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Use of temperature changes and pro-inflammatory biomarkers to diagnose bacterial infections in patients with severe cerebral trauma

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ORIGINAL ARTICLE

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Background: In patients undergoing neurosurgeries, inflammation and infection are strongly related; however, inflammation can be present without infection. Midregional proadrenomedullin (MR-proADM) is a relatively new sepsis biomarker that is rarely used clinically. Recently, the concept of DiffTemp was introduced, that is, a >1°C rise from individual normal temperature accompanied by malaise, as a more accurate definition of temperature assessed as fever. The aim of the present study was to examine the importance of C-reactive protein (CRP), white blood cells, procalcitonin, and MR-proADM levels and DiffTemp.
Methods: This prospective, comparative study had a quantitative approach. Forty-two patients, aged >18 years and presenting with severe cerebral trauma were included from a neurosurgical intensive care unit. The outcome variable was infection; group 0, no infection (n=11); group 1, suspected infection (n=15); and, group 2, confirmed infection (n=16). Group assignments were performed using biomarkers, medical records, bacterial cultures, and International Classification of Diseases-10, and by the clinical assessment of criteria for nosocomial infections by a neurosurgeon.
Results: On comparing groups 1 and 2, MR-proADM and DiffTemp were associated with a higher risk of confirmed infection (odds ratio, 5.41 and 17.14, respectively). Additionally, DiffTemp had a 90.9% specificity in patients with no infection and a 93.8% sensitivity in patients with confirmed infections. CRP and procalcitonin levels were not associated with an increased risk of confirmed infection.
Conclusion: Increased levels of MR-proADM were associated with a higher risk of confirmed infection. DiffTemp was associated with a higher risk of having a confirmed infection.

Keywords: Infection; Fever; DiffTemp; Trauma; Body temperature; Midregional proadrenomedullin

INTRODUCTION

Patients with severe cerebral trauma are susceptible and have a higher risk for developing infections that can be life threatening [1]. Moreover, in these patients, the length of stay (LOS) at the neurosurgical intensive care unit (NICU) and the duration between intensive care and rehabilitation are among the significant factors associated with unfavorable outcomes one year after injury [2]. A recently published multicenter study of complications after severe cerebral trauma showed that infection during the care peri-

od strongly affects the patient's condition in both the short and long terms (1 year after the injury), along with the LOS [1]. A significant clinical sign of suspected infection is increased body temperature that is assessed as fever. Approximately 70% of critically ill patients undergoing neurosurgeries develop fever, although 50% are reported to be due to non-infectious causes such as extreme physiological stress and the inhibition of thermogenesis [3]. Nevertheless, as infection is life threatening and it affects the LOS, it is of utmost importance to prevent, detect, and treat infections [1,2]. However, as tissue damage also triggers an inflammatory immune response, including increased body temperature, it might be a challenge to detect and treat ongoing infections. In the present study, we studied different factors and biomarkers, including C-reactive protein (CRP), white blood cells (WBCs), midregional proadrenomedullin (MR-proADM), and procalcitonin. These biomarkers are clinically used to help diagnose infections in patients with severe cerebral trauma.

Body temperature and the concept of Diff Temp

Elevated body temperature is related to adverse outcomes in critically ill patients, especially in those with severe cerebral trauma. It is associated with long stays in the NICU, increased intracranial pressure, unconsciousness, poor functional status, increased excitatory amino acid release and metabolic demands, and intracerebral edema [4]. The analysis of changes in temperature, rather than the absolute values, may facilitate in reducing the time to antimicrobial therapy [5]. A large cohort study of patients in the NICU concluded that, after controlling for severity of illness, diagnosis, age, and complications, elevated body temperature was independently associated with longer NICU and hospital LOS, a higher mortality rate, and worse outcomes. The study also concluded that it remains to be determined whether the control of elevated temperature can affect these relationships [6].

The prevailing paradigms of normal body temperature as 37°C and fever as > 38°C were established in the mid-19th century by the German physician Wunderlich [6]. Notably, the measurements were performed on patients who were ill, indicating that a large number of them may have been febrile and that axillary measurements were used, which gives only an estimate of peripheral temperature [6,7]. Since then, research has shown that body temperature varies between groups, that is, gender and age [6,8-10], as well as due to temperature gradients within the body [6,9,11-14]. In addition, since 1869, the technical design of thermometers has greatly improved, especially the technical accuracy [6]. This has been confirmed by Mackowiak and Worden [15], who showed that the thermometer used by Wunderlich measured 1.4°C to 2.2°C higher than modern digital devices.

However, as the normal body temperature shows individual variation, a more logical approach is that the same should hold true for the febrile range [16-18]. We tested this hypothesis in a large multicenter study by measuring ear temperatures in 2006 apparently healthy individuals aged [2,4], and 10 to 89 years, of whom 1,700 also claimed that their temperature was assessed as fever by themselves and their children. Interestingly, the results showed that individuals reported at least 1°C increases in body temperatures from the baseline when fever occurred. Based on these results, the concept of Diff Temp was founded, that is, at least a 1°C increase from normal temperature, together with malaise, as an alternative and more accurate definition of temperature assessed as fever [10].

