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Nutritional status, ICU duration and ICU mortality in lung transplant recipients

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Abstract *Objective:* To determine the relation of malnutrition and underlying diagnosis to the length of stay in the Intensive Care Unit (ICU) and to mortality after lung transplantation (LTX).
Design: Retrospective ICU chart review.
Setting: Cardiothoracic ICU in a University hospital.
Patients: Fifty-one consecutive patients who suffered from end-stage lung disease from April 1992 to January 1994.
Interventions: None.
Measurements and results: The median time spent in the ICU was 5 days (range, 2–123 days). Patients with an underlying diagnosis of obstructive lung disease had significantly shorter ICU stays (median 4 days; range, 2–28 days) than those with restrictive lung disease (median 7 days; range, 2–123 days) ($p = 0.005$) or pulmonary hypertension (median 10 days; range, 2–38 days) ($p = 0.041$). Significant differences in ICU duration were ob-served between patients after double lung transplantation (median 10 days; range, 2–123 days) and those after single lung transplantation (median 4 days; range, 2–36 days) ($p = 0.004$). No statistically significant difference in ICU duration was found between patients with different nutritional statuses. In those patients who could not be discharged from the ICU before the 5th day, a body mass index (BMI) below the 25th percentile was a statistically significant risk factor for ICU mortality ($p < 0.05$).
Conclusions: We conclude that the type of transplant procedure and the underlying diagnosis are important predictive indicators of ICU duration. A poor nutritional status (BMI below the 25th percentile) is a risk factor for ICU mortality in cases of patients who stay for 5 days or longer in the ICU.

Key words Lung transplantation · Malnutrition · ICU

Introduction

Over the last decade, lung transplantation (LTX) has become a standard treatment modality in end-stage lung disease. The Intensive Care Unit (ICU) stay after the transplant procedure is a critical time for lung transplant recipients. Severe catabolism, infection, weaning problems and early graft rejection are some of the complications these patients may have to face during their ICU stay. Malnourished general surgical patients are at higher risk for developing postoperative complications compared with well-nourished patients and, as a result, require longer ICU and hospital stays [1–3]. Several studies have shown that patients with end-stage lung disease may be severely malnourished

[4, 5]. In end-stage lung disease, a certain degree of malnutrition may even be advantageous in terms of reduced ventilatory requirements. To date information on the length of stay in the ICU after LTX and its relation to malnutrition is limited. The aim of our study was to examine whether malnutrition was related to the length of stay in the ICU and to the rate of mortality.

Patients and methods

Fifty-one patients underwent LTX at our institution from April 1992 to January 1994. We reviewed their ICU charts and recorded sex, age, diagnosis, preoperative weight, height, date of transplantation, cytomegalovirus (CMV) status of donor and recipient, allograft ischemic time, time on cardiopulmonary bypass, ICU length of stay and length of survival. The assessment of nutritional status was based on the body mass index (BMI), which was calculated by dividing body weight (kg) by the squared height (m). The BMI values thus obtained were compared with percentile values taken from a table valid for the Caucasian, North American population [6]. The patients were divided into two groups: patients with a BMI above the 25th percentile, indicating good nutritional status, and those with a BMI below the 25th percentile, indicating poor nutritional status. The group of patients with a BMI below the 25th percentile included a subgroup of patients with a BMI below the 5th percentile, which indicated severe malnutrition. CMV serology of the donor and the recipient was recorded to determine those patients who were at highest risk for CMV infection. When assessing allograft ischemic time for double lung transplant recipients, the ischemic time of the second lung was noted. The occurrence of severe reperfusion injury immediately after LTX was recorded. Severe reperfusion injury was defined in terms of clinical signs of severely impaired oxygenation and radiological infiltration appearing immediately after transplantation. Patients were discharged from the ICU after extubation when respiratory and hemodynamic stability was achieved. Respiratory stability was defined as follows: no signs of dyspnea when breathing oxygen by mask, a respiratory rate below 25 breaths/min and blood gas values with arterial carbon dioxide tension ($PaCO_2$) less than 55 mmHg and arterial oxygen tension (PaO_2) more than 60 mmHg. Patients were not discharged from the ICU in cases of uncontrolled infection.

