JOURNAL OF INONU LIVER TRANSPLANTATION INSTITUTE

DOI: 10.14744/jilti.2023.36036
J Inonu Liver Transpl Inst 2023;1(3):107–112

Original Research

Predicting Early Post-Transplant Mortality: The Role of ICU Stay in Liver Transplant Recipients with HBV-Related Cirrhosis

Akile Zengin,[1] Yusuf Murat Bag,[2] Yasin Dalda,[3] Bora Barut,[4] Sezai Yilmaz[4]

[1]Department of Gastrointestinal Surgery, Eskisehir Osmangazi University Faculty of Medicine, Eskisehir, Turkiye
[2]Department of General Surgery, Ankara Training and Research Hospital, Ankara, Turkiye
[3]Department of General Surgery, Yesilyurt State Hospital, Malatya, Turkiye
[4]Department of Surgery and Liver Transplant Institute, Inonu University Faculty of Medicine, Malatya, Turkiye

Abstract

Objectives: Liver transplantation is the only treatment option for patients with end-stage liver disease. Hemodynamic, respiratory, and metabolic monitoring in the intensive care unit (ICU) is a vital step after the transplant procedure. While most recipients are discharged from the hospital within postoperative two weeks, some patients stay longer, which increases both morbidity and the costs of liver transplantation. We aimed to explore the implications of ICU stay for post-transplant early mortality.

Methods: This is a retrospective analysis of the liver transplant recipients with Hepatitis B virus (HBV)-related cirrhosis between January 2017 and June 2022. Patients ≥18 years with HBV-related cirrhosis were included in the study. The patients were analyzed in two groups: patients who survived (n=167) and patients with early mortality (n=11) defined as mortality within postoperative 90 days. Various operative and clinical data were compared among the groups.

Results: Post-transplant ICU stay was significantly longer in patients with mortality (11 (7-21) versus 5 (4-7), p<0.001). Although it was not statistically significant, the MELD score (20 (17-25) versus 17 (14-22), p=0.051) and postoperative severe complication rate (63.6% to 34.1%, p=0.058) tended to be higher in the mortality group. We performed a ROC curve analysis and showed that cut-off value for the length of ICU stay was 10.5 days in terms of 90-day mortality. The sensitivity was 64% and the specificity was 94% (the area under the curve = 0.820, 95% CI = 0.651- 0.990, p<0.001). In univariate analyses, duration of operation (HR = 1.005, 95% CI = 1.002-1.009, p=0.002) and ICU stay ≥10.5 days (HR = 19.855, 95% CI = 5.796-68.011, p<0.001) were found as significant variables, but in multivariate analyses, only the ICU stay ≥10.5 days (HR = 17.204, 95% CI = 3.881-76.265, p<0.001) was found as an independent predictor of early post-transplant mortality.

Conclusion: The prolonged ICU stay is an independent predictor of postoperative 90-day mortality in living donor liver transplantation for HBV-related cirrhosis. By using length of ICU stay, high risk patients can be determined and closely monitored for early detection and management of serious complications that may lead to early post-transplant mortality.

Keywords: Complication, cirrhosis, survival, mortality, ICU, LDLT

Please cite this article as "Zengin A, Bag YM, Dalda Y, Barut B, Yilmaz S. Predicting Early Post-Transplant Mortality: The Role of ICU Stay in Liver Transplant Recipients with HBV-Related Cirrhosis. J Inonu Liver Transpl Inst 2023;1(3):107–112".

Address for correspondence: Akile Zengin, MD. Department of Gastrointestinal Surgery, Eskisehir Osmangazi University Faculty of Medicine, Eskisehir, Turkiye
Phone: +90 507 824 08 60 **E-mail:** dr.akile.zengin@gmail.com

Submitted Date: 08.01.2024 **Revised Date:** 11.01.2024 **Accepted Date:** 11.01.2024 **Available Online Date:** 23.01.2024

Liver transplantation is the only viable treatment option for patients with end-stage liver disease.[1] It is the only mode of therapy that provides acceptable survival and improved patient life quality.[2] Liver transplantation is a demanding major abdominal surgery but, establishment of hemodynamic stability, and metabolic monitoring in the intensive care unit (ICU) after the transplant procedure are equally important for a positive outcome of the patients.[3] ICU care of the patients has important implications in terms of the outcome of the liver transplant recipients.[4]

Most recipients are discharged from the hospital within two weeks following the operation. However, some patients stay longer, which increases both morbidity and the cost of liver transplantation.[5] The model for end-stage liver disease-sodium (MELD-Na) is a scoring system that characterizes the severity of the liver disease and enables physicians to prioritize critically ill patients for liver transplantation.[6] It has been shown that patients with higher MELD scores have longer ICU stays.[7] In addition, it was found that prolonged hospital stay is due to complications such as biliary strictures or leaks, early postoperative renal failure, sepsis, and multiorgan dysfunction.[8]

Our aim in the present study is to evaluate the effect of ICU stay on early post-transplant mortality after living donor liver transplantation (LDLT).

