


# Differentiating sepsis from similar groups of symptoms at triage level in emergency care

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## ABSTRACT

*Objectives:* Conditions that have similar initial presentations as sepsis may make early recognition of sepsis in an emergency room (ER) difficult. We investigated whether selected physiologic and metabolic parameters can be reliably used in the emergency department to differentiate sepsis from other disease states that mimic it, such as dehydration and stroke. *Methods:* Loess regression on retrospective follow-up chart data of patients with sepsis-like symptoms ( $N = 664$ ) aged 18+ in a large ER in Hungary was used to visualize/identify cutoff points for sepsis risk. A multivariate logistic regression model based on standard triage data was constructed with its corresponding receiver operating characteristic (ROC) curve and compared with another model constructed based on current sepsis guidelines. *Results:* Age, bicarbonate, HR, lactate, pH, and body temperature had U, V, W, or reverse U-shaped associations with identifiable inflexion points, but the cutoff values we identified were slightly different from guideline cutoff values. In contrast to the guidelines, no inflexion points could be observed for the association of sepsis with SBP, DPB, MAP, and RR and therefore were treated as continuous variables. Compared to the guidelines-based model, the triage data-driven final model contained additional variables (age, pH, bicarbonate) and did not include lactate. The data-driven model identified about 85% of sepsis cases correctly, while the guidelines-based model identified only about 70% of sepsis cases correctly. *Conclusion:* Our findings contribute to the growing body of evidence for the necessity of finding improved tools to identify sepsis at early time points, such as in the ER.

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**KEYWORDS**

sepsis, SIRS, SOFA, clinical patient data, guidelines

**INTRODUCTION**

Sepsis is a life-threatening organ dysfunction that results every year in about six million deaths worldwide [1]. Most of sepsis deaths are preventable by early recognition, but it is frequently underdiagnosed at an early stage due to its undefined appearance [2]. Despite numerous scores and recommendations, there has been much incongruence in and a challenge for the future of finding the ultimate way for best diagnostic practices, especially in the emergency department, where the whole process of recognition and early stabilization begins [3–6]. Along with the basic parameters such as low blood pressure, high or low temperature, increased heart rate, unspecific signs such as altered mental state (AMS) might be a symptom of sepsis [7]; however, AMS can be associated with any kind of transient or permanent brain dysfunction either secondary to toxins or resulting from diminished blood flow. AMS is often mimicked by cognitive disorders and sensory aphasia, which are factors frequently associated with ischemic stroke, thereby enabling stroke to show similarities with sepsis [7] especially in prehospital settings or at triage level. AMS might also be a symptom of dehydration, which – most frequently in the elderly – can also mimic sepsis/associated disorientation [7].

In the early 1990s, sepsis was diagnosed on the basis of systemic inflammatory response syndrome (SIRS) parameters [8, 9] such as body temperature, respiratory rate (RR), heart rate (HR), and the presence of leukocytosis or leukopenia. Due to the limitation of the SIRS criteria definitions, however, they were removed from the newest sepsis definition, although they are not replaced by the quick sequential organ failure assessment score (qSOFA) [10, 11], which is based on systolic blood pressure (SBP), altered mentation, and increased RR). In case of manifest organ dysfunction, the use of the SOFA score is recommended, which is calculated based on oxygenation disturbances ( $\text{PaO}_2/\text{FiO}_2$ ), mental disturbances, decreased mean arterial pressure (MAP) and need for inotropic support, renal involvement, liver dysfunction, and abnormal coagulation [12, 13]. If there is a need for vasopressors to keep MAP above 65 mmHg and serum lactate is higher than 2 mM/l, then the patient is considered to be in septic shock [12]. The predisposition, infection (present or suspected), response (immune system activation) and organ dysfunction (PIRO) concept enables understanding sepsis/septic shock as a complex and multidimensional process, when it is diagnosed, but it does not approximate sepsis diagnosis [14]. Controversy surrounds the use of different sepsis scores and vital parameters along with laboratory results to diagnose sepsis [12, 15]. Therefore, there is a need to come up with a better diagnostic system, especially in the emergency department [15–18] triage where the time limitation does not allow to calculate SOFA score. In most units a blood gas analyzer is available that can present valuable data on the patient in a matter of minutes. One of the most easily measured parameters is lactate. Measurement of lactate levels is still recommended by the Sepsis Six approach, initially developed in 2009 but still applied in recent years [19, 20]. Sepsis Six is also an initial bundle that contributes to timely care including the administration of crystalloids, oxygen, antibiotics in the first hour along with microbiological sampling, measurement of urine



output and lactate levels. The authors are aware that this approach is being challenged, but no other recommendation is available yet.

