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Morbidity and mortality after major liver resection in patients with perihilar cholangiocarcinoma: A systematic review and meta-analysis

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ABSTRACT

Background: Morbidity and mortality after hepatectomy for perihilar cholangiocarcinoma are known to be high. However, reported postoperative outcomes vary, with notable differences between Western and Asian series. We aimed to determine morbidity and mortality rates after major hepatectomy in patients with perihilar cholangiocarcinoma and assess differences in outcome regarding geographic location and hospital volume.
Methods: A systematic review was performed by searching the MEDLINE and EMBASE databases through November 20, 2017. Risk of bias was assessed and meta-analysis and metaregression were performed using a random effects model.
Results: A total of 51 studies were included, representing 4,634 patients. Pooled 30-day and 90-day mortality were 5% (95% CI 3%–6%) and 9% (95% CI 6%–12%), respectively. Pooled overall morbidity and severe morbidity were 57% (95% CI 50%–64%) and 40% (95% CI 34%–47%), respectively. Western studies compared with Asian studies had a significantly higher 30-day mortality, 90-day mortality, and overall morbidity: 8% versus 2% ($P < .001$), 12% versus 3% ($P < .001$), and 63% versus 54% ($P = .048$), respectively. This effect on mortality remained significant after correcting for hospital volume. Univariate metaregression analysis showed no influence of hospital volume on mortality or morbidity, but when corrected for geographic location, higher hospital volume was associated with higher severe morbidity ($P = .039$).
Conclusion: Morbidity and mortality rates after major hepatectomy for perihilar cholangiocarcinoma are high. The Western series showed a higher mortality compared with the Asian series, even when corrected for hospital volume. Standardized reporting of outcomes is necessary. Underlying causes for differences in outcomes between Asian and Western centers, such as differences in treatment strategies, should be further analyzed.

Introduction

Perihilar cholangiocarcinoma (PHC) is a rare tumor arising from the epithelium of the bile duct bifurcation.[1] Even today, the treatment of patients with PHC entails several challenges. Most patients present with advanced disease and obstructive jaundice, requiring preoperative biliary drainage (either by a percutaneous or endoscopic approach), depending on the volume and function of the future remnant liver.[2]

Only a small subset of PHC patients (20%–35%) qualifies for resection,[3,4] generally consisting of resection of the extrahepatic bile duct combined with (extended) hemihepatectomy, including the caudate lobe, complete lymphadenectomy of the hepatoduodenal ligament, and biliary reconstruction (by Roux-en-Y hepaticojejunostomy).[5] These extensive procedures are notoriously high risk, leading to a broad spectrum of postoperative complications with substantial mortality. Postoperative complications after hepatectomy for PHC include but are not limited to bile leakage, hemorrhage, and septic complications; however, liver failure is the most life-threatening event. Hospital volume has been reported to influence postoperative outcomes after major hepatectomy.[6]

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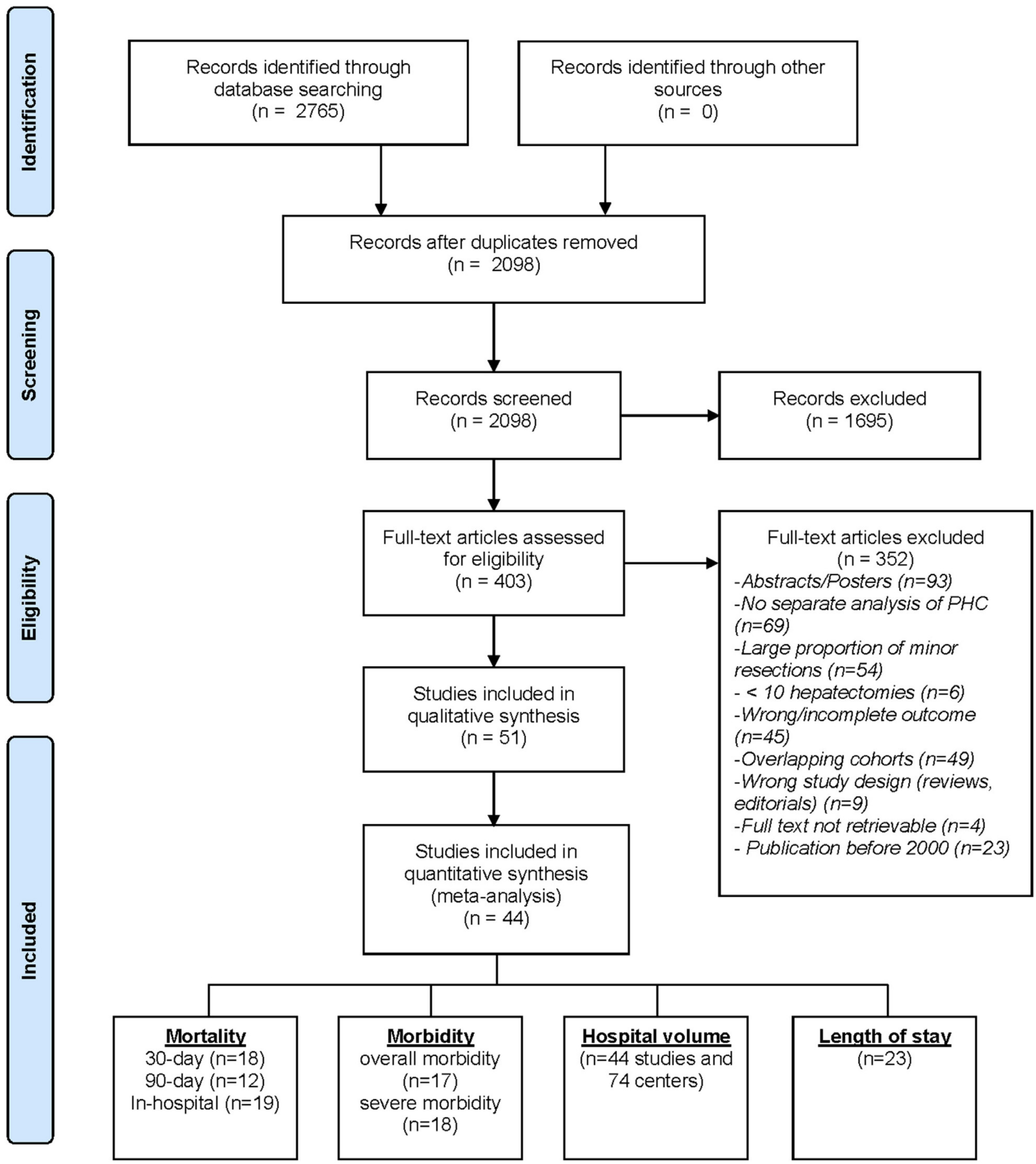

Fig. 1. PRISMA flowchart of included studies.

