Impact of intensive care unit discharge delay after medical clearance on outcomes after liver transplantation

Shirin Salimi
Australian National Liver Transplant Unit https://orcid.org/0000-0002-6168-6988
Keval Pandya
Australian National Liver Transplant Unit
Rebecca J Davis
Royal Prince Alfred Hospital
Michael Crawford
Australian National Liver Transplant Unit
Carlo Pulitano
Australian National Liver Transplant Unit
Simone I Strasser
Australian National Liver Transplant Unit
Geoffrey W McCaughan
Australian National Liver Transplant Unit
Avik Majumdar
Australian National Liver Transplant Unit
Ken Liu (ken.liu@health.nsw.gov.au)
Australian National Liver Transplant Unit https://orcid.org/0000-0002-0453-3168

Research

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Abstract

Background

For general intensive care unit (ICU) patients, ICU discharge delay (ICUDD) has been shown to be associated with increased hospital length of stay (LOS) and acquiring multi-resistant organism (MRO) infections. The impact of ICUDD in liver transplant (LT) recipients is unknown.

Methods

We retrospectively studied consecutive adults who underwent deceased-donor LT between 2011–2019. All patients went to ICU post-operatively then to a specific transplant ward. ICUDD was defined as > 8 hours between a patient being cleared by staff for discharge to ward and the patient leaving ICU.

Results

550 received LT and survived to ward discharge. Median time between clearance for ward and the patient leaving ICU was 25.6 hours (interquartile range 6.6–38.6). The majority (68.4%) of patients experienced ICUDD. No donor or recipient variables were associated with ICUDD. However, patients cleared for discharge early in the week (Sunday-Tuesday) were more likely to experience ICUDD than those cleared on Wednesday-Saturday: 77.5% vs. 62.2% ($P = 0.001$), while patients cleared outside routine work hours were more likely to experience ICUDD than those cleared within working hours (93.6% vs. 66.2%, $P < 0.001$). The median hospital LOS were identical (18 days, $P = 0.96$) and there were no differences in other patient outcomes. Patients who became colonized with MRO in ICU spent longer time there compared to those who remained MRO-free (9 vs. 6 days, $P < 0.001$), however this was not due to ICUDD.

Conclusions

ICUDD post-LT is common and related to logistical factors. It does not prolong hospital LOS and is not associated with adverse patient outcomes or MRO colonization.

Background

Liver transplantation (LT) is a life-saving treatment for select patients with severe liver disease and/or hepatocellular carcinoma. It is a major operation associated with morbidity and patients are often very unwell with decompensated cirrhosis or acute liver failure at the time of transplant. The recipient's physiologic reserve and non-liver comorbidities also factor into the complexity of peri-transplant care. Therefore, routine intensive care unit (ICU) admission post-operatively for optimal monitoring and management is recommended [1].

The decision to discharge a patient from ICU to a hospital ward after LT is a medical one based on the patient's recovery, level of care available on the transplant ward and complications from their underlying liver disease, comorbidities, or the LT itself. Despite medical clearance, timely discharge from ICU can also be impeded by logistical obstacles – primarily a lack of ward bed availability [2]. Meeting time-based targets in other areas of the hospital such as the emergency department has been shown to be associated with reduced in-hospital mortality [3]. Among general ICU patients, discharge delay is associated with prolonged hospitalization and greater risk of acquiring multi-resistant organism (MRO), but no significant difference in mortality [4–6]. However, the impact of ICU discharge delay (ICUDD) on LT recipients has not been specifically examined and previous studies in the general ICU population mostly involved non-LT centers. Therefore, we aimed to assess the prevalence, risk factors and impact of ICUDD after LT in our Australian quaternary-referral center.

