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Review Article

The impact of waiting time and delayed treatment on the outcomes of patients with hepatocellular carcinoma: A systematic review and meta-analysis

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Hepatocellular carcinoma (HCC) is the sixth most diagnosed cancer worldwide. Healthcare resource constraints may predispose treatment delays. We aim to review existing literature on whether delayed treatment results in worse outcomes in HCC. PubMed, Embase, The Cochrane Library, and Scopus were systematically searched from inception till December 2022. Primary outcomes were overall survival (OS) and disease-free survival (DFS). Secondary outcomes included post-treatment mortality, readmission rates, and complications. Fourteen studies with a total of 135,389 patients (delayed n = 25,516, no delay n = 109,873) were included. Age, incidence of male patients, Child–Pugh B cirrhosis, and Barcelona Clinic Liver Cancer Stage 0/A HCC were comparable between delayed and no delay groups. Tumor size was significantly smaller in delayed versus no delay group (mean difference, –0.70 cm; 95% confidence interval [CI]: –1.14, 0.26; $p = 0.002$). More patients received radiofrequency ablation in delayed versus no delay group (OR, 1.22; 95% CI: 1.16, 1.27; $p < 0.0001$). OS was comparable between delayed and no delay in HCC treatment (hazard ratio [HR], 1.13; 95% CI: 0.99, 1.29; $p = 0.07$). Comparable DFS between delayed and no delay groups (HR, 0.99; 95% CI: 0.75, 1.30; $p = 0.95$) was observed. Subgroup analysis of studies that defined treatment delay as > 90 days showed comparable OS in the delayed group (HR, 1.04; 95% CI: 0.93, 1.16; $p = 0.51$). OS and DFS for delayed treatment were non-inferior compared to no delay, but might be due to better tumor biology/smaller tumor size in the delayed group.

Key Words: Hepatocellular carcinoma; Liver cancer; Treatment delay; Time to treatment

INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most diagnosed cancer, and the third most common cause of cancer death worldwide [1]. Generally, prompt treatment after diagnosis is advocated to be the ideal management plan in most patients to prevent progression of the disease. Delays in treatment are believed to worsen survival outcomes by allowing disease spread and progression. However, treatment delays remain an issue that many institutions face. This is because time-to-treatment (TTT) is influenced by a multitude of factors that govern allocation of resources in the management of HCC in healthcare institutions. The consequence is a demand–supply mismatch of patients seeking treatment and treatment availabilities, resulting in a portion of patients suffering from a longer waiting time before receiving intended treatment. Even though prompt treatment after diagnosis is thought to be beneficial to prevent the progression of disease, the effect of delayed treatment on survival outcomes is still unclear.

A literature review by Liao et al. [2] in 2018 concluded that delayed treatment for HCC was associated with worse overall survival (OS) and disease-free survival (DFS). This can be attributed to tumor growth and increased risk of microvascular invasion as a result of a delay in treatment initiation. Since

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then, more observational studies on the impact of delayed treatment in HCC have been published. For example, Xu et al. [3] and Kabir et al. [4] both reported improved OS for patients with delayed treatment, compared to those with no delay. It is hypothesized that treatment delay in these patients includes pre-treatment optimization of patient comorbidities. This explains the improved survival outcomes in patients who underwent rehabilitation in preparation for treatment, compared to patients receiving prompt treatment whilst foregoing a more thorough optimization process. In contrast, Tsilimigras et al. [5], Rao et al. [6], and Govalan et al. [7] reported similar survival between patients with delayed treatment and those without. Conflicting results from various observational studies lead to a conundrum on the important question—whether delayed treatment in HCC is associated with worse survival; and if so, what is the temporal cut-off to define "delayed"? Hence, we aim to perform an updated meta-analysis comparing outcomes of delayed versus no delay in treatment initiation in patients diagnosed with HCC.

MATERIALS AND METHODS

Study selection and search strategy

This systematic review and meta-analysis were performed according to the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) guidelines [8]. The protocol for this systematic review and meta-analysis was registered at PROSPERO (Ref. no: CRD42022381328). A systematic search of the databases PubMed, Embase, The Cochrane Library, and Scopus was conducted for studies published from inception to 1st December 2022. A combination of the following search terms was used: "hepatocellular carcinoma" or "liver cancer", and "time to treatment" or "treatment delay" or "delayed treatment." The search was restricted to the title, abstract, and keywords. The complete search strategy is appended in Supplementary Table 1. Search strategies for other databases were modified accordingly from the initial search strategy done on PubMed based on the database requirements.

Included studies were randomized controlled trials (RCTs)

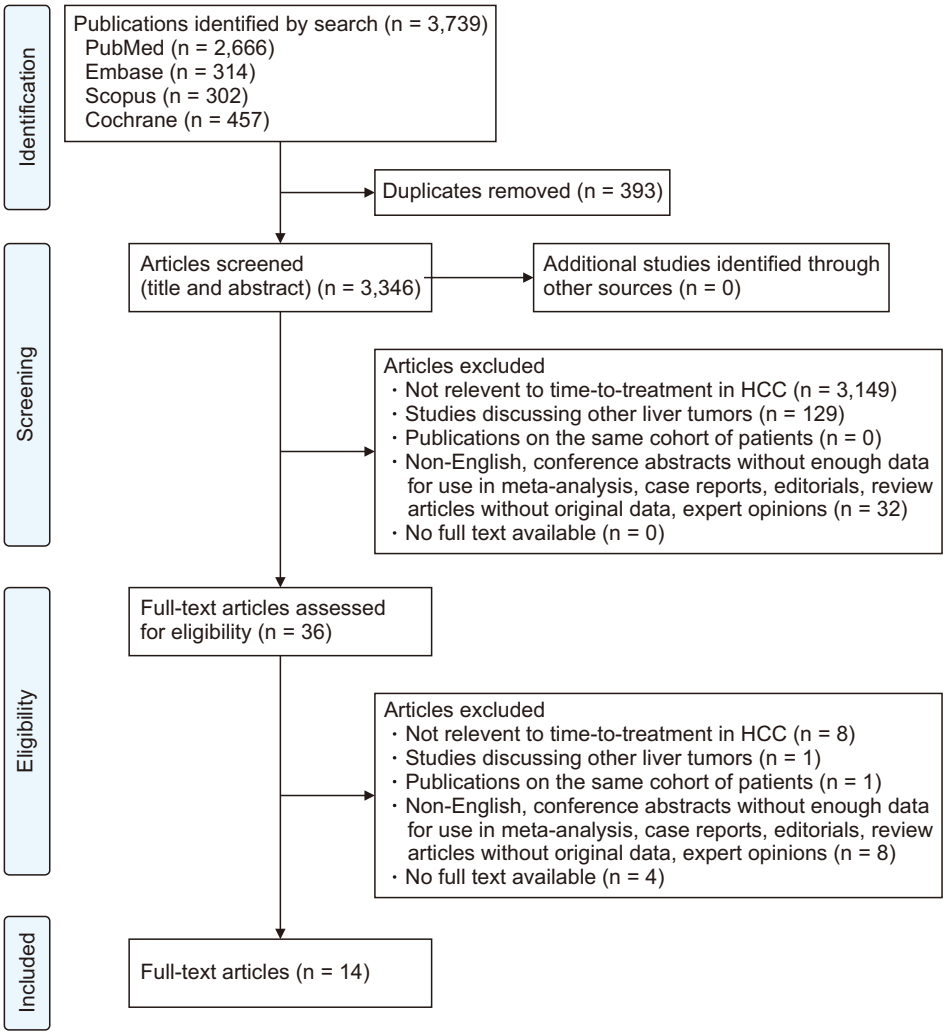

Fig. 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flowchart for study selection.

