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The pringle maneuver for Budd-Chiari syndrome-related orthotopic liver transplantation: an experience from a large referral center

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Abstract

Background Orthotopic liver transplantation (OLT) in Budd-Chiari Syndrome (BCS)-related liver cirrhosis is quite technically challenging due to the difficult handling of an enlarged and congested liver along with the risk of massive intraoperative bleeding. Therefore, we aimed to evaluate the efficacy of occluding the hepatic blood inflow tract by the Pringle maneuver (PM) at the beginning of the hepatectomy phase of BCS-related OLT procedure.

Methods The current retrospective study of prospectively collected data was conducted between 2010 and 2022 in our referral center for OLT. Patients were divided into PM (after 2018) and non-PM (NPM, before 2018) groups. Intraoperative blood loss, packed red blood cell (PC) transfusion, operation time, 30-day mortality, and liver and renal function indexes were collected retrospectively.

Results From a total of 3539 records, a total of 55 patients included in this study; the PM and NPM groups consisted of 17 and 38 patients, respectively. The mean intraoperative blood loss (1418 ± 621 vs. 2240 ± 1591 ml, $p=0.04$) and amount of PC transfusion (418 ± 423 vs. 1263 ± 1557 ml, $p=0.03$) were significantly lower in the PM group. In the NPM group, duration of operation (282 ± 52 vs. 257 ± 32 min) and 30-day mortality rate (16% vs. 0%) were higher, which are statistically nonsignificant but clinically noteworthy.

Conclusion Using the PM can be an effective approach to reducing intraoperative bleeding, PC transfusion, and the length of surgery during OLT for BCS. It decreases the incoming blood to the congested liver, helps porta hepatis collaterals to shrink, and eases the division of hepatic ligaments and diaphragmatic attachments during the hepatectomy phase. These factors potentially facilitate the procedure for surgeons.

Keywords Budd-Chiari syndrome, Liver transplantation, Surgical blood loss, Liver cirrhosis, blood transfusion

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Introduction

Budd-Chiari syndrome (BCS) is a potentially life-threatening disease defined as the obstruction of the hepatic venous outflow tract in the absence of cardiac or pericardial pathology [1]. In patients with progressive BCS that results in liver cirrhosis due to chronic congestion, orthotopic liver transplantation (OLT) from a living or deceased donor is the only effective option, with 10–20% of patients undergoing OLT [2, 3]. Previous studies showed a range of 80–95% and 65–95% for 1- and 5-year survival after BCS-related OLT, respectively [4]. However, blood backflow from enlarged collateral veins can make surgery more challenging due to bleeding and handling of a large and congested liver when it is being divided from its attachments during the hepatectomy phase of OLT. Excessive and uncontrolled bleeding prolongs the surgery, causes unstable hemodynamics in patients, and disturbs the atmosphere of the operating room by increasing the level of stress on surgeons. In addition, previous studies showed that blood transfusion is related to higher morbidity and mortality after OLT [5, 6]. Therefore, reducing intraoperative blood loss and subsequent blood transfusion during OLT in BCS patients represents a crucial therapeutic approach to enhance patient outcomes, mitigate deleterious sequelae, and create a more stable and routine intraoperative phase for surgeons.

Intermittent hepatic inflow occlusion of the portal triad in the hepatoduodenal ligament, the Pringle maneuver (PM), was introduced by James Hogarth Pringle in 1908 to reduce hepatic hemorrhage in trauma patients [7, 8]. The PM during OLT has shown its efficacy in facilitating the hepatectomy phase by decreasing bleeding, blood transfusion, and major postoperative morbidities [9, 10]; however, it has not been investigated in OLT of BCS patients who have patent collateral branches that are at increased risk of massive bleeding. We hypothesized that decreasing the liver's blood inflow by the PM just before releasing the liver during the hepatectomy phase can be an effective approach to reduce intraoperative hemorrhage and blood transfusion and improve the handling of the congested liver in OLT of BCS patients.

