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REVIEW – CANCER RESEARCH

Prognostic role of regulatory T cells in lymphoma: a systematic review and meta-analysis

Fei Peng[1] · You Qin[2] · Shidai Mu[1] · Jingwen Li[1] · Lisha Ai[1] · Yu Hu[1,3]

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Abstract

Purpose The regulatory T cells (Tregs) are a subpopulation of lymphocytes that suppress the immune responses. The prognostic value of Tregs in lymphoma patients remains controversial. Thus, we conducted this meta-analysis to clarify the role of Tregs in the prognosis of lymphoma patients.

Methods We searched PubMed, Embase, and Web of Science to obtain eligible studies that evaluated the prognostic factor of Tregs for lymphoma patients. Hazards ratios (HRs) with the matching 95% confidence intervals (95%CIs) were merged to estimate the prognostic value of Tregs.

Results We finally retrieved 23 eligible studies, including a total of 2269 patients. The overall pooled analysis on all types of lymphomas showed that Tregs had a significantly positive association with prolonged overall survival (OS) (HR = 0.633, 95% CI 0.528–0.758) and progression-free survival (PFS) (HR = 0.451, 95% CI 0.261–0.779). Subgroup analysis indicated that high Tregs were significantly correlated with longer OS in Hodgkin lymphoma, diffuse large B cell lymphoma, and natural killer/T cell lymphoma. However, there was no significant association of Tregs with T cell lymphoma and follicular lymphoma.

Conclusions Increased Tregs indicates a better prognosis for patients with lymphoma. Tregs could be used as a valuable prognostic biomarker of lymphoma patients.

Keywords Regulatory T cells · Lymphoma · Prognosis · Meta-analysis

Abbreviations

Tregs	Regulatory T cells
HR	Hazards ratio
CI	Confidence interval
OS	Overall survival
PFS	Progression-free survival
NHL	Non-Hodgkin lymphoma
HL	Hodgkin lymphoma
MDSCs	Myeloid-derived suppressor cells
FOXP3	Forkhead box P3
NOS	Newcastle–Ottawa Quality Assessment Scale
BCL	B-cell lymphoma
NKTCL	Natural killer/T cell lymphoma
TCL	T cell lymphoma
FL	Follicular lymphoma
DLBCL	Diffuse large B cell lymphoma
IPI	International prognostic index
Th cells	T helper cells
CTLs	Cytotoxic T cells
DCs	Dendritic cells
T cons	Conventional T cells
cAMP	Cyclic adenosine monophosphate
IL-10	Interleukin-10
NK cells	Natural killer cells
RS cells	Reed-Sternberg cells
Tfh	T follicular helper cells
IL-2	Interleukin-2

Fei Peng and You Qin contributed equally to this work.

✉ Lisha Ai
ailisha86@126.com

✉ Yu Hu
dr_huyu@126.com

[1] Institute of Hematology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, No. 1277 Jiefang Avenue, Wuhan 430022, Hubei, China

[2] Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China

[3] Collaborative Innovation Center of Hematology, Huazhong University of Science and Technology, Wuhan 430022, China

Introduction

Lymphoma is a neoplasia of the immune system. Non-Hodgkin lymphoma (NHL) is the main subtype, accounting for around 90%, while the remaining 10% is Hodgkin lymphoma (HL) (Shankland et al. 2012). There are slight geographical variations in the incidence of individual subtypes, with NHL being more common and HL relatively rare in Asia (Saito and Matsuoka 2020). It has been estimated that there will be 85,720 newly diagnosed lymphoma patients and 20,910 deaths in the United States in 2020 (Siegel et al. 2020). Although the striking therapeutic advancements have led to substantial improvements in lymphoma outcomes, the hematological malignancy still threatens human life and impairs the quality of life seriously. Therefore, it is urgent to find more reliable prognostic biomarkers for better control of lymphomas.

Immune cells provide an ideal source for the development of novel prognostic biomarkers due to their ease of detection.The immune components play diverse roles in tumor progression, either inhibiting or promoting tumor growth. The immunosuppressive cells, including myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs), are a rare subpopulation that can impair the antitumorimmunity via suppressing the activity and functions of T cells and natural killer cells (Ai et al. 2019; Finn 2012; Gabrilovich 2017; Giallongo et al. 2016; Görgün et al. 2013; Lv et al. 2019). For example, we have reported that MDSCs are linked with worse prognosis in a variety of malignant tumors (Ai et al. 2018). Tregs, another immunosuppressive subset, has drawn much attention in recent decades.

Tregs prevail as a specialized sub-class of $CD4^+$ T cells with positive nuclear marker forkhead box P3 (FOXP3) (Hori et al. 2003). Multiple lines of studies have demonstrated that increased tumor-infiltrating Tregs predict poor prognosis of patients in most solid tumors, including breast cancer, ovarian carcinoma, hepatocellular carcinoma, etc. (Bates et al. 2006; Curiel et al. 2004; Sun et al. 2017). These findings could be properly explained by its immunosuppressive property and tumor-promoting function. Intriguingly, the opposite results have also been reported in some other solid tumors, such as colorectal cancer, esophageal carcinoma, and head and neck cancer(Shang et al. 2015; Xu et al. 2017).

Similarly, the prognostic impacts of Tregs in lymphoma patients are somewhat controversial. Some literature has reported that the cell count of tumor-infiltrating Tregs is a positive prognostic factor in lymphoma (Carreras et al. 2006, 2019; El-Dien et al. 2017; Greaves et al. 2013; Kim et al. 2009; Lam et al. 2020; Lee et al. 2008; Nakayama et al. 2017; Peng et al. 2011; Saifi et al. 2010; Wang et al. 2018). But more and more studies have questioned the correlation of Tregs with lymphoma outcome (Blaker et al. 2016; Chao et al. 2015; Chetaille et al. 2009; Gjerdrum et al. 2007; Gomez-Gelvez et al. 2016; Kelley et al. 2007; Lundberg et al. 2019; Muenst et al. 2009; Nam et al. 2014; Richendollar et al. 2011; Tzankov et al. 2008). Thus, it is urgent to clarify the prognostic value of Tregs in lymphoma patients based on the findings from the published studies, which were conducted independently with small sample size. To this end, we conducted the present quantitative meta-analysis and found that increased tumor-infiltrating Tregs indicates a better prognosis for patients with lymphoma.