Methods

Patient Selection

This study was approved by the institutional review board (Approval number: 2023/4087). Between January 2017 and June 2022, a total of 178 adult patients received LDLT to treat Hepatitis B virus (HBV)-induced cirrhosis, a condition prevalent in Turkey that accounts for the majority of such liver complications. This selection criteria ensured a homogenous study group, focusing exclusively on individuals who received their first liver transplant (primary LDLT) due to chronic liver disease caused by HBV-related cirrhosis. We divided participants into two categories based on their postoperative outcomes: those who survived beyond the 90-day postoperative period (167 patients) and those who experienced mortality within this timeframe (11 patients). All patients gave written informed consent before the transplant procedure.

Study Parameters

Complications observed during the early postoperative period, which encompasses the first 90 days following surgery, were assessed and instances of death within this timeframe were categorized as early postoperative mortality. The complications were classified according to the Clavien-Dindo classification.[9] Clavien-Dindo grade 3 or higher complications were considered as severe complications. Demographic characteristics including age, and gender; clinical characteristics such as American Society of Anesthesiologists risk classification (ASA), MELD-Na; preoperative laboratory values including alanine aminotransferase (ALT), alanine aminotransferase (ALT), graft-to-recipient weight ratio (GRWR), type of liver graft, warm ischemia time (WIT), cold ischemia time (CIT), duration of ICU stay, operative time, intraoperative blood loss, length of hospitalization were all recorded for each patient.

Statistical Analysis

The Statistical Package for Social Sciences version 25.0 (SPSS v25.0) (IBM Corp., Armonk, N.Y., USA) was used for all statistical analyses. Kolmogorov-Smirnov test was used as the normality tests for the continuous variables. The continuous variables that distributed normally were given as mean±standard deviation (SD). The variables that did not distribute normally were expressed as median (interquartile range). Categoric variables were expressed as number of affected individuals and percentage (%) of the study population. Student t-test and Mann-Whitney U test were used for the comparison of the continuous variables between the study groups. Chi-square and Fisher's exact tests were used for the comparison of the categoric variables. Receiver operating characteristics (ROC) curve analysis was performed for the calculation of the cut-off value for the length of ICU stay. Univariate Cox regression analyses were performed for all variables. Multivariate Cox regression analyses were performed, using all variables with a $p \leq 0.10$ in the univariate analyses, for the determination of independent risk factors for early mortality. The Kaplan-Meier analysis was performed for survival analysis among the groups. Any p-value less than 0.05 was considered statistically significant.

Results

Table 1 summarizes the demographic, clinical, and preoperative laboratory data of the patients in the study groups. Only the duration of ICU stay was significantly higher in the patients with mortality [11 (7-21) versus (4-7), $p<0.001$]. The MELD-Na score among the patients who survived and patients with early mortality was 17 (14-22) and 20 (17-25); respectively ($p=0.051$). The incidence of severe complications in patients who survived and patients with early mortality was 34.1% and 63.6%; respectively ($p=0.058$). Although, patients with early mortality tended to have higher MELD-Na scores and higher serious complication rates, this did not reach statistical significance.

Table 1. Demographics and perioperative characteristics of the patients[x]

