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Original Article

Correlation of IL-6 and TNF-α levels in cerebrospinal fluid and serum in patients with subarachnoid hemorrhage: a meta-analysis

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Abstract: *Objective:* We conducted this study to explore the correlation of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) levels in cerebrospinal fluid (CSF) and serum in the patients with subarachnoid hemorrhage (SAH). *Methods:* Computerized and manual search strategies were performed to retrieve relevant studies. Studies met our inclusion and exclusion criteria were enrolled. Statistical analyses were performed by Comprehensive Meta-analysis 2.0 (Biostat Inc., Englewood, New Jersey, USA). *Results*: A total of seventeen studies were finally included in this meta-analysis, including 449 SAH patients. The results revealed that IL-6 and TNF-α levels in CSF and serum in SAH patients were higher than those in the health control group (CSF: IL-6: SMD = 4.047, 95% CI = 2.651-5.443, $P < 0.001$; TNF-α: SMD = 4.686, 95% CI = 2.475-6.896, $P < 0.001$; Serum: IL-6: SMD = 2.759, 95% CI = 1.110-4.409, $P = 0.001$; TNF-α: SMD = 1.737, 95% CI = 1.358-2.116, $P < 0.001$). Further analysis about cerebral vasospasm (CVS) risk indicated that the IL-6 and TNF-α levels in CSF and serum in the CVS group were significantly higher than those in the non-CVS group (CSF: IL-6: SMD = 2.025, 95% CI = 1.048-3.003, $P < 0.001$; TNF-α: SMD = 0.969, 95% CI = 0.583-1.355, $P < 0.001$; Serum: IL-6: SMD = 4.310, 95% CI = 1.271-7.350, $P = 0.005$; TNF-α: SMD = 1.021, 95% CI = 0.549-1.492, $P < 0.001$). *Conclusion:* Our evidences suggested that IL-6 and TNF-α levels in CSF and serum may be correlated with SAH, which provides a certain of significant guidance for early diagnosis and monitoring of SAH.

Keywords: Correlation, cerebrospinal fluid, serum, subarachnoid hemorrhage, IL-6, TNF-α

Introduction

Subarachnoid hemorrhage (SAH) is a devastating neurological disease that can result from a ruptured aneurysm and has high morbidity and mortality rates that exceeds 50% [1]. Generally, SAH accounts for 5% of all stroke cases, affecting more than 30,000 individuals annually in North America, and half of the patients with SAH are younger than 55 years [2]. It was reported that SAH patients were at risk of developing cerebral vasospasm (CVS), cerebral ischemia, or ischemic neurological deficits [3]. Among which, CVS is the second leading factor causing massive disability and death in SAH patients [4]. Approximately 20% of patients with CVS have ischemic complications in spite of receiving therapy, and more than half of SAH patients die from CVS [5]. SAH is related to medical conditions that include intracranial artery dissections, arteriovenous malformation, mycotic aneurysms, reversible cerebral vasoconstriction syndrome, bleeding disorders, and vasculitis [6, 7]. Despite great advances in the early detection, diagnosis, and proper treatment of SAH, the overall outcome of SAH patients remains poor [8]. Currently, neuroimaging and biochemical markers in cerebrospinal fluid (CSF) and serum/plasma are two areas of extensive biomarker research [9]. One study has shown that the inflammatory response and cytokine release of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) are related to the severity of illness, occurrence of CVS and clinical outcomes in SAH patients [10].

IL-6, a pleiotropic inflammatory cytokine, has a molecular weight of 26 kD and a biological half-life of less than one hour [11]. Generally, IL-6 plays significant roles in immune, hematopoie-

sis, and acute phase responses, which are reactions to many types of inflammatory stimuli [12]. TNF-α, which is produced by activated astrocytes and macrophages, is a pro-inflammatory cytokine that plays a role in the self-propagation of neuronal inflammation [13]. TNF-α exerts it function in the inflammatory response, and it can also initiate a pro-apoptotic pathway, with vascular endothelial cells acting as the major target [14]. A clinical study demonstrated an association between clinical status and inflammation by measuring the inflammatory markers in CSF or serum [15]. Elevated IL-6 and TNF-α levels have been consistently detected in the CSF and serum of SAH patients, and they have been used as evidence of vasospasm via the following observations: transcranial Doppler ultrasound, delayed ischemic deficit and poor SAH outcome [16]. Previous studies have shown that the association between SAH and inflammation may mediate poor outcomes, the elevated levels of TNF-α and IL-6 in CSF and serum provided evidence of vasospasm and poor outcomes in SAH [17, 18]. However, several studies that attempted to correlate TNF-α and IL-6 levels in serum and CSF yielded conflicting results [19, 20]. Therefore, the aim of this study was to explore the correlation of IL-6 and TNF-α levels in CSF or serum with SAH.

Materials and methods

Search strategy

Relevant studies published before April, 2017 that addressed the correlation of IL-6 and TNF-α levels in CSF or serum with SAH were obtained by searching multiple independent computerized databases (PubMed, China BioMedicine (CBM), Web of Science, China National Knowledge Infrastructureand Cochrane Library). Keywords and free words were combined to do the search strategy, such as SAH, primary subarachnoid hemorrhage, acute hemorrhagic cerebrovascular disease, CSF, cytokines, interleukin and tumor necrosis factor, etc.

Study selection

The inclusion criteria were as follows: (1) research topics: the correlation of IL-6 level or TNF-α level in CSF or serum with SAH; (2) study subjects: patients were clinically diagnosed with SAH; (3) outcomes: IL-6 or TNF-α level in CSF or serum were investigated between groups. The exclusion criteria were as follows: (1) articles with only an abstract and summary; (2) animal studies; (3) repetition of published documents; (4) articles with insufficient data; (5) only the latest complete study was considered when selected studies were published by the same author.

