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Predictive role of hepatic venous pressure gradient in bleeding events among patients with cirrhosis undergoing orthotopic liver transplantation

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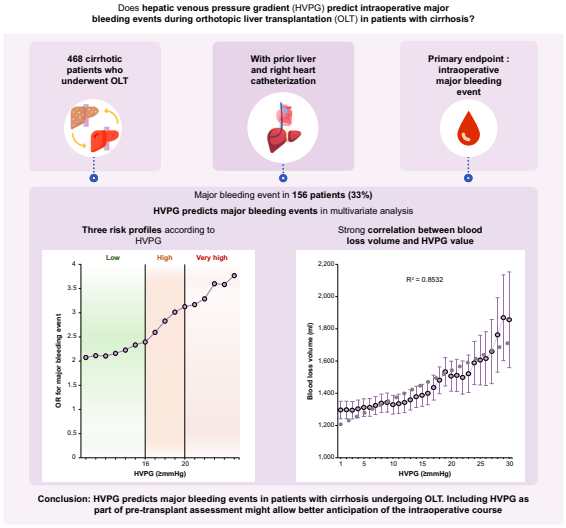
Graphical abstract



Highlights

- HVPG is a predictor of major bleeding events in patients with cirrhosis undergoing OLT.
- Patients can be stratified into three categories based on their risk of major bleeding events.
- Patients with HVPG ≥20 mmHg are at very high risk.
- HVPG value strongly correlates with blood loss volume during OLT.
- HVPG could be systematically included in the pre-transplant assessment to anticipate intraoperative management.

Impact and implications

Major bleeding events during orthotopic liver transplantation (OLT) are associated with poor outcomes but the proportion of this risk related to portal hypertension is unclear. Our work shows that hepatic venous pressure gradient (HVPG), the gold standard for estimating portal hypertension, is a strong predictor of major bleeding events and blood loss volume in patients with cirrhosis undergoing OLT. Three groups of patients can be identified according to their risk of major bleeding events: low-risk patients with HVPG <16 mmHg, high-risk patients with HVPG ≥16 mmHg, and very high-risk patients with HVPG ≥20 mmHg. HVPG could be systematically included in the pre-transplant assessment to anticipate intraoperative course and tailor patient management.

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Predictive role of hepatic venous pressure gradient in bleeding events among patients with cirrhosis undergoing orthotopic liver transplantation

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Background & Aims: Major bleeding events during orthotopic liver transplantation (OLT) are associated with poor outcomes. The proportion of this risk related to portal hypertension is unclear. Hepatic venous pressure gradient (HVPG) is the gold standard for estimating portal hypertension. The aim of this study was to analyze the ability of HVPG to predict intraoperative major bleeding events during OLT in patients with cirrhosis.

Methods: We retrospectively analyzed a prospective database including all patients with cirrhosis who underwent OLT between 2010 and 2020 and had liver and right heart catheterizations as part of their pre-transplant assessment. The primary endpoint was the occurrence of an intraoperative major bleeding event.

Results: The 468 included patients had a median HVPG of 17 mmHg [interquartile range, 13-22] and a median MELD on the day of OLT of 16 [11-24]. Intraoperative red blood cell transfusion was required in 72% of the patients (median 2 units transfused), with a median blood loss of 1,000 ml [575-1,500]. Major intraoperative bleeding occurred in 156 patients (33%) and was associated with HVPG, preoperative hemoglobin level, severity of cirrhosis at the time of OLT (MELD score, ascites, encephalopathy), hemostasis impairment (thrombocytopenia, lower fibrinogen levels), and complications of cirrhosis (sepsis, acute-on-chronic liver failure). By multivariable regression analysis with backward elimination, HVPG, preoperative hemoglobin level, MELD score, and tranexamic acid infusion were associated with the primary endpoint. Three categories of patients were identified according to HVPG: low-risk (HVPG <16 mmHg), high-risk (HVGP ≥16 mmHg), and very high-risk (HVPG ≥20 mmHg).

Conclusions: HVPG predicted major bleeding events in patients with cirrhosis undergoing OLT. Including HVPG as part of pre-transplant assessment might enable better anticipation of the intraoperative course.

Impact and implications: Major bleeding events during orthotopic liver transplantation (OLT) are associated with poor outcomes but the proportion of this risk related to portal hypertension is unclear. Our work shows that hepatic venous pressure gradient (HVPG), the gold standard for estimating portal hypertension, is a strong predictor of major bleeding events and blood loss volume in patients with cirrhosis undergoing OLT. Three groups of patients can be identified according to their risk of major bleeding events: low-risk patients with HVPG <16 mmHg, high-risk patients with HVPG ≥16 mmHg, and very high-risk patients with HVPG ≥20 mmHg. HVPG could be systematically included in the pre-transplant assessment to anticipate intraoperative course and tailor patient management.

Keywords: hepatic venous pressure gradient; liver transplantation; bleeding; cirrhosis; portal hypertension; pre-transplant assessment.

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Introduction

Major bleeding events and massive transfusion[1,2] occasionally occur at the time of orthotopic liver transplantation (OLT) and are associated with high risk of postoperative infection,[3,4] prolonged intensive care unit (ICU) length of stay[3] and death.[5–8] Over the last decades, improvement in perioperative management has reduced transfusion requirements, and transfusion-free OLTs have become more common.[5,9,10] However, there is still substantial variability in transfusion requirements between

patients and centers, with median volumes of red blood cell (RBC) transfusion ranging from 2 to 16 units in the literature,[5] suggesting that reliable tools to predict intraoperative bleeding risk are still lacking.[11]

The risk of bleeding and RBC transfusion during OLT increases with the severity of cirrhosis. The proportion of this risk related to coagulopathy and that related to portal hypertension is unclear.[12–15] In particular, the impact of severity of portal hypertension on the risk of bleeding and transfusion during OLT has not been directly established; available studies mostly used systemic hemodynamic data, and in particular central venous pressure (CVP) as a surrogate measure of portal pressure.[9,10,12,16]

Hepatic vein catheterization with measurement of hepatic venous pressure gradient (HVPG) is the current gold standard for identifying and grading portal pressure.[17] HVPG is calculated by subtracting the free hepatic venous pressure, a measure of systemic pressure, from the wedged hepatic venous pressure, a measure of hepatic sinusoidal pressure.[18] In patients with cirrhosis, without portal vein cavernoma and/or without complete thrombosis of intra and extrahepatic portal vessels, HVPG provides prognostic information on survival and on the risk of decompensation, independently of model for end-stage liver disease (MELD) score.[19] More recently, HVPG has been described as a prognostic factor for 1-year mortality in patients with cirrhosis undergoing elective extrahepatic surgery,[20,21] with thresholds of >16 mmHg and more so ≥20 mmHg being associated with a high risk of post-surgical mortality.[21] HVPG has not been assessed as a predictor of intraoperative bleeding and RBC transfusion during OLT.

The aim of this study was to analyze the ability of HVPG to predict intraoperative major bleeding events (defined by significant bleeding associated with hemodynamic instability) during OLT in patients with cirrhosis.