	Study group (n=178)	Survival group (n=167)	Mortality group (n=11)	P
Age, years	52 (44-59)	52 (45-59)	52 (39-58)	0.541
Gender, male	135 (75.8)	127 (76)	8 (72.7)	0.728
BMI (kg/m^2)	26.34±4.1	26.42±4.05	24.97±4.74	0.257
ASA score				
<3	22 (12.4)	22 (13.2)	-	0.364
≥3	156 (87.6)	145 (86.8)	11 (100)	
MELD-Na score	17 (15-22)	17 (14-22)	20 (17-25)	0.051
Preoperative ALT (U/L)	43.5 (27-71)	44 (28-71)	37 (18-76)	0.338
Preoperative AST (U/L)	63.5 (42-98)	64 (42-98)	56 (43-68)	0.422
Liver graft				
Right	171 (96.1)	160 (95.8)	11 (100)	1
Left	7 (3.9)	7 (4.2)	-	
GRWR (%)	1.02 (0.9-1.17)	1.02 (0.9-1.17)	0.97 (0.91-1.08)	0.781
WIT (minutes)	54 (42-63)	53 (42-63)	56 (45-64)	0.504
CIT (minutes)	80 (57-106.5)	80 (56.76-107)	84 (68-94)	0.931
Operation time (minutes)	504 (480-570)	502 (480-570)	540 (485-690)	0.155
Intraoperative blood loss (ml)	500 (400-700)	500 (350-700)	500 (500-800)	0.241
ICU stay, days	5 (4-7)	5 (4-7)	11 (7-21)	**<0.001**
Hospital stay, days	31 (25-41.26)	31 (25-41)	29 (15-51)	0.387

[x]Results are expressed as: mean±standard deviation, median (interquartile range), or frequency (%); Significant P values are in bold; BMI: Body mass index; ASA: American Society of Anesthesiologists; MELD: Model for End-Stage Liver Disease; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GRWR: Graft-to-recipient weight ratio; WIT: Warm ischemia time; CIT: Cold ischemia time; ICU: Intensive care unit.

We performed ROC curve analyses on the length of ICU stay in association with the occurrence of early mortality in the patients and the cut-off value was determined as 10.5 days. The sensitivity and specificity of the cut-off value were 64% and 94%; respectively. The area under the curve (AUC) was 0.820 (95% CI = 0.651- 0.990, p<0.001) (Fig. 1).

The univariate and multivariate Cox regression analyses for the predictors of early mortality are summarized in Table 2. Operative time (HR = 1.005, 95% CI = 1.002-1.009, p=0.002), length of ICU stay ≥ 10.5 days (HR = 19.855, 95% CI = 5.796-68.011, p<0.001) were significant risk factors of early mortality in univariate analyses. In the multivariate analyses only length of ICU stay≥ 10.5 days (HR = 17.204, 95% CI = 3.881-76.265, p<0.001) was the independent predictor of early mortality. The results of the Kaplan-Meier analyses are summarized in Table 3 and Figure 2. The early mortality rate of the patients with a length of ICU stay <10.5 days versus ≥10.5 days was 2.5% versus 41.2%, respectively (Log-rank Chi-Square = 45.111, p<0.001).

The causes of early mortality were peritonitis due to bile leakage in 3 (27%) patients, sepsis due to an intra-abdominal infected hematoma in 2 (18%)patients, prerenal acute renal failure in 1 patient (9%), SARS-CoV-2 infection in 1 patient (9%), acute cellular rejection and sepsis in 1 patient (9%), portal vein (PV) thrombosis and multiorgan dysfunction in 1 patient (9%), hepatic artery thrombosis (HAT) and intestinal ischemia in 1 patient (9%), and cardiac event in 1 patient (9%).

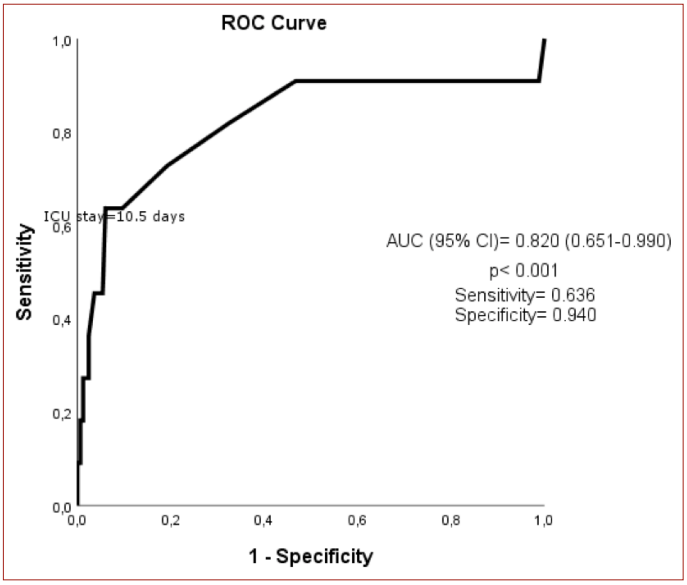

Figure 1. The receiver operating characteristics (ROC) curve for the cut-off value of the length of intensive care unit (ICU) stay in predicting 90-day mortality after living donor liver transplantation (LDLT) for Hepatitis B virus (HBV)-related liver cirrhosis.