Methods

Search strategy

This study was completed following the Standard Guide for Meta-Analysis of Tumor Marker Prognosis Research (Sauerbrei et al. 2018). We systematically searched PubMed, Embase, and Web of Science up to May 2020 to obtain studies regarding the role of Tregs in the outcome of lymphoma patients. We used the following keywords: ("Regulatory T cells" or "Tregs" or "FOXP3") and ("survival" or "outcome" or "prognosis" or "progression" or "mortality" or "recurrence" or "metastasis"). We tried to find more related studies by reviewing the identified reviews, meta-analysis, reports, and other reference lists of related publications. Meanwhile, the "similar articles" function was used to gain more eligible publications.

Selection criteria

Studies that meet the following criteria are included in the present meta-analysis: (i) the prospective or historical cohort studies; (ii) patients diagnosed with lymphoma; (iii) the studies focusing on the association between Tregs and overall survival (OS) or progression-free survival (PFS); (iv) studies providing competent information to calculate hazard ratio (HR) and 95% confidence interval (CI) if HR is not reported directly. In contrast, the exclusion criteria are as follows: (i) case reports, reviews, meeting reports, letters, etc.; (ii) multiple published reports; (iii) studies without enough data to analyze.

Data extraction

Eligible studies were extracted by two researchers independently. Any inconsistency was assessed by the third researcher. The main information of the included studies and patients was collected, including the year of publication, the

name of the first author, country of the study, sample size, follow-up time, age range, and survival data.

Each study was evaluated by two reviewers independently, based on the Newcastle–Ottawa Quality Assessment Scale (NOS). If disagreements occur between researchers, a third researcher will solve differences by discussion. NOS uses a star rating system with a total score of 9 points. Studies scored more than seven points were considered as high-quality studies, otherwise as low-quality studies.

Statistical methods

The effect of Tregs on lymphoma prognosis was quantified by the HR. We extracted HR and 95% CI directly from the literature. If they were not reported, we estimated them by using the methods reported by Parmer et al (Parmar et al. 1998). Heterogeneity among the included studies was analyzed using the I^2 test and χ^2 test (Higgins et al. 2003). A random-effects model was used in the meta-analysis in case of significant heterogeneity ($I^2 \geq 50\%$). Otherwise, the fixed-effects model was used. Significant heterogeneity was analyzed by subgroup analysis and meta-regression. Publishing bias was evaluated by Egger's test and Begg's funnel plot (Egger et al. 1997). The level of significance was set at 0.05. All analyses were performed using Stata 12.0 software.

Results

Selection and characteristics of included studies

A total of 1951 related publications were obtained in the initial retrieve. After screening, 23 studies with a total of 2269 patients were finally included (Fig. 1). The basic characteristics of the included studies were shown in Table 1, displaying a wide distribution of 12 countries. There were 6 studies on HL and 17 on NHL, the latter consisting of 12 on B cell lymphomas (BCL), 3 on natural killer/T cell lymphoma (NKTCL), and 2 on T cell lymphomas (TCL). Of the 12 studies on BCL, 5 focused on follicular lymphoma (FL) and 7 on diffuse large B cell lymphoma (DLBCL). All the studies reported OS, while 9 studies, a total of 732 patients, reported PFS. The NOS scores for all the included studies ranged from 5 to 8.

The prognostic role of FOXP3$^+$ Tregs in the survival of all lymphoma patients

We included 23 studies that reported OS data. Patients with high tumor-infiltrating Tregs density had longer OS with a pooled HR of 0.633 (95% CI 0.528–0.758, $P < 0.001$) and heterogeneity was significant ($\chi^2 = 86.78$, $P < 0.001$; $I^2 = 74.6\%$) (Fig. 2a). Additionally, 9 studies

