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ORIGINAL

Outcome of patients with HCC and liver dysfunction under immunotherapy: a systematic review and meta-analysis

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Abstract

Background and Aims: Immunotherapy-based regimes have changed the management of HCC. However, evidence of efficacy in patients with impaired liver function is unknown. This systematic review and meta-analysis assesses survival of HCC patients and liver dysfunction treated with immunotherapy-based regimens.

Methods: Systematic review and meta-analysis of original articles or abstracts reporting survival (OS) of HCC patients treated with immunotherapy according to liver function between 2017 and 2022. OS according to restricted mean survival time and median OS, and of Child-Pugh B or B/C versus Child-Pugh A were assessed while considering the line of treatment.

Results: Of the 2.2 articles considered, 15 articles recruiting 2.311 patients were included. Of these, 639 (27.7%) were Child-Pugh B and 34 (1.5%) C. Restricted mean survival time was 8.36 (95% CI, 6.15–10.57; $I^2 = 93\%$) months, estimated from 8 studies. The HR was reported in 8 studies for survival between Child-Pugh B versus Child-Pugh A and metanalysis disclosed a 1.65 HR (95% CI,1.45–1.84; $I^2 = 0\%$ heterogeneity; $p = 0.45$). Treatment line data were available for 47% of the patients and 3 studies included patients treated with atezolizumab-bevacizumab in the first line.

Conclusions: The high heterogeneity across studies reflects the incapacity of the current evidence to support the indication of immunotherapy in HCC patients with relevant liver dysfunction. It is mandatory to report complementary information to Child-Pugh classification such as prior liver

Abbreviations: AEs: adverse events; KM: Kaplan-Meier; OS: overall survival; PS: performance status; RMST: Restricted Mean Survival Time; TKI: tyrosine kinase inhibitors.

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decompensation, use of concomitant medication to control ascites, or signs of clinically significant portal hypertension to allow better patient stratification in future studies.

INTRODUCTION

Liver cancer represents the third most deadly cancer worldwide.[1] However, the life expectancy of patients with HCC has dramatically improved in the last years[2] with the incorporation of new treatments based on immunotherapy. Currently, atezolizumab plus bevacizumab[3,4] or tremelimumab plus durvalumab[5] are new standards of care in first-line. Very recently, the combination of camrelizumab plus rivoceranib was superior in comparison to sorafenib in terms of overall survival (OS).[6] Similarly, durvalumab in monotherapy[5] and tislelizumab[7] are noninferior to sorafenib in first-line, ipilimumab in combination with nivolumab[8,9] as well as pembrolizumab were granted accelerated approval by the Food and Drug Administration[10] and the latter recently showed improved OS in comparison to placebo in Asian patients after sorafenib in first-line.[11]

Despite these landmark advances in the field, patients with liver dysfunction as per the Child-Pugh stage have been systematically excluded from the pivotal clinical trials due to the competing risk of death for liver-related events. The sole exception are the nivolumab trials, in which patients with Child-Pugh B 7–8 points without ascites and/or encephalopathy were accepted.[12,13] Thus, the current inclusion/exclusion criteria confine these patients in an orphan condition for systemic treatment. Indeed, no robust evidence exists to recommend any systemic therapy in these patients. Clinical trials testing tyrosine kinase inhibitors (TKI) such as sorafenib,[14,15] lenvatinib,[16] regorafenib,[17] cabozantinib,[18] or with ramucirumab[19] did not include patients with liver dysfunction and data from real-life practice in Child-Pugh B patients with sorafenib showed an OS of 5.2 months in Child-Pugh B and an HR of 2.82, 95% CI, 2.04–3.92; $p < 0.001$ when were compared with Child-Pugh A patients.[20–22] Regardless the lack of any evidence, it has been widely hypothesized that immunotherapy could potentially have a less pronounced impact on liver function and could be safer for HCC patients with liver dysfunction, resulting in improved survival. However, until now only 1 single-arm clinical trial with nivolumab in first-line or after sorafenib[12] has evaluated this population and some immunotherapy-based regimes[23–36] have assessed this special population and reported heterogeneous results.

The aim of this systematic review and meta-analysis was to assess the outcomes of immunotherapy-based regimens in patients with HCC and liver dysfunction as defined by Child-Pugh stage B or C.

METHODS

Search strategy and selection criteria

The review process was conducted according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines. We searched PubMed from November 14, 2017 until March 25, 2022 by formulating keyword searches. The exact query formulated in Pubmed was as follows: "(TS = (hepatocellular carcinoma OR HCC) AND TS = (liver dysfunction OR Child-Pugh B OR Child-Pugh C)" AND TS = (immunotherapy OR nivolumab OR pembrolizumab OR atezolizumab-bevacizumab OR atezolizumab and bevacizumab OR durvalumab-tremelimumab OR durvalumab and tremelimumab OR ipilimumab-nivolumab OR ipilimumab and nivolumab). Duplicate reports were eliminated by scrutinizing the list of aggregated reports. In addition, we manually scanned the reference list of included articles.