Surgical technique, immunosuppression and infection prophylaxis

The operative procedure was performed in a standardized way [7]. When two lungs were implanted, the bilateral sequential method was used. Patients with pulmonary hypertension were transplanted by using cardiopulmonary bypass; in all others cardiopulmonary bypass was used if necessary (e.g. in cases of hemodynamic or ventilatory instability). Immunosuppression was intraoperatively started with 1 g methylprednisolone. Thereafter, 125 mg methylprednisolone was given t.i.d. during the first day. Starting from the 2nd postoperative day, 1 mg/kg of prednisolone was gradually reduced to 0.3 mg/kg within 10 days. Cyclosporine was started postoperatively at a dosage of 0.5 mg/kg as soon as stable hemodynamic and renal function had been achieved. The dosage was increased to 3 mg/kg to obtain a trough whole blood level of 250–300 ng/ml. Azathioprine was started postoperatively at a dosage of 2 mg/kg per day and was adjusted to the leukocyte count. All patients received induction therapy with antilymphocyte globulin (ATG Fresenius) at a dosage of 10 mg/kg per day for 7 days. CMV-positive patients and those with mismatched CMV received CMV hyperimmune globulin

(Cytotect) at a dosage of 1.5 ml/kg per day on days 1, 3, and 7. All patients with mismatched CMV received gancyclovir 5 mg/kg twice daily for 3 weeks.

Nutrition

On the 1st postoperative day, total parenteral nutritional support was started with glucose. Amino acid solutions and fat emulsions were added on the 2nd postoperative day. The standard parenteral all-in-one solutions contained 17% amino acids, 30–50% fat and 30–50% glucose in terms of energy. Enteral nutrition was started as soon as it was tolerated by the patient, which was usually on the 2nd postoperative day. The provided energy demand was 20–40 kcal/kg per day depending on tolerance and estimated requirements. After extubation, a light diet was provided with either enteral or parenteral supplements.

Mechanical Ventilation

Mechanical ventilation was provided with continuous positive pressure ventilation during the initial postoperative period. Thereafter efforts were made to allow spontaneous or at least assisted spontaneous breathing. Target blood gas values were as follows: PaO_2 more than 75 mmHg, pH more than 7.20 and $PaCO_2$ 40–50 mmHg. Higher $PaCO_2$ levels were tolerated, if necessary, to avoid excessive tidal volumes.

Statistical analysis

A patient database was maintained and statistical analyses were carried out by using a statistical software package (Systat 5.1). The Mann-Whitney U test was used to compare differences in ICU duration between different diagnoses, different types of transplantation and different nutritional and CMV statuses. The chi-square test was used to assess associations within groups concerning sex, diagnosis, nutritional and CMV status, type of transplant procedure, development of severe reperfusion injury and ICU mortality. For calculation of the correlations between ICU length of stay and age, allograft ischemic time and time on cardiopulmonary bypass, the Pearson correlation coefficient was used. Multivariate analysis of variance was performed for all the factors mentioned to define the impact of single factors on predicting a need for treatment in the ICU for 5 days or more. Risk factors for ICU mortality were assessed by the same method. A probability value less than 0.05 was considered to be significant.

Results

Fifty-one patients underwent LTX at our institution from April 1992 to January 1994. The mean age of the patients was 44.6 ± 13.3 years (range, 4–66 years). Twenty-three patients were female (45%) and 28 were male (55%). Indications for LTX were obstructive lung disease in 21 patients (41%), restrictive lung disease in 15 (29%), pulmonary hypertension in 9 (18%) and miscellaneous in 6 (12%). In the group of patients with restrictive lung disease, there was one patient on preoperative ventilatory support. The group of patients

suffering from pulmonary hypertension consisted of three patients with primary pulmonary hypertension, two with chronic embolic pulmonary hypertension which could not be treated by pulmonary thrombendarterectomy, three with atrial septal defect and Eisenmenger's complex, and one with lymphangioleiomyoma. The group of patients with miscellaneous diagnoses consisted of three with cystic fibrosis, one with bronchiectasis, one with sarcoidosis and one with bronchiolitis obliterans after heart and lung transplantation.