Patient and methods

Study design and inclusion criteria

We conducted a retrospective monocentric (Beaujon Hospital, Clichy, AP-HP, France) observational study from a prospective database (Fig. S1). This study was approved by the local ethics committee, which waived the need for written informed consent (Institutional Review Board—IRB 00006477—of HUPNVS, Paris 7 University, AP-HP— 13-020). All patients with cirrhosis older than 18 years who underwent liver and right heart catheterizations, with or without transjugular liver biopsy, as part of their pre-transplant assessment between January 2010 and December 2020 and who were thereafter transplanted were included.

The exclusion criteria were the following: combined transplantation (liver-kidney, liver-lung), retransplantation, and complete portal vein thrombosis.

Hemodynamic assessment

In our center, hepatic and right heart catheterizations were performed, using a technique that has been described,[22] as part of the liver-transplant assessment for patients with cirrhosis before listing. Except for rare situations (*e.g.,* emergency listing), hemodynamic assessment was performed in patients in stable clinical condition (compensated or stable decompensated). Briefly, local anesthesia was performed (without intravenous sedation), and an introducer was inserted into the jugular vein under ultrasound guidance using the Seldinger technique. A catheter was then placed in the right or median hepatic vein. Between 2010 and 2012, wedge hepatic venous pressure was measured by 'wedging' a tip-curved catheter (Cook, HNB7.0-38-100-P–NS–MPA) into a small branch of a hepatic vein. Adequate occlusion was confirmed by injection of 5 ml of iodinated radiological contrast medium. A measurement was considered valid when two consecutive measurements from two different veins differed by less than 1 mmHg. Since 2013, wedge hepatic venous pressure has been measured by inflating a 7 French balloon catheter (Lemaitre Vascular; Edwards Lifesciences™) in the right or median hepatic vein. Adequate occlusion was confirmed by injection of 5 ml of iodinated radiological contrast medium. Then, free hepatic venous pressure was obtained. HVPG was calculated as the difference between wedged and free hepatic venous pressures. A measurement was considered valid when two consecutive measurements differed by less than 1 mmHg. Permanent tracings were recorded using Mac-Lab recording system (GE Healthcare).

Right heart hemodynamic measurements including pulmonary artery pressure, right atrial pressure, and pulmonary capillary wedged pressure were also performed using a Swan-Ganz catheter (Edwards Life Sciences™). The cardiac index was measured by the thermodilution method and obtained from the average of 3-5 consecutive measurements obtained by injection of 10 ml of cold (1 to 4 °C) saline.[23]

Anesthetic management

Intraoperative anesthetic management was protocolized. Patients received inhaled or total intravenous anesthesia (left at the discretion of the anesthesiologist) to maintain a Bispectral Index Monitoring value (BIS™, Covidien, Mansfield, MA) between 40 and 60. Fluid resuscitation was guided by hemodynamic monitoring using an arterial line and a pulmonary artery catheter with continuous venous oxygen saturation and thermal cardiac output monitoring (Swan-Ganz COmbo CCO/SVO2; Baxter, Edwards Critical Care Division, Irvine, CA). In exceptional cases where pulmonary artery catheter positioning was impossible, esophageal Doppler or transesophageal echocardiography was used according to anesthesiologist preference and patient severity. Vasopressors were introduced in the case of arterial hypotension defined as a mean arterial blood pressure below 60 mmHg despite appropriate vascular fluid loading. The hemodynamic indexes used as guides for volume expander prescription were measurement of systolic ejection volume and/or cardiac output. 200-250-ml fluid boluses were rapidly administered to maximize stroke volume and/or cardiac output. Fluid administration was stopped if a less than 10% increase in stroke volume resulted from the fluid challenge. Conversely, another 200-250-ml bolus was administered if stroke volume increased more than 10%.

As recommended, prophylactic transfusion of blood products was avoided.[11,24] Coagulation disorders diagnosed from conventional tests were not treated preemptively with blood products in the absence of overt bleeding either before or at the time of OLT. In case of significant bleeding during OLT, platelets, fresh frozen plasma (FFP), and fibrinogen concentrates were transfused to target platelet level above 50,000 $\cdot mm^{-3}$, prothrombin time above 40%, and fibrinogen concentrations around 1.5 $g \cdot L^{-1}$. Tranexamic acid was administered (1 g over 1 h then 10 $mg \cdot kg^{-1} \cdot h^{-1}$ infused until reperfusion) in all patients in the absence of previous history of thromboembolic event or ongoing thrombosis. In the latter cases, the decision of whether to administer tranexamic acid was discussed collegially on a case-by-case basis between

anesthesiologists, hepatologists and surgeons. Cell salvage was used in the absence of sepsis or neoplasia. Hypothermia was prevented by external warming in lower parts of the body and fluid and blood warming. RBC transfusion threshold was 70-80 $g \cdot L^{-1}$ in every patient (80-100 $g \cdot L^{-1}$ in patients with coexisting cardiovascular disease). Management was guided by blood samples (performed at least at the dissection phase, at the end of anhepatic phase, and 15-30 min after reperfusion) to obtain hemoglobin and platelets values, standard tests of hemostasis, lactate, and electrolytes.

The surgical antimicrobial prophylaxis consisted of cephalosporin administration (2 g cefoxitin intravenously at the induction of anesthesia and then 1 g every 2 h). Patients were systematically screened preoperatively for nasal carriage of MRSA (methicillin-resistant *Staphylococcus aureus*) and rectal carriage of ESBL (extended-spectrum beta-lactamase)-producing enterobacterales before surgery. In case of positive findings, antimicrobial prophylaxis was tailored to cover known preoperative carriage (intravenous vancomycin for MRSA and carbapenem or alternatives for ESBL-producing enterobacterales depending on antimicrobial susceptibility testing). Patients were immediately admitted to the ICU after surgery. Extubation was performed within the first postoperative hours after hemodynamic and respiratory stability were achieved.

Surgical management

All liver allografts were harvested by senior surgeons from brain-dead donors or from circulatory death donors (Maastricht-type-III). Piggyback technique and preservation of the inferior vena cava were performed for all OLTs. The use of a temporary porto-caval shunt was decided at the surgeon's discretion, depending on the existence or not of porto-systemic collateral venous circulation. Venovenous bypass was never used.

Outcome analysis

The primary endpoint was the occurrence of an intraoperative major bleeding event defined by the association of (i) significant intraoperative bleeding, namely blood loss ≥1,000 ml and/or RBC transfusion >2 U; [2,25]associated with (ii) significant hemodynamic failure, namely intraoperative maximum norepinephrine dose ≥0.6 $\mu g \cdot kg^{-1} \cdot min^{-1}$. This dose was chosen because it is the median dose received by patients in our cohort.

Secondary endpoints included each component of the primary endpoint (intraoperative blood loss ≥1,000 ml, RBC transfusion >2 U, maximum norepinephrine dose ≥0.6 $\mu g \cdot kg^{-1} \cdot min^{-1}$), blood loss volume, FFP transfusion, platelet transfusion, and postoperative infection, acute renal failure, renal replacement therapy (RRT) requirement during ICU stay, vasopressor infusion duration, ICU length of stay and ICU mortality.