Methods

Patients

A retrospective analysis was performed on consecutive adult deceased-donor LT recipients between July 2011 and June 2019 (8-year period) at a state-wide LT referral center. All patients were transferred to ICU post-operatively then to a specialized transplant hospital ward for recovery until hospital discharge. Our ICU is a "closed" unit where management is led by the attending intensivist with guidance from the medical and surgical LT teams who review the patient on a daily basis. ICUDD was defined as patient transfer out of ICU occurring >8 hours after clearance by medical staff as documented in the medical record by the intensive care doctors or, in the absence of this, by the liver transplant team. Patients were excluded if they died during their initial ICU admission or were discharged home directly from ICU. The study protocol was conducted according to the Declaration of Helsinki and was approved by the Sydney Local Health District Human Ethics Research Committee (RPAH Zone) with a waiver of informed consent (X19-0303).

Clinical Data

Patient demographic and clinical data results were obtained from a prospective LT database and electronic medical records. In patients who survived to discharge from ICU after LT, we compared the following outcomes between those who experienced ICUDD versus those who did not. The primary outcome of interest was the hospital length of stay (LOS) defined as total days in hospital since the LT operation. Secondary endpoints included graft survival (time to re-transplantation or death), patient survival (time to death), total length of ICU stay, ward LOS (time in hospital after initial ICU discharge), unplanned ICU readmission, unplanned hospital readmission and new colonization with MRO. We also compared the above outcomes in patients who became newly colonized with MRO versus those who did not. At our center, all patients undergo a screening swab for methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant Enterococci (VRE), extended spectrum β-lactamase (ESBL)-producing organisms and carbapenem-resistant Enterobacteriaceae (CRE) on entry and exit of ICU and every seven

days in between. New MRO colonization was defined as an initial negative swab followed by a positive swab detected during the patient's ICU admission or within seven days of arrival on the hospital ward. Standard working hours were defined as 0800 to 1700 and the working week was divided into early (Sunday to Tuesday) and late (Wednesday to Saturday) based on previous studies of variations in hospital occupancy [7,8].

Statistical Analysis

Continuous variables were expressed in mean ± standard deviation (SD) or median (interquartile range [IQR]) as appropriate. Differences between subgroups were analyzed using $\chi 2$ or Fisher exact test for categorical variables and Student's t test, Mann-Whitney test, or one-way ANOVA for continuous variables as appropriate. The Kaplan-Meier method with log-rank test was performed to estimate cumulative survival and determine statistical significance. Statistical analysis was performed by Statistical Package for Social Science (SPSS version 23.0, Armonk, NY, USA). A result was considered statistically significant if $P \leq 0.05$.

Results

Patient characteristics

During the study period, 565 patients received LT. Fifteen patients were excluded due to death during the initial ICU admission. A total of 550 patients were included in the final analysis. Patient clinical characteristics are presented in **Table 1**.

The median time between clearance for ward and the patient leaving ICU was 25.6 hours (IQR 6.6-38.6) for the entire cohort. Thus, ICUDD was experienced by the majority of patients (68.4%). In those with ICUDD, the median duration of delay was 30.7 hours (IQR 24.5-52.6). The proportion of patients with ICUDD fluctuated during the study period with 2014-2016 experiencing the greatest rate of ICUDD (74.5%, vs. 59.7% in 2011-2013 and 68.6% in 2017-2019, $P=0.013$). Patients ready for discharge earlier in the week (Sunday to Tuesday) were more likely to experience ICUDD than those cleared later in the week (Wednesday-Saturday; 77.5% vs. 62.2%, odds ratio 1.85, 95% CI 1.28-2.67, $P=0.001$). Patients cleared for discharge outside of routine working hours were more likely to experience ICUDD than those cleared within working hours (93.6% vs 66.2%, odds ratio 0.13, 95% CI 0.04-0.44, $P<0.001$). Patients who were already in ICU prior to LT trended towards having a lower rate of ICUDD (12.7% vs. 19.1%, $P=0.051$). No other donor and recipient variables were associated with ICUDD ($P>0.05$ for all, **Table 1**).