Twenty-seven patients were CMV-seropositive and 24 were CMV-seronegative before transplantation. In the seropositive group ($n = 27$) 16 recipients received CMV-positive grafts and 11 received CMV-negative grafts. In the seronegative group ($n = 24$) 11 recipients received CMV-positive and 13 received CMV-negative grafts. A total of 23 double lung (DLTX) and 28 single lung transplantations (SLTX) were performed. DLTX recipients were significantly younger than SLTX recipients ($p = 0.011$). The mean age of the first group was 39.7 ± 14.9 years (range, 4–65 years), whereas that of the second group was 48.6 ± 10.4 years (range, 17–66 years). Allograft ischemic times of DLTX recipients were significantly longer than those of SLTX recipients (363 ± 51 min versus 247 ± 61 min) ($p < 0.0001$). Cardiopulmonary bypass was used for 20/23 DLTX and for 2/28 SLTX. The average time on cardiopulmonary bypass was 218 ± 79 min.

Body mass index

Nineteen patients (37%) had good nutritional status (BMI over the 25th percentile), whereas 32 patients (63%) had poor nutritional status (BMI below the 25th percentile). Within the first group ($n = 19$) there were six patients with a BMI between the 75th percentile and the 90th percentile, and only one patient with a BMI over the 90th percentile. In the group of patients with a BMI below the 25th percentile ($n = 32$), 14 patients were severely malnourished, with a BMI below the 5th percentile. Patients with a BMI below the 5th percentile were significantly younger compared to those with a BMI above the 5th percentile (37.6 ± 14.4 years versus 47.2 ± 12.0 years) ($p = 0.026$). Five patients with obstructive lung disease ($n = 21$), two with restrictive lung disease ($n = 15$), and one with pulmonary hypertension ($n = 9$) were severely malnourished. The BMI of all patients in the group of miscellaneous diagnoses ($n = 6$) was below the 5th percentile.

Intensive care unit length of stay (Table 1)

The 51 patients spent a total of 567 days in the ICU (Fig. 1). Median time spent in the ICU after transplant-

Table 1 ICU days and ICU mortality for diagnostic groups (*OLD* obstructive lung disease, *RLD* restrictive lung disease, *PH* pulmonary hypertension, *MISC* miscellaneous diagnoses, *DLTX* double lung transplantation, *SLTX* single lung transplantation.)

Group	No.	ICU days		ICU mortality
		median	range	
All	51	5	2–123	9 (17.6%)
Diagnostic groups:				
OLD	21	4[a, b]	2–28	3 (14.3%)
RLD	15	7	2–123	4 (26.7%)
PH	9	10	2–38	1 (11.1%)
MISC	6	6	3–29	1 (16.7%)
Type of transplant procedure:				
DLTX	23	10	2–123	4 (17.4%)
SLTX	28	4[c]	2–36	5 (17.9%)
Influence of transplant procedure within diagnostic groups:				
OLD DLTX	6	5	3–28	1 (16.7%)
OLD SLTX	15	3[d, e]	2–7	2 (13.3%)
RLD DLTX	5	22	5–123	1 (20.0%)
RLD SLTX	10	6.5	2–36	3 (30.0%)

