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Association between serum amyloid A levels and predicting disase severity in COVID-19 patients: a systematic review and meta-analysis

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Abstract. – OBJECTIVE: Global health resources have faced huge challenges from the pandemic coronavirus disease 2019 (COVID-19) since December 2019. Numerous clinical reports have focused on the association of serum amyloid A (SAA) levels with severe COVID-19. However, a systematic analysis synthesizing these findings has not been performed. This meta-analysis aims to systematically review the role of SAA levels in distinguishing among patients with mild, severe, and critical COVID-19.

MATERIALS AND METHODS: A comprehensive literature search was conducted in the PubMed, Embase, and Web of Science databases from the beginning of the COVID-19 outbreak to February 1, 2021. Two investigators independently reviewed suitable studies. Pooled standardized mean differences (SMDs), 95% confidence intervals (CIs), and correlation coefficients (r) were computed using a random-effects model.

RESULTS: We included 19 of 317 titles identified by our search, involving a total of 1806 mild cases and 1529 severe cases. Compared with the mild group, the severe group had markedly higher SAA levels (SMD=1.155, 95% CI 0.89, 1.42). Subgroup analysis revealed that the SAA level differences between the severe group and the mild group were associated with age, sample size, and detection method. Sensitivity analyses showed the credibility and robustness of our results. In addition, in six studies involving 1144 patients with severe COVID-19 and 433 patients with critical COVID-19, SAA was significantly higher in patients with critical COVID-19 (SMD=0.476, 95% CI 0.13, 0.82).

CONCLUSIONS: High circulating SAA levels were markedly associated with COVID-19 severity, especially for subjects aged less than 50 years, compared with patients with mild COVID-19. SAA concentrations were also significantly higher in patients with critical COVID-19 compared with those with severe COVID-19. Further studies in large cohorts are needed to confirm whether the SAA is a useful tool in discriminating among patients with stable COVID-19, those with acute exacerbations, and subjects without disease.

Key Words:
Serum amyloid A (SAA), Severe coronavirus disease 2019 (COVID-19), Systematic review, Meta-analysis.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused the pandemic coronavirus disease 2019 (COVID-19) for the first time in Wuhan, China, in December 2019. As of April 17, 2021, 139 501 934 cases of COVID-19 have been confirmed, with 2 992 193 deaths worldwide[1]. The pneumonia and accompanying multiple organ dysfunction syndrome and respiratory distress syndrome associated with COVID-19 can rapidly progress and lead to death[2,3]. To date, the anti-SARS-CoV-2 immunoglobulin M (IgM) and reverse transcription-PCR (RT-PCR) targeting different SARS-CoV-2 genomic regions, including the ORF1B and nucleocapsid (N), are the most commonly used laboratory diagnostic tests for COVID-19[4], However, they do not appear to play a role in monitoring the progress of the disease. Increased serum amyloid A (SAA) has been reported in COVID-19, and the degree of increase is correlated with disease severity[5]. However, to

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date, the causative, independent, and quantitative contributions of SAA levels to COVID-19 have not yet been thoroughly elucidated. In this study, we conducted a systematic review and meta-analysis of published studies in an attempt to identify the relationship between SAA levels and COVID-19 patients and subsequently investigate the possible roles of SAA in disease monitoring.

Materials and Methods

Search and Selection

We performed a systematic literature search in the PubMed, Web of Science, and Embase databases, with the following medical subject headings and keywords: "serum amyloid A" or "SAA" and "betacoronavirus" or "betacoronavirus 1" or "coronavirus infection" or "coronavirus" or "SARS-CoV-2 OR COVID-19". We did select language restrictions. We also included titles cited in other systematic reviews on SAA and COVID-19. This report reflects the state of the literature as of January 31, 2021.

Three authors (D.Z., W.H., and M.L.) independently selected eligible studies in two stages: (1) screening titles and abstracts and (2) reading full-text articles. We obtained full texts from interlibrary loans and databases or by contacting the corresponding authors. At the end of each stage, the reviewers compared their decisions and resolved discrepancies.

We included all the studies that have addressed inflammatory-related laboratory factors in monitoring severe COVID-19 infection, including retrospective and prospective studies. We excluded duplicate reports, reviews, case reports, animal trials, studies in the form of conference proceedings, and abstracts (**Supplementary Materials**, Excluded with reasons). The exclusion criteria included: (1) insufficient data for detailed analysis, (2) studies that did not differentiate between mild and severe COVID-2019, (3) coronavirus strains other than SARS-CoV-2, and (4) studies with unusable data. In addition, the diagnostic criteria for COVID-2019 were based on RT-PCR. When two or more studies were published by the same authors or institutions, the study having the largest sample size was selected.