Recently there has been some dispute about the usefulness of the otherwise generally recommended classic parameters and approach endorsed by the Surviving Sepsis Guidelines. The reason for this dispute is the controversies regarding, for example, the time to initiation of empiric antibiotic therapy, distinguishing sepsis from noninfectious syndromes, blood cultures and intravenous access catheters, and the use of procalcitonin, as issued by the Infectious Diseases Society of America (IDSA) [21]. This and other arising issues in the early recognition of sepsis focusing on previously unmeasured cofounders [22] make the situation more complicated despite the fact that simple and straight guidelines would be desirable to be able to initiate timely sepsis management.

Little is known about whether basic physiologic and metabolic parameters, in addition to those that form part of prior sepsis diagnostic criteria, could be used for differentiating between sepsis and other conditions with similar initial presentations, such as dehydration and stroke. Therefore, the aim of our study was to assess the relationship profile of basic physiologic and metabolic parameters to sepsis risk, and to simulate clinical decision-making by comparing a data-driven model to a model that is built based on currently existing sepsis guidelines understanding that no classical approach apart from a blend of recommendations and scores are available in the emergency department triage, unlike in an intensive care unit, where laboratory results, invasive monitoring and clinical experience all assist in sepsis care.

## METHODS

### Study population

This analysis is based on a retrospective chart review of patients aged 18 and over of the Emergency Department, Clinical Centre, Semmelweis University, Budapest, Hungary. Patient data with a final discharge diagnosis of sepsis (ICD code A.4190), stroke (I.64H0), and dehydration (E.84H0) were collected and extracted from patients' charts by three of the authors. Confirmation of diagnoses was based on the clinical picture and laboratory and imaging findings confirmed by the senior emergency department specialist on duty in each case. Data for septic and stroke patients were extracted for the period between 13.06.2016 and 12.06.2018, and dehydrated patients' data were extracted for the period between 13.06.2016 and 16.12.2017.

### Outcomes and definitions

Temperature, SBP and diastolic blood pressure (DBP), HR, RR were measured on admission. MAP was calculated as:  $1/3 \text{ SBP} + 2/3 \text{ DBP}$ . Point of care measurement of pH, lactate, and bicarbonate took place at triage level. The diagnosis of sepsis was based on suspected or confirmed infection along with life-threatening organ dysfunction and clinical picture [14]. The diagnosis of stroke was based on National Institutes of Health Stroke Scale and confirmed by CT scan and a structured examination by a neurologist. The diagnosis of dehydration was established by widely accepted diagnostic criteria and confirmed by measuring renal function and



blood electrolytes along with clinical signs of fluid loss, such as capillary refill time, skin turgor, urine output.

### Ethics approval and consent to participate

The study was approved by the Ethics Board of Semmelweis University (49/2018).

### Data management and analysis

Data for only the first hospitalization were kept for re-admitted patients. Those who were hospitalized with more than one of the three groups of symptoms were removed.

We built two models. The first model was driven by our data. For this, we visualized the relationship between sepsis and the continuous variables by creating loess local regression [23, 24] smooth curve fit plots by means of the proc loess procedure (SAS V9.4). If there was a clear inflexion point in the loess curve (where the curve changes from an upward direction to a downward direction or vice versa), then variables were dichotomized: if the predicted probability was above 30% (sample prevalence of sepsis), then the transformed variable was given a value of 1 (indicating higher risk), otherwise it was given a value of 0 (indicating lower risk). If there was no inflexion point, then the original values of the continuous variables were preserved. Logistic regression diagnostics were used to check for influential outliers. Univariate logistic regression models were built for each of the finalized dependent variables (that were either dichotomized or kept original). Then, all variables were entered in a preliminary multivariate logistic regression model. A final multivariate logistic regression model was subsequently built using backwards elimination, where only variables that had statistically significant ( $P < 0.05$ ) Wald chi-square values were kept.

The second model was driven by PoC variables and were dichotomized accordingly. As such, the model included body temperature (risk under 36 °C or above 38 °C), HR (risk above 90 bpm), RR (risk above 22 breaths per minute), lactate (risk above 2 mM/L), SBP/MAP (SBP risk under 100 mmHg or MAP risk under 70 mmHg). All these variables were included in the second model.

