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ORIGINAL SCIENTIFIC REPORT

Expression of Pancreatic Stone Protein is Unaffected by Trauma and Subsequent Surgery in Burn Patients

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Abstract

Background Altered levels of pro-inflammatory markers secondary to trauma or surgery present a major problem to physicians in being prone to interfere with the clinical identification of infectious events.

Methods Patients admitted to Zurich Burn Center between May 2015 and October 2018 with burns ≥10% total body surface area (TBSA) and without infection. Longitudinal analysis of the time course of PSP and routine inflammatory biomarkers [procalcitonin (PCT), C-reactive protein (CRP) and white blood cells (WBC)] over two days after (a) trauma with initial debridement and (b) subsequent burn surgeries was performed. The influence of TBSA, abbreviated burn severity index (ABSI), age and length of operation was investigated using a linear mixed effect regression model.

Results Sixty-six patients (15 female) were included with a mean age of 45.5 ± 18.3 years, median TBSA of 22% (IQR 17) and mean ABSI score 6.8 ± 2.7. PSP was the only biomarker that showed no association with any of the baseline characteristics. Additionally, PSP serum levels did not change over time neither after the burn trauma ($p = 0.832$) nor after secondary procedures ($p = 0.113$), while PCT levels increased significantly after the trauma ($p < 0.001$). Similarly, CRP serum levels were elevated significantly after both trauma and surgery ($p < 0.001$), whereas WBC values demonstrated a significant decline after the trauma ($p < 0.001$).

Conclusion Established biomarkers (WBC, CRP and PCT) demonstrate decisive alterations after tissue destruction caused by burn injuries and subsequent surgical interventions. The robustness of PSP serum levels toward these inflammatory insults is a quality criterion for an upcoming sepsis biomarker.

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Introduction

Bedside clinicians regularly struggle to differentiate between burn- and infection-related inflammation. The burn victim's inherent state of hyperinflammation camouflages infectious events, and microbiological cultures provide results with a delay of 48–72 h after sampling. Both these factors postpone the initiation of targeted antimicrobial and intensive care therapy. Blood biomarkers are supposed to support the clinician's diagnostic and therapeutic decision-making processes but often fail in that respect for lack of sensitivity, specificity, availability or affordability. As to that, altered levels of pro-inflammatory markers secondary to trauma or surgery still present a major problem in being prone to interfere with the clinical identification of infectious events. Modern burn care requires repetitive surgical interventions encompassing large debridements, harvest of skin grafts and additional procedures such as limb amputations contributing to an excessive inflammatory stress response with substantial alterations in hemodynamics as well as endocrine and immune functions [1]. Tissue damage by trauma and surgery comes along with the release of pro-inflammatory cytokines by macrophages and monocytes at the initial site of injury stimulating the synthesis of intra- and extrahepatic acute phase proteins [2]. Consequently, C-reactive protein (CRP) levels increase several 100-fold within 24–48 h [3–5]. Levels of white blood cells (WBC) rise just two hours after surgery followed by a harsh decline after 24 h signifying the anti-inflammatory counterpart of the immune system [6]. Likewise, upsurge of extrahepatic acute phase proteins such as procalcitonin (PCT) serum levels has been reported in response to thermal injury and subsequent procedures [7].

Pancreatic stone protein (PSP) as a promising diagnostic and prognostic marker in critically ill patients has gained increasing attention in recent years [8]. Originally described as a protein constitutively secreted by pancreatic acinar cells to inhibit growth and nucleation of calcium carbonate crystals, insights from more recent studies suggested PSP as acute phase protein activating neutrophil granulocytes in the early phase of infection [9–15]. Our group recently published encouraging results demonstrating PSP's excellent accuracy in sepsis prediction in burn patients—outperforming canonical pro-inflammatory biomarkers such as PCT and CRP [16]. Still, its response to tissue damage by trauma or surgery has hardly been investigated [11]. We hypothesized accordingly that PSP as a marker of inflammation is less/not induced by the inflammatory response to tissue injury as opposed to routinely used biomarkers in a selected burn patient cohort without proven infection or sepsis. The present study investigated the influence of the burn injury itself and subsequent surgical interventions on the serum levels of PSP and commonly used biomarkers (WBC, CRP and PCT) in a cohort of 66 non-infected burn patients.

Methods

Ethics approval

Ethics approval was obtained from the Ethics committee of the University of Zurich, Switzerland, on April 20, 2015 (KEK-ZH-No: 2014-0631).

