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The Analysis Study of Management and Quality of Life of Hepatocellular Carcinoma: A Meta-Analysis and Systematic Review

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ABSTRACT

Background: Hepatocellular carcinoma (HCC) remains one of the leading causes of cancer-related mortality globally, with its incidence steadily rising due to increasing rates of chronic liver diseases. Systemic treatments, including targeted therapies, immunotherapy, and chemotherapy, play a critical role in extending survival and improving quality of life (QoL). This systematic review and meta-analysis aim to evaluate the efficacy of various systemic treatments for HCC while also examining their effects on QoL.

Method: A systematic review and meta-analysis were conducted according to PRISMA 2020 guidelines using the PICO framework. Rigorous screening, data extraction, risk of bias assessment, and statistical analysis were performed to aims to evaluate the efficacy of various systemic treatments for HCC while also examining their effects on QoL.

Results: A total of 88 articles were retrieved from online databases (PubMed, SagePub, Nature and Cochrane). After three rounds of screening, six articles directly relevant to the meta-analysis were selected for full-text reading and analysis. The pooled mean difference (MD) of 2.14 months (95% CI: [1.17, 3.10]) strongly supports the efficacy of systemic treatments in extending the survival of HCC patients.

Conclusion: Management of HCC with systemic treatments demonstrates improved median overall survival. However, quality of life assessments show mixed results, highlighting the importance of considering both survival benefits and patient well-being. Adverse events can significantly impact QoL, underscoring the need for comprehensive treatment strategies that balance efficacy and manage side effects. Future research should prioritize patient-centered outcomes and long-term safety.

Keywords: hepatocellular carcinoma, systemic treatment, quality of life, overall survival

INTRODUCTION

Hepatocellular carcinoma (HCC) remains one of the leading causes of cancer-related mortality globally, with its incidence steadily rising due to increasing rates of chronic liver diseases, particularly cirrhosis and hepatitis B and C infections. As the most common primary liver cancer, HCC presents significant challenges in terms of early detection, treatment, and overall patient survival. Despite advances in diagnostic techniques and therapeutic options, the prognosis for patients with HCC often remains poor, underscoring the urgent need for improved management strategies.[1–3]

The management of HCC is multifaceted, with treatment decisions influenced by a variety of factors, including tumor staging, liver function, and the patient's overall health status. Surgical options such as liver resection and transplantation offer the potential for curative treatment in selected patients, yet the majority of HCC cases are diagnosed at advanced stages when curative therapies are no longer viable. In these cases, systemic treatments, including targeted

therapies, immunotherapy, and chemotherapy, play a critical role in extending survival and improving quality of life (QoL).[4–7]

However, despite the promising results of these systemic treatments, the overall impact on QoL for patients with advanced HCC remains a subject of debate. The toxicities associated with chemotherapy and the potential side effects of immunotherapy and targeted therapies can significantly diminish a patient's functional capacity, leading to a decreased quality of life. As a result, while survival outcomes are crucial, the holistic management of HCC must also address the need for symptom control, management of adverse effects, and overall patient well-being.[8–10]

The relationship between treatment efficacy and QoL is particularly relevant in the context of advanced-stage HCC, where patients may endure prolonged periods of treatment without the possibility of cure. Recent research has highlighted the necessity of incorporating QoL assessments into clinical trials, recognizing that survival benefits alone do not capture the full impact of HCC treatments. QoL measures, such as the ability to perform daily activities, manage symptoms like fatigue and pain, and maintain mental health, are integral to understanding the broader effects of treatment on a patient's life.[11–13]

In addition to treatment efficacy, adverse events associated with systemic therapies remain a key consideration in the management of HCC. Studies have shown that certain therapies, while effective in improving survival, are associated with significant side effects, including fatigue, gastrointestinal disturbances, and hepatic toxicity. These adverse effects can have a considerable impact on patients' daily lives, complicating the therapeutic landscape and highlighting the need for personalized treatment approaches that balance survival benefits with manageable side effects.[14–16]

Given the complexities of managing HCC and the growing importance of patient-centered care, this systematic review and meta-analysis aims to evaluate the efficacy of various systemic treatments for HCC while also examining their effects on QoL.

METHODS

This systematic review and meta-analysis were conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The study utilized the PICO (Population, Intervention, Comparator, and Outcomes) framework.

