Point of care methods to differentiate sepsis from similar groups of symptoms in the emergency department.

PhD thesis

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Budapest

2021

1. Introduction

Sepsis is an extreme challenge to the healthcare providers, being responsible for one in five deaths worldwide (1).

Although with better recognition the number of identified sepsis cases are increasing, there is a substantial difference in mortality in different regions, depending on GDP and the general health of the population.

Early recognition is a key for effective treatment, but sepsis being a highly unspecific group of symptoms, timely management is still a challenge (2).

Under normal circumstances infections are localized and eliminated by the immune system. Depending on the immune status and other individual characteristics (genetic variability, predisposition) infection can trigger systemic inflammation.

Some inflammatory parameters (3,4), such as body temperature, respiratory rate (RR), heart rate (HR), and the presence of leukocytosis or leukopenia were used to diagnose sepsis in the early 1990s. Although the previously widely accepted systemic inflammatory response syndrome (SIRS) criteria are not replaced by the quick sequential organ failure assessment score (qSOFA), based on the blood pressure, respiratory rate and altered mental status. (5), SIRS was eliminated from the newest sepsis definition due to its limitations.

There has been an enormous effort to fine tune early recognition by different scores, but clinical picture and the underlying pathophysiology is too complicated in most cases (6). One of the most useful scores is the Sequential Organ Failure Assessment (SOFA), regarding power, specificity and reactivity focusing on organ involvement i.e. lungs, central nervous system, liver, kidneys, cardiovascular and hemopoietic system (7). Predictive efficacy for in-hospital death of the SIRS and SOFA criteria were recently analyzed by W. Zhang et al. (8). In their retrospective study they found that the SOFA criteria were stronger in sepsis recognition than SIRS criteria.

Sepsis-3 guidelines have been criticised by Sartelli et al. as they were not validated prospectively in a large group of patients. Furthermore, there is also some criticism that data originated mainly from the United States and Germany questioning the useability of these guidelines elsewhere in the world. The most heavily criticised inclusion in the criteria is organ dysfunction as this is not one of the first detectable sign of sepsis. It is

also cumbersome to calculate SOFA score at admission since laboratory parameters are required to do so (9).

The patient is considered to be in septic shock (7), when there is a need for vasopressors to keep mean arterial pressure (MAP) above 65 mmHg and serum lactate is higher than 2 mM/l.

Ideally the whole process of recognition and early stabilization of septic patients begins in the emergency department. However, most of sepsis deaths are preventable by early recognition, due to its undefinied appearance it is very often underdiagnosed or overseen at an early stage (10,11).

The basic parameters like low or high temperature, decreased or increased HR, changes in blood pressure are unspecific predictors, along with the measurement of acute phase proteins and biomarkers such as C-reactive protein (CRP), interleukin-6 (IL-6), procalcitonin and lactate (12).

While altered mental state (AMS) can be a sign of sepsis, it can also be a warning sign in any kind of transient or permanent dysfunction of the brain caused by toxins or as a result of blood flow disturbances (13). Especially in the emergency department or in the prehospital settings factors frequently associated with ischaemic stroke like cognitive disorders or sensomotory aphasia can mimick AMS, thereby enabling stroke to show similarities with sepsis (13). A symptom of dehydration might also reveal AMS, which can also mimic sepsis associated desorientation, especially in the elderly (13). Low blood pressure can affect the blood supply to the brain making it prone for dysfunctioning. The predisposition, infection (present or suspected), response (immune system activation) and organ dysfunction (PIRO) concept, which looks on sepsis/septic shock as a complex and multidimensional process, when it is diagnosed, still does not approximate sepsis diagnosis (14). The use of different sepsis scores and vital parameters along with laboratory results to diagnose sepsis is surrounded by controversy (7,15). In the emergency department (15-18) triage, where the time limitation and lack of specific parameters do not allow to calculate SOFA score, there is a need to come up with a better diagnostic approach. A blood gas analyzer is available in the majority of units that can present valuable data on the patient in a matter of minutes. One of the most easily utilized parameters is lactate which can be measured as routine in arterial or venous blood gas analysis.

