Clinical physiological parameters for the prediction of gram-negative bacterial infection in the emergency department

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Abstract

Background: Early detection and treatment of Gram-negative bacteria (GNB), major causative pathogens of sepsis, may benefit a patient's outcome, since the mortality rate increases by 5–10% for each hour of delayed therapy. Unfortunately, GNB diagnosis is based on blood culture, which is time consuming. Therefore, an economic and effective GNB infection detection tool in the emergency department (ED) is warranted.

Methods: We conducted a retrospective case control-study in the ED of a university-affiliated medical center between January 01, 2014 and December 31, 2017. The inclusion criteria were as follows: (1) age ≥ 18; (2) clinical suspicion of bacterial infection; (3) positive bacterial culture of blood or sputum or urine. Descriptive statistics was performed on patient demographic characteristics, vital signs, laboratory data, infection sites, cultured microorganisms, and clinical outcomes. The accuracy of vital signs to predict GNB infection was identified via logistic regression and receiver operating characteristic (ROC) analysis.

Results: A total of 797 patients were included in this study; the mean age was 71.8 years and 51.3% were male. The results revealed that patients with body temperature ≥ 38.5°C, heart rate ≥ 110 beats per minute, respiratory rate ≥ 20 breaths per minute, and Glasgow coma scale (GCS) < 14, had a 2.3-, 1.4-, 1.9-, and 1.6-fold greater risk of GNB infection, respectively. The area under the curve values for ROC analysis of these measures were 0.70, 0.68, 0.69, and 0.67, respectively.

Conclusion: The four physiological parameters were rapid and reliable independent predictors for early detection of GNB infection.

Background

Gram-negative bacteria (GNB) are more frequently associated than other microbes with severe sepsis and septic shock [1], a potentially life-threatening consequence of the body's inflammatory response to pathogens. There are two theories regarding how GNB trigger these harmful systemic responses. First, bacteria invade blood vessels and produce inflammatory mediators that circulate throughout the body, resulting in systemic inflammation and multiple organ failure. Second, bacteria and their endotoxins induce local inflammation in extravascular tissues that release immune mediators into the bloodstream [2].

Early recognition of these pathogens and appropriate patient disposition are crucial, as numerous studies have demonstrated benefits to patient outcomes [3–6]. One study indicated that failure to implement effective antibiotic therapy within the first 24 hours in GNB sepsis patients may result in a longer hospital stay and a higher mortality rate [7]. The 2018-sepsis-one-hour bundle suggests early administration of antibiotics to patients with suspected infection; antibiotic stewardship was also emphasized as an essential aspect of high-quality sepsis management [8]. At present, the gold standard to diagnose GNB infection is based on bacterial culture, which may take hours or days before the result is known and can lead to delayed treatment decisions.

The inflammatory mediators induced by GNB infection may result in a significant inflammatory response, including fever, tachycardia, and shortness of breath [9]. However, by using clinical parameters, we aimed to discover a prompt, simple, and inexpensive bedside prediction tool to detect GNB infection in the emergency department (ED), to assist clinical physicians with timely antibiotic treatment and enable accurate patient disposition.

Methods

Study design, setting, and participants

This was a retrospective case control-study, conducted in a university-affiliated medical center (Cathay General Hospital, Taipei) in Northern Taiwan; there were 40 ED beds and 800 ward beds, with approximately 55,000 visiting patients annually. The study period was between January 01, 2014 and December 31, 2017. Patients who fulfilled the following inclusion criteria were included: (1) aged above 18 years, (2) suspected of bacterial infection, and (3) positive bacterial culture obtained from blood or sputum or urine obtained in the ED. Patients who were transferred from other hospitals, had out-of-hospital cardiac arrest, were pregnant, or had mixed infections were excluded.

Definition of variables and primary outcome

Suspected bacterial infection is identified by: (1) physician's clinical judgment through chart review and infection related disease codes, or (2) ED clinical parameters that indicate infection, such as severe inflammatory response syndrome (SIRS) and quick sepsis-related organ failure assessment (qSOFA) score. SIRS is defined as a heart rate > 90 beats per minute, respiratory rate > 20 breaths per minute, temperature < 36°C or > 38°C, white blood cell count < 4000 / mm^3 or > 12 000 / mm^3, and band form > 10% [10]. qSOFA score is defined as systolic blood pressure ≤ 100 mmHg, respiratory rate ≥ 22 breaths per minute, and Glasgow Coma Scale < 15 [11]. Two sets of blood cultures, all together four bottles (two aerobic bottles, two anaerobic bottles), were collected from each patient via peripheral venipuncture at two different sites, with a 30-minute interval between sample collections. Positive blood culture is defined as at least two bottles of blood culture yielding the same pathogen [12]. Positive sputum culture is defined as pathogen growth in sputum specimens with fewer than 25 squamous epithelial cells per low-power field [13]. Positive urine culture is defined as pathogen growth > 10^5 colony-forming unit (CFU) per milliliter in clean-catch midstream urine specimens [14].