Materials and methods

Patient selection

The data for this ongoing study was collected prospectively from the hospital database between 2010 and 2022 and analyzed retrospectively in 2024. The inclusion criteria were adult patients (older than 18 years) with a MELD score (model for end-stage liver disease) higher than 15, whose hepatic vein obstruction was proven by contrast-enhanced abdominal computed tomography scan (CTS) or magnetic resonance imaging (MRI), without complete portal vein thrombosis (all were Yerdle 1 or

2) or myeloproliferative disease. Diagnostic confirmation method for BCS was contrast-enhanced abdominal CTS or MRI. From 2018, the PM was used for all BCS-related OLT after a consensus among our transplant surgeons following its initial success. Before that, OLT was performed without the PM.

Data collection

The following variables were collected from the patients' medical records: sex, age, body mass index (BMI), MELD score, intraoperative blood loss (ml), amount of packed red blood cells (ml) (PC, of iso-Group and iso-Rh RBC) transfused, operation time (min), mortality within 30 days. In addition, urine output, JP drain volume, ascites, and biochemistry of blood samples (aspartate aminotransferase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), total and direct bilirubin, international normalized ratio (INR), creatinine (Cr), and hemoglobin (Hb)) were assessed 7 days after surgery. AST, ALT, ALP, and bilirubin were also recorded 90 days after surgery. The volume of intraoperative blood loss was calculated based on the suction container volume and the number of blood-absorbed gauze (normal gauze: 10 ml and long gauze: 100 ml) [11]. BCS was categorized into three types: Type I (truncal type), Type II (radicular type), and Type III (veno-occlusive type) [12].

PM during OLT of BCS

All of the operations were conducted by the same transplant team and we followed a similar protocol for all patients. Since the rate of deceased organ donation is high in our country and its trend has been rising in recent decade, we used deceased donor whole organ OLT [13]. In the PM group, after opening the abdominal layers and inserting the abdominal retractors and aspirating ascites, before performing any dissection, one curved side-biting Satinsky clamp was inserted through the foramen of Winslow. Then, complete occlusion of the hepatoduodenal ligament was done with the closure of the clamp. It seems that the first 2–3 jaw steps were enough to impede the inflow. PM was performed continuously from the beginning of the dissection until the completion of the liver hilum dissection. Next was the liver hilum dissection, separating and ligating hepatic arteries, the common bile duct, and lymphatic tissues. Then, the triangular ligaments were released on the left side and after that on the right side (counterclockwise), followed by the coronary ligament, diaphragm attachments, and finally hepato-renal ligaments. The Satinsky clamp was released afterwards and the rest of the operation was done as a routine OLT procedure. All surgeries were conducted as whole organ transplantation with the caval replacement technique from a deceased brain-dead donor (DBD) without using venovenous bypass, resecting retrohepatic

IVC and then reconstructing it with end-to-end anastomosis by 4–0 Prolene thread to the IVC above and below the grafted liver. Temporary porto-caval shunt was not performed due to surgical complexity, needing expert personal and special training and in order not to increase the duration of the operation and not knowing about its surgical efficacy for BCS-related OLT. Postoperative care was tailored to each patient's specific condition, following established protocols. At our center, the standard management involves initiating heparin therapy shortly after OLT. Once the patient completed 10 days without any signs of acute complications or bleeding, long-term anticoagulation with warfarin was introduced. The goal was to maintain the INR within the therapeutic range of 2 to 3.

Statistical analyses

SPSS software version 26 (IBM Corp. Armonk, NY, USA) was used for statistical analysis. A p -value < 0.05 was considered significant. The continuous and categorical data were presented as mean $\pm$ standard deviation (SD) and frequency (%), respectively. Student's t -test and the chi-square test (or Fisher's exact test) were used for the analysis of normally distributed numerical and categorical variables, respectively, and the Mann-Whitney U test was applied for the analysis of non-normally distributed data. Analysis of covariance (ANCOVA) was conducted between the two groups of study (PM and NPM) and dependent variables (volume of bleeding, amount of PC transfusion, and surgery duration). The rest of the investigated variables were entered as covariates if they met the pre-enrollment criteria. In the ANCOVA model, significant covariates for each dependent variable that were entered to adjust the results were: MELD score ($p = 0.049$) and ascites ($p = 0.033$) for intraoperative bleeding, age ($p = 0.04$) for surgery duration, and MELD score ($p = 0.041$) for PC transfusion. Kaplan-Meier for overall

survival was conducted and Log Rank test (Mantel-Cox) was used to compare the OS between PM vs. NPM. To evaluate the survival and factors affecting it, COX regression model was applied and independent variables were entered as covariate.