and non-RCTs on (a) patients ≥ 18 years old with a diagnosis of HCC who underwent either curative or palliative HCC treatment, and (b) compared outcomes between patients with delayed treatment and no delay. Exclusion criteria were studies (a) on other types of liver cancer, (b) irrelevant to our study question, e.g., did not compare outcomes between delayed treatment and no delayed treatment, (c) no outcome data, (d) on the same cohort of patients, (e) that reported only on transplant patients exclusively, and (f) based on article type (non-English studies, conference abstracts, case report or series, editorials, expert opinions, and review articles without original data). HCC treatment was defined as any form of treatment for HCC—use of either non-operative treatment (locoregional therapy–radiofrequency ablation [RFA], microwave ablation [MWA], transarterial chemoembolization [TACE], selective internal radiation therapy, or systematic therapy with targeted or immunotherapy), or operative treatment (liver resection [LR] or liver transplantation [LT]); studies that included a mix of LR and LT were included in our review. TTT was defined as the time from diagnosis of HCC to the initiation of treatment for HCC. There is no standardized definition of "delayed treatment"; for the purpose of this study, delayed treatment was defined as the definitions used based in the included studies, respectively.

All cross-references were screened for potentially relevant studies not identified by the initial literature search. After removing duplicates, abstracts were screened for potential inclusion screening independently by two authors (FYC, CHFL). Full texts of included studies were reviewed in their entirety, and selected based on the inclusion and exclusion criteria. All discrepancies were resolved after review by the senior author (VGS).

Data extraction

Three authors independently conducted data extraction (FYC, CHFL, KSC). The following variables were extracted from each study: publication details (name of first author, and publication year and country), study characteristics (sample size, sex, age, definition of treatment delay, distribution of patients undergoing modalities of treatment, Child–Pugh score, baseline alpha–fetoprotein, and tumor size). Our primary outcomes were OS and DFS. Our secondary outcomes were

Table 1. Baseline characteristics and patient demographics of the included studies (n = 14) with 14 data sets

No	Author, year	Study design	Study period	Country	Sample size	Age (yr)	Male	Child-Pugh (A/B)	AFP (ng/mL)	Tumor size (cm)	MELD Score
1	Brahmania et al. [20], 2017[a]	Retrospective	Jul 2010–Dec 2013	Canada	No delay: 110 Delayed: 109	NR	NR	NR	NR	NR	NR
2	Chen et al. [21], 2011	Prospective	Jan 2004–Jul 2007	Taiwan	No delay: 100 Delayed: 21	No delay: 64.8 ± 10.3 Delayed: 66.2 ± 9.7	No delay: 59 Delayed: 21	No delay: 88/12 Delayed: 15/6	No delay: 162 ± 402 Delayed: 70.5 ± 129	NR	NR
3	Govalan et al. [7], 2022	Retrospective	2010–2017	United States	No delay: 71,845 Delayed: 16,307	No delay: 60 ± 10 Delayed: 63 ± 9	No delay: 54,802 Delayed: 12,445	NR	Positive: No delay: 41,060 Delayed: 9,110	No delay: 4.0 (2.5–7.0) Delayed: 3.2 (2.2–5.0) No delay: 4.5 ± 3.3[g] Delayed: 3.5 ± 2.1[g]	No delay: 11 (8–17) Delayed: 11 (8–16) No delay: 12.0 ± 6.7[g] Delayed: 11.7 ± 5.9[g]
4	He et al. [16], 2021[b]	Retrospective	2012–2018	China	No delay: 215 Delayed: 17	NR	NR	NR	NR	NR	NR
5	Huo et al. [17], 2007	Retrospective	Feb 1998–Apr 2003	Taiwan	No delay: 96 Delayed: 48	No delay: 68.0 ± 9.4 Delayed: 67.6 ± 10.4	No delay: 71 Delayed: 35	No delay: 65/31 Delayed: 34/14	NR	> 5 cm: No delay: 16 Delayed: 7	No delay: 11.1 ± 2.5 Delayed: 12.3 ± 1.8
6	Kabir et al. [4], 2020[c,d]	Retrospective	2000–2015	Singapore	No delay: 781 Delayed: 82	No delay: 61.7 ± 12.0 Delayed: 60.3 ± 12.0	No delay: 610 Delayed: 66	No delay: 737/44 Delayed: 77/5	NR	No delay: 5.6 ± 4.7 Delayed: 5.1 ± 4.1	NR
7	Lim et al. [18], 2018[c]	Retrospective	Jan 2006–Jun 2016	France	No delay: 50 Delayed: 50	No delay: 65 (59–72) Delayed: 65 (58–73) No delay: 65.3 ± 9.9[g] Delay: 65.3 ± 11.5[g]	No delay: 41 Delayed: 36	NR	No delay: 12 (4–112) Delayed: 9 (5–34)	No delay: 3.7 (2.5–6.4) Delayed: 3.4 (2.6–6.3) No delay: 4.2 ± 3.0[g] Delayed: 4.1 ± 2.8[g]	No delay: 8 (6–9) Delayed: 7 (6–9) No delay: 7.67 ± 2.29[g] Delayed: 7.33 ± 2.29[g]

in-hospital mortality, readmission rates, any morbidity, and major morbidity. OS was defined as the proportion of patients alive at the end of the study or follow-up, and DFS was defined as the proportion of patients who had not died due to HCC. Readmission rate was defined as the proportion of patients who underwent readmission within 90 days post-treatment. Any morbidity and major morbidity were defined as the presence of any complications and complications of Clavien–Dindo ≥ grade 3A, respectively, following initiation of treatment, unless otherwise specified. None of the included studies reported on local and/or regional recurrence. For the purpose of this study, the group receiving delayed treatment (intervention group) are referred to as the delayed group, while the group receiving treatment before the defined cut-off time interval of treatment delay (comparator group) are referred to as the no delay group. For studies that stratified TTT into > 2 groups, the 2 comparator groups were selected based on the most used comparator groups included in other studies. This selection was made by consensus and discussion among the co-authors.