Table 1. Clinical characteristics of LT recipient with and without ICUDD

Characteristic	*All* *n=550*	*No ICUDD* *n=173*	*ICUDD* *n=377*	*P value*
Male	386 (70.2)	128 (74.0)	258 (68.4)	0.19
Age (years)	54 (47-59)	53 (46-60)	54 (47-59)	0.63
Primary indication for LT				0.44
HCC	142 (25.8)	47 (27.2)	95 (25.2)	
Decompensated cirrhosis	378 (68.7)	117 (67.6)	261 (69.2)	
HCV	106 (19.3)	39 (22.5)	67 (17.8)	
Alcohol related liver disease	78 (14.2)	24 (13.9)	54 (14.3)	
Primary sclerosing cholangitis	44 (8.0)	12 (6.9)	32 (8.5)	
NAFLD	43 (7.8)	12 (6.9)	31 (8.2)	
Other	107 (19.4)	30 (17.4)	77 (20.4)	
Acute liver failure	30 (5.5)	9 (5.2)	21 (5.6)	
Retransplantation patient	22 (4.0)	9 (5.2)	13 (3.4)	0.33
Combined liver-kidney transplantation	21 (3.8)	6 (3.5)	15 (4.5)	0.77
Pre-transplant MELD score	19 (14-25)	19 (14-27)	19 (14-24)	0.59
DCD donor	40 (7.2)	11 (6.4)	29 (7.7)	0.58
DRI	1.6 (1.3-1.8)	1.6 (1.3-1.8)	1.6 (1.4-1.8)	0.89
ICU inpatient prior to transplant	81 (14.7)	33 (19.1)	48 (12.7)	**0.051**
MRO colonization prior to ICU admission	138 (25.2)	47 (27.3)	91 (24.2)	0.43
Discharge year				**0.013***
2011-2013	144 (26.2)	58 (40.2)	86 (59.7)	
2014-2016	212 (38.5)	54 (25.6)	158 (74.5)	
2017-2019	194 (35.3)	61 (31.4)	133 (68.6)	
Discharge in early week	267 (48.5)	66 (38.2)	201 (53.3)	**0.001**
Discharge during weekday	429 (78.0)	141 (81.5)	288 (76.4)	0.18
Discharge within working hours	503 (91.5)	170 (98.3)	333 (88.3)	**<0.001**

The data are shown in number (percentage) and median (interquartile range).

*p-value <0.017 for 2011-2013 vs 2014-2016.

DCD, donation after circulatory determination of death; DRI, donor risk index; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ICU, intensive care unit; ICUDD, intensive care unit discharge delay; LT, liver transplantation; MELD, model for end-stage liver disease; MRO, multi-resistant organism; NAFLD, non-alcoholic fatty liver disease.

Patient outcomes

As expected, the median LOS in ICU post-LT was significantly longer in patients who experienced ICUDD compared to those who did not, for both the initial ICU admission (5 vs. 3 days, *P*<0.001) and the total time spent in ICU during the entire hospital admission post LT (6 vs. 5 days, *P*<0.001) (**Table 2**). However, the median hospital LOS was the same between the two groups (18 days, *P*=0.96). After patients were discharged from their initial ICU admission, the ward LOS was, thus, significantly less in the ICUDD group (13 vs. 15 days, *P*=0.020). There were no significant differences in the rate of unplanned ICU and hospital readmission, and MRO colonization between patients with and without ICUDD (*P*>0.05 for all, **Table 2**). After a median follow-up period of 36 months (IQR 13-59 months), there were 54 deaths and 18 re-transplants in our cohort. By Kaplan-Meier analysis, graft and patient survival did not differ between the two groups (Log rank *P*=0.38 and 0.56, respectively; **Figure 1**).

Table 2. Comparison of outcomes between patients with and without ICUDD

Characteristic	*No ICUDD n=173*	*ICUDD n=377*	*P value*
Total hospital LOS (days)	18 (13-29)	18 (13-27)	0.96
Initial ICU admission LOS (days)	3 (2-6)	5 (4-8)	**<0.001**
Total ICU LOS including readmissions (days)	5 (3-8)	6 (5-10)	**<0.001**
Ward LOS (days)	15 (10-22)	13 (8-20)	**0.02**
Unplanned return to operating theater	40 (23.1)	72 (19.1)	0.28
Unplanned ICU readmission	21 (12.1)	29 (7.7)	0.09
Unplanned hospital readmission within 30 days	55 (32.2)	121 (32.7)	0.90
Unplanned hospital readmission within 90 days	86 (50.6)	173 (46.9)	0.42
New colonization with MRO	13 (9.5)	27 (8.6)	0.76

The data are shown in number (percentage) and median (interquartile range).

