance Scale Index 50 and 80%	111 (27.4)	104 (30.1)	7 (11.9)	.
Karnofsky Performance Scale Index > 80%	63 (15.6)	59 (17.1)	4 (6.8)	.
SAPS II (missing =7)	43 [31 ; 58]	43 [31 ; 56]	44 [35 ; 62]	0.09
SOFA (missing =15)	6 [4 ; 9]	6 [4 ; 9]	7 [4 ; 9]	0.43
Treatments during ICU stay				
Steroids (missing =2)	188 (33)	152 (32.1)	36 (37.5)	0.30
Blocking agent (missing =2)	151 (26.5)	125 (26.4)	26 (27.1)	0.89
Chemotherapy (missing =5)	5 (0.9)	3 (0.6)	2 (2.1)	0.16
Catecholamines (miss=2)	363 (63.7)	293 (61.8)	70 (72.9)	0.04
Invasive mechanical ventilation (miss=2)	428 (75.1)	364 (76.6)	64 (67.4)	0.06
Sedation (missing =2)	308 (54)	256 (54)	52 (54.2)	0.98
Renal replacement therapy (missing =6)	98 (17.3)	74 (15.7)	24 (25.3)	0.02
Nutritional status at the end of ICU stay				
Albuminemia - g/L (missing =118)	27.4 [23.6 ; 31.7]	28 [23.9 ; 32.1]	25.5 [22.4 ; 27.9]	<0.01
Transthyretin - mg/L (missing =174)	0.2 [0.1 ; 0.3]	0.2 [0.1 ; 0.3]	0.2 [0.1 ; 0.2]	0.04
Orosomucoid - mg/L (missing =183)	1.8 [1.4 ; 2.1]	1.7 [1.4 ; 2.1]	1.8 [1.5 ; 2.2]	0.40
C Reactive protein - mg/L (missing =101)	44.1 [17.2 ; 86.2]	41.2 [16 ; 81.9]	52.2 [22 ; 112]	0.03
Handgrip test* - kg (miss=2)	22 [13 ; 31]	22 [13 ; 32]	16 [11 ; 26]	<0.01
Bioelectric impedance analysis (missing = 16)				
Fat mass (FM) – kg	20.8 [14.5 ; 30.1]	21.2 [14.3 ; 30.6]	20 [14.6 ; 24.8]	0.26
Fat-free mass (FFM) - kg	55.5 [44 ; 65]	56 [44 ; 65.1]	53.2 [44.2 ; 64]	0.28
Fat-free mass index (FFMi) - kg/m ²	19.1 [16.5 ; 21.9]	19.3 [16.7 ; 22.1]	18.6 [15.7 ; 21.3]	0.09
Appendicular skeletal muscle mass index (aSMi) - kg/m ²	8.2 [6.9 ; 9.7]	8.2 [6.9 ; 9.8]	8.2 [6.7 ; 9.3]	0.42
Phase angle - °	5.2 [4.2 ; 6.6]	5.3 [4.3 ; 6.6]	4.5 [3.5 ; 6.3]	<0.01
ECW/TBW ratio	0.431[0.420 ; 0.473]	0.430[0.419 ; 0.472]	0.434[0.423 ; 0.476]	0.09
Malnutrition§	142 (24.9)	110 (23.2)	32 (33.3)	0.04
ICU length of stay - days	9 [6 ; 15](2 310)	9 [6 ; 15](2 310)	10 [7 ; 16.5](7 118)	0.08

BMI: Body mass index; SAPS II: simplified acute physiology score; SOFA: Sequential Organ Failure Assessment; CRP: C reactive protein and nutritional index; ECW/TBW ratio: extracellular water (ECW)/ total body water (TBW); ICU: intensive care unit.

*19 patients were unable to perform the test and were attributed a 0 kg performance

§Malnutrition according to ESPEN definition 2015 and GLIM definition 2019.

