Effect of vascular resection for perihilar cholangiocarcinoma: A systematic review and meta-analysis

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Objective: To evaluate the effect of vascular resection (VR), including portal vein resection (PVR) and hepatic artery resection (HAR), on short- and long-term outcomes in patients with perihilar cholangiocarcinoma (PHC).

Background: Resection surgery and transplantation are the main treatment methods for PHC that provide a chance of long-term survival. However, the efficacy and safety of VR, including PVR and HAR, for treating PHC remain controversial.

Methods: This study was registered at the International Prospective Register of Systematic Reviews (CRD42020223330). The EMBASE, PubMed, and Cochrane Library databases were used to search for eligible studies published through November 28, 2020. Studies comparing short- and long-term outcomes between patients who underwent hepatectomy with or without PVR and/or HAR were included. Random- and fixed-effects models were applied to assess the outcomes, including morbidity, mortality, and R0 resection rate, as well as the impact of PVR and HAR on long-term survival.

Results: Twenty-two studies including 4091 patients were deemed eligible and included in this study. The meta-analysis showed that PVR did not increase the postoperative morbidity rate (odds ratio (OR): 1.03, 95% confidenceinterval (CI): 0.74-1.42, P = 0.88) and slightly increased the postoperative mortality rate (OR: 1.61, 95% CI: 1.02-2.54, P = 0.04). HAR did not increase the postoperative morbidity rate (OR: 1.32, 95% CI: 0.83-2.11, P = 0.24) and significantly increased the postoperative mortality rate (OR: 4.20, 95% CI: 1.88-9.39, P = 0.0005). Neither PVR nor HAR improved the R0 resection rate (OR: 0.70, 95% CI: 0.47-1.03, P = 0.07; OR: 0.77, 95% CI: 0.37-1.61, P = 0.49, respectively) or long-term survival (OR: 0.52, 95% CI: 0.35-0.76, P = 0.0008; OR: 0.43, 95% CI: 0.32-0.57, P < 0.00001, respectively).

Conclusions: PVR is relatively safe and might benefit certain patients with advanced PHC in terms of long-term survival, but it is not routinely recommended. HAR results in a higher mortality rate and lower overall survival rate, with no proven benefit.

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Abstract

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Introduction

Cholangiocarcinoma is a rare adenocarcinoma that originates from the epithelial cells of bile ducts. Perihilar cholangiocarcinoma (PHC) is the main type of cholangiocarcinoma, accounting for 50% to 67% of cases (1-3). The prognosis of PHC is generally poor because of its anatomical location and aggressive biology. Resection surgery and transplantation are the main treatment methods for PHC that provide a chance of long-term survival (4). The median overall survival (OS) of patients with PHC who undergo curative resection varies from 19 to 39 months (5).

The objective of surgery is to achieve R0 resection. However, PHC usually adheres to or is surrounded by vessels, such as the portal vein or hepatic artery, which makes curative resection difficult to achieve. Therefore, to achieve R0 resection, vascular resection (VR) can be performed during the operation. It has been reported that the proportion of VR during PHC surgery ranges from 15% to 38% (6-10). VR refers to portal vein resection (PVR), hepatic artery resection (HAR) or both. Although VR is performed in many circumstances, controversy still

exists. For PVR, portal vein involvement by PHC was previously considered a sign of unresectability (11). With the development of surgical techniques, PVR has been performed at several clinical centers (12-14). However, the efficacy and safety of PVR for PHC are controversial. Ebata et al. (12) reported that combined portal vein and liver resection can offer long-term survival to some selected patients with advanced PHC. However, Hoffmann et al. (15) found that PVR greatly increased the perioperative morbidity rate and had no benefit for PHC in terms of the oncologic outcomes. In addition, surgical resection with simultaneous HAR for PHC is a demanding procedure (13, 16-18). Similar to PVR, attitudes toward HAR remain inconsistent. Miyazaki et al. (19) reported that HAR had no beneficial effect on prognosis and led to an increase in the perioperative morbidity and mortality rates; thus, the use of HAR may not be justified. Nagino et al. (20) demonstrated that major hepatectomy with HAR could offer a better chance of long-term survival in selected PHC patients.

To date, several meta-analyses have been performed to evaluate the efficacy and safety of VR for PHC patients; however, the results of these studies were inconsistent. By including 2457 patients, Abbas et al. (21) found that PVR may result in survival benefits for some patients with advanced PHC, which was similar to Chen's study (22). However, Wu et al. (23) and Yu et al. (24) found that PVR increases postoperative mortality and morbidity and worsens long-term survival; thus, surgical decisions should be made cautiously. For HAR, Abbas et al. (21) and Yu et al. (24) found that HAR is associated with increased mortality and morbidity without proven survival benefits for PHC patients. In a recent guideline for cholangiocarcinoma from Italy (25), PVR was recommended when there was unilateral portal vein invasion. However, the

recommendation for PVR in this study was limited with a low quality of evidence due to the small number of related studies. Further, hardly any attention was given to HAR in the Italian study. Given these conflicting recommendations, the efficacy and safety of PVR and HAR for treating PHC patients need to be further clarified.

The aim of this study was to systematically review and statistically evaluate the effect of VR, including PVR and HAR, on short- and long-term outcomes in PHC patients.

Materials and methods

Search strategy

This meta-analysis was performed in accordance with the guidelines and review protocols of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement (26). This study was registered at the International Prospective Register of Systematic Reviews (CRD42020223330). Two authors (Y.L. and G.B.L.) conducted a literature search independently using the EMBASE, PubMed, and Cochrane Library databases up to November 28, 2020. The search terms were “hilar cholangiocarcinoma”, “Klatskin’s tumour”, “hepatectomy”, “hepatic artery”, “portal vein” and “vascular resection”. Two authors (Y.L. and G.B.L.) independently reviewed the titles, abstracts and full texts for eligibility on the basis of predesigned inclusion and exclusion criteria. Disagreements were settled through consensus or by the judgment of a third author (Z.W.L). A description of the search strategy is shown in our evidence report (Supporting Table S2). To avoid omission of other studies that were not indexed, the reference lists of the included studies were also reviewed.

Eligibility criteria

106 The inclusion criteria were as follows: (1) humans were used as the research objects; (2)
107 full-text articles published in English; (3) all included subjects were diagnosed with PHC; and
108 (4) all enrolled patients underwent curative surgery, with or without resection of the portal vein
109 or hepatic artery. Records were excluded if they were classified as a case report or letter or if the
110 full text was not available. Studies with inadequate data were excluded. Studies including other
111 malignancies, such as gallbladder cancer, hepatic carcinoma or distal cholangiocarcinoma, were
112 also excluded. In the case of duplicate studies, the latest or most integrated data were chosen for
113 analysis.

114 **Data extraction**

115 Two independent reviewers extracted the following attainable data from the included
116 studies: first author, country, year of publication, inclusive period of study, number of patients,
117 Bismuth-Corlette stage, intraoperative blood loss, 90-day mortality, total morbidity, staging of
118 Union for International Cancer Control Unites (UICC), vascular invasion rate, lymph node
119 metastasis rate, median survival time, 1-, 3-, and 5-year OS, 1-, 3-, and 5-year disease-free
120 survival (DFS), and hazard ratios (HRs) with 95% confidence intervals (CIs) for OS. HRs were
121 obtained in two ways: (1) acquired directly from the article or (2) obtained from Kaplan-Meier
122 survival curves following the methods reported by Tierney et al. (27) and using Engauge
123 Digitizer version 4.1 (SourceForge, Boston, USA).

124 **Quality assessment**

125 The study quality was assessed using the 9-score system of the Newcastle-Ottawa Scale
126 (NOS) (28). The assessment was based on three aspects: (I) selection; (II) comparability; and

(III) outcome. A follow-up duration of at least 2 years was considered adequate. The score provides an assessment of bias for the included studies.

Statistical analysis

The primary purpose of this study was to evaluate the effect of PVR and HAR on long-term outcomes in PHC patients, and the statistical indicators included 1-, 3-, and 5-year OS and 1-, 3-, and 5-year DFS. The secondary purpose of this study was to evaluate the safety of PVR and HAR for PHC patients, and the statistical indicators included 90-day mortality, overall morbidity and the posthepatectomy liver insufficiency (PHI) rate. The 90-day mortality rate included the number of patients who died within 90 days after surgery but excluded the number of patients who died during the operation. Overall morbidity was recorded according to the types of postoperative complications, including intra-abdominal abscess, PHI, bile leakage, vascular complications, etc. (29). Since there was no uniform definition of PHI in the included studies, the PHI rate could only be determined based on individual study reports.

Dichotomous categorical variables were analyzed using the Mantel–Haenszel test. Continuous categorical variables were analyzed using the inverse variance test. The results were expressed using forest plots and presented as odds ratios (ORs) and mean differences (MDs) and 95% CIs. Heterogeneity among studies was assessed using the Cochrane Q-test and P-value. Statistically significant heterogeneity was defined as $I^2 > 50\%$ or a chi-squared P-value < 0.1. When heterogeneity was significant, a random-effects model was applied; otherwise, a fixed-effects model was used. A “leave-one-out” sensitivity analysis was conducted to identify the source of heterogeneity when significant heterogeneity was present. Funnel plots were used to

148 evaluate the presence of significant publication bias.

149 The data syntheses in this meta-analysis were performed using RevMan 5.4 and R software
150 (version 4.0.3). A two-sided $P < 0.05$ was deemed to indicate statistical significance.