The median difference between arterial and venous lactate is only 0,049 mM/l. The Sepsis Six approach, initially developed in 2009 but still applied in recent years (19,20), still recommends the measurement of lactate. 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. This approach is being challenged what the author is aware of but no other recommendation is available yet (21).

At triage level we can only suggest to identify and to use rapidly (turn around time less than 10 minutes) and reliably measurable parameters.

National Early Warning Score (NEWS) is preferably used to detect deterioration over time, therefore it was not feasible to apply in this setting. However, during observation it is still a very useful approach.

In the centre of our research was to find new set of parameters which is easy to use, gives a quick result at triage level in order to enable the clinician to establish the diagnosis of sepsis. However, the use of the neutrophyl-limphocyte ratio (NLR) and the incorporation of that figure in a newly developed scoring system could be the focus of future investigations, but again, not during triage since NLR is a relatively time consuming method.

The creation of more individualised scoring systems (in case of elevated intracranial pressure (ICP) or other diseases requiring higher MAP) may be achievable at a later stage. Although there is no such literature comparing these three entities (sepsis, stroke and dehydration) but given that most emergency room (ER) admissions are due to these set of syndromes, we have chosen arbitrarily these pathologies to make a comparison.

2. Results

2.1. 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 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.

2.2. Inflexion points

No inflexion points were observed for SBP, DBP, MAP, and RR, so these variables were kept as continuous (Fig. 1a-1j).

Age showed a reverse U-shaped curve: higher-risk cutoffs were identified for age 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.

