

## THE DIAGNOSTIC AND PROGNOSTIC VALUE OF SUPAR IN PATIENTS WITH SEPSIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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**ABSTRACT—Background:** Soluble urokinase-type plasminogen activator receptor (suPAR) has the potential to diagnose infectious diseases. Due to the lack of reliable biomarkers and the importance of timely diagnosis for sepsis treatment, we conducted this systematic review and meta-analysis to evaluate the value of suPAR diagnosis and prognosis for sepsis. **Methods:** PubMed, Embase, Web of Science, and Cochrane Library databases were searched for studies, which reported the value of suPAR diagnosis and/or prognosis in patients with sepsis. **Results:** A total of 30 studies involving 6,906 patients were included. Sensitivity and specificity of suPAR for diagnosing sepsis were 0.76 [95% confidence interval (CI), 0.63–0.86] and 0.78 (95% CI, 0.72–0.83), respectively. The area under the summary receiver-operating characteristic curve (AUC) was 0.83 (95% CI, 0.80–0.86). Pooled sensitivity and specificity for predicting mortality were 0.74 (95% CI, 0.67–0.80) and 0.70 (95% CI, 0.63–0.76), respectively, with AUC of 0.78 (95% CI, 0.74–0.82). In addition, AUC for differentiating sepsis from systemic inflammatory response syndrome (SIRS) was 0.81 (95% CI, 0.77–0.84), and the sensitivity and specificity were 0.67 (95% CI, 0.58–0.76) and 0.82 (95% CI, 0.73–0.88), respectively. **Conclusion:** suPAR is a feasible biomarker for timely diagnosis and prognosis of sepsis. Compared with effective value of procalcitonin (PCT) identified by previous meta-analysis, suPAR has similar clinical guiding value, whereas suPAR exhibits higher specificity, which can facilitate the deficiencies of PCT. suPAR also shows a diagnostic value in differentiating sepsis from SIRS. Considering the lack of biomarkers for sepsis and the similar clinical value of suPAR and PCT, suPAR should be considered as a biomarker in clinical practice for sepsis.

**KEYWORDS—**Biomarker, meta-analysis, sepsis, soluble urokinase-type plasminogen activator receptor (suPAR), systematic review

**ABBREVIATIONS—**APACHE II—the Acute Physiology and Chronic Health Evaluation II; AUC—the area under the receiver-operating characteristic curve; CIs—confidence intervals; CRP—C-reactive protein; DOR—diagnostic odds ratio; EWS—early warning score; IL—interleukin; LBP—lipopolysaccharide-binding protein; NLR—negative likelihood ratio; PCT—procalcitonin; PLR—positive likelihood ratio; PRISMA—the preferred reporting items for systematic reviews and meta-analyses; SIRS—systemic inflammatory response syndrome; SROC—summary receiver-operating characteristic; suPAR—soluble urokinase-type plasminogen activator receptor; WOS—web of science

## INTRODUCTION

Soluble urokinase-type plasminogen activator receptor (suPAR) is a soluble form of uPAR which is a membrane-bound receptor for uPA. SuPAR is widely found in body fluids, including plasma, urine, blood, serum, and cerebrospinal fluid. The concentration of suPAR is positively correlated with immune system activity and is a biomarker to indicate the severity and deterioration of the disease, such as arthritis, liver fibrosis, malaria, and bacterial infection (1–5). The concentration is relatively stable under physiological conditions (6, 7). However, when the body is in the state of inflammation or other diseases, the immune system is activated and suPAR level is upregulated, which will greatly increase the content of suPAR in serum (1). Therefore, the level of suPAR has the potential to guide the diagnosis and prognosis of sepsis.

According to the guidelines for sepsis 3.0, sepsis is a disorder of the host's response to infection, resulting in life-threatening organ

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dysfunction (8). It needs to be differentiated from other infections or systemic inflammation such as bacteremia and systemic inflammatory response syndrome (SIRS). Timely diagnosis and accurate treatment are essential to reduce the mortality of sepsis (9). Unfortunately, the current clinical diagnosis of sepsis remains a challenge. Biomarkers are a commonly used diagnostic tool for diseases, with the advantages of fully automatic identification, short turnaround time, and low production costs (1). However, for patients with sepsis, biomarkers that contribute to decision-making are still insufficient. The guidelines of the Surviving Sepsis Campaign (SSC) updated in 2018 only recommend procalcitonin (PCT) as a biomarker for sepsis (10). There is an urgent need for accurate and effective early biomarkers.

Systematic reviews published to date indicate that suPAR has a moderate diagnostic value for bacterial infection or systemic inflammation (11, 12). Backes et al. suggested that suPAR is not specific enough to diagnosing infections, whereas their review included only a limited number of studies (11). However, a large number of subsequent original studies have shown that suPAR has a reliable diagnostic and prognostic value for patients with sepsis. It is still unclear whether suPAR can be an effective biomarker for the diagnosis and prognosis of sepsis. This study was designed to evaluate the timely diagnosis and prognosis efficacy of suPAR in patients with sepsis, to assess the potential of assisting clinical decision-making, and to provide a reference for the clinical application of new biomarkers for sepsis.

## MATERIALS AND METHODS

All methods followed the PRISMA guidelines for conducting this systematic review and meta-analysis (13, 14).

### Data sources and searches

The review authors searched for medical literature before March 2019. The research has been conducted in electronic databases such as the Cochrane Library, PubMed, Excerpt Medica Database (Embase), Web of Science (WOS), and in the reference lists from review articles, irrespective of publication date, status, or language. The search was conducted with the following keywords: *suPAR and sepsis or septicemia or septicemia or septic shock*. Search strategies in Cochrane Library, PubMed, Embase, and WOS can be found in the Supplement, Supplemental Digital Content, <http://links.lww.com/SHK/A930>.

The present meta-analysis includes studies that meet the following criteria:

1. Adult patients with confirmed or suspected sepsis (over 18 years of age). Hospitalization in intensive care unit or emergency department.
2. The studies included the results of suPAR diagnosis and/or prognosis in patients with sepsis. And the selected studies were able to extract information from the  $2 \times 2$  contingency table. Sepsis or infection was diagnosed by the latest reference standard in the original study, such as sepsis3.0, sepsis2.0, and microbiological testing.
3. No publication date, status, or language restrictions were applied. Clinical original articles were included, whereas the secondary study, conference abstracts, editorials, and animal experiments were excluded.