151 **Results**

152 **Literature search**

153 As shown in Figure 1, 1693 records were incipiently included in our search. After the
154 removal of duplicate publications, 1174 studies remained for title and abstract screening, and 642
155 records and 422 records were excluded based on title reading and abstract screening,
156 respectively. Subsequently, 110 full texts were assessed for eligibility. Among them, 88 records
157 were further excluded for the following reasons: not in English (n = 7); abstract form only (n =
158 38); contained other malignancies or benign tumors (n = 2); reconstruction or no reconstruction
159 as comparison item (n = 2); inadequate data (n = 7); and case reports (n = 32). Finally, 22 studies
160 (6-10, 16, 19, 20, 30-43) including 4091 PHC patients were eligible for this systematic review
161 and meta-analysis.

162 **Study characteristics**

163 Study level characteristics are shown in Table 1. All studies were cohort studies published
164 between 1997 and 2020. The total number of patients enrolled was 4,091, and the sample
165 capacities of these studies ranged from 28 to 787 patients. In this meta-analysis, the rates of PVR
166 during curative surgery for PHC varied from 11% to 73%, with an average rate of 27% (6-10, 16,
167 19, 20, 30-43). Compared to PVR, HAR was relatively rare and performed in only 10% of all
168 enrolled patients.

90-day mortality

Eleven studies provided data on 90-day mortality (6, 9, 10, 19, 30, 31, 34, 39, 41-43). The meta-analysis indicated that VR could increase postoperative mortality (OR: 1.66, 95% CI: 1.11-2.48, P = 0.01) (Fig. 2A). A significant difference also existed between the PHC patients with and without PVR, and the pooled OR (95% CI) was 1.61 (1.02, 2.54), with P = 0.04 (Fig. 2B). For patients with and without HAR, the pooled result showed significantly higher mortality among patients who underwent HAR (OR: 4.20, 95% CI: 1.88-9.39, P = 0.0005) (Fig. 2C).

Overall morbidity

Eleven studies containing 2189 patients provided data on overall morbidity (7-10, 16, 19, 32, 39, 41-43). The meta-analysis indicated no difference in morbidity between the patients with and without VR (OR: 1.04, 95% CI: 0.86-1.26, P = 0.68) (Fig. 3A). A similar result was also found when comparing overall morbidity between patients with and without PVR (OR: 1.03, 95% CI: 0.74-1.42, P = 0.88) (Fig. 3B). Furthermore, the meta-analysis indicated that HAR did not increase postoperative morbidity (OR: 1.32, 95% CI: 0.83-2.11, P = 0.24) (Fig. 3C).

Posthepatectomy liver insufficiency

To further explore the impact of VR on PHI, we analyzed this complication alone. Ten studies provided data on PHI (7, 8, 10, 16, 31, 32, 34, 39, 42, 43). The meta-analysis indicated a significantly higher PHI rate among patients with VR (OR: 1.77, 95% CI: 1.37-2.28, P < 0.00001) (Fig. 4A). A similar result was obtained when comparing the PHI rate between patients with and without PVR (OR: 1.60, 95% CI: 1.19-2.16, P = 0.002) (Fig. 4B). For patients with and without HAR, the pooled result showed a significantly higher PHI rate among patients who

underwent HAR (OR: 1.77, 95% CI: 1.23-2.54, P = 0.002) (Fig. 4C).

R0 margin status

Twelve studies containing 2294 patients reported the difference in the R0 margin status (6-9, 16, 30-32, 34, 36, 39, 42). The meta-analysis indicated no difference in the R0 resection rate between patients with and without VR (OR: 0.71, 95% CI: 0.50-1.01, P = 0.06) (Fig. 5A). The analysis between patients with and without PVR showed no statistically significant difference (OR: 0.70, 95% CI: 0.47-1.03, P = 0.07) (Fig. 5B). For patients with and without HAR, the meta-analysis demonstrated a similar outcome (OR: 0.77, 95% CI: 0.37-1.61, P = 0.49) (Fig. 5C).

Long-term survival

Eighteen studies provided data on 1-, 3-, and 5-year OS and DFS (7-10, 16, 19, 20, 31, 32, 34-37, 39-43). The pooled results are shown in Table 2. The pooled analysis showed that patients with VR had worse long-term survival. The meta-analysis showed that the 3- and 5-year OS rates were significantly lower in patients with VR than in those without VR (P < 0.00001), while the 1-year OS was not statistically significant different (OR: 0.94, 95% CI: 0.54-1.64, P = 0.83). In addition, compared with those without PVR, patients with PVR had worse long-term survival (1-year OS: OR: 0.77, 95% CI: 0.49-1.20, P = 0.25; 3-year OS: OR: 0.45, 95% CI: 0.36-0.57, P < 0.00001; 5-year OS: OR: 0.52, 95% CI: 0.35-0.76, P = 0.0008). For patients with and without HAR, the pooled result showed significantly worse long-term survival among patients who underwent HAR (1-year OS: OR: 0.64, 95% CI: 0.11-3.69, P = 0.62; 3-year OS: OR: 0.55, 95% CI: 0.41-0.74, P < 0.0001; 5-year OS: OR: 0.43, 95% CI: 0.32-0.57, P < 0.00001). Meanwhile, there was no difference in the 1-, 3-, or 5-year DFS between patients with and without VR (OR:

1.54, 95% CI: 0.92-2.57, P = 0.10; OR: 1.00, 95% CI: 0.59-1.71, P = 0.99; OR: 0.99, 95% CI: 0.42-2.35, P = 0.98). Furthermore, eight studies provided data on the HR for OS (7, 8, 20, 30, 35, 37, 40, 42). The pooled analysis indicated that VR was relevant to a shorter OS (HR: 1.44, 95% CI: 1.25-1.67, P < 0.001) (Fig. 6A).

Intraoperative blood loss

Eight included studies provided data on intraoperative blood loss (7, 9, 16, 19, 31, 39, 42, 43), and the mean volume of blood loss was significantly greater when VR was performed (MD = 433.66, 95% CI: 91.69–775.63, P = 0.01) (Fig. 6B).

UICC staging

Five studies provided data on UICC staging (8, 9, 32, 34, 42). The proportion of patients diagnosed at UICC stage T3-T4 ranged from 48% to 100% and from 15% to 51% in patients with and without VR, respectively. The meta-analysis indicated a higher UICC staging among patients with VR (OR: 4.72, 95% CI: 1.05-21.12, P = 0.04) (Fig. 6C).

Vascular invasion

Vascular invasion was reported in eight studies (9, 10, 19, 30, 32, 34, 39, 42), and the positive invasion rate ranged from 31% to 88% and from 0% to 86% in patients with and without VR, respectively. The mean vascular invasion rate was 39% in patients without VR, 85% in patients with PVR, and 49% in patients without HAR. Patients who underwent VR had a higher vascular invasion rate (OR: 2.31, 95% CI: 1.70-3.13, P < 0.00001) (Fig. 6D).

Lymph node metastasis

Lymph node metastasis was reported in ten of the included studies (10, 16, 19, 31, 32, 34,

232 39-42). The mean lymph node metastasis rates in patients with and without VR were 55.5% and
233 35.8%, respectively. The mean lymph node metastasis rates in patients with PVR and HAR were
234 52.1% and 62.2%, respectively. As shown in Fig. 7A-7C, the meta-analyses revealed that
235 patients with VR, either PVR or HAR, had a higher lymph node metastasis rate than those
236 without VR (OR: 2.20, 95% CI: 1.80-2.69, $P < 0.00001$; OR: 2.07, 95% CI: 1.64-2.61, $P <$
237 0.00001; OR: 2.68, 95% CI: 1.95-3.68, $P < 0.00001$, respectively).

238 **Discussion**

239 PHC is a rare malignancy that accounts for less than 2% of total human malignancies (44).
240 The tumor often invades the bile duct through the wall and extends to the periductal tissues and
241 adjacent structures (45). Given the anatomical location and aggressive biological characteristics
242 of PHC, most PHC patients are in advanced stages when examined. In fact, despite the use of
243 various imaging tests to assess the tumor status, 40-50% of PHC patients are found to have
244 unresectable tumors during the operation (46, 47). Among them, involvement of the main portal
245 vein, bilateral portal vein and/or hepatic artery branches are important reasons for the
246 unresectability of tumors (46).

247 Surgical resection for PHC is highly technically demanding and could be challenging for
248 hepatobiliary surgeons (48). Due to the changes in surgical philosophy and other aspects, radical
249 surgery for PHC has also undergone great changes. Currently, curative surgery for PHC includes
250 major hepatectomy, bile duct excision, locoregional lymph node dissection, and combined
251 caudate lobectomy (38, 49, 50). Due to local anatomical considerations, vascular invasion is not
252 uncommon in PHC. According to the included studies, the rate of vascular invasion confirmed

by histology ranges from 20% to 87% (9, 10, 19, 30, 32, 34, 39, 42). Furthermore, when the vessel can be reconstructed after resection, vascular invasion is no longer an absolute contraindication for PHC surgery. However, while VR (including PVR and HAR) has been performed at many clinical centers, their effect in patients with PHC remains controversial, and previous comparative studies have reported inconsistent results (19, 30, 38, 49, 51-53).

Due to the complexity of biliary and hepatic resection, the postoperative morbidity rate for PHC is significant, ranging from 36% to 81% (7-10, 16, 19, 32, 41-43). This meta-analysis showed that neither PVR nor HAR increased the incidence of postoperative complications (all $P > 0.05$). PHI seriously affects the patient's recovery and prognosis. The meta-analysis indicated that patients with PVR had a significantly higher incidence of PHI, and a similar result could be found when comparing patients with and without HAR. The reasons for these findings are that PVR and/or HAR may prolong the period of liver ischemia during vascular reconstruction, which may aggravate ischemic damage to the remnant liver (54). To reduce the incidence of PHI, preoperative portal vein embolization (PVE), which was first proposed by Kinoshita et al. (55) and Makuuchi et al. (56) in the 1980s, has been widely performed in many centers before surgery for PHC.

