Journal of Critical Care 52 (2019) 149–155

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.journals.elsevier.com/journal-of-critical-care

Evaluation of MR-proANP and copeptin for sepsis diagnosis after burn injury

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ARTICLE INFO

Keywords:
Burn injury
Sepsis
MR-proANP
Copeptin
PCT

ABSTRACT

Purpose: The significance of the validated biomarkers of sepsis Mid-regional pro-atrial natriuretic peptide (MR-proANP) and copeptin have not been tested in a burn injury setting.
Materials and methods: 42 consecutive patients were included in a prospective observational study. Daily blood specimens collected over the initial 20 days of treatment were quantitatively analysed by immunoluminometric sandwich assay (Kryptor, BRAHMS, Berlin, Germany) for MR-proANP, copeptin and procalcitonin (PCT).
Results: In patients with absence of sepsis, copeptin levels initially increased post-burn injury and thereafter rapidly declined. In contrast, MR-proANP was only slightly elevated within the first few days. MR-proANP [199.8 (115.6; 399.5) vs 160.1 (93.7; 280.6), $P < .007$] and PCT [1.12 (0.32; 2.22) vs 0.32 (0.16; 0.53), $P < .001$] levels were significantly higher on days of sepsis. Copeptin, however, showed no significant differences [20.7 (11.8; 42.2) vs 16.8 (11.0; 30.6), $P = .11$]. Both, MR-proANP and PCT level increases were noted upon the first day of sepsis.
Conclusion: Burn injury itself maybe associated with copeptin and to a lesser degree MR-proANP level increases. Subsequent increases in MR-proANP may be considered diagnostic for sepsis but demonstrated no advantages over PCT. The role of copeptin remains inappropriate for diagnosing sepsis after burn injury (ClinicalTrials.gov number, NCT01055587).

1. Introduction

The burden of septic multiorgan failure continues to challenge the management of severe burn injuries in the intensive care setting [1]. Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to an infection [2]. Severe burn injury itself leads to complex immunologic changes that result in a systemic inflammatory response syndrome the clinical picture of which resembles a systemic infection [3,4]. Coexisting organ dysfunctions may be related to severe trauma, and whether the burn injury itself or sepsis is the trigger is hard to differentiate. The Systemic Inflammatory Response Syndrome (SIRS) criteria for the diagnosis of sepsis have been used until recently but have long been considered unsuitable for burn victims [5]. In 2007, the American Burn Association (ABA) proposed alternative criteria for the definition of sepsis [5]. However, only a weak correlation was found between the ABA criteria and sepsis in burned patients [6,7]. The new sepsis-3 definition [2] has not yet been validated sufficiently in burn patients. In a recent study comparing Sepsis-3 criteria, ABA and modified ABA criteria, the Sepsis-3 was the most predictive. However, no criterion alone had the accuracy to be an ideal diagnostic standard. The authors recommended, that sepsis is clinically assessed, diagnosed, and documented prospectively by the burn team, and not by the application of retrospective criteria [8]. Remarkably, no or only a small number of burn injuries were included when the sepsis-3 definition was developed [9].

Traditional indicators of infection, such as body temperature, white blood cell count (WBC), and C-reactive protein levels, have been found to be unspecific for the diagnosis of sepsis [10-13]. Procalcitonin (PCT) has been widely used for sepsis diagnosis in critical patients in the last two decades. PCT is a 116-amino acid precursor of calcitonin, the physiological synthesis of which is of thyroid C or neuroendrocrine cells of pulmonary and intestinal origin. Presence of microbial toxins, necrotic body cells, and some proinflammatory cytokines (IL-1, IL-6, TNF-α, etc.) increase the expression of the PCT-producing CALC-1 gene in multiple ectopic tissues, including monocytes and adipocytes [14,15]. Elevated values become measurable 2–4 h after onset of the infectious process, peaking at 24–30 h, and rapidly subsiding with recovery [16]. Despite some older studies questioning its usefulness for the early diagnosis of sepsis in burn patients, two recent meta-analyses

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https://doi.org/10.1016/j.jcrc.2019.04.031
0883-9441/

[17,18] suggested that PCT may well be applied for this purpose. These differing views illustrate the continuing controversy in accepting PCT as the ideal marker of sepsis in the burns population [19,20]. Few clinical studies have evaluated other biomarkers, such as IL6, IL10, IL1, IL8, monocytic human leukocyte antigen DR (mHLA-DR), TNFα and Toll-like receptor-9 (TLR-9). The available data do not permit a statement about diagnostic value in burn patients [20]. Hence, overall, there is currently a continued demand for novel predictive biomarkers of sepsis in burns.

