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Risk Factors for Reintubation Related to Non-Airway Failure After Liver Transplantation in Intensive Care Unit: Observational Study

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Abstract: The aim of this observational study was to evaluate the risk factors and predictive indexes of reintubation in patients after liver transplantation in the intensive care unit of a university hospital. The time at the intensive care unit, time on mechanical ventilation, use of noninvasive ventilation, ventilator-associated pneumonia, mortality, sequential organ failure assessment scores (SOFA), simplified acute physiology score (SAPS 3), model for end-stage liver disease (MELD), Child-Pugh (CHILD), Acute Physiology and Chronic Health Disease Classification System II (APACHE II), and balance of risk score (BAR) were correlated with reintubation. The following tests were used for the statistical analysis: Kolmogorov-Smirnov, χ^2, Student's t-test, and regression analysis and receiver operating characteristic (ROC) curve. Two hundred and thirty-seven individuals were analyzed. Among them, 38 (16%) were reintubated. The comparative analysis was performed between reintubated and non-reintubated individuals. The variables analyzed – ventilator associated pneumonia, death, mechanical ventilation time, intensive care unit time, noninvasive ventilation use, MELD score, SAPS 3, BAR, and SOFA third days – after liver transplantation were significantly different ($p < 0.001$). In the multivariate regression analysis, the predictors of reintubation after liver transplantation were ventilator associated pneumonia (*odds ratio* – OR = 10.6; 95% confidence interval – 95%CI 1.04-108.3; p = 0.04) and BAR (OR = 1.18; 95%CI 1.02-1.36; p = 0.02). The highest ROC curves were SOFA third day, MELD, SAPS 3 and BAR scores through the intersections of the sensitivity and specificity curves > 0.70. High values of the BAR score were considered risk factors for reintubation in this study. SOFA third day showed moderate discriminatory power in predicting reintubation after liver transplantation.

Descriptors: Intensive Care Units; Liver; Intubation; General Surgery; Transplantation.

INTRODUCTION

Mechanical ventilation is a life-saving intervention, but the timing of liberation from invasive mechanical ventilation is an important issue for clinicians caring for critically ill intubated patients receiving mechanical ventilation in intensive care units (ICUs).[1] The benefit-risk ratio for extubation has to be assessed on a daily basis. If the patient remains intubated too long, complications associated with prolonged mechanical ventilation may appear.[2] On the other hand, if the patient is extubated too early, reintubation is associated with higher mortality and long-term disability.[3] Extubation failure is defined as the need for reintubation within 24-72 h or up to seven days.[4]

Extubation failure happens due to airway failure caused by upper-airway obstruction and lower-airway obstruction due to aspiration or excessive respiratory secretions. Airway obstruction is related with witnessed aspiration or inability to maintain airway patency because of respiratory secretions, ineffective cough or inability to expectorate. It is necessary repeated nasotracheal aspiration development of atelectasis during the post-extubation period.[4] Extubation failure due to non-airway failure was defined by Epstein and Ciubotaru,[5] and congestive heart failure, respiratory failure due to lung disease and hypoventilation were included in this category.

Several methods for anticipating/managing non-airway failure have been explored, including careful cardiac assessment using brain natriuretic peptide[6] or transthoracic echocardiogram during spontaneous breathing trials spontaneous breathing trials (SBT).[7] Ultrasound and electrical impedance tomography are used to evaluate the heart, diaphragm, pleura, and lungs during the weaning process.[8]

A previous multicenter observational study published in 2018 including 1,514 medical ICU patients who required reintubation has reported the respective incidences of airway failure (45%) and non-airway failure (50%).[9]

The postoperative respiratory complications are one of the main risks of surgery, increasing morbidity and mortality. One of the consequences of acute postoperative respiratory failure is usually linked to tracheal reintubation and extension of invasive mechanical ventilation. Tracheal reintubation is associated with higher mortality rate, increased health care consumption, hospitalization, and time at the ICU.[10]

Surgical outcome of patients after liver transplantation (LTx) is influenced by preoperative physiological status, surgical risk, and appropriate postoperative care. Thus, the importance of risk factors data for morbidity and mortality for this group becomes fundamental. The objectives predictive indexes are to improve ICU performance, correct conduct errors, establish the disease severity and evolution pattern, estimate length of stay, prevent ventilator care, and direct health care assistance after elective LTx.[11] Jaber et al. suggest further studies will be needed to develop and validate scores predicting airway and non-airway failure for success extubation and consequently a decrease in the rate of reintubation.[9]

The aim of this study was to identify the main risk factors and predictive scores for reintubation after LTx.

