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Original Article

Do early procalcitonine levels aid in predicting mortality in burn patients?

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Abstract: Aim: Burn patients in intensive care units (ICU) are at high risk of mortality. Our aim in this stuy is to evaluate the use of first 48 hour procalcitonin level (PCT), C-reactive protein (CRP) and APACHE II score for the prediction of mortality in burn patients admitted to ICU. Material and method: Files of patients with burns admitted to a tertiary centre's burn unit were retrospectively analysed and those with procalcitonin and C-reactive protein level measurements and APACHE II scores within first 48 hours of admittance were included in this study. Patients with comorbidities that would effect PCT and CRP levels such as chronic renal or liver failure were excluded from the study. Patients PCT, CRP and APACHE II scores were compared with the outcome of patients. Results: Seventy patients were included in this study. While CRP levels were lower in patients that were deceased, PCT levels were significantly higher in these patients. In patients with APACHE II score > 20 and PCT > 2 ng/ml, mortality was statistically very significantly higher compared with other patients. Logistical regression analysis showed that high PCT levels and APACHE II scores were important at predicting mortality in these patients. Conclusion: High PCT levels within 48 hours of burns is a predictor of mortality in these patients. Additional studies are required to correctly determine the cut-off value. A modified scoring system including APACHE II and PCT may be useful for better predicting mortality, although larger multi-centered studies are required.

Keywords: Burn, procalcitonin, C-reactive protein, Apache II score

Introduction

The major causes of death in burn patients include type and depth of burn, ratio of burn to body surface area as well as concomitant sepsis, respiratory system insufficiencies and other multiple organ failure [1-3]. It is reported that the early diagnosis, treatment and control of sepsis is an important part of decreasing morbidity and mortality in these patients [4-6]. Procalcitonine (PCT) shows significant increases secondary to sepsis and septic shock secondary to bacterial or fungal infections [7, 8].

Procalcitonine is a prohormone consisting of 116 aminoacids and sysnthesized as a precursor to calcitonine in the thyroid gland. Increases in PCT levels in the first 48 hours is generally seen after serious trauma, burns, multiorgan failure and major surgical prodecures (with our without sepsis), which return to normal after the these conditions subside [7, 9]. Similarly, an increase of 0.15 ng/ml in PCT are seen in patients with chronic renal failure without sepsis or inflammation, decreasing to normal blood level after 3 times hemodialysis [10, 11].

This study aimed to compare and analyse the role of first 48 hour PCT level, C-reactive protein and APACHE II score on the mortality of burn patients in intensive care units.

Material and method

This study was performed at the intensive care burn unit (ICU) of Dr. Lütfi Kirdar Kartal Edu-

Table 1. Correlation of mortality with CRP and PCT levels

	Findings		
	Exitus	Discharge	
	Ave ± S.D. (Median)	Ave ± S.D. (Median)	*P*
CRP (mg/L)	77.28±82.31 (28.25)	106.58±60.70 (110)	[1]*0.049**
PCT (ng/ml)	16.73±28.86 (6)	0.90±0.98 (0.72)	[1]*0.001***
APACHE II	26.03±4.09	12.25±5.82	[2]*0.001***
Burn %	61.26±22.88 (60)	34.85±17.84 (40)	[1]*0.001***

*[1]Mann Whitney U; [2]Student t test. *P < 0.05, **P < 0.01.* Ave ± S.D: Average ± Standart Deviation.

cation and Research Hospital (Istanbul, Turkey). Seventy patients admitted to this center from May 2011 to June 2012, whose full medical documentation and first 48 hour PCT and C-reactive protein (CRP) levels were available, were included in this retrospective study. Exclusion criteria was: age < 2 years, diagnosis of chronic renal failure, hepatic failure (according to patients medical history) and morbid obesity (BMI > 40) and patients who were died in the first 48 hours.

APACHE II scores were calculated within the first 24 hours of admittance for all patients. Procalcitonine measurements were performed using immunoluminometric technique (LUMItest™, B·R·A·H·M·S Diagnostica, Berlin, Germany) and CRP measurment were performed using nephelometric technique (Dade Behring BNII, Germany).

The local ethics committee (Kartal Dr. Lutfi Kirdar Education & Research Hospital Ethics Committee) confirmed that Research and Ethics approval was not required for this study. The need for informed consent was also waived because the study required neither an intervention nor breach of privacy or anonymity.

