#### Research Article / Araștırma Makalesi

Impact of Portal Vein Thrombosis on the Outcomes of Liver Transplantation Portal ven Trombozunun Karaciğer Nakli Sonuçları Üzerindeki Etkisi

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**Abstract:** Portal vein thrombosis (PVT) occurs in up to 17.9% of patients awaiting liver transplantation. It may impact post-liver transplantation survival negatively. The liver transplant procedures performed in our transplant center between January 2020 and June 2021 were screened. Data were collected retrospectively from the electronic folder system. Data, including causes of mortality, recipient gender, age, transplant indication, presence of hepatocellular carcinoma, rejection episodes, number of days in the intensive care unit, hospitalization duration, and complications, were recorded. Patients with no PVT constituted the control group. Patients with PVT were considered as the study group. Student's t-test and the Mann-Whitney U test were used to evaluate the significance of the difference between study groups. Overall, 223 liver transplants were performed within the study period. Three retransplants were excluded from the study. The analysis of 220 liver transplant patients revealed that 18.2% (n=20) of the patients presented with a PVT before liver transplantation. Patients with PVT had a higher rate of non-alcoholic steatohepatitis as an indication of a liver transplant. In addition, the presence of PVT significantly increased surgical mortality and early rejection rates. In correlation with this, the intensive care unit stay was longer in the patient group with PVT. Although the early surgical mortality post-liver transplant was higher in the group with PVT following liver transplantation. Keywords: Portal vein, Thrombosis, Liver transplantation

Özet: Portal ven trombozu (PVT), karaciğer transplantasyonu bekleyen hastaların %17,9 kadarında görülür. Bu durum, karaciğer nakli sonrası sağkalımı olumsuz etkileyebilir. Ocak 2020-Haziran 2021 tarihleri arasında nakil merkezimizde gerçekleştirilen karaciğer nakli ameliyatları tarandı. Veriler geriye dönük olarak elektronik dosya sisteminden toplandı. Alıcının cinsiyeti, yaşı, nakil endikasyonu, hepatosellüler karsinom varlığı, rejeksiyon atakları, yoğun bakım ünitesinde geçirilen gün sayısı, hastanede kalış süresi, komplikasyonlar, mortalite nedenleri ve ilgili risk faktörleri kaydedildi. PVT olmayan hastalar kontrol grubunu oluşturdu. PVT'li hastalar çalışma grubu olarak kabul edildi. Çalışma grupları arasındaki farkın anlamlılığını değerlendirmek için Student testi ve Mann-Whitney U testi kullanıldı. Toplamda, çalışma süresi içinde 223 karaciğer nakli gerçekleştirildi. Yeniden nakil olan 3 hasta çalışmadan çıkarıldı. 220 karaciğer nakli hastası üzerinde yapılan analizler hastaların %18,2'sinin (n=20) karaciğer nakli öncesinde PVT pozitif olduğunu gösterdi. PVT'li hastalar, daha yüksek non-alkolik steatohepatit oranına sahipti. Ek olarak, PVT varlığının cerrahi mortaliteyi ve erken rejeksiyon oranlarını önemli ölçüde arttırdığı gözlendi. Bununla bağlantlı olarak PVT'li hasta

Anahtar Kelimeler: Portal ven, Tromboz, Karaciğer nakli

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# 1. Introduction

Liver transplantation is the ultimate treatment for end-stage liver disease (ESLD) patients (1). However, not all patients with ESLD are eligible for a liver transplant. The absolute contraindications for liver transplantation are severe cardiopulmonary disease, extrahepatic malignancy, active alcohol/substance abuse, active infection/uncontrolled sepsis, and lack of psychosocial support/inability to comply with medical treatment (2). Although portal vein thrombosis (PVT) was classically considered an absolute contraindication for transplantation, owing refined liver to techniques, interventional operative radiological procedures, and increasing surgical experience, liver transplantation can be performed in most patients presenting with PVT (3-6).

Portal vein thrombosis can occur in up to 5-18% of patients on the waiting list (7). A PVT that is non-occlusive and limited to the portal trunk vein allows а physiological reconstruction with an end-to-end anastomosis during liver transplantation (8). This physiological reconstruction of portal flow is correlated with good outcomes posttransplant. On the contrary, a PVT extending to the superior mesenteric vein or the mesenteric vessels, demanding a nonphysiological reconstruction, has been noted to have adverse effects on the clinical outcomes, especially during the first posttransplant year (9).

