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Factors Associated with a Final Diagnosis of Sepsis in Emergency Department Patients with Elevated Procalcitonin—A Single-Center Retrospective Cohort Study

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Abstract

Introduction: The new definition of sepsis is a life-threatening condition caused by an inappropriate host reaction to infection. The existing scoring systems are limited in terms of the performance in an initial evaluation of the patients. Therefore, the diagnosis of sepsis is still largely dependent on clinical training and physician experience. **Objectives**: We aimed to identify factors associated with a final diagnosis of sepsis among patients admitted to the emergency department (ED) with elevated procalcitonin in a Polish population and to describe how clinical severity scoring systems discriminated between patients with and without this diagnosis. **Methods**: In this single-center retrospective cohort study, we included adult (≥18 years) patients admitted to the ED in the period 1.01.2018–30.09.2023 who had elevated procalcitonin concentration (>0.5 μg/L) and were hospitalized. Patients were divided into two groups based on whether a final diagnosis of sepsis was made during the index hospitalization. The primary endpoint was the association of the analyzed baseline characteristics with the final diagnosis of sepsis, assessed with simple and multiple logistic regression; the multivariable model was internally validated with bootstrap resampling. The secondary endpoint was the area under the receiver operating characteristic curve (AUC) of clinical severity scoring systems, calculated in patients with available scores. **Results**: Of 620 hospitalizations (580 patients), 143 (23.1%) involved a final diagnosis of sepsis. In the multiple logistic regression (613 patients, 142 events), procalcitonin (OR: 2.51 per 10-fold increase, 95% CI: 1.80–3.48, $p < 0.0001$), C-reactive protein (OR: 2.39 per 10-fold increase, 95% CI: 1.28–4.47, $p = 0.0063$), and platelet count (OR: 0.87 per $50 \times 10^3/\mu L$, 95% CI: 0.80–0.95, $p = 0.0029$) were associated with a final diagnosis of sepsis. The model had an AUC of 0.790 (optimism-corrected AUC: 0.767). SAPS II, APACHE, and SOFA were available for only 37, 37, and 35 patients, respectively, and were lower in the sepsis group; their AUCs were imprecise and were not formally compared with other scores. **Conclusions**: In patients admitted to the ED with elevated procalcitonin, higher procalcitonin and CRP and a lower platelet count were associated with a final diagnosis of sepsis. These exploratory findings require external validation with standardized diagnostic criteria before they can be used to support the early diagnosis of sepsis.

Keywords: sepsis; emergency department; procalcitonin; clinical severity scores; retrospective cohort

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1. Introduction

1.1. Sepsis Definition

The new definition of sepsis is a life-threatening condition caused by an inappropriate host reaction to infection. The definition was revised three times: in 1992, then in 2001, and last changed in 2016. A 1991 consensus created an initial definition focused on the then-prevailing perspective that sepsis derives from a host's systemic inflammatory response syndrome (SIRS) to infection [1]. A SIRS with multiorgan dysfunction was specifically described as severe sepsis. It could lead to septic shock, which was defined as hypotension induced by sepsis and persisting despite appropriate fluid resuscitation. A 2001 medical committee, recognizing the limitations of these definitions, created an extended list of diagnostic criteria for sepsis. Still, it did not propose any alternative definition because of the lack of supporting evidence [2].

In 2016, the Sepsis-3 Task Force decided against the four stages of sepsis and created new recommendations that differentiated sepsis from an uncomplicated infection [3]. They removed SIRS criteria to identify patients with a worse outcome. Patients with a severe infection are clinically assessed using a Sequential Organ Failure Assessment (SOFA) scoring system. For faster risk assessment, a quick SOFA (qSOFA) scale was designed, which includes symptoms like hypotension, tachypnea, and altered mental status.

Nowadays, even with a more precise, better definition, sepsis is still underdiagnosed or diagnosed with a delay, which leads to serious complications and a high risk of mortality [4].

There are an estimated 150,000 sepsis admissions in the UK annually, with a 30% mortality rate resulting in over 44,000 deaths [5].

1.2. The Causes of Sepsis

Sepsis may have different origins of the primary infection, including the respiratory tract, central nervous system, urinary tract, skin, and abdominal organs [6]. Pneumonia and urinary tract infections are the most common points of focus in bacteremia, septic shock, sepsis, and emergency department (ED) admissions to the intensive care unit for infectious processes [7]. Nevertheless, in the case of many patients, the source of infection remains unresolved [8].

1.3. Differential Diagnosis

Sepsis differential diagnoses include acute conditions like myocardial infarction, pulmonary embolism, pancreatitis, or adrenal insufficiency [9]. Misdiagnosed sepsis can lead to a delay in applying an appropriate treatment, which is an additional burden for the healthcare system and leads to complications, prolonged hospitalization, and a higher mortality rate [10]. It is crucial to diagnose sepsis as early as possible and apply an adequate treatment.

1.4. Sepsis Scoring Systems

Due to the complexity of sepsis, many protocols have been proposed to simplify the diagnostic approach. The most popular scales are SOFA, qSOFA, Simplified Acute Physiology Score (SAPS) II, Acute Physiology and Chronic Health Evaluation (APACHE), Modified Early Warning Score (MEWS), National Early Warning Score (NEWS), and SIRS criteria. However, these instruments were developed for different purposes. SAPS II and APACHE assess the severity of illness and predict mortality in intensive care unit (ICU) patients, SOFA quantifies organ dysfunction, MEWS and NEWS are early warning scores, and qSOFA identifies patients with suspected infection at higher risk of poor outcome. None of them was designed specifically to establish the diagnosis of sepsis. Nevertheless, the existing scoring systems are limited in terms of the performance in an initial evaluation of

the patients. Therefore, the diagnosis of sepsis is still largely dependent on clinical training and physician experience.

1.5. Objectives

We aimed to identify factors associated with a final diagnosis of sepsis among patients admitted to the ED with elevated procalcitonin in a Polish population. We also aimed to describe how clinical severity scoring systems discriminated between patients with and without a final diagnosis of sepsis.

