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Article

Nutritional and Sarcopenia Assessment in Bilateral Lung Transplantation Recipient: Can "The Strongest One" Expect Improved Short-Term Outcomes?

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Abstract: Background: Scant data are available on nutritional status in bilateral lung transplant (BLT) candidates. Methods: All consecutive recipients admitted to the intensive care unit (ICU) of the University Hospital of Padua (February 2016–2020) after bilateral-lung transplant (BLT) were retrospectively screened. Data collected: (i) nutritional indices (body mass index (BMI), albumin level, prognostic nutritional index (PNI), mini nutritional assessment short-form (MNA-SF)); and (ii) muscular indices (creatinine height index (CHI)), skeletal muscle index (SMI), densitometry of paravertebral muscles on chest CT). Results: 108 BLT recipients were enrolled: 55% had a normal BMI, 83% had serum albumin levels > 35 g/L; high PNI and MNA-SF scores were recorded in most of patients. A total of 74% had a "normal or slightly reduced protein state" according to the CHI score; 17% were identified as "sarcopenic" according to muscle densitometry (Hu < 30). Lower serum albumin was associated with longer invasive mechanical ventilation days (IMV) and ICU length of stay (*p*-value for non-linearity < 0.01). PNI and BMI were also associated with an increased ICU length of stay (*p*-value for non-linearity < 0.01). Conclusions: Most of the BLT recipients had normal nutritional and sarcopenia status. Pre-transplant albumin values correlated with the duration of IMV; serum albumin, PNI and BMI were associated with ICU stay. No nutritional or muscle parameters predicted re-intubation, 30-days rejection and overall length of hospital stay.

Keywords: nutrition; lung transplant; muscular assessment; sarcopenia

1. Introduction

Lung transplantation (LT) remains the therapeutic option of last resort for end-stage lung disease. Despite advances in surgical techniques and operative management, LT still has significantly higher morbidity and mortality [1,2]. Several studies have been conducted to investigate factors that negatively affect the prognosis of patients who undergo LT, such as age, underlying disease, bilateral LT, pulmonary hypertension, infections, body mass index (BMI) and malnutrition [3–9]. Indeed, patients who received a bilateral LT often experience severe perioperative stress and critical illness or can be underfed before surgery and all these elements could contribute to a worse postoperative outcome. According to several studies, both physiological and physical vulnerability to stressors leading to adverse health outcomes represent the so called "frailty" concept [10]. This concept was initially associated with aging, but nowadays reflects a biological phenomenon, which occurs in all chronologic age groups [11]. Frailty can result from a combination of multiple domains: physical frailty, sarcopenia, malnutrition, cognitive impairments, multi-morbidity and immune system disfunction [12].

Preoperative malnutrition is correlated with morbidity, mortality, hospital stay and quality of life after surgery in solid organ transplantation (SOT) recipients [13–17], but scant data have been published on LT recipients. Conclusions regarding nutritional assessment and postoperative outcomes in this specific population are heterogenous [18–21].

While it is true that defined nutritional status, such as underweight and severe obesity (BMI > 35 Kg/m^2), has been associated with higher risk of mortality after LT surgery [19,20,22,23], few studies have reported the effect on outcomes of other nutritional indexes, such as albumin, prognostic nutritional index (PNI), mini nutritional assessment (MNA), sarcopenia and the creatinine height index (CHI).

Indeed, nutritional evaluation could have a vital role in recipient assessment, and the consideration of body composition, which helps identify sarcopenic recipients, appears to be significant. Sarcopenia can be evaluated in several different ways, including, but not limited to, computed tomography (CT), which is considered as the gold standard for estimating muscle mass. A significant reduction in cross-sectional area and attenuation of the paravertebral muscles on axial CT images [21] has been shown to predict poor survival, ICU admission [23–25], ventilator-free days and ICU length of stay [26] in critically ill patients, but no results have been reported after LT. The aims of our retrospective study were (i) to describe nutritional and muscular assessment before surgery in LT recipients and (ii) to report correlation among nutritional and muscular assessment, and early post-transplantation outcomes (such as ventilator-days, need of reintubation, duration of ICU stay and 30-day acute rejection).

2. Materials and Methods

Our retrospective single center study received the approval by the local Institutional Ethic Committee (reference number 4539/AO/18) and was conducted in accordance with the principles of Good Clinical Practice outlined in the Declaration of Helsinki. The article was written in accordance with the "Strengthening the reporting of observational studies in epidemiology" checklist.