Data collection

For each patient, we collected heart and liver catheterization data, perioperative clinical and laboratory data immediately before OLT and throughout the intraoperative period, as well as outcome during the ICU stay.

Hemodynamic variables recorded during heart and liver catheterization included heart rate, arterial blood pressure, cardiac index, systemic vascular resistance, pulmonary arterial pressure, right atrial pressure, free hepatic venous pressure, wedged hepatic venous pressure, and HVPG. The period of catheterization (*i.e.*, before or after 2013, when balloon catheters began to be used) and the time elapsed between catheterization and OLT were also recorded.

Preoperative data included demographic data, etiology, and severity of the underlying liver disease as assessed by MELD score and grade of acute-on-chronic liver failure (ACLF), hemoglobin and platelet count, mechanical ventilation, norepinephrine and RRT requirements.

Intraoperative data included blood loss, RBC transfusion, reperfusion syndrome, maximum norepinephrine dose, use of intraoperative temporary porto-caval shunt, infusion of tranexamic acid, surgery duration, and graft cold and warm ischemia time. Postoperative data included acute renal failure, RRT requirement, postoperative infection occurring during ICU hospitalization, vasopressor infusion duration, ICU length of stay, and mortality during ICU hospitalization.

Statistical analyses

Data were compared using the Mann-Whitney *U* or Kruskal-Wallis tests for continuous variables after a normality assessment using Shapiro-Wilk analysis (Table S1). Categorical variables were assessed by the chi-square test or Fisher's exact test where appropriate. Variables achieving a significant p value in univariate analysis (after Bonferroni correction for multiple comparisons) were introduced into a multivariable logistic regression model with backward elimination (exit $p = 0.10$) in complete cases. A bootstrap analysis with 2,000 samples was used to confirm the result of the univariate analysis and the multivariable logistic regression model. Results are expressed as number and percentage or median and interquartile range. Statistical significance was set for a p value <0.05 for all other analyses.

The association between HVPG cut-offs and blood loss volume was analyzed by a linear regression model. Finally, we conducted sensitivity analyses considering the time elapsed between catheterization and OLT (*i.e.,* less than 1 year) on the one hand and the catheterization period (*i.e.*, after 2013, when balloon catheters began to be used) on the other hand. Data handling and analysis were performed using SPSS 22.0 (SPSS Inc., Chicago, IL).

Results

Patient characteristics

Between January 2010 and December 2020, 468 patients with cirrhosis who underwent liver and right heart catheterizations before transplantation were included (Fig. S1). The median duration between catheterization and OLT was 5 months.[2–9] Table 1 shows the main patient characteristics and the hemodynamic values measured at the time of liver and right heart catheterization performed as part of the assessment before OLT. Nine patients (2%) were still receiving terlipressin or octreotide at the time of HVPG measurement because they required emergency listing. The main cause of cirrhosis was excessive alcohol consumption (including 17% of patients not abstinent or abstinent for less than 3 months), and about one-third of patients had hepatocellular carcinoma. Median HVPG was 17 mmHg.[13–22] Table 2 details the main patient characteristics at the time of OLT, the intraoperative events, and the ICU postoperative outcomes. The median MELD score on the day of OLT was 16[11–24] with 12% of the patients (57/468 patients) being transplanted in a context of ACLF. Median intraoperative blood loss was 1,000 ml [575-1,500]. RBC transfusion was required in

Table 1. Patients' main characteristics and liver catheterization data at the time of the liver-transplant assessment.

Patient characteristics	
Age (years)	57 [51-63]
Male sex, n (%)	349 (75)
BMI (kg.m^{-2})	26 [23-30]
Causes of cirrhosis, n (%)	
Excessive alcohol consumption	265 (57)
Metabolic syndrome	108 (23)
HCV infection	110 (24)
HBV infection	59 (13)
Auto-immune hepatitis	18 (4)
Cholestatic liver disease	35 (8)
Hemochromatosis	7 (2)
HCC, n (%)	165 (35)
History of ascites, n (%)	240 (51)
Refractory ascites, n (%)	109 (23)
History of hepatic encephalopathy, n (%)	209 (45)
Esophageal varices, n (%)	
Absent	212 (45)
Small	73 (16)
Large or ligated	183 (39)
History of bleeding event, n (%)	125 (27)
Portal vein thrombosis, n (%)	73 (16)
Active β-blockers intake, n (%)	108 (23)
MELD	14 [10-21]
Hemodynamics values:	
Heart rate (.min^{-1})	74 [64-87]
Mean arterial blood pressure (mmHg)	91 [82-98]
Cardiac index (L.min^{-1}.m^{-2})	3.7 [3.0-4.6]
SVR (dynes.s.cm^{-5})	935 [727-1258]
Free hepatic venous pressure (mmHg)	9 [6-12]
Wedged hepatic venous pressure (mmHg)	27 [21-33]
HVPG (mmHg)	17 [13-22]
PASP (mmHg)	26 [22-33]
PADP (mmHg)	9 [5-12]
mPAP (mmHg)	15 [12-19]
RA pressure (mmHg)	5 [3-7]
PCP (mmHg)	9 [7-12]
HVPG, n (%)	
≤6 mmHg	24 (5)
6-9 mmHg	46 (10)
10-11 mmHg	32 (7)
12-15 mmHg	71 (15)
16-19 mmHg	117 (25)
≥20 mmHg	178 (38)
Duration between catheterization and OLT (months)	5 [2-9]

Results are expressed as number (percentage) or median [interquartile range].
Active β-blocker intake: patients who did not stop β-blocker intake more than 5 days before hemodynamic assessment.
HCC, hepatocellular carcinoma; HVPG, hepatic venous pressure gradient; MELD, model for end-stage liver disease; mPAP, mean pulmonary arterial pressure; OLT, orthotopic liver transplantation; PADP, pulmonary arterial diastolic pressure; PASP, pulmonary arterial systolic pressure; PCP, pulmonary capillary pressure; RA, right atrial; SVR, systemic vascular resistance.

Table 2. Preoperative (within 24 h before OLT), intraoperative characteristics and ICU postoperative outcomes.

