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REVIEW ARTICLE

Accuracy of neutrophil CD64 expression in diagnosing infection in patients with autoimmune diseases: a meta-analysis

Bang-Qin Hu[1,2] · Yi Yang[3] · Chun-Jing Zhao[2] · De-Feng Liu[1] · Fu Kuang[2] · Li-Jun Zhang[4] · Xian Yu[3]

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Abstract

We aimed to systematically evaluate the accuracy of nCD64 in diagnosing infection in patients with autoimmune diseases. Studies were searched in PubMed, Embase, Cochrane Library, China National Knowledge Infrastructure, Wanfang, and Chongqing VIP databases up to October 2018. There was no restriction for language and age. Prospective studies examining the accuracy of nCD64 in diagnosing infection in patients with autoimmune diseases were included. The Quality Assessment of Diagnostic Accuracy Studies-2 tool was used to assess the quality of eligible studies. Stata 15.1 and Meta-DiSc 1.4 software were used for data analysis. Eleven studies fulfilled the inclusion criteria (677 patients, 229 patients with bacterial infection, and 448 without infection). The pooled sensitivity and specificity of nCD64 were 89% (95% confidence interval (CI) 82–93) and 94% (95% CI 91–96), respectively. The pooled positive likelihood ratio and negative likelihood ratio were 14.9 (95% CI 9.3–23.8) and 0.12 (95% CI 0.07–0.20), respectively. The diagnostic odds ratio and area under the summary receiver operating characteristic curve were 123 (95% CI 53–283) and 0.97 (95% CI 0.95–0.98), respectively. The univariate meta-regression analysis showed that region, type of disease, antibiotic therapy, and presentation of nCD64 measurement results were responsible for the heterogeneity. The Deeks' funnel plot asymmetry test showed that there was no publication bias ($p = 0.15$). nCD64 has a good overall diagnostic performance for differentiating infection from disease flare in patients with autoimmune diseases. Further studies are needed to confirm the optimized cutoff value.

Keywords Autoimmune diseases · CD64 · Infection · Meta-analysis · Neutrophil

Introduction

Autoimmune diseases are a spectrum of chronic systemic inflammatory diseases; however, their etiology and mechanism have not been completely illustrated. In the course of a disease, a patient can develop multiple autoimmune diseases simultaneously and experience a wide variety of pathological changes and clinical manifestations. The most indispensable therapeutic modality used against autoimmune diseases is immunosuppressant therapy. However, an accompanying immunocompromised state and recurrent infections can contribute to a fatal outcome [1]. Fever is a common symptom of infection or disease flare in patients with autoimmune diseases. Rheumatologists are often faced with difficulties when it comes to identifying the etiology of autoimmune diseases. Administration of additional or increasing dosages of immunosuppressive agents to improve disease flare can exacerbate infection in those patient populations. Thus, it is of great value to distinguish infection from disease flare in febrile patients with autoimmune diseases in a timely manner.

Prediction of infection has already been extensively studied in patients with various conditions, especially those with sepsis [2], one of the most attractive predictors is a biomarker. However, only a few studies [3–6] have evaluated the diagnostic value of different biomarkers in detecting infection in patients with autoimmune diseases. The conventional markers, for instance, white blood cell count (WBC), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP),

✉ Xian Yu
xiannyyu@outlook.com

1 College of Pharmacy, Chongqing Medical University, Chongqing, China

2 Department of Pharmacy, The Second Affiliated Hospital of Chongqing Medical University, Chongqing, China

3 Phase I Clinical Trial Center, The Second Affiliated Hospital of Chongqing Medical University, Chongqing 400010, China

4 Department of Clinical Laboratory, The Second Affiliated Hospital of Chongqing Medical University, Chongqing, China

lack specificity and are susceptible to immunosuppressive drugs. In recent years, procalcitonin (PCT) shows promise, but the diagnostic performance is moderate [3, 7]. Hence, a new marker for diagnosing infection avoiding the above disadvantages with high sensitivity and specificity is urgently demanded.

The fragment crystallizable (Fc) portion of human immunoglobulin G has three classes of receptors: FcgRI (CD64), FcgRII (CD32), and FcgRIII (CD16). Among them, CD64 is the only high-affinity receptor and is constitutively expressed on macrophages, monocytes, and eosinophils. In healthy individuals, the expression of CD64 on neutrophils (nCD64) is at very low levels. However, when microorganisms and some inflammatory cytokines such as interferon-gamma (IFN-γ) and granulocyte colony-stimulating factor (G-CSF) are present, those stimulating factors can induce significant expression of CD64 on neutrophils [8, 9]. The diagnostic value of nCD64 in the detection of sepsis [10] and neonatal infection [11] has been investigated in previous meta-analyses. Recently, some published studies have focused on the usefulness of nCD64 in diagnosing infection in autoimmune disease patients, but the sample sizes used were small and individual studies showed discordant results. In addition, previous studies have suggested that patients with vasculitis [8], active interstitial pneumonia [12], and Behcet's disease [13] exhibited higher circulating levels of nCD64 during acute exacerbations in the absence of infection. Thus, we aimed to perform this diagnostic meta-analysis to assess the usefulness of nCD64 in diagnosing infection in autoimmune disease patients with fever.

Methods

Search strategy

Before this study was undertaken, a protocol was registered at the PROSPERO (CRD42018114454). We reported this study in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis statement [14]. Studies were systematically searched in PubMed, Embase, Cochrane Library databases, China National Knowledge Infrastructure, Wanfang, and Chongqing VIP databases up to June 2018 by two independent investigators. We updated the literature search of the above electronic databases in October 2018. There was no restriction for language and age. The following MeSH terms and text words were used to locate relevant studies: "receptors," "IgG," "fc receptor," "CD64," "neutrophils," "infection," "sepsis," "septic shock," "bacteremia," "systemic inflammatory response syndrome," "septicemia," "autoimmunity," and "autoimmune disease." For additional studies, we also screened the relevant references listed in the searched papers and reviews. We had also contacted relevant authors for further details.