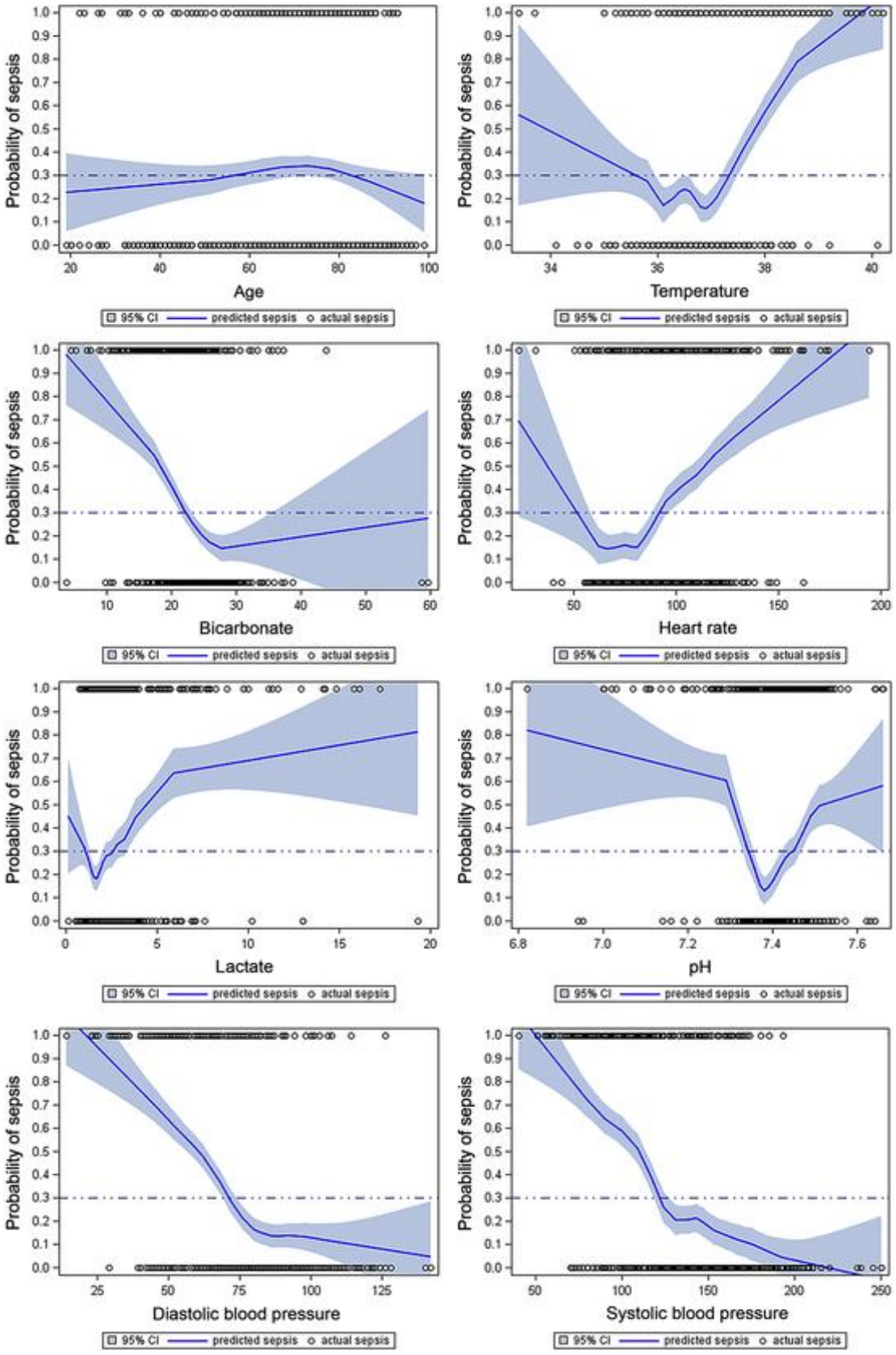

Figure. 1 Loess regression plots depicting the relationship between the predicted probability of sepsis and a. age, b. body temperature, c. bicarbonate level, d. heart rate, e.

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 $P = 0.3$

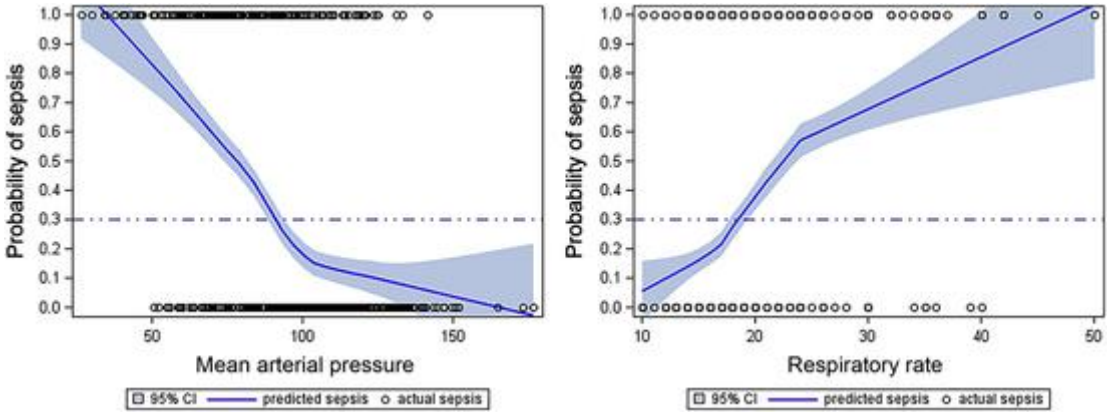

Figure. 1 Continued

2.3. Univariate and multivariable analyses

In the univariate analysis of the data-driven model, RR and old age, bicarbonate, HR, lactate, pH, and temperature were positively associated; and MAP was inversely associated with sepsis risk.

In the final multivariable analysis, RR and higher-risk age, bicarbonate, HR, 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.

In summary, compared to the guidelines-based model, the data-driven final model contained additional variables (age, pH, bicarbonate) and did not 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).

