REVIEW ARTICLE

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Portal Pressure Impact on Clinical Outcome after Major Hepatectomy: A Systematic Review and Meta-Analysis

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Abbreviations:
PHLF - posthepatectomy liver failure;
PVP - portal venous pressure;

ABSTRACT

Aim of the study: To systematically review the evidence regarding the association between portal venous pressure (PVP) after hepatectomy and posthepatectomy liver failure (PLHF) or other postsurgical outcomes.
Materials and methods: We searched PubMed, Scopus and Web of Science for studies assessing post-hepatectomy PVP (or its variation) and reporting its association with PHLF or other postsurgical outcomes. We performed a random-effects meta-analysis for the association between development of PHLF and post-hepatectomy PVP and its variation. Heterogeneity was assessed using Q-Cochran test and I2 statistic. Quality assessment was performed considering ROBINS-1 Cochrane tool.
Results: Four studies, assessing 439 patients, met the eligibility criteria and were included in this systematic review. The meta-analyses, including 3 studies, demonstrated that patients developing PHLF did not have a significantly higher post-hepatectomy PVP when compared to the remainder (1.98; 95%CI=-1.44-5.39; p=0.256; I2=2%), but had a significantly higher PVP variation (increase) during hepatectomy (1.65; 95%CI=1.15-2.15; p<0.001; I2=0%). The quality of the studies allowed to consider the robustness of the conclusions as "median".
Conclusions: An increased PVP variation following hepatectomy associates with a higher risk of PHLF, but the same was not observed for the absolute value of post-hepatectomy PVP.
Key words: hepatobiliary surgery, liver, portal venous pressure, portal inflow modulation, posthepatectomy liver failure, meta-analysis

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INTRODUCTION

Currently, major hepatectomy, traditionally defined as the resection of three

or more hepatic segments, constitutes the standard treatment of many benign or malignant liver diseases (1). Over the past 15 years, there has been an increase in survival and a decrease in morbidity in patients undergoing major hepatectomy or liver transplantation (1–5). However, despite this advancement, post-hepatectomy liver failure (PHLF), which mortality approaches 50%, is still frequent (1). Currently, the key point of liver function recovery after a major hepatectomy is the liver's ability to regenerate (4,6). Implementation of strategies to increase hepatic regeneration and prevent PHLF have shown promising results. Such strategies include selective portal embolization performed before major hepatectomy (7), and iterative hepatectomy. These strategies have allowed to achieve a new perspective, wherein limiting factor is not the size and location of the lesions, but the future liver reserve after hepatectomy (6).

Simultaneously to the development of these new strategies focused on liver regeneration, recent studies have suggested that hemodynamic factors of liver circulation, in particular excessive portal venous pressure (PVP) in the remaining hepatic volume, can cause severe endothelial sinusoidal injury followed by hepatic dysfunction (1,4,6). However, despite these pathological mechanisms described in clinical and experimental models (4,6,8–13), published experience about the clinical effects of portal hyperperfusion after major hepatectomy, and particularly its possible association with PHLF, has not been systematically reviewed. Therefore, in this study, we performed a systematic review of studies assessing post-hepatectomy PVP (or its post-hepatectomy variation) and its association with occurrence of PHLF or other major complication events.

MATERIAL AND METHODS

Search strategy and selection criteria

We followed PRISMA statement(14) for conducting and reporting systematic reviews. The

research protocol was registered at the International Prospective Register of Systematic Reviews with the following registration number: CRD42020135879.

We searched PubMed, Scopus and Web of Science in the last quarter of 2019, using the MeSH terms and keywords "portal venous pressure", "portal inflow modulation", "posthepatectomy liver failure" (complete query available in *table 1*).

The inclusion criteria consisted of studies assessing humans, measuring PVP after hepatectomy and assessing its association with PHLF or other outcomes, such as liver function deterioration and postoperative mortality. It was not applied any exclusion criteria based on the language or date of publication.

After duplicates removal, screening by title and abstract reading was independently performed by two authors. The full texts of potentially eligible studies were then independently assessed by two authors. Data from included studies were independently extracted by two authors, according to a previously built specific form. Missing data were requested to the authors of the primary study. Any disagreement was solved by consensus.