Table 2: Association and prediction of one-year death depending on nutritional and functional assessment at the end of ICU stay and characteristics on admission

Variables	OR	CI OR 95%	p-value	AUC [95 % CI]
Handgrip test*	0.97	[0.95 ; 0.99]	<0.01	0.7 [0.64 ; 0.75]
FFMI*	0.94	[0.88 ; 1.00]	<0.01	0.67 [0.61 ; 0.72]
aSMI*	1.02	[0.97 ; 1.07]	0.41	0.67 [0.61 ; 0.72]
Phase angle*	1	[0.96 ; 1.04]	0.94	0.67 [0.61 ; 0.72]
ECW/TBW ratio*	2.1	[0.06 ; 71.17]	0.68	0.67 [0.62 ; 0.73]
Low handgrip score - kg: 14 (F) or 27 (M)§	1.54	[1.19 ; 2.00]	<0.01	0.68 [0.63 ; 0.74]
FFMI < 16.5 (F) or < 20 (M) - kg/m²§	1.16	[0.92 ; 1.46]	0.20	0.64 [0.59 ; 0.7]
aSMi < 7 (F) or < 8.5 (M) - kg/m²§	1.11	[0.89 ; 1.40]	0.35	0.64 [0.59 ; 0.7]
Phase angle < 4.9° (F) or < 5.3° (M)§	1.20	[0.95 ; 1.53]	0.13	0.65 [0.6 ; 0.71]
ECW/TBM > 0.475 (F) or > 0.426 (M)§	1.22	[0.97 ; 1.54]	0.09	0.65 [0.6 ; 0.71]
Malnutrition§-§§	1.37	[1.07 ; 1.76]	0.01	0.65 [0.6 ; 0.71]
Albuminemia < 30 g/L	1.56	[1.08 ; 2.24]	0.01	0.63 [0.56 - 0.69]
Transthyretin < 0.2 mg/L	1.21	[0.90 ; 1.64]	0.20	0.58 [0.5 - 0.66]
Orosomuroid > 1.8 mg/L	1.11	[0.82 ; 1.49]	0.51	0.53 [0.45 - 0.61]
C reactive protein > 40 mg/L	1.29	[0.97 ; 1.72]	0.08	0.58 [0.51 - 0.64]
Model 1**				
Age 50 and 60 years	1.00	[0.62 ; 1.64]	0.99	0.74[0.69 ; 0.80]
Age 60 and 70 years	1.35	[0.9 ; 2.03]	0.15	
Age > 70 years	1.58	[1.05 ; 2.37]	0.03	
Age < 50 years	1		<0.01	
Chronic kidney disease	1.42	[1.04 ; 1.93]	0.03	
Cancer	1.77	[1.35 ; 2.34]	<0.01	
Karnofsky Performance Scale Index 50 and 80%	0.76	[0.42 ; 1.35]	0.35	
Karnofsky Performance Scale Index < 50%	1.61	[1.07 ; 2.42]	0.02	
Karnofsky Performance Scale Index > 80%	1		<0.01	
Low handgrip score - kg: 14 (F) or 27 (M)	1.44	[1.1 ; 1.89]	0.01	
Malnutrition§§	1.27	[0.97 ; 1.64]	0.08	
Model 2**				
Age 50 and 60 years	1.02	[0.55 ; 1.88]	0.95	0.71[0.66 ; 0.76]
Age 60 and 70 years	1.77	[1.07 ; 2.93]	0.03	
Age > 70 years	2.23	[1.34 ; 3.69]	<0.01	
Age < 50 years				
Albuminemia < 30 g/L	1.33	[0.91 ; 1.95]	0.15	
Malnutrition§§	1.53	[1.11 ; 2.11]	0.01	

FFMI: fat-free mass index; aSMi: appendicular skeletal muscle mass index

* In all analyses, variables are considered linearly and adjusted for age and sex.

