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*Observational Study*

**The role of international normalised ratio (INR) in nonpulmonary sepsis screening: a prospective observational study**

INR in nonpulmonary sepsis screening

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## **Abstract**

### **BACKGROUND**

Currently, there is a lack of sepsis screening tools that can be widely used worldwide. Pulmonary sepsis can be of sufficient concern to physicians due to their noticeable symptoms, which usually rely less on screening tools.

### **AIM**

To investigate the efficiency of the international normalised ratio (INR) for the early rapid recognition of adult nonpulmonary infectious sepsis.

### **METHODS**

This is a prospective observational study. A total of 108 sepsis patients and 106 nonsepsis patients were enrolled according to relevant inclusion and exclusion criteria. Commonly used clinical indicators, such as WBC, neutrophil count, lymphocyte count, neutrophil-lymphocyte count ratio (NLCR), platelets (PLT), prothrombin time, INR, activated partial thromboplastin time and quick Sequential [Sepsis-related] Organ Failure Assessment (qSOFA) scores, were recorded within 24 h after admission. The diagnostic performances of them were analyzed and compared through multivariate logistic regression analysis, Spearman correlation and receiver operating characteristic curve (ROC) analysis.

### **RESULTS**

The INR value of the sepsis group was significantly higher than that of the nonsepsis group. INR has superior diagnostic efficacy for sepsis, with an area under the curve value of 0.918, when those preexisting diseases which significantly affect coagulation function were excluded. The diagnostic efficacy of the INR was more significant than that of NLCR, PLT and qSOFA ( $P < 0.05$ ). Moreover, INR levels of 1.17, 1.20, and 1.22 could be used as low - to medium-high risk predictor of nonpulmonary infectious sepsis, respectively.

## CONCLUSION

The INR is a promising and easily available biomarker for diagnosis, and it can be used as one of the indicators for early screening of adult nonpulmonary infectious sepsis. When its value is higher than the optimal cutoff (1.22) value, high vigilance is required for adult nonpulmonary infectious sepsis.

**Key Words:** Sepsis; Coagulopathy; International normalised ratio; Screening Tool; qSOFA

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**Core Tip:** The international normalised ratio (INR) has high specificity and sensitivity in the early identification of adult nonpulmonary source of sepsis. Sepsis is highly suspected when the INR value exceeds 1.22 in patients with non-pulmonary infection, especially for those patients without preexisting underlying disease or medication history that affects coagulation function. Due to its low cost, fast detection and easy interpretation, INR is suitable for the primary screening of sepsis for emergency patients, outpatient patients, particularly in low and middle-income countries.

## INTRODUCTION

The incidence of sepsis has been increasing year by year, and it has become one of the leading causes of death in ICU patients [1]. Studies have confirmed that sepsis results in a "bimodal" distribution of death times, which are early death within a few days and late death within a few weeks or months [2 3]. Early death is mainly caused by an aggressive inflammatory response, while persistent immunosuppression leads to late death. Owing to the mechanism of late immunosuppression not being clear,

immunomodulatory treatment is not yet very effective, and more than 40 Large clinical studies of early anti-inflammatory therapy have also failed; early recognition might be an important way to improve the treatment of sepsis in the short term [4]. At present, Sepsis-3 is newly defined as sequential impairment of organ function due to suspected infection along with the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score increased 2 points or more [5], which emphasizes organ dysfunction caused by infection. Although Sepsis-3 increased the specificity of in-hospital diagnosis [6], it was not widely used in clinical practice because of its multiple complex indicators; it is difficult to carry out rapidly and widely in low and middle-income areas, especially in emergency and outpatient departments and in nonintensive care units. The quick SOFA (qSOFA) score, as a fast, simple and noninvasive screening tool, is widely used in clinical practice. However, Askim *et al* found that qSOFA score had a low sensitivity to screen sepsis [7], and Williams *et al* found that the sensitivity was only 29.7% when the qSOFA score was  $\geq 2$  points for screening sepsis [8]. Thus, qSOFA score as a rapid screening tool for sepsis remains controversial.