Since the extension of the thrombus in the portal vein is crucial for deciding the reconstruction technique and treatment options, a classification for its staging has been proposed. Yerdel et al. proposed a classification in their article published in 2000 (10). Their clinical study showed that the Yerdel classification could predict the outcome in patients with PVT undergoing liver transplantation.

In this single-center retrospective study, we aimed to analyze the prognosis, complication rate, and clinical outcomes of liver transplant recipients with PVT and without PVT.

# 2. Materials and Methods

This retrospective single-center study was conducted our institution's at Hepatopancreaticobiliary Surgery and Liver Transplantation unit. It was approved by our institutional ethical review committee (22.11.2022-141). All patients gave written consent for the use of their medical data in the context of this study. Patients who received a live donor liver transplant between January 2020 and June 2021 were retrospectively reviewed. Patients older than 18 years with at least a one-year follow-up duration were included in the study.

immunosuppression Induction was administered during the transplant and on postoperative day 4 with 40 mg intravenous basiliximab. Clinical follow-up protocol after liver transplant included management of immunosuppression. maintenance The standard regimen for immunosuppression comprised calcineurin inhibitors (cyclosporine/tacrolimus), corticosteroids, and mycophenolate mofetil. In the case of renal toxicity due to calcineurin inhibitors, a switch to the mammalian target of rapamycin inhibitors (sirolimus, everolimus) was made. After discharge, patients were followed once per week for two months at the liver transplant clinic by an experienced hepatologist and a transplant surgery fellow. After two months, patients were seen once per month and at intervals of 3 to 6 months after one year. Patient-related data were obtained from outpatient medical records and the institutional electronic data collecting system. In addition, causes of mortality and other parameters, including recipient gender, age, presence indication. transplant of hepatocellular carcinoma (HCC), rejection episodes, number of days in the intensive care unit, hospitalization duration, and complications, were recorded.

Additionally, preoperative computed tomography or Doppler reports of these patients were reviewed. *Late mortality* was defined as death after 6-month posttransplant. *Surgical mortality* has been defined as any death, regardless of cause, occurring within 30 days after surgery in or out of the hospital. Early rejection was considered when graft rejection occurred any time from the first week after the transplant to 3 months afterward. Patients with no thrombosis in the portal vein constituted the control group. Patients with PVT were considered as the study group. The PVT group was further evaluated and classified according to the Yerdel classification. The two groups were subject to comparative analysis.

## Statistical analysis

Data analysis was performed using the IBM SPSS Statistics 25.0 (IBM Corporation, NY. program. Armonk, US) The Kolmogorov-Smirnov test was used to determine whether the distribution of discrete numerical variables was close to normal, and Levene's test was used to check the homogeneity of variances. Descriptive statistics were expressed as means±standard deviations or medians [minimum-maximum], while categorical variables were expressed as the number of cases and percentages. Student's t-test was used when the number of independent groups was two. On the other hand, the significance of the difference between more than two independent groups was evaluated by One-Way ANOVA, Mann-Whitney U, or Kruskal Wallis tests. Pearson's  $\chi^2$  test was used in categorical data analysis unless otherwise stated. If the expected frequency was below 5 in at least  $\frac{1}{4}$  of the cells in the 2x2 crosstabs, the categorical data were evaluated with Fisher's exact probability test.

In contrast, the  $\chi^2$  test with continuity correction was used when the expected frequency was between 5-25. In the analysis of the categorical data, the Fisher Freeman Halton test was used if the expected frequency was below 5 in at least <sup>1</sup>/<sub>4</sub> of the cells. The p value was considered significant when it was lower than 0,05.

## 3. Results

During the study period, 223 live donor liver transplant procedures were performed. Three patients undergoing re-transplant were excluded from the study. In total, 220 patients were included in the study. The follow-up duration was 19 [3-51] months. Patient demographics are listed in Table 1.