### Study selection

Two review authors (QH, HX) independently assessed the studies to be included based on the titles, abstracts, and keywords. If a study was found relevant to our topic, at least two reviewers will further evaluate the full text to determine whether it meets the inclusion criteria or not. In case of inconsistencies between the reviewers, the third reviewer (JL) will be consulted. To further ensure the eligibility of a study, the authors have been consulted when additional information is needed in the study, for example, the details of results and methods or allocation concealment. A study diagram was prepared for this purpose to demonstrate the entire process of literature research and the selection of studies.

### Data extraction and quality assessment

The data were extracted by two review authors independently (TS, PY) and the resulting differences were resolved by the third reviewer (KY). The extracted data included lead author, publication year, country of origin, and participant characteristics (age, sex, and hospitalization, prevalence, mortality rate, and the measured time of suPAR levels). The optimal cutoff threshold, values for sensitivity, specificity, true-positive, true-negative, false-positive, and false-negative, and the area under the receiver-operating characteristic (ROC) curve (AUC). Where data were missing, a letter will be written to the authors to request for the data. If the letter brings about no response after 4 weeks, an e-mail will be sent. Still no response, we will use estimates based on available data. The outcomes which cannot be pooled or analyzed are described in the literature.

Two review authors (J Liu, J Lu) evaluated each involved study independently; they applied the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (15). The quality and bias of the included studies were assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) (16) by two independent authors (J Liu, J Lu). In case of any inconsistencies, agreement has been reached through discussion among all the authors. The quality has been assessed from two perspectives, including risk of bias and applicability concerns. The summary charts have been made to show the assessment of the risk of bias (Fig. S1, Supplemental Digital Content, <http://links.lww.com/SHK/A930>).

### Data synthesis and analysis

This study used StataSE14.0 (StataCorp; College Station, Tex) to analyze the extracted data. The Spearman correlation coefficient was used to evaluate the threshold effect of suPAR diagnosis and prognostic accuracy. The pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR) were calculated. The accuracy of the diagnostic and prognostic effects was evaluated by constructing a summary receiver-operating characteristic (SROC) curve. AUC reflects the accuracy of diagnostic experiments, 0.5 to 0.7 indicates low accuracy, 0.7 to 0.9 indicates moderate accuracy, and  $>0.9$  indicates high accuracy. Heterogeneity was assessed by  $Q$  test (significant heterogeneity if  $P < 0.05$ ) and  $I^2$  test (significant heterogeneity if  $I^2 > 50\%$ ). If substantive heterogeneity ( $I^2 > 50\%$ ) exists, univariate meta-regression and subgroup analysis are performed to analyze the sources of heterogeneity. The tested items of meta-regression analysis were from the baseline characteristics table. The median cutoff values of the included studies were calculated, and the studies were divided into high cutoff point subgroup (cutoff values  $\geq$  the median) and low cutoff point subgroup (cutoff values  $<$  the median). Based on the results, forest plots were made to demonstrate the cumulative effect of suPAR. Deek's funnel plot was used to assess the publication bias. The  $\alpha$  value was set at 0.05.

## RESULTS

A flow chart of the study selection process (Fig. 1) was prepared according to the PRISMA guidelines (17). After reviewing the title and abstract, 111 articles were screened for full-text review. Of these, 81 articles failed to meet the inclusion criteria. Only 30 studies fulfilled all criteria. Among them, Georgescu et al. (18, 19) and Kofoed et al. (20, 21) produced two articles from two different studies, respectively. In summary, 30 studies involving 6,906 patients were included in our systematic review and meta-analysis.

The baseline characteristics of the 30 identified studies (18–47) are summarized, as shown in Table 1. Of the included studies (18, 21–23, 26, 27, 30, 31, 35, 37–40, 42, 44, 45, 47), 17 studies including 2,722 patients reported the results of suPAR in the diagnosis of sepsis, and 19 studies including 5,622 patients reported the usefulness of suPAR for predicting poor outcomes in sepsis (19, 20, 22, 24, 25, 27–30, 32–34, 36, 38, 39, 41, 43, 44, 46). Of these, there were eight studies reported the diagnostic value of suPAR in bacterial sepsis (18, 21, 23, 27, 31, 35, 40, 42), and eight reported the results about the value of suPAR predicting mortality from bacterial sepsis (19, 20, 25, 27, 32–34, 41). In addition, five studies investigated the effect of suPAR in differentiating sepsis from SIRS

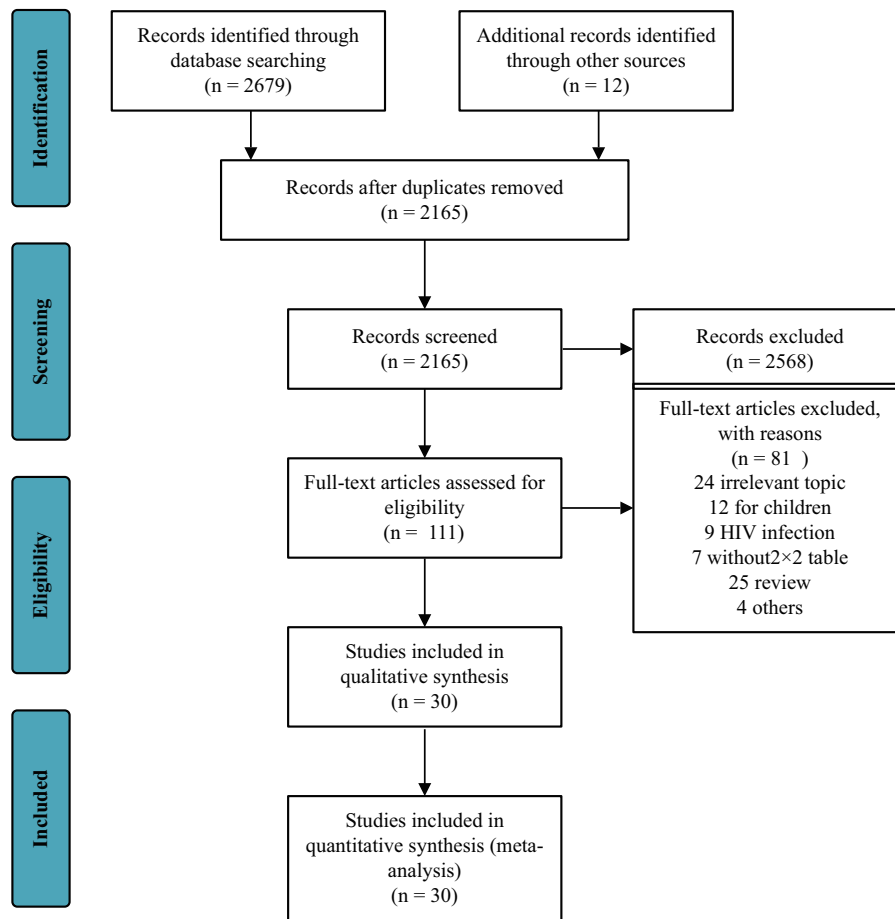


Fig. 1. PRISMA (preferred reporting items for systematic reviews and meta-analyses) flow diagram and exclusion criteria.

