https://doi.org/10.31925/farmacia.2023.3.8 **ORIGINAL ARTICLE**

PREDICTIVE VALUES OF PRESEPSIN AND C-REACTIVE PROTEIN ON PROGNOSIS IN SEVERE BURNS

BOGDAN NITESCU [1,2], BOGDAN PAVEL [2,3]*, IRINA ANDRA TACHE [4], IOANA ANASTASIA POP [2], COSMIN ION BALAN [1,5], STEFAN SORIN ARAMA [6,8], SEBASTIAN ISAC [3], ADRIAN STREINU-CERCEL [7,8], TALAPAN DANIELA [7,8], PITIGOI DANIELA [7,8], VICTORIA ARAMA [7,8]

[1] *"Carol Davila" University of Medicine and Pharmacy, Doctoral School, Bucharest, Romania*
[2] *Clinical Emergency Hospital of Plastic, Reconstructive Surgery and Burns, Bucharest, Romania*
[3] *"Carol Davila" University of Medicine and Pharmacy, Department of Functional Sciences, Bucharest, Romania*
[4] *University Politehnica of Bucharest, Department of Automatic Control and Systems Engineering, Romania*
[5] *"Prof. CC Iliescu" Emergency Institute for Cardiovascular Diseases, 1st Department of Cardiovascular Anaesthesiology and Intensive Care, Bucharest, Romania*
[6] *"Carol Davila" University of Medicine and Pharmacy, Department - Dental Medicine II, Bucharest, Romania*
[7] *"Carol Davila" University of Medicine and Pharmacy, Department of Infectious Disease, Epidemiology, Microbiology, Parasitology, Virusology, Diabetes and Endocrinology, Bucharest, Romania*
[8] *"Matei Balş" National Institute of Infectious Disease, Bucharest, Romania*

**corresponding author: bogdan.pavel@umfcd.ro*

Manuscript received: February 2023

Abstract

Burn patients are at risk of sepsis, hemodynamic instability, and high mortality due to burn-induced inflammation. Inflammatory biomarkers, such as presepsin (PSP) and C-reactive protein (CRP), predict these outcomes. Low albumin, blood iron, and platelet levels indicate sepsis in severe burns. A prospective study with 121 patients and 355 blood samples examined these biomarkers and their correlation with vasopressor use.The CRP cut-off for sepsis prediction was >194 mg/L (AUC: 0.631). Biomarkers complement clinical criteria and wound cultures but do not diagnose sepsis. CRP >180 mg/L and PSP >868 pg/mL indicated vasopressor use (AUC: 0.63 and 0.68). Patients with CRP <180 mg/L and PSP <868 pg/mL had low hemodynamic instability risk. Univariate and multivariate analyses identified PSP, platelet count, and the Abbreviated Burn Severity Index (ABSI) as mortality predictors, excluding CRP. PSP >867 pg/mL (AUC: 0.685) predicted disease. Timely intervention based on predictive values aids antibiotic treatment selection in burn patients with multi-drug resistance. In summary, PSP, CRP, and other biomarkers predict sepsis, hemodynamic instability, and mortality in burn patients. Combining biomarkers with clinical criteria improves decision-making. Predictive values guide timely interventions, addressing infections and selecting antibiotics. These findings have significant implications for managing burn patients.

Rezumat

Pacienții cu arsuri sunt expuși riscului de sepsis, instabilitate hemodinamică și mortalitate ridicată din cauza inflamației induse de arsuri. Biomarkerii inflamatori, cum ar fi presepsina (PSP) și proteina C reactivă (CRP), pot avea valoare predictivă. Nivelurile scăzute de albumină, fier din sânge și trombocite indică sepsisul în cazul arsurilor grave. Un studiu prospectiv cu 121 de pacienți și 355 de probe de sânge a examinat acești biomarkeri și corelația lor cu utilizarea vasopresoarelor. *Cut-off*-ul CRP pentru predicția sepsisului a fost > 194 mg/L (AUC: 0,631). Biomarkerii completează criteriile clinice și culturile de plagă, dar nu diagnostichează sepsisul. CRP > 180 mg/L și PSP > 868 pg/mL au indicat utilizarea vasopresoarelor (AUC: 0,63 și 0,68). Pacienții cu CRP < 180 mg/L și PSP < 868 pg/mL au avut un risc scăzut de instabilitate hemodinamică. Analizele univariate și multivariate au identificat PSP, numărul de trombocite și indicele de severitate a arsurilor abreviat (ABSI) ca predictori de mortalitate, excluzând CRP. Intervenția în timp util, bazată pe valorile predictive, ajută la selectarea tratamentului cu antibiotice la pacienții cu arsuri și rezistență la medicamente. În concluzie, PSP, CRP și alți biomarkeri sunt factori predictibili pentru sepsis, instabilitatea hemodinamică și mortalitatea la pacienții cu arsuri. Combinarea biomarkerilor cu criteriile clinice îmbunătățește procesul decizional.

