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ORIGINAL ARTICLE

Global and regional long-term survival following resection for HCC in the recent decade: A meta-analysis of 110 studies

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Abstract

Surgical resection for HCC remains a major curative treatment option, but it is unclear whether there are differences in outcomes by region and whether outcomes have improved over time. We aimed to estimate pooled overall survival (OS), recurrence-free survival (RFS), and complication rates in patients with hepatocellular carcinoma (HCC) following curative surgical resection and to compare outcomes by region and by time period. In this systematic review and meta-analysis, we searched Pubmed, Embase, and Cochrane databases from inception to May 15, 2020. We selected studies reporting

Abbreviations: AFP, alpha-fetoprotein; CI, confidence interval; DAA, direct-acting antiviral; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IFN, interferon; MELD, Model for End-Stage Liver Disease; OS, overall survival; RFS, recurrence-free survival.

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OS, RFS, and complications in adult patients with HCC undergoing curative surgical resection. Two authors independently searched the literature and extracted the data. We screened 6983 articles and included 110 eligible studies with 82,392 patients, with study periods spanning from 1980–2017. The global pooled 1-year and 5-year survival rates were 88.9% (95% confidence interval [CI] 87.1–90.4) and 56.2% (95% CI 52.8–59.6) for OS and 71.1% (95% CI 67.6–74.3) and 35.2% (95% CI 32.5–38.0) for RFS, respectively. Five-year OS was higher in Asia (57.03%) than in other regions (Europe 48.3%; North America 48.0%; and South America 49.5%); $p = 0.002$. Five-year RFS was higher in patients with hepatitis B virus versus patients with hepatitis C virus (34.8% vs. 24.1%; $p = 0.02$). There was no significant improvement in 5-year OS and RFS over time. The pooled rate for complications was 27.6% (95% CI 23.4–32.3), with 9.7% (95% CI 6.3–14.7) classified as major. One-year OS after surgical resection for HCC is excellent (~90%). However, 5-year OS (~55%) and RFS (~35%) are still poor, suggesting that long-term care is suboptimal. Greater efforts are required to improve survival through enhanced surveillance and preventing recurrence through antiviral therapy.

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 (LT) and radiofrequency ablation (RFA), are the only curative therapies for HCC. However, LT and RFA are limited by organ availability, tumor size constraints, local expertise, and resources.[2–5] Outcome data for surgical resection for HCC may vary by region due to differences in patient factors, diverse etiologies for liver disease, and surgical expertise.[6–8] For example, hepatitis B virus (HBV) is the predominant cause of HCC in Asia except for Japan, whereas hepatitis C virus (HCV) and alcohol are the dominant causes of HCC in North America and Europe. In the recent decade, the introduction of effective and well-tolerated oral antiviral therapies for patients with HBV and HCV infection,[9,10] the aging of the population with viral hepatitis,[11–15] as well as the emergence of nonalcoholic fatty liver disease (NAFLD) as a major cause of HCC with its associated comorbidities[16–19] could all have affected the outcomes of patients with HCC undergoing partial hepatectomy.

Therefore, through a systematic review and meta-analytic approach, we aimed to estimate surgical outcomes (overall survival [OS], recurrence-free survival [RFS], and complications) following primary liver resection for HCC globally and stratified by region. Our secondary aims were to compare survival outcomes between studies from the last 10 years versus those prior and identify factors associated with survival outcomes.

METHODS

In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement, we conducted and reported the meta-analysis as recommended for meta-analyses of observational studies (Table S1).[20]

Search strategy and selection criteria

We searched PubMed, Embase, and the Cochrane Library databases from inception to May 15, 2020, for original full-text research articles using search terms based on “HCC,” “resection,” and “survival,” as developed in collaboration with a medical librarian (C.W.) from the Lane Medical Library at Stanford University (Stanford, CA, USA). Details of the search terms and study selection criteria are available in the Supporting Information. Briefly, we included original research studies published as full-text articles that provided data on (1) adults aged 18 years or older with HCC who had undergone primary surgical resection with curative intent without pre-operative neo-adjuvant HCC treatment, and (2) OS and or RFS outcomes. We excluded (1) studies with fewer than 100 patients to avoid bias introduced by small studies, (2) studies with a median follow-up time of less than 2 years since our goal was to focus on long-term outcomes, and (3) studies that focused on particular subgroups of HCC (e.g., macrovascular invasion, large HCC only).

Two authors independently searched the databases for relevant articles and 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. We extracted data from eligible studies using a case report form developed explicitly for this study. We performed a quality assessment of included studies using scales also developed for this review based on the Newcastle-Ottawa scale for retrospective studies and Cochrane risk of bias tool for randomized control trials.[21,22]

Statistical analysis

We used a random-effects model to determine pooled estimates of demographic and clinical characteristics of patients with HCC. We also used a random-effects model to estimate pooled percentages and 95% confidence intervals (CIs) of median, 1-year, 3-year, and 5-year OS and RFS. We performed preplanned analyses to determine whether there were sufficient data available for the following subgroups: median study year (which would better reflect the study population than publication year as the latter may significantly lag behind), 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 5-year OS and RFS for variables with available data such as age, tumor number, tumor size, AFP levels, platelet levels, and whether the resection was performed at a tertiary center.

We assessed for interstudy heterogeneity with the Higgins' and Thompson's I^2 statistics derived from Cochran's Q test and with heterogeneity considered significant if $I^2 > 50\%$.[23] We used Egger's test and funnel plot to assess for publication bias. All statistical analyses were carried out with the meta-packages in R statistical software (version 3.6.1). The study was conducted according to the Helsinki Declaration of 1975, as revised in 2008.

