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Research Article

JOURNAL OF SURGERY AND RESEARCH

ISSN: 2640-1002

The Time-related role of early pH, Base excess and Lactate for the Development in Sepsis in Polytrauma patients. An analysis using the IBM Watson Trauma Pathway Explorer

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Abstract

Triaging is essential for treating polytrauma patients. The Watson Trauma Pathway Explorer® represents an outcome prediction tool that prognosticates adverse events being Systemic Inflammatory Respiratory Syndrome and sepsis within 21 days and death within 72 h. We intended to compare the time-dependent role of pH, base excess (BE) and lactate for sepsis development in these patients. Retrospective data from 3653 patients were used. According to sepsis development, two groups were formed. pH, BE and lactate values were measured until up to 48 h after admission to our trauma bay. Differences in these three factors were analyzed between the two groups. Each factor (pH < 7.35; BE < -2 mmol/L; lactate > 2 or 4 mmol/L) was tested regarding its predictive quality, adjusted for ISS, age and gender. Threshold values at each timepoint were calculated. Between the two groups, differences in pH existed within the first 4 h, and for BE within the first six hours. Lactate values differed from the second hour onwards. pH (< 7.35; p = 0.035) and lactate (> 4 mmol/L; p = 0.006) at 4 h as well as BE at 6 h (< - 2 mmol/L; p = 0.022) were independent predictors for sepsis. Threshold values for pH were acidic for the first two hours, compared to BE within the first six hours. The insights indicating a time window of avoiding sepsis may allow referencing and promote timely measures while minimizing complications. Analysis of further surrogative parameters is required to warrant a more precise prediction.

Keywords: Watson Trauma Pathway Explorer; Polytrauma; Sepsis

Introduction

Triaging of polytrauma patients is essential after admission to trauma bay. Besides clinical evaluation, numerous laboratory parameters are considered to evaluate injury severity and risk of subsequent adverse events (AE) such as systemic Inflammatory Respiratory Syndrome (SIRS), sepsis and death [1-11]. Anticipation and awareness of such aspects may be helpful in treatment decisions, being pharmaceutical or operative. The Watson Trauma Pathway Explorer® represents an outcome prediction tool that prognosticates the occurrence of SIRS and sepsis within 21 days and death within 72h [2-8,12]. The tool is based on an internal data base from more than 3500 patients with ongoing admission. Its main advantage is the ability to reference values according to fixed time points since admission, thereby allowing for continuous re-assessment. Lactate is an established parameter in estimating the risk for sepsis and mortality of polytrauma patients [1,7,9-11]. It is often a sign of hypoperfusion [13] but can also suggest a disease state or adrenergic process, for example in polytrauma cases [14-17]. Here, trauma-caused cell debris may lead to an immunologic response resembled

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Citation: Philipp Vetter, Jan Hambrecht, Cédric Niggli, Hans-Christoph Pape, Ladislav Mica. The time-related role of early pH, base excess and lactate for the development in sepsis in polytrauma patients. An analysis using the IBM Watson Trauma Pathway Explorer. Journal of Surgery and Research. 6 (2023): 283-291.

Received: July 15, 2023
Accepted: July 24, 2023
Published: August 18, 2023

Vetter P, et al., J Surg Res 2023
DOI:10.26502/jsr.10020311

as SIRS [18]. This, in turn, can further complicate into sepsis in a severe or shock state, accompanied by multiple organ damage and hypotension [19,20]. The association between lactate levels and AE generally appears to be linear [10,21,22] and related to injury severity [23,24]. This could explain the heterogenic aspect of lactate cut-off values indicating a substantial risk for AE, including a threshold of > 2 [mmol/L] [25,26], intermediately elevated values (2.0 - 3.9 [mmol/L]) [9,27,28] and a value greater than 4.0 [mmol/L] [10,11]. In combination with changes over time in the posttraumatic course, decision making on the basis of this parameter can be very challenging. Base excess (BE) is a parameter for acid-base dysbalance and physiologically lies within -2 and +2 mmol/L. In the trauma setting, it often implies tissue hypoperfusion by means of acidosis [29-31] and was found to be a predictive factor for mortality in polytrauma patients [32]. pH, on the other hand, represents a direct parameter that comprises the effects of oxygen debt, metabolic dysbalance (e.g. indicated by BE) and compensatory mechanisms [33]. Its comprehensiveness makes acidotic values (< 7.35) indicative of a serious morbidity, although the high rate of confounding aspects makes it less sensitive to minor changes [30,34]. Our aim was to analyze the time-dependent of pH, BE and lactate for sepsis development in polytrauma patients.