Literature inclusion and exclusion criteria

The studies were included if they fulfilled the fowling criteria: (1) studies that included autoimmune disease patients suspected of infection; (2) studies that involved collection of blood samples from participants to detect nCD64; (3) studies that presented true positive (TP), false positive (FP), false negative (FN), and true negative (TN) results of the diagnostic tests performed to detect infection; (4) studies that conducted diagnostic accuracy tests with prospective data collection; (5) studies that involved diagnosing an autoimmune disease based on each classification or diagnostic criteria; and studies that used microbiological culture or polymerase chain reaction (PCR), clinical symptoms, biochemical or radiological or imaging evidence, or obvious effects observed by physicians after empirical antibacterial therapy to confirm an infection.

The following studies were excluded: (1) reviews, case reports, letters, conference papers, editorials, and expert opinions; (2) studies with less than ten samples; (3) studies that included healthy persons as controls; and (4) studies with incomplete data.

Data extraction and qualitative assessment

Two reviewers independently identified the studies and extracted the data to obtain information on the studies. The following characteristics were extracted: name of first author, region, publication year, study design, type of disease, diagnostic criteria for autoimmune disease, definition of infection, cutoff value, prevalence of infection, sample size, detecting instrument, whether the samples were collected before antibiotic therapy, analytical method, source of CD64 antibody reagents, and presentation of nCD64 measurement results. The number of TP, FP, FN, and TN was extracted or calculated.

The Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool [15] was used to assess the methodological quality of the included trials by two independent authors. Disagreements between the two authors were resolved by consensus.

Statistical analysis

Stata software version 15.1 (Stata Corporation, College Station, TX, USA) and Meta-DiSc software version 1.4 (http://www.hrc.es/investigacion/metadisc_en.htm) were used for this meta-analysis. The bivariate mixed-effects regression model was used to calculate the pooled pairs of sensitivity and specificity, the pooled positive and negative likelihood ratios, and the summary diagnostic odds ratio along with their 95% confidence interval (CI) [16]. A summary receiver operating characteristic (SROC) curve analysis was performed to evaluate the overall diagnostic accuracy. Fagan's nomogram was used to calculate the post-test probability. When between-study heterogeneity existed, Cochran's Q test and I^2 index were calculated. I^2 values of 25%, 50%, and 75% were nominally assigned as low, moderate, and high estimates, respectively. The presence of a threshold effect on the diagnostic accuracy of nCD64 was evaluated using the Spearman correlation coefficient between the logits of sensitivity and specificity. In addition to the heterogeneity that was likely due to the threshold effect, univariate meta-regression analysis and subgroup analysis were performed to explore the sources of potential heterogeneity in sensitivity and specificity. The covariates included the following elements: region (whether the trial was conducted in Asia), disease (whether the type of disease was systemic lupus erythematosus), expression (whether CD64 molecules per cell was used as the presentation of nCD64 measurement results), sampling (whether samples was collected before antibiotic therapy), instrument (whether the detecting instrument was BD FACSCalibur), and size (whether the sample size was equal or greater than 30). p values less than 0.05 were considered significant. Publication bias was tested by Deeks' funnel plot asymmetry test.

Results

Literature search and study characteristics

We initially retrieved 961 studies by electronic searching, and 2 more relevant studies were identified in the bibliographies of original studies. Of the 961 studies, 364 were from PubMed, 485 from Embase, 31 from Cochrane Library, 18 from China National Knowledge Infrastructure, 55 from Wanfang, and 8 from Chongqing VIP. Among these studies, 944 studies that were repeatedly published, categorized as review articles, involved animal or in vitro experiments, with irrelevant topics, and categorized as conference abstracts were excluded by screening the title and abstract; the remaining 19 possible correlative studies were scrutinized in a full-text review. Among the 19 studies, 8 could not be used to reconstruct the 2 × 2 table. Thus, 11 studies fulfilled our eligibility criteria and were included in the final analysis (Fig. 1).

A total of 677 patients were included, comprising 229 infected patients and 448 non-infected patients. The included studies were published from 2002 to 2018, eight studies were published in English, and three [17–19] were published in Chinese. In addition to one study [18] that recruited adults and children, the other ten studies only recruited adult patients. These studies consisted of five [12, 17, 19–21] patients with rheumatoid arthritis, three [18, 22, 23] with systemic lupus erythematosus, two [8, 9] with systemic autoimmune diseases, and one [24] with inflammatory bowel disease. Most of the studies used a FACSCalibur flow cytometer (Becton-Dickinson) for nCD64 measurement. The CD64 antibody reagents in nine studies were provided by the Becton-Dickinson company, and those in the two remaining studies [9, 24] were from Dako and Medarex. The prevalence of infection across studies ranged from 21 to 57%. The characteristics of the included studies are shown in Table 1.

Quality assessment of the included studies

The methodological quality assessment of original diagnostic trials was carried out by using QUADAS-2 tool. It mainly consisted of four parts that cover patient selection, index test, reference standard, flow, and time interval between index test and reference standard test. The first three parts were evaluated for clinical applicability, and all four parts were evaluated for risk of bias. As shown in Table 2, none of the studies presented all of the above items. The most obvious limitation of original studies is the lack of report blinding. However, the methodological quality was moderate, and the included studies had high clinical applicability.