Keywords: sepsis, presepsin, C-reactive protein, albumin, vasopressor, burns

Introduction

Sepsis has always been a subject prone to debate in the medical field. The definition, diagnosis, and treatment of sepsis remain ongoing topics to this day. Despite the latest progress made in the medical sciences, sepsis still remains the major cause of death, since one in three patients still dies of sepsis in hospitals [1].

Diagnosing sepsis in burn patients is a significant problem. Burns, one of the most severe types of traumatic injuries, are one of the main causes that lead to sepsis due to the impairment of the immune

response and the loss of the skin barrier. Recognising sepsis in an enhanced inflammatory response state, like the condition of a major burn patient, is very difficult and challenging. Burn injuries are a serious matter of public health and have a grave social and psychological impact on patients. A total of 28 - 65% of deaths related to severe burn injuries are linked to sepsis [2].

The third definition is based on a suspected or documented infection associated with two or more Sequential Organ Failure Assessment (SOFA) score points. The third definition of sepsis is broadly accepted in the medical field, but when applied to burn pathology, it is not yet an accepted consensus. In 2007, the American Burn Association (ABA) modified the systemic inflammatory response syndrome (SIRS) criteria included in the second definition in order to accommodate the term sepsis with the severity of the inflammatory response in severe burns. Thus, ABA concluded that all of the patients with a total burn surface area (TBSA) greater than 20% have SIRS, or they need to have 3 or more SIRS modified criteria if under 20% TBSA. One example of modified criteria is thrombocytopenia (< 100.000/μL, after the third day of resuscitation), as demonstrated by Housinger *et al*. that burn patients present low thrombocyte levels before developing sepsis, which is why our team included this biomarker in our study [3-5]. The ABA consensus acknowledges the lack of correlation between inflammatory markers and the diagnosis of sepsis in burn patients and the lack of correlation between these markers and the prognosis [6].

Over the last decade, a series of sepsis-related biomarkers have been tested in order to aid in the definition of sepsis in burn patients. Procalcitonin (PCT) and IL-6 are some of the most promising sepsis markers, along with presepsin (PSP, soluble CD-14 subtype) and CRP. PCT measurement has limitations because it is useful only in the acute phase after burn injury, while IL-6 is a tool to differentiate the blood stream infection from the inflammation status, although IL-6 is high in all severe burn patients [2, 7-9].

Presepsin is a 13-kDa protein that is a truncated N-terminal fragment of CD14, the receptor for lipopoly-saccharide (LPS) and LPS binding protein (LBP). PSP is very useful in the diagnosis of sepsis because its levels specifically increase in the blood of septic patients. Studies show a wide range of cut-off values for PSP in relation to sepsis, from 300 to 600 pg/mL. Also, AUC-ROC values vary significantly for this marker [10, 11]. Various authors place the cut-off value of PSP at 600 pg/mL to distinguish bacterial and non-bacterial infections in non-burn patients [2, 8, 12]. Specific for burn pathology, a study performed on 41 patients in Turkey in 2012-2013 revealed a cut-off value for PSP of 542 pg/mL [2]. There is one case report in burns that states that PSP can also increase in non-septic burns, being an inflammation marker [13].

We focused our attention in our study on PSP, CRP, albumin and iron. We included the correlation of presepsin levels, albumin, sideremia, and CRP in order to indicate cut-off values for sepsis and PSP and CRP to create a predictable tool (cut-off) for vasopressor requirements in burn patients, given the fact that there is no medical consensus for the predictive values of these markers.

We enlisted the plasma iron levels as a criterion because of their inflammatory indicator properties; anaemia is one of the many complications of sepsis, and the blood iron values decrease rapidly in severe burn injuries. This assumption was hard to make because we can correct the iron deficiency easier and faster than we can eliminate a bacterial infection [14]. Another marker we monitored was the serum albumin level, trying to correlate it with inflammatory markers since albumin levels decrease in severe burn patients.

Given the fact that burn patients who develop septic shock have a reserved prognosis, we consider that it is of real interest to use the values of CRP and PSP in order to predict which patients are at risk for septic shock, thus further needing hemodynamic support. It is possible that if we establish what the cut-off values of these markers are, we could use various techniques for preventing septic shock, such as expanding the identification panel of germs, enhancing antibiotic therapy, including immunoglobulin therapy, vasopressor support, or off-label techniques such as extracorporeal clearance using cytokine filters [15].

