



Characteristics and outcomes of hepatocellular carcinoma patients with macrovascular invasion following surgical resection: a meta-analysis of 40 studies and 8,218 patients

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Background: Guidelines recommend that hepatocellular carcinoma (HCC) patients with portal vein tumor thrombosis (PVTT) and/or hepatic vein tumor thrombosis (HVTT) should undergo systemic therapy. However, recent data suggest that surgical resection may be beneficial in selected cases, but outcomes are heterogenous. We aimed to estimate pooled overall survival (OS), recurrence free survival (RFS) and complication rates in HCC patients with macrovascular invasion (MVI) following surgical resection.

Methods: In this systematic review and meta-analysis, two investigators independently searched PubMed, Embase, and Cochrane databases from inception to Nov 10, 2020, without language restrictions, for studies reporting outcomes of adult HCC patients with MVI who underwent liver resection with curative intent.

Results: We screened 8,598 articles and included 40 studies involving 8,218 patients. Among all patients with MVI, the pooled median OS was 14.39 months [95% confidence interval (CI): 10.99–18.84], 1-year OS was 54.47% (95% CI: 46.12–62.58%) and 3-year OS was 23.20% (95% CI: 16.61–31.42%). Overall, 1- and 3-year RFS were 27.70% (95% CI: 21.00–35.57%) and 10.06% (95% CI: 6.62–15.01%), respectively. Among patients with PVTT, median OS was 20.41 months in those with segmental/2nd order involvement compared to 12.91 months if 1st order branch was involved and 6.41 months if the main trunk was involved. The pooled rate of major complications was 6.17% (95% CI: 3.53–10.56%).

Conclusions: Overall median survival was 14.39 months for HCC patients with MVI following resection. Median survival was higher in PVTT with segmental/2nd order involvement at 20.41 versus 6.41 months if the main trunk was involved.

Keywords: Hepatocellular carcinoma (HCC); resection; portal vein; macrovascular invasion (MVI); recurrence

Submitted Oct 10, 2021. Accepted for publication Mar 23, 2022.

doi: 10.21037/hbsn-21-419

View this article at: <https://dx.doi.org/10.21037/hbsn-21-419>

Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer death worldwide (1), with an overall 5-year survival of less than 20% (2). Surgical resection, along with liver transplantation and radiofrequency ablation, are the only curative therapies for HCC (3). However, portal vein tumor thrombosis (PVTT) is present in more than a quarter of cases at the point of diagnosis, while hepatic vein tumor thrombosis (HVTT) is present in around 13% (4-6). These are often considered a contraindication to surgical treatment. As a result, patients with tumor macrovascular invasion (MVI) are classified as Barcelona Clinic Liver Cancer (BCLC) stage C, with treatment options limited to mostly palliative systemic therapy. Prognosis is poor, with untreated patients having a median overall survival (OS) of around 6–8 months and a 1-year survival of 25% (2,7-9).

More recently, data from Asia and the US suggest a survival benefit with surgical resection in well selected HCC patients with MVI (10-12). However, available data are heterogenous likely due in part to the inclusion of patients with tumor thrombus that involved different anatomic levels of the vasculature in different studies. Therefore, the primary purpose of this study was to conduct a systematic review and meta-analysis to evaluate OS, recurrence free survival (RFS) and perioperative complications of HCC patients with MVI who underwent liver resection with curative intent. Our secondary aims were to evaluate the effect of different anatomic sub-classes of MVI on clinical outcomes, as well as to identify factors associated with survival and recurrence. We present the following article in accordance with the PRISMA reporting checklist (available at <https://hbsn.amegroups.com/article/view/10.21037/hbsn-21-419/rc>).

Methods

In accordance with the PRISMA statement, we conducted and reported the meta-analysis as recommended for meta-analyses of observational studies (Appendix 1) (13).

Search strategy and selection criteria

We searched PubMed, Embase, and the Cochrane Library databases from inception to Nov 10, 2020 for original full-text research articles, using search terms based on “HCC”, “resection”, and “survival” as developed in collaboration

with a medical librarian (CW) from the Lane Medical Library at Stanford University, CA, USA. Details of the search terms and study selection criteria are available in the Appendix 1. Briefly, we included original research studies published as full-text articles that provided data on adults aged ≥ 18 years with HCC and portal vein and/or hepatic vein invasion who had undergone primary surgical resection with curative intent and reported OS and/or RFS outcomes. In order to discern the impact of liver resection on survival outcomes of patients with MVI, we excluded studies with patients who received neo-adjuvant therapy for HCC.

Two authors independently searched the databases for relevant articles, screened through them by title and abstract review, followed by a full-text review of potentially eligible articles. Discordance was resolved by consensus or consultation with a third and senior author. Data was extracted from eligible studies using a case report form developed for this study. Quality assessment of included studies was performed using scales developed for this review based on the Newcastle-Ottawa scale (NOS) for retrospective studies (14).