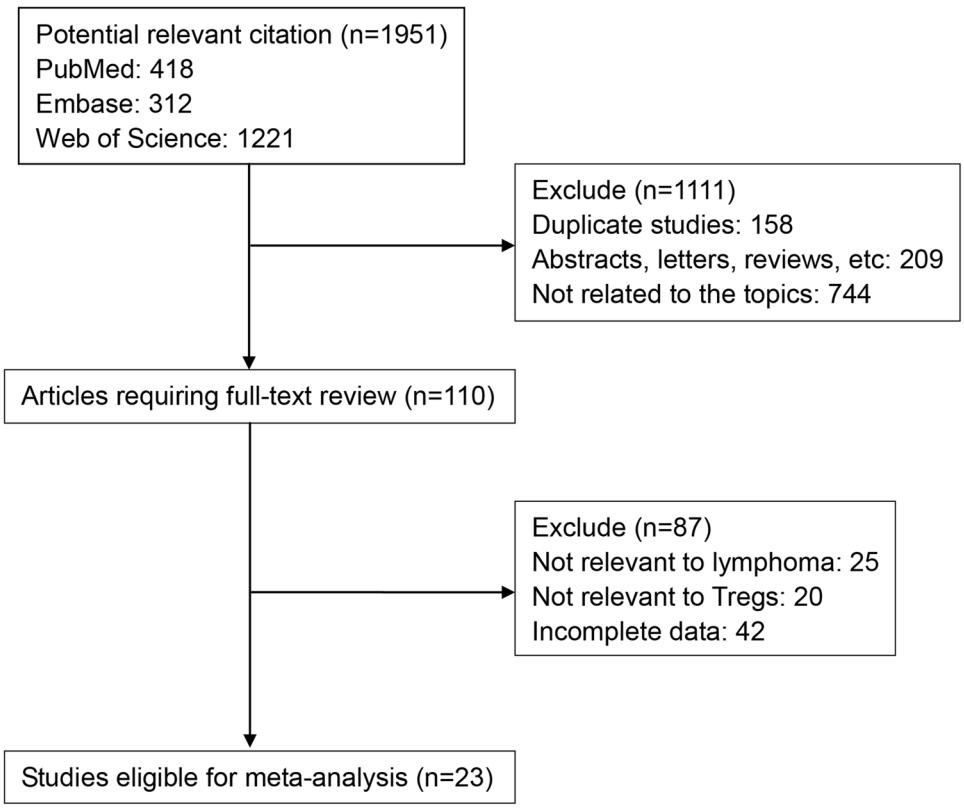

Fig. 1 Flow diagram of selecting relevant studies included in the meta-analysis

Table 1 Characteristics of studies included in the meta-analysis

Study	Year	Country	Cancer type	Sample size	Cut off	Age	Follow-up month median (range)	Method	Treatment	NOS score	HR	HR method
Greaves, Paul	2013	UK	HL	113	125/HPF	NR	16.5 (2–40)	Tissue microarrays	No	8	Estimated	OS
Kelley, T. W	2007	USA	HL	98	25/HPF	29 (4–84)	103.2 (11–238.8)	Tissue microarrays	No	6	Estimated	OS, PFS
Chetaille, B	2009	France	HL	132	IHC score = 1	NR	NR	Whole-tissue sections	No	8	Reported	OS, PFS
Muenst, S	2009	Switzerland	HL	244	27 cell/mm^2	NR	NR	Whole-tissue sections	No	6	Reported	OS
Wang, Chaoyu	2018	China	HL	95	25%	31.5 (7–82)	NR	Whole-tissue sections	No	5	Reported	OS, PFS
Tzankov, A.1	2008	Switzerland	HL	280	27 cell/mm^2	42	244	Tissue microarrays	No	8	Estimated	OS
Nakayama, S	2017	Japan	DLBCL	82	4000 cell/cm^2	68.3	NR	Whole-tissue sections	No	6	Reported	OS
Carreras, Joaquim	2019	Western	DLBCL	106	NR	57 (26–88)	97.56 (0.24–276.24)	Whole-tissue sections	No	5	Estimated	OS
El-Dien, Marwa M	2017	Egypt	DLBCL	44	NR	54 (12–82)	9.5 (1–105)	Whole-tissue sections	No	6	Estimated	OS
Nam, S. J	2014	Korea	DLBCL	109	NR	NR	43 (16–178)	Whole-tissue sections	No	6	Estimated	OS, PFS
Chao, C	2016	USA	DLBCL	80	NR	NR	NR	Tissue microarrays	No	7	Estimated	OS
Gomez-Gelvez, J. C	2016	USA	DLBCL	74	17%	59.1 (20–91)	49.2 (7.2–144)	Tissue microarrays	Yes	6	Reported	OS, PFS
Lee, Na-Ri	2008	Korea	DLBCL	96	2.3%	58 (20–83)	16 (1–132)	Tissue microarrays	No	6	Reported	OS
Saifi, M	2010	France	FL	100	86 cell/mm^2	58 (48–69)	24 (12–108)	Whole-tissue sections	No	6	Estimated	OS
Tzankov, A.2	2008	Switzerland	FL	86	4.5 cell/mm^2	57	126	Tissue microarrays	No	8	Estimated	OS
Carreras, J	2019	Spain	FL	97	5%	55 (26–93)	5.6 (1.1–13.0)	Whole-tissue sections	No	8	Estimated	OS
Blaker, Y. N	2016	Norway	FL	52	Median	54 (34–77)	118 (68–300)	Tissue microarrays	Yes	7	Reported	OS, PFS
Richendollar, B. G	2011	USA	FL	88	3%	58 (24–89)	(6–19.7)	Tissue microarrays	No	6	Reported	OS
Kim, W. Y	2009	Korea	NKTCL	64	50 cell/0.4mm^2	50 (10–79)	NR	Whole-tissue sections	No	8	All	OS, PFS
Lam, Sio Teng	2020	China	NKTCL	81	52.5/HPF	45 (16–79)	28.9 (1.127–11.493)	Whole-tissue sections	Yes	6	Reported	OS, PFS
Peng, R. J	2011	China	NKTCL	27	22.89/HPF	41 (13–68)	NR	Whole-tissue sections	No	7	Reported	OS, PFS
Lundberg, J	2019	Sweden	TCL	35	200 cell/mm^2	57 (18–73)	141.6 (68.4—172.8)	Whole-tissue sections	No	6	Estimated	OS
Gjerdrum,L.M	2007	Denmark	TCL	86	Median	66 (33–88)	120 (2–360)	Whole-tissue sections	No	8	Reported	OS

HL Hodgkin lymphoma, *DLBCL* diffuse large B cell lymphoma, *FL* follicular lymphoma, *NKTCL* natural killer/T cell lymphoma, *TCL* T cell lymphoma