Results

Demographic characteristics

From a total of 3,539 OLT records between 2010 and 2022 in our center, a total of 68 patients had BCS; seven patients had underlying myeloproliferative disease, and three patients younger than 18 years old were excluded from this study. Patients were divided into PM and non-PM groups, which consisted of 17 (30.9%) and 38 (69.1%) patients, respectively. There was no significant difference between the two groups regarding their sex, age, BMI, weight, height, and MELD score (Table 1). In addition, the type of BCS was not significantly different between the two groups ($p = 0.638$).

Intraoperative bleeding and PC transfusion

The mean intraoperative blood loss was significantly lower in the PM group ($1,418 \pm 621$ ml vs. $2,240 \pm 1,591$ ml, $p = 0.045$ in t -test, $p = 0.040$ in ANCOVA, Fig. 1 (section A)). Accordingly, the amount of PC transfusion was significantly lower in the PM group (418 ± 423 ml vs. $1,263 \pm 1,557$ ml, $p = 0.033$ in t -test, $p = 0.034$ in ANCOVA, Fig. 1 (section B)). Although the operation lasted longer in the NPM group, the difference was not statistically significant ($p = 0.066$); however, after adjusting for age, the level of significance dropped to $p = 0.044$ in ANCOVA model.

Mortality and liver and renal indices after OLT

The 30-day mortality rate was 16% ($n = 6$) in the NPM group. Two patients died due to primary non-function (on day 1), three due to hepatic artery thrombosis (HAT)

Table 1 Demographic and outcomes of OLT due to BCS with and without pringle maneuver

Variables	Pringle Group ($n = 17$)	Non-Pringle Group ($n = 38$)	P -value
Male gender	8 (47.1%)	20 (52.6%)	0.702
Age (year)	36.88 ± 10.18	34.97 ± 10.43	0.530
BMI (kg/m^2)	23.71 ± 3.61	23.64 ± 3.51	0.947
Weight (kg)	66.24 ± 12.19	66.37 ± 10.74	0.968
Height (m)	1.67 ± 0.09	1.68 ± 0.09	0.803
MELD Score	19.12 ± 5.75	19.50 ± 6.51	0.836
Operation time (min)	256.76 ± 31.57	282.37 ± 51.96	0.066
30-day mortality	0	6 (15.8%)	0.083
Overall mortality	1 (5.9%)	10 (26.3%)	0.077
Type of Budd-Chiari syndrome			
Type I - truncal type	6 (35.3%)	11 (28.9%)	0.638
Type II - radicular type	11 (64.7%)	27 (71.1%)	
Type III - venoocclusive type	0	0	

BMI: body mass index, kg: kilogram, m: meter, MELD: model for end-stage liver disease, min: minute