A Receiver Operating Characteristic (ROC) curve was built for both final logistic regression models to test their accuracies. The ROC curve is a plot that shows the true positive rate (sensitivity) against the false positive rate (1-specificity) for different cutpoints of a model or test [25], allowing for the tradeoff between sensitivity and specificity, since an increase in one is connected to a decrease in the other. The area under the ROC curve shows the accuracy: an area of 1 is considered a perfect model or test, whereas an area of 0.5 is considered a failed model or test (0.90–1 is excellent, 0.8–0.9 is good, 0.7–0.8 is fair, 0.6–0.7 is poor, and 0.5–0.6 is fail).

Frequencies and percentages for categorical variables and means calculations with their corresponding standard deviations (SDs) for continuous variables, univariate odds ratios (ORs) and multivariate adjusted odds ratios (aORs) with their corresponding 95% confidence intervals (95% CI) are reported. Data management and analysis were performed in SAS V9.4.

## RESULTS

### Sample description

Charts of 228 sepsis patients, 274 dehydration patients, and 228 stroke patients were extracted. Altogether 40 observations were deleted because they were repeat visits, and altogether 26



Table 1. Description of sample characteristics

Characteristic	N (%) or mean (SD)	Range
<i>Demographic characteristics</i>		
Gender		
Female	359 (54.1)	N/A
Male	305 (45.9)	N/A
Age-years	70.2 (15.7)	19-99
<i>Vital parameters</i>		
Body temperature - °C	36.9 (0.9)	32.3-40.2
Respiratory rate - per minute	18.7 (6.1)	10-50
Heart rate - per minute	91.0 (23.2)	23-194
Systolic blood pressure - mmHg	135.3 (36.2)	40-250
Diastolic blood pressure - mmHg	75.7 (19.9)	14-142
Mean arterial pressure - mmHg	95.6 (23.8)	26.3-176.7
<i>Point of care test results</i>		
Lactate level - mM/L	2.6 (2.2)	0.1-19.3
pH	7.40 (0.09)	6.82-7.66
Bicarbonate level - mM/L	22.9 (5.3)	3.7-59.6
<i>Diagnosis</i>		
Sepsis	205 (30.9)	N/A
Stroke	215 (32.4)	N/A
Dehydration	244 (36.7)	N/A

Note: N/A - not applicable.

observations (13 patients) were removed from the data because those patients had presented with more than one of the three diagnoses of interest. No influential outliers were identified. Therefore, the final analysis data set included a total of 664 patients with one observation each: 205 (30.9%) were septic, 244 (36.7%) were dehydrated, and 215 (32.4%) were stroke patients; about half (54.1%) were female and the mean age was 70.2 years (SD = 15.7). Table 1 shows the mean (SD) values and the ranges for the vital parameters and the PoC results.

## Inflexion points

No inflexion points were observed for SBP, DBP, MAP, and RR, therefore these variables were kept as continuous (Fig. 1a-j). Age showed a reverse U-shaped curve: higher-risk cutoffs were identified for ages between 56 years and 83 years. Body temperature showed a W-shaped curve: higher-risk cutoffs were identified for temperatures under 35.6 °C and above 37.3 °C. Bicarbonate and HR showed U-shaped curves: higher-risk cutoffs were identified at under 22.3 mM/L for bicarbonate, and under 53 bpm and above 91 bpm for HR. Lactate and pH showed V-shaped curves: higher-risk cutoffs were identified at 1 mM/L or under and above 2.5 mM/L for lactate, and under 7.34 and above 7.45 for pH.

## Univariate and multivariate analyses

In the univariate analysis of the data-driven model, RR and higher-risk age, bicarbonate, HR, lactate, pH, and temperature were positively associated; and MAP was inversely associated with sepsis risk (Table 2). In the final multivariate analysis, RR and higher-risk age, bicarbonate, HR,