Data extraction and quality assessment

Relevant information from selected articles was extracted by two independent investigators and recorded on a predefined form. Specifically, the following data were obtained: first author, time of publication, country, ethnicity, language, age, gender, number of cases, control group and detection method. The two investigators evaluated the quality of the included studies in light of the critical appraisal skill program (CASP) criteria (http://www.casp-uk.net/). The CASP criteria are standardized as the following 11 aspects: whether the study addresses a clearly focused issue (CASP01); whether an appropriate method was employed to answer their question (CASP02); whether the cases were recruited in an acceptable way (CASP03); whether the controls were selected in an acceptable way (CASP04); whether the exposures were accurately measured to minimize bias (CASP05); what confounding factors have the authors accounted for or have the authors considered as potential confounding factors in the design or analysis (CASP06); whether the results of this study are complete (CASP07); the precision of the results (CASP08); whether the results are reliable (CASP09); whether the results be can applied to the local population (CASP10); and whether the results of the study fit with other available evidence (CASP11). Discrepancies in the CASP scores for each of the included articles were further addressed by a third reviewer through group discussion and consultation.

Statistical analysis

Our meta-analysis was performed using Comprehensive Meta-analysis 2.0 (Biostat Inc., Englewood, New Jersey, USA). The standard mean difference (SMD) with its 95% confidence interval (95% CI) was utilized for evaluating the associations of IL-6 or TNF-α levels in CSF or serum in patients with SAH. The Z test was per-

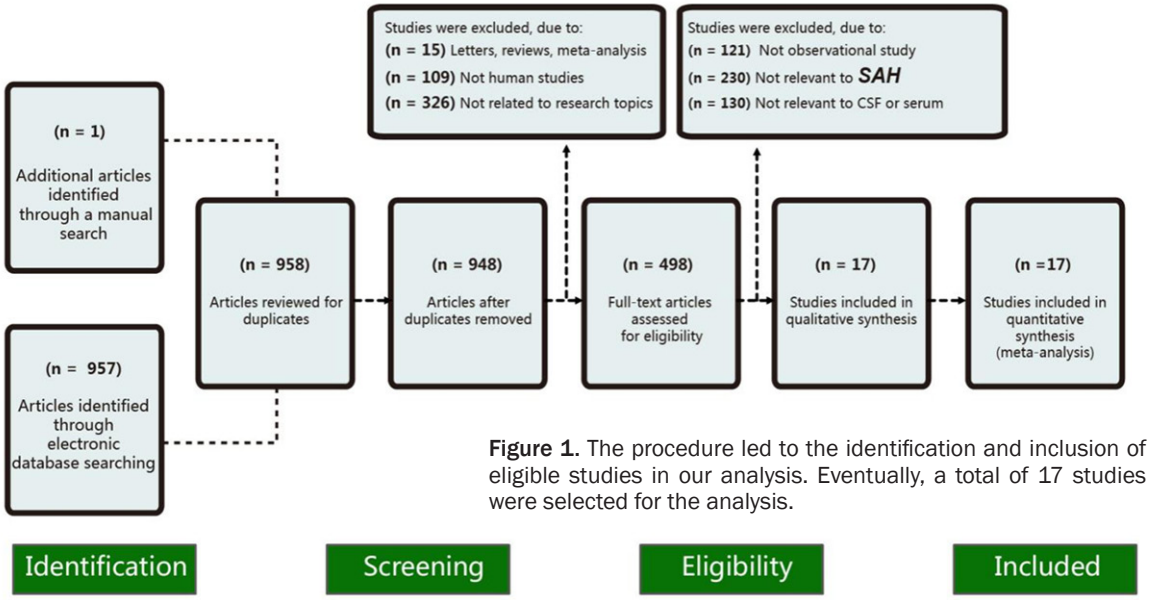

Figure 1. The procedure led to the identification and inclusion of eligible studies in our analysis. Eventually, a total of 17 studies were selected for the analysis.

formed to determine the significance of the overall effect [21]. A forest plot was drawn to reflect the values of SMD and 95% CI between the study groups. To assess the heterogeneity across studies, we calculated Cochran's *Q*-statistic (significance level of $P \leq 0.05$) and I^2 test [22, 23]. The degrees of heterogeneity were low, moderate and high, which correspond to I^2 values of 25%, 50% and 75%, respectively. For the presence of heterogeneity, a random-effects model was utilized; otherwise, a fixed-effects model was applied [24]. Multiple meta-regression analysis was used to evaluate the potential heterogeneous sources, and the Monte Carlo simulation method was used to perform corrections for multiple tests [22, 25]. A sensitivity analysis was conducted to assess whether the results were affected after exclusion of any single selected study. The funnel plots, classic fail-safe N and the Egger's linear regression test were constructed to determine whether a publication bias was present [26-28]. All tests were two-sided, and $P < 0.05$ was considered statistically significant.

Results

Included studies

Figure 1 presents the procedure used to identify the inclusion of eligible studies in our analysis. We initially retrieved 958 studies through our manual and electronic database search. There were 10 duplicates, 15 letters or reviews, 109 non-human studies and 326 non-related articles that were considered ineligible and thus excluded. The remaining 498 studies were further reviewed, among which 481 were excluded because 121 were non-observational studies, 230 were irrelevant to SAH and 130 were irrelevant to CSF or serum. Finally, 17 studies were enrolled in this study, which included a total of 449 SAH patients [18, 29-45]. These selected studies were published between 1993 and 2013 and included subjects in both Asian (n = 13) and Caucasian (n = 4) populations. Among these studies, 1 was performed in Sweden, 1 in Poland, 2 in Germany, 10 in China, 2 in Korea and 1 in Japan. **Table 1** illustrated the baseline characteristics of these 17 studies in detail.