Purpose/hypothesis

To study the importance of CRP, WBC, procalcitonin, and MR-pro-ADM levels and Diff Temp defined as an increase of > 1°C in individual body temperature for the early detection of ongoing infection in patients with severe cerebral trauma.

METHODS

Study design

The study had a prospective, comparative design with a quantitative approach.

Sample

The inclusion criteria were as follows: patients aged > 18 years who were referred to the NICU with severe cerebral trauma and had the lowest non-sedated reaction level scale (RLS) scores from 3 to 8 in the first 24 hours after injury.

Setting

The present study was conducted at an NICU consisting of 14 beds at a university hospital in middle Sweden that served over one million inhabitants. In March 2017, a pilot study was conducted over two weeks for feasibility. After adjusting the logistics for data collection, the study was conducted from October 2017 to April 2018. The patient, or his/her next of kin, was informed in writing and orally at admission to the NICU by the attending (RN).

The research RN at the NICU was responsible for performance and follow-up, together with the project leader (MSL). Patients aged 18 years and above with acute cerebral trauma admitted to the NICU were included. The patients were followed up multiple times daily during their stay. Based on a power of 0.80 and $P < 0.05$, the required sample size was calculated as 21 patients (7

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patients per group). However, a total of 42 patients were included, with no dropouts. Data on age, sex, and cerebral trauma diagnosis were obtained from patient medical records. Observations of vital parameters, that is, RLS score, intracranial pressure, blood pressure, pulse, breathing, pain estimation, drugs, cultures, and treatments were recorded via patient records and monitoring protocols. After the end of the care period, the course of the illness was compiled through a review of the patient's journal.

Outcome

The study outcome was infection. After the study was performed, the main author (AT), the responsible neurosurgeon (MN), and the project leader (MSL) retrospectively reviewed the medical records for biomarkers, clinical signs and symptoms, vital parameters, intracranial pressure, International Classification of Diseases-10, and criteria for nosocomial infection. Assessments of no infection, suspected infection, and confirmed infection were then performed by the responsible neurosurgeon (MN). Most patients were administered a single dose of prophylactic antibiotics during the surgery [19,20].

Group 0: no infection (n = 11); this group consisted of patients who did not have any clinical symptoms of infection or abnormal blood levels of CRP, WBC, procalcitonin, and MR-proADM and abnormal radiographs. Group 1: suspected infection (n = 15); this group consisted of patients who had clinical symptoms of infection, such as increased oxygen demand, and/or abnormal blood levels of CRP, WBC, procalcitonin and MR-proADM, and/or abnormal radiographs. All the patients in this group had negative blood, sputum, and urine cultures and no visual signs of postoperative wound infection (swelling, redness, tenderness, and pus). Group 2: confirmed infection (n = 16); this group consisted of patients with abnormal blood levels of CRP, WBC, procalcitonin, or MR-proADM and/or abnormal radiographs and/or clinical symptoms, such as increased oxygen demand. All the patients included in this group had positive blood, sputum, or urine culture and/or visual signs of postoperative wound infection (swelling, redness, tenderness, and pus).

The average care time at the NICU where the study was performed was 3.5 days, which is comparable to other NICUs in the country. A total of 919 medical care events occurred between 2018 and 2020. While 131 medical care events having durations from 11 to 30 days had an occupancy of 42% in the NICU, 374 medical care events having durations from 1–3 days had an occupancy of only 16%. This shows how LOS is the most important factor in hospital occupancy (Fig. 1). Table 1 gives an overview of the infection diagnoses of the included patients in groups 1 and 2.

Confounders

All the 42 patients were treated according to the NICU clinical routine without any intervention, which means that patients were administered intravenous doses of paracetamol (4,000 mg daily). Paracetamol is known to decrease the body temperature by 0.4°C [21], with an induction time of 30–60 minutes and a half-life of 1.9–2.5 hours [22]. The patients were administered 1,000 mg paracetamol four times a day, at 6 AM, 12 AM, 6 PM, and 12 PM. As paracetamol and diurnal variation are considered as confounders, the measurement point for the analysis of body temperature was decided as 6 AM to minimize the risk of its effect on body temperature. As no significant difference was found between the body temperatures measured in the right and left ears, the mea-

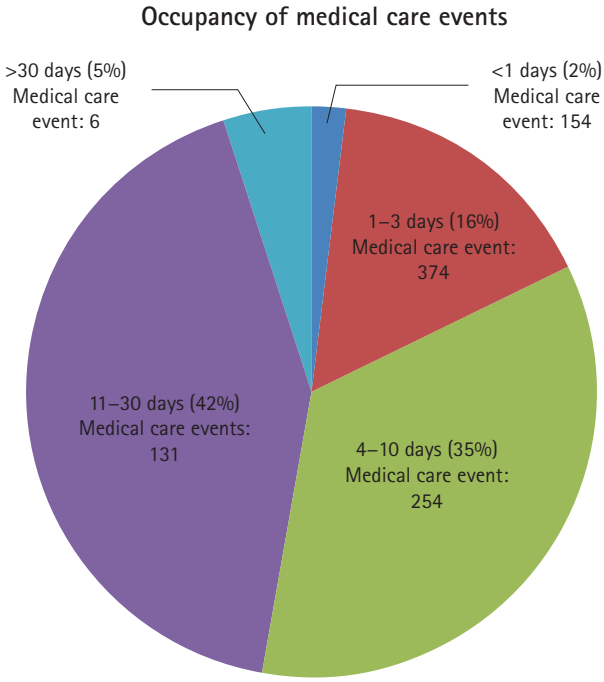

Fig. 1. The average care time at the neurosurgical intensive care unit where the study was performed.