Methods

Patient cohort

Retrospective data from 3653 patients (1996-2022) from our institutional database, with ongoing implementation, were used for analysis in the Watson Trauma Pathway Explorer. We included polytrauma patients aged ≥ 16 years with an Injury Severity Score (ISS) ≥ 16 [35] retrospectively. Complete datasets were required. Excluded were patients that had not survived until admission or patients that were referred from external hospitals. According to the development of sepsis within the observational period of 21 days, two groups were formed. For all patients, pH, BE and lactate values were measured at previously defined time points (admission, 1, 2, 3, 4, 6, 8, 12, 24, and 48 h) after admission to our trauma bay at the University Hospital Zurich [5,7,8].

Definition of sepsis

Based on the most extreme values in leucocyte count, respiratory rate, heart rate and temperature, the SIRS score was calculated each day [36]. It was calculated for the time frame of hospitalization. Sepsis was defined as a SIRS score ≥ 2 with a focus of infection [19], and had to occur within the observational time frame of 21 days.

Laboratory analysis

Lactate levels [mmol/L] as well as pH and Base excess [mmol/L] were measured at the Institut für Klinische Chemie at the University of Zurich in a standardized blood gas analyzer (Radiometer ABL 825 Flex, Radiometer RSCH GmbH, Thalwil, Switzerland) The same procedure of measurement was applied at each time point.

Statistical analysis

Patients' baseline characteristics are described as means with standard deviations (SD) for numerical variables, as medians with interquartile ranges (IQR) for ordinal data and as percentages for binary variables. An unpaired t-test for numerical variables and a Mood's median test for ordinal variables were used for assessing differences between the two groups. Differences between groups according to the presence of sepsis were analyzed using the Mann-Whitney-U-Test due to a missing normal distribution according to a Q-Q-plot and an unequal variance.

Binary logistic regression was performed to analyze pH, BE and lactate as independent prediction factors for sepsis. Analysis was corrected for ISS, age and gender, as these factors were previously confirmed as notable factors [10,21, 22,37-39]. For this binary logistic regression, groups were split according to generally accepted threshold values of pH (< 7.35), BE (< -2 mmol/L) and lactate (> 2 or 4 mmol/L) [10,11,25,26].

Calculation of threshold values between the two groups (sepsis development) at each timepoint was performed according to the closest top-left threshold method, presenting the threshold point closest to the top-left corner of the receiver operating characteristic.

SPSS 29.0 (IBM SPSS Statistics 29) served for data analysis. The level of significance was set a $p < 0.05$.

Ethical approval

This study was conducted according to the guidelines for good clinical practice and the Helsinki guidelines. Research was based on the TRIPOD statement, representing a guideline for multivariable prediction model [40]. Ethical approval for analysis of patient data was granted by the ethical committee of the University Hospital Zurich and the government of Zurich upon the development of the database (Nr. StV: 1-2008) and reapproved for development of the Watson Trauma Pathway Explorer® (BASEC 2021-00391).

Results

Patient cohort

We included 3653 patients with a mean age of 45.8 ± 20.2 years, with 73.4% being male (Table 1). Sepsis cases displayed higher values for the (New) Injury Severity Score (NISS), Injury Severity Score (ISS) and the Acute Physiology and Chronic Health Evaluation (APACHE)-II-Score, as well as a younger age.

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Table 1: Baseline characteristics of the total patient cohort and groups according to development of sepsis. pH, BE and lactate values are shown from admission onwards. Age [years], temperature [°C], Systolic blood pressure [mmHg], Prothrombin time [%], Hemoglobin [g/dL], CRP [mg/L], PCT [ng/mL], Lactate [mmol/L].