Data synthesis and meta-analysis

Figure 2 schematically showed the forest plot of sensitivity and specificity of nCD64 in the diagnosis of infection in patients with autoimmune diseases. Sensitivity (TP rate) reflects the probability of actual patients to show positive diagnostic test results. By contrast, specificity (TN rate), reflects the probability of nonpatients to show negative diagnostic test results simultaneously. The pooled sensitivity and specificity of all studies in our meta-analysis were 89% (95% CI 82–93) and 94% (95% CI 91–96), respectively. The area under the SROC curve (AUC) was 0.97 (95% CI 0.95–0.98), and the diagnostic odds ratio (DOR) was 123 (95% CI 53–283), indicating a high diagnostic accuracy (Fig. 3). Likelihood ratios (LRs) are a composite index comprehensively reflecting those two independent parameters; it can be distinguished into positive likelihood ratio (PLR) and negative likelihood ratio (NLR). PLR is the ratio of TP rate to FP rate, while NLR is the ratio of FN rate to TN rate. The pooled PLR was 14.9 (95% CI 9.3–23.8) in our meta-analysis, suggesting that a person with infection was about 15 times more likely to have a positive test than a person with disease activity. Moreover, the pooled NLR was 0.12 (95% CI 0.07–0.20), indicating individuals with disease activity were about ten times more likely to have a negative test than individuals with infection. A method based on the Bayes' theorem that combines the application of LRs and pretest probability of a disease to predict the post-test probability of the disease, and can be visually

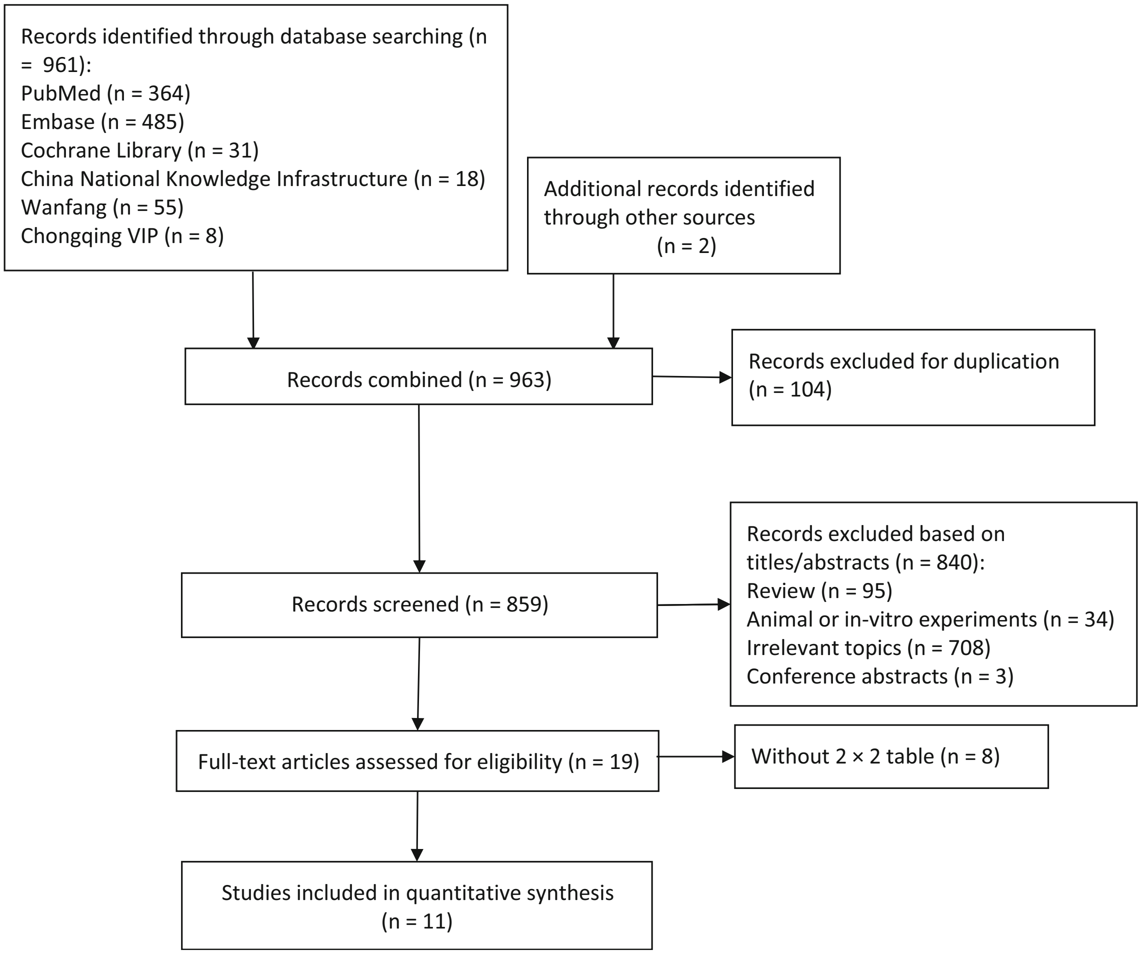

Fig. 1 Flow diagram of the selection process

presented using the Fagan's nomogram [27]. The Fagan's nomogram can be used to show the probability of a patient to develop a disease once the test results are known. The pretest probability of having infection was 34%. As we know, the pretest probability increases with a positive test and decreases with a negative test. The Fagan's nomogram indicated that the nCD64 detection would raise the post-test probability to 88% and decrease the post-test probability to 6% (Fig. 4), suggesting a practical and clinical value to perform the nCD64 test.

Heterogeneity assessment and meta-regression analysis

The I^2 test revealed that the pooled sensitivity and specificity were 49.25% (95% CI 14.09–84.41) and 0% (95% CI 0–92.20), respectively, which showed high heterogeneity among studies. No statistically significant difference was observed when exploring for the threshold effect (Spearman's correlation coefficient = − 0.388; $p = 0.238$), suggesting that non-threshold effect factors were the source of heterogeneity. A univariate meta-regression analysis was performed to determine the source of heterogeneity among included studies. Results showed that type of disease influenced sensitivity, while region, type of disease, whether sample was collected before antibiotic therapy, and the presentation of nCD64 measurement results accounted for the heterogeneity of specificity (Fig. 5). Results of subgroup analysis implied a good diagnostic value of nCD64, which was similar to the total population (Table 3).

Evaluation of publication bias

Deeks' funnel plot asymmetry test showed that publication bias was not statistically significant ($p = 0.15$).