$p < 0.05$: [a]OLD versus RLD, [b]OLD versus PH, [c]SLTX versus DLTX, [d]OLD SLTX versus OLD DLTX, [e]OLD SLTX versus RLD SLTX
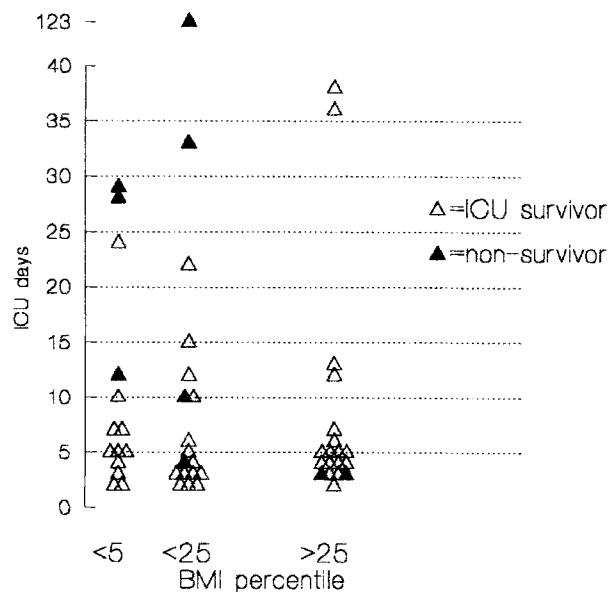

Fig. 1 ICU days and ICU mortality of lung transplant recipients grouped according to nutritional status

ation was 5 days (range, 2–123 days). The diagnostic groups had significantly different median lengths of ICU stay. Patients with obstructive lung disease had significantly shorter ICU stays than patients with restrictive lung disease ($p = 0.005$) or those with pulmonary hypertension ($p = 0.041$). Patients who had

Table 2 ICU duration and ICU mortality of the three nutritional groups (*BMI* body mass index)

Group		BMI < 5th percentile	BMI 5th–25th percentile	BMI > 25th percentile
All	No.	14	18	19
	ICU days median (range)	6 (2–29)	4.5 (2–123)	5 (2–38)
ICU survivors	No.	11	14	17
	ICU days median (range)	5 (2–24)	3.5 (2–22)	5 (2–38)
Non-survivors	No.	3	4	2
ICU mortality	%	21.4%	22.2%	10.5%

Table 3 Causes of death in the ICU (*OLD* obstructive lung disease, *PH* pulmonary hypertension, *RLD* restrictive lung disease, *CF* cystic fibrosis, *DLTX* double lung transplantation, *SLTX* single lung transplantation)

BMI (percentile)	Age	Diagnosis	TX	Reperfusion injury	ICU days	Cause of death
< 5th	51	OLD	DLTX		28	Bronchus dehiscence
	21	CF	DLTX	yes	29	Gram-negative sepsis
	48	RLD	SLTX		12	Cytomegalovirus pneumonia
5–25th	58	RLD	SLTX	yes	33	*Candida albicans* pneumonia, sepsis
	62	OLD	SLTX		4	*Pseudomonas aeruginosa* pneumonia, sepsis
	50	RLD	SLTX		10	Mycobacterium tuberculosis pneumonia
	46	RLD	DLTX		123	*Pseudomonas aeruginosa* pneumonia
> 25th	57	PH	DLTX	yes	3	Reperfusion injury
	49	OLD	SLTX	yes	3	Reperfusion injury

undergone DLTX spent a significantly longer time in the ICU than those who had undergone SLTX ($p = 0.004$). This difference was also observed in the group of patients with obstructive lung disease. Patients with obstructive lung disease who had undergone DLTX had a significantly longer ICU stay than those who had undergone SLTX ($p = 0.026$). A similar trend, although not statistically significant due to the large range in ICU duration, was detected within the group with restrictive lung disease. Owing to the small sample size, statistical analyses were not performed for the other diagnostic groups.

No statistically significant difference in ICU duration was found between the three groups of various nutritional statuses when all patients or only the ICU survivors were analysed (Table 2). The number of non-survivors within the three nutritional groups was too small for statistical anlysis. No statistically significant influence on the length of stay in the ICU of age, sex, CMV-status, allograft ischemic time and time on cardiopulmonary bypass was detected.