Preoperative characteristics (within 24 h before OLT)	
Ascites, n (%)	255 (55)
Hepatic encephalopathy, n (%)	60 (13)
Sepsis within the last 15 days, n (%)	81 (17)
Spontaneous bacterial peritonitis	37 (8)
Urinary tract infection	15 (3)
Bacteremia	11 (2)
Pneumonia	7 (1)
Other	11 (2)
β-blocker intake, n (%)	210 (45)
TIPS, n (%)	20 (4)
Hemoglobin (g/L)	112 [93-131]
Platelet count (x10^9/L)	87 [62-133]
Factor V (%)	60 [40-83]
Fibrinogen (g/L)	2.1 [1.3-2.8]
MELD	16 [11-24]
ACLF, n (%)	57 (12)
Grade of ACLF, n (%):	
Grade 1	11 (2)
Grade 2	22 (5)
Grade 3	24 (5)
CLIF-C ACLF score	55 [45-64]
SOFA	0 [0-4]
Mechanical ventilation, n (%)	13 (3)
Norepinephrine, n (%)	19 (4)
RRT, n (%)	21 (5)
Intraoperative characteristics	
Blood loss (ml)	1,000 [575-1,500]
RBC transfusion, n (%)	291 (62)
Number of RBCs units transfused (U)	2 [0-3]
Maximum norepinephrine dose (μg.kg^{-1}.min^{-1})	0.6 [0.3-0.9]
FFP transfusion, n (%)	198 (42)
Major bleeding event, n (%)	156 (33)
Blood loss ≥1,000 ml and maximum norepinephrine dose ≥0.6 μg kg^{-1}.min^{-1}, n (%)	58 (12)
RBC transfusion >2 U and maximum norepinephrine dose ≥0.6 μg kg^{-1}.min^{-1}, n (%)	16 (3)
RBC transfusion >2 U and blood loss ≥1,000 ml and maximum norepinephrine dose ≥0.6 μg kg^{-1}.min^{-1}, n (%)	82 (18)
Platelet transfusion, n (%)	149 (32)
Reperfusion syndrome, n (%)	241 (52)
Intraoperative temporary porto-caval shunt, n (%)	82 (18)
Intraoperative infusion of tranexamic acid, n (%)	365 (78)
Surgery duration (min)	310 [270-355]
Cold ischemia time (min)	413 [440-504]
Warm ischemia time (min)	45 [37-50]
ICU postoperative outcomes	
Vasopressor infusion duration (hours)	8 [2-24]
Vasopressor infusion duration ≥24 h	142 (30)
Acute renal failure, n (%)	103 (22)
RRT, n (%)	66 (14)
Infection, n (%)	143 (31)
ICU length of stay (days)	9 [7-16]
ICU length of stay >15 days, n (%)	122 (26)
ICU mortality, n (%)	22 (5)

Results are expressed as number (percentage) or median [interquartile range]. Only sepsis occurring within the last 15 days prior to OLT were considered. All patients had received at least 72 h of antibiotics and had no fever or leukopenia <0.5 G/L at the time of OLT.[51]
ACLF, acute-on-chronic liver failure; FFP, fresh frozen plasma; ICU, intensive care unit; MELD, model for end-stage liver disease; OLT, orthotopic liver transplantation; RBC, red blood cell; RRT, renal replacement therapy; SOFA, sequential organ failure assessment; TIPS, transjugular intrahepatic portosystemic shunt.

72% of cases (291/468 patients), with a median of 2 [0-3] packed RBC units transfused. ICU mortality was 5% (22/468 patients). Additional patient characteristics at the time of HVPG measurement and at the time of OLT are provided in Table S2.

Predictors of major intraoperative bleeding events

The primary endpoint of a major intraoperative bleeding event was met in 156 patients (33%) including 58 patients (12%) with intraoperative blood loss ≥1,000 ml and intraoperative maximum norepinephrine dose ≥0.6 μg·kg^{-1}·min^{-1}, 16 patients (3%) with RBC transfusion >2 U and intraoperative maximum norepinephrine dose ≥0.6 μg·kg^{-1}·min^{-1}, and 82 patients (18%) with intraoperative blood loss ≥1,000 ml, RBC transfusion >2 U and intraoperative maximum norepinephrine dose ≥0.6 μg·kg^{-1}·min^{-1}. Features associated with major intraoperative bleeding events by univariate analysis are detailed in Table 3. Among these factors, HVPG was significantly higher in patients who met

Table 3. Preoperative features associated with the primary endpoint by univariate analysis.

	Whole population (N = 460)			Balloon catheter population (n = 373)		
	Primary endpoint					
	No (n = 304)	Yes (n = 156)	*p* value	No (n = 245)	Yes (n = 128)	*p* value
Patients' characteristics and liver and right heart catheterization data at the time of the OLT assessment						
Age (years)	58 [51-63]	56 [48-62]	0.031	58 [53-64]	56 [49-62]	0.037
Male sex, n (%)	222 (73)	120 (77)	0.365	182 (74)	98 (77)	0.629
BMI ($kg.m^{-2}$)	26 [24-30]	26 [23-29]	0.138	26 [24-30]	26 [23-30]	0.322
Excessive alcohol consumption, n (%)	173 (57)	87 (56)	0.816	139 (57)	68 (53)	0.505
History of HCC, n (%)	126 (41)	38 (24)	**<0.001**	109 (45)	34 (27)	**0.001**
Esophageal varices, n (%)	157 (52)	93 (60)	0.104	126 (51)	77 (60)	0.108
History of bleeding event, n (%)	68 (22)	53 (34)	0.007	48 (20)	42 (33)	0.005
Portal vein thrombosis, n (%)	36 (12)	35 (22)	0.003	32 (13)	26 (20)	0.067
Active β-blockers intake, n (%)	71 (23)	36 (23)	0.947	71 (29)	36 (28)	0.862
SVR ($dynes.s.cm^{-5}$)	1,011 [739-1,316]	852 [706-1,099]	**0.001**	1,016 [747-1,327]	850 [696-1,072]	**0.001**
HVPG (mmHg)	16 [11-21]	20 [15-24]	**<0.001**	16 [12-21]	20 [16-24]	**<0.001**
mPAP (mmHg)	16 [12-20]	15 [12-18]	0.267	15 [12-19]	15 [12-18]	0.557
RA pressure (mmHg)	5 [3-7]	5 [2-7]	0.201	5 [3-7]	5 [2-7]	0.135
PCP (mmHg)	9 [7-12]	9 [6-13]	0.804	9 [6-12]	9 [6-12]	0.693
Preoperative characteristics (within 24 h before OLT)						
Ascites, n (%)	142 (47)	107 (69)	**<0.001**	114 (47)	87 (68)	**<0.001**
Hepatic encephalopathy, n (%)	27 (9)	31 (20)	**0.001**	23 (9)	25 (20)	0.005
TIPS, n (%)	11 (4)	9 (6)	0.284	10 (4)	8 (6)	0.354
Sepsis, n (%)	38 (13)	42 (27)	**<0.001**	21 (9)	29 (23)	**<0.001**
Hemoglobin (g/L)	118 [98-137]	98 [82-118]	**<0.001**	120 [100-138]	98 [83-115]	**<0.001**
Platelet count (G/L)	93 [66-142]	77 [53-121]	**0.002**	99 [69-149]	79 [55-125]	**0.002**
Factor V (%)	66 [47-90]	48 [32-68]	**<0.001**	69 [47-92]	49 [33-69]	**<0.001**
Fibrinogen (g/L)	2.2 [1.6-2.9]	1.8 [1.1-2.4]	**<0.001**	2.3 [1.7-3.1]	1.9 [1.1-2.4]	**<0.001**
RRT, n (%)	7 (2)	21 (13)	**<0.001**	5 (2)	14 (11)	**<0.001**
MELD score	14 [10-21]	21 [13-29]	**<0.001**	14 [10-20]	20 [13-29]	**<0.001**
ACLF, n (%)	22 (7)	33 (21)	**<0.001**	15 (6)	28 (22)	**<0.001**

