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Journal of Human Physiology
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ARTICLE

The Regulatory B Cell in Active Systemic Lupus Erythematosus Patients: A Systemic Review and Meta-analysis

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ARTICLE INFO

Article history
Received: 23 December 2019
Accepted: 7 February 2020
Published Online: 31 May 2020

Keywords:
Regulatory B cell
Systemic lupus erythematosus
Percentage
Autoimmunity
Meta-analysis

ABSTRACT

Background: The study of regulatory B cells (Bregs) in systemic lupus erythematosus (SLE) has been in full swing in recent years, but the number and function of Bregs in SLE patients have also present quite contradictory results. Therefore, we conducted a meta-analysis to verify the changes in Bregs in active SLE. Methods: We identified studies reporting the proportions of Bregs in SLE patients by searching Pubmed, Embase, Web of Science, Cochrane and CNKI. Due to the degree of heterogeneity is very high, we used a random effects model to assess the mean differences in percentages of Bregs between active SLE and controls. Then, sensitivity analysis and subgroup analysis were performed to verify potential sources of heterogeneity. Results: Seven eligible articles involving 301 active SLE patients and 218 controls were included in the meta-analysis. The pooled percentages of Bregs were found no significant difference between active SLE patients and healthy controls [0.259, (−1.150, 1.668), p = 0.719], with great heterogeneity (I^2 = 97.5%) . The result of sensitivity analysis showed that exclusion of any single study or single article did not materially resolve the heterogeneity, but after excluding the article conducted by Cai X and his colleagues, the percentages of Bregs were significantly higher in active SLE than those in controls [1.394, (0.114,2.675), p = 0.033]. The results of subgroup analysis revealed that when the disease activity was judged by SLEDAI score ≥ 5, the percentages of Bregs were significantly lower in the SLE groups than in the control groups[-1.99,(-3.241,-0.739), p = 0.002], but when the threshold of SLEDAI score ≥ 6 chosen for active SLE, the percentages of Bregs were significantly increased in the SLE groups[2.546,(1.333,3.759), p < 0.001]. Meanwhile, other subgroup analysis based on the different phenotypes of Bregs, diagnostic criteria, enrolled research countries, treatment status, and organ involvement did not differ in proportion of Bregs between SLE patients and controls. Conclusions: The study implies that Bregs may play a role in the pathogenesis of active SLE, and the thresholds of SLEDAI score to distinguish between active and inactive SLE patients are important factors affecting the percentages of Bregs.

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 DOI: https://doi.org/10.30564/jhp.v2i1.1594

1. Introduction

Systemic lupus erythematosus (SLE) is an autoimmune connective tissue disease involving multiple organs, which is common in young women. There are excessive activation of various immune cells and secretion of autoantibodies, and antigen-antibody complexes formed by binding of autoantibodies to antigens are deposited on skin, joints and other positions to cause tissue damage and diseases. In recent years, the role of regulatory B cells (Bregs) in SLE has been attracted widespread attention. This type cells interact with $CD4^+$ T cells by secreting cytokines , directly contacting among cells, and involving in immune responses, which are closely related to the pathogenesis and disease activity of SLE.

Bregs are a subgroup of B cells, which play a role in immune regulatory mainly through the secretion of regulatory cytokines such as interleukin(IL)-10 and transforming growth factor (TGF) –β and expression of inhibitory antibodies that inhibit pathogenic T cells and autoreactive B cells [1]. The hypothesis of regulatory B cells can suppress the immune system was first proposed in the 1970s, and they are capable of producing inhibitory antibodies to maintain this inhibitory function [2]. The regulatory function of B cells in autoimmune diseases was first discovered by Janeway et al. in experimental autoimmune encephalomyelitis (EAE) in murine. They found B cells are not required for EAE induction, but may play an immunomodulatory role in EAE from acute to complete recovery [3]. With the further research on Bregs, it has been found that there are many subtypes of Bregs, such as marginal B cells, IL-10-producing Bregs (Br1 or B10), TGF-β-producing Bregs (Br3), Foxp3-expressing Bregs and other Bregs that have cytotoxic effects [4].