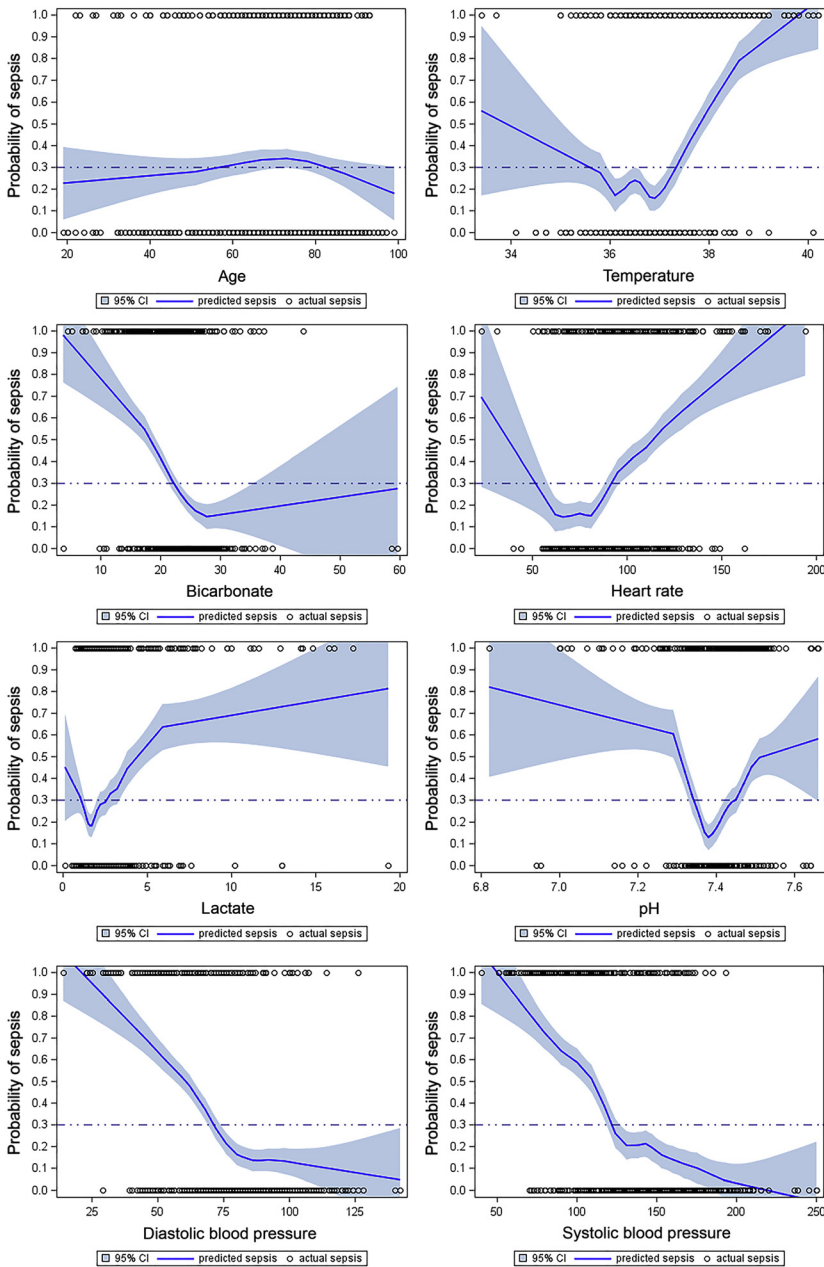


Fig. 1. Loess regression plots depicting the relationship between the predicted probability of sepsis and a. age, b. body temperature, c. bicarbonate level, d. heart rate, e. lactate, f. pH, g. diastolic blood pressure, h. systolic blood pressure, i. mean arterial pressure, and j. respiratory rate.

Note: The high-risk vs. low-risk cutoff level based on actual population prevalence is marked with a dotted line at  $P = 0.3$



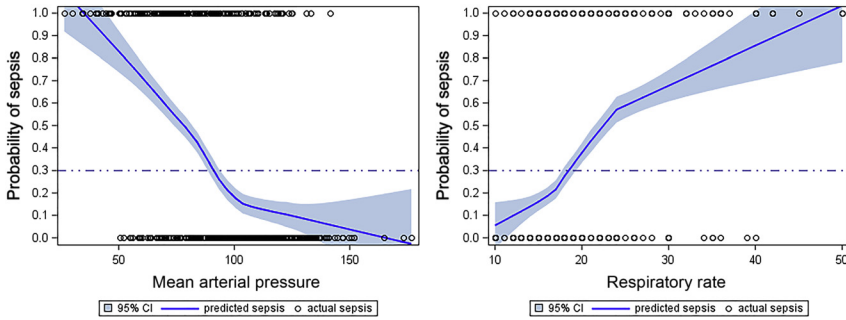


Fig. 1. Continued

Table 2. Univariate and multivariate associations with sepsis – data-driven model

