Primary graft nonfunction in liver transplantation: can we predict? A single-center experience

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The Abstract has been presented at 25th Annual Congress of the International Liver Transplantation Society (ILTS) Toronto, Canada, May 15–18, 2019.
Received: 23 October 2020
Revised: 15 November 2020
Accepted: 15 November 2020
Published: 18 May 2021

The Egyptian Journal of Surgery 2021, 40:216–223

Background
Primary nonfunction (PNF) after liver transplantation is a lethal condition, requiring immediate retransplantation. The precise cause is not well known yet. The aim of this study is to determine the incidence of PNF in our liver recipients, potential risk factors, and outcome.
Patients and methods
A total of 248 adult liver transplant recipients from 2014 till 2017 at our Transplant Unit were included after excluding nine patients for missing data. Of 248 patients, five (2%) had PNF; two of these patients have been excluded for the purpose of data analysis, as they had machine perfusion (One Liver Assist, and the other Organox). Of the non-PNF 243 recipients, 36 patients receiving livers from donors undergoing in-situ normothermic regional perfusion or ex-situ normothermic perfusion were not included, leaving 207 patients, so the total number was 210 patients.
Donor and graft variables studied including age, BMI, serum sodium, cold ischemia time, warm ischemia time, operative time, graft type, and severity of steatosis. Recipient variables included primary liver disease; United Kingdom Model for End-Stage Liver Disease (UKELD) score; posttransplant biochemistry; potential risk factors, including dialysis, inotropes, mechanical ventilation, and pretransplant portal vein thrombosis; hospital and ICU stay; and patient survival.
Results
UKELD score was the only significant recipient variable (P=0.044). Among donor and graft variables, notably all PNF patients received donation after circulatory death grafts. Posttransplant laboratory values were strikingly worse, clearly indicating more pronounced hepatic and renal impairment in PNF group. Creatinine levels on days 1, 3, and 5 were significantly worse. Hospital and ICU stays were longer for PNF group, with ICU stay significantly longer [median of 7 vs. 2 days (P=0.014)], with no death in PNF group.
Conclusion
The main risk factors for PNF in our practice were donation after circulatory death grafts and more sick (higher UKELD) recipients.

Keywords:
early allograft dysfunction, liver transplantation, primary non-function

Egyptian J Surgery 40:216–223

1110-1121

Introduction

The treatment of choice in patients with end-stage liver disease is liver transplantation. Improvements in surgical techniques, preservation modalities, and immunosuppressants have led to an increase in successful liver transplantation and improved long-term graft and patient survival [1]. Primary nonfunction (PNF) after liver transplantation is a life-threatening emergency requiring immediate retransplantation [2].

The terminology used to describe PNF is not widely agreed upon [3]. In the literature, the diagnostic criteria of PNF often vary dramatically [4–10]. Diagnosis is based on the recipient's clinical and laboratory assessment, typically excluding issues with the liver graft's vascular supply. Coagulative necrosis is pathologically seen in an allograft biopsy of the liver [1,11,12]. Progressive increase in serum transaminases within 48 h of transplantation, uncorrectable coagulopathy, metabolic acidosis, hepatorenal syndrome, and hemodynamic instability are classic signs of PNF [13].

The reported incidence of PNF in literature varies between 0.9 and 7.2% [13]. Unlike kidney transplantation, there are few studies specifically looking at short-term graft survival in liver transplant patients, and the reported occurrence of

PNF among the various liver transplant recipients varies widely (range, 2–14%) [1].

It is likely that many different factors result in PNF, and there remains no reliable and objective way to predict PNF. Overall patient survival rates following PNF are extremely poor without retransplantation [1]. Older donors, steatotic livers, livers from donation after circulatory death (DCD) donors, prolonged ischemic times, and high-risk recipients have been reported to be established risk factors for the development of PNF [3,14,15].

The main objective of this study was to determine the incidence of PNF in our liver transplant program and to identify potential diagnostic criteria/risk factors for this lethal complication. We also sought to review the outcome of patients experiencing PNF.