In our research, we also aimed to validate our hospital protocol of drawing PSP and CRP twice a week and to observe the outcome of associating epinephrine and norepinephrine support with septic shock patients. In a meta-analysis on vasopressor agents published in 2015, the authors found that norepinephrine has a 11% rate of reducing mortality compared with other vasoactive substances and has the lowest hemodynamic side-effect impact [16].

Materials and Methods

This prospective study includes 121 patients consecutively selected after their admission in the Intensive Care Unit (ICU) and admitted patients in the Clinical Emergency Hospital of Plastic, Reconstructive Surgery and Burns, Bucharest, Romania (CEHPRSB) between May 2018 and December 2021. Our hospital is representative on a national scale, being the only hospital in Romania exclusively dedicated to plastic surgery pathology and having the only ICU compartment exclusively dedicated to burn patients. Thus, our patients are admitted from all over the country. We collected demographic data, including age and sex. We established inclusion criteria in the study: total burn surface area

> 20% associating or not with airways burn. We also included exclusion criteria in the study: COVID-19-positive patients, immunosuppressive therapy, human immunodeficiency virus (HIV) infection, tuberculosis, pre-existing kidney disease or coagulopathies, and severe comorbidities that had an impact on the patient's immune system. Following the admission to the hospital, an ABSI score was performed on all the patients. From 121 patients, 355 sampling time points were collected. According to our hospital's ICU protocol, sepsis was declared positive based on wound culture (positive) and ABA criteria. Tissue biopsy culture was not available in our hospital at that moment.

For microbiologic diagnosis, we used wound prelevates, endotracheal aspirates, blood, and urinary cultures. The ICU protocol includes burn wound swabs and endotracheal aspirates at admission if the patient has an inhalation injury. This type of procedure is repeated twice a week; urinary samples are analysed once a week; and blood cultures are drawn if needed in patients presenting with shivering or fever (temperature > 38.5°C). Culture isolates are incubated at 37°C in an incubator (Memmert, Germany). Blood tests were drawn for PSP and CRP twice a week (Monday and Thursday), as well as iron, albumin and platelet levels. For blood cell count, we used AcT5 dif CP (Beckman Coulter, Germany); for measuring CRP, albumin and iron levels, we used Konelab-20i/20XTi (Thermo Electron Corporation, Finland); and for PSP values, Vidas and Bio Merieux VITEC (France) were used. For the parameters used in this study, the Kolmogorov-Smirnov test was performed to assess the presence or absence of a normal distribution. Our data are presented as the average values ± standard deviation for the age and as the median (interquartile range, IQR, 25% - 75%) for PCR, PSP, albumin and iron using PATON, and Area Under Curve values of receiver operator's characteristics (AUC-ROC) were performed for analysis in diagnosing sepsis. We also performed a univariate analysis and, for variables achieving a p value less than 0.01, a full model of multivariable logistic regression according to the enter algorithm. We defined hemodynamic instability as the inability to maintain a main arterial blood pressure > 65 mmHg without a vasopressor (despite volemic resuscitation). The results were considered statistically significant with a P value < 0.05. This study was approved by the ethics committee of the Clinical Emergency Hospital of Plastic Reconstructive Surgery and Burns.

Results and Discussion

Results

From the 121 patients in our study group, 67 (55%) suffered from sepsis and 54 (45%) were non-sepsis. From the 121 patients, 77 died (64%). Also, 71 (59%) patients needed vasopressor support, while 50 didn't need vasopressor agents. From the 71 patients who were hemodynamically unstable, 58 (81%) died. Patient characteristics are shown in Table I.

From these 121 patient groups, we enlisted a total of 355 values of CRP, PSP, iron, albumin, and platelet levels, and we categorised their median values according to septic and non-septic groups and also mortal and non-mortal groups. The median values and IQR of 25% - 75% of the parameters enlisted above are shown in Table I.

Table I

Individual patient characteristics, PSP, CRP, iron, albumin, and thrombocytes in sepsis and non-sepsis groups, survivors and non-survivors groups, and vasopressor and non-vasopressor groups (median IQR 25% - 75%).