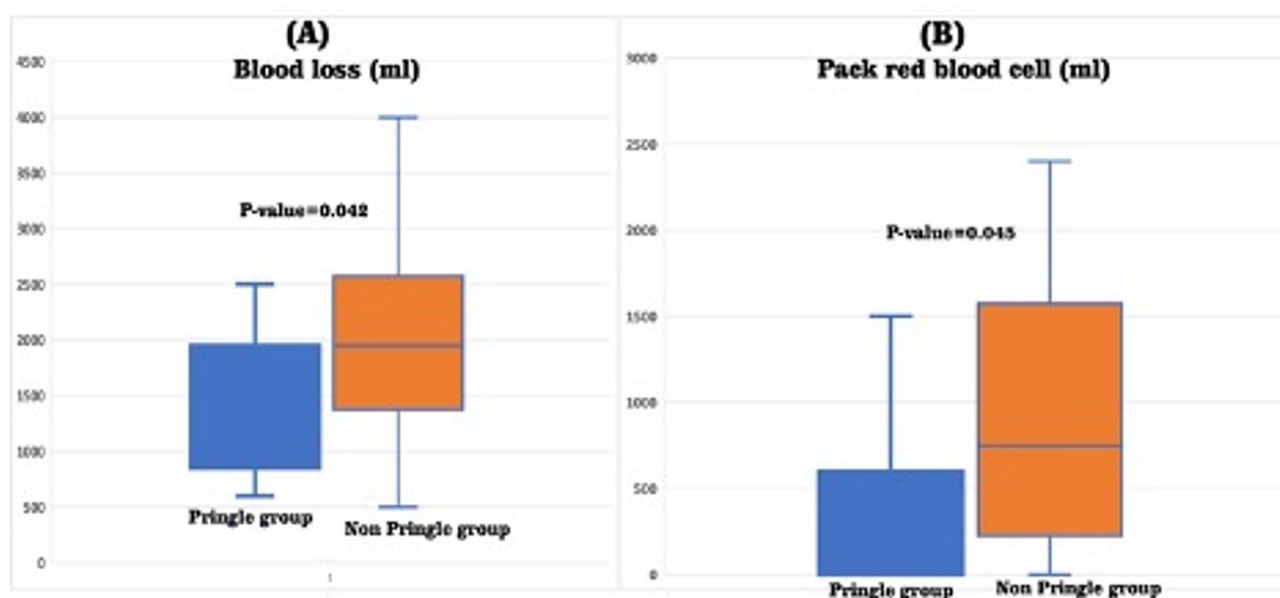


Fig. 1 The comparison of mean intraoperative blood loss (section **A**) and packed red blood cells transfusion (section **B**) between the Pringle and non-Pringle groups (Blood loss: $1,418 \pm 621$ vs. $2,240 \pm 1,591$ ml, respectively) (PC transfusion: 418 ± 423 vs. $1,263 \pm 1,557$ ml, respectively)

(no further timing specification), of which one also had portal vein thrombosis, and one due to sepsis (day 25). While the rate of 30-day mortality was 0% in the PM group, the difference was not statistically significant ($p=0.083$) though it is clinically noteworthy. However, the overall mortality throughout the study period (till 2024) was 6% (one patient) in PM group (happened 60 days post-OLT due to venous thromboembolic events (VTEs)) and 26.3% (10 patients, other deaths beyond 30 days were COVID-19 (day 476), sepsis (day 287), myocardial infarction (day 112), and VTEs (day 33)) in NPM ($p=0.077$). The Kaplan-Meier plot is shown in Fig. 2. Log rank test ($p=0.086$) and COX regression model were all statistically non-significant between groups and no influential factor was found (age, sex, BMI, MELD, and technique were entered into the model).

As summarized in Table 2, serum levels of liver enzymes, bilirubin, and INR were not statistically different between the two groups except for day-7 ascites volume ($p=0.045$). Although serum Cr after 7 days was higher in the NPM group, the difference was not statistically significant ($p=0.154$). Finally, urine output was not significantly different between the two groups after 7 days.

Discussion

Most previous similar studies on the PM were done on liver resection surgeries [14], and none of them focused on BCS as a rare indication for OLT. Due to encountering a large and congested liver in a small and packed space, liver handling is difficult during OLT, and there

is a fear of massive intraoperative hemorrhage and the need for blood transfusion when the liver is divided from its attachments and ligaments during the hepatectomy phase; this could be one reason why some surgeons are terrified to operate on BCS patients or frustrated about obtaining good postoperative outcomes. It seems theoretically that occluding the hepatoduodenal ligament can serve as a temporary measure to mitigate the bleeding tendencies resulting from portal hypertension.

To the best of our knowledge, this is the first study to investigate the effect of the PM on BCS-related OLT candidates who are at high risk of intraoperative hemorrhage and blood transfusion due to hepatic venous outflow tract obstruction, liver congestion, and collateral openings. The PM should be used after entering the abdomen and before completing the hepatectomy phase when the liver is going to be divided from its attachments; that is the phase with the high risk of bleeding and difficult handling due to a large, congested organ. In this regard, our results showed that BCS patients who underwent OLT with the PM had a significantly lower intraoperative hemorrhage and PC transfusion. Previous studies showed intraoperative blood loss is a predictor of poor outcomes in short- and long-term follow-up after OLT [15]. In addition, it was shown that excessive blood loss and blood transfusion are associated with reduced graft survival, increased septic episodes, prolonged ICU stays, and higher costs to the healthcare system [16, 17]. Besides, the association between intraoperative blood transfusion, the effects on immunomodulation, and a higher risk of postoperative complications including