RESULTS

Study selection and study characteristics

We screened 6983 articles, removed 2337 duplicates, reviewed titles and abstracts of 4646 articles, identified and reviewed the full text of 673 potentially eligible articles, and finally selected 110 studies involving 82,392 patients from four continents/regions and 15 countries that met our study inclusion/exclusion criteria (Figure 1). Of these, 95 studies were from Asia, six from Europe, four from North America, one from South America, none from Africa, and four from multiple regions. Eighty-three studies had a median study year before 2010, and 27 studies had a median study year from 2010 and later. The study sample size ranged from 100 to 23,107. Details of individual study characteristics are reported in Table S2, while each study's patient and tumor characteristics are summarized in Table S3. The quality assessment for each study is provided in Tables S4 and S5. All studies were of high quality (n = 108) except two of moderate quality, and none were of low quality.

Study patient characteristics, overall/global and by region or time period

Study patient characteristics are given in Table 1A,B, and the provided data for these analyses are listed in Table S6. Overall, most of the patients were male (80.85%, 95% CI 79.06–82.52), and the pooled mean age was 57.92 years (95% CI 56.36–59.47) (Table 1A). Most patients (62.47%, 95% CI 56.8–67.83) had cirrhosis, and the pooled mean Model for End-Stage Liver Disease (MELD) score was 7.75 (95% CI 7.17–8.34). The most common underlying liver disease was HBV infection (64.77%, 95% CI 58.02–70.98), followed by alcohol (20.9%, 95% CI 13.66–30.62), and HCV infection (17.88%, 95% CI 13.13–23.88). The pooled mean AFP level was 89.36 ng/ml (95% CI 63.48–115.23). With regard to tumor characteristics, the pooled mean tumor size was 5.01 cm (95% CI 4.6–5.43), the proportion of patients with poorly differentiated HCC was 22.95% (95% CI 18.47–28.14), the proportion with macrovascular invasion was 15.6% (95% CI 8.92–25.87), and the proportion with Barcelona Clinic Liver Cancer stage C was 4.82% (2.50–9.11). The pooled median follow-up was 43.37 months (95% CI 40.04–46.98).

By time period, there was a lower MELD score in studies 2010 and after compared with before 2010 (7.00 vs. 7.91; $p = 0.002$). Otherwise, the study, patient, and tumor characteristics for studies before 2010 and those after 2010 were similar (Table 1B).

By region, there were significant differences in the sex and age distribution ($p < 0.0001$ and $p = 0.0003$, respectively), with patients from Asia more likely male (81.64%, 95% CI 79.72–83.42) than patients from North America (67.46%, 95% CI 64.17–70.58), South America (65.35%, 95% CI 55.59–73.96), and Europe (78.75%, 95% CI 74.9–82.15). In addition, patients from North America (56.64 years, 95% CI 46.43–66.85) and Asia (57.28 years, 95% CI 55.64–58.91) were younger than those from Europe (64.56 years, 95% CI 61.43–67.70) (Table 1A). More patients from Asia had HBV (68.92%, 95% CI 62.76–74.48) than those from Europe (16.96%, 95% CI 14.94–19.18), North America (16.26%, 95% CI 14.09–18.69), or South America (7.92%, 95% CI 4.01–15.05) ($p < 0.0001$), and more patients from Europe had HCV (45.15%, 95% CI 22.7–69.76) compared with those from Asia (15.54%, 95% CI 10.99–21.51), North America (27.99%, 95% CI 14.66–46.78), or South

