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Review Article

Heparin-binding Protein as a Diagnostic and Prognostic Marker of Infections: A Systematic Review and Meta-analysis

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Abstract. Heparin-binding protein (HBP) is a granule protein derived from neutrophils, located in secretory vesicles and neutrophilic granules, also known as cationic antimicrobial protein of 37 kDa (CAP37) or azurocidin. This study evaluates the diagnostic and prognostic value of HBP levels in relation to infection, organ dysfunction, and mortality in adult patients. A systematic review and meta-analysis were conducted by searching PubMed, Web of Science, EMBASE, and the Cochrane Database from their inception through June 2024. Original studies assessing HBP levels' diagnostic and prognostic utility in predicting infection and disease severity in critically ill adult patients were included. The primary outcome was the diagnostic and predictive role of HBP in infection and severity. The Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool was used to evaluate bias risk. A total of 56 studies involving 11,486 patients were included. Pooled analysis showed HBP had a sensitivity of 0.87 (95% CI, 0.82–0.91), specificity of 0.87 (95% CI, 0.79–0.92), and an AUC of 0.93 (95% CI, 0.91–0.95) for infection diagnosis. For prognostic assessment, sensitivity was 0.77 (95% CI, 0.74–0.80), specificity was 0.72 (95% CI, 0.68–0.76), and AUC was 0.81 (95% CI, 0.78–0.85). HBP outperformed procalcitonin (PCT), C-reactive protein (CRP), and white blood cell count (WBC) in diagnosing and predicting critical illness. No publication bias was detected. HBP demonstrates high sensitivity and specificity for diagnosing infections in critically ill adult patients. Additionally, it effectively predicts disease progression, including organ dysfunction and mortality, surpassing traditional biomarkers such as PCT, CRP, and WBC. All that cannot be true for subjects with severe neutropenia.

Keywords: Heparin-binding protein; Systematic review, Meta-analysis, Diagnosis, Prognosis, Infectious disease, Sepsis, Organ failure, Mortality.

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Introduction. Critically ill diseases, such as sepsis, trauma, and multiple organ dysfunction, are life-threatening conditions.[1,2] It is one of the main determinants of the mortality rate in the intensive care unit (ICU). Early identification of critically ill patients with severe infections or poor outcomes is an ongoing clinical challenge for intensive care unit doctors. Blood biomarkers, such as PCT (procalcitonin), WBC, and

CRP, may provide information for severe infections.[3] Sequential Organ Failure Assessment (SOFA) score and Acute Physiology and Chronic Health Evaluation (APACHE II) have been validated for risk stratification of critical illness.[4,5] However, no single biomarker in Critically ill has been identified as a gold standard.

Heparin-binding protein (HBP) is a granule protein derived from neutrophils and located in secretory vesicles and neutrophilic granules, which is also called cationic antimicrobial protein of 37 kDa (CAP37) or leukocidin.[6] In neutrophils, HBP contributes to the regulation of endothelial permeability. HBP was considered a promising novel biomarker in infectious diseases due to the role of HBP in intravascular neutrophil activation.[7,8] In addition, HBP has been considered a predictive biomarker for the progression of organ dysfunction induced by sepsis, such as circulatory failure, respiratory failure, and acute kidney injury.[9] There is also a growing body of studies showing that a high concentration of HBP in plasma is associated with disease severity, especially mortality and organ failure.[9-12] The level of HBP in the blood of healthy people is very low, generally no more than 10 ng/ml. When an infection occurs, HBP levels change with the severity of the disease. Multiple studies have indicated that HBP is associated with various types of infection, showing elevated levels across different infections.[13] Moreover, it is considered to possess good predictive value in forecasting the occurrence, progression, and prognosis of severe infections and septic shock. In addition, recently increasing studies have illustrated that HBP has important predictive value for the prognosis of the critically ill.[12,14] Increased levels of coronary sinus HBP could serve as valuable indicators for predicting myocardial injury-related cardiogenic shock after cardiac surgery.[11] A high level of HBP in plasma upon ICU admission is connected to occurrences of respiratory and circulatory failure throughout the ICU period, which correlates with an elevated 30-day mortality rate.[15] Hence, HBP may serve as an effective biomarker for rapid clinical assessment of critical illness. However, comprehensive evaluation regarding the diagnostic efficacy of infection and prognostic ability of HBP in critically ill adult patients was warranted. Therefore, the role of HBP in the diagnosis of infection and the predictive value in critically ill adult patients were evaluated in this systematic review and meta-analysis.