Baseline characteristic	Overall patient sample N = 3653	Patients with developed Sepsis N = 547	Patients without developed sepsis N = 3106	p-value
Age (mean, SD)	45.8 ± 20.2	42.8 ± 18.1	46.3 ± 20.5	0.0002
Male	73.4%; N=2681	78.6%; N=430	72.4%; N=2251	-
Early death within 72h	19.3%; N=708	1.46%; N=8	22.5%; N=700	-
Blunt trauma	91.3%; N=3336	94.7%; N=518	90.7%; N=2818	-
Head injury	38.3%; N=1400	44.8%; N=245	37.2%; N=1155	-
BMI at admission (mean, SD)	25 ± 4.4	25.9 ± 4.4	24.8 ± 4.3	<0.001
ISS (median, IQR)	25 (17–34)	30 (25–41)	25 (17–34)	<0.001
NISS (median, IQR)	34 (25–50)	41 (33–50)	34 (24–48)	<0.001
APACHE II at admission (median, IQR)	14 (7–21)	17 (11–21)	13 (6–21)	<0.001
GCS at admission (median, IQR)	10 (3–15)	3 (3–14)	11 (3–15)	<0.001
Temperature at admission (mean ± SD)	35.5 ± 1.7	35.4 ± 1.7	35.6 ± 1.7	0.131
Systolic blood pressure at admission (mean ± SD)	130.7 ± 27.6	128.5 ± 27.7	131.2 ± 27.5	0.0715
Prothrombin time at admission (median ± IQR)	84 (65–97)	80 (61–92)	85 (66–98)	0.1257
Hemoglobin at admission (mean ± SD)	11.4 ± 4	11 ± 2.8	11.5 ± 4.2	0.005
CRP at admission (mean ± SD)	13.74 ± 41.21	23.15 ± 62.96	11.94 ± 35.32	< 0.001
pH at admission (mean ± SD)	***7.31 ± 0.13***	***7.30 ± 0.15***	***7.32 ± 0.13***	***0.00632***
pH at 1 h (mean ± SD)	***7.31*** ± 0.15	***7.29*** ± 0.13	***7.31*** ± 0.15	< 0.001
pH at 2 h (mean ± SD)	***7.33*** ± 0.12	***7.32*** ± 0.09	***7.33*** ± 0.13	0.002
pH at 3 h (mean ± SD)	***7.34*** ± 0.14	***7.33*** ± 0.19	***7.35*** ± 0.13	0.003
pH at 4 h (mean ± SD)	***7.36*** ± 0.14	***7.35*** ± 0.08	***7.36*** ± 0.15	0.003
PCT at admission (mean ± SD)	1.23 ± 4.3	0.48 ± 0.56	1.15 ± 4.86	0.559
BE at admission (mean ± SD)	***-3.77 ± 5.27***	***-4.29 ± 4.97***	***-3.67 ± 5.32***	***< 0.001***
BE at 1 h (mean ± SD)	-4.57 ± 5.29	-5.23 ± 5.14	-4.40 ± 5.31	< 0.001
BE at 2 h (mean ± SD)	-4.05 ± 4.51	-4.45 ± 4.32	-3.94 ± 4.56	0.009
BE at 3 h (mean ± SD)	-3.67 ± 4.24	-4.16 ± 3.75	-3.54 ± 4.34	0.001
BE at 4 h (mean ± SD)	-3.05 ± 3.81	-3.40 ± 3.89	-2.96 ± 3.79	0.034
Lactate at admission (mean, SD)	***2.94 +- 2.53***	***2.94 +- 2.27***	***2.94 +- 2.58***	***0.943***
Lactate at 1 hours (mean, SD)	2.76 +- 2.42	2.77 +- 2.15	2.75 +- 2.48	0.941
Lactate at 2 h (mean ± SD)	2.63 ± 2.35	2.95 ± 2.45	2.54 ± 2.32	0.035
Lactate at 3 h (mean ± SD)	2.58 ± 2.25	2.89 ± 2.32	2.50 ± 2.23	0.011
Lactate at 4 h (mean ± SD)	2.51 ± 2.14	2.90 ± 2.33	2.41 ± 2.07	< 0.001
Lactate at 6 h (mean ± SD)	2.33 ± 1.87	2.63 ± 1.85	2.24 ± 1.87	0.00123
Lactate at 8 h (mean ± SD)	2.13 ± 2.44	2.46 ± 1.74	2.05 ± 2.59	0.00851
Lactate at 12 h (mean ± SD)	1.69 ± 1.37	2.10 ± 1.55	1.58 ± 1.30	< 0.001
Lactate at 24 h (mean ± SD)	1.38 ± 1.15	1.71 ± 1.17	1.30 ± 1.22	< 0.001
Lactate at 48 h (mean ± SD)	1.19 ± 1.02	1.47 ± 1.00	1.09 ± 1.01	< 0.001

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Parameter levels according to the development of sepsis

Between the two groups according to sepsis development, differences in pH existed from admission on and persisted for slightly more than four hours (Figure 1). Similar results were observed for BE, which differed over roughly six hours.

