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META-ANALYSIS

Roles of Tregs in development of hepatocellular carcinoma: A meta-analysis

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Abstract

AIM: To assess systematically the association between regulatory T cells (Tregs) and hepatocellular carcinoma (HCC).

METHODS: We searched Medline, Embase and Wanfang databases for literature on the populations of Tregs in HCC patients and controls, using the pooled OR and 95%CIs for assessment. There were no limitations with respect to publication date or language. The references of qualifying articles were also searched. We excluded studies with unclear data or overlapping studies. Twenty-three studies met our criteria, and the quality of these studies was assessed using the Scottish Intercollegiate Guidelines Network (SIGN). The meta-analysis of association between Tregs and HCC was undertaken using the random-effects approach, as described by DerSimonian and Laird. Subgroup analysis was performed when at least three studies were available. Potential publication bias was assessed by visual inspection of the funnel plot, and an asymmetric plot suggested possible publication bias.

RESULTS: Twenty-three studies with a total of 1279 HCC patients and 547 healthy volunteers as controls were enrolled. The frequency of circulating Tregs in HCC patients was 87% higher than in healthy controls (OR = 1.87, 95%CI: 1.49-2.34). The frequency of Tregs in the HCC tumor microenvironment was significantly higher than that in tumor-surrounding tissue and biopsy specimens from healthy livers (OR = 4.04, 95%CI: 2.10-7.79, P = 0.000; OR = 2.869, 95%CI: 2.16-3.82, P = 0.000). However, subgroup analyses based on the different types of tumors or patient characteristics such as tumor size, tumor number or α fetoprotein (AFP) levels in HCC patients, showed that populations of Tregs as a whole were not significantly changed between groups (P > 0.05 for all).

CONCLUSION: There is an obvious association between Tregs and pathogenesis of HCC. Further well-designed clinical studies are warranted to illustrate the potential role of Tregs in HCC.

Key words: Hepatocellular carcinoma; Regulatory T cells; Meta-analysis; Tumor escape; Cellular immunity

Core tip: Association of increased populations of regulatory T cells (Tregs) with impaired immune response in hepatocellular carcinoma (HCC) patients has been proposed. This study systematically quantified the strength of this association by meta-analysis. The available literature revealed that HCC patients have more Tregs in

the circulation and tumor tissue. However, more well-designed clinical studies are needed to investigate further the potential role of Tregs in the pathogenesis of HCC, because subgroup analyses based on other tumors or patient characteristics did not show any positive correlation between Tregs and such pathological states.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the major health problems worldwide, resulting in > 600000 patients dying from this disease annually[1]. Accumulating evidence shows that the tumor is immunogenic. The frequent finding of tumor infiltrating lymphocytes in this malignancy suggests that an immune response is triggered by the tumor. Studies have shown that different types of T lymphocytes exert various functions in the tumor microenvironment. The $CD4^+$ regulatory T lymphocyte (Treg) subsets have been shown to exert a negative effect on antitumor immunity by suppressing effector T lymphocytes[2,3].

The same tumor-related immune reaction has also been found in the HCC microenvironment, suggesting that it is rational to develop immunotherapy for HCC. Classic therapies for HCC (such as liver resection, liver transplantation, radiofrequency ablation, and transarterial chemoenbolization) often do not provide a complete cure, because half of the treated patients experience tumor recurrence within 3 years; let alone a large number of patients who are undiagnosed until an advanced stage has been reached[4]. In view of these facts, new treatment strategies, such as immunotherapy, are warranted, aiming at providing more efficient and selective targeting of tumor cells by inducing or boosting the existing tumor-specific immune response. Identification of the exact roles that various anti-tumor immune cells may play calls for formation of novel therapeutic strategies.

Tregs, which usually express $CD25^+$, are naturally present in the immune system, accounting for 5%-10% of $CD4^+$ T cells. Tregs can result in suppression of both $CD4^+$ and $CD8^+$ T cell activation and proliferation both *in vitro* and *in vivo* in various ways, including cell-cell contact and secretion of immunosuppressive cytokines such as transforming growth factor (TGF)-β, interleukin (IL)-10 and IL-35[5]. The frequency and function of Tregs have been reported in hepatitis B infection and it is believed that Tregs are the most important determining factor of prognosis of hepatitis B patients[6]. The development of HCC is believed to be associated with hepatitis B virus (HBV). HBV infection accounts for > 60% of liver cancer cases in developing countries and < 25% of cases in developed countries. Therefore, it is desirable to establish whether Tregs play a potential role in the progression of HCC and its clinical significance. We assume that with more information gathered about the role of Tregs in development of HCC, the more effective immunotherapy may become available in the future. This systematic review evaluated the available evidence for the functions of Tregs in HCC patients and aimed to establish the clinical importance of Tregs in HCC patients.

