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Original Article

The role of procalcitonin and C-reactive protein in predicting candidemia in reanimation intensive care unit and burn unit patients

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Abstract

Aim: Predicting the diagnosis of candidemia remains a challenge for physicians. It is difficult to distinguish candidemia from other potential conditions, especially in patients under intensive care. Although blood culture is the gold standard in diagnosis, there is continued search for other markers that may be used for early prediction.
This study intended to assess if procalcitonin (PCT) and C-reactive protein (CRP) may be able to guide the course of Candidemia.
Materials and Methods: The study included patients over the age of 18 admitted to the Reanimation Intensive Care Unit and Burn Unit between June 2018 and June 2019 whose blood cultures exhibited growth of Candida species (spp.). Moreover, the patients' blood cultures were also tested for Gram negative and Grow positive bacterial growth that may accompany Candida species (spp.). For all patients, we recorded the PCT and CRP values three times.
Results: This study examined sixty-six patients exhibiting growth of Candida spp. in their blood cultures; 42 (64%) cases had no accompanying bacterial growth in their culture (Group 1). In addition to the growth of Candida spp., the blood cultures showed that 16 patients also had Gram-negative bacteremia (Group 2), and eight patients had Gram-positive bacteremia (Group 3). When a cut-off value of 0.5 ng/mL was considered for all candidemia patients, the first assessments did not show a statistically significant high value ($p=0.053$). However, when evaluated with bacteremia, the first PCT results were higher in patients with Gram-negative bacteremia. PCT and CRP changes over time were statistically significant based on two-way repeated measures comparisons ($p<0.05$). There was a positive correlation between PCT values and mortality ($p<0.01$).
Conclusion: We believe that the decrease in PCT and CRP values are helpful while clinically monitoring patients with candidemia.

Keywords: Candidemia; C-reactive protein; procalcitonin

INTRODUCTION

The term Candidemia is defined as the presence of Candida species in the blood. Candida in blood cultures should never be considered contaminants and should be evaluated as causative pathogens. Patients hospitalized in intensive care and burn units tend to develop invasive fungal infections due to risk factors that are often unavoidable (1).

Blood culture is the gold standard for diagnosing candidiasis. However, blood cultures take several days to cultivate these organisms. On the other hand, candidemia is difficult to distinguish from bacterial bloodstream infections, especially since clinical symptoms can easily be confused without microbiological evidence. This situation leads to the search for other clues beside the blood culture that may help with early diagnosis. Procalcitonin (PCT) is a precursor of calcitonin that is normally produced by thyroid C-cells; in the inflammatory process, it is secreted by peripheral blood mononuclear cells and liver (2). C-reactive protein (CRP) is one of the first acute phase proteins discovered. It has been named C-reactive protein because it precipitates the somatic C-polysaccharide of Streptococcus pneumoniae (3). CRP production is part of the acute phase response to most inflammation, infection, and tissue damage. These biomarkers have been used to

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help diagnose bacterial infections, but their role in fungal infections is open to debate (4-6).

The goal of this study was to evaluate the time period until blood culturing is concluded and treatment is initiated in patients diagnosed with candidemia; in addition, we planned to evaluate the significance of CRP and PCT values while monitoring patients during this process.

MATERIALS and METHODS

Hospital setting and patients

This study was conducted in a tertiary care university hospital with a 1350-bed capacity in Eastern Turkey. Reanimation intensive care and burn intensive care patients hospitalized between June 2018and June 2019 who exhibited Candida species growth in their blood culture were retrospectively included in the study; all patients in the study were over the age of 18. Patients who solely had Candida spp. growth in their blood cultures were classified as group 1, those with both Candida spp. and Gram negative bacterial growth were group 2, and patients with Candida spp. and gram positive growth were group 3. PCT and CRP values were recorded from the day that blood samples were taken for culturing, as well as one day before (first assessment) and one day after. The CRP and PCT results were also recorded from day two-three (second assessment) and days five-seven (third assessment) after the first blood was taken for culturing. In our hospital, the reference range used in the evaluation of PCT is 0-0.5 ng/dL, and for CRP is 0.035 mg/dL. Antifungal treatment time was also determined according to the day culturing was performed. The date of the blood culture was calculated according to the day of hospitalization.