Data Extraction

Two reviewers (F.G. and Y.L.) filtered the abstracts and collected data independently. Furthermore, a third reviewer (C.T.) assessed these articles and solved any arisen argument. The following data from each study were collected: (1) first author and publication year; (2) characteristics of the study, such as gender and age; (3) study design type; (4) grouping data (mild and severe case, N, the mean ± SD of SAA); and (5) SAA detection method.

The included studies all were performed in China. Patient status was defined based on the New Coronavirus Pneumonia Prevention and Control Program (6th and 7th editions) published by the Chinese National Health Committee[6,7]. Patients with uncomplicated illness were those without radiologic findings of pneumonia, whereas those with mild disease had respiratory symptoms, fever, and findings consistent with pneumonia upon chest imaging examination. A severe case was defined clinically as having respiratory distress with a respiratory rate of ≥ 30/min, an oxygenation index (oxygen partial pressure/fraction of inspired oxygen) of ≤ 300 mm Hg, and a resting pulse oxygen saturation (SpO_2) of $\leq 93\%$. A critically ill case was defined as patients with shock, respiratory failure requiring mechanical ventilation, or simultaneous failure in another organ requiring intensive care unit monitoring.

Literature Quality Assessment

We used the Newcastle-Ottawa Scale (NOS) to assess the quality of literature[8]. Three independent reviewers (C.T., L.S., and Y.S.) assessed the risk of bias according to the recommendations of PRISMA. The NOS evaluated nine questions, with one point for each satisfactory answer. Studies achieving six or more points were considered to be of high quality.

Statistical Analysis

The main outcome of the meta-analysis was the difference in SAA values among patients with mild, severe, and critical COVID-19. In this regard, the standard mean differences (SMDs) with 95% confidence intervals (CIs) of the continuous data extracted from eligible studies were calculated. $p < 0.05$ was considered statistically significant. In some studies, mean and standard deviation were estimated from the median and quartiles of SAA levels[9,10].

Heterogeneity of SMDs across studies was assessed using the Q statistic ($p < 0.10$ was considered statistically significant). Heterogeneity between studies was assessed using the I^2 statistic ($I^2 < 25\%$, no heterogeneity; I^2 between 25% and

50%, moderate heterogeneity; I^2 between 50% and 75%, large heterogeneity; $I^2 > 75\%$, extreme heterogeneity)[11,12]. A random-effects model was applied to calculate the corresponding 95% confidence intervals and pooled SMDs. Funnel plots, means of Begg's adjusted rank correlation tests, and Egger's regression asymmetry tests were used to assess potential publication bias ($p < 0.05$ was considered statistically significant)[13]. Sensitivity analysis was applied to determine reliability and stability[14]. Subgroup analysis and meta-regression analyses were also performed to further assess the sources of heterogeneity according to age, SAA detection method, sample size, and city. All statistical analyses were performed using Excel and STATA statistical package version 12.0 (STATA version 12.0, Stata Corporation, College Station, TX, USA).

Results

Characteristics of Eligible Studies

A flow chart describing the study selection is presented in Figure 1. The characteristics of the nineteen studies investigating the SAA in severe COVID-19 versus mild cases are presented in Table I[15-33]. These studies consisting of seventeen retrospective studies and two cross-sectional studies. All included studies were published as full articles in 2020. SAA concentrations were tested by immunonephelometry in two of the articles, cytometry in one article, and via colloidal gold in one article. The nineteen studies included eight conducted in Wuhan and eleven in other regions of China. High methodological quality was found in the studies of Zeng et al[15], Liu et al[18], Li et al[19], Yang et al[20], Chen et al[21], Li et al[23], Xu et al[25], Wang et al[27], Liu et al[29], Yu et al[31], Fu et al[33]. The studies of Shi et al[16], Xu et al[17], Mo et al[22], Xia et al[24], Zhao et al[26], Zhang et al[28], Dong et al[30] and Chen et al[32] had low methodological quality.