Participants

A priori sample size estimation for Wilcoxon matched-pairs signed-rank test was performed using GPOWER 3.1 resulting in a necessary number of 57 patients (given $\alpha = 0.05$, power = 0.9, effect size = 0.4) [17]. Between May 2015 and October 2018, patients with burns $\geq$10% TBSA admitted to our burn center were asked for participation and consent. Affected TBSA was determined using Lund Browder Charts. Exclusion criteria were age $<$18 years, current infection at admission, immunosuppressive medication and burn injuries older than 6 h. All patients received comprehensive oral and written information on the present study and had to sign the informed consent. Close relatives and authorized representatives were asked for consent by proxy, if the patient was unable to agree due to the extent of the injury.

Patient-related data

Besides demographic and trauma-related data, clinical parameters were extracted from the patients' chart retrospectively and collected in the case report form for 14

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consecutive days from admission. The latter included: blood count, electrolytes, inflammatory markers (PCT, CRP), liver, kidney and pancreas function. Above that, vital signs as well as data on circulatory support, ventilation and mental status were collected in order to closely study pathophysiological changes with regard to infection and sepsis. Clinical parameters at the timepoint of blood sampling were chosen for analysis at 6 am daily. Methods of serum/plasma biomarker measurement are given as supplemental material 1.

Exclusion of patients with occurring infection, sepsis or death

Patients with an infectious or septic event occurring five days or less after either admission or a procedure were excluded from the present analysis to avoid confounding effects. We used the centers for disease control and prevention (CDC) definition for hospital acquired infections [18]. Sepsis was defined according to the Third International Consensus Definition for Sepsis and Septic Shock (Sepsis-3) [19]. Likewise, patients with a fatal course within the first three days were excluded from the present analysis.

Definition of admission and subsequent burn procedures

At the Zurich Burn Center, every burn victim with TBSA $\geq$10% undergoes an initial debridement. The initial debridement includes a bath of the whole patient and complete shaving with removal of blisters and debris using povidone iodine solution (Betadine®). Escharotomy is performed where necessary. After that, the patients have daily dressing changes with polyhexanide solution (Prontosan®) until definitive extent and depth of the burn wounds can be evaluated. The patients usually get excision and temporary/definitive coverage within the next 72 h. Where temporary wound coverage is necessary, we use allografts (Euroskin®). Thus, *admission* is referred to as the trauma with initial debridement with *T*0 defined as measurement at admission, *T*1 as next day measurement at 6 am and *T*2 as measurement 24 h hours later. In contrast, *burn procedures* are defined as subsequent operations performed after the first debridement with *T*0 being the measurement at 6 am at the day of the operation and *T*1, *T*2 as measurement 24 and 48 h later, respectively.

Statistical analysis

Discrete values are expressed as counts with percentages, while continuous variables are presented as mean ± standard deviation (SD) or median with interquartile range (IQR) as appropriate. Spearman's rank correlation ρ with Bonferroni correction for multiple testing was performed to identify associations between levels of biomarkers at *T*0, *T*1, *T*2 and selected baseline characteristics. Logarithmic (log10) transformation of PSP, CRP, PCT and WBC was performed to achieve Gaussian distribution. Differences between time points were tested using a linear mixed effect regression model with random intercepts. The influence of selected baseline characteristic on the time course of the biomarkers was tested by adding a covariate to the mixed effects regression model. All tests were two-tailed; $p < 0.05$ was considered significant. Data were analyzed using Jamovi [The jamovi project (2019). *jamovi* (version 1.0.5) https://www.jamovi.org] and GraphPad Prism version 6.00 for Macintosh (GraphPad Software, La Jolla California USA).

Results

Baseline characteristics

One hundred and four patients with burns $\geq$10% TBSA were enrolled between May 2015 and October 2018, of which 66 patients (15 female) were selected for the current study according to the criteria mentioned in the method section (Fig. 1). Mean age was 45.5 ± 18.3 years, median TBSA was 22% [IQR 17], and mean ABSI score was 6.8 ± 2.7. All patients underwent an initial debridement at admission [median time: 65 (IQR 30) minutes]. Fifty-nine burn procedures were recorded for the present study with a median length of 140 [IQR 155] minutes.