Lactate, on the other hand, showed no initial differences between groups, but differed from the second hour onwards until the end of the observational period of 21 days.

Parameters as independent predictors for sepsis

Binary logistic regression revealed pH (<7.35; $p = 0.035$), lactate (> 4 mmol/l; $p = 0.006$) at 4 h and BE at 6 h (< - 2 mmol/L; $p = 0.022$) as independent predictors (Figure 2), representing a statistically significant model ($p = 0.037$). There was a tendency for lactate with a cut-off of 2 mmol/l at 2 h to also be significantly predictive ($p = 0.052$).

pH, BE and lactate showed a correlation with each other (pH – lactate: $r = -0.654$; $p < 0.001$; pH – BE: $r = 0.804$; $p < 0.001$; BE – lactate: $r = -0.730$; $p < 0.001$).

Analysis was corrected for ISS, age and gender, as each parameter at admission showed a correlation with the ISS (pH: $r = -0.256$; $p < 0.001$; BE: $r = -0.247$; $p < 0.001$; lactate: $r = 0.193$; $p < 0.001$) and age (pH: $r = 0.048$; $p = 0.016$; BE: $r = 0.06$; $p = 0.002$; lactate: $r = -0.049$; $p = 0.007$), Additionally, lactate and pH at admission were higher in men (lactate: $p < 0.001$; pH: $p < 0.001$).

Time-dependent threshold values for sepsis.

The threshold values for pH were in the acidic range (< 7.35) for the first two hours after admission before reaching the lower limit of the normal range and turning more neutral thereafter (Figure 3).

For BE, threshold values initially revolved around – 4 mmol/L in the first four hours before reaching the lower limit of the normal range at around six hours, from there on also trending towards the central neutral range (Figure 4).

Lactate has been analyzed in a previous study [7] regarding this aspect and is therefore not depicted in an analogous manner.