Discussion

On the clinical context of autoimmune diseases, clinicians are frequently faced with challenges when distinguishing infection from disease flare in a febrile patient. Administrating immunosuppressive drugs to infected patients may often lead to prolonged hospitalization, extra hospital charges, and even life-threatening complications. Establishing the correct

Table 1 Characteristics of studies included in this systematic review

Author	Year	Region	Study design	Type of disease	Diagnostic criteria for disease	Definition of bacterial infection	Samples collected before antibiotic therapy	The source of anti-CD64 antibodies	Analytical method
Allen [8]	2002	North America	PR + RR	Autoimmune diseases[a]	Unclear	Microbiological culture positive	No	BD	FCM
Matsui [12]	2006	Asia	PR + CR	RA	ACR1987	Microbiological culture positive or PCR confirmed	Yes	BD	FCM
Wolfgang Tillinger 24]	2008	Europe	PR	IBD	Unclear	Microbiological culture positive	Unclear	Medarex	FCM
Hussein [9]	2010	Africa	PR	Autoimmune diseases[b]	RA: ACR1987 SLE: ACR 1997	Microbiological culture positive	Yes	Dako	FCM
Nishino [20]	2010	Asia	PR	RA	ACR1987	Microbiological culture positive clinical infection	No (38 patients had been treated with antibiotics)	BD	FCM
El-Said [22]	2010	Africa	PR	SLE	ACR 1997	Clinical infection	NO	BD	FCM
Mokuda [21]	2012	Asia	PR	RA	ACR1987	Microbiological culture positive or PCR confirmed	Yes	BD	FCM
Li [17]	2013	Asia	PR	RA	ACR1987	Microbiological culture positive	Unclear	BD	FCM
Xu19]	2016	Asia	PR	RA	ACR1987	Microbiological culture positive	Unclear	BD	FCM
Chen [18]	2018	Asia	PR + RR	SLE	2009 revised criteria of SLICC	Unclear	Unclear	BD	FCM
Echeverri [23]	2018	South America	PR	SLE	ACR 1997	Microbiological culture positive	Unclear	BD	FCM

Detecting instrument	the presentation of nCD64 measurement results	Cut-off value	Sample size (n)	Infection prevalence (%)	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
BD FACSCalibur	CD64 molecules per cell	2000 mol/cell	71	38	23	4	4	40	85	91
BD FACSCalibur	CD64 molecules per cell	2000 mol/cell	257	21	51	7	4	195	93	97
BD FACSCalibur	CD64 molecules per cell	10,000 mol/cell	49	44.9	21	1	1	26	96	97
BD FACSCalibur	Mean fluorescence intensity (MFI)	43.5 MFI/cell	36	50	17	2	1	16	94	89
BD FACSCalibur	CD64 molecules per cell	2000 mol/cell	61	41	19	2	6	34	76	94
Beckman Coulter machine	The percentage of neutrophil expressing CD64	17.6%	20	50	10	0	0	10	100	100
BD FACSCalibur	CD64 molecules per cell	1800 mol/cell	40	38	14	2	1	23	96	92
Beckman coulter eptcs XL	The percentage of neutrophil expressing CD64	71.11%	50	30	13	1	2	34	87	98
BD FACSCanto II	CD64 index	3.47	42	43	17	2	1	22	94	92
BD FACSCalibur	CD64 index	0.464	24	50	10	2	2	10	82	80
Beckman Coulter Navios TM	Mean fluorescence intensity (MFI)	2.04	27	44	7	2	5	13	58	87

RA, rheumatoid arthritis; *SLE*, systemic lupus erythematosus; *IBD*, inflammatory bowel disease; *BD*, Becton-Dickinson company; *PR*, prospective recruitment; *CR*, continuous recruitment; *RR*, random recruitment; *FCM*, flow cytometer

[a] RA, 21 patients; SLE, 8 patients; gout, 8 patients; spondyloarthropathy, 4 patients; dermatomyositis, 2 patients; familial Mediterranean fever, 1 patient

[b] RA, 24 patients; SLE, 19 patients

ACR1987, the 1987 revised criteria of the American College of Rheumatology [25]; ACR1997, the 1997 revised criteria of the American College of Rheumatology [26]

Table 2 Quality assessment of the included studies using the Quality Assessment of Diagnostic Accuracy Studies-2 tool

Studies	Risk of bias				Applicability		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Allen 2002	Unclear	High	Low	Low	Low	Low	Low
Matsui 2006	Low	Unclear	Unclear	Low	Low	Low	Low
Wolfgang Tillinger 2008	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
Hussein 2010	Unclear	Unclear	Unclear	Low	Low	Low	Low
Nishino 2010	Unclear	Unclear	Unclear	Low	Low	Low	Low
El-Said 2010	Unclear	High	Low	Low	Low	Low	Low
Mokuda 2012	Unclear	Unclear	Unclear	Low	Low	Low	Low
Li 2013	Unclear	High	Unclear	Unclear	Low	Low	Low
Xu 2016	Unclear	Unclear	Unclear	Low	Low	Low	Low
Chen 2018	Unclear	High	Unclear	Unclear	Low	Low	Low
Echeverri 2018	Unclear	High	Low	Low	Low	Low	Low

diagnosis is the most essential premise. Researchers had concentrated on various biomarkers such as mannose binding lectin, high mobility group box chromosomal protein 1, and those that could be good markers of disease activity [6]. In addition, soluble triggering receptors expressed on myeloid cell type 1 [4], mean platelet volume [5], delta neutrophil index [6], and molecular signatures [28] were also studied as differential diagnostic tools in patients with autoimmune diseases who developed an infection, but these studies were conducted individually. A previous meta-analysis [3] including