**Table 1.** Demographic and clinical characteristics of the patients

Age (years)	51,4±13,2
Age range (years)	18-79
Gender	
Male	152 (69.1%)
Female	68 (30.9%)
Etiology	
HBV	59 (%26.8)
HCV	12 (%5.5)
NASH	42 (%19,1)
Cryptogenic	52 (%23.6)
Autoimmune	13 (%5.9)
Alcoholism	16 (%7.3)
PBS	10 (%4.5)
Others	19 (%8.6)
Complications	52 (%23.6)
Late mortality	15 (%6.8)
Surgical mortality	17 (%7.7)
Early rejection	67 (%30.5)
ICU stay (days)	1 (1-26)
Hospitalization (days)	16 (1-130)
Follow-up duration (months)	19 (3-51)

The mean age of patients was  $51,4\pm13,2$ years. The male gender was predominant, constituting 69,1% of the cohort. The leading causes of liver failure were Hepatitis B (n=59, 26.8%), cryptogenic (n=52, 23.6%) and nonalcoholic steatohepatitis (NASH) (n=42, 19.1%). The overall complication rate was 23,6% (n=52). Late mortality was recorded in 6,8% (n=15) of the patients. Surgical mortality rate was 7,7% (n=17) and early rejection rate was 30,5% (n=67). The mean intensive care unit stay was 1 [1-26] days, while the mean hospitalization required after the transplant was 16 [1-130] days.

There were 40 (18,2%) patients with portal vein thrombosis. The extent of the portal vein thrombosis was defined using the Yerdel classification. Twenty-five patients had Yerdel Class 1 (62,5%), seven had Yerdel Class 2, seven had Yerdel class 3, and only one had Yerdel Class 4 PVT (Figure 1). In cases with Yerdel 3 or Yerdel 4 PVT, the

portal vein was dissected until the confluence of the splenic vein and superior mesenteric vein, particularly if there is stricture and it is not possible to provide patency by thrombectomy. The strictured segment was removed and replaced by a cadaveric iliac vein graft previously harvested and kept at -80 Celcius degree. The graft was anastomosed to the confluence for portal vein reconstruction. In cases without portal vein stenosis but inadequate portal blood flow, venography was performed perioperatively, and procedures such as balloon dilatation (to the splenic vein or superior mesenteric vein) or thrombectomy were performed as necessary. The portal flow was assessed after these procedures to ensure optimal portal perfusion.



Figure 1. The distributions of the patients according to the Yerdel classification (n=40)

The demographic characteristics and collected variables were compared between the patients with no PVT and PVT (Table 2).

Table 2. Compa	rison of demog	raphic and clinic	al characteristics	according to the	study groups

Age (years)	51.0±13.6	53.0±11.0	0.399†
Gender			0.144‡
Male	120 (%66.7)	32 (%80.0)	
Female	60 (%33.3)	8 (%20.0)	
Etiology			
HBV	52 (%28.9)	7 (%17.5)	0.203‡
HCV	8 (%4.4)	4 (%10.0)	0.238¶
NASH	32 (%17.8)	10 (%25.0)	0.407‡
Cryptogenic	37 (%20.6)	15 (%37.5)	0.038‡
Autoimmune	12 (%6.7)	1 (%2.5)	0.471¶
Alcoholism	14 (%7.8)	2 (%5.0)	0.742¶
PBS	10 (%5.6)	0 (%0.0)	0.215¶
Others	17 (%9.4)	2 (%5.0)	0.538¶
Complications	39 (%21.7)	13 (%32.5)	0.210‡
Late mortality	13 (%6.7)	3 (%7.5)	0.740¶
Surgical mortality	9 (%5.0)	8 (%20.0)	0.004¶
Early rejection	49 (%27.2)	18 (%45.0)	0.043‡
ICU stay (days)	1 (1-26)	2 (1-12)	0.009¥
Hospitalization (days)	16 (7-130)	16 (1-58)	0.674¥
Follow-up duration (months)	19 (3-51)	18 (6-50)	0.930¥

† Student's t test, ‡ Continuity corrected  $\chi^2$  tests, ¶ Fisher's exact probability test, ¥ Mann Whitney U test.

There was no statistical difference in terms of age and gender. The etiology of cryptogenic liver failure was higher in the group with PVT (p=0.038). Surgical mortality was 5% (n=9) in the no PVT group, whereas it was 20% (n=8) in the PVT group (Figure 2).