Association between baseline characteristics and inflammatory biomarkers

Table 1 shows the Spearman's rank correlation ρ with corresponding *p* values for each time point according to the baseline characteristics. Age and length of the procedure were not associated with any of the biomarkers tested. TBSA demonstrated moderate to strong correlations with PCT, CRP and WBC serum levels after trauma, while it was significantly associated with PCT and CRP after burn procedures. ABSI was not associated with the biomarkers tested except for PCT at *T*1 and *T*2 after admission. Of note, PSP was the only biomarker that showed no association with any of the baseline characteristics.

Biomarker kinetics in response to trauma and initial debridement

A linear mixed effect regression model with random intercepts was applied to evaluate differences between the

time points. Figure 2 depicts the biomarker levels in response to the trauma and initial debridement. PSP serum levels did not alter significantly within the first two days ($p = 0.078$). PCT and CRP serum levels showed a significant increase within the first 48 h after the trauma ($p < 0.001$). WBC was increased at admission followed by a decline over the next two days signifying the immunosuppressive counterpart ($p < 0.001$).

A covariate was included in the linear mixed effect regression model to further corroborate a potential influence of the baseline characteristics (age, TBSA, ABSI, length of procedure). Only age was significant in the model for PSP time course ($p = 0.042$), but did not affect the main result ($p = 0.078$). None of the baseline characteristics had a significant effect on PCT time course. ABSI score had a significant effect in the model for CRP time course ($p = 0.041$), but did not affect the main result ($p < 0.001$). The time course of WBC was significantly influenced by TBSA ($p < 0.001$), ABSI score ($p = 0.001$) and length of procedure ($p = 0.007$), but did not change the main result, respectively ($p < 0.001$).

Biomarker kinetics in response to burn surgery

Figure 3 demonstrates the biomarker levels in response to burn procedures. Again, PSP serum levels did not show significant alterations secondary to the surgical trauma in the linear mixed effect model ($p = 0.26$). Likewise, PCT levels did not show significant changes within 48 h ($p = 0.16$). CRP values increased significantly within the first 24 h ($p < 0.001$) followed by a rather steady state. WBC serum levels did not vary significantly in response to surgery ($p = 0.105$).

The time courses of PSP and PCT were unaffected by all baseline characteristics. Length of procedure demonstrated a significant effect on the time course of CRP ($p = 0.011$) without changing the main result ($p = 0.004$). Though, adjusting the WBC model for length of procedure changed the main effect ($p = 0.044$), while TBSA had a significant