Data collection and assignment to case and control groups

The retrospective chart review method was used to acquire data of patients who fulfilled the inclusion criteria. Demographic characteristics, including vital signs (obtained at the ED triage), laboratory data, infection sites, cultured microorganisms, qSOFA scores, SIRS criteria, and clinical outcomes, were obtained by an emergency physician (Table 1). In total, 903 bacteria-infected ED patients were initially recruited, with a total of 797 patients included in the study. Exclusions (106 patients) were made for insufficient data, presence of mixed infections, occurrence of an out-of-hospital cardiac arrest, transferal

of patients treated at other hospitals, or pregnant patients (Figure 1). The recruited patients were further divided into two groups based on the culture result, with 278 patients assigned to the GNB group and 519 patients to the non-GNB group. All variables were compared between the two groups, and the accuracy of clinical parameters to predict GNB infection were also analyzed.

Ethical statement

This study was approved by the institutional Review Board of the Cathay General Hospital and was conducted according to the Declaration of Helsinki. This was an observational study; the need for informed consent from the patients was not necessary.

Statistical analysis

We used SPSS 23.0 for Mac (SPSS Inc., Chicago, IL, USA) to perform statistical analysis. Continuous data were presented as mean ± standard deviation (SD), while categorical variables were presented as percentages. Independent samples *t*-test, the Mann–Whitney, or Wilcoxon test were used to analyze continuous variables. Pearson's chi-square test or Fisher's exact test was used for categorical variables. Logistic regression was performed to evaluate the prediction of GNB infection among the four clinical parameters that showed significant difference ($p < 0.05$) between the GNB and the non-GNB group (Table 2). The optimal cut-off point of each clinical parameter used to predict GNB infection was calculated via Youden index. The area under the receiver operating characteristic curve (AUROC) was then used to evaluate GNB prediction discrimination ability (Table 3).

Results

A total of 797 patients were included in this study. The male to female ratio was approximately equal. The mean ± SD age was 71.8 ± 17.2 years, and the GNB group was older than the non-GNB group at 77.0 ± 1.2 and 69.0 ± 17.5 years, respectively. Glasgow coma scale (GCS), heart rate, respiratory rate, and body temperature were significantly different (*p*-value < 0.01, 0.02, <0.01, 0.01) between GNB and non-GNB group. The mean ± SD of GCS was lower in the GNB group (10.9 ± 3.8) than the non-GNB group (11.9 ± 4.0). Heart rate, respiratory rate, and body temperature were higher in the GNB group than the non-GNB group for 105.0 ± 25.2, 21.9 ± 6.6, 37.7 ± 1.5, and 100.0 ± 29.5, 20.3 ± 6.9, 37.0 ± 4.3, respectively.

The median C-reactive protein (CRP) was 7.9 (interquartile range [IQR]: 3.1–17.4) in the GNB group, which was higher than that in the non-GNB group, 5.5 (IQR: 1.3–12.9). The prevalence of pneumonia, urinary tract infection, intra-abdominal infection, and bacteremia was moderately higher in the GNB group than in the non-GNB group at 37.1%, 55.8%, 17.3%, and 36.7%, respectively. The percentage of qSOFA score ≥ 2 and SIRS criteria ≥ 3 were both significantly higher in the GNB group, at 50.7% and 39.6%, respectively, than the non-GNB group, at 38.3% and 24.5%, respectively. The most frequently identified bacterium from the blood and the urine specimen was *Escherichia coli* (38%); while the most frequently identified pathogen from the sputum was *Pseudomonas aeruginosa* (40%) (Figure 3).