Methods

Search strategy. A comprehensive systematic search was performed across PubMed, Embase, Scopus, and the Cochrane Library using a combination of Medical Subject Headings (MeSH) terms and free-text keywords. The following search terms were included: "Heparin-Binding Protein" (HBP), "Sepsis," "Diagnostic Accuracy," and "Biomarkers." Boolean operators (AND/OR) were applied for optimal search sensitivity. The detailed search strategy, including full Boolean logic and MeSH terms, is provided in Supplementary

Study Selection. Two researchers screened the titles and abstracts of all retrieved papers by themself. The following inclusion criteria were used: (1) study participants (adults ≥ 18 years old), (2) intervention (measurements of HBP), (3) diagnosis performance in infection or prognostic performance in critically ill of HBP levels compared to other potential biomarkers, (4) The data available from the studies included were sufficient to create a 2 × 2 contingency table, which was either obtained from the original article or derived from the provided dataset or figures. Meeting abstracts, editorials, reviews, letters, case reports, and animal and cell experiments were excluded. Full-text papers were obtained if either of the researchers argued that the abstract and title were suitable. After obtaining the full papers of potentially relevant studies, two researchers independently evaluated each study's eligibility on the basis of the inclusion/exclusion criteria. Full-text papers of screened titles and abstracts in accordance with the inclusion criteria were assessed for final eligibility. The conflicting viewpoints on research eligibility were resolved through consensus negotiations or by seeking input from independent researchers (**Figure 1**).

Data extraction and quality assessment. Two investigators independently extracted data by applying the same standard to record the study design, publication year, country, number of study participants, participant clinical characteristics, HBP levels, biomarkers other than HBP, study outcomes, and so on. Furthermore, among the included studies, data were extracted to establish a 2 × 2 contingency table to evaluate the ability of HBP to diagnose infection in disease and predict prognosis, such as mortality and organ failure, in adult patients.

The risk of bias in the included studies was evaluated by two independent reviewers applying the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool.[17] We evaluated with QUADAS-2 four potential areas of bias. These four areas include: (1) Patient selection, (2) Evaluation test, (3) Gold standard, and (4) Flow and timing. "yes", "no," or "unclear" were scored in each criterion.

Evidence synthesis. A pooled sensitivity, specificity, and AUC with the corresponding 95% CIs were calculated by applying a bivariate random-effects meta-analysis model. A hierarchical summary receiver operating characteristic (ROC) curve model was performed, and the area under the summary ROC curve with CIs was evaluated from different diagnostic and prognostic studies. In addition, the extent of heterogeneity of the

Detailed Search Strategy:

- PubMed
- Embase
- Scopus
- Cochrane Library

Search Terms and Boolean Logic:

("Heparin-Binding Protein" OR "HBP" OR "HBP biomarker") AND ("Sepsis" OR "Severe sepsis" OR "Septic shock") AND ("Diagnostic Accuracy" OR "Sensitivity" OR "Specificity" OR "ROC Curve")

MeSH Terms Used:

- "Sepsis"[MeSH]
- "Heparin-Binding Protein"[MeSH]
- "Biomarkers"[MeSH]
- "Diagnostic Tests, Routine"[MeSH]

Filters Applied:

- **Language:** English
- **Study Type:** Clinical trials, cohort studies, case-control studies
- **Publication Date:** From 2009 to 2024