All statistical analyses were performed using IBM SPSS 22.0 for Windows. Descriptive statistics were performed. Also, quantitative data was compared using Student t test for normally distributed data, Mann Whitney U test for non-normally distributed data. Qualitative data was compared using Chi-Square test and Continuity Correction (Yates) test. Logistical analysis was used for multivariate analysis. Diagnostic screening test data was used for calculation of sensitivity, specificity and determination of cut-off points. Parameters with non-normal distribution of data were also analysed with Spearman's rho correlation analysis. Statistical significance was accepted as P < 0.05.

Results

A total of 70 patients with an average age of 40.77±22.47 years (range 2-91 years, 16 female (22.9%) and 54 males (77.1%) were included in the study. Average ICU stay was 15.34±17 days (median 9 days, range 4-76 days). Thirty patients (42.9%) died during ICU care and 40 (57.1%) were transfered to burn care services. Cuases for burn were fire in 40%, electrical burn in 24.3%, synthetic thinner in 12.9%, boiling water in 5.7%, petrol in 2.9%, hot oil in 2.9%, gas in 2.9% and other causes in 8.6%.

There was a statistically significant difference between patients that were died vs those who were discharged for CRP level, PCT level, APACHE II scores and burn percentage (**Table 1**). A statistically significant difference was found between patients who were died and discharged in procalcitonin levels, APACHE II scores, PCT & APACHE II combined, and burn percentage. A moderate positive correlation was observed between PCT levels and burn percentage (r=0.492, P < 0.01). A similar moderate positive correlation was found between PCT levels and APACHE II scores (r=0.523, P < 0.01).

When procalcitonin levels between 0-3 and above 3 were compared, there was a 21.30 times higher risk for mortality in patients with PCT > 3. (ODDS Ratio: 21.30, 95% CI: 5.30-85.64). Patients with APACHE II score above 20 had 36.83 times higher risk of mortality than those with APACHE II below 20. (ODDS Ratio: 36.83, 95% CI: 9.41-144.13). When APACHE II score and PCT > 3 was combined, patients with APACHE II > 20 and PCT > 3 had a 58.50 times higher risk of mortality than those with APACHE II < 20 and/or PCT < 3 (ODDS Ratio: 58.5, 95% CI: 7.06-484.972).

Patients with over 60-80% burns were found to have 5.78 times higher risk of mortality than those with lower percentages. (ODDS Ratio: 5.78, 95% CI: 1.11-30.25). This risk increased to 15.26 time in those with over 80% burns. (ODDS Ratio: 15.26, 95% CI: 1.82-128.33).

Table 2. Comparison between patient parameters

		Findings		*P*
		Exitus	Discharge	
		n (%)	n (%)	
PCT	> 3	19 (86..4%)	3 (13..6%)	[1]0.001**
	0-3	11 (22.9%)	37 (77.1%)	
APACHE II	> 20	26 (86.7%)	6 (15%)	[1]0.001**
	< 20	4 (13.3%)	34 (85%)	
PCT & APACHE II	Pct > 2 & APACHE II > 20	19 (63.3%)	2 (5%)	[1]0.001**
	Others	11 (36.7%)	38 (95%)	
Burn Percentage (%)	< 20%	2 (6.7%)	8 (20%)	[2]0.001**
	20-40%	1 (3.3%)	9 (22.5%)	
	40-60%	11 (36.7%)	20 (50%)	
	60-80%	7 (23.3%)	2 (5%)	
	≥ 80%	9 (30%)	1 (2.5%)	
PCT	< 0.5	4 (13.3%)	16 (40%)	[2]0.001**
	0.5-2	5 (16.7%)	19 (47.5%)	
	2-10	10 (33.3%)	5 (12.5%)	
	≥ 10	11 (36.7%)	0 (0%)	
APACHE II	0-10	0 (0%)	16 (40%)	[2]0.001**
	10-20	4 (13.3%)	18 (45%)	
	20-30	22 (73.3%)	6 (15%)	
	≥ 30	4 (13.3%)	0 (0%)	

*[1]Continuity correction (Yates) test, [2]Ki-Kare test, **P < 0.01.*

Table 3. Sensitivity and Specificity of PCT for predicting mortality

Procalcitonin Level	Sensitivity	Specificity	PPV	NPV	Diagnostic Accuracy
1	86.67	70.00	68.42	87.50	77.14
2	70.00	87.50	80.77	79.55	80.00
3	63.33	92.50	86.36	77.08	80.00
4	63.33	95.00	90.48	77.55	81.43
5	56.67	100.00	100.00	75.47	81.43
7	50.00	100.00	100.00	72.73	78.57

PPV: Positive Predictive Values; NPV: Negative Predictive Values.