Patients and methods

Adult patients undergoing liver transplantation at our hospital between October 1, 2014 and October 1, 2017 were considered. Those receiving livers from donors undergoing in-situ normothermic regional perfusion (NRP) or ex-situ normothermic perfusion were excluded, as well as those receiving liver containing bowel grafts. PNF was defined as graft loss or patient death within two weeks of transplantation, excluding those losses secondary to hepatic artery thrombosis, biliary problems, recurrent primary disease, or acute rejection. Patient survival was defined as time elapsed from transplantation to patient death. The total number was 210 patients, comprising three PNF patients and 207 non-PNF patients.

Recipient demographic data; date of transplantation and retransplantation; primary liver disease; United Kingdom Model for End-Stage Liver Disease (UKELD) score [16]; posttransplant laboratory values [alanine aminotransferase, bilirubin, creatinine, prothrombin time, and day 1 lactate (first lactate once back on ITU)]; potential risk factors, including dialysis/chronic kidney disease, inotropes, mechanical ventilation, and pretransplant portal vein thrombosis (PVT); hospital and ICU stay; and patient survival. Data were prospectively recorded on the electronic patient record (EPIC Systems, Madison, Wisconsin, USA).

Donor and graft variables included donor demographic data, including age, height, weight, BMI, serum sodium (mmol/l), cold and warm ischemia times, graft type; whether donation after brain-stem death or DCD and postperfusion liver biopsy result of the graft; operative time was also included. Donor graft steatosis was graded as minimal to severe (minimal <5%, mild 5–33%, moderate 33–66%, and severe >66%). The grading of graft steatosis was performed on a routine postreperfusion biopsy of the liver allograft performed at the end of the transplant operation before closure. For the purpose of this study, we considered only moderate and severe steatosis (33–66 and >66%).

Statistical analysis

Summary of data are presented as median (range). Statistical analyses were performed with SPSS statistical software (IBM, SPSS Statistics 20, Chicago, Illinois, USA) using the χ^2 test or the Fisher's exact test for qualitative variables and Student's t test for continuous variables. Statistical significance was indicated by P values of less than 0.05.

Results

A total of 248 adult liver transplant recipients from 2014 till 2017 at our Transplant Unit were included after excluding nine patients for missing data. Of 248 patients, five (2%) had PNF; two out of these have been excluded for the purpose of data analysis, as they had machine perfusion (One Liver Assist, and the other Organox). Of the non-PNF 243 recipients, 36 patients receiving livers from donors undergoing in-situ normothermic regional perfusion or ex-situ normothermic perfusion were not included as well, leaving 207 patients, so the total number was 210 patients.

Among 210 liver transplant recipients, three (1.4%) underwent retransplantation owing to PNF of the primary allograft (group B); the remaining 207 patients had primary graft function (group A). All patients with PNF underwent retransplantation.

The characteristics of the recipients are provided in Table 1. There have been no major variations between the two groups in age or etiology of underlying liver pathology. No patients transplanted for acute liver failure experienced PNF. At the time of transplant, patients with graft failure had a significantly higher UKELD score compared with non-PNF group (59 vs. 55), with a *P* value of 0.044. No patients with PNF were on dialysis, inotropes, or mechanical ventilation before transplantation (Table 1); only one patient in the PNF group had previous PVT before transplant.

Between the two groups, donor and graft parameters were not substantially different apart from type of graft

Table 1 Recipients characteristics

Variables	Overall (210)	No-PNF (207)	PNF (3)	*P* value
Number	210	207	3	
Age (median)	55 (17–74)	55 (17–74)	48 (36–52)	0.210
Underlying liver disease				
Viral	26 (12.4)	25 (12.1)	1 (33.3)	0.267
ArLD	47 (22.4)	45 (21.7)	2 (66.7)	0.064
NASH	44 (21)	44 (21.3)	0	0.834
PSC	35 (16.7)	35 (16.9)	0	0.435
PBC	20 (9.5)	20 (9.7)	0	0.571
AIH/Cholestasis (%)	4 (1.9)	4 (1.9)	0	0.808
Acute liver failure (%)	8 (3.8)	8 (3.9)	0	0.728
Other (%)	26 (12.4)	26 (12.6)	0	0.442
HCC (%)	42 (20)	40 (19.3)	2 (66.7)	0.670
UKELD score (median)	56	55	59	0.044*
Risk factors				
PreTx dialysis/CKD	19 (9)	19 (9.2)	0	0.582
PreTx inotropes	13 (6.2)	13 (6.3)	0	0.654
PreTx mechanical ventilation	13 (6.2)	13 (6.3)	0	0.654
PreTx PVT	19 (partial PVT-9)	18 (partial PVT-8)	1 (partial PVT-1)	0.024

Data are median (range) or *n* (%). AIH, autoimmune hepatitis; ArLD, alcohol related liver disease; CKD, chronic kidney disease; HCC, hepatocellular carcinoma; NASH, non-alcoholic steato-hepatitis; PBC, primary biliary cirrhosis; PNF, primary nonfunction; PSC, primary sclerosing cholangitis; PVT, portal vein thrombosis; UKELD, United Kingdom Model for End-Stage Liver Disease.