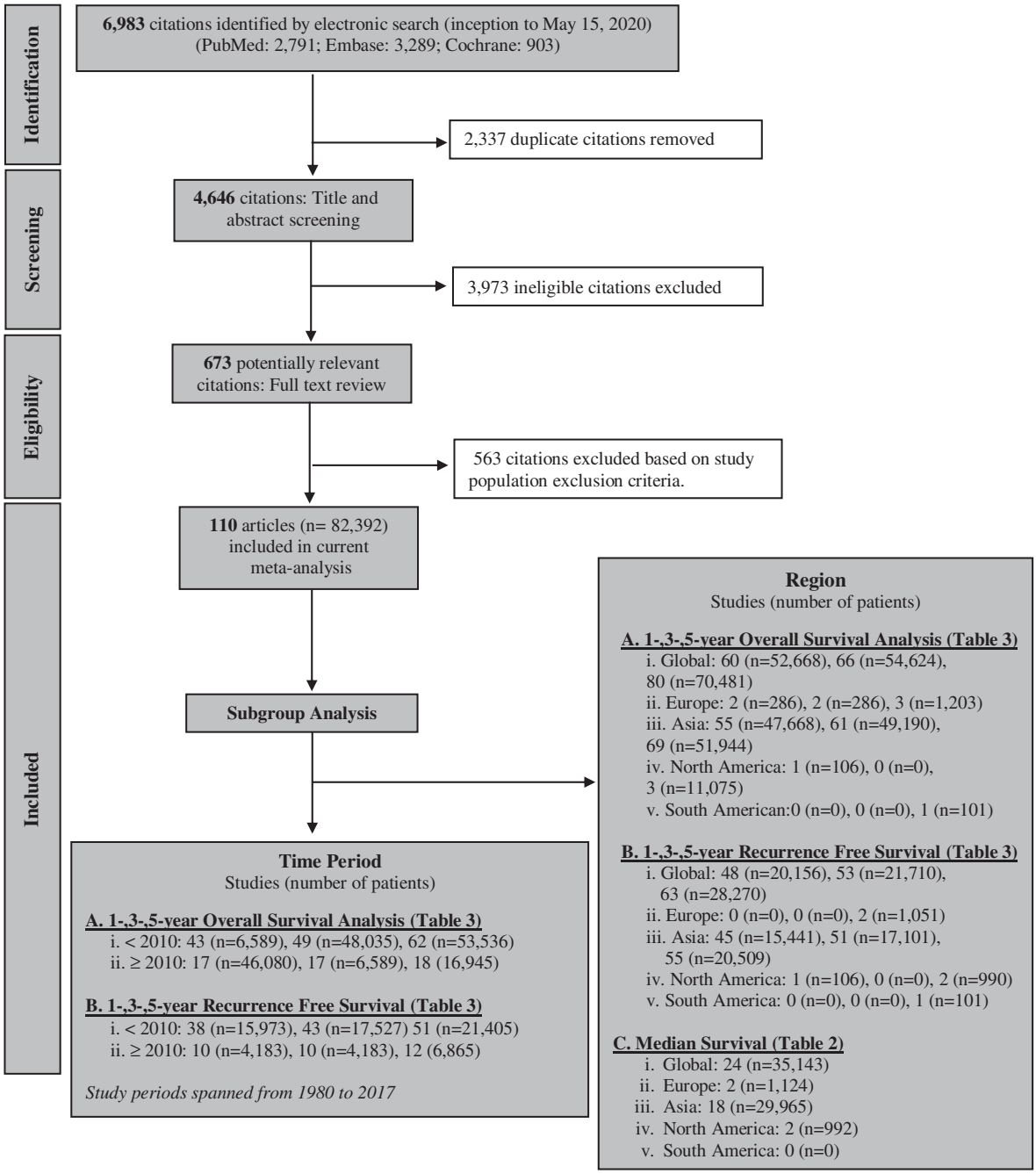

FIGURE 1 Flow chart of literature search and study selection

America (33.66%, 25.14–43.4) (p = 0.001). Notably, the mean AFP from Asian studies was higher than those from Europe (164.73 vs. 13.04, p < 0.0001). Tumor size and the proportions of patients with poorly differentiated histology were similar among the regions.

Overall survival

Overall, 24 studies (35,143 patients) provided data for median OS (Asia, 18 studies, 29,965 patients; Europe, 2 studies, 1124 patients; and North America, 2 studies, 992 patients). The pooled median OS was 48.7 months (95% CI 35.72–66.39) (Table 2). The 1-year (60 studies, 52,668 patients), 3-year (66 studies, 54,624 patients), and 5-year OS (80 studies, 70,481 patients) were 88.85% (95% CI 87.13–90.37), 69.93% (95% CI 66.93–72.77), and 56.20% (95% CI 52.77–59.58), respectively (Table 3).

By time period, the 1-year OS of studies before 2010 versus 2010 and later was 88.35% (95% CI 86.32–90.11) versus 90.03% (95% CI 86.58–92.66) (p = 0.37); and 5-year OS of studies before 2010 versus 2010 and later was 55.17% (95% CI 52.22–58.08) versus 59.89% (95% CI 48.49–70.31) (p = 0.43) (Table 3).

By region, the 1-year OS was high across regions at 88.91% (95% CI 87.08–90.51) for Asia, 85.34% (95% CI 66.21–94.54) for Europe, and 87.74% (95% CI 80.02–92.74) for North America (no available 1-year OS data for South America) (Table 3). However, the 5-year OS was notably higher for Asia (57.03%, 95% CI 53.13%–60.84%) compared with other regions (Europe 48.30%, 95% CI 45.48–51.12; North America 48.04%, 95% CI 44.43–51.67; and South America 49.50%, 95% CI 39.89–59.15) (p = 0.002). For countries with available data, we also provided country-level 5-year OS (Figure 2). In total, data from at least two studies were available for six countries (USA, Italy, China, Japan, Korea, and Taiwan), with data from only one study available for four countries (Brazil, Germany, Hong Kong, and Singapore). The highest 5-year OS was observed for South Korea (69.11%), followed by Japan (64.35%) and Singapore (59.09%). The lowest 5-year OS was observed for Germany (44.03%), followed by USA (48.04%) and Italy (48.83%).

The studies included in the analyses of OS and RFS are listed in Table S7.

Recurrence-free survival

The 1-year (48 studies, 20,156 patients), 3-year (53 studies, 21,710 patients), and 5-year RFS (63 studies, 28,270 patients) were 71.05% (95% CI 67.59–74.28), 45.79% (95% CI 42.95–48.67), and 35.17% (95% CI 32.48–37.97), respectively (Table 3).

By time period, the 1-year and 5-year RFS of studies before 2010 versus 2010 and beyond did not change significantly (Table 3).

By region, the 5-year RFS in Asia, Europe, North America, and South America were 35.12% (95% CI 32.11–38.26), 37.67% (95% CI 28.43–47.9), 36.14% (95% CI 26.44–47.11), and 40.59% (95% CI 31.48–50.41), respectively (p = 0.72) (Table 3).

As with OS, we presented country-level 5-year RFS for countries with available data (Figure 2). The 5-year RFS was highest in Italy (43.73%), Brazil (40.59%) and South Korea (38.75%), and lowest in Hong Kong (26.47%) and Singapore (29.55%).