ICU, intensive care unit; ICUDD, intensive care unit discharge delay; LOS, length of stay; LT, liver transplantation; MRO, multi-resistant organism.

Figure 1. Survival analyses. Kaplan-Meier analyses of cumulative liver graft survival (A) and overall survival (B) in patients with no intensive care unit discharge delay (ICUDD) and patients with ICUDD.

Of the original study cohort, 451 patients (82.0%) had adequate MRO screening data, of whom 40/451 acquired a new MRO infection during their ICU initial admission (8.9%). The MRO acquired were: MRSA (n = 2, 0.5%), VRE (n = 38, 8.4%). There were no cases of ESBL or CRE acquisition. These patients had a longer initial ICU post-LT compared to those who did not acquire a new MRO (9 vs. 6 days, $P<0.001$). However, this difference in time was not associated with ICUDD which was similar between the two groups 67.5% in those with newly colonized MRO vs. 69.8% without newly colonized MRO, $P=0.76$). Conversely, the proportion of patients already colonized with MRO prior to their LT admission did not differ in those with and without ICUDD (24.2% vs. 27.3% colonized with MRO, respectively, $P=0.43$). No donor or recipient variables were associated with new MRO colonization in ICU ($P>0.05$ for all; **Table 3**). New MRO colonization in ICU was associated with greater total hospital LOS (26 days vs. 18 days), total ICU LOS (6 vs. 9 days), and rate of unplanned ICU readmission (27.5% vs. 9.5%) compared to those who did not acquire new MRO ($P<0.01$ for all). However, no differences were seen in graft and patient survival between the two groups (Log rank $P=0.61$ and 0.47, respectively; **Supplementary Figure 1**).

Table 3. Characteristics of patients who did vs did not acquire MRO colonization during ICU admission post-LT

Characteristic	*No infection acquired* *n=411*	*Infection acquired* *n=40*	*p-value*
Male	292 (71.0)	26 (65.0)	0.42
Age (years)	55 (47-59)	57 (50-61)	0.09
Discharge year			**0.011***
2011-2013	88 (97.8)	2 (2.2)	
2014-2016	161 (87.0)	24 (13.0)	
2017-2019	162 (92.0)	14 (8.0)	
Hospital inpatient prior to transplant	188 (45.7)	14 (35.0)	0.78
ICU inpatient prior to transplant	55 (13.4)	5 (12.5)	0.88
ICUDD	287 (69.8%)	27 (67.5%)	0.76
Duration of delay in those with ICUDD (hours)	31 (24-53)	33 (28-74)	0.25
Total hospital LOS (days)	18 (13-27)	26 (15-49)	**0.007**
Initial ICU admission LOS (days)	4 (3-7)	7 (5-11)	**<0.001**
Ward LOS (days)	13 (8-21)	18 (10-30)	0.06
Total ICU LOS including readmissions (days)	6 (4-9)	9 (6-16)	**<0.001**
Unplanned return to operating theater	84 (20.4)	10 (25)	0.50
Unplanned ICU readmission	39 (9.5)	11 (27.5)	**0.001**
Unplanned hospital readmission within 30 days	130 (32.2)	12 (30.8)	0.86
Unplanned hospital readmission within 90 days	196 (48.8)	17 (43.6)	0.54

The data are shown in number (percentage) and median (interquartile range).

*p-value <0.017 for 2011-2013 vs 2014-2016.

ICU, intensive care unit; ICUDD, intensive care unit discharge delay; LOS, length of stay; LT, liver transplantation; MRO, multi-resistant organism.