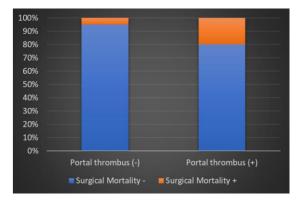


Figure 2. The comparison of surgical mortality according to the presence of portal thrombus

This difference was statistically higher in the PVT group (p=0.004). The early rejection rate was 27,2% (n=49) in the no PVT group and 45% (n=18) in the PVT group. Early rejection was recorded significantly higher in the PVT group compared to the no PVT group (p=0.043). In line with these findings, the ICU stay was significantly longer in the patients with PVT [1 (1-26) vs. 2 (1-12), p=0,009].

For further analysis, patients with PVT were divided into two groups, Yerdel 1-2 (n=32) and Yerdel 3-4 (n=8). Comparative analysis between these groups revealed that surgical mortality was higher in the Yerdel 1-2 group, with a rate of 21,9% (n=7) compared to the other groups (p=0.004) (Figure 3).

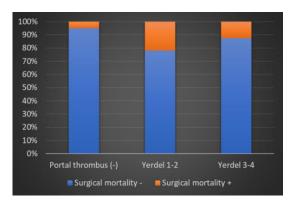


Figure 3. The distribution of the cases according to surgical mortality rates in Yerdel 1-2, Yerdel 3-4 and no portal thrombus groups shown in a stacked column chart

Moreover, the early rejection rate was higher in the Yerdel 3-4 group, with a rate of 75% (n=6) in comparison to the other groups (p=0.008) (Table 3). Among all cases with PVT, thrombectomy was performed in one case with Yerdel 1 PVT, and this patient underwent re-thrombectomy on the 10th day after LT due to recurrence of PVT. One case with Yerdel 3 PVT, who underwent balloon dilatation and iliac vein graft implantation, developed portal vein stenosis within the first month after the procedure. Subsequently, angiographic balloon dilatation was performed. Both cases had an uneventful postprocedural course without any complications.

Age (years)	51.0±13.6	53.3±10.6	51.7±13.0	0.671†
Gender				0.224‡
Male	120 (%66.7)	25 (%78.1)	7 (%87.5)	
Female	60 (%33.3)	7 (%21.9)	1 (%12.5)	
Etiology				
HBV	52 (%28.9)	6 (%18.8)	1 (%12.5)	0.318‡
HCV	8 (%4.4)	4 (%12.5)	0 (%0.0)	0.139¶
NASH	32 (%17.8)	8 (%25.0)	2 (%25.0)	0.575‡
Cryptogenic	37 (%20.6)	11 (%34.4)	4 (%50.0)	0.054‡
Autoimmune	12 (%6.7)	1 (%3.1)	0 (%0.0)	0.815¶
Alcoholism	14 (%7.8)	2 (%6.3)	0 (%0.0)	>0.999¶
PBS	10 (%5.6)	0 (%0.0)	0 (%0.0)	0.565¶
Others	17 (%9.4)	1 (%3.1)	1 (%12.5)	0.350¶
Complications	39 (%21.7)	10 (%31.3)	3 (%37.5)	0.322‡
Late mortality	13 (%6.7)	3 (%9.4)	0 (%0.0)	0.834¶
Surgical mortality	$9(\%5.0)^{a}$	$7(\%21.9)^{a}$	1 (%12.5)	0.005¶
Early rejection	$49(\%27.2)^{b}$	12 (%37.5)	$6(\%75.0)^{b}$	0.010‡
ICU stay (days)	1 (1-26)	2 (1-12)	2.5 (1-3)	0.067¥
Hospitalization (days)	16 (7-130)	15 (1-39)	20.5 (3-58)	0.387¥
Follow-up duration (months)	19 (3-51)	18 (6-50)	19.5 (6-37)	0.939¥

**Table 3.** Comparison of the demographic and clinical characteristics of patients according to the presence

 and extent of portal thrombosis using Yerdel classification

*†* One-way analysis of variance (One-Way ANOVA), *‡* Pearson's  $\chi^2$  test, ¶ Fisher Freeman Halton test, ¥ Kruskal Wallis test. a: The difference between the group with portal thrombus and Yerdel 1-2 group is statistically significant (*p*=0.004), *b*: The difference between the group without portal thrombus and Yerdel 3-4 group is statistically significant (*p*=0.008).

## 4. Discussion and Conclusion

Liver transplantation can be performed in patients with PVT, especially if it is not occlusive and limited to the portal vein trunk (10,11). However, thrombosis is challenging for the surgeon, particularly when it extends the mesenteric vessels. Therefore. to technically a relatively more physiologic endto-end anastomosis of the portal vein is preferred; however, more complex reconstructions may be necessary in cases with extended PVT (12). It was reported that the annual incidence of PVT in patients with cirrhosis ranged between 5% and 17,9% (13).