Atrial natriuretic peptide (ANP), thus named due to a prodominant cardiogenic origin, counteracts the effects of the renin–angiotensin–aldosterone system at the level of renal tubule sodium reabsorption, cell growth and vascular tone. Its physiological effects include a decrease in blood pressure and diuretic and natriuretic properties. The hormonal effects are exerted on circulatory system barohomeostasis and endothelial permeability [21,22]. Polymorphonuclear neutrophil and macrophage mediated innate and acquired immunological responses are also modulated by ANP [23,24]. It has been shown to regulate transcription factors, mainly including NF-κB [25]. Prohormone (pro-ANP) is the precursor of mature ANP that represents the carboxyl-terminal amino acids 99–126 [26]. MR-proANP is the amino terminal of the prohormone (also termed NT-pro-ANP or pro-ANP1–98) and as a consequence secreted in equal measure as the mature ANP derivative. Nevertheless the half life of MR-proANP is significantly longer, lending this quality as a more reliable molecule for analysis [27]. MR-proANP has been shown to be stable for up to 24 h at 20 °C in whole blood [28]. Some studies indicate that an increase in ANP or proANP occurs in septic patients [29-31]. In addition, the extent of this increase has been correlated with the severity of the disease [30,31] and a worse prognosis [21,22,29,30,32].

Copeptin (CT-proAVP), a 39-amino acid-long glycosylated peptide, is the C-terminal part of the arginine vasopressin (AVP) precursor. Thus, synthesized in the hypothalamus in an equimolar ratio as AVP [33]. The physiological function of AVP is to promote renal water retention, thereby contributing to osmotic and cardiovascular homeostasis [34]. Conversely to mature AVP, the copeptin assay is extremely stable in plasma or serum ex vivo. The ex vivo stability (<20% loss of recovery) was reported to be 7 days at room temperature increasing to 14 days at 4 °C [34]. Vasopressin (AVP) is recognized as a major hypothalamic stress hormone, as a consequence its co-metabolite copeptin has been considered as a marker of non-specific stress responses [35,36]. AVP can be stimulated by different stressors, e.g., cardiac arrest, shock and ischaemic stroke [37-39], but its role in sepsis is not yet clearly defined. While some studies have shown that copeptin is able to differentiate between septic and non-septic patients [40-42], other studies have not confirmed this relationship [38,43,44]. Furthermore, the extent of the increase seems to reflect the disease severity in septic patients [42,45,46] and was correlated with a poor prognosis [42,45,46].

No data is currently available regarding the diagnostic value of MR-proANP and copeptin in patients after burns. The aim of the present study was to investigate possible trauma-related changes and the diagnostic performance of MR-proANP and copeptin in sepsis after burn injury.

2. Material and methods

2.1. Subjects and study design

Ethics approval was acquired on August 28, 2009 from the Saxon State Chamber of Medicine (EK-BR-29/09–1). The prospective study included all patients with a burned total body surface area (TBSA) > 15% within a period of 15 months who were admitted within 24 h after burn injury to the intensive care unit (ICU) of a regional burn centre. Written informed consent was obtained from all participants. The following criteria led to the study exclusion: patient age < 18 years old, history of congestive heart disease (New York Heart Association score > 2), severe liver disease (> Child A), chronic renal failure [Glomerular filtration rate (GFR) category > G2 (Classification of Chronic Kidney Disease Based on GFR category)], coexisting polytrauma and immunosuppressive therapy. Patients considered for palliative care were also not included in the study.

2.2. Burn care protocol

Initial fluid infusion, calculated according to Parkland's formula at 4 mL/kgBW/% burned TBSA was thereafter titrated to maintain a urine output of 0.5 mL/kgBW/h. Unstable cardiovascular function triggered vasopressor support and/or 20% human albumin infusion. Serum albumin was maintained above 25.0 g/L. Administration of Human albumin was avoided within 8 h after injury. Enteral nutrition was commenced within 6 h of admission or at the earliest opportunity thereafter. Completion of burn wound excision and grafting was aimed within 72 h, whereby a maximum of 20% of the burned surface area would be excised at a single sitting. Thereafter operations were repeated every 2–3 days as required. Prophylactic antibiotics was not standard practice.