Correlation between IL-6 and TNF-α levels in CSF and SAH

Among the 17 selected studies, 12 reported a correlation between IL-6 levels in CSF and SAH. Significant heterogeneity was found among studies ($I^2 = 96.843\%$, $P_h < 0.001$); therefore, a random-effects model was utilized. The results of the meta-analysis showed that higher levels of IL-6 were found in the CSF patients with SAH when compared with the health control group (SMD = 4.047, 95% CI = 2.651-5.443, $P < 0.001$; **Figure 2A**). An analysis of the incidence of CVS revealed IL-6 levels in CSF were significantly higher in the CVS group than that in the non-CVS group (SMD = 2.025, 95% CI = 1.048-

Table 1. Baseline characteristics of ten included studies

First author	Country	Ethnicity	Language	Study type	CASP scores	Total	Sample size		Gender (M/F)		Age (years)		Method
							Case	Control	Case	Control	Case	Control	
Mathiesen T (1993)	Sweden	Caucasians	English	Non-RCT	9	30	12	18	NR	NR	NR	18 ± 2	ELISA
Osuka K (1998)	Japan	Asians	English	Non-RCT	10	33	24	9	10/14	NR	56.0 ± 2.4	NR	ELISA
Tang YL (2000)	China	Asians	Chinese	Non-RCT	10	40	20	20	11/9	NR	48.2 (25~65)	NR	ELISA
Fassbender K (2001)	Germany	Caucasians	English	Non-RCT	11	55	35	20	14/21	8/12	56.0 ± 10.0	40.0 ± 9.0	ELISA
Kwon KY (2001)	Korea	Asians	English	Non-RCT	9	31	19	12	6/13	5/7	51.7 (34~69)	46.5 (29~65)	ELISA
Hendryk S (2004)	Poland	Caucasians	English	RCT	9	15	8	7	NR	NR	NR	NR	RIM
Li JH (2004)	China	Asians	Chinese	Non-RCT	10	46	26	20	14/12	NR	49.2 (0.17~72)	NR	ELISA
Zhang ZL (2005)	China	Asians	Chinese	Non-RCT	9	52	32	20	17/15	8/12	30.90 ± 15.06	35.40 ± 9.50	RIM
Schoch B (2007)	Germany	Caucasians	English	Non-RCT	11	64	18	46	4/14	11/35	52 ± 12	56 ± 12	ELISA
Wang ZG (2007)	China	Asians	Chinese	Non-RCT	9	55	35	20	16/19	8/12	65.2 ± 13.3	61.3 ± 10.2	ELISA
Zhang LG (2008)	China	Asians	Chinese	Non-RCT	10	69	27	42	10/17	24/18	51.8 (17~68)	43.9 (26~73)	ELISA
Ni W (2011)	China	Asians	English	RCT	11	46	20	26	16/4	8/18	53 ± 6	54 ± 11	ELISA
Lee JH (2012)	Korea	Asians	English	Non-RCT	9	16	10	6	2/8	3/3	66.2 (46~79)	43.3 (4~63)	ELISA
Liu ZW (2012)	China	Asians	Chinese	Non-RCT	10	55	45	10	28/17	4/6	38.30 ± 11.1	37.40 ± 9.50	ELISA
Liu BG (2012)	China	Asians	Chinese	Non-RCT	10	54	41	13	18/23	5/8	52.40 ± 5.6	43.9 ± 7.2	ELISA
Jiang JQ (2013)	China	Asians	Chinese	Non-RCT	9	102	52	50	29/23	26/24	69.26 ± 5.37	68.84 ± 6.73	ELISA
Xie X (2013)	China	Asians	English	Non-RCT	11	72	36	36	NR	NR	NR	NR	ELISA

ELISA: enzyme-linked immunosorbent assay; RIM: radio-immunity method; NR: not reported; RCT: randomized controlled trial; CASP: critical appraisal skills programme.

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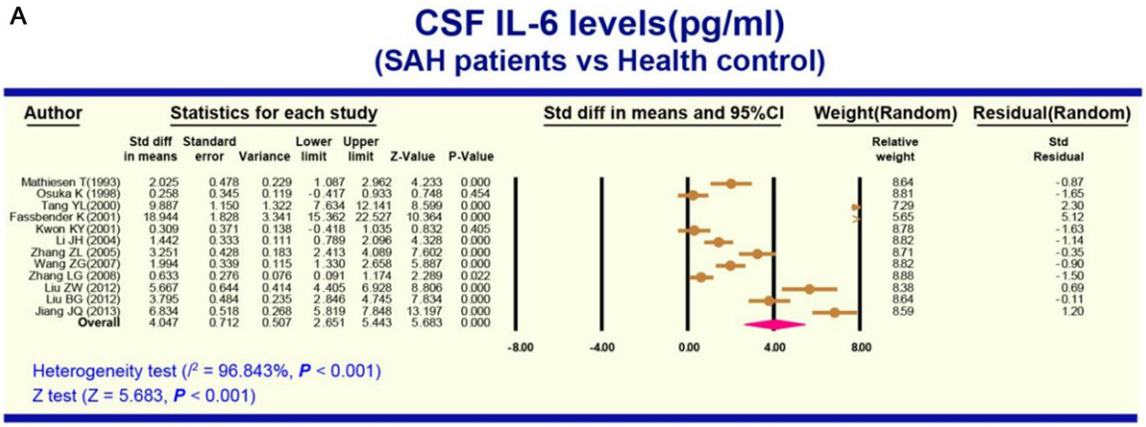

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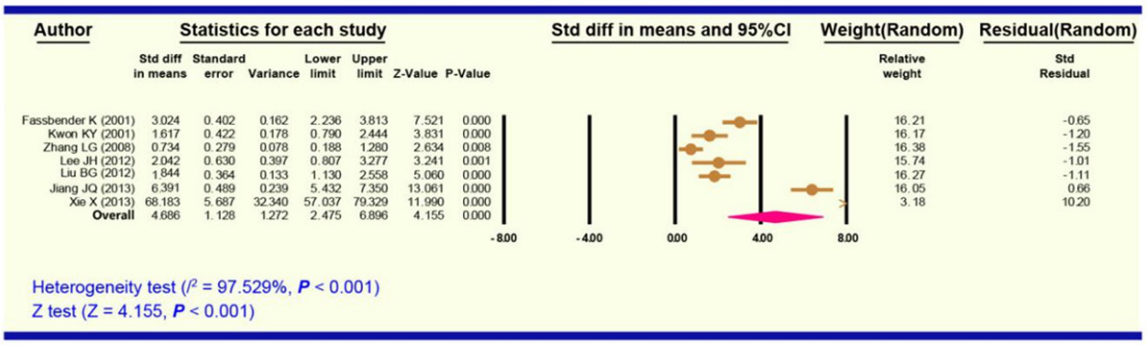