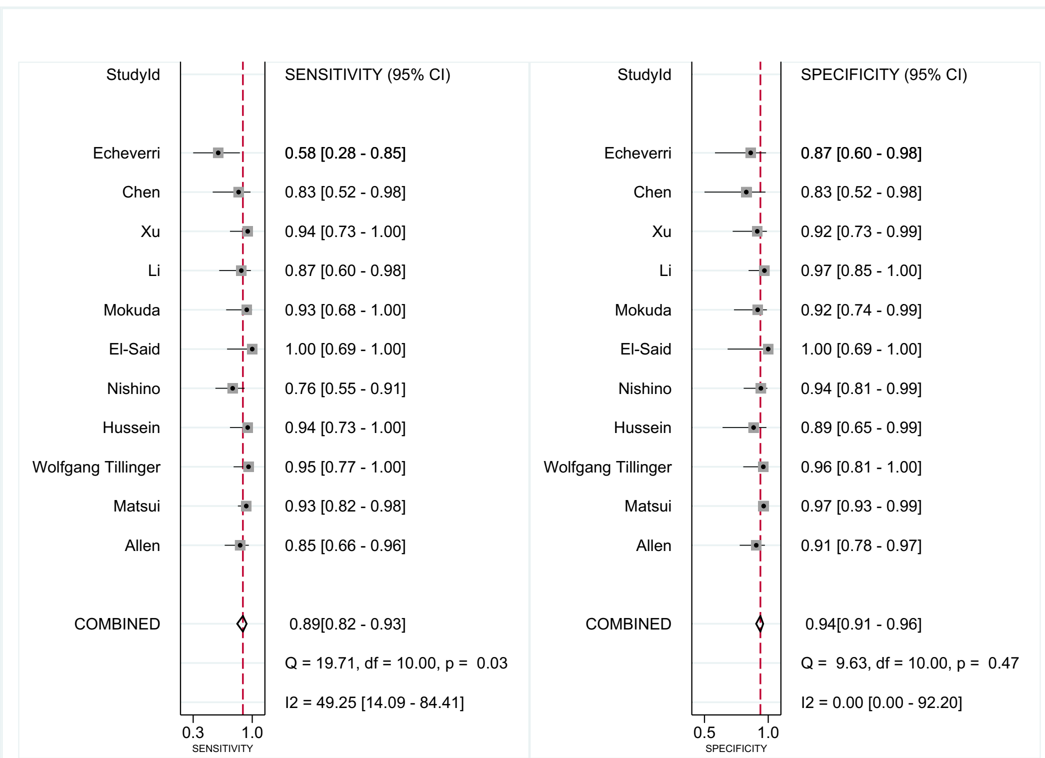

Fig. 2 Forest plot of the sensitivity and specificity of nCD64 for the diagnosis of infection in patients with autoimmune diseases. Forest plot of the sensitivity and specificity of each individual study, pooled sensitivity and specificity, and I^2 statistic for heterogeneity

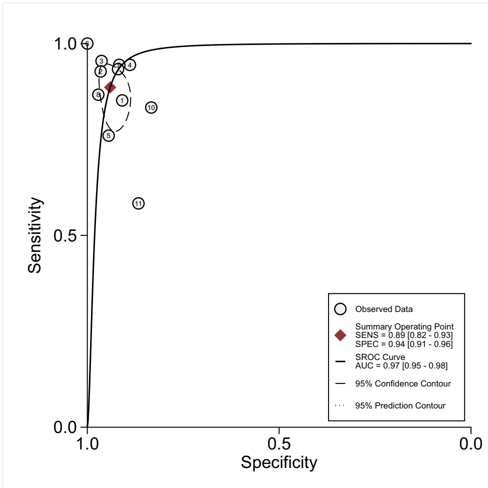

Fig. 3 Summary receiver operating characteristic graph of included studies. Summary receiver operating characteristic graph with 95% confidence contour and 95% prediction contour of nCD64 for the diagnosis of infection in patients with autoimmune diseases

nine studies had evaluated the effectiveness of serum PCT in diagnosing bacterial infections in patients with autoimmune diseases; results showed that the AUC value was 0.91 (95% CI 0.88–0.93), which indicated a good diagnostic value. However, the pooled sensitivity and specificity of serum PCT for diagnosing bacterial infections were 75% (95% CI 63–84) and 90% (95% CI 85–93), respectively; a low sensitivity indicated that serum PCT is not a good marker.

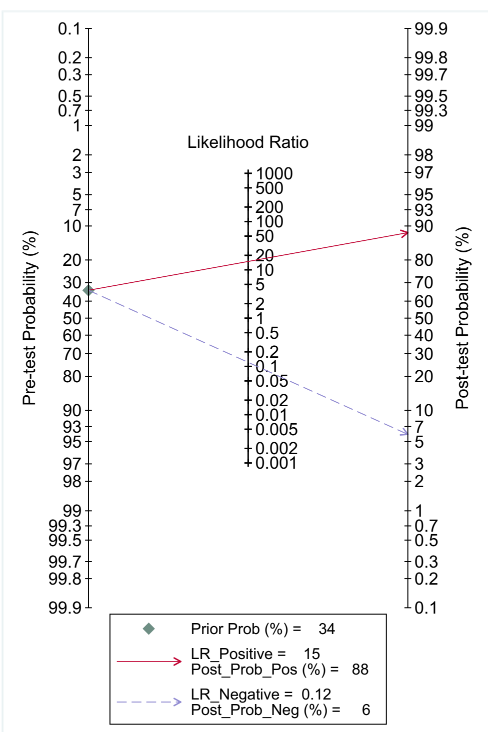

Fig. 4 Fagan's nomogram for likelihood ratios and the probability for nCD64 for the diagnosis of infection in patients with autoimmune diseases