The population included adult patients diagnosed with hepatocellular carcinoma (HCC) undergoing various systemic treatments, compared to control or alternative treatments. The primary outcomes of interest were median overall survival (OS) and quality of life (QoL) assessments. Secondary outcomes included adverse events, treatment complications, and other QoL-related factors.

Eligibility Criteria

Studies were included if they involved adult patients diagnosed with HCC and receiving systemic treatments. Eligible studies had to report data on primary or secondary outcomes, and included randomized controlled trials (RCTs), cohort studies, or case-control studies published in peer-reviewed journals. Both prospective and retrospective designs were considered. Studies were excluded if they involved non-adult patients, lacked comparative outcome data, or were non-peer-reviewed articles, conference abstracts, case reports, or studies with fewer than 10 participants.

Data Sources and Search Strategy

The search strategy involved multiple data sources, including PubMed, SagePub, Nature, and Cochrane. A comprehensive search was conducted using keywords related to "hepatocellular carcinoma," "systemic treatment," "quality of life," and "overall survival." Medical Subject Headings (MeSH) terms were applied to enhance the search, and studies published in English were included. Manual screening of reference lists from relevant studies and reviews was conducted to identify additional eligible articles.

Study Selection

The selection of studies followed a two-step process. Initially, titles and abstracts were independently screened by two reviewers to exclude studies that did

not meet the inclusion criteria. Full-text articles of potentially eligible studies were then retrieved and evaluated against the eligibility criteria. Any disagreements during this process were resolved through discussion or consultation with a third reviewer. The study selection process was summarized using a PRISMA flow diagram.

Data Extraction

Two reviewers independently extracted data using a standardized extraction form, which included study characteristics (design, publication year, sample size), patient demographics, systemic treatments, and reported outcomes. Any discrepancies were resolved through discussion or consultation with a third reviewer. All extracted data were cross-verified for accuracy and completeness.

Risk of Bias

The risk of bias in each trial was assessed across six domains using the RevMan 5.4 tool (Cochrane, UK). These domains included sequence generation, allocation concealment, blinding, attrition bias, selective outcome reporting, and other potential sources of bias. Trials were categorized as having high, low, or unclear bias in each domain, with detailed justifications provided for each determination.