Meta-Analysis

The random-effects meta-analysis showed that patients with severe COVID-19 exhibited increased SAA levels compared with mild cases (SMD=1.155, 95% CI 0.89, 1.42; Figure 2). No significant change was found when any study was excluded using a random-effects model during sensitivity analyses, which indicated that the result was statistically robust (Figure 3). Subgroup analyses were performed to find the heterogeneity source (Table II). When divided by sample size, the number of participants more or less than 100 both showed average SAA levels that were markedly increased in patients with severe COVID-19 compared with mild cases (SMD 1.07, 95% CI 0.77 to 1.36, $p < 0.001$; SMD 1.4 6, 95% CI 0.78 to 2.14, $p < 0.001$). When stratified by age, SAA levels in the severe group with mean age ranges of 39–50 (SMD 1.53, 95% CI 1.10

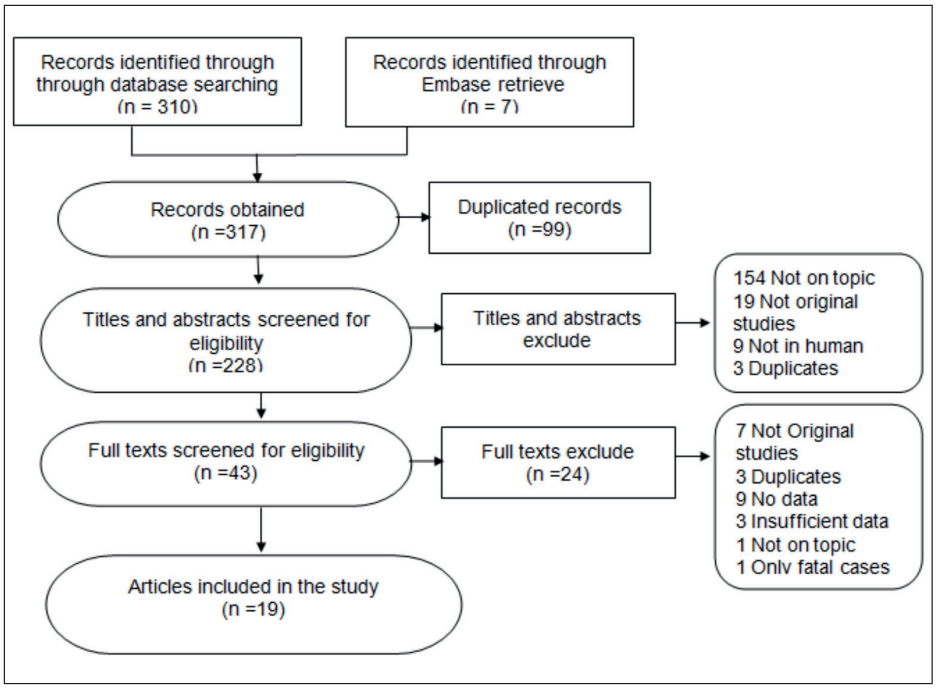

Figure 1. Flow chart showing the Literature Search and Selection. Specific reasons for exclusion of studies are also shown.

Table I. Characteristics of 19 studies included in the meta-analysis.

Author	Study design	NOS	COVID-19 mild group				COVID-19 severe group				Detection methodt
			N	Age (years)	Gender (F/M)	SAA mean ± SD/median (IQR)	N	Age (years)	Gender (F/M)	SAA mean ± SD/median (IQR)	
Zeng JK	R	7	36	54 (22-86)	16/20	99.5 (3.6-237.9)	41	62 (29-88)	13/28	115.4 (17.9-248.3)	Immunonephelometry
Shi YL	R	5	150	-	84/66	25.78 (4.63-156.15)	8	-	4/4	200 (187.35-250.33)	Immunonephelometry
Xu B	R	5	80	56 (44-67)	50/30	83.62 (11.59-202.50)	45	60 (46-67)	14/31	292.32 (153.03-301)	Cytometry
Liu SL	R	6	194	43 (33-57)	103/91	3.91 (1-18.79)	31	64 (45-66)	14/17	48.57 (9.3-469.16)	Colloidal Gold
Li H	R	6	60	57.32 ± 11.52	32/28	123.57 ± 75.81	56	66.55 ± 12.05	19/37	171.91 ± 56.89	-
Yang RR	R	6	61	-	-	67.04 (43.14-102.06)	11	-	-	140.20 (58.21-265.18)	-
Chen MQ	R	6	47	42.04 ± 15.96	23/24	109.52 ± 85.63	24	56.92 ± 15.87	4/20	169.92 ± 66.56	-
Mo XN	R	5	102	-	-	40.42 ± 56.62	16	-	-	198.32 ± 55.12	-
Li L	R	7	22	39.1 ± 12.2	10/12	96.53 ± 31	12	52.1 ± 14.2	5/7	260.58 ± 54.58	-
Xia XT	R	5	32	62.25 ± 15.07	17/15	176.59 (37.833-300)	31	64.55 ± 14.88	13/18	300 (194.83-300)	-
Xu J	R	6	125	39.84 ± 15.09	57/67	87.64 ± 34.85	30	50.97 ± 13.55	10/20	137.00 ± 70.23	-
Zhao K	R	5	19	49 (36-65)	12/9	57 (27-121)	18	55(46-63)	4/14	501 (313-721)	-
Wang D	C	7	72	44 (32-60)	43/29	40.6 (13.6-141)	71	65 (53-69)	27/44	477.7 (209-996)	-
Zhang QH	R	5	47	61(54-67)	29/18	10.84 (5.99-55.15)	27	72 (58-81)	9/18	106.05 (52.05-167.62)	-
Liu Q	C	7	59	49 (33-57)	28/31	14.7 (7.43-28.69)	25	52 (45-67)	11//14	65.75 (14.3-117.8)	-
Dong YL	R	5	94	40 (32-56)	60/34	71.25 (19.08-342.93)	53	60 (49-64)	24/29	685.5 (282.05-730.25)	-
Yu YL	R	6	239	-	-	5.42 (4.39-7.87)	862	-	-	24.74 (5-129.3)	-
Chen RH	R	5	345	67.3 ± 12.1	163/182	166.65 (43.93-250.3)	155	60.9 ± 13.8	62/93	198.8 (153.2-241.8)	-
Fu J	R	6	22	40.77 ± 9.06	11/11	89.78 ± 54.75	13	60.08 ± 15.51	11/2	144.29 ± 57.33	-