	Sepsis	**Non - sepsis**	**Survivors**	**Non - Survivors**	**Vasopressor**	**Non - vasop***
Number	**55% (67)**	**45% (54)**	**36% (44)**	**64% (77)**	**59% (71)**	**41% (50)**
Age (years) (mean ± std)	62.19 ± 16.02	54.17 ± 16.69	61.19 ± 16.79	50.47 ± 14.62	61.12 ± 16.85	55.04 ± 16.08
Gender (m/f)	43/24	32/22	29/15	46/31	43/28	32/18
PSP (pg/mL)	1702 (1220 - 2834.5)	470.5 (328.5 - 629)	631 (392 - 1050)	1225.5 (2238 - 603.25)	1452 (671 - 2805)	191 (116 - 276)
CRP (mg/L)	203 (160.5 - 261.5)	173.5 (131 - 214.5)	168 (122 - 210)	202 (257 - 158.5)	208 (161 - 269)	174 (131 - 219.5)
Iron (sideremia - µg/dL)	23 (13 - 42.75)	28 (15 - 42.25)	27 (18 - 43.25)	23 (12 - 41.75)	22 (11 - 44)	26 (15 - 41)
Albumin (mg/L)	28.46 (30.3 - 26.85)	30.35 (32.92 - 27.92)	30.95 (33.37 - 28.3)	28.7 (26.8 - 30.5)	28.25 (25.95 - 30.5)	29.9 (32.1 - 27.8)
Platelet (nr./µL)	211 (132 - 317.5)	228 (149 - 351)	282 (433 - 187)	191 (116 - 276)	172 (272 - 108)	236 (159 - 365)

*PSP = presepsin, CRP = C-reactive protein

Univariate analysis of the logistic regression revealed the following results for albumin, sideremia (blood iron levels), CRP, PSP, platelet levels, the use of vasopressors, and ABSI (Table II). Following this analysis, we considered PSP, platelets, and ABSI statistically significant and calculated a multivariate analysis for these 3 parameters. We observed that the ABSI maintained the best p-value (Table III).

Table II

Univariate analysis of serum markers (albumin, sideremia, CRP, PSP, PLT, vasopressor requirement and ABSI) on mortality

	OR (CI 95%)	P value
Albumin	0.82(0.76 - 0.88)	< **0.001**
Sideremia	0.99 (0.99 - 1.00)	= 0.68
CRP	1.00 (1.0021 - 1.0076)	< **0.001**
PSP	1.00 (1.002 - 1.0006)	< **0.001**
PLT	0.99 (0.9934 - 0.9967)	< **0.001**
Vasopressor	2.24 (1.39 - 3.61)	< **0.001**
ABSI	1.79 (1.35 - 2.37)	< **0.001**

*PSP = presepsin, CRP = C-reactive protein, PLT = platelets, ABSI = Abbreviated Burn Severity Index

Table III

Multivariate regression analysis

	OR (CI 95%)	p value
PSP	0.85(0.78 - 0.92)	0.04
PLT	4.04 (2.25 - 7.27)	0.03
ABSI	1.04(1.02 - 1.06)	0.005

*PSP = presepsin, CRP = C-reactive protein, PLT = platelets, ABSI = Abbreviated *Burn* Severity Index; The results were considered statistically significant for a p value < 0.05

The ROC-AUC curves of sepsis patients used for albumin, sideremia and CRP are shown in Figure 1, and we obtained the following cut-off values: sensibility and specificity (Table IV). The ROC-AUC curves for vasopressors, which were used as parameters for CRP and PSP, are shown in Figure 2, and we obtained the following cut-off values: sensibility and specificity (Table V). The ROC-AUC curve analysis for presepsin (PSP) to predict disease is presented in Figure 3, and the cut-off value, sensibility, and specificity are shown in Table VI. On the other hand, the following microbial agents were identified: *Pseudomonas spp*., 40%; *Staphylococcus aureus*; *Klebsiella spp*.; and *Acinetobacter spp*., approximately 10% each.

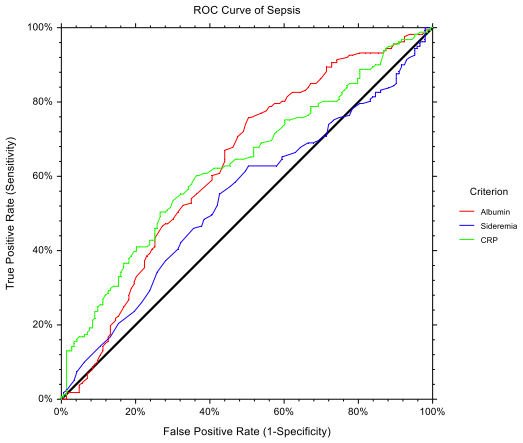

Figure 1.

Comparison of ROC curves for albumin, sideremia and C-reactive protein (CRP) in the diagnostic in septic patients

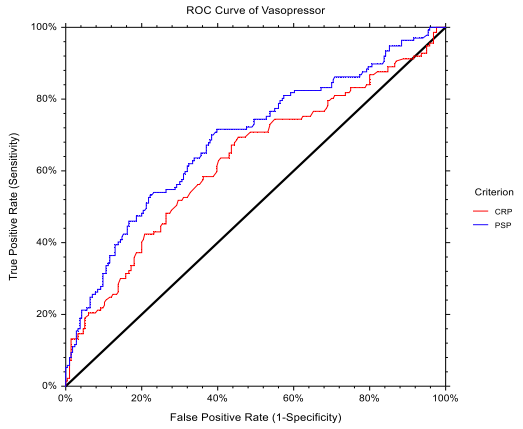

Figure 2.