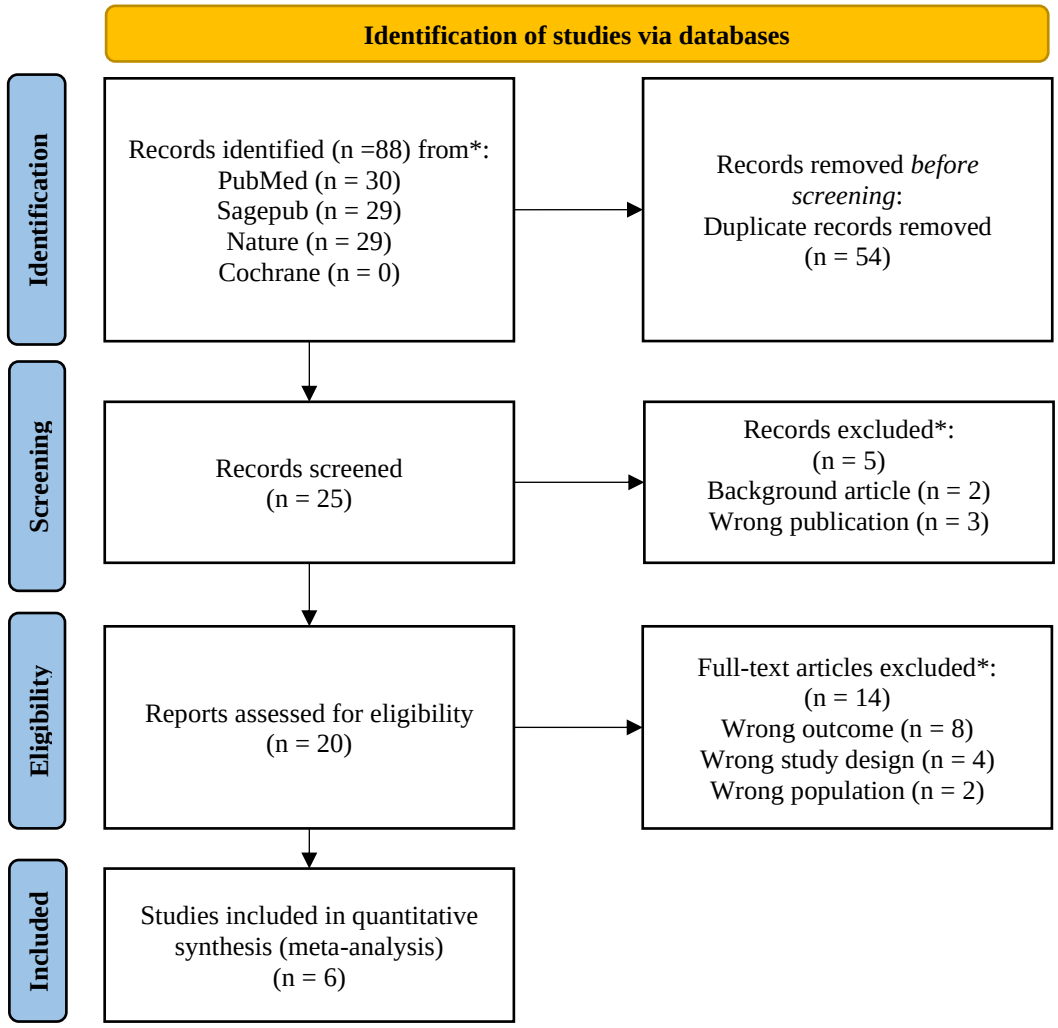

Figure 1. Search strategy and selection of studies for the meta-analysis.

Data Synthesis and Analysis

Data were synthesized and analyzed using Review Manager (RevMan) version 5.4. For continuous outcomes, mean differences (MDs) with 95% confidence intervals (CIs) were calculated. For dichotomous outcomes, odds ratios (ORs) with 95% CIs were pooled using a random-effects model. Heterogeneity among studies was assessed using the I^2 statistic. Subgroup analyses were performed to explore potential differences based on factors such as patient age, sex, and baseline risk. Sensitivity analyses assessed the robustness of findings by excluding studies with high risk of bias. Publication bias was evaluated using funnel plots and Egger's test. All analyses were conducted using RevMan software, version 5.4 (Cochrane Collaboration, Copenhagen, Denmark).

RESULT

A total of 88 articles were retrieved from online databases (PubMed, SagePub, Nature and Cochrane). After three rounds of screening, six articles directly relevant to the systematic review were selected for full-text reading and analysis. The characteristics of the studies are showed in Table 1 and 2

Table 1. Characteristics of studies included in the systematic review

Author	Origin	Study Design	Sample Size	Result
Abou-Alfa, et al.[17] (2018)	USA	RCT	707	The trial demonstrated significantly improved overall survival with cabozantinib compared to placebo. Median overall survival was 10.2 months with cabozantinib versus 8.0 months with placebo (HR for death, 0.76; 95% CI, 0.63–0.92; P = 0.005). Median progression-free survival was also longer with cabozantinib at 5.2 months versus 1.9 months with placebo (HR for progression or death, 0.44; 95% CI, 0.36–0.52; P < 0.001). Objective response rates were 4% for cabozantinib and <1% for placebo (P = 0.009).
Bruix, et al.[18] (2017)	Spain	RCT	573	Between May 14, 2013, and Dec 31, 2015, 843 patients were screened, and 573 were randomized to regorafenib (n=379) or placebo (n=194) for efficacy analysis. Regorafenib significantly improved overall survival with a hazard ratio of 0.63 (95% CI, 0.50–0.79; one-sided P < 0.0001). Median survival was 10.6 months (95% CI, 9.1–12.1) with regorafenib versus 7.8 months (6.3–8.8) with placebo.
Chie, et al.[19] (2015)	Taiwan	RCT	171	Patients treated with ablation had higher odds of quality-of-life (QoL) deterioration compared to embolization (dyspnea: *P* = 0.019; appetite loss: *P* = 0.018; body image: *P* = 0.035)