Intensive care unit mortality and causes of death (Table 3)

Nine (17.6%) of the 51 patients died in the ICU (Fig. 1). The causes of death were infection (6), severe reperfusion injury (2) and bronchus anastomosis dehiscence (1).

The overall mortality rate of the three nutritional groups did not differ significantly (Table 2). However, patients with a BMI below the 25th percentile had a significantly higher rate of ICU mortality, if they could not be discharged from the ICU before the 5th day. Nineteen patients with a BMI below the 25th percentile ($n = 32$) stayed 5 days or longer in the ICU. Six of them died in the ICU. Ten patients with a BMI above the 25th percentile ($n = 19$) stayed 5 days or longer, and all of them survived. This difference in the rate of ICU mortality between these two groups from the 5th day onward was statistically significant ($p < 0.05$). Six patients developed severe reperfusion injury, of whom four died. Thus, the patients who

developed severe reperfusion injury showed a significantly higher mortality rate than all other patients ($p < 0.001$). No statistically significant influence on ICU mortality of age, sex, diagnosis, type of transplant procedure, CMV-status, allograft ischemic time and time on cardiopulmonary bypass could be demonstrated.

Analysis of variance

Predictors for an ICU stay of 5 days or more were the type of transplant procedure and the underlying diagnosis ($r = 0.454, p = 0.004$). Predictors for ICU mortality were the development of severe reperfusion injury and a BMI below the 25th percentile ($r = 0.507$, $p = 0.0008$).

Discussion

The early postoperative days are a critical period for lung transplant recipients. The underlying diagnosis plays an important role in the postoperative course. Davis et al. [8] found differences in the need for ventilatory support and ICU treatment in a group of 83 patients after SLTX. Patients with obstructive lung disease spent less time in the ICU (2.3 ± 2.3 days) compared to patients with idiopathic pulmonary fibrosis (12 ± 19.9 days) or primary pulmonary hypertension (7.8 ± 8.6 days) ($p < 0.05$). These data are in agreement with our findings. Patients with obstructive lung disease have a rather uncomplicated postoperative course and require intensive care only for a short period. Patients with obstructive lung disease after SLTX had the shortest ICU duration of all our patients. However, these patients are at risk for hyperinflation of the native lung, which may cause mediastinal shift and a higher rate of mortality and morbidity [9].

Patients who undergo DLTX have significantly better postoperative pulmonary function and a trend toward better survival compared to those who undergo SLTX [10]. Thus, it was surprising that the DLTX patients of our patient population had a prolonged ICU stay. The characteristics of DLTX candidates differ from those of SLTX candidates. Although the former may be younger, their condition is usually more severe, because many of them suffer from chronic infectious lung disease (i.e. cystic fibrosis or bronchiectasis). Right-ventricular dysfunction is an additional risk factor in patients who undergo DLTX for pulmonary hypertension. The allograft ischemic times of DLTX recipients are longer than those of SLTX recipients and cardiopulmonary bypass is more often necessary in DLTX. In patients requiring cardiopulmonary bypass

for LTX, statistically significant increases in the length of intubation and the number of hospital deaths occur [11]. However, it has also been demonstrated that in DLTX the use of cardiopulmonary bypass does not seem to affect the outcome adversely as expressed in terms of the time until extubation and the time spent in the ICU [12]. Since, in our study population, cardiopulmonary bypass was used in the majority of patients who underwent DLTX but in only two who underwent SLTX, it was not possible to distinguish between the effects of cardiopulmonary bypass and DLTX itself on outcome.

If cardiopulmonary bypass is necessary for LTX, the transplanted lung is reperfused with activated blood elements, that may exacerbate the reperfusion injury. Reperfusion injury is caused by a variety of mechanisms [13]. Evidence of mild reperfusion injury was observed in nearly all our patients. In most cases this remains short-lived, whereas the development of severe reperfusion injury is associated with an increased mortality rate. Severe reperfusion injury developed in six patients, of which four died. Two died immediately; while lung dysfunction led to a prolonged ICU stay, in the other two patients, and ultimately they died from infection.