Whether PVR increases postoperative mortality remains controversial. The portal vein bifurcation lies directly posterior to the hepatic duct confluence and therefore frequently shows tumor involvement. To achieve R0 resection, curative surgery might therefore require concomitant resection of the portal vein bifurcation. Most studies have indicated that patients with PVR have a higher mortality rate than those without PVR, ranging from 0% to 19% and

from 0% to 16%, respectively (6, 7, 19, 30, 31, 34, 39, 41, 43), but other studies have shown inconsistent results. In 2014, Tamoto et al. (42) reported 0% mortality in patients with PVR and 15% mortality in patients without PVR, which was similar to She's study (9). This meta-analysis showed that PVR might increase mortality. However, the mean mortality rate was 4.0% in patients without PVR and 6.2% in patients with PVR. These results showed that although PVR increased mortality, it was to an acceptable level. Compared to PVR, the effect of HAR on mortality was similar. All five included studies showed that patients with HAR had a higher mortality rate than those without HAR. The meta-analysis showed that HAR greatly increased mortality ($P = 0.0005$). The mean mortality rate was 1.7% in patients without HAR and 5.4% in patients with HAR. Consequently, it seems that HAR is more likely to significantly increase mortality.

The resection margin is a vital prognostic factor for PHC surgery. In most surgical series that have included patients treated with hepatectomy combined with extrahepatic biliary resection, an R0 margin was obtained in 55-90% of patients (6-9, 16, 30-32, 34, 36, 39, 42). Although R1 resection has shown some benefit to survival when compared to nonoperative treatment, R0 margins should be achieved as far as possible (57-59). This meta-analysis showed no difference in the R0 resection rate between patients with and without PVR, and a similar result could be found when comparing patients with and without HAR. The mean R0 resection rates were 76%, 69% and 70% in patients without VR, with HAR and with PVR, respectively. Although patients with VR had disease of a more advanced stage, the validity of VR in terms of obtaining a better surgical margin still should be considered in such patients. Combined with

previous studies, we seem to be able to conclude that VR (including PVR and HAR) can achieve a higher R0 resection rate because these patients can only achieve R1 resection or even R2 resection if VR is not performed. Of course, this conclusion needs to be further verified.

The results of the survival analysis showed that patients with PVR had poorer OS than those without VR, although the 1-year OS was not statistically significant different. These results seem to imply that the surgical oncologic outcome of patients with PVR is worse than that of patients without PVR. However, subsequent analysis found that patients with PVR had more advanced disease and higher positive lymph node metastasis, both of which are adverse prognostic factors (60). Furthermore, some studies have shown that patients with PVR have a significant survival advantage over unresectable patients (9, 20, 32). Considering that PVR did not increase the postoperative morbidity rate and slightly increased the mortality rate, it seems that PVR is acceptable for selected patients. At present, there is no uniform conclusion on the selection of suitable patients for PVR. The invasion of both portal branches strongly contraindicates hepatic resection and this has been sustained by different guidelines (61-63). In addition, patients with distant metastatic disease or involvement of aortocaval or truncal nodes are unlikely to benefit from resection (64). Therefore, we suggest that PVR could be performed in PHC patients with a preoperative or intraoperative finding of unilateral portal vein invasion and without a distant metastatic event. Besides, considering the increased incidence of PHI associated with PVR, surgical decision should be made cautiously according to the physical condition of patients. However, the meta-analysis showed that HAR did not increase postoperative morbidity and achieved an acceptable R0 resection rate but significantly increased postoperative mortality.

316 Meanwhile, for long-term survival, the 1-, 3-, and 5-year OS rates in patients with HAR were
317 59.57%, 43.90% and 27.81%, respectively, and 64.71%, 54.12% and 46.75% in patients without
318 HAR, respectively. These results showed that HAR has not been demonstrated to benefit PHC
319 patients in terms of safety and long-term survival.

320 High heterogeneity was found in the analysis of several covariates, especially R0 margin
321 status ($I^2 = 70$, $P = 0.009$), intraoperative blood loss ($I^2 = 89\%$, $P < 0.00001$) and UICC staging
322 ($I^2 = 85\%$, $P < 0.0001$). For R0 margin status, through a "leave-one-out" sensitivity analysis, we
323 found that one study (7) may have contributed to the heterogeneity. In Mizuno's study, patients
324 without VR had earlier tumor statuses, with a significantly lower proportion of T4 stage patients
325 than those with VR (either PVR or HAR), at 25% versus 85%, respectively. Therefore, the R0
326 resection rate in patients without VR was markedly higher than in those with VR, either PVR or
327 HAR (84.7%, 68.8% and 63.7%, respectively). Moreover, the sample size of the study was
328 extremely large, and therefore the effect on heterogeneity was large. After removing Mizuno's
329 study, similar results were obtained that neither PVR nor HAR improved the R0 resection rate.
330 In addition, for the high heterogeneity found in the analysis of intraoperative blood loss, the
331 possible reasons were as follows: 1) the year of publication of the included studies ranged from
332 1997 to 2020, and advances in surgical techniques across this relatively long period could lead to
333 large differences in intraoperative parameters, such as intrahepatic blood loss; 2) surgical
334 experience varies among clinical centers, and intraoperative blood loss thus varies among
335 different centers; and 3) although all PHC patients underwent hepatectomy, the extent of liver
336 resection varied depending on the location of the tumor, thus resulting in a difference in

intraoperative blood loss. Likewise, for the obvious heterogeneity found in the analysis of UICC staging, after checking the details, we found that two studies (8, 32) may have contributed to the heterogeneity. In these studies, a much higher proportion of patients with VR were diagnosed at UICC stage T3-T4.

This review has several limitations that should be mentioned. First, there were no randomized trials on this topic, and all eligible studies were observational studies. Second, a large number of studies were excluded due to either inadequate data or the lack of an effective comparison group. Third, data were missing in a few of the included studies, and the statistical power was relatively low. Last, the retrospective study design has inherent limitations, and inherent information bias in the original studies can always cause problems.

Conclusions

In conclusion, PHC is an uncommon and aggressive disease with a poor long-term prognosis. PVR is relatively safe and might confer benefits to certain patients with advanced PHC in terms of long-term survival. HAR is related to increased mortality and has not been demonstrated to benefit long-term survival, which should be considered before performing this procedure. Data from randomized controlled trials are required to further prove the findings in this study.

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Table 1(on next page)

Studies included in the current meta-analysis

Table 1 Studies included in the current meta-analysis

Study (Year)	Country	Period	No of Patients	Male, %	Age (median or mean)	Blood loss (ml)	90-day mortality,	Overall morbidity,	R0, %	Hepatic insufficiency,
Wang et al. (2015)	China	2005-2012	PVR:16	4(25%)	53	980±511	0(0%)	6(38%)	NR	0(0%)
			HAR:24	18(75%)	60	1175±713	1(4%)	10(42%)	NR	1(6%)
			No VR:114	70(61%)	57	527±596	4(4%)	40(35%)	NR	2(2%)
Dumitracu et al. (2017)	Romania	1996-2014	PVR:21	17(81%)	56	3475±2925	2(10%)	NR	15(71%)	4(19%)
			No VR:102	53(52%)	59	400±2483	5(5%)	NR	80(78%)	27(26%)
Ebata et al. (2003)	Japan	1979-2000	PVR:52	35(67%)	60.3	NR	NR	44(85%)	36(69%)	14(27%)
			No VR:108	81(75%)	60.2	NR	NR	85(79%)	95(88%)	21(19%)
Nagino et al. (2010)	Japan	1997-2009	PVR:92	NR	60	NR	NR	NR	NR	NR
			HAR:62	NR	60	NR	NR	NR	NR	NR
			No VR:211	NR	NR	NR	NR	NR	NR	NR
Hoffmann et al. (2015)	Germany	2001-2012	PVR:21	9(43%)	65	NR	4(19%)	NR	12(57%)	12(57%)
			No VR:39	28(72%)	68	NR	5(13%)	NR	23(59%)	17(44%)
Peng et al. (2016)	China	2005-2012	HAR:26	18(69%)	59	327 ± 146	NR	15(58%)	22(85%)	5(19%)
			No VR:35	20(57%)	63	400 ± 209	NR	15(43%)	28(80%)	3(9%)
Schimizzi et al (2017).	United States	1998-2015	PVR:19	10(53%)	62	NR	NR	13(68%)	14(74%)	3(16%)
			HAR:12	6(50%)	52	NR	NR	6(50%)	8(67%)	0(0%)
			No VR:170	69(41%)	66	NR	NR	114(67%)	119(70%)	7(4%)
Hemming et al. (2011)	United States	1999-2010	PVR:42	NR	NR	NR	NR	NR	NR	NR
			No VR:53	NR	NR	NR	NR	NR	NR	NR