Assessment of study quality

Two authors (FYC, CHFL) independently performed a quality assessment of the included studies. Observational studies were assessed using the Newcastle–Ottawa scale (Supplementary Table 2) [9]. Only observational studies of sufficient quality (defined as articles with a score > 6) were included. Disagreements between authors were resolved by discussion with the senior author (VGS).

Statistical analysis

Study variables were extracted to Microsoft Excel 365 (Microsoft®). For continuous variables, which were expressed only in median and range or interquartile range, mean and standard deviation were estimated from the median and range

Table 1. Continued

No	Author, year	Study design	Study period	Country	Sample size	Age (yr)	Male	Child-Pugh (A/B)	AFP (ng/mL)	Tumor size (cm)	MELD Score
8	Ong et al. [19], 2022	Retrospective	Jan 2011–Jul 2017	Singapore	No delay: 106 Delayed: 109	No delay: 68.49 ± 10.68 Delayed: 68.62 ± 9.43	No delay: 83 Delayed: 77	NR	NR	NR	NR
9	Rao et al. [6], 2021	Retrospective	Jan 2008–Jul 2017	Unites States	No delay: 500 Delayed: 104	NR	NR	NR	NR	NR	NR
10	Singal et al. [22], 2013	Retrospective	Jan 2005–Jun 2012	United States	No delay: 50 Delayed: 115	NR	No delay: 38 Delayed: 93	No delay: 50/50 Delayed: 72/42	NR	NR	NR
11	Tsai et al. [15], 2018[e,f]	Retrospective	2004–2010	Taiwan	No delay: 21,123 Delayed: 2,124	No delay: 63.03 ± 12.17 Delayed: 64.59 ± 12.04	NR	NR	NR	NR	NR
12	Tsilimigras et al. [5], 2021	Retrospective	2000–2017	United States	No delay: 537 Delayed: 238	No delay: 68 (59–74) Delay: 67 (59–74) No delay: 67.0 ± 11.2[g] Delayed: 66.7 ± 11.1[g]	No delay: 391 Delayed: 186	NR	400: No delay: 87 Delayed: 35	No delay: 5.0 (3.0–8.5) Delayed: 4.5 (3.0–7.5) No delay: 5.5 ± 4.1[g] Delayed: 5.0 ± 3.4[g]	NR
13	Wagle et al. [13], 2022	Retrospective	2001–2015	United States	No delay: 7,245 Delayed: 1,205	NR	No delay: 4,863 Delayed: 812	NR	NR	NR	NR
14	Xu et al. [3], 2019[b]	Retrospective	2004–2012	United States and Puerto Rico	No delay: 7,115 Delayed: 4,987	No delay: 62.8 ± 11.8 Delayed: 62.0 ± 10.3	No delay: 5,055 Delayed: 3,716	NR	Elevated: No delay: 3,446 Delayed: 2,628	> 5 cm: No delay: 2,584 Delayed: 1,269	No delay: 13.0 ± 8.6 Delayed: 13.1 ± 8.5

All continuous variables are expressed in mean ± standard deviation or median (interquartile range) unless otherwise stated. All categorical variables are expressed as n (%) unless otherwise stated.

AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma; MELD, Model for End-stage Liver Disease; NR, not reported.

[a]Values included in this study are from the hazard ratio for wait time expressed per 30 days. [b]Values included in this study are from the cohort defining treatment delay as > 60 days (data comparing other cut-offs were excluded). [c]Values included in this study is obtained after propensity score matching. [d]Values included in this study are from the cohort defining treatment delay as > 90 days (data comparing other cut-offs were excluded). [e]Values included in this study are from the data sets of cohorts ≤ 30 days and 61–180 days (other data sets were excluded). [f]Histology of liver cancer in this study does not explicitly mention HCC, assumed that study includes only HCC and excludes other liver cancers based on reading of article. [g]Mean and standard deviation were calculated from median and range/interquartile range using methods described by Wan et al. [10].

values using the methods described by Wan et al. [10]. Meta-analysis was performed using RevMan 5.4 (Review Manager 5.4, The Nordic Cochrane Centre). For cumulative OS and DFS, hazard ratio (HR) and standard error (SE) were estimated indirectly, according to the methods described by Parmar et al. [11]. Pooled HR was calculated through the inverse-variance method using the natural logarithm of HR (ln[HR]) and SE [12]. For studies that used both univariate and multivariate analysis to assess the impact of treatment delay, the effect size from the multivariate analysis was used in our pooled analysis. Heterogeneity was assessed using Cochrane's Q, and quantified by I^2. Heterogeneity was defined by $I^2 > 50\%$. A random-effect model was used when $I^2 > 50\%$, while a fixed-effect model was used when $I^2 \leq 50\%$. Statistical significance was defined as $p < 0.05$. Publication bias was investigated using funnel plots. Subgroup analysis was performed on patients who received LR only, and for studies with delayed treatment defined as > 90 days.

RESULTS

The systematic search identified 3,739 articles from the four databases. An existing literature review by Liao et al. [2] in 2018 on the impact of delayed treatment in HCC was also screened for potential references for inclusion in our study. After removal of the duplicates, there were 3,346 articles. Titles and abstracts of all the identified articles were screened. The remaining 36 articles underwent full-text review, of which 14 articles were included in the final analysis [3-7,13-21]. Two studies reported on the same cohort of patients [14,22], of which the more recent study by Singal et al. [14] reporting on a larger sample size was included. Fig. 1 appends the PRISMA diagram for the study selection process, while Supplementary Fig. 1 appends the funnel plots.

Study characteristics

We included 14 studies with 135,389 patients (delayed n = 25,516, no delay n = 109,873) [3-7,13-21]. There was 1 prospective study with 121 patients (delayed n = 21, no delay n = 100) [21], and 13 retrospective studies with 135,049 patients (delayed n = 25,386, no delay n = 109,663) [3-7,13-20], of which 2 studies, by Lim et al. [18] in 2018 and Kabir et al. [4] in 2020, used propensity score matching (PSM) analysis. In addition, Kabir et al. [4] used both inverse probability of treatment weighting and PSM to derive their patient cohorts; only the PSM cohort was analyzed in our study. Six studies performed both univariate and multivariate analysis on the impact of treatment delay on outcomes [5-7,13,20,21]. Tsilimigras et al. [5] presented outcomes of delayed treatment in two groups (Barcelona Liver Cancer Clinic [BCLC]–0/A group and BCLC–B/C group); individual outcomes of each group were recorded separately in our

Table 2. Summary of effect size of different study variables and outcomes between patients with hepatocellular carcinoma receiving delayed treatment and no delay