2. Patients and Methods

2.1. Study Design and Participants

In this single-center retrospective cohort study, we included adult (≥18 years) patients admitted to the ED in the period 1.01.2018–30.09.2023 who had elevated procalcitonin concentration (>0.5 μg/L) and were hospitalized in the National Medical Institute of the Ministry of the Interior and Administration (Warsaw, Poland). Procalcitonin was measured in all ED patients in whom any infection was suspected. Eligible patients were identified by searching the laboratory records for all ED patients with procalcitonin >0.5 μg/L in the study period, and the discharge summary of each identified patient was then reviewed. The cut-off of 0.5 μg/L was chosen because it is the upper limit of the reference range in our hospital laboratory, and higher values are reported as abnormal. The 620 included hospitalizations concerned 580 patients, of whom 38 were hospitalized more than once during the study period; each eligible hospitalization was analyzed as a separate observation. The study is reported in accordance with the STROBE guidelines. Patients were divided into two groups based on the final diagnosis related to the index hospitalization: (i) patients with a final diagnosis of sepsis and (ii) patients with a final diagnosis other than sepsis.

The final diagnosis of sepsis was made by the treating physicians and recorded in the discharge summary. It was established in routine care by different physicians on the basis of their clinical judgement. No institutional sepsis protocol based on the Sepsis-3 criteria was in use, no uniform diagnostic criteria were imposed for the purpose of this study, and the physicians had access to procalcitonin, CRP and other laboratory results. All discharge summaries were reviewed, and the data were extracted from the medical records by one investigator (K.K.) without independent verification by a second investigator. All patients without sepsis had a laboratory-confirmed inflammatory response. This group included, among others, patients with intestinal ischemia and acute pancreatitis, in whom elevated procalcitonin may also have reflected a developing systemic infection, whereas there were no patients with other non-infectious causes of elevated procalcitonin, such as vasculitis or medullary thyroid carcinoma.

Under Polish law (Act of 5 December 1996 on the Professions of Physician and Dentist), a retrospective analysis of medical records collected during routine care does not constitute a medical experiment and does not require approval of a bioethics committee. The data were pseudonymized before analysis, and the study was conducted with the consent of the hospital management. Individual informed consent was not required because of the retrospective design and the use of pseudonymized data collected during routine care. The study was conducted in accordance with the Declaration of Helsinki.

2.2. Data Collection

We collected patients' data from the electronic medical records.

Epidemiological and demographic data included sex, age, and the source of infection (urosepsis, pneumonia, abdomen, skin infection, catheter, or unknown).

Clinical data included the duration of symptoms before admission, temperature, heart rate, respiratory rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), SpO2, FiO2, and Glasgow Coma Scale (GCS) score.

Laboratory findings included: blood-gas pO2 [mmHg], procalcitonin [µg/L], C-reactive protein (CRP) [mg/L], D-dimers [µg/L], creatinine [mg/dL], urea [mg/dL], bilirubin [mg/dL], hematocrit, white blood cell (WBC) count [10^3/µL], platelet count [10^3/µL], pH, lactates [mmol/L], K^+ [mmol/L], Na^+ [mmol/L], HCO_3^- [mmol/L], and base excess [mmol/L]. Blood gas analyses were performed on venous samples; therefore, the pO2 values do not reflect arterial oxygenation. For all clinical and laboratory variables, the first value recorded in the ED was used.

We analyzed the following comorbidities and risk factors: chronic kidney disease, heart failure, neoplastic disease, chronic obstructive pulmonary disease, diabetes, obesity, alcohol addiction, drug addiction, recent injury or surgery, acquired immunodeficiency syndrome (AIDS), dialysis, vascular access port, chemotherapy lately, immunosuppressants, and steroid therapy.

In terms of treatment applied, we collected data about the duration of hospitalization, the antibiotics used in the ED (beta-lactams: penicillin derivatives, cephalosporins, and carbapenems, fluoroquinolones, metronidazole, vancomycin, clindamycin, clarithromycin, amikacin, co-trimoxazole, linezolid), the number of antibiotics used in the ED, the time to the antibiotic, the use of norepinephrine, and the use of oxygen. Further, we compared the in-hospital mortality between the groups.

We also analyzed the following clinical severity scoring systems: SAPS II, APACHE, SOFA, MEWS, NEWS, qSOFA, and SIRS criteria. APACHE II and the original version of NEWS (2012) were used; for NEWS, a GCS score ≤ 13 was regarded as an altered level of consciousness. SAPS II, APACHE and SOFA were not calculated for the purpose of this study but were taken from the medical records of patients admitted to the ICU; they were calculated on the first day of ICU stay from the first parameters measured and the first samples obtained in the ED. MEWS, NEWS, qSOFA and the number of SIRS criteria were calculated from the first vital signs and laboratory results recorded in the ED. ED scores were not calculated if any of their components was missing (10 patients for MEWS, NEWS and SIRS criteria, and 9 patients for qSOFA).

2.3. Study Endpoints

The primary endpoint of this study was the association of the analyzed baseline characteristics with the final diagnosis of sepsis, presented as an odds ratio (OR) with 95% CI. The secondary endpoint of this research was the area under the curve (AUC) in the receiver operating characteristic (ROC) analysis of the included clinical severity scoring systems for discriminating between patients with and without a final diagnosis of sepsis.

2.4. Statistical Methods

Statistical analysis was performed with GraphPad Prism Version 10.4.1 (GraphPad Software, Boston, MA, USA), and the multivariable model was fitted and validated in Python 3 (NumPy, SciPy, and scikit-learn libraries). Continuous variables with a non-normal distribution were presented as median (IQR), and normally distributed variables were presented as means (SD). Categorical variables were shown as counts (percentages). The normality of data distribution was assessed with the Shapiro–Wilk test. Non-normally distributed variables were compared between the groups with the Mann–Whitney U test, while normally distributed variables were analyzed with Student's *t*-test. Categorical data were analyzed using Fisher's exact test. First, a general Fisher's exact test was conducted to assess the proportionality of source distribution for the source of infection. Then, each