MATERIALS AND METHODS

Search strategy

Two authors independently carried out a literature search using Medline (1950 to December 2012), Embase (1980 to December 2012), and Wanfang (1998 to December 2012) databases to identify studies on Tregs in patients with HCC and in controls. The following medical subject headings (MeSH) and key words were used: "T-lymphocytes, regulatory", "Tregs", "regulatory T cells", "T regulatory cells", "$CD4^+CD25^+FoxP3^+$ T cells", "$CD4^+CD25^+$T cells", "carcinoma, hepatocellular", "hepatocellular carcinoma", "liver neoplasms", and "liver tumor". There was no language limitation. The "related articles" function was used to broaden the search. All references cited in the studies were also reviewed to identify additional published articles missed in the retrieval, until no further relevant studies were identified. We searched all the publications up to the end of December 2012.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) publications in all languages; (2) appropriate study design: case-control, cohort, cross-sectional and clinical trial; (3) report of the frequency of Tregs in peripheral blood or tumor tissue; (4) study population of HCC patients; and (5) patients who did not receive any immunotherapy or chemotherapy that could have influenced their immune reactions. The exclusion criteria were as follows: (1) unclear and confusing data; and (2) overlapping studies (in studies with overlapping cases or controls).

Data extraction

Two authors independently retrieved the following data from all eligible studies: first author's name, publication year, country of study, type of study, number of patients included, patient characteristics, frequency of Tregs in the peripheral blood and/or tumor tissue, and frequency of Tregs divided by various features of the tumor and/or patients. In case of doubt, the authors were contacted for further information to ensure accuracy. When there was disagreement over eligibility of a study, an additional reviewer assessed the article until a consensus was reached.

Quality assessment

Critical appraisal was done by two reviewers and graded on strength of evidence using the revised grading sys-

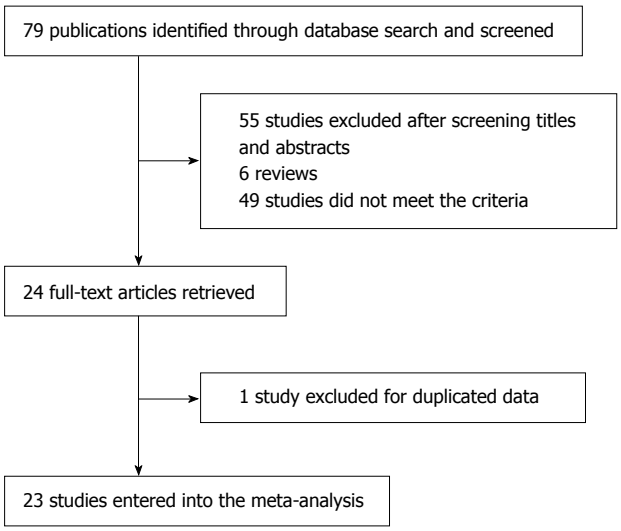


Figure 1 Flow diagram showing study methodology for measurement of regulatory T cells in hepatocellular carcinoma.

tem of the Scottish Intercollegiate Guidelines Network (SIGN)[7]. If disagreement existed on the assigned grade, studies were reassessed until a consensus was reached.