Table 2 Donor and graft characteristics

Variables	Overall (210)	No-PNF (207)	PNF (3)	*P* value
Age	50 (15–76)	50 (29–51)	50 (29–51)	0.492
Height (cm)	173 (150–198)	173 (150–198)	169 (160–170)	0.237
Weight (kg)	80 (43.4–132.5)	80 (43.4–132.5)	75 (70–90)	0.965
BMI (kg/m^2)	26.01 (16.74–46.93)	26.01 (16.74–46.93)	27.34 (25.95–31.51)	0.376
Na (mmol/l)	149 (129–178)	149 (129–178)	145 (141–150)	0.444
Cause of death (CVA %)	129 (61.4)	127 (61.4)	2 (66.6)	
Cold ischemia time (min)	509 (50–1140)	510.5 (50–1140)	474 (413–733)	0.825
Warm ischemia time (min)	44 (22–113)	44 (22–113)	50 (43–76)	0.169
Operative time (min)	424.5 (256–700)	424.5 (256–700)	480 (450–540)	0.189
Type of graft				
DBD donor	160 (76.2)	160 (77.3)	0	0.013*
DCD donor	50 (23.8)	47 (22.7)	3 (100)	
Postperfusion liver biopsy showing moderate or severe steatosis	9 (4.3)	9 (4.3)	0	0.712

Data are presented as median (range) or *n* (%). CVA, cerebrovascular accident; DBD, donation after brain-stem death; DCD, donation after circulatory death; PNF, primary nonfunction.

received (Table 2). Notably only DCD livers experienced PNF in our series. Height, weight, and secondary (anastomotic) warm ischemia time were not significantly different between the two groups. Stroke as a cause of death [cerebrovascular accident (CVA %)] was common in both groups. Among those experiencing PNF, donors were not substantially older, and high donor BMI was also not found to be a causative factor. Donor serum sodium also did not differ significantly between groups. None of the PNF group patients received either moderately or severely steatotic grafts, which has been confirmed by time zero biopsy.

When posttransplant laboratory values of both groups were compared (Table 3, Fig. 1), most of the parameters obviously differed, showing a more pronounced impairment of both liver and kidney function in the PNF group. Creatinine (μmol/l) on days 1, 3, 5 and bilirubin on day 5 were significantly worse in patients with PNF (P=0.021, 0.020, 0.017, and 0.012, respectively).

Not surprisingly, both hospital and ICU stays were longer for the PNF group (Table 4), with ICU stay significantly longer, with median of 7 days for PNF group versus 2 days for the no-PNF (P=0.014) (Fig. 2).

Table 3 Posttransplant laboratory values

Variables	Overall	No-PNF (207)	PNF (3)	*P* value
ALT (u/l) day 1	488	486	871	0.288
Bilirubin (μmol/l) day 1	49	49.00	100.00	0.119
Creatinine (μmol/l) day 1	105	103	164	0.021
PT (sec) day 1	19.4	19.30	29.60	0.942
Lactate (mmol/l) day 1	1.3	1.3	4.59	0.114
ALT (u/l) day 3	308	308	508	0.405
Bilirubin (μmol/l) day 3	42.50	42.00	131.00	0.086
Creatinine (μmol/l) day 3	86	86	205	0.020
PT (sec) day 3	14.00	13.95	32.60	0.161
ALT (u/l) day 5	192	192	924	0.541
Bilirubin (μmol/l) day 5	47	45	225	0.012
Creatinine (μmol/l) day 5	70	70	189	0.017
PT (s) day 5	14.00	13.50	34.90	0.469
ALT (u/l) day 7	147	146	970	0.497
Bilirubin (μmol/l) day 7	35	34.50	158	0.069
Creatinine (μmol/l) day 7	65	65	135	0.532
PT (s) day 7	13.00	13.00	16.35	0.099

Data are presented as medians. ALT, alanine aminotransferase; PNF, primary nonfunction.