Study (Year)	Country	Period	No of Patients	Male, %	Age (median or mean)	Blood loss (ml)	90-day mortality,	Overall morbidity,	R0, %	Hepatic insufficiency,
Tamoto et al. (2014)	Japan	2005-2009	PVR:36	25(69%)	68.5	1902±1287	0(0%)	21(58%)	28(78%)	2(6%)
			No VR:13	10(77%)	68	1980±867	2(15%)	10(77%)	12(92%)	2(15%)
Higuchi et al. (2018)	Japan	2000-2016	PVR:56	38(68%)	69.5	NR	3(5%)	NR	35(63%)	NR
			HAR:19	13(68%)	67.0	NR	3(16%)	NR	12(63%)	NR
			No VR:174	126(72%)	70.0	NR	3(2%)	NR	115(66%)	NR
Lee et al. (2009)	Korea	2001-2008	PVR:38	NR	NR	NR	NR	NR	NR	NR
			HAR:5	NR	NR	NR	NR	NR	NR	NR
			No VR:259	NR	NR	NR	NR	NR	NR	NR
Igami et al (2009)	Japan	2001-2008	PVR:69	NR	NR	NR	NR	NR	NR	NR
			HAR:53	NR	NR	NR	NR	NR	NR	NR
			No VR:176	NR	NR	NR	NR	NR	NR	NR
She et al. (2020)	China	1989-2016	PVR:17 HAR:5	14(64%)	57.0	2875±1875	1(5%)	11(50%)	10(45%)	NR
			No VR:68	49(72%)	67.5	1465±4925	11(16%)	41(60%)	38(56%)	NR
Kondo et al. (2004)	Japan	1999-2002	PVR:6	NR	NR	NR	NR	NR	NR	NR
			HAR:8	NR	NR	NR	NR	NR	NR	NR
			No VR:26	NR	NR	NR	NR	NR	NR	NR
Jong et al. (2012)	United States	1984-2010	PVR:51	29(57%)	66	NR	9(18%)	NR	34(67%)	NR
			No VR:173	100(58%)	66	NR	26(15%)	NR	115(66%)	NR
Miyazaki et al. (2007)	Japan	1981-2004	PVR:34	18(53%)	64	1975 ± 1474	3(9%)	13(38%)	NR	NR
			HAR:9	7(78%)	59	1726 ± 1253	3(33%)	7(78%)	NR	NR
			No VR:118	77(65%)	65	1523 ± 1147	5(4%)	42(36%)	NR	NR

Study (Year)	Country	Period	No of Patients	Male, %	Age (median or mean)	Blood loss (ml)	90-day mortality,	Overall morbidity,	R0, %	Hepatic insufficiency,
Muñoz et al. (2002)	United States	1990-2001	PVR:10	7(70%)	61	NR	NR	NR	NR	NR
			No VR:18	5(28%)	66	NR	NR	NR	NR	NR
Klempnauer et al. (1997)	Germany	1971-1995	PVR:40	NR	NR	NR	NR	NR	30(73%)	NR
			HAR:1	NR	NR	NR	NR	NR	NR	NR
			No VR:77	NR	NR	NR	NR	NR	55(71%)	NR
Matsuyama et al. (2016)	Japan	1992-2014	PVR:54	39(72%)	70	1981 ±1926	2(4%)	38(70%)	43(80%)	4(7%)
			HAR:44	27(61%)	69	2212 ±2192	4(9%)	36(82%)	35(80%)	5(11%)
			No VR:74	55(74%)	69	1929±1387	3(4%)	61(82%)	55(74%)	6(8%)
Yu et al. (2017)	China	2006-2014	PVR:10	NR	55.40	NR	NR	16(84%)	NR	0(0%)
			HAR:9	NR						
			No VR:76	43(57%)	61.03	NR	NR	45(59%)	NR	4(5%)
Mizuno et al. (2020)	Japan	2001-2018	PVR:157	49(31%)	67	1498±1805	3(2%)	145(48%)	108(69%)	54(34%)
			HAR:146	NR	67	1491±1146	2(1%)	NR	93(64%)	49(34%)
			No VR:484	162(33%)	69	1078±891	1(0%)	242(50%)	410(85%)	102(21%)
Song et al. (2009)	Korea	1989-2005	PVR:51	NR	NR	NR	5(10%)	24(47%)	NR	NR
			No VR:208	NR	NR	NR	6(3%)	82(39%)	NR	NR

Abbreviations: VR, vascular resection; PVR, portal vein resection; HAR, hepatic artery resection; NR, not retrievable; UICC, Union for International Cancer Control Unites.

Table 2(on next page)

Meta-analysis results of pooled survival in all included studies

Table 2 Meta-analysis results of pooled survival in all included studies

	Group	I2	Pooled OR	95 %CI	P value
1-year OS	VR	55%	0.94	0.54-1.64	0.83
	PVR	48%	0.77	0.49-1.20	0.25
	HAR	78%	0.64	0.11-3.69	0.62
3-year OS	VR	35%	0.56	0.46-0.68	<0.00001
	PVR	21%	0.45	0.36-0.57	<0.00001
	HAR	42%	0.55	0.41-0.74	<0.0001
5-year OS	VR	27%	0.48	0.40-0.58	<0.00001
	PVR	54%	0.52	0.35-0.76	0.0008
	HAR	0%	0.43	0.32-0.57	<0.00001
1-year DFS	VR	3%	1.54	0.92-2.57	0.10
3-year DFS	VR	0%	1.00	059-1.71	0.99
5-year DFS	VR	0%	0.99	0.42-2.35	0.98

Abbreviations: OR, Odds Ratio; CI, confidence interval; VR, vascular resection; PVR, portal vein resection; HAR, hepatic artery resection; OS, overall survival; DFS, disease free survival.

Figure 1

Flow chart showing the study selection process.

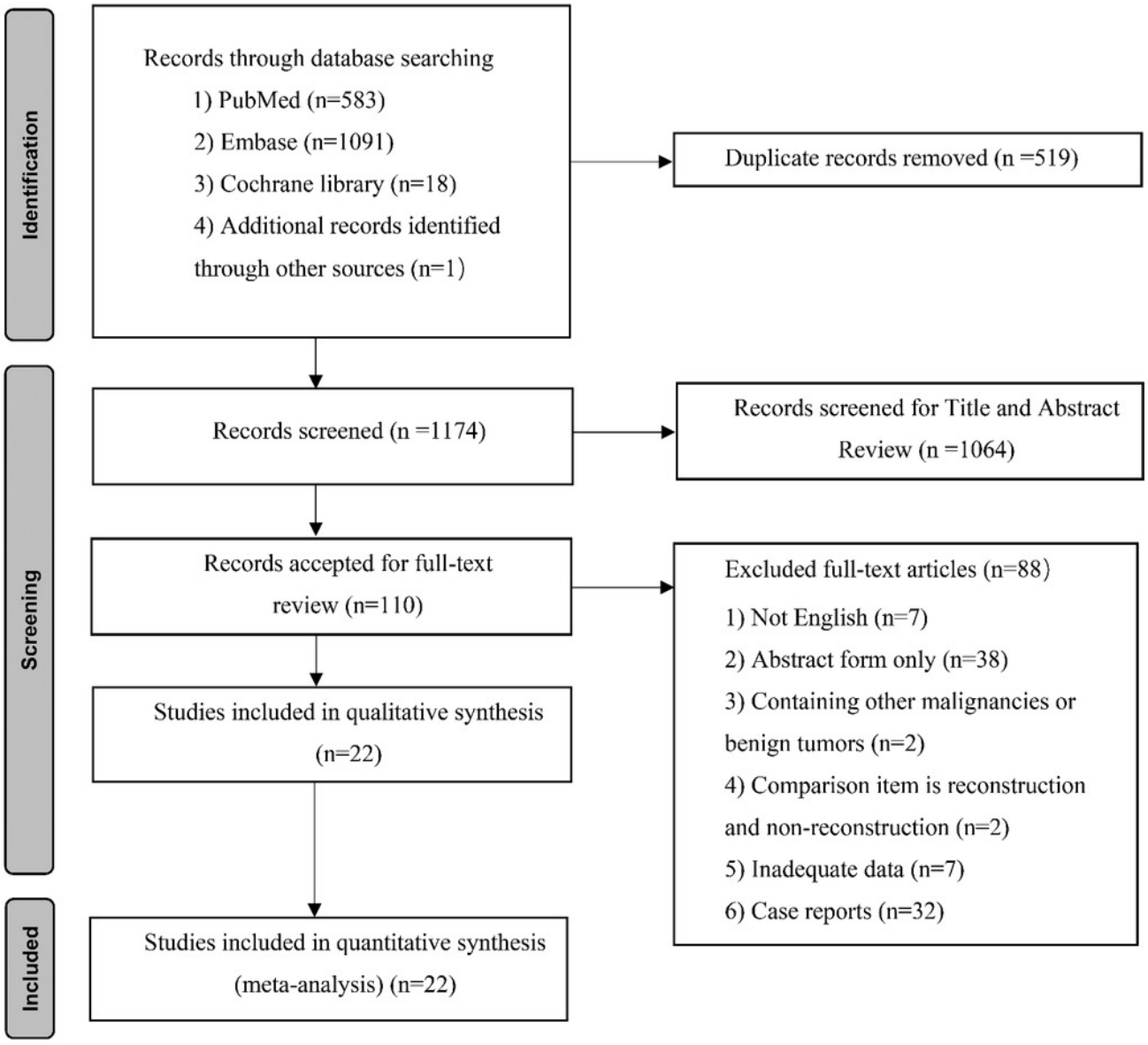


Figure 2

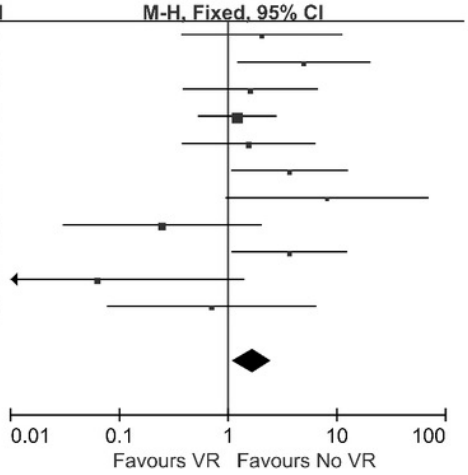
Meta-analysis of studies on 90-day mortality.