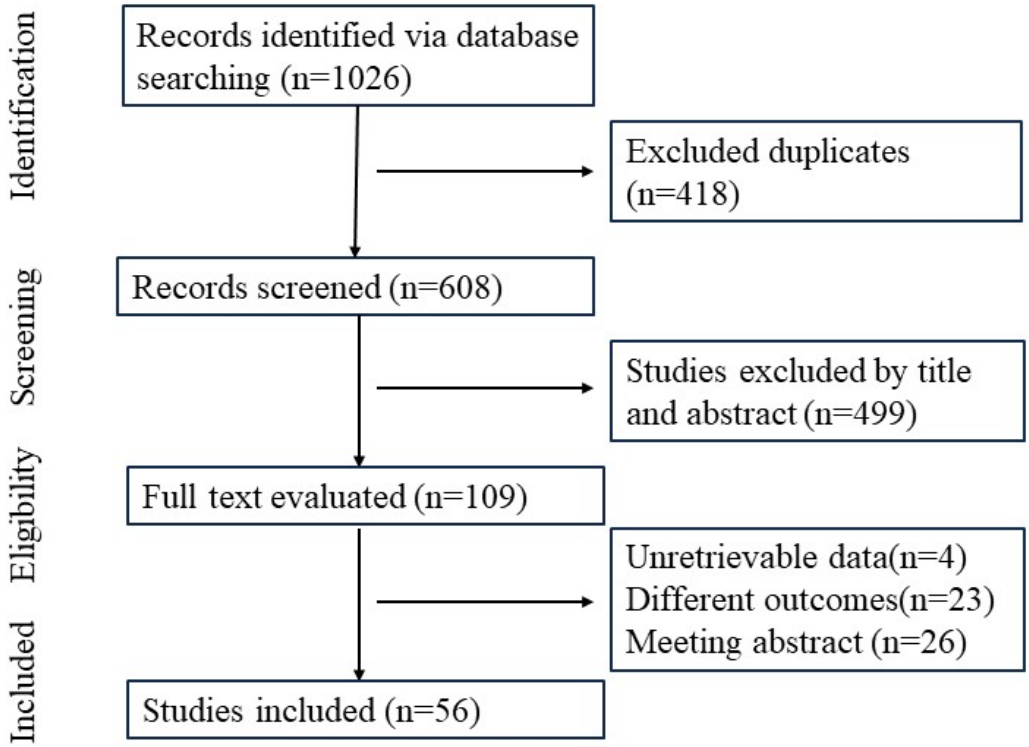
Figure 1. A flow diagram of included studies for systematic review.

included studies was quantified by the I2 statistic, and subgroup analyses were conducted to find potential sources of heterogeneity. Study design, sample size, time of study, and country were included in predefined subgroups. Potential publication bias was assessed by Deeks' test.[18] The CIs and p-values were calculated analytically. Statistical analyses were performed by applying STATA MP17 and R software. All statistical tests were conducted with a two-tailed approach, and the statistical significance threshold was defined as $p < 0.05$.

Results. A flow diagram of included studies for systematic review was reported in **Figure 1**, which demonstrates the selection process of included studies. One thousand twenty-six studies were retrieved in our database search, and 418 studies were excluded after removing duplications. Moreover, 499 studies were further excluded after screening the titles and abstracts. Therefore, 56 studies were included after a full-text review,[6,10,11,15,19-70] and 23 studies were excluded. **Table 1** displays the features of the included studies. The included studies were published from 2009 to 2024. Twenty studies were performed in China, nineteen studies were conducted in Sweden, and seventeen studies were conducted in other countries. All included studies evaluated the role of HBP in diagnosing infection and predicting clinical outcomes in critically ill adult patients. Overall, the aggregate study population included a total of 11486 adult patients with infectious diseases and critically ill patients. HBP levels were used to elevate the role in adult patients. The mean age ranged between 18 and 94 years. In addition, there were 24 studies evaluating the diagnostic role of HBP, 29 studies assessing the prognostic role of HBP, and three studies evaluating both the diagnostic and predictive role of HBP. Because some researchers suggested diagnostic or prognostic accuracy separately for patients in studies, these studies were divided into two or three parts. Therefore, 38 dataset analyses were performed in the diagnosis study, and 45 dataset analyses were performed in the prognosis study.

Risk of bias assessment. Problematic QUADAS items were: 1. Was a consecutive or random sample of patients enrolled? 2. Was a case-control design avoided? 3. Did the study avoid inappropriate exclusions? 4. Were the index test results interpreted without knowledge of the results of the reference standard? 5. If a threshold was

Table 1. Characteristics of the included studies.