Comparison of ROC curves for C-reactive protein (CRP) and presepsin (PSP) in the identification of the vasopressor requirement

Table IV

Predictive values of albumin, sideremia, and CRP in sepsis using ROC curves

	Albumin (g/dL)	Blood iron level - sideremia (µg/dL)	CRP (mg/L)
Optimal cut-off	**≤ 30.3**	**≤ 24**	**> 194**
Sensitivity	75.7%	54.76%	64.6%
Specificity	50%	58%	58.7%
PPV*	63%	59%	64%
NPV**	64%	53%	58%
Youden index	0.26	0.12	0.23
AUC-ROC (CI 95%) *	0.631 (0.564 - 0.69)	0.542 (0.474 - 0.603)	0.631 (0.564 - 0.689)
p value	< 0.001	= 0.209	< 0.001

*PPV = positive predictive value; *NPV = negative predictive value; *CI = Confidence interval; *CRP = C-reactive protein; *AUC-ROC = Area under curve values of receiver operator's characteristics. The results were considered statistically significant for a p value < 0.05; *Sensitivity is the probability of a positive test result, conditioned on the individual truly being positive; **Specificity is the probability of a negative test result, conditioned on the individual truly being negative

Table V

Diagnostic performance of CRP and PSP in predicting hemodynamic instability using ROC curves

	CRP (mg/L)	PSP (pg/mL)
Optimal cut-off	**> 180**	**> 868**
Sensitivity	69.3%	71.5%
Specificity	54.6%	60.2%

	CRP (mg/L)	PSP (pg/mL)
PPV*	49%	53%
NPV*	73.6%	76.8%
Youden index	0.24	0.31
AUC-ROC (CI 95%) *	0.63 (0.564 - 0.687)	0.68 (0.625 - 0.741)
p value	< 0.001	< 0.001

*PSP = presepsin, CRP = C-reactive protein. The results were considered statistically significant for a p value < 0.05; Pairwise comparison (they are not different): CRP to PSP ROC difference -0.05; CI 95% -0.13 to 0.015; p = 0.120

Table VI

Diagnostic performance of PSP in predicting mortality using ROC curves

Optimal cut-off	**> 867 PSP (pg/mL)**
Sensitivity	64.35%
Specificity	69.11%
PPV*	79.57%
NPV*	50.9%
Youden index	0.33
AUC-ROC (CI 95%) *	0.685 (0.624 - 0.738)
p value	< 0.001

*PSP = presepsin. The results were considered statistically significant for a p value < 0.05

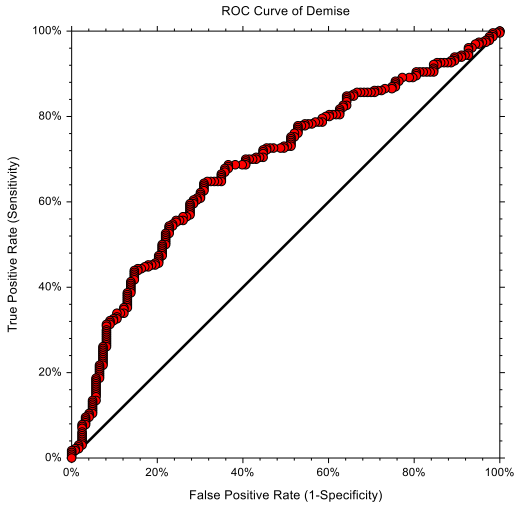

Figure 3.

ROC curve analysis for presepsin (PSP) to predict mortality

Predicting the development of septic shock in burn patients has been challenging for intensivists for many years. Previous studies that tried to identify a tool for predicting hemodynamic instability were generally based on heart rate, blood pressure, or derived indexes such as the shock index [17-19]. A very few studies tried to include other markers than heart rate or blood pressure, such as PTT or INR [20].

In this study, we tried to identify optimal cut-off values for PSP and CRP for highly predicting the onset of hemodynamic instability in the severe burn patient secondary to septic shock. The ROC-AUC analysis detected the cut-off values presented in Table VI. The CRP has a ROC-AUC value of 0.63, and the PSP has an AUC value of 0.68. The values we obtained for PSP and CRP in recognising hemodynamic instability indicate that these biomarkers should not be used alone for prediction. Identifying values greater than 0.8 for these markers would have aided our clinical practise in taking evidence-based decisions to implement different methods of hemodynamic monitoring in sepsis. These methods would include complex hemodynamic monitoring such as Swan-Ganz, PiCCO, and VolumeView and would also take into account off-label sepsis therapies such as immuno-globulin administration or the use of cytokine-filter dialysis [21-24].