Table 2. Cox regression analysis evaluating the predictors of 90-day mortality after LDLT for HBV related-cirrhosis.

Variable	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI Lower-Upper	p	Hazard ratio	95% CI Lower-Upper	p
Age, years	0.977	0.924-1.033	0.405	-	-	-
Gender, male	0.862	0.229-3.251	0.827	-	-	-
BMI (kg/m^2)	0.916	0.787-1.065	0.254	-	-	-
ASA score ≥3	24.741	0.011-57122.628	0.417	-	-	-
MELD score	1.089	0.992-1.194	0.072	1.049	0.951-1.157	0.340
Preoperative ALT (U/L)	0.996	0.984-1.007	0.466	-	-	-
Preoperative AST (U/L)	0.997	0.988-1.005	0.473	-	-	-
Graft type, right	0.047	0-28793.250	0.653	-	-	-
GRWR (%)	0.551	0.032-9.379	0.680	-	-	-
WIT (minutes)	1.004	0.975-1.034	0.786	-	-	-
CIT (minutes)	0.999	0.982-1.016	0.882	-	-	-
Operation time (minutes)	1.005	1.002-1.009	0.002	1.002	0.998-1.007	0.328
Intraoperative blood loss (ml)	1.001	1-1.001	0.081	1	0.999-1.001	0.753
ICU stay ≥10.5 days	19.855	5.796-68.011	<0.001	17.204	3.881-76.265	<0.001
Hospital stay, days	0.989	0.953-1.027	0.573	-	-	-

LDLT: Living donor liver transplantation; HBV: Hepatitis-B virus; CI: Confidence interval; BMI: Body mass index; ASA: American Society of Anesthesiologists; MELD: Model for End-Stage Liver Disease; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GRWR: Graft-to-recipient weight ratio; WIT: Warm ischemia time; CIT: Cold ischemia time; ICU: Intensive care unit.

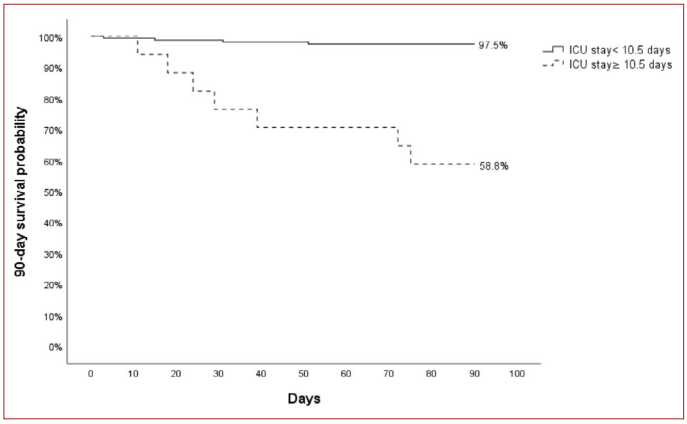

Figure 2. Kaplan–Meier 90-day survival graph of patients with living donor liver transplantation (LDLT) for Hepatitis B virus (HBV)-related liver cirrhosis according to the length of intensive care unit (ICU) stay with a cut-off value of 10.5 days.

Discussion

We have evaluated the duration of ICU stay and its implications in the post-transplant 90-day mortality in patients who received LDLT for HBV related cirrhosis. The study is unique in terms of the results for we have found that patients with an ICU stay longer than 10.5 days had higher early mortality in LDLT recipients.

Factors such as undiagnosed heart diseases prior to liver transplantation, high MELD score, Hepatitis C virus as the cause of end-stage liver disease, post-transplant infections, gastrointestinal bleeding, rejection, and renal failure cause prolonged hospitalization durations, and an increased risk of mortality.[8] Stratigopoulou et al.[4] showed that an ICU stay longer than 3 days affects the length of hospitalization, early mortality rates, and post-transplant survival. It is known that a high preoperative MELD score is a predictive factor that affects graft and recipient survival.[10] Furthermore, a high MELD score prolongs the duration of ICU care in the post-transplant period.[7] Bayrak et al.[1] stated that a MELD score of 19 can predict 30-day mortality of the recipients following the liver transplant. Niewińsk et al.[3] analyzed the results of 150 patients and reported that MELD scores greater than 16 were closely correlated with the length of postoperative ICU stay.

