Independent Predictors for Primary Non-Function after Liver Transplantation

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Primary non-function (PNF) after liver transplantation has been found to be the most common cause of early graft loss, which accounts for up to 36% of such failures. The cause of PNF is not known. The purpose of this study was to identify factors associated with and independently predictive of PNF after liver transplantation. Four hundreds twenty-four liver transplants performed at the Charles O. Strickler Transplant Center, University of Virginia were retrospectively reviewed. PNF was defined as the failure of an allograft after revascularization with no discernable cause, leading either to retransplantation or to patient death. Risk factors were analyzed using the Pearson chi-square test for univariate analysis and logistic regression for multivariate analysis. Factors found to be associated with PNF included: female recipient (6.4% vs. 2.6%, $p=0.045$), African-American donor (9.5% vs. 3.2%, p=0.043), inter-racial donor to recipient transplantation (9.5% vs. 2.8%, $p=0.008$), severe encephalopathy pretransplant (11.1% vs. 3.1%, $p=0.034$), pretransplant recipient PTT > 50 seconds (10.9% vs. 2.8%, $p=0.004$), portal vein reconstruction with conduit (15.0% vs. 3.5%, $p=0.011$), and downsizing of graft (22.9% vs. 3.8%, $p=0.007$). Logistic regression identified the use of donor iliac vein conduit for the portal vein reconstruction (p=0.003, odds ratio=3.15, 95% confidence interval: 1.49-6.64) and the racial difference between donor and recipient ($p=0.012$, odds ratio=2.31, 95% confidence interval: 1.20-4.45) to be independent predictors of PNF. The exact cause of these findings, whether physiologic or immunologic, remains unknown. If confirmed in larger data sets, the attention to these factors may minimize the possibility of PNF in non-emergency situations.

Key Words: Risk factor, primary non-function, liver transplantation

INTRODUCTION

Primary non-function (PNF), as first described by Shaw et al.,[1] is the most common cause of early graft failure and is associated with a high mortality and morbidity. The evaluation of the pathogenesis of PNF is impeded by the lack of a clear definition or uniform diagnostic criteria, and also by the wide variation in the reported incidence. Published definitions have included "initial poor hepatic function",[2] "immediate graft failure with elevated liver enzymes, little or no bile output, encephalopathy, and coagulopathy",[3] "postoperative status 72 hours, characterized by liver failure",[4] and "failure to demonstrate function immediately after liver transplantation with pathological evidence of ischemic necrosis for which no specific technical cause could be identified".[5] PNF represents the failure of an allograft soon after revascularization with no discernible cause, which leads either to retransplantation or to patient death. It is always considered to be a diagnosis of exclusion that can be made only in retrospect.[6,7] With such vagueness in definition, the reported incidence of PNF varies from 0.6% to 24%, with most centers reporting a range from 2% to 10%.[2,3,8-12]

Nonetheless, PNF has been found to be the most common cause of early graft loss after liver transplantation, accounting for up to 30-36% of such failures.[3,5] The diagnosis of PNF is made when a graft fails to demonstrate evidence of initial function following the transplantation without any technical or immunological causes. This diagnosis must be made rapidly in order to

determine the need for retransplantation. In spite of the successful clinical trials of prostaglandins in treating PNF,[13-16] the most definitive treatment for PNF remains as retransplantation.[17] Because PNF is loosely defined only in terms of the complete failure of an allograft, a successful treatment without retransplantation calls into question the accuracy of its very diagnosis.[6] Without retransplantation, deaths will occur early in the posttransplant period due to sepsis, irreversible brain injury, and multiple organ system failures.[14]

Although several potential mechanisms for PNF have been postulated, the exact cause is not yet known. The mechanisms can be divided and discussed in terms of donor-related factors (old age, unstable vital signs, use of vasoactive drugs, macrovesicular steatosis, ischemic time, nutritional status, etc) and recipient-related factors (reduced-size graft, endotoxin, and hepatotoxic drugs, etc).

Although it appears that there are many conditions that may predispose a patient to PNF, it remains a seemingly random event. This study was undertaken to determine the risk factors associated with and independently predictive of PNF after liver transplantation using a single center experience.