(A) 90-day mortality rate in patients with and without VR; (B) 90-day mortality rate in patients with and without PVR; (C) 90-day mortality rate in patients with and without HAR.

A

Study or Subgroup	VR Events	VR Total	No VR Events	No VR Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Dumitracu 2017	2	21	5	102	4.4%	2.04 [0.37, 11.31]
Higuchi 2018	6	75	3	174	4.8%	4.96 [1.21, 20.38]
Hoffmann 2015	4	21	5	39	8.1%	1.60 [0.38, 6.74]
Jong 2012	9	51	26	173	27.9%	1.21 [0.53, 2.78]
Matsuyama 2016	6	98	3	74	9.2%	1.54 [0.37, 6.39]
Miyazaki 2007	6	43	5	118	6.6%	3.66 [1.06, 12.71]
Mizuno 2020	5	303	1	484	2.2%	8.10 [0.94, 69.70]
She 2020	1	22	11	68	14.7%	0.25 [0.03, 2.03]
Song 2009	5	51	6	208	6.1%	3.66 [1.07, 12.51]
Tamoto 2014	0	36	2	13	10.2%	0.06 [0.00, 1.41]
Wang 2015	1	40	4	114	5.8%	0.71 [0.08, 6.50]
Total (95% CI)		**761**		**1567**	**100.0%**	**1.66 [1.11, 2.48]**
Total events	45		71			

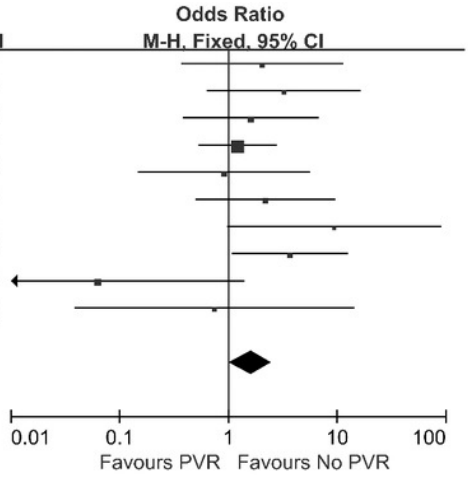
Heterogeneity: Chi² = 16.12, df = 10 (P = 0.10); I² = 38%
Test for overall effect: Z = 2.46 (P = 0.01)



B

Study or Subgroup	PVR Events	PVR Total	No PVR Events	No PVR Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Dumitracu 2017	2	21	5	102	5.7%	2.04 [0.37, 11.31]
Higuchi 2018	3	56	3	174	5.1%	3.23 [0.63, 16.46]
Hoffmann 2015	4	21	5	39	10.4%	1.60 [0.38, 6.74]
Jong 2012	9	51	26	173	35.7%	1.21 [0.53, 2.78]
Matsuyama 2016	2	54	3	74	8.9%	0.91 [0.15, 5.64]
Miyazaki 2007	3	34	5	118	7.5%	2.19 [0.50, 9.66]
Mizuno 2020	3	157	1	484	1.8%	9.41 [0.97, 91.11]
Song 2009	5	51	6	208	7.8%	3.66 [1.07, 12.51]
Tamoto 2014	0	36	2	13	13.1%	0.06 [0.00, 1.41]
Wang 2015	0	16	4	114	4.1%	0.74 [0.04, 14.46]
Total (95% CI)		**497**		**1499**	**100.0%**	**1.61 [1.02, 2.54]**
Total events	31		60			

Heterogeneity: Chi² = 10.23, df = 9 (P = 0.33); I² = 12%
Test for overall effect: Z = 2.05 (P = 0.04)



C

Study or Subgroup	HAR Events	HAR Total	No HAR Events	No HAR Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Higuchi 2018	3	19	3	174	10.4%	10.69 [1.99, 57.36]
Matsuyama 2016	4	44	3	74	42.4%	2.37 [0.50, 11.11]
Miyazaki 2007	3	9	5	118	9.9%	11.30 [2.17, 58.85]
Mizuno 2020	2	146	1	484	9.5%	6.71 [0.60, 74.52]
Wang 2015	1	24	4	114	27.8%	1.20 [0.13, 11.20]
Total (95% CI)		**242**		**964**	**100.0%**	**4.20 [1.88, 9.39]**
Total events	13		16			

Heterogeneity: Chi² = 4.46, df = 4 (P = 0.35); I² = 10%
Test for overall effect: Z = 3.49 (P = 0.0005)

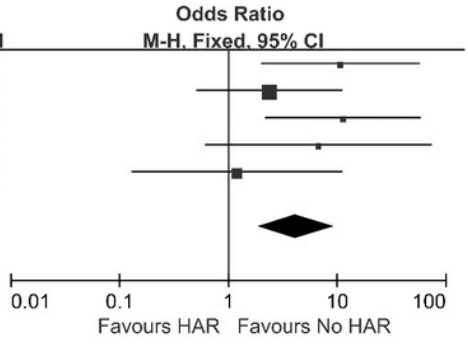


Figure 3

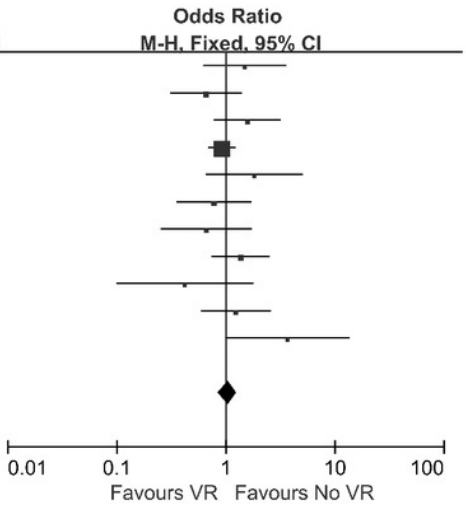
Meta-analysis of studies on overall morbidity.

(A) overall morbidity rate in patients with and without VR; (B) overall morbidity rate in patients with and without PVR; (C) overall morbidity rate in patients with and without HAR.

A

Study or Subgroup	VR Events	VR Total	No VR Events	No VR Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Ebata 2003	44	52	85	108	4.2%	1.49 [0.62, 3.60]
Matsuyama 2016	74	98	61	74	8.4%	0.66 [0.31, 1.40]
Miyazaki 2007	20	43	42	118	5.9%	1.57 [0.78, 3.19]
Mizuno 2020	145	303	242	484	48.0%	0.92 [0.69, 1.22]
Peng 2016	15	26	15	35	2.7%	1.82 [0.65, 5.07]
Schimizzi 2017	19	31	114	170	6.7%	0.78 [0.35, 1.71]
She 2020	11	22	41	68	5.0%	0.66 [0.25, 1.73]
Song 2009	24	51	82	208	8.5%	1.37 [0.74, 2.53]
Tamoto 2014	21	36	10	13	3.0%	0.42 [0.10, 1.79]
Wang 2015	16	40	40	114	6.2%	1.23 [0.59, 2.59]
Yu 2017	16	19	45	76	1.4%	3.67 [0.99, 13.69]
Total (95% CI)		**721**		**1468**	**100.0%**	**1.04 [0.86, 1.26]**
Total events	405		777			

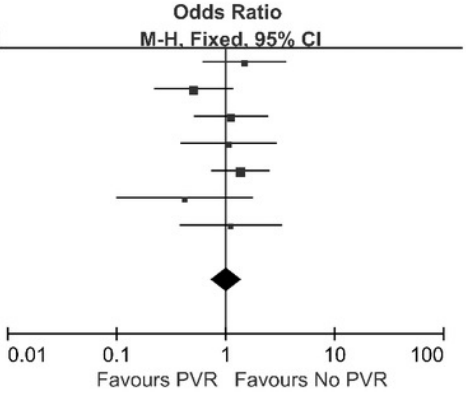
Heterogeneity: Chi² = 12.61, df = 10 (P = 0.25); I² = 21%
Test for overall effect: Z = 0.41 (P = 0.68)



B

Study or Subgroup	PVR Events	PVR Total	No PVR Events	No PVR Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Ebata 2003	44	52	85	108	11.8%	1.49 [0.62, 3.60]
Matsuyama 2016	38	54	61	74	21.2%	0.51 [0.22, 1.17]
Miyazaki 2007	13	34	42	118	16.1%	1.12 [0.51, 2.46]
Schimizzi 2017	13	19	114	170	10.1%	1.06 [0.38, 2.95]
Song 2009	24	51	82	208	23.8%	1.37 [0.74, 2.53]
Tamoto 2014	21	36	10	13	8.5%	0.42 [0.10, 1.79]
Wang 2015	6	16	40	114	8.6%	1.11 [0.38, 3.28]
Total (95% CI)		**262**		**805**	**100.0%**	**1.03 [0.74, 1.42]**
Total events	159		434			

Heterogeneity: Chi² = 5.78, df = 6 (P = 0.45); I² = 0%
Test for overall effect: Z = 0.15 (P = 0.88)



C

Study or Subgroup	HAR Events	HAR Total	No HAR Events	No HAR Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Matsuyama 2016	36	44	61	74	27.0%	0.96 [0.36, 2.54]
Miyazaki 2007	7	9	42	118	4.3%	6.33 [1.26, 31.88]
Peng 2016	15	26	15	35	17.7%	1.82 [0.65, 5.07]
Schimizzi 2017	6	12	114	170	24.5%	0.49 [0.15, 1.59]
Wang 2015	10	24	40	114	26.5%	1.32 [0.54, 3.24]
Total (95% CI)		**115**		**511**	**100.0%**	**1.32 [0.83, 2.11]**
Total events	74		272			

Heterogeneity: Chi² = 7.12, df = 4 (P = 0.13); I² = 44%
Test for overall effect: Z = 1.18 (P = 0.24)

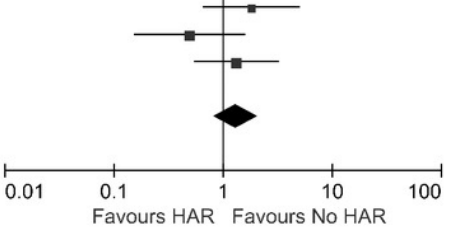


Figure 4

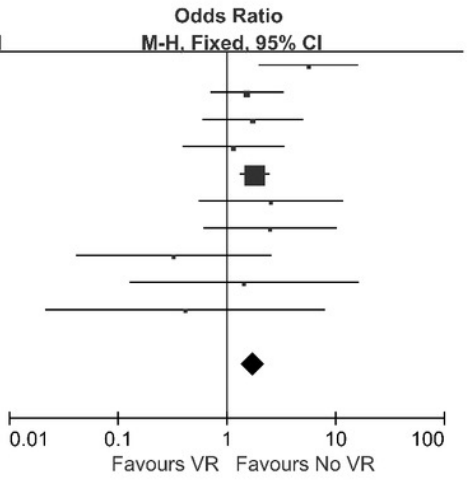
Meta-analysis of studies on posthepatectomy liver insufficiency (PHI).