Eight (3.9%) recipients without PNF died in the first year compared with none with PNF (Fig. 3).

Discussion

Donor organ scarcity pushes transplant professionals to consider suboptimal organs, and avoiding or even minimizing PNF would provide substantial gains. The diagnostic criteria for PNF were focused on clinical experience and liver transplant policies of almost 20 years ago [17].

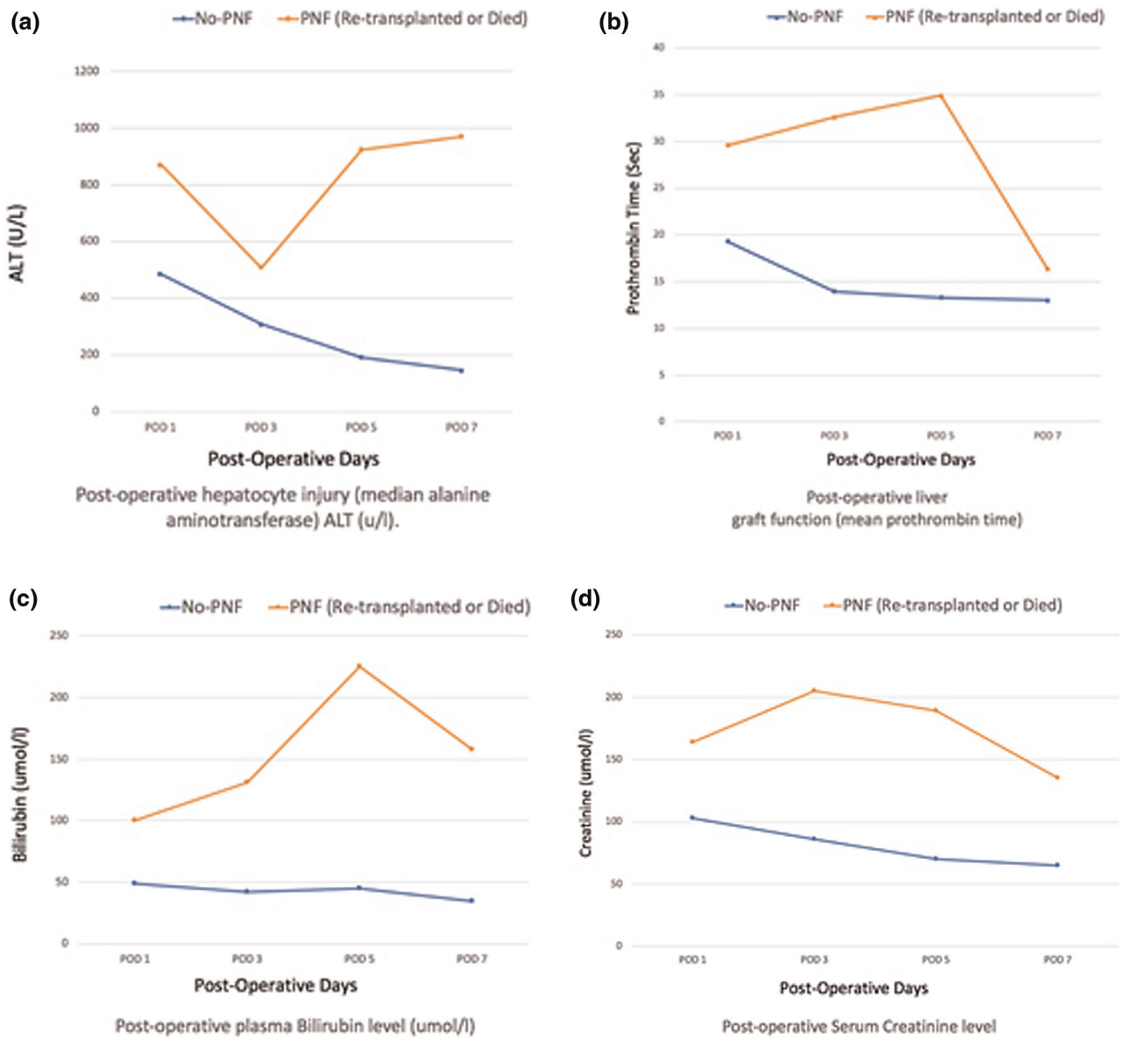
We had a PNF incidence of 2% in out-transplant recipients from October 2014 till October 2017. When compared with published data, it is within the range mentioned in literature which varies between 0.9 and 7.2% [13]. This is significantly less than 5.8% stated by Johnson and colleagues utilizing the Scientific Registry of Transplant Recipients (SRTR) database of more than 10 000 patients and less than 6–9.2% claimed by a single-center series [18–20]. Similar to our finding, of the 2130 orthotopic liver transplants conducted in a single US center, they documented 2.2% PNF cases [12].

