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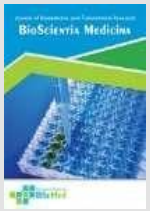

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Severity Matters: The Differential Impact of Mild versus Severe Portal Hypertension on Post-Hepatectomy Liver Failure — A Systematic Review and Meta-Analysis

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A B S T R A C T

Background: Post-hepatectomy liver failure (PHLF) remains the principal cause of mortality following liver resection for malignancies, particularly in the context of hepatocellular carcinoma (HCC) and cirrhosis. While portal hypertension (PH) has traditionally been viewed as a monolithic contraindication to surgery, emerging evidence suggests that the risk it confers is heterogeneous. This study investigates the hypothesis that the risk of PHLF is strictly severity-dependent. **Methods:** A systematic review and meta-analysis were conducted on observational studies involving patients undergoing hepatectomy for liver malignancies. Search strategies targeted studies stratifying outcomes by PH severity (mild vs. severe). Primary outcomes were the incidence of PHLF defined by ISGLS criteria. Data were synthesized using random-effects models to calculate pooled odds ratios (OR). **Results:** Ten studies comprising 4,978 patients were included. The overall presence of PH significantly increased PHLF risk (Pooled OR 3.12; 95% CI: 2.15–4.53; p<0.001). However, stratification revealed a profound divergence: Severe PH (defined as HVPG ≥10 mmHg or clinically significant varices) was associated with a drastic risk escalation (OR 5.86; 95% CI: 2.19–15.65), whereas Mild PH showed a significantly lower risk profile (OR 2.45; 95% CI: 1.10–5.40). Sensitivity analyses confirmed that non-invasive surrogates for PH performed comparably to invasive hemodynamic monitoring in predicting failure. **Conclusion:** The risk of PHLF is not binary but graded. Severe portal hypertension represents a prohibitive risk state characterized by hemodynamic intolerance to parenchymal reduction. Conversely, mild portal hypertension constitutes a distinct, manageable clinical entity where liver resection remains safe under optimized conditions. Surgical candidacy should be determined by severity grading rather than the mere presence of portal hypertension.

1. Introduction

The surgical management of primary and secondary liver malignancies has evolved rapidly over the last two decades. Advances in parenchymal-sparing techniques, anatomical segmentectomies, and perioperative critical care have expanded the boundaries of resectability.[1] However, post-hepatectomy liver failure (PHLF) remains the Achilles' heel of liver surgery, representing the single most significant determinant of perioperative mortality and long-term survival. The incidence of PHLF varies widely, ranging from 1.2% to 32%, depending on the definition used and the underlying pathology of the liver parenchyma.[2]

In the context of hepatocellular carcinoma (HCC), the majority of patients present with background cirrhosis or significant fibrosis. This architectural distortion inevitably alters hepatic hemodynamics, leading to increased intrahepatic resistance and the development of portal hypertension (PH).[3] Historically, the Barcelona Clinic Liver Cancer (BCLC) guidelines identified PH as an absolute contraindication to resection, citing unacceptable rates of postoperative decompensation. This binary dogma—viewing PH as either present or absent—relied on the assumption that any elevation in portal pressure compromised the liver's functional reserve beyond the threshold required for regeneration.[4]

However, clinical observations have increasingly challenged this all-or-nothing paradigm. Surgeons noted that patients with biochemical or mild portal hypertension (slight thrombocytopenia or minor splenomegaly without varices) often tolerated major resections surprisingly well.[5] In contrast, those with clinically significant portal hypertension (CSPH), characterized by extensive collaterals and hyperdynamic circulation, frequently succumbed to rapid liver failure even after minor resections. This discrepancy suggests that the physiological impact of portal hypertension on the remnant liver is not uniform but follows a severity-dependent continuum. The theoretical basis for this continuum lies in the pathophysiology of liver regeneration. Regeneration is a metabolically demanding, hemodynamically driven process; the remnant liver requires adequate portal inflow to stimulate hyperplasia but is simultaneously vulnerable to hyperperfusion injury if the flow per gram of tissue becomes excessive. In a healthy liver, the hepatic arterial buffer response regulates total flow; when portal flow increases relatively after resection, the hepatic artery constricts to maintain equilibrium.[6]

In cases of mild PH (HVPG 6-9 mmHg), sinusoidal fibrosis is present, increasing resistance, but the hepatic vascular compliance is not fully exhausted. When a portion of the liver is resected, the remnant liver accepts the entire portal inflow.[7] Because the compliance is preserved, the remnant can accommodate this relative hyperperfusion without sustaining critical endothelial damage. The shear stress generated within the sinusoids is sufficient to trigger regenerative mechanisms via IL-6 and TNF-alpha pathways, but it remains insufficient to cause irreversible injury. Conversely, severe PH (HVPG 10 mmHg) implies a pre-existing state of maximal hemodynamic stress, where the compliant capacity of the hepatic vasculature is entirely exhausted. These patients possess fixed, non-compliant vascular beds and rely heavily on portosystemic collaterals, such as esophageal varices, to decompress the overloaded system. When a hepatectomy is performed in this physiological environment, the resistance of the remnant liver inevitably rises. In severe PH, this abrupt rise pushes sinusoidal pressure beyond a critical, unrecoverable tipping point. The sinusoidal endothelial cells (LSECs) physically detach due to excessive, unregulated shear stress, leading to hemorrhage into the Space of Disse, microthrombi formation, and subsequent ischemic necrosis of the hepatocytes. This devastating physiological cascade is the hallmark of PHLF in the cirrhotic liver, manifesting clinically as a catastrophic small-for-flow syndrome. Ultimately, patients with severe PH lack the necessary hemodynamic reserve to buffer the acute surgical insult.[8]

