ORIGINAL ARTICLE

Portal vein thrombosis and renal dysfunction: a national comparative study of liver transplant recipients for NAFLD versus alcoholic cirrhosis

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SUMMARY

The prevalence of portal vein thrombosis (PVT), renal dysfunction (RD), and simultaneous PVT/RD in liver transplantation (LT) is poorly understood. We analyzed the prevalence of PVT, RD, simultaneous PVT/RD, and the outcomes of adult recipients of LT for nonalcoholic fatty liver disease (NAFLD) and alcoholic liver disease (ALD) between 2006 and 2016 in the United States. We found that the prevalence of PVT (7.2% → 11.3%), RD (33.8% → 39.2%), and simultaneous PVT/RD (2.4% → 4.5%) has increased significantly over the study period (all *P*-values <0.05). NAFLD patients had a higher proportion of PVT (14.8% vs. 9.2%), RD (45.0% vs. 42.1%), and simultaneous PVT/RD (6.5% vs. 3.9%; all *P*-values <0.05). 90-day mortality was 3.8%, 6.3%, 6.8%, and 9.8% for PVT(−)/RD(−), PVT(−)/RD(+), PVT(+)/RD(−), and PVT(+)/RD(+) recipients, respectively ($P < 0.01$). 5-year survival was 82.1%, 75.5%, 74.8%, and 71.1% for PVT(−)/RD(−), PVT(−)/RD(+), PVT(+)/RD(−), and PVT(+)/RD(+) recipients, respectively ($P < 0.05$). In conclusion, the prevalence of PVT, RD, and simultaneous PVT/RD has increased among LT recipients, especially for those with NAFLD. The short- and long-term outcomes of recipients with PVT, RD, and simultaneous PVT/RD were inferior to patients without those risk factors irrespective of their indication for LT. No differences in patient outcomes were found between ALD and NAFLD recipients after stratification by risk factors.

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Key words
alcoholic liver disease, interaction, liver transplantation, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, overall survival, perioperative mortality, portal vein thrombosis, renal dysfunction

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Introduction

Portal vein thrombosis (PVT) and renal dysfunction (RD) are common complications of end-stage liver disease [1–4]. Recent studies have shown that 10–15% of liver transplant (LT) recipients have partial or complete PVT at the time of their surgeries [5,6], and up to 50% have one or more episodes of acute kidney injury while on the waiting list [7].

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Multiple factors contribute to the development of PVT and RD in cirrhotic patients [3,8]. Cirrhosis leads to an imbalance between anti-thrombotic factors (e.g., antithrombin III and proteins C and S) [9,10], and pro-thrombotic and pro-inflammatory mediators that predispose to the development of venous thrombosis [11,12], especially where the blood flow is reduced such as in the portal system from the increased resistance of the intrahepatic vascular bed [8,13]. The additional presence of hypotension from systemic vasodilation [14,15] and intravascular contraction from the formation of ascites [14] activate the angiotensin-aldosterone cascade [14] with subsequent arterial vasoconstriction and drop in the glomerular filtration rate [7,11,12].

Over the last few decades, transplant centers have become more liberal in listing patients with PVT or RD [5,16–18]. These changes are multifactorial and supported by several studies suggesting that candidates with PVT or RD can be successfully transplanted with reasonable outcomes [4,16,17,19–21].

Previous investigators have shown that among LT candidates, the risk of PVT and RD is significantly higher in patients with NAFLD than in patients with other types of liver disease [22–26]. Since NAFLD has become the fastest growing indication for LT in most high-income countries [27], we speculated that the number of patients undergoing LT with PVT, RD, or simultaneous PVT/RT might have also increased over the years.

The primary aim of the current study was to assess the trends in the prevalence of PVT, RD, or simultaneous PVT/RD for LT patients undergoing surgery for NAFLD and alcoholic liver disease (ALD) in the United States (US). The secondary aim was to determine the clinical impact of simultaneous PVT/RD on patients transplanted for NAFLD compared to patients with alcoholic liver disease (ALD), as they represent the two most common indications for LT in developed countries [26].

Patients and methods

Dataset and inclusion and exclusion criteria

The United Network for Organ Sharing (UNOS) registry was used to select patients transplanted between January 1, 2006 and January 1, 2016, for NAFLD or ALD, in the United States [28]. Eligible criteria were adult age (≥18 years) and liver grafts from deceased donors. Exclusion criteria were multiple indications for LT as the presence of simultaneous NAFLD and viral hepatitis, NAFLD and ALD. Other exclusion criteria were hepatic malignancies except for hepatocellular carcinoma, the use of partial grafts or multi-visceral transplants such as simultaneous liver and renal transplants, and ABO-incompatible organs.

Hypothesis

We tested the null hypothesis that the prevalence of PVT, RD, and simultaneous PVT/RD did not change over the study period. The secondary hypothesis was that there might be an interaction between PVT and RD with a subsequent negative impact on patients' survival. Interaction between PVT and RD was defined as an effect greater than the sum of the effects of each variable. Specifically, we hypothesized that the risk of postoperative mortality in patients with simultaneous PVT/RD was greater than the sum of the risks of perioperative mortality because of PVT or RD alone.

Study population

A total of 12 770 potential candidates were screened. After excluding 3771 patients for the reasons detailed in Fig. 1, a total of 8999 recipients were included in the study population. Because of the retrospective design, the number of patients who were included was fixed.

Data regarding the presence or absence of PVT was missing in 195 subjects. For these patients, we speculated that they did not have PVT since most transplant programs would lean toward the reporting of PVT rather than not since PVT is a risk factor when adjusting for the outcomes that are made available to the public in the United States. Therefore, patients with missing information about the status of the portal vein were included in the group of recipients with no PVT. Sensitivity analysis was subsequently performed to determine if the inclusion of patients with unknown PVT in the group of patients with PVT changed the overall results of the study. No further imputations were made for any of the other variables.

The REporting of studies Conducted using Observational Routinely collected health Data (RECORD) Statement [29], an extension of the STROBE guidelines [30], was used to conduct and report the results of this study. The approval from our institution's ethics review board was waived because the data used for this study was anonymous and available to the public.

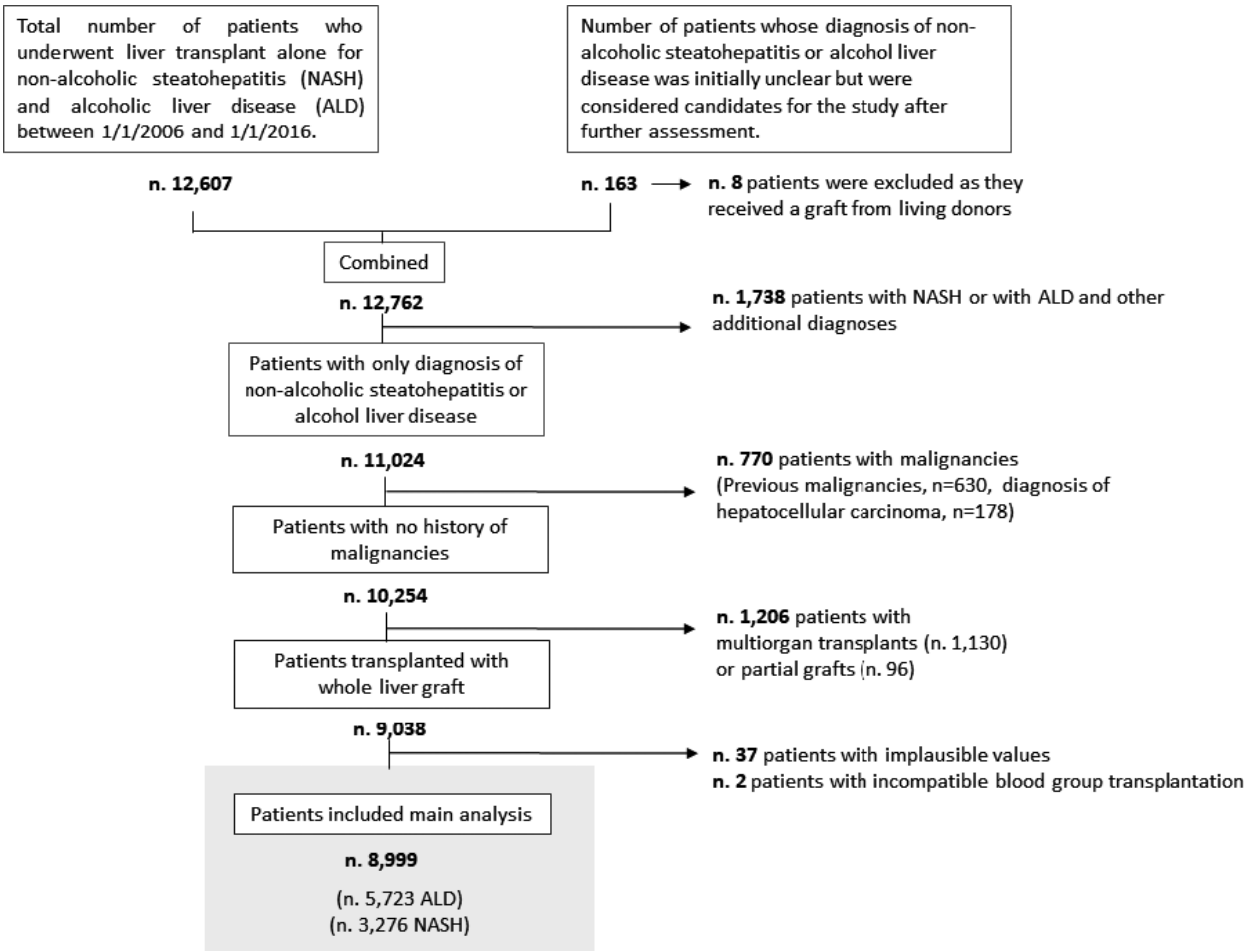


Figure 1 Flow chart showing the number of adult patients who underwent whole organ deceased donor liver transplantation in the United States between January 1, 2006 and January 1, 2016, for alcoholic liver disease (ALD) or nonalcoholic steatohepatitis (NAFLD) who were included in the study. We screened 12 770 patients. After excluding 3771 recipients, the study population comprised 8999 adults, 3276 with NAFLD (36.4%), and 5723 with ALD (63.6%).