Following ROC-AUC analysis, we can state that patients with CRP values < 180 mg/dL and PSP < 868 pg/mL are very unlikely to become hemodynamically unstable, which is very valuable information for the intensivist physician and helps in putting the patient in the relatively safe zone.

Our secondary interest was to identify cut-off values of CRP, albumin, and sideremia for septic patients. The results after ROC-AUC analysis did not lead to obtaining a value greater than 0.8 (albumin AUC 0.631, iron blood levels AUC 0.542, CRP 0.631). Our AUC values for CRP range between other ROC-AUC values reported for this marker in septic buns (0.463 - 0.749) [25, 26]. These observations led us to the idea that declaring sepsis in severe burn patients only based on usual markers such as CRP, albumin, and iron levels and wound culture alone is not highly predictive for declaring infection. The low prediction power of CRP (IL-6 induced) could be potentially explained by the complexity of sepsis signalling pathways. On the other hand, burn inflammatory response (due to long-term healing) can coexist with sepsis, so this could explain why CRP (a common marker for burn inflammatory response and sepsis) cannot distinguish well between sepsis and inflammation. Wound culture in correlation with ABA criteria and/or PSP and PCT values is the desired protocol to be achieved in emerging economic countries for diagnosis algorithms [27]. Future studies are needed in order to establish optimum cut-off values for PSP in burn patients (very few studies have been conducted until now), but it seems to be a very promising bio-marker in other types of sepsis [28-30]. PCT is a well-known biomarker for sepsis, but its cutoff values are not homogenous among different studies in burns [2, 31, 32].

The uni- and multi-variate analysis of our survival group *vs.* mortality group identified as highly predictive

markers for mortality low values of PSP, platelets, and an increased ABSI score.

The predictive values of PSP in estimating mortality in burn patients (AUC-ROC = 0.6850) are not so high but are comparable with its cut-off value in predicting patients' mortality in a non-burn ICU (AUC-ROC = 0.703) [33].

PSP could also play a role in predicting sepsis not only in thermal burns but also in chemical burns, knowing that these kinds of skin burns are more severe and also prone to infection. PSP could help initiate prompt and targeted antibiotic therapy [34-36].

Our internal protocol for diagnosing sepsis uses wound cultures, inflammatory markers such as CRP and PSP (along with other daily blood tests), and ABA-modified sepsis criteria. These parameters help us identify septic patients and implement early and targeted antibiotic therapy. Although these criteria are helpful, we consider that including wound biopsy culture will aid our practise even better, and this is a new direction in plastic surgery practise all over the world that is only available in highly developed economic countries.

This study has certain limitations that should be acknowledged. Firstly, our internal protocol involved collecting CRP and PSP markers from patients only twice a week, specifically on Mondays and Thursdays. This protocol may have resulted in a delay between the sample collection and the onset of symptoms, potentially overlooking any hemodynamic instability that could have occurred during the intervening days. Furthermore, the sample size utilised in this study may have posed limitations in terms of statistical power and generalizability.

Conclusions

Our data analysis revealed that PSP and CRP have moderate sensitivity and specificity in predicting hemodynamic instability onset in severe burn patients, with PSP having better predicting values compared to CRP. A moderate sensitivity and specificity of the usually obtained main serum markers - CRP, albumin and sideremia - in predicting sepsis in severe burn patients compared to the clinical criteria and tissue biopsy cultures was observed. Our study confirms that PSP, ABSI and platelets were predictors of death. Although PSP alone has moderate sensitivity and specificity in predicting mortality, it could be taken into account for sepsis prediction.

Conflict of interest

The authors declare no conflict of interest.