Table 1. Descriptive statistics of diagnoses across categories of infection

Variable	Suspected Infection (n=15)	Confirmed infection (n=16)
Pneumonia	7	15
Meningitis	5	3
Urosepsis	0	2
Central venous catheter infection	0	1
Unclear	5	0

Patients in the same group can have two simultaneous diagnoses.

surement from the right ear at 6 AM was used in the statistical analysis [23].

Measurements

Biochemical and inflammatory markers

To monitor biochemical markers and the inflammation status, daily blood samples were taken for the analysis of high-sensitivity CRP (hs-CRP), WBC, procalcitonin, and MR-pro-ADM levels at 5 AM in conjunction with regular sampling. The time is described in days. Time 1 refers to day one of admission to the NICU. This means that one value of each biomarker was analyzed each day during the NICU stay. The body temperature measured at 6 AM was analyzed, which means one value of body temperature was analyzed each day during the NICU stay. The samples were drawn at this specific time to avoid other confounding factors, such as medications and operations, as much as possible. All the samples, except that taken for the MR-proADM analysis, were analyzed within 24 hours at the Diagnostic Center, Östergötland County Council. The samples for MR-proADM were stored in Biobank 935 before analysis. hs-CRP levels were analyzed using the immuno-turbidimetric analysis (Roche Diagnostics, Basel, Switzerland); WBC levels, automated analysis system (Cell-Dyn Sapphire; Abbott Scandinavia AB, Stockholm, Sweden); procalcitonin levels, luminescence (Roche Diagnostics, Basel, Switzerland); and, MR-pro-ADM levels, time-resolved amplified cryptate emission (Brahms, Hennigsdorf, Germany).

Body temperature

Using ear measurements is a routine method for assessing body temperature in the NICU. Special thermometers were provided by the research team for this study. Body temperature measurements were performed using infrared technology in both the ears (Genius 2; Medtronic, Boston, MA, US). Body temperatures were measured simultaneously from the right and the left ears every 4 hours between 6 AM and 12 PM, and when required in conjunction with a changed condition, throughout the care period. In the present study, DiffTemp was used to compare the individual morning body temperatures (6 AM) from one day to the next. All the thermometers were calibrated and set to measure the actual temperature without predetermined additions for adjustments to another measurement site (Medtronic). With respect to circadian rhythm and the intravenous administration of paracetamol, temperature measurements at 6 AM were chosen for estimating DiffTemp.

Statistical analysis

Data were inserted into IBM SPSS ver. 27 (IBM Corp., Armonk, NY, USA) for analysis. The outcome variable was a record of infection in the patient record [23]. Data were analyzed using descriptive statistics, Shapiro-Wilk tests to determine normality, and Spearman correlation to determine the correlation between variables. Differences between groups were analyzed using the Kruskal-Wallis one-way analysis of variance (ANOVA) or one-way ANOVA. Multinomial logistic regression was performed to calculate DiffTemp. Multinomial logistic regression with a goodness-of-fit test was performed to compare it to the traditional assessment of fever (> 38°C). The differences between the infection groups were then compared. A mixed-effects logistic regression analysis was used to analyze the parameters related to an increased risk of confirmed infection. Sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) for DiffTemp were analyzed using Crosstabs. Statistical significance was set at $P < 0.05$ [19,20].

A Shapiro-Wilk test was used to determine whether levels of MR-proADM, CRP, WBC, and procalcitonin and body temperature (ear) were normally distributed, and Spearman correlation coefficients were calculated to estimate correlations between variables included in the regression analysis. Of the included variables, only body temperature was normally distributed. WBC, CRP, MR-proADM, and procalcitonin levels were non-normally distributed, irrespective of the category of infection (no infection, suspected infection, confirmed infection). A significant weak uphill linear correlation was found between the levels of procalcitonin and CRP (spearman's rho = 0.346, $P = 0.000$), between MR-proADM and CRP (spearman's rho = 0.244, $P = 0.000$), and procalcitonin and MR- proADM (spearman's rho = 0.262, $P = 0.000$).

RESULTS

The study included 42 patients, all of whom were acutely admitted to the NICU. Men and women had mean NICU stays of 15 days and 12 days, respectively. Of the 42 patients, 27 were ≥ 60 years old and 15 were < 60 years old; and, 48% of the patients were aged ≥ 60 years and 20% of patients aged < 60 years had confirmed infections during hospital care. Table 2 and Fig. 2 provide an overview of the distribution of included biomarkers and body temperature across the categories of infection.