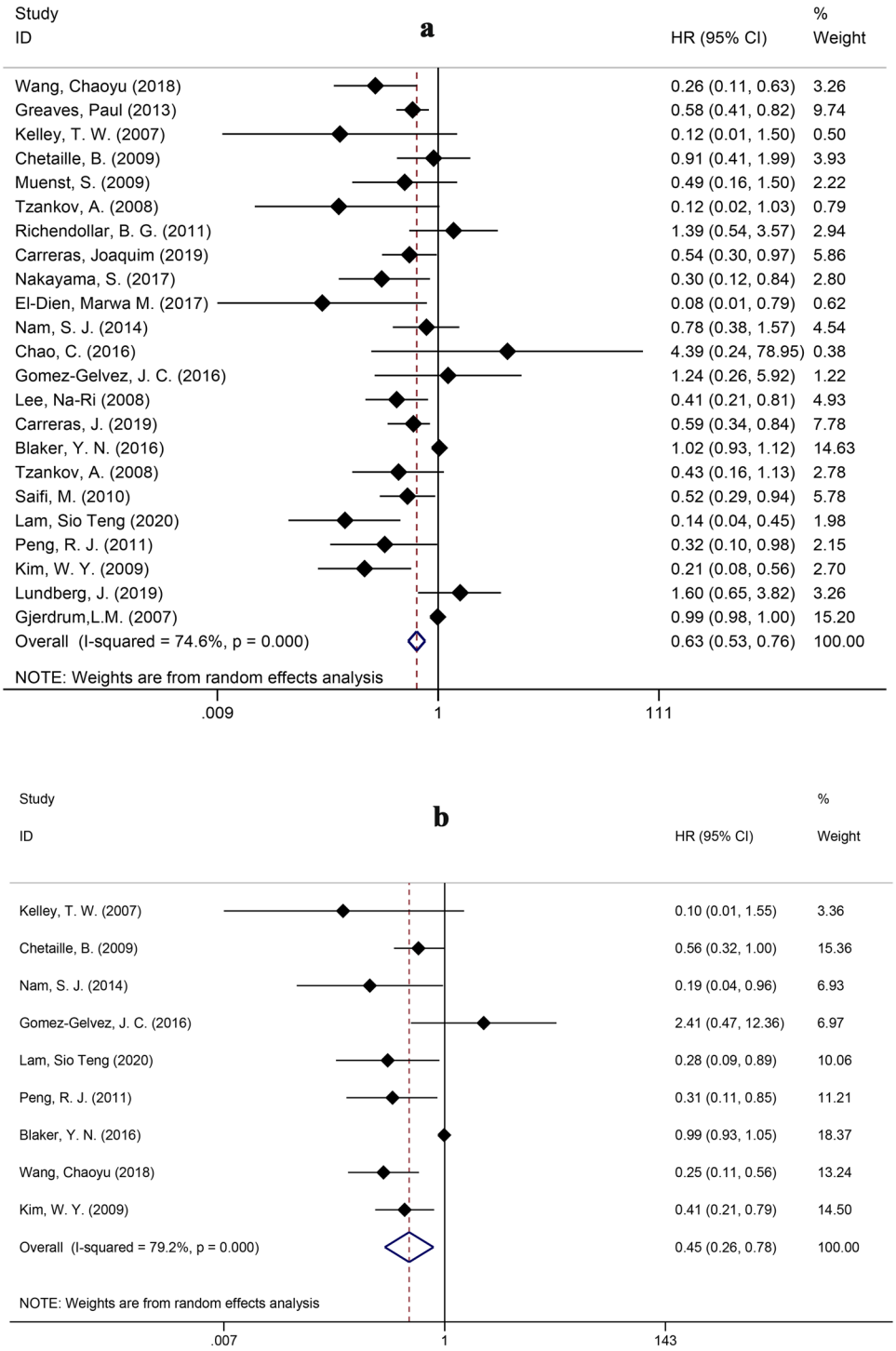

Fig. 2 Forest plots showing the relationship between Tregs and the prognosis of lymphoma. **a** OS; **b** PFS

reported PFS. Similarly, elevated Tregs were associated with longer PFS, indicating a prolonged survival (HR = 0.451, 95% CI 0.261–0.779, $P = 0.004$). Statistical heterogeneity among these 9 studies was also observed ($\chi^2 = 38.47$, $P < 0.001$; $I^2 = 79.27\%$) (Fig. 2b).

Group analysis on the role of FOXP3$^+$ Tregs in the prognosis for different types of lymphomas

To demonstrate the prognostic value of Tregs in diverse subtypes of lymphomas, we conducted a subgroup analysis

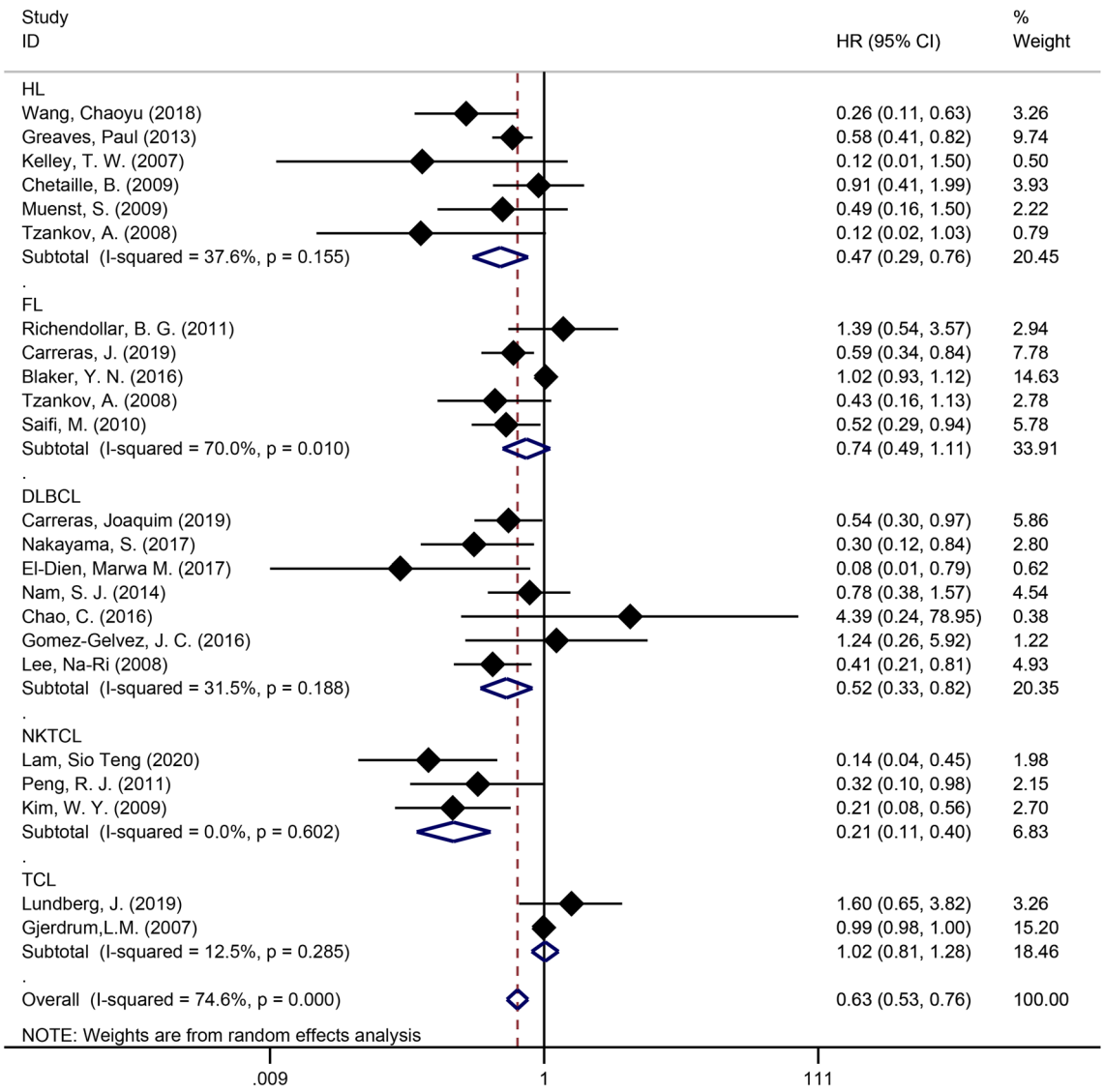

Fig. 3 Subgroup analysis of OS by subtype of lymphoma. *HL* Hodgkin lymphoma, *FL* follicular lymphoma, *DLBCL* diffuse large B cell lymphoma, *NKTCL* natural killer/T cell lymphoma, *TCL* T cell lymphoma