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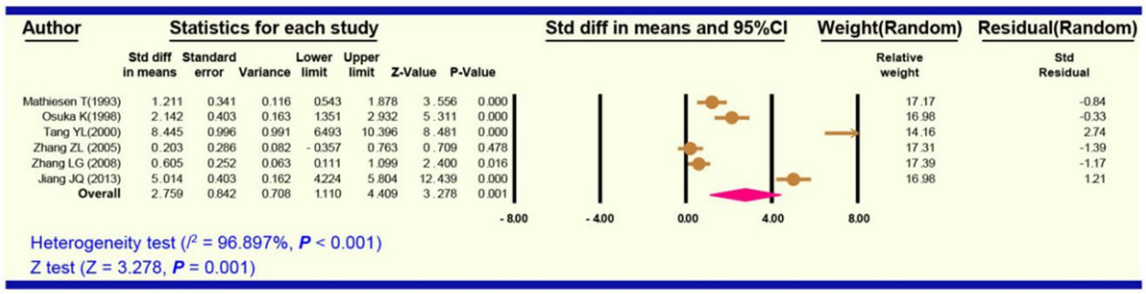

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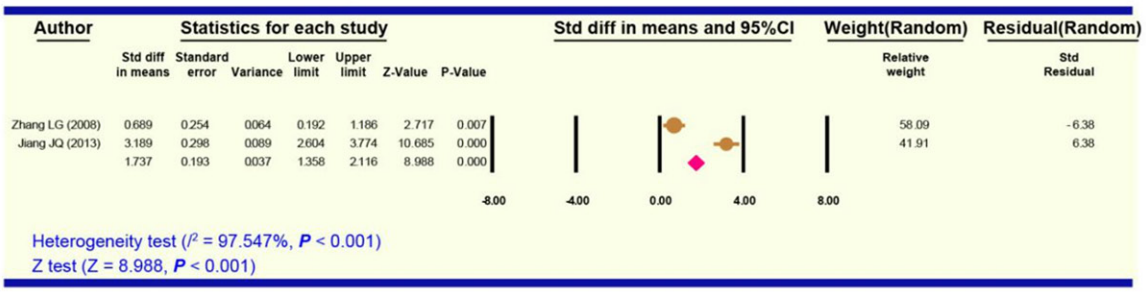

Figure 2. Forest plots for comparisons of IL-6 and TNF-α levels in CSF and serum between SAH patients and the health control group (SAH: subarachnoid hemorrhage, CSF: cerebrospinal fluid, A: CSF IL-6 levels, B: CSF TNF-α levels, C: Serum IL-6 levels, D: Serum TNF levels).