We extracted data that included the year of publication, study design (i.e., whether the study was prospective or retrospective), sample size, patients characteristics (mean and median age, sex ratio, body mass index, malign or benign diagnosis, functional status, and American Society of Anaesthesiologists (ASA) score), frequency of potentially patient-related factors of poor prognosis (malignancy, hepatitis, pre-operative jaundice, preoperative cholangitis, cirrhosis, alcohol consumption, smoking, diabetes mellitus, obesity), frequency of surgical procedure-related factors associated with por prognosis (future liver remnant and intra-operative blood transfusion), procedures and techniques used, PVP values (including post-hepatectomy and pre-hepatectomy values and/or its variation) and methods used to measure it, defined PVP cut-off reported to be associated to worsening outcomes, frequency of patients developing PHLF (50/50 criteria and International Study Group of Liver Surgery (ISGLS) criteria) and

Table 1 - Search query – number of articles searched

Mesh terms	Pubmed	Scopus	Web of science	Total
Portal venous pressure	5088	4874	2853	12815
Portal inflow modulation	31	58	112	201
Posthepatectomy liver failure	301	538	395	1234
Total	5420	5470	3360	14250

respective PVP values, and also other outcomes whose association with PVP was measured including cytolysis and coagulation function, morbidity (Clavien-Dindo Score), mortality and survival.

Risk of bias

Quality assessment of primary studies was performed independently by two authors by applying the ROBINS-I tool (a Cochrane risk of bias tool to assess non-randomized studies) (15). The Cohen kappa statistic (16) was used to quantify agreement between the investigators. Disagreements between the authors over the risk of bias assessment were solved by consensus.

Statistical analysis

We were only able to quantitatively pool information for the comparison of post-hepatectomy PVP and PVP variation between patients developing and not developing PHLF. For studies not reporting the standard-deviation or standard-error for each group, the standard deviation of each group was extrapolated from the SD of the total. It was performed a random-effects meta-analysis of mean differences following the restricted maximum likelihood method. Heterogeneity was assessed using both the Q-Cochran test and the I^2 statistic – a Q-Cochran p value less than 0.10, and an I^2 greater than 50% were considered indicative of substantial heterogeneity. Software R (meta package) was used for statistical analysis. The significance threshold used was $p < 0.05$.

RESULTS

Literature search

The process of study selection is illustrated in *figure 1* (PRISMA flow diagram). A total of 3987 records were initially retrieved. After removing duplicates