Each measure of diagnostic accuracy reflects some specific aspects of a diagnostic procedure. In the present study, the pooled sensitivity and specificity indicated that nCD64 was an effective diagnostic marker. However, both of these measures have limitations, that is, they change in the opposite direction as the cutoff value changes. Alternatively, the AUC is a good indicator of overall diagnostic accuracy; the closer the AUC value is to 1, the better the diagnostic performance of a test. Our AUC value showed an excellent diagnostic accuracy. In the clinical practice, however, the AUC is not easy to interpret. By contrast, the LRs are more clinically meaningful. With LRs, we can adapt the results of a test to patients. The further LRs are from 1, the higher the probability for the presence or absence of a disease. In most circumstances, we consider PLR above 10 as a strong evidence to rule in diagnoses, while with NLR below 0.1, we can rule out diagnoses [29]. Our NLR is a bit high; hence, we speculate that the special reason may be related to the moderate sensitivity. The sensitivity of nCD64 test is affected by collecting blood samples after antibiotic treatment, which may lead to a negative test in patients with infection. Due to lack of data, we did not conduct a subgroup analysis for this factor. However, this result is much less than 1; that means for patients who showed a negative nCD64 test result, performing the nCD64 test is helpful for ruling out a possible infection. In addition, the results of the post-test probability indicate that performing the nCD64 test is of great importance in clinical practice. We performed a subgroup analysis to explain the high heterogeneity between studies, which also suggested that nCD64 had high diagnostic accuracy. In a word, our meta-analysis results suggested that nCD64 had a good diagnostic performance in detecting infection in patients with autoimmune diseases.

Neutrophils are very important immune cells in the human body and are the host's first line of defense against the invasion of foreign pathogens. The activation of neutrophils results in respiratory burst and degranulation in order to combat infections [30]. However, when neutrophils are excessively activated, it may trigger the development of some autoimmune diseases [31]. This finding may explain the results of previous retrospective case-series studies [8, 12, 13], which showed that nCD64 expression may be upregulated in vasculitis, active interstitial pneumonia, and Behcet's disease in the absence of infection. However, we could not perform a subgroup analysis of those diseases as there was insufficient data, but we still cannot ignore those confounding factors. It is worth noting that glucocorticoids can inhibit the overactivation of neutrophils [31], and other immunosuppressive agents can also affect the count and function of neutrophils. However, a recent trial [32] had concluded that neutrophil count did not affect the expression of nCD64. Other previous trials also confirmed that the blood nCD64 level in autoimmune disease patients is unaffected by the use of immunosuppressive agents, and the specific mechanism is

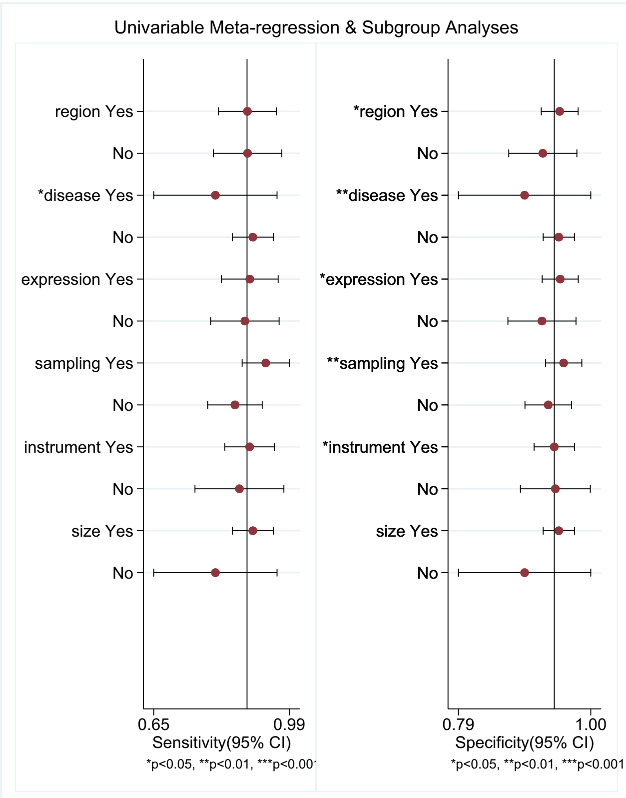

Fig. 5 Univariate meta-regression and subgroup analysis. The covariates included region (whether the trial was conducted in Asia), disease (whether the disease was systemic lupus erythematosus), expression (whether the presentation of nCD64 results was CD64 molecules per cell), sampling (whether samples was collected before antibiotic therapy), instrument (whether the detecting instrument was BD FACSCalibur), and size (sample size ≥ 30)

unknown [8, 12]. In addition, nCD64 as a credible biomarker to facilitate testing is feasible for the following reasons. First, with a stimulating factor, an initial increase of blood nCD64 levels after 4–6 h suggest that nCD64 [8] can be detected as early as PCT, which maintaining a plateau between 8 and 24 h [33]. Second, in terms of time cost, quantitative measurements of nCD64 can be conducted more easily and rapidly (within 2 h) compared with microbiological cultures or PCR testing of specimens. Finally, in the clinical setting, the stability of samples is crucial to the reliability of test results. The nCD64 was confirmed to be stable within 72 h at 4 °C and 36 h at room temperature in stored blood samples [24]. Commercial analyte-specific reagent kits and automatic analysis software [34] today allow those with no experience to perform this test and finally achieve consistent, reliable results.