All consecutive adult patients admitted to our ICU at the Padua University Hospital after the first bilateral LT, between 10 February 2016 and 11 February 2020, were retrospectively evaluated and enrolled. Predefined exclusion criteria were: (i) patients that underwent single or a second LT, (ii) a previous diagnosis of musculoskeletal diseases, and (iii) hospital admission before the LT.

All screened LT recipients had at least one complete nutritional screening and a chest CT scan performed 6 months before surgery. For each enrolled patient, baseline characteristics were collected from electronic health records. Nutritional indexes and sarcopenia assessment by the CHI score and densitometry of paravertebral muscles on chest CT were analyzed.

2.1. Nutritional Indexes

According to the evidence available in the literature, we selected three of the most reliable instruments for evaluation of nutritional status: prognostic nutritional index (PNI), the mini nutritional assessment short-form (MNA-SF) and the creatinine height index (CHI), which have shown promise as prognostic indicators for critically ill patients.

(i) BMI is calculated as weight (kg) divided by height (m^2). Weight ranges are based on the World Health Organization (WHO) classification scheme: underweight (<18.5 kg/m^2); normal weight (18.5–24.9 kg/m^2); overweight (25–29.9 kg/m^2); and obese (>30 kg/m^2) [27,28];

(ii) The prognostic nutritional index (PNI), which is calculated as the product between the serum albumin level and total lymphocyte count in the peripheral blood [29,30]. A reference value is still missing. Our median value (i.e., 50) was used to distinguished between "high PNI" versus "low PNI" recipients;

(iii) The mini nutritional assessment short-form (MNA-SF) is a shorter and faster screening version of the MNA, validated for the assessment of nutritional problems in elderly populations [31]. In the MNA-SF, there are six items totaling 14 points (decrease in food intake in the previous three months, involuntary weight loss in the previous three months, mobility, psychological stress or acute disease in the previous three months, neuropsychological problems, and BMI or calf circumference). Based on the total score, patients were divided into three different categories of nutritional status ("well-nourished": 12–14; "at risk": 8–11; "malnourished": 0–7).

2.2. Sarcopenia Indexes

(i) The CHI score [32] was calculated by a standard formula as follows: CHI = (1⁄4 Daily urinary creatinine of patient/daily expected urinary creatinine for individuals of same height and sex) $\times$ 100. The expected value for daily urinary creatinine was obtained from reference charts. Based on CHI, nutritional status was classified as normal for CHI > 90%, mild malnutrition for CHI 80% to 90%, moderate malnutrition for CHI 60% to 80% and severe malnutrition for CHI < 60%;

(ii) Paravertebral muscular densitometry: two musculoskeletal imaging radiologists, each possessing a decade of experience, gathered the mean Hounsfield Unit (Hu) value for the right paravertebral muscle at the level of the 12th dorsal vertebra through manual segmentation and extraction of Hu values. Muscle loss was defined as values < 30 Hu, according to the literature [24];

(iii) The SMI was computed as skeletal muscle cross-sectional area (cm^2), detected at CT scan, divided by body surface area (BSA) [33–35], but a reference value is still missing.

2.3. Statistical Analysis

Baseline characteristics of patients were summarized through descriptive statistics (number, proportion, median, interquartile range (IQR)). Normal distribution of the variables was verified by Skewness and Kurtosis tests.

We conducted univariate analysis to model dichotomous (unsuccessful weaning and early acute rejection) with the aim to identify significant predictors. Adjusted odds ratio (OR) controlling for all the other predictors and 95% confidence intervals (CIs) were calculated from the model. A log-gamma-logistic regression was further conducted to analyze continuous outcomes (mechanical ventilation days, ICU stay duration, hospital days). As regards the gamma models, the marginal effect was calculated as a partial derivative of the expected marginal. The results were reported as average marginal effect (AME), 95% CIs, and *p*-value. For no-linear association, the "restricted cubic spline" model was used, and the significant associations were reproduced considering gender difference.

Statistical significance was defined as *p* values < 0.05. All analyses were conducted using R version 4.1.0 software (R Foundation for Statistical Computing), "Regression Modeling Strategies" [32] and "Marginal Effects for Model Objects packets" [33].