SAA, serum amyloid A; IQR, interquartile range; COVID-19, coronavirus 2019; NOS, Newcastle-Ottawa quality assessment scale; R, retrospective; C, cross-sectional.

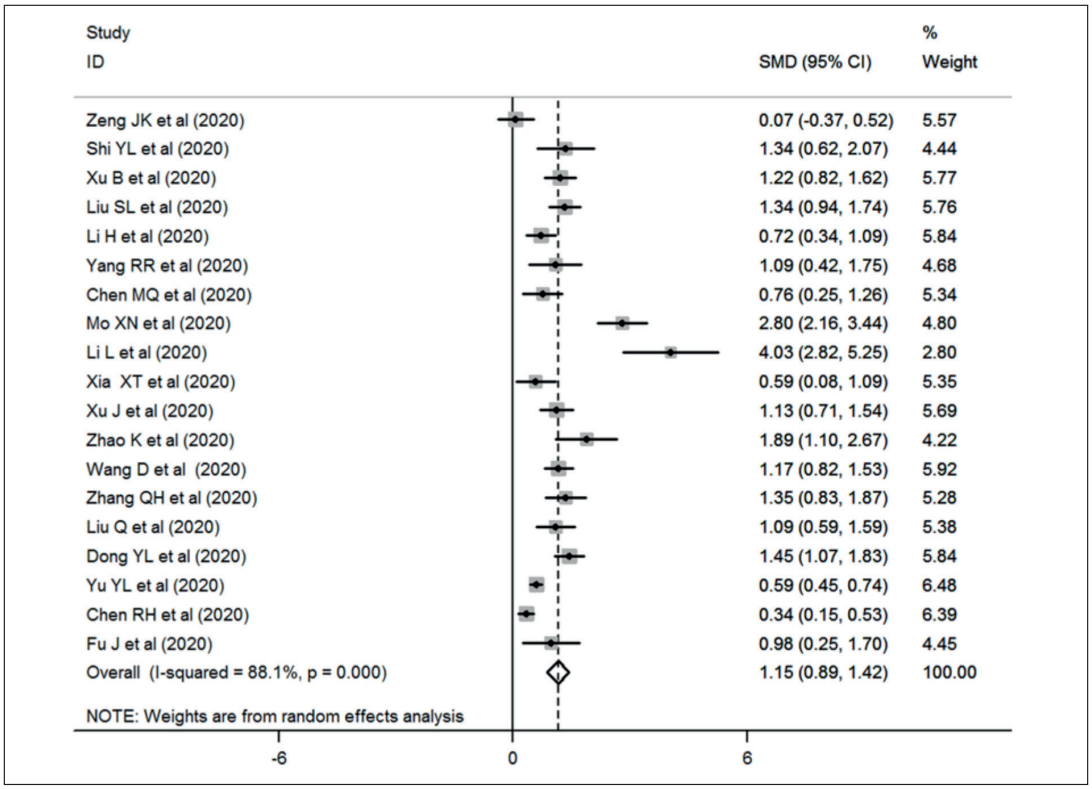

Figure 2. Forest Plot of serum amyloid A level differences between severe COVID-19 group and mild group. The pooled effect size was estimated using random-effects model.