Suspected sepsis triggered a standardized diagnostic and therapeutic protocol. Vascular access lines were exchanged immediately and blood, urine and burn wound cultures were taken. Chest X-ray and a contemporary bronchoscopy with quantitative cultures of bronchoscopic bronchoalveolar lavage (BAL) specimens were also acquired. Piperacillin/tazobactam constituted empirical antibiotic therapy as standard until targeted antibiotic therapy was implemented upon receiving microbiological results. In cases of suspected wound-induced sepsis early surgical debridement was executed.

2.3. Sepsis criteria

Within our institution, suspicion of sepsis is based on clinical experience, including observation of the following: a deterioration in the patient's general medical state, elevation or drop in body temperature, increasing tachycardia and tachypnea, confusion, hemodynamic instability, increased fluid requirements and gastrointestinal dysfunction. These are evaluated in combination with coinciding alterations in blood glucose levels and/or increase in lactate and base deficit. Sepsis was defined if both firstly antibiotic therapy was started and secondly either the infection was microbiologically confirmed and/or antibiotic therapy led to improvement in the patient's clinical condition. Confirmation of microorganisms in blood cultures or BAL specimens (BAL with $\geq 10^4$ CFU / mL) was regarded as positive.

2.4. Biomarker measurement

Daily blood specimens were collected at admission and for a maximum of 20 days post burn or limited until patient ICU discharge or death. Fresh drawn blood was centrifuged at the bedside at 3000 rpm for 15 min and stored at −80 °C until assayed. In this way the attending physician was blinded to biomarker levels at the time of sampling. The MR-proANP and copeptin levels were determined by a specific 'sandwich' immunofluorescent assay (Kryptor, B.R.A.H.M.S., Berlin, Germany) in EDTA plasma. According to the manufacturer, a normal plasma level of MR-proANP is <46.1 pmol/L [47]. The median plasma copeptin level was reported to be 4.2 pmol/L in healthy volunteers [34].

2.5. Data collection

The recording of injury characteristics, demographic data and vital parameters was carried out using a patient data management system (ICU Data, IMESO, Gießen). Patients were assessed on admission using an Acute Physiology and Chronic Health Evaluation II (APACHE II) score and a Sequential Organ Failure Assessment (SOFA) score [48]. Daily SOFA scores were calculated during the study period. The SOFA score on day 1 was defined as that obtained at 0600 h on the day

following admission. Thereafter scores were recorded at 0600 h at 24-h intervals. All patients were allocated daily into two categories: 'non-septic' and 'septic'. Patients continued to be classified as 'septic' for four days following diagnosis of sepsis. Data analysis was executed up to the first sepsis event and included the following four treatment days. Subsequent sepsis episodes were disregarded. The rationale of this approach was to exclude any potential influence, and thus error, caused by biomarkers measured during the first sepsis episode on subsequent sepsis episodes.

To determine the natural course of biomarkers after burn injury, data collected before the first septic event were analysed. To exclude the potential interference of sepsis, data inclusion was ceased two days before the diagnosis of sepsis. Non-septic and septic day parameter comparisons were only investigated in patients who developed sepsis.

Relative changes of biomarkers that occurred within a 7-day period surrounding the septic event were analysed at the following points in time (T): the day of infection-2 (T-2), the day of infection-1 (T-1), the day of infection (Inf), the day of infection+1 (T + 1), the day of infection+2 (T + 2), the day of infection+3 (T + 3), and the day of infection+4 (T + 4).

2.6. Statistical analysis

The results are presented descriptively as medians (50th percentile) and interquartile ranges (i.e., the interval between the 25% and 75% quartiles). The data were analysed by Normal Q–Q plots and Shapiro–Wilk tests to test for normal distribution, with outcome an increased likelihood of null hypothesis rejection. Non-parametric Mann–Whitney *U* tests were applied to single univariate comparisons between groups and non-parametric Wilcoxon tests for comparisons between two time points. Box plots were used for graphical presentation. Fisher exact testing or the Spearman correlation coefficient were used where relationships were noted between categorical parameters. A correlation coefficient $r > 0.5$ was considered clinically relevant. The alpha level of the study was $P = .05$ with applied Holm correction of significance levels of individual parameter changes. The evaluation was performed using the R program for Windows version 3.01.