Pro-inflammatory biomarkers and body temperature

Table 3 provides an overview of the statistical differences in biomarkers and body temperature between the different groups. On

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Table 2. Descriptive statistics of variables across categories of infection

Variable	Total	No Infection (n=11)	Suspected Infection (n=15)	Confirmed infection (n=16)
Age (yr)	62±14 (20–88)	62±10	61±17	65±14
NICU stay (day)	14±9 (2–43)	10±10	14±10	17±8
Sex (male:female)	26:16	3:8	11:4	12:4
hs-CRP (mg/L)	73.11±75.72	41.90±54.02	82.25±81.54	74.09±73.80
WBC ($\times 10^9$/L)	12.56±5.94	10.99±3.02	11.22±3.41	14.10±7.60
Procalcitonin (μg/L)	0.55±2.79	0.39±0.50	0.28±0.34	0.83±4.01
MR-ProADM (nmol/L)	1.10±0.64	1.23±1.34[a]	0.99±0.33	1.16±0.49
Body temperature (°C)	37.12±0.81	37.16±0.72	36.97±0.84	37.24±0.80

Values are presented as mean±standard deviation (range) or mean±standard deviation.
NICU, neurosurgical intensive care unit; hs-CRP, high-sensitivity C-reactive protein; WBC, white blood cell; MR-proADM, midregional proadrenomedullin.
[a]MR-proADM was high in this group due to an extreme outlier.

analyzing all the groups together, on the day of admission to the NICU, the mean baseline hs-CRP was 25 mg/L. On day 2, the levels increased more than two-fold to a mean of 68 mg/L, and it further doubled to 135 mg/L on day 4. The mean hs-CRP then steadily decreased from day 5, and continued to decrease over time. hs-CRP levels decreased to the same levels as those displayed on the first day of admission on day 19 during the NICU stay (Fig. 3).

Fig. 4 shows hs-CRP differences between the infection groups. All the three infection groups had the same hs-CRP peaks on day 4, although the hs-CRP peaks were higher in the suspected infection and confirmed infection groups than that in the no infection group. One patient in group 0 (no infection) underwent a re-operation, which explains the high hs-CRP levels in CRP 13 in the graph.

Mixed-effects logistic regression

On comparing the groups with suspected and confirmed infections, WBC and MR-proADM levels and body temperature were related to the increased risk for confirmed infection, whereas CRP and procalcitonin levels were not. The WBC level had a 1.09% risk of confirmed infection ($P=0.002$; odds ratio (OR), 1.09; 95% confidence interval [CI], 1.036–1.166), and MR-proADM had a 5.41 risk of confirmed infection ($P=0.000$; OR, 5.41; 95% CI, 2.20–13.28).

Multinomial logistic regression of traditional assessment of body temperature vs. DiffTemp when comparing infection groups Traditional assessment of body temperature, that is, fever assessed as body temperature >38°C, did not show a significant risk relation with a higher risk of having a confirmed infection. DiffTemp, however, was associated with a 150% higher risk of having a confirmed infection ($P=0.001$; OR, 150.00; 95% CI, 8.378–2,685.505) as compared to no infection. DiffTemp was also related to a 17.14% higher risk of having a confirmed infection ($P=0.014$; OR, 17.14; 95% CI, 1.78–164.97) as compared to suspected infection. A goodness-of-fit test showed that the model fits the data well.

Fig. 5 shows that only one patient out of 10 in group 0 (no infection) had an increase of body temperature >1°C. In group 1 (suspected infection), 8 out of 15 patients had no increase, whereas 7 patients had increases of >1°C in body temperature. In group 2 (confirmed infection), 15 out of 16 patients had increases of >1°C in temperature. DiffTemp had a 90.9% specificity for classifying no infection, and a 93.8% sensitivity for classifying confirmed infection. The DiffTemp specificity in patients with suspected infection was 53.3%, and the sensitivity was 46.7%. DiffTemp had an NPV of 52.6% for no infection and 42.1% for suspected infection, and a PPV of 65.2% for confirmed infection and 30.4% for suspected infection.

DISCUSSION

CRP is one of the most frequently used biomarkers for diagnosing an infectious process. Normal levels of CRP are defined as <10 mg/L, and <5 mg/L using a highly sensitive technique. The secretion of CRP begins within 4–6 hours of the stimulus. Elevations in serum CRP are most prominent in systemic infections caused by Gram-negative and Gram-positive bacterial infections. Chronic inflammation, surgery, trauma, burns, and other conditions can alter CRP concentrations. It is almost always supplemented by other blood tests and/or physical examination [24]. The CRP results from our study are in concordance with the results of other studies [25,26]. The CRP curve in Fig. 3 represents the CRP levels from the first day of admission. The peak on day 4 was homogenous for almost all the patients across the categories of infection, although the group without infection had a lower peak. The peak is probably explained by surgery since all the patients underwent surgeries within 2 days of admission to the