source was compared with all other sources combined, using a Bonferroni-corrected significance threshold of $0.05/6 \approx 0.0083$. Simple logistic regression was performed for all the following variables: demographic and epidemiologic data, clinical data, laboratory findings, comorbidities, and risk factors. In the simple logistic regression, a *p*-value was calculated with the Wald test, while the 95% CI was computed using profile likelihood; for estimates close to the significance threshold, the two methods may lead to different conclusions. Variables with a *p*-value < 0.1 in the simple logistic regression were considered for the multiple logistic regression. Collinearity was assessed with variance inflation factors (VIF) and Spearman correlation coefficients (ρ); urea and DBP were excluded because of their strong correlation with creatinine ($\rho = 0.76$) and SBP ($\rho = 0.71$), respectively, although no VIF exceeded 2.3. Procalcitonin and CRP were log10-transformed because of their skewed distributions, and platelet count was expressed per $50 \times 10^3/\mu L$. Patients with missing data for any of the variables were excluded (complete-case analysis), so the final model included 12 variables and 613 patients with 142 events (approximately 12 events per variable). In the multiple logistic regression, 95% CIs and *p*-values were calculated with the Wald method. The discrimination of the model was assessed with the AUC, its overall performance with the Brier score, and its calibration with the Hosmer–Lemeshow test and the calibration slope. Internal validation was performed with 1000 bootstrap samples to obtain the optimism-corrected AUC and calibration slope. Because some patients were hospitalized more than once, a sensitivity analysis was performed with one hospitalization per patient, and cluster-robust standard errors accounting for repeated hospitalizations were calculated. The optimal cut-offs of the predicted probability, procalcitonin, and CRP were determined with the Youden index. ROC curves of the clinical severity scoring systems were constructed separately for each score in patients with available data. For scores that were lower in the sepsis group, lower values were treated as indicating a final diagnosis of sepsis. Because the scores were available for different subsets of patients, the AUCs were not compared formally. For all other cases, a two-sided *p*-value below 0.05 was considered statistically significant; apart from the infection-source comparisons, no correction for multiple comparisons was applied, and these *p*-values should be regarded as nominal.

3. Results

3.1. Baseline Characteristics

Our cohort included 620 hospitalizations of 580 patients admitted to ED with a procalcitonin level above 0.5 µg/L; 143 (23.1%) hospitalizations involved a final diagnosis of sepsis. Table 1 presents the baseline characteristics of the included patients divided into two groups: those without a final diagnosis of sepsis (further: no sepsis) and those with a final diagnosis of sepsis (further: sepsis). The groups did not differ in the sex distribution (48.8% vs. 44.8% females in no sepsis vs. sepsis, $p = 0.4453$) and age (median 72.0 years, IQR: 60.0–81.5 vs. median 72.0 years, IQR: 58.0–82.0, $p = 0.5528$). However, the groups differed in several clinical and laboratory findings. The sepsis cohort compared to no-sepsis cohort had higher temperature (median 36.7 °C, IQR: 36.5–37.2 vs. median 36.7 °C, IQR: 36.5–37.0, $p = 0.0253$), heart rate (median 100 min^{-1}, IQR: 82.0–114.0 vs. median 94 min^{-1}, IQR: 80.0–110.0, $p = 0.0493$), procalcitonin concentration (median 8.66 µg/L, IQR: 2.03–34.5 vs. median 1.47 µg/L, IQR: 0.82–4.43, $p < 0.0001$), CRP concentration (median 201.0 mg/L, IQR: 137.3–282.6 vs. median 144.9 mg/L, IQR: 57.8–240.5, $p < 0.0001$), creatinine concentration (median 1.90 mg/dL, IQR: 1.22–3.53 vs. median 1.38 mg/dL, IQR: 0.96–2.53, $p < 0.0001$), urea concentration (median 80.5 mg/dL, IQR: 57.0–140.8 vs. median 63.0 mg/dL, IQR: 39.3–107.8, $p = 0.0003$), and lactates (median 2.50 mmol/L, IQR: 1.70–4.10 vs. median 2.20 mmol/L, IQR: 1.50–3.40, $p = 0.0211$), and lower systolic blood pressure (median 105.0 mmHg, IQR: 87.0–130.0 vs. median 117.0 mmHg, IQR: 100.0–134.3, $p = 0.0003$), diastolic

blood pressure (median 65.0 mmHg, IQR: 54.0–80.0 vs. median 70.0 mmHg, IQR: 59.0–81.0, $p = 0.0217$), Glasgow Coma Scale score (median 15.0, IQR: 14.0–15.0 vs. median 15.0, IQR: 14.0–15.0, $p = 0.0064$), platelets (median 187 [$10^3/\mu L$], IQR: 120–252 vs. median 228 [$10^3/\mu L$], IQR: 159–322, $p < 0.0001$), HCO_3^- concentration (median 22.0 mmol/L, IQR: 18.9–23.9 vs. median 23.1 mmol/L, IQR: 20.0–25.6, $p = 0.0008$), and base excess (median −2.5 mmol/L, IQR: from −5.3 to 0.0 vs. median −1.0 mmol/L, IQR: from −3.9 to 1.3, $p = 0.0012$). Patients from the sepsis group had a vascular access port more often as a risk factor (11.9% vs. 5.9%, $p = 0.0256$). The groups did not differ in any other analyzed comorbidities or risk factors.

Table 1. The baseline characteristics of included patients are divided into groups based on the final diagnosis. Statistically significant differences are bolded.

Parameter	No Sepsis ($n = 477$)	Sepsis ($n = 143$)	*p*-Value
Demographic data			
Sex, female	233 (48.8%)	64 (44.8%)	0.4453
Age, years	72.0 (60.0–81.5)	72.0 (58.0–82.0)	0.5528
Clinical and laboratory findings			
Symptoms duration, days	3.0 (1.0–5.0)	3.0 (1.0–5.0)	0.9048
Temperature, °C	**36.7 (36.5–37.0)**	**36.7 (36.5–37.2)**	**0.0253**
Heart rate, bpm	**94.0 (80.0–110.0)**	**100.0 (82.0–114.0)**	**0.0493**
Respiratory rate, min^{-1}	16.0 (16.0–18.0)	17.0 (16.0–18.0)	0.1874
SBP, mmHg	**117.0 (100.0–134.3)**	**105.0 (87.0–130.0)**	**0.0003**
DBP, mmHg	**70.0 (59.0–81.0)**	**65.0 (54.0–80.0)**	**0.0217**
SpO2, %	96.0 (94.0–98.0)	96.0 (93.0–98.0)	0.5050
Blood-gas pO2, mmHg	34.0 (26.2–48.5)	38.7 (28.0–53.2)	0.0446
FiO2, fraction	0.21 (0.21–0.21)	0.21 (0.21–0.30)	0.1581
GCS score	**15.0 (14.0–15.0)**	**15.0 (14.0–15.0)**	**0.0064**
Procalcitonin, µg/L	**1.47 (0.82–4.43)**	**8.66 (2.03–34.5)**	**<0.0001**
CRP, mg/L	**144.9 (57.8–240.5)**	**201.0 (137.3–282.6)**	**<0.0001**
D-dimers, µg/L	2537 (1451–5387)	3592 (1652–6722)	0.0726
Creatinine, mg/dL	**1.38 (0.96–2.53)**	**1.90 (1.22–3.53)**	**<0.0001**
Urea, mg/dL	**63.0 (39.3–107.8)**	**80.5 (57.0–140.8)**	**0.0003**
Bilirubin, mg/dL	0.75 (0.40–1.40)	0.70 (0.43–1.26)	0.7315
HCT, mean (SD)	34.67 (7.16)	34.32 (7.36)	0.6078
WBC, $10^3/\mu L$	13.6 (9.3–18.6)	14.3 (8.3–21.0)	0.8574
PLT, $10^3/\mu L$	**228 (159–322)**	**187 (120–252)**	**<0.0001**
pH	7.40 (7.34–7.44)	7.40 (7.33–7.44)	0.7409
Lactates, mmol/L	**2.20 (1.50–3.40)**	**2.50 (1.70–4.10)**	**0.0211**
K^+, mmol/L	4.0 (3.6–4.7)	4.2 (3.5–5.0)	0.1593
Na^+, mmol/L	135.0 (131.0–139.0)	136.0 (132.0–140.0)	0.4671
HCO_3^-, mmol/L	**23.1 (20.0–25.6)**	**22.0 (18.9–23.9)**	**0.0008**
BE, mmol/L	**−1.0 (from −3.9 to 1.3)**	**−2.5 (from −5.3 to 0.0)**	**0.0012**
Comorbidities and risk factors			
Chronic kidney disease	129 (27.0%)	48 (33.6%)	0.1399