In clinical practice, the clinical symptoms of patients with pulmonary infections are often conspicuous, which are likely to arouse the vigilance and attention of clinicians. Therefore, for outpatients with pulmonary infection, sepsis screening tools usually are less necessary. While these patients with nonpulmonary infections, such as abdominal and urinary tract infections, are more likely to deteriorate into sepsis or septic shock, with the incidence of both as high as 50% [9]. Therefore, these patients are more likely to need tools for rapid sepsis screening. Usually, a good screening tool should not only have sufficient sensitivity and specificity but also be able to reflect the physiological characteristics of the disease.

Sepsis is a severe systemic inflammatory response that manifests with widespread inflammation, as well as endothelial and coagulation dysfunction [10]. A mass of studies has shown that sepsis patients are associated with different degrees of coagulopathy, which exists over the whole process in sepsis [11]. Stimulated by inflammatory factors, coagulopathy appears from the early pro-coagulant state of sub-clinical symptoms to

the DIC at the terminal stage <sup>[12]</sup>. The platelet count, an indicator of coagulopathy status, also appear in the diagnostic criteria of sepsis-3 <sup>[13]</sup>. Thus, further exploration of the indicators of coagulation function status is expected to develop new screening tools for sepsis. Currently, There are many tools for coagulation function tests, such as conventional coagulation examinations (including parameters: <sup>10</sup> prothrombin time (PT), activated partial thromboplastin time (APTT), international normalised ratio (INR), etc), thromboelastography (TEG) <sup>[12]</sup>, rotational thromboelastometry (ROTEM) <sup>[14]</sup>, etc. However, TEG and ROTEM are more commonly used in cardiovascular surgery to evaluate platelet function, coagulation and fibrinolytic systems, and blood transfusion in the early resuscitation stage of trauma patients <sup>[15 16]</sup>. In addition, TEG and ROTEM cannot be routinely performed in medical institutions at all levels. In contrast, the conventional coagulation examinations can be used as screening tools for the early and rapid identification of sepsis. In particular, the development of Point-of-Care INR Test (POCT) further shorten its detection time <sup>[17]</sup>. Currently, blood cells analysis, as a routine test, has been widely performed in clinical practice. Thus, the purpose of this study was to explore the efficiency of routine indicators of blood cells and coagulation function in the early rapid recognition of adult nonpulmonary infectious sepsis.

## **MATERIALS AND METHODS**

### ***Study population***

This was a prospective observational study with a small sample size conducted in the Department of the Emergency and Intensive Care Unit of the First Affiliated Hospital of Chongqing Medical University, which is a 3200-bed tertiary care teaching hospital with an annual load of approximately 154,000 patients. Patients with suspected infection were enrolled in this study from August 2019 to July 2020. The study was approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University in compliance with the Declaration of Helsinki.

According to the Sepsis-3 criteria, the study subjects were divided into nonsepsis and sepsis groups. There were not consecutive patients enrolled. The inclusion criteria were

the following: age >18 years old and not limited by sex; and patients with confirmed nonpulmonary infections. The exclusion criteria were the following: age <18 years old; patients with some preexisting diseases which their coagulation function could be notably affected: such as chronic liver diseases, hematologic system diseases, or patients who had previously undergone long-term treatment with immunosuppressants or anticoagulants, and those patients with incomplete data. The sex, age, and other basic data of all of the included patients were recorded. Acute Physiology and Chronic Health Evaluation II (APACHE II), Sequential [Sepsis-related] Organ Failure Assessment (SOFA) and quick SOFA (qSOFA) scores were assessed on the day of admission within 24 h. These indicators, WBC, neutrophil count (N#), lymphocyte count (L#), neutrophil-lymphocyte count ratio (NLCR), platelets (PLT), prothrombin time (PT), INR and activated partial thromboplastin time (APTT), were also recorded along with the assessment of APACHE II, SOFA and qSOFA scores. Patients are assigned to the sepsis group when their SOFA score increases by 2 or more points, that is, when they met the diagnostic criteria for sepsis-3.