In our analyses of 220 liver transplant patients, 18,2% (n=20) presented with a PVT prior to liver transplantation. This finding is in line with the rates reported in the literature (13,14). However, patients with PVT had a higher rate of NASH as an indication of a liver transplant. In addition, the presence of PVT significantly increased surgical mortality and early rejection rates. In correlation with this, the length of ICU stay was longer in the patient group with PVT.

In our study, *surgical mortality* was defined as death within 30 days after surgery, and it was found to be significantly higher in the PVT group. This result suggested that PVT might

impact the early mortality rate, especially in post-liver transplant patients with Yerdel Class 1-2 PVT. The data available in the literature on the effect of PVT on the outcomes of liver transplantation are unclear and focused on the type of portal vein anastomosis (9,10). However, our results show a correlation and a predictable pattern between Yerdel classification and the outcome of liver transplants.

Portal vein thrombosis can be a cause or a consequence of liver disease deterioration (14). Indeed, PVT is more frequently recorded in patients with advanced liver cirrhosis (15). However, a prospective study including more than a thousand patients with compensated cirrhosis showed no cause-and-effect relationship between the presence of PVT and liver function deterioration (16). The findings in our study support this since the late mortality rates were similar in both PVT and no PVT groups following liver transplantation (p=0,74).

Although the results of this study obtained statistically significant differences between Yerdel 1-2 and 3-4 groups in terms of surgical mortality and early rejection, our numbers are relatively small to make generalizations (32)

patients in Yerdel 1-2 group and 8 patients in the Yerdel 3-4 group). The comparison of these groups required complex statistical analyses; thus, comprehensive clinical studies with a higher number of patients are required for solid conclusions. Additionally, the surgical risk factors of the patients, such as co-morbidities, previous abdominal surgeries, smoking status, and ASA (American Society of Anesthesiology) scores, were not evaluated. This condition may lead to misinterpretation of the results due to the absence of these variables. Another weakness of our study was that complications were not classified according to the Clavien-Dindo classification. The Clavien-Dindo classification is a widely used tool to evaluate the severity of surgical complications, and it stratifies the complications according to their management. Due to the retrospective nature of our study, a Clavien-Dindo chart was not feasible. Therefore, an overall complication rate was given rather than a detailed profile.

The presence of PVT was associated with a higher early rejection rate in our study. Early allotransplant rejection involves the activation of platelets and intravascular coagulation cascade, which can trigger thrombosis of the graft vessels. (17). Additionally, patients with liver cirrhosis have low levels of procoagulant factors, resulting in a new, rebalanced hemostasis (18). However, whether these acquired hemostatic alterations

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facilitate the PVT or alter the post-transplant outcome has not yet been confirmed (19,20).

Since the underlying mechanisms are not well defined, the management of patients with PVT prior to liver transplantation is another point of discussion. Despite inadequate clinical evidence, anticoagulation with low-molecular-weight heparin or vitamin K antagonists has been recommended (21).

Currently, there are no consensus guidelines on the management of PVT prior to liver transplantation. Furthermore, current guidelines do not propose definitive treatment strategies for patient management and optimization of liver transplant outcomes in this patient group.

In our study, the number of patients with Yerdel 1 or 2 PVT was much higher than those with Yerdel 3 or 4. Even though this difference is because Yerdel 1 and Yerdel 2 PVT cases are much more common than Yerdel 3 or 4, this finding should be considered while evaluating the results. Nevertheless, this study showed that the late mortality rates were not inferior in patients with PVT following live donor liver transplantation. Although the surgical mortality was higher in the group with PVT, the underlying variables could not be identified in this study. Further, prospective trials should be designed to clinical investigate underlying risks comprehensively.

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#### Ethics

**Ethics Committee Approval:** This study has been approved by Istinye University Training and Research Hospital Ethical Review Committee (Decision no:141, Date: 22.11.2022).

**Informed Consent:** Written informed consent was obtained from all participants who participated in this study.

Authorship Contributions: Surgical and Medical Practices: EE, AD. Concept: EE. Design: EE. Data collection and processing: EE and AD. Analysis and Interpretation: AD. Literature Search: AD. Writing: EE and AD

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