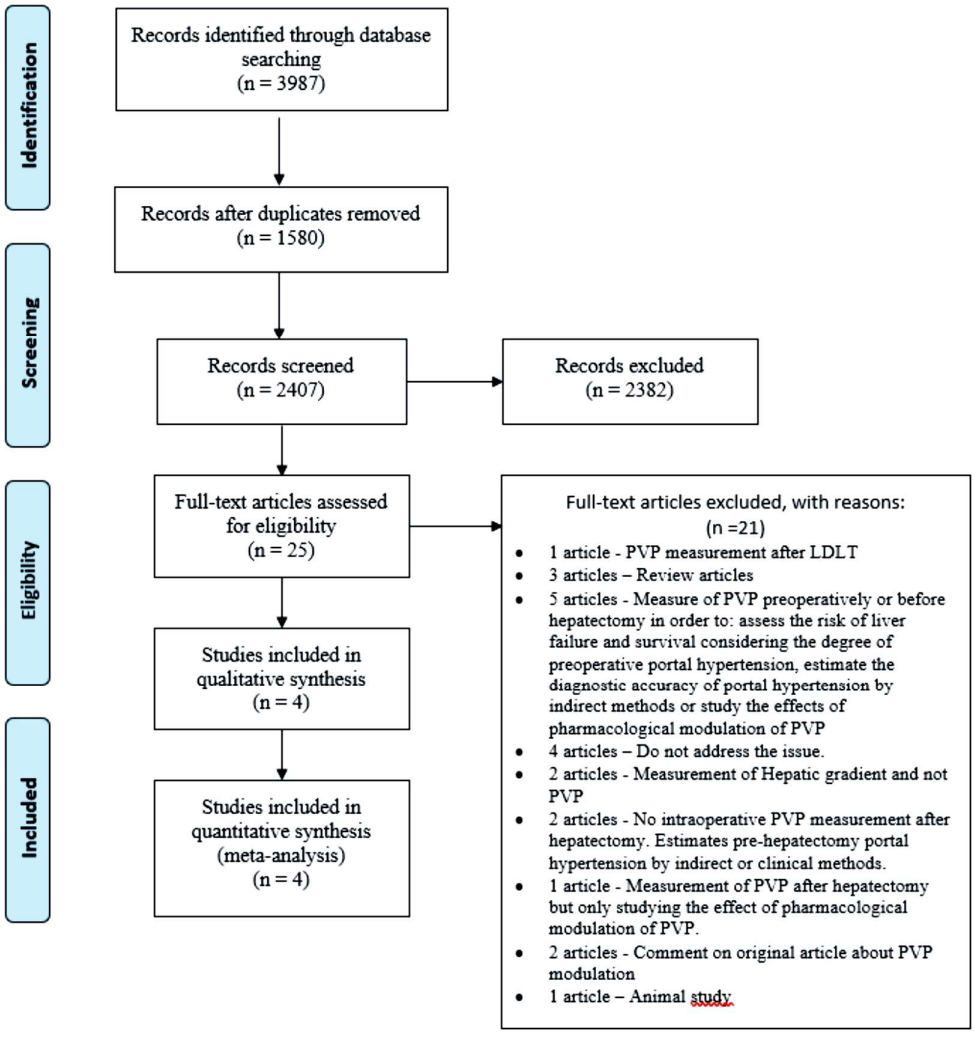

Figure 1 - PRISMA Flow Diagram

(n=1580), 2407 articles were screened. Among them, 2382 articles were excluded by title or abstract reading. Of the 25 studies fully read, 21 studies were excluded (17–37), so that 4 studies were included in this systematic review (1,38–40).

Characteristics and quality of included studies

The characteristics of included studies are shown in *table 2* and *table 3*. The 4 included studies were published between 2013 and 2019 and included a total of 439 patients. Three of those studies had a prospective design (1,39,40).

Looking at the factors that may influence the study analysis, only two studies provided information on the body mass (39,40), one included information on the functional status, ASA score and previous alcohol and smoking habits(39), three studies discriminated the percentage of patients with diabetes mellitus (1,38,39), and all consider the extent of liver resection. Regarding the presence of cirrhosis, one study included 3 patients CHILD A (40), two studies did not include cirrhotic patients (1,39), while Iida et al. did not explicitly report the percentage of cirrhotic patients, but all patients had an acceptable risk score including hepatic clearance function(38). The perioperative blood transfusion was considered in two studies (1,39) and only one study included one patient submitted to two-stage hepatectomy (39). According to the ISGLS classification, 3 studies reported 10%, 37.5% and 13.4% of patients with PHLF grade B and C (38–40), while Allard et al only reported patients with PHLF grade C (10.5%).

In three studies portal venous pressure was measured by direct puncture of the portal vein using a needle/catheter attached to a transducer (1,39,40), while in one study it was performed by introducing a tube into the round ligament (38). Three studies presented results for post-hepatectomy PVP values (1,39,40), while PVP variation before and after hepatectomy was reported by three studies (38–40). One study concluded that increased PVP after hepatectomy is associated with deteriorated liver coagulation function (39). Considering only the risk of developing

Table 2 - Characteristics of the studies included in the systematic review

Study (Publication Year)	Country	Design	Patients	Age (μ±SD)	Malignant Diagnosis (%)	Cirrhosis Grade (ISGLS Classification)(%)	Operative procedures (% Major hepatectomy)	ROBINS-I Risk of bias tool
Allard et al (2013)	France	Prospective Randomized Controlled	277	52.7 ± 16	66%	Grade C 10,5%	100%	Low
Iida et al (2016)	Japan	Retrospective	35	PHLF: 60,1±12,7 Ø : 64,1±8,1	n.m.	Grade B and C 37,5%	100% Right hepatectomy	Moderate
Carrapita et al (2019)	Portugal	Prospective Controlled	30	62.47±11.42	76.67%	Grade B and C 10%	73,33%	Moderate
Bogner et al (2019)	Germany	Prospective Controlled	97	MH: 61,4±11,8 CG: 56,2±14,5	86,6%	Grade B and C 13,4%	69,1%	Moderate

μ: mean; SD: standard deviation; PHLF: Posthepatectomy liver failure; Uncomplicated group: Ø; n.m: not mentioned. MH: Major hepatectomy group; CG: control group (minor hepatectomy)