Transplant recipients are susceptible to infection and have a high risk of severe sepsis and infections that reduce graft and patient survival.[11, 12] The liver prevents sepsis induced tissues and organs damage.[13] It regulates the levels of the proinflammatory cytokines and chemokines in the circulation. Kupffer cells are the first line of defense against enteric bacteria, and microbial and environmental toxins originating from the intestinal tract.[14]

Pereira et al.[15] reported that there was a correlation between the 28-day mortality and the number of organ systems that failed during the ICU stay, the arterial lactate

Table 3. Results of Kaplan-Meier survival analysis for 90-day mortality in the patients with LDLT for HBV related-cirrhosis

	90-day mortality, n (%)	Log-rank Chi-Square	p
ICU stay <10.5 days (n=161)	4 (2.5)	45.111	<0.001
ICU stay ≥10.5 days (n=17)	7 (41.2)		

LDLT: Living donor liver transplantation; HBV: Hepatitis-B virus; ICU: Intensive care unit.

level on the postoperative third day in the ICU, and the INR. In LDLT, the duration of ICU stay in after the transplant procedure has high sensitivity and specificity in predicting the incidence of acute renal injury.[5] Postoperative renal dysfunction may occur due to the presence of hepatorenal syndrome before transplantation or post-transplant graft dysfunction, prolonged use of sympathomimetic agents, and the drugs that are used during the ICU stay that may cause acute tubular injury.[16]

The liver possess blood supply from the portal vein, hepatic artery, and inferior vena cava due to hepatic outflow. More than one vascular anastomoses are required in liver transplantation and complications can emerge at any anastomotic site.[2] Arterial complications are more common than venous complications.[2] HAT affects approximately 2-12% of patients with liver transplantation and can lead to graft loss and patient mortality.[2] This risk increases 5.76 times if hepatic artery anastomosis is performed to the supraceliac aorta via an interposition graft.[17] The mortality after re-transplantation for HAT was reported to be 40%.[18] In one of our patients, the reason for mortality was HAT. The hepatic artery anastomosis in this patient was performed using a graft extending from the supraceliac aorta. Portal vein complications have devastating results in LDLT and it is less frequently encountered.[2] The bile duct epithelium is supplied by the hepatic artery. For this reason, arterial complications may cause biliary ischemia that results in biliary strictures, bile leakage, and biloma.[19] Bile leakage constitutes 5-10% of early complications of transplantation.[2] Acute cellular rejection, another postoperative complication typically occurs within the first 90 days after transplantation,[2] and it causes high morbidity and mortality rates.[4] Three patients died due to peritonitis due to bile leakage, and 1 patient died due to acute cellular rejection in our series. In our clinic, the rate of bile leakage is 1.7% and the rate of bile complications is well below the rates stated in the literature.

The retrospective single-center design of our study and the low volume of the patients were the main limitations of our study. Although the MELD-Na score was close to significant in predicting 90-day mortality, it was not statistically significant. It may be meaningful in a larger case series study. Furthermore, we analyzed the effect of the duration of ICU stay on the early postoperative outcome of the recipients and we did not include the long-term outcome of the patients. It is important that we see long-term results to evaluate whether the transplanted liver is affected by the length of stay in intensive care.

Conclusion

In conclusion, our study indicated that the prolonged ICU stay was predictive for the determination of 90-day mortality risk following LDLT for HBV-related cirrhosis. The high-risk patients with an ICU stay longer than 10.5 days can be closely monitored for any complications and treated in the early period.

Disclosures

Ethics Committee Approval: Inonu University Review Board (Approval number: 2023/4087).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – A.Z., Y.M.B.; Design – Y.M.B., Y.D.; Supervision – S.Y., B.B.; Materials – S.Y., B.B.; Data collection – A.Z., Y.D.; Analysis and/or interpretation – Y.M.B., A.Z.; Literature search – A.Z.; Writing – A.Z., Y.M.B.; Critical review – S.Y., B.B.