Statistical analysis

We used a random-effects model to determine pooled estimates of demographic and clinical characteristics of HCC patients with MVI. We also used a random-effects model to estimate pooled percentages and 95% confidence intervals (CI) of median, 1-, 3-, and 5-year OS and RFS. We performed pre-planned analyses if there were sufficient data available for the following subgroups: studies that included PVTT only versus PVTT and/or HVTT, sub-classification of PVTT (as recommended by the Liver Cancer Study Group of Japan and the Cheng’s classification) (15,16), country/region, alpha-fetoprotein (AFP) levels, number of tumor nodules, tumor histology, status of hepatic function, presence of cirrhosis and etiology of the underlying liver disease. We performed meta-regression to evaluate factors associated with 3- and 5-year OS and RFS for variables with available data such as age, etiology of liver disease, presence of cirrhosis, tumor number, tumor size, sub-classification of MVI, AFP levels and platelet levels.

We assessed for inter-study heterogeneity with the Higgins’ and Thompson’s I^2 statistics derived from the Cochran’s Q test, with heterogeneity considered significant if $I^2 > 50\%$ (17). We utilized the Egger’s test and the funnel plot to assess for publication bias. All statistical analyses

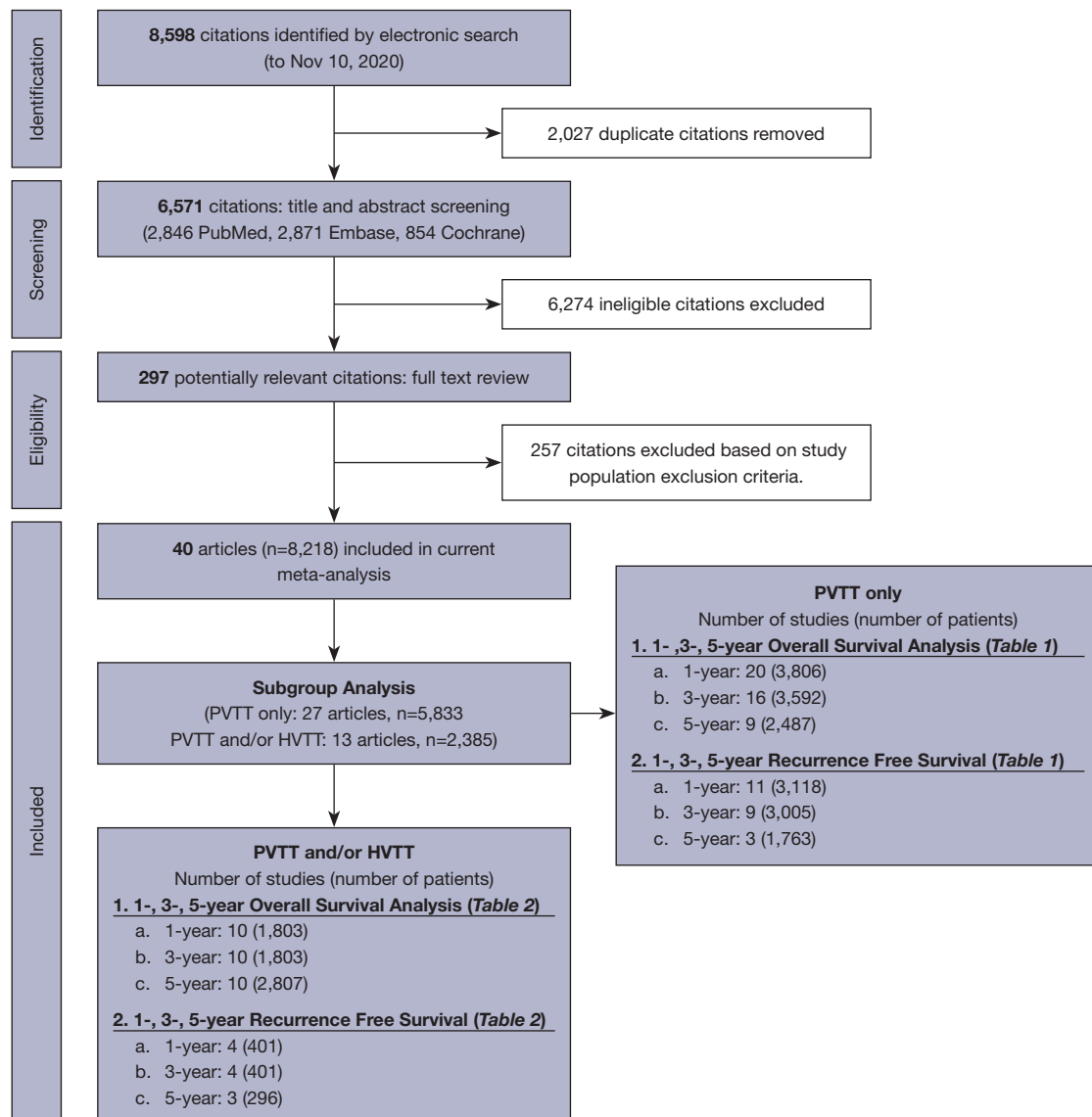


Figure 1 Flow chart of systematic literature search and screening for analysis of HCC resection outcomes in patients with MVI. PVTT, portal vein tumor thrombosis; HVTT, hepatic vein tumor thrombosis; HCC, hepatocellular carcinoma; MVI, macrovascular invasion.

were carried out with the meta-packages in R statistical software (version 3.6.1).