#### ***Defining suspected infection and low-medium-high risk of sepsis***

The first suspected infections were defined as a combination of antibiotics (either orally or intravenously) and body fluid cultures (pleural effusion, blood, abdominal effusion, urine, etc). We need make sure that the combination of culture and antibiotics occurred within a specific time frame. If antibiotics were given first, culture samples need be obtained within 24 h. If culture samples were performed firstly, antibiotics must be given within 24 h. The time at which either of the above two events occurred was defined as the "onset" of infection. The sites of infection in deep tissue were determined by CT scan, while superficial lesions could be identified by physical examination. In order to obtain the predictive efficacy of different INR values on the low, medium and high risk of sepsis, we defined the positive predictive rate below 10%, around 50% and above 85% as low, medium and high risk of sepsis, respectively.

### ***Relevant biomarkers and determination***

Peripheral venous blood samples were collected immediately after admission. Peripheral blood cell (including WBC, L#, N#, NLCR, PLT) were analyzed by the Sysmex XN-9000 (Kobe, Japan) through flow cytometry, and coagulation tests (including INR, PT, APTT) were measured with the Sysmex CS-5100 (Shanghai, China). All the tests were carried out in the Medical Laboratory of our hospital according to the standard procedures, the quality of which have been certified by the American Society of Pathologists (CAP).

### ***Statistical analysis***

The SPSS software, version 24.0 (IBM Corp. Armonk, New York, USA), and MedCalc software, version 19.0 (MedCalc Software, Belgium), were used for statistical analysis. All of the measured data in this study were subject to normal distributions, which were analyzed by the Kolmogorov-Smirnov test. Data were expressed as mean  $\pm$  SD. For comparisons of two independent group of samples, Student's *t*-test was employed. The chi-square test was used to compare the composition ratio between the two groups. Logistic regression analysis was performed to analyze the significance of INR in the early identifying of sepsis, through the univariate and multivariate analysis (forward, LR). The receiver operating characteristic (ROC) curves were plotted by the software. INR, PT, PLT, WBC, NLCR and qSOFA were compared for their efficacy in the early identification of sepsis, according to the area under their ROC curves (AUC). The cut-off points, sensitivities, specificities, positive predictive values, and negative predictive values of these indicators were, respectively, calculated to evaluate their diagnostic efficiency. Relationship of INR value with SOFA Score and APACHE II Score were analyzed through Spearman's rank correlation.

## **RESULTS**

### ***Patient enrolment and comparison of baseline characteristics***



301 patients were initially enrolled in this study, of whom 201 met all the inclusion criteria and were identified as study subjects (Figure 1). The baseline characteristics of the patients are shown in Table 1. There were no differences between the nonsepsis and sepsis groups in sex, age, or infection site (all  $P > 0.05$ ), indicating that the baseline data were comparable.

The comparison of WBC, NLCR, INR, PLT, PT, APTT and other indices and levels between the sepsis and nonsepsis groups is shown in Table 2, and it was found that all of them were significantly higher in the sepsis group than in the nonsepsis group ( $P < 0.05$ ).

### Efficiency of the INR in screening for sepsis

#### Analysis of factors influencing the identification of sepsis

##### Screening the indicators that can identify sepsis

Univariate and multivariate analyses for the diagnosis of sepsis showed that WBC, NLCR, the INR, PLT, PT, APTT and qSOFA were of significance in the diagnosis of sepsis ( $P < 0.05$ ) (Table 3). Logistic regression multivariate analysis was performed on WBC, NLCR, the INR, PLT, PT, APTT and qSOFA, among which WBC, NLCR, the INR, PLT and PT were statistically significant (OR=0.875, 95%CI=0.772-0.992,  $P=0.037$ ; OR=1.145, 95%CI =1.069-1.226,  $P < 0.001$ ; OR=27.106, 95%CI =5.038-145.825,  $P < 0.001$ ; OR=0.981, 95%CI =0.97-0.991,  $P < 0.001$ ; OR = 1.475, 95%CI =1.032-2.106,  $P=0.033$ , respectively); Thus, WBC, NLCR, the INR, PLT and PT were associated with the diagnosis of sepsis, while APTT and qSOFA were not.