References

1. Bayrak V, Gürkök MÇ, Aydemir FD, Ergün B, Egeli T, Durukan NŞ, et al. The predictive value of MELDNa (model for end-stage liver disease-sodium) and mean platelet volume/platelet count for patients' 30-day mortality after liver transplantation. Clin Exp Hepatol 2022;8(2):111–7.
2. Craig EV, Heller MT. Complications of liver transplant. Abdom Radiol 2021;46:43–67.
3. Niewińsk G, Raszeja-Wyszomirska J, G\lówczyńska R, Figiel W, Zając K, Kornasiewicz O, et al. Risk factors of prolonged ICU stay in liver transplant recipients in a single-center experience. In: Transplantation Proceedings. Elsevier; 2018. p. 2014–7.
4. Stratigopoulou P, Paul A, Hoyer DP, Kykalos S, Saner FH, Sotiropoulos GC. High MELD score and extended operating time predict prolonged initial ICU stay after liver transplantation and influence the outcome. PLoS One 2017;12(3):e0174173.
5. Ali AY, William KY, Emad N, Mogawer MS, Elshazli MM, Youssof M, et al. Effect of duration of intensive care unit stay on outcomes of adult living donor liver transplant recipients. In: Transplantation

Proceedings. Elsevier; 2019. p. 2425–9.
6. Hernaez R, Liu Y, Kramer JR, Rana A, El-Serag HB, Kanwal F. Model for end-stage liver disease-sodium underestimates 90-day mortality risk in patients with acute-on-chronic liver failure. J Hepatol. 2020;73(6):1425–33.
7. Foxton MR, Al-Freah MA, Portal AJ, Sizer E, Bernal W, Auzinger G, et al. Increased model for end-stage liver disease score at the time of liver transplant results in prolonged hospitalization and overall intensive care unit costs. Liver Transpl. 2010;16(5):668–77.
8. Smith JO, Shiffman ML, Behnke M, Stravitz RT, Luketic VA, Sanyal AJ, et al. Incidence of prolonged length of stay after orthotopic liver transplantation and its influence on outcomes. Liver Transpl. 2009;15(3):273–9.
9. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240(2):205.
10. Dudek K, Kornasiewicz O, Remiszewski P, Zieniewicz K, Wróblewski T, Krawczyk M. Results of liver transplantation from old donors. In: Transplantation Proceedings. Elsevier; 2014. p. 2762–5.
11. Altunisik Toplu S, Bayindir Y, Yilmaz S, Yalçınsoy M, Otlu B, Kose A, et al. Short-term experiences of a liver transplant centre before and after the COVID-19 pandemic. Int J Clin Pract. 2021;75(10):e14668.
12. Yeşiler Fİ, Şahintürk H, Zeyneloğlu P, Haberal M. Posttransplant Pneumonia Among Solid Organ Transplant Recipients Followed in Intensive Care Unit. Exp Clin Transplant Off J Middle East Soc Organ Transplant. 2021;20(1):83–90.
13. Foreman MG, Mannino DM, Moss M. Cirrhosis as a risk factor for sepsis and death: analysis of the National Hospital Discharge Survey. Chest. 2003;124(3):1016–20.
14. Ren Y, Zhang L, Xu F, Han D, Zheng S, Zhang F, et al. Risk factor analysis and nomogram for predicting in-hospital mortality in ICU patients with sepsis and lung infection. BMC Pulm Med. 2022;22:1–11.
15. Pereira R, Bagulho L, Cardoso FS. Acute-on-chronic liver failure syndrome-clinical results from an intensive care unit in a liver transplant center. Rev Bras Ter Intensiva. 2020;32:49–57.
16. Feltracco P, Barbieri S, Galligioni H, Michieletto E, Carollo C, Ori C. Intensive care management of liver transplanted patients. World J Hepatol. 2011;3(3):61.
17. Stange BJ, Glanemann M, Nuessler NC, Settmacher U, Steinmüller T, Neuhaus P. Hepatic artery thrombosis after adult liver transplantation. Liver Transpl. 2003;9(6):612–20.
18. Pinto LEV, Coelho GR, Coutinho MMS, Torres OJM, Leal PC, Vieira CB, et al. Risk factors associated with hepatic artery thrombosis: analysis of 1050 liver transplants. ABCD Arq Bras Cir Dig São Paulo. 2021;33.
19. Shaji Mathew J, Kumar KS, Nair K, Thankamony Amma BSP, Krishnakumar L, Balakrishnan D, et al. Antegrade hepatic artery and portal vein perfusion versus portal vein perfusion alone in living donor liver transplantation: a randomized trial. Liver Transpl. 2019;25(9):1353–62.