Table 1. *Cont.*

Parameter	No Sepsis (n = 477)	Sepsis (n = 143)	p-Value
Heart failure	176 (36.9%)	62 (43.4%)	0.1709
Neoplastic disease	171 (35.8%)	48 (33.6%)	0.6900
COPD	25 (5.2%)	10 (7.0%)	0.4132
Diabetes	142 (29.8%)	46 (32.2%)	0.6047
Alcohol addiction	40 (8.4%)	9 (6.3%)	0.4832
Drug addiction	1 (0.2%)	1 (0.7%)	0.4084
Injury or surgery	3 (0.6%)	1 (0.7%)	>0.9999
AIDS	2 (0.4%)	0 (0.0%)	>0.9999
Dialysis	31 (6.5%)	15 (10.5%)	0.1436
Vascular access port	**28 (5.9%)**	**17 (11.9%)**	**0.0256**
Chemotherapy lately	43 (9.0%)	7 (4.9%)	0.1596
Immunosuppressants	8 (1.7%)	4 (2.8%)	0.4861
Steroid therapy	13 (2.7%)	7 (4.9%)	0.2769

Categorical data is presented as the number (percentage) of patients. Continuous data is presented as median (IQR) unless indicated otherwise. Abbreviations: BE, base excess; bpm, beats per minute; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; DBP, diastolic blood pressure; GCS, Glasgow coma scale; HCT, hematocrit; PLT, platelets; SBP, systolic blood pressure; and WBC, white blood cells count.

3.2. Treatment Applied and Outcomes

Antibiotics applied in ED were more often used in patients from a sepsis group (67.8% vs. 57.2%, $p = 0.0254$). A significant difference was found for vancomycin (13.3% vs. 1.3%, $p < 0.0001$) and beta-lactams (61.5% vs. 40.0%, $p < 0.0001$), but not for other antibiotic groups. In a sub-analysis of beta-lactam groups, cephalosporins and carbapenems were more frequently used in a sepsis group compared to no-sepsis groups (49.7% vs. 34.0%, $p = 0.0008$ and 8.4% vs. 2.1%, $p = 0.0011$, respectively). At the same time, there was no difference regarding penicillin derivatives. Patients from the sepsis group had more antibiotics used in ED (median 1.0, IQR: 0.0–2.0 vs. median 0.0, IQR: 0.0–1.0, $p < 0.0001$). They also more frequently received norepinephrine (46.2% vs. 14.7%, $p < 0.0001$).

Patients from a sepsis group had significantly higher in-hospital mortality rates (41.3% vs. 19.9%, $p < 0.0001$). The hospitalization of sepsis patients lasted for a median of 8.0 days, IQR: 4.0–19.0, while of patients from a no-sepsis group for a median of 10.5 days, IQR: 4.5–19.0 ($p = 0.3351$). All detailed data regarding treatment applied to patients and their outcomes is presented in Table 2.

Table 2. Treatment applied and in-hospital mortality for included patients divided into groups based on final diagnosis. Statistically significant differences are bolded.

Parameter	No Sepsis (n = 477)	Sepsis (n = 143)	p-Value
Antibiotics used in ED	**273 (57.2%)**	**97 (67.8%)**	**0.0254**
Beta-lactams	**191 (40.0%)**	**88 (61.5%)**	**<0.0001**
Penicillin derivatives	21 (4.4%)	10 (7.0%)	0.2717
Cephalosporins	**162 (34.0%)**	**71 (49.7%)**	**0.0008**
Carbapenems	**10 (2.1%)**	**12 (8.4%)**	**0.0011**
Fluoroquinolones	82 (17.2%)	27 (18.9%)	0.6189

Table 2. *Cont.*

Parameter	No Sepsis (n = 477)	Sepsis (n = 143)	p-Value
Metronidazole	43 (9.0%)	13 (9.1%)	>0.9999
Vancomycin	**6 (1.3%)**	**19 (13.3%)**	**<0.0001**
Clindamycin	2 (0.4%)	1 (0.7%)	0.5453
Clarithromycin	1 (0.2%)	1 (0.7%)	0.4084
Amikacin	1 (0.2%)	0 (0.0%)	>0.9999
Co-trimoxazole	2 (0.4%)	0 (0.0%)	>0.9999
Linezolid	1 (0.2%)	1 (0.7%)	0.4084
Number of antibiotics used in ED	**0.0 (0.0–1.0)**	**1.0 (0.0–2.0)**	**<0.0001**
Time to antibiotic, hours	3.0 (2.0–6.0)	3.0 (1.1–5.0)	0.0657
Norepinephrine	**70 (14.7%)**	**66 (46.2%)**	**<0.0001**
Oxygen	111 (23.3%)	41 (28.7%)	0.2226
Hospitalization duration, days	10.5 (4.5–19.0)	8.0 (4.0–19.0)	0.3351
In-hospital mortality	**95 (19.9%)**	**59 (41.3%)**	**<0.0001**

Categorical data is the number (percentage) of patients, while continuous data is the median (IQR). Abbreviations: ED, emergency department.