3. Results

3.1. Patients, injury characteristics and outcome parameters

The study included 42 patients. Median patient age was 53 years [34.25; 65.75], including 28 patients who were male (66.7%). Median burn injury was 28.75% TBSA [22; 35.5] with an abbreviated burn injury index (ABSI) of 8 [7; 9]. Inhalation injury afflicted 7 patients (16.7%).

During the observation period, sepsis was observed in 27 patients (64.3%). The median date of sepsis onset was day 6 [5; 8.5]. Five patients died (11.9%), three of these through sepsis related causes. Two other patients died further along the course of non-sepsis aetiology. Biometric data, injury characteristics and outcome parameters are summarized in Table 1.

The dominant cause of sepsis was the burn wound (19 patients), followed by pneumonia (6 patients) and abdominal infection (one patient). Additionally, there was one catheter-related blood stream infection. In 20 patients, a positive blood culture was obtained. In 6 patients, infection was confirmed by BAL specimens or via autopsy. In one patient, no evidence of bacteria was detected.

3.2. Natural course of biomarkers after burn injury

At admission, MR-proANP was slightly increased and remained stable at this level in the first days after trauma. Significant changes did not occur within the first 6 days (Fig. 1A). In contrast, copeptin was markedly increased on the day of admission. Subsequently, the levels of this marker decreased rapidly but remained above normal [base

Table 1
Patients, injury characteristics and outcome parameters.

$n = 42$	Median [IQR], n (%)
Burned TBSA (%)	28.75 [22; 35.5]
Full thickness burn (%)	23.5 [15; 29.75]
Inhalation injury	7 (16.7)
ABSI	8 [7; 9]
Baux score	79.5 [63; 97.75]
Age (y)	53 [34.25; 65.75]
Gender, male	28 (66.7)
SOFA at admission	2 [1; 3.75]
APACHE II on day 1	10.5 [8; 13.75]
Sepsis	27 (64.3)
Mechanical ventilation	20 (47.6)
CRRT	4 (9.5)
Days of hospital stay	31.5 [16.25; 47]
Mortality	5 (11.9)

TBSA = total body surface area, ABSI = abbreviated burn severity index, APACHE II = acute physiological and chronic health evaluation II, SOFA = sequential organ failure assessment, CRRT = continuous renal replacement therapy, IQR = interquartile range.

68.72 pmol/L (32.9; 155.5) vs t1 23 pmol/L (12.5; 41.2), $P < .001$ and t1 vs t2 13.6 pmol/L (25; 24.7), $P < .001$]. The first non-significant decrease was observed from day 2 to day 3 (Fig. 1B). PCT levels increased during the first days after injury, peaking on day 2 (on day of admission, 0.06 μg/L [0.04; 0.11]; on day 2, 0.22 μg/L [0.12; 1.79]. Subsequently, these levels decreased yet remained above normal (Fig. 1C).

On the day of the accident, no correlation between burned TBSA and the level of biomarkers was found (MR-proANP $r = 0.14$, $P = .4$; copeptin $r = 0.12$, $P = .45$; PCT: $r = 0.121$, $P = .457$). There was also no clinically relevant correlation between burned TBSA and peak biomarker levels over the clinical course (MR-proANP $r = 0.11$, $P = .51$; copeptin $r = 0.19$, $P = .23$; PCT: $r = 0.471$, $P = .002$).

Patients with and without inhalation injury showed no difference in the levels of biomarkers on the day of admission [MR-proANP 57.8 pmol/L (33.8; 84.7) vs 70.5 pmol/L (33.4; 182.3), $P = .34$; copeptin 59.9 pmol/L (46.8; 119.1) vs 82.3 pmol/L (53.1; 139.6), $P = .61$]; PCT: 0.05 μg/L [0.04; 0.15] vs. 0.05 μg/L [0.04; 0.11], $P = .315$).

3.3. Biomarkers for sepsis

In patients with sepsis, a total of 309 days were analysed; 125 non-septic and 184 septic days. For MR-proANP and PCT, significantly higher levels were measured on septic days compared to non-septic days. In contrast, copeptin levels were comparable between septic and non-septic days. This was also the case for WBC counts and maximum daily temperatures.

Septic days were associated with significantly higher SOFA scores (Table 2). Moreover, there was a correlation between SOFA scores and MR-proANP levels ($r = 0.55$, $P < .0001$), copeptin levels ($r = 0.58$, $P < .0001$) and PCT levels ($r = 0.661$, $P < .0001$). The SOFA-Score was not clinically correlated with WBC counts ($r = 0.32$, $P = .42$) and maximum temperature per day (Tmax, $r = 0.37$, $P < .001$).

