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ASSOCIATION BETWEEN CHANGE IN SERUM PROCALCITONIN AND 28-DAY OUTCOMES IN PATIENTS WITH PRESUMED BACTERIAL SEPSIS
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ASSOCIATION BETWEEN CHANGE IN SERUM PROCALCITONIN AND 28-DAY OUTCOMES IN PATIENTS WITH PRESUMED BACTERIAL SEPSIS

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ABSTRACT

Introduction: **Sepsis remains a major cause of mortality worldwide despite the increase in deaths due to non-communicable diseases. Poor diagnostic capability and delay in confirming appropriateness of therapy are major contributors to these poor outcomes. Procalcitonin has emerged as a useful tool for diagnosis and prediction of clinical outcomes in patients with sepsis.**

Materials and methods: **The study was conducted as an observational cohort study at the Kenyatta National hospital. Patients with presumed bacterial sepsis were evaluated for procalcitonin levels on admission and 48 hours after initiation of treatment. Patients were allocated to the 2 study arms on the basis of the change in their procalcitonin levels over the initial 48 hours, with unexposed being those with a decline greater than 30% and exposed having a rise in procalcitonin levels or a decline of less than 30%. Outcomes were documented after a 28-day follow-up period.**

Results: **More patients (16.9%) died in the exposed than the unexposed study arm (7.4%); however, this difference was not statistically significant (p=0.075). Duration of hospital stay was longer in the exposed study arm (9 days vs 12) but this was also not statistically significant (p=0.077).**

Conclusion: **Procalcitonin kinetics may not be a useful predictor of clinical outcomes in non-ICU setting.**

INTRODUCTION

Despite advances in health and hygiene, infectious diseases still account for a large proportion of morbidity and mortality worldwide. According to the WHO Global burden of disease update of 2015, infectious and parasitic conditions were found to account for about 13% of disease-adjusted life years (DALYs) globally and 32% in Africa [1]. An overwhelming majority of infection-related hospitalisations occur in developing countries, particularly sub-Saharan Africa, where resources for diagnosis and treatment of infections are still limited.

The cost of infectious diseases remains high. A study of patients with sepsis and septic shock in an ICU in Brazil found the average cost of management per patient to be over 17,000 US dollars and roughly 1,600 US dollars per day [2].

While Africa bears majority of the burden of disease of sepsis, it is also resource constrained. A survey of ICU health workers found that only 1.2%of respondents had the necessary resources to implement the Surviving sepsis campaign guidelines [3]. In a study conducted at 2 hospitals in Uganda, it was found that inadequacy of material resources and personnel was a predictor of mortality in patients with sepsis [4]. Based on this data, it can be inferred that besides having a larger population at risk of sepsis, clinical outcomes in Africa are worse as compared to those in high-income countries.

Given the high prevalence of sepsis worldwide, great emphasis has been placed on early and effective treatment. Rapid initiation of appropriate treatment in patients with severe infections has been found to reduce in-hospital mortality [5].

Analysis of clinical outcomes in sepsis has revealed that mortality rates still remain high particularly in severe sepsis and septic shock. Several studies have been carried out to determine prognostic factors and predictors of mortality in an attempt to identify patients requiring more aggressive interventions.

Surrogate markers of infection have shown promise in prediction of mortality outcomes. C-reactive protein has been validated by several studies for this purpose but has been found to have poor correlation with the clinical predictors [6]. Other markers that have been used as predictors of clinical outcomes include B type natriuretic peptide, copeptin and serum lactate [7,8].

Procalcitonin:

Procalcitonin was first described as a marker of sepsis by Assicott et al in 1993, who found high levels of a calcitonin-like substance and normal levels of mature calcitonin in patients with various infections [9]. Procalcitonin (PCT) is a 116-amino acid peptide that is a precursor of the hormone calcitonin. It is encoded by the gene CALC-1 located on chromosome 11, along with CGRP-1.