				and surgery (dyspnea: *P* = 0.099; appetite loss: *P* = 0.100; body image: *P* = 0.038).
Kudo, et al.[20] (2018)	Japan	RCT	954	Between March 1, 2013, and July 30, 2015, 1492 patients were recruited, and 954 eligible patients were randomized to lenvatinib (n=478) or sorafenib (n=476). Median survival with lenvatinib (13.6 months, 95% CI 12.1–14.9) was non-inferior to sorafenib (12.3 months, 95% CI 10.4–13.9; HR 0.92, 95% CI 0.79–1.06).
Ryoo, et al.[21] (2021)	South Korea	RCT	398	In the HRQoL analysis, 271 patients received pembrolizumab, and 127 received placebo. From baseline to week 12, changes in global health status/QoL scores were stable and similar between the groups. The proportions of patients who improved, remained stable, or deteriorated across functional and symptom domains were generally comparable. Time to deterioration in abdominal swelling, fatigue, and pain was also similar between pembrolizumab and placebo based on the EORTC QLQ-HCC18 analysis.
Zhu, et al.[22] (2019)	USA	RCT	292	Between July 26, 2015, and Aug 30, 2017, 292 patients were randomized to ramucirumab (n=197) or placebo (n=95). At a median follow-up of 7.6 months, ramucirumab significantly improved median overall survival (8.5 months vs. 7.3 months; HR 0.710, 95% CI 0.531–0.949; *P* = 0.0199) and progression-free survival (2.8 months vs. 1.6 months; HR 0.452, 95% CI 0.339–0.603; *P* < 0.0001). Objective response rates did not differ significantly (5% vs. 1%; *P* = 0.1697). Median time to deterioration in FHSI-8 scores (3.7 vs. 2.8 months; HR 0.799; *P* = 0.238) and ECOG performance status (HR 1.082; *P* = 0.77) showed no significant differences. Grade 3 or worse adverse events were more

				common with ramucirumab, including hypertension (13% vs. 5%), hyponatremia (6% vs. 0%), and increased aspartate aminotransferase (3% vs. 5%). Serious adverse events occurred in 35% of ramucirumab patients versus 29% of placebo patients. Three deaths in the ramucirumab group were related to treatment-emergent adverse events.

Table 2. Characteristics of studies included in the meta-analysis

No.	Author	Intervention	Total Sample	Quality of Life Assessment	Median Overall Survival						
					Experimental			Control			MD (FE, 95% CI)
					Mean	SD	Total	Mean	SD	Total	
1.	Abou-Alfa, et al.[17] (2018)	Cabozantinib vs placebo	707	Grade 3 or 4 adverse events occurred in 68% of cabozantinib patients versus 36% of placebo patients. The most common high-grade adverse events with cabozantinib were palmar–plantar erythrodysesthesia (17%), hypertension (16%), elevated aspartate aminotransferase (12%), fatigue (10%), and diarrhea (10%).	10.2	12.1359	470	8.0	9.3772	237	2.20 [0.58, 3.82]
2.	Bruix, et al.[18] (2017)	Regorafenib vs placebo	573	Adverse events occurred in all patients receiving regorafenib (100%) and 93% of placebo recipients. Common grade 3 or 4 treatment-emergent events with regorafenib included hypertension (15% vs. 5% with placebo), hand–foot skin reaction (13% vs. 1%), fatigue (9% vs. 5%), and diarrhea (3% vs. 0%). Among 88 deaths during the study (50 with regorafenib and 38 with placebo),	10.6	14.8515	379	7.8	10.5928	194	2.80 [0.69, 4.91]

				seven (2%) in the regorafenib group and two (1%) in the placebo group were considered related to the study drug.							
3.	Chie, et al.[19] (2015)	Surgery vs ablation vs embolization	171	Patients treated with ablation had higher odds of quality-of-life (QoL) deterioration compared to embolization (dyspnea: *P* = 0.019; appetite loss: *P* = 0.018; body image: *P* = 0.035) and surgery (dyspnea: *P* = 0.099; appetite loss: *P* = 0.100; body image: *P* = 0.038).	10.7	11.22	53	8.9	9.45	65	1.80 [-2.00, 5.60]
4.	Kudo, et al.[20] (2018)	lenvatinib versus sorafenib	954	Lenvatinib delayed clinically meaningful deterioration in role functioning, pain, diarrhea, and nutrition compared to sorafenib. However, the overall EORTC QLQ-C30 summary score was not significantly different between the two treatments (*P* = 0.07).	13.6	16.6899	478	12.3	21.096	476	1.30 [-1.11, 3.71]
5.	Ryoo, et al.[21] (2021)	Pembrolizumab vs placebo	398	Time to deterioration in abdominal swelling, fatigue, and pain was also similar between pembrolizumab and placebo based on the EORTC QLQ-HCC18 analysis.	13.9	19.2315	271	10.6	13.0976	127	3.30 [0.07, 6.53]