In our patients, there was no significant difference in age between both recipient groups, with no patients who presented with acute liver failure subsequently developing PNF after transplant. There has been an evidence that the extent of recipient illness could have an effect on early posttransplant results. A high MELD transplant score (cut-off values of 25 or 30) has been thought to be associated with decreased posttransplant survival for 3 and 12 months [21–24]. The analysis of Al-Freah *et al.* [17] data clarified that after adjusting for other pretransplant and posttransplant variables, neither MELD (as continuous or categorical variable) nor its components were correlated with PNF. This result was in agreement with Johnson *et al.* [18], who in the study of the SRTR database of 10 545 patients used the same description of PNF and did not show any association of MELD with PNF. The UKELD score in UK has been stated to be a more accurate transplant waiting list predictor of mortality than MELD or MELD-Na [16]. In our recipients, patients with graft failure had significantly higher UKELD score at transplant (59 vs. 55, P=0.044).

PNF-associated factors concentrated largely on the seriousness of the recipient's disease. Life support, artificial ventilation, inotropes, and hemodialysis were more commonly seen in those with PNF in the Johnson *et al.* [18] univariate model. In a number of single-center trials, the role of life support influencing outcomes after transplantation has been studied. In a study by Markmann *et al.* [25], using a multivariate model, primary graft survival was decreased by pretransplant mechanical ventilation. On the contrary, in our cohort, there were no patients at all in PNF group that have been on dialysis, inotropes, or mechanically ventilated at the time of transplant with only one patient who had previous PVT before transplant.

Donor factors presumed to be linked to graft failure included age more than 40, African American race, CVA as a cause of mortality, DCD grafts, steatotic and split livers, and prolonged ischemic times. Offering organ replacement for individuals in desperate need of an allograft, and the use of these expanded criteria

Figure 1



(A) Post-operative hepatocyte injury (median alanine aminotransferase) (ALT), (B) Liver allograft function (median prothrombin time), (C) Bilirubin and (D) Creatinine measured during the first week after transplant.

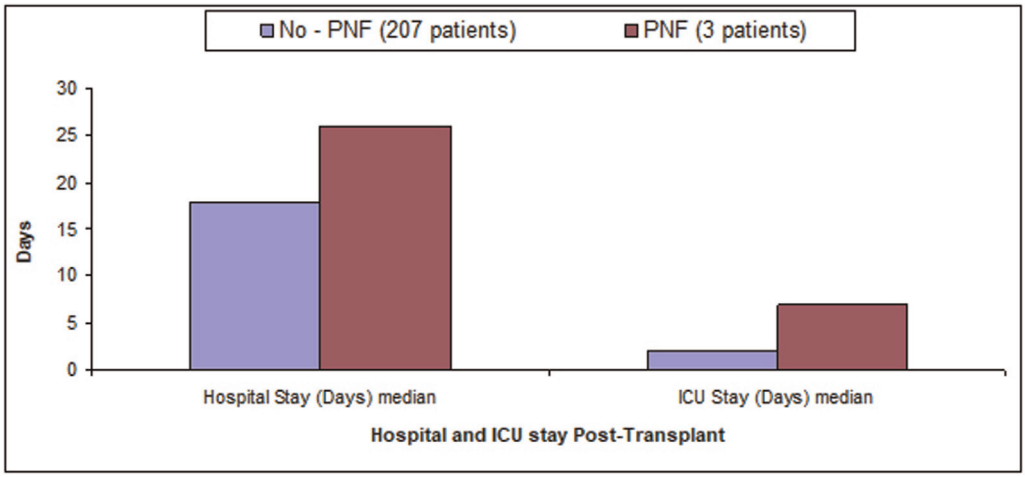
Table 4 Recipient hospital, ICU stay and survival