Human Bregs are categorized mainly as either transitional ($CD19^+CD24^{high}CD38^{high}$) or memory ($CD24^{high}CD27^+$) [5,6]. The production of proinflammatory factors by $CD4^+$T cells can be inhibited by $CD19^+CD24^{high}CD38^{high}$ Bregs, relying on IL-10, CD80 and CD86, but not TGF-β [6]. $CD19^+CD25^{high}CD86^{high}CD1d^{high}$ Bregs produce IL-10 and TGF-β that inhibit $CD4^+$T cells proliferation and enhance expression of FoxP3 and T lyphocyte antigen 4 in regulatory T cells [7]. $CD24^{high}CD27^+$ Bregs also regulate the production of TNF-α by producing IL-10 [6]. Therefore, human Bregs are not a single phenotype, but regardless of phenotype, most of their regulatory function depends on IL-10. Although there are few studies on human regulatory B cells, evidence suggested that they may become targets for the treatment of human immune diseases in the future.

Despite these evidences, we still lack confidence in the beneficial effects that therapeutic Bregs may have on SLE patients. The use of Breg-based therapies should be based on changes in the number of Bregs and/or impaired regulatory function associated with the pathogenesis of SLE. However, the results of studies on the number of Bregs in active SLE patients and normal healthy people are quite contradictory; the frequency of Bregs in SLE patients is reduced or increased [8-14]. Importantly, the role of Bregs in SLE is also controversial. It is conceivable that quantifying Breg's strategy is crucial to draw conclusions about Breg subtypes. In addition, differences in patients recruitment (research country, diagnostic criteria, treatment status, disease activity, organ involvement) may also be the cause of significant differences in the literature. However, to the best of our knowledge, no source of these inconsistent results has been studied. It is still unclear that the quantitative and qualitative changes about Bregs in SLE, but immunotherapy based on Bregs shows promising therapeutic power, thus we performed this meta-analysis to obtain more information about Bregs in SLE patients, explore the reasons for inconsistent sources of results, and gain a more detailed understanding of the role of Bregs in the pathogenesis of SLE.

2. Methods

2.1 Search Strategy

The literature search was conducted in Pubmed, Embase, Web of Science, Cochrane and CNKI using the MeSH terms "regulatory B cell" and "systemic lupus erythematosus" and their combination. We searched for relevant studies that were updated to October 20, 2019. All potentially eligible articles were also considered except for murine experiments, reviews and conference abstract superseded by publication. There were no limits on geographical location and ethnicity.

2.2 Eligibility Criteria

Studies that fulfilled the following criteria were included: (1) evaluating the levels of Bregs in SLE patients and controls; (2)the levels of Bregs were presented as ratio of Bregs to total lymphocytes(%); (3) available as a full text article; (4) providing mean (standard deviation/ standard error) or median (range/ interquartile range); (5) case-control study. Reviews, studies about murine experiments, conference abstracts that were not published as full-length articles were not included.

2.3 Data Extraction

Two independent researchers selected and recorded eligible articles. The other researchers were consulted to reach a consensus when any divergence occurred. The following

DOI: https://doi.org/10.30564/jhp.v2i1.1594

information was extracted from the studies: first author's name, publication time, regions where the authors performed studies, diagnostic criteria, Breg definition, treatment status, threshold of SLEDAI chosen to define active SLE, the number of patients and controls, the frequency of Bregs(%). When the medians and ranges (or interquartile ranges) were provided in studies instead of means and standard deviations, we calculated the means and standard deviations by estimation methods [15]. The quality of included studies was evaluated by the Newcastle-Ottawa Quality Assessment Scale (NOS).

2.4 Statistical Analysis

We used the I^2-statistic to explore the heterogeneity among studies. The I^2 values of 25, 50, and 75%, respectively, were used as evidence of low, medium, and high heterogeneity. When the pooled results were in high heterogeneity, a random effects model was used, and a fixed-effects model was used in the case of low heterogeneity or no heterogeneity. We performed other analysis when heterogeneity was high, including subgroup analysis and publication bias to explore heterogeneity. We explored the heterogeneity of researches by drawing forest plots to visualize the results more intuitively. By examining funnel plot asymmetry using the Begger and Egger tests ($p \geq 0.05$), we assessed the publication bias. We also performed a sensitivity analysis to test the robustness of the original results. All statistical analysis were performed using Stata software (ver.15.0). This meta-analysis was conducted according to the PRISMA guidelines.