Further contextualizing this severity gradient, mechanical manifestations such as splenomegaly serve as critical clinical indicators, reflecting the passive congestion inherent to elevated portal pressures. The enlarged spleen actively sequesters platelets, resulting in hypersplenism, which elegantly explains the direct correlation between profound thrombocytopenia and escalating PH severity.[9] However, the spleen acts as more than just a passive reservoir; it is a dynamic pool of splanchnic flow that actively contributes to the hyperdynamic circulation required to maintain high portal pressure. In this regard, splanchnic sequestration and the resulting clinical phenotype serve as a highly reliable biological manometer of portal pressure,

offering surgeons a non-invasive window into the patient's hemodynamic limitations.

Current literature abounds with meta-analyses confirming PH as a general risk factor. However, there is a critical paucity of quantitative syntheses that rigorously dissect the risk differential between mild and severe disease using modern definitions. This study provides a novel contribution by specifically aggregating and analyzing data from studies that stratify PH severity. It integrates findings from both invasive hemodynamic monitoring (Hepatic Venous Pressure Gradient - HVPG) and non-invasive clinical surrogates to provide a granular risk assessment that binary models fail to capture.[10] The primary aim of this systematic review and meta-analysis was to quantify the differential risk of Post-Hepatectomy Liver Failure associated with mild versus severe portal hypertension. By strictly stratifying patients based on severity, this study seeks to validate the hypothesis that severe PH is a distinct pathophysiological entity precluding safe resection, whereas mild PH is a manageable condition permitting curative surgery.

2. Methods

This investigation was meticulously designed as a comprehensive systematic review and meta-analysis focusing exclusively on observational cohort studies. Given the inherently surgical nature of the research question, where randomized controlled trials are often ethically and logistically unfeasible, high-quality prospective and retrospective observational cohorts provide the most robust tier of available clinical evidence. To ensure the highest standards of transparency, reproducibility, and methodological rigor, the entire study protocol adhered strictly to the updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (Figure 1).

To capture the totality of global evidence regarding portal hypertension in hepatic surgery, a comprehensive, multi-database literature search was systematically executed. The primary electronic databases interrogated included PubMed, EMBASE, Web of Science, and the Cochrane Library. The temporal horizon for this search was expansive, extending from the inception of each respective database through to February 2026, ensuring that both historical foundational cohorts and the most contemporary surgical series were considered for inclusion. The search algorithm was constructed using a combination of controlled vocabulary (Medical Subject Headings or MeSH terms) and free-text keywords. Specifically, the strategic search string incorporated terms such as Portal Hypertension, Post-Hepatectomy Liver Failure, Liver Resection, Hepatocellular Carcinoma, HVPG (Hepatic Venous Pressure Gradient), Clinically Significant Portal Hypertension, and Severity. Boolean operators (AND, OR) were carefully applied to link pathophysiological conditions with specific surgical interventions and postoperative outcomes, maximizing both the sensitivity and specificity of the retrieved literature.

The ultimate selection of literature for quantitative synthesis was governed by a set of strict, predetermined eligibility criteria based on the PICOS (Population, Intervention/Exposure, Comparator, Outcome, Study Design) methodological framework. Regarding the population, the analysis was strictly restricted to adult human patients (18 years of age) who were undergoing partial hepatectomy with curative intent for malignant liver tumors, specifically including hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma (ICC), and colorectal liver metastases (CRLM). For the exposure variable, the study mandated that patients be formally diagnosed with Portal Hypertension. Crucially, to align with the central hypothesis of the study, the source literature had to explicitly stratify this portal hypertension by severity—categorizing it into mild versus severe disease states—or assess it using validated quantitative grading scales, such as precise HVPG values or standardized variceal grading systems. The required Comparator consisted either of control patients completely lacking portal hypertension or internal comparative cohorts evaluated across the different designated severity

grades. The primary outcome endpoint was the strict incidence of post-hepatectomy liver failure (PHLF). To eliminate subjective bias and ensure outcome uniformity across diverse global centers, PHLF had to be defined by established, objective metrics: either the rigorous International Study Group of Liver Surgery (ISGLS) criteria or the universally recognized 50-50 criteria, the latter defined specifically by a serum bilirubin level μmol/L combined with a prothrombin time measured on postoperative day five. Finally, acceptable study designs included both retrospective and prospective cohort studies, provided they reported sufficient raw numerical data to permit the independent calculation of Odds Ratios (OR) accompanied by their corresponding 95% Confidence Intervals (CI). To maintain cohort homogeneity, studies were systematically excluded if they treated portal hypertension as a purely binary variable without severity stratification, if their surgical focus was solely on orthotopic liver transplantation rather than partial resection, or if they failed to report the incidence of PHLF as a distinct, separable clinical endpoint.