Variables	Overall (210)	No-PNF (207)	PNF (3)	*P* value
MEAF[a]	4.81 (1.06–9.85)	4.77 (1.06–9.57)	6.92 (5.78–9.85)	0.042[a]
Hospital stay (days)	18 (7–140)	18 (7–140)	26 (15–32)	0.402
ICU Stay (days)	2 (1–58)	2 (1–58)	7 (6–21)	0.014[a]
Mortality (30 days)	2 (1)	2 (1)	0	0.864
Mortality (1 year)	8 (3.8)	8 (3.9)	0	0.728

Data are presented as median (range) or *n* (%). PNF, primary nonfunction.
[a]We have to be cautious in interpreting MEAF in PNF as it might not be reliable because we treat the recipient with FFP once a decision to retransplant is made.

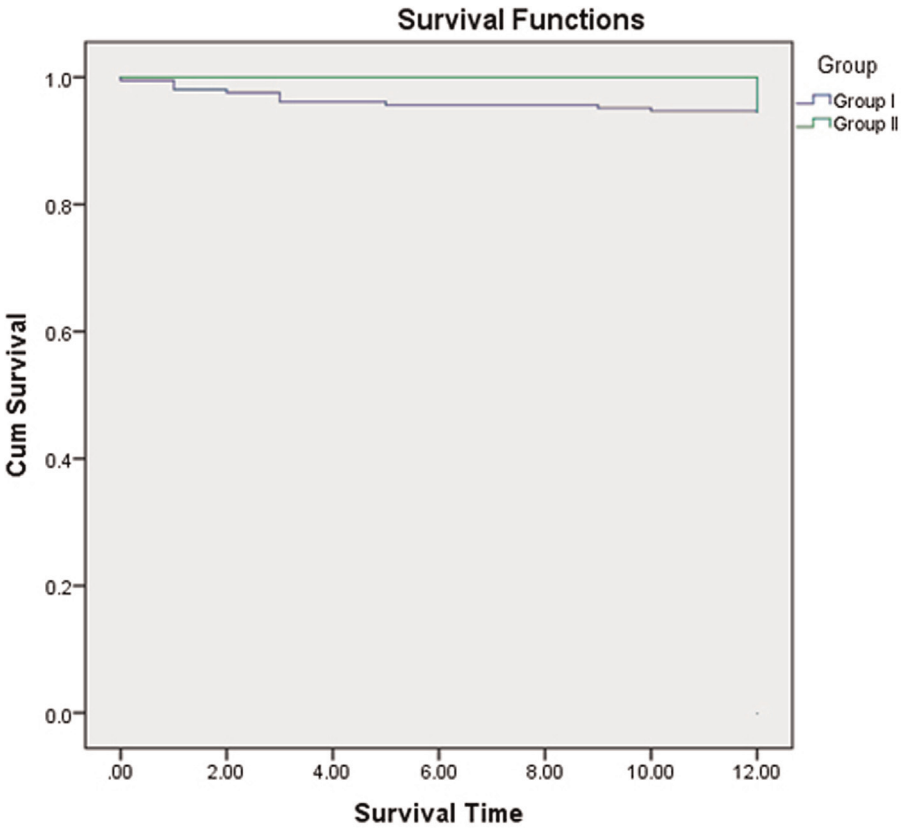
donors, in the meantime, could lead to early allograft dysfunction and a greater likelihood of primary graft nonfunction (PNF) [3,14,15,26]. With respect to the effect of graft and donor performance on the occurrence of PNF, the existing literature varied. Makowka *et al.* [7] found no effect on the occurrence of PNF from donor variables. Others found that split grafts, steatotic grafts, longer periods of cold or warm ischemia, older donors, donor weight greater than 100 kg, anhepatic phase length, and DCD

Figure 2



Hospital and ICU stay after transplant.

Figure 3



Kaplan–Meier survival curves (in months) for the PNF (group B) and no-PNF (group A). PNF, primary nonfunction.

grafts were correlated with poor function of the graft [4,5,18,27,28].