on individual lymphomas, including HL, FL, DLBCL, NKTCL, and TCL (Fig. 3). High density of Tregs was linked with longer OS in HL (HR = 0.471, 95% CI 0.293–0.760, $P = 0.002$), DLBCL (HR = 0.523 95% CI 0.334–0.818, $P = 0.004$), and NKTCL (HR = 0.211, 95% CI 0.112–0.399, $P < 0.001$), whereas no significant correlation of Tregs with the OS for TCL patients (HR = 1.017, 95% CI 0.809–1.280, $P = 0.883$) and FL patients (HR = 0.738, 95% CI 0.490–1.110, $P = 0.144$) were found. Heterogeneity was significant for FL ($\chi^2 = 13.35$, $I^2 = 70.0\%$), but not significant for HL ($\chi^2 = 8.02$, $I^2 = 37.6\%$), DLBDL ($\chi^2 = 8.75$, $I^2 = 31.5\%$), NKTCL ($\chi^2 = 1.01$, $I^2 < 0.1\%$), and TCL ($\chi^2 = 1.14$, $I^2 = 12.5\%$).

Risk-adjusted analysis

Among all the included studies, 12 reported the results of a multi-factor analysis of OS (Fig. 4a). The risk-adjusted analysis showed that upregulated Tregs indicated a better OS with a pooled HR of 0.679 (95% CI 0.551–0.837, $P < 0.001$). But the heterogeneity was significant ($\chi^2 = 50.21$, $I^2 = 78.9\%$). This finding implies that the high density of tumor-infiltrating Tregs was an independent prognostic factor of the OS in lymphoma patients.

Only five studies provided the multivariate-adjusted analysis of PFS (Fig. 4b). The pooled HR of the multivariate-adjusted analysis showed that the density of Tregs was

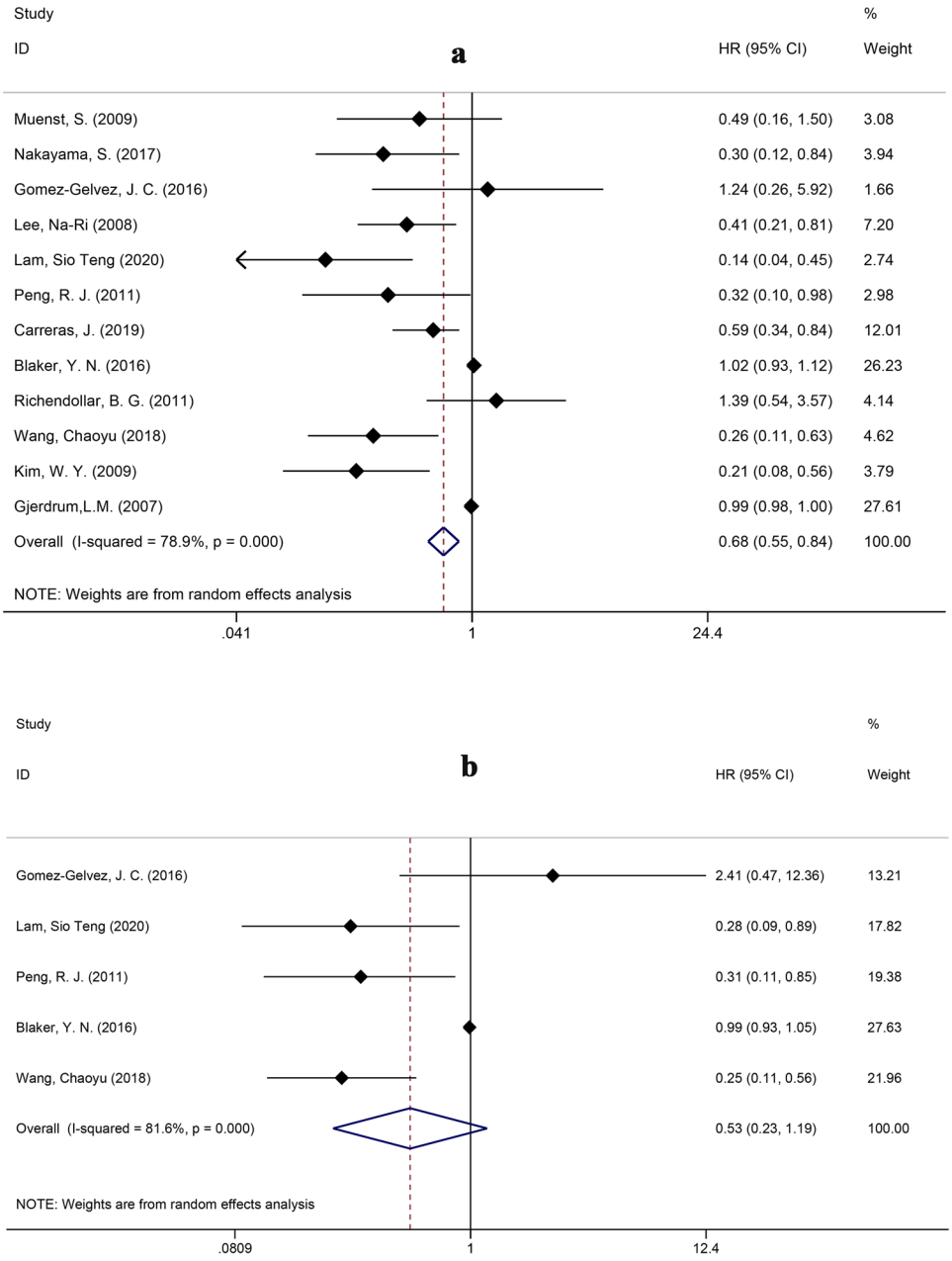

Fig. 4 Forest plots of multivariate analysis showing the relationship between Tregs and lymphoma. **a** OS; **b** PFS

not significantly associated with PFS (HR = 0.525, 95% CI 0.231–1.195, $P = 0.125$).