(22, 31, 42, 45, 47). Most of the included studies tested suPAR levels at admission or within 24 h after admission, thus the test results can reflect the timely diagnostic and prognosis value of suPAR. All included studies used an enzyme-linked immunosorbent assay kit (most of them used ViroGates, Birkerød, Denmark) to test the level of suPAR. The optimal cutoff threshold of each study was retrospectively determined based on the ROC curve. The median cutoff value for suPAR in the included studies where it was used for the diagnosis of sepsis was 7.5 ng/mL (range: 2.7–12.0 ng/mL), and the median cutoff value where it was used for mortality prediction was 9.6 ng/mL (range: 6.3–14.3 ng/mL).

#### Diagnostic value of suPAR for sepsis

The pooled sensitivity of suPAR in diagnosing sepsis was 0.76 [95% confidence interval (CI), 0.63–0.86;  $I^2 = 93.71\%$ ,  $Q = 254.49$  ( $P < 0.01$ )] and the specificity was 0.78 [95% CI, 0.72–0.83;  $I^2 = 78.46\%$ ,  $Q = 74.29$  ( $P < 0.01$ ); Fig. 2]. The PLR and NLR were 3.5 (95% CI, 2.6–4.7) and 0.30 (95% CI, 0.18–0.50), respectively, and the DOR was 12 (95% CI, 6–24). The AUC was 0.83 (95% CI, 0.80–0.86; Fig. 3), indicating that suPAR has a moderate diagnostic accuracy in sepsis.

As for publication bias, there was no significant difference detected by Deek's funnel plot ( $P = 0.20$ ; Fig. S2, Supplemental Digital Content, <http://links.lww.com/SHK/A930>). In addition, there was no significant difference in threshold effects

(Spearman correlation coefficient = 0.007;  $P = 0.98$ ). Because of the non-negligible heterogeneity in the included studies, we used univariate meta-regression and subgroups to analyze sources of sensitivity and specific heterogeneity. The region, clinical setting, reference standard for diagnosis sepsis, tested sample, measured time, and type of assay kit for detecting the level of suPAR were used as covariates. Meta-regression analysis showed that the tested variables failed to explain the source of heterogeneity in sensitivity and specificity (Fig. S3 Supplemental Digital Content, <http://links.lww.com/SHK/A930>). Subgroup analysis is presented in Table 2.

#### Prognostic value of suPAR for sepsis mortality

Twelve studies reported the results of suPAR used to predict mortality in sepsis patients. As shown in Figure 4, the pooled sensitivity of suPAR for predicting mortality of sepsis was 0.74 [95% CI, 0.67–0.80;  $I^2 = 67.96\%$ ,  $Q = 56.18$  ( $P < 0.01$ )] and the specificity was 0.70 [95% CI, 0.63–0.76;  $I^2 = 88.73\%$ ,  $Q = 159.69$  ( $P < 0.01$ )]. The PLR and NLR were 2.5 (95% CI, 2.0–3.0) and 0.38 (95% CI, 0.30–0.47), respectively, and the DOR was 7 (95% CI, 5–9). The AUC was 0.78 (95% CI, 0.74–0.82; Fig. 5), indicating that suPAR has moderate accuracy in predicting sepsis mortality.

No significant threshold effects were found in these studies (Spearman correlation coefficient = 0.257;  $P = 0.29$ ). However, Deek's funnel plot showed a publication bias ( $P = 0.01$ ;