Results

Study selection and study characteristics

We screened 8,598 articles, removed 2,027 duplicates, reviewed titles and abstracts of 4,646 articles, identified and reviewed the full text of 297 potentially eligible articles and finally selected 40 studies involving 8,218 patients from

8 countries/regions that met our study inclusion/exclusion criteria (Figure 1, Tables 1,2). Of the included studies, 34 were from Asia, 4 from Europe, 1 from North America and 1 from multiple regions. The study sample size ranged from 12 to 1,517. Details of individual study characteristics are reported in Appendix 1, while each study's patient and tumor characteristics are summarized in Appendix 1. The quality assessment for each study is shown in Appendix 1. Overall, 38 studies were of high quality, 2 studies were of moderate quality, and none were of low quality.

Table 1 OS and RFS after liver resection in patients with HCC and only PVTT (not inclusive of patients with HVTT)

Country/region	n/n	1-year, % (95% CI)	P	n/n	3-year, % (95% CI)	P	n/n	5-year, % (95% CI)	P
OS*									
Global	20/3,806	51.77 (40.71–62.65)	–	16/3,592	20.16 (11.52–32.87)	–	9/2,487	21.19 (11.16–36.54)	–
By country/region*									
China	15/3,411	46.68 (34.93–58.81)	<0.0001	12/3,228	15.65 (7.69 – 29.23)	<0.0001	6/2,166	18.25 (8.15 – 35.95)	<0.0001
Japan	1/29	62.10 (43.62–77.63)		1/29	24.10 (11.94–42.65)		1/29	17.20 (7.34–35.27)	
Korea	2/74	72.43* (61.21–81.39)		1/43	42.00 (28.33–57.02)		0/0	–	
Taiwan	1/247	85.00 (79.98–88.93)		1/247	68.00 (61.93–73.52)		1/247	61.00 (54.78–66.89)	
France	1/45	30.80 (19.12–45.60)		1/45	20.50 (11.11–34.71)		1/45	15.40 (7.49–29.03)	
RFS*									
Global	11/3,118	22.67 (16.97–29.60)	–	9/3,005	7.05 (4.99–9.87)	–	3/1,763	0.65 (0.01–26.72)	–
By country*									
China	8/2,999	20.29 (14.27–28.02)	0.15	7/2,917	6.22 (4.39–8.75)	0.04	2/1,718	0.10** (0.00–31.83)	0.12
Korea	2/74	31.17 (19.73–45.48)		1/43	16.00 (7.77–30.09)		0/0	–	
France	1/45	32.50 (20.51–47.33)		1/45	11.60 (5.01–24.63)		1/45	11.60 (5.01–24.63)	

n/n, studies/patients; *, some studies encompassed multiple regions, so they were included in the global analysis but not in the regional/country analysis; **, all $I^2 > 65.2$ with P value <0.05, except for values marked. OS, overall survival; RFS, recurrence free survival; HCC, hepatocellular carcinoma; PVTT, portal vein tumor thrombosis; HVTT, hepatic vein tumor thrombosis.

Study patient characteristics, overall and by presence of PVTT only or PVTT and/or HVTT

Study and patient characteristics are shown in *Table 3*, and the studies that provided data for these analyses are listed in *Appendix 1*. Overall, the majority of patients were male (86.80%, 95% CI: 83.39–89.59%), and the pooled mean age was 52.93 years (95% CI: 51.15–54.70) (*Table 3*). More than three-quarter of patients (79.49%, 95% CI: 65.30–88.87%) had cirrhosis, and the pooled mean Model for End-Stage Liver Disease (MELD) score was 7.34 (95% CI: 6.23–8.45). The most common underlying liver disease was hepatitis B virus (HBV) infection (74.37%, 95% CI: 61.77–83.90%),

followed by hepatitis C virus (HCV) infection (16.16%, 95% CI: 7.63–31.04%) and alcohol (4.92%, 95% CI: 3.00–7.98%). The pooled mean AFP level was 892.91 ng/mL (496.50–1,289.32) (*Appendix 1*). With regards to tumor characteristics, the pooled mean tumor size was 7.43 cm (95% CI: 5.44–9.42), the proportion of patients with poorly differentiated HCC was 36.99% (95% CI: 13.08–69.61%), and the proportion with lymphatic invasion was 11.97% (95% CI: 8.48–16.65%) (*Appendix 1*). The proportion of patients that underwent anatomical resection (6 studies, 517 patients) and non-anatomical resection (5 studies, 493 patients) were 73.60% (95% CI: 44.61–90.61%) and 36.92% (95% CI: 19.14–59.15%) respectively. The pooled

Table 2 OS and RFS after liver resection in patients with HCC from studies that included PVTT and/or HVTT