Subgroup analysis and sensitivity analysis

To verify the source of heterogeneity, we performed the meta-regression and sensitivity analysis for OS (Table 2). Studies were grouped according to the region (Eastern or Western), sample size (≥ 100 or < 100), study quality (NOS scores ≥ 7 or < 7), treatment (yes or no), and detection method (whole-tissue sections or tissue microarrays). A similar association of Tregs with OS was acquired in the subgroup analysis, also with significant heterogeneity. However, the heterogeneity was slightly reduced in the subgroup analysis based on the region.

Further, we conducted a sensitivity analysis. As shown in Fig. 5a, studies by Gjerdrum et al. (Gjerdrum et al. 2007) and Blaker et al. (Blaker et al. 2016) had an evident impact on the results of OS, suggesting that these two studies may be the main source of heterogeneity. After excluding these two studies, the pooled HR was 0.508 (95% CI 0.392–0.657) for OS with lower heterogeneity ($\chi^2 = 36.21$, $P = 0.005$; $I^2 = 44.8\%$). Similarly, after dropping the study of Blakeret al, the pooled HR was 0.387 (95% CI 0.257–0.585) for PFS with lower heterogeneity ($\chi^2 = 9.61$, $P < 0.001$; $I^2 = 27.1\%$) (Fig. 5b), suggesting that our results were reliable.

Table 2 Subgroup analysis and meta-regression

Subgroup analysis	No. of studies	No. of patients	Pooled HR (95% CI)		Overall effect *P* value	Meta regression (*P* value)	Heterogeneity	
			Fixed	Random			I^2 (%)	*P* value
Region						0.015		
Western	14	1565	0.986 (0.975, 0.997)	0.844 (0.725, 0.982)	0.028		60.90%	0.002
Eastern	9	704	0.385 (0.289, 0.513)	0.354 (0.244, 0.515)	< 0.001		35.30%	0.136
Sample size						0.988		
< 100	16	1185	0.986 (0.975, 0.997)	0.668 (0.544, 0.821)	< 0.001		76.80%	< 0.001
> 100	7	1084	0.589 (0.462, 0.751)	0.589 (0.462, 0.751)	< 0.001		0.00%	0.561
NOS score						0.503		
< 7	13	1017	0.522 (0.404, 0.675)	0.496 (0.332, 0.740)	0.001		53.00%	0.012
> 7	10	1252	0.986 (0.975, 0.997)	0.771 (0.645, 0.921)	0.004		76.10%	< 0.001
Detection method						0.813		
Whole-tissue sections	14	1288	0.985 (0.974, 0.996)	0.505 (0.353, 0.722)	< 0.001		78.10%	< 0.001
Tissue microarrays	9	981	0.963 (0.883, 1.051)	0.664 (0.429, 1.028)	0.066		70.70%	< 0.001
Treatment						0.716		
Yes	3	207	1.012 (0.923, 1.108)	0.547 (0.411, 0.729)	< 0.001		81.60%	0.004
No	20	2062	0.985 (0.974, 0.996)	0.573 (0.135, 2.119)	0.404		74.90%	< 0.001

HR hazards ratio, *NOS* Newcastle–Ottawa Quality assessment scale

Intriguingly, there was no change in the relationship between Tregs and the OS in HL, DLBCL, NKTCL, and TCL after excluding the studies by Gjerdrum et al. (2007) and Blaker et al. (2016). However, after excluding the study of Blaker et al. (2016), the subgroup analysis showed that high Tregs were linked with longer OS in FL (HR = 0.613, 95% CI 0.423–0.889, $P = 0.010$).

Publication bias

To investigate publication bias, we conducted Begg's test and Egger's test. Grounded on the results of sensitivity analysis, two studies reported by Gjerdrum et al. and Blaker et al. were excluded. The Funnel plot was symmetric in both OS (Fig. 6a) and PFS (Fig. 6b). The results of Begg's test (OS: $P = 0.131$, PFS: $P = 0.266$) and Egger's test (OS: $P = 0.154$, PFS: $P = 0.58$) indicated that there was no publication bias regarding the included studies.

Discussion

For some types of lymphoma, the stage is inadequate to determine patients' outcome (Matasar and Zelenetz 2008). In this case, other factors, like the international prognostic index (IPI), can be utilized to evaluate the prognosis and classify patients into high-risk or low-risk groups. However, IPI is only applicable to some specific types due to the heterogeneity of lymphomas. Thus, it is urgent to develop more prognostic biomarkers so that hematologists and oncologists can clarify the prognosis of lymphoma patients more accurately. Tregs, an immunosuppressive subpopulation of T cells, play a key role in tumor development by modulating the tumor immune microenvironment. To explore the value of Tregs in the outcome of lymphoma, we conducted this study. To the best of our knowledge, it is the first meta-analysis to analyze the association of Tregs with the prognosis of lymphoma patients.

Our meta-analysis study included 23 publications with a total of 2269 patients. We showed that lymphoma patients with a higher density of tumor-infiltrating Tregs had significantly longer OS and PFS. The analysis of OS presented significant heterogeneity ($I^2 = 74.6\%$). To identify the source of heterogeneity, we performed subgroup analysis and mate-regression. Our results in Table 2 show that the region of studies may be one key source of heterogeneity. Moreover, we identified two studies that largely attributed heterogeneity through sensitivity analysis (Blaker et al. 2016; Gjerdrum et al. 2007). After excluding those studies, the association of Tregs with the prognosis was similar to the previous analysis, suggesting that our results are quite reliable.