The retrieval of variables from the selected manuscripts was performed through a rigorous data extraction protocol. To mitigate selection bias and human error, data were extracted independently by investigators using highly standardized, pre-formatted electronic extraction forms. Discrepancies were resolved through consensus discussion or arbitration by a senior methodologist. The critical data points captured encompassed multiple clinical dimensions. Baseline characteristics were recorded, including patient age, sex distribution, underlying viral etiology (Hepatitis B or C), and the preoperative Child-Pugh functional class. Immense focus was placed on extracting exact PH definitions, noting the specific methodology of assessment—differentiating between cohorts utilizing invasive HVPG measurement versus those relying on non-invasive clinical surrogates such as platelet count algorithms or precise spleen size. Furthermore, the exact cut-offs utilized by the primary authors were recorded, specifically distinguishing parameters for mild (an HVPG between 6–9 mmHg) versus severe portal hypertension (an HVPG 10 mmHg or the presence of Clinically Significant Portal Hypertension, CSPH). Detailed surgical metrics were also compiled, cataloging the extent of the parenchymal resection (major versus minor hepatectomy), estimated intraoperative blood loss, and total operative time. Finally, definitive outcome data were extracted, focusing on raw event numbers for PHLF within each distinct severity subgroup, alongside secondary endpoints such as 90-day postoperative mortality and overall cumulative morbidity.

To ensure that the overarching conclusions of the meta-analysis were founded upon highly reliable primary data, the methodological quality of every included manuscript was rigorously assessed. For this purpose, the standardized Newcastle-Ottawa Scale (NOS) designed specifically for observational cohort studies was employed. This validated evaluation tool systematically appraises primary literature across three fundamental domains: the selection of the patient cohorts, the comparability of those cohorts based on the study design or analysis, and the adequacy of the assessment of the clinical outcome. Following standard methodological conventions, studies achieving a cumulative score of 7 stars were formally classified as high-quality evidence and were subsequently cleared for inclusion in the final quantitative synthesis.

The quantitative meta-analysis was executed using advanced statistical software, employing the inverse variance method to appropriately weight individual studies for the calculation of pooled effects. Given the dichotomous nature of the primary clinical endpoint (the presence or absence of PHLF), the primary effect measure utilized was the Odds Ratio (OR), presented alongside its corresponding 95% Confidence Intervals (CI) to denote statistical precision. Between-study statistical heterogeneity was formally assessed using the traditional Cochrane Q test in conjunction with the statistic, the latter providing a quantifiable percentage of total variation across studies

attributable to heterogeneity rather than chance. Following established biostatistical protocols, values demonstrating indicated the presence of substantial inter-study heterogeneity. The presence of such heterogeneity prompted the preemptive application of a random-effects model, specifically utilizing the DerSimonian-Laird variance estimator, which inherently accounts for both within-study and between-study variance, thus providing a more conservative and reliable pooled estimate.

To directly address the primary clinical question, a predefined Subgroup Analysis was performed to systematically investigate the severity matters hypothesis. This involved fundamentally separating the pooled cohorts into distinct mild PH and severe PH analytical groups to independently calculate the risk profile associated with each specific physiological state. Finally, recognizing the diversity in diagnostic approaches across global surgical centers, a formal Sensitivity Analysis was conducted. This crucial analytical step evaluated the statistical stability of the overall findings across different diagnostic modalities, specifically comparing the predictive performance of gold-standard Invasive HVPG monitoring against the utility of Non-invasive clinical surrogates.