Two reviewers (I.E.H. and M.S.-Z.) independently selected potentially relevant studies based on title and abstract reading. Full-text articles were then gathered and assessed for eligibility by the same 2 independent reviewers. In case of discrepancies, consensus was reached after discussion with the senior author (M.R.). When an author had more than 1 publication on the same topic, the most recent was selected to avoid overlapped populations.

To be eligible, original articles or abstracts presented to international conferences in the last 5 years (list of conferences in Supplemental Table 1, http://links.lww.com/HEP/A46) had to report survival outcomes according to liver function (Child-Pugh A, Child-Pugh B, Child-Pugh C, or Child-Pugh B/C). We excluded studies where immunotherapy was combined with locoregional treatments or with TKIs.

Outcome of interest

The outcome of interest was the survival of HCC patients with liver dysfunction treated with immunotherapy regardless of the line of treatment. As the primary outcome, the restricted mean survival time (RMST) was used instead of the median OS since RMST summarizes information as time-to-event up to a fixed point, considering the entire survival curve, whereas median OS only provides information on a fixed point of the

curve[37–39] or estimation of relative risk by means HR, requiring proportional hazard as a methodological condition. Considering that the studies did not report these data, we used the Guyot et al.[40] algorithm to extract the necessary information from the reported Kaplan-Meier (KM) curves in each study. The Guyot algorithm was used in studies to obtain survival data. Due to the heterogeneity of follow-up between studies, 2 approaches were adopted with respect to RMST, 1 with the follow-up described in each individual study and 1 with a cut-off time-point at 12 months of follow-up.

As sensitivity analysis, median OS by KM were also collected and analyzed as well as reported HR of survival of Child-Pugh B or Child-Pugh B or C patients versus Child-Pugh A.

Data analysis

Two authors extracted data by using a pre-established form. In addition to the usual bibliometric variables, information on the following variables was also collected: duration of inclusion; study design; the number of patients treated in the study; number of patients treated with immunotherapy; the number of treated patients according to liver function (Child-Pugh A, B/C, B or C); BCLC stage; median follow-up; percentage of patients treated in first-line, second-line, third-line, or fourth-line; percentage of patients according to performance status (PS); median OS; survival HR between the different groups of interest; time to treatment discontinuation; rate of adverse events (AEs); incidence of grade ≥ 3 AE; rate of treatment discontinuation.

Critical appraisal was carried out independently by 2 reviewers (I.E.H. and M.S.-Z.) using the National Institutes of Health (NIH) Quality Assessment Tool for observational cohort and cross-sectional studies.[41]

The between-reviewer agreement was assessed in terms of methodological quality and the decision to include studies by means of Kendall and kappa coefficients and their 95% CI, respectively.

The RMSTs, calculated using the restricting time (tau) ~~the time~~ of the last follow-up, and the RMSTs calculated using as the restricting time (tau) of 12 months or last follow-up (if the last follow-up was >12 mo) with the 95% CI from each study, estimated from each study with the Guyot et al.[40] algorithm, were used to compute the pooled RMST and their 95% CI were determined using the random-effects model described by Der Simonian and Leir[42] with the *metagen* command of R. Heterogeneity was evaluated by means of I^2 statistic. Values of I^2 of 25%, 50%, and 75% were considered as low, moderate, and high heterogeneity levels.[43] The χ^2 test was performed to evaluate statistical significance for the level of heterogeneity, considering a p-value < 0.1 as the threshold. The same strategy was followed for the sensitivity analyses, median OS and HR (Child-Pugh B or C vs. A and Child-Pugh B vs. A).

For primary analysis, a funnel plot was constructed to assess publication bias, and metaregression was planned using the following parameters: inclusion of Child-Pugh C patients (yes/no) and treatment line (only first line vs. multiple lines), the rate of AE, the rate of AE grade III and the treatment duration time using the *metareg* command of R.

All statistical analyses were performed using RStudio Team 2018 software (RStudio: Integrated Development for R. RStudio Inc., Boston, MA), except the calculation of RMST, performed using SAS software, v9.4 (SAS Institute, Cary, North Carolina, USA). The level of significance was set at 2-sided 5%.

None of the funding sources of the group had any role in the study design, data collection, data analysis, data interpretation, or writing of the report. All authors had access to the study data and reviewed and approved the final manuscript.

RESULTS

Figure 1 shows the flowchart of the study and the process to retrieve, screen, and ultimately, use the selected studies according to the methods described above. A total of 2246 AQ5 articles were retrieved based on the search terms. After initial screening, 186 articles not relevant for the study were excluded and 36 potential study reports were assessed for eligibility at the full-text level. Thereafter, 21 articles were excluded and 15 studies were finally included for meta-analysis (1 clinical trial and 14 observational studies),[13,23–36] 4 of these being abstracts.[25–28]

Between reviewer agreement for the inclusion process was 0.75 (95% CI, 0.70–0.80), as assessed by the kappa coefficient. There was disagreement with respect to 4 studies and it was resolved by a third reviewer (M.R.).