The mortality percentage was higher in the GNB group (27.7%) than the non-GNB group (24.8%). The optimal cut-off point for the clinical parameters to predict GNB infection among ED adult bacteria-infected patients, calculated via Youden index, are as follows: body temperature ≥ 38.5°C, heart rate ≥ 110 beats per minute, respiratory rate ≥ 20 breaths per minute, and GCS < 14. Logistic regression showed that patients with each of these parameters had, respectively, a 2.3-, 1.4-, 1.9-, and 1.6-fold greater risk of GNB infection. The AUROC, adjusted by age ($p < 0.01$), chronic kidney disease (CKD) ($p < 0.01$) and uremia under dialysis, in predicting GNB infection among ED adult bacteria-infected patients, showed body temperature ≥ 38.5°C and had an acceptable discrimination ability at 0.7 (0.66–0.74) (Figure 2).

Discussion

It is crucial to quickly identify the pathogens in septic patients and make a prompt decision in a busy ED, as the mortality rate may increase up to 10% with every hour of delayed diagnosis [15]. Unlike the time-consuming blood culture, assessment of clinical physiological parameters has the advantage of being immediate and easy to acquire in the ED. SIRS criteria and qSOFA scores were both used to identify sepsis via clinical parameters. However, the relative accuracy of these tools for the identification of sepsis remains under debate [16], and none of these have been used to predict GNB infection yet.

This study identified the key clinical physiological parameters that could predict GNB infection in the ED by reviewing medical records of adult patients with suspected bacterial infection. The vital signs that correlated with GNB infection were body temperature, heart rate, respiratory rate, and GCS. We determined that the cut-off points of body temperature of ≥ 38.5°C and heart rate ≥ 110 beats per minute were higher than the SIRS criteria of > 38°C and > 90 beats per minute. These were probably related to the systemic inflammation, which could include effects induced by the GNB, such as increased vascular permeability, leukocyte-endothelial adhesion, and neuroendocrine dysregulation [2]. The circulating GNB endotoxin may further precipitate organ dysfunction and shock status, with consequences of poor perfusion to the central nervous system and changes in GCS [2]. In this study and other reports, the respiratory tract was one of the most common infection sites for GNB [17], resulting in pneumonia and increased respiratory rates.

Prior medical history did not show a significant difference between the GNB and the non-GNB group, making it difficult to predict GNB infection using these methods. However, higher prevalence of CKD and uremia under dialysis were noted in the non-GNB group. A similar finding was noted in a previous study conducted by Berman and colleagues, who concluded that instead of GNB, the major pathogens in infected dialysis patients were gram-positive cocci [18]. In patients with CKD, *Escherichia coli* and *Staphylococcus aureus* accounted for the majority of bloodstream infections, while *Staphylococcus aureus* was especially prominent in CKD patents with an estimated glomerular filtration rate < 30 mL per minute per 1.73 m^2 [19].

This study demonstrated a significantly higher CRP level in the GNB group than the non-GNB group. Ryuzo and colleagues discovered a similar result, where CRP and interleukin-6 were higher in gram-

negative bacteremia than in gram-positive bacteremia in intensive care unit patients [1]. Another study also showed CRP and procalcitonin as effective predictors of bloodstream GNB infection [20]. Although laboratory data may act as potential indicators of GNB infection, it still requires time to obtain the result, and this may jeopardize the early treatment strategy. Furthermore, despite several newly developed molecular rapid diagnostic tools being available for the early detection of these pathogen species, these tools are not widely used in most medical facilities due to their unavailability and expense [21-24].

To our knowledge, this was the first study conducted to evaluate physiological parameters to predict GNB infection in the ED. However, this study also has some limitations. First, some valuable information and data may be missing due to the nature of a retrospective study setting. Second, this was a single-center study and thus the bacterial species detected may have a selection bias. Third, the study was conducted in a tertiary medical center, where the disease severity of the visiting patients may be higher. Fourth, several unmeasured confounding factors may exist, such as the severity of underlying diseases and the time of treatment. Fifth, clinical parameters were obtained only once after arrival at the ED, while initial vital signs may better reflect the original patient status rather than the vital signs obtained after treatment. Thus, further research is needed to validate the findings of this study.

Conclusion

Clinical physiological parameters, including body temperature ≥ 38.5°C, heart rate ≥ 110 beats per minute, respiratory rate ≥ 20 breaths per minute, and GCS < 14, were four rapid, simple, and cost-effective independent predictors that could detect GNB infection early in the ED.