This gene has been found to possess pluripotentiality in the sense that a variety of products can be expressed from this single locus. Regulation of expression varies depending on the cells involved, the stimulus for cellular activation (eg sepsis) and the sensitivity of individual cells to this activation. The end result being calcitonin production following hormonal and metabolic stimuli whereas procalcitonin is produced mainly in

response to sepsis [10]. Concentrations of procalcitonin in non-septic individuals are usually less than 0.1 ng/mL.

PCT has been found to have very rapid kinetics during sepsis, rising to a detectable level within 3 to 4 hours of development of infection. It reaches its peak level within 6 hours and remains elevated for up to 24 hours after initiation of appropriate treatment [11].

PCT has a wide clinical utility. It has been found to be useful in diagnosis of sepsis [12], differentiating between bacterial and viral sepsis, and also in determining severity of sepsis [13]. PCT levels may also be elevated in some fungal and severe malarial infections.

In terms of clinical outcomes, various studies have shown a correlation between elevated PCT levels and critical illness [14]. A multicenter prospective trial done in Germany also confirmed that PCT is a reliable predictor of 28-day mortality in community-acquired pneumonia [15].

Study Justification:

Microbiological culture and sensitivity have previously been used as the gold standard to guide antibiotic therapy. However, it's unreliable due to low sensitivity and long turnaround time and may impact patient outcomes. Validation of procalcitonin for outcome prediction would be useful in more guiding therapy, thus helping to improve outcomes.

MATERIALS AND METHODS

This prospective comparative cohort study was conducted at the Kenyatta national hospital between December 2010 and June 2011. The study population consisted of patients presenting to the Kenyatta National Hospital A&E with features of systemic inflammation of suspected bacterial origin (based on clinical picture) and expected to be admitted to either the medical wards or Intensive Care Unit (ICU). These were identified by the AACP/SCCM 2008 guidelines.

Consecutive sampling was used to achieve a calculated sample size of 89 in each study arm. All patients above the age of 13 years presenting with clinical features of the systemic inflammatory response syndrome (SIRS) as documented by the admitting doctor were screened and interviewed. We excluded patients who had been on antibiotics within the preceding seven days, and those with non-infective inflammatory conditions including pancreatitis and burns. Patients with sepsis of surgical and gynaecological origin such as abscesses were also excluded as the investigator had no influence over the time to intervention.

All suitable candidates with an initial PCT level above 0.5ng/mL were recruited after seeking written consent from either the patient or guardian. Subjects were followed up and PCT levels repeated after 48 hours. Other standard laboratory and radiological investigations were requested where applicable.

The study variable was decline in PCT level over the initial 48 hours following admission. Based on the studies by Charles et al [16], the cut-off was set as 30%. An unexposed case was defined as any patient whose PCT level declined by more than 30% and was therefore expected to have a good outcome. On the other hand, an exposed case was defined as any patient whose PCT levels either increased or declined by less than 30%;

these were expected to have a poor outcome.

Blood samples drawn from each participant were centrifuged and plasma samples frozen for CRP and PCT assays which were run at the end of the data collection period. A human procalcitonin immunoassay was used to perform the procalcitonin levels. The test used in this study (Roche PCT) has been found to have a high sensitivity, with an ability to detect levels as low as 0.02ng/mL.

Patients were reviewed daily to determine their clinical outcomes, and these were documented at the end of the 4-week period. Those patients who were discharged from the hospital before the end of the study period were followed up by means of a telephone call to document their survival outcomes. An intention-to-treat approach was used for those patients who were lost to follow-up after discharge from the hospital.

All assays were run according to protocol and specific manufacturer's instructions where applicable. All laboratories conduct internal quality controls and participate in external quality assessment from time to time. Data collected was verified and analysis was done using the Statistical Package for Social Scientists (SPSS) version14.0.