Our study had some limitations. A previous meta-analysis [35] concluded that nCD64 represented a useful biomarker of bacterial infection; their results demonstrated that the sensitivity and specificity was only 76% and 85%, respectively, and a publication bias existed. Unlike the previous meta-analysis, our meta-analysis expanded the retrieval database to avoid retrieval bias and focused only on the area of autoimmune diseases and found that nCD64 can be used to accurately diagnose patients with autoimmune diseases. In addition, Deeks' funnel plot asymmetry test showed that publication bias did not exist. Even so, we still could not ignore some limitations in our meta-analysis. First, most of the included studies did not discuss the blind method, which may result in the overestimation of accuracy. Thus, specification of reports needs to be emphasized. Second, the presentation of nCD64 measurement results varied between each trail, and

Table 3 Results of subgroup analysis of the diagnostic accuracy of neutrophil CD64 expression in patients with autoimmune disease

Subgroup	Studies	Sample size	Sensitivity (%)	95%CI	Specificity (%)	95%CI	PLR	95%CI	NLR	95%CI	DOR	95%CI	AUC	95%CI
All	11	677	89	82–93	94	91–96	14.9	9.3–23.8	0.12	0.07–0.20	123	53–283	0.97	0.95–0.98
Type of disease														
RA	5	450	89	81–94	96	92–97	20.2	11.6–35	0.11	0.06–0.20	177	72–437	0.97	0.95–0.98
RA/SLE	8	521	87	77–93	94	91–97	15.7	8.8–28.1	0.13	0.07–0.25	117	41–332	0.97	0.95–0.98
Region														
Asia	6	474	88	81–93	95	91–97	17.5	9.8–31.1	0.12	0.07–0.21	143	58–354	0.97	0.95–0.98
Other	5	203	90	73–97	93	85–97	12.2	5.4–27.5	0.10	0.03–0.33	118	21–676	0.96	0.94–0.97
The presentation of nCD64 measurement results														
Molecular/cell	5	478	89	81–94	95	91–97	17.6	10.1–30.9	0.1	0.07–0.21	152	59–392	0.97	0.96–0.98
Other	6	199	90	75–96	92	85–96	11.4	5.6–23.4	0.12	0.05–0.30	95	24–376	0.95	0.93–0.97
Detecting instrument														
BD FACSCalibur	8	538	89	82–93	94	90–96	14.9	8.8–25.4	0.12	0.07–0.19	127	54–299	0.97	0.95–0.98
Sample size														
≥ 30	8	606	90	84–94	95	92–97	17.1	10.8–27.2	0.11	0.07–0.17	159	76–334	0.97	0.96–0.99

the cutoff values of nCD64 differed greatly; thus, we could not determine the optimized cutoff value. Third, the definition of infection complications in each original trial varied. In particular, El-Said et al. [22] used only the clinical criteria to diagnose infection. Finally, interobserver and intraobserver variations, performance of different laboratory tests, and use of different batches of the same reagents can also affect the results. Therefore, forming a unified presentation of nCD64 measurement results should be conducted in future studies.

In conclusion, our meta-analysis indicates that neutrophil CD64 expression can be a sensitive and specific marker for differentiating infection from disease flare in febrile patients with autoimmune diseases. However, due to lack of optimized cutoff value, more large-blinded prospective cohort studies must be carried out to evaluate its accuracy in the field of autoimmune diseases.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Hellmann DB, Petri M, Whiting-O'Keefe Q (1987) Fatal infections in systemic lupus erythematosus: the role of opportunistic organisms. Medicine (Baltimore) 66(5):341–348
2. Larsen FF, Petersen JA (2017) Novel biomarkers for sepsis: a narrative review. Eur J Intern Med 45:46–50. https://doi.org/10.1016/j.ejim.2017.09.030
3. Wu JY, Lee SH, Shen CJ, Hsieh YC, Yo PH, Cheng HY, Chan RC, Lee CC, Chang SS (2012) Use of serum procalcitonin to detect bacterial infection in patients with autoimmune diseases: a systematic review and meta-analysis. Arthritis Rheum 64(9):3034–3042. https://doi.org/10.1002/art.34512
4. Lin C, Hsieh S, Keng L et al (2016) Prospective evaluation of procalcitonin, soluble triggering receptor expressed on myeloid cells-1 and C-reactive protein in febrile patients with autoimmune diseases. PLoS One 11(4):e153938. https://doi.org/10.1371/journal.pone.0153938
5. Ryu HJ, Seo MR, Choi HJ et al (2018) Mean platelet volume as a marker for differentiating disease flare from infection in Behcet's disease. Int J Rheum Dis 21(8):1640–1645. https://doi.org/10.1111/1756-185X.13008
6. Ospina FE, Echeverri A, Zambrano D, Suso JP, Martínez-Blanco J, Cañas CA, Tobón GJ (2016) Distinguishing infections vs flares in patients with systemic lupus erythematosus. Rheumatology (Oxford, England) 56(suppl_1):i46–i54. https://doi.org/10.1093/rheumatology/kew340
7. Song GG, Bae SC, Lee YH (2015) Diagnostic accuracies of procalcitonin and C-reactive protein for bacterial infection in patients with systemic rheumatic diseases: a meta-analysis. Clin Exp Rheumatol 33(2):166–173
8. Allen E, Bakke AC, Purtzer MZ, Deodhar A (2002) Neutrophil CD64 expression: distinguishing acute inflammatory autoimmune disease from systemic infections. Ann Rheum Dis 61(6):522–525. https://doi.org/10.1136/ard.61.6.522
9. Hussein OA, El-Toukhy MA, El-Rahman HS (2010) Neutrophil CD64 expression in inflammatory autoimmune diseases: its value in distinguishing infection from disease flare. Immunol Investig 39(7):699–712. https://doi.org/10.3109/08820139.2010.491520
10. Wang X, Li ZY, Zeng L, Zhang AQ, Pan W, Gu W, Jiang JX (2015) Neutrophil CD64 expression as a diagnostic marker for sepsis in adult patients: a meta-analysis. Crit Care (London, England) 19(1):245. https://doi.org/10.1186/s13054-015-0972-z
11. Jia LQ, Shen YC, Hu QJ, Wan C, Wang T, Chen L, Wen FQ (2013) Diagnostic accuracy of neutrophil CD64 expression in neonatal infection: a meta-analysis. J Int Med Res 41(4):934–943. https://doi.org/10.1177/0300060513489799
12. Matsui T, Ohsumi K, Ozawa N et al (2006) CD64 on neutrophils is a sensitive and specific marker for detection of infection in patients with rheumatoid arthritis. J Rheumatol 33(12):2416–2424
13. Ureten K, Ertenli I, Oztürk MA (2005) Neutrophil CD64 expression in Behçet's disease. J Rheumatol 32(5):849–852
14. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 151(4):264–269
15. Whiting PF, Rutjes AWS, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, Leeflang MM, Sterne JA, Bossuyt PM, QUADAS-2 Group (2011) QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 155(8):529–536. https://doi.org/10.7326/0003-4819-155-8-201110180-00009
16. Gatsonis C, Paliwal P (2006) Meta-analysis of diagnostic and screening test accuracy evaluations: methodologic primer. AJR Am J Roentgenol 187(2):271–281. https://doi.org/10.2214/AJR.06.0226
17. Li DH, Li Y, Ju J et al (2013) Neutrophil CD64 expression in rheumatoid arthritis patients complicated with infection (in chinese). Chin J Lab Med 36(1):77–79. https://doi.org/10.3760/cma.j.issn.1009-9158.2013.01.019
18. Chen FF, Zhang QY, Xing J et al (2018) Clinical value of peripheral blood neutrophil CD64 index in identifying SLE complicated with bacterial infection and active SLE. J Mod Lab Med 33(3):14–17. https://doi.org/10.3969/j.issn.1671-7414.2018.03.005
19. Xu QY, Ding ZX, Zhou YL et al (2016) Usefullness of neutrophil CD64 index as a marker to differentiate between infection and disease flare in patients with rheumatoid arthritis. J Jiangsu Univ (Med Edn) 26(5):444–448. https://doi.org/10.13312/j.issn.1671-7783.y160132
20. Nishino J, Tanaka S, Kadono Y, Matsui T, Komiya A, Nishimura K, Tohma S (2010) The usefulness of neutrophil CD64 expression in the diagnosis of local infection in patients with rheumatoid arthritis in daily practice. J Orthop Sci 15(4):547–552. https://doi.org/10.1007/s00776-010-1498-5
21. Mokuda S, Doi O, Takasugi K (2012) Simultaneous quantitative analysis of the expression of CD64 and CD35 on neutrophils as markers to differentiate between bacterial and viral infections in patients with rheumatoid arthritis. Mod Rheumatol 22(5):750–757. https://doi.org/10.1007/s10165-011-0587-4
22. El-Said EE, Ali SR, El-Sheshtawy FA (2010) Neutrophil CD64 in diagnosis of infection in systemic lupus erythematosus patients. Egypt J Hosp Med 41:600–617
23. Echeverri A, Naranjo-Escobar J, Posso-Osorio I, Aguirre-Valencia D, Zambrano D, Castaño GL, Martínez JD, Cañas CA, Tobón GJ (2018) Neutrophil CD64 expression, procalcitonin and presepsin are useful to differentiate infections from flares in SLE patients with SIRS. Lupus 27(7):1130–1139. https://doi.org/10.1177/0961203318763740