Meta-regression of factors associated with survival

Meta-regression of study-level demographic, clinical, and biochemical characteristics for potentially relevant factors with sufficient data demonstrated that age, AFP level, platelet count, tumor number, tumor size, and whether the resection was performed at a tertiary center were not significantly associated with 5-year OS (Table 4). Of these characteristics, only a higher tumor number was inversely associated with 5-year RFS (coefficient −0.18, $p < 0.0001$), meaning that the more the number of tumors, the poorer the RFS.

Complications

Globally, pooled complication rates were 27.6% (95% CI 23.35–32.28, 20 studies, 6402 patients) for overall complications and 9.73% (95% CI 6.34-14.65, 14 studies, 4968 patients) for major complications (defined as Clavien-Dindo classification III/IV) (Table 2).

Subgroup analyses

The pooled estimates of 1-year (3 studies, 701 patients) and 3-year (3 studies, 877 patients) OS in Child-Pugh class A patients was 86.90% (95% CI 81.43–90.94) and 69.12% (95% CI 63.63–74.12), respectively (Table S8).

The pooled 5-year OS of patients with HBV (4 studies, 485 patients) was 48.26% (95% CI 34.31–62.69), similar to that of patients with HCV (3 studies, 555 patients) at 57.84% (95% CI 53.68–61.88) (p = 0.22). However, the 5-year RFS of patients with HBV (4 studies, 227 patients) was significantly higher at 34.80% (95% CI 28.89–41.23) compared to patients with HCV (4 studies, 677 patients) at 24.10% (95% CI 18.47–30.79) (p = 0.02) (Table S8).

Due to insufficient data, we were not able to provide qualitative pooled summary data for the other subgroups. However, we provided summary data for each study in Table S8.

Sensitivity analysis

One study consisting of a disproportionately large number of patients (10,085 out of a total sample size of 16,945) from the USA was excluded from the analysis of studies with median study year after 2010. After excluding the dominant large study, the 5-year global OS was 60.73% (95% CI 48.79–71.5), similar to that of the main analysis of 59.89% (95% CI 48.49–70.31).

Heterogeneity and publication bias

There was substantial heterogeneity among studies (all I^2 statistic > 80%). The funnel plot (Figures S1 and S2) and Egger's test were not suggestive of publication bias for the analysis of 5-year OS and 5-year RFS (p = 0.16 and p = 0.93, respectively).

DISCUSSION

In this extensive systematic review and meta-analysis of 110 studies and 82,392 patients from 15 countries, we determined that patients with HCC who underwent curative surgical resection had a 1-year and 5-year OS of 89% and 56%, respectively. While the excellent

TABLE 1 Study, patient, and tumor characteristics

(A) Overall/global and by region

	Overall/global[a]		North America		South America		Europe		Asia		
	Number of studies (N)		Number of studies (N)		Number of studies (N)		Number of studies (N)		Number of studies (N)		
	Number of patients (n)	Mean/median/% (95% CI)/range	Number of patients (n)	Mean/median/% (95% CI)/range	Number of patients (n)	Mean/median/% (95% CI)/range	Number of patients (n)	Mean/median/% (95% CI)/range	Number of patients (n)	Mean/median/% (95% CI)/range	*P*
Study characteristics[b]											
Median study year	**110** 82,392	**2007** (1995–2014)	**4** 11,961	**2003** (2001–2010)	**1** 101	**2007**[c] (2004–2007)	**6** 2025	**2008** (1998–2011)	**95** 62,147	**2007** (2004–2010)	0.67
Tertiary referral center (%)	**22** 29,197	**20.00%**	**0** 0	—	**0** 0	—	**0** 0	—	**21** 28,187	**22.11%**	—
Median follow-up duration (months)	**78** 47,508	**43.37** (40.04–46.98)	**1** 10,085	**57.9**[a] (56.88–59.14)	**0** 0	—	**4** 1410	**38.77** (26.73–56.23)	**69** 29,855	**43.17** (39.46–47.22)	0.0001
Patient characteristics[b]											
Male (%)	**110** 82,392	**80.85** (79.06–82.52)	**4** 11,961	**67.46** (64.17 – 70.58)	**1** 101	**65.35**[c]	**6** 2025	**78.75** (74.90–82.15)	**95** 62,147	**81.64** (79.72–83.42)	<0.0001
Age (years)	**61** 42,475	**57.92** (56.36–59.47)	**3** 11,075	**56.64** (46.43–66.85)	**0** 0	—	**5** 1873	**64.56** (61.43–67.70)	**51** 24,918	**57.28** (55.64–58.91)	0.0003
Platelet (10^3)	**28** 18,370	**155.68** (145.60–165.76)	**0** 0	—	**0** 0	—	**4** 1684	**158.45** (121.38–195.51)	**24** 16,686	**155.26** (144.36–166.17)	0.87
MELD	**12** 7088	**7.75** (7.17–8.34)	**2** 990	**7.05** (6.83–7.26)	**0** 0	—	**4** 1666	**8.25** (7.49–9.02)	**5** 2346	**7.40** (6.74–8.07)	0.01
Cirrhosis (%)	**73** 56,357	**62.47** (56.80–67.83)	**2** 1770	**45.45** (18.56–75.28)	0 0	—	**4** 950	**84.19** (22.10–99.01)	**65** 52,088	**62.83** (57.33–68.02)	0.42
Diabetes (%)	**10** 8330	**13.40** (09.22–19.09)	0 0	—	0 0	—	0 0	—	**10** 8330	**14.43** (10.06–20.26)	—
Alcohol (%)	**12** 6666	**20.90** (13.66–30.62)	0 0	—	0 0	—	0 0	—	**9** 2802	**24.67** (15.24–37.37)	—
HBV (%)	**91** 65,350	**64.77** (58.02–70.98)	**2** 990	**16.26** (14.09–18.69)	**1** 101	**7.92**[c] (4.01 – 15.05)	**3** 1209	**16.96** (14.94 – 19.18)	**83** 58,441	**68.92** (62.76 – 74.48)	<0.0001
HCV (%)	**66** 52,355	**17.88** (13.13–23.88)	**3** 1876	**27.99** (14.66–46.78)	**1** 101	**33.66**[c] (25.14–43.40)	**3** 1209	**45.15** (22.70–69.76)	**57** 44,560	**15.54** (10.99–21.51)	0.001