Our study confirmed that elevated Tregs was associated with better outcomes in lymphoma patients, which is in disagreement with the studies on most types of solid tumors (Shang et al. 2015). The potential underlined mechanisms regarding the positive relationship between Tregs and lymphoma outcomes may be due to the specific immunosuppressive functions of Tregs. First, Tregs may directly induce the death of malignant B cells, which might be supported by the study reported by Lindqvist et al. (2011). In this study,

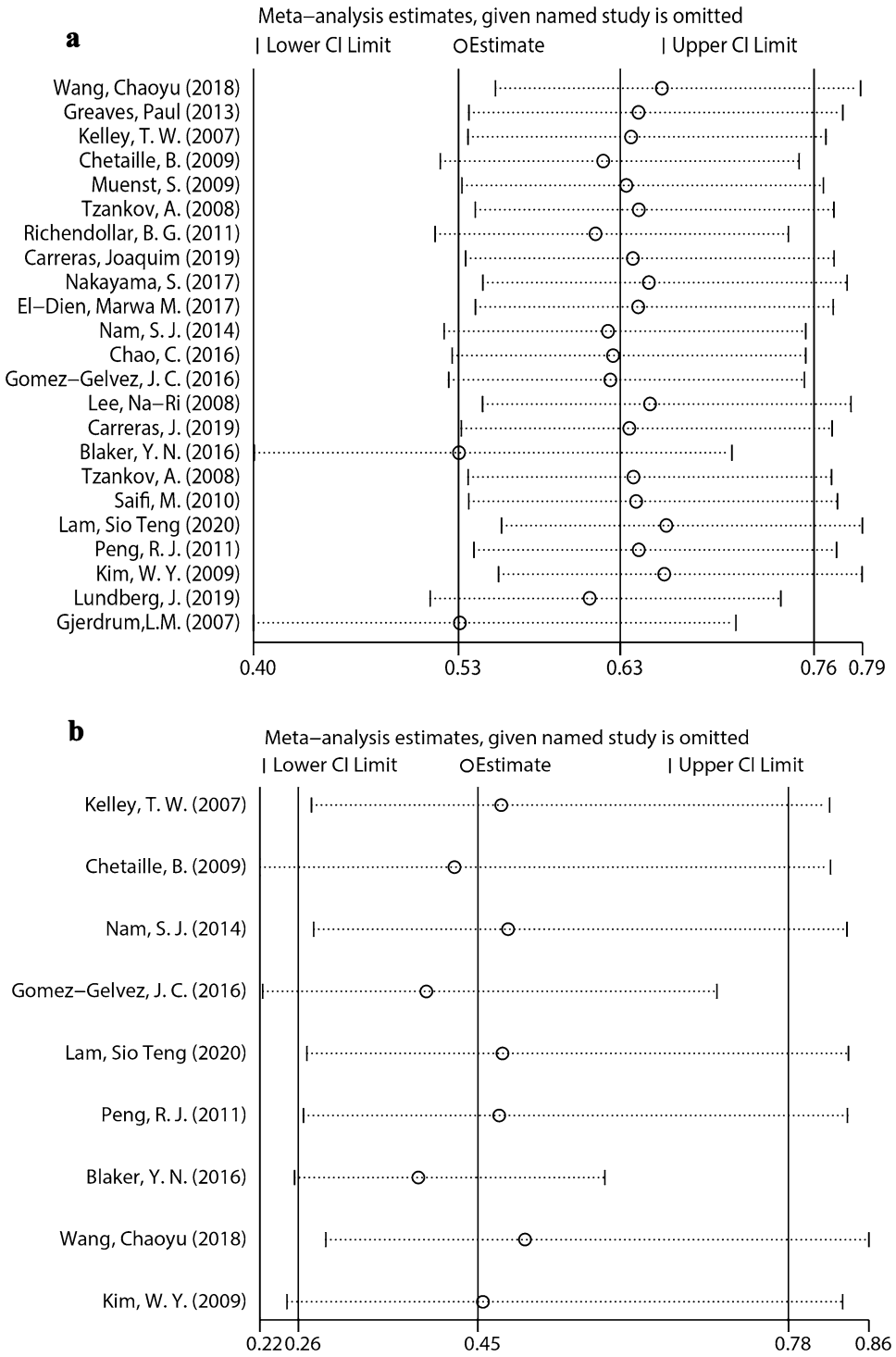

Fig. 5 Sensitivity analysis of the overall pooled study. **a** OS; **b** PFS

the authors found that $CD4^+FOXP3^+$ Tregs isolated from patients with B cell malignancy are able to kill autologous leukemic B cells in vitro. Second, Tregs may suppress the T helper (Th) cells and promote the apoptosis of cytotoxic T cells (CTLs) (Najafi et al. 2019), which might properly explain the reasons for the positive prognostic value of Tregs in NKTCL. Additionally, the lack of functional Th cells may impair B cells (Ueno 2016), which might be an indirect way of Tregs to affect the prognosis of BCL. Third, Tregs can function in suppressing the activity of other immune components, such as dendritic cells (DCs) and NK cells (Ring et al. 2010, 2015).

The molecular mechanisms regarding the immunosuppressive properties of Tregs in hematological malignant