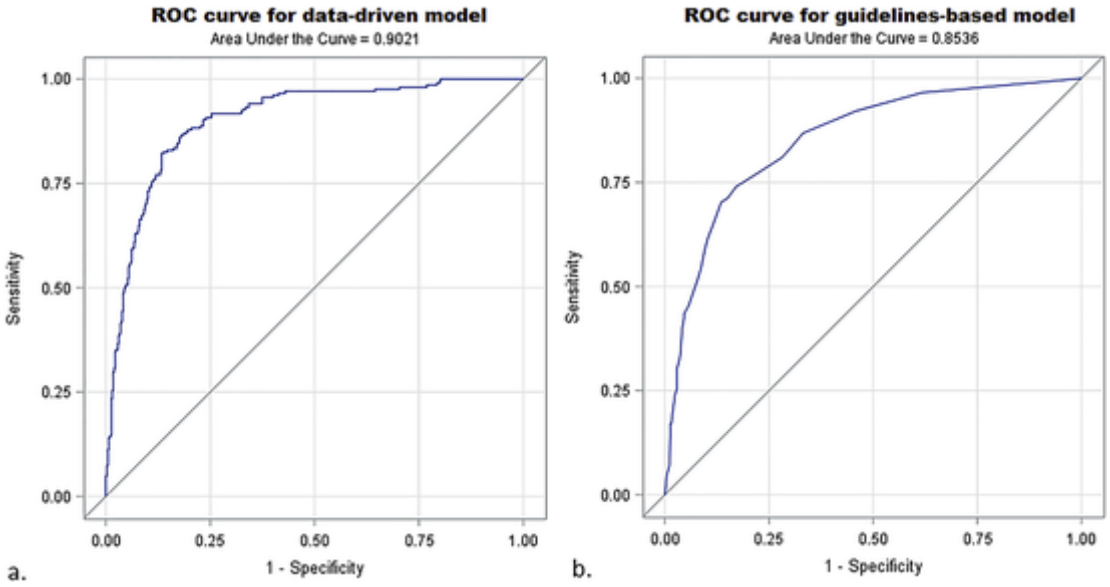

Figure. 2 A Receiver Operating Characteristics (ROCs) curve showing the true positive rate against the false positive rate for the different possible cutoff points of a. the data-driven final multivariable regression model (Area Under the Curve = 0.9021) and b. the guidelines-based multivariable model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

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%.

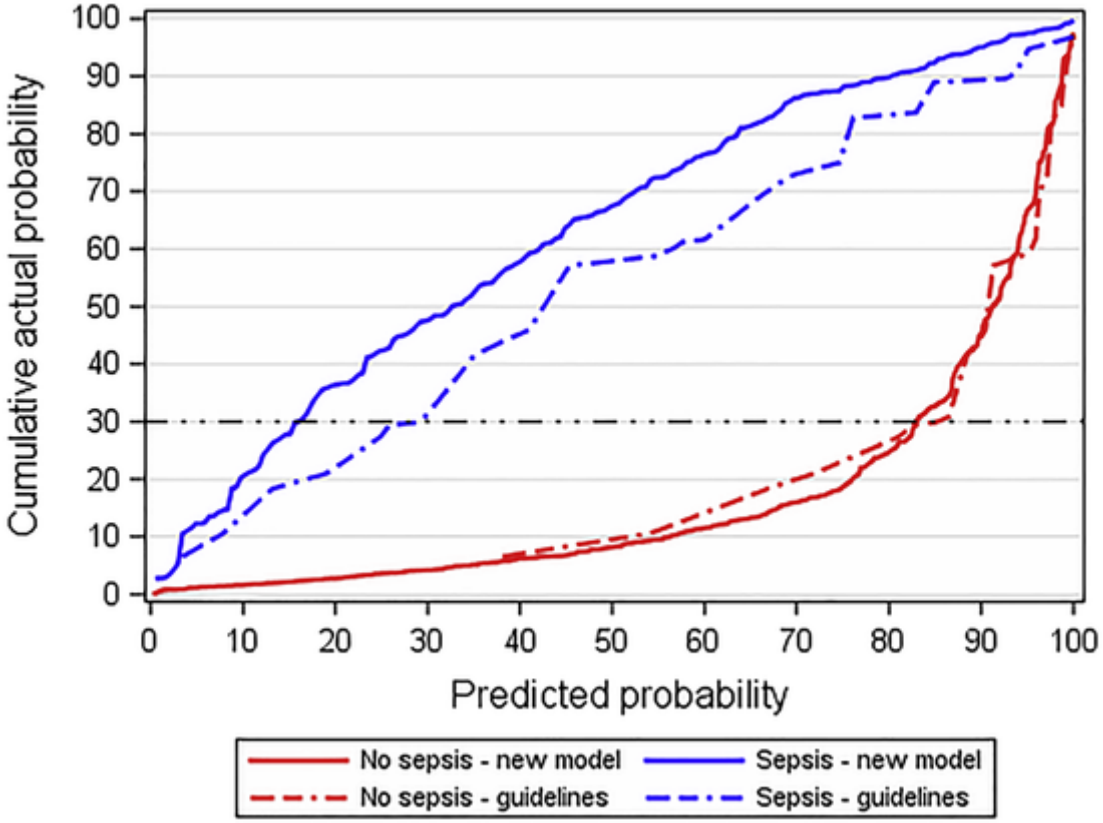

Figure. 3 A curve showing the cumulative predicted probability against the predicted probability for both the data-driven model and the guidelines-based model. *Note:* The dotted black line shows the actual probability of $P = 0.3$. The solid blue and red lines depict the data-driven new model, and the 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.