TABLE 1. Characteristics of included studies

Study type	Author	Year	Country	Study design	Clinical setting	Reference standard	Sample size	Age, y	Morbidity, %	Cutoff <sup>1</sup> , ng/mL	Mortality, %	Cutoff <sup>2</sup> , ng/mL	Tested sample	Measured time	Type of assay kit
P	Agustin Julián-Jiménez	2019	Spain	MPR	ED	Sepsis-3	136	84.5	NA	NA	9.5	7.1	Plasma	D0	ViroGates
D	Jing-jing Zhao	2018	China	PR	ICU	Sepsis: International Guidelines for Management of Severe Sepsis and Septic Shock; SIRS: the 1991 ACCP/SCCM	88	62.5	63.0 <sup>*</sup>	5.5	NA	NA	Serum	D0	ViroGates
D	L Lazaridis	2018	Greece	PR	ICU	Sepsis-3	100	61.3	50.0 <sup>†</sup>	8.4	NA	NA	Serum	D1	ViroGates
P	Xiaoling Wu	2017	China	PR	ICU	Berlin definition	162	57.2	NA	NA	30.4	14.3	Plasma	D0	ViroGates
D&P	Mian Zeng	2016	China	PR	ICU	Sepsis: International Guidelines for Management of Severe Sepsis and Septic Shock; SIRS: the 1991 ACCP/SCCM	126	59.0	73.9	9.5	37.8	12.0	Plasma	D1	USCN Life Science
D	Xuan Liu	2016	China	PR	ICU	SCCM/ESICM/ACCP/ATS/SIS international sepsis definitions	137	69.5	NA	NA	17.1	10.8	Plasma	D1	ViroGates
D&P	Walea S. Khater	2016	Egypt	PR	ICU	2001 International Sepsis Definitions Conference criteria	80	68.9	50.0	4.4	60.0	6.3	Serum	D1	Quantikine
P	Panagiotis Tsirigotis	2016	Greece	PR	ICU	SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions	105	66.6	NA	NA	36.2	7.6	Serum	D1	ViroGates
D	Mitra Barati	2015	Iran	PR	ICU	International guidelines Based on the American College of Chest Physicians/ Society of Critical Care Medicine (ACCP/SCCM) Sepsis Directory	107	62.4	48.2 <sup>‡</sup>	8.5	NA	NA	Plasma	D1	USCN Life Science
P	Anca Meda Georgescu1	2015	Romania	PR	ICU	The 1991 ACCP/SCCM	67	NA	62.5 <sup>§</sup>	9.5	71.6	10.6	Plasma	D1	ViroGates
D&P	Anca Meda Georgescu2	2015	Romania	PR	ICU	Blood cultures	49	71.0	28.6	9.9	77.6	11.5	Serum	D0	ViroGates
D	Anne J. M. Looen	2014	Netherlands	RR	ED	Blood cultures	125	62.2	16.0	7.5	NA	NA	Serum	NA	ViroGates
D	M. Reichsoellner	2014	Austria	PR	ED	Blood cultures	159	65.9	69.2	7.6	NA	NA	Plasma	D0	ViroGates
D	Matti Vänskä	2014	Finland	PR	NA	Guidelines of the American College of Chest Physicians/Society of Critical Care Medicine	99	56.0	21.2	4.0	NA	NA	Plasma	D0	ViroGates
P	R. B. Raggam	2014	Austria	PR	ED et al.	Blood cultures	902	63.0	NA	NA	13.0	9.2	Plasma	D0	ViroGates
D&P	Katia Donadello	2014	Belgium	PR	ICU	the criteria proposed by the International Sepsis Forum	258	62.0	36.4	5.6	18.1	10.2	Serum	D0	ViroGates
D	Martin Hoenigl	2013	Austria	PR	ED	Blood cultures	132	67.3	41.7	7.9	NA	NA	Serum	D0	ViroGates
P	B. Suberviola	2013	Spain	PR	ICU	2001 International Sepsis Definitions Conference criteria	137	62.6	NA	NA	29.9	9.6	Serum	D0	ViroGates
D	Selcuk Kaya	2013	Turkey	PR	NA	Blood cultures	118	46.8	45	5.9	NA	NA	Serum	D1	ViroGates
P	Evangelos J. Giannarellou-Bourboulis	2012	Greece	MPR	ICU et al.	2001 International Sepsis Definitions Conference criteria	1914	66.1	NA	NA	21.9	12.0	Serum	D1	ViroGates
D&P	R. Uusitalo-Seppala	2012	Finland	PR	ED	Blood cultures	539	61.0	9.1	6.6	6.1	6.4	Plasma	D0	ViroGates
P	R. Huittunen	2011	Finland	PR	NA	Blood cultures	132	62.0	NA	NA	13.6	11.0	Plasma	D1	ViroGates
D&P	Athina Sava	2011	Greece	MPR	ICU et al.	SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions	180	58.4	73.9	10.5	27.8	12.9	Serum	D1	ViroGates
D	Gürdal Yilmaz	2011	Turkey	PR	NA	SIRS criteria defined in 1992	138	43.6	61.6	2.8	NA	NA	Plasma	D0	ViroGates
D&P	Alexander Koch	2011	Germany	PR	ICU	SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions	273	64.0	72.2	8.0	35.9	8.0	Serum	D0	ViroGates
P	T. Molkänen	2011	Finland	PR	NA	Blood cultures	59	NA	NA	NA	32.2	9.3	Serum	D2-5	ViroGates
P	K. Kofoed	2008	Denmark	PR	ED et al.	SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions	151	56.0	NA	NA	6.0	6.6	Plasma	D0	Luminex
D	K. Kofoed	2007	Denmark	PR	ED et al.	SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions	151	56.0	63.6	2.7	NA	NA	Plasma	D0	Luminex
P	Holger Jon Møller	2006	Denmark	PR	NA	Blood cultures	141	83.5	NA	NA	16.3	8.3	Plasma	D0	NA
P	P. Wittenhagen	2004	Denmark	MPR	NA	Blood cultures	141	64.0	NA	NA	17.0	10.0	Plasma	D1	NA

Three different sets of data in the Jing-jing Zhao's study: <sup>†</sup>represents the rate of sepsis; <sup>‡</sup>represents the rate of sepsis from SIRS. Two different sets of data in the Mitra Barati's study: <sup>\*</sup>represents the rate of sepsis from SIRS; <sup>§</sup>represents infection rate of sepsis. ARDS, acute respiratory distress syndrome; D&P, diagnosis and prognosis value; ED, emergency department; ICU, intensive care unit; MPR, multicenter prospective recruitment; NA, not available; P, prognosis value; PR, prospective recruitment; RR, retrospective recruitment; SIRS, systemic inflammatory response syndrome. Cut-off<sup>1</sup>: the cutoff value of prevalence; Cut-off<sup>2</sup>: the cutoff value of mortality. D0: the measured time of suPAR was at the time of admission; D1: the measured time of suPAR was within 24 h of admission; D2-5: the measured time of suPAR was within 2 to 5 days of admission.



