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ORIGINAL ARTICLE

High values of procalcitonin in non-septic patients with thermal and airway burns – an early severity predictor?

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Abstract: *Purpose – Combined airway burns with cutaneous burns is a further negative prognostic factor in burn patients. In this study we tried to identify the most relevant negative prognostic factors at admission in a relatively homogeneous population.*

Methods – In this study, ten young patients who suffered from skin and airway burns following a fire in a club, admitted to our ICU department, were included. At the intake, ABSI and APACHE II scores were calculated, and a series of biomarkers were also collected. The correlation and associations between gravity scores and biomarkers was then calculated using the Spearman correlation and Chi square tests.

Results – Based on data analysis, we found very high values of ABSI 8.9 ± 1.4 and APACHE II 25.4 ± 2.79 scores, procalcitonin (46.16 ± 68.18 ng/ml), white blood cells (41.26 ± 15.66 × 103/mm3), hematocrit (51.6 ± 7.31 %), and low corrected albumin values (22.08 ± 4.66 g/l). The statistical analysis revealed a good correlation between gravity scores and values of PCT and low albumin levels ($p < 0.05$). The mortality was also associated with the need for vasopressor support from the beginning ($p < 0.05$).

Conclusions – Adverse prognostic factors that we have identified in this group of young patients with skin burns and airway include: increased values of the severity scores and PCT, low values of corrected albumin and vasopressor support necessary at admission.

INTRODUCTION

Burns represent one of the most aggressive injuries of the human body known for high mortality, thus raising major public health issues such as increased length of hospitalization and recuperation, along with psychological and physiological traumas, all these leading to increased costs [1-4].

Burns-induced mortality rate is globally increased, and surprisingly high in the developing countries, including Europe's burn centers, where it ranges between 1.4% and 18% [5]. The high mortality is associated with a number of factors, including long-term severity of burn driven inflammatory response of the host, secondary human body frailty and abnormal response to further injuries like sepsis [6, 7]. The association of airways' and cutaneous burns induces a supplemental increase of the inflammatory response, difficult to quantify because of the inaccurate evaluation of the burns from the surface of the lungs and burn degree same time [8]. Consequently, in the case of mixed cutaneous-and-airway burns the mortality increases,

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despite the usage of advanced techniques to support lung function (Extracorporeal membrane oxygenation – ECMO) [9-12]. On the other hand, in the beginning, it is unclear whether a patient has both cutaneous and airway burns, as for the latter it might take up to 48 hours to observe any clinical manifestations. As such, the airways' burns assumption is made based on anamnesis and correlation between the high incidence of airways burns and the increased surface of cutaneous burns [11]. If one can clinically suppose an airways burn (in this case a bronchoscopy is usually performed for a certain diagnosis), there is no toll to quantify its' impact on the inflammatory response of human body. Currently, there is just an indirect estimation of their aggression on the human body using either dedicated markers or severity scores. Despite the wide availability of severity scores as Acute Physiology And Chronic Health Evaluation (APACHE II and APACHE III), Abbreviated Burn Severity Index (ABSI), and biomarkers (such as microalbuminuria, serum albumin, C-reactive protein, procalcitonin (PCT)), both used to estimate the severity of cutaneous burn injuries, they are not sufficiently standardized for the estimation of mortality risk in case of combined thermal and airway burns [13-16].

Considering the increased mortality and likeliness of combined burns complications, it is paramount to know the severity degree and the prognosis of the burn evolution from the beginning.

In the current study, we evaluated the absolute values of serological markers and severity scores upon admission to the Intensive Care Unit (ICU) in a group of young adult patients who presented both cutaneous and airway burns following the fire in a club in Bucharest, Romania and we studied their correlation with mortality.

MATERIAL AND METHOD

This study includes the victims of a fire at a club in Bucharest, in the night of 29-30 October 2015, all of them hospitalized that night in the Intensive Care Unit of the Emergency Hospital for Plastic Reconstructive Surgery and Burns, in Bucharest. All admitted patients underwent surgery (non-excisional debridement) and subsequently, they were connected to artificial breathing devices, central venous and urinary catheters being placed on them too.