3. Results

Overall, 114 patients who underwent bilateral lung transplant (BLT) in our center between February 2016 and February 2020 were screened. According to eligibility criteria, 108 (94,7%) patients were included in the study (see study flow-chart in Figure 1). Baseline characteristics of participants are described in Table 1.

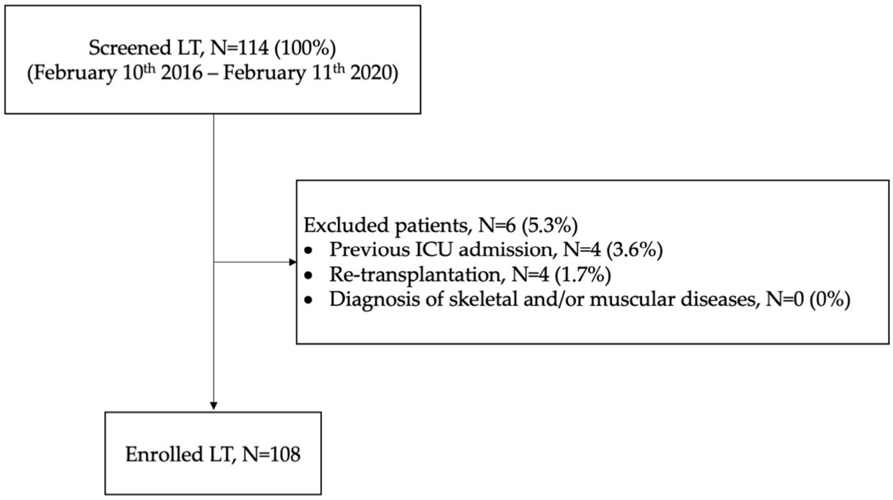


Figure 1. Flowchart.

Table 1. Baseline characteristics of the enrolled LT patients.

	Over-All Population, n = 108
Baseline characteristics	
Age, years	52 [43–60]
Male gender, n (%)	72 (67%)
Weight, Kg	69 [57–83]
IBW, Kg	64 [59–70]
BSA, m^2	1.84 [1.61–1.99]
Admission from home, n (%)	108 (100)
Comorbidities	
Arterial hypertension, n (%)	33 (30%)
Diabetes mellitus, n (%)	19 (18%)
Chronic kidney disease, n (%)	2 (2%)

Data are expressed as number and (percentage) or median and [interquartile range]. Abbreviations: IBW, ideal body weight; BSA, body surface area; Kg, kilogram.

3.1. Description of Preoperative Nutritional and Muscular Status

As described in Table 2, among the patients enrolled, 55% (n = 59) were classified as normal weight according to BMI classification, with albumin values in normal range for 83% (n = 89) of participants. Patients were categorized into PNI-high and PNI-low groups based on a PNI threshold of 50, with 56 patients (52%) falling into the PNI-high group, and 52 patients (48%) into the PNI-low group. MNA-SF score detected the higher number of malnourished patients or patients at risk of malnutrition (21%, n = 23 and 3%, n = 3).

Table 2. Preoperative nutritional and muscular screening of the enrolled LT patients.

	Over-All Population, n = 108
Nutritional indexes	
BMI, kg/m^2	23 [21–27]
Underweight, <18.50 kg/m^2	12 (11%)
normal weight, 18.50–24.90 kg/m^2	59 (55%)
Overweight, >30.00 kg/m^2	37 (34%)
albumin, g/L	39 [36–42]
<35 g/L	18 (17%)
35–55 g/L	90 (83%)
prealbumin, mg/L	232 [186–276]
PNI	50 [4–54]
PNI-high group, >50	52 (48%)
PNI-low group, <50	56 (52%)
MNA-SF score	13 [12–14]
MNA-SF < 7, malnourished	3 (3%)
MNA-SF 8–11, risk of Malnutrition	23 (21%)
MNA-SF > 12, normal nutritional status	82 (76%)
Muscular indexes	
CHI, %	80 [59–100]
muscular density, Hu	36.90 [31.80–41.30]
SMI, cm^2/BSA	36.50 [31.70–40.80]
sarcopenia, n (%)	14 (17)

Data are expressed as number and (percentage) or median and [interquartile range]. Abbreviations: BMI, body mass index; n, number; PNI, prognostic nutritional index; MNA-SF, mini nutritional assessment short-form; CHI, creatinine height index; SMI, skeletal muscle index ; BSA, body surface area; n, number.