TABLE 1 (Continued)

(A) Overall/global and by region

	Overall/global[a]		North America		South America		Europe		Asia		
	Number of studies (N)		Number of studies (N)		Number of studies (N)		Number of studies (N)		Number of studies (N)		
	Number of patients (n)	Mean/median/% (95% CI)/range	Number of patients (n)	Mean/median/% (95% CI)/range	Number of patients (n)	Mean/median/% (95% CI)/range	Number of patients (n)	Mean/median/% (95% CI)/range	Number of patients (n)	Mean/median/% (95% CI)/range	*P*
Tumor characteristics[b]											
Tumor number	**4**	**2.67** (0.50–4.83)	0	—	0	—	0	—	**3**	**1.65** (1.27–2.02)	—
	3068		0		0		0		982		
Tumor size	**32**	**5.01** (4.60–5.43)	**3**	**6.33**	0	—	**3**	**5.31** (3.84–6.78)	**26**	**4.84** (4.34–5.33)	0.56
	23,975		11,075	(3.22–9.45)	0		499		12,401		
Macrovascular invasion (%)	**22**	**15.60** (8.92–25.87)	0	—	0	—	0	—	**21**	**15.79** (8.79–26.73)	—
	10,850		0		0		0		10,311		
Poorly differentiated histology (%)	**44**	**22.95** (18.47–28.14)	**2**	**18.55**	0	—	0	—	**40**	**22.98** (18.15–28.64)	0.12
	20,601		992	(16.25–21.09)	0		0		18,060		
BCLC C (%)	**25**	**4.82** (2.50–9.11)	0	—	0	—	**1**	**16.43**[a]	**23**	**5.12** (2.68 – 9.56)	—
	11,223		0		0		0		10,882		
AFP (ng/ml)	**19**	**89.36** (63.48–115.23)	0	—	0	—	**2**	**13.04** (8.46–17.62)	**16**	**164.73** (122.34–207.11)	<0.0001
	15,257		0		0		1124		11,610		

(B) By time period

	Before 2010		2010 and after		
	Number of studies (N)		Number of studies (N)		
	Number of patients (n)	Mean/median/% (95% CI)	Number of patients (n)	Mean/median/% (95% CI)	*p*
Study characteristics[a]					
Median study year	**83**	**2005** (1995–2009)	**27**	**2011** (2010–2014)	<0.0001
	60,870		21,522		
Tertiary referral center (%)	**17**	**20.48%**	**5**	**18.52%**	1
	27,602		1595		
Median follow-up duration (months)	**54**	**44.97** (40.49–49.94)	**24**	**39.96** (35.03–45.59)	0.17
	27,737		19,771		
Patient characteristics[a]					
Male (%)	**83**	**80.56** (78.63–82.36)	**27**	**81.72** (77.41–85.36)	0.61
	60,870		21,522		

(Continues)

TABLE 1 (Continued)

(B) By time period	Before 2010		2010 and after		
	Number of studies (N)		Number of studies (N)		
	Number of patients (n)	Mean/median/% (95% CI)	Number of patients (n)	Mean/median/% (95% CI)	*p*
Age (years)	**44** 25,577	**58.66** (56.98–60.35)	**17** 16,898	**56.00** (52.90–59.10)	0.14
Platelet (10^3)	**20** 13,631	**155.63** (142.41–168.85)	**8** 4739	**156.00** (143.10–168.89)	0.97
MELD	**10** 6166	**7.91** (7.34–8.48)	**2** 922	**7.00** (6.87–7.13)	0.002
Cirrhosis (%)	**56** 47,698	**62.56** (55.95–68.73)	**17** 8659	**62.23** (50.87–72.39)	0.96
Diabetes (%)	**9** 7795	**14.87** (10.02–21.50)	**1** 535	**11.03**[a]	—
Alcohol (%)	**10** 5863	**19.39** (11.70–30.40)	**2** 803	**29.18** (21.99–37.58)	0.14
HBV (%)	**69** 55,929	**63.14** (55.02–70.57)	**22** 9421	**69.69** (57.80–79.42)	0.35
HCV (%)	**56** 46,784	**19.19** (13.81–26.02)	**10** 5571	**11.90** (5.12–25.27)	0.27
Tumor characteristics[a]					
Tumor number	**3** 2789	**2.67** (0.50–4.83)	**1** 279	**1.57**[a]	—
Tumor size	**25** 10,607	**5.11** (4.57–5.64)	**7** 13,368	**4.66** (4.05–5.27)	0.28
Macrovascular invasion (%)	**19** 8992	**15.33** (7.99–27.41)	**3** 1858	**17.27** (12.74–23.00)	0.73
Poorly differentiated histology (%)	**31** 12,630	**24.81** (20.30–29.94)	**13** 7971	**19.00** (10.69–31.49)	0.35
BCLC C (%)	**16** 6034	**4.89** (2.82–8.34)	**9** 2527	**4.54** (0.84–21.15)	0.93
AFP (ng/ml)	**15** 13,894	**103.74** (72.93–134.55)	**4** 1363	**61.11** (−5.51–127.73)	0.26

Abbreviations: AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; MELD, Model for End-Stage Liver Disease.