In the 15 included studies ~~2.311~~ patients were treated with immune checkpoint inhibitors (ICIs), and the specific ICI was nivolumab in 6 studies (n = 585),[13,23,24,26,29,30] atezolizumab plus bevacizumab in 3 studies (n = 428),[25,28,36] pembrolizumab or nivolumab in 2 studies (n = 126),[28,31] ipilimumab plus nivolumab/pembrolizumab in 1 study (n = 48)[35] and a variety of ICIs in 3 studies (n = 1124).[32–34] In total, 639 (27.7%) patients were classified as Child-Pugh B and 34 (1.5%) as Child-Pugh C.[27,29,31,33,35] Three of the studies included only Child-Pugh B patients[13,26,30] and 1 study included Child-Pugh B and C patients only.[27]

Patients Child-Pugh B and C patients

The treatment line was described in 319 patients (47.1%),[13,23,26–28,30,36] of which 212 patients (66.5%) were in the first line, 93 (29.2%) in the second line, and 14 (4.9%) in the third line. Only 3 of the 15 studies[13,28,30] reported the BCLC stage in Child-Pugh B or C patients but in none of these studies was the OS

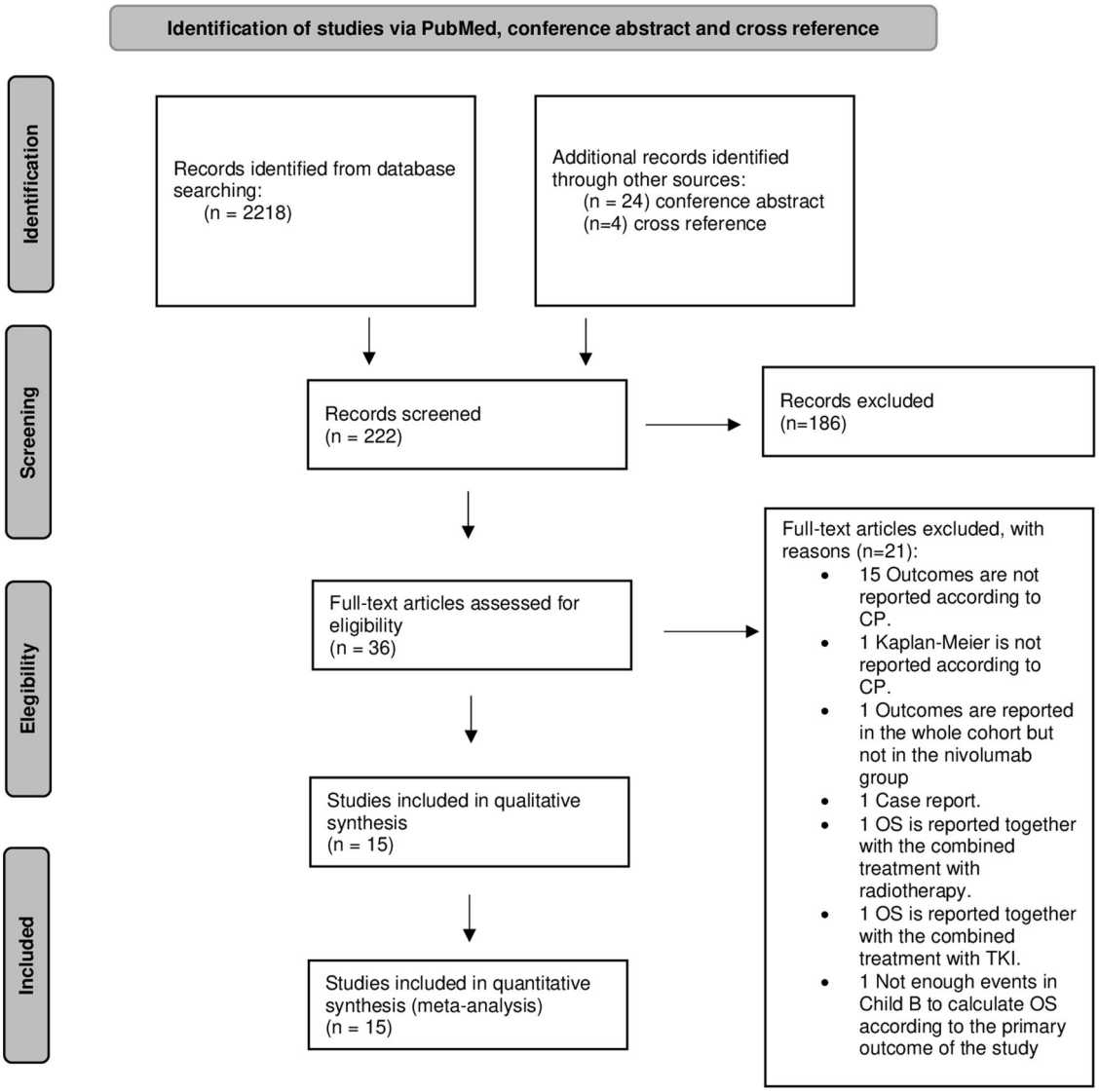

FIGURE 1 PRISMA flow diagram of study selection. Abbreviations: CP, Child-Pugh; OS, overall survival; TKI, tyrosine kinase inhibitor.

analyzed according to the BCLC stage. The main characteristics of the included studies are summarized in Table 1. PS, median follow-up, median treatment duration, rate of AEs, and rate of treatment discontinuation based on the Child-Pugh classification when available are reported in Table 2.