3. Results

3.1 Literature Search

We searched the database for 1779 articles that might be eligible. The flow chart about the screening process of literatures is shown in Figure 1. We excluded 1677 articles by screening headlines and abstracts. Then 16 duplicated articles were excluded, 15 articles were not case-control trials, 15 articles were not for SLE patients, 14 articles were conference abstract superseded by publications, 17 articles did not provide relevant data, and 18 articles could not obtain full-text information. Therefore, this meta-analysis included a total of seven articles [8-14].

3.2 Study Characteristics

All main characteristics of the included studies are presented in Table 1. These studies were published between 2014 and 2019. The analysis included 301 active SLE patients and 218 controls from seven eligible articles. Of these articles, five were conducted in China [8,10,12-14], one in Israel [11] and one in Germany [9]. The diagnose criteria of SLE varied across studies. All controls were healthy people without any autoimmune disease. We regarded all studies as case-control studies and scored them using the NOS, and all studies had a scored of 5-6.

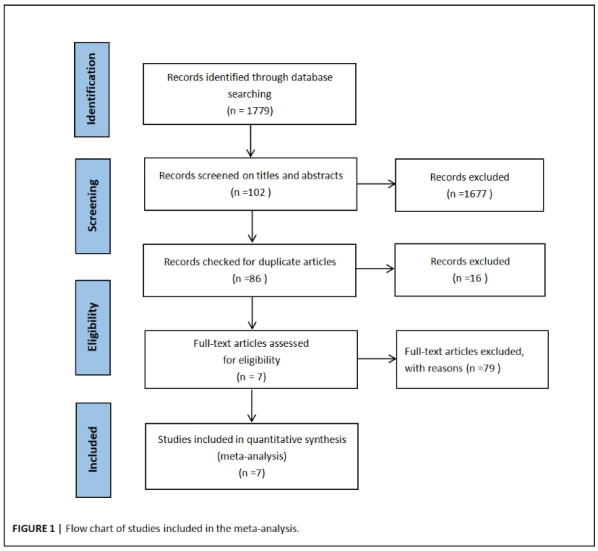

FIGURE 1 | Flow chart of studies included in the meta-analysis.

Table 1. Characteristics of studies included in the meta-analysis

References	Region	Diagnosis criteria	Treatment status	Threshold of SLEDAI for active SLE	Breg definition	Case (n)	Control (n)	Bregs in case (mean±SD,%)	Bregs in control (mean±SD,%)	NOS score
Cai X et al.	China	1997	Not report	≥5	IL-10+CD19+	38	20	1.54±0.64	4.35±1.00	6
					CD19+CD24highCD38high	38	20	1.26±0.45	3.14±0.87	
Heinemann K et al.	Germany	*ACR	Partial treated	>4	IL-10+	34	21	5.50±4.80	17.00±7.00	5
					CD19+CD24highCD38high	34	21	1.60±2.60	1.50±1.10	
Wang H et al.	China	1982	Partial treated	>5	CD19+CD24highCD38high	30	30	2.70±1.97	0.38±0.33	5
Vadasz Z et al.	Israel	1992	Untreated	Not report	CD19+CD25high	21	20	18.50±3.05	11.00±1.65	5
Wang T et al.	China	1997	Not report	Not report	CD19+CD24highCD38high	56	35	39.83±21.39	8.74±3.97	5
Yang X et al.	China	1997	Treated	≥6	CD19+CD5+CD1dhigh	16	15	4.90±1.27	1.63±0.99	5
					IL-10+CD19+	6	6	3.44±0.69	1.15±0.45	
Wang Z et al.	China	1997	Untreated	≥5	CD19+CD24highCD38high	28	30	2.10±1.09	4.07±1.48	5

Notes: *ACR without detailed description

3.3 Meta-Analysis of the Breg Percentages in Active SLE Patients and Publication Bias

Initially, we compared the percentages of Bregs in active SLE patients and healthy controls, regardless of the Breg definitions were used. A total of ten studies were available in seven eligible articles, and five studies reported higher percentage of Bregs in active SLE patients than those in the control group [10-13], three studies reported decreased percentages [8,14]. In addition, the simultaneous analysis of two different subtypes of Breg in two studies from one articles yielded conflicting results [9]. Surprisingly, in the overall analysis, there was no significant difference in any studies [0.259, (−1.150, 1.668), p = 0.719, Figure 2]. Meanwhile, the heterogeneity was 97.5% (p < 0.001) by I^2 statistic and thus very high, and a random effect model was used for meta-analysis. The Egger test showed no publication bias (t = 0.13, p = 0.898, Figure 3).