Fig. 1 Flow diagram

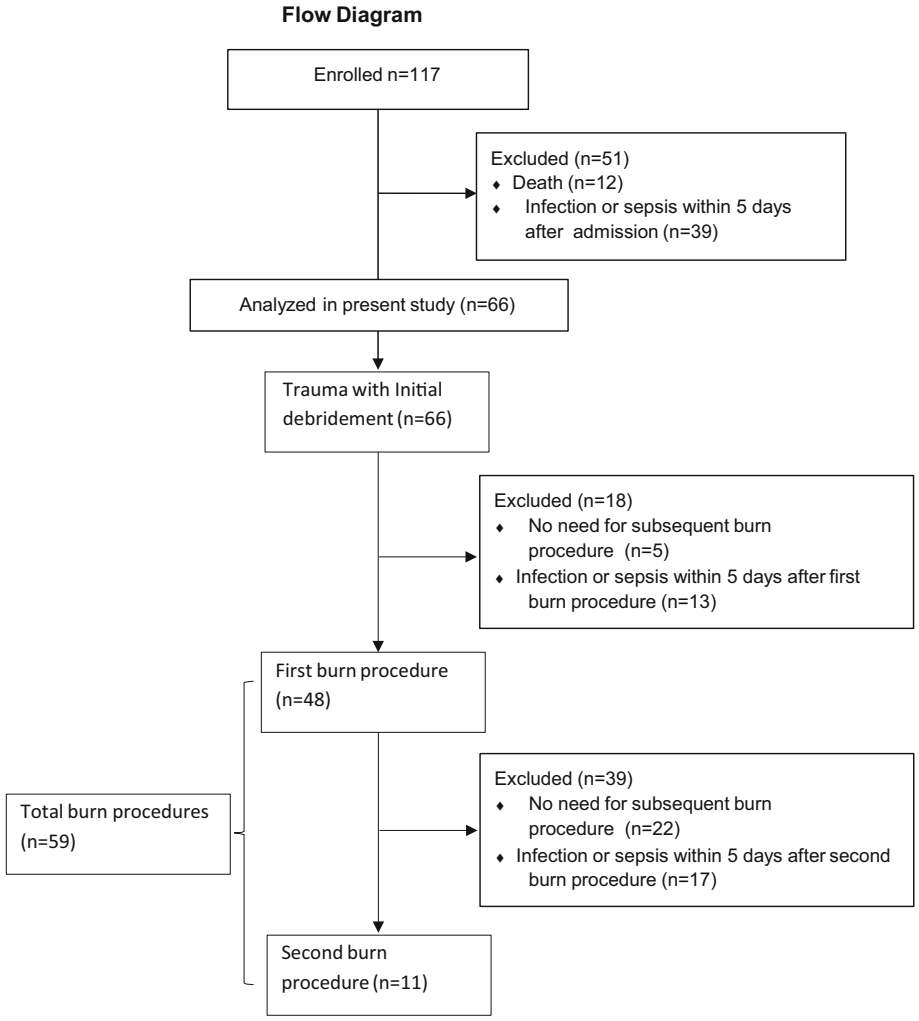

Table 1 Spearman's rank correlation ρ with corresponding p values for each time point according to the baseline characteristics

		Trauma and initial debridement											
		PSP			PCT			CRP			WBC		
		*T*0	*T*1	*T*2	*T*0	*T*1	*T*2	*T*0	*T*1	*T*2	*T*0	*T*1	*T*2
Age	ρ	.133	.269	.313	.084	.044	− .059	.317	.187	.072	− .194	− .180	− .281
	p value	.314	.045	.020	.626	.770	.660	.012	.163	.585	.130	.176	.031
TBSA	ρ	.084	.139	.084	− .160	**.560****	**.637****	− .082	.156	**.550****	**.520****	**.402****	− .094
	p value	.527	.307	.542	.352	**.000**	**.000**	.524	.248	**.000**	**.000**	**.002**	.477
ABSI	ρ	.135	.220	.259	− .035	**.460****	**.370****	.129	.163	.267	.274	.329	− *.061*
	p value	.314	.104	.059	.841	**.001**	**.005**	.323	.226	.041	.033	.012	*.647*
Length of procedure	ρ	–	− .104	− .127	–	.235	.291	–	.147	.296	–	.292	.112
	p value	–	.444	.354	–	.115	.027	–	.276	.022	–	.026	.399
		Subsequent procedures											
		PSP			PCT			CRP			WBC		
		*T*0	*T*1	*T*2	*T*0	*T*1	*T*2	*T*0	*T*1	*T*2	*T*0	*T*1	*T*2
Age	ρ	.175	.039	.026	− .172	− .118	− .031	− .006	.161	.262	− .097	− .168	− .193
	p value	.210	.778	.862	.223	.392	.832	.965	.223	.060	.474	.203	.163
TBSA	ρ	.164	.045	.089	**.531****	**.484****	.346	**.443****	**.384****	.239	.045	.031	.259
	p value	.242	.746	.549	**.000**	**.000**	.015	**.001**	**.003**	.088	.742	.818	.059
ABSI	ρ	.212	.096	.079	.222	.143	.121	.192	.224	.254	.025	− .094	− .082
	p value	.128	.489	.597	.113	.301	.411	.157	.091	.073	.851	.481	.560
Length of procedure	ρ	–	− .094	.136	–	.177	.181	–	.306	.237	–	− .164	− .001
	p value	–	.493	.356	–	.195	.212	–	.019	.090	–	.214	.995

Bonferroni correction for multiple testing was performed setting $\alpha \leq 0.005$. ** indicates $p \leq 0.005$, these results are marked in bold. Upper part of the table depicts the correlations for the trauma and initial debridement, while lower part refers to subsequent burn procedures

influence ($p = 0.041$), but did not change the main result ($p = 0.105$).

Median PSP serum value of all six measurements (*T*0–*T*2 of trauma/initial debridement and *T*0–*T*2 of burn procedures) ranged between 26.2 and 33.2 ng/ml resulting in a grand median of 30 ng/ml. Additional comparison of those six measurements revealed no difference in the Friedman test ($p = 0.166$; 99% CI: 0.151–0.170).