Nutritional status of patients based on CHI was as follows: 50% had normal nutritional status, 24% had mild malnutrition, 22% had moderate malnutrition and 4% had severe malnutrition. Median SMI value was 36.50 and sarcopenia was detected in only 17% (n = 14) of the cohort.

3.2. Relationship between Preoperative Nutritional and Muscular Status and Outcomes

Days of IMV, need of re-intubation or tracheostomy, the duration of ICU and hospital stays and early acute rejection are summarized in Table 3.

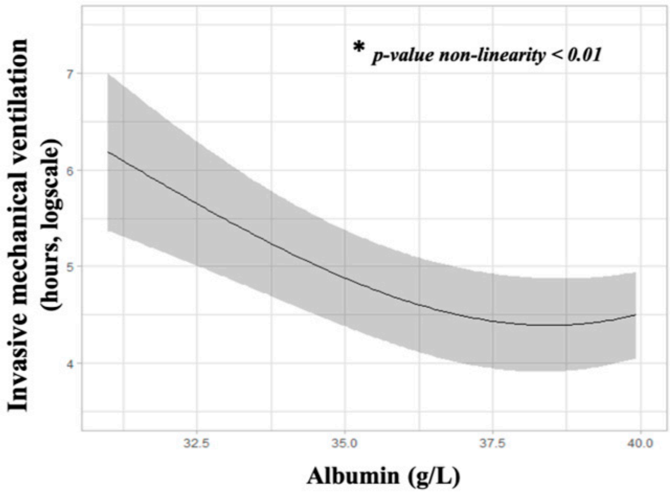
Table 3. Outcomes.

	Over-All Population, n = 108
Invasive mechanical ventilation, hours	33 [21–96]
Re-intubation, n (%)	17 (16%)
Tracheostomy, n (%)	32 (30%)
ICU stay, days	9 [6–21]
Hospital stay, days	33 [28–46]

Data are expressed as a number and (percentage) or median and [interquartile range]. Abbreviations: n, number; ICU, intensive care unit.

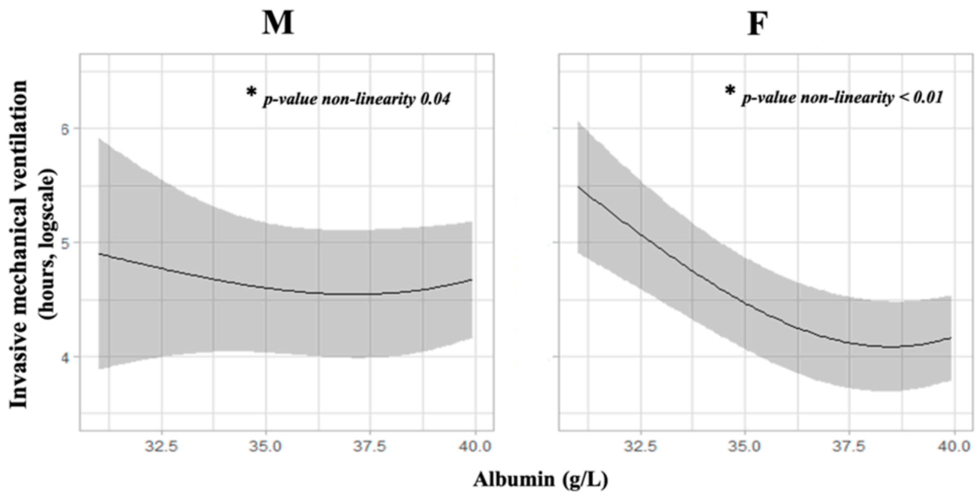
3.2.1. Relationship between Albumin Values and IMV

According to the univariable Gamma model (Figure 2), a preoperative albumin value can predict IMV days following a non-linearity relation (range 30–35 g/L: effect −1.67 h [2.45–0.89], p-value for non-linearity < 0.01). Thus, this reduces the time of IMV as plasma levels rise, especially for the female patients (as shown in Figure 3).



Range	Effect (hours)	95% IC	
25 – 30 g/L	−1.80	−2.64	−0.97
30 – 35 g/L	−1.67	−2.45	−0.89
35 – 40 g/L	−0.38	−0.79	0.04

Figure 2. Relationship between albumin and invasive mechanical duration. Abbreviations: CI, confidential interval.