Mann-Whitney *U* test used for continuous variables. Chi-square test used for categorical variables. Results are expressed as number (percentage) or median [interquartile range]. After Bonferroni correction, the *p* value was considered significant when it was 0.002 or lower. Significant *p*-values are shown in bold. The primary endpoint was the occurrence of an intraoperative major bleeding event defined by the association of (i) significant intraoperative bleeding, namely blood loss ≥1,000 ml and/or RBC transfusion >2 U; associated with (ii) significant hemodynamic failure, namely intraoperative maximum norepinephrine dose ≥0.6 $\mu g\ kg^{-1}.min^{-1}$. Data to assess the primary endpoint were missing for 8 patients. Analyzes were conducted on 460 patients.
ACLF, acute-on-chronic liver failure; HCC, hepatocellular carcinoma; HVPG, hepatic venous pressure gradient; MELD, model for end-stage liver disease; mPAP, mean pulmonary arterial pressure; PCP, pulmonary capillary pressure; RA, right atrial; RRT, renal replacement therapy; SVR, systemic vascular resistance; TIPS, transjugular intrahepatic portosystemic shunt.

the primary endpoint than in those who did not (20[15–24] *vs.* 16,[11–21] $p < 0.0001$). The prevalence of the primary endpoint according to various ranges of HVPG is shown in Fig. S2. Other features associated with major intraoperative bleeding reflected severity of cirrhosis at the time of OLT (MELD score, ascites, encephalopathy), hemostasis impairment (thrombocytopenia, lower hemoglobin and fibrinogen levels), and complications of cirrhosis (sepsis, ACLF). The prevalence of the primary endpoint according to HVPG and MELD score thresholds is presented in Fig. 1.

All features reaching a significant *p* value after Bonferroni's correction were included in a multivariable logistic regression model with backward elimination together with two intraoperative parameters known to influence bleeding complications, namely tranexamic acid infusion and temporary portocaval shunting. As shown in Table 4, HVPG, preoperative hemoglobin level, MELD score, and tranexamic acid infusion were independently associated with the primary endpoint. After bootstrap resampling, HVPG and preoperative hemoglobin level remained associated with the primary endpoint (Table S3). One mmHg increase in HVPG was associated with a 4.0% increase in the odds of major intraoperative bleeding, whereas tranexamic acid infusion reduced the risk almost two-fold. A 90% sensitivity for the primary endpoint was reached for HVPG ≥10 mmHg (specificity 18%). A 90% specificity for the primary endpoint was reached for HVPG >25 mmHg (sensitivity 20%).

Severity of portal hypertension and major intraoperative bleeding: low- and high-risk thresholds of HVPG

After identifying HVPG as an independent predictor of intraoperative major bleeding events, we sought to define thresholds of HVPG associated with different risk levels. Three categories of patients were identified for the primary endpoint based on HVPG thresholds known to have prognostic value in cirrhosis[18] (Fig. 2A): low-risk patients (HVPG <16 mmHg), patients at high-risk (HVPG ≥16 mmHg), and patients at very high-risk (HVPG ≥20 mmHg). Similar associations between HVPG and each component of the primary endpoint were observed (Fig. S3).

Secondary endpoints

The prevalence of secondary endpoints is displayed in Table 2. Table S4 shows the features associated with each component of the major intraoperative bleeding composite criterion (intraoperative blood loss ≥1,000 ml, RBC transfusion >2 U, intraoperative maximum norepinephrine dose ≥0.6 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Associations of HVPG with other secondary endpoints are presented in Table 5. Interestingly, HVPG was associated with each component of major intraoperative bleeding and with FFP transfusion, platelet transfusion, postoperative acute renal failure, vasopressor infusion duration and ICU length of stay.

We found that HVPG thresholds associated with low-, high-, and very high-risk of major intraoperative bleeding remained

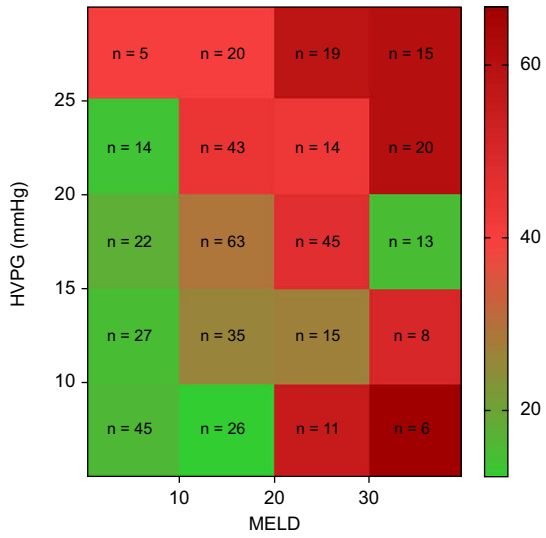

Fig. 1. Heatmap showing the prevalence of the primary endpoint according to the HVPG and MELD score thresholds. The color of the boxes represents the prevalence of the primary endpoint in each sub-population according to the threshold categories of HVPG and MELD. The number of patients in each sub-population according to HVPG and MELD threshold categories is indicated (n). The primary endpoint was the occurrence of an intraoperative major bleeding event defined by the association of (i) significant intraoperative bleeding, namely blood loss ≥1,000 ml and/or RBC transfusion >2 U; associated with (ii) significant hemodynamic failure, namely intraoperative maximum norepinephrine dose ≥0.6 μg $kg^{-1}.min^{-1}$. HVPG, hepatic venous pressure gradient (mmHg); MELD, model for end-stage liver disease.

discriminant when considering each component of the primary endpoint separately (Fig. S3). In addition, patients in the low-risk population required a shorter duration of vasopressor infusion than patients in the high-risk and very high-risk populations: respectively 4 h^{1-24} *vs.* 8 h^{2-24} and 12 h^{3-24} ($p = 0.001$). Similarly, ICU length of stay was shorter in the low-risk population than in the high- and very high-risk populations: 8 $days^{6-15}$ *vs.* 9 $days^{7-15}$ and 10 $days,^{7-18}$ respectively ($p = 0.030$). We also observed that major intraoperative bleeding events were associated with a worse prognosis (Table S5).

Finally, we demonstrated a strong correlation between blood loss volume and HVPG values (linear regression coefficient r^2 = 0.853, p <0.01) (Fig. 2B).

Secondary analyses

We conducted sensitivity analyses to assess whether the time elapsed between catheterization and OLT (*i.e.,* less than 1 year) or the catheterization technique used (*i.e.,* balloon catheters) impacted our results. The results of univariate and multivariable analyses confirm the role of HVPG values in predicting major bleeding events during OLT (Tables 3,4 and S6,S7).

We also performed subgroup analyses according to different MELD ranges, ACLF status, etiology of liver disease, β-blocker treatment at the time of HVPG and use of tranexamic acid during OLT. Results are displayed in Fig. 3.

As tranexamic acid infusion remains an independent predictor of major intraoperative bleeding events in multivariable analysis, we conducted a subgroup analysis comparing patients who received tranexamic acid and those who did not (Table S8).

Finally, we also investigated whether factors reflecting surgical complexity and coagulation failure (*i.e.,* portal vein thrombosis, platelet count, fibrinogen level and international normalized ratio [INR]) would improve the prediction of major bleeding events (Table S9). In this model, only HVPG and history of portal vein thrombosis remained significantly associated with the primary endpoint. Fig. S4 shows the prevalence of the primary endpoint according to high HPVG value (≥16 mmHg) and history of portal vein thrombosis.