The literature reports that the morbidity and mortality of these high-risk operations vary widely. Overall morbidity ranges from 26%[7] to as high as 68%.[8] Mortality rates have been reported between 1.4%[4] and 18%,[9] and major differences between the Asian and Western series exist.[10]

Because of the low prevalence of PHC, evidence on outcomes of resection for PHC mainly consists of observational case series and cohort studies. The aim of this systemic review and meta-analysis was to determine the incidence of morbidity and mortality after major hepatectomy in patients with PHC and to assess possible differences in outcomes between Asian and Western populations and high- and low-volume centers.

Methods

This systematic review and meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement and the Meta-analysis of Observational Studies in Epidemiology (MOOSE)

Table I
Study characteristics

Author	Country	Inclusion period	Liver resections (N)	Yearly volume	Mean age (years)	Female patients n (%)	Mean BMI	ASA 3-4 n (%)	BC type	Resection type LH/ELH/RH/ERH	PVE n (%)	Vascular resections *n* (%)	PBD n, (%)
Western studies													
Abdel-Wahab et al[13]	Egypt	1995-2010	159	11	53	65 (41)	—	—	—	104/0/55/0	0 (0)	0 (0)	72 (45)
Baton et al[14]	France	1984-2003	59	3	60	23 (39)	—	—	III-IV	32/7/6/13	14 (24)	7 (12)	48 (81)
Dumitrascu et al[16]	Romania	1996-2012	70	4	59	30 (43)	—	—	—	34/0/21/15	0	v:17 (24)	15 (21)
Farges et al[8]*	France	1997-2008	366*	3	62	132 (36)	24	—	I-IV	182/-/184/-	—	v: 88 (24)	179 (49)
Gerhards et al[18]	NL	1983-1998	32	2	60	12 (38)	—	—	I-IV	18-/-/14/-	—	v:* (9) a:* (8)	27 (84)
Govil et al[19]	UK	2009-2015	36	7	58	14 (39)	-	-	III-IV	23/-/13/-	—	v:19 (53) a:10 (28)	14 (39)
Grandadam et al[20]	France	1997-2007	38	4	—	17 (45)	—	—	III	—	14 (36)	v:1 (3)	13 (33)
Hemming et al[22]	USA	1999-2010	95	9	64	36 (38)	—	—	III-IV	29/-/66/-	36 (38)	v:42 (44) a:5 (5)	84 (88)
Hoffmann et al[23]	Germany	2001-2012	60	5	67	23 (38)	—	—	II-IV	12/13/7/28	3 (5)	v:21 (35)	33 (55)
IJitsma et al[24]	NL	1986-2001	42	3	60	22 (52)	—	—	—	19/1/12/5	—	v:7 (17) a:4 (10)	42 (100
Kimura et al[10]	UK	1995-2014	103	5	58	44 (43)	—	13 (13)	—	43/-/60/-	4 (4)	v:45 (44) a:4 (4)	83 (81)
Konsta-doulakis et al[30]	USA	1988-2006	51	3	62	20 (39)	—	—	I-IV	28/0/0/20	1 (2)	16 (31)	29 (57)
Matsuo et al[37]	USA	‘91-‘08	129	8	65	53 (41)	—	—	—	45/8/56/16	—	v:16 (12)	—
Molina et al[38]	Spain	2007-2014	32	5	64	13 (40)	—	—	II-IV	13/3/7/9	—	v:23 (72)	19 (59)
Nuzzo et al[41]	Italy	1992-2007	376*	2	64	162 (43)	—	—	I-IV	179/3/69/103	79 (21)	v:38 (10) a:8 (2)	316 (84)
Olthof et al[9]	NL	2000-2015	125	8	63	44 (35)	24	18 (14)	I-IV	27/14/9/36	7 (6)	v:36 (29)	113 (90)
Papoulas et al[58]	Israel	2004-2009	15	3	49	—	—	—	III-IV	5/0/11/0	—	—	—
Rea et al[43]	USA	1979-1997	46	2	60	21 (46)	—	—	II-III	25/0/17/4	0 (0)	—	35 (76)
Ribero et al[44]	USA + Italy	1996-2013	133*	4	66	49 (37)	—	—	II-III	43/10/24/56	32 (24)	v:28 (21) a:1 (1)	98 (74)
Vaccarezza et al[56]	Argentina	1994-2008	40	3	58	15 (38)	—	—	II-IV	17/-/22/-/1	3 (8)	v:5 (13) a:2 (5)	19 (47)
Zervos et al[55]	USA	—	31	—	70	15 (48)	—	—	—	12/1/16/2	—	—	—
Total: 2,038													
Asian studies													
Chen et al[15]	China	2000-2007	45	6	35	13 (28)	—	—	III-IV	19/-/26/-	0 (0)	—	24
Cheng et al[7]	China	2001-2010	171	19	56	58 (34)	—	—	III-IV	107/13/24/15	36 (21)	v: 22 (13) a: 5 (3)	72 (42)
Furusawa et al[17]	Japan	1990-2012	144	7	69	104 (72)	—	14 (10)	I-IV	40/-/95/-	84 (58)	v: 13 (9) a: 4 (3)	122 (85)
Hasegawa et al[21]	Japan	1990-2003	49	4	65	20 (41)	—	—	I-IV	18/4/17/6	0 (0)	3 (6)	43 (88)
Kaneoka et al[25]	Japan	1997-2007	29	3	65	11 (38)	—	—	—	13/-/13/-	8 (28)	v: 13 (45) a: 6 (21)	—
Kang et al[26]	Korea	2005-2010	33	6	65	11 (33)	—	—	III-IV	0/0/8/25	11 (33)	—	29 (88)
Kawabata et al[27]	Japan	2010-2016	40	7	71	14 (35)	23	2 (5)	III-IV	1/14/0/4	15 (38)	v: 4 (10)	27 (68)
Kawarada et al[28]	Japan	1976-2000	65	3	66	16 (24)	—	—	I-IV	0/7/0/9	16 (24)	—	57 (88)
Khuntikeo et al[29]	Thailand	1999-2002	30	10	53	9 (30)	—	—	—	4/0/15/11	—	—	0 (0)
Kimura et al[10]	Japan	1995-2014	80	4	68	34 (42)	—	12 (15)	—	26/-/53/-	36 (45)	v: 11 (14) a: 3 (4)	70 (88)
Kow et al[31]	Korea	1995-2010	127	9	62	50 (39)	—	—	III	24/10/48/35	14 (11)	—	76 (60)
Kuriyama et al[32]	Japan	2011-2015	23	6	70	10 (43)	—	—	III-IV	12/2/16/8	4 (17)	v: 14 (61) a: 3 (13)	—
Kurosaki et al[33]	Japan	1987-2005	56	3	64	20 (36)	—	—	—	—	0 (0)	25 (45)	—
Li and Jiang[34]	China	1998-2010	25	2	62	11 (44)	—	—	III-IV	11/0/14/0	—	v: 18 (72) a: 9 (36)	—
Lim et al[35]	Korea	2000-2012	26	2	64	8 (31)	23.5	—	I-II	5/1/13/0	7 (27)	—	21 (81)
Liu et al[36]	China	1989-2004	40	3	65	15 (38)	—	—	I-IV	12/2/23/2	15 (38)	v: 11 (28)	12 (30)