### Comparative analysis of ROC curves

ROC curve analysis displayed that the INR had the largest AUC value for the diagnosis of sepsis: 0.918(95%CI: 0.857-0.959) (Figure 2, Table 4). The AUC values for other biomarkers were, respectively, as follows: PT 0.868 (95%CI: 0.796-0.921); PLT 0.841(95%CI: 0.766-0.9); NLCR 0.83 (95%CI: 0.754-0.891); qSOFA 0.638 (95%CI: 0.548-0.721) and WBC 0.599 (95%CI: 0.508-0.684). The sensitivity, specificity, positive

predictive value (PPV), and negative predictive value (NPV) for WBC, NLCR, the INR, PT, PLT and qSOFA are depicted in Table 4. The sensitivity and specificity were 90.0% (95%CI: 80.5%-95.9%) and 84.48% (95%CI: (72.6%-92.7%)), and the PPV and NPV were 87.5% (95%CI: 79.3%-92.8%) and 87.5% (95%CI: 77.5%-93.4%), respectively, when the INR cutoff value was 1.22.

### **The correlation of INR with SOFA Score and APACHE II Score, and low-medium-high risk of sepsis according to INR**

Since SOFA Score and Apache II Score are not Gaussian distribution, Spearman's rank correlation method was used. It can be found that there is a strong correlation between INR value and SOFA Score ( $r=0.660$ , 95%CI: 0.574-0.731,  $P < 0.001$ ), while there is a weak correlation between INR value and Apache II Score ( $r=0.457$ , 95%CI: 0.341-0.560,  $P < 0.001$ ). When INR value was less than or equal to 1.17, 1.20 and greater than or equal to 1.22, respectively, with PPV of 8.24%, 55.6% and 87.5%, there were low, medium, and high risk of sepsis. (Figure 3)

## **DISCUSSION**

Early diagnosis and timely treatment of sepsis can improve the prognosis and reduce the mortality of sepsis. Although Sepsis-3 revealed organ dysfunction caused by infection, it is difficult to diagnose early for patients who have severe infections not reaching significant organ failure [13]. In clinical practice, blood culture is still used to diagnose sepsis. Due to culture will take a longer time and has a less positive rate, it usually lead to delayed and missed diagnoses of sepsis. Exploring for new and effective markers for the screening of sepsis is necessary. Zboromyrska *et al* studied multiplex real-time polymerase chain reaction, the Magicplex<sup>TM</sup> Sepsis test (MP), the specificity of which was up to 95%, while the sensitivity was only 29% [18]. Lei *et al* found that members of the miR-148 family (miR-148A/B and miR-152) were candidate biomarkers for sepsis by studying the Gene Expression Omnibus dataset GSE12624, but further study is required to evaluate the diagnostic performance [19]. Guo *et al* found that the

AUC value of miR-495 in the diagnosis of sepsis was 0.915 when the cutoff value was 0.655, the sensitivity was 89.5%, and the specificity was 83.0% [20]. Although all these new markers have their own advantages, the disadvantage is that their detection takes a long time, costs a lot, and limited efficiency, which is difficult to carry out in economically underdeveloped areas. As we learn more about the pathophysiology of sepsis, we may be able to go back and develop new screening indicators for tests routinely performed in the laboratory.

Coagulopathy is one of the characteristic pathophysiological changes of sepsis, which exists across the whole process in sepsis and is a critical factor for the occurrence, development and prognosis of sepsis [21]. With the persistence of infection or sepsis, the consumption of coagulation factors and decrease of platelets will occur, as well as the bleeding and dysfunction of the skin, mucous membranes and other organs, constituting DIC (disseminated intravascular coagulation) [22]. Therefore, the indicators related to coagulation function have great potential to be used as screening indicators for sepsis. Zhang *et al* found that the AUC of PT for the diagnosis of sepsis was 0.806 when the cutoff value was 20, and the sensitivity and the specificity were 83.54% and 65.22%, respectively [23]. In this study, we investigated common indicators of coagulation function and some markers of inflammation, such as WBC, NLCR, PLT, INR, PT, APTT, and qSOFA scores, in the identification efficiency of adult nonpulmonary infectious sepsis. As for procalcitonin, there have been quite a lot of relevant studies reported [24-29]. In addition, procalcitonin (PCT) is not a routine test item that can be carried out in all economically backward areas. Here, we mainly analyzed the most commonly used test indicators. Our results showed that the INR had the highest efficiency in the diagnosis of adult nonpulmonary infectious sepsis, compared with WBC, NLCR, PLT, PT, APTT and qSOFA. Lyons PG *et al* found that coagulopathy was closely related to the severity and mortality of sepsis, and with the extension of the INR, the more severe that the sepsis was, the higher that the mortality was [30]. Recent studies of COVID-19 patients with secondary bacterial infection have