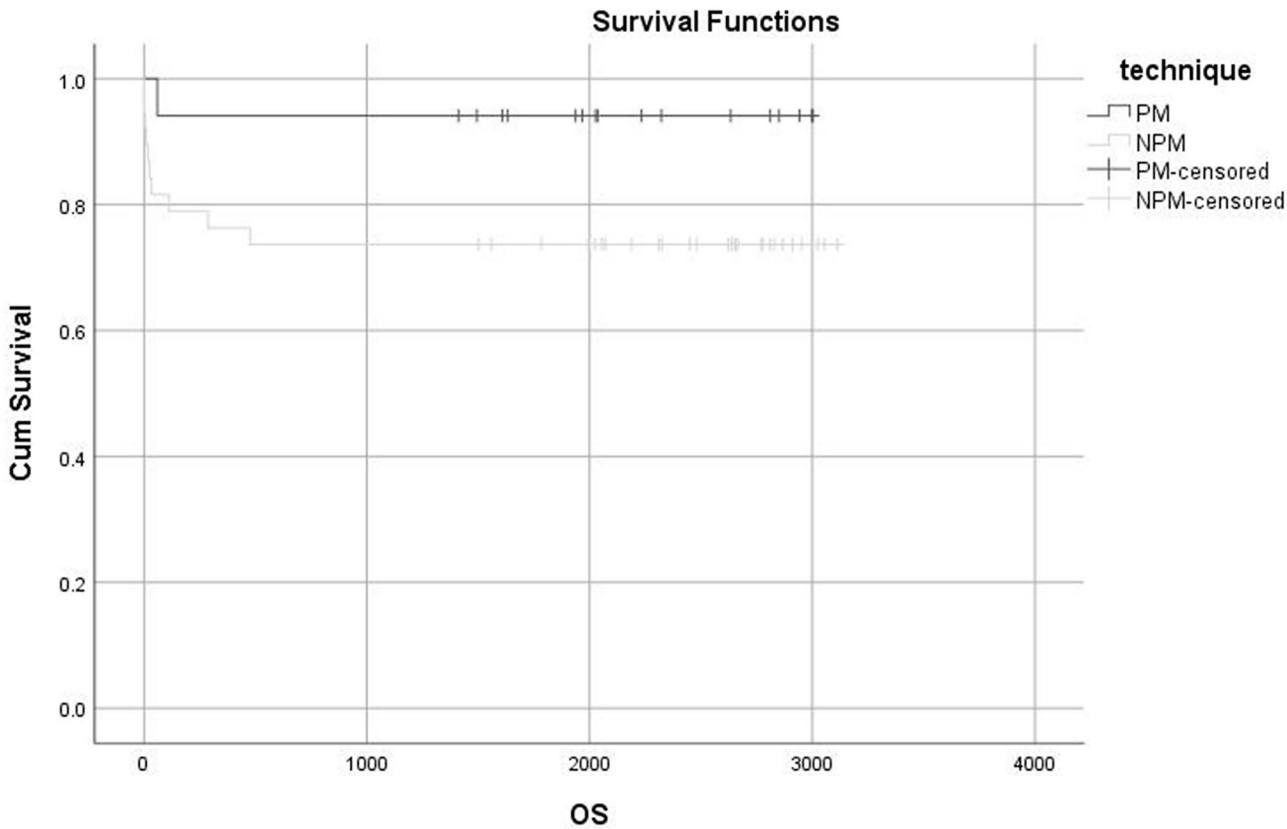


Fig. 2 Kaplan-Meier for overall survival and log rank test between the pringle and non-pringle groups ($p=0.086$)