Maeno et al[57]	Japan	1981-2002	19	1	64	9 (43)	–	–	–	10/1/3/4	–	v: 2 (10)	17 (89)
Nagino et al[4]	Japan	1977-2010	574	17	64	195 (34)	–	–	I-IV	187/110/177/43	207 (36)	v: 207 (36) a: 75 (13)	482 (84)
Nanashima et al[39]	Japan	1997-2008	33	3	68	15 (45)	–	–	III-IV	20/0/12/0	8 (24)	–	–
Noji et al[40]	Japan	2000-2015	209	14	68	61 (29)	–	–	–	100/0/109/0	–	v: 107 (51) a: 29 (14)	169 (81)
Otani et al[42]	Japan	1990-2006	21	1	69	6 (29)	–	–	II-IV	10/0/11/0	–	v: 8 (14) a: 0 (0)	–
Sano et al[45]	Japan	1980-2004	126	5	64	37 (29)	–	–	–	55/8/61/2	64 (51)	v: 21 (17) a: 4 (3)	98 (78)
Shimada et al[46]	Japan	1985-2001	30	2	61	14 (47)	–	–	II-IV	17/0/8/5	8 (27)	v: 9 (30) a: 6 (20)	–
Shimizu et al[47]	Japan	1984-2008	174	7	71	64 (37)	–	–	III-IV	88/0/84/0	–	v: 49 (28) a: 10 (6)	–
Tan et al[48]	China	2002-2010	51	6	63	16 (31)	–	–	IV	15/0/18/0	–	v: 13 (25)	–
Tsuchikawa et al[49]	Japan	1980-1997	40	2	65	12 (30)	–	–	I-IV	13/8/5/11	–	v: 8 (20) a: 1 (3)	–
Unno et al[50]	Japan	2001-2008	125	18	66	33 (26)	–	–	I-IV	51/0/74/0	12 (37)	v: 41 (33) a: 4 (3)	–
Wang et al[52]	China	2008-2013	70	14	59	39 (55)	–	–	II-IV	44/0/26/0	–	0 (0)	57 (81)
Wang et al[51]	China	2009-2012	38	13	58	16 (42)	–	–	III-IV	28/0/10/0	0 (0)	v: 4 (10) a: 15 (39)	7 (18)
Xiong et al[53]	China	2002-2012	78	8	60	47 (37)	–	16 (21)	I-IV	48/3/18/9	8 (10)	v: 14 (18) a: 5 (7)	32 (41)
Yamanaka et al[54]	Japan	1980-1998	25	1	70	12 (48)	–	–	–	11/0/14/0	–	v: 12 (48) a: 10 (40)	–
Total: 2,596													

BC, Bismuth-Corlette; *(E)LH*, (extended) left hemihepatectomy; *(E)RH*, (extended) right hemihepatectomy; *PBD*, preoperative biliary drainage; *PVE*, portal vein embolization; *BMI*, body mass index; *v*, portal vein; *a*, hepatic artery; –, not reported.

* Multicenter studies (yearly volume was adjusted for the number of centers contributing to these studies).

guideline. The protocol of this study was registered in PROSPERO under registration number CRD42018093348.

Eligibility criteria

We aimed to identify all studies reporting on morbidity and mortality after hepatectomy in patients with PHC. We included both retrospective and prospective observational studies containing original data that reported on *both* overall morbidity and mortality after hepatectomy in patients with PHC and were published after the year 2000. Case reports, conference abstracts, and reviews were excluded. Studies with a minimum of 10 hepatectomies were eligible for inclusion because case reports or small case series are more prone to selection bias. Studies that included patients undergoing external bile duct resection without major hepatectomy were only included if the proportion of patients not undergoing major hepatectomy was <10% of the total amount of included patients. In the case of a mixed population (eg, including gallbladder carcinoma or distal cholangiocarcinoma), studies were excluded if there was no separate reporting of outcomes for patients with PHC. Studies including intrahepatic cholangiocarcinoma invading the hilum were included because many authors consider this a similar disease requiring the same surgical procedures.[11] No language restrictions were applied. To avoid double counting of patients in multiple publications from the same institution regarding the same or overlapping inclusion periods, only the most recent or largest series were included.