Statistical analysis

The statistical analysis of data was conducted with IBM SPSS Statistics 22.0 (SPSS Inc., Chicago, IL, USA) software. Variables showing normal distribution were recorded as mean and standard deviation(SD); variables not showing normal distribution were recorded as "interquartile" (IQ) with median value. Variable changes over time were analyzed by using the Wilcoxon test for the analysis of variance (Friedman test) in paired comparisons. The One simple t-test and Independent T-test were used to compare the means. Statistical significance was accepted as $p < 0.05$.

The present study was approved by the Inonu University Medical Faculty non-interventional Ethical Committee. (approval no: 2020/444).

RESULTS

This study examined sixty-six patients exhibiting growth of Candida species (spp.) in their blood cultures, 42 (64%) cases had no accompanying bacterial growth in their culture (Group 1). In addition to the growth of Candida spp., the blood cultures showed that 16 (24.2%) patients also had Gram-negative bacteremia (Group 2), and 8 (12.1%) patients had Gram-positive bacteremia (Group 3). Table 1 displays the mean PCT and CRP values from 3 assessments according to groups. The cases consisted of 38 (57.6%) males and 28 (42.4%) females. The mean±SD of patients was 48.9±19.3 (min 18, max 93). When a cut-off value of 0.5 ng/mL was considered for all candidemia patients, the first PCT assessment did not show a statistically significant high value (p=0.053). However, when evaluated with bacteremia, the first PCT results were higher in patients with Gram-negative bacteremia compared to those without. In general, PCT elevation in the second and third assessments and CRP elevation in all three assessments were statistically significant in candidemia patients (Table 2). PCT and CRP changes over time were statistically significant based on two-way repeated measures comparisons (p<0.05).

Table 1. With respect to group, PCT (ng/mL) and CRP (mg/dL) values in the three assessments and the number of patients

Accompanying bacteremia		CRP first	CRP(2.)	CRP(3.)	PCT first	PCT(2.)	PCT(3.)
Only candidemia	Mean	10.7212	10.1297	8.2627	2.1220	1.7183	.7377
	N	42	38	37	39	33	29
	Std. Deviation	5.73159	6.13008	5.76968	3.47003	2.87871	.87172
Candidemia accompanied by	Mean	12.0841	10.3508	7.5023	8.7917	2.0440	1.9775
Gram-negative bacteremia	N	16	13	13	15	14	12
	Std. Deviation	5.26310	5.35636	3.83892	25.55898	3.22312	2.19453
Candidemia accompanied by	Mean	13.2075	17.9257	10.4243	1.6563	2.2343	2.8614
Gram-positive bacteremia	N	8	7	7	8	7	7
	Std. Deviation	4.00995	6.01267	4.34563	3.29090	4.44457	4.41513
Total	Mean	11.3530	11.1202	8.3547	3.6755	1.8696	1.3574
	N	66	58	57	62	54	48
	Std. Deviation	5.44594	6.38084	5.22410	12.93008	3.13493	2.17725

Table 2. The statistical significance of PCT (ng/mL) and CRP (mg/dL) values in the three assessments

	Cut off value = 0.5 ng/mL					
	t	df	Sig. (2-tailed)	Mean Difference	95% Confidence Interval for the Difference	
					Lower	Upper
PCTfirst	1.934	61	.058	3.17555	-.1081	6.4592
PCT(2.)	3.210	53	.002	1.36963	.5140	2.2253
PCT(3.)	2.728	47	.009	.85735	.2251	1.4896

	Cut off value= 0.35 mg/dL					
	t	df	Sig. (2-tailed)	Mean Difference	95% Confidence Interval for the Difference	
					Lower	Upper
CRPfirst	16.414	65	.000	11.00295	9.6642	12.3417
CRP(2.)	12.855	57	.000	10.77017	9.0924	12.4479
CRP(3.)	11.568	56	.000	8.00474	6.6186	9.3909

In the comparison of assessments made on the same day, there was a statistical difference between the first PCT assessment of group 1 and 2, and the third PCT assessments of group 1 & 2, group 2 & 3 and group 1 & 3 ($p<0.05$), no differences were detected in the other comparisons (Table 3).