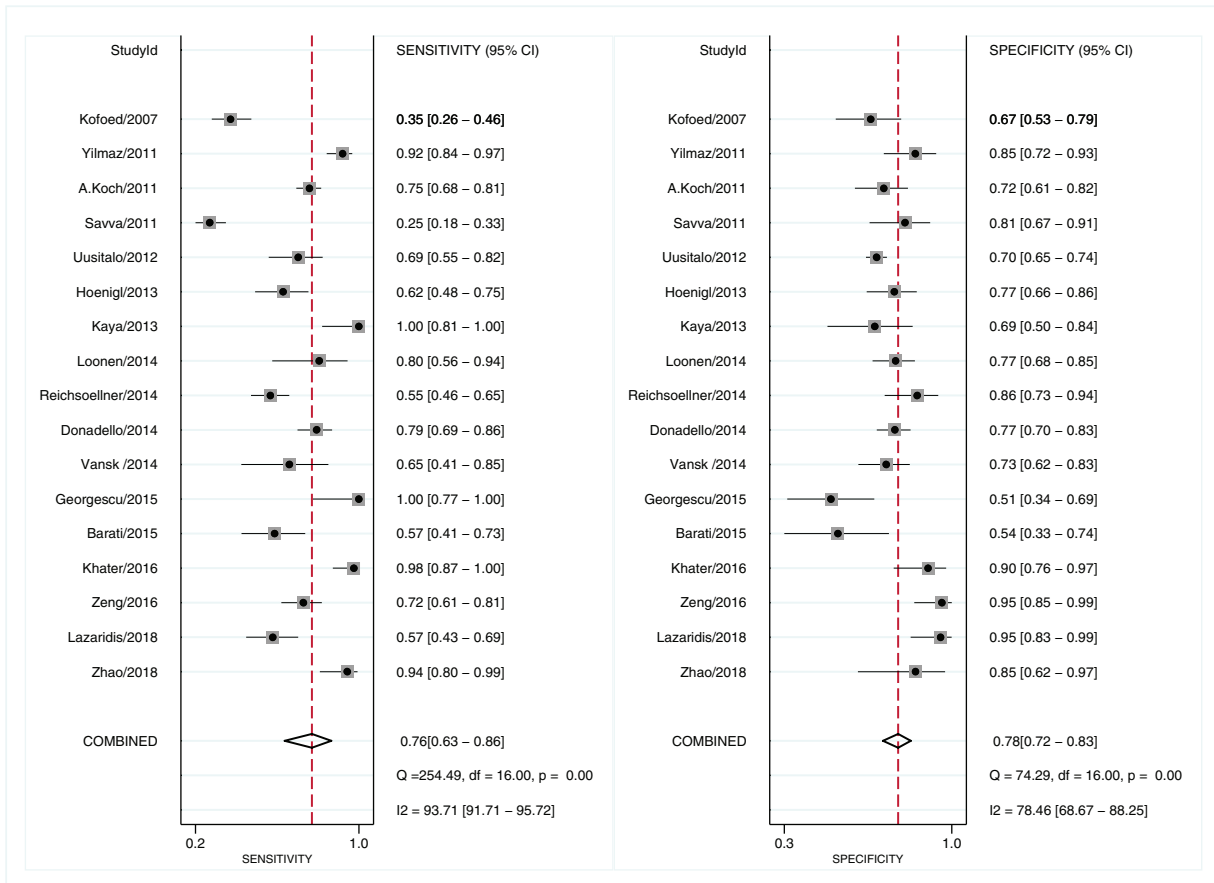


FIG. 2. Forest plot of the sensitivity and specificity of suPAR for the diagnosis of sepsis.

Figure S4, Supplemental Digital Content, <http://links.lww.com/SHK/A930>). In the meta-regression analysis, heterogeneity sources among the study were assessed by using the multicenter design, region, clinical setting, reference standard for diagnosis sepsis, tested sample, measured time, and type of assay kit. The findings showed that the multicenter design and region significantly accounted for the heterogeneity of sensitivity. As for the heterogeneity of specificity, clinical setting, reference standard for diagnosis sepsis, and the suPAR-level measured time showed significant statistical difference (Figure S5, Supplemental Digital Content, <http://links.lww.com/SHK/A930>). The subgroup analysis is presented in Table 2.

#### Subgroup analysis of the diagnostic and prognostic value of suPAR

As for the diagnostic value of suPAR in differentiating sepsis from SIRS, the pooled sensitivity and specificity were 0.67 [95% CI, 0.58–0.76;  $I^2 = 68.45%$ ,  $Q = 12.68$  ( $P = 0.01$ )] and 0.82 [95% CI, 0.73–0.88;  $I^2 = 61.65%$ ,  $Q = 10.43$  ( $P = 0.03$ )], respectively. The PLR and NLR were 3.7 (95% CI, 2.4–5.8) and 0.40 (95% CI, 0.30–0.53), respectively. The DOR was 9 (95% CI, 5–18), and the AUC was 0.81 (95% CI, 0.77–0.84).

The sensitivity and specificity for diagnosing bacterial sepsis were 0.81 [95% CI, 0.57–0.94;  $I^2 = 92.44%$ ,  $Q = 92.63$  ( $P < 0.01$ )] and 0.73 [95% CI, 0.66–0.79;  $I^2 = 72.00%$ ,  $Q = 25.00$  ( $P < 0.01$ )]. The PLR and NLR were 3.1 (95%

CI, 2.3–4.0) and 0.25 (95% CI, 0.10–0.66), respectively. The DOR was 12 (95% CI, 4–38), and the AUC was 0.79 (95% CI, 0.75–0.82). The pooled sensitivity and specificity for predicting mortality of bacterial sepsis were 0.68 [95% CI, 0.59–0.76;  $I^2 = 59.87%$ ,  $Q = 17.44$  ( $P = 0.01$ )] and 0.77 [95% CI, 0.66–0.85;  $I^2 = 89.31%$ ,  $Q = 65.47$  ( $P < 0.01$ )], respectively. The PLR and NLR were 2.9 (95% CI, 2.1–4.1) and 0.41 (95% CI, 0.34–0.51), respectively, and the DOR was 7 (95% CI, 5–10). The AUC was 0.77 (95% CI, 0.73–0.81).

In the subgroup analysis of diagnostic studies based on cutoff value, the studies reported cutoff value  $< 7.5$  ng/mL showed the pooled sensitivity and specificity were 0.85 [95% CI, 0.67–0.94;  $I^2 = 95.12%$ ,  $Q = 143.57$  ( $P < 0.01$ )] and 0.77 [95% CI, 0.70–0.82;  $I^2 = 84.31%$ ,  $Q = 51.14$  ( $P < 0.01$ )], respectively. The PLR and NLR were 3.6 (95% CI, 2.5–5.4) and 0.20 (95% CI, 0.08–0.50), respectively, and the DOR was 18 (95% CI, 5–66). The AUC was 0.83 (95% CI, 0.80–0.86). As for the cutoff value  $\geq 7.5$  ng/ml, the pooled sensitivity and specificity were 0.66 [95% CI, 0.50–0.78;  $I^2 = 92.42%$ ,  $Q = 105.54$  ( $P < 0.01$ )] and 0.79 [95% CI, 0.69–0.87;  $I^2 = 79.87%$ ,  $Q = 39.74$  ( $P < 0.01$ )], respectively. The PLR and NLR were 3.2 (95% CI, 2.1–4.9) and 0.43 (95% CI, 0.29–0.64), respectively, and the DOR was 7 (95% CI, 4–15). The AUC was 0.80 (95% CI, 0.76–0.83).

In the subgroup analysis of prognostic studies based on cutoff value, the studies reported cutoff value  $< 9.6$  ng/mL

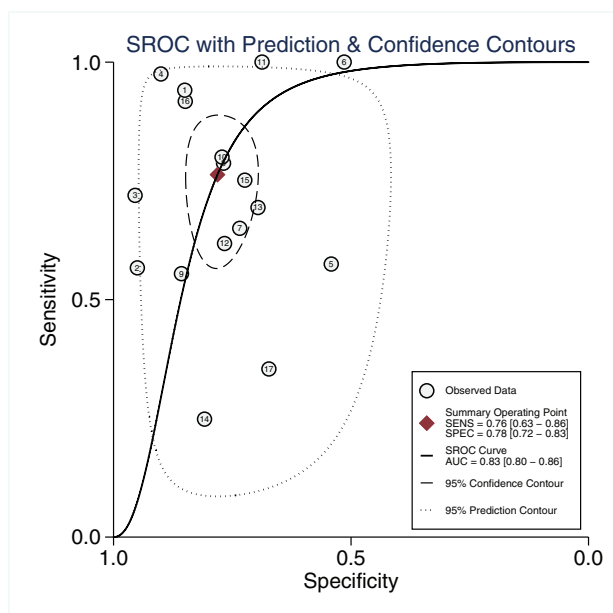


FIG. 3. Summary receiver-operating characteristics curve for studies evaluating the diagnosis value of suPAR for sepsis.