Table 3 - Other variables considered in the studies

First author name	♀:♂	Body mass index	Functional status (Karnofsky index)	ASA score (Median)	Alcohol consumption	Smoking	Diabetes Mellitus	Future Liver	Remnant Peroperative blood transfusion
Carrapita et al	18:12	26,78 ± 4,48	100%	2	2 (6,67%)	6 (20%)	7 (23,33%)	0,65 ± 0,18	9 (30%)
Allard et al	142:135	not reported	not reported	not reported	not reported	not reported	23 (8,3%)	not reported	114(41,16%)
Lida et al	not reported	not reported	not reported	not reported	not reported	not reported	22,86%	not reported	not reported
Bogner et al	Major Hepatectomy Group: 29:38 Control Group: 16:14	Major Hepatectomy: 25,7 ±4,6 Minor Hepatectomy: 25,7 ±3,9	not reported	not reported	not reported	not reported	not reported	not reported	not reported

Table 4 - results of the studies included in the systematic review

Study (Publication Year)	PVP cut off poor prognosis (mm Hg)	Primary outcome	Secondary outcome	Conclusions
Allard et al (2013)	PVP post hep ≥ 22 (PHLF grade C)		PVP ≥ 22 mmHg is an independent factor for the occurrence of PHLF grade C (RR=4.24; 95% IC: 1.89-16.40; P<0.05)	⇒ PVP post hep is an independent predictive factor of PHLF and 90-day mortality after major liver resection in patients without cirrhosis
	PVP post hep ≥ 21 (Mortality and Bilirubin peak)	Bilirubin peak greater than 120 µmol / L	PVP ≥ 21 mmHg is an independent factor for mortality (RR=5.37; 95% IC: 1.87-15.39; P<0.05)	⇒ PVP post hep ≥ 21 mmHg is the cut off for worst outcome
Iida et al (2016)	υPVP ≥ 2.2	-	υPVP≥2.2 mm Hg is an independent factor for the occurrence of PHLF grade B and C (OR=3.11; 95% IC: 1.536-8.183; P<0.05)	⇒ PVP increase ≥ 2.2 mmHg following right hepatectomy is a risk factor for PHLF
Carrapita et al (2019)	υPVP ≥ 1.5 PVP post hep ≥ 12.5	Deterioration of coagulation at 24h, 5th and 30th day	υPVP≥2 mm Hg is an independent factor for the occurrence of major complications (OR=0.124; 95% IC: 0.018-0.837; P<0.05)	⇒ PVP increase during hepatectomy influences the deterioration of liver function in the postoperative period ⇒ A PVP increase ≥ 2 mmHg after hepatectomy, compared to baseline, rises the risk of major complications
Bogner et al (2019)	-	No association between υPVP with any other clinic-pathological variables	υPVP has a significant and independent association with PHLF Grade B and C (OR=1.154; 95% IC: 1.018-1.307; P<0.05) Þ	⇒ The extent of intraoperative PVP increase was found as an immediate and independent predictor of PHLF ⇒ υPVP has higher predictive value of PHLF than pure post resection PVP value.

PVP post hep: Posthepatectomy portal venous pressure; PHLF: posthepatectomy liver failure; υPVP: Portal venous pressure variation during hepatectomy; Bilirubin peak: Peak of bilirubin greater than 120 µmol / L.

PHLF, Allard et al defined a PVP cut off after hepatectomy of 22 mmHg for the occurrence of grade C of this syndrome (RR= 4.24: 95% IC: 1.88-16.40; p<0.05) (1), while Carrapita et al found a PVP cut off after hepatectomy predicting PHLF (grade B and C) of 12.5 mmHg (39), as shown in *table 4*. If it is considered the variation of PVP that occurs during hepatectomy, and not just the measurement of PVP at the end of hepatectomy, we detect a 2.2 mmHg cut off as a predictor of PHLF grade B and C (OR= 0.124; 95% IC: 0.018-0.837; p<0.05) in one study (38), and a 2,2 mmHg cut off predicting major complications (OR= 0.124; 95% IC: 0.018-0.837; p<0.05) (39). All studies concluded that the elevation of PVP after hepatectomy increases the risk of PHLF, according to the ISGLS criteria, as shown in *table 2* (1,38–40).

Meta-analytical results

Two studies compared patients with and without PHLF on their post-hepatectomy PVP values (39,40). Both studies reported a higher post-hepatectomy PVP mean value in the PHLF group when compared to the remaining patients. The pooled meta-analytical PVP mean difference between the two groups was not significantly different (1.98; 95% CI=-1.44; 5.39; p=0.256), with no substantial heterogeneity detected (I2=2%; p=0.313) (*figure 2*).