Of all the patients, 21 (31.8%) died. There was a positive correlation between PCT values and mortality rate ($p<0.01$). As there was no difference between the two genders in terms of mortality, gender did not have an effect on death rate ($p>0.05$).

The time elapsed between the date that candida-positive blood was taken for culturing and the date of hospitalization was mean±SD, 27.04 ± 15.17 days. For patients in the reanimation intensive care unit, the time elapsed between candida-positive blood being drawn and admission was mean±SD 26.68±15.97 days, this duration was 27.77± 16.02 days for patients in the burn unit ($p=0.769$, t -.261, 95% CID lower -9.43, upper 7.25). The time between blood being drawn and culture results being reported was mean±SD 4.47±1.4 days. Treatment was initiated 2.07±2.65 days after the blood culture was conducted.

Table 3. Differences in PCT-CRP between the candidemia groups in terms of same day assessments

		p	t	95% Confidence for the difference (Lower) (Upper)
PCT first assess.	Group1-Group2	**0.003**	-1.007	(-20.85) (7.51)
PCT first assess.	Group1-Group3	0.782	0.349	(-2.22) (3.15)
PCT first assess.	Group2-Group3	0.169	0.778	(-11.9) (26.21)
PCT 2. assess.	Group1-Group2	0.809	-3.42	(-2.24) (1.59)
PCT 2. assess.	Group1-Group3	0.260	-0.390	(-3.19) (2.16)
PCT 2. assess.	Grup2- Grup3	0.451	0.451	(-3.72) (3.34)
PCT 3. assess.	Group1-Group2	**0.000**	-1.896	(-2.65) (0.17)
PCT 3. assess.	Group1-Group3	**0.000**	-1.267	(-6.20) (1.96)
PCT 3. assess.	Group2-Group3	**0.035**	-0.495	(-5.02) (3.25)
CRPfirst assess.	Group1-Group2	0.503	-0.827	(-4.66) (1.93)
CRPfirst assess.	Group1-Group3	0.144	-1.169	(-6.76) (1.79)
CRPfirst assess.	Group2-Group3	0.382	-0.530	(-5.52) (3.27)
CRP 2. assess.	Group1-Group2	0.837	-0.116	(-4.06) (3.62)
CRP 2. assess.	Group1-Group3	0.830	-3.10	(-12.86) (-2.72)
CRP 2. assess.	Group2-Group3	0.946	-2.89	(-13.07) (-2.07)
CRP 3. assess.	Group1-Group2	0.305	0.441	(-2.71) (4.23)
CRP 3. assess.	Group1-Group3	0.666	-0.938	(-6.81) (2.48)
CRP 3. assess.	Group2-Group3	0.575	-1.552	(-6.87) (1.03)

There was no statistically significant correlation between mortality rate due to candida infection and gender, treatment initiation time and the Candida species (Table 4).

Table 4. Comparison of mortality rate due to candida infection and gender, treatment initiation time and the Candida species

		Mortality rate (%)	--P-- X^2
Gender	Female	%39.3 (11/28)	P=0.379 X^2=0.775
	Male	%28.9 (11/38)	
Duration between the start of blood culture - initiation of treatment	3 days or less	%32.6 (15/41)	P=0.959 X^2=0.003
	4 days or more	%33.3 (5/10)	
Species of Candida	*C. albicans*	%42.9 (3/7)	P=0.385 X^2=3.073
	C. tropicalis	%0.0 (0/2)	
	C. glabrata	%57.1 (4/7)	
	C. parapsilosis	%30.0 (15/50)	

DISCUSSION

In this study, we evaluated adult cases of candidemia who were being monitored in the Reanimation and Burn Units, where critical patients are typically found, within one year period. Within this time period, 66 cases of candidemia were retrospectively identified. A single center study from Japan evaluated 11 cases of candidemia within a similar time span. In these fungemia cases, Bamba et al. evaluated the significance of presepsin as well as PCT and CRP. Two patients had concomitant bacterial presence, four had PCT elevation, and one patient had mild CRP elevation. Five (45%) patients were male. The rate of mortality was 36%. Of the patients who died, three were male and one was female. The species present in the blood culture of mortal cases were *C. tropicalis* in two and *C. albicans* in one patient (9). In our study, 38 (57.6%) patients were male. Of all the cases, 21 (31.8%) were mortal. A positive correlation was observed between PCT values and mortality ($p<0.01$). Gender and the species of Candida did not have an effect on death rate ($p>0.05$) (Table 4).