During the time period surrounding the septic event (day −2 to day +4), there were differences in the profiles of MR-proANP and copeptin (Fig. 2A and B). MR-proANP increased significantly from day −1 to the day of infection [100.5 (84.4; 260.4) vs. 201.7 (91.7; 384.1), $P = .003$] and then remained at this elevated level until T + 4 after infection. Copeptin, however, showed no significant changes during the period around the infection. The first significant increase in PCT levels was observed between T-1 and Inf ($P = .021$), with the largest increase from Inf to T + 1. The peak PCT level was measured on T + 1 (1.57 μg/L [0.43; 3.4]) (Fig. 2C).

4. Discussion

To our knowledge, this is the first study to investigate the diagnostic value of MR-proANP and copeptin in septic burn patients. First, we

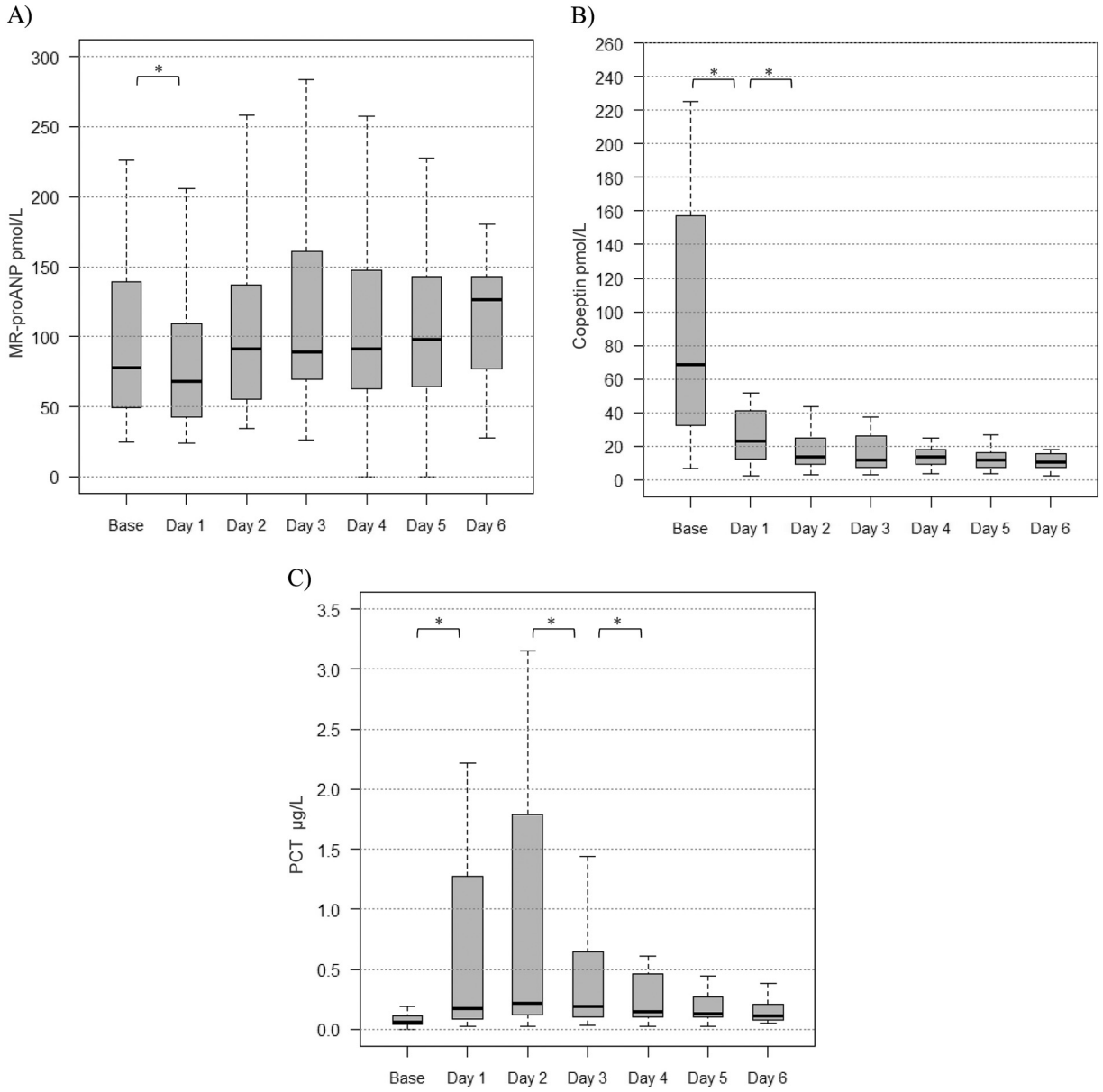

Fig. 1. Time course of MR-proANP (A), copeptin (B) und PCT (C) levels from the day of admission (baseline) to day 6 after burn injury. The symbols indicate a statistically significant difference compared to the previous day ($P < .05$).

analysed the natural course of these biomarkers after burn injury. While there was a burn-induced increase in both parameters, the increase in copeptin was more pronounced and decreased rapidly within the first day after burn injury. MR-proANP was only slightly elevated on admission day and subsequently remained stable at this level. The burned TBSA or the presence of inhalation trauma did not influence the extent of the increase. The maximum levels of biomarkers measured during the further course or the disease was not correlated with burned TBSA. Trauma-induced increases have been described for copeptin [33,49,50]. Our results suggest that burn shock appears to be a very strong stimulator of the copeptin response. The underlying mechanisms may involve typical pathophysiological alterations in burn shock characterized by complex cardiovascular dysfunction, hypovolaemia, the liberation of multiple proinflammatory mediators and reactive oxygen species [3,51,52]. Koch et al. [38] found a strong correlation between copeptin and both biomarkers of endothelial dysfunction and systemic regulators of vascular tone. Copeptin has a biological stress mediated release, in a similar manner to vasopressin (with which it shares the same precursor) and CRH-ACTH-cortisol hormones [38]. The dynamics of the concentration levels as noted above provide the interest and potential use of copetin and MR-pro-ANP as early markers of sepsis during the clinical course after restitution of burn shock.

Accordingly, in our study, we reveal that the levels of MRpro-ANP are significantly higher on days with sepsis than on non-sepsis days,

Table 2
Infection markers and SOFA scores on non-septic and septic days.

	Non-septic days, Median [IQR]	Septic days, Median [IQR]	*P*-value
MR-proANP (pmol/L)	160.1 [93.7; 280.6]	199.8 [115.6; 399.5]	<0.007
Copeptin (pmol/L)	16.8 [11.0; 30.6]	20.7 [11.8; 42.2]	0.11
PCT (µg/L)	0.32 [0.16; 0.53]	1.12 [0.32; 2.22]	<0.001
WBC (10^9/L)	11.75 (10.1; 14.4)	11.75 (10; 13.3)	0.99
Tmax (°C)	37.9 (37.7; 38.1)	37.7 (37.4; 38.2)	0.448
SOFA	3 (2; 4.25)	5 (2; 9.25)	< 0.001

MR-proANP = midregional pro-atrial natriuretic peptide, PCT = procalcitonin, WBC = white blood cell, Tmax = maximum temperature per day, SOFA = Sequential Organ Failure Assessment Score, IQR = interquartile range.