6.	Zhu, et al.[22] (2019)	ramucirumab vs placebo	292	Median time to deterioration in FHSI-8 scores (3.7 vs. 2.8 months; HR 0.799; *P* = 0.238) and ECOG performance status (HR 1.082; *P* = 0.77) showed no significant differences. Grade 3 or worse adverse events were more common with ramucirumab, including hypertension (13% vs. 5%), hyponatremia (6% vs. 0%), and increased aspartate aminotransferase (3% vs. 5%). Serious adverse events occurred in 35% of ramucirumab patients versus 29% of placebo patients. Three deaths in the ramucirumab group were related to treatment-emergent adverse events.	8.5	14.9456	197	7.3	9.327	95	1.20 [-1.61, 4.01]

The risk of bias analysis for the studies on the management and quality of life of hepatocellular carcinoma (HCC) revealed a generally low risk across key domains. Most of the included studies, such as Abou-Alfa et al. (2018), Bruix et al. (2017), and Kudo et al. (2018), clearly documented random sequence generation and allocation concealment, reducing the potential for selection bias and ensuring that treatment effects could be reliably assessed. However, there was no significant risk of bias in random sequence generation, allocation concealment, and blinding in all included studies, which all had a clear approach to both.

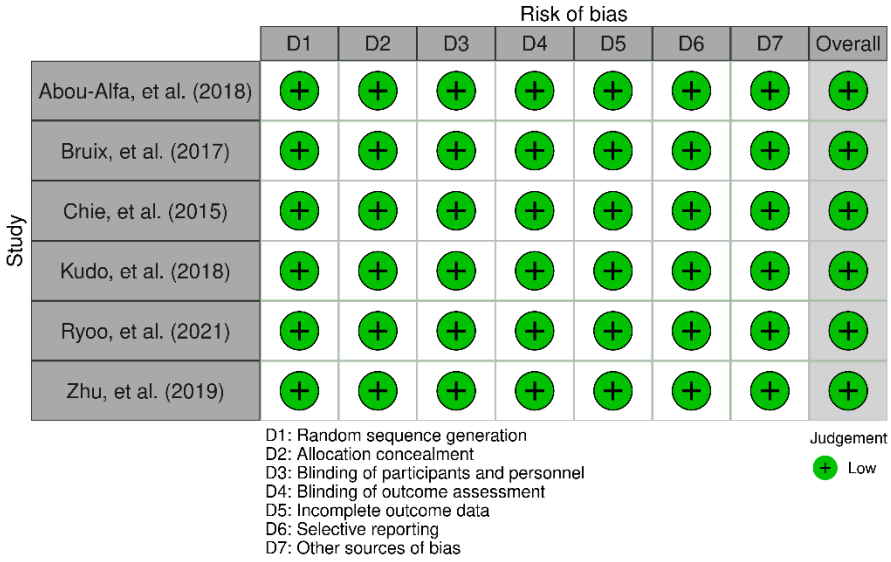

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Blinding of participants and personnel was well-controlled in the majority of trials, such as those by Abou-Alfa et al. (2018), Bruix et al. (2017), and Kudo et al. (2018), which is important for minimizing performance bias. Given the nature of the interventions, where blinding would be feasible, the risk of performance bias was considered low. Similarly, blinding of outcome assessment was conducted effectively across all studies, ensuring that detection bias was minimized and that outcome measures were objective and reliable. Incomplete outcome data were generally well-managed, with low risk observed in the majority of studies due to comprehensive follow-up and well-defined outcomes. The studies demonstrated minimal evidence of selective reporting, as most adhered to pre-specified outcomes.

No significant risk was identified in relation to the handling of incomplete data or selective reporting in any of the studies reviewed.