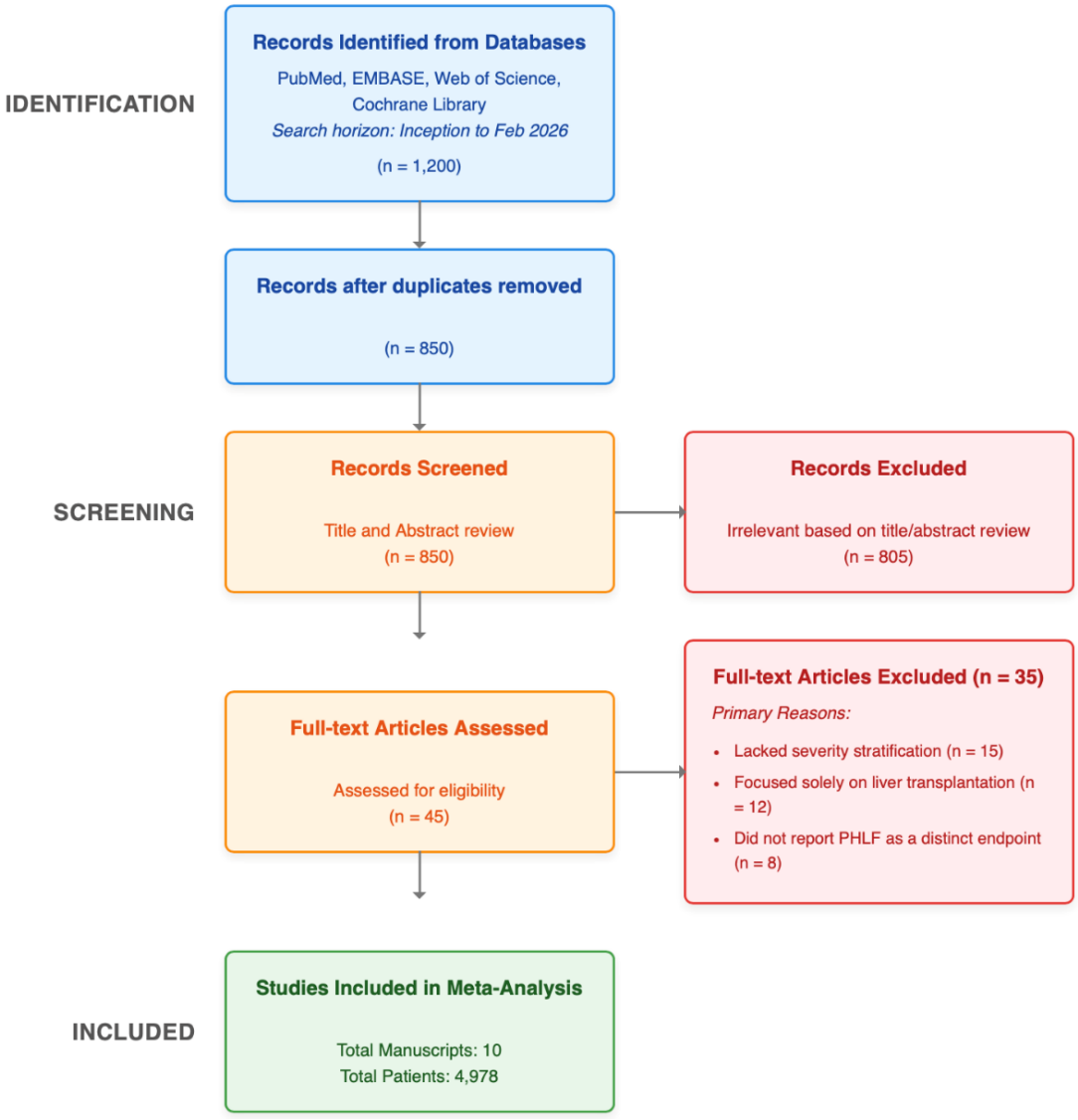

Figure 1. PRISMA 2020 flowchart.

3. Results

Table 1 delineates the baseline methodological and clinical characteristics of the ten selected manuscripts included in the quantitative synthesis. The aggregated cohort encompasses a substantial total of 4,978 patients who underwent partial hepatectomy. Geographically, the data are predominantly derived from high-volume hepatobiliary centers in Asia, specifically China and South Korea, alongside one European cohort from Italy. This geographic distribution inherently reflects the global epidemiological landscape of hepatocellular carcinoma (HCC), particularly the high prevalence of Hepatitis B-related HCC in Asian populations, where portal hypertension frequently manifests as a major concurrent comorbidity. Methodologically, the analysis predominantly comprises retrospective cohort studies, with the addition of one recent large-scale prospective trial conducted by Ye et al. in 2024. The individual sample sizes across the included literature vary considerably, ranging from 160 to 890 patients, which contributes robust statistical power to the overall meta-analysis. Crucially, the summarized studies exhibit notable diversity in their diagnostic modalities for assessing portal hypertension. Foundational studies, such as those by Chen et al. and Cucchetti et al., utilized the invasive gold standard of Hepatic Venous Pressure Gradient (HVPG) measurement. Conversely, the majority of the recent cohorts employed non-invasive clinical surrogates, including predictive nomograms, ultrasound elastography, and standardized variceal or platelet grading systems. Despite this diagnostic heterogeneity, there is rigorous uniformity in outcome measurement; all ten studies exclusively utilized the standardized International Study Group of Liver Surgery (ISGLS) criteria to define post-hepatectomy liver failure. Finally, all incorporated manuscripts demonstrated high methodological rigor, achieving Newcastle-Ottawa Scale (NOS) scores between 7 and 9.