Statistical analysis

Statistical analyses were performed using STATA 12 software (StataCorp LP, College Station, TX, United States). Statistical heterogeneity of results was appraised using heterogeneity tests including Q^2, I^2, and τ^2 statistics. For Q statistics, $P < 0.01$ was considered significant. I^2 values of 25%, 50% and 75% were used as evidence of low, moderate and high heterogeneity, respectively[8]. We also used τ^2 statistics because in most subgroups, there were few articles[9]. According to the results of heterogeneity tests, we selected fixed/random effects models for meta-analysis with the "metan" command. The ORs and 95%CIs for determination of Tregs were calculated using the random-effects approach, as described by DerSimonian *et al*[10]. Subgroup analysis was performed when at least three studies were available[11]. The credibility of outcomes in this meta-analysis was validated by the sensitivity analysis that was performed by sequential omission of individual studies or by omitting studies without high quality. Potential publication bias was assessed by visual inspection of the funnel plot, and an asymmetric plot suggested possible publication bias[12]. In addition, we also performed an Egger linear regression test at the $P < 0.01$ level of significance to assess the publication bias[13].

RESULTS

Search results and study description

Based on the predefined search strategy, 79 potentially relevant publications were identified. After screening titles and abstracts, 55 publications were excluded, comprising six reviews and 49 articles that did not meet the inclusion criteria. Full text for the remaining 24 studies was retrieved and reviewed in detail. No relevant publications were found by examination of references attached to these 24 studies. Duplicate data were identified in one publication[14] and this was excluded from the analysis. Finally, 23 studies[15-37] met the predefined inclusion criteria and entered the meta-analysis. A flow diagram of the search is shown in Figure 1.

Table 1 Baseline information of studies included in the meta-analysis

Ref.	No. of HCC patients	No. of controls	Year of study	Country of study
Unitt *et al*[15]	25	48	2005	United Kingdom
Ormandy *et al*[16]	84	21	2005	Germany
Guo *et al*[17]	22	12	2006	China
Fu *et al*[18]	123	47	2007	China
Peng *et al*[21]	63	40	2007	China
Yang *et al*[20]	28	26	2007	China
Cao *et al*[19]	33	20	2007	United States
Yu *et al*[22]	58	15	2008	China
Zhang *et al*[23]	100	20	2008	China
Huang *et al*[28]	93	24	2010	China
Kuang *et al*[26]	28	26	2010	China
Wang *et al*[27]	46	32	2010	China
Yoshizawa *et al*[24]	57	31	2010	Japan
Zhang *et al*[25]	49	25	2010	China
Thakur *et al*[33]	28	15	2011	Indian
[1]Fan *et al*[30]	138	-	2011	China
Liu *et al*[32]	40	28	2011	China
Aleem *et al*[29]	15	10	2011	Egypt
Feng *et al*[31]	42	15	2011	China
Wang *et al*[34]	30	30	2011	China
Yang *et al*[37]	60	20	2012	China
Wu *et al*[36]	78	12	2012	China
Chen *et al*[35]	39	30	2012	China