Critical appraisal, as assessed by the National Institutes of Health Quality Assessment Tool,[41] indicated that 2 studies had a high risk of bias, 12 moderate risk, and 1 low risk. Between-reviewer concordance of this issue was 0.71 (95% CI, 0.30–1.00), as assessed by the Kendall coefficient.

Quantitative synthesis of OS in patients Child-Pugh B and C

RMST in patients Child-Pugh B only was 8.36 months (95% CI, 6.15–10.57; $I^2 = 93\%$; heterogeneity test $p < 0.0001$, Figure 2) in the 8 studies where KM figures were available. RMST in patients Child-Pugh B or C was 8.24 months (95% CI, 6.14–10.34; $I^2 = 92\%$; heterogeneity test $p < 0.0001$) in the 9 studies where KM figures were available. RMST at 12 months or the end of follow-up if it was before of that point, was 6.13 months (95% CI, 5.02–7.24; $I^2 = 89\%$; heterogeneity test $p < 0.0001$; Supplemental Figure 1, http://links.lww.com/HEP/A47).

Median OS in Child B only was 6.05 (95% CI, 4.60–7.49; $I^2 = 82\%$) (Figure 3). The pooled reported actuarial OS curve in Child B can be found in Supplemental Figure 4 (http://links.lww.com/HEP/A50). Median OS in Child B and C was 5.60 (95% CI, 4.30–6.91; $I^2 = 80\%$; $p < 0.0001$; Supplemental Figure 2, http://links.lww.com/HEP/A48) months.

Figure 4 shows the HR of survival between Child-Pugh B/C versus Child-Pugh A (HR, 1.85; 95% CI, 1.51–2.26; $I^2 = 61\%$; heterogeneity test $p = 0.018$).

TABLE 1 Characteristics of studies included in meta-analysis

References	Study design	ICI type	Patients treated with ICI (n)	CP-B, n (%)	CP-C, n (%)	1st line[c], n (%)	2nd line[c], n (%)	3rd line[c], n (%)	BCLC stage[d], n (%)
Finkelmeier et al.[29]	Retrospective	Nivolumab	34	14 (41.2)	1 (2.9)	NA	NA	NA	NA
Kambhampati et al.[30]	Retrospective	Nivolumab	18	18 (100)	0	5 (27.8)	13 (72.2)	0	B: 4 (22); C: 14 (78)
Scheiner et al.[31]	Retrospective	Pembrolizumab/ Nivolumab	65	28 (43.1)	5 (7.7)	NA	NA	NA	NA
Fessas et al.[24]	Retrospective	Nivolumab	233	75 (32.2)	0	NA	NA	NA	NA
Choi et al.[23]	Retrospective	Nivolumab	203	71 (35)	0	1 (1.4)	56 (78.9)	14 (19.7)	B: 2 (2.8); C: 69 (97.2)
Pinato et al.[33]	Retrospective	A variety of ICIs	341	81 (23.8)	9 (2.6)	NA	NA	NA	NA
Kudo et al.[13]	Phase I-II, label	Nivolumab	49	49 (100)	0	25 (51)	24 (49)	0	A: 2 (4); B: 8 (16); C: 36 (73); D: 3 (6)
Ng et al .[32]	Retrospective	A variety of ICIs	114	21 (18.4)	0	NA	NA	NA	NA
Pinato et al.[a][34]	Retrospective	A variety of ICIs	394	12 (3)	0	NA	NA	NA	NA
			275	82 (29.8)	0	NA	NA	NA	NA
Ha et al.[b][25]	Retrospective	Atezolizumab-Bevacizumab	50	5 (10)	0	NA	NA	NA	NA
Chapin et al.[b][26]	Retrospective	Nivolumab	48	48 (100)	0	48 (100)	0	0	NA
Wong et al.[b][27]	Retrospective	Pembrolizumab/ Nivolumab	61	44 (72.1)	17 (27.9)	NA	NA	NA	NA
Wong et al.[35]	Retrospective	Ipilimumab and nivolumab or pembrolizumab	48	6 (24)	2 (8)	48 (100)	0	0	NA
Kim et al.[b][28]	Retrospective	Atezolizumab-Bevacizumab	176	37 (21)	0	37 (100)	0	0	NA
D'Alessio et al.[36]	Retrospective	Atezolizumab-Bevacizumab	202	48 (23.8)	0	48 (100)	0	0	NA
Total			2311	639	34	212	93	14	

Abbreviations: CP-B, Child-Pugh B; CP-C, Child-Pugh C; ICI, immune checkpoint-inhibitors; NA, not available.
[a]Two different cohorts were included: FDA data set (n = 394) and multi-institutional data set (n = 275).
[b]ABSTRACT presented at international conferences.
[c]Treatment line.
[d]BCLC stage refers to the number of patients among Child-Pugh B or C.