Supplementary Figure 1. Survival analyses. Kaplan-Meier analyses of cumulative liver graft survival (A) and overall survival (B) in patients who did not become newly colonized with a multi-resistant organism infection and patients who did become colonized.

Financial cost of ICUDD

The daily cost of an Australian ICU bed was recently estimated at $4,375 AUD (approximately $3,325 USD) per patient [9]. The daily cost of a bed on our LT ward in 2019-2020 was $535 AUD (approximately $407 USD). Therefore, we calculated each day of ICUDD incurred an extra cost of $3,840 AUD ($2,921 AUD) or $160 AUD ($122 USD) per hour to the health system. This equates to a cost of $28,830 vs $21,150 AUD ($21,932 vs. $16,090 USD, $P<0.001$) per patient for the initial LT admission in those with vs. without ICUDD based on median LOS.

Discussion

Post-LT care is financially- and resource-intense with all patients requiring ICU admission [10,11]. We present the first study to assess the prevalence and clinical impact of ICUDD in LT recipients. We followed 550 patients undergoing deceased donor LT and found the majority (68.4%) experienced ICUDD >8 hours. Unsurprisingly, patients with ICUDD spent longer time in ICU, however, there were no differences in total hospital LOS or patient outcomes including MRO colonization. Our results suggest that ICUDD is mainly due to factors related to hospital bed management rather than donor, recipient or operative factors. We observed a higher proportion of ICUDD at our center compared to previous studies of the general ICU population (68% vs. 27-50%) [2,4]. This likely reflects the need for all our LT patients to stepdown to a specific transplant ward limiting bed availability, whereas non-LT ICU patients may have the option of recovering in one of several general hospital wards. Predictors of ICUDD in our study were discharge earlier in the week, and discharge outside of routine working hours which are congruent with previous reports [2,4]. A single-center study of 652 ICU discharges, similarly observed that discharges occurring on Saturday to Monday were more likely to experience ICUDD (2.17 times) compared to discharges occurring on Tuesday to Friday [2]. These authors also noted that rates of ICUDD increased proportionately as ICU bed occupancy (a reflection of hospital occupancy) increased from 40% to 80%. In a separate prospective study of 955 general ICU patients across five Australian hospitals, Tiruvoipati et al. found that after-hours discharges were three times more likely to result in ICUDD (34% vs. 10%) [4]. These predictors may point to times when free beds are likely to be occupied already. Indeed previous studies have shown peak hospital bed occupancy in early in the working week (Monday and Tuesday) [7,8]. Despite evidence showing after-hours discharges may lead to increased risk of readmission and death [12–14], this has not translated into poorer outcomes for patients with ICUDD [2,4]. Indeed, we also did not detect any negative impact of ICUDD on post-LT outcomes including graft survival, patient survival and unplanned readmission rates. We also observed identical total hospital LOS between patients who experienced ICUDD and those who did not. This suggests that the patient convalescence process (including regaining mobility and functional status, progression of diet, etc.), begins in the ICU and not only after a patient is discharged to the ward. Indeed, at our center, all post-LT patients are routinely seen by physiotherapists