Characteristic	Sepsis		Univariate	Preliminary multivariate	Final multivariate
	No N (%) or mean (SD)	Yes N (%) or mean (SD)	OR (95%CI)	aOR (95%CI)	aOR (95%CI)
Total	459 (100%)	205 (100%)	–	–	–
<i>Demographic characteristics</i>					
Gender					
Female	260 (72.4)	99 (27.6)	ref	ref	
Male	199 (65.2)	106 (34.8)	<b>0.7 [0.5-1.0]</b>	0.8 [0.5-1.2]	–
Age					
Under 56 or above 83 years	182 (74.3)	63 (25.7)	ref	ref	ref
Between 56 and 83 years	277 (66.1)	142 (33.9)	<b>1.5 [1.1-2.1]</b>	<b>1.7 [1.04-2.7]</b>	<b>1.7 [1.1-2.8]</b>
<i>Vital parameters</i>					
Body temperature					
Between 35.6 °C and 37.3 °C	380 (79.7)	97 (20.3)	ref	ref	ref
Under 35.6 °C or above 37.3 °C	79 (42.2)	108 (57.8)	<b>5.4 [3.7-7.7]</b>	<b>3.3 [2.0-5.3]</b>	<b>3.4 [2.1-5.4]</b>
Respiratory rate, per minute	16.9 (4.3)	22.8 (7.5)	<b>1.2 [1.2-1.3]</b>	<b>1.1 [1.1-1.2]</b>	<b>1.1 [1.1-1.2]</b>
Heart rate					
Between 53 and 91 per minute	324 (82.4)	69 (17.6)	ref	ref	ref
Under 53 or above 91 per minute	135 (49.8)	136 (50.2)	<b>4.7 [3.3-6.7]</b>	<b>2.6 [1.6-4.2]</b>	<b>2.7 [1.7-4.3]</b>

(continued)



**Table 2. Continued**

Characteristic	Sepsis		Univariate	Preliminary multivariate	Final multivariate
	No N (%) or mean (SD)	Yes N (%) or mean (SD)	OR (95%CI)	aOR (95%CI)	aOR (95%CI)
Mean arterial pressure, mmHg	103.2 (20.4)	78.4 (21.8)	<b>0.95 [0.94-0.95]</b>	<b>0.95 [0.94-0.96]</b>	<b>0.95 [0.94-0.96]</b>
<i>Point of care test results</i>					
Lactate level					
Between 1.0 and 2.5 mM/L	329 (76.5)	101 (23.5)	ref	ref	ref
Under 1.0 or above 2.5 mM/L	130 (55.6)	104 (44.4)	<b>2.6 [1.8-3.6]</b>	1.5 [0.9-2.4]	-
pH					
Between 7.34 and 7.45	335 (78.8)	90 (21.2)	ref	ref	ref
Under 7.34 or above 7.45	124 (51.9)	115 (48.1)	<b>3.1 [2.2-4.4]</b>	<b>1.7 [1.1-2.7]</b>	<b>1.6 [1.04-2.6]</b>
Bicarbonate level					
22.3 mM/L and above	315 (80.2)	78 (19.8)	ref	ref	ref
Under 22.3 mM/L	144 (53.1)	127 (46.9)	<b>3.6 [2.5-5.0]</b>	<b>2.0 [1.3-3.2]</b>	<b>2.1 [1.3-3.3]</b>

Note: Statistically significant values are bolded.

*Table 3. Multivariate associations with sepsis – guidelines-based model*

Characteristics	Sepsis		Multivariate analysis
	No N (%)	Yes N (%)	aOR (95%CI)
Body temperature			
Between 36 °C and 38 °C	410 (76.2)	128 (23.8)	ref
Under 36 °C or above 38 °C	49 (38.9)	77 (61.1)	<b>3.5 [2.2-5.7]</b>
Heart rate			
90 per minute or under	318 (82.2)	69 (17.8)	ref
Above 90 per minute	141 (50.9)	136 (49.1)	<b>3.2 [2.1-4.9]</b>
Respiratory rate			
22 per minute or under	414 (78.3)	115 (21.7)	ref
Above 22 per minute	45 (33.3)	90 (66.7)	<b>3.8 [2.3-6.1]</b>
Lactate level			
2 mM/L or under	293 (77.9)	83 (22.1)	ref
Above 2 mM/L	166 (57.6)	122 (42.4)	<b>1.7 [1.1-2.5]</b>
Blood pressure measures			
SBP 100 mmHg or above and MAP 70 mmHg or above	430 (76.1)	135 (23.9)	ref
SPB under 100 mmHg or MAP under 70 mmHg	29 (29.3)	70 (70.7)	<b>6.1 [3.8-9.7]</b>