MATERIALS AND METHODS

Four hundreds twenty-four liver transplants performed at the University of Virginia Health System were reviewed. Donor parameters that were considered included age, hemodynamic stability, use of vasoactive drugs, liver function test, duration of hospitalization, and estimated ischemic time. Liver biopsies were not routinely performed. When biopsied to assess fat content on the basis of clinical parameters such as obesity, old age, and alcohol history of the donor, grafts with more than 30% macro-steatosis were discarded. All grafts were preserved with University of Wisconsin (UW) solution, and the immunosuppression consisted of cyclosporine or tacrolimus, corticosteroids, and sometimes azathioprine or mycophenolate mofetil.

If a graft never demonstrated evidence of initial function following transplantation without any

technical or immunological causes, the condition was diagnosed as PNF. The clinical picture included signs of total hepatic failure such as little or no bile output, stage IV coma, renal failure, hemodynamic instability, as well as biochemical features consistent with signs of irreversible damage to the graft such as massive rise in transaminases, unrelenting daily rise in bilirubin, incorrigible coagulopathy, lactic acidosis, and hypoglycemia. Other possible causes of early graft failure (technical, immunological, infectious, etc) were excluded after reviewing the clinical course, operative findings, pathology reports, radiologic findings, laboratory data, and autopsy findings.

Recipient-related risk factors for PNF included the following: demographics, number of transplants, liver disease, pretransplant CMV/VZV/EBV status, pretransplant liver function assessed by Child-Turcotte-Pugh (CTP) score, type of vascular or bile duct reconstruction, and type of graft (downsized or whole). Donor-related factors were as follows: demographics, duration of admission, cause of brain death, preoperative CMV status, cold or warm ischemic times, HLA matching, and recipient/donor body weight ratio.

For univariate analysis, variables were analyzed using the Pearson chi-square test. All values were expressed as a percentage of the group from which they were derived. A value of $p < 0.05$ was considered significant. Logistic regression was then performed to identify independent predictors for PNF after liver transplantation. Variables with a $p < 0.05$ in the univariate analysis were entered into a forward stepwise logistic regression analysis to estimate the odds ratio (OR) of PNF (dependent variables) and the presence or absence of potential prognostic factors (independent variables). The odds ratio was defined as the exp [beta-coefficient] with 95% confidence intervals (95% CI). Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) software for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

The diagnosis of PNF was made in 17 cases (4.0%). In the first month post transplant, PNF

was the most common cause (37%) of graft loss (46 cases) and was the most common indication (57%) for the need of retransplantation (21 cases). Overall (50 cases), hepatic artery thrombosis was the most common indication for retransplantation (32%) followed by PNF (24%). Five of the 17 patients with PNF died, and 12 were retransplanted within 13 days. Of 12 patients who underwent retransplantation, 3 died within 2 weeks of retransplantation, 5 died from sepsis, and 1 from stroke between 2 weeks and 1 month post-retransplant, and 3 survived for more than 1 year after retransplantation.

According to the univariate analysis, female recipients were found to be associated with PNF after liver transplantation, as shown in Table 1. The incidence of PNF in 156 female recipients was 6.4%, significantly higher than that of male recipients (2.6%, p=0.045). PNF occurred more frequently after transplantation from the 42 African-American donors (9.5%) versus 375 Caucasian donors (3.2%, p=0.043). Transplants between different races, such as African-American donors to Caucasian recipients or Caucasian donors to African-American recipients, also showed a significantly higher incidence of PNF (9.5% of 74 cases, p=0.008), compared to the 2.8% of 326 transplants between similar races. The severity of pretransplant encephalopathy was associated with PNF (p=0.034). The incidence of PNF in the recipi-

Table 1. Significant Risk Factors for PNF after Liver Transplantation

Variables	Category	Incidence(%)	Number	p-value
Recipient gender	male	2.6	268	
	female	6.4	156	0.045
Donor-to-recipient race	white-to-white	2.8	324	
	white-to-black	8.3	36	
	black-to-white	10.5	38	
	black-to-black	0	2	0.062
	between same races	2.8	326	
	between different races	9.5	74	0.008
Donor race	Caucasian	3.2	375	
	African-American	9.5	42	0.043
Preop. encephalopathy	none	2.4	168	
of recipient	1 - 2	3.8	183	
	3 - 4	13.0	23	
	unresponsive	0	4	0.085
	< moderate	3.1	351	
	> severe	11.1	27	0.034
Preop. PTT (sec)	< 30	0	53	
of recipient	30 - 40	4.0	177	
	40 - 50	2.1	96	
	50 - 60	8.1	37	
	> 60	16.7	18	0.014
	> 50	10.9	45	
	< =50	2.8	317	0.004
Portal vein anastomosis	end-to-end	3.5	375	
	conduit	15.0	20	0.011
Hepatic allograft	reduced	22.2	9	
	whole	3.8	394	0.007