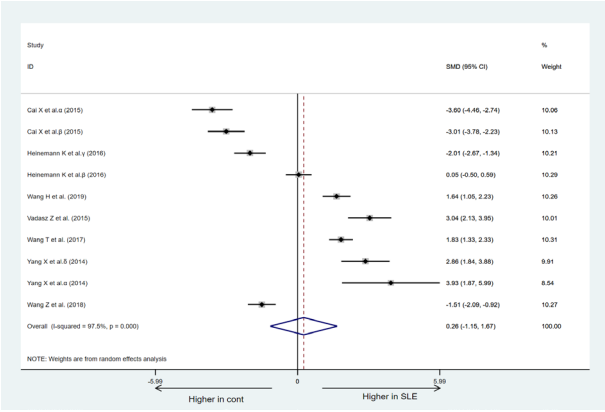

Figure 2. Forest plot of the percentage changes of Bregs in active SLE patients compared with the controls. α: Bregs were gated by IL-10$^+$CD19$^+$; β: Bregs were gated by CD19$^+$CD24^{high}CD38^{high}; γ: Bregs were gated by IL-10$^+$; δ: Bregs were gated by CD19$^+$CD5$^+$CD1d^{high}

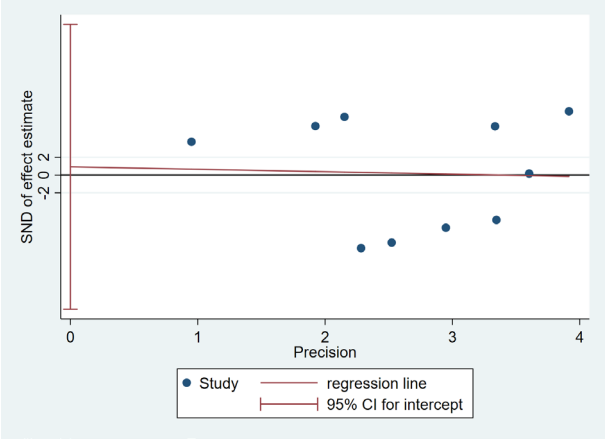

Figure 3. Publication bias analysis using Egger linear regression and Begg rank correlation test

3.4 Sensitivity Analysis and Subgroup Analysis

Due to the high heterogeneity of the results, we performed a sensitivity analysis. Then, considering the different phenotypes of Bregs, diagnostic criteria, enrolled regions, threshold of SLEDAI chosen for active SLE definition, treatment status, and organ involvement are potential factors that may lead to bias in the results, we performed a subgroup analysis based on these factors.

Firstly, we performed sensitivity analysis to explore potential sources of heterogeneity. Exclusion of any single study or single article did not materially resolve the heterogeneity. But after excluding the article conducted by Cai X and his colleagues [8], the percentages of Bregs were significantly higher in active SLE than those in controls [1.394, (0.114,2.675), p = 0.033].

Then, we hypothesized that the main cause of unexpected results may be the inconsistent definition of Bregs. Therefore, we performed a subgroup analysis based on the Bregs definition to explore potential sources of heterogeneity. There are several subtypes in the selected articles, which can roughly divide Bregs into two groups: based on IL-10$^+$ and CD19$^+$(Table 2). To our surprise, no matter whether Breg was based on IL-10$^+$ or CD19$^+$, there was no statistical difference between SLE patients and control groups. When Bregs were gated based on IL-10$^+$, the percentages of Bregs in active SLE were comparable to those in the controls [-0.783,(-3.526,1.960), p = 0.576, Figure 4] [8,9,13]. Meanwhile, pooled analysis of nine studies revealed the proportion of Bregs defined as CD19$^+$ cells did not differ significantly between active SLE patients and healthy controls [0.517,(-0.979,2.014), p = 0.498, Figure 5] [8,10-14].