RESULTS

A total of 1,238 patients were screened between December 2010 and June 2011. Of these, 286 (23.1%) met the SIRS criteria for presumed sepsis and were interviewed. 15 patients declined to give consent as they were unwilling to undergo repeated venipuncture and four other patients were excluded due to suspicion of a surgical cause of sepsis (1 peritonitis, 2 abscess and 1 pancreatitis). One patient developed a severe cutaneous drug reaction and was excluded because antibiotic treatment was withheld. 51 patients had negative baseline PCT results (levels below 0.5ng/mL) and were dropped from the study. Seven patients were discharged, and 11 others died before the initial 48 hours lapsed and were excluded from analysis.

This gave a total of 197 participants; 108 of these had a drop in PCT of more than 30% and were assigned to the unexposed arm. The remainder of the study participants had either a drop in PCT of less than 30% or a rise in PCT at 48 hours and were assigned to the exposed arm.

Baseline population characteristics: The demographic characteristics of the study population was found to be as summarized in Table 1 below.

Table 1

Baseline demographic characteristics

	UNEXPOSED	EXPOSED	TOTAL	p-VALUE
EMPLOYMENT STATUS: EMPLOYED	35 (32.4%)	37 (41.6%)	72 (36.5%)	0.375
SELF-EMPLOYED	28 (25.9%)	22 (24.7%)	50 (25.4%)	
UNEMPLOYED	45 (41.7%)	30 (33.7%)	75 (38.1%)	
LEVEL OF EDUCATION: NONE	10 (9.3%)	9 (10.1%)	19 (9.6%)	0.976
PRIMARY	50 (46.3%)	41 (46.1%)	91 (46.2%)	
SECONDARY	39 (36.1%)	33 (37.1%)	72 (36.5%)	
TERTIARY	9 (8.3%)	6 (6.7%)	15 (7.6%)	
MARITAL STATUS: MARRIED	84 (77.8%)	73 (82.0%)	157 (79.7%)	0.563
SINGLE	17 (15.7%)	14 (15.7%)	31 (15.7%)	
SEPARATED	4 (3.7%)	1 (1.1%)	5 (2.5%)	
WIDOWED	3 (2.8%)	1 (1.1%)	4 (2.0%)	
GENDER: MALE	58 (53.7%)	51 (57.3%)	109 (55%)	0.613
GENDER: FEMALE	50 (46.3%)	38 (42.7%)	88 (45%)	
AGE (years): MEAN	41.30	45.55	43.22	0.046
AGE: MEDIAN	38	45	40.0	

Baseline laboratory parameters: QQ plots were created for all baseline laboratory parameters to determine the normality of distribution. All baseline laboratory parameters had a non-normal distribution and analysis to determine significance in the differences between the 2 study arms was therefore done using non-parametric methods.

Analysis of the baseline laboratory parameters determined that the 2 arms were comparable for all variables except baseline PCT level (Table 2). This was found to be higher in the unexposed group (median 107.49) as compared to the exposed group (88.7). This difference was found to be statistically significant (p= 0.021).

Table 2

Comparison of baseline laboratory parameters in the 2 study arms

	GROUP	Mean	Median	p-value
WBC	Unexposed	12.1841	11.6000	
	Exposed	11.7798	12.1500	.936
NEUT %	Unexposed	77.566	79.250	
	Exposed	72.170	75.800	.963
ABS NEUT	Unexposed	9.6103	9.2750	
	Exposed	8.9498	9.6200	.878
ESR	Unexposed	43.59	41.50	
	Exposed	36.90	36.00	.560
CRP	Unexposed	177.1988	183.9400	
	Exposed	164.6865	134.6600	.499
PCT (0)	Unexposed	21.0988	2.6850	
	Exposed	4.5200	.8375	.021

Clinical outcomes: Clinical outcomes were recorded as either death or discharge. Duration of hospital stay (time to event) was recorded as number of days. Of the total population of 197, 174 (88.3%) were discharged while 23 (11.7%) had died by the end of the study period. 8 patients (7.4%) in the unexposed group died as compared to 15 (16.9%) in the exposed group.