Variables and outcomes

The demographic and the clinical variables used for this study were the primary indication for LT (NAFLD or ALD) recipients' age, sex, ethnicity, body mass index (BMI) at time of LT, the severity of liver disease by the calculated model for end-stage liver disease (MELD) score without exception points [31], the status of the portal vein, the need for preoperative dialysis, the serum creatinine level before LT, the presence of transjugular intrahepatic portosystemic shunt (TIPSS), history of diabetes, history of previous abdominal surgeries, history of spontaneous bacterial peritonitis, presence of ascites, cold ischemia time, donor age, donor sex, and donor race.

Portal vein thrombosis was defined as the presence of a clinically relevant intraluminal clot conditioning partial or complete occlusion of the portal vein irrespective of its duration or extension. The diagnosis of PVT was made before LT or at the time of LT.

Using the conventional definition of acute kidney injury/RD in cirrhosis [32], we classified patients with RD if their preoperative serum creatinine level was ≥1.5 mg/dl as previously reported by other investigators [3,33] or if they need dialysis within one week before LT.

BMI was estimated using the World Health Organization formula [34]: BMI equal to the weight (kg)/height $(m)^2$. MELD score was calculated using the formula proposed by Malinchoc *et al.* [35]: $3.78 \times \ln$ [serum bilirubin (mg/dl)] + $11.2 \times \ln$ [INR] + $9.57 \times \ln$ [serum creatinine (mg/dl)] + 6.43.

Statistical analysis

Continuous variables with normal distribution are reported using the mean and standard deviation (SD).

Median and interquartile ranges are used for nonparametric variables. Frequencies and percentages are used to report categorical variables. Analysis of variance, χ^2, and Kruskal–Wallis tests were used for summary statistics, and all estimates were adjusted when multiple comparisons were performed. Postoperative patient survival was estimated using the date of LT and the date of the last follow-up, death, or the study completion date (January 1, 2016), whichever date came first. Logistic regression was used to determine the odds ratio for 90-day perioperative mortality after adjusting for age, sex, ethnicity, and MELD score. Poisson regression analysis was used to determine if there were independent factors associated with the prevalence of RD, PVT, or simultaneous PVT/RD with the specific intent to assess if there was an association with the number of patients transplanted for NAFLD or the year of transplant surgery. The Kaplan–Meier method [36] was used to estimate the proportion of patients who were alive after surgery. The log-rank test [37] was used to compare survival functions among groups. Censoring occurred when patients underwent retransplantation, or if patients were still alive at the time of their last follow-up or completion of the study. The Cox proportional-hazards model [38] was used to estimate unadjusted and adjusted hazard ratios (HRs) of LT recipients. Two-tailed P values of less than 0.05 were considered statistically significant and Bonferroni adjustment was used when multiple comparisons were performed. Statistical analyses were performed using SPSS 26 software.

Results

Study population characteristics

Patients with ALD represented 63.6% of the population (n: 5723) while the remaining 36.4% (n: 3276) had NAFLD. The mean age at transplantation was 55 years (SD ±9), 69% of patients were males, 11.2% had PVT, 43.2% had RD, and 4.8% had simultaneous PVT/RD. The prevalence of PVT, RD, and simultaneous PVT/RD was significantly higher in patients with NAFLD in comparison with patients with ALD ($P < 0.001$; Fig. 2). The demographic and clinical characteristics of the study population stratified by primary indication for LT are reported in Table 1.

Prevalence of portal vein thrombosis, renal dysfunction, or both

The prevalence of PVT, RD, and simultaneous PVT/RD increased over time (Fig. 3a). Patients with PVT

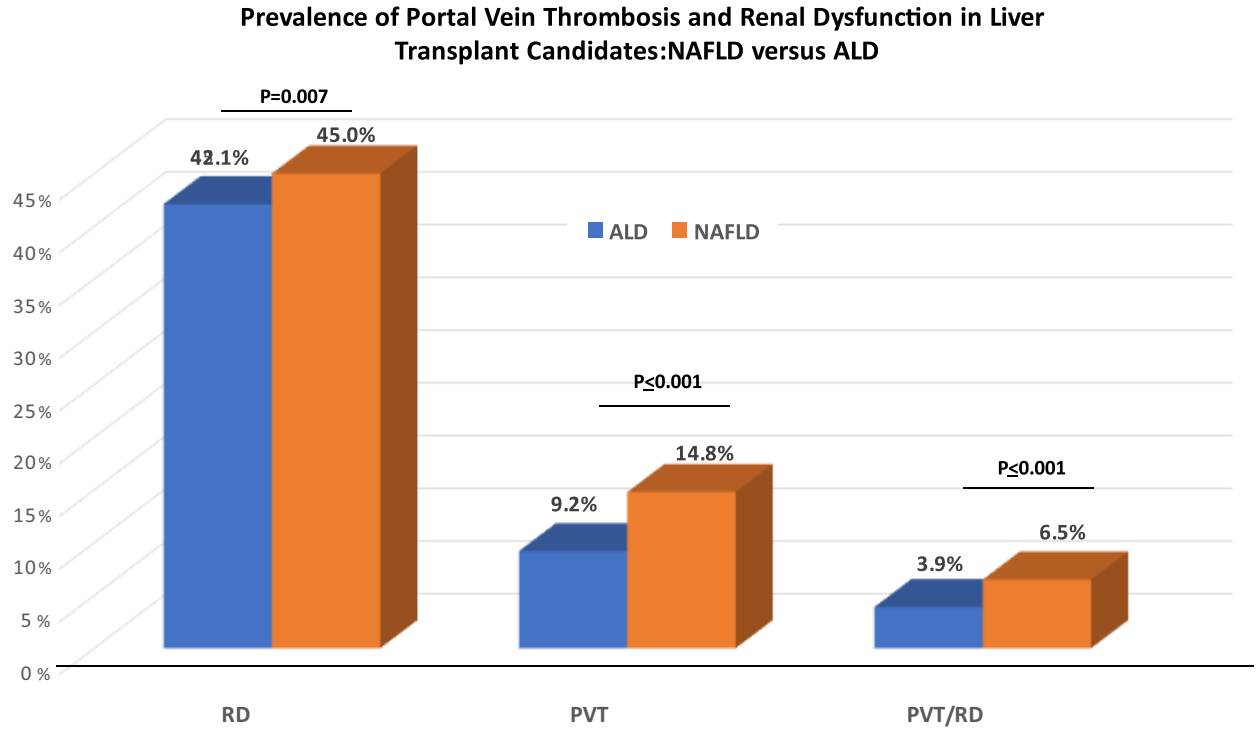


Figure 2 Prevalence of portal vein thrombosis (PVT), renal dysfunction (RD), and simultaneous portal vein thrombosis and renal dysfunction (PVT/RD) in adult patients undergoing deceased donor liver transplantation for nonalcoholic steatohepatitis (NAFLD) compared with alcoholic liver disease (ALD).