Abbreviations

GNB: Gram-negative bacteria

ED: Emergency department

ROC: Receiver operating characteristic

SIRS: Severe inflammatory response syndrome

qSOFA: Quick sepsis-related organ failure assessment

CFU: Colony-forming unit

SD: Standard deviation

AUROC: Area under the receiver operating characteristic curve

GCS: Glasgow coma scale

CRP: C-reactive protein

IQR: Interquartile range

CKD: Chronic kidney disease

Declarations

Ethics approval and consent to participate

This study was approved by the institutional Review Board of the Cathay General Hospital and was conducted according to the Declaration of Helsinki.
Due to the retrospective setting of this study, the need for informed consent from the patients was not necessary.

Consent for publication

Not applicable.

Availability of data and material

All data generated or analyzed during this study were included in this manuscript.

Competing interests

All authors denied any conflict of interest.

Funding

Not applicable.

Author contributions

CPH, HYC, WLC, JHC, CCH, PHW, and JYC designed and conceived this study, HYC and CPH wrote the manuscript. JYC performed the statistical analysis. JHC, WLC, and CCH provided professional suggestions. All authors read and approved the final manuscript.

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Tables

Table 1. Demographics of emergency department adult patients with bacterial infection.

Characteristics	Total patients (n=797)	GNB (n=278)	Non-GNB (n=519)	*p*-value
Age (mean ± SD)	71.8 ± 17.2	77.0 ± 1.2	69.0 ± 17.5	< 0.01
Male (%)	51.3%	47.5%	53.4%	0.11
Vital signs (mean ± SD)				
Glasgow coma scale	11.5 ± 4.0	10.9 ± 3.8	11.9 ± 4.0	< 0.01
SBP (mmHg)	96.0 ± 37.3	98.0 ± 35.0	94.9 ± 38.5	0.26
Heart rate (n/min)	101.7 ± 28.1	105.0 ± 25.2	100.0 ± 29.5	0.02
Respiratory rate (n/min)	20.8 ± 6.8	21.9 ± 6.6	20.3 ± 6.9	< 0.01
Body temperature (°C)	37.3 ± 3.6	37.7 ± 1.5	37.0 ± 4.3	0.01
Laboratory data (median, IQR)				
WBC ($10^3/mm^3$)	11.6 (8.1–16.6)	12.3 (8.8–17.1)	11.4 (7.9–16.4)	0.13
CRP (mg/dL)	6.6 (2.0–14.8)	7.9 (3.1–17.4)	5.5 (1.3–12.9)	< 0.01
Infection sites (%)				
Pneumonia	26.3%	37.1%	20.6%	< 0.01
Urinary tract infection	22.1%	55.8%	4.0%	< 0.01
Intra-abdominal infection	11.4%	17.3%	8.3%	< 0.01
Soft tissue infection	3.1%	3.2%	3.1%	0.90
Infectious endocarditis	0.8%	1.4%	0.4%	0.10
CNS infection	0.1%	0.4%	0%	0.17
HIV infection	0.4%	0.0%	0.6%	0.20
Bacteremia	14.3%	36.7%	23.3%	< 0.01
Medical history (%)				
Diabetes	13.2%	11.9%	13.9%	0.43
Malignancy	18.1%	16.5%	18.9%	0.41
Chronic kidney disease	12.5%	6.1%	12.0%	< 0.01
Uremia under hemodialysis	2.9%	0.7%	4.9%	< 0.01
COPD	1.6%	2.2%	1.3%	0.39
Liver cirrhosis	4.9%	3.6%	5.6%	0.21

Autoimmune disease	2.0%	2.2%	1.9%	0.82
qSOFA ≥ 2 (%)	42.7%	50.7%	38.3%	< 0.01
SIRS ≥ 3 (%)	29.7%	39.6%	24.5%	< 0.01
Mortality (%)	26.7%	27.7%	24.8%	0.37

GNB, gram-negative bacteria; SD, standard deviation; SBP, systolic blood pressure; IQR, interquartile range; WBC, white blood cell; CRP, C-reactive protein; CNS, central nervous system; HIV, Human immunodeficiency virus; COPD, chronic obstructive pulmonary disease; qSOFA, quick sepsis related organ failure assessment; SIRS, systemic inflammatory response syndrome.

Table 2. Predicting gram-negative bacterial infection by specific clinical physiology parameters of adult patients with bacterial infection in emergency department, identified by logistic regression.

