Beta-Adrenergic Receptor Blockers and Hepatocellular Carcinoma Survival. A Systemic Review and Meta-Analysis

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Abstract

Introduction

Pre-clinical data has revealed that beta-adrenergic stimulation can affect the growth and progression of different types of malignancies. Beta-adrenergic receptor blockers have been associated with improved survival in patients with many types of cancer. We performed a meta-analysis to investigate the association between beta-blocker use and hepatocellular carcinoma (HCC) prognosis.

Methods

In this meta-analysis, a full search was conducted using PubMed, the Cochrane library, and Embase to identify all relevant studies published up to May 2021. Available hazard ratios (HRs) were extracted for overall survival (OS), cancer-specific survival (CSS) and pooled using a random effects meta-analysis.

Results

Four studies involving 7252 patients with HCC met the inclusion criteria and were included in the systemic review. Three studies that reported OS data of 5148 patients were included in the meta-analysis. The random-effects model showed that beta-blocker use was associated with significantly improved OS in HCC (HR = 0.69, 95% CI = 0.54-0.88, P = 0.0031), without significant heterogeneity (I^2 = 41%; Q = 6.42, P = 0.18)

Conclusion

This meta-analysis suggested that beta-blocker use can be associated with prolonged OS of patients with HCC.

Introduction

Liver cancer is the fourth-highest cause of cancer-related deaths worldwide. Hepatocellular carcinoma (HCC) is the predominant form of liver cancer, accounting for 75–85% of cases [1]. Treatment options for HCC include surgical hepatectomy in selected patients with limited disease, and liver transplantation performed in highly selected patients. Radiofrequency or microwave ablation is recommended in cases of unresectable patients [2]. The treatment of choice for intermediate stages could be arterially directed therapies, including chemoembolism, radioembolism or simple embolism [3]. Multi-kinase inhibitors for systemic therapy, such as sorafenib and lenvatinib, mainly target vascular endothelial growth factor receptors (VEGFRs). Recently, PD-L1 immune-checkpoint inhibitors plus anti-VEGF inhibitors (atezolizumab and bevacizumab) was approved as an initial treatment for patient with unresectable or metastatic HCC [4].

HCC commonly develops in the background of liver cirrhosis caused by chronic hepatic inflammation and fibrosis [5]. A meta-analysis of randomized trials on beta-blockers for the prevention of variceal bleeding

in patients with liver cirrhosis showed a reduction in the risk of HCC but not HCC mortality [6]. Pre-clinical data have revealed that beta-adrenergic stimulation can affect the growth and progression of different types of malignancies [7]. Beta-adrenergic receptor blockers have been associated with a reduced risk of cancer and better survival among patients with many types of cancers [8, 9]. However, no randomized trial has been designed to study the association between beta-blocker use and HCC cancer survival. However, some retrospective studies of HCC have shown an association between improved survival and beta-blocker use [10–13].

Therefore we reviewed existing studies and conducted a meta-analysis on the end of survival in patients with HCC receiving beta-blockers.

Material And Methods

Literature search and study selection

We conducted our systematic review and meta-analysis in accordance with the PRISMA guidelines [14]. A full search was conducted in PubMed, the Cochrane library, and Embase to identify all relevant studies published up to May 2021. We searched for titles and abstracts containing the following keywords: 'beta-adrenergic inhibitors, beta-blockers, propranolol, metoprolol, atenolol, carvedilol' and 'Hepatocellular carcinoma, Liver cancer' and 'survival, mortality'. The search was conducted on May 2021. All abstracts and full texts were checked by two researchers (H.C. and S.H.L). Studies were eligible for inclusion if they were published as full papers in English. Any discrepancies were discussed and resolved between the two authors. During the initial search, 116 articles were identified, of which four duplicate articles were excluded. Abstracts were reviewed and excluded if the article was about review articles, non-HCC outcomes, no use of beta-blockers, and no survival data. The remaining four papers were reviewed in full to ensure that a systemic review was possible and that adequate and sufficient data were available (Fig. 1.).