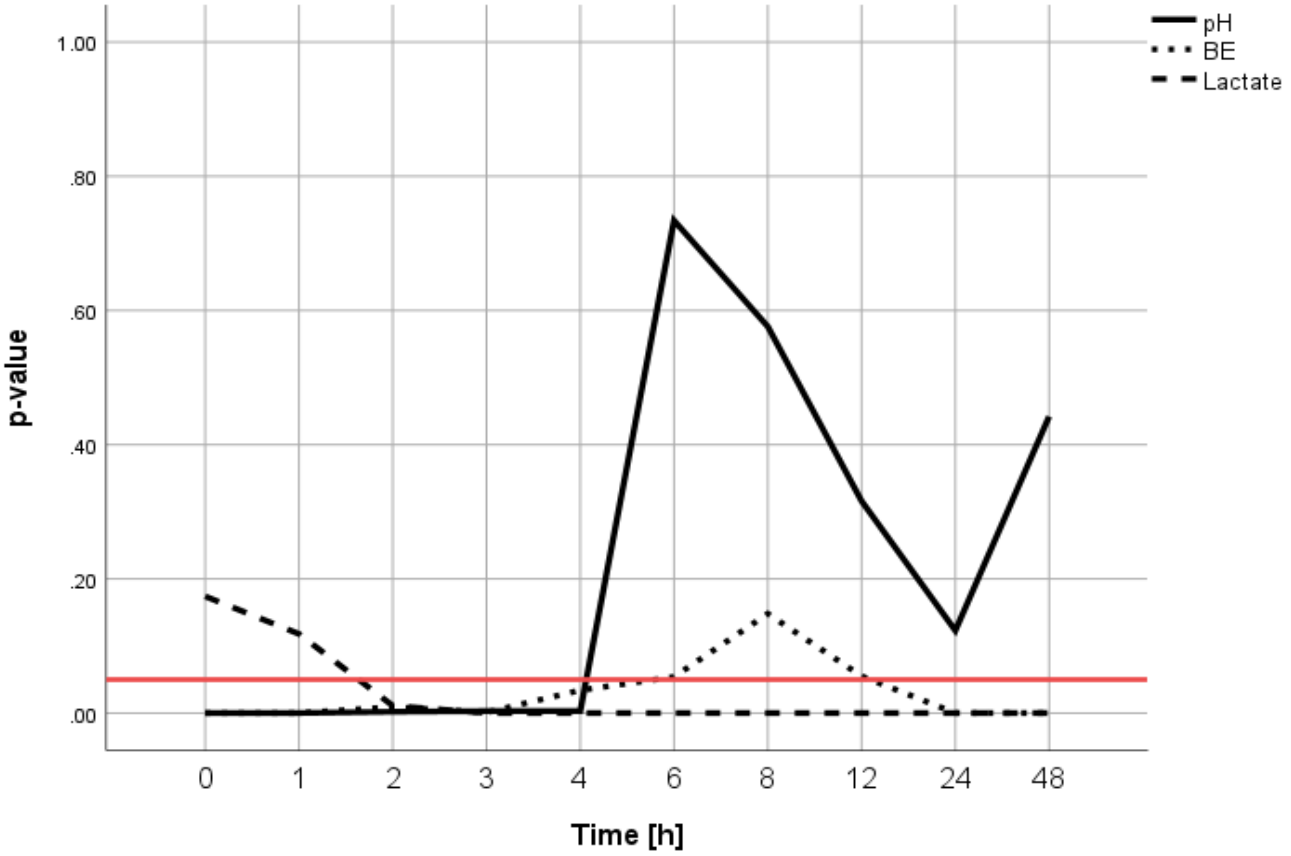

Figure 1: Comparison of parameter levels between the sepsis and non-sepsis group. There were significant differences in pH (continuous line) from admission onwards, which persisted for slightly more than 4 hours. Similar results were observed for BE (dotted line), which differed over roughly 6 hours. Lactate (dashed line), on the other hand, showed no initial differences between groups, but differed from the second hour onwards. The straight horizontal red line indicates the level of significance ($p = 0.05$).

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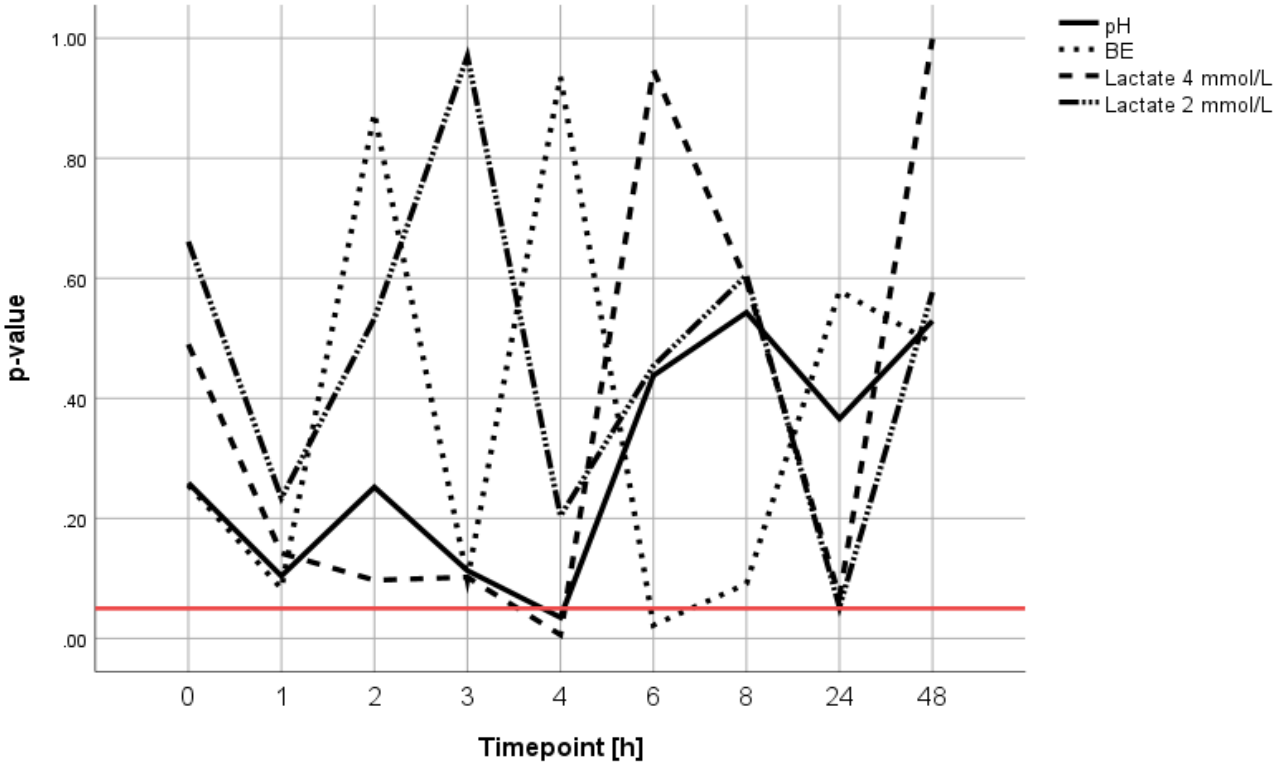