No	Study variables and/or outcomes	No. of data sets	Total number of patients (delayed/no delay)	No. of patients (%)		Effect size, OR (95% CI)/ MD (95% CI)/ HR (95% CI)[a]	*p*-value	I^2 (%)	Model used
				Delayed	No delay				
Demographics and histopathological findings									
1	Age (yr)	9	125,719 (23,966/101,753)	NA		–0.17 (–1.09, 0.76)	0.72	90	RE
2	Male	10	111,087 (23,162/87,925)	17,487 (75.5)	66,013 (75.1)	1.07 (0.95, 1.20)	0.26	65	RE
3	Child's B cirrhosis	4	1,293 (266/1,027)	82 (30.8)	113 (11.0)	1.49 (0.62, 3.61)	0.37	77	RE
4	Tumor size (cm)	4	89,890 (16,677/73,213)	NA		–0.70 (–1.14, –0.26)	0.002*	59	RE
5	BCLC-0/A staging	3	1,040 (403/637)	322 (79.9)	547 (85.9)	0.75 (0.29, 1.92)	0.55	79	RE
6	MELD score	4	100,498 (21,392/79,106)	NA		0.12 (–0.39, 0.62)	0.65	86	RE
7	Surgical resection	6	102,157 (21,779/80,378)	6,667 (30.6)	18,946 (23.6)	1.10 (0.20, 5.99)	0.92	89	RE
8	RFA	3	88,438 (16,443/71,995)	2,842 (17.3)	10,611 (14.7)	1.22 (1.16, 1.27)	< 0.0001*	0	FE
Outcomes									
9	Overall survival	13	134,955 (25,298/109,657)	NA		1.13 (0.99, 1.29)	0.07	92	RE
10	Disease-free survival	4	1,211 (418/793)	NA		0.99 (0.75, 1.30)	0.95	66	RE
11	Overall survival with TTT defined as 90 days	7	99,109 (18,101/81,008)	NA		1.04 (0.93, 1.16)	0.51	57	RE
13	Overall survival in surgical delay	4	13,840 (5,357/8,483)	NA		0.92 (0.87, 0.98)	0.01*	0	FE

BCLC, Barcelona Liver Cancer Clinic; CI, confidence interval; FE, fixed-effects; HR, hazard ratio; I^2, heterogeneity; MD, mean difference; MELD, Model for End-stage Liver Disease; NA, not applicable; OR, odds ratio; RE, random-effects; RFA, radiofrequency ablation; TTT, time-to-treatment.

[a]OR and 95% CI was used for dichotomous outcomes, MD and 95% CI was used for continuous outcomes, and HR and 95% CI was used for time-to-event outcomes.

*$p < 0.05$.

Table 3. Clinical characteristics and details of treatment received in the included studies (n = 14) with 14 data sets

No	Author, year	Treatment delay cut-off	Treatment modalities	Time-to-treatment	Treatment compli-cations	1-year OS (%)	1-year DFS (%)	5-year OS (%)	5-year DFS (%)
1	Brahmania et al. [20], 2017	96 days[c]	RFA: No delay: 110 Delayed: 109	96 days (75–139)	NR	NR	NR	NR	NR
2	Chen et al. [21], 2011	5 wk	RFA: No delay: 100 Delayed: 21	NR	NR	NR	NR	NR	NR
3	Govalan et al. [7], 2022	90 days	LT: No delay: 6,299 Delayed: 1,696 LR: No delay: 10,459 Delayed: 1,287 Any type of ablation: No delay: 10,507 Delayed: 2,809	NR	NR	NR	NR	NR	NR
4	He et al. [16], 2021	60 days[d]	NR	NR	NR	NR	NR	NR	NR
5	Huo et al. [17], 2007	60 days	TACE: No delay: 48 Delayed: 56 PAI: No delay: 35 Delayed: 29 PEI: No delay: 18 Delayed: 15	NR	NR	No delay: 97 Delayed: 86	NR	NR	NR
6	Kabir et al. [4], 2020[a]	90 days[e]	LR: No delay: 781 Delayed: 82	NR	NR	NR	NR	NR	NR
7	Lim et al. [18], 2018[a]	90 days	LR: No delay: 50 Delayed: 50	3 mon (1.8–4.6)	No delay: 8 Delayed: 18	No delay: 100 Delayed: 96	No delay: 94 Delayed: 88	No delay: 80 Delayed: 81	No delay: 48 Delayed: 37
8	Ong et al. [19], 2022	42 days	NR	42 days (0–445)	NR	NR	NR	NR	NR
9	Rao et al. [6], 2021	90 days	NR	46 days (29–74)	NR	NR	NR	NR	NR
10	Singal et al. [22], 2013	90 days	LT: No delay: 5 Delayed: 1 LR: No delay: 4 Delayed: 23 TACE: No delay: 34 Delayed: 53 RFA: No delay: 4 Delayed: 12 Systemic therapy: No delay: 3 Delayed: 26	1.7 mon (0.1–42.5)	NR	No delay: 89.80 Delayed: 63.70	NR	NR	NR
11	Tsai et al. [15], 2018[b]	< 30 days vs. 61–180 days[f]	NR	NR	NR	NR	NR	NR	NR
12	Tsilimigras et al. [5], 2021	90 days	LR: No delay: 537 Delayed: 238	60 days (34–100)	No delay: 197 Delayed: 79	NR	NR	No delay: 63.70 Delayed: 64.90	No delay: 33.50 Delayed: 42.40
13	Wagle et al. [13], 2023	90 days	NR	1 mon (1–3)	NR	NR	NR	NR	NR
14	Xu et al. [3], 2019	60 days[d]	LR: No delay: 7,115 Delayed: 4,987	50 days (29–86)	NR	NR	NR	NR	NR

All continuous variables are expressed in mean ± standard deviation, or median (interquartile range) unless otherwise stated. All categorical variables are expressed as n (%) unless otherwise stated.

RFA, radiofrequency ablation; DFS, disease-free survival; NR, not reported; LR, liver resection; LT, liver transplantation; OS, overall survival; PAI, percutaneous acetic acid injection; PEI, percutaneous ethanol injection; TACE, transarterial chemoembolization.

[a]Values included is this study is obtained after propensity score matching. [b]Histology of liver cancer in this study does not explicitly mention HCC, assumed that study includes only HCC and excludes other liver cancers based on reading of article. [c]Values included in this study are from the hazard ratio for wait time expressed per 30 days. [d]Values included in this study are from the cohort defining treatment delay as > 60 days (data comparing other cut-offs were excluded). [e]Values included in this study are from the cohort defining treatment delay as > 90 days (data comparing other cut-offs were excluded). [f]Values included in this study are from the data sets of cohorts ≤ 30 days and 61–180 days (other data sets were excluded).