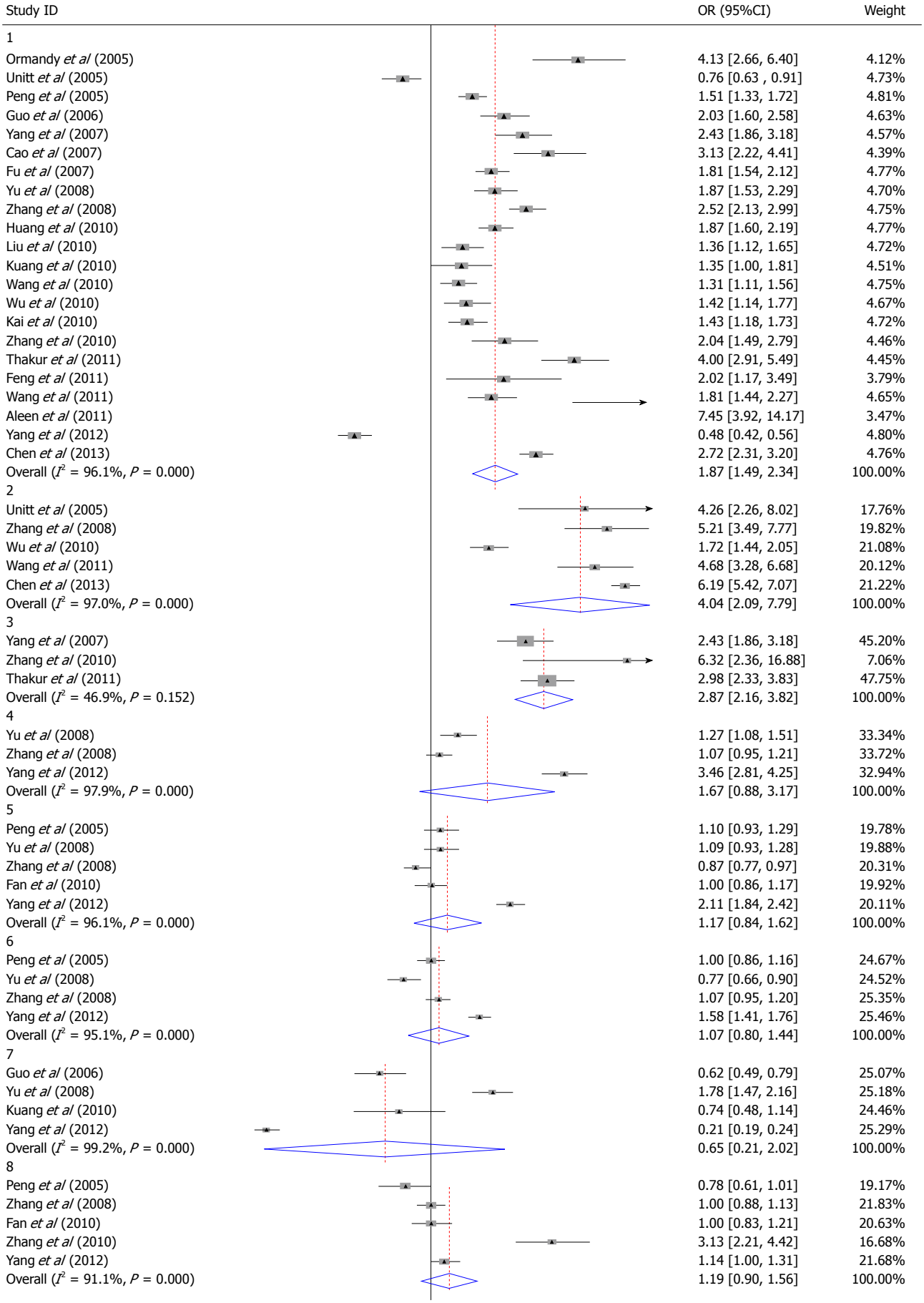
[1]Study data used for subgroup analysis. HCC: Hepatocellular carcinoma.

Study characteristics

In this study, 1279 HCC patients and 547 healthy volunteers as controls were enrolled. The age of the patients ranged from 44.5 to 71 years and that of the controls was 41.1-56 years. Sex distribution of the two groups was 57.1%-91.4% in male and 46.2%-93.3% in female. Information about the year of publication and the country in which the study was performed is listed in Table 1.

Meta-analysis

The main results of this meta-analysis are listed in Figure 2 and Table 2. Meta-analysis of a total of 22 studies showed that the frequency of circulating Tregs in HCC patients was 87% higher than in healthy controls (OR = 1.87, 95%CI: 1.49-2.34, $P = 0.000$), although there was significant between-study heterogeneity (P value of $Q^2 = 0.000$, $I^2 = 96.1\%$, $\tau^2 = 0.2741$). The frequency of Tregs in the HCC tumor microenvironment was significantly higher than that in tumor-surrounding tissue and biopsy specimens from healthy livers (OR = 4.04, 95%CI: 2.10-7.79, $P = 0.000$; OR = 2.869, 95%CI: 2.16-3.82, $P = 0.000$). Between-study heterogeneity was also observed (P value of $Q^2 = 0.000$, $I^2 = 97.0\%$, $\tau^2 = 0.5250$; P value of