Patients with PCT between 2-10 were at 3.5 times risk (ODDS Ratio: 3.5, 95% CI: 1.05-11.69), and those with PCT above 10 were at 22.58 more risk (ODDS Ratio: 22.58, 95% CI: 2.71-187.97) than those with lower PCT levels. Patients with APACHE II score between 20-30 had a 18.33 times risk (ODDS Ratio: 18.33, 95% CI: 5.65-59.63) and those with APACHE II above 30 had a 5.2 times risk when compared to patients with lower scores (ODDS Ratio: 5.2, 95% CI: 0.55-48.96). PCT levels, APACHE II scores and burn percentages for patients who were deceased and survived are shown in **Table 2**.

Procalcitonin was found to have the highest diagnostic value when above 2. APACHE II was found to have the best predictive value for mortality when above 20. The sensitivity, specificity, positive predictive and negative predictive values plus diagnostic accuracy for PCT above 1 ng/ml were 86.7%, 70%, 68.4%, 87.5% and 77.1%; for PCT above 2 ng/ml were 70%, 87.5%, 80.8%, 79.6% and 80%; PCT above 3 ng/ml were 62.3%, 92.5%, 83.3%, 77.0% and 80% for APACHE II above 20 were 86.7%, 87.5%, 83.9%, 89.8% and 87.1% respectively. (**Tables 3**, **4**; **Figures 1**, **2**)

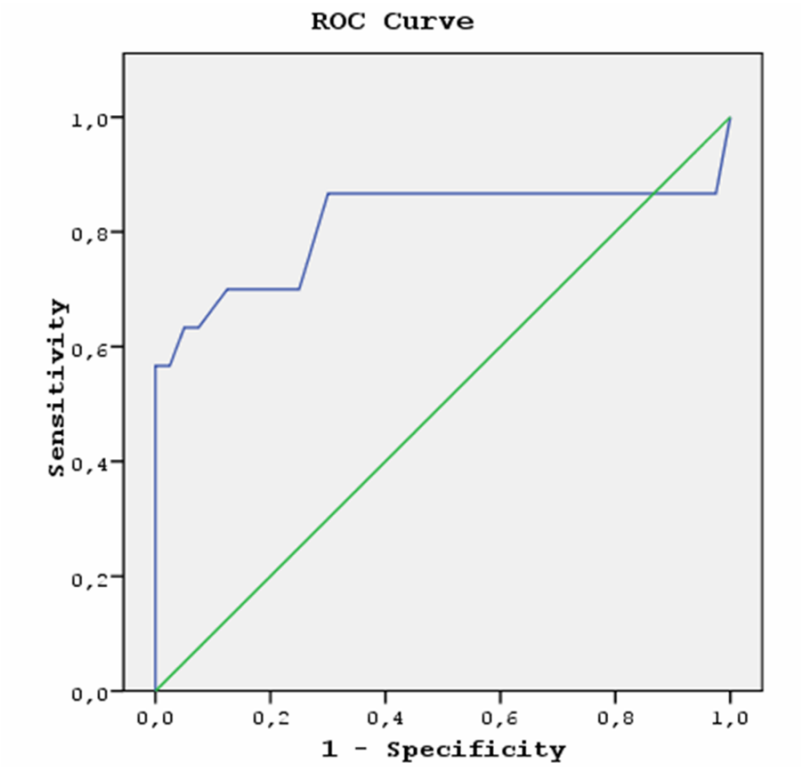
When regression analysis of the effects of procalcitonin levels, APACHE II scores and burn percentages were performed, the model was found to be statistically significant (P < 0.001), the Negelkerke R square level was 0.680, the models explanitory coefficient was found as 85.7%. The effect of procalcitonin level and APACHE II score were found to be statistically significant (P < 0.05, P < 0.01). Loss of patient was found to be 6.068 times more for high procalcitonin levels and 12.550 times more for high APACHE II score. The effect of burn percentage on the model was not statistically significant (P > 0.05) (**Table 5**).