TABLE 2 Secondary characteristics of studies included in meta-analysis

References	Child-Pugh B, n (%)		Performance status, n (%)			Median follow-up (mo)	Median treatment duration (mo)	Rate of adverse event, n (%)			Rate of treatment discontinuation, n (%)	
	CP-B 7	CP-B >7	PS 0	PS 1	PS >1			CP-A	CP-B	CP-C	CP-A	CP-B
Finkelmeier et al.[29]	NA	NA	7 (20.6)	24 (70.6)	3 (8.8)	3.3	2	NA	NA	NA	NA	NA
Kambhampati et al.[30]	9 (50)	9 (50)	NA	NA	1 (6)	18	2.3		17 (94)	—		16 (89)
Scheiner et al.[31]	NA	NA	32 (49)	NA	NA	11.2	NA	10 (31)	12 (43)	—	NA	NA
Fessas et al.[24]	NA	NA	44 (28)	99 (63.1)	13 (8.3)	8	4	NA	NA	—	NA	NA
Choi et al.[23]	41 (57.8)	30 (42.2)	82 (40.4)	98 (48.3)	23 (11.3)	5.6	0.9	5 (17.9)	1 (32.4)	—	115 (87.1)	63 (88.7)
Pinato et al.[33]	NA	NA	NA	NA	19 (5.6)	NA	NA	111 (50)	22 (34)	2 (29)	NA	NA
Kudo et al	37 (76)	11 (22)	NA	NA	NA	16.3	2.3		25 (51)	—		47 (96)
Ng et al.[32]	13 (61.9)	8 (38.1)	70 (61.4)	30 (35.1)	4 (3.5)	NA	NA	70 (75.3)	9 (42.9)	—	NA	NA
Pinato et al.[a][34]												
FDA	NA	NA	244 (86.1)	178 (43.8)	NA	NA	NA	NA	NA	—	NA	NA
MI	NA	NA	62 (17.4)	179 (50.1)	NA	15.3	NA	NA	NA	—	NA	NA
Ha et al.[b][25]	NA	NA	NA	NA	NA	NA	NA	NA	NA	—	NA	NA
Chapin et al.[b][26]	NA	NA	NA	NA	NA	NA	NA	NA	NA	—	NA	NA
Wong et al.[b][27]	19 (43.2)	25 (56.8)	NA	NA	NA	2.3	NA	NA	NA	NA	NA	NA
Wong et al.[35]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Kim et al.[b]	NA	NA	NA	NA	NA	NA	NA	123 (88.5)	35 (94.6)	—	NA	NA
D'Alessio et al.[36]	21 (43.8)	27 (56.2)	127 (63)	70 (35)	5 (2)	9	NA	82 (53)[c] 74 (48)[d]	19 (40)[c] 22 (46)[d]	—	NA	NA

Abbreviations: CP-B, Child-Pugh B; CP-C: Child-Pugh C; NA, not available; PS, performance status.
[a]Two different cohorts were included: FDA data set (n = 394) and MI (Multi-institutional data set) (n = 275).
[b]ABSTRACT presented at international conferences.
[c]Patients experiencing adverse events of any grade related to atezolizumab.
[d]Patients experiencing adverse events of any grade related to bevacizumab.

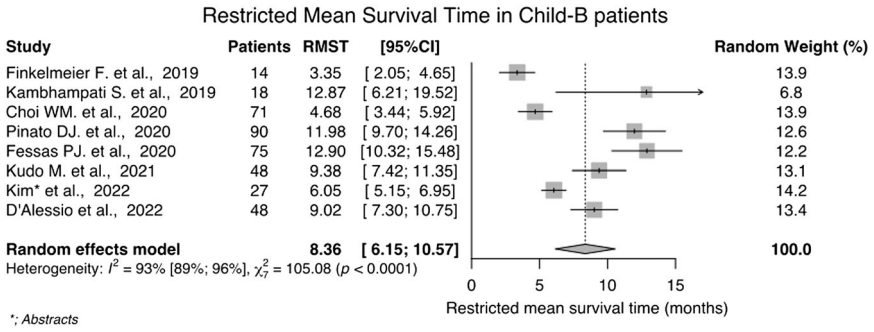

FIGURE 2 Restricted mean survival time (RMST) (tau = 12 or end of follow-up) in Child-Pugh B only.