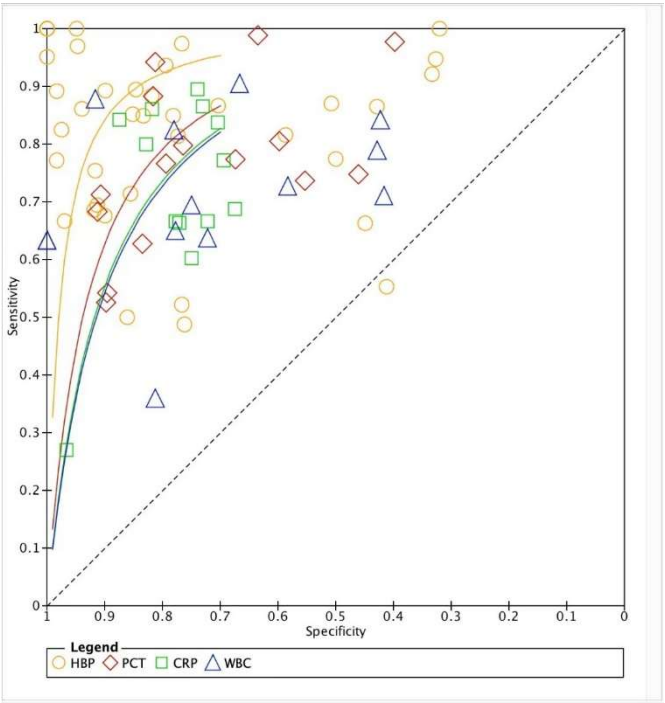


Figure 2. Characteristic curves of HBP, PCT, CRP, and WBC for diagnosing infection. HBP: Heparin-binding protein; PCT: Procalcitonin; CRP: C-reactive protein; WBC: White Blood Cell.

used, was it pre-specified? 6. Is the reference standard likely to correctly classify the target condition? 7. Were the reference standard results interpreted without knowledge of the results of the index test? 8. Was there an appropriate interval between index test(s) and reference standard? 9. Did all patients receive a reference standard? 10. Did patients receive the same reference standard? 11. Were all patients included in the analysis?

Accuracy of HBP in diagnosing infection. For the accuracy of HBP in diagnosing infection, HBP has the best discriminative power to differentiate infection from non-infection. The area under the summary ROC curve was 0.93 (95% CI, 0.91–0.95) for HBP (**Figure 2**), 0.85 (95% CI, 0.81–0.88) for PCT, 0.83 for CRP (95% CI, 0.79–0.86), and 0.80 (95% CI, 0.76–0.83) for WBC. Sensitivity and specificity of HBP for diagnosing infectious disease were 0.87 (95% CI, 0.82–0.91) and 0.87 (95% CI, 0.79–0.92), 0.81 (95% CI, 0.71–0.88) and 0.76 (95% CI, 0.67–0.83) for PCT, 0.74 (95% CI, 0.65–0.81) and 0.78 (95% CI, 0.72–0.83) for CRP, 0.72 (95% CI, 0.64–0.79) and 0.78 (95% CI, 0.62–0.89) for WBC.

The value of HBP levels in predicting organ failure in critically ill adult patients. The utility of HBP levels was assessed in 12 studies to predict the future occurrence of organ failure. These studies displayed significantly higher HBP levels in adult patients who subsequently developed organ failure compared to those patients without organ failure. In our study, the area under the summary ROC curve was 0.84 (95% CI, 0.80–0.87) (**Figure 3**) for HBP in predicting organ failure, and sensitivity and specificity of HBP for diagnosing organ failure was 0.80 (95% CI, 0.75–0.84) and 0.72 (95% CI, 0.62–0.80). Increased plasma concentrations of HBP are correlated with an imminent risk of developing sepsis, circulatory failure, and the severity of infection in adult patients.[10] Increased HBP levels upon admission to the

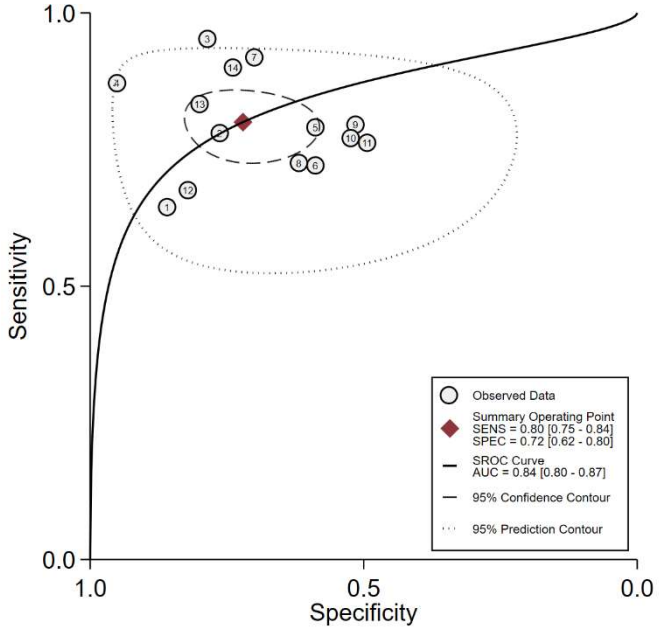


Figure 3. reports the characteristic curves of HBP for prognosing organ failure in infectious diseases and other diseases. HBP: Heparin-binding protein.