References

1. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, Machado FR, Mcintyre L, Ostermann M, Prescott HC, Schorr C, Simpson S, Wiersinga WJ, Alshamsi F, Angus DC, Arabi Y, Azevedo L, Beale R, Beilman G, Belley-Cote E, Burry L, Cecconi M, Centofanti J, Coz Yataco A, De Waele J, Dellinger RP, Doi K, Du B, Estenssoro E, Ferrer R, Gomersall C, Hodgson C, Møller MH, Iwashyna T, Jacob S, Kleinpell R, Klompas M, Koh Y, Kumar A, Kwizera A, Lobo S, Masur H, Mehta S, Mehta Y, Mer M, Nunnally M, Oczkowski S, Osborn T, Papathanassoglou E, Perner A, Puskarich M, Roberts J, Schweickert W, Seckel M, Sevransky J, Sprung CL, Welte T, Zimmerman J, Levy M, Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. *Intensive Care Med.*, 2021; 47(11): 1181-1247.
2. Madenci OC, Yakupoglu S, Benzonana N, Yucel N, Akbaba D, Kaptanagası AO, Evaluation of soluble CD14 subtype (presepsin) in burn sepsis. *Burns*, 2014; 40(4): 664-669.
3. Boehm D, Menke H, Sepsis in Burns—Lessons Learnt from Developments in the Management of Septic Shock. *Medicina*, 2022; 58: 26.
4. Greenhalgh DG, Sepsis in the burn patient: a different problem than sepsis in the general population. *Burn Trauma,* 2017; 5: 23.
5. Tridente A, Sepsis 3 and the burns patient: do we need Sepsis 3.1? *Scars Burn Heal*., 2018; 14: 4.
6. Greenhalgh DG, Saffle JR, Holmes JH 4th, Gamelli RL, Palmieri TL, Horton JW, Tompkins RG, Traber DL, Mozingo DW, Deitch EA, Goodwin CW, Herndon DN, Gallagher JJ, Sanford AP, Jeng JC, Ahrenholz DH, Neely AN, O'Mara MS, Wolf SE, Purdue GF, Garner WL, Yowler CJ, Latenser BA, American Burn Association consensus conference to define sepsis and infection in burns. *J Burn Care Res*., 2007; 28(6): 776-790.
7. Ali FT, Ali MAM, Elnakeeb MM, Bendary HNM, Presepsin is an early monitoring biomarker for predicting clinical outcome in patients with sepsis. *Clin Chim Acta*., 2016; 1;460: 93-101.
8. Endo S, Suzuki Y, Takahashi G, Shozushima T, Ishikura H, Murai A, Nishida T, Irie Y, Miura M, Iguchi H, Fukui Y, Tanaka K, Nojima T, Okamura Y, Usefulness of presepsin in the diagnosis of sepsis in a multicenter prospective study. *J Infect Chemother*., 2012; 18(6): 891-897.
9. Becker KL, Snider R, Nylen ES, Procalcitonin in sepsis and systemic inflammation: a harmful biomarker and a therapeutic target. *Br J Pharmacol*., 2010; 159: 253-264.
10. Wright SD, Ramos RA, Tobias PS, Ulevitch RJ, Mathison JC, CD14, a receptor for complexes of lipopolysaccharide (LPS) and LPS binding protein. *Science*, 1990; 249(4975): 1431-1433.
11. Vodnik T, Kaljevic G, Tadic T, Majkic-Singh N, Presepsin (sCD14-ST) in preoperative diagnosis of abdominal sepsis. *Clin Chem Lab Med.*, 2013; 51(10): 2053-2062.
12. Giavarina D, Carta M, Determination of reference interval for presepsin, an early marker for sepsis. *Biochem Med (Zagreb).*, 2015; 25(1): 64-68.
13. Hayashi M, Yaguchi Y, Okamura K, Goto E, Onodera Y, Sugiura A, Suzuki H, Nakane M, Kawamae K, Suzuki T, A case of extensive burn without sepsis