Literature search strategy

A search was performed in the PubMed and EMBASE databases on November 20, 2017. A clinical librarian (F.E.) was consulted on the search strategy. The following key words and Medical Subject Headings (MeSH) terms were used for both databases: biliary tract neoplasms/surgery, cholangiocarcinoma/surgery, Klatskin tumor/surgery, hilar cholangiocarcinoma, perihilar cholangiocarcinoma, hepatectomy, liver resection, postoperative complications, morbidity, and mortality. The complete search string can be found in Supplementary Table I. Additional hand screening was performed of reference lists of included articles.

Study selection

Study selection was performed in three phases according to the PRISMA statement (Fig 1). Abstracts were screened for eligibility by two independent researchers (E.R. and L.C.F.), using Covidence online software (Covidence, Roende, Denmark). Any discrepancies were resolved by a third reviewer (A.M.S.). Two independent researchers (L.C.F. and A.M.S.) screened full texts and selected studies for inclusion in the systematic review and the meta-analysis. Discrepancies at this stage were resolved by discussion and consensus.

Data collection

Data collection was performed by two investigators (L.C.F. and A.M.S.) using predesigned data extraction forms. Collected data included study characteristics (author, publication year, study design, inclusion period), hospital characteristics (volume, geographical location), patient characteristics (age, sex, comorbidities), preoperative characteristics (biliary drainage, Bismuth-Corlette classification, portal vein embolization), operative characteristics (type of operation, number of procedures, vascular reconstruction), and postoperative events (mortality, intensive care unit admission, length of hospital stay, postoperative morbidity, Clavien-Dindo classification). Study authors were not contacted for additional data.

Risk of bias

Risk of bias was assessed by two independent researchers (A.M.S. and L.C.F.) using the Joanna Briggs Institute ([JBI] Faculty of Health Sciences, The University of Adelaide, South Australia) checklist for case series. Any discrepancies were resolved in a consensus meeting. The predefined criteria for each of the 10 questions in the JBI checklist—used to award low, unclear, or high risk of bias—is presented in Supplementary Table II. A risk-of-bias graph displays overall risk of bias for each item on the JBI checklist across all included studies. Risk of bias per individual study is displayed in a risk-of-bias summary table. Risk of bias across studies was assessed, including the risk of publication, detection, and reporting bias.

Statistical analysis

Categorical values are represented as numbers and percentages, continuous data as mean ± standard deviation (SD) or median and range. For meta-analysis on mortality, studies were considered comparable if they used the same time interval for mortality (either 30-day mortality, 90-day mortality, or in-hospital mortality), and only data of comparable studies were included in the meta-analysis. For overall morbidity, only studies reporting both major and minor complications (using the Clavien-Dindo classification or a comparable definition) were included in the meta-analysis. Regarding severe morbidity, only studies reporting on Clavien-Dindo grade III and IV complications or a comparable definition (eg, major complications requiring surgical, endoscopic or radiological reintervention, and/or life-threatening complications) were included in the meta-analysis.

To analyze length of hospital stay, we used the method proposed by Wan et al[12] to estimate the sample mean and standard deviation from provided medians. Meta-analysis was performed by inverse variance weighting with a random effects model using the meta package (v 4.9-2) for R software (v 3.4.3). Results were presented in forest plots, providing an estimate of the mean proportion with a 95% confidence interval (CI).

Heterogeneity was assessed using the I^2 statistic. An I^2 value of 50% or more was considered as significant heterogeneity and led to the use of a random effects model. Univariate and bivariate metaregression were performed using the metafor package (v 2.0-0) for R software for Asian versus Western publications and hospital volume as a continuous value. In addition, meta-regression for high-volume versus low-volume centers were performed using various cutoffs for high-volume centers. Distribution of hospital volume across Asian and Western centers was compared using the Mann-Whitney *U* test using SPSS 25 software (IBM, Armonk, NY, USA).

Results

A total of 2,765 records were identified through database searching (Fig 1). After removal of duplicates, 2,098 records were screened for eligibility. This resulted in the screening of 403 full texts and the inclusion of 51 studies.[4,7–10,13–58] Hand screening of reference lists yielded no additional articles eligible for inclusion.

Study characteristics

The 51 studies included in this systematic review comprise a total of 4,634 patients, with the largest study including 574 patients (Table I).[4] Four studies were multicenter, leading to a total of 79 centers included in this review.[8,10,41,44] A total of 20 studies originated from Western countries (United States, Europe, Egypt, and Israel), whereas 30 studies originated from Asian countries (Japan, China, Korea, Thailand, and India). One study reported on a combined cohort (United Kingdom and Japan) and presented results individually per center.[10]

Six studies evaluated their own results through time by dividing patients according to the period in which they underwent surgery.[4,17,18,28,36,45] In general, the morbidity and mortality rates decreased through time in these studies.

The number of patients undergoing preoperative biliary drainage was reported in 19 studies, with percentages varying from 0% (0 of 30)[29] to 100% (42 of 42).[24] Preoperative portal vein embolism (PVE) was described in 19 studies, with a range of 0%–58% (84 of 144).[17] Only 1 study treated patients with neoadjuvant chemotherapy (in 69% of the study population).[32]

Critical appraisal and risk of bias

Figure 2 presents the overall risk of bias for each item of the JBI checklist across all included studies. The study-level risk of bias for each individual study is presented in Supplementary Fig 1.