Figure 2: Significance of pH (continuous line), BE (dotted line) and lactate (dashed line/mixed dashed and dotted line) being independent predictors of sepsis adjusted for ISS, age and gender. Binary logistic regression revealed a pH < 7.35 and lactate > 4 mmol/L at 4 h after admission and a BE < -2 mmol/L 6 h after admission as independent predictors of sepsis. The straight horizontal red line indicates the level of significance (p = 0.05).

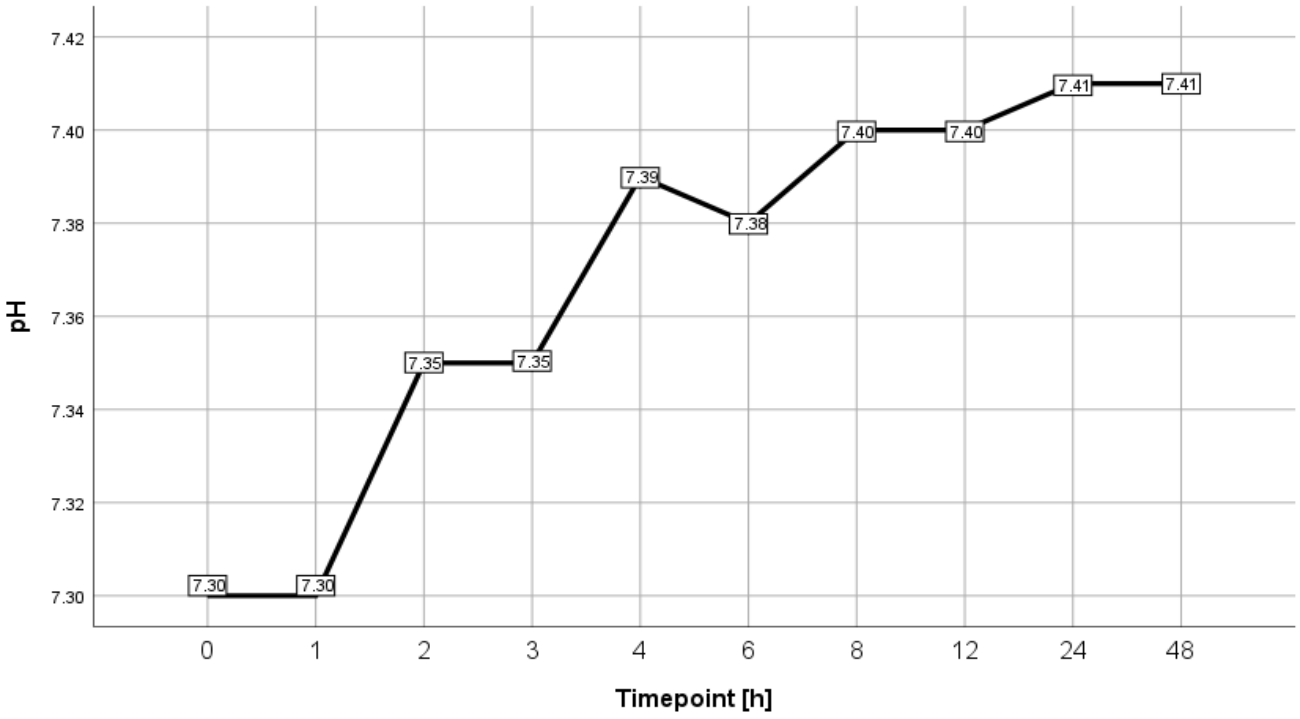

Figure 3: Time-dependent threshold values for pH for sepsis according to the closest top-left threshold method. Values were acidic for the first two hours after admission before reaching the lower limit of the normal range and turning more neutral thereafter.