METHODS

Observational prospective study based on the analysis of the records contained in the Adult Transplant ICU database of the Clinics Hospital at the Universidade Estadual de Campinas (HC-UNICAMP). We analyzed the data of patients submitted to liver transplantation and required reintubation during the ICU stay between 2013 and 2018. The HC-UNICAMP database is managed by a trained and exclusive professional, who prospectively feeds the information collected through the medical records, in order to keep the patient's identity confidential. The project was approved by the Ethics Committee of the Faculty of Medical Sciences of Campinas by the report No. 1,240,556.

Eligibility criteria for enrolling patients in the study were age over than 18 years old and all transplant patients admitted to the ICU for anesthetic recovery and extubated. Patients who didn't have complete data in the medical records in the database and those who underwent liver transplantation combined with the renal transplantation were excluded from the study.

All subjects underwent the weaning and extubation protocol and needed non-invasive ventilation developed by the multidisciplinary team of the ICU, which is available in the "Clinics Hospital UNICAMP Adult ICU Procedures Manual", accordingly with Brazilian Mechanical Ventilation Guidelines (2013).

For the data analysis, the subjects were divided into two groups:

- Reintubated group, which included patients who needed reintubation in the ICU at the time of admission until discharge from the ICU;
- Non-reitubated group, which included patients undergoing liver transplantation who weren't reintubated.

The variables and characteristics analyzed and correlated to reintubation were redistributed in the pre, intra and postoperative LTx moments. In the pre-operative period, the variables were the model for end-stage liver disease (MELD) and Child-Pugh (CHILD).

The MELD score was implemented in 2002 to estimate the severity of liver disease and the mortality prognosis of patients on the liver transplantation waiting list. Through the patients' medical records, the MELD values recorded by the medical team during the outpatient follow-up while they were waiting for transplantation were captured.[12]

In the intraoperative period, it was used the balance of risk score (BAR). In the BAR score, the variables used were donor age (years), cold ischemia time (hour), retransplantation (yes / no), ICU days with artificial life support (mechanical ventilator), recipient age (years), and MELD value without special punctuation.[13]

In the postoperative period, the general demographic characteristics of the studied population were analyzed, such as age, body mass index (BMI), gender, and primary diagnosis of the disease. Other variables included were mechanical ventilation time (MV), ICU and hospitalization times, and use of noninvasive ventilation. Death rate, ventilator assisted pneumonia (VAP), sequential organ failure assessment score (SOFA), Acute Physiology and Chronic Health Disease Classification System II (APACHE II), mortality by APACHE II, Child-Pugh (CHILD), simplified acute physiology score (SAPS 3), mortality by SAPS 3, and need for reintubation were investigated.

For the calculation of the SOFA of the first and third day of length of stay ICU, the variables that evaluate the systemic function of six organs were used, as proposed by Vincent et al.[14]

To calculate APACHE II, the final equation proposed by Knaus et al.[15] was used and calculated online through the *Sfar* system that integrates the database software.

The SAPS 3 score is composed of 20 different variables, divided into three parts: demographic variables, reasons for ICU admission, and physiological variables. These variables represent the degree of disease impairment and health status assessment prior to hospital admission, indicating pre-morbid condition. In South America, the index was calibrated with a value of 1.3, the relation between observed and expected mortality (SAPS 3 mortality).[16]

Statistical analysis

Quantitative variables were expressed as means (standard deviation) or medians (interquartiles 25-75%) and compared using the Student's t-test or the Wilcoxon test. Qualitative variables were compared using the χ^2 test or the Fisher's test.

For qualitative variables, absolute (n) and relative (%) frequency were adopted. Observed the normality of data distribution, Kolmogorov-Smirnov test, qualitative variables with χ^2 test, quantitative variables with normal distribution, Student's t-test, quantitative variables with abnormal distribution, and Mann-Whitney test were used.

The multinomial logistic regression allows simultaneous comparison of reintubed group and non-reintubed group with risk factors and predictive indexes. A multivariate multinomial logistic model was established. Interactions between variables were tested, variables with $p < 0.05$. *Odds ratios* (ORs) with 95% confidence intervals (CIs) for response were calculated using "factors the reintubation" as the reference category.