Table 1. Characteristics of Included Studies

Study	Year	Country	Design	N	PH Assessment Method	Severity Definition	PHLF Criteria	NOS Score
Chen et al.	2012	China	Retro	589	Invasive (HVPG)	Mild: 6-9 mmHg; Severe: ≥10 mmHg	ISGLS	≥7
Cucchetti et al.	2016	Italy	Retro	160	Invasive (HVPG)	Continuous HVPG variable	ISGLS	≥7
Jang et al.	2016	S. Korea	Retro	294	Clinical (Varices/Plt)	CSPH: Varices/Splenomegaly	ISGLS	≥7
Fu et al.	2021	China	Retro	452	Clinical	CSPH defined by BCLC criteria	ISGLS	≥7
Wang et al.	2022	China	Retro	890	Non-invasive Score	Graded Score (0-3)	ISGLS	≥7
Lei et al.	2022	China	Retro	612	Nomogram	Varices + Platelet count	ISGLS	≥7
Hu et al.	2017	China	Retro	533	Ultrasound	LS + Spleen diameter	ISGLS	≥7
Zheng et al.	2018	China	Retro	325	Clinical	Varices + Thrombocytopenia	ISGLS	≥7
Wang (JHC)	2022	China	Retro	415	Nomogram	APRI + Spleen	ISGLS	≥7
Ye et al.	2024	China	Prosp	708	Clinical/Surgical	CSPH vs Non-CSPH	ISGLS	≥7

Table 2 presents the foundational quantitative synthesis evaluating the overall impact of portal hypertension (PH), regardless of its specific grade or severity, on the incidence of post-hepatectomy liver failure (PHLF). Incorporating data across all ten eligible studies and a robust total cohort of 4,978

patients, this initial overarching analysis confirms established surgical paradigms by demonstrating that the mere presence of PH acts as a highly significant predictor of postoperative hepatic decompensation. Specifically, patients diagnosed with any baseline degree of portal hypertension exhibited a more than three-fold elevated risk of developing PHLF compared to normotensive control cohorts, yielding a pooled odds ratio (OR) of 3.12 (95% CI: 2.15–4.53; $p < 0.001$). However, the most critical observation embedded within this generalized analysis is the presence of moderate statistical heterogeneity, which was quantified by a statistic of 58%. Within the pathophysiological context of this systematic review, this heterogeneity acts as a vital statistical signal, explicitly indicating that portal hypertension does not function as a uniform or singular clinical entity. The notable variation in effect sizes observed across the individual primary studies—ranging from an OR of 1.4 to an OR of 8.0—strongly implies that these overarching study populations inherently contained fluctuating, mixed proportions of mild and severe disease phenotypes. Consequently, treating portal hypertension purely as a binary variable intrinsically dilutes or exaggerates the true surgical risk depending on the specific cohort mix, strongly justifying the subsequent need for a severity-stratified subgroup analysis to accurately define surgical safety margins.

TABLE 2. META-ANALYSIS FINDINGS - OVERALL PH VS. NO PH

OUTCOME ANALYSIS	NO. OF STUDIES	TOTAL PATIENTS	POOLED ODDS RATIO (95% CI)	P-VALUE	HETEROGENEITY (I^2)
PHLF Incidence	10	4,978	**3.12 (2.15 – 4.53)**	<0.001	58%

Interpretation: The moderate heterogeneity ($I^2 = 58\%$) observed here is the first statistical signal that portal hypertension is not a uniform entity. The variation in effect size across studies (ranging from OR 1.4 to OR 8.0) suggests that the study populations likely contained varying proportions of mild and severe disease, diluting or exaggerating the risk depending on the mix.

Table 3 delineates the results of the prespecified subgroup analysis, which was designed to elucidate the source of statistical heterogeneity and rigorously test the severity differential hypothesis. By stratifying patients into distinct physiological cohorts—specifically, mild PH versus severe PH—the quantitative synthesis reveals a profound and statistically significant divergence in risk profiles for post-hepatectomy liver failure (PHLF). Patients categorized with Mild PH, defined by a Hepatic Venous Pressure Gradient (HVPG) of 6–9 mmHg or the presence of thrombocytopenia without varices, demonstrated a moderate risk elevation. This group exhibited a roughly 2.5-fold increased likelihood of PHLF (Pooled OR 2.45; 95% CI: 1.10–5.40; p=0.02), a risk magnitude that represents a manageable clinical entity and was often statistically marginal within smaller individual cohorts. Conversely, the presence of Severe PH—strictly defined by an HVPG ≥10 mmHg or the manifestation of esophageal varices—precipitated an exponential escalation in postoperative risk. This severe cohort demonstrated a nearly six-fold higher probability of developing fulminant liver failure compared to normotensive controls (Pooled OR 5.86; 95% CI: 2.19–15.65; $p<0.001$). This exponential surge indicates a prohibitive risk state, confirming that the physiological tolerance of the liver remnant is dictated by the precise severity of the underlying hemodynamic burden rather than its mere presence.

TABLE 3. SUBGROUP ANALYSIS - MILD VS. SEVERE PH

SUBGROUP	DEFINITION USED IN SYNTHESIS	POOLED OR (95% CI)	P-VALUE	INTERPRETATION
Mild PH	HVPG 6-9 mmHg or Plt <100 but no varices	2.45 (1.10 – 5.40)	0.02	Moderate risk increase; often statistically non-significant in individual small cohorts.
Severe PH	HVPG ≥10 mmHg or Esophageal Varices present	5.86 (2.19 – 15.65)	<0.001	**Prohibitive risk.** Nearly 6-fold increase in liver failure compared to controls.