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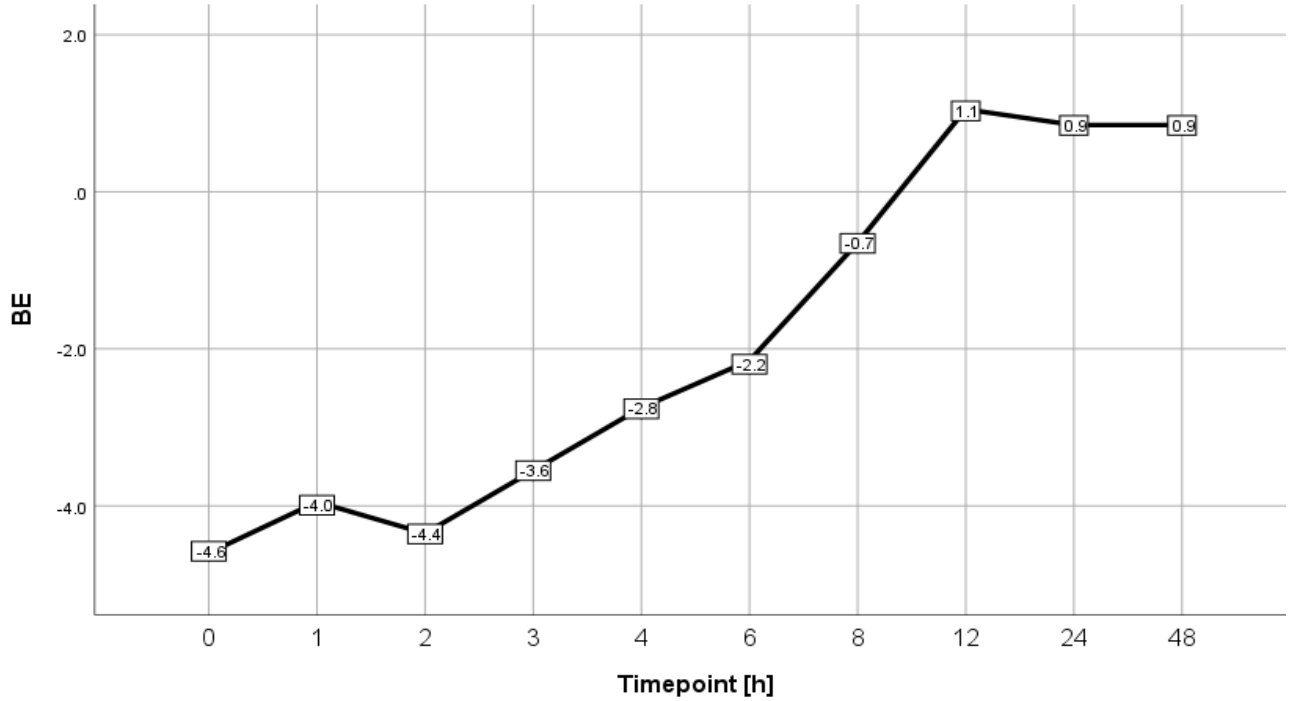

Figure 4: Time-dependent threshold values of BE for sepsis according to the closest top-left threshold method. After initial values of around -4 mmol/L, values reaching the lower limit of the normal range at around 6 hours and from there on trended towards more neutral ranges. Values are given as [mmol/L].