To calculate the sensitivity and specificity of the patient's severity scores in predicting the reintubation rate, the receiver operating characteristic curve (ROC) was performed.

RESULTS

The flow diagram reports numbers of individuals included at each group in the study, completing the follow-up.

Table 1 describes the general characteristics of the population studied. The values of the variables were expressed as median, Q1-Q3 and frequency as a percentage of the variables. The age was from 54 to 57 years old, male prevalence (174 individuals), and body mass index (BMI) of 29.3 [30.9-34.6] kg/m^2. The primary diagnoses were hepatitis by C virus with liver cirrhosis (46.6%), and cirrhosis alcoholic liver disease (19.4%) of the total of 237 individuals analyzed.

The death rate, prevalence of VAP, time of mechanical ventilation, use of noninvasive ventilation, length of hospital stay ICU, hospitalization, value of the SOFA in the third day, SAPS 3, and BAR showed statistically significant higher values $p < 0.05$ in the reintubation group compared with non-reintubation group. The variables were expressed as medians, percentage, and significance in Table 2.

Table 3 shows in the multivariate analysis BAR score and the VAP were predictive factors for reintubation.

It has been observed that the area under the curve (AUC) the ROC for SOFA score third days was 0.7 (95%CI 0.59-0.82; p = 0.001), SAPS 3 0.64 (95%CI 0.52-0.77; p = 0.02), BAR 0.65 (95%CI 0.2-0.77; p = 0.01) and MELD 0.62 (95%CI 0.48-0.76; p = 0.04) in Fig. 1 showed moderate discriminatory power in predicting reintubation after liver transplantation. However, there was no statistical difference between them.

Table 1. General demographic characteristics and descriptive analysis of the studied population.

Analyzed variables	Median	Q1-Q3 ST	Frequency (%)	Overall
Pre-operative				
Age (years old)	57	54-57		237
Gender				
Male			174 (73.4)	237
Female			63 (26.6)	
BMI (kg/m²)	29.3	30,9-34.6		237
Indication of LTx				
Hepatitis C virus			110 (46.4)	237
Cryptogenic			38 (16)	
Alcoholism			46 (19.4)	
Hepatitis B Virus			15 (6.3)	
Autoimmune			7 (3)	
Other reasons			21 (8.8)	
Comorbidities				
Hypertension			62 (26)	237
Diabetes mellitus			57 (24)	
Renal insufficiency			1 (0.4)	
Alcoholism			67 (28.3)	
Smoking			46 (19)	
Heart insufficiency			0	
Chronic Renal insufficiency			4 (1.7)	
CHILD				
A			38 (16)	126
B			42 (17.7)	
C			46 (19.4)	
MELD	17	14.5-17.7		237
Intraoperative				
BAR	12	11-12		237
Postoperative				
APACHE II	16	16.2-17.6		237
APACHE II mortality	24	26.2-30.3		237
SAPS 3	9	11.9-15.7		237
Mortality			60 (25.3)	

Q1-Q3: quartiles; ST: standard deviation; BMI: body mass index; LTx: liver transplantation; CHILD: Child-Pugh; MELD: model for end-stage liver disease; BAR: balance of risk score; APACHE II: Acute Physiology and Chronic Health Evaluation; SAPS 3: simplified acute physiology score.

Table 2. Descriptive analysis and comparisons between reintubated and non-reintubated groups.