Discussion

The present study investigated the time course of PSP and three established inflammatory markers (WBC, CRP and PCT) in response to trauma and surgery in 66 burn patients without infection. We selected these patients from a larger cohort of 117 subjects in order to study the inflammatory impact of tissue damage following thermal injuries and burn procedures without the confounding effect of infectious events. In a first step, the authors performed a correlation analysis to reveal potential associations between four baseline characteristics (age, TBSA, ABSI and length of procedure) and the level of the four biomarkers both at admission and in response to surgery. Bonferroni correction was used for multiple testing in this 12 × 4 correlation matrix. Interestingly, age was not correlated with any of the biomarker levels. This result is in line with previous findings for PCT levels in adults showing no age dependency, whereas PCT levels are known to be elevated early after birth [20, 21]. Similar to PCT, Schlapbach et al. demonstrated PSP levels to be rather constant in healthy adult patients, but to be fairly elevated in infants [22]. CRP and leukocyte levels are reported to change with age, but to stay within the normal range [23, 24]; especially comorbidity-related chronic inflammation, e.g., due to cardiovascular diseases or diabetes mellitus, is supposed to be responsible for (within the range-) elevated CRP serum levels in the senium. The present study cohort was about 46 ± 18 years old with few comorbidities, so that our findings are concordant with the previous data [25]. Moreover, the correlation analysis showed strong associations between levels of PCT, CRP and WBC and the trauma severity after admission with initial debridement. Trauma severity was represented by TBSA and the ABSI

score. The latter encompasses TBSA, inhalation injury, gender, third-degree burn and age. The correlation indices were higher regarding TBSA as compared to the ABSI score, which might be explained by the fact that the ABSI score includes variables that do not necessarily have an influence on the biomarker alterations, such as age and gender. This became even more evident after subsequent burn procedures, where the ABSI score demonstrated no associations with the biomarker levels. Still, the amount of skin that was excised, debrided and replaced by autologous grafts—dependent on the individual TBSA—seems to trigger (sterile) inflammation with elevations of PCT and CRP serum levels. These results support data from previous studies showing a positive correlation between the PCT/CRP and trauma severity in and beyond burns [4, 26–30]. Interestingly, none of the biomarker levels was correlated with the length of the procedure both at admission and after subsequent surgery. This suggests that the length of an operation alone does not affect inflammatory processes with alterations of the studied biomarkers, but rather the extent of tissue damage by trauma and surgery. Strikingly, PSP levels were not correlated with trauma severity or the ABSI score—neither at admission nor after burn procedures. This absent association is a crucial quality criterion of PSP as a sepsis biomarker, which we did not find for the routinely used markers.

In a second step, we performed a longitudinal comparison using a linear mixed effect regression model. We demonstrated that PSP serum levels did not vary significantly within 48 h after both the initial trauma and subsequent burn procedures. These findings are largely in line with a previous study of polytraumatic patients demonstrating only mild undulations of PSP values in non-infected patients within the first 48 h after trauma (10–22 ng/ml) [10]. In 2015, our group demonstrated in a cohort of 120 patients undergoing elective cardiac surgery that the use of cardiopulmonary bypass—considered as highly inflammatory insult—had no effect on the time course of PSP within 72 h after surgery. In contrast, patients undergoing sternotomy had a significantly steeper rise of postoperative PSP levels as opposed to those subjected to a minimally invasive approach—yet, infected patients were not excluded from this analysis. However, the three routinely used biomarkers of the present study showed significant alterations in response to the trauma, while CRP was the only biomarker that exhibited a significant rise after surgery. This reflects previous findings demonstrating PCT serum levels to rise in response to the immediate inflammatory burst of the burn injury as well as subsequent surgical traumata with elevations of up to 2.0 ng/mL [7, 27, 28, 31]. Likewise, CRP levels are reported to increase several 100-fold within 24–48 h after thermal injuries as well as after surgery, which is reflected by the present study [4, 5, 29].

The inflammatory response to thermal injuries has been well documented [32]. In contrast, the inflammatory impact of burn surgery encompassing large tangential or total excisions with sizeable harvest of skin grafts has hardly been introduced to literature so far. Valvis et al. found the immune response to skin trauma to be dependent on the etiology of injury in a mouse model of burn and excision [33]. Acute cytokine induction was faster after burn trauma as opposed to that of excision injury with excessive IL-6 release stimulating the proliferation of polymorphonuclear leukocytes. The present study is closely in line with these findings, as the leukocyte profile was immediately elevated after burn injury, but it showed insignificant undulations within the normal range after excision surgery. Likewise, CRP and PCT serum levels—triggered as hepatic and extrahepatic acute phase proteins by the cytokine burst after tissue damage—demonstrated a considerably steeper and faster increase after the burn injury as compared to after the surgical trauma. Of note, these temporal changes were not observed for PSP—neither after trauma nor after surgery. Together with our latest findings demonstrating PSP's excellent discrimination in sepsis prediction, these results underline its distinctive role rather in infectious scenarios than in sterile inflammation [16].