Outcome of interest

The primary outcome of this study was to assess the association between beta-blocker use and overall survival (OS) and cancer-specific survival (CSS) in patients with HCC.

Data extraction and risk of bias assessment

Two researchers (H.C. and S.H.L.) independently extracted the following data from all selected articles: first author, country, study period, study design, characteristics of enrolled patients, and hazard ratios (HRs) with 95% confidence intervals (CIs) for OS and CSS. If data were not provided directly, we requested that the author provide the available data [11]. Quality assessment of the included studies was based on the Newcastle-Ottawa Scale for assessing the quality of non-randomised studies [15]. One researcher (H.C.) assessed the quality in the beginning and the second (S.H.L.) checked the assessments.

Statistical analysis

This study was planned to evaluate the association between beta-blocker use and OS and CSS in patients with HCC. Only one study was published for CSS [13], thus, these patients were included in our review and tables, but excluded from the meta-analysis for OS. Another study included a resectable and curable HCC cohort, however reported only relapse-free survival data for them, thus this cohort was excluded from the review and meta-analysis [10].

Effect measures for the outcomes of survival included adjusted and/or unadjusted HRs and 95% CIs. Pooled HRs and corresponding 95% CIs for OS were shown by forest plots. Since the clinical and methodological heterogeneity were known, we used a random-effects model to calculate the pooled HRs and their 95% CIs, even though there was no between-study heterogeneity in statistics (Fig. 2). The heterogeneity across studies was tested using the chi-squared Q test and I^2 metric statistic. There was marked heterogeneity if P-value ≤ 0.10 and/or I^2 was $> 50\%$. All P-values were two-sided, and statistical significance was set at $P < 0.05$. All statistical analyses were performed using R software (version 4.0.3; http://www.r-project.org).

Results

Study selection

The selection process for the included studies is described in the CONSORT diagram provided in Fig. 1. Four studies involving 7252 patients with HCC met the inclusion criteria and were included in the systemic review. Three studies reported only OS outcomes [10–12], while the other one showed only CSS as the endpoint [13]. Thus, three studies involving 5148 patients were included in the meta-analysis [10–12], and meta-analysis for CSS was not performed.

Study characteristics

The characteristics of the included studies are summarized in Table 1. Two original studies included HCC patients only [10, 13], and the other two studies included other cancer patients and cancer-free patients, respectively. [11] and [12]:

Table 1
Summary of selected studies

Study	Design	Patient characteristics	BB	No BB	BB medication	Out-come	Definition of BB use
Chang et al. (10)	RS	Unresectable or metastatic HCC	1560	3120	Propranolol	OS	Within 1 year prior to the initial palliative treatment
Boas et al. (11)	RS	HCC initially treated with TAE	68	236	Mixed	OS	Seven days prior through 30 days after TAE
Lee et al. (12)	RS	HCC with cirrhosis and hepatic encephalopathy	78	86	Propranolol	OS	At least 90 days after the diagnosis of hepatic encephalopathy
Udumyan et al. (13)	RS	Primary HCC diagnosed	714	1390	Mixed	CSS	In the 90 days before HCC diagnosis

BB, beta-blocker; RS, retrospective study; HCC, hepatocellular carcinoma; TAE, transarterial embolization; OS, overall survival; CSS, cancer-specific survival; Mixed, use of various beta-blockers;

One study investigated the effect of propranolol on OS in patients with unresectable or metastatic HCC [10]. The other study evaluated the association adjuvant medication including use of beta blocker at the time of HCC embolization or ablation and survival [11]. The third study investigated whether propranolol treatment was associated with outcomes for cirrhotic patients with hepatic encephalopathy, and subgroup analysis showed a significant association between propranolol treatment and mortality in patients with HCC [12]. The last study assessed beta-blockers and CSS of HCC in a Swedish national cohort [13]. They reported that beta-blockers, particularly the non-selective type, are associated with cancer mortality in patients with primary HCC (HR = 0.82, $P = 0.005$).