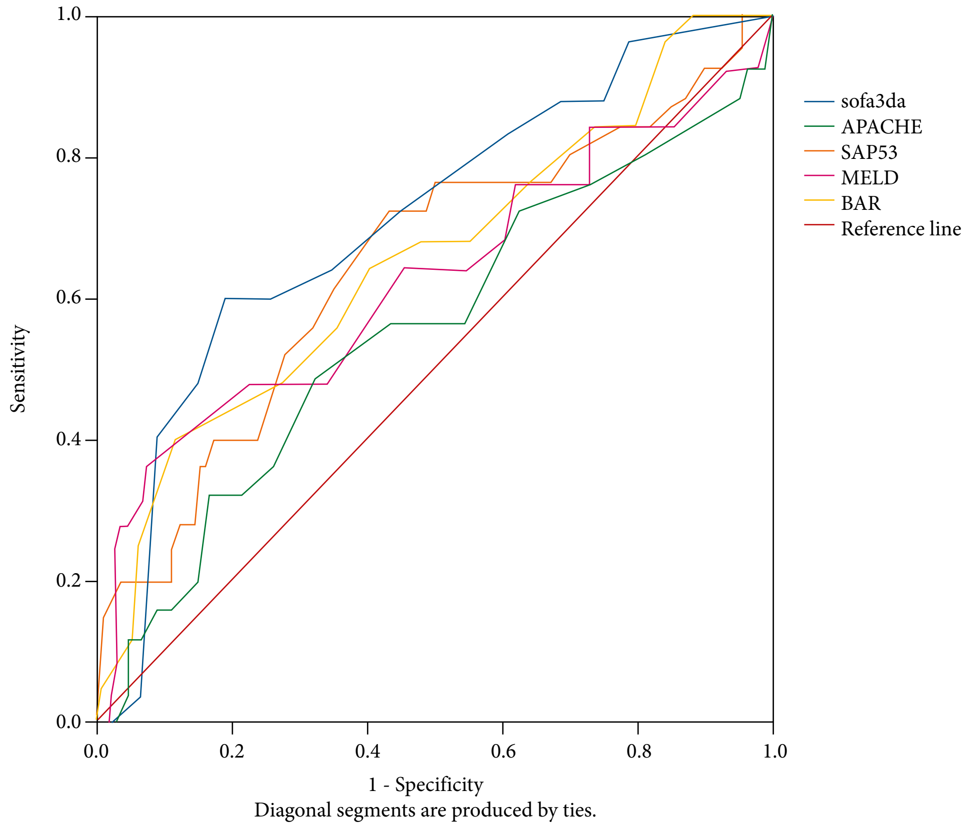
Variables	Reintubated N = 38		Non-reintubated N = 199		P-value
	M [Q1-Q3]	Frequency (%)	M [Q1-Q3]	Frequency (%)	
Pre-operative					
Age (years old)	57 [54.2-57.2]		56 [49.2-57.5]		0.54
Gender					
Male		26 (15)		147 (85)	0.48
Female		12 (18.8)		52 (81.2)	
BMI (kg/m²)	27.7 [28.6-44.0]		29.7 [30.4-33.9]		0.94
CHILD					
A		7 (18.4)		31 (15.6)	0.76
B		5 (13.2)		37 (18.6)	
C		9 (23.7)		37 (18.6)	
MELD	19 [11.7-21.2]		17 [14.4-17.7]		0.54
Intraoperative					
BAR	14 [12-16]		11 [11-12]		0,01*
Postoperative					
Mortality		22 (57.9)		38 (19.1)	<0.001*
VAP		8 (21.1)		4 (2.0)	<0.001*
Time MV (days)	6 [5-19]		1 [1-3]		<0.001*
Length of stay ICU (days)	14 [16-32]		4 [5-7]		<0.001*
Use of NIV		25 (65.8)		49 (24.6)	<0.001*
Hospitalization time (days)	16 [19-24]		24 [26-44]		<0.001*
SOFA	10 [8-10]		8 [7-8]		0.27
SOFA third day	10 [8-10]		8 [8-9]		<0.001*
SAPS 3	47 [43.5-53.9]		41 [41.2-44]		0.03*
Mortality SAPS 3	13 [14.1-28.9]		7 [10.1-13.7]		0.03*
APACHE II	16 [15.4-18.9]		16 [16.1-17.6]		0.67
Mortality APACHE II	24 [23.8-33.9]		24 [25.9-30.5]		0.69
Need of Re-Tx	3 [7.9]		12 [6]		0.66

M: median; Q1-Q3: quartiles; BMI: body mass index; CHILD: Child-Pugh; MELD: model for end-stage liver disease; BAR: balance of risk score; VAP: ventilator associated pneumonia; MV: mechanical ventilation; ICU: intensive care unit; NIV: noninvasive ventilation; SOFA: sequential organ failure assessment; SAPS 3: simplified acute physiology score; APACHE II: Acute Physiology and Chronic Health Evaluation; Re-Tx: liver transplantation; *p<0.05.

Table 3. Multivariate logistic regression analysis for the study of risk factors reintubation in relation to the variables MV time (days), use of NIV, VAP, BAR and SAPS3.

Variables	95%CI	OR	P-value
Intraoperative			
BAR	1.02-1.36	1.18	0.02
Postoperative			
MV time (days)	0.99-1.01	1.04	0.06
Use VNI, n (%)	0.96-9.68	3.05	0.05
VAP, n (%)	1.04-108.3	10.6	0.04
SAPS 3	0.99-1.09	1.04	0.07

MV: mechanical ventilation; NIV: non-invasive ventilation; VAP: ventilator associated pneumonia; BAR: balance of risk score; SAPS 3: Simplified Acute Physiology Score; 95%CI: 95% confidence interval for OR; OR: odds ratio; *p<0.05.