All the three studies compared patients with and without PHLF on their post-hepatectomy PVP variation (38–40). All these studies reported a higher mean PVP increase in the PHLF group, comparing to the group without this postoperative complication. Patients developing PHLF had a significantly higher PVP increase compared to the remainder (1.65; 95%CI=1.15;2.15; p<0.001), with no heterogeneity detected (I2=0%; p=0.649) (*figure 3*).

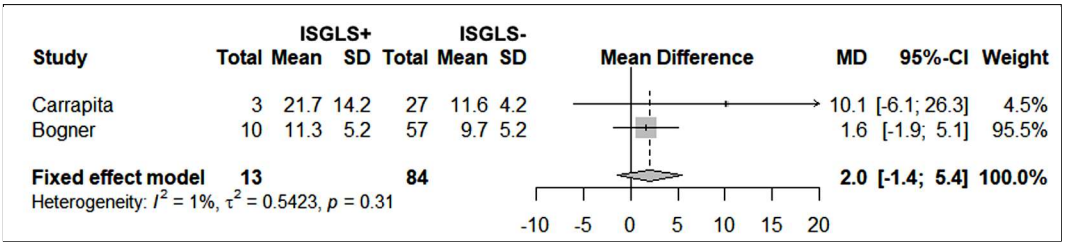

Figure 2 – Forestplot of pooled meta-analytical posthepatectomy portal venous pressure mean difference

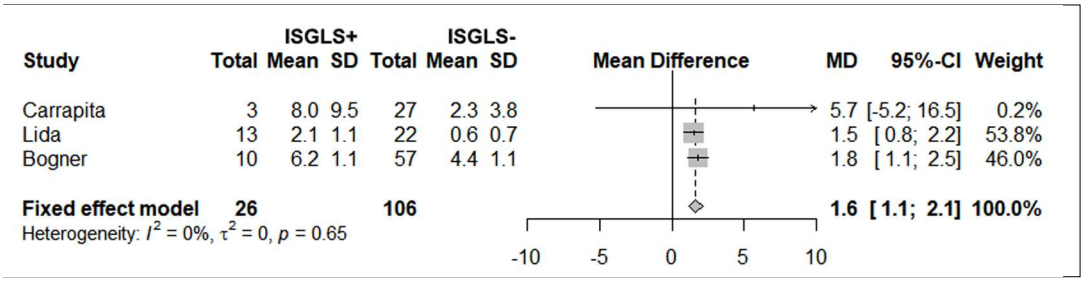

Figure 3 – Forestplot of pooled meta-analytical portal venous pressure variation mean difference

Quality of studies

Regarding the quality of the studies, the ROBINS-I tool, which is a Cochrane risk of bias tool to assess non-randomized studies of interventions expressed in *table 2* and *table 5*, allowed to consider the included studies as having low or moderate risk of bias for all domains. It was found an increased risk of confounding bias in one study because of the high number of influencing factors included, although it was minimized by stepwise selection (39). Three studies present a risk of misclassification of exposure because they do not consider other factors that may influence the analysis studied, namely diseases and previous habits, functional status and perioperative blood transfusion (1,38,40). The risk of performance bias was considered in three studies, because it was not explained if the surgical team was always the same, which was minimized by standardization of the procedure (1,38,40). In addition, one study was considered to have limited internal validity because of its retrospective nature(38), while three studies were considered to have limited validity on account of their small sample size (38–40).

DISCUSSION

This systematic review suggests that patients who develop PHLF exhibit an increase in PVP during major hepatectomy which is significantly higher to that observed in patients who do not have this postoperative syndrome. This reinforces the importance of intraoperative measurement of PVP. On the other hand, this review suggests that the isolated measurement of PVP after hepatectomy is not enough, since this absolute value is not significantly different in groups with or without PHLF. In addition, in this review the cut off variance found in the studies included was explicit, if only the measurement of PVP after hepatectomy is considered. Probably, the difference in the PVP cut off after hepatectomy predicting PHLF observed in the two included studies (22 mmHg versus 12.5 mmHg) is not only be related to the difference in the inclusion criteria of patients with PHLF (grade C versus grade B and C). This discrepancy reflects the variability of PVP to which several factors contribute, namely the PVP before hepatectomy.