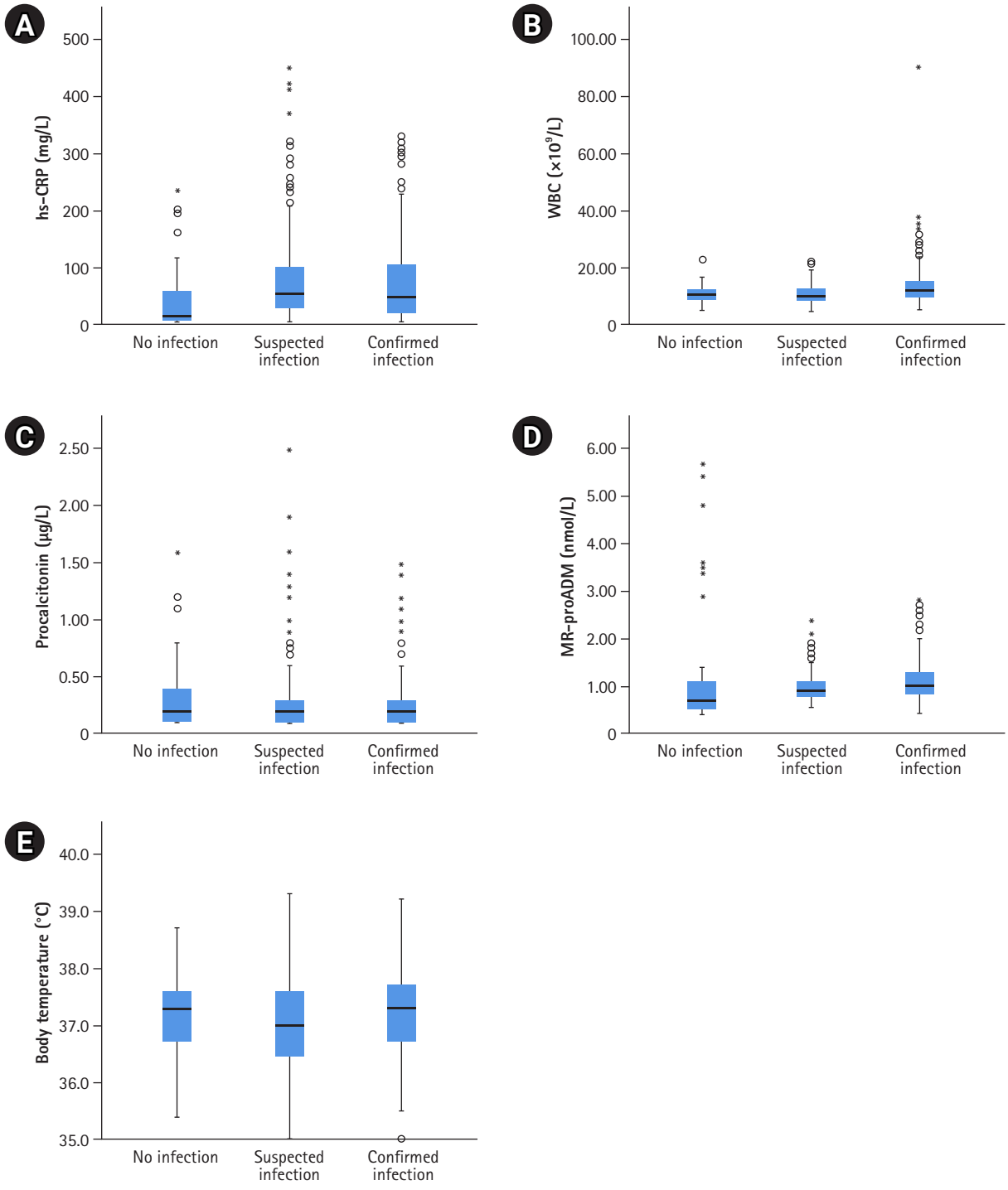

Fig. 2. Boxplots of (A) high-sensitivity C-reactive protein (hs-CRP), (B) white blood cell (WBC), (C) procalcitonin, (D) midregional proadrenomedullin (MR-proADM) levels, and (E) body temperature by infection group. The boxes represent the interquartile ranges (25th to 75th percentiles), the thick black line in the box is the 50th percentile (median), and the bars represent the range of results, excluding outliers. Circles are "outliers" and asterisks are "extreme outliers." No infection, n=11; suspected infection, n=15; confirmed infection, n=16. Two patients were excluded from Fig. 2C (group 2) due to extreme outliers affecting the readability of the figure. Analyzed using the independent-samples Kruskal-Wallis test.

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Table 3. Statistical differences between the groups

Variable	No infection vs. suspected infection (*P*-value)	No infection vs. confirmed infection (*P*-value)	Suspected infection vs. confirmed infection (*P*-value)
hs-CRP	<0.001	<0.001	0.180
WBC	0.890	<0.001	<0.001
Procalcitonin	0.209	0.769	0.218
MR-proADM	0.003	<0.001	0.008
Body temperature	0.185	0.587	0.009

hs-CRP, high-sensitivity C-reactive protein; WBC, white blood cell; MR-proADM, midregional proadrenomedullin.