Discussion

After previous analyses [5-8], the Watson Trauma Pathway Explorer® allowed time-dependent insights on the role of pH, BE and lactate regarding the prediction of sepsis in polytrauma patients. The main finding of our study are the early differences in pH, BE and lactate for patients developing sepsis after polytrauma. More specifically, acidic values in pH, BE and lactate were found to be relevant independently within six hours after admission. Threshold values also showed that pH and BE normalized within three to six hours. The parameters are confirmed in their (early) clinical relevance in association with posttraumatic complications [29-34, 41-45], as values differed early, while corrected for injury severity according to the ISS, age and gender [10,21,22,37-39]. There was a respective correlation between the three factors of interest. pH, due to its comprehensiveness, is interpreted as a value affected by BE and lactate. However, it is not only seen in the mere light of bleeding [33], but must also be seen in a multifactorial etiology, associated with the immune system related to complement pathway activation [46-48]. Regarding the time course, threshold values could be defined, being less severe than values in studies reporting on mortality rates [30,32-34]. These intermediately altered parameters may help the treating trauma team to assume when values should return to the normal range, which appears to revolve around the 6 h mark [30]. It appears that this time frame of 4 to 6 h after admission represents the time window of avoiding sepsis. Besides facilitated immediate treatment or prevention measures, being pharmaceutical (fluids, pain relievers, antibiotics, vasopressors or corticosteroids) or surgical (damage-control surgery vs. early total care), the outcome prediction tool allows for constant re-assessment when the patient may have been stabilized hemodynamically but is yet subject to major treatment. In this case, treatment should also be aimed at avoiding an exuberant physiologic response, possibly manifesting in the form of immunosuppression-triggered sepsis. Ultimately, the regression of the researched laboratory parameters to physiological ranges is concordant with the theory of SIRS and CARS (Compensatory Anti-inflammatory Response Syndrome) [49,50], as the early inflammatory response (SIRS) is followed by CARS. Limitations of this study mainly include the non-consideration of patient related confounding variables (e.g. morbidities, injuries according to body region) as well as changes in treatment methods over the long time-frame of inclusion. Restricting confounding was intended by correcting for age, gender and ISS. The short time period for recording the values of interested is due to their exclusive measurement on our interne intensive care units. Our insights ought to provide guidance for the treatment of polytrauma patients in reference to the analyzed parameters. In doing so, anticipation and timely measures shall be facilitated to maximize therapeutic effects while minimizing the risk for complications. Despite the advancements in polytrauma patient analysis using the

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Watson Trauma Pathway Explorer®, analysis and inclusion of further surrogative parameters is required to warrant a more precise prediction.

Conclusion

Between the two groups according to the development of sepsis, differences in pH existed within the first 4 hours, compared to BE within the first 6 hours. Lactate showed no initial differences between groups but differed from the second hour onwards. Binary logistic regression identified pH (< 7.35) and lactate (> 4 mmol/l) at 4 h as well as BE at 6 h (< - 2 mmol/L; p = 0.022) as independent predictors for sepsis. Threshold values for pH between groups were acidic for the first two hours after admission before reaching the lower limit of the normal range. For BE, threshold values initially revolved around – 4 mmol/L in the first 4 hours before reaching the lower limit of the normal range at around 6 hours. Our insights ought to provide guidance for the treatment of polytrauma patients in reference to the analyzed parameters. In doing so, anticipation and timely measures shall be facilitated to maximize therapeutic effects while minimizing the risk for complications. Despite the advancements in polytrauma patient analysis using the Watson Trauma Pathway Explorer®, analysis and inclusion of further surrogative parameters is required to warrant a more precise prediction.

Comment: Watson Trauma Pathway Explorer © by Ladislav Mica and IBM®.

Author contributions

P.V.: Data curation, Formal analysis, Investigation, Software, Visualization, Writing – original draft.

J.H.: Data curation, Project administration, Software, Writing - review & editing.

C.N.: Data curation, Project administration, Software, Writing - review & editing.

H.-C.P: Data curation, Project administration, Software, Writing - review & editing.

L.M.: Conceptualization, Data curation, Investigation, Methodology, Project administration,

Resources, Supervision, Validation, Writing - review & editing.

Conflict of interest

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest, or nonfinancial interest in the subject matter or materials discussed in this paper. The authors declare no conflict of interest related to the submitted study.

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Citation: Philipp Vetter, Jan Hambrecht, Cédric Niggli, Hans-Christoph Pape, Ladislav Mica. The time-related role of early pH, base excess and lactate for the development in sepsis in polytrauma patients. An analysis using the IBM Watson Trauma Pathway Explorer. Journal of Surgery and Research. 6 (2023): 283-291.