[a]Some studies encompassed multiple regions; these were included in the global analysis but not in the regional analysis.

[b]All $I^2 > 93.0$ for regions with more than two studies; all *p* values for available I^2 were < 0.05.

[c]Insufficient studies for pooled analysis.

[a]All $I^2 > 93.0$; all *p* values for available I^2 were < 0.05.

TABLE 2 Median survival and complication rates of curative resection for HCC

	Number of studies (n)	Study reference number[a]	Number of patients (n)	Median survival (months) or complications (%) (95% CI)	*p*
Median survival[b] (months)					
Global[b]	24	5,10,20,35,41,42,51,53,56,59,65,69,72,73,75,83,86,89,92,96,104,105,106,108	35,143	48.69 (35.72–66.39)	
By region[c]					
Europe	2	20,53	1124	51.28 (38.48–68.34)	0.76
Asia	18	5,10,42,51,56,59,65,69,72,73,75,83,86,89,104,105,106,108	29,965	55.18 (48.11–63.29)	
North America	2	41,92	992	41.24 (16.55–102.75)	
South America	0	—	—	—	
Complications[d] (%)					
All	20	2,20,37,40,42,45,53,54,56,60,61,76,77,79,80,83,87,89,90,93	6402	27.60 (23.35–32.28)	<0.0001
Minor[e]	11	2,16,29,30,45,54,56,76,79,87,105	3320	20.02 (13.32–28.95)	
Major[f]	14	2,11,16,29,32,40,45,54,56,65,76,79,87,105	4968	9.73 (6.34–14.65)	

[a]Supplemental file reference numbers.
[b]All I^2 > 96.0 for regions with more than two studies; all *p* values for available I^2 were < 0.05.
[c]Some studies encompassed multiple regions; these were included in the global analysis but not in the regional analysis.
[d]All I^2 > 93.0; all *p* values for I^2 are < 0.05.
[e]Clavien-Dindo classification Grade I or II (any deviation from the normal postoperative course, with or without the need for specific pharmacological intervention).
[f]Clavien-Dindo classification Grade III or IV (complications that require procedural intervention or life-threatening complications requiring intensive care unit support).

1-year OS suggests good surgical expertise and short-term postoperative management, the 5-year OS of only slightly more than half suggests potential for improvement. The 1-year RFS of 71% suggests that patient selection, as well as rescue therapies, remain important. The 5-year RFS of only 35% is particularly concerning and suggests that recurrence is probably a significant cause of poor long-term survival. In addition, OS is overall higher than RFS, which suggests that most patients with recurrent HCC are generally asymptomatic and/or eligible for additional HCC treatment. Therefore, it is important to survey patients for recurrence even after curative treatment such as surgical resection, so that any recurrence can be detected early and hopefully at a treatable stage.

Another important finding of our study is the similar short-term and intermediate-term outcomes among the regions but significantly higher long-term 5-year OS and RFS in studies from Asia. These observations suggest that there may not be much difference in surgical techniques or patient selection among the regions. However, there may be a significant difference among the regions in the rate of tumor recurrence and/or early tumor detection, both of which present important implications for improving the current 5-year OS and RFS. The predominant cause of liver disease in Asia was HBV. Effective and well-tolerated antiviral agents such as nucleoside and nucleotide analogues for treatment of HBV have been available in Asia for more than a decade, which may help explain the higher long-term RFS and OS in studies from Asia.[24,25] Preoperative antiviral treatment has also been shown to reduce microvascular invasion, an important risk factor for recurrence.[26]

Meanwhile, there was a higher proportion of patients with HCV from Europe (45%) and South America (34%) versus Asia (16%). However, interferon (IFN)–free direct-acting antiviral (DAA) therapies for HCV did not become available until 2014, and the studies providing data for 5-year OS and RFS of patients with HCV in the current meta-analysis were all conducted before 2015 before the advent of DAAs. As such, it is likely that most patients with HCV included in this meta-analysis were not treated with IFN-based regimens due to substantial treatment-associated side effects, besides their lower sustained virological response rates.[27] In fact, the treatment rate during the IFN era for HCV was only about 10% in a large population-based U.S.

TABLE 3 Overall survival (A) and RFS (B) of patients with HCC after curative resection, overall and by time period or region