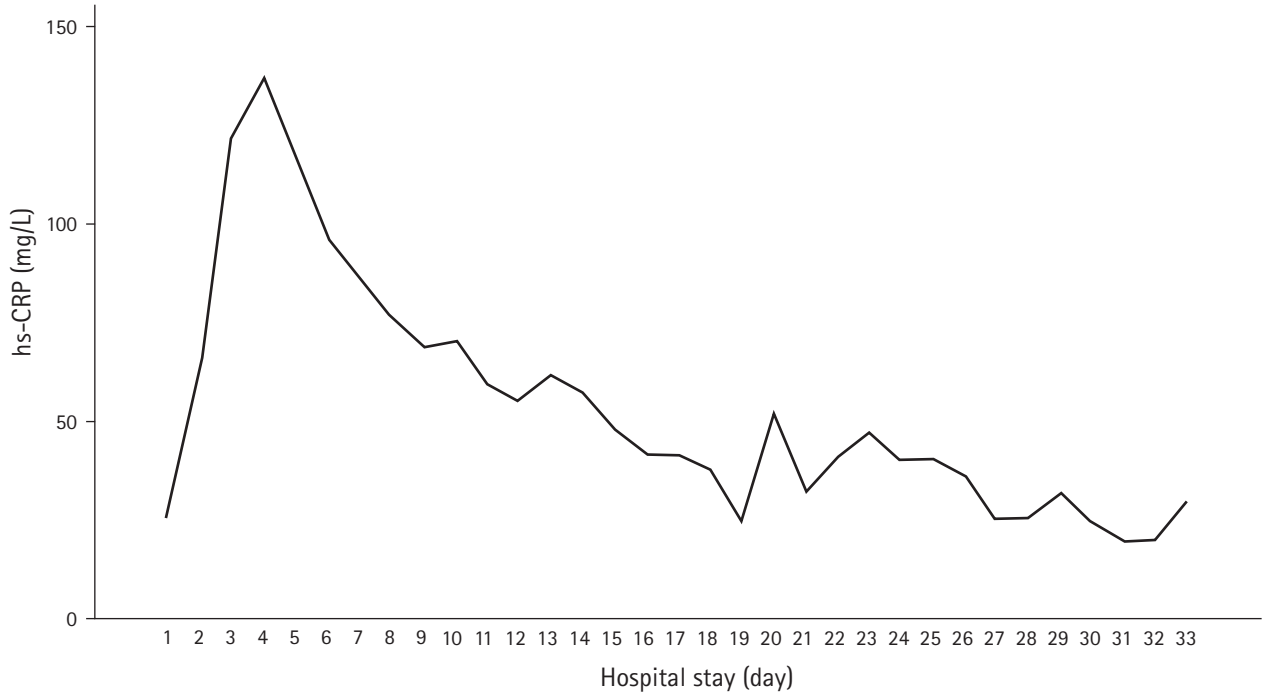

Fig. 3. High-sensitivity C-reactive protein (hs-CRP) levels displayed over time during hospital stay in 42 patients in the neurosurgical intensive care unit.

NICU. Another reason could be cerebral trauma, which causes inflammation and, therefore, elevated CRP levels. In addition, CRP levels started to decrease after day 5, regardless of antibiotic use or other treatments for bacterial infection, which indicates that the increased levels solely depended on surgery and cerebral trauma and not on an infectious agent. Surgery and cerebral trauma are therefore confounders for CRP levels [26,27]. This explains why a postoperative increase in CRP levels was not assessed as a sign of suspected infection by the responsible neurosurgeon in the study.

Normal variations in WBC are defined as 3.5 to 8.8 $\times 10^9$/L for individuals above the age of 16 years. Elevated WBC levels are common in bacterial infections. The WBC levels can double within hours after a stimulus, for example, a pathogen. When comparing the groups with suspected and confirmed infections, the WBC count was associated with a small risk for confirmed infection. A study by Riley and Rupert found that the WBC count is a suggestive but not a definitive marker for the presence of significant infection [28].

Procalcitonin is a precursor of calcitonin. Procalcitonin levels are low in healthy humans (< 0.05 μg/L). The levels of procalcitonin start to increase in 4–12 hours in case of systemic infection. Procalcitonin has also been identified as a prognostic factor in sepsis [29], and it has recently become the gold standard for identifying sepsis and confirming infection [30,31]. According to Sudhir et al. [32] procalcitonin proved to be an excellent indicator of sepsis with a sensitivity of 94%. Another study by Jekarl et al. [33] concluded that procalcitonin could support and predict the unfavorable prognosis of sepsis based on third international consensus definitions for sepsis and septic shock, whereas the diag-