Several studies have shown that patients with end-stage lung disease may be severely malnourished [4, 5]. It is generally accepted that malnourished surgical patients are at a higher risk for developing postoperative complications compared with well-nourished patients and, as a result, require longer ICU stays [1–3]. It has already been shown that, in liver transplant recipients, the degree of preoperative malnutrition is predictive of postoperative morbidity and mortality [14]. In cases of moderately and severely malnourished liver transplant recipients, a significant increase was found in the number of days during which ventilatory support was required as well as in the number of days spent in the ICU and in the hospital. Interestingly, this strong correlation between nutritional status and ICU duration was not found in our lung transplant recipients. However, a correlation was observed between poor nutritional status and ICU mortality after a prolonged ICU stay. Even the most severely malnourished patients with a BMI below the 5th percentile did not require a longer ICU stay. But this subgroup was significantly younger than the rest of our study population, a fact which suggests that malnutrition was counteracted by younger age. In some patients, low body mass may even prove advantageous in terms of metabolic economy and subsequent reduced ventilatory requirements.

There is slight evidence that poorly nourished heart and lung transplant recipients with cystic fibrosis are more likely to succumb to post-transplantation hazards [15]. In our study, this was clearly confirmed in cases of lung transplant recipients. A BMI below the

25th percentile significantly increased the risk of ICU mortality if the patient could not be discharged before the 5th ICU day. This indicates that poor nutritional status is an important risk factor in cases of prolonged ICU stay (5 days or more) but does not play such a significant role in cases of early ICU death. Surgical injury is associated with a high risk of protein loss. The loss of body tissue may be minimal and of little consequence in a patient with normal nutritional status and a brief ICU duration, but when the stay is prolonged and the patient is nutritionally depleted, a variety of clinical events associated with the catabolic state have been known to occur [16]. These alterations include immunosuppression characterized by an increase in the frequency of nosocomial infections [17], a decrease or delay in wound healing and tissue repair [18] as well as loss of muscle strength and diminished activity [19]. Catabolically induced inspiratory muscle weakness may contribute to a prolonged weaning period and to postoperative respiratory failure [20]. Thus lung transplant recipients with good nutritional status may tolerate an ICU stay that is prolonged by complications.

In the early postoperative period, the main threat to survival after LTX is infection [21, 22]. In our study group, infection was the cause of death in six patients. All of them had BMIs below the 25th percentile. The donor lung has been known to influence substantially the development of infection after LTX [23]. Unfortunately the bacteriological status of the donor lung is often not available before LTX is performed. Thus a selection of organs on the basis of very recent bacteriology is not feasible. The only strategy to decrease the risk of infection would be to improve the nutritional status of the most malnourished lung transplant candidates. It has been shown in other malnourished patients that preoperative nutritional support can significantly decrease postoperative mortality [24].

Although ICU mortality was not affected by nutritional status in our patients, mortality was increased in malnourished patients who stayed 5 days or longer in the ICU. In the postoperative period, when the catabolic drive is high and is enhanced by the administration of glucocorticoids, the nutritional status should be maintained. To maintain the nutritional status, sufficient amounts of amino acids and calories have to be given. Frequently, the amount of calories has to be reduced in order to permit weaning from the ventilator, because many patients show ventilatory insufficiency during a prolonged ICU stay. A new approach is the administration of the human growth hormone. Due to its anabolic properties, human growth hormone enhances protein synthesis and tissue repair and could help malnourished patients who undergo a prolonged ICU stay [16]. Human growth hormone therapy was successfully used in three lung transplanted patients, who could not be weaned from the ventilator [25].

We conclude that the type of transplant procedure and the underlying diagnosis are important predictive indicators of ICU duration. Moreover, our study clearly proved that in cases of lung transplant recipients, poor nutritional status markedly enhanced the risk of ICU mortality from the 5th day onward. Thus strategies that improve or maintain nutritional status should be applied before LTX. Postoperative nutritional interventions need further evaluation.

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