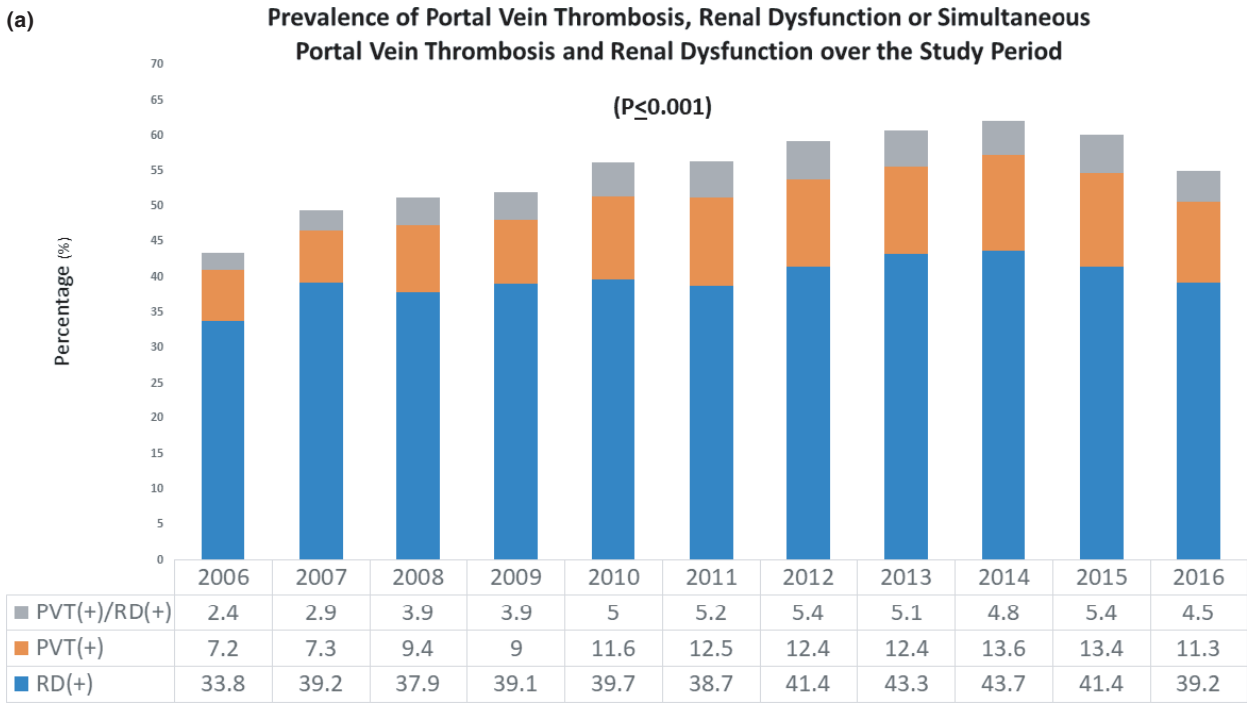
Table 1. Demographic and clinical characteristics of liver transplant recipients and donors.

Characteristics Number of patients, (%)	Total *N* = 8999, (100)	Nonalcoholic steatohepatitis *N* = 3276, (36.4)	Alcohol liver disease *N* = 5723, (63.5)	*P* value
Recipient				
Age, mean (SD) – year	55.1 (9.0)	58.0 (8.3)	53.5 (8.9)	**<0.001**
Male sex – *n* (%)	6199 (68.9)	1794 (54.8)	4405 (77.0)	**<0.001**
Race – *n* (%)				
Caucasian	7295 (81.1)	2791 (85.2)	4504 (78.7)	**0.014**
African American	272 (3.0)	55 (1.7)	217 (3.8)	**<0.001**
Hispanic	1214 (13.5)	353 (10.8)	861 (15.0)	**<0.001**
Asian	113 (1.3)	38 (1.2)	75 (1.3)	0.37
Other	105 (1.2)	39 (1.2)	66 (1.2)	0.87
Diabetes – *n* (%) – *n* (%)	2565 (28.5)	1616 (49.3)	949 (16.6)	**<0.001**
Body mass index, mean (SD)	29.8 (6.0)	32.4 (6.1)	28.2 (5.4)	**<0.001**
Underweight – *n* (%)	86 (1.0)	16 (0.5)	70 (1.2)	**<0.001**
Normal weight – *n* (%)	1655 (18.5)	250 (7.7)	1405 (24.6)	**<0.001**
Overweight – *n* (%)	2852 (31.8)	763 (23.4)	2989 (36.6)	**<0.001**
Obese (Class I) – *n* (%)	2458 (27.4)	1054 (32.4)	1404 (24.6)	**<0.001**
Obese (Class II) – *n* (%)	1347 (15.0)	780 (23.9)	567 (9.9)	**<0.001**
Obese (Class III) – *n* (%)	567 (6.3)	395 (12.1)	172 (3.0)	**<0.001**
TIPSS – *n* (%)	854 (9.5)	310 (9.5)	544 (9.5)	0.95
Renal dysfunction – *n* (%)	3884 (43.2)	1475 (45.0)	2409 (42.1)	**0.007**
Serum creatinine ≥1.5 mg/dl – *n* (%)	3860 (42.9)	1468 (44.8)	2392 (41.8)	**0.005**
Dialysis one week before transplant – *n* (%)	1179 (13.1)	392 (12.0)	787 (13.8)	**0.007**
Spontaneous bacterial peritonitis – *n* (%)	842 (9.4)	217 (6.6)	625 (10.9)	**<0.001**
Previous abdominal surgeries – *n* (%)	3156 (35.1)	1500 (45.8)	1656 (28.9)	**<0.001**
Presence of ascites – *n* (%)	4673 (52.1)	1780 (54.5)	2893 (50.8)	**0.037**
MELD, mean (SD)	25.1 (9.4)	24.1 (8.9)	25.8 (9.5)	**<0.001**
Functional status, mean (SD)	48.5 (23.4)	50.6 (23.6)	47.3 (23.1)	**<0.001**
Length of hospital stay, days, median (IQR) – days	10 (7–18)	10 (7–17)	10 (7–18)	0.79
Mortality during the index admission – *n* (%)	359 (4.0)	142 (4.3)	217 (3.8)	0.21
30-day mortality – *n* (%)	266 (3.0)	102 (3.1)	164 (2.9)	0.27
90-day mortality – *n* (%)	472 (5.2)	171 (5.2)	301 (5.3)	0.48
1-year mortality – *n* (%)	811 (9.0)	313 (9.6)	498 (8.7)	0.94
Donor Age, mean (SD) – year	43.9 (17.1)	43.7 (17.1)	43.9 (17.2)	0.49
Cold ischemia time, median (IQR) – h	6.2 (5.0–8.0)	6.1 (4.9–8.0)	6.2 (5.0–8.0)	0.10

MELD, model for end stage liver disease; TIPSS, trans-jugular intrahepatic porto-systemic shunt.

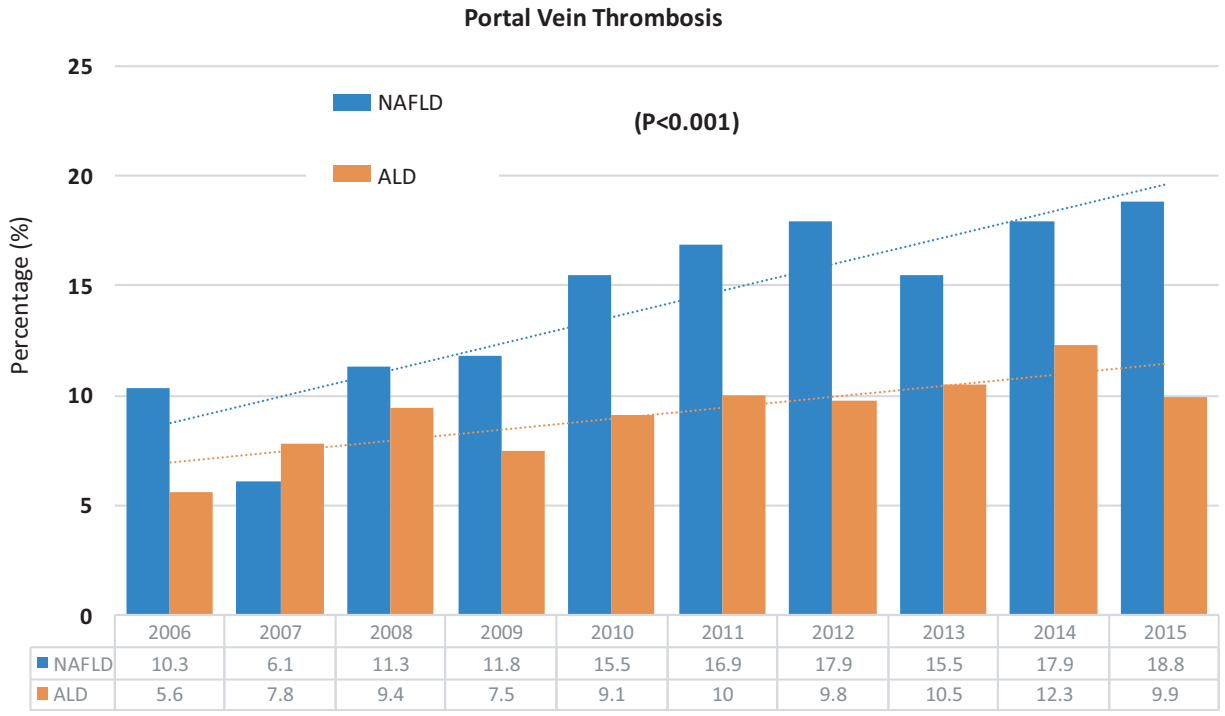
The *P* values reported with bold characters are statistically significant.