Region	Number of studies (N) Number of patients (n)	1 year (%) (95% CI)	p	Number of studies (N) Number of patients (n)	3 years (%) (95% CI)	p	Number of studies (N) Number of patients (n)	5 years (%) (95% CI)	p
OS[a]									
Global[b]	**60**	**88.85**		**66**	**69.93**		**80**	**56.2**	
	52,668	(87.13–90.37)		54,624	(66.93–72.77)		70,481	(52.77–59.58)	
By region[a]									
Europe	**2**	**85.34**	0.8	**2**	**64.24**	0.2	**3**	**48.3**	0.002
	286	(66.21–94.54)		286	(54.82–72.69)		1203	(45.48–51.12)	
Asia	**55**	**88.91**		**61**	**70.26**		**69**	**57.03**	
	47,668	(87.08–90.51)		49,190	(67.08–73.25)		51,944	(53.13–60.84)	
North America	**1**	**87.74**		**0**	—		**3**	**48.04**	
	106	(80.02–92.74)		0			11,075	(44.43–51.67)	
South America	**0**	—		0	—		**1**	**49.5**	
	0			0			101	(39.89–59.15)	
By time period[a]									
Year < 2010	**43**	**88.35**	0.37	**49**	**68.9**	0.37	**62**	**55.17**	0.43
	6589	(86.32–90.11)		48,035	(66.11–71.55)		53,536	(52.22–58.08)	
Year ≥ 2010	**17**	**90.03**		**17**	**72.84**		**18**	**59.89**	
	46,080	(86.58–92.66)		6589	(64.36–79.93)		16,945	(48.49–70.31)	
RFS[a]									
Global[b]	**48**	**71.05**		**53**	**45.79**		**63**	**35.17**	
	20,156	(67.59–74.28)		21,710	(42.95–48.67)		28,270	(32.48–37.97)	
By region[a]									
Europe	**0**	—	0.01	**0**	—	—	**2**	**37.67**	0.72
	0			0			1051	(28.43–47.90)	
Asia	**45**	**70.81**		**51**	**45.95**		**55**	**35.12**	
	15,441	(67.16-74.20)		17,101	(42.99-48.94)		20,509	(32.11–38.26)	
North America	**1**	**83.96**		**0**	—		**2**	**36.14**	
	106	(75.71–89.79)		0			990	(26.44-47.11)	
South America	**0**	—		**0**	—		**1**	**40.59**	
	0			0			101	(31.48-50.41)	
By time period[a]									
Year < 2010	**38**	**70.28**	0.29	**43**	**44.3**	0.07	**51**	**34.35**	0.4
	15,973	(66.13–74.11)		17,527	(41.53-47.10)		21,405	(31.97–36.81)	
Year ≥ 2010	**10**	**73.88**		**10**	**52.38**		**12**	**38.62**	
	4183	(68.34–78.75)		4183	(44.13–60.51)		6865	(29.24–48.94)	

Abbreviation: OS, overall survival.

[a]All I^2 > 82.0 except for North America and South America due to the low number of studies; all *p* values for available I^2 were < 0.05.

[b]Some studies encompassed multiple regions; these were included in the global analysis but not in the regional analysis.

study of over 70,000[28]; hence, it is likely that well less than 10% of patients with HCV-related HCC received HCV treatment prior to 2015. Meanwhile, effective and well-tolerated antiviral therapy for HBV has been available since 1998, and about 50% of patients with HBV-related HCC received antiviral treatment in a multinational study of patients from the USA, Taiwan, and Korea.[24] Therefore, the higher prevalence of HBV in Asian studies and higher rate of antiviral use with HBV may explain the higher survival outcomes seen in studies from Asia as compared with other regions such as Europe. With the advent of DAAs since 2015, this disparity may decrease in the future, as long-term survival outcomes following surgical resection have the potential to improve with increasing use of DAAs for patients with HCV-related HCC. Recent data from the

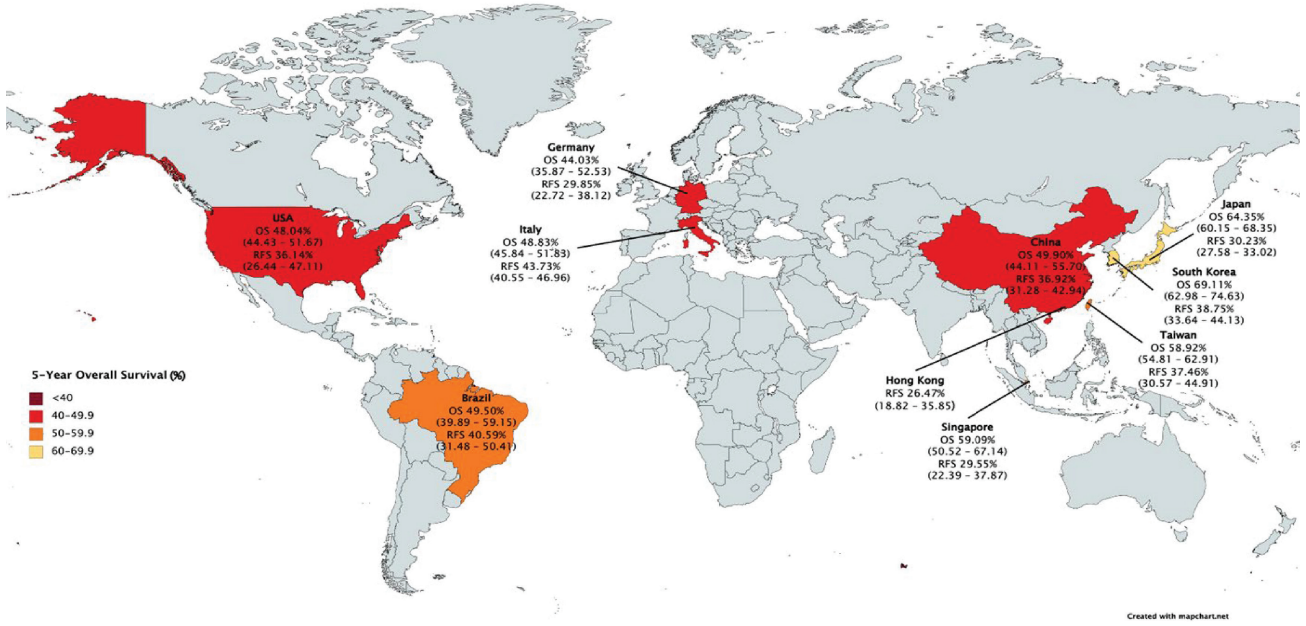

FIGURE 2 Country-level 5-year overall and recurrence free survival (RFS) after curative resection for hepatocellular carcinoma (HCC)

USA and Asia have consistently shown lower overall and liver-related mortality in patients with HCV-related HCC following HCV cure with DAA therapy, independent of types of HCC treatment.[9,29]

One strategy for improving long-term survival outcomes is increasing the uptake of antiviral treatment in patients with HCC. In a multicenter cohort study involving 2518 HBV-related HCC cases, only 17% of patients were on HBV antiviral therapy at the time of HCC diagnosis, and only half received HBV antiviral therapy at any time before or after HCC diagnosis, highlighting the massive care gap[24,30] and a significant opportunity for intervention. New systemic therapies for HCC may present additional adjuvant options, but more data are required, as most of these treatments are not as accessible or as well tolerated.