and dieticians while still in the ICU and are encouraged to sit out of bed and begin mobilizing as soon as appropriate. In contrast, the aforementioned study by Tiruvoipati et al. found a small but significant increase in total hospital LOS by one day in patients with ICUDD compared to those without [4]. This difference was entirely due to the ICUDD time (median delay 24 hours) since the median time spent in hospital after ICU discharge was identical in both groups (5 days). The authors proposed that a certain amount of time is required by the treating team to prepare a patient for discharge regardless of time spent in ICU after the discharge decision. Our patients (regardless of ICUDD status) experienced a much longer median hospital LOS of 18 days versus five days in Tiruvoipati et al. cohort [4]. However, patients who experienced ICUDD in our study also had significantly shorter stays in the LT ward after discharge from ICU compared to those without ICUDD (13 vs. 15 days), again suggesting some of the convalesce occurred in ICU. Although ICUDD does not appear to significantly impact the individual LT patient, it does have wider resource implications both economically and clinically. We calculated the cost of ICUDD to the health system which was similar to that reported in other studies: approximately $1-2 USD per minute while a patient remains unnecessarily in ICU [15]. Of concern, the annual cost of critical care medicine is increasing over time – doubling between 2000 and 2010 [16]. Furthermore, ICUDD either prevents or delays the availability of ICU facilities for others who are in need which may indirectly result morbidity and/or mortality to these patients. Clearly, ICUDD is a costly and important problem which is also difficult to solve. Regarding new MRO colonization, our results confirmed previous studies which showed prolonged time spent in ICU and prolonged total hospital LOS were associated with increased risk. However, this extra time did not result from ICUDD since the rate and duration of ICUDD between patients who did and did not acquire new MRO were similar. Instead, these patients remained in ICU/hospital longer because they needed ongoing care suggesting they were patients who were sicker and/or experienced more complications post-LT. Thus, it does not appear new MRO colonization can be reduced by addressing ICUDD. Other risk factors for new MRO colonization in these patients include the need for broad-spectrum antibiotics, invasive procedures and catheters and prolonged intubation [5], although these were not specifically examined in the present study. MRO infection during ICU has been reported to be associated with an increased morbidity, healthcare costs and even mortality [17–19]. However, this was not demonstrated in our cohort. Nonetheless, this serves as a reminder that all clinicians should practice good antibiotic stewardship, hand hygiene and other infection control measures on all patients. The main strength of our study lies in our large cohort of LT patients spanning multiple years. However, several limitations should be acknowledged. First, the retrospective nature of this study relies on the accuracy and completeness of data found in medical records. Second, the exact reason(s) behind ICUDD is not recorded at our center leaving it up to speculation. However, we expect it would be akin to other studies with lack of ward bed availability being the most common (74-81%) [2,4]. Similarly, other undesirable patient consequences from ICUDD reported in other studies such as delirium or sleep disturbance are not routinely captured in our LT database and could not be studied. Finally, this single center study may not reflect the situation in other institutions. Indeed, each LT center has its own unique caseload, bed management procedures, and logistics which would determine ICUDD. However, our results were largely consistent with those found in the general ICU population in Australia [2,4]. Indeed, our results should be confirmed with larger multi-center studies.

Conclusions

Our study is the first to assess the prevalence and clinical impact of ICUDD in LT recipients. In conclusion, ICUDD post-LT is common and is most likely due to logistical factors. Discharge delay was not associated with prolonged hospital LOS or adverse patient outcomes. Although prolonged time in ICU was associated with increased risk of new MRO colonization, this was not directly contributed to by ICUDD.

Declarations

Ethics approval and consent to participate

The study protocol was conducted according to the Declaration of Helsinki and was approved by the Sydney Local Health District Human Ethics Research Committee (RPAH Zone) with a waiver of informed consent (X19-0303).

Consent for publication

Not applicable.

Availability of data and materials

The dataset generated and analysed during the current study are not publicly available as this would compromise patient confidentiality, but the dataset is available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

SS and KP acquired, analyzed and interpreted the data, drafted the article, and critically revised the article. RJD, MC, CP, SIS, GWM and AM interpreted the data and critically revised the article. KL created the study concept and design, interpreted the data, drafted the article, and critically revised the article. All authors have read and approved the final manuscript.

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Not applicable.

Abbreviations

CRE, carbapenem-resistant Enterobacteriaceae. DCD, donation after circulatory determination of death. DRI, donor risk index. ESBL, extended spectrum β-lactamase. HCC, hepatocellular carcinoma. HCV, hepatitis C virus. ICU, intensive care unit. ICUDD, intensive care unit discharge delay. IQR, interquartile range. LOS, length of stay. LT, liver transplantation. MELD, model for end-stage liver disease. MRO, multi-resistant organism. MRSA, methicillin-resistant *Staphylococcus aureus*. NAFLD, non-alcoholic fatty liver disease. SD, standard deviation. VRE, vancomycin-resistant Enterococci.