Table 2 Investigated Post-OLT variables

Variable		Pringle Group (<i>n</i> = 17)	Non-Pringle Group (<i>n</i> = 38)	<i>p</i> -value
AST	Day 7	57.76 ± 79.41	160.06 ± 501.16	0.409
	Day 90	27.38 ± 14.31	22.35 ± 8.89	0.149
ALT	Day 7	177.71 ± 182.818	219.74 ± 244.34	0.533
	Day 90	27.88 ± 15.77	22.92 ± 10.2	0.203
ALP	Day 7	414.71 ± 294.27	392.91 ± 235.61	0.744
	Day 90	183.81 ± 91.232	184.03 ± 102.135	0.994
Total bilirubin	Day 7	1.64 ± 2.01	2.58 ± 4.95	0.453
	Day 90	1.16 ± 0.8	0.9 ± 0.45	0.164
Direct bilirubin	Day 7	0.89 ± 1.27	1.32 ± 2.51	0.507
INR	Day 7	1.23 ± 0.28	1.46 ± 1.04	0.379
Serum Cr	Day 7	0.89 ± 0.30	1.06 ± 0.44	0.154
Hb	Day 7	8.87 ± 1.44	9.56 ± 1.71	0.157
JP Drain	Day 7	582.35 ± 723.045	794.86 ± 1118.159	0.479
Urine output (ml/kg)	Day 7	< 0.5 ml/kg	2 (11.8%)	0.728
		0.5-1 ml/kg	10 (58.8%)	
		> 2 ml/kg	5 (29.4%)	
Ascites	Day 7	0	8 (47.1%)	0.045
		1	3 (17.6%)	
		2	4 (23.5%)	
		3	2 (11.8%)	
			15 (41.7%)	
			18 (50%)	
			2 (5.6%)	
			1 (2.8%)	

AST: aspartate aminotransferase, ALT: alanine transaminase, ALP: alkaline phosphatase, INR: international normalized ratio, Cr: creatinine, Hb: hemoglobin

gastrointestinal, intra-abdominal, infections, and/or pulmonary complications, longer recovery, and a higher rate of reoperation were reported repeatedly [18, 19]. Therefore, theoretically and based on our findings, PM can potentially prevent these aforementioned complications. Although it was statistically nonsignificant, mortality was higher in NPM, which may relate to improvement in learning curve of our surgical team, the sample size, or factors that were not investigated in this study. Three deaths in the NPM group were related to HAT, despite not being specified whether it was happened early or late in the post-operative course. Surgical technique, center experience, inflammation, which is related to the amount of intraoperative and postoperative blood products transfusions, extent of endothelial injury and amount of arterial manipulation, which correlates with the duration of the operation and amount of bleeding are among the numerous risk factors that have been proposed for HAT [20, 21]. HAT after BCS-related OLT is a sophisticated issue, hence, it seems PM could help lower the risk of HAT through shortening the length of surgery and decreasing the amount of transfusion. However, PM occludes arterial flow to the liver and it may irritate the hepatic artery and impose a risk of HAT by endothelial damaging, which needs a thorough investigation [22]. Similar to our results, Choi et al. showed that occlusion of the hepatoduodenal ligament with the PM can reduce intraoperative bleeding during the hepatectomy phase of liver resection [9]. They also stated that it is not necessary to completely block the inflow with a tight squeeze in order to perform the PM. A simple application of a loosely placed vascular clamp can effectively achieve the goal of reducing bleeding during a hepatectomy [9]. Another concern relating to the high rate of intraoperative blood loss in patients who underwent OLT is acute kidney injury (AKI). Massive intraoperative blood loss can increase the risk of pre-renal and subsequently renal AKI due to prolonged renal hypoperfusion, which was associated with longer hospital stays and increased mortality and morbidity rates [23, 24]. With regard to our results, day-7 serum Cr and urine output were not significantly different between the PM and NPM groups.

More studies on OLT for BCS with and without PM are needed and there are still important concerns about the safety of this maneuver with regard to congestion and bleeding risk in viscera and reperfusion syndrome after de-clamping of portal vein [25]. The PM itself does not insult the recipient's own liver, indeed, due to obstructing the venous flow from the gastrointestinal tract and spleen, congestion and lactic acidosis may encounter after releasing the clamp and may induce reperfusion syndrome [25], which didn't evaluate in this study, however, no bleeding from viscera was observed during or after surgery. To let the congested liver shrink and collapse the

porta hepatis collaterals and prepare the liver by releasing from the surrounding ligaments during the hepatectomy phase, we needed one clamping period of fewer than 45 min for all cases; however, reperfusion syndrome may occur as a natural problem in case of prolonged portal vein clamping. In addition, in cirrhotic patients who have high portal vein pressure and those who have partial portal vein thrombosis, due to the increase in portal vein pressure, the blood entering the liver decreases and enter the collateral vessels, it seemed that the PM does not have much effect on collateral vessels.