Another strategy for improving long-term survival outcomes is early detection of recurrence and optimal management of tumor recurrence. A study of 734 patients with HCC that underwent resection found that lack of tumor surveillance was an independent predictor of mortality.[7] Unfortunately, as shown in a recent meta-analysis, the adherence rate for HCC surveillance was generally very poor at 24% among patients with cirrhosis. However, the true rate is likely only about 10%, because most studies included in this meta-analysis were drawn from academic centers and or studies without a strict definition of surveillance.[31,32] In addition, a recent analysis of the U.S. Truven Health MarketScan Research Database revealed a compliance to HCC surveillance in only 8.8% of patients with cirrhosis.[33] Therefore, greater emphasis needs to be placed on enhancing surveillance following resection; currently, there are no specific recommendations for how to survey patients following resection among hepatology society practice guidelines.[2–4] 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.[34]

Disappointingly, our study did not find a significant difference in the 5-year OS between studies before 2010 versus studies from 2010 and after. The similar outcomes may be related to the fact that selection criteria for resection have remained relatively constant over time; thus, there were no significant differences in patient and tumor characteristics over time, as also shown in our study. On the other hand, the observed lack of improvement over time may still be a true reflection of the current situation if there has been no significant improvement over time in the availability of adjuvant antineoplastic treatment, adherence to HCC surveillance, and or the linkage to care for patients with viral hepatitis. Indeed, a recent large-scale nationwide study in the USA involving almost 95,000 patients with HBV found that only 49% of those with HCC received antiviral therapy.[35]

We acknowledge the following limitations. There was a relative paucity of data from Europe, North America, and South America, as well as a complete lack of data from the Eastern Mediterranean and African regions. This paucity highlights the need for more studies from these regions with information on characteristics and postresection outcomes of patients with HCC, especially for Africa.[36] This is particularly relevant, as incident cases of liver cancer have increased by 35% between 2007 and 2017, with 819,000 deaths in 2017 globally.[37] Additionally,

TABLE 4 Meta-regression of variables associated with OS and RFS after surgical resection

	5-year OS (months)				5-year RFS (months)			
	Number of studies (N) Number of patients (n)	Coefficient	95% CI	*p*	Number of studies (N) Number of patients (n)	Coefficient	95% CI	*p*
Age, per year	**45** 34,896	0.0228	−0.0013–0.0469	0.0635	**37** 18,893	−0.0131	−0.0347–0.0085	0.2349
Tumor number	**3** 2770	−0.1433	−0.3396–0.0531	0.1527	**3** 2770	−0.176	−0.2362 to −0.1158	<0.0001
Tumor size, cm	**24** 19,506	−0.0191	−0.0499–0.0117	0.2237	**19** 9426	0.0102	−0.0187–0.0391	0.4890
AFP (per 1 ng/ml increase)	**13** 13,289	0	−0.0001–0.0002	0.8243	**11** 6925	0	−0.0001–0.0001	0.3451
Platelet per (10^3) increase	**21** 14,726	−0.0031	−0.0131–0.0070	0.5478	**16** 9324	−0.0006	−0.0096–0.0085	0.9042
Tertiary center	**41** 42,436	−0.0593	−0.3645–0.2458	0.7031	**30** 11,776	0.063	−0.2041–0.3300	0.6438

there was a lack of data on outcomes for major underlying liver-disease etiologies such as NAFLD and alcohol-associated liver disease[38]; further studies are needed to examine the outcomes for these populations. Finally, we were not able to perform subgroup analyses for patients with and without cirrhosis and patients with different tumor stage and characteristics due to lack of survival outcomes for these specific subgroups.

In summary, we found excellent 1-year OS after surgical resection for HCC (~90%) without significant regional variation, suggesting that surgical techniques and immediate postoperative management are likely to be near optimal. However, 5-year OS (~55%) and RFS (~35%) are still poor overall, although rates were higher for Asia, a region with predominantly HBV-related HCC. The poorer long-term outcomes suggest that there is substantial room for improvement in long-term medical care. Greater efforts are required to improve survival by preventing HCC recurrence through antiviral therapy for those with viral-related HCC and early detection of tumor recurrence through enhanced surveillance.

CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Data collection, data interpretation, and review and/or critical revision of the manuscript: All authors. *Data analysis:* Eunice Yewon Lee, B.Y., Daniel Q. Huang, Margaret L. P. Teng, and Mindie H. Nguyen. *Manuscript draft*: Margaret L. P. Teng, Daniel Q. Huang, R.F.R.T., and Mindie H. Nguyen. *Study design:* Rosyli F. Reveron-Thornton, Margaret L. P. Teng, Daniel Q. Huang, and Mindie H. Nguyen. *Study supervision and guarantor of the article:* Daniel Q. Huang and Mindie H. Nguyen. *Study concept:* Mindie H. Nguyen. All authors approved the final version of the manuscript.

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