However, only 1.5% of patients were Child-Pugh C. Figure 5 shows the HR of survival between Child-Pugh B versus Child-Pugh A (HR, 1.65; 95% CI, 1.45–1.84; I^2 = 0% 95% CI, 0%–75%; heterogeneity test p = 0.4502)

Of the 15 included studies, 3 comprised 90 Child-Pugh B patients treated with atezolizumab and bevacizumab in first-line[25,28,36] and the pooled median OS was 5.70 (95% CI, 4.87–6.54; I^2 = 0% with 95% CI, 0%–89.6%; heterogeneity test p < 0.4779) while RSMT was not estimable. In addition, 3 studies included 93 patients in second-line-only and their pooled median OS was 5.09 (95% CI, 1.54–8.64; I^2 = 82.6%; heterogeneity test p < 0.0031).

Heterogeneity assessment

Both I^2 value and funnel plot (Supplemental Figure 3, http://links.lww.com/HEP/A49) revealed a high statistical heterogeneity among the studies. Sensitivity analysis was therefore assessed by the leave-one-out method (Table 3). However, the sensitivity result showed that heterogeneity remained high (I^2 > 90.4%) (Table 3). The meta-regression approach reveals that the inclusion of Child-Pugh C patients had no impact in terms of reducing the global heterogeneity (p-value = 0.0755, I^2 = 90.6%). ~~Details on the meta-regressio~~nalysis including the safety profile and treatment duration ~~time i~~ited by the small number of the study included and is reported in the Supplemental Material (http://links.lww.com/HEP/A51). Finally, only 5 studies evaluated whether the treatments were first-line (p-value = 0.7860, I^2 = 86.9%).

DISCUSSION

The incorporation of immunotherapy in the field of liver cancer has been a breakthrough. The safety profile was not compared head-to-head to TKIs but it was felt to be adequate, thus raising high expectations for its use in patients with impaired liver function who are conventionally excluded from pivotal trials. In the CheckMate040 study the safety and initial efficacy signal of Nivolumab in patients with Child-Pugh B 7–8 was assessed.[13] This study suggested that nivolumab bears clinical activity and an acceptable safety profile in patients with HCC who have a mild liver function that might prevent the use of other therapies.

The results of CheckMate040[12] as well as the hope of the Scientific Community concerning the safety profile of immunotherapy-based treatments opened the question about considering ICIs in patients with liver dysfunction.

The median OS in Child-Pugh B or C was 5.60 (95% CI, 4.30–6.91; I^2 = 80%; p < 0.001) months. There is

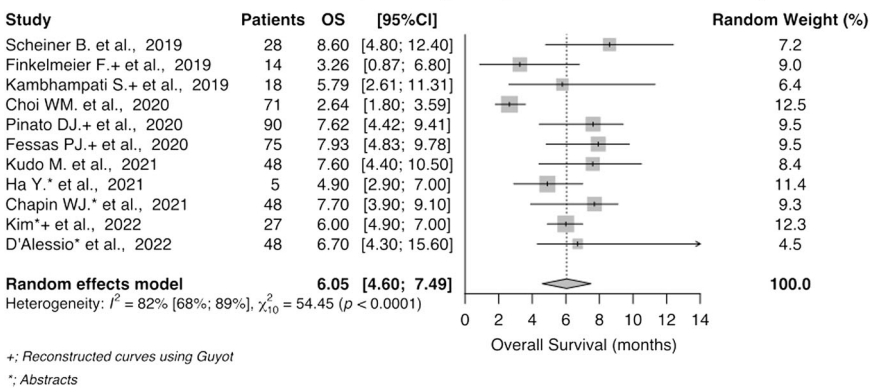

FIGURE 3 OS in Child-B patients (adding reconstructed KM curves). Abbreviations: KM, Kaplan-Meier; OS, overall survival.

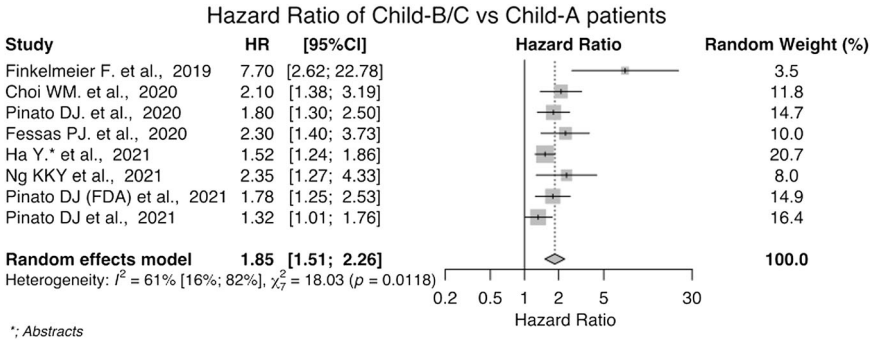

FIGURE 4 HR of Child-Pugh B/C versus Child-Pugh A patients.