(a)



	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
PVT(+)/RD(+)	2.4	2.9	3.9	3.9	5	5.2	5.4	5.1	4.8	5.4	4.5
PVT(+)	7.2	7.3	9.4	9	11.6	12.5	12.4	12.4	13.6	13.4	11.3
RD(+)	33.8	39.2	37.9	39.1	39.7	38.7	41.4	43.3	43.7	41.4	39.2

(b)



	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
NAFLD	10.3	6.1	11.3	11.8	15.5	16.9	17.9	15.5	17.9	18.8
ALD	5.6	7.8	9.4	7.5	9.1	10	9.8	10.5	12.3	9.9

Figure 3 Longitudinal analysis of the prevalence of portal vein thrombosis (PVT), renal dysfunction (RD), and simultaneous portal vein thrombosis and renal dysfunction (PVT/RD) in adult patients undergoing deceased donor liver transplantation for nonalcoholic steatohepatitis (NAFLD) or alcoholic liver disease (ALD) in the United States between 2006 and 2016 (Panel a). Longitudinal analysis of the prevalence of portal vein thrombosis (PVT) (Panel b), renal dysfunction (RD) (Panel c), and simultaneous portal vein thrombosis and renal dysfunction (PVT/RD) (Panel d) in adult patients undergoing deceased donor liver transplantation for nonalcoholic steatohepatitis (NAFLD) compared with alcoholic liver disease (ALD).

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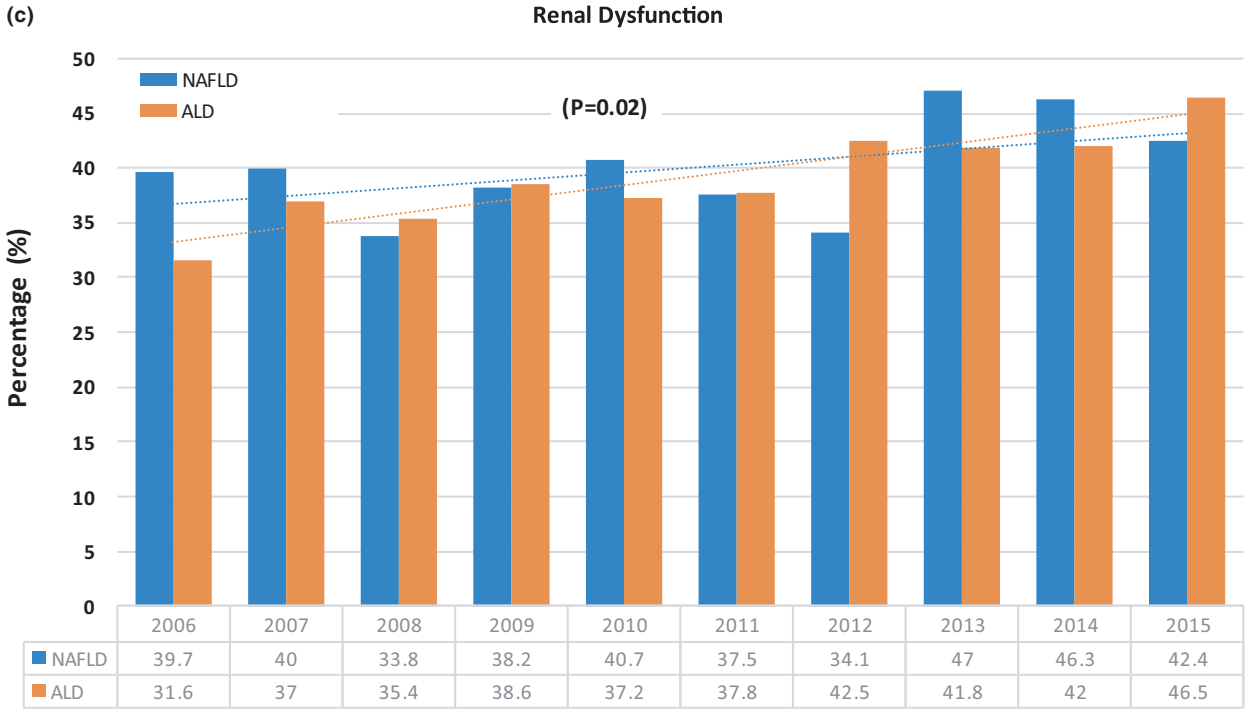
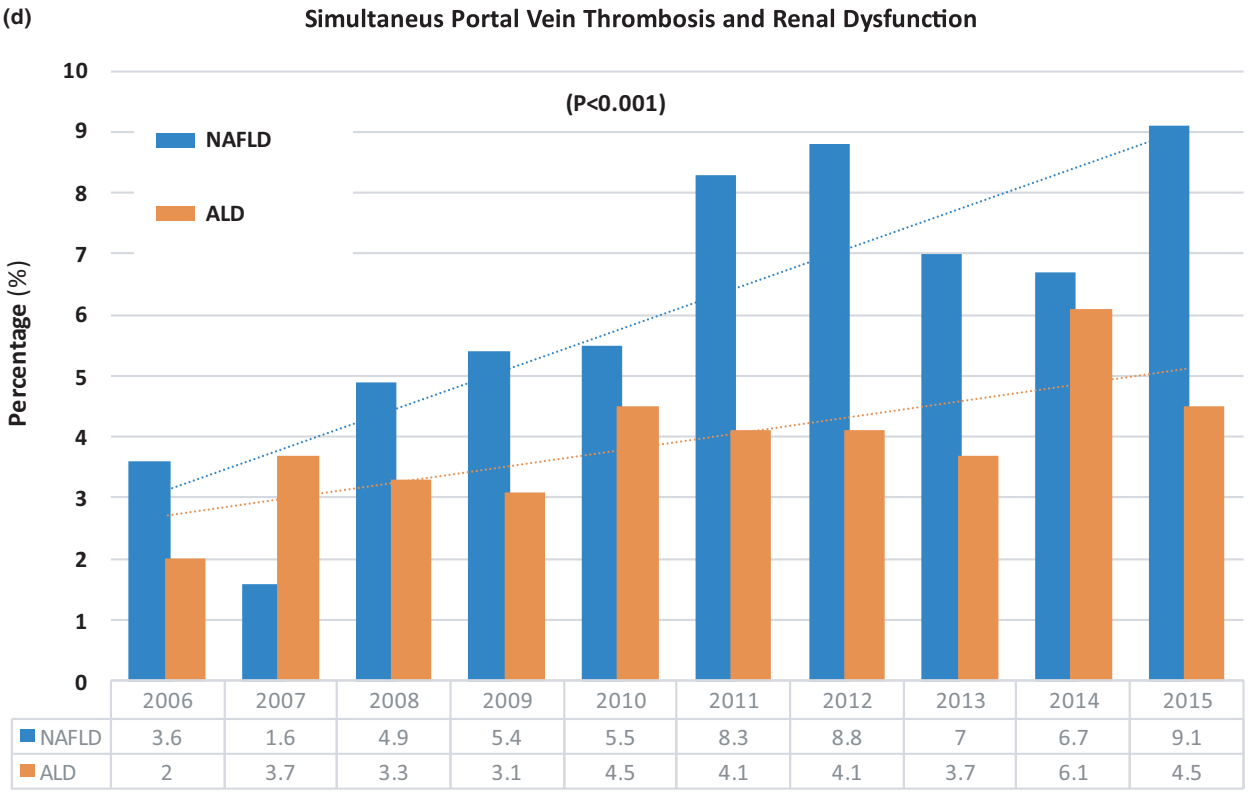


	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
NAFLD	39.7	40	33.8	38.2	40.7	37.5	34.1	47	46.3	42.4
ALD	31.6	37	35.4	38.6	37.2	37.8	42.5	41.8	42	46.5



	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
NAFLD	3.6	1.6	4.9	5.4	5.5	8.3	8.8	7	6.7	9.1
ALD	2	3.7	3.3	3.1	4.5	4.1	4.1	3.7	6.1	4.5

Figure 3 Continued.

Table 2. Demographic and clinical characteristics of liver transplant recipients with portal vein thrombosis compared to patients without portal vein thrombosis.

Characteristics Number of patients, (%)	PVT(+) *N* = 1015, (11.2)	PVT(−) *N* = 7984, (88.7)	*P* value
Recipient			
Age, mean (SD) – year	57.2 (8.1)	54.8 (9.0)	**<0.001**
Male sex – *n* (%)	727 (71.6)	5472 (68.5)	**0.04**
Race – *n* (%)			
Caucasian	803 (79.1)	6492 (81.3)	0.92
African American	24 (2.3)	248 (3.1)	0.19
Hispanic	164 (16.1)	1050 (13.1)	**0.008**
Asian	7 (0.6)	106 (1.3)	0.08
Other	17 (1.6)	88 (1.1)	0.1
Diabetes – *n* (%)	392 (38.6)	2173 (27.2)	**<0.001**
Body mass index, mean (SD)	30.6 (5.6)	29.6 (6.0)	**<0.001**
Underweight (BMI <18.5), *n* (%)	9 (0.9)	76 (1)	0.83
Normal weight (BMI 18.5–24.9), *n* (%)	125 (12.3)	1518 (19.2)	**<0.001**
Overweight (BMI 25–29.9), *n* (%)	300 (29.6)	2536 (32.1)	0.15
Obese class I (BMI 30–34.9), *n* (%)	324 (32.0)	2118 (26.8)	**<0.001**
Obese class II (BMI 35–39.9), *n* (%)	183 (18.1)	1161 (14.7)	**0.003**
Obese class III (BMI ≥40), *n* (%)	72 (7.1)	494 (6.3)	0.26
TIPSS – *n* (%)	86 (8.4)	768 (9.2)	0.46
Dialysis one week before transplant – *n* (%)	133 (13.1)	1046 (13.1)	0.94
Serum creatinine ≥1.5 mg/dl – *n* (%)	438 (43.2)	3422 (42.9)	0.85
Spontaneous bacterial peritonitis, *n* (%)	125 (12.3)	717 (9.0)	**0.003**
Previous abdominal surgeries, *n* (%)	400 (39.4)	2756 (34.5)	**0.008**
Presence of ascites, *n* (%)	536 (53.0)	4137 (52.0)	0.56
MELD, mean (SD)	24.1 (9.3)	25.3 (9.3)	**<0.001**
Functional status, mean (SD)	46.2 (22.0)	48.8 (23.5)	**0.001**
Renal dysfunction, *n* (%)	438 (43.2)	3446 (43.2)	0.99
Length of hospital stay, days, median (IQR) – days	10.7 (7–19)	10 (7–17)	0.14
Mortality during the index admission – *n* (%)	67 (6.6)	292 (3.7)	**<0.001**
30-day mortality – *n* (%)	50 (4.9)	216 (2.7)	**<0.001**
90-day mortality – *n* (%)	82 (8.1)	390 (4.9)	**<0.001**
1-year mortality – *n* (%)	135 (13.3)	676 (8.5)	**<0.001**
Donor age, mean (SD) – year	44.1 (17.2)	43.8 (17.1)	0.69
Cold ischemia time, median (IQR) – h	6.3 (5.1–8.0)	6.1 (4.9–7.9)	**0.029**