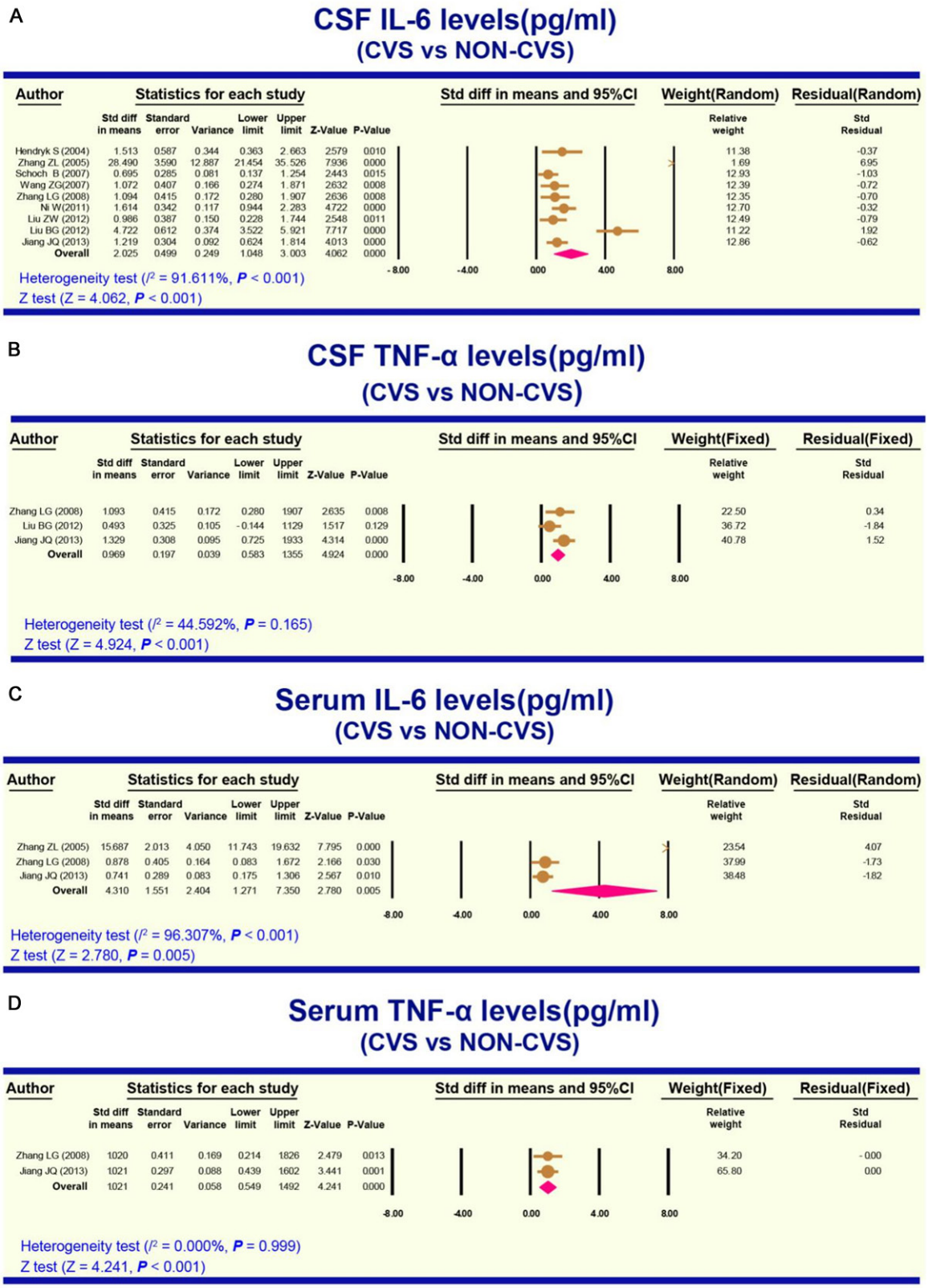

Figure 3. Forest plots for comparisons of IL-6 and TNF-α levels in the CSF and serum between CVS and non-CVS groups (SAH: subarachnoid hemorrhage, CSF: cerebrospinal fluid, CVS, cerebral vasospasm, A: CSF IL-6 levels, B: CSF TNF-α levels, C: Serum IL-6 levels, D: Serum TNF levels).

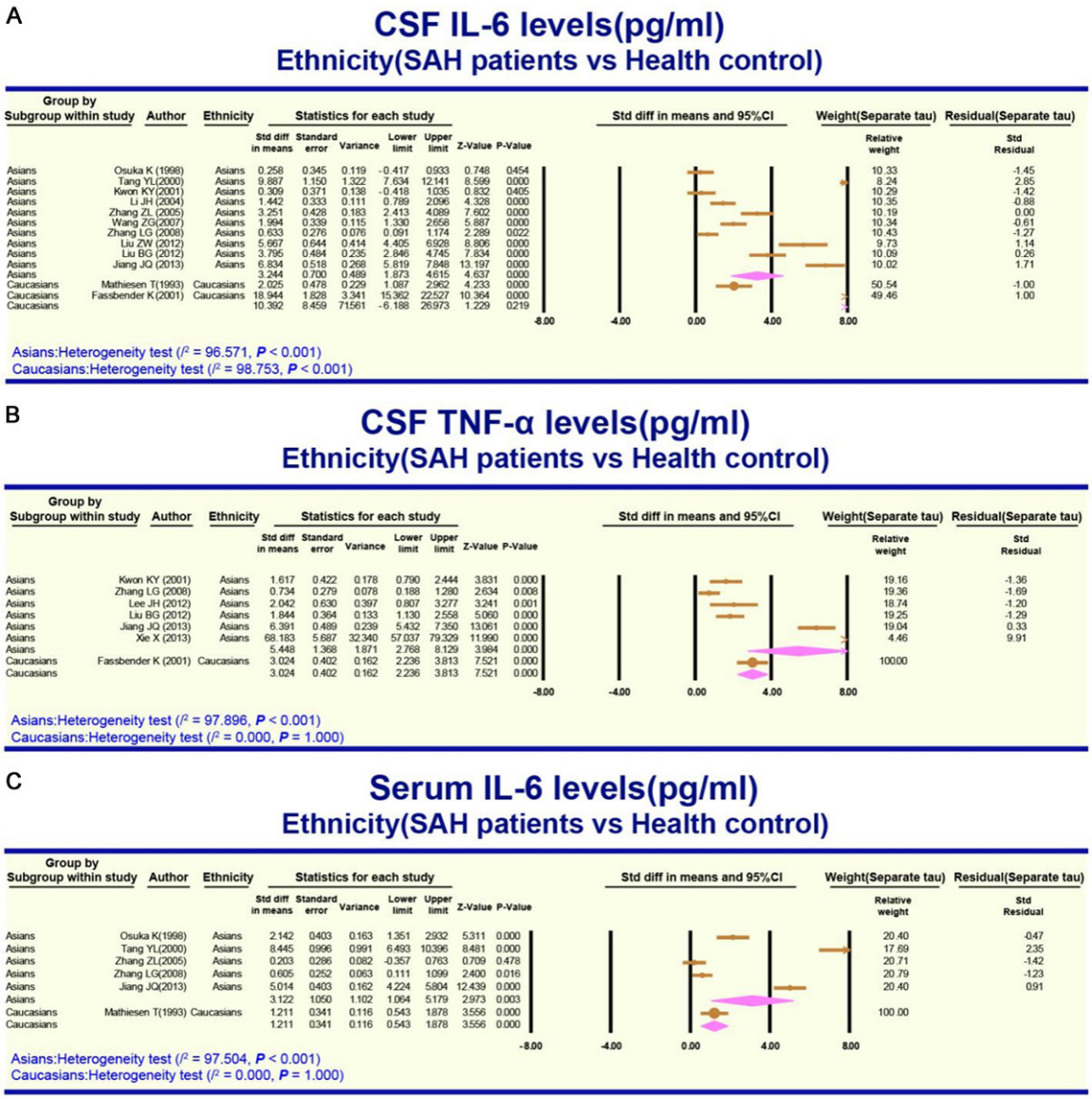

Figure 4. Forest plots based on ethnicity for comparisons of IL-6 and TNF-α levels in CSF and serum between SAH patients and the health control group (SAH: subarachnoid hemorrhage, CSF: cerebrospinal fluid, A: CSF IL-6 levels, B: CSF TNF-α levels, C: Serum IL-6 levels).