Study ID
OR (95%CI)
Weight
1
Ormandy et al (2005) 4.13 [2.66, 6.40] 4.12%
Unitt et al (2005) 0.76 [0.63 , 0.91] 4.73%
Peng et al (2005) 1.51 [1.33, 1.72] 4.81%
Guo et al (2006) 2.03 [1.60, 2.58] 4.63%
Yang et al (2007) 2.43 [1.86, 3.18] 4.57%
Cao et al (2007) 3.13 [2.22, 4.41] 4.39%
Fu et al (2007) 1.81 [1.54, 2.12] 4.77%
Yu et al (2008) 1.87 [1.53, 2.29] 4.70%
Zhang et al (2008) 2.52 [2.13, 2.99] 4.75%
Huang et al (2010) 1.87 [1.60, 2.19] 4.77%
Liu et al (2010) 1.36 [1.12, 1.65] 4.72%
Kuang et al (2010) 1.35 [1.00, 1.81] 4.51%
Wang et al (2010) 1.31 [1.11, 1.56] 4.75%
Wu et al (2010) 1.42 [1.14, 1.77] 4.67%
Kai et al (2010) 1.43 [1.18, 1.73] 4.72%
Zhang et al (2010) 2.04 [1.49, 2.79] 4.46%
Thakur et al (2011) 4.00 [2.91, 5.49] 4.45%
Feng et al (2011) 2.02 [1.17, 3.49] 3.79%
Wang et al (2011) 1.81 [1.44, 2.27] 4.65%
Aleen et al (2011) 7.45 [3.92, 14.17] 3.47%
Yang et al (2012) 0.48 [0.42, 0.56] 4.80%
Chen et al (2013) 2.72 [2.31, 3.20] 4.76%
Overall (I^2 = 96.1%, P = 0.000) 1.87 [1.49, 2.34] 100.00%
2
Unitt et al (2005) 4.26 [2.26, 8.02] 17.76%
Zhang et al (2008) 5.21 [3.49, 7.77] 19.82%
Wu et al (2010) 1.72 [1.44, 2.05] 21.08%
Wang et al (2011) 4.68 [3.28, 6.68] 20.12%
Chen et al (2013) 6.19 [5.42, 7.07] 21.22%
Overall (I^2 = 97.0%, P = 0.000) 4.04 [2.09, 7.79] 100.00%
3
Yang et al (2007) 2.43 [1.86, 3.18] 45.20%
Zhang et al (2010) 6.32 [2.36, 16.88] 7.06%
Thakur et al (2011) 2.98 [2.33, 3.83] 47.75%
Overall (I^2 = 46.9%, P = 0.152) 2.87 [2.16, 3.82] 100.00%
4
Yu et al (2008) 1.27 [1.08, 1.51] 33.34%
Zhang et al (2008) 1.07 [0.95, 1.21] 33.72%
Yang et al (2012) 3.46 [2.81, 4.25] 32.94%
Overall (I^2 = 97.9%, P = 0.000) 1.67 [0.88, 3.17] 100.00%
5
Peng et al (2005) 1.10 [0.93, 1.29] 19.78%
Yu et al (2008) 1.09 [0.93, 1.28] 19.88%
Zhang et al (2008) 0.87 [0.77, 0.97] 20.31%
Fan et al (2010) 1.00 [0.86, 1.17] 19.92%
Yang et al (2012) 2.11 [1.84, 2.42] 20.11%
Overall (I^2 = 96.1%, P = 0.000) 1.17 [0.84, 1.62] 100.00%
6
Peng et al (2005) 1.00 [0.86, 1.16] 24.67%
Yu et al (2008) 0.77 [0.66, 0.90] 24.52%
Zhang et al (2008) 1.07 [0.95, 1.20] 25.35%
Yang et al (2012) 1.58 [1.41, 1.76] 25.46%
Overall (I^2 = 95.1%, P = 0.000) 1.07 [0.80, 1.44] 100.00%
7
Guo et al (2006) 0.62 [0.49, 0.79] 25.07%
Yu et al (2008) 1.78 [1.47, 2.16] 25.18%
Kuang et al (2010) 0.74 [0.48, 1.14] 24.46%
Yang et al (2012) 0.21 [0.19, 0.24] 25.29%
Overall (I^2 = 99.2%, P = 0.000) 0.65 [0.21, 2.02] 100.00%
8
Peng et al (2005) 0.78 [0.61, 1.01] 19.17%
Zhang et al (2008) 1.00 [0.88, 1.13] 21.83%
Fan et al (2010) 1.00 [0.83, 1.21] 20.63%
Zhang et al (2010) 3.13 [2.21, 4.42] 16.68%
Yang et al (2012) 1.14 [1.00, 1.31] 21.68%
Overall (I^2 = 91.1%, P = 0.000) 1.19 [0.90, 1.56] 100.00%