Another aim when it comes to testing a novel sepsis biomarker in clinical routine is to approach a reliable normative value determined in different patient populations. Therefore, we calculated the grand median of all six measurements resulting in 30 ng/ml. This value is higher than that reported in Schlapbach et al.'s (10.2 ng/ml) and Keel et al.'s study (15.6 ng/ml), which is most likely due to the baseline inflammatory response present in burns.

The mechanism by which PSP reacts to inflammation either from surgical stress or from infection is yet unclear. Animal experiments by Graf et al. as well as Reding et al. demonstrated that the pancreas as the main locus of synthesis senses remote organ damage and systemic stress via cytokine storms and responds by secreting PSP, particularly when associated with infectious/septic events [9, 34]. Similarly, previous clinical studies on PSP performed by our group suggested that—although surgical trauma has a measurable impact on PSP levels—the slope of the rise in PSP levels more specifically mirrors infectious conditions above a reactive increase of this secretory protein upon surgical trauma [11]. Canonical inflammatory markers such as circulating levels of CRP and WBC, on the other hand, appear to primarily reflect surgical trauma, without enabling an identification of infectious or septic processes at an incipient stage of the disease. Once released in the bloodstream, PSP plays a role in activating neutrophils and aggregating bacteria [10]. Likewise, PSP has been