Country/region	n/n	1-year, % (95% CI)	P	n/n	3-year, % (95% CI)	P	n/n	5-year, % (95% CI)	P
OS*									
Global	10/1,803	60.07 (49.22–70.00)	–	10/1,803	27.34 (19.36–37.10)	–	10/2,807	19.78 (13.85–27.44)	–
By country/region*									
China	5/830	54.83 (41.60–67.41)	<0.0001	5/830	17.62** (15.17–20.36)	<0.0001	2/607	11.47* (9.16–14.25)	<0.0001
Japan	1/651	80.00 (76.75–82.90)		1/651	56.60 (52.76–60.36)		2/917	32.42 (19.01–49.51)	
Taiwan	0/0	–		0/0	–		1/76	15.70 (9.12–25.68)	
France	1/26	38.00 (21.73–57.50)		1/26	20.00 (8.73–39.52)		1/26	13.00 (4.55–31.91)	
Italy	1/62	53.30 (49.93–65.27)		1/62	30.10 (20.02–42.56)		1/62	20.00 (11.83–31.78)	
Spain	1/12	66.70 (37.62–86.93)		1/12	33.30 (13.07–62.38)		1/12	22.20 (6.81–52.68)	
United States	0/0	–		0/0	–		1/165	14.00 (9.49–20.17)	
RFS*									
Global	4/401	45.30 (38.00–52.79)	–	4/401	20.88 (11.36–35.22)	–	3/296	17.66 (13.72–22.42)	–
By country*									
China	1/105	51.90 (42.39–61.27)	0.03	1/105	7.90 (4.05–14.84)	0.003	0/0	–	0.59
Italy	1/62	31.70 (21.37–44.21)		1/62	20.80 (12.45–32.66)		1/62	15.60 (8.52–26.85)	
Spain	1/12	58.30 (30.74–81.50)		1/12	43.70 (19.88–70.83)		1/12	21.90 (6.66–52.41)	

n/n, studies/patients; *, some studies encompassed multiple regions, so they were included in the global analysis but not in the regional/country analysis; **, all $I^2 > 89.2$, all P value for available I^2 were < 0.05 . OS, overall survival; RFS, recurrence free survival; HCC, hepatocellular carcinoma; PVTT, portal vein tumor thrombosis; HVTT, hepatic vein tumor thrombosis.

median follow-up was 16.60 months (95% CI: 12.35–20.85).

When studies including only PVTT (without HVTT) were compared against studies including PVTT and/or HVTT, the two groups were distinct in terms of age with the former being significantly younger (50.93 years, 95% CI: 49.62–52.24 versus 57.86 years, 95% CI: 52.46–63.27, $P=0.01$) but similar in terms of gender ($P=0.54$) and presence of cirrhosis ($P=0.56$).

OS

Overall analysis (OS)

Overall, 21 studies (3,909 patients) provided data for median OS (Asia 17 studies, 3,611 patients; Europe 3 studies, 133 patients; North America 1 study, 165 patients). The pooled median OS was 14.39 months (95% CI: 10.99–18.84) (Table 4). The 1-year (30 studies, 5,609 patients), 3-year

Table 3 Study and patient characteristics

Characteristics	Overall		PVTT only		PVTT and/or HVTT		P*
	n/n	Mean/median/% (95% CI)	n/n	Mean/median/% (95% CI)	n/n	Mean/median/% (95% CI)	
Study characteristics							
Median study year	40/8,218	2007	27/5,833	2007	13/2,385	2004	0.21
Median follow-up (months)	9/1,161	16.60 (12.35–20.85)	8/1,133	17.14 (12.66–21.62)	1/28	11.00 (7.70–14.30)	0.06
Patient characteristics							
Male (%)	35/6,128	86.80 (83.39–89.59)	26/4,316	86.99 (82.56–90.42)	9/1,812	85.28 (81.11–88.66)	0.54
Age (years)	31/4,389	52.93 (51.15–54.70)	22/2,953	50.93 (49.62–52.24)	9/1,436	57.86 (52.46–63.27)	0.01
Platelet (10 ⁹ /L)	12/2,221	196.60 (174.45–218.75)	8/1,080	195.68 (163.72–227.65)	4/1,141	195.68 (163.72–227.65)	0.94
MELD score	5/928	7.34 (6.23–8.45)	5/928	7.34 (5.93–8.76)	0/0	–	–
Cirrhosis (%)	24/3,930	79.49 (65.30–88.87)	20/3,531	78.30 (60.73–89.39)	4/399	84.51 (64.74–94.19)	0.56
Alcohol (%)	6/890	4.92 (3.00–7.98)	4/428	4.44** (2.85–6.85)	2/462	5.78 (2.65–12.15)	0.56
HBV (%)	29/5,290	74.37 (61.77–83.90)	21/3,454	80.92 (71.73–87.64)	8/1,836	49.75 (19.75–79.93)	0.055
HCV (%)	16/2,622	16.16 (7.63–31.04)	12/1,447	13.84 (5.63–30.19)	4/1,175	41.23 (35.30–47.43)	0.42
Child-Pugh class A (%)	28/5,051	96.21 (93.23–97.91)	21/3,924	93.76 (89.99–96.17)	7/1,127	99.87 (93.85–100.00)	0.051
Child-Pugh class B (%)	27/4,886	4.25 (2.43–7.34)	21/3,924	6.24 (3.83–10.01)	6/962	0.26 (0.01–7.62)	0.07

n/n, studies/patients; *, between PVTT only and PVTT and/or HVTT; **, all $I^2 > 54.6$ with P value < 0.05 , except for values marked; PVTT, portal vein tumor thrombosis; HVTT, hepatic vein tumor thrombosis; MELD, Model for End-Stage Liver Disease; HBV, hepatitis B virus; HCV, hepatitis C virus.

(26 studies, 5,395 patients) and 5-year OS (19 studies, 4,574 patients) were 54.47% (95% CI: 46.12–62.58%), 23.20% (95% CI: 16.61–31.42%) and 20.29% (95% CI: 14.23–28.08%), respectively (Table 5 and Appendix 1).