	Odds ratio	95% CI	*p*-value
BT ≥ 38.5°C	2.30	1.90–3.83	< 0.01
RR ≥ 20/min	1.91	1.51–2.92	< 0.01
GCS < 14	1.57	1.38–2.50	< 0.01
HR ≥ 110 beats/min	1.38	1.27–2.30	0.04

BT, body temperature; RR, respiratory rate; GCS, Glasgow coma scale; HR, heart rate

Table 3. Adjusted AUROC for gram-negative bacterial infection prediction by clinical physiology parameters of adult patients with bacterial infection in emergency department.

	AUROC	95% CI	*p*-value
BT ≥ 38.5°C	0.70	0.66–0.74	< 0.01
RR ≥ 20 /min	0.69	0.65–0.72	< 0.01
GCS < 14	0.68	0.64–0.72	< 0.01
HR ≥ 110 beats/min	0.67	0.63–0.71	< 0.01

AUROC, Area under the Receiver Operating Characteristic; BT, body temperature; RR, respiratory rate; GCS, Glasgow coma scale; HR, heart rate

Figures

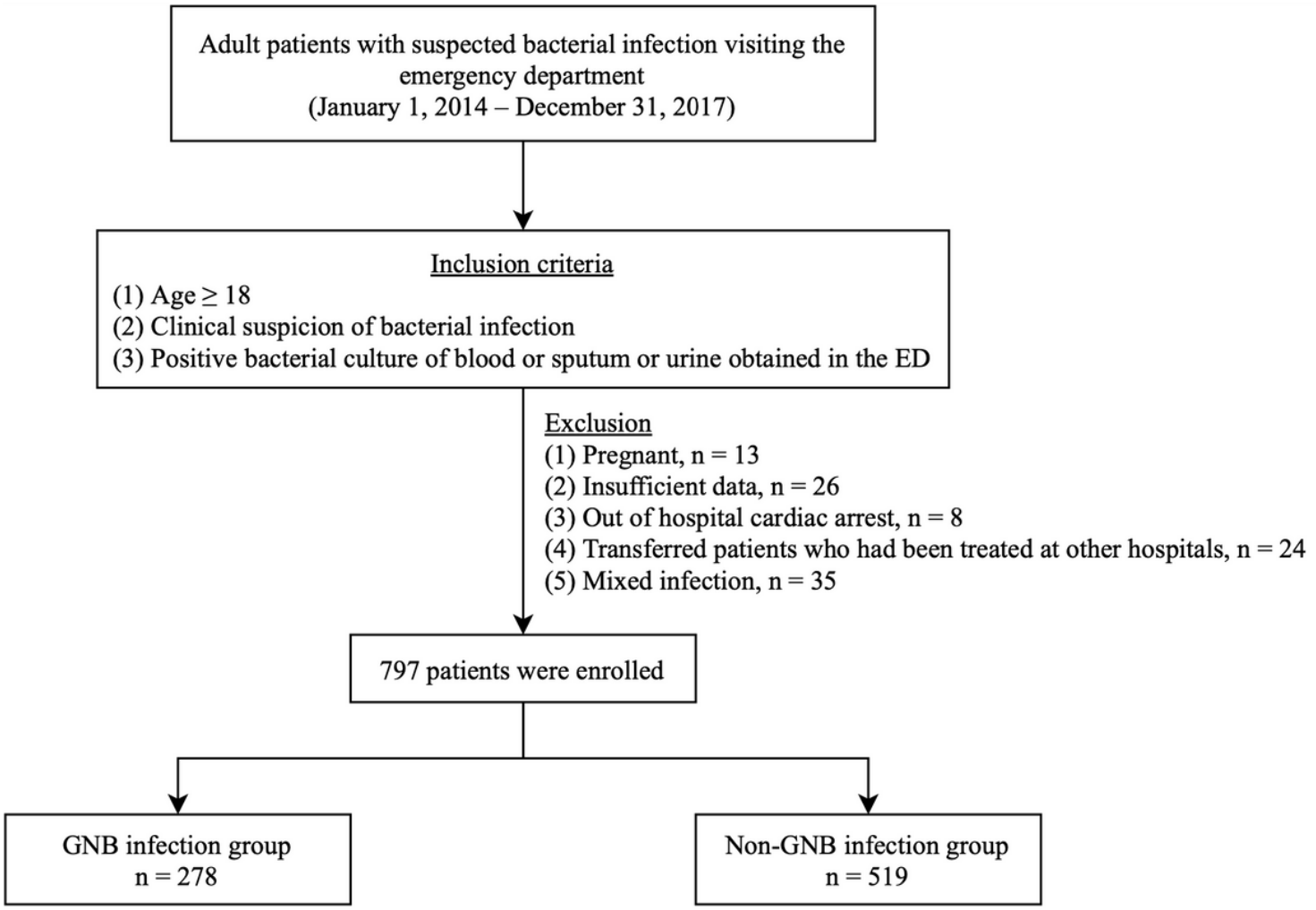

Figure 1

Flowchart of this study

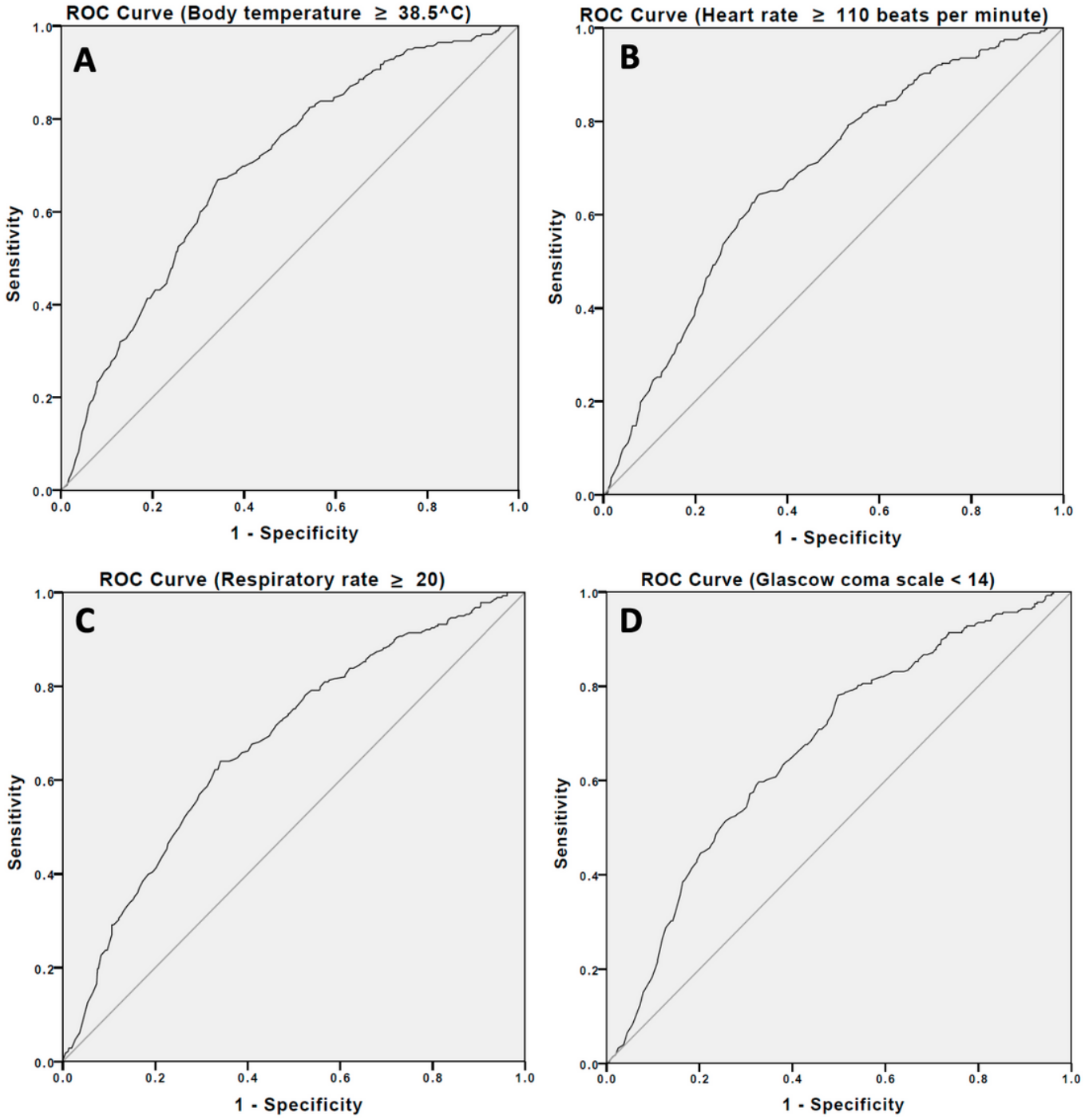

Figure 2

A. Area under the curve of body temperature ≥ 38.5°C; B. heart rate ≥ 110 beats per minute; C. respiratory rate ≥ 20 breaths per minute; D. Glasgow coma scale < 14 to predict gram negative bacterial infection in the emergency department