The Newcastle–Ottawa quality assessment scale was used to assess the quality of the studies. Scores ranged from 7 to 8 for individual studies (supplementary Table 1).

Meta-analysis

Three studies that reported OS data were included in the meta-analysis for OS [10–12]. A random-effects model was used to conduct the meta-analysis. The pooled results indicated that beta-blockers were associated with better OS in patients with HCC (HR = 0.69, 95% CI = 0.54–0.88, $P = 0.0031$). There was no significant heterogeneity among the three studies ($I^2 = 41\%$; $Q = 6.42$, $P = 0.18$). Forest plot for the three studies is shown in Fig. 2.

Discussion

This meta-analysis showed that beta-blocker use could be related to the prolonged survival of patients with HCC. To our knowledge, this is the first meta-analysis to the association between beta-blockers and OS in patients with HCC.

The effect of beta-blockers on the incidence and prognosis has been extensively reported in several cancers, including lung, breast, ovary and prostate cancers [16–20]. A retrospective study of non-small-cell lung cancer patients who received definitive radiotherapy showed that beta-blocker use was associated with improved distant metastasis-free survival (HR = 0.67), disease-free survival (HR = 0.74), and OS (HR = 0.78) [16]. The meta-analysis of breast cancer suggested that the use of beta-blockers significantly reduced the risk of cancer death among women with breast cancer (HR = 0.50) [17]. A cohort study of ovarian cancer reported that a long duration of beta-blocker use was associated with better OS (HR = 0.26) and disease-specific survival (HR = 0.25) [18]. Lu et al. suggested that beta-blocker use was an independent favorable prognostic factor for CSS in a meta-analysis of prostate cancer (HR = 0.85) [19].

Pre-clinical studies have suggested that beta-adrenergic signaling plays a role in cancer development, including that of HCC. Wu et al. reported that beta 2-adrenergic receptor (ADR) signaling sustained HCC cell proliferation and survival through the negative regulation of autophagy [21]. Norepinephrine/epinephrine promotes HCC cell invasion via alpha 1A- and beta 2-ADRs and prevents anoikis via beta 2-ADR [22]. Beta 2-ADR-mediated activation of YB-1 stimulates epithelial-to-mesenchymal transition and HCC metastasis [23]. An *in vitro* study including HCC cells showed that beta-ADR blockers inhibited cancer cell proliferation, invasion, and migration [24].

In a clinical trial of breast cancer patients, preoperative beta-blockers reduced intratumoral mesenchymal polarization and stimulated immune cell infiltration in cancer [25]. This provided the evidence that beta-blockers could enhance the anti-tumor immune response. In addition, beta-blockers reduced the risk of HCC development in patient with cirrhosis, which is a well-known risk factor for HCC [6, 26, 27].

These preclinical and clinical findings suggest that beta-blockers have anti-tumor effects by inhibiting tumor progression and metastasis [28]. Therefore, the better OS of beta-blocker use patients in our analysis could be related to the reduction of cancer progression linked to inhibition of beta-ADR signaling in HCC pathology.

Previous studies have suggested that beta-blockers could enhance the effect of HCC treatment (e.g., tyrosine kinase inhibitor and embolization) Boas et al. reported that beta-blockers are responsible for improving survival in HCC patients who were treated with embolization [11]. Chang et al. suggested that the beta-blocker propranolol may have a synergistic effect with sorafenib, radiotherapy and embolization [10]. The xenograft model with HCC cells showed that inhibition of beta 2-ADR signaling by beta-blockers led to increased autophagy, HIF1α destabilization, tumor growth suppression, and enhanced anti-tumor activity of sorafenib [21]. Beta-blockers suppress endothelial cell proliferation and arrest tumor angiogenesis, which is one of the resistance mechanisms of chemoembolization in HCC [29–31]. In addition, VEGF-induced Src-ERK pathways in HUVECs were inhibited by beta-blockers [32]. Therefore,

beta-blocker use in HCC patients may improve the efficacy of anti-tumor treatment, potentially resulting in better survival.