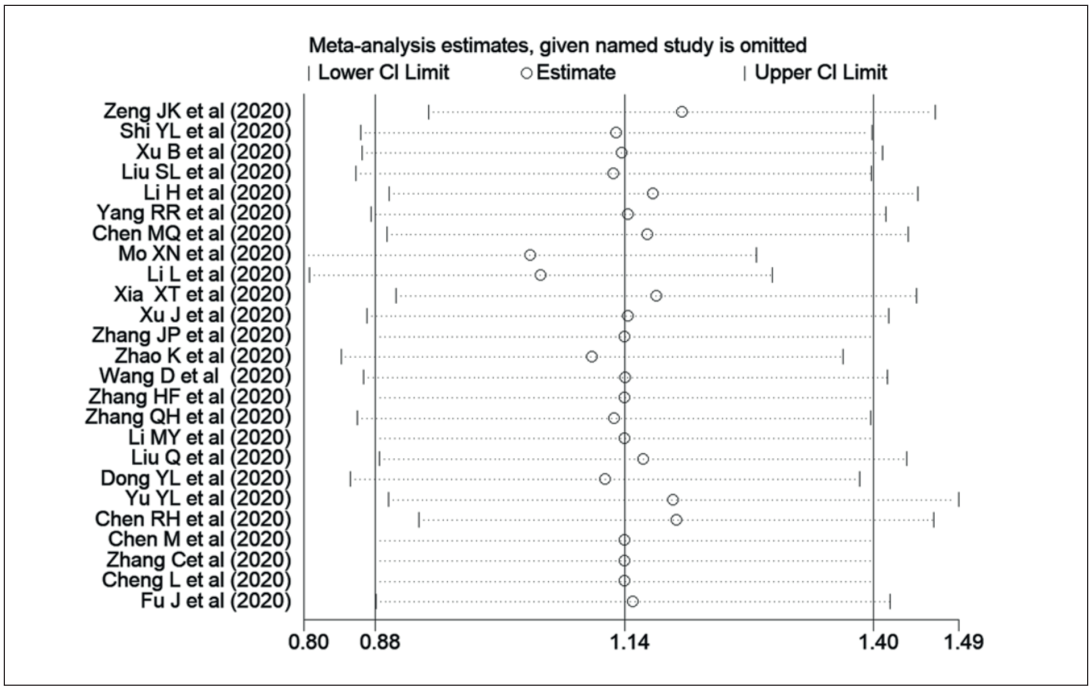

Figure 3. Sensitivity Analysis of SAA level difference between severe COVID-19 group and mild group by excluding one study at a time. The horizontal axis represented the SMD value and its 95% confidence interval. The SMD effect size was estimated using random-effects model.

Table II. Subgroup of serum amyloid A (SAA) level differences between severe group and mild group.

Variable	Subgroup	Study number	SMD (95% CI)	Heterogeneity		
				X^2	I^2	*p*-value
Total	All studies	19	1.18 (1.00 to 1.36)	30.75	57.7%	0.004
Sample size	> 100	13	1.07 (0.77 to 1.36)	111.47	89.2%	< 0.001
	≤ 100	6	1.46 (0.78 to 2.14)	32.99	84.8%	< 0.001
Age	≤ 50	9	1.53 (1.10 to 1.97)	47.19	83%	< 0.001
	51-59	4	0.70 (0.16 to 1.24)	31.84	90.6%	< 0.001
	≥ 60	3	0.87 (0.44 to 1.30)	5.06	60.5%	0.08
	Unknown	3	1.11 (0.37 to 1.86)	11.82	83.1%	0.003
City	Wuhan	11	1.17 (0.82 to 1.53)	77.54	87.1%	< 0.001
	Others	8	1.14 (0.65 to 1.63)	72.63	90.5%	< 0.001
Detection	Unknown	15	1.10 (0.84 to 1.38)	107.9	87%	< 0.001
	Immunonephelometry	2	0.68 (-0.57 to 1.92)	8.5	88.2%	0.004
	Cytometry	1	1.22 (0.82 to 1.62)	-	-	-
	Colloidal Gold	1	4.03 (2.82 to 5.25)	-	-	-
Study design	Retrospective	17	1.16 (0.87 to 1.46)	146.03	89%	< 0.001
	Cross-sectional	2	1.15 (0.86 to 1.44)	0.07	0.0	0.790

The SMD effect size estimated using random-effects model; SAA, serum amyoid A; SMD were SAA level difference between severe group and mild group.