showed the pooled sensitivity and specificity were 0.72 [95% CI, 0.66–0.77;  $I^2 = 0.00\%$ ,  $Q = 7.07$  ( $P = 0.53$ )] and 0.65 [95% CI, 0.58–0.72;  $I^2 = 85.11\%$ ,  $Q = 53.74$  ( $P < 0.01$ )], respectively. The PLR and NLR were 2.1 (95% CI, 1.6–2.6) and 0.43 (95% CI, 0.34–0.56), respectively, and the DOR was 5 (95% CI, 3–8). The AUC was 0.74 (95% CI, 0.70–0.78). As for the cutoff value  $\geq 9.6$  ng/ml, the pooled sensitivity and specificity were 0.74 [95% CI, 0.61–0.84;  $I^2 = 82.06\%$ ,  $Q = 50.17$  ( $P < 0.01$ )] and 0.72 [95% CI, 0.64–0.83;  $I^2 = 91.43\%$ ,  $Q = 105.01$  ( $P < 0.01$ )], respectively. The PLR and NLR were 3.0 (95% CI, 2.1–4.1) and 0.35 (95% CI, 0.24–0.51), respectively, and the DOR was 9 (95% CI, 5–14). The AUC was 0.81 (95% CI, 0.77–0.84).

### DISCUSSION

This meta-analysis shows that suPAR has moderate diagnosis and prognosis value for sepsis. The pooled data of 17

studies, including 2,722 patients, showed that the AUC of suPAR in the diagnosis of sepsis was 0.83. A total of 19 studies, including 5,622 patients, showed the AUC of the prognosis value of suPAR was 0.78. This indicates that elevated suPAR levels are associated with a high risk of poor outcomes of sepsis. In subgroup analysis, the AUC of diagnosis and prognosis value for bacterial sepsis were 0.79 and 0.77, respectively. Furthermore, suPAR also demonstrated moderate diagnostic value to discriminate between sepsis and SIRS with an AUC of 0.81 in the pooled data.

Currently, the PCT is the only biomarker recommended in the SSC guidelines, and demonstrates that PCT can help clinical decision-making in patients with sepsis (11). Serum C-reactive protein (CRP) is also a widely studied biomarker in sepsis patients. Although CRP can be used to indicate acute inflammation, its specificity is relatively low, which limits its application in the diagnosis of sepsis (48). For PCT, a meta-analysis by Chengfen Y et al. (49) showed that PCT is a promising diagnostic biomarker for sepsis with a pooled sensitivity and specificity of 74% and 70%, respectively. Because the biomarkers mentioned above lack specificity for sepsis and the levels may be elevated in other inflammatory diseases, these biomarkers are more useful for ruling out sepsis than for ruling it in (50). Compared with the diagnosis value of PCT identified by previous meta-analysis, we found that suPAR and PCT have similar diagnostic accuracy. More importantly, suPAR exhibited higher specificity (PCT: 70% vs suPAR: 78%) than PCT and CRP, suggesting that suPAR has an advantage in identifying nonsepsis populations and is more distinguishable than other biomarkers in patients with different inflammatory diseases (41). Therefore, suPAR has the potential to complement existing biomarker defects.

Identifying of sepsis from noninfectious original SIRS is critical for clinical diagnosis and treatment. The sepsis 3.0 guidelines emphasize the existence of dysregulation of host response to infection and organ dysfunction caused by infection in the definition of sepsis (8). However, SIRS only reflects the appropriate immune response, not the immune response disorder because its pathological mechanism is infection and the concomitant inflammatory response. Regarding the accuracy of suPAR in distinguishing between sepsis and SIRS, Wentao Ni

TABLE 2. Subgroup analysis of the diagnostic and prognostic value of suPAR based on different variables

Study type	Variables	Studies, no. (patients, no.)	Sensitivity (95% CI)	Specificity (95% CI)	PLR (95% CI)	NLR (95% CI)	DOR (95% CI)	AUC (95% CI)
Diagnostic value	Sepsis	17 (2722)	0.76 (0.63–0.86)	0.78 (0.72–0.83)	3.50 (2.60–4.70)	0.30 (0.18–0.50)	12 (6–24)	0.83 (0.80–0.86)
	Sepsis from SIRS	5 (637)	0.67 (0.58–0.76)	0.82 (0.73–0.88)	3.70 (2.40–5.80)	0.40 (0.30–0.53)	9 (5–18)	0.81 (0.77–0.84)
	Bacterial Sepsis	8 (1316)	0.81 (0.57–0.94)	0.73 (0.66–0.79)	3.10 (2.30–4.00)	0.25 (0.10–0.66)	12 (4–38)	0.79 (0.75–0.82)
	Cutoff <7.5 ng/mL	8 (1471)	0.85 (0.67–0.94)	0.77 (0.70–0.82)	3.60 (2.50–5.40)	0.20 (0.08–0.50)	18 (5–66)	0.83 (0.80–0.86)
	Cutoff $\geq 7.5$ ng/mL	9 (1251)	0.66 (0.50–0.78)	0.79 (0.69–0.87)	3.20 (2.10–4.90)	0.43 (0.29–0.64)	7 (4–15)	0.80 (0.76–0.83)
Prognostic value	Sepsis	19 (5622)	0.74 (0.67–0.80)	0.70 (0.63–0.76)	2.50 (2.00–3.00)	0.38 (0.30–0.47)	7 (5–9)	0.78 (0.74–0.82)
	Bacterial Sepsis	8 (2114)	0.68 (0.59–0.76)	0.77 (0.66–0.85)	2.90 (2.10–4.10)	0.41 (0.34–0.51)	7 (5–10)	0.77 (0.73–0.81)
	Cutoff <9.6 ng/mL	9 (2386)	0.72 (0.66–0.77)	0.65 (0.58–0.72)	2.10 (1.60–2.60)	0.43 (0.34–0.56)	5 (3–8)	0.74 (0.70–0.78)
	Cutoff $\geq 9.6$ ng/mL	10 (3236)	0.74 (0.61–0.84)	0.75 (0.64–0.83)	3.00 (2.10–4.10)	0.35 (0.24–0.51)	9 (5–14)	0.81 (0.77–0.84)

AUC, area under the receiver-operating characteristic curve; CI, confidence interval; DOR, diagnostic odds ratio; NLR, negative likelihood ratio; PLR, positive likelihood ratio.