Range	Gender	Effect (hours)	95% CI	
25 – 30 g/L	M	−0.44	−1.51	0.64
	F	−2.80	−3.93	−1.68
30 – 35 g/L	M	−0.39	−1.39	0.62
	F	−2.59	−3.64	−1.54
35 – 40 g/L	M	0.08	−0.42	0.58
	F	−0.60	−1.20	0.01

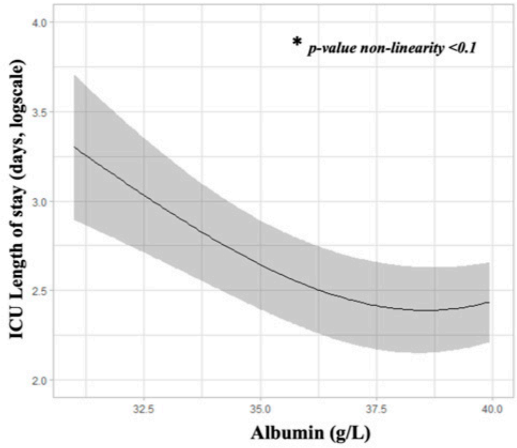
Figure 3. Relationship between albumin and invasive mechanical duration in males and females. Abbreviations: CI, confidential interval; M, male; F, female.

On the contrary, the other nutritional and muscular parameters did not show any significance (Table S1).

3.2.2. Relationship between Albumin Value, PNI Score, BMI and ICU Long-Stay

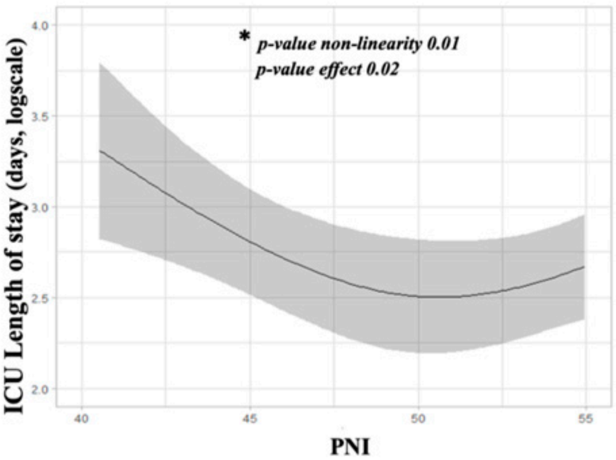
The length of stay in ICU was related to albumin (range 30–35 g/L: effect −0.84 days [1.23–0.45], *p*-value for non-linearity < 0.01), to PNI (range 25–40: effect −1.79 days [3.09, −0.50], *p*-value for non-linearity = 0.01) and to BMI (range 20.7–27.40 kg/m^2: effect

0.34 days [0.03–0.68], p-value for linearity 0.04) (Figure 4A–C). Reduced ICU length of stay was associated with higher serum albumin and PNI levels and with lower BMI.



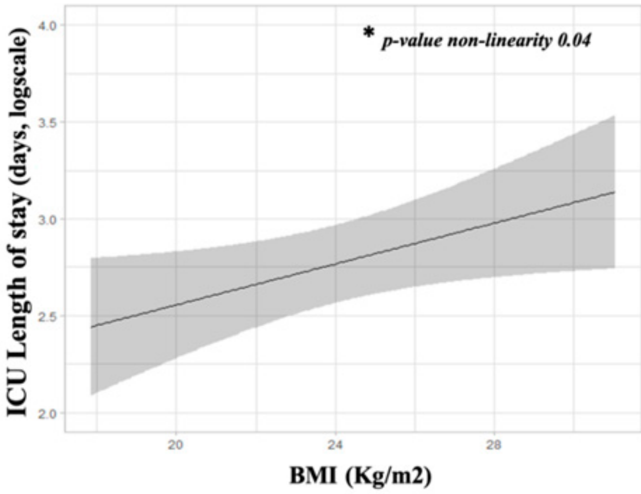
Range	Effect (days)	95% CI	
25 – 30 g/L	−0.91	−1.32	−0.49
30 – 35 g/L	−0.84	−1.23	−0.45
35 – 40 g/L	−0.21	−0.41	−0.01

(**A**)



Range	Effect (days)	95% CI	
25 – 40	−1.79	−3.09	−0.50
40 – 55	−0.70	−1.34	−0.06

(**B**)



Range	Effect (days)	95% CI	
20.7 – 27.4 Kg/m2	0.34	0.03	0.68

(**C**)

Figure 4. Relationship between pre-transplant, albumin (**A**), PNI (**B**) and BMI (**C**) with ICU length of stay. ICU, intensive care unit; CI, confidential interval; PNI, prognostic nutritional index; BMI, body mass index.