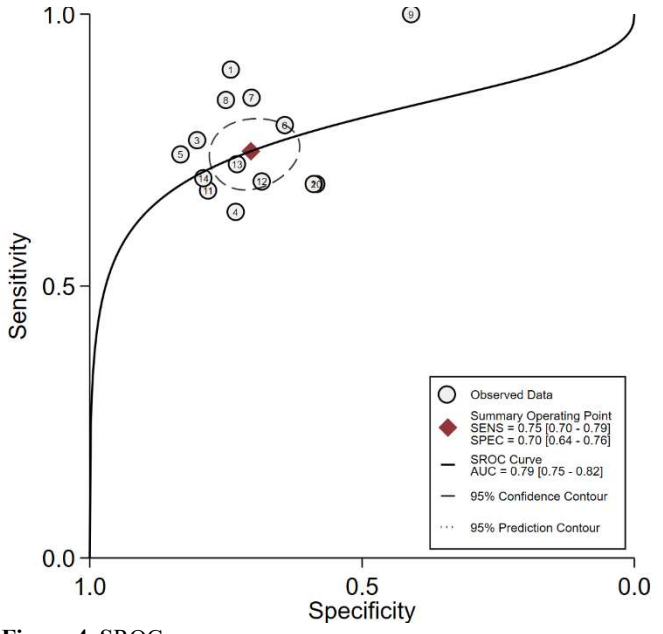


Figure 4. SROC curve.

intensive care unit were linked to the development of severe acute kidney injury within the initial 7 days.[71]

Value of HBP levels in predicting mortality in adult patients. All 14 studies evaluating the value of HBP level determination in predicting mortality in adult patients showed a significant elevation of HBP levels in non-survivors compared with that in survivors. The area under the summary ROC curve was 0.79 (95% CI, 0.75–0.82) for HBP (**Figure 4**). The sensitivity and specificity of HBP for diagnosing mortality were 0.75 (95% CI, 0.70–0.79) and 0.70 (95% CI, 0.64–0.76). A study showed that patients with sepsis with a decreased HBP greater than 50% in 48 hours had a greater than 90% chance of survival. However, patients with sepsis with decreased HBP in 48 hours less than 4% had a nearly 90% 30-day all-cause mortality rate.[27] Conversely, one study showed that there was no association between a single HBP level and 28-day mortality.[35]

Value of HBP levels in predicting the outcome of critically ill adult patients. The association between HBP level and the outcome of critically ill adult patients was evaluated in our systematic review and meta-analysis. The results suggested that all of those with worsening conditions (including mortality and organ dysfunction) had higher HDP levels than those in stable or healthy state. In addition to mortality and organ dysfunction, the association between HBP level and the severity of diseases in adult patients has been reported in many studies. One study reported that HBP is an important biomarker in patients with ST-segment elevation typical of myocardial infarction.[32] Another study demonstrated that HBP could predict the risk of severe acute pancreatitis in advance.[38] In our present study, the area under the summary ROC curve was 0.81 (95% CI, 0.78–0.85) for HBP, and the sensitivity and specificity of HBP for prognosis in adult patients were 0.77 (95% CI, 0.74–0.80) and 0.72 (95% CI, 0.68–0.76) (**Figure 5**). However, one study reported that there was no association between HBP level and disease severity in patients with acute pancreatitis.[57]