Besides the clinical studies assessed in this systematic review, there are also experimental studies, explaining the pathological processes underlying the association between PVP increase and PHLF (1,6,10–12). These studies allowed to clarify some mechanisms through which the portal venous hyperperfusion induces deleterious effects on the liver parenchyma, particularly the increase in cell death by apoptosis and oxidative

Table 5 - Risk of bias ROBINS-I assessment tool (Cochrane risk of bias tool to assess non-randomized studies)

	Allard et al (2013)	Iida et al (2016)	Carrapita et al (2019)	Bogner et al (2019)
Bias due to confounding	Moderate	Moderate	Moderate	Moderate
Bias in selection of participants into the study	Low	Low	Low	Moderate
Bias in classification of interventions	Low	Moderate	Low	Low
Bias due to deviations from intended interventions	Low	Low	Low	Low
Bias due to missing data	Low	Moderate	Low	Low
Bias in measurement of outcomes	Low	Low	Low	Low
Bias in selection of the reported result	Moderate	Moderate	Moderate	Moderate
Overall bias	Low	Moderate	Moderate	Moderate

stress mediated by humoral and inflammatory response.

Furthermore, it is now known that the transhepatic flow regulation mechanism, which is equal to hepatic arterial flow plus portal venous flow, is related to the so-called artery buffer response, which allows to compensate an elevation of the portal venous flow with a constriction of the hepatic artery, mediated by the decrease of the adenosine phosphatase concentration (so-called "adenosine washout hypothesis") (28). The problem arises when this mechanism is not enough to compensate the abrupt and sharp rise in portal pressure/flow, particularly in the presence of liver injury, namely steatosis, cirrhosis, prolonged exposure to chemotherapeutic agents or prolonged intra-operative ischemia. In these circumstances, the tolerance threshold for portal hyperperfusion is decreased, resulting in need for greater future liver remnant (4,13). This can explain the need for a greater graft volume in cirrhotic patients, whose over dynamic circulation status could result, with higher probability, in liver failure after LDLT (4).

Currently, in LDLT, targets have been met to establish criteria to define in which situations the risk of graft liver failure is increased. For this purpose, much contributed Govil et al. (41), which confirmed the achievements of previous studies and proposed recommendations. They presented the concept of small-for-flow, confirming that graft dysfunction, although multifactorial, is associated with high portal pressure and flow, establishing limits to portal flow and pressure in order to avoid this syndrome and suggested that both should be considered to avoid the portal steal syndrome. In addition, these authors suggest that, in LDLT, a portal flow greater than 4 times the right portal vein flow of the donor (that is>360 ml/min per 100 g graft weight) or the combination of PVP > 15 mmHg and a portal flow greater than 2 times the basal flow of the right portal vein of the donor (that is > 180 ml/ min per 100 g graft weight), significantly increases the risk of small-for-flow syndrome (41). However, such indications are not yet supported by adequate scientific evidence. This review has some limitations, namely the limited number of studies, rendering it impossible to perform subgroup analysis or meta-regression. Nevertheless, the need for such methods is curbed by the low heterogeneity observed. In addition, the high number of factors which predispose to PHLF and could influence the PVP/PHLF relation, besides not being all described in all the studies, may promote the occurrence of confounding. Another limitation is the small number of patients participating in each study included in this review, resulting in decreased precision of the obtained estimates. Additional limitations include the disparity in the design and methodology of published studies, namely the inclusion of patients with different grades of liver failure after hepatectomy, the adoption of different PVP predictive cut-offs of PHLF, and lack of information on outcomes other than PHLF, such as mortality.

However, despite these limitations, this systematic review has also some strengths. In particular, its search was performed in three different bibliographic databases, with no definition of exclusion criteria based on publication language or date. This is the first systematic review with meta-analysis assessing the association between PVP and PHLF, and points to the potential importance of assessing PVP during hepatectomy, by assessing the relative increase in PVP during hepatectomy, rather than the absolute value of PVP measured after hepatectomy. Taking this into account, future research should try to define cut off(s) of PVP increment corresponding to relevant increases in the risk of PHLF. This would contribute to define indications of portal influx modulation, with the goal of decreasing the incidence of PHLF and, therefore, mortality after major hepatectomy.

CONCLUSION

The relative increase in PVP during hepatectomy is associated with increased occurrence of PHLF, contrarily to what has been observed for the absolute value of PVP after hepatectomy. Standardizing the methodology for PVP measurement and defining PVP variance cut-offs, not only may allow to predict which patients may be in increased risk of PHLF, but also opens a door to the implementation of strategies for portal inflow modulation.

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Disclosure of interest

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