(A) PHI rate in patients with and without VR; (B) PHI rate in patients with and without PVR; (C) PHI rate in patients with and without HAR.

A

Study or Subgroup	VR Events	VR Total	No VR Events	No VR Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Dumitracu 2017	9	21	12	102	2.7%	5.63 [1.96, 16.13]
Ebata 2003	14	52	21	108	11.3%	1.53 [0.70, 3.32]
Hoffmann 2015	12	21	17	39	5.8%	1.73 [0.59, 5.04]
Matsuyama 2016	9	98	6	74	7.0%	1.15 [0.39, 3.38]
Mizuno 2020	103	303	108	484	62.3%	1.79 [1.30, 2.47]
Peng 2016	5	26	3	35	2.3%	2.54 [0.55, 11.77]
Schimizzi 2017	3	31	7	170	2.2%	2.49 [0.61, 10.23]
Tamoto 2014	2	36	2	13	3.1%	0.32 [0.04, 2.58]
Wang 2015	1	40	2	114	1.1%	1.44 [0.13, 16.28]
Yu 2017	0	19	4	76	2.1%	0.41 [0.02, 8.01]
Total (95% CI)		**647**		**1215**	**100.0%**	**1.77 [1.37, 2.28]**
Total events	158		182			

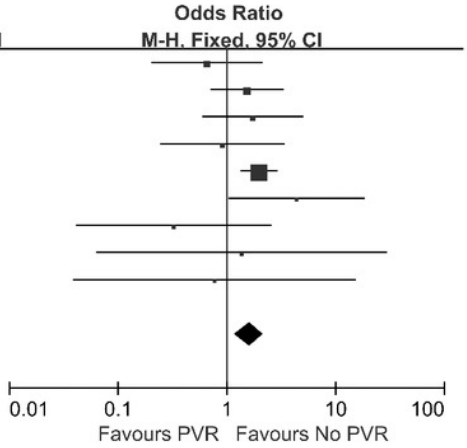
Heterogeneity: Chi² = 9.37, df = 9 (P = 0.40); I² = 4%
Test for overall effect: Z = 4.42 (P < 0.00001)



B

Study or Subgroup	PVR Events	PVR Total	No PVR Events	No PVR Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Dumitracu 2017	4	21	27	102	11.4%	0.65 [0.20, 2.12]
Ebata 2003	14	52	21	108	15.2%	1.53 [0.70, 3.32]
Hoffmann 2015	12	21	17	39	7.8%	1.73 [0.59, 5.04]
Matsuyama 2016	4	54	6	74	7.1%	0.91 [0.24, 3.38]
Mizuno 2020	54	157	102	484	49.9%	1.96 [1.32, 2.91]
Schimizzi 2017	3	19	7	170	1.8%	4.37 [1.03, 18.55]
Tamoto 2014	2	36	2	13	4.2%	0.32 [0.04, 2.58]
Wang 2015	0	16	2	114	1.0%	1.36 [0.06, 29.67]
Yu 2017	0	10	4	76	1.6%	0.77 [0.04, 15.30]
Total (95% CI)		**386**		**1180**	**100.0%**	**1.60 [1.19, 2.16]**
Total events	93		188			

Heterogeneity: Chi² = 8.38, df = 8 (P = 0.40); I² = 5%
Test for overall effect: Z = 3.11 (P = 0.002)



C

Study or Subgroup	HAR Events	HAR Total	No HAR Events	No HAR Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Matsuyama 2016	5	44	6	74	9.7%	1.45 [0.42, 5.07]
Mizuno 2020	49	146	108	484	81.5%	1.76 [1.17, 2.64]
Peng 2016	5	26	3	35	5.1%	2.54 [0.55, 11.77]
Schimizzi 2017	0	12	7	170	2.5%	0.87 [0.05, 16.17]
Wang 2015	1	18	2	114	1.3%	3.29 [0.28, 38.33]
Total (95% CI)		**246**		**877**	**100.0%**	**1.77 [1.23, 2.54]**
Total events	60		126			

Heterogeneity: Chi² = 0.78, df = 4 (P = 0.94); I² = 0%
Test for overall effect: Z = 3.05 (P = 0.002)

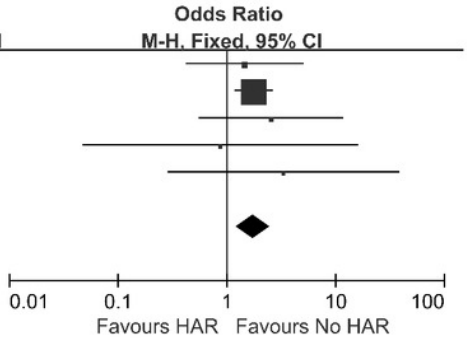


Figure 5

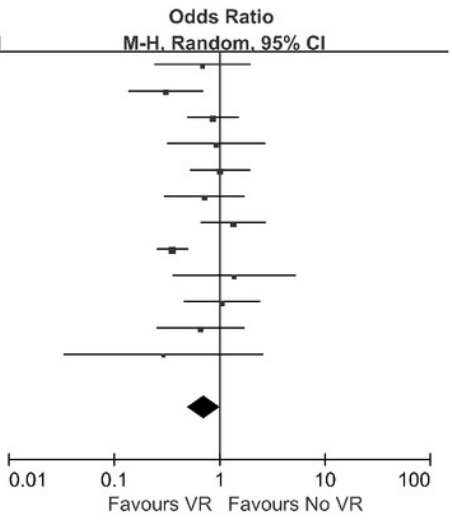
Meta-analysis of studies on R0 margin status.

(A) R0 resection rate in patients with and without VR; (B) R0 resection rate in patients with and without PVR; (C) R0 resection rate in patients with and without HAR.

A

Study or Subgroup	VR Events	VR Total	No VR Events	No VR Total	Weight	Odds Ratio M-H, Random, 95% CI
Dumitracu 2017	15	21	80	102	6.6%	0.69 [0.24, 1.98]
Ebata 2003	36	52	95	108	8.7%	0.31 [0.13, 0.70]
Higuchi 2018	47	75	115	174	11.8%	0.86 [0.49, 1.51]
Hoffmann 2015	12	21	23	39	6.5%	0.93 [0.32, 2.72]
Jong 2012	34	51	115	173	10.6%	1.01 [0.52, 1.96]
Klempnauer 1997	30	41	61	77	8.1%	0.72 [0.30, 1.73]
Matsuyama 2016	78	98	55	74	9.9%	1.35 [0.66, 2.76]
Mizuno 2020	201	303	410	484	14.7%	0.36 [0.25, 0.50]
Peng 2016	22	26	28	35	4.8%	1.38 [0.36, 5.30]
Schimizzi 2017	22	31	119	170	8.6%	1.05 [0.45, 2.43]
She 2020	10	22	38	68	7.4%	0.66 [0.25, 1.73]
Tamoto 2014	28	36	12	13	2.2%	0.29 [0.03, 2.60]
Total (95% CI)		**777**		**1517**	**100.0%**	**0.71 [0.50, 1.01]**
Total events	535		1151			

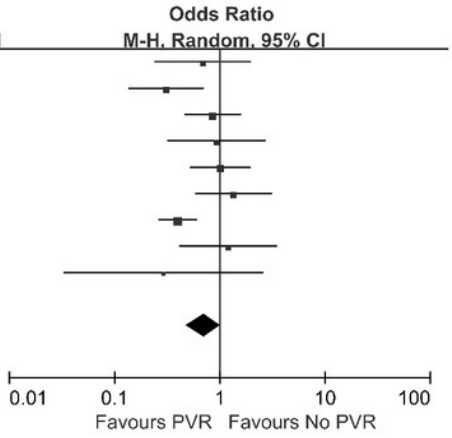
Heterogeneity: Tau² = 0.18; Chi² = 24.65, df = 11 (P = 0.01); I² = 55%
Test for overall effect: Z = 1.90 (P = 0.06)