Table 3

Clinical Outcomes

STUDY ARM	NO OF EVENTS (n, %)	SURVIVAL (n, %)
PCT decline >30%	8 (7.4%)	100 (92.6%)
PCT decline <30%	15 (16.9%)	74 (83.1%)
TOTAL	23 (11.7%)	174 (88.3%)

Eleven patients died before the initial 48-hour follow-up was over and were thus excluded from analysis. Survival analysis using the log rank (Mantel-Cox) test where the event was mortality and discharge was right-censored revealed no significant difference between the two groups (p=0.075) i.e. the study variable was not an independent determinant of clinical outcome.

For analysis of the duration of hospital stay, the event was taken as discharge and mortality was right-censored. Median hospital stay for the unexposed group was 9 days as compared to 12 days for the exposed group. However, this difference was not statistically significant (p =0.077).

Table 4

Duration of hospital stay

	UNEXPOSED	EXPOSED
Median duration (days)	9	12
Interquartile range	6-14	7-16

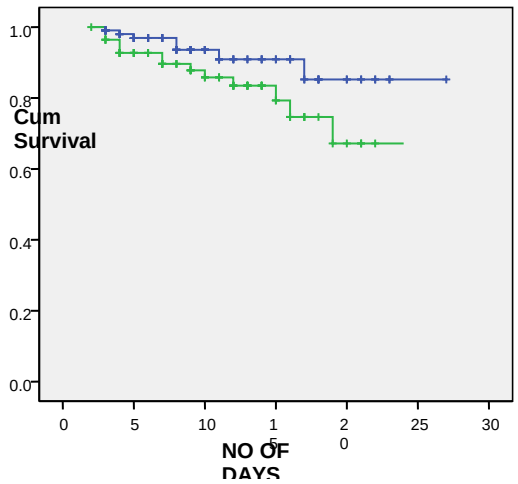

Fig 1: Time to Mortality

Effect of baseline parameters on outcome: Cox regression model was created for baseline laboratory parameters. Hazard function analysis showed no relation between the baseline parameters and clinical outcome i.e. the baseline parameters did not confound the relationship between group and survival.

Table 8

Relationship between baseline parameters and clinical outcome

	p-value	**95% CI**	
		Lower	**Upper**
WBC	.824	.731	1.484
NEUT	.924	.954	1.044
ABSNEUT	.925	.600	1.589
ESR	.778	.988	1.016
CRP	.149	.992	1.001
PCT (0)	.331	.991	1.026