ROC: receiver operating characteristic; SOFA third dia: sequential organ failure assessment score third day; APACHE II: Acute Physiology and Chronic Health Evaluation; SAPS 3: simplified acute physiology; MELD: model for end-stage liver disease; BAR: balance of risk score; ICU: intensive care unit.

Figure 1. ROC curve of SOFA third day, APACHE II, SAPS 3, MELD and BAR scores at the end of reintubation probability of patients after liver transplantation in ICU.

DISCUSSION

It was observed in the current study that the risk factors for reintubation were BAR score and VAP in multivariate analysis. In similar studies, the main of reintubation factors were preoperative infection control, ABO blood type incompatibility in blood transfusion, postoperative pneumonia, and development of graft dysfunction.[17]

Despite of the scarcity of studies and literature referring to reintubation predictor scores after LTx, Magalhães et al.[18] observed that cold ischemia time, a variable used in the BAR score still in the intraoperative period, was a predictor of pulmonary complications after LTx. In view of the variables analyzed in the BAR score, Bhangui et al.[19] observed that young patients with a low MELD value are viable and safe candidates to be extubated still on the operating room after LTx. Ferraz Neto et al.[20] reported that patients after LTx with BAR values below 18 showed longer ICU stay for respiratory complications and survival below 80%, corroborating the findings of the current study, in which the BAR score showed good discriminating power through AUC in predicting reintubation and through multivariate analysis (OR = 1.18; 95%CI 1.02-1.36; p = 0.02).

Some complications are inherent in ICU admission after LTx surgery, such as pressure injury, sepsis, pulmonary complications, VAP, delirium, global muscle weakness, and reintubation.[10] In the current study, 16% of the patients were reintubed. In a systematic study, it was observed that in eight studies reintubation rate in patients who were extubated immediately after transplantation was from 0 to 11% and in patients who were extubated in the conventional way in the ICU it was from 0 to 36%.[22] The reintubation generates high hospital costs; the average LTx cost in Brazil is around R$ 17,367, corresponding to 31.9% in the surgical unit and 25.3% in ICU.[23]

Prolonged mechanical ventilation may also increase right ventricular after load and even induce venous congestion of the liver graft, especially in those with pre-existing tricuspid regurgitation and raised pulmonary artery pressures (which is not uncommon in end-stage liver disease patients).[24] When comparing the reintubated group with the non-orotracheal reintubation

(Retot) group, it can be observed that the ICU time values (14 [16-32] days and 4 [5-7] days, < 0.001), mechanical ventilation time (6 [5-19] and 1 [1-3] days < 0.001) and mortality 57.9% *vs*. 19.1% were significantly higher in the reintubated group.

Metabolic alteration, nutritional deficiency, low body weight, loss of muscle mass, decreased mobility of the rib cage impaired by ascites and increased respiratory work caused by increased intra-abdominal pressure are some of the factors that contribute to weakness of the diaphragm muscle in individuals with liver disease on the waiting list transplantation.[25] Some authors have observed through diaphragmatic ultrasound examinations that 79% of individuals who underwent LTx had right diaphragm paralysis in more than half of these patients, caused by abdominal surgery combined with anesthesia.[26] Duarte et al. also observed through surface electroneuromyography examination lower effectiveness of the diaphragm muscle after ICU extubation on liver transplantation, thus presenting greater difficulty for the individual to perform resistance breathing.[25] Weak diaphragm decreases an individual's chances of successful spontaneous ventilation and successful extubation of ventilatory support.

Respiratory complications in the postoperative abdominal period are multifactorial and partially related to atelectasis due to pulmonary hypoventilation, collapse of the alveolar, retained secretions and diaphragmatic dysfunction. The use of the non-invasive ventilation (NIV) technique can improve lung volume by combining effects positive expiratory pressure (PEEP) and inspiratory pressure support, which together provide reduction in respiratory work, increased pulmonary ventilation, reopening of collapsed alveolar and improved gas exchange. Failure in NIV indications and treatment protocols inevitably reflects increased reintubation, mortality rate, prolonged mechanical ventilation, length of ICU, hospitalization, and morbidity. However, studies are needed to evaluate the benefits, indications, contraindications, and protocols for NIV administration after liver transplantation.[27]