All studies were retrospective, although 8 studies prospectively collected their data.[7,15,16,23,36,37,53,55] Incomplete reporting of clinical information (Bismuth-Corlette type, biliary drainage, resection procedure, PVE, and comorbidities) and outcomes occurred in approximately 83% (41 of 51) and 22% (11 of 51) of included studies, respectively. These findings suggest a moderate to high risk of detection bias. Also, 43% (22 of 51) of the included studies do not describe inclusion of consecutive patients, suggesting a substantial risk of selection bias.

Postoperative mortality

Of the 51 included studies reporting on postoperative mortality, a total of 42 studies adequately provided time definitions for mortality. There were 18 studies reporting on 30-day mortality, accounting for 1,638 patients (Fig 3). The pooled 30-day mortality rate of these studies was 5% (95% CI 3%–7%). A total of 12 studies reported on 90-day mortality, accounting for 1,924 patients. Pooled 90-day mortality rate of these studies was 9% (95% CI 6%–12%). In-hospital mortality was described by 19 studies, comprising 1736 patients. Pooled in-hospital mortality rate was 8% (95% CI 6%–11%). The remaining 9 studies did not provide a clear definition of mortality and therefore were not included in the meta-analysis (Supplementary Table III). Four studies reporting on both 30-day mortality and 90-day mortality all presented a higher mortality rate at 90 days.[4,17,22,58] Liver failure was the most frequent reported cause of death.

Overall and severe morbidity

Overall morbidity, including minor complications (Clavien-Dindo grade I/II), was adequately reported in 17 studies, accounting for 2,190 patients (Fig 4). The pooled overall morbidity rate was 57% (95% CI 50%–64%).

A total of 25 studies reported on overall morbidity without a sufficient definition of morbidity. Unpooled outcomes of these studies are presented in Supplementary Table IV. Severe morbidity, defined as Clavien-Dindo grade III/IV, was adequately reported by 17 studies, accounting for a total of 1,770 patients (Fig 4). The pooled severe morbidity rate of these studies was 40% (95% CI 34%–47%). None of the included studies specifically reported the number of patients requiring ICU admission.

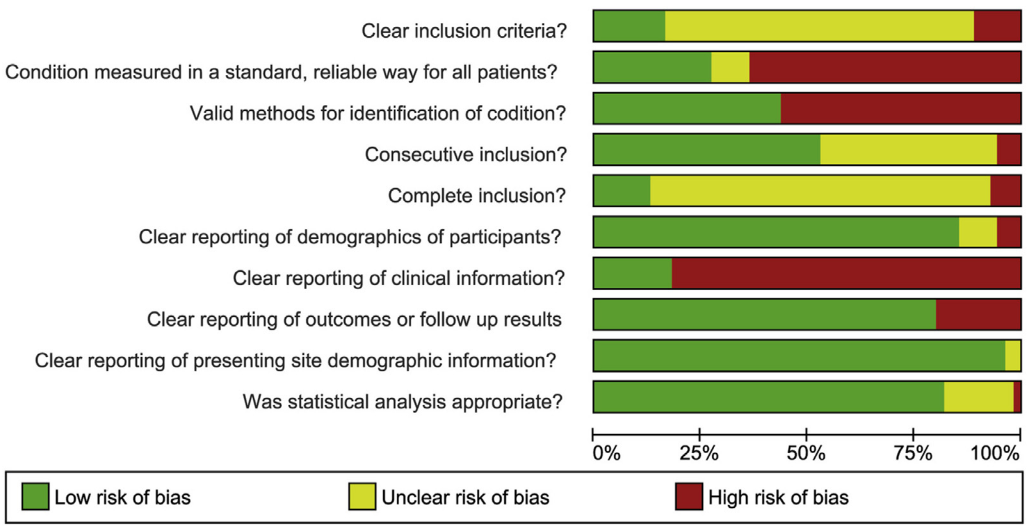

Fig. 2. Risk of bias graph. Overall risk of bias across all included studies.

Western versus Asian studies

Metaregression comparing outcomes from Western studies with outcomes from Asian studies showed significant differences in mortality (30-day, 90-day, and in-hospital) in favor of the Asian studies (Fig 3). The 30-day and 90-day mortality for Western centers was 8% and 12% (95% CI 6%–11% and 10%–15%), respectively, compared with 2% and 3% (95% CI 2%–4% and 2%–5%) for Asian centers ($P < .001$). In-hospital mortality in Western centers was 13% (95% CI 5%–28%) compared with 7% (95% CI 5%–10%) in Asian centers ($P = .233$).

Pooled overall morbidity in the Western studies was 63% (95% CI 53%–72%) and 54% in the Asian series (95% CI 45%–63%, $P = .206$; Fig 4). Pooled severe morbidity was 43% in the Western series (95% CI 34%–52%) and 37% in the Asian series (95% CI 27%–48%, $P = .424$).

Hospital volume

The median annual volume of hepatectomies performed for PHC in this systematic review was 4. Of 1 center, annual volume could not be calculated because the inclusion period of that study was not provided.[55] Of the 79 included centers in this review, only 11 centers performed 8 or more hepatectomies for PHC per year.[4,9,13,22,29,31,40,50–52] We observed 18 of 31 (58%) Asian centers that performed ≥4 procedures per year, and 9 of 20 (45%) Western centers performed ≥4 procedures per year. The median of all the Asian centers was 6 procedures per year compared with a median of 4 procedures in the Western centers ($P = .524$).

On univariate metaregression, hospital volume (as a continuous value) was not significantly associated with 30-day mortality, 90-day mortality, in-hospital mortality, overall morbidity, or severe morbidity (Table II).