Discussion

The present study shows the impact of portal hypertension level, measured by HVPG, on the risk of major intraoperative bleeding events defined by significant blood loss or RBC transfusion associated with hemodynamic instability requiring vasopressors during OLT. Of note, the association between HVPG and major bleeding persists after adjusting for multiple potential confounders related to liver disease severity (MELD score) and complications (sepsis, ACLF) and to conventional hemostatic parameters/abnormalities (thrombocytopenia, lower fibrinogen levels). HVPG strongly correlates with blood loss and thresholds (<16 mmHg; between16 and 20 mmHg and ≥20 mmHg) can be proposed to categorize risk levels of major bleeding and to help clinicians anticipate intra- and postoperative management.

A significant decrease in blood loss and blood product requirements has been observed over the last decades during OLT and our median blood loss and RBC transfused per patient of 1,000 mL and 2 U, respectively, are consistent with those reported by other centers.[2,26,27] However, the OLT procedure is still associated with a high risk of bleeding in certain subgroups of patients[16,28,29] and one-third of patients experienced major bleeding events in our cohort. Abnormal results of standard hemostasis tests have long been held responsible for the major bleeding risk of patients with end-stage liver disease. However, it is now widely accepted that the hemostatic system of those patients remains well balanced, as a result of simultaneous changes in pro- and anti-hemostatic systems, and that current coagulation tests are unable to accurately predict bleeding risk.[30] Several models and nomograms have been developed to identify

Table 4. Features associated with the primary endpoint by a multivariable logistic regression model.

	Whole population (N = 460)		Balloon catheter population (n = 373)	
	Primary endpoint	*p* value	Primary endpoint	*p* value
Preoperative hemoglobin	0.858 [0.771-0.956]	**0.005**	0.848 [0.754-0.954]	**0.006**
HVPG	1.040 [1.009-1.072]	**0.010**	1.049 [1.012-1.087]	**0.010**
Preoperative MELD score	1.032 [1.004-1.059]	**0.023**	1.040 [1.008-1.073]	**0.013**
Intraoperative infusion of tranexamic acid	0.586 [0.352-0.978]	**0.041**	–	–
Intraoperative temporary porto-caval shunt	–	–	0.509 [0.228-1.135]	0.099

Multivariable logistic regression with backward elimination (exit $p = 0.10$). Results presented as odds ratio [95% CI]. Significant *p*-values are shown in bold. The primary endpoint was the occurrence of an intraoperative major bleeding event defined by the association of (i) significant intraoperative bleeding, namely blood loss ≥1,000 ml and/or red blood cell transfusion >2 U; associated with (ii) significant hemodynamic failure, namely intraoperative maximum norepinephrine dose ≥0.6 μg $kg^{-1}.min^{-1}$.
HVPG, hepatic venous pressure gradient; MELD, model for end-stage liver disease.

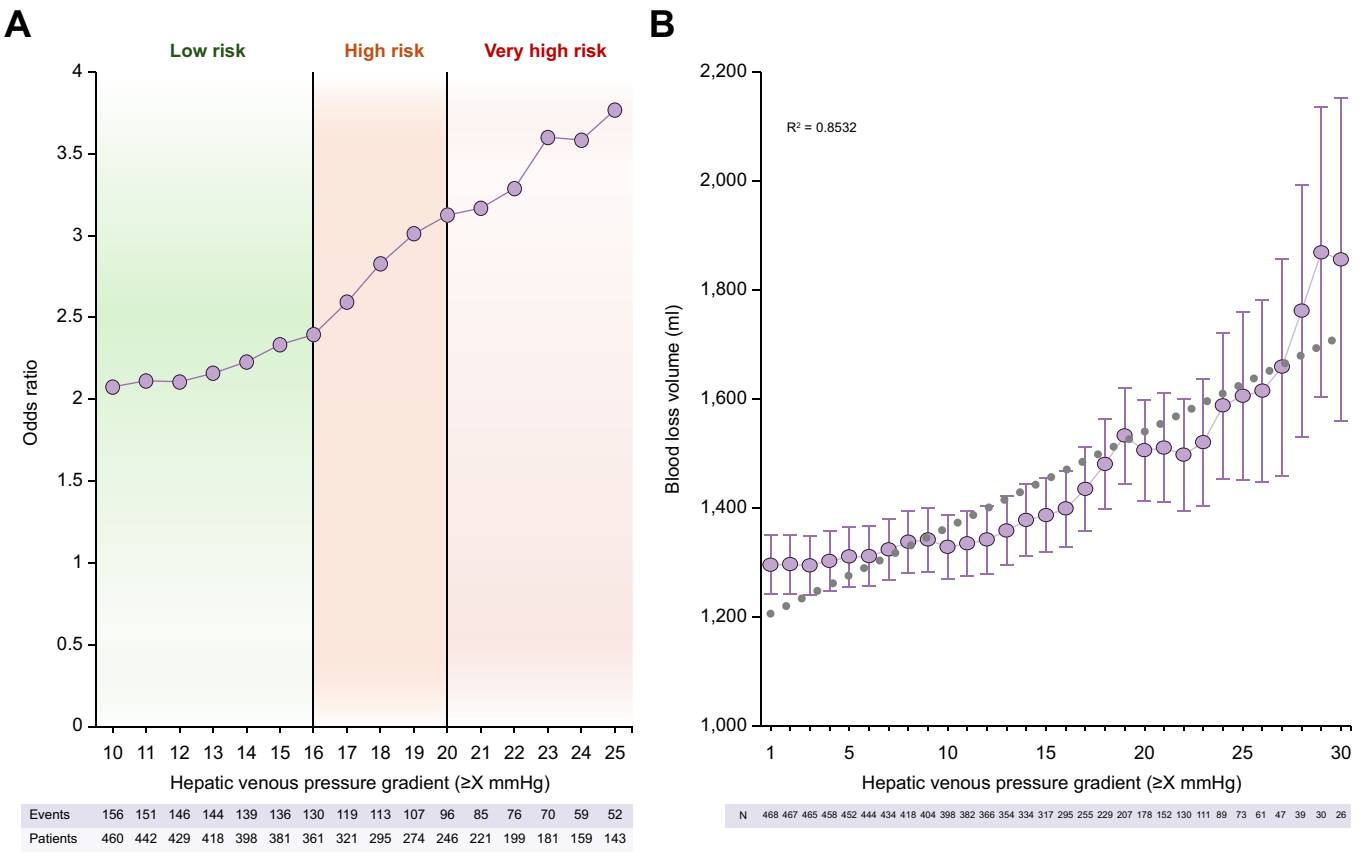

Fig. 2. Effect of HVPG on the risk of major intraoperative bleeding event and on intraoperative blood loss volume. (A) Impact (odds ratio) of different HVPG cut-offs on the risk of major intraoperative bleeding events using logistic regression. Major intraoperative major bleeding event was defined by the association of (i) significant intraoperative bleeding, namely blood loss ≥1,000 ml and/or RBC transfusion >2 U; associated with (ii) significant hemodynamic failure, namely intraoperative maximum norepinephrine dose ≥0.6 μg $kg^{-1}.min^{-1}$. (B) Correlation between different HVPG cut-offs and intraoperative blood loss volume using a linear regression model. Red circles and bars represent mean (SEM). HVPG, hepatic venous pressure gradient; RBC, red blood cell.