Hydroelectrolytic rebalancing started from the operating room with a crystalloid solution (Ringer lactate), following the Parkland protocol (4 ml/kgc/Total Burn Surface Area-TBSA), while in patients who could not maintain a Mean Arterial Pressure (MAP) > 65 mmHg, epinephrine was administered in continuous perfusion from the beginning. Patients were admitted to ICU between 00:00 and 03:00 on 30 October, and the first set of blood tests was harvested at 6:00 on 30 October. To determine the quantitative procalcitonin (PCT) values, the testers arrived after about 48 hours from admission.

We estimated the severity of the patients' burns using ABSI and APACHE II scores.

In, order to estimate the appropriate level of serum albumin under hypovolemic conditions, we corrected it in accordance to the hematocrit (Ht) level, using the following formula:

$$corrected\ albumin\ level\ = measured\ albumin\ level\ \times \frac{normal\ Ht}{measured\ Ht}$$

where normal hematocrit (Ht) is 45% for men and 40% for women.

For the determination of the blood cells count, the Ac-T 5 diff CP (Beckman Coulter, Germany) was used. The biochemical markers were measured using the Konelab-20i/20XTI (Thermo Electron Corporation, Finland). Coagulation parameters were determined using the ACL-7000 instrument (Instruments Laboratory, Italy). PCT was assessed using the VIDAS, bio Merieux VITEK, France.

The conduct of this study was approved by the Ethics Committee of the Emergency Hospital for Plastic Reconstructive Surgery and Burns (number 5/10 July 2017).

Statistical analysis

The data is presented as the average ± standard deviation for quantitative variables, and absolute frequencies and relative frequencies, respectively for the qualitative variables. Batch variance analysis was performed with the Levene test. For the analysis of the difference between the environments the t-student test was used together with the calculation of the confidence intervals. For the correlation analysis Spearman correlation coefficient and chi-square nonparametric test were employed. In addition, for the correlation analysis we performed Percentile Bootstrap Correlation in order to calculate the Pearson parametric correlation coefficient. Confidence intervals for the value of the t test and the Pearson correlation coefficient were obtained through the bootstrap method with 10,000 and 1,000 replications, respectively. The results were considered statistically significant for a p value <0.05. For the statistical analysis IBM SPSS 18.0 and several R packages, such as wBoot, were used.

RESULTS

During the night of 29-30 October 2015, ten patients (seven male and three women) were admitted in our ICU. The deep cutaneous burn lesions (3rd degree) ranged between 5% and 50% of the body surface area and the age range of admitted patients was 18 to 40 years old. Their ABSI scores were between 7 and 11, associating a mortality between 10% and 60 - 80% and the APACHE II score ranged between 23 and 30, which is associated with a 46% to 70.3% mortality at admission. In Table 1 we report demographical data, several laboratory measures describing the admission conditions and, for some of them, the measures sampled 30 hours after admission.

Table 1. Characteristics of the patients included in the study

	Values
WBC (1000/ml)	41.26 ± 15.66
PLT (1000/ml)	142.5 ± 50
APTT (sec)	40.27 ± 10.76
INR	1.87 ± 0.45
pH	7.04 ± 0.11
Temperature (^{0}C)	35.95 ± 0.61
Albumin (g/l)	25.95 ± 4.52
Corrected Albumin (g/l)	22.08 ± 4.66
PCT (ng/dl)	46.16 ± 68.18
Creatinine (mg/dl)	1.39 ± 0.53
TGO (mg/dl)	70.8 ± 38.31
TGP (mg/dl)	54 ± 43.28
One month mortality (%)	80%
One year mortality (%)	90%
WBC (1000/ml)	41.26 ± 15.66
PLT (1000/ml)	142.5 ± 50
APTT (sec)	40.27 ± 10.76
INR	1.87 ± 0.45
pH	7.04 ± 0.11
Temperature (^{0}C)	35.95 ± 0.61
Albumin (g/l)	25.95 ± 4.52

Note: TBSA III = Total Burn Surface Area 3rd degree, WBC = white blood cells, PLT = platelets, APTT = activated partial thromboplastin time, INR = international normalized ratio, Corrected Albumin represents corrected values of albumin according to hematocrit, PCT = procalcitonin, TGO = glutamic oxaloacetic transaminase, TGP = glutamate-pyruvate transaminase.