Bivariate metaregression

When corrected for hospital volume, the Asian centers showed a negative correlation with 30-day mortality (z-value −3.727, $P < .001$) and 90-day mortality (z-value −6.997, $P < .001$). In hospital mortality, overall morbidity and severe morbidity were not significantly influenced by geographic origin (Asian/Western) when corrected for hospital volume. When corrected for geographic origin (Asian/Western), severe morbidity increased with increasing hospital volume (z-value 2.069, $P = .039$). The effect of hospital volume on overall morbidity was negative, although not significant (z-value −0.015, $P = .091$)

High versus low volume with cutoffs at 4, 6, and 8 hepatectomies per year

In Supplementary Table V, results of univariate and bivariate metaregressions are presented, using a cutoff of 4, 6, and 8 procedures per year for high-volume centers. Univariate metaregression using cutoffs of 4 and 6 hepatectomies per year, showed that 30-day mortality was lower in high-volume centers (eg, performing more than 4 or 6 hepatectomies per year) compared with low-volume centers (z-value −0.025, $P = .049$). This association was not found when the results were corrected for geographic location ([Asian/Western]; z-value 0.018, $P = .114$).

Length of hospital stay

A total of 23 studies, accounting for 2,061 patients, reported on length of hospital stay. There were 12 studies that only reported median length of hospital stay. Overall, pooled hospital stay was 29 days (95% CI 27–31 days). The pooled hospital stay for the Western series was 18 days (95% CI 17–19 days), and the pooled hospital stay for the Asian series was 42 days (95% CI 34–52 days, $P < .001$).

Discussion

This comprehensive systematic review on morbidity and mortality of major hepatectomy for PHC patients totaled 51 studies, reporting on a total of 4,634 patients from 79 centers worldwide. Meta-analysis revealed a 30-day mortality rate of 5%, 90-day and in-hospital mortality rates of 9%, a severe morbidity rate of 40%, and an overall morbidity rate of 57%. These outcomes showed substantial heterogeneity across studies. We observed a significant difference in mortality rates in the Western and Asian studies in favor of the Asian studies, even when corrected for hospital volume. Hospital volume alone had no significant influence on mortality or morbidity.

Although an inverse relationship has been presented in the literature between case volume and perioperative mortality in liver surgery,[6] we were unable to detect an association between hospital volume and mortality in this study. The median annual volume of hepatectomies performed for PHC in this systematic

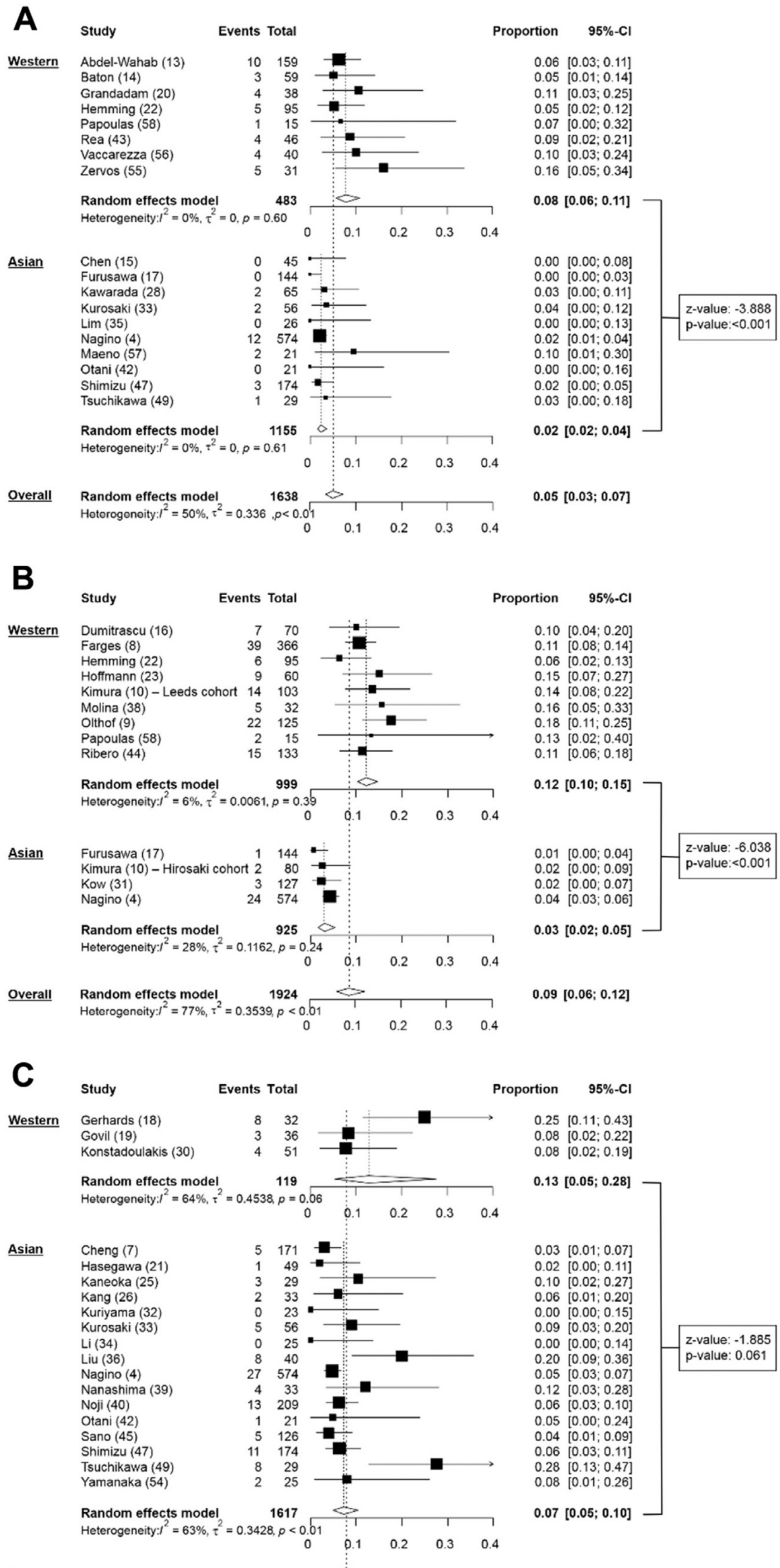

Fig 3. Forest plots of reported mortality (Asian versus Western countries). (*A*) 30-day mortality. (*B*) 90-day mortality. (*C*) In-hospital mortality.