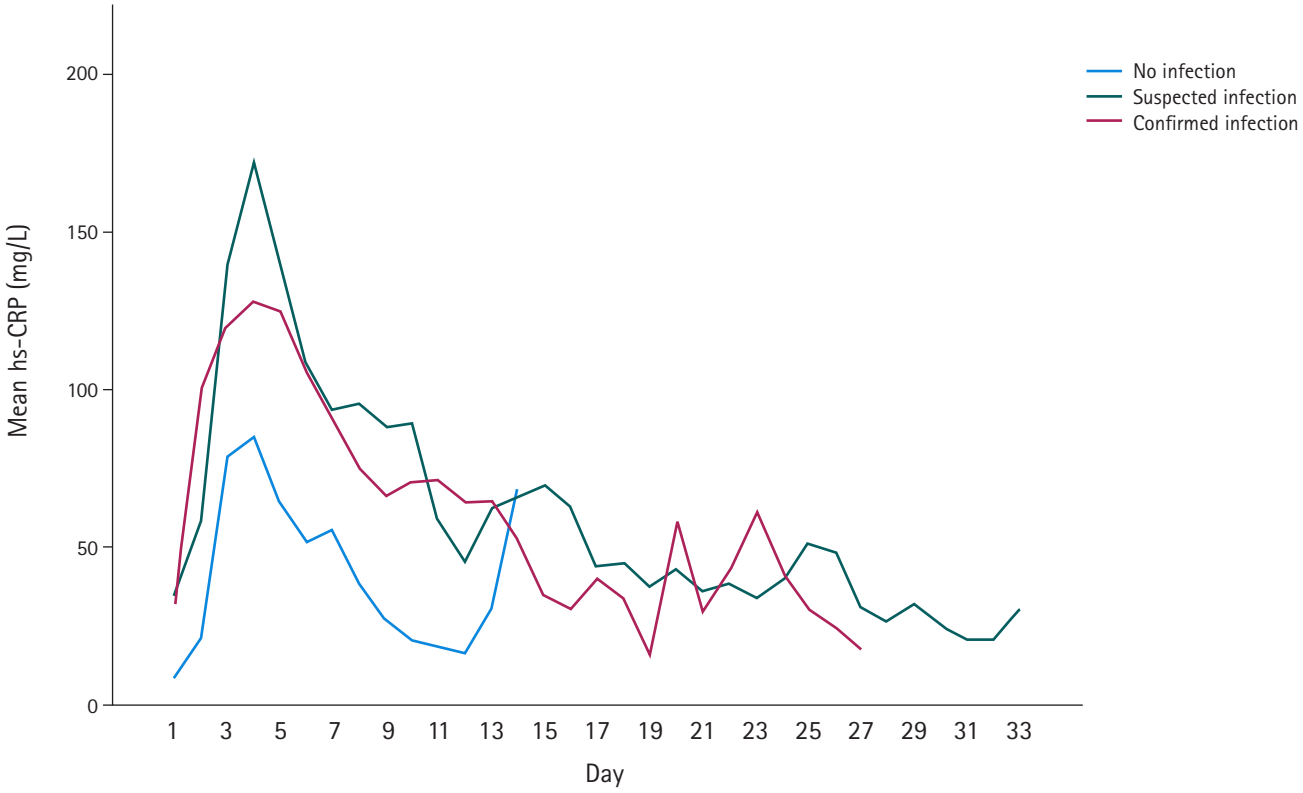

Fig. 4. Mean high-sensitivity C-reactive protein (hs-CRP) levels over time across the categories of infection. No infection, n=11; suspected infection, n=15; confirmed infection, n=16.

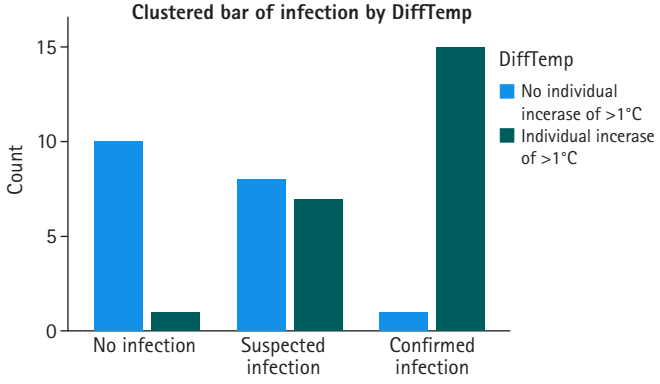

Fig. 5. Bar graph of the different infection groups that were organized by temperature change (defined by DiffTemp, i.e., having or not having an individual increase of >1°C) during hospital stay.

nostic potential of procalcitonin requires further evaluation. Taylor et al. [34] concluded that sepsis could be reduced using procalcitonin administration. In our present study, however, increased procalcitonin levels indicated no increased risk for infection. A study in patients with traumatic brain injury (TBI) in the NICU concluded that procalcitonin was useful for mortality prediction, but not for sepsis prediction [35]. A study by Oconnor et al. [36], which had similar settings, concluded that procalcitonin appeared to correlate with the severity of TBI and mortality. Additionally, Oconnor et al. [36] concluded that procalcitonin could not distinguish between systemic inflammatory response syndrome (SIRS) and sepsis because procalcitonin elevation correlated with the severity of injury. Sinaga et al. [37] found that procalcitonin levels are predictors of SIRS. Hence, TBI and SIRS could be confounders for procalcitonin levels, which are probable reasons for the results obtained for procalcitonin in our present study.