Discussion

Burns continue to be a serious medical problem as it not only effect the skin but all vital

Table 4. APACHE II score versus mortality

APACHE II	Sensitivity	Specificity	PPV	NPV	Diagnostic Accuracy
15	100.00	75.00	75.00	100.00	85.71
18	100.00	82.50	81.08	100.00	90.00
19	90.00	82.50	79.41	91.67	85.71
20	86.67	87.50	83.87	89.74	87.14
22	83.33	90.00	86.21	87.80	87.14
23	80.00	92.50	88.89	86.05	87.14
24	73.33	92.50	88.00	82.22	84.29
25	73.33	95.00	91.67	82.61	85.71
26	66.67	97.50	95.24	79.59	84.29
27	60.00	97.50	94.74	76.47	81.43
28	43.33	97.50	92.86	69.64	74.29
29	30.00	97.50	90.00	65.00	68.57



Area Under the Curve

Test Result Variable(s): procalcitonin

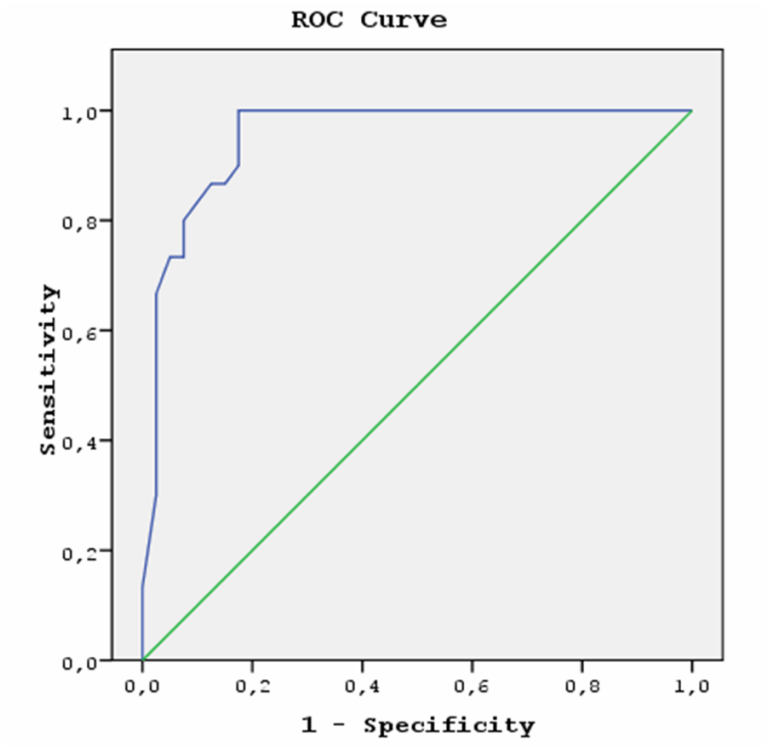
Area	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
,813	,062	,000	,691	,935

Figure 1. ROC Curve and AUC for PCT.

systems. Advanced age, co-morbidities, burn percentage, sepsis and multi-organ failure are important risk factors for mortality. ICU admission also carries serious risk in these patients [12, 13]. Scoring systems such as APACHE II, SAPS, SOFA and PRISM for pediatric patients, are frequently used for predicting mortality in ICU patients. However none of these scoring systems are specific or include parameters for burn patients. They are therefore not accurate in predicting mortality in this specific group of patients.

Pavoni et al reported that SAPS and SOFA scores, burn percentage, burn degree, development of sepsis, presence of inhalation burn, development of respiratory insufficiency, time of escarotomy and time spent in ICU were predictors of mortality in burn patients [13]. There are several studies that foresee a value of PCT in predicting mortality in these patients. In our study, we aimed to demonstrate the predictive value of PCT for burn patients' mortality. Seoane et al found a correlation between PCT and hypoperfusion in burn patients [14]. However, their study also found no significant difference between patients with sepsis, serious sepsis and septic shock. SOFA, another ICU scoring system was also analysed and showed no correlation with PCT in these patients.

Most studies regarding PCT have been conducted on patients with sepsis with the aim of determining its use for predicting mortality [9, 14-16]. While there are studies



Area Under the Curve

Test Result Variable(s): apache

Area	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
,952	,025	,000	,904	1,000

Figure 2. ROC Curve and AUC for APACHE II.