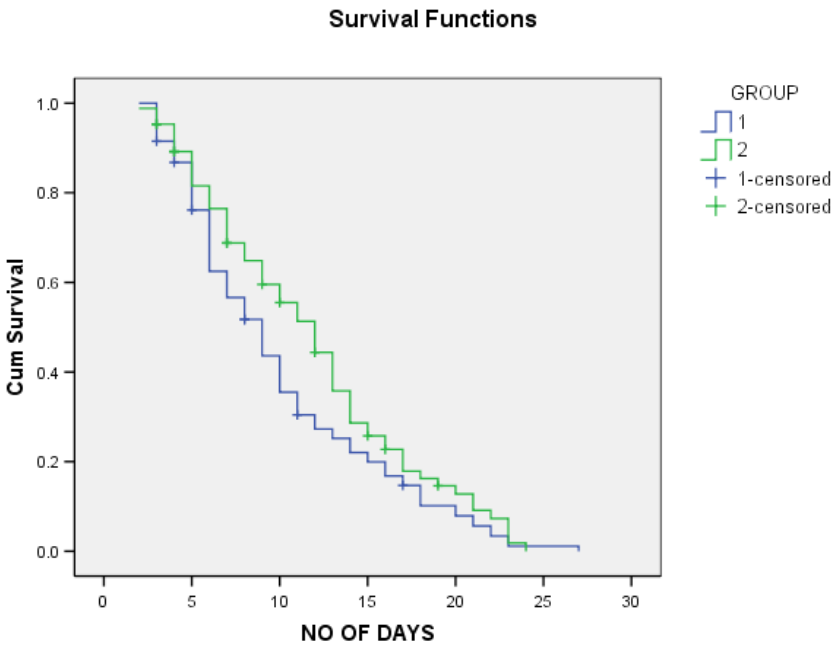

Fig 2: Time to discharge

Effect of other factors on outcome: Chi square test was used to analyse the effect of the severity of illness on clinical outcomes. Severity of illness (SIRS category) was found to have an effect on outcome, though this association was weak (p=0.044). Demographic characteristics were found not to have a significant effect on the relationship between the study variable and clinical outcome based on linear regression analysis.

Table 9

Effect of demographic characteristics on outcome

CHARACTERISTIC	p-VALUE
Age	0.268
Gender	0.523
Marital Status	0.659
Employment status	0.795
Level of Education	0.861

DISCUSSION

Mortality rate was higher in the exposed group than the unexposed group. Despite this finding, the study variable was found not to be a determinant of clinical outcome. This may be explained by the fact that the number of events was very small thus it was not possible to demonstrate statistical significance.

Exclusion of mortalities that occurred before the initial 48-hour follow-up period could also have explained the lack of association between clinical outcome and the study variable. The possibility of confounding factors that were not analysed in this study cannot be completely excluded. An attempt was made to control for the effect of some of these possible factors such as baseline laboratory parameters. The only parameter that demonstrated significant difference between the two study arms was baseline PCT level, which interestingly was higher in the unexposed group.

Previous studies such as that by Ghorbani et al [13] have shown a direct correlation between PCT and severity of illness. It would therefore have been expected that mortality would have occurred more frequently in the unexposed group. The fact that this did not occur suggests that perhaps other, stronger factors were at play. In particular, these results suggest that the PCT kinetics were indeed more reliable than the single baseline value in determining the outcomes. This is in keeping with findings of other studies such as that by Charles et al [16].

This study was done in patients presenting with any form of bacterial infection regardless of site or severity. As regards the severity of illness, majority of our patients had SIRS and therefore can be said to have had mild disease. It would therefore be expected that they would have had a good outcome. This may explain the finding of slightly better clinical outcomes than previous studies with a mortality rate of 11.7% as compared to 18% in other studies. However, it is of note that there were other patients who were not included in this analysis due to the fact that they died

before the initial 48-hour follow-up period.

A large number of previous studies have been done in the ICU setting, on critically ill patients. The fact that this study was done on patients with mild disease and the heterogeneity of the population in terms of severity of illness could be another factor that affected our findings. It is possible that our results may have been different if we had analysed each SIRS category separately. However, the number of patients with severe sepsis and septic shock were very few and this study was not powered for sub-group analysis of these in relation to outcome.

Due to the diverse clinical entities that were studied, it was not possible to create a uniform protocol of care for all patients. It was assumed that all patients received timely and appropriate care under their respective clinicians and wards. This may not necessarily have been the case. In addition, due to logistical issues, timing of treatment and availability/ cost of medications was not assessed in this study, but it may have contributed to the final outcome.

The Kenyatta National Hospital is a referral hospital that caters for a wide catchment area. More often than not, there is a shortage of bed space in the critical care unit. All the patients recruited into this study were managed in the medical wards, without regard to the severity of their illness. This may have had an impact on the outcomes, given the fact that most deaths occurred relatively early in the study period. Previous studies were mostly done in ICU settings meaning patients were followed up from the first day of onset of sepsis, whereas this study was done on community-acquired sepsis. The duration of illness was therefore widely varied in our study. This may also have had an impact on our findings.

CONCLUSION

Our results suggest that PCT kinetics over the initial 48 hours of treatment may not be useful in determining clinical outcomes.

RECOMMENDATION

Further studies need to be carried out on a larger population, with sub-analysis split according to severity of sepsis.

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