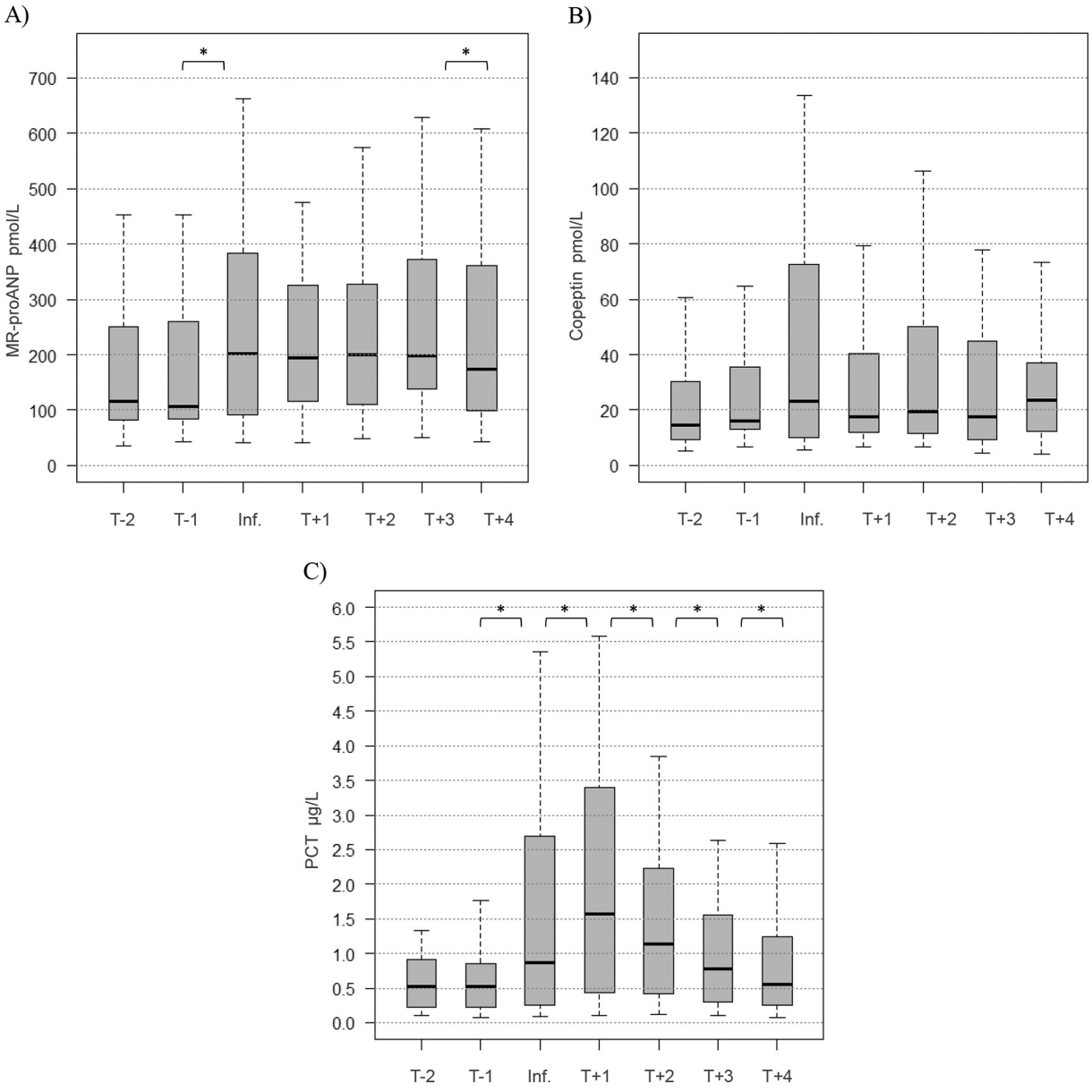

Fig. 2. Time course of MR-proAVP (A), copeptin (B) and PCT (C) levels during the time period immediately surrounding the occurrence of sepsis (Inf) from day 2 prior to infection (T-2) to day 4 after infection (T + 4). The symbols indicate statistically significant differences compared to the previous day ($P < .05$).

analogous to the findings for PCT. For copeptin, however, there was no difference between septic and non-septic days. In concordance to the literature [12,13], neither WBC counts nor temperature discriminated between sepsis and non-septic days. To better explore the dynamic changes that occur during episodes of sepsis, we investigated a 7-day period surrounding the beginning of sepsis (Fig. 2). MR-proANP levels increased significantly from day −1 to the day of infection and then remained at this elevated level until day 4 post-infection (Fig. 2A). In contrast, copeptin did not significantly change during this time period (Fig. 2B). In comparison, PCT significantly increased for the first time on the day of infection, and the median maximum level was measured on the 1st day after infection (Fig. 2C).

With regard for MR-proANP, our results agree with those presented in a prospective study on critically ill patients performed by Wang and colleagues. The median levels of proANP (ng/mL) on admission to the ICU were 87.22 in patients with SIRS, 1533.30 in those with sepsis, 1098.73 in those with severe sepsis, and 1933.94 in those with septic shock. As the severity of the disease increased, the level of proANP gradually increased. On admission, among patients with sepsis, severe sepsis, or septic shock, circulating levels of pro-ANP were significantly higher in non-survivors than in survivors [31]. These results correspond to those presented in another study of ICU patients performed by Liu and colleagues. The authors found that ANP levels were significantly higher in septic patients than in patients with non-infectious SIRS. Moreover, ANP values were correlated with the severity of sepsis and had better predictive power than was found for PCT [30]. The mechanism of ANP elevation in sepsis is not fully understood. Some authors consider ANP and proANP to be markers of cardiac dysfunction in sepsis patients [53-56]. ANP levels have also been shown to be related to IL6 production and could consequently be viewed as a marker of inflammation [57]. It may be expressed in various immune cells after a septic stimulus attenuating the inflammatory response. Anti-inflammatory activities include reduction of pro-inflammatory mediators and decreasing TNFα synthesis [58]. ANP has also been reported to counteract TNFα-induced endothelial permeability and the adhesion and attraction of inflammatory cells [59]. Mazul-Sunko and colleagues [55] detected significantly higher proANP levels in septic patients who developed acute respiratory distress syndrome [55]. In contrast, in a