§Adjustment for age.

** Multivariate logistic regression analyses

§§Malnutrition according to ESPEN definition 2015 and GLIM definition 2019.

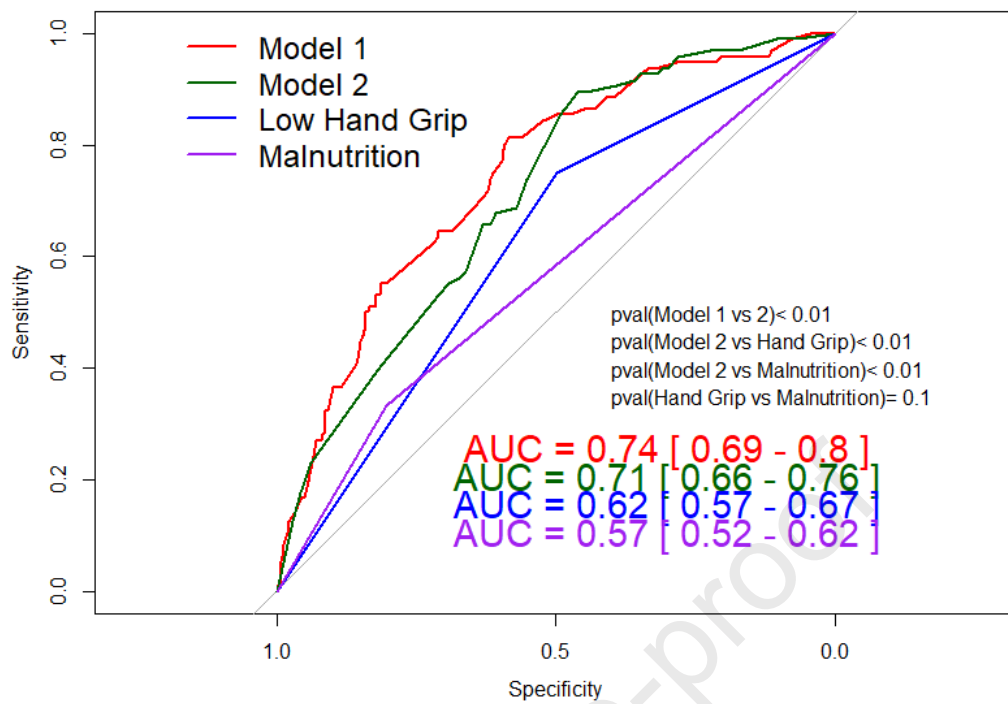


Figure 1: Prediction of one-year mortality according to main characteristics during ICU stay and nutritional and physical assessment at the end of ICU stay.

Model 1: Age, chronic kidney disease, cancer, Karnofsky Performance Scale Index, low handgrip score: cut-off values 14 (F) or 27 (M), and malnutrition

Model 2: Characteristics of the patients depending on albuminemia, handgrip score and malnutrition at the end of ICU stay