to 1.97, $p < 0.001$) and 51–59 (SMD 0.7, 95% CI 0.16 to 1.24, $p < 0.001$) years were higher than those in the mild group, but not in patients > 60 years old. When stratified by outbreak city, regardless of whether patients were from Wuhan, the severe groups had significantly higher average SAA levels than mild cases (SMD 1.17, 95% 0.82 to 1.53, $p < 0.001$; SMD 1.14, 95% 0.65 to 1.83, $p < 0.001$). Meta-regression was performed to further identify the sources of heterogeneity (Table III). The p values from meta-regression analysis with the covariate of SAA detection method, age, city, sample size, and study design were 0.757, 0.266, 0.858, 0.442, and 0.922, respectively. Thus, no covariate significantly contributed to the between-study heterogeneity. Egger's or Begg's test was used to assess for publication bias, and a trend toward publication bias was observed (Begg, $p = 0.142$; Egger, $p = 0.001$). When the trim-and-fill method was used to correct the results, eight potential missing studies were required in the left side of the funnel plot to ensure symmetry (Figure 4). The adjusted SMD was reduced (SMD 0.68, 95% CI 0.40 to 0.97, $p < 0.001$).

Subsequently, the meta-analyses of SAA levels between the critical COVID-19 group and the severe group were performed in six studies (Figure 5, Table IV). They comprised a total of 1144 patients with critical COVID-19 (mean age 66.36 ± 13.29 years) and 433 patients with severe COVID-19 (mean age 61.09 ± 14.18). Compared with the severe group, the critical group had significantly higher average SAA levels (SMD 0.476, 95% 0.13 to 0.82, $p = 0.001$). Significant heterogeneity was found between studies ($I^2 = 76.6\%$, $p < 0.001$). Sensitivity analysis indicated that pooled SMD values were not substantially altered when single studies were removed, indicating that the results of the meta-analysis were

Table III. Meta-regression of serum amyloid A level differences between severe group and mild group.

Covariates	β	SE	T	*p* values	95% CI	Tau^2	Adjusted R^2 (%)
Detection	1.06	0.20	0.31	0.757	0.70 to 1.59	0.50	-7.29%
Age	0.83	0.14	-1.15	0.266	0.59 to 1.17	0.45	2.93%
City	0.93	0.36	-0.18	0.856	0.41 to 2.10	0.51	-9.47%
Sample size	0.75	0.26	-0.79	0.442	0.36 to 1.59	0.50	-6.08%
Study design	0.94	0.57	-0.10	0.922	0.26 to 3.39	0.51	-9.72%

β, regression coefficients; SE, standard error of regression coefficients; Tau 2, study between the component of variation size; adjusted R2(%), the current covariate can explain the size of heterogeneity.

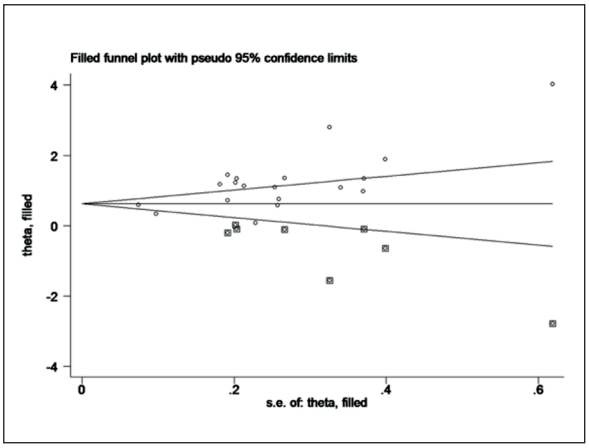

Figure 4. Funnel plot of studies investigating severe COVID-19 group and mild group after trimming and filling. Dummy studies and genuine studies are represented by enclosed circles and free circle, respectively.

robust (Figure 6). No evidence of publication bias was observed (Begg, p = 1.000; Egger, p = 0.235).

Discussion

COVID-19 has rapidly spread across the world since December 2019 and precipitated a global crisis. The most common initial clinical symptoms of patients with COVID-19 are cough, fever, fatigue, and the usual development of bilateral multiple lobular and subsegmental areas of consolidation within 15 days after symptom onset[34,35]. The consolidation usually clears quickly but progresses to bilateral ground-glass opacity[34]. Serial chest radiographs are helpful in the screening and monitoring of the clinical course[36,37], but their interpretation can be confounded by a lack of available experienced radiologists, similar imaging characteristics as pneumonia caused by other viruses, inter-observer variability, and the frequently suboptimal quality of images photographed in isolation wards to avoid the epidemic spreading to other patients[38,39].