This study has several limitations. First, this meta-analysis was based on retrospective studies, which could increase the risk of bias. Further, the enrolled HCC patients were not uniform between the studies in clinical situations. In addition, each study had its specific definition of 'beta-blocker exposure', and thus the duration and the timing of beta-blocker use were not homogeneous. However, it should be noted that the between-study heterogeneity was acceptable in this analysis ($I^2 < 50\%$). Second, beta-blockers are a wide and heterogeneous group of molecules that act as competitive and reversible antagonists of beta 2-ADRs [33]. The class effect of beta-blockers can cause different anti-cancer effects [13]. However, we could not analyze the effect of the type of beta-blocker because two of the three studies in this analysis investigated propranolol. Third, a dose-response meta-analysis was not performed because of the lack of relevant data. Lastly, CSS data was available in one published article and the meta-analysis for CSS was not conducted. Future studies are warranted to evaluate CSS and beta-blockers in patients with HCC.

Conclusions

Despite the above limitations, the current study provided strong evidence for the effect of beta-blocker use on OS in patients with HCC. Considering published clinical data and preclinical investigations, the cytotoxic effect of beta-blockers on cancer cells and the synergistic effect with standard treatment for HCC might be responsible for the benefit of beta-blockers. Further prospective studies should be conducted to confirm these findings.

Declarations

Author Contributions: Conceptualization, H.C. ; methodology, H.C.; software, H.C.; validation, H.C., S.H.L.; formal analysis, H.C.; investigation, H.C., S.H.L.; resources, H.C., S.H.L.; data curation, H.C., S.H.L.; writing—original draft preparation, H.C.; writing—review and editing, H.C., S.H.L.; visualization, H.C.; supervision, H.C.; project administration, H.C.; All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

Compliance with Ethical Standards

No approval of research ethics committees was required to accomplish the goals of this study because systemic review and meta-analysis was conducted with previously published articles.