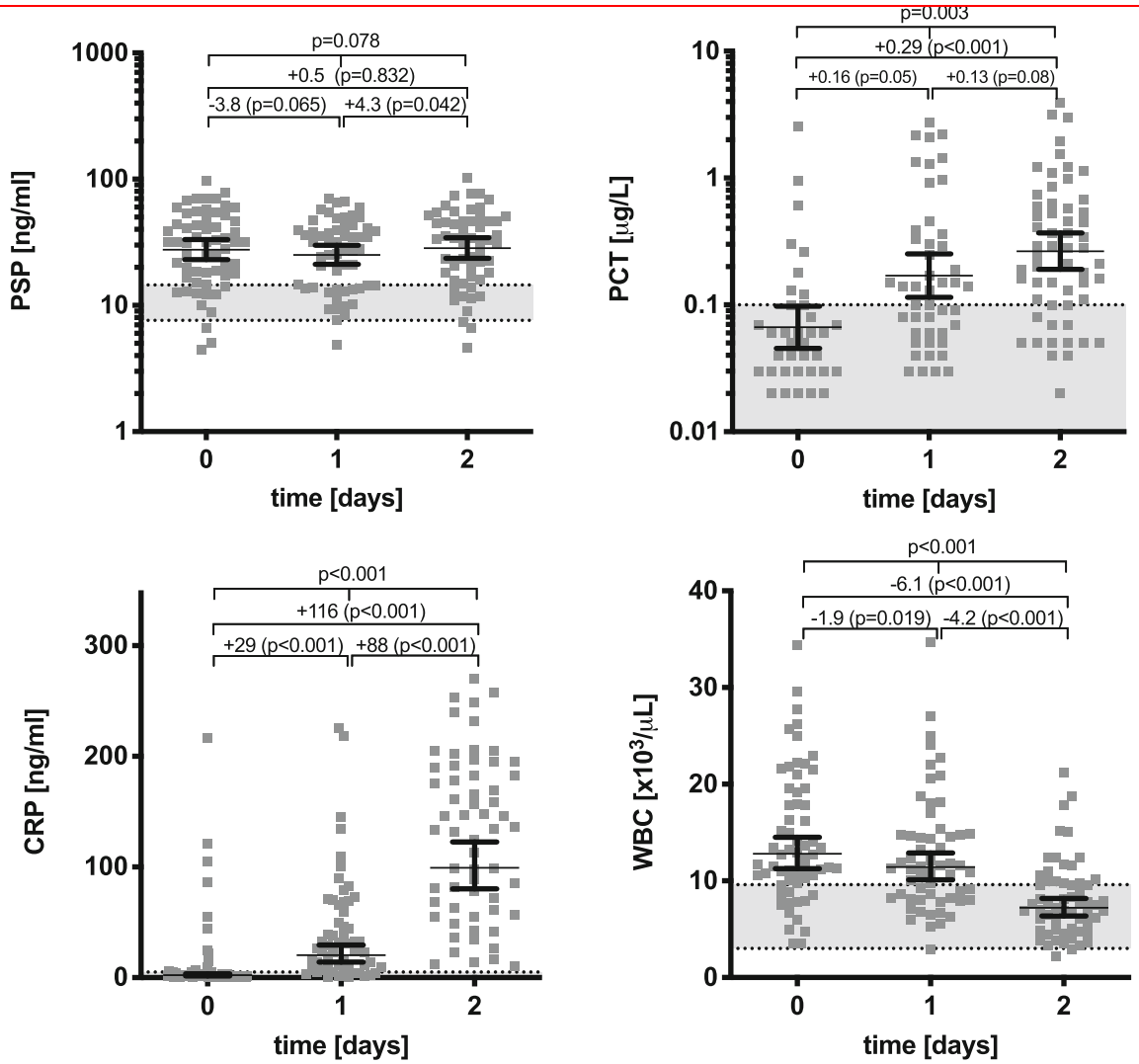

Fig. 2 Time course of all biomarkers at admission and subsequent two days as scatter plots and geometric mean with 95% CI. Differences between time points were calculated by a linear mixed effects regression model with random intercepts. Whereas WBC ($p < 0.001$), CRP ($p < 0.001$) and PCT ($p = 0.003$) serum levels demonstrated significant alterations after trauma and initial debridement, PSP serum levels did not vary significantly ($p = 0.078$). Dotted lines with horizontal bars in light grey depict the range of normal values

demonstrated to bear a high degree of structural homology with lectins, which are calcium-dependent glycan-binding proteins known to have a diverse range of functions, including adhesion and signaling receptors in homeostasis and innate immunity [8]. Consequently, we assume that PSP has a special (specific) role in the sepsis pathway as compared to rather unspecific markers like CRP and WBC, but explanatory approaches on a molecular level remain elusive.

In summary, our results suggest that PSP is superior to established biomarkers in terms of its robustness towards confounding inflammatory insults such as tissue damage by trauma or surgery in burn patients. Posttraumatic and postoperative altered levels of pro-inflammatory markers like PCT or CRP still present a major problem to clinicians as they commonly interfere with the clinical identification of infectious events. This impediment has to be addressed in novel sepsis biomarker research—or as Honore et al. puts it in a letter to the Journal of Critical Care in 2016: "The struggle to differentiate inflammation from infection in severely burned patients: time to send better biomarkers into the arena?" [35]. We think that the answer is simply "yes," as mortality owing to sepsis in extensive burn injuries remains substantial [32, 36]. Against this background, the present study represents another crucial step on