A great amount of COVID-19 studies reported that the abnormalities in clinical laboratory parameters were related to COVID-19 severity, particularly in severe and critically ill patients[40]. SARS-CoV-2 antibody is usually increased at a later stage of COVID-19[41] and is therefore unsuitable as a marker for monitoring disease progression. An increased neutrophil-to-lymphocyte ratio, a fairly common occurrence in disease severity[42], is a potential marker for disease activity. However, lymphocyte counts are affected by treatment with intravenous immunoglobulins and steroids, as well as the presence of bacterial infections or other superimposed viral infections, making it less meaningful for monitoring the

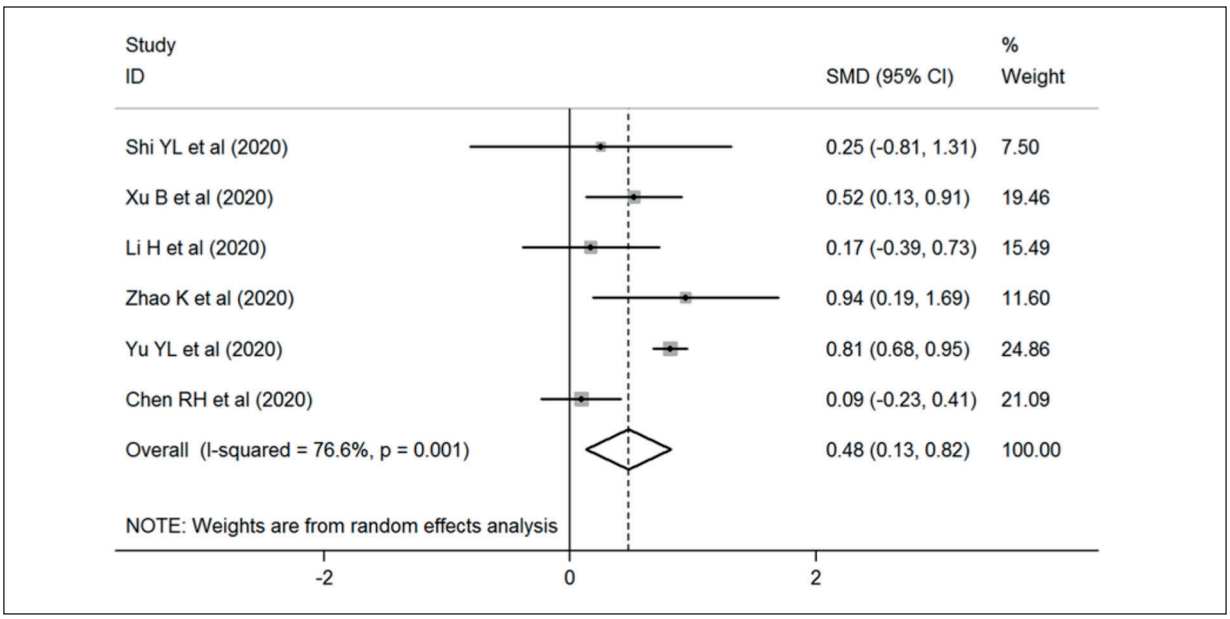

Figure 5. Forest Plot of serum amyloid A level differences between critical COVID-19 group and severe group. The pooled effect size was estimated using random-effects model.

Table IV. Summary of the studies on critical COVID-19 vs severe group included in the meta-analysis.

Author	Study design	NOS (stars)	COVID-19 severe group				COVID-19 critical group				Detection methodt
			N	Age (years)	Gender (F/M)	SAA mean ± SD/median (IQR)	N	Age (years)	Gender (F/M)	SAA mean ± SD/median (IQR)	
Shi YL	R	5	8	-	4/4	200 (187.35-250.33)	6	-	1/5	234.77 (174.28-298.38)	Immunonephelometry
Xu B	R	5	45	60 (46-67)	14/31	292.32 (153.03-301)	62	70 (60.25-76.75)	20/42	301 (258.48-301)	Cytometry
Li H	R	6	56	66.55 ± 12.05	19/37	171.91 ± 56.89	16	64.06 ± 13.36	6/10	181 ± 40.66	-
Zhao K	R	5	18	55 (46-63)	4/14	501 (313-721)	13	66 (56-74)	4/9	1359 (499-1795)	-
Yu YL	R	6	862	-	-	24.74 (5-129.3)	288	-	-	117.4 (72.76-197.1)	-
Chen RH	R	5	155	60.9 ± 13.8	62/93	198.8 (153.2-241.8)	48	64.1 ± 13.6	10/38	191.25 (162.5-255.8)	-

SAA, serum amyloid A; IQR, interquartile range; COVID-19, coronavirus 2019; NOS, Newcastle-Ottawa quality assessment scale; R, retrospective; C, cross-sectional.