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study. There were two studies that reported multiple cut-offs for treatment delay; for these studies, TTT cut-off of 60 days for Xu et al. [3] and TTT cut-off of 90 days for Kabir et al. [4] were used for the purpose of this study. The median wait time from diagnosis to treatment of HCC reported in 8 studies ranged (1 month to 96 days) [3,5,6,13,14,18-20]. One study used TTT cut-off of 30 days [15], 3 studies used 60 days [3,16,17], and 7 studies used 90 days [4-7,13,14,18]. Ong et al. [19] used TTT cut-off of 42 days, while Chen et al. [21] used TTT cut-off of 5 weeks. Brahmania et al. [20] presented HR for wait time expressed per 30 days. Tsai et al. [15] compared several different TTT intervals with a reference TTT of < 30 days, of which data sets of the cohort with a TTT of 61–180 days were extracted.

Patient demographics and treatment received

Table 1 summarizes the study characteristics and patient demographics of individual studies. Four studies reported on patients with LR [3-5,18], 2 studies on those with RFA [20,21], 1 study with TACE/percutaneous acetic acid injection (PAI)/percutaneous ethanol injection (PEI) [17], 2 on multiple treatment methods used for HCC [7,14], and 5 studies that did not specify the type of treatment received [6,13,15,16,19]. Age, incidence of male patients and Child–Pugh B cirrhosis, BCLC–0/A HCC were comparable between the delayed treatment and the no delay group (Table 2). Tumor size was significantly smaller in the delayed treatment (mean difference [MD], –0.70 cm; 95% confidence interval [CI], –1.14, 0.26; $p = 0.002$), compared to the no delay group. Four studies reported the Child–Pugh status of patients [4,14,17,21], of which a majority had Child–Pugh A liver cirrhosis (n = 1,153/1,348 [85.5%]). Three studies presented on BCLC staging [5,14,18], of which a large proportion of HCC were BCLC 0/A (n = 869/1,039 [83.6%]). Table 3 summarizes the details of treatment received, and survival outcomes reported in individual studies. There were more patients who received RFA (odds ratio [OR], 1.22; 95% CI, 1.16, 1.27; $p < 0.0001$) in the delayed treatment versus the no delay group. The incidence of patients who received LR was comparable between delayed treatment and no delay.

Oncological outcomes

Thirteen studies involving 135,174 patients (delayed n = 25,407, no delay n = 109,767) reported on OS [3-7,13-18,20,21].

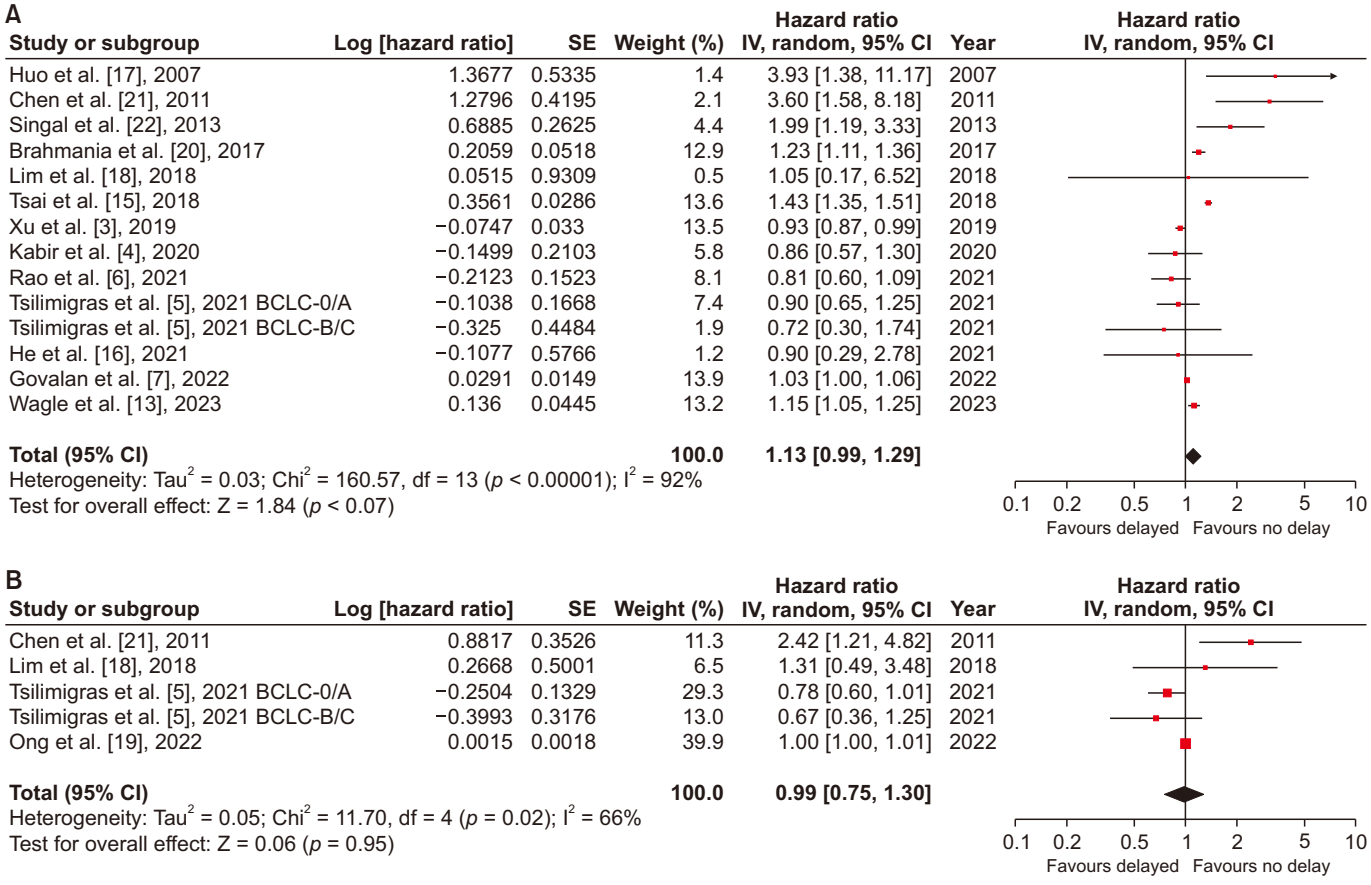

Fig. 2. Comparison of (A) overall survival and (B) disease-free survival between delayed treatment and no delay in patients with hepatocellular carcinoma. BCLC, Barcelona Liver Cancer Clinic; CI, confidence interval; SE, standard error.

OS was comparable between delay and no delay in treatment for HCC (HR, 1.13; 95% CI, 0.99, 1.29; p = 0.07) (Fig. 2A). There was considerable heterogeneity among the studies (I^2 = 92%, p < 0.001).

Four studies involving 1,211 patients (delayed n = 418, no delay n = 793) reported on DFS [5,18,19,21]. Pooled results showed comparable DFS between the delayed and no delay groups (HR, 0.99; 95% CI, 0.75, 1.30; p = 0.95) (Fig. 2B). There was considerable heterogeneity among the studies (I^2 = 66%, p = 0.02).