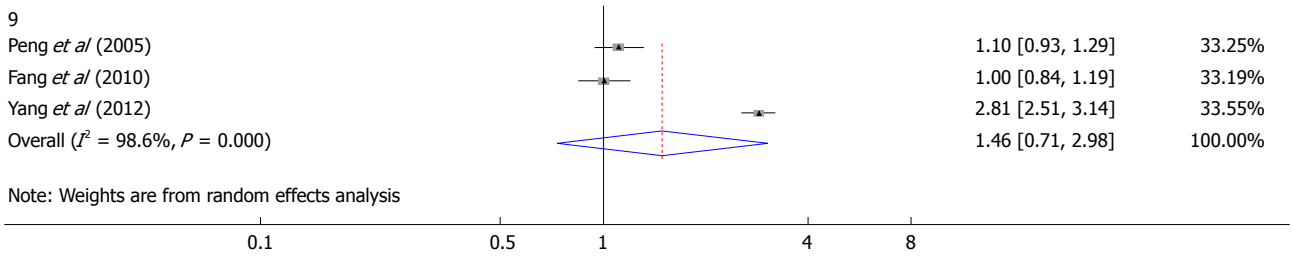


Figure 2 Integrated forest plot of pooled OR with 95%CI for this meta-analysis (corresponding to Table 2).

Table 2 Summary of odds ratios and 95%CIs in this meta-analysis

Items	OR		Heterogeneity			
	OR (95%CI)	*P* value	Q^2	τ^2	I^2 (%)	*P* value
Ciculating populations of Tregs between HCC patients and health controls	1.868 (1.489-2.344)	0	539.28	0.2741	96.1	0
Populations of Tregs in the tumor and surrounding tissues	4.040 (2.094-7.794)	0	133.41	0.5250	97.0	0
Populations of Tregs in the tumor and the normal liver tissues	2.869 (2.157-3.817)	0	3.77	0.0282	46.9	0.152
Populations of Tregs among HCC patients with different tumor numbers (one tumor mass or more)	1.670 (0.879-3.171)	0.117	94.91	0.3138	97.9	0
Populations of Tregs among HCC patients with different tumor sizes (smaller or larger than 5 cm)	1.170 (0.844-1.620)	0.346	102.41	0.1325	96.1	0
6 Populations of Tregs between HCC patients with or without capsule	1.073 (0.798-1.442)	0.642	61.48	0.0682	95.1	0
Populations of Tregs among HCC patients in different TNM stages (Ⅰ/Ⅱ *vs* Ⅲ/Ⅳ)	0.646 (0.207-2.021)	0.453	365.99	1.3338	99.2	0
Populations of Tregs between HCC patients with or without HBV infection	1.189 (0.904-1.564)	0.216	45.02	0.0856	91.1	0
Populations of Tregs among HCC patients with different AFP levels (lower or higher than 20 ng/mL)	1.458 (0.714-2.975)	0.3	143.21	0.3916	98.6	0

HCC: Hepatocellular carcinoma; HBV: Hepatitis B virus; AFP: Alpha-fetoprotein; Tregs: Regulatory T cells.

Q^2 = 0.152, I^2 = 46.9%, τ^2 = 0.0280). Sensitivity and subgroup analyses were conducted to identify the causes of significant heterogeneity, however, it was still not possible to eliminate the observed heterogeneity.

Based on the different types of tumors or patient characteristics, subgroup analyses were conducted. Our results showed that the frequency of Tregs between the groups divided by tumor size, tumor number or AFP levels of HCC patients did not differ significantly between the groups ($P > 0.05$ for all).

Publication bias

Funnel plot and Egger's test were performed to assess the publication bias of this meta-analysis. As shown in Figure 3, in the meta-analysis investigating the circulating Tregs populations between HCC patients and healthy controls, the funnel plot's shape seemed asymmetrical, and the *P* value of the Egger test was 0.036, which was > 0.01 but < 0.05. In view of the statistical power of the Egger test when < 25 cases were included, we cautiously drew the conclusion that publication bias might have been present in this meta-analysis.

DISCUSSION

Although many studies on the pathogenetic role of Tregs in the development of HCC have been done in the past decade, the results are controversial. Those conflicting results may partly have been due to the relatively small sample size of the individual studies and sampling effects. Thus, it was necessary to carry out a meta-analysis, a statistical procedure for combining results from published studies to acquire a more precise estimation of the major effect, and to identify the potential role of Tregs in the development of HCC.