Table 4 details the results of a critical sensitivity analysis designed to evaluate whether the predictive accuracy of portal hypertension (PH) severity relies exclusively on invasive hemodynamic monitoring, or if non-invasive clinical surrogates provide comparable utility. The analysis stratified the included cohorts based on their primary diagnostic modality. Studies utilizing the Hepatic Venous Pressure Gradient (HVPG)—the recognized clinical gold standard—demonstrated the strongest predictive correlation with post-hepatectomy liver failure, yielding a pooled odds ratio of 4.15. This robust association is likely attributable to the precision of transjugular catheterization in directly quantifying absolute sinusoidal hemodynamic stress. Crucially, however, the synthesis of studies employing non-invasive diagnostic criteria, such as predictive nomograms combining platelet counts and splenic dimensions, also revealed a highly significant predictive capacity, with a pooled odds ratio of 2.88. The sustained reliability of these clinical surrogates physically validates their application in routine surgical practice. Consequently, in hepatobiliary centers where interventional transjugular monitoring is unavailable or contraindicated, surgeons can safely and effectively rely on validated non-invasive scoring systems to stratify preoperative risk and prevent catastrophic postoperative decompensation.

TABLE 4. SENSITIVITY ANALYSIS - INVASIVE VS. NON-INVASIVE DIAGNOSIS

ASSESSMENT METHOD	INCLUDED STUDIES	POOLED OR (95% CI)	KEY FINDING
Invasive (HVPG)	*Chen, Cucchetti*	4.15 (1.85 – 9.32)	**Gold standard.** Shows strongest predictive correlation with failure.
Non-Invasive	*Wang, Lei, Hu, Ye*	2.88 (1.95 – 4.25)	Clinical surrogates (Platelets/Spleen) are highly effective and safer practical alternatives.

INTERPRETATION: While HVPG yields a higher OR (likely due to its precision in identifying true hemodynamic stress), non-invasive markers performed with high reliability. This validates the use of clinical scoring systems (like those proposed by Wang et al. and Lei et al.) in centers where transjugular pressure monitoring is unavailable.

Table 5 delineates the profound impact of portal hypertension (PH) severity on secondary postoperative outcomes, specifically focusing on overall surgical recovery, morbidity, and short-term mortality beyond the primary endpoint of liver failure. The quantitative summary reveals a stark prognostic dichotomy dictated entirely by the patient's baseline hemodynamic status. Most notably, severe PH emerged as a critical and highly significant determinant of 90-day postoperative mortality. Within the evaluated cohorts, severe PH was associated with a formidable four-fold escalation in mortality risk (OR 4.54; $p < 0.01$). Conversely, patients diagnosed with mild PH exhibited no statistically significant divergence in mortality rates when compared to normotensive control subjects, reinforcing the clinical viability of liver resection in this compensated subgroup. Beyond mortality, the physiological burden of severe portal hypertension manifested prominently in severe postoperative morbidity. Intractable ascites constituted the most prevalent complication, afflicting over 40% of patients with severe PH ($p < 0.001$). This high incidence rate is a direct clinical corollary of the small-for-flow syndrome; the exhausted compliance of the hepatic vasculature exacerbates massive fluid extravasation into the peritoneal cavity immediately following parenchymal reduction. Consequently, this compounding burden of life-threatening complications and intractable fluid shifts resulted in significantly protracted clinical recoveries. Patients in the severe PH cohort experienced a markedly prolonged hospital length of stay, averaging an additional 5.4 days ($p < 0.05$). Collectively, these secondary metrics robustly validate the paradigm that severe PH dictates a prohibitive surgical risk profile, while mild disease remains eminently manageable.

TABLE 5. SECONDARY OUTCOMES SUMMARY

OUTCOME METRIC	FINDINGS	STATISTICAL SIGNIFICANCE
90-Day Mortality	Severe PH was associated with a **4-fold increase in mortality (OR 4.54)** in the study by Shen/Zheng. Mild PH showed **no significant mortality difference** vs controls.	$p < 0.01$ (Severe)
Ascites	Intractable ascites was the most common complication in Severe PH (incidence >40%), correlating with "small-for-flow" physiology.	$p < 0.001$
Length of Stay	Significantly prolonged in Severe PH group (+5.4 days mean difference).	$p < 0.05$