study on patients with community-acquired pneumonia, MR-proANP levels showed only a small but statistically significant increase in patients with positive bacteraemia (92.8 pmol/L vs. 84.3 pmol/L, $p = .04$). The performance of MR-proANP in detecting bacteraemia was less accurate than that of PCT. The authors concluded that MR-proANP poorly predicts bacteraemia in these patients [29]. In an Emergency Department population, proANP (in contrast to PCT) was not able to discriminate septic from non-septic patients, similar to findings for copeptin [43].

Copeptin has been the subject of various studies in septic patients. In another observational study performed in patients presenting to an Emergency Department, copeptin was able to identify septic patients. In this setting, a ROC analysis showed that the performance of copeptin and PCT was similar (0.845 and 0.861, respectively). The authors concluded that copeptin may have a promising diagnostic and prognostic role in the management of sepsis [40]. A post mortem study illustrated significantly elevated copeptin concentrations in sepsis, which were correlated with C-reactive protein, procalcitonin and IL6 values [60]. However, these findings have varied among reports. In a recent study by Koch and colleagues performed in ICU patients, sepsis had no impact on copeptin levels, in agreement with the findings of the present study. Moreover, copeptin concentrations were correlated with disease severity independent of the presence of sepsis. Elevated copeptin levels were found in cases with renal failure, metabolic disturbances and impaired tissue perfusion [38]. We also observed a correlation between peak SOFA scores and copeptin levels (as well as MR-proANP levels). This may confirm the suggestion that copeptin reflects hemodynamic imbalance and a stress state rather than infection-specific changes [50,61]. Alternatively, copeptin plasma concentrations might not be different between adult patients with and without shock. A possible indication of dysfunctional vasopressin regulation in severe sepsis [41]. Inflammatory mediators may affect copeptin expression and compromise AVP synthesis and secretion [62]. This would be consistent with a study on neutropenic patients, in which the lack of increase in copeptin was associated with bacteraemia [44].

The current study has several recognizable limitations. Due to the small number of patients, we could not differentiate between gram-positive and gram-negative sepsis, and this may have influenced the levels and time courses of biomarkers. A larger multi-center study would address this issue and may validate the results, including analysis of possible confounders influencing immune response (e.g. fluid used for burn resuscitation, timing of surgery and amount of blood transfusion). Another crucial point is the diagnosis of sepsis. There is no accepted gold standard for the diagnosis of sepsis in burn patients [9]. The current study adopted a practical approach combining clinical signs of infection with microbiological confirmation, when possible, or at least a positive effect of initiated antibiotic therapy. This method was underscored by recently published ISBI guidelines [63]. The cohort of the current study includes patients with moderate burn injuries, thus conclusions can only be extrapolated to those with extensive burn injuries with caution. The strengths of this study include its prospective design and blinding of the attending physician to the biomarker levels at the time of sampling during treatment.

5. Conclusion

In this population of severe burn patients, both copeptin and, to a lesser extent, MR-proANP were elevated in first days after trauma. During the further course of treatment, MR-proANP but not copeptin was able to discriminate septic from non-septic patients and showed a significant increase on day of infection, comparable to the dynamics of PCT. All parameters were correlated with disease severity. In conclusion, MR-proANP can be used to detect sepsis but does not provide the additional information provided by PCT. These results do not support the use of copeptin as a biomarker of septic complications in this patient group.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest statement

None of the authors have any financial arrangements or potential conflicts of interest regarding this article to declare.

Acknowlegdements

The authors are particularly grateful for the statistical support from Martin Mogk, MoReData (statistical office) GmbH, Kerkrader Str. 11, D-35394 Giessen, Germany.

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