There has not been much documentation of the effect of donor age on PNF. Donor age was not shown to increase the incidence of PNF [29] in a single-center study of 400 liver transplants, and other studies have verified this obvious lack of association of donor age with PNF [30–32]. In our donors, we had similar findings as the donor age was almost identical for both groups with a median age of 50 years. On the contrary, a review of The National Institute of Diabetes and Digestive and Kidney Diseases Liver Transplantation Database looking at donor age and outcome found that donor age was substantially and autonomously linked to PNF. According to their

findings, older donors (>50) raised the PNF odds ratio by 1.57 (95% confidence interval, 1.25–1.96) and by 2.01 (95% confidence interval, 1.62–2.49) for ages greater than 60 relative to the comparison cohort consisting of donors less than 40 years [33].

Both cold and warm ischemic times have been presumed a major risk factor for both early allograft dysfunction as well as PNF [1,12]. In our cohort, both secondary (anastomotic) warm ischemia time and cold ischemia time did not differ between groups. Other parameters such as height, weight, warm ischemia time and stroke as a cause of death (CVA %) were not significantly different as well.

Despite the occurrence of PNF in liver transplantation using DCD grafts was higher in patients of Taner *et al*. [2] than in regular donor grafts, this was still comparable to the overall incidence of PNF as stated in the SRTR. Abt *et al*. [14] also recorded that 6.4% of brain-dead donors experienced PNF versus 11.8% of donors following circulatory death. Interestingly, in our patients, all donors in PNF groups were DCD donors. Donor BMI and serum Na did not differ significantly between groups (P=0.098 and 0.997). Remarkably, none of the PNF group patients received either moderately or severely steatotic grafts.

High posttransplant AST levels suggest acute graft injury and PT represents synthetic graft function and are both within the current PNF criteria in the United Kingdom and the United States [34,35]. Bilirubin in previous reports correlated with graft dysfunction [36]. In our patients, not surprisingly, most laboratory parameters after transplant differed massively showing more severe impairment of both liver and kidney functions in the PNF group. Creatinine (μmol/l) days 1, 3, and day 5, and bilirubin day 5 were significantly different (P=0.021, 0.020, 0.017, and 0.012, respectively).

The Liver Donor Risk Index, the extended donor criteria, and the 'balance of risk' score were created to minimize risk for PNF and to better qualify suboptimal allografts [37–39]. New biomarkers can help to predict risk for PNF, including miRNAs. Finally, recent preclinical research indicates that treatment with Rho-kinase inhibitor could prevent extensive ischemia-reperfusion injury in steatotic grafts without significant systemic adversity providing pharmacological interventional possibilities in the use of fatty allografts [40].Earlier liver retransplantation in patients with graft failure within the first week after transplantation is assumed to lead to greater survival relative to retransplantation between the second and fourth weeks [19,41]. All three patients with PNF were retransplanted within the first week post primary transplant. They have been retransplanted on postoperative days 3, 4, and 5.

Taner *et al*. [2] reported poor patient survival outcome after retransplant. Similarly, a retrospective Korean single-center study reported retransplant to be associated with worse outcome whatever the cause [42], and similar findings were concluded by others [43,44]. In our patient follow-up up to 1 year, we had no death in the PNF group. Understandably, both hospital and ICU stays were much longer for the PNF group being retransplanted. In Taner *et al* cohort of patients, survivors beyond the first few days, both hospital and ICU stays were prolonged as well [2].

Conclusion

In conclusion, this study touches a lethal complication of liver transplantation, that is, PNF, and reconsider its potential risk factors. Our study has various limitations. First, it reflects a single-center experience, and, thus, it is important to assess carefully the applicability of such findings to other patient populations. Second, some operative data such as blood loss volume and need for intraoperative transfusion were lacking and were thus not included in our study. Early posttransplant findings might have been affected by these variables. Finally, this study did not provide immunosuppression details; however, all patients were managed according to our standard immunosuppression protocol.

Authorship contribution

Mohamed Ghazaly participated in research design, participated in the performance of the research, did data analysis, and participated in the writing of the paper, as well as involved in approval of the final draft to be published. Veena Surendrakumar participated in the performance of the research, participated in data analysis, and approval of the final draft to be published. Navneet Tiwari participated in the performance of the research, and participated in data analysis, revision of scientific content, and approval of the final draft to be published. Pulkit Sethi participated in the performance of the research, revision of scientific content, and approval of the final draft to be published.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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