3.3. Source of Infection

Fisher's exact test showed significantly different proportions of sources of infection between patients from sepsis and no-sepsis groups ($p = 0.0003$). In an analysis of each source of infection compared to all others combined, urosepsis and catheter were significantly more frequent sources of infection in sepsis patients compared to no-sepsis patients (32.2% vs. 20.3%, $p = 0.0045$ and 5.6% vs. 0.8%, $p = 0.0014$, respectively); both differences remained significant after Bonferroni correction (threshold $p = 0.0083$). Other sources of infection were not significantly different between the groups (Figure 1).

3.4. Clinical Scoring Systems

SAPS II was available for 37 patients (23 with and 14 without sepsis), APACHE for 37 patients (23 and 14), and SOFA for 35 patients (21 and 14), whereas qSOFA was available for 611 patients and MEWS, NEWS, and SIRS criteria for 610 patients (143 with sepsis for each). Patients from a sepsis group compared to those from a no-sepsis group had lower scores on the SAPS II scale (mean 47.22 ± 21.00 vs. mean 66.64 ± 22.77, $p = 0.0122$, Figure 2A) and higher scores on the MEWS (median 2.0, IQR: 1.0–4.0 vs. median 2.0, IQR: 1.0–3.0, $p = 0.0005$, Figure 2D), and NEWS scales (median 4.0, IQR: 2.0–7.0 vs. median 3.0, IQR: 1.0–5.0, $p = 0.0001$, Figure 2E). There was also a significant difference between the analyzed groups in the distribution of qSOFA scores ($p < 0.0001$, Figure 2F) and the number of SIRS criteria ($p = 0.0433$, Figure 2G). There was no significant difference between the groups regarding APACHE ($p = 0.0905$, Figure 2B) and SOFA scores ($p = 0.0821$, Figure 2C).

In the ROC analysis for the discrimination between patients with a final diagnosis of sepsis and those without a final diagnosis of sepsis, the AUC was 0.7671 (95% CI: 0.6006–0.9336, Figure 3A) for SAPS II, 0.7019 (95% CI: 0.5268–0.8770, Figure 3B) for APACHE, and 0.6735 (95% CI: 0.4879–0.8591, Figure 3C) for SOFA. As these three scores were lower in the sepsis group, these AUCs reflect discrimination with lower values indicating sepsis; with the opposite direction, the AUCs would be 0.23, 0.30, and 0.33, respectively. The AUCs of qSOFA, MEWS, NEWS, and SIRS criteria were 0.6196, 0.5942, 0.6066, and 0.5571,

respectively (Figure 3D–G). Only 32 patients had all seven scores; because the scores were available for different subsets of patients, the AUCs were not compared formally.

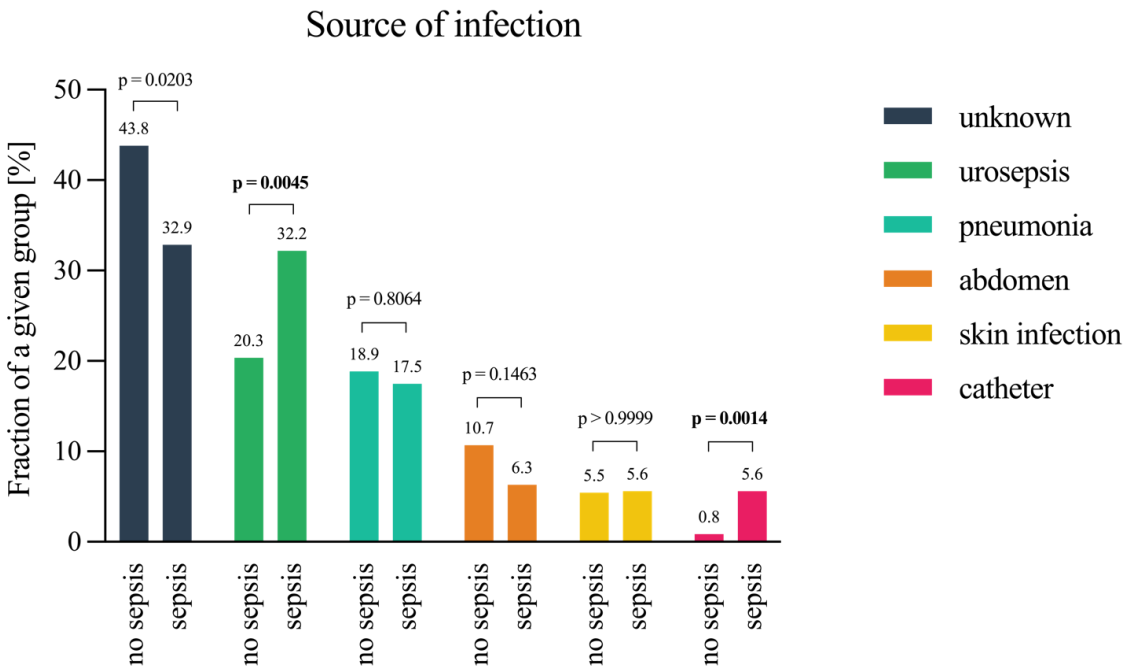


Figure 1. The comparison of the source of infection frequency between patients with and without a final diagnosis of sepsis. Numbers above the columns present the fraction (percentage) of total in a given group. Fisher's exact test showed significantly different proportions of sources of infection between the groups ($p = 0.0003$). The *p*-values above the columns represent the findings from comparing the proportion of a given source versus all other sources between the two groups. Statistically significant differences are bolded (taking into account Bonferroni correction for multiple comparisons and adjusted threshold *p*-value of 0.0083).