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Figures

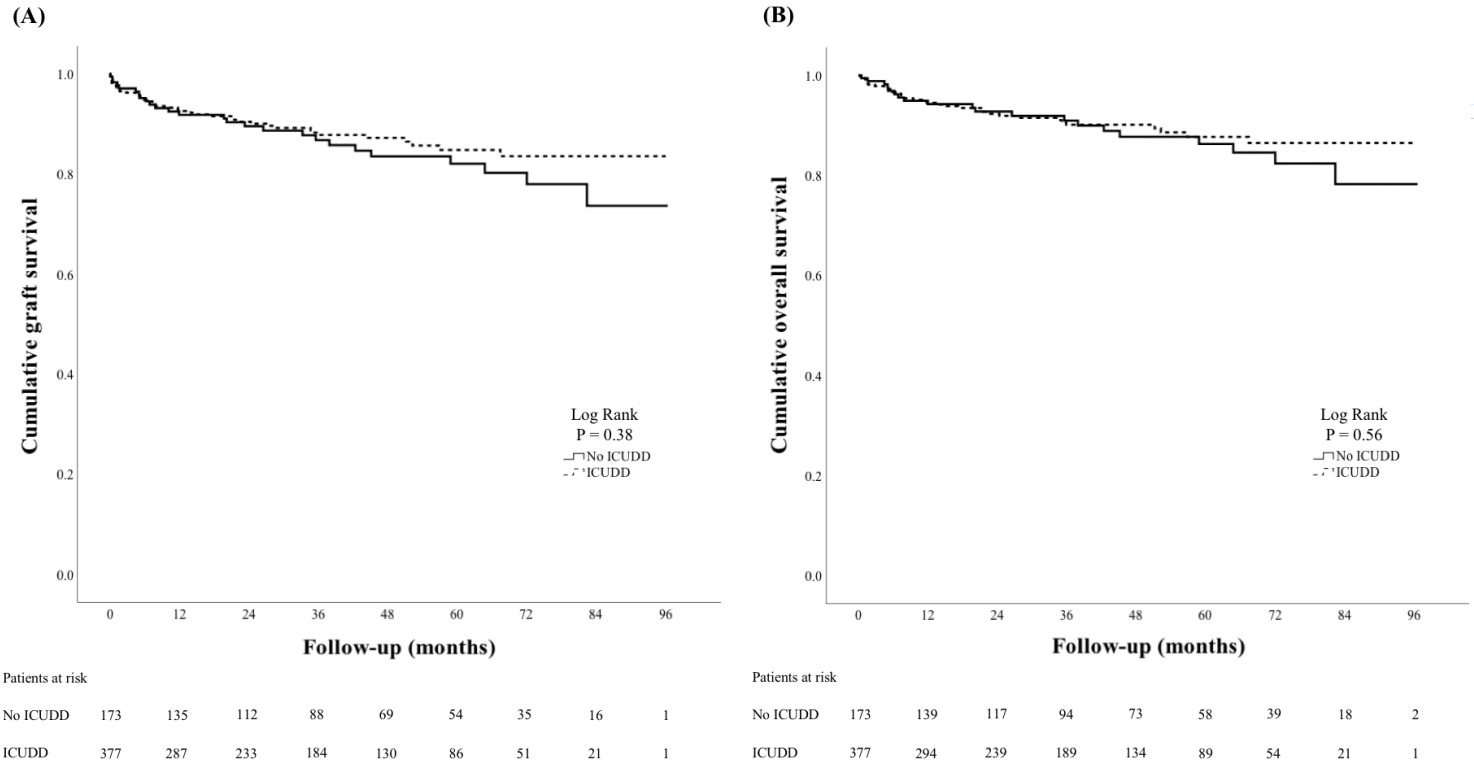

Figure 1

Survival analyses. Kaplan-Meier analyses of cumulative liver graft survival (A) and overall survival (B) in patients with no intensive care unit discharge delay (ICUDD) and patients with ICUDD.

Supplementary Files

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- Supplementaryfigure11.tiff