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Figures

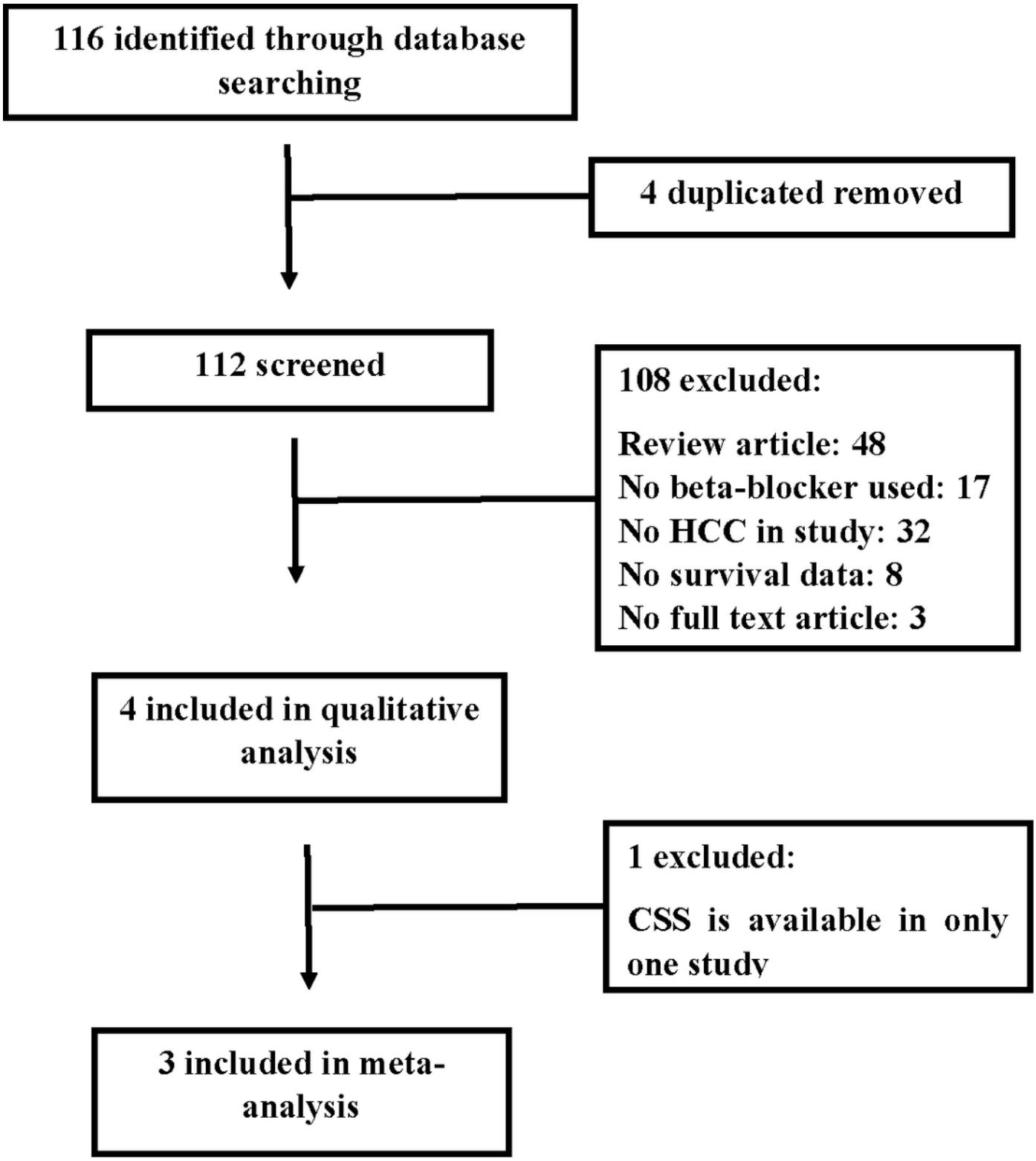

Figure 1

Flow chart on the article selection process

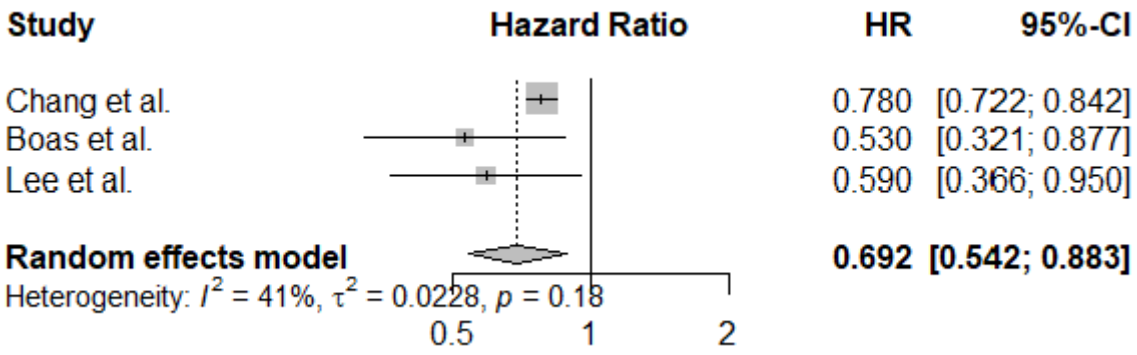

Figure 2

Forest plot of overall survival according to beta-blocker use in patients with hepatocellular carcinoma

Supplementary Files

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