Table 2. Subgroup analysis based on different definitions of Bregs in patients with SLE

Definition of Bregs	Number of studies	Test of association		
		SMD	95%CI	P value
Association with IL-10-positive	3	-0.783	(-3.526,1.960)	0.576
IL-10+CD19+	2	0.106	(-7.272,7.484)	0.978
IL-10+	1	-2.007	(-2.672,-1.342)	-
Association with CD19-positive	9	0.517	(-0.979,2.014)	0.498
IL-10+CD19+	2	0.106	(-7.272,7.484)	0.978
CD19+CD24highCD38high	5	-0.186	(-1.856,1.483)	0.827
CD19+CD5+CD1dhigh	1	2.86	(1.841,3.879)	-
CD19+CD25high	1	3.037	(2.127,3.948)	-

From the articles we collected, it was found that the researchers did not agree on the diagnostic criteria for active SLE patients. Six of the studies were based on the 1997 diagnostic criteria [8,12-14], one based on the 1982 ACR standard [10], and three studies showing only the ACR criteria without specific years [9,11]. Therefore, we conducted

DOI: https://doi.org/10.30564/jhp.v2i1.1594

a subgroup analysis to explore whether it is a source of heterogeneity. However, our subgroup analysis showed no statistically significant difference between the percentages of Bregs calculated using the 1997 diagnostic criteria and the ACR diagnosis criteria [0.008,(-2.203,2.219), p = 0.994 for subgroup of 1997, 0.340,(-2.137,2.817), p = 0.788 for subgroup of ACR, Figure 6].

More and more recent studies have shown that SLE has geographical and ethnic differences [16], so we assumed that the heterogeneity was caused by the different countries of the research population. There are differences in the prevalence and incidence of SLE in different countries, which may have a certain impact on the percentages of Bregs. Of the ten studies, seven were conducted in China [8,10,12-14], two in Germany [9], and one in Israel [11]. However, by subgroup analysis, the percentages of Bregs in each subgroup of SLE patients and controls was still not statistically significant(Figure 7).

Our results revealed that choosing the SLEDAI score to distinguish thresholds between active SLE and inactive SLE may result in heterogeneity. We attributed the study with a SLEDAI score of >4 to the ≥5 group [9], and the study with a score of >5 to the ≥6 group [10]. Therefore, ultimately all studies could be divided into three subgroups, "≥5" group, "≥6"group and "not reported" group(Figure 8). When the disease activity was judged by SLEDAI score ≥ 5, the percentages of Bregs were significantly lower in the SLE groups than in the control groups[-1.99,(-3.241,-0.739), p = 0.002] [8,9,14], but when the threshold of SLEDAI score ≥ 6 chosen for active SLE, the percentages of Bregs were significantly increased in the SLE groups[2.546,(1.333,3.759), p < 0.001] [10,13].

Previous study suggested that glucocorticoid therapy can increase the frequency of Bregs in patients with SLE [17]. The subgroup treatment status analysis of this meta-analysis showed no statistically significant differences among studies receiving drug therapy or those partially receiving drugs or no drug therapy(Figure 9). Given the fact that most patients who enrolled in the current studies received medication and the differences in the use of drugs, the possible effects of the treatment require further evaluation.

SLE can involve many organs, and lupus nephritis (LN) is a typical major organ involving of SLE. In all articles, Heinemann K et al. [9] compared the percentages of two different Breg subtypes in LN with the healthy control group. The data showed that the percentages of Bregs in active LN was not statistically different from the healthy controls[-1.010,(-2.882, 0.863), p < 0.291].

To assess the impact of disease activity further, we analyzed the percentages of Breg in active SLE versus in inactive SLE and in inactive SLE versus in healthy controls. The results presented are also not statistically significant.

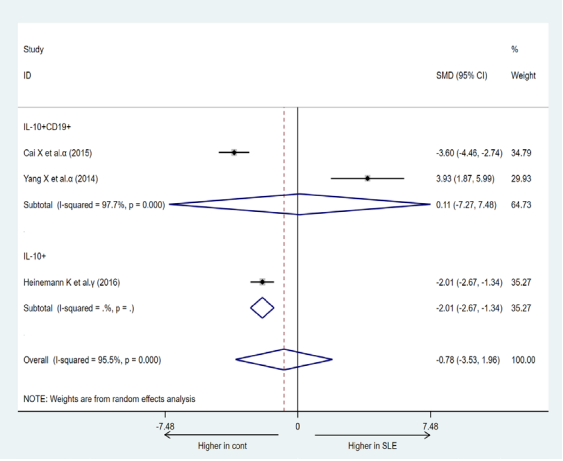

Figure 4. Subgroup analysis based on IL-10$^+$ as definition of Bregs in SLE patients