3. Discussion

Our research 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 cut-off values are slightly different from the cutoff values that are used in current sepsis guidelines. Additionally, while guidelines have set cut-off values for other variables, we found sepsis risk for those variables linear and therefore 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 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°C or above 38°C *body temperature* (3,4). While we found a W-shaped curve that indicates both lower and higher body temperatures (under 35.6°C and above 37.3°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°C and 36°C the risk is the same as between 36°C and 37.3°C, and therefore SIRS might over-diagnose the risk of sepsis at lower temperatures (between 35.6°C and 36°C) and under-diagnose at higher temperatures (between 37.3°C and 38°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 (90,91). 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 (3,4). 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 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 (92). 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 (3,4). 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 (7). 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 stay in the multivariable model as a correlate. There has been an ongoing debate on alternative signs or predictors such as 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 a result of it (93), and Marik argues that lactate is not an accurate indicator of tissue hypoxia, because experimental models have failed to demonstrate cellular hypoxia in sepsis (94). 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 might be interpreted cautiously in septic patients, or that at least lactate *per se* may not be a pure indicator of severity of circulatory derangement (95). 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 ≤100 mmHg and by SOFA for MAP <70 mmHg might be easy and user-friendly values (7,96). 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 (97). We understand that no direct correlation can be established between MAP/SBP and tissue perfusion (97). However, our results suggest that higher target pressures might be set in terms of fluid and vasoactive therapy.

Normal *pH values* are described as those between 7.35-7.45, 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 (98). This, however, is not a characteristic pathophysiological pathway in sepsis (99).

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 (100), 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, so 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 multivariable model, this might somewhat control for 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.

4. 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 have better accuracy and better differentiating 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 target 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).

5. Bibliography of the candidate's publications

Related to the thesis

1. **Molnár G**, Gyarmathy VA, Takács J, Sándor S, Kiss B, Fazakas J, Kanizsai PL. (2021) Differentiating sepsis from similar groups of sysmptoms at triage level in emergency care Physiol Int, 108, 1: 106-120. **IF: 1,410***

*Expected value

2. **Molnár G**, Gyarmathy VA, Zádori N, Hegyi P, Kanizsai P. (2021) Severe Hypertriglyceridemia-Induced Acute Pancreatitis. Case Rep Gastroenterol, 15, 1: 218-224.

3. Xantus G, Kiss B, **Molnar G**, Matheson C, Gyarmathy VA, Kanizsai PL. (2021) Lactate reloaded–reevaluation of the importance of lactate monitoring in the management of adult sepsis in the emergency department. BIOCELL, 45, 3: 445–449. **IF: 2,821***

*Expected value

4. Saeed K, González Del Castillo J, Backous C, Drevet S, Ferrer R, Gavazzi G, Gluck E, Jensen JU, Kanizsai P, Ruiz-Rodríguez JC, **Molnar G**, Fazakas J, Umpleby H, Townsend J, Schuetz P. (2019) Hot topics on procalcitonin use in clinical practice, can it help antibiotic stewardship? Int J Antimicrob Agents, 54, 6: 686-696. **IF: 4,621***

*Expected value

5. Kanizsai P, **Molnár Gy**, Sztudva R, Berényi T, Hornyák I. (2018) Does level of training predetermine the success rate of prehospital sepsis assessment? A prospective survey on early recognition. Developments in Health Sciences, 1, 2: 33-38.

Not related to the thesis

1. **Molnar Gy**, Roberts G, Thorpe C. (2013): Improving data capture on obstetric anaesthesia procedures and complications – role of coding International Journal of Obstetric Anaesthesia, 22: 34.

Cumulative impact factor of the candidate's publications: **8,852*** *Expected value