Tregs, especially $CD4^+CD25^+Foxp3^+$ Tregs, are one of the most widely investigated types of immune cells because of their specific inhibitory function in the pathogenesis of tumors. Several mechanisms contribute to the negative regulation of immunity in the tumor microenvironment, such as: (1) direct lysis of effector T cells through release of granzyme B and perforin; (2) induction of apoptosis of effector T cells through deprivation of IL-2 by high-affinity CD25; (3) modulation of maturation and function of dendritic cells by cell-cell contact-dependent mechanisms involving cytotoxic T lymphocyte antigen-4; and (4) release of inhibitory cytokines including TGF-β, IL-10, IL-35 and prostaglandin E2 to modulate effector cell immune responses[38].

As a potential immunotherapy strategy for HCC, Treg deletion has been shown to impair tumor growth[39]. However, some critical issues with regard to human Tregs require further investigation for the purpose of forming a clinical immunotherapy strategy. One issue is the lack

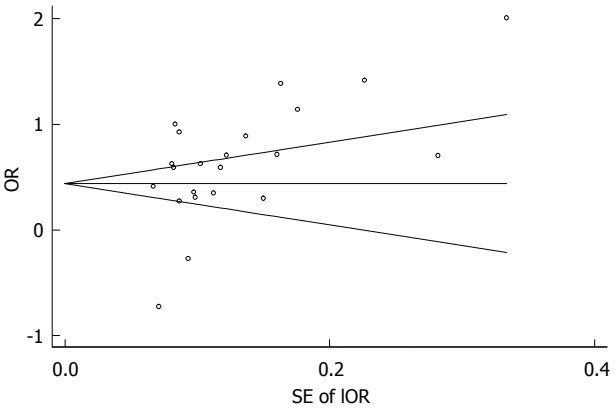


Figure 3 Funnel plot for publication bias test in the meta-analysis investing the circulating populations of Regulatory T cells between hepatocellular carcinoma patients and healthy controls.

of specific markers for human Tregs. Transcription factor Forkhead box (Fox)p3 is believed to be the most important regulatory factor for the differentiation and functional maintenance of $CD4^+CD25^+$ Tregs. Therefore, $CD4^+CD25^{high}$ and Foxp3 are regarded as the specific markers for human $CD4^+CD25^+$ Tregs cells. However, with the discovery of Foxp3 mRNA in activated $CD25^-$ T cells, researchers perceive that not all Foxp3-positive cells are Tregs[40]. Recent genome-wide analyses have revealed several regions that show different patterns of DNA methylation or histone modification between Tconv cells and Tregs in humans. It is likely that Foxp3-dependent gene regulation and Treg cell epigenome-dependent regulation have distinct roles in determining the whole Treg-cell-type gene expression pattern and complement mutually in the expression of certain specific genes in Tregs. Thus, it is recognized that together with Foxp3 expression, the Treg cell-specific DNA hypomethylation pattern can be a reliable marker for defining functional Tregs as a distinct cellular entity[41].

Another issue is the plasticity of Tregs. Recently, human $Foxp3^+CD4^+$ T cells were divided into three types of cells based on the detection of peripheral blood CD45RA and CD25, Foxp3 expression, cytokine secretion, and *in vitro* inhibitory effects on T cells: (1) $CD45RA^+CD25^{low}Foxp3^{low}CD4^+$ T cells; (2) $CD45RA^-CD25^{hi}Foxp3^{hi}CD4^+$ T cells; these two types of cells have strong immunosuppressive activity *in vitro*; and (3) $CD45RA^-CD25^{low}Foxp3^{low}CD4^+$ T cells; these cells secrete cytokines to promote T cell proliferation, but do not have immunosuppressive activity[42]. Previous studies have demonstrated that suppressive activities of $Foxp3^+$ cells are correlated with the DNA methylation status of the *FOXP3* CNS2 region[41].