Subgroup analyses by presence of PVTT only or PVTT and/or HVTT and by country/region (OS)

Among studies that provided data for PVTT only (without HVTT), median OS was 12.97 months (95% CI: 10.48–16.06) (Table 4). The 1-year (20 studies, 3,806 patients), 3-year (16 studies, 3,592 patients) and 5-year OS (9 studies, 2,487 patients) were 51.77% (95% CI: 40.71–62.65%), 20.16% (95% CI: 11.52–32.87%) and 21.19% (95% CI: 11.16–36.54%) (Table 1, Appendix 1), respectively.

Among studies that provided data for PVTT and/or HVTT, median OS was 16.83 (95% CI: 10.12–27.98) (Table 4). The 1-year (10 studies, 1,803 patients), 3-year (10 studies, 1,803 patients) and 5-year OS (10 studies, 2,807 patients) were 60.07% (95% CI: 49.22–70.00%), 27.34% (95% CI: 19.36–37.10%) and 19.78% (95% CI:

13.85–27.44%), respectively (Table 2, Appendix 1). There were no significant differences in 1-, 3- and 5-year OS between the PVTT only group versus the PVTT and/or HVTT only group (all $P > 0.32$).

Country/region level data for OS, where available, are shown in Tables 1, 2, 5. For OS, most of the studies ($n=20$) came from China, with other countries contributing 1–2 studies each. The studies included in the analyses of OS are listed in Appendix 1.

Subgroup analyses by sub-classification of PVTT

There were significant differences in the median OS among patients with different levels of vascular invasion. The median OS among patients with segmental/2nd order portal vein branch involvement was 20.41 months (95% CI: 15.16–27.48; 3 studies, 612 patients), versus 12.91 months (95% CI: 9.97–16.72; 3 studies, 466 patients) among patients with 1st order branch involvement and 6.41 months (95% CI: 5.07–8.10; 2 studies, 214 patients) among those with main portal vein trunk/superior mesenteric vein (SMV)

Table 4 Median survival, complication rates, operation time and blood loss of liver resection for HCC with MVI

Outcomes and complications	Number of studies	Number of patients	Refer to sub-header
Median survival (months)			
Overall	21	3,909	14.39 (10.99–18.84)
PVTT only	13	2,437	12.97 (10.48–16.06)
PVTT and/or HVTT	8	1,472	16.83 (10.12–27.98)
All complications (%)			
Overall	13	1,698	30.52 (23.60–38.44)
PVTT only	8	1,039	27.37 (19.72–36.63)
PVTT and/or HVTT	5	659	36.59 (24.44–50.72)
Minor complications (%)			
Overall	9	669	24.87 (20.09–30.36)
PVTT only	6	474	21.44 (17.15–26.45)*
PVTT and/or HVTT	3	195	31.79 (25.64–38.66)*
Major complications (%)			
Overall	16	1,687	6.17 (3.53–10.56)
PVTT only	12	1,327	4.86 (2.10–10.82)
PVTT and/or HVTT	4	360	9.17 (6.59–12.61)*
Operation time (min)			
Overall	9	1,253	219.42 (182.77–256.07)
PVTT only	5	749	185.89 (181.06–190.73)
PVTT and/or HVTT	4	504	146.96 (137.32–156.60)
Blood loss (mL)			
Overall	8	1,290	655.76 (434.94–876.58)
PVTT only	6	824	618.28 (342.81–893.75)

*, all $I^2 > 57.4$ with P value < 0.05 , except for values marked. HCC, hepatocellular carcinoma; MVI, macrovascular invasion; PVTT, portal vein tumor thrombosis; HVTT, hepatic vein tumor thrombosis.

involvement, $P < 0.0001$.

The pooled 1-year OS for segmental and second-order branch involvement, first-order branch involvement and main trunk/SMV involvement were 57.04% (95% CI: 38.92–73.45%), 42.16% (95% CI: 22.71–64.38%) and 19.59% (95% CI: 8.75–38.23%), respectively (Table 6).

The pooled 3-year OS for segmental and second-order branch involvement, first-order branch involvement and main trunk/SMV involvement were 28.55% (95% CI: 21.47–36.86%), 17.85% (95% CI: 4.94–47.60%) and 0.00% (95% CI: 0.00–100.00%), respectively (Table 6 and Appendix 1).

There were insufficient studies reporting 5-year OS for meta-analysis.

RFS

Overall analysis (RFS)

Overall, the 1-year (15 studies, 3,519 patients), 3-year (13 studies, 3,406 patients) and 5-year RFS (6 studies, 2,059 patients) were 27.70% (95% CI: 21.00–35.57%), 10.06% (95% CI: 6.62–15.01%) and 4.31% (95% CI: 0.61–24.76%), respectively (Table 5, Appendix 1). The pooled

Table 5 OS and RFS after liver resection in patients with HCC and MVI with only PVTT and in those with PVTT and/or HVTT