B

Study or Subgroup	PVR Events	PVR Total	No PVR Events	No PVR Total	Weight	Odds Ratio M-H, Random, 95% CI
Dumitracu 2017	15	21	80	102	8.7%	0.69 [0.24, 1.98]
Ebata 2003	36	52	95	108	11.6%	0.31 [0.13, 0.70]
Higuchi 2018	35	56	115	174	15.0%	0.86 [0.46, 1.60]
Hoffmann 2015	12	21	23	39	8.5%	0.93 [0.32, 2.72]
Jong 2012	34	51	115	173	14.3%	1.01 [0.52, 1.96]
Matsuyama 2016	43	54	55	74	11.4%	1.35 [0.58, 3.14]
Mizuno 2020	108	157	410	484	19.2%	0.40 [0.26, 0.60]
Schimizzi 2017	14	19	119	170	8.5%	1.20 [0.41, 3.51]
Tamoto 2014	28	36	12	13	2.8%	0.29 [0.03, 2.60]
Total (95% CI)		**467**		**1337**	**100.0%**	**0.70 [0.47, 1.03]**
Total events	325		1024			

Heterogeneity: Tau² = 0.16; Chi² = 15.92, df = 8 (P = 0.04); I² = 50%
Test for overall effect: Z = 1.82 (P = 0.07)



C

Study or Subgroup	HAR Events	HAR Total	No HAR Events	No HAR Total	Weight	Odds Ratio M-H, Random, 95% CI
Higuchi 2018	12	19	115	174	19.8%	0.88 [0.33, 2.35]
Matsuyama 2016	35	44	55	74	21.0%	1.34 [0.55, 3.30]
Mizuno 2020	93	146	410	484	27.8%	0.32 [0.21, 0.48]
Peng 2016	22	26	28	35	15.1%	1.38 [0.36, 5.30]
Schimizzi 2017	8	12	119	170	16.3%	0.86 [0.25, 2.97]
Total (95% CI)		**247**		**937**	**100.0%**	**0.77 [0.37, 1.61]**
Total events	170		727			

Heterogeneity: Tau² = 0.47; Chi² = 13.43, df = 4 (P = 0.009); I² = 70%
Test for overall effect: Z = 0.69 (P = 0.49)

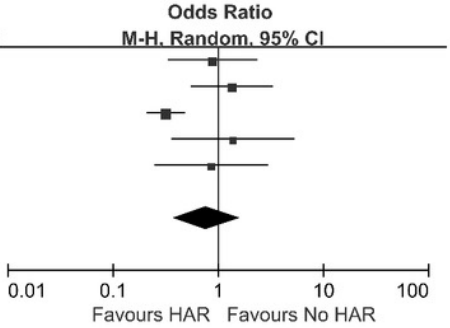
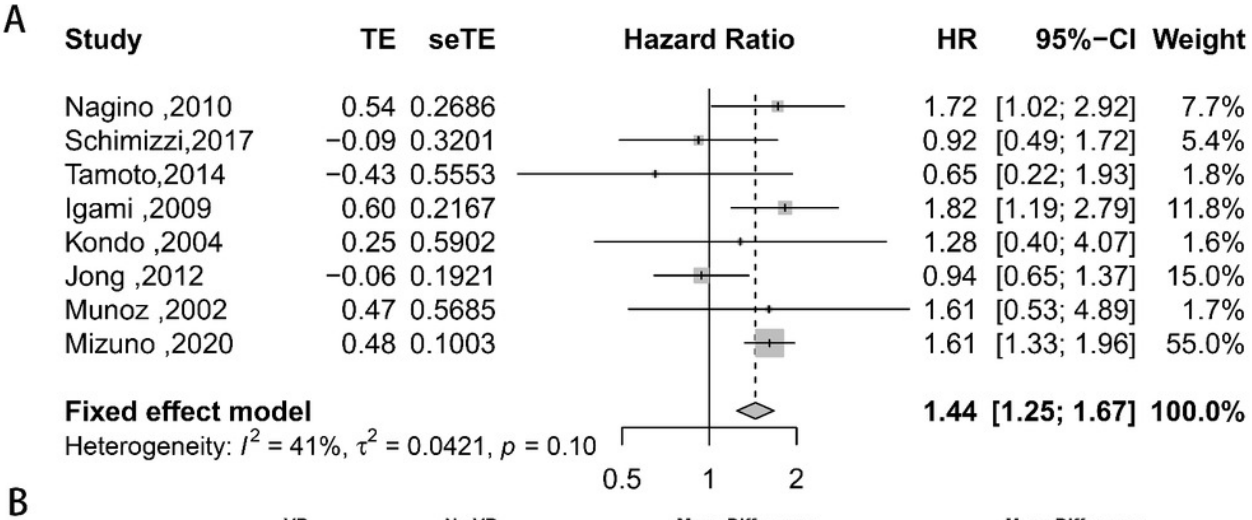


Figure 6

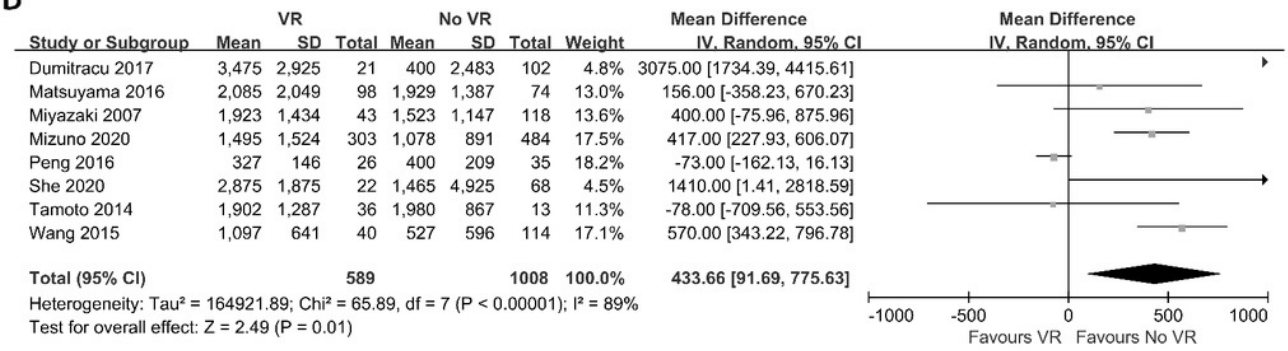
Funnel plots of main results in patients with and without VR.

(A) overall survival; (B) intraoperative blood loss; (C) proportion of Ⅲ,Ⅳ stage according to UICC staging systems; (D) vascular invasion confirmed by histology.

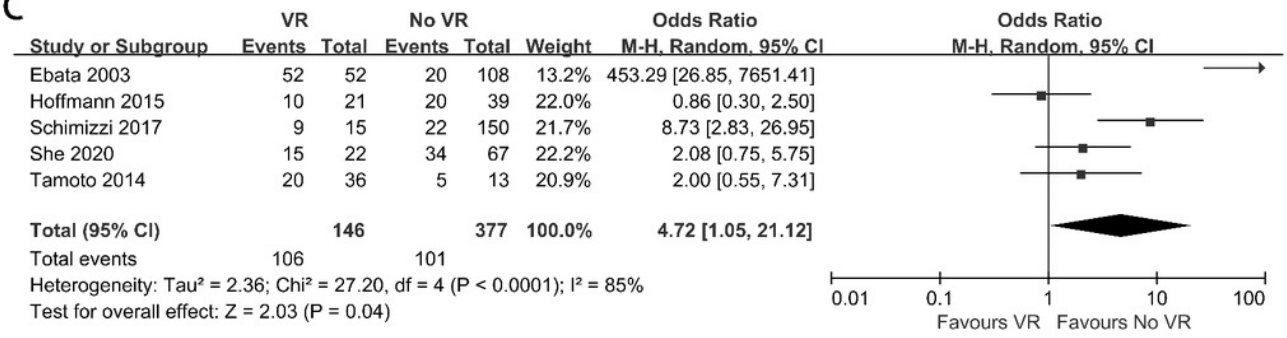
A


Study TE seTE Hazard Ratio HR 95%−CI Weight
Nagino ,2010 0.54 0.2686 1.72 [1.02; 2.92] 7.7%
Schimizzi,2017 −0.09 0.3201 0.92 [0.49; 1.72] 5.4%
Tamoto,2014 −0.43 0.5553 0.65 [0.22; 1.93] 1.8%
Igami ,2009 0.60 0.2167 1.82 [1.19; 2.79] 11.8%
Kondo ,2004 0.25 0.5902 1.28 [0.40; 4.07] 1.6%
Jong ,2012 −0.06 0.1921 0.94 [0.65; 1.37] 15.0%
Munoz ,2002 0.47 0.5685 1.61 [0.53; 4.89] 1.7%
Mizuno ,2020 0.48 0.1003 1.61 [1.33; 1.96] 55.0%
Fixed effect model 1.44 [1.25; 1.67] 100.0%
Heterogeneity: I^2 = 41%, τ^2 = 0.0421, p = 0.10
0.5 1 2

B


VR No VR Mean Difference Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI IV, Random, 95% CI
Dumitracu 2017 3,475 2,925 21 400 2,483 102 4.8% 3075.00 [1734.39, 4415.61]
Matsuyama 2016 2,085 2,049 98 1,929 1,387 74 13.0% 156.00 [-358.23, 670.23]
Miyazaki 2007 1,923 1,434 43 1,523 1,147 118 13.6% 400.00 [-75.96, 875.96]
Mizuno 2020 1,495 1,524 303 1,078 891 484 17.5% 417.00 [227.93, 606.07]
Peng 2016 327 146 26 400 209 35 18.2% -73.00 [-162.13, 16.13]
She 2020 2,875 1,875 22 1,465 4,925 68 4.5% 1410.00 [1.41, 2818.59]
Tamoto 2014 1,902 1,287 36 1,980 867 13 11.3% -78.00 [-709.56, 553.56]
Wang 2015 1,097 641 40 527 596 114 17.1% 570.00 [343.22, 796.78]
Total (95% CI) 589 1008 100.0% 433.66 [91.69, 775.63]
Heterogeneity: Tau² = 164921.89; Chi² = 65.89, df = 7 (P < 0.00001); I² = 89%
Test for overall effect: Z = 2.49 (P = 0.01)
-1000 -500 0 500 1000
Favours VR Favours No VR