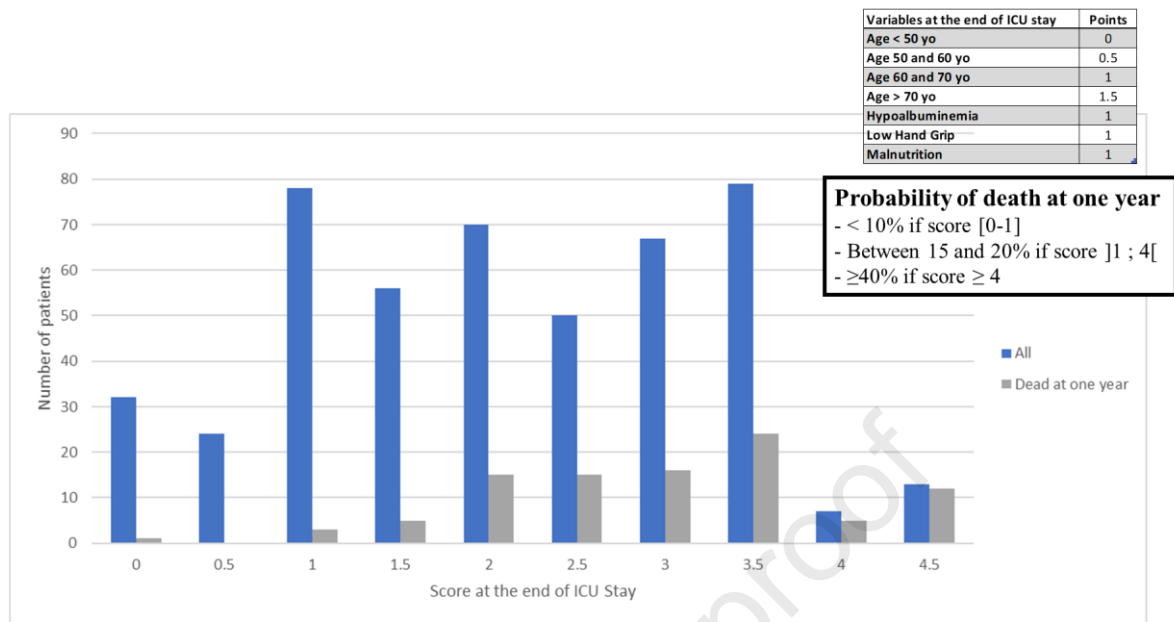


Figure 2: The Nutritional and Functional State at ICU Discharge Score (NUFID score) for prediction of death at one year depending on nutritional and physical assessment at the end of ICU stay

Hypoalbuminemia = Albuminemia < 30 g/L

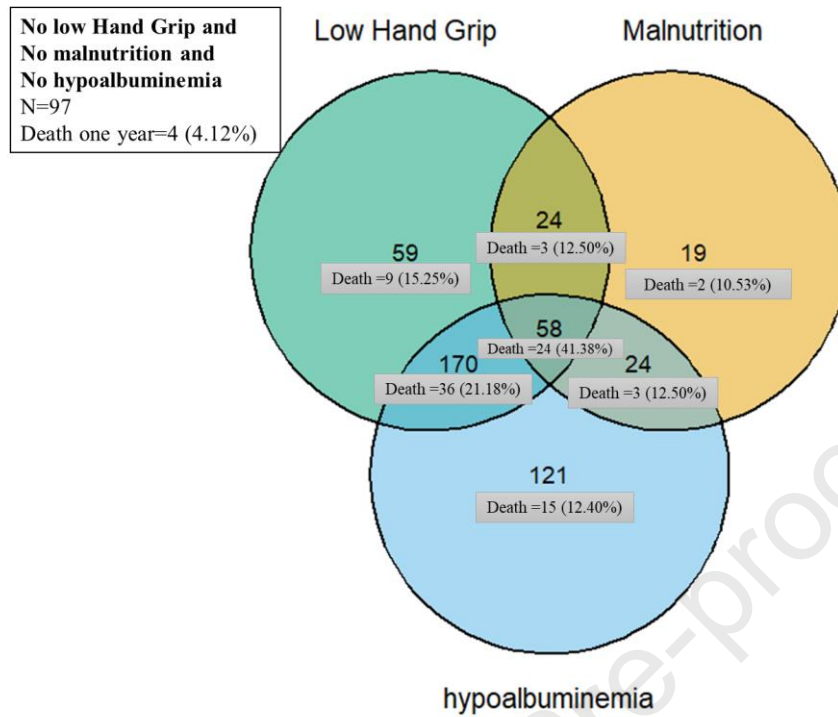


Figure 3: Distribution of the patients at the end of ICU stay and associated death rate at one year depending on their Hand grip test, PINI score and presence of malnutrition.

PINI: prognostic inflammatory and nutritional index