In our study, when all candidemia groups were evaluated collectively, there was no statistical significance in the first PCT assessment ($p=0.058$) (Table 2). When evaluated with bacteremia, the first PCT results were higher in patients with Gram negative bacteremia compared to those without. In the literature, Gram negative bacteremia had a stronger correlation to PCT elevation in comparison to candidemia and Gram positive bacteremia. A study by Thomas-Ruddel and colleagues reported that PCT elevation was significantly greater in Gram-negative bacteremia when compared to Gram-positive bacteremia and candidemia ($p<0.001$) (5).

In our study, we evaluated the changes in CRP and PCT in cases of candidemia as well as in cases of candidemia accompanied by Gram-negative bacteremia and candidemia with Gram-positive bacteremia (Table 1). In candidemia not accompanied by bacteremia, there were still changes during observation. When evaluating the third assessment (control blood taken one week after blood culture was performed) of all groups, patients with candidemia demonstrated a PCT value of mean±SD 0.737±0.87 ng/mL; this value was mean±SD 1.97±2.19 ng/mL in patients with Gram-negative bacteremia, and mean±SD 2.86 ±4.41 ng/mL in patients with Gram-positive bacteremia. Contrary to what is widely known, this result implies that PCT follow-up is only viable in patients with candidemia alone. Nevertheless, the limited number of patients with concomitant bacteremia may indicate that clinical trials with more patients are required.

When evaluating all candidemia cases in our study, it was determined that PCT elevation in the second and third assessments and CRP elevation in all three assessments were statistically significant (Table 2). Previous research has found that collective evaluation of CRP, PCT, and IL-6 increases the sensitivity and specificity of diagnosing Candida sepsis (8).

In contrast, candidemia accompanied by bacteremia may exhibit confusing CRP and PCT follow-up results. In a systematic analysis study, Cortegiani and colleagues advised that PCT should not be used in the differential diagnosis of candidemia and bacteremia (7). In the comparison of assessments with respect to day, there was a statistical difference between the first PCT assessment of group 1 and 2, and the third PCT assessments of group 1 & 2, group 2 & 3 and group 1 & 3 ($p<0.05$), no differences were detected in the other comparisons (Table 3). These results suggest that the bacteremia accompanying candidemia may have a more substantial influence on PCT than it does on CRP.

The time between candida-positive blood being taken for culturing and the date of hospitalization was mean±SD, 27.04 ± 15.17 days. For patients in the reanimation intensive care unit, the time elapsed between candida-positive blood being drawn and admission was mean±SD 26.68±15.97 days, this duration was 27.77± 16.02 days for patients in the burn unit. No statistical difference was observed between the two units in terms of the time of detecting Candida spp. in blood culture and hospitalization ($p=0.769$).

The duration between the first and second PCT assessment was three days, and between the first and third PCT assessment was one week. The time between blood being drawn and culture results being reported was mean±SD 4.47±1.4 days. Treatment was initiated 2.07±2.65 days after the blood culture was conducted. The significant ($p< 0.05$) drop in PCT and CRP values following initiation of antifungal treatment suggests that PCT and CRP may be viable follow-up markers.

CONCLUSION

A recent study by Wu et al. stated that the collective evaluation of ΔPCT and ΔCRP may be more effective in distinguishing candidemia (10). Our study was designed retrospectively and this caused some limitations. The control group could not be evaluated retrospectively because the follow-up measurements were not regular. Future prospective studies should be conducted with control groups to fully understand the value of PCT and CRP follow-up in monitoring candidemia patients. Alongside this, we believe that the decrease in follow-up PCT and CRP values could be useful in clinical monitoring and should be taken into consideration.

Conflict of interest : The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical approval: The present study was approved by The Inonu University Medical Faculty non-interventional Ethical Committee. (Approval no: 2020/444).

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