C


VR No VR Odds Ratio Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI M-H, Random, 95% CI
Ebata 2003 52 52 20 108 13.2% 453.29 [26.85, 7651.41]
Hoffmann 2015 10 21 20 39 22.0% 0.86 [0.30, 2.50]
Schimizzi 2017 9 15 22 150 21.7% 8.73 [2.83, 26.95]
She 2020 15 22 34 67 22.2% 2.08 [0.75, 5.75]
Tamoto 2014 20 36 5 13 20.9% 2.00 [0.55, 7.31]
Total (95% CI) 146 377 100.0% 4.72 [1.05, 21.12]
Total events 106 101
Heterogeneity: Tau² = 2.36; Chi² = 27.20, df = 4 (P < 0.0001); I² = 85%
Test for overall effect: Z = 2.03 (P = 0.04)
0.01 0.1 1 10 100
Favours VR Favours No VR

D

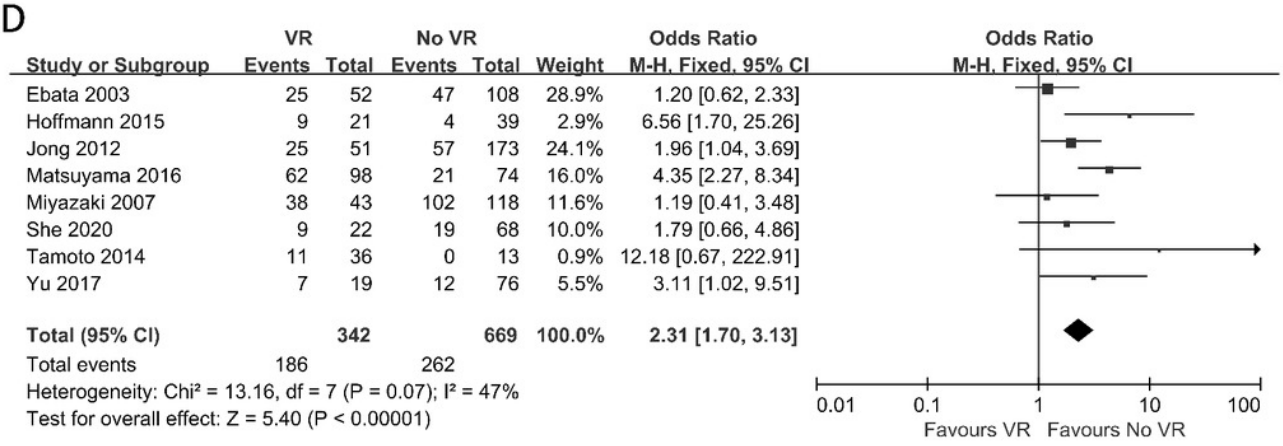

VR No VR Odds Ratio Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI M-H, Fixed, 95% CI
Ebata 2003 25 52 47 108 28.9% 1.20 [0.62, 2.33]
Hoffmann 2015 9 21 4 39 2.9% 6.56 [1.70, 25.26]
Jong 2012 25 51 57 173 24.1% 1.96 [1.04, 3.69]
Matsuyama 2016 62 98 21 74 16.0% 4.35 [2.27, 8.34]
Miyazaki 2007 38 43 102 118 11.6% 1.19 [0.41, 3.48]
She 2020 9 22 19 68 10.0% 1.79 [0.66, 4.86]
Tamoto 2014 11 36 0 13 0.9% 12.18 [0.67, 222.91]
Yu 2017 7 19 12 76 5.5% 3.11 [1.02, 9.51]
Total (95% CI) 342 669 100.0% 2.31 [1.70, 3.13]
Total events 186 262
Heterogeneity: Chi² = 13.16, df = 7 (P = 0.07); I² = 47%
Test for overall effect: Z = 5.40 (P < 0.00001)
0.01 0.1 1 10 100
Favours VR Favours No VR

Figure 7

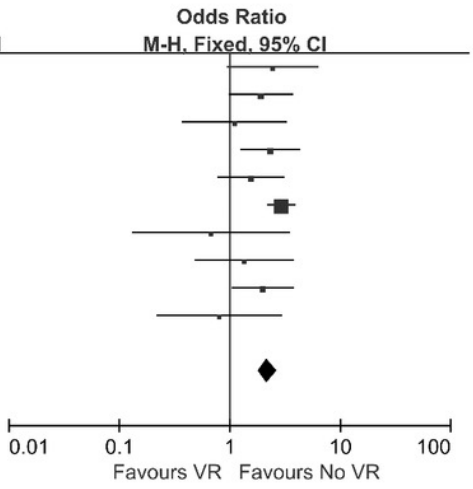
Meta-analysis of studies on lymph node metastasis.

(A) lymph node metastasis rate in patients with and without VR; (B) lymph node metastasis rate in patients with and without PVR; (C) lymph node metastasis rate in patients with and without HAR.

A

Study or Subgroup	VR Events	VR Total	No VR Events	No VR Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Dumitracu 2017	12	21	36	102	4.2%	2.44 [0.94, 6.35]
Ebata 2003	29	52	43	108	9.8%	1.91 [0.98, 3.72]
Hoffmann 2015	8	21	14	39	4.8%	1.10 [0.37, 3.29]
Matsuyama 2016	53	98	25	74	10.3%	2.31 [1.24, 4.31]
Miyazaki 2007	24	43	53	118	9.9%	1.55 [0.77, 3.13]
Mizuno 2020	191	303	179	484	40.2%	2.91 [2.16, 3.91]
Muñoz 2002	3	10	7	18	2.8%	0.67 [0.13, 3.51]
Peng 2016	16	26	19	35	4.9%	1.35 [0.48, 3.78]
Song 2009	19	51	48	208	9.4%	1.98 [1.03, 3.80]
Tamoto 2014	12	36	5	13	3.9%	0.80 [0.21, 2.98]
Total (95% CI)		**661**		**1199**	**100.0%**	**2.20 [1.80, 2.69]**
Total events	367		429			

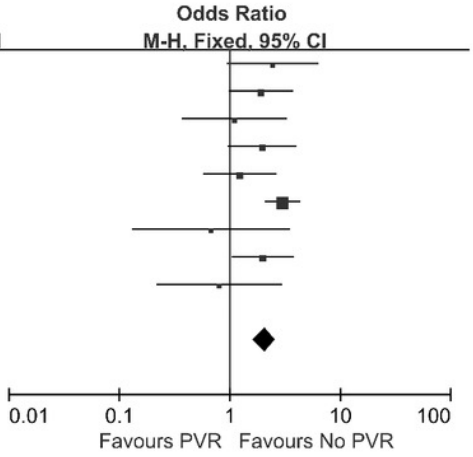
Heterogeneity: Chi² = 11.32, df = 9 (P = 0.25); I² = 20%
Test for overall effect: Z = 7.67 (P < 0.00001)



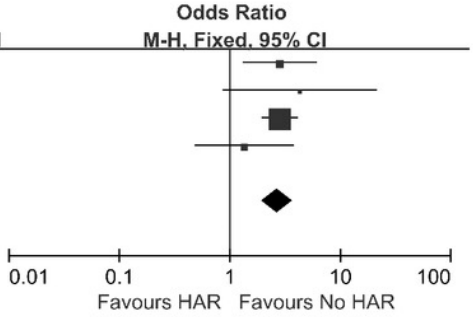
B

Study or Subgroup	PVR Events	PVR Total	No PVR Events	No PVR Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Dumitracu 2017	12	21	36	102	5.4%	2.44 [0.94, 6.35]
Ebata 2003	29	52	43	108	12.6%	1.91 [0.98, 3.72]
Hoffmann 2015	8	21	14	39	6.2%	1.10 [0.37, 3.29]
Matsuyama 2016	27	54	25	74	10.7%	1.96 [0.96, 4.02]
Miyazaki 2007	17	34	53	118	12.1%	1.23 [0.57, 2.63]
Mizuno 2020	100	157	179	484	32.4%	2.99 [2.06, 4.35]
Muñoz 2002	3	10	7	18	3.6%	0.67 [0.13, 3.51]
Song 2009	19	51	48	208	12.1%	1.98 [1.03, 3.80]
Tamoto 2014	12	36	5	13	5.0%	0.80 [0.21, 2.98]
Total (95% CI)		**436**		**1164**	**100.0%**	**2.07 [1.64, 2.61]**
Total events	227		410			

Heterogeneity: Chi² = 10.79, df = 8 (P = 0.21); I² = 26%
Test for overall effect: Z = 6.15 (P < 0.00001)



C

Study or Subgroup	HAR Events	HAR Total	No HAR Events	No HAR Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Matsuyama 2016	26	44	25	74	16.3%	2.83 [1.31, 6.12]
Miyazaki 2007	7	9	53	118	3.6%	4.29 [0.86, 21.53]
Mizuno 2020	91	146	179	484	66.8%	2.82 [1.92, 4.13]
Peng 2016	16	26	19	35	13.3%	1.35 [0.48, 3.78]
Total (95% CI)		**225**		**711**	**100.0%**	**2.68 [1.95, 3.68]**
Total events	140		276			

Heterogeneity: Chi² = 2.12, df = 3 (P = 0.55); I² = 0%
Test for overall effect: Z = 6.08 (P < 0.00001)