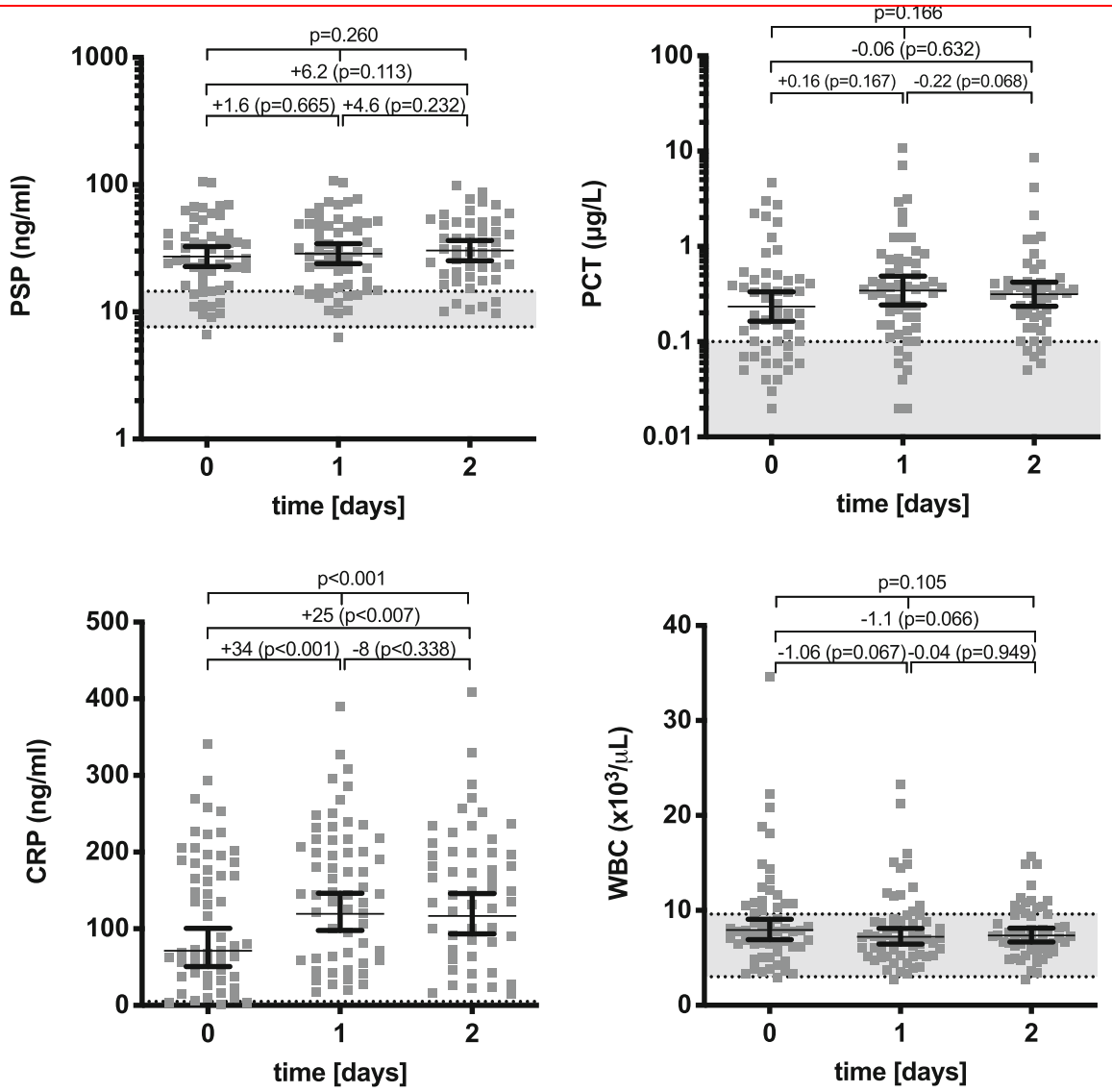

Fig. 3 Time course of all biomarkers before (*T*0) and after (*T*1, *T*2) burn procedure as scatter plots and geometric mean with 95% CI. Differences between time points were calculated by a linear mixed effects regression model with random intercepts. PSP serum levels showed no alterations ($p = 0.26$) within in the ensuing 48 h. Likewise, PCT levels nearly varied ($p = 0.166$), while CRP serum levels showed a significant increase within the first 24 h ($p < 0.001$). WBC showed no significant alterations in response to surgery ($p = 0.105$). Dotted lines with horizontal bars in light grey depict the range of normal values

the way to test a potentially helpful biomarker for early sepsis detection in burns.

The present study does not answer the question to which extent PSP levels might increase in infected patients in response to surgery. A potential interaction between infectious courses and additional tissue damage by surgery with regard to PSP serum alterations needs to be clarified in future studies. Given the single-center design of our study, there is no external validation of our data, which has to be addressed in future work. Likewise, measurement of biomarkers was performed only once per 24 h, neglecting potential alterations between these intervals. Moreover, the influence of the type of surgery (e.g., surgical vs. chemical debridement) needs to be evaluated in future studies. The high number of excluded patients due to the strict inclusion and exclusion criteria represents a further limitation of the study.

Conclusion

Established biomarkers (WBC, CRP and PCT) demonstrate decisive alterations after tissue destruction caused by burn injuries and subsequent surgical interventions. The

robustness of PSP serum levels towards these inflammatory insults induced by tissue damage is a quality criterion for an upcoming sepsis biomarker.

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Compliance with ethical standards

Conflict of interest Rolf Graf is inventor of an assay covered by Patent No: EP 2185937 B2 "Method for Assaying sepsis in Humans", which is owned by the University of Zurich (Zurich, Switzerland). This does not alter the authors' adherence to all the policies on sharing data and materials.

Ethical approval Ethics approval was obtained from the Ethics committee of the University of Zurich, Switzerland on April 20th 2015 (KEK-ZH-No: 2014-0631).

Informed consent Informed consent was obtained from all individual participants included in the study.

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