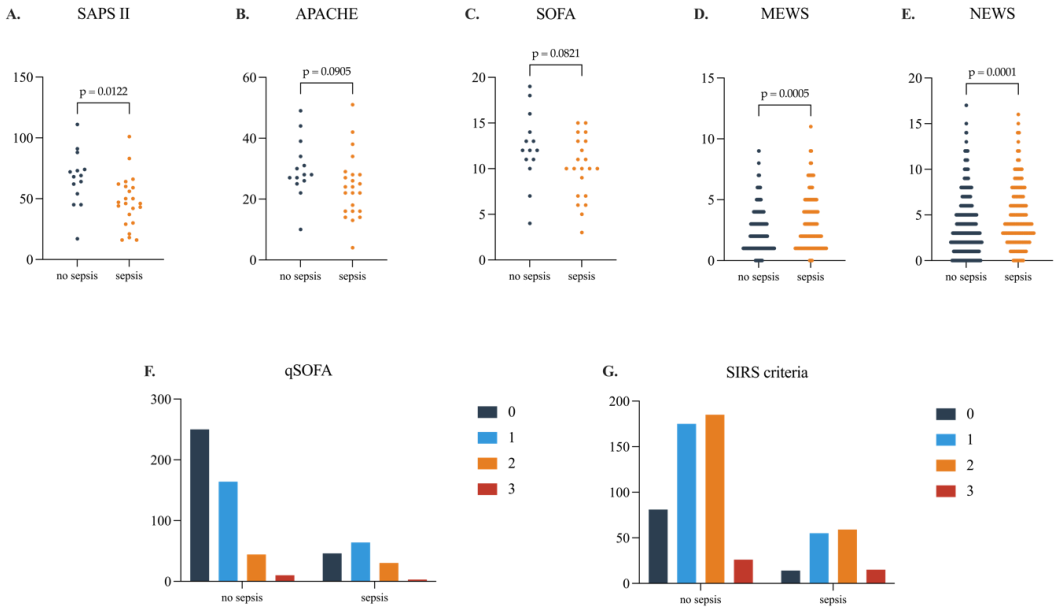


Figure 2. The comparison of the SAPS II, APACHE, SOFA, MEWS, and NEWS scale scores and qSOFA and SIRS criteria number distributions between patients with and without a final diagnosis of sepsis. (**A**) SAPS II; (**B**) APACHE; (**C**) SOFA; (**D**) MEWS; (**E**) NEWS; (**F**) qSOFA; (**G**) SIRS criteria.

Depending on the data distribution, Student's *t*-tests or Mann–Whitney tests were used for numerical scales. Fisher's exact test was used for categorical data (qSOFA, SIRS criteria). Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; MEWS, Modified Early Warning Score; NEWS, National Early Warning Score; qSOFA, quick SOFA; SAPS, Simplified Acute Physiology Score; SIRS, systemic inflammatory response syndrome; and SOFA, Sequential Organ Failure Assessment.

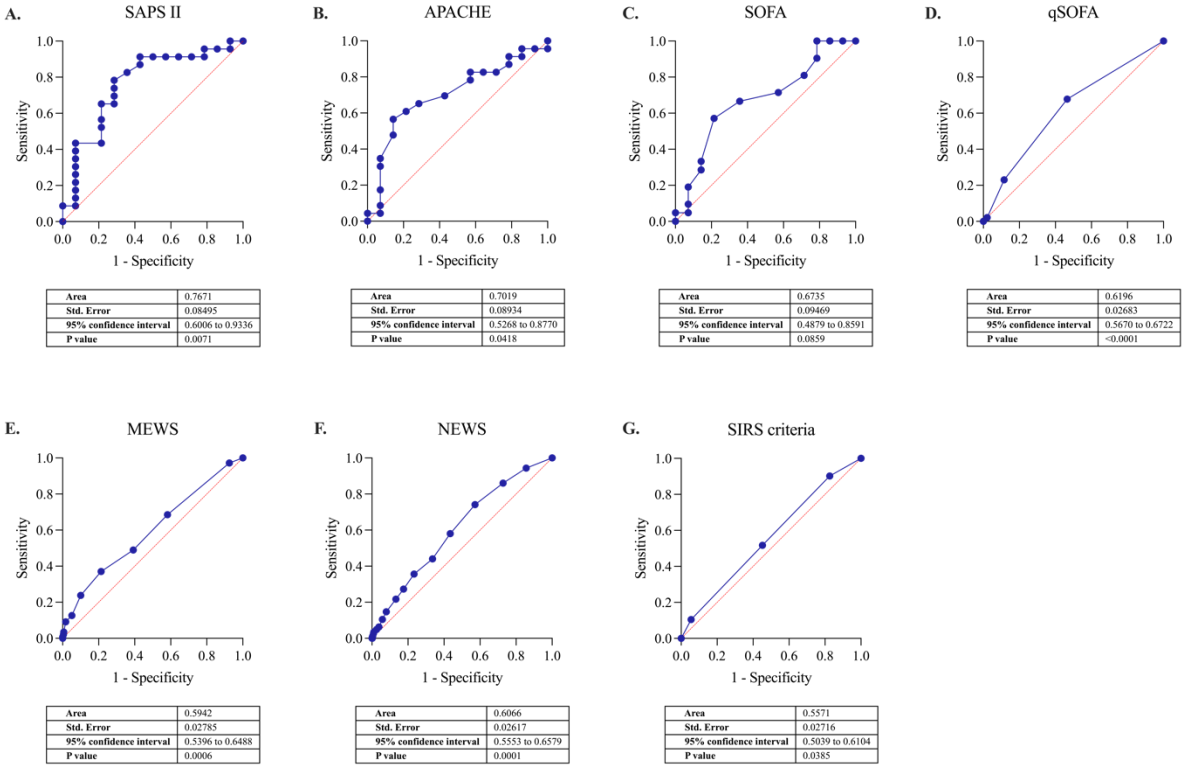


Figure 3. The results of the ROC analyses for scales: SAPS II, APACHE, SOFA, qSOFA, MEWS, NEWS, and SIRS criteria for discriminating between patients with and without a final diagnosis of sepsis. (**A**) SAPS II; (**B**) APACHE; (**C**) SOFA; (**D**) qSOFA; (**E**) MEWS; (**F**) NEWS; (**G**) SIRS criteria. Blue line, ROC curve; red dashed line, line of no discrimination. The following data were presented below the plot for each ROC analysis: AUC with standard error, 95% CI, and a *p*-value. Number of patients (with sepsis) included in each analysis: SAPS II 37 (23), APACHE 37 (23), SOFA 35 (21), qSOFA 611 (143), MEWS 610 (143), NEWS 610 (143), and SIRS 610 (143). For SAPS II, APACHE, and SOFA, lower scores were treated as indicating a final diagnosis of sepsis. Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; AUC, the area under the curve; CI, confidence intervals; MEWS, Modified Early Warning Score; NEWS, National Early Warning Score; qSOFA, quick SOFA; ROC, receiver operating characteristic; SAPS, Simplified Acute Physiology Score; SIRS, systemic inflammatory response syndrome; and SOFA, Sequential Organ Failure Assessment.