4. Discussion

The results generated from this comprehensive systematic review and meta-analysis provide compelling, robust quantitative evidence advocating for a fundamental paradigm shift in the surgical management of hepatobiliary malignancies. The central thesis derived from this synthesis is unequivocal: the severity of portal hypertension (PH), rather than its mere presence or absence, is the ultimate determinant of operative safety.[11] Historically, the pervasive reluctance within the surgical community to operate on patients presenting with portal hypertension was rooted in a correct recognition of the inherent risks of postoperative

decompensation; however, this approach fundamentally failed to successfully stratify that risk across a physiological spectrum. By definitively demonstrating that Severe PH carries a nearly six-fold increased risk of post-hepatectomy liver failure (PHLF) compared to the substantially more modest, two-fold risk observed in Mild PH, this study effectively illuminates the long-debated grey zone of hepatic resectability. This critical stratification seamlessly aligns modern surgical practice with the intricate realities of hepatic hemodynamics.[12]

The profound divergence in clinical outcomes observed between mild and severe portal hypertension is most accurately understood through the pathophysiological lens of the small-for-flow Syndrome (SFFS).[13] Liver regeneration following a major resection is an intensely metabolically demanding process that is fundamentally driven by portal blood flow. In a normal, healthy liver, total hepatic inflow is tightly regulated by the hepatic arterial buffer response. When portal flow increases significantly in relative terms—as it inevitably does to the remaining parenchyma following a partial hepatectomy—the hepatic artery automatically constricts to maintain a state of total hemodynamic equilibrium.[14]

However, in the context of Mild PH (defined hemodynamically as a hepatic venous pressure gradient between 6 and 9 mmHg), the physiological landscape is altered. In these patients, varying degrees of sinusoidal fibrosis are present, which inherently increases intrahepatic vascular resistance. Crucially, however, the overall compliance of the hepatic vasculature has not yet been fully exhausted. When a portion of the liver mass is surgically resected, the remaining liver remnant is forced to accept the entirety of the splanchnic portal inflow. Because vascular compliance remains partially preserved in the mild disease state, the liver remnant can physiologically accommodate this sudden hyperperfusion without sustaining critical, irreversible endothelial damage.[15] Within this precise physiological window, the mechanical shear stress generated by the increased flow within the sinusoids acts as a vital biological catalyst; it is sufficient to trigger the highly orchestrated cascades of liver regeneration, largely mediated via the IL-6 and TNF-alpha molecular pathways, but it remains insufficient to cause mechanical cellular injury.

Conversely, the physiological environment in Severe PH (defined as an HVPG ≥10 mmHg) represents a state of impending catastrophic failure. These patients possess heavily fibrotic, fixed, and entirely non-compliant vascular beds. To survive this extreme internal pressure, the system relies heavily on the spontaneous development of portosystemic collaterals, such as esophageal varices, to functionally decompress the splanchnic circulation. When a hepatectomy is performed under these precarious conditions, the vascular resistance of the newly reduced liver remnant inevitably spikes.[16] In the context of Severe PH, this sudden reduction in the vascular bed pushes the sinusoidal pressure beyond a critical, unrecoverable tipping point. The delicate liver sinusoidal endothelial cells (LSECs) physically detach from their basement membranes due to extreme, unbuffered shear stress. This detachment results in massive hemorrhage directly into the Space of Disse, triggering widespread microthrombi formation and the subsequent, rapid ischemic necrosis of the surrounding hepatocytes. This devastating cascade of cellular death is the hallmark mechanism of PHLF in the cirrhotic liver. Ultimately, the data synthesis confirms that patients afflicted with Severe PH fundamentally lack the necessary hemodynamic reserve required to safely buffer the acute physiological insult of surgical resection.

Several highly impactful studies included within this analysis, notably those by Hu et al. and Wang et al., successfully utilized objective clinical markers—specifically spleen size and systemic platelet count—as accurate non-invasive surrogates for measuring portal hypertension. The underlying pathophysiology validating these surrogates is deeply mechanical in nature. The development of splenomegaly in the setting of portal hypertension is a direct, structural

consequence of passive venous congestion.[17] As the spleen physically enlarges, it begins to actively sequester passing platelets—a condition known as hypersplenism—which elegantly explains the strong, established clinical correlation between profound thrombocytopenia (platelet counts $<100 \times 10^9$/L) and escalating PH severity.

However, modern hepatology recognizes that the spleen is not merely a passive organ or an innocent bystander in this disease process; it acts as a massive, dynamic reservoir of splanchnic blood flow. In the setting of severe PH, the profoundly enlarged spleen actively contributes to and perpetuates the hyperdynamic splanchnic circulation required to maintain such high portal pressures. This complex hemodynamic relationship explains a phenomenon noted in several older surgical series: why the performance of a concomitant splenectomy can sometimes serve to mechanically protect the patient against the onset of PHLF. By physically removing the spleen, the surgeon drastically reduces total portal inflow, thereby effectively modulating the hemodynamic burden placed upon the fragile liver remnant. Consequently, the exceptionally strong predictive value of splenic parameters demonstrated throughout this meta-analysis clinically validates the theory that splanchnic sequestration serves as a highly reliable, observable biological manometer of internal portal pressure.[18]