TIPSS, transjugular intrahepatic portosystemic shunt; MELD, model for end-stage liver disease.

The *P* values reported with bold characters are statistically significant.

represented 7.2% of the cohort in 2006 compared to 11.3% in 2016 ($P < 0.001$). Similar trends were observed for RD that increased from 33.8% to 39.2% ($P < 0.001$) and for simultaneous PVT/RD that increased from 2.4% to 4.5% ($P < 0.001$).

The increasing prevalence of PVT (Fig. 3b), RD (Fig. 3c), and simultaneous PVT/RD (Fig. 3d) was more pronounced in patients with NAFLD than in patients with ALD (All *P* for trends <0.05).

Poisson regression analysis showed that the increasing prevalence of PVT, RD, or both was due to the growing proportion of patients transplanted for NAFLD after adjusting for recipient age, sex, ethnicity, MELD score, BMI, and year of transplantation. NAFLD was an independent risk factor for the increasing prevalence of PVT (adjusted rate ratio 1.41; 95%CI 1.22–1.62; $P < 0.001$), RD (adjusted rate ratio 1.14; 95% CI 1.06–1.23; $P < 0.001$), and simultaneous PVT/RD (adjusted rate ratio 1.65; 95% CI 1.34–2.05; $P < 0.001$).

Risk factors for portal vein thrombosis

In addition to NAFLD, other risk factors for PVT were recipient age, male sex, Hispanic ethnicity, history of diabetes, obesity, spontaneous bacterial peritonitis, previous abdominal surgeries, and the MELD score (Table 2). At multivariate analysis, NAFLD remained the second strongest risk factor for PVT after

Table 3. Adjusted odds ratios for portal vein thrombosis in adult patients undergoing deceased donor liver transplantation.

	Portal vein thrombosis		
Risk factor	Adjusted OR	95% CI	*P*-value
NAFLD	1.45	1.24–1.69	**<0.001**
Male gender	1.31	1.12–1.54	**<0.001**
Age	1.02	1.01–1.03	**<0.001**
Race			
Caucasian	Reference	–	
Hispanic	1.35	1.12–1.62	**0.001**
BMI	1.01	1.00–1.02	0.012
Diabetes	1.36	1.18–1.57	**<0.001**
Spontaneous bacterial peritonitis	1.62	1.32–2.00	**<0.001**
Abdominal surgeries	1.15	0.99–1.32	0.057
MELD	0.99	0.98–0.99	**0.016**

NAFLD emerged as an independent factor for portal vein thrombosis with an adjusted odds ratio of 1.45 (95% CI 1.24–1.69) after accounting for age, sex, race, body mass index (BMI), diabetes, history of spontaneous bacterial peritonitis, previous abdominal surgeries, and the MELD score.

The *P* values reported with bold characters are statistically significant

spontaneous bacterial peritonitis, (adjusted odds ratio of 1.45; 95% CI 1.24–1.69; $P \leq 0.001$; Table 3).

Risk factors for renal dysfunction

Other than NAFLD, other risk factors for RD were recipient age, Hispanic ethnicity, diabetes, obesity, ascites, spontaneous bacterial peritonitis, history of TIPSS, previous abdominal surgeries, and the MELD score (Table 4). At multivariate analysis, NAFLD remained the third strongest risk factor for RD after diabetes and the presence of ascites (adjusted odds ratio = 1.28; 95% CI 1.12–1.46; $P \leq 0.001$; Table 5).

Risk factors for simultaneous portal vein thrombosis and renal dysfunction

NAFLD was also an important risk factor for simultaneous PVT/RD. Other risk factors were age, Hispanic ethnicity, obesity, diabetes, and spontaneous bacterial peritonitis (Table 6). At multivariate analysis, NAFLD remained the strongest risk factor for simultaneous PVT/RD (adjusted odds ratio 1.61; 95% CI 1.28–2.04; $P < 0.001$) after accounting for age, ethnicity, diabetes, BMI, history of spontaneous bacterial peritonitis, and MELD score (Table 7).

Perioperative mortality

Irrespective of their primary indication for LT, recipients with simultaneous PVT/RD had a 30 days, 90 days, and at 1-year mortality of 6.4%, 9.8%, and 16.9% in comparison with 2.1%, 3.8%, and 6.5% in patients without PVT or RD ($P < 0.001$; Fig. 4a). Comparisons between the respective perioperative mortality rates between NAFLD and ALD recipients showed no statistically significant differences (Table 8).

Patient survival

The median follow-up of the entire cohort was 50.0 (IQR 25.1–85.1) months. The 5-year survival of all recipients without PVT and without RD was 82.1% (95% CI 80.9–83.3). For all patients with RD alone, the survival rate was 75.5% (95% CI 74.3–77.5), for all patients with PVT alone the survival rate was 74.8% (95%CI 71.9–77.9) and for all patients with simultaneous PVT/RD, the survival rate was 71.1% (95% 70.1–73.9; all pairwise comparisons: $P < 0.05$).

Cox regression analysis showed that PVT, RD, and simultaneous PVT/RD were independent risk factors of poorer survival after adjusting for recipient age, sex, ethnicity, diabetes, BMI, MELD, history of previous abdominal surgeries, ascites, TIPSS, spontaneous bacterial peritonitis, donor age, and year of transplantation. The adjusted hazard ratio for RD was 1.45 (95% CI 1.30–1.61; $P \leq 0.0001$), for PVT was 1.29 (95% CI 1.05–1.58; $P = 0.012$), and for simultaneous PVT/RD was 2.11 (95% CI 1.73–2.56; $P \leq 0.0001$).

Contrary to our hypothesis, no statistically significant interaction on patient survival was found between PVT

Table 4. Demographic and clinical characteristics of liver transplant recipients with renal dysfunction compared to patients without renal dysfunction.

Characteristics Number of patients, (%)	RD (+) *N* = 3884, (43.1)	RD (−) *N* = 5115, (61.2)	*P* value
Recipient			
Age, mean (SD) – year	54.9 (9.0)	54.3 (8.7)	**0.001**
Male sex – *n* (%)	2649 (68.2)	3550 (69.4)	0.22
Race – *n* (%)			
Caucasian	3082 (79.4)	4213 (82.4)	**<0.001**
African American	134 (3.5)	138 (2.7)	0.039
Hispanic	578 (14.9)	636 (12.4)	**<0.001**
Asian	47 (1.2)	66 (1.3)	0.73
Other	43 (1.1)	62 (1.2)	0.64
Diabetes – *n* (%)	1307 (33.7)	1511 (29.5)	**<0.001**
Body mass index, mean (SD)	30.7 (6.3)	29.9 (5.8)	**<0.001**
Underweight (BMI <18.5), *n* (%)	35 (0.9)	51 (1.0)	0.63
Normal weight (BMI 18.5–24.9), *n* (%)	657 (17.0)	998 (19.5)	**0.001**
Overweight (BMI 25–29.9), *n* (%)	1174 (30.4)	1678 (32.9)	**0.009**
Obese class I (BMI 30–34.9), *n* (%)	1053 (27.3)	1405 (27.5)	0.71
Obese class II (BMI 35–39.9), *n* (%)	636 (16.5)	711 (13.9)	**0.001**
Obese class III (BMI ≥40), *n* (%)	303 (7.9)	264 (5.2)	**<0.001**
TIPSS – *n* (%)	374 (9.6)	722 (14.1)	**<0.001**
Dialysis one week before transplant – *n* (%)	1179 (30.4)	0 (0)	**<0.001**
Serum creatinine ≥ 1.5 mg/dl – *n* (%)	3860 (99.4)	0 (0)	**<0.001**
Spontaneous bacterial peritonitis, *n* (%)	417 (10.4)	425 (8.3)	**<0.001**
Previous abdominal surgeries, *n* (%)	1334 (34.3)	1822 (35.6)	**0.002**
Presence of ascites, *n* (%)	1733 (44.8)	2940 (57.7)	**<0.001**
MELD, mean (SD)	31.4 (8.7)	20.4 (6.6)	**<0.001**
Functional status, mean (SD)	38.6 (22.6)	56.0 (21.1)	**<0.001**
Length of hospital stay, days, median (IQR) – days	13 (8–22)	9 (7–15)	**<0.001**
Mortality during the index admission – *n* (%)	211 (5.5)	148 (2.9)	**<0.001**
30-day mortality – *n* (%)	150 (3.9)	116 (2.3)	**<0.001**
90-day mortality – *n* (%)	262 (6.7)	210 (4.1)	**<0.001**
1-year mortality – *n* (%)	457 (11.8)	354 (6.9)	**<0.001**
Donor Age, mean (SD) – year	42.3 (16.6)	45.0 (17.4)	**<0.001**
Cold ischemia time, median (IQR) – h	6.3 (5–8)	6.1 (4.9–8.0)	0.5

MELD, model for end stage liver disease; TIPSS, trans-jugular intrahepatic porto-systemic shunt.