only 1 study in Child-Pugh [redacted]. For this reason, the OS and RMST analyses were performed excluding Child-Pugh C patients as they show a different degree of liver dysfunction. However, no significant differences were found (median OS in Child-Pugh B or C was 5.60; 95% CI, 4.30–6.91 vs. 6.05; 95% CI, 4.60–7.49 in Child Pugh B) due to the low proportion of Child-Pugh C patients. The HR of survival between Child-Pugh B versus Child-Pugh A (HR, 1.65; 95% CI, 1.45–1.84; $I^2 = 0\%$; $p = 0.4502$) are the most important results of our study. All these data serve to frame the current outcome of patients and tempers the high expectancy of ICs in this unserved population. However, these systematic review and meta-analysis show that the target population "patients with liver dysfunction" is heterogeneous and almost all the publications defined them only according to the Child-Pugh score without considering co-factors such as PS, tumor burden or line of treatment. The limitations of Child-Pugh score for the assessment of liver function have already been questioned by some authors[44,45] and it was indeed removed from the BCLC classification in 2018 and 2022.[2,46] Nevertheless, the Child-Pugh score is still used for this purpose because alternative scores such as MELD or ALBI do not completely solve all the Child-Pugh limitations. As known, a major change in liver function reserve, and therefore in prognosis, takes place when the patients develop decompensation such as ascites.[47] However, despite the presence of slight ascites or transient episodes of hepatic encephalopathy, patients may still belong to Child-Pugh A class if bilirubin and prothrombin are within an adequate range. This also applies to the ALBI score that may be useful to stratify the patients but does not capture the presence of ascites and the potential simultaneous impairment of renal function. Inclusion and exclusion criteria in pivotal trials solved the limitations of the wide Child-Pugh A category, with the exclusion of patients with a specific parameter that reflects an increased risk of death, and which may compete with cancer-related death. In clinical practice, liver function should be assessed from a holistic perspective before starting systemic treatment surpassing the limitations of the mere Child-Pugh classification. This is crucial as well as the adequate evaluation of liver function during the treatment as recently proposed by Cabibbo et al.[48]

The high heterogeneity observed in our study evidenced that the current information concerning this population is not reliable. Indeed, this could be due to the characterization of patients, study design, management of the patients included or other factors. Traditionally, patients with liver dysfunction are considered a special population but the characterization of that population must consider more than just liver function in order to offer proper granularity. In this systematic review only 3 of the 15 studies reported both the liver dysfunction and the evolutionary stage of the HCC.[13,28,30] It is already known that the prognosis of HCC is conditioned not only by the presence of preserved liver function, but also by other important

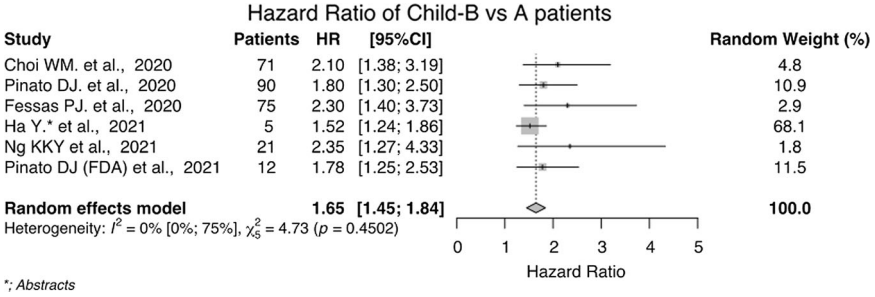

FIGURE 5 HR of Child-Pugh B versus Child-Pugh A patients.

AQ6 **TABLE 3** Leave-one-out analysis

Omitting study	RMST (95% CI)	I^2 (%)
Finkelmeier et al.[29]	8.77 (6.54–10.99)	89.7
Kambhampati et al.[30]	7.73 (5.57–9.90)	92.4
Choi et al.[23]	8.61 (6.11–11.11)	92.1
Pinato et al.[33]	7.46 (5.42–9.49)	90.0
Fesas et al. (2020)	7.35 (5.36–9.35)	89.8
Kudo et al.[13]	7.87 (5.60–10.14)	91.8
Wong et al.[27,35]	8.18 (5.96–10.40)	92.7
Kim et al.[a][28]	8.46 (5.66–11.26)	92.7
D'Alessio et al.[a][36]	8.12 (5.82–10.43)	92.7

Abbreviation: RMST, restricted mean survival time.

parameters such as PS and tumor burden. Therefore, the results are flawed if only liver function is considered in the analysis.