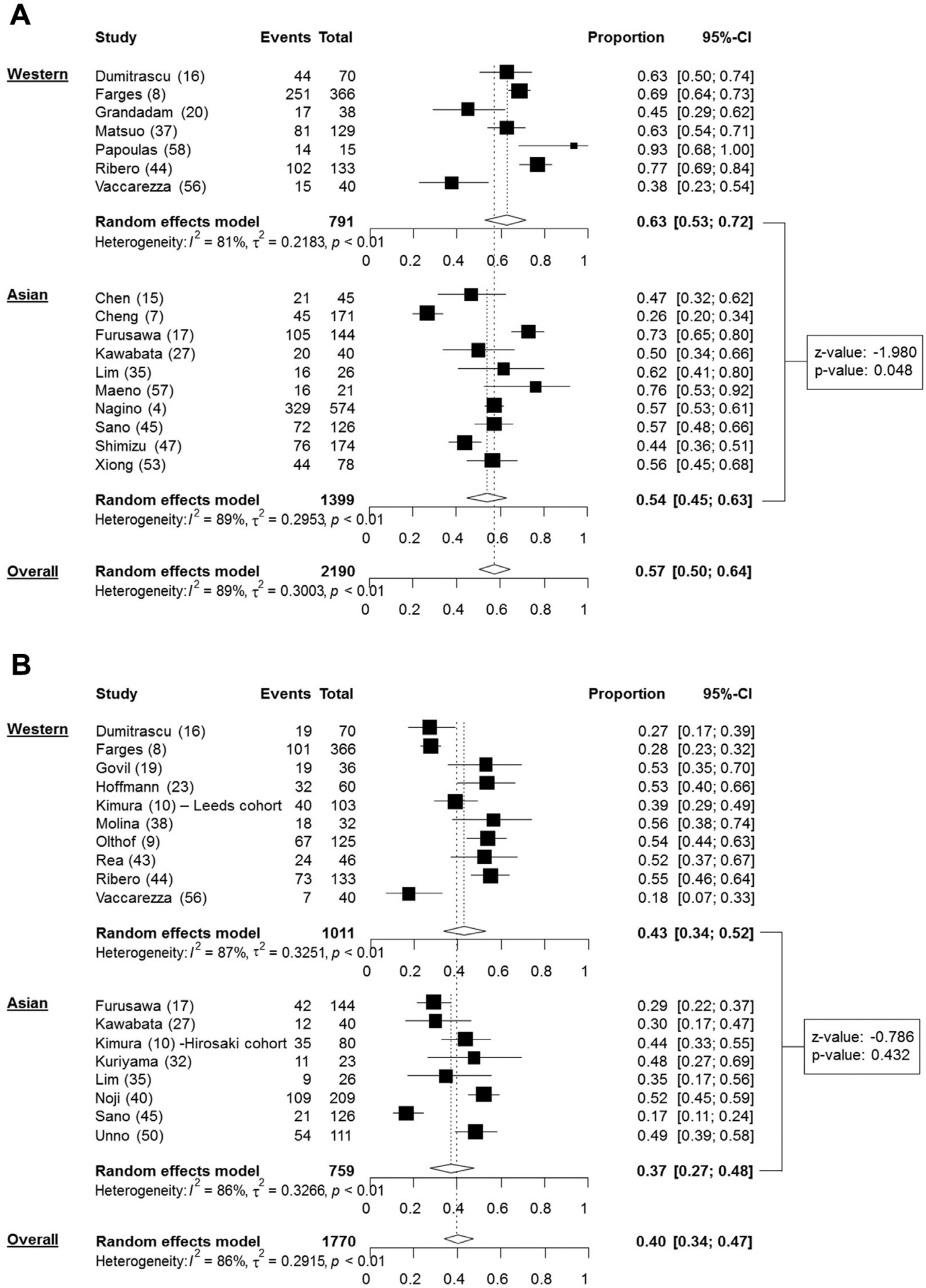

Fig 4. Forest plots of reported morbidity (Asian versus Western countries). (*A*) Overall morbidity. (*B*) Severe morbidity.

review was 4, with only 11 studies having an annual volume of more than 8 hepatectomies.[4,9,13,22,29,31,40,50–52] Although we chose to use hospital volume as a continuous value, we also performed our analyses with cutoffs of 4, 6, and 8 procedures per year. This resulted in a significantly lower 30-day mortality in high-volume centers performing more than 4 or 6 procedures per year compared with low-volume centers. When corrected for geographic origin, this association was not significant. The scarcity of high-volume centers may have hampered the detection of this association. Also, as part of this study, we calculated the annual volume based on hepatectomies performed for PHC, not accounting for potential experience derived from hepatectomies for other indications.

When corrected for geographic location (Asian/Western), increasing hospital volume was associated with higher severe morbidity. This contrasting finding may reflect a referral bias of more complex patients to high-volume centers.

We observed relatively more centers with a hospital volume above the median of 4 procedures per year in Asia (18 of 31, 58%) compared with Western countries (9 of 20, 45%), although this difference was not significant. Because of a higher prevalence of PHC in Asian countries, and therefore more experience in treating

Table II
Univariate and bivariate metaregression: The effect of hospital volume and geographic location on mortality and morbidity