The *P* values reported with bold characters are statistically significant.

and RD ($P = 0.85$) indicating that the effects of PVT and RD were additive but not synergistic.

Pairwise comparison of the 5-year survival of patients with NAFLD versus patients with ALD showed no significant differences between the two groups (78.3% vs. 79.3%; log-rank $P = 0.78$). Similar findings were also observed for the 5-year survival of NAFLD versus ALD patients without PVT or RD (79.9% vs. 78.4%; log-rank $P = 0.72$), with RD only (71.7% vs. 75.2%; log-rank $P = 0.059$), with PVT only (73.9% vs. 72.9%; log-rank $P = 0.84$), and with simultaneous PVT/RD (66.1% vs. 70.6%; log-rank $P = 0.70$).

In both groups, patients without PVT or RD had significantly better survival than patients with RD only, PVT only, and with simultaneous PVT/RD ($P < 0.001$; Fig. 5). On the other hand, the clinical impact of PVT alone or in combination with RD was more pronounced in patients with NAFLD compared to ALD recipients (Fig. 6).

Discussion

To the best of our knowledge, this study is the first that analyzed the trends of the prevalence of PVT, RD, or simultaneous PVT/RD at a national level, and the first that assessed the clinical effects that these conditions had on the short- and the long-term outcomes of adult LT recipients. Using data from patients who underwent

Table 5. Adjusted odds ratios for renal dysfunction in adult patients undergoing deceased donor liver transplantation.

	Renal dysfunction		
Risk factor	Adjusted OR	95% CI	*P* value
NASH	1.28	1.12–1.46	**≤0.001**
Male gender	1.18	1.04–1.34	**0.01**
Age	1.04	1.03–1.05	**≤0.001**
Race			
Caucasian	Reference		
African American	0.94	0.68–1.29	0.72
Hispanic	0.80	0.69–0.96	**0.009**
BMI	1.01	0.99–1.01	0.09
Diabetes	1.67	1.47–1.89	**≤0.001**
Spontaneous bacterial peritonitis	1.04	0.87–1.25	0.64
Abdominal surgeries	1.08	0.96–1.22	0.16
MELD	1.21	1.20–1.22	**≤0.001**
TIPSS	0.78	0.65–0.92	**0.005**
Ascites	1.30	1.08–1.57	**0.005**

NAFLD emerged as an independent factor for renal dysfunction with an adjusted odds ratio of 1.28 (95% CI 1.12–1.46) after accounting for age, sex, race, body mass index (BMI), diabetes, history of spontaneous bacterial peritonitis, previous abdominal surgeries, the MELD score, placement of transjugular intrahepatic portosystemic shunt (TIPSS), and presence of ascites.

The *P* values reported with bold characters are statistically significant.

a LT for NAFLD and ALD between 2006 and 2016 in the United States, we found that there has been a significant increase in the percentage of LT recipients with PVT, RD, or simultaneous PVT/RD. Specifically, over a decade, the proportion of LT recipients with PVT rose from 7.2% to 11.3%, a relative increase of 57%, the proportion of patients with RD rose from 33.8% to 39.2%, a relative increase of 16%, and the proportion of patients with simultaneous PVT/RD rose from 2.4% to 4.5%, a relative increase of 87%.

The increasing prevalence of PVT, RD, and simultaneous PVT/RD was more pronounced in NAFLD patients than in recipients with ALD. In particular, we found that the overall prevalence of RD, PVT, and simultaneous PVT/RD was, respectively, 45%, 14.8%, and 6.5% for patients with NAFLD in comparison with 42%, 9.2%, and 3.9% for patients with ALD.

The rising trends of PVT, RD, and simultaneous PVT/RD are probably multifactorial. Over the last fifty years, since the first successful LT was performed by Starzl and colleagues in 1967 [39], transplant centers have gained more expertise in managing patients with RD and PVT and have become more liberal in accepting candidates with those risk factors [40–42]. Another consideration is that, in most high-income countries, the number of patients undergoing LT for NASH [28,43,44] has grown significantly [28,43,44].

Previous studies have indicated that patients with NASH are at an increased risk for RD [24] and PVT [22–26]. In a recent meta-analysis by Musso *et al.* [24] using data from 33 studies reporting the prevalence of RD in patients with NAFLD, NAFLD emerged as an independent risk factor for RD irrespective of the presence or not of diabetes and hypertension, two of the most common causes of renal failure in the world [24]. The link between NAFLD and RD has also been confirmed by other investigators who have indicated that patients with NAFLD have an increased level of oxidative stress as well pro-inflammatory cytokines that induce endothelial damage, renal injury, and thrombotic complications [22–26].

Recent evidence also suggests that RD alone is a predisposing factor for thrombosis [45,46]. The hypercoagulable state observed in patients with RD is secondary to of high levels of acute-phase proteins in addition to endothelial cell dysfunction [46]. These two conditions induce a chronic activation of the coagulation cascade, as shown by an elevated level of thrombin-antithrombin complexes and lower levels of endogenous anticoagulants such as protein C and protein S and antithrombin [47].

The data of our study corroborated those observations as NAFLD resulted as an independent risk factor for PVT, RD, and simultaneous PVT/RD, after accounting for confounders such as age, sex, BMI, diabetes, and other important clinical characteristics. Additional findings worth mentioning were that LT recipients with PVT [18], RD [48], or simultaneous PVT/RD had

Table 6. Demographic and clinical characteristics of liver transplant recipients with simultaneous portal vein thrombosis and renal dysfunction compared to patients with portal vein thrombosis alone, renal dysfunction alone, and without portal vein and without renal dysfunction.

Characteristics Number of patients, (%)	PVT(+)/RD(+) *N* = 438, (4.8)	PVT(+)/RD(−) *N* = 577, (6.4)	PVT(−)/RD(+) *N* = 3446, (38.2)	PVT(−)/RD(−) *N* = 4538, (50.4)	*P*-value
Recipient					
Age, mean (SD) – year	56.6 (7.8)	56.2 (8.1)	54 (9.2)	54.0 (8.8)	**<0.001**
Male sex – *n* (%)	316 (72.1)	411 (71.2)	2315 (68.0)	3139 (69.2)	0.1
NAFLD – *n* (%)	212 (48.4)	274 (47.5)	1263 (36.7)	1527 (33.6)	**<0.001**
ALD – *n* (%)	226 (51.6)	303 (52.5)	2183 (63.3)	3011 (66.4)	**<0.001**
Race – *n* (%)					
Caucasian	332 (75.8)	471 (81.6)	2719 (79.9)	3742 (82.5)	**<0.001**
African American	10 (2.3)	14 (2.4)	123 (3.6)	124 (2.7)	0.09
Hispanic	81 (18.5)	83 (14.4)	490 (14.4)	553 (12.2)	**<0.001**
Asian	3 (0.7)	4 (0.7)	44 (1.3)	62 (1.4)	0.37
Other	11 (2.5)	5 (0.8)	29 (0.8)	57 (1.3)	**0.01**
Body mass index, mean (SD)	31.4 (5.9)	31.0 (5.5)	30.7 (6.3)	29.7 (5.8)	**<0.001**
Underweight (BMI <18.5), *n* (%)	4 (0.9)	5 (0.9)	30 (0.9)	46 (1.0)	0.47
Normal weight (BMI 18.5–24.9), *n* (%)	54 (12.4)	71 (12.3)	594 (17.4)	927 (20.4)	0.25
Overweight (BMI 25–29.9), *n* (%)	130 (29.8)	170 (29.5)	1030 (30.2)	1508 (33.2)	**<0.001**
Obese class I (BMI 30–34.9), *n* (%)	135 (31.0)	189 (32.8)	904 (26.5)	1216 (26.8)	0.003
Obese class II (BMI 35–39.9), *n* (%)	73 (16.7)	110 (19.1)	561 (15.5)	601 (13.2)	**<0.001**
Obese class III (BMI ≥40), *n* (%)	40 (9.2)	32 (5.5)	262 (7.7)	232 (5.1)	**<0.001**
Diabetes – *n* (%)	192 (43.8)	238 (41.2)	1103 (32.4)	1273 (28.1)	**<0.001**
TIPSS – *n* (%)	44 (10.0)	95 (16.5)	328 (9.6)	627 (13.8)	**<0.001**
Dialysis one week before transplant – *n* (%)	133 (30.4)	0	1046 (30.7)	0	**<0.001**
Serum creatinine ≥1.5 mg/dl – *n* (%)	438 (100)	0	3422 (99.3)	0	**<0.001**
MELD, mean (SD)	31.1 (8.6)	19.0 (5.9)	31.6 (8.6)	20.6 (6.6)	**<0.001**
Functional status, mean (SD)	36.7 (21.7)	53.4 (19.4)	38.7 (22,6)	56.3 (21.3)	**<0.001**
Ascites, *n* (%)	201 (46.0)	335 (58.3)	1511 (44.5)	2605 (57.4)	**<0.001**
Abdominal surgeries, *n* (%)	170 (38.8)	230 (39.9)	1151 (33.8)	1592 (35.1)	**0.001**
Spontaneous bacterial peritonitis, *n* (%)	61 (13.9)	64 (11.1)	356 (10.5)	361 (8.0)	**<0.001**
Length of hospital stay, days, median (IQR) – days	13 (8–25)	9.5 (7–16)	13 (8–22)	9 (7–15)	**<0.001**
Mortality during the index admission – *n* (%)	33 (7.6)	34 (5.9)	175 (5.1)	114 (2.5)	**<0.001**
30-day mortality – *n* (%)	28 (6.4)	22 (3.8)	119 (3.5)	94 (2.1)	**<0.001**
90-day mortality – *n* (%)	43 (9.8)	39 (6.8)	215 (6.3)	171 (3.8)	**<0.001**
1-year mortality – *n* (%)	74 (16.9)	61 (10.6)	378 (11.1)	293 (6.5)	**<0.001**
Donor age, mean (SD) – year	41.8 (16.5)	45.9 (17.5)	42.4 (16.6)	44.9 (17.4)	**<0.001**
Cold ischemia time, median (IQR) – h	6.4 (5.2–8.1)	6.2 (5.0–7.9)	6.2 (5–8)	6.0 (4.9–8.0)	0.15