Short-term outcomes following the initiation of treatment

Two studies involving 875 patients (delayed n = 288, no delay n = 587) reported on the incidence of post-operative complications in patients who received LR only [5,18]. Tsilimigras et al. [5] reported post-operative complication of 33.2% in the delayed treatment group (n = 79/238), and 36.7% in the no delay group (n = 197/537); however, this did not reach statistical significance (p = 0.35). Lim et al. [18] reported higher post-operative complications in the delayed treatment, compared to the no delay group (delayed n = 18/50 [36.0%], no delay n = 8/50 [16.0%], p = 0.02).

Two studies involving 875 patients (delayed n = 288, no delay n = 587) reported on the incidence of major complications (Clavien–Dindo Grade ≥ III) [5,18]. Tsilimigras et al. [5] reported statistically significantly lower major complications (Clavien–Dindo Grade ≥III) in the delayed, compared to the no delay group (delayed n = 16/238 [6.7%], no delay n = 69/537 [12.8%], p = 0.01). Lim et al. [18] reported similar incidence of major complications (Clavien–Dindo Grade III to IV) in the delayed and no delay groups (delayed n = 5/50 [10.0%], no delay n = 1/50 [2.0%], p = 0.39).

Only one study reported on 90 days re-admission and mortality: Tsilimigras et al. [5] reported 90 days readmission rates of 4.6% (n = 11/238) and 6.1% (n = 33/537) in the delayed treatment and no delay group, respectively (p = 0.40). They also reported similar 90 days mortality between the delayed treatment and the no delay group (delayed n = 5/238 [2.1%], no delay n = 18/537 [3.4%], p = 0.34).

Subgroup analysis based on time cut-off and type of treatment

In view of the heterogeneity of time cut-off used in the included studies, we performed a subgroup analysis on the most used TTT cut-off (i.e., 90 days) to define delayed treatment. Seven studies including 99,109 patients (delayed n = 18,101, no delay n = 81,008) compared OS between patients with TTT ≥ 90 days and < 90 days after the diagnosis of HCC [4-7,13,14,18]. Pooled HR showed comparable OS between the delayed and no delay group (HR, 1.04; 95% CI, 0.93, 1.16; p = 0.51) (Fig. 3A). Heterogeneity was significant among the studies (I^2 = 57%, p = 0.02).

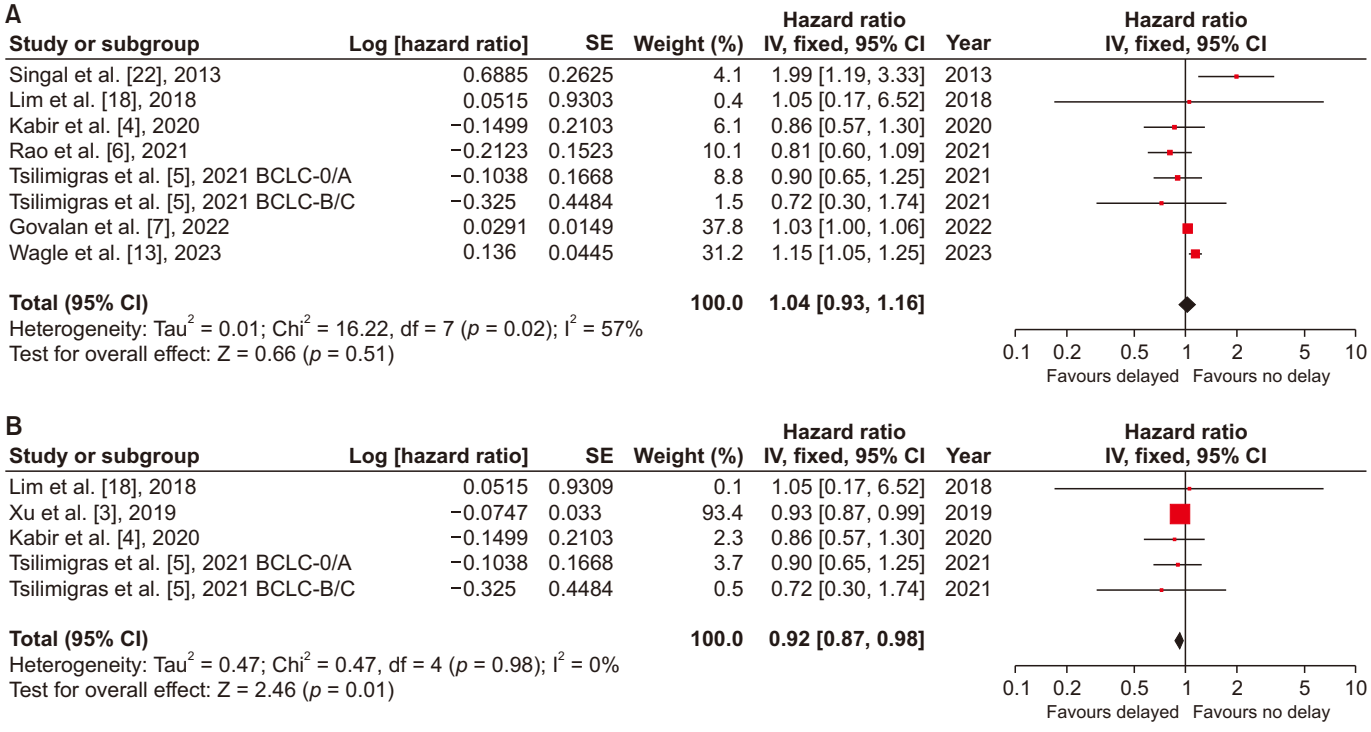

Fig. 3. Subgroup analysis comparing overall survival between delayed treatment and no delay in patients with hepatocellular carcinoma with (A) time-to-treatment cut-off defined as 90 days, and (B) received liver resection only. BCLC, Barcelona Liver Cancer Clinic; CI, confidence interval; SE, standard error.

Subgroup analysis was also performed for patients who received LR only; four studies involving 13,840 patients (delayed n = 5,357, no delay n = 8,483) reported on OS [3-5,18]. Of the included studies, three studies defined TTT as > 90 days [4,5,18], while one study defined TTT as > 60 days [3]. Pooled HR showed statistically significantly better OS in the delayed group (HR, 0.92; 95% CI, 0.87, 0.98; $p = 0.01$) (Fig. 3B). Heterogeneity was not significant among the studies ($I^2 = 0\%$, $p = 0.98$). In view of the significant weight of included studies allocated to the study by Xu et al. [3], after excluding the study by Xu et al. [3], sensitivity analysis was performed to exclude that study; OS was comparable between delayed treatment and no delay (HR, 0.87; 95% CI, 0.69, 1.12; $p = 0.28$).