3.003, P < 0.001; **Figure 3A**). According to the subgroup analysis of ethnicity, SAH patients had higher CSF levels of IL-6 than the health control group in the Asian populations (SMD = 3.244, 95% CI = 1.873-4.615, P < 0.001), but no statistical correlation was found in the Caucasian populations (SMD = 10.392, 95% CI = -6.188-26.973, P = 0.219; **Figure 4A**). Seven studies examined the correlation between TNF-α levels in CSF and SAH. A random-effects model was applied to examine the existence of significant heterogeneity (I^2 = 97.529%, P_h < 0.001). The results indicated that TNF-α levels in CSF were markedly higher in patients with SAH than in the health control group (SMD = 4.686, 95% CI = 2.475-6.896, P < 0.001; **Figure 2B**). According to the incidence of CVS in SAH patients, TNF-α levels in CSF in the CVS group were remarkably higher than those in the non-CVS group (SMD = 0.969, 95% CI = 0.583-1.355, P < 0.001; **Figure 3B**). A subgroup analysis based on ethnicity suggested that TNF-α levels in CSF in SAH patients were higher than those in the health control group in both the Asian and Caucasian populations (Asian populations: SMD = 5.448, 95% CI = 2.768-8.129, P

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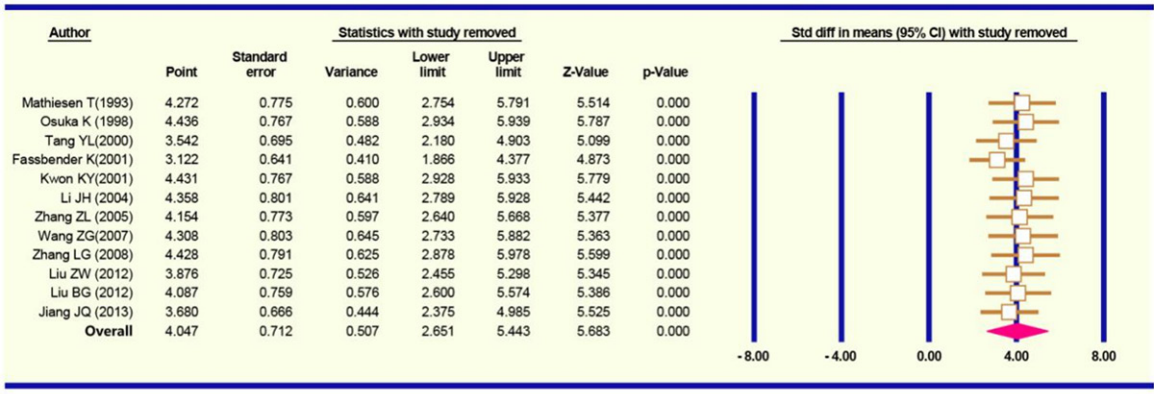

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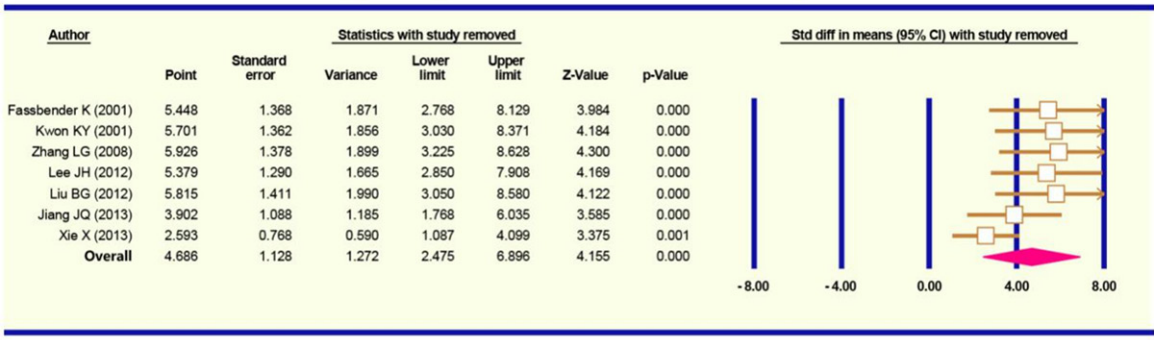

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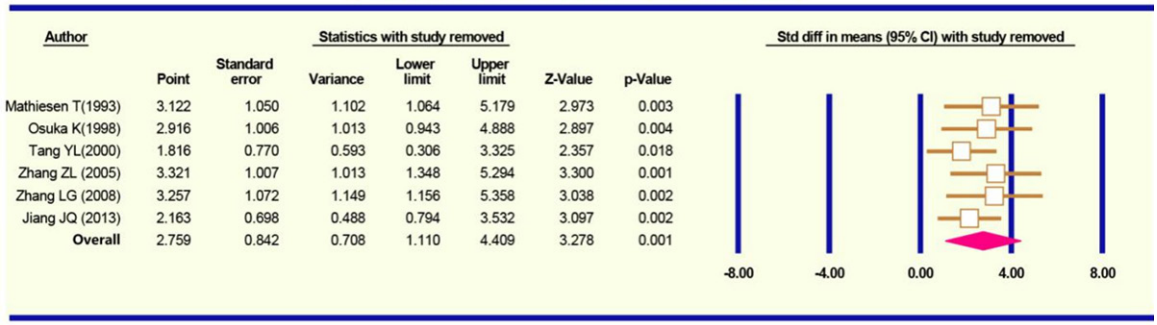

Figure 5. Sensitivity analyses for comparisons of IL-6 and TNF-α levels in CSF and serum between SAH patients and the health control group (SAH: subarachnoid hemorrhage, CSF: cerebrospinal fluid, A: CSF IL-6 levels, B: CSF TNF-α levels, C: Serum IL-6 levels).

< 0.001; Caucasian populations: SMD = 3.024, 95% CI = 2.236-3.813, $P < 0.001$; **Figure 4B**).