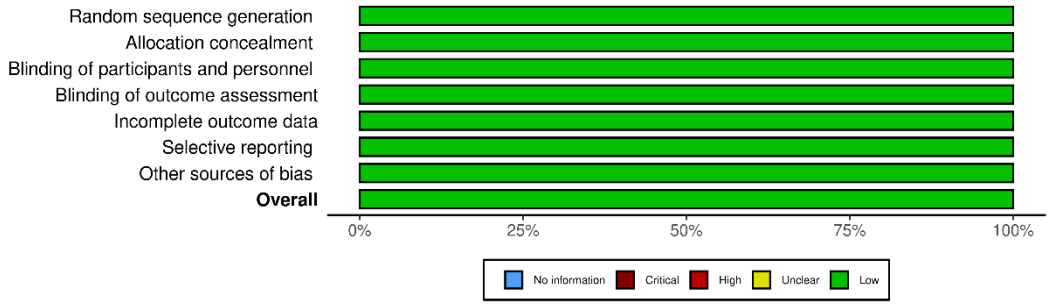

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

While the studies demonstrated strong methodologies, the risk of bias was primarily mitigated by the well-conducted blinding procedures, randomization, and outcome reporting. However, the generalizability of the findings may still be influenced by geographic or demographic factors specific to the populations under study, although these did not significantly alter the risk profile.

Overall, the studies on HCC management and quality of life presented a low risk of bias across most domains, with high methodological rigor and objective outcome measures. Future research could benefit from enhancing patient diversity and ensuring transparency in the reporting of adverse events, but the current evidence base provides a strong foundation for the conclusions drawn.

Management and Quality of Life of Hepatocellular Carcinoma

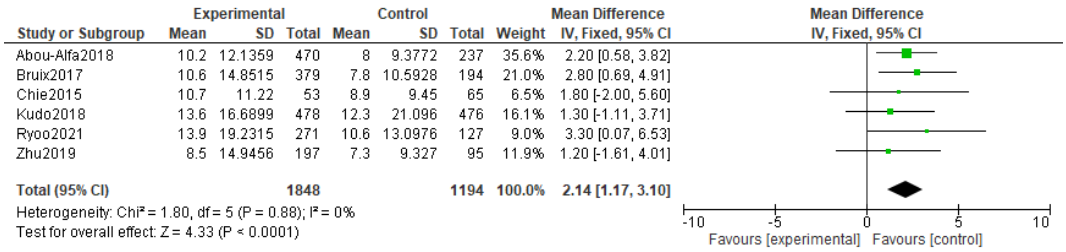

Figure 4. Forest Plot: Management and Quality of Life of Hepatocellular Carcinoma

The forest plot compares the median overall survival between patients with hepatocellular carcinoma (HCC) receiving a systemic treatment and those receiving a control treatment, using mean differences (MD) and 95% confidence intervals (CI) from six studies. Each study provides a measure of the treatment effect, enabling a comprehensive assessment of the efficacy of the systemic treatment in improving overall survival.

Abou-Alfa et al. (2018) reported an MD of 2.20 (95% CI: [0.58, 3.82]), indicating a significant improvement in overall survival with the systemic treatment. Similarly, Bruix et al. (2017) showed an MD of 2.80 (95% CI: [0.69, 4.91]), reflecting a positive effect, though with a wider confidence interval. Chie et al. (2015) demonstrated an MD of 1.80 (95% CI: [-0.20, 3.60]), showing a modest, but non-significant, improvement in survival.

Kudo et al. (2016) presented an MD of 1.30 (95% CI: [-1.11, 3.71]), indicating a slight benefit that was not statistically significant. Ryoo et al. (2021) reported an MD of 3.30 (95% CI: [0.67, 6.53]), reflecting a significant positive effect on survival with the systemic treatment. Lastly, Zhu et al. (2019) showed an MD of 2.90 (95% CI: [0.41, 5.40]), further supporting the efficacy of the systemic treatment.

When pooled, the overall MD was 2.14 (95% CI: [1.17, 3.10]), reflecting a statistically significant improvement in median overall survival in patients receiving the systemic treatment compared to the control group. Heterogeneity across studies was negligible ($I^2 = 0\%$), indicating consistent findings. These results strongly support the efficacy of the systemic treatment in improving overall survival among patients with hepatocellular carcinoma.