Country/region	n/n	1-year, % (95% CI)	P	n/n	3-year, % (95% CI)	P	n/n	5-year, % (95% CI)	P
OS*									
Global	30/5,609	54.47 (46.12–62.58)	–	26/5,395	23.20 (16.61–31.42)	–	19/4,574	20.29 (14.23–28.08)	–
By country/region*									
China	20/4,241	48.77 (39.14–58.49)	<0.0001	17/4,058	17.40 (11.26–25.93)	<0.0001	8/2,773	16.13 (8.61–28.16)	<0.0001
Japan	2/680	79.24 (76.02–82.12)		2/680	41.82 (20.97–66.05)		3/946	28.21 (16.64–43.60)	
Korea	2/74	72.43** (61.21–81.39)		1/43	42.00 (28.33–57.02)		0/0	–	
Taiwan	1/247	85.00 (79.98–88.93)		1/247	68.00 (61.93–73.52)		2/323	35.59 (11.01–71.15)	
France	2/71	33.44* (23.48–45.13)		2/71	20.32 (12.51–31.25)		2/71	14.52 (8.07–24.74)	
Italy	1/62	53.30 (40.93–65.27)		1/62	30.10 (20.02–42.56)		1/62	20.00 (11.83–31.78)	
Spain	1/12	66.70 (37.62–86.93)		1/12	33.30 (13.07–62.38)		1/12	22.20 (6.81–52.68)	
United States	0/0	–		0/0	–		1/165	14.00 (9.49–20.17)	
RFS*									
Global	15/3,519	27.70 (21.00–35.57)	–	13/3,406	10.06 (6.62–15.01)	–	6/2,059	4.31 (0.61–24.76)	–
By country*									
China	9/3,104	22.81 (15.45–32.33)	0.002	8/3,022	6.35 (4.63–8.65)	<0.0001	2/1,718	0.10* (0.00–31.83)	0.37
Korea	2/74	31.17 (19.73–45.48)		1/43	16.00 (7.77–30.09)		0/0	–	
France	1/45	32.50 (20.51–47.33)		1/45	11.60 (5.01–24.63)		1/45	11.60 (5.01–24.63)	
Italy	1/62	31.70 (21.37–44.21)		1/62	20.80 (12.45–32.66)		1/62	15.60 (8.52–26.85)	
Spain	1/12	58.30 (30.74–81.50)		1/12	43.70 (19.88–70.83)		1/12	21.90 (6.66–52.41)	

n/n, studies/patients; *, some studies encompassed multiple regions, so they were included in the global analysis but not in the regional/country analysis; **, all $I^2 > 66.0$ with P value <0.05, except for values marked. OS, overall survival; RFS, recurrence free survival; HCC, hepatocellular carcinoma; MVI, macrovascular invasion; PVTT, portal vein tumor thrombosis; HVTT, hepatic vein tumor thrombosis.

proportion of recurrences that were intrahepatic (10 studies, 1,701 patients) and extrahepatic (7 studies, 494 patients) were 56.61% (95% CI: 43.65–68.73%) and 38.75% (95%

CI: 16.42–67.07%) respectively.

Among studies that provided data for PVTT only (without HVTT), the 1-year (11 studies, 3,118 patients),

Table 6 OS and RFS after liver resection in patients with HCC patients by sub-classification of PVTT

PVTT sub-classification	n/n	1-year, % (95% CI)	P	n/n	3-year, % (95% CI)	P	n/n	5-year, % (95% CI)	P	n/n	Median survival (months) (95% CI)	P
OS												
Segmental & second-order branch ^a	3/396	57.04 (38.92–73.45)	0.02	3/396	28.55 (21.47–36.86)	0.72	1, 20	21.75 (8.77–44.57)	0.98	3, 612	20.41 (15.16–27.48)	<0.0001
First-order branch ^b	4/223	42.16 (22.71–64.38)		3/172	17.85 (4.94–47.60)		1, 21	19.00 (7.31–41.10)		3, 466	12.91 (9.97–16.72)	
Main trunk & SMV ^c	3/101	19.59 (8.75–38.23)		2/70	0.00** (0.00–100.00)		1, 50	0.00 (0.00–100.00)		2, 214	6.41** (5.07–8.10)	
RFS												
Segmental & second-order branch ^a	1/308	16.98 (13.19–21.59)	<0.0001	1/308	5.50 (3.44–8.67)	1.00	0, 0	–	–	–	–	–
First-order branch ^b	2/129	3.67 (2.32–5.76)		1/78	0.00 (0.00–100.00)		0, 0	–		–	–	
Main trunk & SMV ^c	2/51	0.24** (0.01–8.70)		1/20	0.00 (0.00–100.00)		0, 0	–		–	–	

n/n, studies/patients; ^a, segmental & second-order branch corresponds to Cheng's classification I and Japan's VP classification VP1 and VP2; ^b, first-order branch corresponds to Cheng's classification II and Japan's VP classification VP3; ^c, main trunk & SMV corresponds to Cheng's classification III and Japan's VP classification VP4; **, all available $I^2 > 72.9$ and all P value for available I^2 were < 0.05 , except for values marked. OS, overall survival; RFS, recurrence free survival; HCC, hepatocellular carcinoma; PVTT, portal vein tumor thrombosis; SMV, superior mesenteric vein.

3-year (9 studies, 3,005 patients) and 5-year RFS (3 studies, 1,763 patients) were 22.67% (95% CI: 16.97–29.60%), 7.05% (95% CI: 4.99–9.87%) and 0.65% (95% CI: 0.01–26.72%), respectively (Table 1).

Subgroup analyses by presence of PVTT only or PVTT and/or HVTT and by country/region (RFS)

Among studies that provided data for PVTT and/or HVTT, the 1-year (4 studies, 401 patients), 3-year (4 studies, 401 patients) and 5-year RFS (3 studies, 296 patients) were 45.30% (95% CI: 38.00–52.79%), 20.88% (95% CI: 11.36–35.22%) and 17.66% (95% CI: 13.72–22.42%), respectively (Table 2).