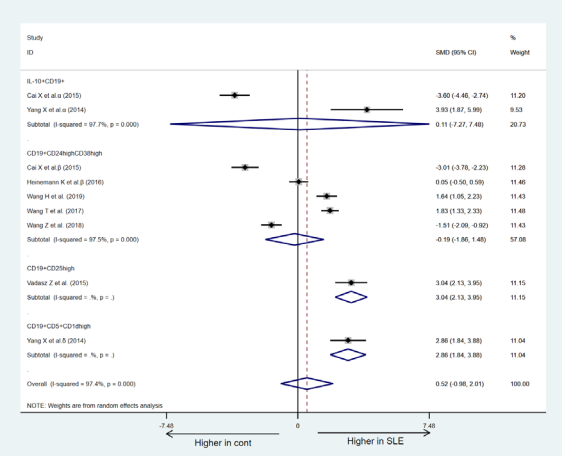

Figure 5. Subgroup analysis based on CD19$^+$ as definition of Bregs in SLE patients

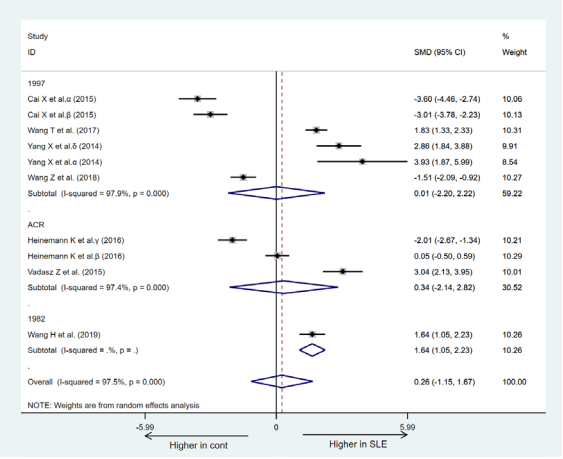

Figure 6. Subgroup analysis based on different diagnose criterion in SLE patients

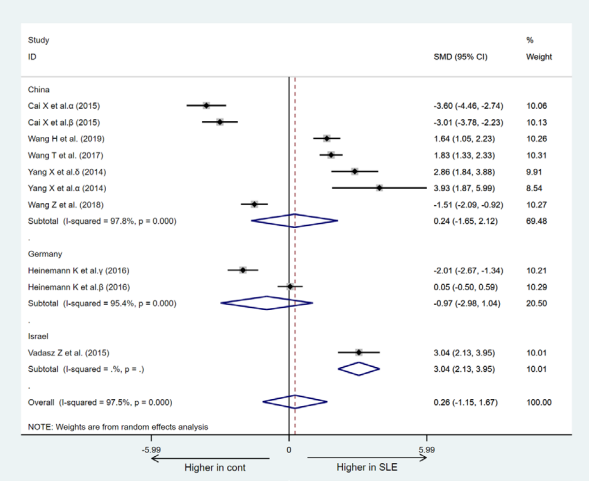

Figure 7. Subgroup analysis based on different study regions in SLE patients

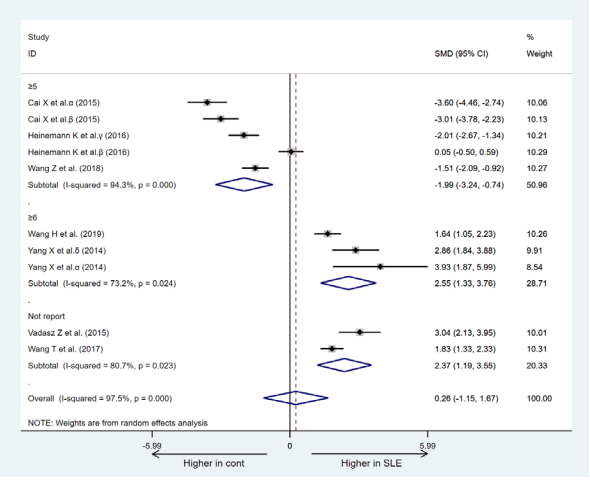

Figure 8. Subgroup analysis based on different thresholds of SELDAI chosen for active SLE definition in SLE patients