For these variables, the values presented are mean ± standard deviation. Gender distribution and mortality after one month and one year are also provided in Table 1. Blood tests revealed: high levels of white blood cells (WBC) of 41.26 ± 15.66/mm3, elevated hematocrit (Ht) level51.6 ± 7.31%, albumin values of 25.95 ± 4.52 g/dl (uncorrected) and 22.08 ± 4.66 g/dl (corrected), creatinine level of 1.39 ± 0.53 mg/dl, glutamic oxaloacetic transaminase (TGO) values of 70.8 ± 38.31 mg/dl and glutamate-pyruvate transaminase (TGP) levels of 54 ± 43.28 mg/dl.

Forty-eight hour procalcitonin (PCT) values were extremely elevated: 49.85 ± 67.34 ng/ml (PCT was measured in eight patients). The coagulation parameters activated partial thromboplastin time (APTT), international normalized ratio (INR), and platelets (PLT) we report in Table 1 were measured at 30 hours from admission (the second set of analysis) because at the first set there were no changes (first set: APTT = 29.3 ± 3.01, INR = 1.15 ± 0.18, PLT = 306.2 ± 108.47). So we found: APTT = 40.27 ± 10.76 seconds, INR = 1.87 ± 0.45, PLT = 142.5 ± 50*103/ml. The pH values of 7.04 ± 0.11 presented in the table were obtained from central venous blood samples after the central venous catheters were placed. The temperature at admission had a mean value of 35.95 ± 0.61 Celsius degrees. Of the ten patients in ICU eight needed vasopressor support at admission and also during the next days.

Table 2 presents values of serological markers, Total Burn Surface Area 3rd degree in terms of mean ± standard deviation, and the number of patients who required vasopressor support with epinephrine (norepinephrine from the second day) from the admission, considering the total study group and the subgroup of those who did not survived.

Table 2. Values of serological markers, total burn surface area (TBSA) and norepinephrine status in the study group and subgroup

	Total	Non Survivors	p value
Albumin (g/l)	25.95 ± 4.52	24.63 ± 3.97	0.26
Corrected Albumin (g/l)	22.08 ± 4.66	21.25 ± 4.62	0.35
PCT (ng/ml)	46.16 ± 68.18	65.88 ± 71.52	0.35
Hematocrit (%)	51.6 ± 7.31	51.19 ± 5.07	0.43
WBC (1000/ml)	41.26 ± 15.66	44.00 ± 16.22	0.36
Norepinephrine	8 (10)	8	0.03
TBSA III (%)	25.7 ± 16.73	29.62 ± 16.27	0.30

Note: WBC = white blood cells, PCT = procalcitonin, Corrected Albumin represents corrected values of albumin according to hematocrit. TBSA III = Total Burn Surface Area 3rd degree. Data are presented as mean ± standard deviation.

In the case of norepinephrine requirements association chi-

square test were performed.

Statistical significance is considered for a p value < 0.05. We performed parametric t-tests for the above variables in order to assess whether there are sizeable differences between the values recorded for all patients versus the values for those that died. Due to the existence of abnormal values for TBSA and PCT 48 hrs, we have eliminated TBSA values exceeding 8, and PCT 48H values under 200. Table 3 presents two versions of the t-tests: regular tests assuming unequal variances, and bootstrap tests with 10000 replications.

Table 3. T-tests and bootstrap confidence intervals

Parameter	T-test value	P-value	Bootstrap confidence interval limits			
			Lower 95%	Upper 95%	Lower 90%	Upper 90%
Corrected albumin	0.37421	0.7134	-2.90235	4.7619	-2.52655	4.1034
TBSA	-0.50211	0.6227	-17.32	9.86	-2.3798	4.0939
PCT	-0.38325	0.7093	-105.1441	8.8855	-100.0322	5.32
WCB (divided by 100)	-0.36157	0.7228	-16.404	8.845175	-13.9097	7.57075
TBSA>8	-0.28615	0.7793	-15.71875	11.5	-13.75	9.25
PCT48h <200	-0.4898	0.6367	-37.916	19.39814	-32.02486	14.458
Albumin	0.65438	0.5223	-2.195	4.57	-1.575	4.21
Hematocrit	0.16848	0.8683	-4.50495	5.85595	-3.6257	5.1709

All results show that differences between the two samples are non-significant at 90% confidence level. Further, we investigated the correlations between severity scores (ABSI and APACHE II), procalcitonin (PCT) and corrected albumin using the Spearman non-parametric (rank) correlation coefficient. Table 4 shows that these correlations are significant at 10% significance level. We pursued a more in-depth analysis of the correlations between the above variables calculating the Pearson parametric correlation coefficient using the Percentile Bootstrap Correlation Method available in the package wBoot of R. intervals obtained after 1000 replications.