showing high level of plasma presepsin (sCD14-ST). *Burns Open*, 2017; 1(1): 33-36.
14. Jiang Y, Jiang FQ, Kong F, An MM, Jin BB, Cao D, Gong P, Inflammatory anemia-associated parameters are related to 28-day mortality in patients with sepsis admitted to the ICU: a preliminary observational study. *Ann Intensive Care*, 2019; 9(1): 67.
15. Honore PM, Hoste E, Molnár Z, Jacobs R, Joannes-Boyau O, Malbrain MLNG, Forni LG, Cytokine removal in human septic shock: Where are we and where are we going?. *Ann Intensive Care*, 2019; 9(1): 56.
16. Avni T, Lador A, Lev S, Leibovici L, Paul M, Grossman A, Vasopressors for the Treatment of Septic Shock: Systematic Review and Meta-Analysis. *PLoS One*, 2015; 10(8): e0129305.
17. Cao H, Eshelman L, Chbat N, Nielsen L, Gross B, Saeed M, Predicting ICU hemodynamic instability using continuous multiparameter trends. *Annu Int Conf IEEE Eng Med Biol Soc.*, 2008; 2008: 3803-3806.
18. Potes C, Conroy B, Xu-Wilson M, Newth C, Inwald D, Frassica J, A clinical prediction model to identify patients at high risk of hemodynamic instability in the pediatric intensive care unit. *Crit Care.*, 2017; 21(1): 282.
19. Rahman A, Chang Y, Dong J, Conroy B, Natarajan A, Kinoshita T, Vicario F, Frassica J, Xu-Wilson M, Early prediction of hemodynamic interventions in the intensive care unit using machine learning. *Crit Care.*, 2021; 25(1): 388.
20. Eshelman LJ, Lee KP, Frassica JJ, Zong W, Nielsen L, Saeed M, Development and evaluation of predictive alerts for hemodynamic instability in ICU patients. *AMIA Annu Symp Proc.*, 2008; 2008: 379-383.
21. Jarczak D, Kluge S, Nierhaus A, Use of intravenous immunoglobulins in sepsis therapy: a clinical view. *Int J Mol Sci.*, 2020; 21(15): 5543.
22. Akil A, Ziegeler S, Reichelt J, Rehers S, Abdalla O, Semik M, Fischer S, Combined use of CytoSorb and ECMO in patients with severe pneumogenic sepsis. *Thorac Cardiovasc Surg.*, 2021; 69(3): 246-251.
23. Zhang Z, Xu X, Yao M, Chen H, Ni H, Fan H, Use of the PiCCO system in critically ill patients with septic shock and acute respiratory distress syndrome: a study protocol for a randomized controlled trial. *Trials*, 2013; 14: 32.
24. Slagt C, Helmi M, Malagon I, Groeneveld AB, Calibrated versus uncalibrated arterial pressure waveform analysis in monitoring cardiac output with transpulmonary thermodilution in patients with severe sepsis and septic shock: an observational study. *Eur J Anaesthesiol.*, 2015; 32(1): 5-12.
25. Lavrentieva A, Kontakiotis T, Lazaridis L, Tsotsolis N, Koumis J, Kyriazis G, Bitzani M, Inflammatory markers in patients with severe burn injury: what is the best indicator of sepsis? *Burns*, 2007; 33(2): 189-194.
26. Bargues L, Chancerelle Y, Catineau J, Jault P, Carsin H, Evaluation of serum procalcitonin concentration in the ICU following severe burn. *Burns*, 2007; 33(7): 860-864.
27. Zhang Yy, Ning Bt, Signaling pathways and intervention therapies in sepsis. *Sig Transduct Target Ther.*, 2021; 6: 407.
28. Zhang P, Zou B, Liou YC, Huang C, The pathogenesis and diagnosis of sepsis post burn injury. *Burns Trauma.*, 2021; 9: tkaa047.
29. Memar MY, Baghi HB, Presepsin: A promising biomarker for the detection of bacterial infections. *Biomed Pharmacother.*, 2019; 111: 649-656.
30. Zhang J, Hu ZD, Song J, Shao J, Diagnostic value of presepsin for sepsis: A systematic review and meta-analysis. *Medicine (Baltimore)*, 2015; 94(47): e2158.
31. Pavel BI, Vatasoiu LMV, Stanculea AT, High values of procalcitonin in non-septic patients with thermal and airway burns - an early severity predictor. *Romanian J Mil Med.*, 2019; 122(3): 22-28.
32. Pavel B, Popescu MR, Skolozubova D, Flutur E, Voiculescu VM, Brezeanu AC, Early low level of procalcitonin is associated with a favorable outcome in a case of a surviving patient with 80% body surface area thermal burn. *Am J Case Rep.*, 2021; 22: e934052.
33. Wen MY, Huang LQ, Yang F, Ye JK, Cai GX, Li XS, Ding HG, Zeng HK, Presepsin level in predicting patients' in-hospital mortality from sepsis under sepsis-3 criteria. *Ther Clin Risk Manag.*, 2019; 15: 733-739.
34. Secara CA, Catrina AM, Voinea OC, Dinu SS, Hîrjău AC, Șerbănescu LG, Serban D, Smarandache GC, Haidoiu C, Radu S, Tudor C, Costea DO, Comandasu M, Dascalu AM, Păuna A, Tudosie MS, *In vivo* assessment of skin chemical burns in exposure to vesicants and the efficacy of an antidote formula in different pharmaceutical forms, an experimental approach. *Farmacia*, 2022; 70(3): 456-464.
35. Petca A, Negoita S, Petca RC, Borislavschi A, Calo IG, Popescu VG, Sinescu RD, Bacterial pathogens isolated from surgical site infections and their antibiotic - susceptibility. *Farmacia*, 2021; 69(4): 741-748.
36. Sanya DRA, Onésime D, Vizzarro G, Jacquier N, Recent advances in therapeutic targets identification and development of treatment strategies towards Pseudomonas aeruginosa infections. *BMC Microbiol.*, 2023; 23(1): 86