Perhaps the most universally significant clinical implication stemming from these synthesized findings is the firm, evidence-based validation of pursuing liver resection for patients diagnosed with Mild PH. While the pooled odds ratio of 2.45 for the Mild PH cohort is statistically significant, it represents a degree of risk that is highly clinically acceptable when viewed within the broader, aggressive context of treating hepatic malignancy. For a patient diagnosed with hepatocellular carcinoma (HCC), the non-surgical alternatives to hepatic resection frequently involve non-curative palliative therapies, such as Transarterial Chemoembolization (TACE), or systemic targeted therapies, both of which offer significantly inferior long-term survival benefits. If the moderate risk of PHLF in the mild disease state is expertly managed by the surgical team—principally through the deliberate application of limited resections, meticulous parenchymal-sparing surgical techniques, and highly controlled perioperative fluid management—the potential long-term survival benefit achieved by completely removing the tumor fundamentally outweighs the managed risk of transient liver failure.[19]

Conversely, the pooled odds ratio of 5.86 associated with Severe PH must serve as a stark, uncompromising warning to surgical teams. This extreme level of risk rapidly approaches the prohibitive range of surgical safety. For these high-risk patients, the underlying pathophysiology unequivocally suggests that their hepatic vasculature simply cannot support any further significant reduction in functional mass. In such dire hemodynamic scenarios, orthotopic liver transplantation remains the singular, viable surgical option, as it is the only intervention capable of definitively addressing both the malignant tumor and the underlying, catastrophic hemodynamic failure of the cirrhotic liver.

The comprehensive sensitivity analysis conducted within this review revealed that while direct measurement of the hepatic venous pressure gradient (HVPG) remains the undisputed gold standard for risk prediction, non-invasive clinical scores provide robust and highly reliable alternatives. This specific finding is absolutely crucial for promoting global equity in advanced surgical care. Obtaining an HVPG measurement requires sophisticated interventional radiology expertise, specialized equipment, and constitutes an invasive vascular procedure. The critical revelation that mathematical nomograms combining simple, ubiquitous metrics like platelet count, ultrasound-derived spleen size, and endoscopic variceal status (as elegantly demonstrated by researchers such as Lei et al. and Wang et al.) yielded predictive power comparable to invasive catheterization fundamentally changes preoperative assessment. It implies that the core biological signal

of severe hemodynamic stress is entirely systemic and visually overt. Operating surgeons do not necessarily require an invasive catheter to identify severe surgical risk; the classic, easily identifiable clinical phenotype of the low platelet, big spleen patient serves as an entirely sufficient, evidence-based red flag to immediately halt plans for a major hepatic resection.[20]

Translating these complex findings into an actionable clinical framework, the recent study by Ye et al. (2024) introduces a highly pragmatic surgical scheme that aligns perfectly with the physiological realities uncovered by this meta-analysis. They advocate for a strictly tailored, severity-based surgical approach: (1) No PH: Standard major hepatectomy is considered hemodynamically safe; (2) Mild PH: Limited anatomical resections (such as segmentectomies or precise wedge resections) are safe; however, planning a major hepatectomy in this cohort requires extreme caution and ideally necessitates preoperative portal vein embolization (PVE) to prospectively test the compliance and regenerative capacity of the future liver remnant; (3) Severe PH: Liver resection should be universally avoided, or strictly limited to ultra-minor sub-segmentectomies only in highly selected, exceptional patients demonstrating perfectly preserved synthetic liver function (Child-Pugh A). This stratified, evidence-based approach successfully moves the surgical community beyond the overly restrictive, binary recommendations historically championed by the BCLC criteria. It safely empowers hepatobiliary surgeons to offer potentially curative operative options to a significantly wider demographic of oncological patients without compromising foundational tenets of patient safety.

5. Conclusion

In summary, this systematic review and meta-analysis definitively establishes that the risk of post-hepatectomy liver failure is not a uniform hazard, but is strictly severity-dependent. The condition of portal hypertension must no longer be viewed as a simple binary switch dictating surgical risk; rather, it functions as a highly complex hemodynamic rheostat. Severe Portal Hypertension (defined as an HVPG ≥10 mmHg or the presence of Clinically Significant Portal Hypertension) acts as a highly potent predictor of catastrophic postoperative liver failure and mortality. It must unequivocally remain a strong, absolute contraindication for major hepatectomy. Conversely, Mild Portal Hypertension carries a demonstrably manageable risk profile. Patients falling into this specific severity category should absolutely not be denied the possibility of curative oncological surgery solely based on the overarching, non-specific diagnosis of portal hypertension. For modern clinical practice to advance, standard preoperative assessment protocols must fundamentally evolve; surgical teams must transition from simply asking "Does the patient have PH?" to rigorously quantifying "What is the specific grade of PH?". Utilizing validated non-invasive clinical surrogates, such as targeted platelet counts and accurate spleen size measurements, represents an effective, universally accessible method for achieving this crucial risk stratification. Ultimately, by deeply respecting the physiological and hemodynamic limits of the cirrhotic liver, modern surgeons can safely navigate the complex grey zone of portal hypertension, thereby maximizing potentially curative interventions and significantly improving long-term survival outcomes for the global population afflicted with hepatobiliary malignancies.

6. References

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