also reported that prolonged INR time is a monitoring indicator in severe patients, and the longer the INR time is, the worse the prognosis of patients is [31-33]. This study also found that there was a strong correlation between INR value and SOFA Score ( $r = 0.660$ ). Due to SOFA Score was correlated with the prognosis of sepsis, which also suggested that INR had a good predictive value of nonpulmonary infectious sepsis from another perspective. In particular, when INR was less than or equal to 1.17, 1.20 and greater than or equal to 1.22, there were low, medium and high positive predicted rates of sepsis. All the above related studies have indicated that INR could be used as one of the early screening indicators for sepsis. While, there are many underlying diseases that can affect INR. Although relevant conclusions in this study were drawn under corresponding exclusion criteria, it is true that in clinical practice, there are still a small number of potentially infected patients with those underlying diseases that cannot be detected at the first time. For this condition, when their INR reach the high-risk value of sepsis, *e.g.*, more than 1.22, they still need to be considered highly suspected of sepsis because they are at higher risk of adverse outcomes when they are missed.

As for qSOFA, many studies have found it to be of low sensitivity as a sepsis screening tool [7]. Our study also confirmed that the sensitivity of qSOFA was only 28.57%, the specificity was 79.31%, and the AUC was 0.638 (% 95CI: 0.548 - 0.721). However, because qSOFA is a non-invasive and fast screening method, setting it as a preliminary screening is still feasible. Because infection and stress can cause neutropenia and lymphopenia, neutrophil lymphocyte count ratio (NLCR) has attracted more and more attention of clinical researchers [34]. Fuss J *et al* found that the NLCR level of sepsis in burn patients was significantly higher than in common burn patients [35]. Relevant studies have also found that NLCR could be a simple and feasible indicator for the prediction of sepsis after percutaneous nephrolithotomy [36]. Our study showed that the diagnostic value of NLCR in diagnosing adult nonpulmonary infectious sepsis was lower than that of the INR.

Platelets play an important role in sepsis because they are at the intersection of the immune system, coagulation cascade and endothelial cells [37 38]. Patients who had sustained thrombocytopenia or a drop in PLT of >30% during their ICU stay had higher mortality [39]. Therefore, thrombocytopenia was considered to be an independent risk factor for death in patients with sepsis or septic shock [40]. However, as one of the diagnostic criteria for Sepsis-3, Hossein *et al* found, when the platelet count was less than  $229 \times 10^9$ , the sensitivity and specificity of the diagnosis of acute appendicitis were only 24% and 75%, respectively [41]. Similarly, our study also showed that when the platelet count was less than  $180 \times 10^9/L$ , the sensitivity and specificity of the diagnosis of sepsis were 80.0% and 82.76% respectively, which were still lower than those of the INR. Furthermore, the base range of platelets was larger, and the sensitivity was lower, which could easily lead to delayed diagnosis of sepsis with delayed treatment and increased mortality of sepsis patients. Therefore, whether INR could replace platelet count as one of the indicators of SOFA score in sepsis criteria in the future still needs further studies with large sample size and multiple centers.

## **CONCLUSION**

The INR has high specificity and sensitivity in the early identification of adult nonpulmonary infectious sepsis. When the INR value exceeds 1.22 in patients with non-pulmonary infection, sepsis should be highly suspected, especially for those patients without preexisting underlying disease or medication history that affects coagulation function. Due to its low cost, rapid detection and easy interpretation of the results, it is particularly suitable for the preliminary screening of sepsis in emergency patients, outpatient patients and patients in economically backward areas.



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