MELD, model for end-stage liver disease; TIPSS, transjugular intrahepatic portosystemic shunt.

The *P* values reported with bold characters are statistically significant.

Table 7. Adjusted odds ratios for simultaneous portal vein thrombosis and renal dysfunction in adult patients undergoing deceased donor liver transplantation.

	Portal vein thrombosis and renal dysfunction		
Risk factor	Adjusted OR	95% CI	*P* value
NASH	1.61	1.28–2.04	**≤0.001**
Male gender	1.49	1.18–1.88	**≤0.001**
Age	1.03	1.02–1.05	**≤0.001**
Race			
Caucasian	Reference	–	
African American	0.89	0.46–1.72	0.74
Hispanic	1.24	0.95–1.61	0.1
BMI	1.01	0.99–1.02	0.26
Diabetes	1.54	1.24–1.92	**≤0.001**
Spontaneous bacterial peritonitis	1.47	1.09–1.98	**0.01**
Abdominal surgeries	1.19	0.96–1.48	0.1
MELD	1.07	1.06–1.08	**≤0.001**
TIPSS	0.82	0.59–1.14	0.27
Ascites	1.49	0.99–2.25	0.053

NAFLD emerged as an independent factor for simultaneous portal vein thrombosis and renal dysfunction with an adjusted odds ratio of 1.61 (95% CI 1.28–2.04) after accounting for age, sex, race, body mass index (BMI), diabetes, history of spontaneous bacterial peritonitis, previous abdominal surgeries, the MELD score, placement of transjugular intrahepatic portosystemic shunt (TIPS), and presence of ascites.

The *P* values reported with bold characters are statistically significant.

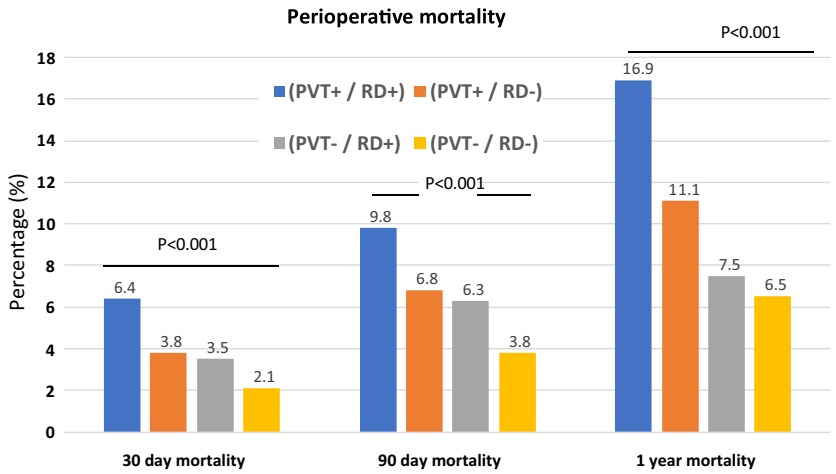


Figure 4 Perioperative mortality of liver transplant recipients stratified by the presence or absence of portal vein thrombosis (PVT), renal dysfunction (RD), or simultaneous portal vein thrombosis and renal dysfunction (PVT/RD). Patients with simultaneous PVT/RD had the highest perioperative mortality at 30 days, 90 days, and at 1-year, followed by patients with PVT only, RD only, and patients without PVT or RD who had the lowest perioperative mortality risk.

higher perioperative mortality and lower long-term survival rates than patients without those conditions. In comparison with patients with no risk factors whose 5-year survival was 82%, recipients with one risk factor had a 5-year survival of 75%, and patients with simultaneous PVT/RD had a 5-year survival of 71%. It is important to notice that, despite the 5-year survival of patients with simultaneous PVT/RD was the lowest among the groups, their survival was abundantly higher than 50%, a value commonly referred to as the lowest acceptable survival rate to justify LT [49].

In comparison with patients with ALD, NAFLD recipients were older, more frequently obese, hypertensive, diabetic, and with RD. These findings confirmed

Table 8. Perioperative mortality at 30 days, 90 days, and at 1-year after liver transplantation.

Mortality	NASH (%)	ALD (%)	*P* value
30-days			
PVT(−)/RD(−)	2.1	2.1	0.81
PVT(−)/RD(+)	3.6	3.5	0.84
PVT(+)/RD(−)	3.6	4.0	0.84
PVT(+)/RD(+)	6.6	6.2	0.86
90-days			
PVT(−)/RD(−)	3.5	3.9	0.55
PVT(−)/RD(+)	6.2	6.5	0.74
PVT(+)/RD(−)	7.3	6.3	0.24
PVT(+)/RD(+)	9	8	0.33
1 year			
PVT(−)/RD(−)	6.6	6.4	0.09
PVT(−)/RD(+)	11.7	10.8	0.73
PVT(+)/RD(−)	9.9	11.2	0.28
PVT(+)/RD(+)	17.5	16.4	0.09

Patients were stratified by the presence or absence of portal vein thrombosis (PVT) and renal dysfunction (RD) before their surgeries. Comparisons were performed between patients with nonalcoholic liver disease (NAFLD) and patients with alcoholic liver disease (ALD).

previous observations reporting that NAFLD patients have worse physical conditions than patients with other types of liver disease [25,50]. Because of the higher comorbidity index, we anticipated that NAFLD patients, especially those with PVT or simultaneous PVT/RD would experience a significantly lower survival than patients transplanted for ALD [24,51,52]. Contrary to our speculations, their survival was not significantly different as previously reported by other investigators [50,53,54]. Although the long-term survival between the two groups was similar, other studies have reported that the immediate postoperative mortality of NAFLD patients is higher, mainly because of infections and cardiovascular complications [42,55]. Contrary to those observations, in our population, we found that the 1-year mortality of NAFLD patients was equivalent to the 1-year survival of patients affected by ALD (7.3% vs. 9.1%; $P = 0.25$; data not shown). Further analysis has also shown that there were no significant differences in the cause of death between the two groups, with infections and cardiovascular complications being the most common reasons for patients' demise for both ALD and NAFLD recipients (Data not shown).

One of the unexpected findings of our study was that after adjusting for the primary cause of liver disease, sex, age, ethnicity, BMI, presence of diabetes, and history of previous abdominal surgeries, spontaneous bacterial peritonitis was one of the strongest predictors for PVT with an odds ratio of 1.55. To the best of our knowledge, no other studies have reported a similar observation in LT recipients. The only publication that signaled that spontaneous bacterial peritonitis might be a risk factor for PVT in cirrhotic patients was by Nadinskaia *et al.* [56] who reported that Child-Pugh class B and C, the presence of hepatocellular carcinoma, the history of surgical azygoportal disconnection, and the presence of any intra-abdominal acute conditions that included spontaneous bacterial peritonitis were predictors for PVT. Therefore, it is conceivable that intra-peritoneal infections or other noninfectious inflammatory processes can induce a locoregional pro-thrombotic condition that predisposes to the formation of PVT. Yet, this hypothesis should be tested in future studies.