Table 4. Spearman correlations

Correlation	Correlation Coefficient	p value
ABSI - APACHE II	0.54	0.053
APACHE II - Corrected Albumin	-0.59	0.036
ABSI - PCT	0.73	0.019
APACHE II - PCT	0.73	0.019

Table 5 presents the values of the correlation coefficient, the standard error as well as the 90% or 95% confidence

Table 5. Pearson correlations: results from the Percentile Bootstrap Correlation Method, 1000 replications

Variables	Mean coefficient	Standard error	Confidence interval		
			Lower Limit	Upper Limit	Level
ABSI , Apache II	0.4904211	0.2582198	0.008991	0.8477	90%
ABSI , PCT	0.5594826	0.1655465	0.2769	0.8614	95%
Apache II, PCT	0.5487429	0.208531	0.1969	0.9677	95%
Apache II, Corrected Albumin	-0.5645653	0.2334818	-0.8677	-0.151	90%

Bronchoscopic aspects at 48 hours did not reveal severe changes, most of them related to mild or moderate impairment of the lungs (Grade 0-2), only one exception with severe lesions (Grade 3) being identified. Following the Berlin criteria for the classification of acute respiratory distress syndrome (ARDS), nine patients presented mild ARDS and only one moderate ARDS upon admission to ICU.

We have obtained a good correlation between the APACHE II score at admission and the procalcitonin values (at 48 hours), ABSI score and procalcitonin and also between the

APACHE II score and albumin (Table 3).

One month after admission, two of the ten patients survived and after one year, one patient survived.

DISCUSSION

Upon arrival, patients showed signs of increased burn severity including high values of PCT (at 48 hours from admission), WBC, APACHE II & ABSI scores, and Ht, as well as low levels of albumin. Eight of the ten admitted patients required vasopressor support from the beginning.

It is known that PCT, a molecule secreted by the thyroid, intestine, liver, kidney, muscle and adipocytes under the action of TNFα and IL-1β has elevated values especially in bacterial sepsis [17] and not in viral infections [18] and also has a rapid kinetic growth from the first few hours of injury to a maximum of 12 hours [19]. PCT is also increased in septic burned patients. Several studies were performed for identifying a cut-off value for sepsis in burned patients, the yielded values ranging from 0.5 ng/ml to 1.5 ng/ml [20-23]. The highest PCT values reported for non septic patients were 2.3 ± 3.7 ng/ml [20].

Nevertheless, PCT was also found to be increased in non-septic states by systemic inflammatory response syndrome-SIRS, which is logical considering that its secretion is stimulated by TNFα and IL-1β. Additionally, it has been noticed that in complex visceral liver/spleen plus thoracic trauma the PCT values go up to 9.37 ± 2.71 ng/ml [24], consequently elevated values were also found in other SIRS states [25, 26]. In burns it was found that PCT grows even in the absence of infection, so patients who associate PCT values > 2 ng/ml within the first 48 hours of admission have a mortality of 65% at 50 days [27]. According to the American Burns Association criteria (ABA) [28], we had just one patient who presented sepsis criteria in the first 48 hours, so the high PCT values observed in our patients (46.16 ± 68.18 ng/ml) were explained by an extremely aggressive inflammatory response to burn. Our opinion is that this reaction was induced not only by skin burns but also by pulmonary injury so that high PTC values on admission may also indicate an associated airway burn in patients who have such a suspicion.

Serum albumin is a marker of severity in critical patients and is associated with an increased mortality [29, 30]. Low levels of serum albumin and urinary albumin occur by increasing vascular permeability induced by pro-inflammatory mediators in SIRS or sepsis [31, 32]. Patients with burn injuries lose their albumin by increasing the capillary permeability induced by pro-inflammatory mediators and the serum albumin value correlates with the burned surface, so at a burned surface of 60%, serum albumin (at admission) is around 1.95 ± 0.02 g/l [33, 34, 35]. In a recent study, it was found that in patients with burn driven injuries an albumin value < 2 g/l is correlated with a mortality > 80% [36]. For our patients, the value of serum albumin on admission was 25.95 ± 4.52 g/dl and corrected albumin was 22.08 ± 4.66 g/dl. We consider it more useful to report corrected albumin values considering that patients have high hematocrit variations as most of them are hemoconcentrated at admission. In all of the studies we considered, the serum albumin values were presented without being adjusted to the hematocrit value.