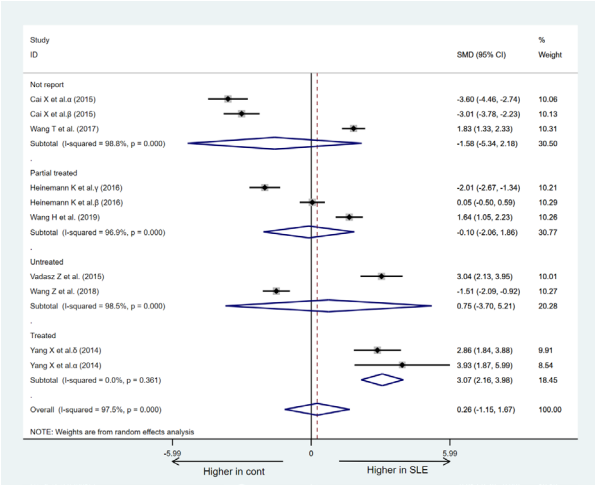

Figure 9. Subgroup analysis based on different treatment status in SLE patients

4. Discussion

B cells are one of the main components of specific immunity, and play a positive regulatory role mainly by initiating and activating immunity. Including secretion of antibodies, antigen presentation, production of inflammation and immunoregulatory factors, providing synergistic stimulation signals, etc. It is known that T cells have immunoregulatory functions, and whether B cells have regulatory subpopulations has become a research hotspot in recent years. Increased or decreased percentage of Bregs has been reported in patients with active SLE [8-14]. Therefore, we conducted further research on these results. However, meta-analysis results found no significant difference in percentages of Bregs between active SLE patients and healthy controls. Since the results showed great heterogeneity (I^2> 90), sensitivity analysis and subgroup analysis was subsequently performed to evaluate the possible effect of several factors on the percentages of Bregs, and the results indicated that different thresholds of SLEDAI chosen for defining active SLE might influence the frequency.

When studying Bregs, it is important to determine their phenotype. Previous research found that Bregs can produce IL-10, TGF-β, and Foxp3. One subtype of Bregs mainly secrete IL-10, which can inhibit the differentiation of T helper cells 1 (Th1) and T helper cells 17 (Th17) , and reduce the production of inflammatory cytokines through dendritic cells [18]. Such IL-10-producing Bregs are called B10 cells. In humans, B10 cells account for less than 1% of the total number of B cells in the blood. Human Bregs include $CD19^{+}CD24^{high}CD38^{high}CD1d^{high}$ and $CD19^{+}CD24^{high}CD27^{+}$, etc [19]. The relationship between development and differentiation of these subtypes of Bregs is unclear. In addition, Breg functioning involves CD40, TLR, B cell receptor, CD19, CD1d, etc [20]. In this study, no statistically significant difference was found in the different statistical strategies of Bregs subtype classification. Normal frequencies were observed when $IL\text{-}10^{+}$ was chosen to define Bregs [-0.783, (-3.526,1.960), p = 0.576] [8,9,13]. The percentages of Breg based on $CD19^{+}$ did not show a significant difference between the patients and the control group [0.517 , (-0.979, 2.014), p = 0.498] [8,10-14]. Considering that some studies only mentioned $IL\text{-}10^{+}$ Bregs, but did not mention the specific Bregs subtypes that secreted IL-10, and the research sample size was insufficient, further researches on the frequency of Bregs with different subtypes are needed in the future.

Since SLE is a heterogeneous disease, the diagnosis is not always so simple. From American College of Rheumatology (ARA) established the SLE classification standard in 1971 [21], many changes have taken place in the diag-

DOI: https://doi.org/10.30564/jhp.v2i1.1594

nostic criteria for SLE. The effect of different diagnostic criterion on the percentages of Bregs was not found in our study, and the results showed no statistical significance. However, the underlying causes and mechanisms leading to this result need to be further clarified in the future.

Recently, many studies have shown that there are significant regional differences in the incidence, clinical manifestations, and mortality of SLE. Khan A et al. [22] showed that significant regional differences existed in the clinical manifestations of SLE in Khyber Pakhtunkhwa compared to other regions through cross-sectional studies. In addition, Yen EY et al. [23] found that the United States since 1968, mortality of SLE has declined, but it remains higher than mortality in non-SLE, and there were significant gender, ethnic, and regional differences. Therefore, we hypothesized that differences in the study regions may result in variability in the results, but unexpectedly, the analysis results showed that the percentages of Breg in SLE patients from different regions was comparable to these of the healthy control group. We considered that most of researches originated in China, while the sample size of other countries was small, China had a large land area, a large span of latitudes and longitudes, different environments and ethnicities, which would also cause heterogeneity of Bregs in SLE patients. Thus, a larger sample size studies are needed for analysis.