One relevant output of our study is that these results reflect the complexity of the OS analysis within the setting of the current HCC landscape. The same treatment is given to HCC patients who are in a different treatment-line, and who have different tumor burden, prior pattern of progression or even transition to a next line because of toxicity in the absence of tumor progression.[49] If the analysis merely concentrates on the drug received, as we have found in this systematic review, the results just add ~~unrobust~~ information and even more importantly, they do not provide useful data for clinical-decision making. Indeed, what emerges is that simply reporting the median OS provides faulty figures. This is relevant when carrying out comparisons across studies. The 5.70 months median survival in first-line treatment with atezolizumab and bevacizumab in Child-Pugh B patients seems similar to the median survival with sorafenib reported in the GIDEON study with a median OS in Child-Pugh B of 5.2 months.[20] Similarly, median OS with sorafenib in Child-Pugh B was of 4.6 months in the meta-analysis of McNamara et al.[22] and 4.2 with lenvatinib.[50] However, those results carry the same limitations that we mentioned above: data were not adjusted according to the tumor stage or history of HCC progression. In this regard, Ogushi et al.[51] analyzed the value of lenvatinib in Child-Pugh A/B patients. Even if the authors did not report the median OS of the cohort, they showed that BCLC stage and Child-Pugh points were the factors associated with OS.

As exposed above, the main limitation of the present systematic review and meta-analysis is represented by the high heterogeneity among the studies included. A potential strategy to manage it could have been to perform a metanalysis of individual patient data. In addition, the analysis of OS in patients receiving immunotherapy at different treatment-lines hampers any robust interpretation. However, we reported the survival outcomes of patients treated in first-line with atezolizumab in combination with bevacizumab as well as of those in second-line only. Besides, the retrospective profile of the majority of the included studies with heterogeneous radiologic assessment schedules and criteria prevented the reliable evaluation of response to treatment and duration of response.

While waiting for potential prospective randomized trials to inform the benefit of treatment in this frail population, systematic reviews and meta-analysis that include observational studies may help to identify robust information and/or point out the aspects that need improvement to generate adequate information that would impact in clinical management of the strata of patients not included in the pivotal trials. Accordingly, the main messages of this systematic review are; (a) the current available data on the use of immunotherapy-based regimens in patients with liver dysfunction derive mainly form observational studies, the results are heterogeneous and it is not possible to make recommendations due to the limited information in the field. There is a need of prospective studies and clinical trials (randomized or not) to answer this relevant clinical question. (b) The pivotal clinical trials have to reflect the use of Child-Pugh score as inclusion criteria, but the patient characterization should detail if the patients included are compensated or decompensated. There are several tools to complement the Child-Pugh score such as prior liver cirrhosis decompensation, the use and dose of concomitant medication to control ascites and the assessment of signs clinically significant of portal hypertension by indirect parameters; (c) the post hoc analysis of prospective/retrospective cohort studies can be used to generate hypotheses but the assessment of HCC patient outcome according to liver dysfunction as an isolated factor of analysis should be seen as a faulty approach. In conclusion, the minimum information required to perform sub-group analysis is the following: HCC evolutionary stage, PS, tumor burden, history/current liver complications at the time of starting onco-specific treatment, the treatment-line where the analysis is performed, follow-up time, and status (alive/dead/loss of the follow-up) of the patients at the time of the analysis.

CONFLICT OF INTEREST

AQ9 AQ13 AQ11

M.S.-Z. is on the speakers' bureau for and received grants from Bayer. He received grants from MSD, BTG, Eisai and Roche. V.S. consults for LEO Pharma. He received grants from Bayer. S.M.-M. is on the speakers' bureau for and received grants from Bayer. He received grants from Eisai, Roche, and MSD. E.M. is on the speakers' bureau for Roche and Sirtex. He received grants from Roche. N.L. consults for, advises, and received grants from Bayer. ~~He~~ consults for and advises AstraZeneca and UniversalDX. ~~He~~ is on the speakers' bureau for Roche. ~~He~~ received congress inscriptions

from Eisai, ~~lectures from AEEH, Escola Universitaria d'infermeria de Sant Pau, HUCA, BCLC.~~ G.I. received grants from Bayer. A.F. consults for, advises, and is on the speakers' bureau for Boston Scientific. He consults for and advises Guerbert, Exact Science and ~~Sirex~~. H consults for and is on the speakers' bureau for Bayer and Roche. He consults for AstraZeneca. He is on the speakers' bureau for Gilead and MSD. J.R. received educational/training fees from Amgen, AstraZeneca, Boehringer Ingelheim, Janssen-Cilag, Novartis, and Lilly. J.B. consults for, received grants from and is on the speakers' bureau for Bayer and BTG. He consults for and is on the speaker's bureau for Ipsen, Eisai, Terumo, and Sirtex. He consults for Arqule, Novartis, BMS, Kowa, Gilead, Bio-Alliance, Roche, AbbVie, MSD, Astra-medimmune, Incyte, Quirem, Adaptimmune, Lilly, Basilea, Nerviano, Sanofi, ~~Tahio~~ and Universal DX. M.R. received consultancy fees and/or travel support, lecture fees, and research grants from Bayer. She received consultancy fees and/or travel support and received lecture fees from Gilead ~~and~~ BM~~S~~. She received consultancy fees and/or travel support and research grants from Roche and Ipsen. ~~She received consultancy fees and/or travel support and lecture fees from Lily.~~ She received consultancy fees and/or travel support from BTG, AstraZeneca, Boston Scientific , Abbive, Geneos Therapeutics, and UniversalDx. I.E.H. has nothing to report.

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