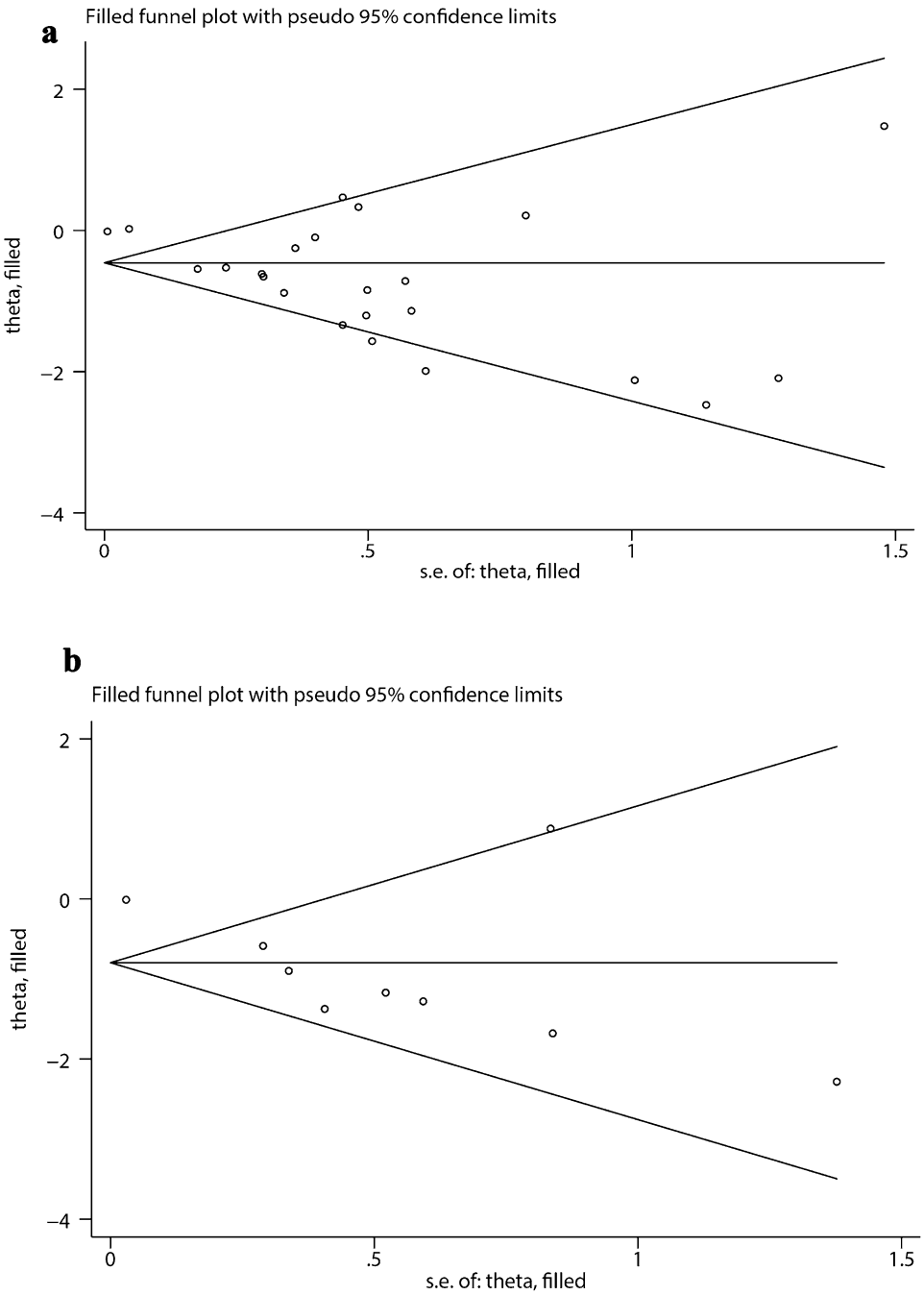

Fig. 6 Publication bias of the present meta-analysis. **a** OS; **b** PFS

diseases have been extensively reported. First, Tregs inhibits the function of conventional T cells (Tcons) and DCs through increasing cyclic adenosine monophosphate (cAMP) expression (Borsellino et al. 2007), leading to inhibition of the proliferation and cytokine production of Tcons (Rueda et al. 2016). Also, with decreased expressions of costimulatory molecules and increased expressions of inhibitory molecules, elevated expression of cAMP can inhibit the antigen-presenting function of DCs (Ring et al. 2010, 2015). Besides, Tregs suppresses immune response through releasing inhibitory immunomodulatory molecules, such as Interleukin-10 (IL-10) and transforming growth factor-β (TGF-β). IL-10 can promote the depletion of T cells in the tumor by regulating the expression of inhibitory receptors (Li et al. 2017; Sawant et al. 2019). TGF-β can impair the activity of natural killer cells (NK cells) and CTLs (Najafi et al. 2019). Additionally, Tregs also can induce NK cells and $CD8^+$ T cell death dependent on Granzyme B and perforin (Cao et al. 2007). Collectively, Tregs exerts immunosuppressive effects through direct contact and release of cytokines.

Lymphomas are a group of hematological malignancies consisting of various subtypes with substantial heterogeneity and diversity of clinical and biological characteristics. Thus, it is reasonable to sub-analyzed the prognostic role of Tregs in different subtypes of lymphoma. Our subgroup analysis showed that a higher density of Tregs was associated with better prognosis in HL, DLBCL, and NKTCL, but with a neutral prognostic claim in TCL and FL. Reed-Sternberg cells (RS cells), characteristic of HL, are maintained by various cytokines. The background of inflammation suppressed by Tregs can inhibit cytokine production. There are many potential pathways as RS cells express various surface receptors (Khan 2006). DLBCL is a subtype of lymphoma with high incidence. Tregs inhibit B cell proliferation directly by inducing its apoptosis (Zhao et al. 2006). Besides, Tregs can inhibit the function of B cells indirectly via suppressing the function of T follicular helper cells (Tfh) (Marinova et al. 2007). About NKTCL, in addition to inhibiting NK cells function and inducing NK cells to death, Tregs highly express CD25, which is a high-affinity receptor of IL-2. IL-2 is necessary for the proliferation and maintenance of NKT cells. Tumor-infiltrating Tregs may compete for IL-2 with tumor cells, resulting in the deprivation of IL-2. So, Tregs improve the clinical prognosis and play the antitumor roles in NKTCL. In TCL, the function of Tregs seems particularly complicated. On one hand, the malignant cells are T lymphocyte, which could be suppressed by Tregs. On the other hand, some studies showed that the cancerous cells could be Tregs-derived (Bonzheim et al. 2008; Roncador et al. 2005). We need more research about the relationship between TCL or FL and Tregs.

Some limitations should be noted in this meta-analysis. First, considering the limited number of studies on NKTCL ($n=3$) and TCL ($n=2$), the conclusion regarding these subtypes should be interpreted with caution. Second, after excluding two studies that largely attribute heterogeneity, there was still heterogeneity yet, which might be caused by laboratory testing methods and reagents. Third, the literature enrolled did not include unpublished studies. Although the publication bias was tested, the prognostic role of Tregs in lymphoma patients may be overestimated.

Conclusions

Lymphoma patients with a higher density of tumor-infiltrating Tregs have a better prognosis. This is helpful to develop individualized treatment strategies. It is meaningful to conduct further research about Tregs and its subtypes, which can help us find new immunotherapy targets.

Author contributions FP and YQ collected and analyzed the data, wrote the paper. FP, YQ, SM and JL analyzed the data and wrote the paper. LA and YH conceived and designed this study, analyzed the data, wrote the paper. All authors read and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest The authors have declared that no competing interest exists.

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