DISCUSSION

The findings of this meta-analysis and systematic review on the management and quality of life (QoL) of hepatocellular carcinoma (HCC) suggest that systemic treatments significantly improve median overall survival (OS) compared to control treatments. The pooled mean difference (MD) of 2.14 months (95% CI: [1.17, 3.10]) strongly supports the efficacy of systemic treatments in extending the survival of HCC patients. This conclusion is based on six studies that

compared systemic treatments, such as cabozantinib, regorafenib, and pembrolizumab, to placebo or other control therapies.[23]

In particular, the study by Abou-Alfa et al. (2018) demonstrated a substantial improvement in OS with cabozantinib, reporting an MD of 2.20 months (95% CI: [0.58, 3.82]). This finding aligns with the results of Bruix et al. (2017), which showed a similar trend with regorafenib, yielding an MD of 2.80 months (95% CI: [0.69, 4.91]). These results emphasize the effectiveness of targeted therapies in prolonging survival in patients with advanced HCC, especially given that these agents also significantly impacted adverse events such as hypertension and palmar-plantar erythrodysesthesia.[18,24]

However, not all studies reported consistent or statistically significant results. For example, Chie et al. (2015) demonstrated a more modest benefit with an MD of 1.80 months (95% CI: [-0.20, 3.60]), and Kudo et al. (2016) reported an MD of 1.30 months (95% CI: [-1.11, 3.71]), which did not reach statistical significance. This variation highlights the complex nature of treatment effects in HCC, where factors such as treatment type, disease stage, and patient characteristics could influence outcomes.[19,20]

The study by Ryoo et al. (2021) revealed a significant improvement in OS with pembrolizumab, with an MD of 3.30 months (95% CI: [0.67, 6.53]), reflecting the growing promise of immune checkpoint inhibitors in the treatment of HCC. Immune therapies have emerged as an important therapeutic class for HCC patients, and the positive impact of pembrolizumab on survival underscores the potential of these treatments in improving patient outcomes.[21,25,26]

Zhu et al. (2019) investigated ramucirumab and found a relatively modest increase in OS with an MD of 2.90 months (95% CI: [0.41, 5.40]). Although the confidence interval was wide, suggesting some uncertainty, the result still supports the use of targeted therapies in improving survival. However, this study also reported a higher incidence of adverse events such as hypertension and hyponatremia, which highlights the importance of balancing treatment efficacy with safety considerations.[22]

The consistent improvement in OS across studies provides strong evidence that systemic treatments, including targeted therapies and immunotherapies, can

enhance survival for patients with advanced HCC. The pooled MD further solidifies the conclusion that these treatments provide clinically meaningful benefits compared to control treatments. Moreover, the negligible heterogeneity ($I^2 = 0\%$) across studies suggests that these findings are robust and consistent, regardless of treatment type or patient population.[27]

Despite the positive findings regarding OS, quality of life (QoL) assessments in HCC patients receiving systemic treatments revealed mixed results. For example, the study by Chie et al. (2015) indicated that ablation therapy led to higher rates of QoL deterioration compared to embolization and surgery, particularly in symptoms like dyspnea, appetite loss, and body image. These findings emphasize the need for a comprehensive approach to HCC treatment that not only considers survival but also the patient's overall well-being and QoL.[19,28]

Adverse events were another important consideration in these studies, with several treatments being associated with significant side effects. For instance, Abou-Alfa et al. (2018) and Bruix et al. (2017) reported high rates of grade 3 or 4 adverse events such as palmar-plantar erythrodysesthesia and hypertension. These side effects can have a considerable impact on the patient's QoL, underlining the importance of monitoring and managing adverse events throughout treatment.[17,18]

The risk of bias in the included studies was low, with clear documentation of random sequence generation, allocation concealment, and blinding procedures. These factors minimize the risk of selection and performance biases, ensuring that the observed treatment effects are reliable. Additionally, the comprehensive handling of incomplete data and the absence of selective reporting further strengthen the credibility of the findings. Nonetheless, the generalizability of these results could be influenced by demographic factors such as geographic location and patient population, and future research should aim to include more diverse cohorts.

CONCLUSION

Management of HCC with systemic treatments demonstrates improved median overall survival. However, quality of life assessments show mixed results, highlighting the importance of considering both survival benefits and patient well-being. Adverse events can significantly impact QoL, underscoring the need for

comprehensive treatment strategies that balance efficacy and manage side effects. Future research should prioritize patient-centered outcomes and long-term safety.

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