Outcome		Univariate				Bivariate			
		Estimate	*Z* value	95% CI	*P* value	Estimate	*Z* value	95% CI	*P* value
30-day mortality	Asian	-0.050	*-3.888*	-0.075- -0.025	**< .001**	-0.049	*-3.727*	-0.075- -0.023	**< .001**
	Volume	-0.001	*-0.746*	-0.004-0.002	.456	-0.000	*-0.002*	-0.002-0.002	.998
90-day mortality	Asian	-0.090	*-6.038*	-0.120- -0.061	**< .001**	-0.101	*-6.997*	-0.129–0.073	**< .001**
	Volume	-0.005	*-1.121*	-0.012-0.003	.262	0.002	*1.664*	-0.000-0.005	.096
In hospital mortality	Asian	-0.064	*-1.885*	-0.132-0.003	.061	-0.048	*-1.650*	-0.106-0.009	.099
	Volume	-0.001	*-1.300*	-0.004-0.007	.193	-0.001	*-0.927*	-0.004-0.001	.354
Overall morbidity	Asian	-0.055	-1.980	-0.109- -0.006	**.048**	-0.038	*-0.465*	-0.199-0.122	.122
	Volume	-0.001	-1.302	-0.004-0.007	.193	-0.015	*-1.825*	-0.031-0.001	.068
Severe morbidity	Asian	-0.053	-0.786	-0.183-0.078	.432	-0.113	-1.689	-0.245-0.018	.091
	Volume	0.011	1.369	-0.005-0.026	.171	0.017	2.069	0.001-0.033	**.039**

patients with PHC, we expected hospital volume to play a substantial role in these differences. However, even when corrected for hospital volume (as continuous values) Asian centers showed lower 30-day and 90-day mortality. Several studies have specifically addressed the differences in outcomes according to geographic location. Kimura et al[10] compared patients from Hirosaki, Japan, with patients from Leeds, United Kingdom. Results from this study showed comparable severe morbidity rates but a significantly lower 90-day mortality in the Japanese population. Olthof et al[59] compared two Western patient series (AMC, Amsterdam, the Netherlands, and Memorial Sloan Kettering Cancer Center, New York, NY, USA) and a series from Hokkaido, Japan, showing major differences in patient characteristics, treatment strategies, perioperative outcomes, and survival between Eastern and Western PHC cohorts.

Differences in Asian and Western populations may potentially play a role in the observed differences in outcomes after hepatectomy for PHC. Patient characteristics differ among regions, with a higher incidence of obesity in Western populations. Because body mass index and the American Society of Anesthesiologists classification were rarely reported in the included studies, we could not quantify differences in populations in this review.

Not only differences in epidemiology, but also differences in treatment approaches may have effected outcome variations across studies. Policy on preoperative biliary drainage differs, especially regarding the use of nasobiliary drainage, which is advocated in Asian centers but rarely used in Western hospitals.[10] However, the debate on which patients to drain and whether this should be undertaken by percutaneous or endoscopic biliary drainage, currently remains undecided.[2] Preoperative PVE increases the volume of future remnant liver and is more commonly performed in Asia.[59] Also, the length of hospital stay tends to be longer in the Asian series, as was demonstrated in this review.

This review has several limitations. First is the substantial risk of bias, as discussed earlier in this report. Because of the rarity of PHC, available evidence consists solely of observational studies. The majority of included studies is retrospective and generally of poor quality. Although many studies only present the most severe complications rather than the number of complications, the lack of inclusion of consecutive patients suggests potential underreporting of negative results. It is likely that a certain amount of publication bias exists on this topic because centers with poor outcomes may not be eager to publish those results. We excluded studies reporting on fewer than 10 hepatectomies. Although this may have introduced some degree of selection bias, it is likely that these studies report on biased samples (ie, only reporting a small series of patients with favorable outcomes). Furthermore, we could not identify any publications fulfilling the inclusion criteria for this systematic review originating from Australia, Africa, or Canada.

We only included publications after the year 2000 in this systematic review. However, some of the included studies represent patients over a long timeframe and we were unable analyze their results separately. Advances in surgical techniques, perioperative management, and technical improvements obviously had an impact on outcomes through time. Six studies evaluated their own results through time, showing decreased morbidity and mortality rates in later periods.[4,17,18,28,36,45]

It is important to note that reporting and grading of morbidity and mortality varied widely among studies. In-hospital, 30-day and 90-day mortality were described for mortality, whereas 9 studies provided no definition of mortality. Studies reporting on both 30-day and 90-day mortality showed an increased mortality rate at 90 days compared with 30 days, which supports the notion that reporting 30-day mortality significantly underestimates surgery-related death.[4,17,22] Moreover, only 3 studies provided a clear period in which morbidity was observed. Clear definitions of overall morbidity, and grading of severity (such as the Clavien-Dindo system[60], or the International Study Group of Liver Surgery criteria for bile leakage,[61] posthepatectomy liver failure,[62] and hemorrhage[63]) were often lacking, and separate complications were often not specified. Patients with complex complications require prolonged treatment and hospital stay, which might progress into slow deterioration, ultimately leading to the patient's death after more than 30 days. It is therefore crucial to report mortality in this patient category at 90 days.

In this review, we addressed the issue of different definitions of outcomes by performing our meta-analysis only on subgroups with comparable outcome criteria. Because we could include 51 studies accounting for 4,634 patients, it was possible to do this subgroup analysis with preservation of statistical power.

The variability of criteria to report outcomes encountered in this systematic review stresses the need for standardized reporting of surgical complications. This is especially of importance in studies on PHC patients because this disease is rare and evidence mainly consists of small observational studies. The results of this review underscore the need for an international multicenter, prospective registration of PHC patients undergoing surgical resection, with predefined standardized outcomes. For such a registry, but also for future single-center studies, we propose that reports on surgical outcomes for resection of PHC should at a minimum contain the items presented in Supplementary Table VI.

Most studies report only the most severe complication per patient, and it is known that many patients experience more than one complication.[17] It is important to take into account that the occurrence of more than one complication can be of major clinical importance to the individual patient. By using the comprehensive complication index as a measurement for overall morbidity, all events a patient experiences with their respective severity can be integrated into a single score.[64]

In conclusion, this comprehensive systematic review and meta-analysis of observational studies showed high morbidity and mortality rates after major hepatectomy in PHC patients. When corrected for geographic localization, higher hospital volume was associated with increased severe morbidity. This association may reflect a referral bias. The Western series showed a higher mortality in comparison with the Asian series, even when corrected for annual hospital volume. Treatment strategies in Asian and Western centers should be studied and compared to further investigate causes for different outcomes. The incomplete reporting and variation in criteria to report outcomes encountered in this systematic review stress the need for standardized outcome reporting for PHC.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.surg.2019.01.010.

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