MR-proADM is a precursor of adrenomedullin. Adrenomedullin is acts as both a cytokine and a hormone [38]. It is suggested that it has multiple physiological functions, including being directly bactericidal [39]. Adrenomedullin also has diuretic effects, and it works as an immune-modulator and a potent vasodilator. Elevated levels of interleukin-1β and tumor necrosis factor stimulate the production of adrenomedullin [39]. MR-proADM is a marker used to diagnose and evaluate the prognosis of sepsis [40]. In the present study, we found that MR-proADM was related with a significantly increased risk for having a confirmed infection. In 2018, Önal et al. [40] identified MR-proADM as a prognostic marker that stratified the mortality risk in patients with sepsis. Önal et al. [40] also concluded that it may be helpful in the early identification and individual risk assessment of sepsis, and it may also facili-

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tate the subsequent clinical management of sepsis and septic shock.

The main and interesting findings in the present study are the promising results of using DiffTemp and MR-proADM in clinical practice. The results suggest that using MR-proADM in combination with DiffTemp could clinically help in detecting ongoing infection in patients with cerebral trauma early on and differentiate between possible and confirmed infections. This would not only help in early diagnosis and treatment, but it could also potentially help decrease the LOS and thereby reduce the financial burden. In our results, we found that the traditional assessment of body temperature with a cutoff value set to 38°C was not associated with a significant risk of having a confirmed infection on analyzing and comparing groups with suspected and confirmed infection. Using the new definition, DiffTemp showed a 17.14% higher risk of having a confirmed infection on analyzing the same two groups. This could further reinforce the hypothesis that DiffTemp is superior to traditional fever assessment. Furthermore, DiffTemp had a 90.9% specificity in patients with no infection and 93.8% sensitivity in patients with confirmed infection. Thus, DiffTemp can potentially be used to confirm infection in patients with other symptoms and/or abnormal biomarkers. It can also potentially be used to rule out infection in patients with no other symptoms and/or abnormal biomarkers. The detection of infection early on using DiffTemp could lead to decreased LOS, hospital occupancy, and complication rate from infections. Since DiffTemp is a new term, there are no previous studies with similar settings for comparison. Nevertheless, another study of patients in the NICU concluded that elevated body temperature independently contributes to the increased LOS [6], which supports our results since patients with confirmed infection had the longest LOS and 15 of 16 patients with confirmed infection had increased body temperatures according to DiffTemp.

The longest LOS across all the infection categories was found in patients with confirmed infection, followed by that of patients with suspected infections, whereas patients with no infection had the shortest LOS. It is well known that a longer LOS is associated with a higher risk of developing a nosocomial infection [41]. In the present study, we were unable to confirm whether these patients developed a nosocomial infection because of a longer LOS or if they had a longer LOS because they developed a post-surgical or nosocomial infection.

A previous study from an acute care hospital showed a correlation between higher age and nosocomial infections, and it concluded that daily infection rates were 59% in patients aged >60 years and 40% in younger patients [42]. In our present study, we found a lower infection rate, especially in younger subjects: patients aged >60 years had a 48% rate of infection (13/27), whereas patients below the age of 60 had a 20% rate (3/15). The rate difference between our study and the previous study may be due to differences in settings. The previously mentioned study included patients admitted to an acute care hospital, and our current study included patients with severe cerebral trauma admitted to the NICU. The difference could also be due to the small sample size in the present study. Taken together, the results suggest that MR-proADM and the assessment of temperature in fever as DiffTemp would enhance recovery and reduce LOS after severe brain injury by detecting ongoing infection early on. However, randomized placebo-controlled trials are needed to confirm this.

Limitations of the study

The sample size was small, and our 42 patients and the infection groups were not equally distributed. To draw more conclusions, a larger study should be conducted. In addition, hospital stays varied widely between and within the groups of patients. However, patients were followed up during the entire hospital stay, and the number of repeated measurements over time was large in all the patients, which increased the amount of analyzed data.

In the present study, we used bacterial cultures. Patients with negative bacterial cultures but positive clinical signs and biomarkers were included in the suspected infection group. This means that some patients in this group had an inflammatory process, whereas others had an infectious process that could not be objectively identified. However, MR-proADM and DiffTemp showed promising results in distinguishing patients with suspected infection from those with confirmed infection. An advantage of the present study is that it mirrors the current clinical difficulty in confirming infectious processes and presents new methods for the guidance and investigation of infection.

Conclusion

DiffTemp and MR-proADM were associated with an increased risk of infection in patients with severe cerebral trauma, whereas CRP and procalcitonin did not show any significantly increased risks of infection. DiffTemp is a new concept for assessing fever, which we found to be superior to the traditional predetermined fever temperature assessment (>38°C), but further studies are needed.

ARTICLE INFORMATION

Ethics statement

Ethical approval was granted by the Ethics Committee of the Fac-

ulty of Health Sciences, Linköping University, Sweden (2016 / 159-31). Informed consent was obtained for the handling of sensitive personal data and storage of samples in the biobank facility.

Conflict of interest

No potential conflict of interest relevant to this article.

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Conceptualization: EG, MSL, MN. Data curation: EG, MSL, MN. Formal analysis: AT, EG, MSL, NK. Funding acquisition: MSL. Methodology: NK. Project administration: MSL. Visualization: AT. Writing–original draft: AT, EG, MSL. Writing–review & editing: AT, EG, MSL, MN, NK.

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