Although our results showed the benefits of PM during OLT of BCS-related liver cirrhosis for the first time, it should be interpreted considering several limitations. First, the exact duration of the PM was not recorded, indeed, it didn't exceed more than 45 min. We recommend future studies to investigate the incidence and severity of reperfusion syndrome during and after the OLT of BCS with and without the PM. Although PM was investigated in other liver surgeries, the number of included patients were limited due to unknown results and consequences, therefore, our findings and complex statistical analysis should be interpreted cautiously. Higher amounts of bleeding, longer length of surgery, higher mortality rates, and postoperative complications such as HAT in NPM group may correlate with the surgical team's experience, which got improved during a learning curve since 2010. This study is from a large center with the highest referral rate for transplant surgery and unfortunately, the etiologies of BCS were not recorded. Although patients with myeloproliferative disease were not included, other thrombogenic disease such as paroxysmal nocturnal hemoglobinuria, anti-phospholipid syndrome, Proteins S and C deficiency were not investigated. We didn't face any intestinal congestion related to PM, which may relate to opening collateral at the diaphragm and splenorenal shunt that transfer the blood to IVC. As long as we kept our PM as short as possible, intestinal congestion would not be a serious problem during OLT of BCS patients. However, it is a potential threat and surgeons may encounter it in prolonged clamping. We did not evaluate the safety and efficacy of PM through a randomized trial, and after 2018, all included patients were candidates for OLT with PM, therefore we suggest conducting a randomized clinical trial with longer follow-ups. For hepatectomy phase "hilar dissection first" method could be use, which is a viable option was applied neither in our center nor in this study because it may have unknown outcomes and needs further investigations. The V-V bypass has been proposed to decrease the amount of bleeding by decompressing the pressure, however, we did not apply this step and the aim of this study was only dedicated to evaluate the PM. We recommend future studies to use V-V bypass along with the PM

to evaluate their efficacies. Finally, the amount of bleeding and duration of surgery were not separated based on stages of the operation; these number may differ between PM and NPM groups during hilar dissection or liver mobilization periods.

Conclusion

The PM is an effective approach during OLT for BCS patients after entering the abdomen and before releasing the liver's attachments, reducing intraoperative blood loss and blood transfusion and shortening the surgery duration without significant damage to the graft. The PM decreases blood flow to the congested liver, facilitates shrinkage of open porta hepatis collaterals, and eases division of hepatic ligaments and diaphragmatic attachments during the hepatectomy phase, potentially enhancing procedural ease for surgeons.

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Author contributions

K.K.: Conceptualization, Methodology, Validation, Investigation, Resources, Data Curation, Writing - Original Draft, Writing - Review & Editing, Supervision, Project administration, Funding acquisition. A.S.: Conceptualization, Methodology, Validation, Investigation, Resources, Data Curation, Writing - Original Draft, Writing - Review & Editing, Supervision, Project administration, Funding acquisition. H.N.: Conceptualization, Methodology, Validation, Investigation, Resources, Data Curation, Writing - Original Draft, Writing - Review & Editing, Supervision, Project administration. E.S.: Methodology, Formal analysis, Investigation, Writing - Original Draft, Writing - Review & Editing, Visualization. A.E.: Formal analysis, Writing - Original Draft, Writing - Review & Editing, Visualization. M.J.: Methodology, Validation, Resources, Data Curation, Writing - Original Draft, Writing - Review & Editing, Supervision, Project administration. M.E.: Conceptualization, Methodology, Validation, Investigation, Resources, Data Curation, Writing - Original Draft, Writing - Review & Editing, Supervision, Project administration. S.N.: Methodology, Validation, Investigation, Resources, Data Curation, Writing - Original Draft, Writing - Review & Editing, Supervision, Project administration, Funding acquisition.

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None.

Data availability

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

All procedures performed in this study were in accordance with the ethical standards of institutional and national research committee and with 1964 Helsinki declarations and its later amendments. The protocol of this study was approved by the institutional review board of the Shiraz University of Medical Sciences. Written informed consent was obtained from all of the participants before the enrollment.

Consent for publication

N/A.

Competing interests

The authors declare no competing interests.

Conflict of interest

none to be declared.

Ethical considerations

All procedures performed in this study were in accordance with the ethical standards of institutional and national research committee and with 1964 Helsinki declarations and its later amendments. The protocol of this study was approved by the institutional review board of the Shiraz University of Medical Sciences. Written informed consent was obtained from all of the participants before the enrollment.

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