patients at higher risk of bleeding and/or need for transfusion during OLT, but they are either cumbersome and difficult to translate into clinical practice, or suboptimal.[2,16,31–33]

While the association between portal hypertension and intraoperative course during OLT, especially blood loss and RBC transfusion, has long been suspected, the potential of HVPG, the gold standard for estimating portal venous pressure, to predict the risk of major bleeding events during OLT has been poorly investigated. Child-Pugh and MELD scores, which have been shown to predict major bleeding during OLT,[2,16] only offer partial and/or indirect information on the degree of portal hypertension. Clinical signs of portal hypertension, such as a previous history of variceal bleeding, have also been described as a risk factor for large RBC transfusion requirements.[32] Other evidence of the role of portal hypertension in the literature is based on systemic surrogate measures of portal hypertension such as CVP and is underpinned by the pathophysiological hypothesis of an association between hypervolemia, portal hypertension, and increased intraoperative bleeding. In this way, some studies showed that a low CVP strategy (a restrictive fluid management policy and sometimes phlebotomy) may reduce RBC transfusion requirements during OLT, implicating portal congestion in intraoperative bleeding.[9,10,12,16,34] These data were supported by Giannini *et al.* in 2014 who suggested a correlation between portal pressure and blood volume in patients with cirrhosis[35] and by Massicotte *et al.* who showed that phlebotomy during the dissection phase of OLT decreased portal vein pressure.[36,37] In the same way, Choi *et al.* found that maintenance of relative hypovolemia (assessed by a high stroke volume variation) resulted in reduced blood transfusion requirements in OLT recipients.[38,39]

Table 5. Association between HVPG value and secondary endpoints.

		HVPG	*p*
FFP transfusion (n = 468)	*Yes* (n = 198)	19 [15-24]	**<0.001**
	No (n = 270)	16 [10-21]	
Platelet transfusion (n = 468)	*Yes* (n = 149)	18 [14-24]	**0.043**
	No (n = 319)	17 [12-22]	
Postoperative infection (n = 468)	*Yes* (n = 143)	18 [14-23]	0.17
	No (n = 325)	17 [12-22]	
Postoperative acute renal failure (n = 377)	*Yes* (n = 103)	19 [15-24]	**0.02**
	No (n = 274)	17 [13-22]	
Postoperative renal replacement therapy (n = 468)	*Yes* (n = 66)	19 [14-24]	0.07
	No (n = 402)	17 [13-22]	
Vasopressor infusion duration ≥24hr (n = 466)	*Yes* (n = 142)	19 [13-24]	**0.011**
	No (n = 324)	17 [12-21]	
ICU length of stay>15d (n = 455)	*Yes* (n = 122)	19 [14-24]	**0.007**
	No (n = 333)	17 [12-22]	
ICU mortality (n = 468)	*Yes* (n = 22)	16 [10-22]	0.83
	No (n = 446)	17 [13-22]	

Mann-Whitney *U* test used. Results are expressed as median [interquartile range]. Significant *p*-values are shown in bold.
FFP, fresh frozen plasma; HVPG, hepatic venous pressure gradient; ICU, intensive care unit.

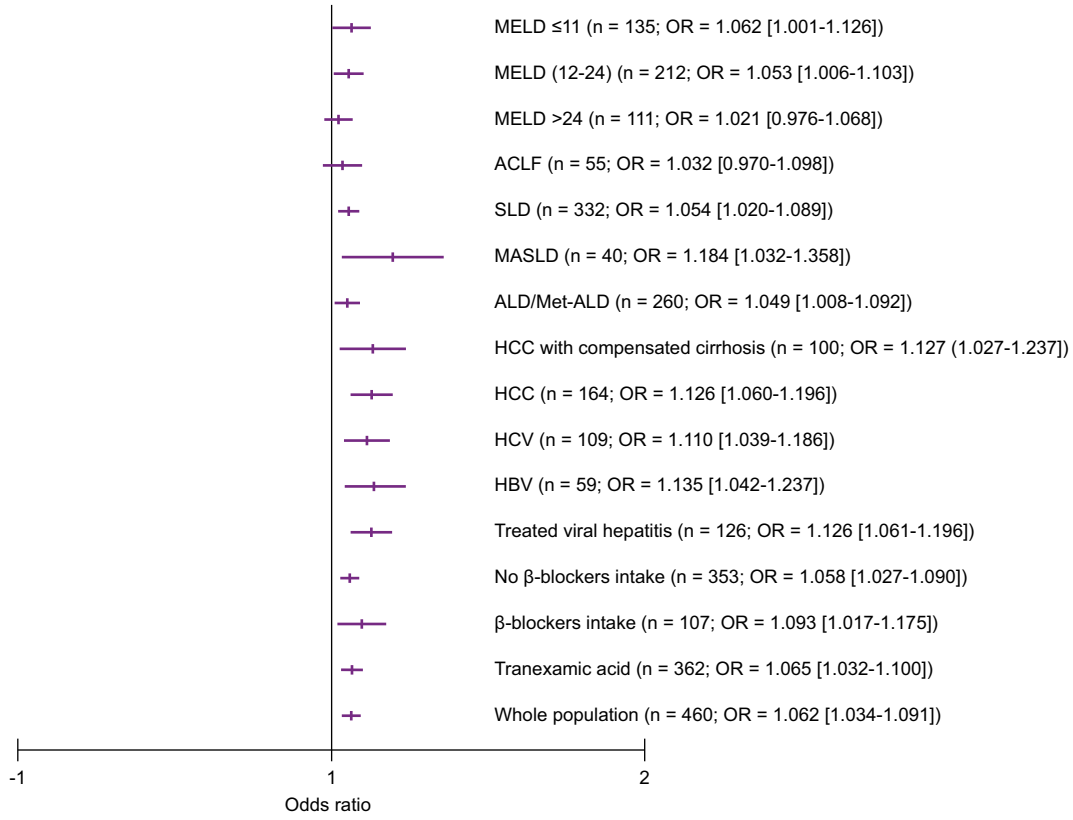

Fig. 3. Effect (OR) of HVPG on the risk of major intraoperative bleeding event among different subpopulations. Logistic regression used. Results are presented as OR [95% CI]. Major intraoperative major bleeding event was defined by the association of (i) significant intraoperative bleeding, namely blood loss ≥1,000 ml and/or RBC transfusion >2 U; associated with (ii) significant hemodynamic failure, namely intraoperative maximum norepinephrine dose ≥0.6 μg $kg^{-1}.min^{-1}$. ACLF, acute-on-chronic liver failure; ALD, alcohol-related liver disease; HCC, hepatocellular carcinoma; MASLD, metabolic dysfunction-associated steatotic liver disease; Met-ALD, MASLD and increased alcohol intake; OR, odds ratio; RBC, red blood cell; SLD, steatotic liver disease.[52–54]

Recently, Sanahuja *et al.* investigated the association between HVPG and transfusion requirements and blood loss during OLT and found no clear associations between portal hypertension and either bleeding or transfusion.[40] However, all OLTs were performed using temporary porto-caval shunt, thereby limiting the external validity of the results. Indeed, while intraoperative porto-caval shunt is often used in the absence of portal hypertension, its value in patients with cirrhosis and portal hypertension is more debated. Recently a panel of experts performed a systematic review of the literature and recommended against its routine use.[41] In our study, a temporary porto-caval shunt was used in 18% of patients and HVPG predicted major bleeding events independently of its use, suggesting that HVPG level may help in selecting patients who may benefit the most from intraoperative porto-caval shunt.