Our analysis has several strengths and limitations. In comparison with other studies, we had the advantage of using a national registry that included all patients transplanted in the United States. It is important to keep in mind, however, that granular information on some variables that were clinically important for our study, such as the degree and chronicity of PVT or if the patients were receiving anticoagulation therapy at the time of transplantation, were not available. Consequently, we could not test if there were differences in the postoperative outcomes of LT patients based on the duration of PVT (acute versus chronic), the extension of the thrombosis (involvement of the main portal vein or involvement of tributary branches), the degree of occlusion (complete or partial thrombosis), or treatment (ongoing anticoagulation) [57]. We are fully aware that portal vein thrombosis is not a binary risk factor, and that chronicity and the extension of the disease play a very important role in the outcomes of patients undergoing LT. While a partial PVT has inconsequential effects on postoperative outcomes [19], a complete and chronic PVT might require a nonanatomical vein reconstruction that increases the complexity and duration of the operation. Therefore, the insufficient information on the degree and the chronicity of PVT available in our dataset did not allow further analyses in this regard. Despite this limitation, we think that the results of our study are clinically important as irrespective of its extension or duration (partial or complete/chronic or acute), PVT remains an independent risk factor for increased perioperative mortality and lower survival rate of LT recipients as suggested by other investigators almost two decades ago [19].

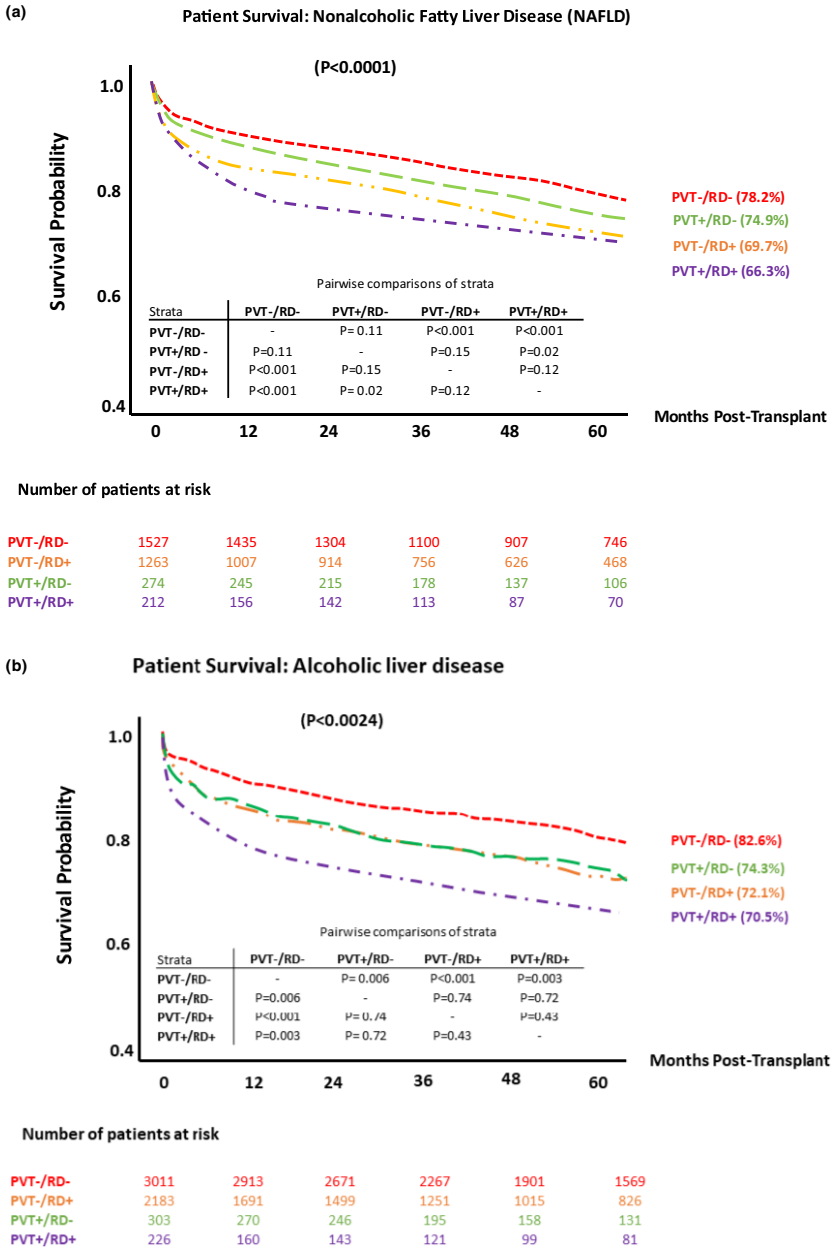


Figure 5 Kaplan–Meier survival functions of first-time recipients of deceased donor liver graft transplants for nonalcoholic steatohepatitis (Panel a), and for alcoholic liver disease (Panel b). Patients were stratified based on the presence or absence of preoperative renal dysfunction (RD+; yellow color), portal vein thrombosis (PVT+; green color), simultaneous renal dysfunction and portal vein thrombosis (PVT+/RD+; purple color), and absence of portal vein thrombosis or renal dysfunction (PVT−/RD−; red color).

Because of the retrospective design, our results need to be interpreted with caution. Only the fittest patients who underwent LT were included. Therefore, we recognize that the impact of PVT, RD, and simultaneous PVT/RD is probably more significant than what was found in this study because of the selection bias of its participants.

An additional limitation is our definition of RD. In this study, we used the preoperative serum creatinine level of 1.5 mg/dl to define patients with RD. This classification has been proposed by other investigators in the past [3,33,58] based on data from cirrhotic patients with hepatorenal syndrome [59]. However, the use of preoperative serum creatinine does not provide enough information on the etiology, the degree, and the chronicity of RD. On the other hand one of the advantages of using serum creatinine is that it is easily available and it is the most common parameter to measure

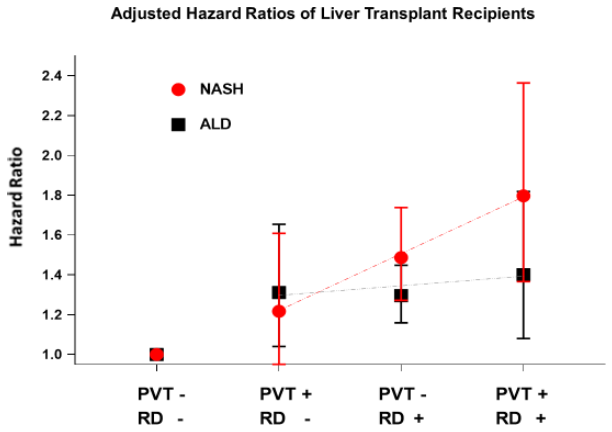


Figure 6 Adjusted hazard ratios for the death of patients undergoing liver transplantation for nonalcoholic steatohepatitis (NAFLD; red color) and alcoholic liver disease (ALD; black color). Hazard ratios were adjusted for recipient age, sex, and race. Patients without portal vein thrombosis (PVT) and renal dysfunction (RD) represented the reference group (HR = 1). The effects of renal dysfunction alone or in combination with portal vein thrombosis on patients' survival were more pronounced in patients with NAFLD than in ALD recipients, although statistically not significant.

renal function [58]. Therefore, although a better definition of RD would have been preferable, the use of the serum creatinine level was the only feasible method available to us to identify patients with impaired renal function before LT.

Our study presents some opportunities for future research in the clinical management of transplant candidates. Transplant centers should be aware that NASH patients are at an increased risk of PVT, RD, and simultaneous PVT/RD in comparison with patients with other types of liver disease. Therefore, they might require more frequent assessments of the status of their portal vein and their renal function while on the waiting list. This should also apply to patients with spontaneous bacterial peritonitis as they seem to have a higher prevalence of PVT. Current guidelines do not recommend screening for kidney disease in the absence of traditional risk factors [60]. Our study, however, suggest that individuals with NAFLD should be screened for RD even in the absence of classical risk factors such as hypertension and diabetes.

Patients with preoperative PVT, RD, or simultaneous PVT/RD are at increased perioperative mortality, and therefore, transplant centers should be aware of the risk factors associated with those conditions. More importantly, further research is needed to better understand what are the mechanisms that link NAFLD to PVT and RD and if these mechanisms can be modified.

In conclusion, our study indicates that in the United States, the number of patients undergoing LT with PVT, RD, or simultaneous PVT/RD has significantly increased over time, especially among recipients with NAFLD. Contrary to our expectations, we did not observe a negative synergistic interaction on patient survival between PVT and RD. Also, despite the higher prevalence of PVT, RD, and simultaneous PVT/RD in NAFLD patients, their survival was comparable to patients with ALD. This finding suggests that for selected recipients with PVT, RD, or simultaneous PVT/RD, the outcomes after LT are within the acceptable limits irrespective of their primary indication for LT.

Authorship

MM: designed the study, performed some of the statistical analyses, and wrote the manuscript. CFC and DD: designed the study and edited the manuscript. JD: performed statistical analyses and edited the manuscript. AC-S, SD, JB, VR, SG, CK, HL, CH, AT, HAH, BE and AH: edited the manuscript. RBA: designed the study, supervised all the statistical analyses, and edited the manuscript.

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Conflict of interest

The authors declare no conflicts of interest.

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