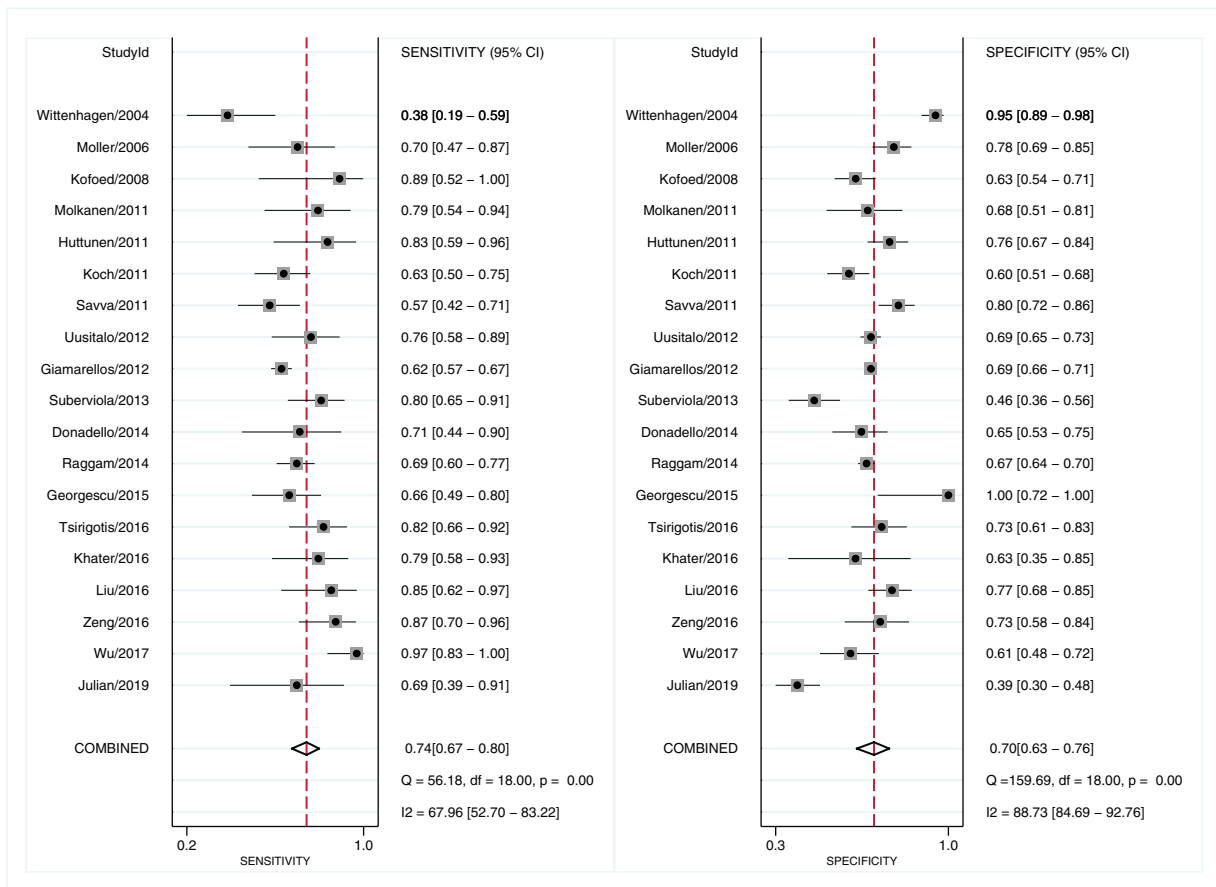


FIG. 4. Forest plot of sensitivity and specificity of suPAR for the prediction of mortality in sepsis.

et al. (12) considered suPAR as a low accurate biomarker (AUC = 0.68). Interestingly, our study found that suPAR has a promising diagnostic value (AUC = 0.81) for differentiating sepsis from noninfectious original SIRS. Moreover, it better differentiates between infectious and noninfectious causes of critical illness than CRP, lipopolysaccharide-binding protein (LBP), and interleukin (IL)-6. This suggests that the level of suPAR has the potential to identify infectivity from noninfectivity (51), which will improve the clinical guidance value of suPAR and aid decision-making.

Existing biomarkers fail to show the ideal accuracy for predicting sepsis mortality (52, 53). A meta-analysis by Liu et al. (54) found that the PCT levels at admission were moderately accurate for the prognosis of sepsis, with sensitivity of 76% and specificity of 64%. Compared with the identified effect value of PCT we found that suPAR was slightly better in terms of specificity of prognostic value (PCT: 64% vs suPAR: 70%). Although the value of using suPAR alone to prognosis sepsis is limited, the elevated suPAR levels in the initial stage is still associated with a high risk of death. Wentao Ni et al. (12) showed that the mortality rate of bacterial infection increased by 3.37 times with the elevated suPAR level. A primary study reported that the use of combined indicators to predict sepsis mortality can be effective in improving accuracy (43). And this study suggested that combining the Acute Physiology and Chronic Health Evaluation II (APACHE II) score with the serum suPAR level could be a

measurement for predicting sepsis outcomes. Due to the limitation of suPAR in prognosis sepsis, further investigation is required to evaluate the predictive efficacy of suPAR in combination with other indicators.

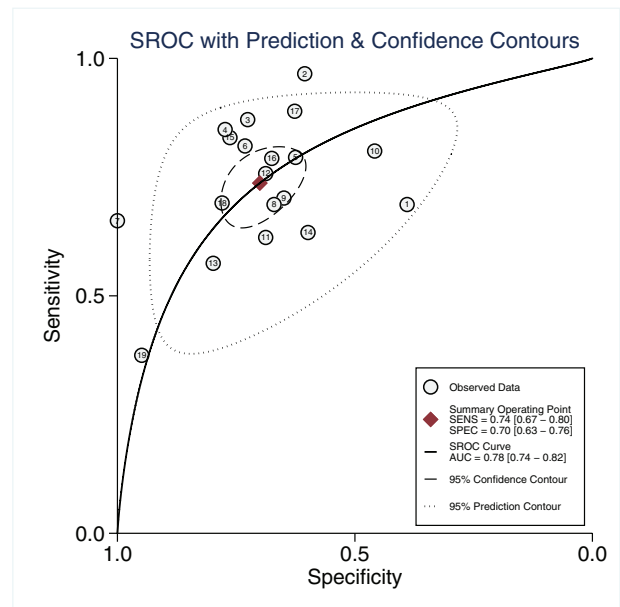


FIG. 5. Summary receiver-operating characteristics curve for evaluating prediction value of mortality of suPAR in sepsis.