Note: Statistically significant values are bolded.





pH, and temperature were positively associated; and MAP was inversely associated with sepsis risk – gender and lactate did not stay in the final model as significant correlates. Table 3 shows the results of the guidelines-based model. In summary, compared to the guidelines-based model, the data-driven final model contained additional variables (age, pH, bicarbonate) and did not

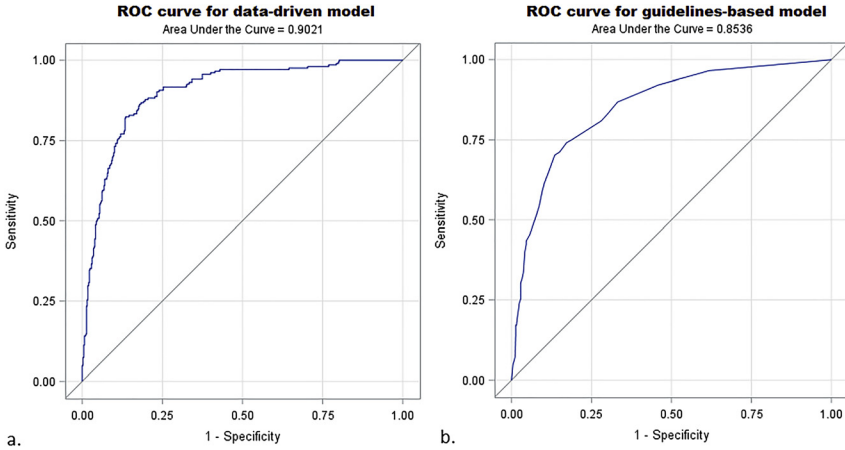


Fig. 2. A Receiver Operating Characteristics (ROCs) curve showing the true positive rate against the false positive rate for the different possible cutoff points of a. the data-driven final multivariate regression model (Area Under the Curve = 0.9021) and b. the guidelines-based multivariate model (Area Under the Curve = 0.8536)

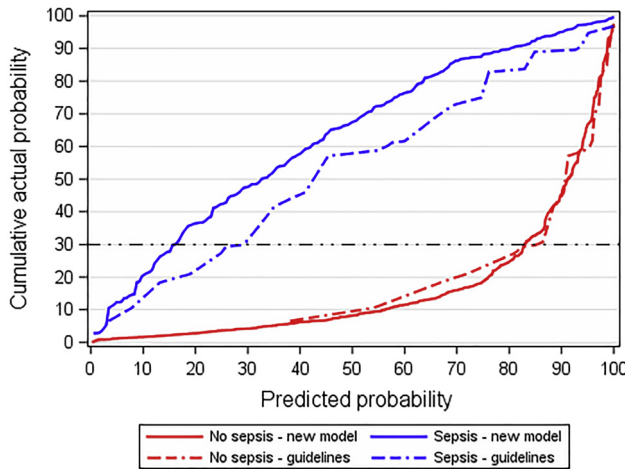


Fig. 3. A curve showing the cumulative predicted probability against the predicted probability for both the data-driven model and the guidelines-based model.

Note: The dotted black line shows the actual probability of  $P = 0.3$ . The solid blue and red lines depict the data-driven new model, and the dotted blue and red lines depict the guidelines-based model, showing about 85% true positives for the data-driven model and about 70% true positives for the guidelines-based model, and showing about the same true negatives for both



include lactate. The area under the ROC curve was 0.9021 for the data-driven model, and 0.8536 for the guidelines-based model (Fig. 2).

Fig. 3 shows the relationship between predicted probability and cumulative actual probability for both models. As seen in the section of the curves above the reference line at  $y = 30$ , when a cut-off for the predicted probability is set at the actual probability (30% – which is the reference line at  $y = 30$ ), then the data-driven model correctly identifies about 85% of the cases (true positives: the blue curve above the dotted line) and incorrectly identifies 15% of non-cases (false positives: the red curve above the dotted line). In contrast, the guidelines-based model had a true positive rate of about 70% and a false positive rate of about 15%.