3.5. Simple Logistic Regression Results

In the simple logistic regression of baseline characteristics variables, the following factors were associated with the final diagnosis of sepsis: procalcitonin (OR: 1.016, 95% CI: 1.010–1.022, $p < 0.0001$), temperature (OR: 1.355, 95% CI: 1.084–1.6991, $p = 0.0078$), heart rate (OR: 1.010, 95% CI: 1.002–1.018, $p = 0.0185$), SBP (OR: 0.9861, 95% CI: 0.9785–0.9934, $p = 0.0003$), GCS score (OR: 0.9219, 95% CI: 0.8611–0.9893, $p = 0.0208$), HCO_3^- (OR: 0.9644, 95% CI: 0.9329–0.9973, $p = 0.0327$), platelets (OR: 0.9966, 95% CI: 0.9949–0.9982, $p < 0.0001$), CRP (OR: 1.004, 95% CI: 1.002–1.006, $p < 0.0001$), urea (OR: 1.004, 95% CI: 1.001–1.006, $p = 0.0032$), creatinine (OR: 1.122, 95% CI: 1.038–1.215, $p = 0.0037$), bilirubin (OR: 0.9141, 95% CI: 0.8235–0.9855, $p = 0.0472$), and a vascular access port (OR: 2.164, 95% CI: 1.128–4.043, $p = 0.0171$). Moreover, DBP (OR: 0.9896, 95% CI: 0.9787–1.000, $p = 0.0585$) and lactates

(OR: 1.048, 95% CI: 1.003–1.103, $p = 0.0547$) met the $p < 0.10$ criterion for inclusion in the multiple logistic regression.

3.6. Multiple Logistic Regression and Model Performance

In the multiple logistic regression, including 613 patients (142 with sepsis) with complete data, the following factors were independently associated with a final diagnosis of sepsis: procalcitonin (OR: 2.505 per 10-fold increase, 95% CI: 1.803–3.482, $p < 0.0001$), CRP (OR: 2.391 per 10-fold increase, 95% CI: 1.280–4.468, $p = 0.0063$), and platelet count (OR: 0.8719 per $50 \times 10^3/\mu L$ increase, 95% CI: 0.7967–0.9543, $p = 0.0029$). SBP ($p = 0.0750$) and a vascular access port ($p = 0.2744$) were not significantly associated with the outcome after adjustment, and neither was bilirubin (OR: 0.9177, 95% CI: 0.8299–1.015, $p = 0.0941$), which is consistent with the lack of difference between the groups in Table 1 ($p = 0.7315$). The complete results of multiple logistic regression are presented in Table 3. The model had an AUC of 0.790 (95% CI: 0.747–0.832), and after internal validation, the optimism-corrected AUC was 0.767 and the calibration slope 0.88. The Brier score was 0.142, compared with 0.178 for a model assigning the observed prevalence to all patients, and the Hosmer–Lemeshow test did not indicate poor calibration ($p = 0.84$). At a predicted probability cut-off of 0.20, the sensitivity was 76.1% and the specificity 70.1%. Procalcitonin alone had an AUC of 0.747; at a cut-off of 6.5 µg/L, its sensitivity was 57.3% and specificity 81.1%. CRP alone had an AUC of 0.640; at a cut-off of 114 mg/L, its sensitivity was 86.0% and specificity 39.3%. In the sensitivity analysis including one hospitalization per patient (572 patients, 132 events), the results were similar: procalcitonin (OR: 2.496 per 10-fold increase, 95% CI: 1.770–3.518), CRP (OR: 2.836 per 10-fold increase, 95% CI: 1.416–5.680), and platelet count (OR: 0.877 per $50 \times 10^3/\mu L$ increase, 95% CI: 0.798–0.964) remained associated with a final diagnosis of sepsis, and the use of cluster-robust standard errors did not change any of the conclusions.

Table 3. The results of a multiple logistic regression between the listed factors and the final diagnosis of sepsis ($n = 613$, 142 events). Variables with $p < 0.05$ are bolded.

Variable	Odds Ratio	95% CI	*p*-Value
Procalcitonin, per 10-fold increase	**2.505**	**1.803 to 3.482**	**<0.0001**
Temperature, °C	1.178	0.9033 to 1.537	0.2262
Heart rate, bpm	1.006	0.9962 to 1.016	0.2280
SBP, mmHg	0.9923	0.9838 to 1.001	0.0750
GCS score	0.9560	0.8775 to 1.042	0.3035
Lactates, mmol/L	1.032	0.9776 to 1.089	0.2557
HCO_3^-, mmol/L	1.004	0.9561 to 1.053	0.8873
PLT, per $50 \times 10^3/\mu L$	**0.8719**	**0.7967 to 0.9543**	**0.0029**
CRP, per 10-fold increase	**2.391**	**1.280 to 4.468**	**0.0063**
Creatinine, mg/dL	1.088	0.9727 to 1.217	0.1400
Bilirubin, mg/dL	0.9177	0.8299 to 1.015	0.0941
Vascular access port	1.537	0.7112 to 3.320	0.2744

Abbreviations: bpm, beats per minute; CI, confidence interval; CRP, C-reactive protein; GCS, Glasgow Coma Scale; PLT, platelets; and SBP, systolic blood pressure. Procalcitonin and CRP were log10-transformed, and the odds ratios are given per 10-fold increase; for PLT, per $50 \times 10^3/\mu L$ increase; for the other continuous variables, per one-unit increase. Urea and DBP were excluded because of collinearity with creatinine and SBP, respectively. Confidence intervals and *p*-values were calculated with the Wald method. Model performance: AUC 0.790 (optimism-corrected 0.767), calibration slope 0.88 (optimism-corrected), Brier score 0.142, Hosmer–Lemeshow test $p = 0.84$.

4. Discussion

In this cohort of patients admitted to the ED with procalcitonin >0.5 µg/L, almost one in four had a final diagnosis of sepsis. Higher procalcitonin and CRP and a lower platelet count were associated with this diagnosis in the multiple logistic regression, and the model showed moderate discrimination after internal validation. SAPS II, APACHE, and SOFA were available for only a small subset of patients, and their AUC estimates were imprecise.

Patients with a final diagnosis of sepsis had a numerically shorter length of hospitalization than patients with a final diagnosis other than sepsis, although the difference was not statistically significant. In-hospital mortality was higher in the former group, which may partly explain the observed difference in hospital stays.