DISCUSSION

Early diagnosis and the prompt initiation of treatment remain key principles in the management of cancers. The avoidance of treatment delay can be attributed to the fear of tumor and disease progression. Early initiation of treatment has been associated with better oncological outcomes in various cancers, such as breast, prostate, non-small cell lung cancer, and colon cancers [23,24]. While a literature review performed by Liao et al. [2] in 2018 summarized the existing evidence on the impact of delayed treatment in HCC, newer studies have been published since then, and warrant an updated meta-analysis. This meta-analysis demonstrated that OS and DFS in delayed treatment was non-inferior, compared to no delay in treatment for HCC. However, the majority of the included studies were retrospective in nature, and patients who received delayed treatment had smaller tumor size.

Delay in treatment is a major concern and fear both clinicians and patients have, due to the risk of tumor progression and the upstaging of disease. A recent meta-analysis by Nathani et al. [25] on 20 studies with 1,374 HCC lesions showed that the pooled tumor doubling time (TDT) was 4.6 months. This raises the concern of whether delayed treatment may worsen prognosis with an increased tumor burden. Our study did not show any significant difference in OS and DFS between delayed treatment and no delay. This finding is unexpected, as delay in treatment is concerning for tumor progression, worsening survival outcomes. Hence, this finding needs to be explained. One postulate would be the tumor biology of the included patients. Studies have suggested that HCC exhibits logarithmic growth (initial rapid growth, followed by subsequent indolent growth with increasing tumor size) [26-29]. However, it is also important to note that the tumor biology for HCC varies. Rich et al. [30] demonstrated heterogeneous tumor growth patterns in the Western cohort, with one-fourth exhibiting rapid tumor growth (defined as TDT < 90 days), and over one-third with indolent growth (defined as TDT > 365 days). Indolent tumor growth has been suggested to result in lower mortality, compared to rapid tumor growth (HR, 0.61; 95% CI, 0.40–0.95) [30]. Patients in the delayed treatment group may have better tumor biology with longer TDT, resulting in non-inferior survival outcomes, compared to the no delay group. However, none of the included studies described TDT, which limits the interpretation of our study.

The diverse definitions of treatment delay in the included studies, ranging 30 to 96 days, could contribute to bias in our main analysis. With a majority of studies (n = 7/14, 50.0%) defining delayed treatment as TTT > 90 days, we performed a subgroup analysis on these studies. Similarly, the subgroup analysis also showed non-inferior OS for delayed treatment (TTT > 90 days), compared with no delay (HR, 1.04; 95% CI, 0.93–1.16; $p = 0.51$). Potential factors contributing to this unexpected outcome are explored in this discussion.

Additionally, the concept of immortal time bias is important when interpreting the results of our study. Immortal time bias is also referred to as time-dependent bias, and happens usually in observational studies; it occurs when treatment exposure occurs after the initiation of a study, and analysis does not take into account this discordance between the time of initiation of study and the time treatment started [31]. For example, in the context of this study, a patient under the delayed treatment group would have started later compared to the no delay group; however, survival was analyzed from the initiation of the study (which would likely correspond to the time of diagnosis of HCC). Survival of the delayed treatment group may appear similar to no delay due to "immortal time" (defined as time between the start of the study to the initiation of the treatment), when this may in fact be shorter. When analyzing time-dependent outcomes like survival, immortal time bias needs to be addressed separately through the use of other types of analysis, such as time-dependent Cox models, instead of the standard Cox regression models [32]. The Standard Cox regression models have been shown to significantly overestimate treatment effects (which in this study, may have overestimated the survival benefit delayed treatment has, compared with no delay) [32].

To date, there are several existing guidelines for the diagnosis and management of HCC, including the BCLC guidelines, and the Hong Kong Liver Cancer (HKLC) staging system [33,34]. Management of HCC is largely divided into curative and palliative treatments. Our study defined "treatment" as any curative or palliative treatment for HCC. This was to ensure an adequate sample size for meaningful quantitative analysis. However, this does introduce heterogeneity in the analysis, and hence our results need to be discussed, and put into context. Of all included studies, there were 4 on LR [3-5,18], 1 on TACE/PAI/PEI [17], 2 on RFA/MWA [20,21], and 7 with mixed treatment modalities [6,7,13-16,19]. The type of treatment received reflects the stage of HCC at the point of diagnosis (e.g., systemic therapy will not be offered for the curative treatment of small HCC). Hence, we compared the patient demographics and type of treatment received between the delayed treatment and no delay groups. Patients with delayed treatment had smaller

tumor size (MD, −0.70 cm; 95% CI, −1.14, −0.26; p = 0.002) and higher incidence of RFA (OR, 1.22; 95% CI, 1.16, 1.27; $p \leq$ 0.0001). RFA is a recommended treatment option for patients with good pre-morbid function, liver function (Child–Pugh) and small early-stage tumors (size ≤ 3 cm) in several existing guidelines, including the BCLC and HKLC staging system [33,34]. Early stage and/or smaller HCC have been shown to bear better prognosis, where early stage tumors have 5-year survival exceeding 70%, compared to advanced stage HCC with median survival of 1–1.5 years [35-37]. While our study failed to show any significant difference in stage of tumor, this may be confounded by the small sample size of 3 studies (n = 1,040 patients). It is difficult to draw definitive conclusions in view of the heterogenous population with varied treatments received.

Nevertheless, in view of this heterogeneity of treatment options received, subgroup analysis was performed to analyze patients who underwent LR only and for whom no heterogeneity was noted (I^2 = 0%). Interestingly, subgroup analysis of patients who underwent LR for HCC showed that delayed treatment was associated with superior OS, compared to no delay (HR, 0.92; 95% CI, 0.87–0.98; p = 0.01). This is unexpected, as delay in treatment should have worse survival, compared to no delay; Johnson et al. [38] showed that delayed surgery results in worse OS for breast, lung, and colon cancer. However, factors to consider would include reasons for delayed treatment. Delayed treatment may be due to the need for pre-operative nutritional and functional optimization to improve post-operative outcomes [39]. Delay in treatment may also be due to the need for pre-operative liver augmentation due the risk of post-hepatectomy liver failure, especially for patients with underlying liver cirrhosis [40]. Although these techniques require a delay of surgical resection by several weeks, there is potential in improving perioperative and long-term outcomes [4].