## DISCUSSION

Our study provides further evidence that improved tools to identify sepsis at early time points, such as in the emergency room are much needed. We found that while some variables indeed have non-linear associations with sepsis risk and therefore require binarization, the binary cutoff values are slightly different from the cutoff values that are used in current sepsis guidelines. Additionally, while guidelines have set cutoff values for other variables, we found sepsis risk for those variables linear, which makes their binarization inappropriate. Moreover, compared to the guidelines-based model, the data-driven final model contained additional variables such as age, pH, and bicarbonate (that are – to our knowledge – not present in any of the guidelines for sepsis diagnosis), and did not include lactate (an important predictor in current guidelines). Finally, the data-driven model proved to be superior to the guidelines-based model in identifying sepsis cases.

SIRS postulates sepsis risk under  $36\text{ }^{\circ}\text{C}$  or above  $38\text{ }^{\circ}\text{C}$  *body temperature* [8, 9]. While we found a W curve that indicates both lower and higher body temperatures (under  $35.6\text{ }^{\circ}\text{C}$  and above  $37.3\text{ }^{\circ}\text{C}$ ) as risk factors for sepsis, our findings indicate that the risk limits of infection-induced temperature change might be shifted towards higher temperatures. As such, we found that between  $35.6\text{ }^{\circ}\text{C}$  and  $36\text{ }^{\circ}\text{C}$  the risk is the same as between  $36\text{ }^{\circ}\text{C}$  and  $37.3\text{ }^{\circ}\text{C}$ , and therefore SIRS might over-diagnose the risk of sepsis at lower temperatures (between  $35.6\text{ }^{\circ}\text{C}$  and  $36\text{ }^{\circ}\text{C}$ ) and under-diagnose at higher temperatures (between  $37.3\text{ }^{\circ}\text{C}$  and  $38\text{ }^{\circ}\text{C}$ ). This might suggest that while accurate measurements of body temperature will play an important role in the diagnosis of sepsis, hypothermia and normal body temperature range still remain to be defined more clearly [26, 27]. Our results also indicate that no fever is needed to have elevated sepsis risk, but a febrile condition might already be a risk indication.

SIRS also predicates sepsis risk at a *heart rate* above 90 bpm [8, 9]. While our results support this as an upper value, we also identified a lower limit (a HR under 53 bpm) under which there was increased sepsis risk. Currently, a lower HR value is not included in any sepsis guideline recommendation, although it is understood that bradycardia in sepsis might be associated with sepsis-induced myocardial dysfunction that might impair survival [28]. We would therefore recommend taking into consideration HR values below about 50 bpm as higher-risk – in addition to the currently used value of above 90 bpm – when considering the diagnosis of sepsis.

*Respiratory rate* above 22 breaths per minute is another sepsis risk criterion [8, 9]. Given that we found no inflexion point for this variable, risk related to RR appears to be a sliding scale as opposed to a real cutoff: the higher the RR the higher the risk of patients having sepsis.



One of the criteria of severe sepsis is a serum *lactate level* above 2 mM/L [12]. While our results suggest that a 2 mM/L cutoff point might be somewhat low (compared to our cutoff point of 2.5 mM/L), we also identified a cutoff of 1 mM/L or under. Interestingly enough, though, lactate did not persist in the multivariate model as a correlate. There has been an ongoing debate on the use of lactate as an accurate biomarker of septic shock. Garcia-Alvarez et al. dispute that lactate is a precedent of sepsis and propose that it is rather its result [29], and Marik argues that lactate is not an accurate indicator of tissue hypoxia, because experimental models have failed to demonstrate cellular hypoxia in sepsis [30]. Our finding that in an ER setting sepsis was not associated with lactate levels but with pH instead, appears to confirm this proposition. Indeed, other researchers failed to demonstrate direct connections among oxygen carrying capacity, mixed venous oxygen saturation and levels of lactate, along with lacking evidence of direct tissue hypoxia in sepsis – it is therefore not surprising that we did not find lactate levels to be associated with sepsis. Therefore, we provide further evidence that net lactate levels should be interpreted cautiously in septic patients, or that at least lactate *per se* may not be a pure indicator of the severity of circulatory derangement [31]. Considering that we found two cutoff points of lactate risk, further clarification is needed how lactate levels lower than 1 mM/L (or even lactate in general) are associated with sepsis.

With regard to *blood pressure*, the defined cut off values used by qSOFA for SBP  $\leq 100$  mmHg and by SOFA for MAP  $< 70$  mmHg might be easy and user-friendly values [12, 32]. We, however, found no inflexion point but rather a sliding scale. In addition, our findings suggest that the previously defined MAP of 65 mmHg might be too permissive in terms of perfusion pressure [33]. We understand that no direct correlation can be established between MAP/SBP and tissue perfusion [33]. However, our results suggest that higher target pressures might be set in terms of fluid and vasoactive therapy [34].