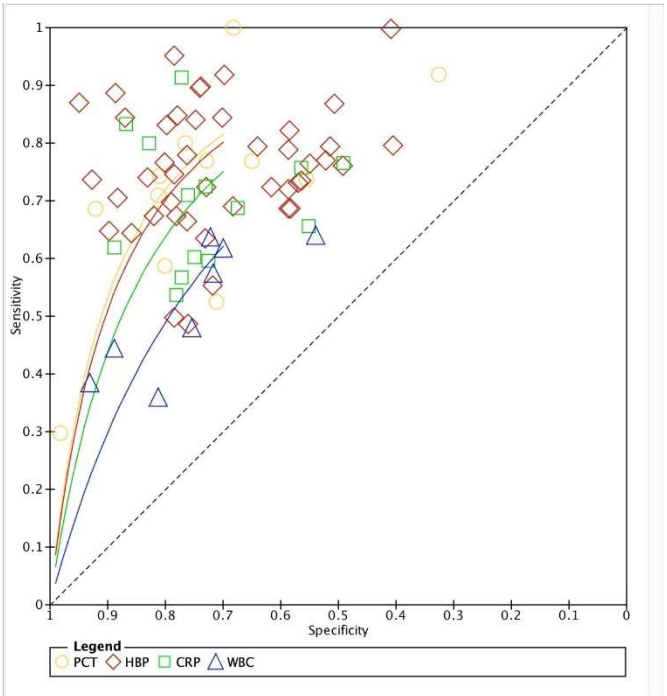


Figure 5. The characteristic curves of HBP, PCT, CRP, and WBC for predicting the outcome of critically ill. HBP: Heparin-binding protein; PCT: Procalcitonin; CRP: C-reactive protein; WBC: White Blood Cell.

Subgroup analysis. Subgroup analysis of retrospective studies (AUROC, 0.94) showed a better diagnostic

accuracy of infection for HBP than that prospective (AUROC, 0.91). HBP tends to conduct better before 2020 (AUROC, 0.97) than after 2020 (including 2020) studies (AUROC, 0.90). Studies were performed on different countries that displayed similar accuracy in identifying infectious diseases. Regarding sample size, the subgroup analysis of studies from less than 200 demonstrated HBP has better discriminative power to differentiate infectious disease and non-infectious disease than that greater than 200. However, for the prognostic role of HBP in our present study, the subgroup analysis of studies from different study types, study years, and sample sizes illustrated similar results. HBP showed a better prognostic ability than Sweden and other countries in our present subgroup analysis.

Significant heterogeneity was observed in the overall analysis and subgroup analyses. However, no evidence of a threshold effect was found, which indicated that a specific cutoff point did not influence the variability in the results.

Discussion. In our systematic review and meta-analysis, we found that HBP was more accurate biomarkers for infection than CRP, PCT and WBC levels. In addition, HBP also showed good predictive ability for prognosis in critical illness, especially mortality and organ failure.

For clinicians, the early identification of infections remains a challenge. Due to the emergence of antibiotic resistance, it is widely agreed that antibiotics should not be prescribed for every suspected infection. Thus, a better specific biomarker for infection would be most beneficial. HBP is a promising, innovative biomarker for predicting sepsis and sepsis-induced organ failure, which is derived from neutrophils and was first reported by Adam Linder.[10] Based on the predefined protocol, in our present systematic review and meta-analysis, which included 56 studies from several countries, we demonstrated the role of HBP in the diagnosis of infectious diseases and the development of organ failure and mortality in critically ill adult patients. The plasma HBP levels were detected in a prospective study, which included 233 subjects and was performed in 2009 to investigate human infection.[10] The study concluded that there was a strong association between high HBP levels and infection or the development of sepsis with organ dysfunction.[10] After that, HBP could be considered a useful clinical marker for infectious diseases, including sepsis. In our present study, we have summarized the diagnostic efficacy of HBP in infectious diseases. We illustrated that HBP had the best discriminative capability to distinguish infectious diseases from non-infectious diseases when compared with PCT, CRP, or WBC. As the application of biomarkers and validated clinical scoring systems becomes more prevalent in clinical practice, there has been a surge of interest in the diagnostic value of their combined utilization. Several studies have reported that HBP was combined with another biomarker to diagnose sepsis.[10,21,27,29,72] Combining HBP, PCT, and lactate may raise the diagnostic role compared to single biomarkers.[64] Therefore, combining HBP with existing biomarkers or validated clinical scoring systems could improve diagnostic accuracy for infection.