Overall, antibiotics were prescribed more often in the ED to patients with a final diagnosis of sepsis. They received vancomycin and beta-lactams more commonly, but the significant difference was restricted to cephalosporins and carbapenems. This shows that prescribing physicians might have suspected a severe infection early in the ED, and therefore, those patients more often received a wide-spectrum antibiotic therapy. Similarly, the more frequent use of norepinephrine in the sepsis group (46.2% vs. 14.7%) describes the treatment applied rather than an independent diagnostic factor, as vasopressor requirement is itself part of the definition of septic shock.

When analyzing the underlying infection source, two that differed between the patients in the sepsis and no-sepsis groups were urosepsis and a catheter. Moreover, a vascular access port was more frequent in the sepsis group and was associated with a final diagnosis of sepsis in the simple logistic regression, although not after adjustment. Although the presence of a port alone does not prove a catheter-related source of infection, this finding draws attention to the potential iatrogenic cause of sepsis. Although much has been done in recent decades in the field of the aseptic approach, further improvements are still required.

We found that higher procalcitonin, higher CRP, and lower platelet count were associated with a final diagnosis of sepsis, whereas low SBP and a vascular access port were associated with this diagnosis only in the simple logistic regression. These parameters can be easily assessed at admission. However, these results should be interpreted with caution. The final diagnosis was made by the treating physicians, who knew the procalcitonin and CRP results, and platelet count is a component of the SOFA score used to identify organ dysfunction in sepsis. Therefore, the observed associations may partly reflect how the diagnosis was established rather than provide independent diagnostic information (incorporation bias). Our findings regarding procalcitonin align with the landmark study by Hausfater et al., in which procalcitonin was found to be the only independent variable associated with a diagnosis of systemic infection [11]. Further, Ko et al. found that low platelets are independent predictors of septic shock development in patients with sepsis [12], although this outcome and population differ from ours.

Surprisingly, we found that lactates were not independently associated with the final diagnosis of sepsis. This is counterintuitive since lactates are one of the main assessed factors in this clinical scenario and are easily performed in blood gas tests. The high heterogeneity of our cohort, which has many comorbidities, could explain this.

Finally, SAPS II and APACHE had the highest AUCs among the analyzed scales; however, this finding should be interpreted with caution. These scores, as well as SOFA, were available for only 35–37 patients admitted to the ICU, and all three were lower in patients with sepsis. In this subset, the comparison group probably consisted of critically ill patients with other conditions, which may explain the inverse direction. Moreover, SAPS II and APACHE were designed to assess the severity of illness and prognosis in the ICU, not to diagnose sepsis, and the confidence intervals of their AUCs were wide. We obtained values similar to those of a recent study by Liengswangwong et al., which assessed several

scoring systems for early prediction of septic shock in diabetic patients with sepsis [13]. The AUC for SAPS II was 0.685 compared to 0.7671 in our study, and the AUC for APACHE was 0.661 compared to 0.7019 in our research. On the other hand, they found SOFA to perform better than we found it. However, we only had the SOFA score for a limited number of patients, which might have influenced the results. Moreover, it must be underlined that Liengswangwong et al. evaluated the utility of these scales in diabetic patients with sepsis for septic shock prediction. At the same time, we assessed these scoring systems in patients with a procalcitonin concentration > 0.5 μg/L in relation to a final diagnosis of sepsis.

Our study was limited to the index hospitalization. Biza et al. showed in an ED-based cohort in Ethiopia that readmissions are common among sepsis survivors [14], which indicates that outcomes after discharge are also clinically relevant in ED sepsis cohorts, although they were beyond the scope of our analysis.

5. Limitations

We must mention a few limitations of our study, which may prevent drawing firm conclusions and can introduce some bias. First, the sepsis group comprised few patients compared to those without a final diagnosis of sepsis. There is a high heterogeneity, both intragroup and intergroup. Although we conducted a multiple logistic regression, residual confounding cannot be excluded, and with approximately 12 events per variable the estimates may be unstable. Moreover, 38 patients were hospitalized more than once, so not all observations were independent; however, the sensitivity analysis including one hospitalization per patient gave similar results. Further, the inclusion criterion of procalcitonin concentration > 0.5 μg/L was used to ease patients' identification but limited the interpretation of the results and their generalizability to patients with normal or unmeasured procalcitonin and to those who were not hospitalized.

The following limitation is the reliance on medical records, which was associated with a lack of data for some patients and a limited guarantee of data completeness. Different physicians made the final sepsis diagnosis, which increased the variability, and the data were extracted by a single investigator without independent verification. No uniform diagnostic criteria were applied, and patients could not be reclassified according to the Sepsis-3 criteria, because baseline SOFA scores and the time of suspected infection could not be reliably established from the records. The no-sepsis group was defined by the absence of a sepsis diagnosis and may include both patients with infection without sepsis and patients with non-infectious causes of elevated procalcitonin. Moreover, procalcitonin and CRP were known to the diagnosing physicians, and several variables associated with the outcome are components of the SOFA score, which may have led to an overestimation of these associations; we did not fit a separate model without these variables. Procalcitonin concentrations are also influenced by kidney function, and although creatinine was included in the multiple logistic regression, chronic kidney disease and dialysis, which did not differ significantly between the groups, were not included as separate covariates, and no stratified analysis was performed.

Last, data regarding scoring systems were available only for very few patients, which might have influenced the obtained results and limited their interpretation. These scores were available only for patients admitted to the ICU, which introduces selection bias. Finally, the multiple logistic regression was exploratory. Although procalcitonin and CRP were log-transformed, the other continuous variables were entered as linear terms. The model was validated only internally, and the cut-offs were derived and evaluated in the same cohort, which probably overestimates their performance. External validation is therefore required before the model or the cut-offs can be used in clinical practice.

6. Conclusions

To conclude, we found that higher procalcitonin, higher CRP, and a lower platelet count were associated with a final diagnosis of sepsis in patients admitted to the ED with procalcitonin > 0.5 µg/L. The analysis of clinical severity scoring systems was limited by the small number of patients with available scores and does not allow us to rank them. These exploratory findings may help generate hypotheses for future prospective studies using standardized diagnostic criteria aimed at developing and validating prediction models for sepsis in the ED.

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Institutional Review Board Statement: The study was a retrospective analysis of pseudonymized medical records. Under Polish law, such an analysis does not constitute a medical experiment and does not require approval of a bioethics committee (see Section 2.1).

Informed Consent Statement: Patient consent was waived due to the retrospective design of the study and the use of pseudonymized data collected during routine care.

Data Availability Statement: The data presented in this study are available from the corresponding author upon reasonable request, subject to institutional approval and data protection regulations.

Conflicts of Interest: The authors declare no conflicts of interest.

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