Patients submitted to LTx have higher risk for developing VAP and severe respiratory complications because of complex surgical procedure, immunosuppression, intraoperative blood component transfusion, severe encephalopathy, pleural exudate, large bleeding, longer ICU time and need for reintubation.[27] Postoperative VAP was reported by some authors as a predictor of reintubation.[17,28] However, in the current study, VAP values were higher in the Retot group than in the non-reintubated group – 21.1% ($n = 8$) and 2% ($n = 4$), $p < 0.001$ and considered as a predictive factor for the reintubation in the postoperative period through multivariate analysis (OR = 10.6; 95%CI 1.04-108.3; $p = 0.04$).

The MELD score values were obtained in the preoperative evaluation of LTx candidates, but it can be observed that it presents light discriminating power through AUC (0.62; 95%CI 0.48-0.76; $p = 0.04$) in predicting reintubation after transplantation, corroborating with other studies, which observed that the score MELD was not only a predictor of mortality, but also a predictive of respiratory failure and extubation time after LTx.[4,8]

The SAPS 3 score was not designed to be representative of all patient types, especially in specific areas or individual types of disease, as it was performed in the general ICU population. Therefore, external validation is important before applying this score to any type of patient, such as surgical patients. However, some studies report that the SAPS 3 prediction score has proved to be a useful tool for verifying patients in need of greater care and for the very evolution of high-risk surgical patients, and may be applied.[16] Articles on the use of the SAPS 3 score as a predictive factor of reintubation after LTx are scarce in the literature to discuss the positive findings of the use of the score found in the present study.

The values of SOFA in the third day were significantly different between the studied groups: in the reintubated group it was 10 (8-10) and in the non-reintubated 8 (8-9). Huang et al. observed that the SOFA score of patients who developed postoperative LTx respiratory failure on the second day was associated with an increase in the SOFA score value compared to patients without acute respiratory failure (8.1 ± 3.4 *vs*. 4.9 ± 1.8, $p < 0.001$).[29] In a similar study, but with a group of patients after cardiac surgery, they found a SOFA value (6.9 ± 2.6) and a predictor of reintubation.[30] Jaber et al.[9] showed that certain risk factors were specific to non-airway failure (non-obese status, SOFA score ≥ 8). SOFA scores that increase by about 30% during hospitalization are associated with mortality of at least 50%.

To date, few studies have been found on the topic. There are different predictors indexes that need be collected more accurately or more systematically, which would allow achieving C-statistics of 0.8 or greater.

The study has certain limitations and strengths requiring discussion. First, it was not possible to evaluate and compare the risk factors for reintubation related to the airway failure in present study. The correct classification non-airway failure in extubation was defined by two authors, but none of them studied and applied this term in patients after transplantation.[9] Second, this pragmatic non-interventional observational study reflected Brazil ICU practices in real life. Some specific risk factors airway, such as cough strength determined using a peak flow system, rapid shallow breathing index, maximal inspiratory and expiratory pressures or airway occlusion pressure, were evaluated and practiced by physiotherapists, however not all ICUs have this professional present 24 hours a day. The present study also demonstrated the strength of this observational study, which sought identify risk factors and predictive indexes that can be accessible to a multidisciplinary team and assist in safe and early extubation this pragmatic non-interventionist observational study. A further step would be to try to create an own index and try to outperform the SOFA index.

CONCLUSION

The high values of the BAR and SOFA scores should be constantly monitored by the multiprofessional team in the liver transplant ICUs, not only as predictor of survival, but a predictor of reintubation after LTx. Reintubation is considered of the main and frequent complications in the ICU and related with mortality.

AUTHORS' CONTRIBUTION

Substantive scientific and intellectual contributions to the study: Agostini APRA, Figueiredo LC, Martins LC and Falcao ALE; **Conception and design:** Agostini APRA, Figueiredo LC, Martins LC, Tonella RM and Ratti LSR; **Technical procedures:** Boin IFSF; **Analysis and interpretation of data:** Heidemann A, Martins LC; **Statistics analysis:** Heidemann A; **Manuscript writing:** Agostini APRA; **Critical revision:** Agostini APRA, Figueiredo LC, Martins LC, Falcao ALE, Tonella RM, Ratti LSR, Boin IFSF and Heidemann A.

DATA AVAILABILITY STATEMENT

All dataset were generated or analyzed in the current study.

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