24. Tillinger W, Jilch R, Jilma B, Brunner H, Koeller U, Lichtenberger C, Waldhör T, Reinisch W (2009) Expression of the high-affinity IgG receptor FcRI (CD64) in patients with inflammatory bowel disease: a new biomarker for gastroenterologic diagnostics. Am J Gastroenterol 104(1):102–109. https://doi.org/10.1038/ajg.2008.6
25. Arnett FC, Edworthy AM, Bloch DA et al. (1988) The American rheumatism association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 31(3):315–324. https://doi.org/10.1002/art.1780310302
26. Hochberg MC (1997) Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 40(9):1725–1726
27. Akobeng AK (2007) Understanding diagnostic tests 2: likelihood ratios, pre- and post-test probabilities and their use in clinical practice. Acta Paediatr (Oslo, Norway : 1992) 96(4):487–491. https://doi.org/10.1111/j.1651-2227.2006.00179.x
28. Mackay M, Oswald M, Sanchez-Guerrero J, Lichauco J, Aranow C, Kotkin S, Korsunsky I, Gregersen PK, Diamond B (2016) Molecular signatures in systemic lupus erythematosus: distinction between disease flare and infection. Lupus Sci Med 3(1):e000159. https://doi.org/10.1136/lupus-2016-000159
29. Deeks JJ, Altman DG (2004) Diagnostic tests 4: likelihood ratios. BMJ 329(7458):168–169. https://doi.org/10.1136/bmj.329.7458.168
30. Badwey JA, Karovsky ML (1980) Active oxygen species and the functions of phagocytic leukocytes. Annu Rev Biochem 49:695–726. https://doi.org/10.1146/annurev.bi.49.070180.003403
31. Liu L, Wang YX, Zhou J, Long F, Sun HW, Liu Y, Chen YZ, Jiang CL (2005) Rapid non-genomic inhibitory effects of glucocorticoids on human neutrophil degranulation. Inflamm Res 54(1):37–41. https://doi.org/10.1007/s00011-004-1320-y
32. Shi SJ, Zhang J, Wu Q, Li J (2015) Diagnostic value of neutrophil CD64 for bacterial infection in patients with hematologic malignancies after chemotherapy. J Exp Hematol 23(3):852–855. https://doi.org/10.7534/j.issn.1009-2137.2015.03.048
33. Dandona P, Nix D, Wilson MF, Aljada A, Love J, Assicot M, Bohuon C (1994) Procalcitonin increase after endotoxin injection in normal subjects. J Clin Endocrinol Metab 79(6):1605–1608
34. Icardi M, Erickson Y, Kilborn S, Stewart B, Grief B, Scharnweber G (2009) CD64 index provides simple and predictive testing for detection and monitoring of sepsis and bacterial infection in hospital patients. J Clin Microbiol 47(12):3914–3919
35. Li S, Huang X, Chen Z, Zhong H, Peng Q, Deng Y, Qin X, Zhao J (2013) Neutrophil CD64 expression as a biomarker in the early diagnosis of bacterial infection: a meta-analysis. Int J Infect Dis 17(1):e12–e23

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