The present meta-analysis, including 23 case-control studies with a total of 1279 cases and 547 controls, provides the most comprehensive assessment to date of the effect of Tregs in the pathogenesis of HCC. The main results of the meta-analysis of a total of 22 studies showed that the circulating population of Tregs among HCC patients was 87% higher than that of healthy controls. Populations of Tregs in the HCC tumor microenvironment were significantly larger than those in tissues adjacent to tumors and healthy liver biopsy specimens. The subgroup analyses as stratified according to different clinical features in patients with HCC showed no obvious relationship in terms of circulating populations of Tregs (all $P > 0.05$). These features included tumor size, tumor number, tumor capsule, TNM stage, HBV infection, and AFP levels. However, it is worthy of note that most subgroup analyses included no more than five studies. As a whole, our meta-analyses demonstrated a definite relationship of Tregs with the pathogenesis of HCC. Both the circulating and tissue Tregs in HCC patients were increased compared with healthy controls, and they might have contributed to the immune tolerance of tumors. The subgroup analyses raised the suggestion that more well-designed clinical studies are needed to disclose the clinical roles of Tregs in the different stages of tumor formation. Our meta-analysis demonstrated the relationship between frequency of Tregs and pathological state of HCC. Therefore, further studies should pay more attention to the effect of Tregs on survival of HCC patients and clinical identification of different subtypes of human Tregs, as well as their precise role in the development of HCC. They could help with the development of an immunotherapy strategy directed towards Tregs to reinforce antitumor immunity and improve life expectancy. In addition, all items mentioned in the subgroup analyses should be investigated further to improve our understanding.

Several limitations to our meta-analysis should be considered. First, all the studies included were retrospective case-control studies, thus, it should not be considered to be evidence of the highest quality. However, in light of the scarcity of high-quality evidence in this field, data from these studies still can be informative. Second, the degree of statistical heterogeneity between the included studies cautions against over-interpretation of our results. Efforts have been made to diminish the influence of the observed heterogeneity by involving a prior decision to use the random-effect model and sensitivity analysis. In addition, variability in the study design and the selection of patients, controls and the immune labels for Tregs (some studies have identified $CD4^+CD25^+$ T cells as Tregs while others consider $CD4^+CD25^+Foxp3^+$ T cells as Tregs) was present in our meta-analysis. Finally, although a comprehensive literature search strategy and meticulous document retrieval were performed independently by two authors, the fact that the 23 articles included six graduate theses suggests that publication bias may not have been revealed by the asymmetric shape of the funnel plot and the *P* value of Egger's test.

In conclusion, the meta-analysis of available data suggests that there is a significant association between the high expression of Tregs and the development of HCC. Nevertheless, more well-designed clinical studies still need to be done to elucidate the exact relationship between Tregs and tumor development, and not only the

frequency of Tregs either in the circulating or tumor microenvironment.

COMMENTS

Background

Hepatocellular carcinoma (HCC) is still a major health problem worldwide. Increasing number of studies have revealed the immunogenic role of tumors and the mechanisms by which malignant cells escape immune attack. Regulatory T cells (Tregs) play a critical role in tumor escape, but the association between Tregs and HCC is currently unclear.

Research frontiers

Over the past three decades, many studies have been performed to understand the association between the number of Tregs and the pathological stage of liver cancer. However, there have been no systematic reviews to investigate these associations.

Innovations and breakthroughs

Based on this meta-analysis, both the circulating and tissue populations of Tregs in HCC patients were found to be higher than in healthy controls. However, subgroup analyses based on tumor size and other features did not show any difference between the two groups. These findings have not been quantified in previous studies.

Applications

Immunotherapy for HCC has been investigated to fill up the insufficiency of the classic methods. An exploration of the association between Tregs and HCC may help us to understand the mechanism of tumor immunity.

Terminology

Tumor escape refers to the ability of tumors to evade destruction by the immune system. Theories concerning possible mechanisms by which this takes place involve both cellular and humoral immunity, and also co-stimulatory pathways related to CD28 antigens and CD80 antigens. Tregs are a component of the immune system that suppress immune responses of other cells. Tregs come in many forms, with the most well-understood being those that express CD4, CD25, and Forkhead box (Fox)p3 ($CD4^+CD25^+$ regulatory T cells, or Tregs). Mouse models have suggested that modulation of Tregs can treat autoimmune disease and cancer, and facilitate organ transplantation.

Peer review

The authors analyzed the role of Tregs in the development of HCC through a systematic review and meta-analysis, showing that both the circulating and tissue populations of Tregs are higher among HCC patients. The topic is very interesting and the report is well written.

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