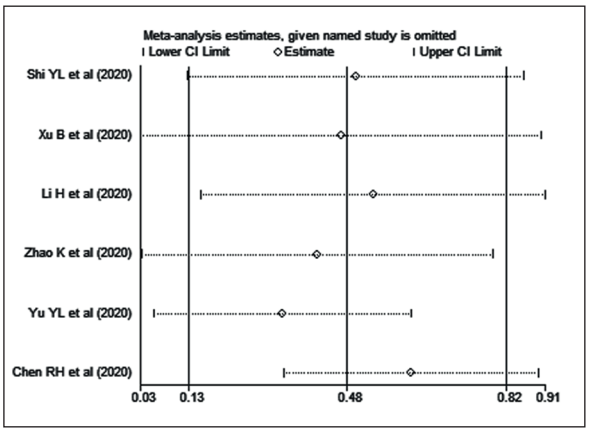

Figure 6. Sensitivity Analysis of SAA level difference between critical COVID-19 group and severe group by excluding one study at a time. The horizontal axis represented the SMD value and its 95% confidence interval. The SMD effect size was estimated using random-effects model.

disease activity of COVID-19. Other biomarkers, including lactate dehydrogenase (LDH), aspartate aminotransferase (AST), and alanine aminotransferase (ALT), have been associated with severe and critically ill disease[40,43,44]. Because these enzymes can originate from different organs, such as the liver, heart, and skeletal muscles, disease conditions in these organs also result in their abnormal elevation. Thus, a change in LDH, AST, and ALP activities may not be specific enough for monitoring COVID-19 infection.

During the progression from mild to severe/critical COVID-19 disease, an increasing trend of ferritin, SAA, procalcitonin, IL-6, PCT, and CRP and a decreasing trend of prealbumin and/or albumin have been frequently observed[45,46], indicating the crucial role of these markers in predicting COVID-19 course and severity. SAA, one of the normal constituents of blood serum, is synthesized prominently in the liver. SAA comprises four families of molecules, among which SAA1 and SAA2 are the most prominent members of the acute phase response proteins; their serum levels rise sharply with infection, trauma, and other stimuli (including the acute inflammatory stimulus)[47]. Yip et al[39] performed profiling technology combining mass spectrometry with a surface-enhanced biochip and found that SAA was substantially higher in patients with SARS compared with control patients with different bacterial or viral infections; furthermore, SAA concentrations correlated well with the extent of pneumonia[39]. Circulating SAA is approximately 10-fold greater than CRP levels in physiologic levels, suggesting that SAA may be more sensitive than CRP in detecting minor inflammation[48].

The precise mechanism for the increase of SAA concentration in patients with COVID-19 remains unknown. These patients are characterized by diffuse alveolar damage[49], Multiple inflammatory factors, including IL-6 and IL-1, are produced and secreted by diffuse alveolar damage stimuli. Given that IL-6 and IL-1 can rapidly induce a 1000-fold increase in SAA in a synergistic manner[50], we postulated whether SAR-CoV-2 targets alveolar macrophages and causes increased IL-6, which subsequently results in increased SAA levels. However, further investigations are needed.

In this meta-analysis, we found that (a) SAA levels were significantly higher in patients with severe COVID-19 compared with mild subjects, and the magnitude of the differences (278%) was enough to allow clear discrimination; and (b) SAA levels were significantly higher in patients with critical COVID-19 compared with severe groups. Further studies in large cohorts are needed to determine whether the SAA is useful to discriminate among patients with mild, severe, and critical COVID-19 and subjects without disease. Notably, the differences in the SAA levels between patients with severe and critical COVID-19 observed in our study (163% in critical COVID-19) suggest that this biomarker may be particularly useful for the identification of patients with critical COVID-19.

This review has some limitations worth noting. First, the studies evaluated in the present review often involved small sample sizes and were largely limited to cases in a single country. Second, most of the studies were less likely to include healthy controls, with a predominant patient population from China. Furthermore, Egger's tests and funnel plots showed strong publication bias, which may originate from the tendency of researchers and editors to report positive results. Third, the exact timeline of laboratory sample collection and serial sample measurements is lacking. Finally, most of the studies were retrospective in design, incomplete, and failed to report final outcomes due to the need for rapid publishing during the current pandemic.

Conclusions

Our results demonstrate that circulating SAA levels are significantly higher in patients with severe COVID-19 compared with mild cases.

However, the magnitude of the reported difference was reduced after trim-and-fill adjustment. Furthermore, SAA levels in patients with critical COVID-19 are significantly higher than those in severe patients. These findings suggest that high SAA levels are closely associated with COVID-19 disease conditions. SAA and the other biomarkers discussed may be used to monitor disease activity and treatment in patients with COVID-19.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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