There were differences in 1-, 3- and 5-year RFS between the PVTT only (without HVTT) group versus the PVTT and/or HVTT only group (P=0.02 for 1-year, P=0.03 for 3-year, P=0.05 for 5-year).

RFS data, by subclassification of PVTT are shown in Table 6.

Country/region level data for RFS, where available, are shown in Tables 1,2,5. The studies included in the analyses of RFS are listed in Appendix 1.

Meta-regression of factors associated with survival

Meta-regression of study-level demographic, clinical, and biochemical characteristics for potentially relevant factors with sufficient data did not show any significant association with 5-year OS including age (15 studies, 2,242 patients), cirrhosis (10 studies, 1,237 patients), platelets (7 studies, 1,531 patients), HBV infection (13 studies, 2,441 patients), HCV infection (11 studies, 1,869 patients) or tumor size (8 studies, 1,335 patients) (Appendix 1).

Complications, blood loss and operative time

Overall, pooled complication rates were 30.52% (95% CI: 23.60–38.44%; 13 studies, 1,698 patients) for overall complications and 6.17% (95% CI: 3.53–10.56%; 16 studies, 1,687 patients) for major complications (defined as Clavien-Dindo classification III/IV) (Table 4). Subgroup analysis for complication rates in studies reporting outcomes in PVTT only versus PVTT and/or HVTT were similar to the overall analysis (Table 4). The pooled operative time and blood loss in the overall analysis was 219.42 (95% CI: 182.77–256.07) min

and 655.76 (95% CI: 434.94–876.58) mL, respectively.

Additional subgroup analyses

We collected survival data when available for various subgroups (AFP <400 ng/mL, AFP ≥400 ng/mL, presence and absence of cirrhosis, presence of HBV, viral versus non-viral etiology of liver disease, isolated hepatic vein involvement and open versus minimally invasive approaches for surgery). As there were insufficient data to perform meta-analysis, we reported the data in the form of a systematic review in [Appendix 1](#).

Heterogeneity and publication bias

There was moderate heterogeneity among most of the studies (I^2 statistic >54.6%, except for the analysis for alcohol as an etiology of liver disease where heterogeneity was low). The funnel plot ([Appendix 1](#)) and Egger's test did not suggest potential publication bias ($P=0.13$) for 5-year OS.

Discussion

In this systematic review and meta-analysis of 40 studies and 8,218 patients from 8 countries/regions, we determined that HCC patients with MVI who underwent surgical resection with curative intent had a 1- and 3-year OS of 54.5% and 23.2%, respectively. Among studies that reported outcomes for PVTT only (without HVTT), the 1- and 3-year OS were 51.8% and 20.2%, while among studies that reported outcomes for PVTT and/or HVTT, the 1- and 3-year OS were 60.1% and 19.8% respectively. Overall, 1- and 3-year RFS were 27.8% and 10.1%, with similar outcomes in the PVTT only (without HVTT) group (22.7% and 7.1% respectively) and better outcomes in the PVTT and/or HVTT group (45.3% and 20.9%), however, there were limited studies (≤ 4) that provided RFS data for the PVTT and/or HVTT subgroup and these findings require cautious interpretation. By contrast, a meta-analysis of phase III trials for the treatment of advanced HCC reported a median OS of 10 months for sorafenib; a recent randomized trial demonstrated a median OS of 13 months for lenvatinib and the Imbrave150 trial reported a median OS of 19.2 months with atezolizumab and bevacizumab (18-22). These data suggest that the median survival of resected patients with MVI in general (14 months) may be comparable to that of systemic therapy (2,8), although caution is required in interpreting these data as the current study was not designed to compare

outcomes between liver resection and systemic therapy.

Furthermore, in patients with segmental or 2nd order PVTT, median OS was 20.4 months, 1-year OS was 57% and 3-year OS approached 30%, suggesting that surgical resection in this situation may be superior to the multi-kinase inhibitors and comparable to atezolizumab plus bevacizumab. In addition, many patients from countries of lower socioeconomic status do not have access to the newer systemic therapies such as lenvatinib or atezolizumab plus bevacizumab or are unable to afford such costly treatment. Ongoing systemic therapy is often associated with multiple systemic side effects including increased bleeding risk, severe immune associated hepatitis or dermatitis, further complicating the management of these complex patients who are already struggling with poor hepatic reserve and impaired quality of life (23,24). Therefore, surgery may be a viable alternative option in the setting of segmental or 2nd order PVTT (25). Our data is in line with a recent study by Govalan *et al.* (10) which was published after our search was performed. The authors evaluated 11,259 HCC patients with American Joint Commission on Cancer (AJCC) 7th clinical stage TNM (26) T_{3B}N₀M₀ and demonstrated that those who underwent resection had a median OS of 21 versus 8 months in those that received systemic therapy. Of note, only 3% of the cohort in the Govalan study received surgery, suggesting that these were highly selected patients, compared with 38% that received systemic therapy. Taken together, these data suggest that a personalized approach should be adopted for HCC patients with MVI, especially those with segmental or 2nd order PVTT, contrary to the latest AJCC 8th edition staging system where any MVI or invasion into adjacent organs are both considered as T4 (27). However, caution must be exercised when interpreting the results, as patients with MVI who underwent liver resection were likely to be highly selected and potentially had fewer comorbidities than those undergoing systemic therapy. In addition, the mean age of patients who underwent resection was only 53 years, younger than the patients included in most clinical trials for systemic therapy (28).