Another plausible reason for improved survival with delayed LR may be retrospective selection bias and resource allocation priority, i.e., patients with more advanced disease were allocated earlier surgery dates, compared to those with early disease. This phenomenon has been referred to as the 'waiting time paradox' by clinicians, whereby more advanced and/or poorly differentiated HCC was referred more urgently for treatment, resulting in lower odds for delayed treatment [7]; patients in the delayed treatment group may hence consist of patients with HCC that was slow growing and less aggressive, which has better prognosis, compared to rapidly growing tumors [36,37]. This was similarly described in one of the included studies; Xu et al. [3] who studied 12,102 patients showed a lower proportion of patients with HCC > 5 cm and poorly-differentiated/undifferentiated tumor in the delayed treatment group, and concluded that delayed treatment is associated with improved survival; they postulated that their findings may be due to tumor biology, rather than the presence of delayed treatment alone. However, in view of the high weight and large sample size of their study, we performed a sensitivity analysis excluding their study, which failed to show statistically significantly better OS (HR, 0.87; 95% CI, 0.69–1.12) in patients with LR only. Caution should be taken to conclude that delayed LR is associated with superior OS in HCC; randomized trials would be needed to prove the above point, but would be challenging, since intentional delay of treatment is considered unethical, unless for the purpose of pre-operative optimization with intent to improve post-operative outcomes and survival.

Other patient demographics and tumor characteristics, such as the presence of hepatitis B, poor tumor differentiation, and Asian population, are risk factors predictive of more rapid tumor growth [25]. Large tumor size is also associated with poor prognostic indicators, such as macro and microvascular invasion, and technical difficulties posing the risk of positive resection margins [41]. A PSM study by Kabir et al. [4] in 2020 on 863 patients undergoing surgical resection as definitive HCC treatment reported no significant difference in OS between delayed (> 90 days) and non-delayed LR (≤ 90 days) (HR, 0.86; 95% CI, 0.57–1.30; p = 0.47). In contrast, a prospective by Chen et al. in 2011 on 121 patients who underwent RFA showed that delayed initiation of RFA (> 5 weeks) was independently associated with worse OS (HR, 3.59; 95% CI, 1.58–8.18; p = 0.002) [21]. A plausible reason for the differences in findings obtained may be due to the difference in demographics; Kabir et al. [4] studied a patient cohort with mean tumor size of 5.55 ± 4.64 cm, while Chen et al. [21] only included HCC with a maximum tumor diameter of 5 cm. However, Tsilimigras et al. [5] performed subgroup analysis of BCLC−0/A stage HCC and BCLC−B/C stage HCC; they showed that delayed treatment was not independently associated with worse OS in both subgroups (BCLC−0/A stage: HR = 0.90, 95% CI = 0.65–1.25, p = 0.53; and BCLC−B/C stage: HR = 0.72, 95% CI = 0.30–1.74, p = 0.47, respectively). As explained earlier, pooled tumor size in our study was smaller in the delayed treatment group, which may confound survival outcomes.

LT remains an attractive but scarce cure for HCC, especially for patients with underlying cirrhosis. Our review had two studies that included patients who underwent LT [7,14]. A meta-analysis by Menahem et al. [42] showed that LT is associated with improved DFS compared with LR after the 3-year mark (LT, 74.2% vs. 54.4%; OR, 0.24; 95% CI, 0.07–0.80; p = 0.02) and improved OS after the 10 year mark (LT, 50.0% vs. LR, 29.8%; OR, 0.40; 95% CI, 0.23–0.68; p < 0.001). Due to differences in survival outcomes between LT and LR, we excluded studies that examined the survival outcomes of patients who received LT exclusively, as this may further introduce heterogeneity to our study; we included studies that included a mix of LT and other treatment modalities to avoid dilution to our sample size (n = 8,001/88,317 patients received LT in the two studies); removal of these two studies would result in decrease in the sample size by 65.2%. Questions may be raised as to whether this would further create heterogeneity due to misrepresenta-

tion of the population (by only including studies with a mix of LT; however, patients undergoing LT comprised only a small proportion of the entire study sample size (n = 8,001/135,389, 5.9%).

Additionally, patients awaiting LT are placed on a waitlist, and are selected and prioritized for LT based on a strict selection criteria (such as the MELD score) [43]. Tumor progression may result in drop-out from LT, and bridging therapy may be considered in patients with long waiting time for LT [44,45]. Waiting time for LT is dependent on a variety of factors - availability of transplant services, organ supply and demand, and social determinants [46-48]; locally in Singapore, the estimated waiting time for LT is one year, but is dependent on a variety of factors [49]. This raises the concern of whether there will be significant progression of tumor, given that the estimated tumor doubling rate is 4.6 months [25]. Interestingly, studies have shown that long waiting time in LT predicts longer survival post-LT in patients with HCC [50,51]. Short waiting time of < 90 days to LT has been shown to be associated with worse OS [52]; this may be due to the inclusion of patients with aggressive tumors, posing a high risk for post-LT recurrence. This is further reinforced by the "ablate and wait" strategy, where HCC, which fell outside the Milan criteria and underwent ablation followed by LT, had similar oncological outcomes compared to HCC that were within the Milan criteria, and underwent upfront LT [53]. In view of the heterogenous approach toward patients undergoing LT, patients undergoing LT should be separately analyzed.

This main strength of this study is that it is an updated systematic review with additional meta-analysis comparing the oncological and short-term treatment outcomes between delayed versus no treatment delay in HCC. We included studies with patients who underwent a variety of HCC treatment modalities (both curative and palliative), and performed subgroup analysis to reduce heterogeneity.

However, there are several limitations to our study. The majority of the included studies were retrospective observational studies. However, quality assessment was performed for the included studies, and all of the included studies had at least moderate quality evidence. Additionally, the majority of the studies in this paper were conducted only in Asia and the Unites States, especially with a large proportion of patients originating from Asian countries, despite including HCC globally. Hence, the generalizability of our results might be compromised. However, this could be attributed to the epidemiological distribution of liver cancer, where 75% occurs in Asia [54]. Patient demographics and tumor characteristics were also heterogenous, and were not reported in any study. Differences in demographics and tumor characteristics may confound survival outcomes, as described in our discussion earlier. We were unable to perform a meta-analysis on our secondary outcomes of post-treatment mortality, readmission rates, and complications, because of the low number of studies reporting on outcomes. Subgroup analysis was also not performed for other treatment modalities for HCC, because of the low number of studies reporting on outcomes, as well as for DFS. Patients who received LT exclusively were also not included in our analysis, due to the unique characteristics of LT as described earlier; we included studies with a mix of LT and other treatment modalities to avoid dilution to sample size, but otherwise, LT only comprised a small proportion of the entire cohort (n = 8,001/135,389, 5.9%). Lastly, this study does not clearly define the subgroup of HCC that would benefit from a modest treatment delay, as it is dependent on disease factors, patient factors, and available treatment options.

CONCLUSION

Our meta-analysis demonstrated that delayed treatment may be non-inferior compared to no delay in patients with smaller HCC in terms of OS and DFS, but findings are limited in view of the retrospective nature of studies with selection bias. Prospective, well-designed, and randomized studies with similar patient demographics, tumor characteristics, and definitions of delayed TTT should be conducted to validate our findings.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.14701/ahbps.23-090.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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