The SLEDAI score can be used to judge the condition of SLE. Different scores indicate differences in disease activity, which determine the use of different doses of glucocorticoid and the choice of different immunosuppressants [24]. Our results revealed that active SLE could cause heterogeneity by choosing different thresholds of SLEDAI score. When SLEDAI score ≥ 5 was defined as active SLE, the percentages of Bregs in patients with active SLE were significantly lower than those in the healthy control group [-1.99, (-3.241-0.739), $p = 0.02$] [8,9,14]; however, the percentages of Bregs in patients with active SLE were significantly higher than control groups, when SLEDAI score ≥ 6 as the activity standard [2.546, (1.333, 3.759), $p < 0.001$] [10,13]. Considering that higher thresholds of SLEDAI score in recruited SLE patients may indicate a more severe conditions, Bregs seems to be positively correlated with disease activity in SLE, but this does not explain that the percentages of Bregs in SLE patients with a slightly lower SLEDAI score were lower than in healthy controls. Therefore, the changes of Bregs in the process of SLE disease need to be further studied.

Drug treatment for patients with SLE includes glucocorticoid, hydroxychloroquine, cyclophosphamide, and azathioprine etc. Previous studies showed that glucocorticoid therapy can increase the frequency of Bregs in patients with SLE [17]. However, the use of cyclophosphamide appeared to reduce the amount of Bregs [25]. Results of the subgroup analysis based on treatment status did not reveal a statistical difference between patients who received drug therapy and untreated patients. Drugs for SLE are diverse, and each SLE patient enrolled in the studies received different treatment status and used different drugs. Thus the possible effects of different treatment modalities on Bregs need to be further evaluated in the future.

Recently, studies by Szabó K et al. and Makiyama A. et al. found that activated T helper cells, especially Th1 cells, were associated with the promotion of B cell differentiation in SLE patients [26-27]. On the one hand, Bregs can secrete IL-10, TGF-β and other related factors, inhibit the conversion of Th0 to Th1 and Th2, reduce the production of inflammatory factors such as TNF-α and IFN-γ, and down-regulate autoimmune response and excessive immunity [28-29]; On the other hand, Bregs can exert immunoregulatory effects by affecting the number and function of Tregs [30]; Bregs can also suppress the immune response through cell-to-cell contact, such as by contacting CD40 / CD40L with effector T cells and causing T cells death [31]. It seems that the Bregs and T cells can interact and influence each other. In the past, Zhang SX et al. [32] systematically reviewed and performed a meta-analysis about the proportion of Tregs in patients with SLE, the results showed that the percentages of Tregs in SLE patients was significantly lower than those in healthy controls. Considering the correlation between Bregs and Tregs, we evaluated the proportion of Bregs in SLE patients, and analyzed the relevant influencing factors to obtain more evidence about Bregs in the pathogenesis of SLE, which may aid in the development of approaches to the therapeutic modalities employing the use of Bregs.

The present study has certain limitations. First of all, not all research-related information is publically available, such as the duration of the disease, specific information on the use of drugs or treatments, etc., and we did not contact the corresponding authors in time to obtain more information, which prevented us from comprehensive investigation of the disease course and the effect of drugs on the percentages of Bregs. Second, our assessment of the factors affecting the percentages of Bregs was inadequate. Faced with a high degree of heterogeneity, more SLE patients who are in different backgrounds and disease status need to be studied, which may help to clarify the role and changes of Bregs in SLE disease process better.

5. Conclusion

In summary, our meta-analysis results suggest that Bregs may play a role in the pathogenesis of active SLE, and the

 DOI: https://doi.org/10.30564/jhp.v2i1.1594

thresholds of SLEDAI score to distinguish whether SLE patients are active or not are important factors affecting the percentages of Bregs. Our findings support the notion that Bregs status is important in patients with SLE, but we cannot determine how Bregs have changed throughout the course of SLE. Due to the evidence is still limited, more and further large-scale and well-designed randomized controlled trials are urgently needed.

Author Contributions

MHY: study design. LL and LL: data collection. CXH, WYH and SJC: statistical analysis. CXH: paper writing. MHY: paper revision. All authors approved the submitted version of the manuscript.

Funding

This work was supported by funding from the National Natural Science Foundation of China Grants [81760286].

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