Correlation between IL-6 and TNF-α level in serum and SAH

The correlation between IL-6 level in serum and SAH was reported in 6 studies. The significant heterogeneity found among studies led to the selection of a random-effects model (I^2 = 96.897%, $P_h < 0.001$). The results of the meta-analysis demonstrated that higher level of IL-6 in serum was found in SAH patients than in the health control group (SMD = 2.759, 95% CI = 1.110-4.409, P = 0.001; **Figure 2C**). Further analysis concerning CVS risk showed that the

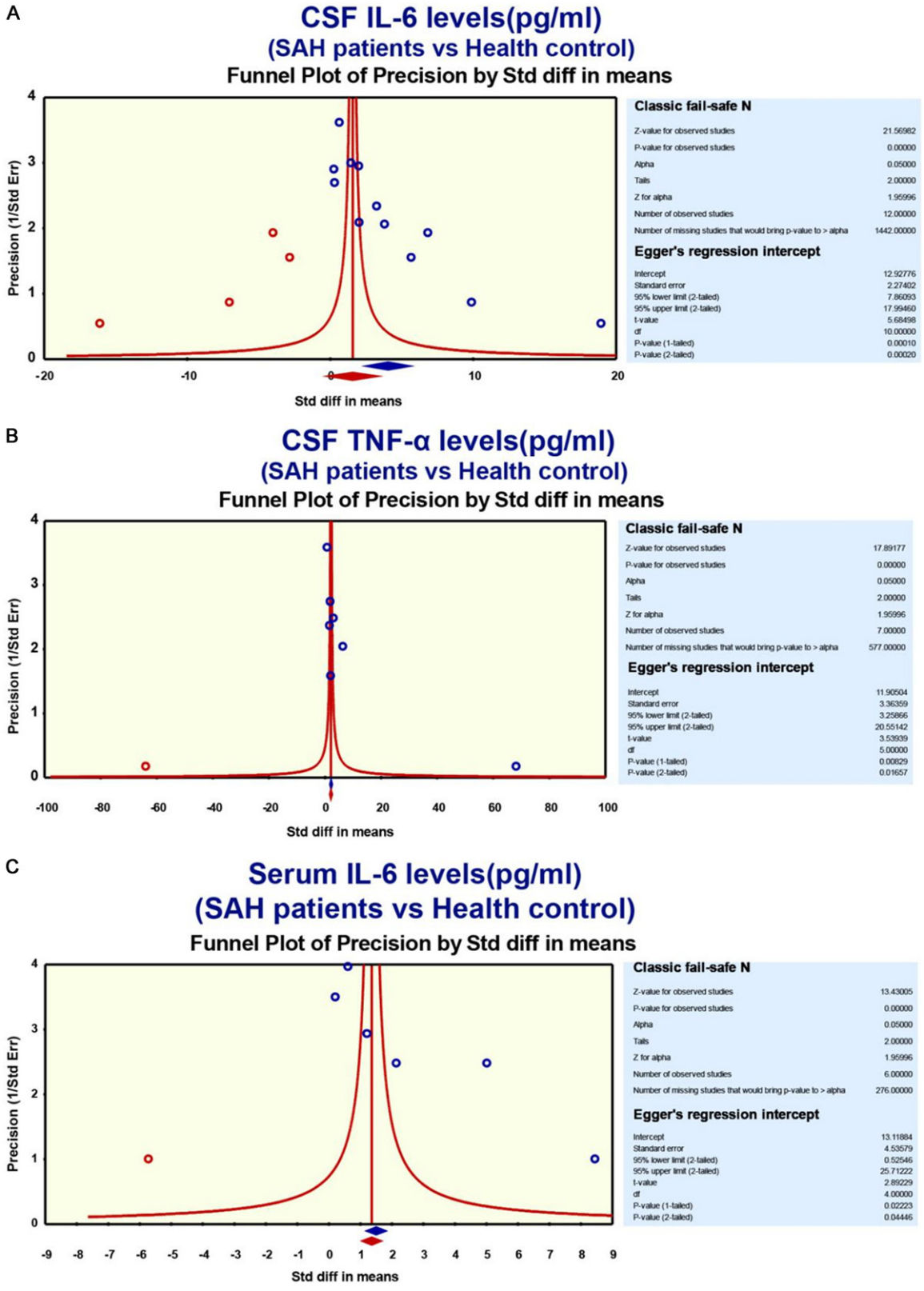

Figure 6. Publication bias for comparison of IL-6 and TNF-α level in CSF and serum between SAH patients and the health control group (SAH: subarachnoid hemorrhage, CSF: cerebrospinal fluid, A: CSF IL-6 levels, B: CSF TNF-α levels, C: Serum IL-6 levels).

Table 2. Meta-regression analysis of potential source of heterogeneity

Outcomes	Heterogeneity factors	Coefficient	SE	t	*P* (Adjusted)	95% CI	
						LL	UL
CSF IL-6	Year	0.368	0.285	1.290	0.423	-0.289	1.025
	Ethnicity	10.219	4.795	2.130	0.170	-0.837	21.276
	Sample size	0.011	0.046	0.240	0.990	-0.095	0.118
	Language	0.686	0.408	1.680	0.812	-0.212	1.585
CSF TNF-α	Year	1.491	3.354	0.440	0.817	-9.182	12.163
	Ethnicity	2.984	44.963	0.070	1.000	-140.107	140.075
	Sample size	0.179	0.521	0.340	0.968	-1.477	1.836
	Language	1.364	0.890	1.530	0.970	-0.815	3.542
Serum IL-6	Year	-0.073	0.590	-0.120	1.000	-2.610	2.465
	Ethnicity	-2.920	7.154	-0.410	0.962	-33.698	27.860
	Sample size	-0.001	0.154	-0.010	1.000	-0.662	0.660
	Language	0.256	1.732	0.150	0.890	-4.553	5.065

Notes: SE: Standard Error; LL: Lower Limit; UL: Upper Limit; 95% CI: 95% confidence interval.

serum level of IL-6 was higher in the CVS group than in the non-CVS group (SMD = 4.310, 95% CI = 1.271-7.350, P = 0.005; **Figure 3C**). An ethnicity-stratified analysis indicated that serum levels of IL-6 were higher in SAH patients than in the health control group in both the Asian and Caucasian populations (Asian populations: SMD = 3.122, 95% CI = 1.064-5.179, P = 0.003; Caucasian populations: SMD = 1.211, 95% CI = 0.543-1.878, P < 0.001; **Figure 4C**). Two studies examined the correlation between TNF-α level in serum and SAH. A random-effects model was applied to identify the existence of significant heterogeneity (I^2 = 97.547%, P_h < 0.001). The results indicated that serum levels of TNF-α were markedly higher in SAH patients than in the health control group (SMD = 1.737, 95% CI = 1.358-2.116, P < 0.001; **Figure 2D**). According to the CVS risk found in SAH patients, serum levels of TNF-α in the CVS group were remarkably higher than those in the non-CVS group (SMD = 1.021, 95% CI = 0.549-1.492, P < 0.001; **Figure 3D**).