Early elevation of HBP is involved in the severity of adult patients.[35] Significantly increased HBP levels are related to a substantially elevated risk for complications in adult patients.[43] Several studies have demonstrated that most patients with aggravation of the disease have an increased HBP level ranging from 11 to 266 ng/mL.[11,56] Previous studies have also demonstrated that HBP serves as a significant predictor of mortality. One study showed that plasma HBP greater than 13.47 ng/mL was related to increased deceased patients (died), with an AUC of 0.81, a sensitivity of 0.90, and a specificity of 0.74.[19] Moreover, HBP is utilized as a diagnostic and monitoring biomarker in clinical settings to assess organ dysfunction resulting from sepsis.[43] However, HBP also has displayed a certain predictive role in organ failure in infectious diseases and other diseases.[52,56,60] Linder et al. illustrated the predictive and diagnostic role of HBP in 2009.[10] The study showed that the level of HBP increased at least 12 hours before signs of organ dysfunction at a cutoff value of 15 ng/mL in severe sepsis. HBP is increased prior to the development of organ failure in COVID-19.[46] In addition, increased plasma levels of HBP at ICU admission were independently related to multiple organ dysfunction syndrome (MODS) and early death after resuscitation from cardiac arrest.[54] In our meta-analysis, we synthesized the current evidence to display how HBP can help clinically in the monitoring of organ dysfunction in infectious diseases and other diseases. HBP plays a significant role in the pathogenesis of organ dysfunction in sepsis, specifically by causing an increase in capillary permeability.[73] This mechanism helps explain why HBP is a more effective prognostic biomarker than CRP and PCT in the detection of organ dysfunction in sepsis. In addition, some studies indicated that HBP not only predicts mortality and organ failure but also provides some indication of disease progression. One study confirmed that HBP contributed to the early identification of COPD, which illustrated that the level of HBP in the acute exacerbation group (147 ng/ml) is higher than that in the stable group (50.69 ng/ml).[26] In another study, elevated levels of coronary sinus HBP were helpful markers for predicting myocardial injury-related cardiogenic shock after cardiac surgery.[11] However, more large clinical studies are needed to establish the optimal cutoff for HBP clearance in predicting organ dysfunction and mortality.

To the best of our knowledge, the present study stands as the most comprehensive meta-analysis to date, effectively synthesizing the existing data on the role of

HBP in adult patients, which includes the diagnosis of infection and the prognosis of critically ill adult patients.[72,74,75] In a previous systematic review and meta-analysis, HBP had a better diagnostic role in identifying sepsis among patients presenting with signs of systemic infection than PCT and CRP, which included 26 studies published up to 2019.[74] In our present study, we assessed the diagnostic capability of HBP for infectious diseases and evaluated its prognostic potential in predicting critically ill outcomes, which included 56 studies up to 2024. Collectively, our findings revealed that HBP illustrates not only both high sensitivity and specificity in the identification of infectious diseases but also a high prognostic role in the identification of the critically ill. In terms of clinical significance, HBP serves as a crucial diagnostic aid in detecting and ruling out infectious diseases among patients presenting with signs and symptoms of infection.[31] In addition, HBP levels are increased before the development of aggravation of disease, including organ dysfunction and mortality.[56] Moreover, this will probably lead to improved outcomes for adult patients with infectious diseases and critically ill adult patients. All the articles reported

As highlighted by Fisher et al. (2022),[76] variations influence the dynamics of circulating HBP levels in neutrophil activation and mobilization, raising concerns about its reliability in immunocompromised patients. Moreover, Chen and Ma (2024)[77] emphasize that alternative infection markers may be necessary for this patient population to enhance early detection and differentiation between infectious and non-infectious causes of fever and inflammation. Given these limitations, clinicians should be cautious when interpreting HBP levels in patients with neutropenic fever, frequently found in hematologic malignancies, and consider complementary biomarkers and clinical scoring systems to improve diagnostic accuracy.[78]

However, our present study, which also excluded neutropenic patients, has several limitations. First, variations across countries, study types, and years may contribute to heterogeneity in the pooled outcomes, potentially diminishing the precision of sensitivity and specificity measurements. Second, this study only included studies in which the language is English, and more studies in other languages are needed in future studies. Furthermore, there is limited usefulness in pooling studies comparing healthy adults and cases with studies looking at a cohort of patients with a reasonable likelihood of having the target condition.

Conclusions. While HBP has demonstrated significant utility as a biomarker for infections in critically ill patients, its reliability is reduced in individuals with hematologic malignancies, particularly those experiencing severe neutropenia. Patients with conditions such as leukemia or those undergoing intensive chemotherapy often exhibit depleted neutrophil counts, which can significantly impact the release and detection of HBP. To enhance its clinical applicability, standardized cutoff values and future multicenter studies are recommended.

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