3.2.3. Additional Outcomes

Among the preoperative variables, nutritional status and muscular index did not predict reintubation rate, hospital length of stay or acute graft rejection, in the univariable Gamma models as reported in Tables S2–S5.

4. Discussion

In this retrospective cohort of 108 adults undergoing bilateral LT, nutritional and muscular status before surgery were analyzed. Most LT patients presented a nutritional and muscular profile within the normal limits. After considering other clinical factors, we found that only a few laboratory and anthropometric values are predictive of ICU stay and IMV days. Lower albumin values were associated with longer IMV duration and ICU-days, while prolonged ICU stay was correlated to poorer PNI scores and higher BMI values. To our knowledge, this study is the first to provide a multiparametric nutritional, muscular and sarcopenia description in a wide cohort of LT recipients.

Our study highlighted the value of preoperative BMI, a simple and well-known immuno-nutritional indicator. Historically, obese LT recipients have been linked with poor post-surgical outcomes [27]. Patients classified as obese (BMI $\geq$ 30 kg/m^2) prior to transplantation had markedly shorter post-transplant survival times, with up to a fivefold higher odds ratio of death compared to normal weight patients, referred to as the reference group [27,36,37]. Based on these studies, BMI was incorporated as a component of the lung allocation score, a method of prioritizing LT candidates introduced in 2005 [38,39]. In the most recent 2014 update to the guidelines, class I (BMI $\leq$ 35 kg/m^2) and II-III obesity ($\geq$35 kg/m^2) is now considered an absolute and relative contraindication to LT [40]. No previous correlations are reported among BMI and ICU stay and BMI's role as the sole measure of nutrition status in LT candidates is now being questioned.

In our cohort, lower albumin values and poorer PNI score (which is derived by albumin value) were associated with longer duration ICU stay but not with survival. Regarding PNI score and ICU days, no previous data are available, but large community-based studies have shown a link between low serum albumin and an increase in the length of stay in ICU and postoperative complications [41,42]. A lower albumin value is associated with worse outcomes across a myriad of patient cohorts, including trauma [43], major surgery [44], emergency medical admissions [45,46]. In a retrospective single-center cohort study, Thongprayoon et al. [47] reported that in 14,075 hospitalized adult patients admitted at Mayo Clinic Hospital in Rochester, MN, a serum albumin level at admission of 3.5 g/dL or lower was associated with higher risk of acute respiratory failure requiring mechanical ventilation. Similar results were also obtained in other studies [48].

Based on this assumption, several nutritional indexes have been developed with the aim to improve patient's outcome LT. PNI has been classified as a valid indicator of malnutrition in patients affected by cancer, liver cirrhosis [49], chronic renal failure [50,51], and, more recently, in LT recipients [20]. Kim et al. evaluated the database of Severance Hospital at Yonsei University, collecting data on 132 patients who underwent single or double LT, and they reported that a low preoperative PNI score was an independent predictor of overall survival among LT recipients [21].

No nutritional or muscle parameters predicted the need for re-intubation, the onset of rejection at 30 days and the length of hospital stay in our cohort of LT recipients. We hypothesized that re-intubation and acute rejection graft could have a multifactorial pathogenesis, and this could be explained, at least in part, by the absence of significance. Considering muscular indexes, two retrospective studies have investigated the CHI value. Schewebel et al. enrolled 78 LT candidates with lower CHI score in 45% of the cohort; lower CHI scores have been correlated to higher risk of respiratory failure and mortality (up to 31.4%) [21].

In a cohort of 167 patients on prolonged IMV, Datta et al. described 75% of malnourished cases, and CHI-score represents a stronger predictor of successful weaning [29]. No significant results concerning CHI score were reported in this study. This could be explained, at least in part, by the lower prevalence of malnutrition in our study cohort.

Similar findings were described by Chohan et al. who investigated malnutrition using a different score named 'nutritional risk index' (NRI). According to their findings, NRI was not prognostic of post-transplant outcomes. Moreover, LT candidates with high malnutrition risk were able to maintain their weight pre-transplant and demonstrated considerable weight gain in the first-year post-transplant [52].