ents with more than a severe degree of encepha-
lopathy (grade 3) was 11.1% out of 27 cases, while
the incidence of PNF in the recipients with less
than a moderate degree of encephalopathy was
3.1% out of 351 cases. PNF occurred more fre-
quently in the group of 45 recipients with a
pretransplant partial prothombin time (PTT)
greater than 50 seconds (10.9%) versus recipients
with PTT less than 50 seconds (2.8% of 317 cases,
p=0.004). The use of an iliac vein conduit from
cadaveric donors for portal vein reconstruction
(between recipient superior mesenteric vein and
graft portal vein) in recipients with portal vein
thrombosis had an increased incidence of PNF,
15.0%, compared to 3.5% for the end-to-end portal
reconstruction (p=0.011). Transplants with a re-
duced-size liver graft also had a significantly
higher incidence of PNF (22.2% of 9 cases) com-
pared to the transplants with a whole graft (3.8%
of 394 cases, p=0.007).

There was no significant difference in the in-
cidence of PNF in terms of the following: number
of transplants, age of donor and recipient, donor
gender, the gender combination of both recipient
and donor, recipient race, recipient liver disease,
donor and recipient pretransplant CMV status,
recipient pretransplant VZV status, recipient
pretransplant EBV status, recipient ABO blood
type, ABO match, donor ABO blood type, reci-
pient Rh blood type, donor Rh blood type,
recipient/donor body weight ratio, degree of HLA
matching and HLA mismatching, pretransplant
CTP score of recipients, warm and cold ischemic
time of grafts, duration of donor admission, and
cause of brain death of donors.

The logistic regression identified the use of the
donor iliac vein conduit for portal vein recon-
struction (p=0.003, odds ratio=3.15, 95% confi-
dence interval: 1.49-6.64) and racial mismatching
between donor and recipient (p=0.012, odds ratio=
2.31, 95% confidence interval: 1.20-4.45) to be
independent predictors of PNF.

DISCUSSION

Although the exact cause of PNF is not yet
known, several potential mechanisms have been
reported. Donor age may be one consideration.

Ploeg at al. reported an increase in the incidence
of PNF with livers from donors who were more
than 50 years of age.[18] By contrast, several studies
have found no increase in the incidence of PNF
among donors older than 50 years, and it has been
concluded that there are no scientific reasons to
exclude an organ for transplantation based on age
alone.[19-22]

Another potential cause of PNF is the hemody-
namic status of the donor, which is usually asso-
ciated with the use of vasoactive drugs such as
epinephrine or vasopressin. The results of several
discriminant analyses, however, revealed that
these traditional parameters of donor assessment
are inefficient in predicting poor graft function
after transplantation.[7,23] Moreover, the incidence
of PNF with the livers from non-heart beating
donors has been reported to be no different from
that of heart-beating cadaveric donors.[24]

Macrovesicular steatosis in the donor liver has
been indicated as a cause of PNF. Since Todo et
al. reported 2 cases of PNF after liver trans-
plantation from fat infiltrated livers,[25] others have
also found an association between steatosis and
PNF in both clinical[18,22,26] and animal studies.[27]
The histological and experimental evidence of fat
accumulation in steatotic allografts that cause
compression of sinusoidal space with a decrease
in liver blood flow has been reported.[28,29]
However, not all fatty livers resulted in PNF, and
not all PNF grafts were fatty.[30]

Despite the fact that University of Wisconsin
solution has significantly lowered the incidence of
PNF,[31,32] increased cold ischemic time still results
in an increased incidence of PNF[18,33] because cold
preservation slows but does not prevent cellular
metabolic processes.[34] Related to cold preserva-
tion, the nutritional status of the donor has also
been a topic of many investigations. Several
studies using animal models have reported that
nutritional support is important to improving
organ viability and function by reducing possible
injuries from cold preservation.[35,36] However, the
opposite (i.e. fasting confers a resistance to warm
and cold ischemia) has been also reported.[37]