The suPAR measurement time of the included studies was concentrated at the time of admission or within 24 h after admission. Therefore, these results suggest that the level of suPAR could be a timely and effective criterion for the diagnosis and prognosis of sepsis. There are early clinical screening tools, such as early warning score (EWS), which predicts sepsis by analyzing available electronic data (55). EWS shows extremely opposite sensitivity and specificity of 0.16 and 0.97, respectively (56). Although EWS has good specificity, its low sensitivity significantly reduces diagnostic accuracy. In addition, the cumbersome testing items included in the score also increase the difficulty of clinical practice (57). Unlike other early detection indicators of sepsis, as a biomarker, suPAR has non-negligible advantages, including fully automated identification, short turnaround time, and low production costs.

At present, there is no gold standard for diagnosing sepsis; no tool for selecting, evaluating, and de-escalating treatment; and no reliable biomarker for allocating risk profiles or predicting outcome (58). In addition, accurate and timely diagnosis can provide a strong guarantee for screening high-risk populations and improving clinical courses and outcomes (59). Examination of a disease-specific biomarker may help in the identification, early diagnosis and prevention of disease, and monitoring during treatment (60). Clinicians are constantly seeking biomarkers to diagnosis sepsis and distinguish sepsis from SIRS. The SSC guidelines recommended only one biomarker in clinical practice, the PCT (10), which is insufficient to aid the diagnosis and clinical decision of sepsis. Therefore, effective biomarkers are needed to promote the diagnosis of sepsis and to monitor the course of the disease. Our study suggests that suPAR is a promising biomarker for sepsis. To assess the potential of suPAR assisting clinical decision-making, we compared the effect size of suPAR for sepsis with that of PCT identified in previous meta-analysis (49, 54). The level of suPAR has the similar clinical guiding value to PCT, whereas suPAR exhibits higher specificity than PCT in the diagnosis and prognosis of sepsis. Hence, suPAR can partially facilitate the deficiencies of PCT in terms of specificity. In addition, the level of suPAR has the potential to identify infectivity from noninfectiousness, which will improve the clinical guiding value of suPAR and aid decision-making. Considering the lack of biomarkers for sepsis and the similar clinical value of suPAR and PCT, suPAR has the potential value in the clinical practice for sepsis patients.

According to the sepsis 3.0 guidelines, it is a need to identify sepsis from SIRS (8). In previous studies, to the best of our knowledge, most systematic reviews focused on the relationship between suPAR and bacterial infection or SIRS (11, 12). The sepsis was treated as one of the subgroups for preliminary analysis. In addition, the number of included original studies is limited. The meta-analysis by Wentao Ni et al. (12) focused on bacterial infections and only studied bacterial-induced sepsis, whereas the pathogenic microorganisms of sepsis include bacteria, fungi, viruses, and parasites. The sepsis population they studied was not representative enough for sepsis. They found that suPAR is ineffective in distinguishing sepsis from SIRS. However, in our study, suPAR showed an effective ability to distinguish sepsis from SIRS, thus indicating that suPAR has the

potential to identify infectivity from noninfectiousness. In addition, Ni et al. only studied sepsis in a subgroup analysis and did not analyze the heterogeneity of effective values of suPAR for sepsis. They cannot rule out a substantive heterogeneity or analyze the sources of heterogeneity. Considering the lack of representative sepsis patients and the inadequate information and analysis of sepsis, the conclusions of previous studies can hardly guide clinical practice and cannot be directly applied to sepsis patients. The clinical value of suPAR in the diagnosis, prognosis, and therapeutic guidance of sepsis still needs to be well defined.

Compared with meta-analyses of interventions including randomized controlled trials, those including diagnostic studies have more publication bias (61). Publication bias exists in studies which reported the prognostic value. Excluding studies without enough data could contribute to publication and reporting bias. Thus, the prognosis value of suPAR may be overestimated. As for the significant degree of heterogeneity, we performed meta-regression and subgroup analysis to explore the source of heterogeneity. Meta-regression analysis revealed that no tested variables substantially affected the sensitivity and specificity of suPAR for sepsis diagnosis. However, due to the diversity of reference standards for diagnosis sepsis among included studies, univariate meta-regression cannot fully explain the impact of the reference standard on heterogeneity, thus it should be carefully considered. Through analysis of prognosis studies, it was found that multicenter design and region have an impact on the heterogeneity of sensitivity, and the clinical setting, reference standards, and measurement time affect the heterogeneities of specificity. Given the impact of different types of infectious original in sepsis on heterogeneity, we found no significant reduction in the heterogeneity of bacterial sepsis. There were no significant threshold effects in both diagnostic and prognostic studies. As shown in Table 1, higher cutoff points ( $\geq 7.5$  ng/mL for diagnostic studies;  $\geq 9.6$  ng/mL for prognostic studies) indicate a higher specificity of suPAR for sepsis diagnosis and prognosis. Minimal evidence of sensitivity heterogeneity was obtained in prognostic studies at lower cutoff points, indicating that the cutoff value of suPAR can also account for the heterogeneity.

There are several limitations in the current meta-analysis. First, the level of suPAR is associated with a variety of diseases, including sepsis and malignant tumors, kidney damage, and inflammatory bowel disease. The influencing factors of other diseases such as different complications may lead to confounding factors, which is difficult to assess in included studies. Second, it is hard to obtain raw data for each included study, which restricts us to determine the optimal cutoff point for suPAR for the sepsis diagnosis and prognosis. Third, due to the lack of original studies comparing the effective value of suPAR and PCT in patients with sepsis, it is hard to obtain accurate results. However, the trend can still be drawn by comparing the results with the existing meta-analysis of the diagnostic and prognostic value of PCT for sepsis. It is a need for further investigation is required to compare the clinical value of suPAR and that of PCT in patients with sepsis. Finally, although we have analyzed the source of heterogeneity through meta-regression and subgroup analysis, the substantial heterogeneity in the results should still be considered carefully.



## CONCLUSIONS

In conclusion, the results of this systematic review and meta-analysis suggest that suPAR is a feasible biomarker for patients with sepsis. Compared with the diagnosis and prognosis value of PCT identified by previous meta-analysis, the level of suPAR has the similar clinical guiding value to PCT, whereas suPAR exhibited a higher specificity than PCT which can partially facilitate the deficiencies of PCT. In addition, the elevated level of suPAR also has the potential to identify sepsis from SIRS of noninfectious origin, which is helpful in aiding decision-making and improves the clinical guiding value of suPAR. Further investigation is required to evaluate the predictive efficacy of suPAR in combination with other indicators. Considering the lack of reliable biomarkers for sepsis, the effective clinical value of suPAR, and the importance of timely diagnosis for the treatment of sepsis, suPAR should be considered as a biomarker in clinical practice for patients with sepsis.

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