Regarding the muscular–skeletal profile, one of the more recent developments in this topic of research is the use of CT imaging to quantify muscle mass, and recently, this application has been extended to critically-ill patients [24,25,53,54].

Our results suggest that muscular assessment, in the form of muscle index, was not associated with worse short-term outcomes. In a retrospective cohort study by Kelm et al. of 36 adult LT recipients, in the pre-transplant muscle mass detected on CT scan 6 months prior to surgery, the median muscle index was 40.2 cm^2 and lower values were associated with worse survival and increased hospital LOS. We consider that the difference with our study cohort could be explained by different methods used: in our study we consider a muscle index normalized by BSA, while in the paper of Kelm et al. a pure muscular tool (i.e., measure of muscle surface area) was considered [54]. Recently, Swaminathan et al. in a cohort of 515 LT recipients conducted a frailty assessment, and thoracic sarcopenia was one of variable investigated [55]. In that cohort of study, a prevalence of 51.3% of frail patients according to the transplant-specific frailty index was reported, but no association was found between thoracic sarcopenia and short-term outcomes after LT [55]. Recently, a growing interest has been reported on the assessment of frailty in solid organ transplantation recipients and in LT candidates, as reported by the paper of Singer et al. which proposed the Lung Transplant Frailty Scale (LT-FS) as a disease-specific physical frailty measure with higher predictive capability of delisting/death face [56]. In addition, Singer et al. have proposed a frailty measurement according to sub-phenotypes; they identified a hyperinflammatory, sarcopenic sub-phenotype in LT candidates, associated with worse disability, higher risk of waitlist delisting or death and reoperation, and longer post-transplant hospital stay [12].

This study has some limitations. Firstly, are the retrospective design of the study and the single center nature of the experience. Second, although many nutritional indexes have been proposed, they could be influenced by many factors; for example, PNI has been proposed as a simple marker for evaluation of nutritional status, but many factors (drugs, diseases, age) could influence the serum albumin level and lymphocyte count. Finally, in our study, we did not used any standardized measure of physical frailty, such as the recent "Lung Transplant Frailty Scale" [56]; these innovative tools, as a combination of different domains (symptoms, signs, diseases, disabilities or laboratory measurements) exhibited superior construct and predictive validity for clinical outcomes of death or delisting from the waitlist [11].

5. Conclusions

In the present study, we found that most patients have a good nutritional profile and assessment of skeletal mass prior to lung transplant. We analyzed relationships among preoperative nutritional variables and postoperative outcomes, reporting some statistical significance. Pre-transplant serum albumin values correlated with the duration of IMV, while serum albumin, PNI and BMI were associated with prolonged ICU stay. On the contrary, the proposed indicators of sarcopenia did not show any correlation with the investigated outcomes. These findings suggest that the preoperative albumin value, BMI and PNI-score, which can be easily obtained or calculated, are useful markers for identifying LT recipients at a higher risk of longer ICU stay and prolonged IMV. Further studies are necessary to validate our results and to investigate, on a larger sample, newer associations between nutritional/muscular status and outcomes of interest.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/transplantology4040021/s1, Table S1: Univariable Gamma model for IMV; Table S2: Univariable Gamma model for reintubation; Table S3: Univariable Gamma model for overall hospital LOS; Table S4: Univariable Gamma model for 30-day rejection; Table S5: Main findings.

Author Contributions: Conceptualization, S.C., A.B., P.N., N.S., D.L., B.M.B., C.G., F.R. and C.L.; methodology, A.B., D.L., G.L., D.G. and C.L.; formal analysis: A.B., G.L., D.G., C.G. and N.S.; data curation, A.B., S.C., M.N., M.B. (Martina Biscaro), M.B. (Mara Bassi), G.F., D.L., T.A.G. and P.Z.; writing—original draft preparation, A.B., S.C., M.N., C.L., D.L., M.B. (Mara Bassi), B.M.B., G.L., C.G., D.G. and F.R.; writing—review and editing, P.N., M.N., M.B. (Martina Biscaro), M.B. (Mara Bassi), N.S., G.F., T.A.G. and P.Z.; supervision, M.B. (Martina Biscaro), M.B. (Mara Bassi), B.M.B., F.R., P.N. and A.B. All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Data supporting results will be available after a proper request.

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Conflicts of Interest: The authors declare no conflict of interest.

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