Predicting major bleeding events during OLT is of major interest for the individualization of perioperative management. Herein, we provide thresholds of HVPG that may allow for preoperative identification of patients at high risk of bleeding, thus enabling surgical teams to anticipate patient blood management strategies to reduce blood product exposure and transfusion-associated complications and costs. Importantly, we show that the predictive ability of HVPG is independent of other factors frequently associated with bleeding (*e.g.,* preoperative hemoglobin and fibrinogen levels and MELD score) and of some specific target interventions to reduce it (*e.g.*, tranexamic acid infusion and temporary porto-caval shunting).[2,26,27,42] Furthermore, we performed subgroup analyses confirming the association between HVPG and major bleeding events in several subpopulations (according to low and intermediate MELD score, indication for OLT and use of tranexamic acid) except those with MELD scores >24 in whom HVPG was no longer reliable.

By specifying intraoperative risk assessment, HVPG – together with other features including preoperative hemoglobin concentration and MELD – could be included in a decision algorithm to adapt perioperative patient management. First, HVPG might help tailor intraoperative hemodynamic monitoring. Indeed, while routine use of invasive arterial and CVP monitoring as a minimum standard of practice is strongly recommended, the routine use of pulmonary arterial catheter or transesophageal echocardiogram is more debated and could be restricted to patients at a high risk of intraoperative major bleeding events.[38] Second, HVPG could be used to select patients who may benefit the most from intraoperative strategies that minimize blood loss, such as restrictive fluid management (outside transfusion) policy and intraoperative cell salvage. In the same way, while the utilization of prothrombin complex concentrates is not routinely recommended, their use during OLT might be of interest in patients with high HVPG as an alternative to FFP because of their low volume, which limits the negative impact of FFP on portal hypertension and on coagulation through hemodilution and hypothermia.[43] Third, identifying patients at high risk of major bleeding during OLT could help to determine whether to perform a temporary porto-caval shunt.

Based on HVPG being a risk factor for major bleeding, transjugular intrahepatic portosystemic shunt (TIPS) placement before OLT seems logical to decrease bleeding risk in patients with high HVPG values. The small number of patients with TIPS in our cohort did not allow us to address this. Dedicated studies are needed to answer this question, also considering that some groups reported that TIPS was associated with additional technical difficulties during OLT.[44,45]

Improving the prediction of intraoperative major bleeding events could also have a major impact on the postoperative management of these patients. Several studies suggested a significant association between RBC transfusion volume and short- or middle-term mortality after OLT.[5,7,8] Longer ICU and hospital length of stay and higher rates of postoperative infection were also reported in patients who required RBC transfusion.[3,4] In our study, HVPG level was associated with postoperative acute renal failure, vasopressor infusion duration and ICU length of stay, but not with postoperative infection or ICU mortality. Therefore, in an era where the necessity of a systematic hospitalization in ICU after OLT is debated, with some teams promoting a "fast-tracking" strategy bypassing ICU, improvement of the preoperative assessment of patients seems essential.[46–48]

HVPG is mostly used to diagnose portal hypertension and define its severity, and to assess patient prognosis (*e.g.* the risks of death and of decompensating events such as portal hypertension-related bleeding), response to pharmacological treatments of portal hypertension, and risk of decompensation and mortality after hepatic and non-hepatic surgery.[49] Our study raises the question of whether to include HVPG measurement as part of routine pre-transplant assessment of patients with cirrhosis to stratify the risk of major intraoperative events and help the clinician to anticipate and personalize patient management. Whether HVPG could be used with MELD in a graft allocation algorithm to optimize the evaluation of the benefit risk ratio of OLT in patients with cirrhosis remains to be investigated.

Our study has some limitations. First, its retrospective design may have biased the results, and prospective validation of the ability of HVPG to predict intraoperative course would further strengthen our results. However, the database was prospectively filled out, thus limiting the risk of error in the analysis. Second, it must be acknowledged that HVPG is one of several risk factors for bleeding and we cannot exclude that other features not considered in this retrospective analysis would have an impact on intraoperative major bleeding events. Furthermore, HVPG can be modified in case of an acute event and its predictive ability may therefore be limited in certain subpopulations of severe patients, such as those with high MELD score or ACLF at the time of OLT. Third, this is a monocentric study. However, the large number of patients included, and the use of a bootstrap analysis might compensate for this limitation and enable the extrapolation of our results to other centers. Fourth, as the study spans more than 10 years, it is possible that surgical and anesthetic practices have changed over time. Nevertheless, anesthetic management has always followed a standardized written protocol following guidelines and excluding in particular preventive transfusion of blood products.[11,24] Moreover, sensitivity analyses gave the same results. Fifth, our primary endpoint is debatable but it is pragmatic and based on thresholds consistent with the literature.[2,50] Finally, while the time elapsed between HVPG measurement and OLT and the catheterization period (*i.e.,* after 2013) may have impacted our results, sensitivity analyses confirmed the predictive value of HVPG.

In conclusion, this study provides evidence for including HVPG measurement in the pre-transplant assessment of patients with cirrhosis to predict the risk of major bleeding events. A pragmatic approach based on high- and low-risk HVPG thresholds can be used, together with MELD, and preoperative hemoglobin level, to anticipate the risk and adapt perioperative management. Using HVPG may also help select appropriate high-risk populations for future studies that will investigate bleeding treatment strategies during OLT.

Abbreviations

ACLF, acute-on-chronic liver failure; CVP, central venous pressure; FFP, fresh frozen plasma; HVPG, hepatic venous pressure gradient; ICU, intensive care unit; INR, international normalized ratio; MELD, model for end-stage liver disease; OLT, orthotopic liver transplantation; RBC, red blood cell; RRT, renal replacement therapy; TIPS, transjugular intrahepatic portosystemic shunt.

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Conflict of interest

The authors of this study declare that they do not have any conflict of interest.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

MG, PJ participated in research design, in the writing of the paper, in the performance of the research and in data analysis. SS participated in the writing of the paper and in the performance of the research. CT, PD, FD, FD, PAF, ML, AP, AR, OR, TTS, ML participated in the performance of the research. SV participated in the performance of the research and in data analysis. PER, EW participated in research design, in the writing of the paper, in the performance of the research and in data analysis.

Data availability statement

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

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Ethics approval

The Institutional Review Board—IRB 00006477—of HUPNVS, Paris 7 University, AP-HP— 13-020 approved the study.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2024.101051.

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Author names in bold designate shared co-first authorship

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