Normal *pH values* are described as those between 7.35–7.45 [34], and indeed we found a sepsis risk outside this exact interval. Although pH is an easily measurable parameter that has not been explicitly pinpointed yet as a factor in diagnosing sepsis, it seems that our findings might give basis to pH measurement along with or instead of other metabolic parameters, such as lactate. Even though the extent of pH change is influenced by a variety of parameters, lactate *per se* is not likely to affect pH unless clear lactate acidosis is diagnosed [35]. This, however, is not a characteristic pathophysiological pathway in sepsis [36].

To our knowledge, *bicarbonate* has not been used in the diagnosis of sepsis. The normal levels for serum bicarbonate are postulated to be between 22 and 29 mM/L [37], and we indeed found an increased sepsis risk under 22.3 mM/L. We found no indication for an upper risk cutoff value.

A defined risk cutoff level for bicarbonate might help to differentiate sepsis from other disease states that mimic it, such as dehydration and stroke. Caution should be exercised, though, when using bicarbonate as a definitive parameter because of the commonly ill-defined origin of acidosis.

Additionally, *age* has not been identified as a sepsis risk in any scoring system. In their study of 47,475 patients, Inada-Kim et al. found a gradual increase in the number of admissions with increasing age until age 85, when the number of admissions started to decline [16]. Our findings that the risk of sepsis was highest between the ages of 56 years and 83 years correspond with the results of the above study, suggesting this age range as a probability variable in assessing the risk of sepsis.



Some limitations of this study are noteworthy. First, this analysis is based on a retrospective chart review of mostly elderly adult patients, therefore our results might not be generalizable to other age groups. However, most septic patients are elderly, and since age – albeit as a binary variable – was included in the final multivariate model, this might somewhat counteract this limitation. Moreover, not all patients admitted to the emergency room (ER) were assessed for the parameters examined in this study, but only those where the physician in charge considered such evaluation necessary. Our goal was not to assess sepsis risk among all ER admissions, but to differentiate the diagnosis among those patients that present with conditions that mimic sepsis, such as stroke and dehydration. Additionally, the study is based on a single center retrospective dataset, and therefore our findings might not be representative of all patient populations, either in Hungary or in other countries. This study focused only on early recognition and not on survival, and therefore survival data are unavailable.

## CONCLUSIONS

We can conclude that in addition to some SIRS and qSOFA parameters that are easy to measure at triage level, other easily measurable variables, such as pH, bicarbonate levels, and age might be useful in the diagnosis of sepsis in the ER and provide better accuracy and predictive power than the tools provided by current sepsis guidelines. Since the currently used sepsis criteria are rather unspecific, our results suggest that the model and its variables that we constructed in this analysis and that proved to have excellent predictability might be such a tool that would aid in a more specific identification of sepsis in the first line of care. Therefore, future studies should duplicate our analysis with these variables in order to confirm our findings. Ideally, a new tool might be developed that would help rapid and early identification of sepsis in the triage, enabling the physician to perform the necessary actions that contribute to lower mortality. Our findings contribute to the growing body of evidence in the quest of finding improved tools to identify sepsis at early time points, such as in the emergency room [15–18].

*Authors' contribution:* Gyula Molnár collected the data, was involved in the study design, and wrote the paper. V. Anna Gyarmathy designed the study, performed data management and analysis, designed and created the figures, designed the tables, and wrote the paper. Johanna Takács performed data management and analysis, contributed to the creation of the figures, created the tables, and wrote the paper. Szilárd Sándor and Bálint Kiss collected the data and contributed to writing the paper. János Fazakas provided recommendations for the analysis and revised the manuscript. Péter L. Kanizsai was involved in the study design, supervised data collection, and wrote the paper. All authors provided final approval of the version submitted for publication.

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## LIST OF ABBREVIATIONS

AMS	Altered mental state
aOR	adjusted odds ratio
CI	confidence intervals
DBP	diastolic blood pressure
ER	emergency room
HR	heart rate
MAP	mean arterial pressure
OR	odds ratio
PIRO	predisposition, infection (present or suspected), response (immune system activation) and organ dysfunction
PoC	point of care
qSOFA	quick sequential organ failure assessment score
ROC	receiver operating characteristic
RR	respiratory rate
SBP	systolic blood pressure
SD	standard deviations
SIRS	systemic inflammatory response syndrome

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