Despite survival being fair in segmental or 2nd order PVTT, 1-year RFS is poor (17%), emphasizing the need for early detection of tumor recurrence in these patients. A study of 734 HCC patients that underwent resection found that lack of tumor surveillance was an independent predictor of mortality (29). We suggest imaging be obtained every 4 months for the first 2 years after surgery, then twice a year thereafter, in line with the National Comprehensive Cancer Network guidelines (30). More data are required

regarding the use of neo-adjuvant and adjuvant therapy among patients with MVI undergoing resection, given the extremely high recurrence rate.

However, it should be noted that in the setting of tumor involvement of the first order branch or main trunk PV/SMV, the median survival rates were much poorer (12.9 and 6.4 months respectively). Such patients should be considered for systemic therapy rather than invasive surgery.

Regardless of the vascular extent of tumor thrombus and types of therapy, the outcome of patients with advanced HCC is dismal. This highlights the importance of increasing compliance to primary HCC surveillance among patients at risk for HCC, to increase the likelihood of such patients being diagnosed before the development of MVI. Unfortunately, compliance to HCC surveillance has been reported to be very poor in the real world, with most HCC patients diagnosed at a late stage (31-35). A recent nationwide USA study of 82,427 patients with cirrhosis reported that HCC surveillance took place in barely 10% of patients (32). Therefore, there is an urgent need to improve compliance to HCC surveillance and linkage to care (33,36).

In the current study, majority of the included patients (74%) had HBV as the underlying etiology for liver disease, followed by HCV (16%). Although treatment with antivirals has been shown to improve survival and reduce recurrence after HCC treatment (37,38), there is gross under-utilization of anti-viral treatment (37-40). In a multi-center study involving 2,518 patients with HBV-related HCC from the USA and Asia, only 17% of patients were on anti-viral therapy at the time of HCC diagnosis, and only half received HBV anti-viral therapy at any time, highlighting a substantial care gap (38,41) and a significant opportunity for intervention.

We acknowledge the following limitations. There were a lack of data for major underlying liver disease etiologies such as non-alcoholic fatty liver disease (NAFLD) (42) and alcohol-associated liver disease (43), and further studies are needed to examine the outcomes for these populations, especially since the burden of NAFLD and alcohol-associated liver disease are rising. Due to poorer surveillance rates among patients with alcohol-associated liver disease and NAFLD compared with viral-associated liver disease, the proportion of patients with advanced HCC stage and MVI at presentation may increase, therefore, more outcome data for these subgroups are required (35,44). There was marked variation in outcomes among countries/regions, with studies from Taiwan and Japan reporting 1-year OS of around 80% or more, while studies from other

countries such as China and France reported 1-year OS of 49% and 33% respectively. However, there were few studies from countries outside of China, and a complete lack of data from South America, Africa and the Middle East. More data are required to accurately determine survival outcomes in these countries. In addition, the outcomes from the sub-classification of PVTT should be interpreted with caution as some of the subgroup analyses only contained a limited number of studies. There were insufficient data among the included studies regarding cases where tumor thrombus crossed the portal vein bifurcation from left to right, or vice versa without entering the main portal vein. More studies are required to evaluate outcomes in this subgroup. The observational nature of the included studies, moderate heterogeneity and the lack of certain data points are further limitations to this study. In addition, this study was not designed to compare the outcomes of surgical resection with systemic therapy, and more data in this area are required.

Conclusions

HCC patients with PVTT and HVTT generally have poor survival after surgical resection, though the median survival is comparable to patients who receive systemic therapy. However, survival is particularly poor if the main portal vein trunk/SMV or 1st order portal vein is involved, suggesting that invasive surgical treatment should be avoided in this setting. On the other hand, more favorable median survival is observed in patients with segmental or 2nd order branch portal vein invasion, suggesting that surgical resection may be a reasonable option in select patients.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at <https://hbsn.amegroups.com/article/view/10.21037/hbsn-21-419/rc>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://hbsn.amegroups.com/article/view/10.21037/hbsn-21-419/coif>). MHN has received research grants from Glycotest, Gilead, B. K. Kee Foundation, and National Cancer Institute; MHN serves on the Advisory Board of Intercept,

Laboratory of Advanced Medicine, Bayer, Eisai, Gilead, Novartis, Janssen, Eli Lilly, and Exact Sciences. DQH has received a research grant from the National Medical Research Council [Singapore (MOH-000595-01)] and the Exxon-Mobil NUS Scholarship for Clinicians (MOH-000595-01); DQH serves on the Advisory Board of Eisai. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Huang DQ, Tran A, Tan EX, Nerurkar SN, Teh R, Teng MLP, Yeo EJ, Zou B, Wong C, Esquivel CO, Bonham CA, Nguyen MH. Characteristics and outcomes of hepatocellular carcinoma patients with macrovascular invasion following surgical resection: a meta-analysis of 40 studies and 8,218 patients. *HepatoBiliary Surg Nutr* 2022;11(6):848-860. doi: 10.21037/hbsn-21-419