Table 5. Logistical Regression Analysis for PCT, APACHE II and Burn percentage

	B	S.E.	P	Exp (B)	95% CI	
					Lower	Upper
Burn (%)			0.533			
20-40%	-0.928	1.549	0.549	0.395	0.019	8.231
40-60%	0.169	1.194	0.887	1.184	0.114	12.295
60-80%	1.445	1.530	0.345	4.242	0.211	85.125
≥ 80%	1.340	1.604	0.403	3.820	0.165	88.582
PCT > 3	2.088	0.911	0.022*	8.068	1.353	48.120
APACHE II > 20	2.530	0.825	0.002**	12.550	2.489	63.270
Constant	-2.508	1.100	0.023	0.081		

P < 0.05, P < 0.01. CI: Confidence intervals.

analysing the correlation between PCT and CRP in patients with sepsis, they are few in number. There are even fewer studies on the correlation of PCT and CRP with mortality in burn patients. In their study on the value of admittance PCT for short term mortality in ICU, Meng et al reported a link between high PCT concentration and organ dysfunction and insufficiency, postoperative complications and bad outcome [15]. PCT ≥ 10 ng/mL was found to be significant in predicting short term mortality. Also, PCT-Q test was found to be more valuable at predicting short term mortality when compared to APACHE II and CRP.

Travaglino et al reported a positive correlation between PCT and APACHE II scores in patients with sepsis [17]. A seperate study reported that PCT and CRP were worse predictors of mortality in septic patients, when compared to APACHE II scores [16]. Similar to reports in literatüre, our study also found that CRP levels were lower in patients who were deceased when compared to those who survived. We therefore do not beleive that CRP can be an indicator of mortality in these patients.

In a cohord of 175 burn patients, Kim et al compared PCT at 48th hour and mortality [18]. Mortality was 10% in patients with PCT 0.05-0.49 ng/ml, 14.3% for patients with PCT between 0.5-0.99 ng/ml, 31.6% for PCT between 1-1.99 ng/ml, 60.9% for PCT between 2-4.99 ng/ml and 84.7% for patients with PCT of 20 ng/ml. The authors concluded that there was an increased mortality (> 60%) in patients with PCT above 2 ng/ml when compared to those below 2 ng/ml. The authors recommend antibiotics for patients with PCT > 2 ng/ml at 48th hour, although prophylactic antibiotic use is not routinely recommended in burn patients, However, this study included all patients hospi-

talized for burns, not just those in ICU. Similar to reports in literature, when PCT levels and mortality were compared, PCT was found to be higher in patients who were deceased in our study. Mortality was 16.33 times higher in patients with PCT > 2 ng/ml, 3.5 times higher for PCT 2 ng/ml-10 ng/ml and 22.56 times higher for PCT > 10 ng/ml. These rates are clearly higher than those reported by Kim et al and can be explained as mortality is multi-factorial in these patients (age, burn percentage and degree, comorbidities etc.) [18]. Data from our study suggests that prophylactic antibiotics may not be required for burn patients with PCT < 2 ng/ml as these patients' mortality is low. However, larger prospective studies are required for a definative suggestion to be made.

Our primary aim in this study was to study the correlation between PCT and mortality in burn patients admitted to ICU and to also determine if the combination of PCT with APACHE II score would be more helpful in determining mortality. Unlike studies in literatüre, we found that in patients with both PCT > 3 ng/ml and APACHE II > 20, mortality was 90.47%. Mortality was 81.25% in patients with only APACHE II > 20 and 80.76% for those with only PCT > 3 ng/ml. Logistic regression analysis demonstrated a significant effect of higher APACHE II scores and PCT levels on mortality.

Conclusion

High mortality is expected in patients admitted to ICU for burns. CRP and PCT are especially used for the diagnosis and followup of patients with sepsis. CRP measured within the first 48 hours is not an important predictor of mortality in these patients. A high PCT level in addition to high APACHE II score shows increased mortality in these patients. A high PCT level with the addition of a high APACHE II score can be effectively used for predicting mortality. A modified scoring system including both APACHE II and PCT levels may be useful in better predicting mortality in this group of patients. However, more studies are required to determine the correct cut-off level of PCT.

Disclosure of conflict of interest

None.

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