The APACHE II score is known as a severity score that is used to estimate mortality in intensive care units [37]. Its correlation with mortality is applicable to burn patients [38, 39] and also to acute respiratory distress syndrome (ARDS) patients [40, 41]. In our group, the high APACHE II scores have been interpreted as being induced by an extreme inflammatory response probably induced by thermal and airway burns. The ABSI score is a good indicator of the severity of a thermal injury and seems to estimate quite well the burning severity in patients with airway burns [42, 43]. ABSI score has a similar prognostic value compared to APACHE II in estimating the severity of patients with both cutaneous and airway burns. ABSI and APACHE II predict a similar mortality and the correlation of their scores is at the p = 0.05 limit. In our patients, the WBC count at admission was extremely high 41.26 ± 15.66 *103/ml. These elevated values can be only partially explained by hemoconcentration because the mean value of the hematocrit was just slightly elevated. WBC count is also increased in other situations with a systemic inflammatory response but not to those values reported in our group [44, 45].

The mean serum creatinine value, at 6 hours after admission, was 1.39 mg/dl, which may be due to hypovolemia induced by renal hypoperfusion. On the other hand, elevated transaminases with predominantly TGO/TGP increased ratio may be explained by their release from the burn cutaneous area rather than by hepatic hypoperfusion. The triad: acidosis, hypothermia and coagulopathy has a poor prognosis in polytraumatized patients and in burn patients [46]. This triad is particularly presents in patients with cutaneous and airway burns. All the patients with skin and airway burns showed severe metabolic acidosis at admission. Coagulopathy did not immediately appear but emerged in the next 30 hours. Hypothermia (temperature under 35.5°C degrees) was present in just two patients at admission, and the mean value was about 35.95 Celsius degrees. The absence of hypothermia can be explained by the very short time until the patients were brought to the hospital, the fire being located in a club in Bucharest,

relatively close to the hospital. Thus, out of the three parameters of the triad, in our patients, only 2 of them were present.

These changes of PCT, WBC and high APACHE II and ABSI scores can be explained by an extreme inflammatory reaction or septic shock. This inflammatory reaction could be caused by thermal cutaneous lesions and/or airway burns. Although we found a good correlation between the APACHE II score & PCT & corrected albumin, and also between ABSI score & PCT, we did not find a statistically significant correlation between the burn lesions surface or depth and the biological parameters. So we can state that the inflammatory reaction was determined by a mixed cause represented by the thermal cutaneous lesions and airway burns. For patients with airway burns, the etiology may be thermal or chemical. In most of our cases, bronchoscopy did not reveal significant structural changes in the upper airways, which led us to the idea that pulmonary injury was mixed, thermal and chemical. Although we did not obtain statistically significant changes, we found an increase in WBC, PCT and TBSA III values in the case of non-survivors compared to the mean values obtained in the entire group of patients. Yet, a statistically significant difference was obtained with regard to vasopressor support, so all eight patients requiring vasopressor support at the admission died in the first month.

The patients who survived one month from the incident, had PCT values at 48 hours of 3.14 ng/ml and 0.41 ng/ml, respectively, corrected albumin of 22.3 g/l and 28.45 g/l, respectively, while the APACHE II values were 24 and 23 respectively, and ABSI scores were 8 and 7 respectively. These were also the only patients who did not require vasopressor support at admission.

CONCLUSIONS

The association of airway burns to the cutaneous thermal lesions is linked to an increased mortality even in young patients. There is no dedicated marker or score for the assessment of the combined cutaneous and airways burns aggression on the human body but an association of markers and scores could improve the evaluation of the burn severity. The negative prognostic factors we identified in our group were high PCT values at 48 hours, low corrected albumin levels, vasopressor requirements and elevated APACHE II and ABSI scores. The WBC count and TBSA could be also considered in establishing the severity of the cases.

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