Source of heterogeneity

The sensitivity analysis showed that all of the studies included in the meta-analysis had no significant effect on the SMD values for the correlation of IL-6 or TNF-α levels in serum or CSF with SAH (**Figure 5A-C**). The funnel plot was symmetrical, which suggested no obvious publication bias. The classic fail-safe N together with the Egger's linear regression test further confirmed that a significant publication bias was found among the included studies (both P < 0.05) (**Figure 6A-C**). Multiple meta-regression analysis showed that age, ethnicity, sample size and language were neither the main sources of heterogeneity, nor the key factors affecting the overall effect (P > 0.05, **Table 2**).

Discussion

The present meta-analysis was constructed to investigate the correlation of the levels of IL-6 and TNF-α in CSF or serum with SAH. Our meta-analysis results suggest that the levels of IL-6 in the CSF and serum were higher in SAH patient than in the health control group, indicating that these two cytokines in CSF and serum may be associated with SAH. This can be explained by the fact that when SAH occurred, a local inflammatory reaction in the brain tissue activated a massive release of cytokines, including IL-6 and TNF-α. The identification of related signal transduction molecules also activated a variety of kinases in cells, which increased the flow velocity in the basilar artery in the brain and further increased the incidence of CVS in SAH patient [40].

One of the findings in this meta-analysis showed that the levels of IL-6 in the CSF and serum of SAH patient were higher than those in the health control group, suggesting the increased level of IL-6 in CSF and serum may be associated with the onset of SAH, especially CVS. It is well-known that higher IL-6 levels are closely associated with various diseases, such as type

2 diabetes mellitus, cardiovascular disease, acute brain injury, acute cerebral ischemia, and cancer growth [46, 47]. IL-6 is related to increased endothelial permeability in the central nervous system (CNS) and upregulation of molecular mediators in ischemic brain injury (eg. leukotrienes and prostaglandins (PG)), both of which might cause further brain injury in SAH [48]. Additionally, IL-6 can activate PG and COX cascade reaction by increasing production of cyclooxygenase 2 protein. Together, these substances led to the production of PG and further contributed to the occurrence of CVS [49]. Furthermore, a series of reactions initiated by IL-6 play significant roles in stimulating intracranial vascular spasm, causing increases in vascular resistance and critical pressure, as well as reductions in blood flow velocity and blood flow, thus aggravating cerebral ischemia, hemorrhage, inflammatory reactions and vascular spasm and greatly exacerbating the clinical symptoms of SAH patients [34]. In accordance with our results, SAH patients generally showed elevated IL-6 levels in serum, CSF, cerebral extracellular fluid, and peripheral veins [50]. Furthermore, Schoch *et al*. provided strong evidence that IL-6 was significantly elevated in SAH patients with unfavorable outcome [37].

Another finding in our meta-analysis indicated that the levels of TNF-α in the CSF and serum of SAH patient were higher than those in the health control group, suggesting the increased levels of TNF-α in CSF and serum may be associated with the onset of SAH. TNF-α is a pro-inflammatory cytokine that is associated with SAH-related endothelial cell apoptosis, oxidative stress, and recruitment of inflammatory mediators of vasospasm [51]. Additionally, TNF-α plays an important role in the inflammatory cascade and host defense against infections, which was identified as a potential therapeutic target for autoimmune disease [52]. One study provided evidence that apoptosis occurred when endothelial cells were exposed to specific inducers, such as TNF-α; therefore, TNF-α together with the caspase-dependent cascades were believed to play important roles in SAH-induced apoptosis [53]. In fact, increased circulating TNF-α is related to more severe secondary brain injury in other conditions, including intra-cerebral hemorrhage and ischemic stroke [54]. At the cellular level, TNF-α may be involved in SAH via the pleiotropic effects, such as activation of mitogen-activated protein kinases (MAPK) and promotion of downstream inflammatory cascade by promoting the synthesis of adhesion molecules with other cytokines [18]. Additionally, TNF-α plays a significant role in the onset of cerebral vasoconstriction and hemolysis-induced vascular injury, and both human and animal studies have demonstrated a role for TNF-α in CVS [55, 56]. Jayaraman *et al.* reported an essential role for TNF-α in the development of SAH in an association with poor outcomes [20]. In this meta-analysis, our results confirmed TNF-α as a circulating inflammatory marker related to poor SAH outcomes in humans.

Given the influence of ethnicity on the levels of IL-6 and TNF-α in SAH, subgroup analyses were constructed based on ethnicity. The ethnicity-stratified analysis showed that the levels of TNF-α in CSF and IL-6 in serum were higher in SAH patients than in the health control group in both Asian and Caucasian populations. However, the CSF levels of IL-6 were higher in SAH patients than in the health control group in the Asian populations, but no statistical correlation was found in the Caucasian populations. These differences between ethnicity subgroups could be attributed to geographical, environmental and genetic factors.

Some limitations should be addressed while interpreting the results of the present meta-analysis. First, the 17 studies included in the analysis involved only Caucasians and Asians, whereas other ethnicities were inapplicable in the meta-analysis, which could contribute to a selection bias. Second, the lack of original data from some of the included studies restricted a further assessment. For example, an analysis of the ethnicity subgroups for TNF-α level in serum was not conducted because of insufficient data. Moreover, with the restrictions of the search parameters and a lack of persons who were proficient in other language, only studies published in English and Chinese were included into our meta-analysis, studies published in other languages were not included.

In conclusion, our findings demonstrated that the levels of IL-6 and TNF-α in CSF and serum may be associated with SAH, and they could be used as important biological indicators for early diagnosis and monitoring for SAH.

Disclosure of conflict of interest

None.

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