At least in the pediatric population, reduced-
size allografts have been noted to have a higher
incidence of PNF, although the mechanisms have
not been specifically addressed. D'Alessandro et

al. reported that there were no failures resulting from PNF among children who received whole livers, whereas PNF was the most common reason (20%) for retransplantation in those who received reduced livers.[3] This association between PNF and reduced-size livers was also demonstrated by Ploeg et al.[18]

Some experimental animal and clinical studies have suggested that endotoxin from bowel flora could be a potential source of liver injury during the operation.[38,39] Endotoxin directly affects mitochondrial function and is mediated by nitric oxide.[40] It is possible that the exposure to endotoxin and liver injury could occur in the donor, particularly following severe trauma.[41] In addition, graft damage can be caused by many drugs, whether used before or after transplantation. Cyclosporine and its metabolites,[42] as well as azathioprine, some antibiotics, and amphotericin B,[43] all have hepatotoxic effects.

The wide variety of definitions for PNF in the literature spans a continuum from potentially reversible dysfunction to complete and irreversible graft failure. We strictly defined PNF, as an immediate, complete failure of a liver graft without discernible cause, leading to either retransplantation or patient death. According to this definition, diagnosis can be made only in retrospect through the exclusion of other technical or immunological causes. Using this definition, only the portal vein reconstruction and donor-recipient racial disparity were independent predictors of PNF.

Univariate analysis illustrated that the recipient being female, the donor being African-American, racial disparity between donor and recipient, severe encephalopathy and prolonged PTT of the recipient, use of iliac vein conduit for portal reconstruction secondary to portal vein thrombosis, and downsizing of the graft were significant risk factors for PNF after liver transplantation. Multivariate analysis using these significant variables identified racial differences between donor and recipient and the type of portal vein reconstruction to be independent predictors of PNF after transplantation.

Although we have not established a criteria for the selection of potential donors, many well-known risk factors for PNF that were reconsi-

dered were donor age, hemodynamic stability, use of vasoactive drugs, liver function test, duration of hospitalization, and estimated ischemic time. If a donor had risk factors for significant macrovesicular steatosis of liver such as obesity, old age, or a history of alcohol use, a liver biopsy was performed to assess the fat content. Donated livers with more than a 30% macro-steatosis were discarded. Our overall incidence of PNF was similar to previous reports.[7,18,44]

The effect of race of the donor and recipient on the outcome of clinical liver transplantation has been discussed. Pillay et al. and Eckhoff et al. reported that there was no significant difference in graft survival when a liver was transplanted between black and white Americans and vice versa, though the incidence of PNF was not studied separately.[45,46] On the recipient side, Devlin et al. demonstrated no significant difference in either patient or graft survival among the different races (north European origin, European/ Mediterranean origin, Middle East/central Asian origin, and Afro-Caribbean origin) in the early postoperative period. However, at 1, 3, and 5 years after transplantation, the Afro-Caribbean group had a significantly lower level of patient survival.[47] However, no significant difference was found in the incidence of PNF between different races of recipients, but rather, a higher incidence of PNF was found among grafts from African-American donors (by univariate analysis) and for interracial combinations between Caucasians and African-Americans (by univariate and multivariate analyses). These data, if confirmed in large studies, may support the concept that there are significant differences in outcomes based on ethnic background.

The normal liver receives approximately 75% of its blood flow from the portal vein. For a successful liver transplantation, portal venous inflow must be at an adequate volume. Like recurrent portal vein thrombosis after liver transplantation using donor iliac vein conduit, PNF can occur as a result of decreased blood flow into the graft due to steal through pre-existing hepatopedal collateral circulation,[48] even if no evident obstruction or stenosis is found. Although the recurrence of portal vein thrombosis after liver transplantation has been reported,[49] a correlation between a

previous portal vein thrombosis and PNF is new. This association suggests that the intraoperative portal flow measurement or increased utilization of routine post-operative ultrasound may be indicated after a difficult portal reconstruction.

Without a full understanding of the cause of PNF, predicting and avoiding PNF will remain a challenge. Although many transplant programs try to avoid PNF by considering known risk factors, it still remains the major cause of early irretrievable graft failure. Although PNF is not yet preventable, steps can be taken to minimize its occurrence. If the correlation between PNF and racial combination or low portal blood flow can be confirmed, attention to these factors in donor allocation or in the recipient operation with the ligation of collaterals, respectively, may minimize the possibility of this dreaded outcome.

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