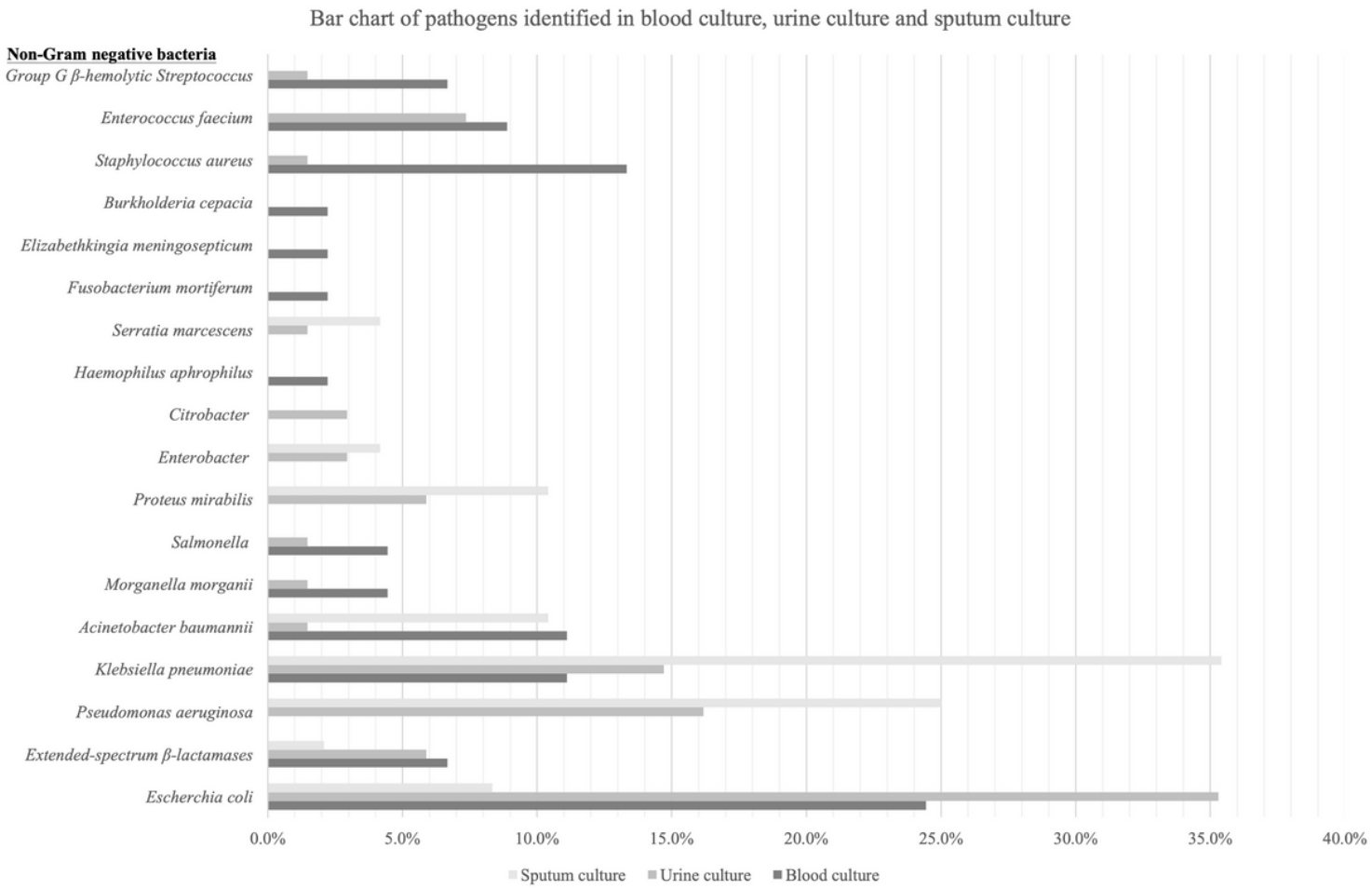

Figure 3

Bar chart of pathogens identified in blood culture, urine culture, and sputum culture