Original Article

The Value of Procalcitonin and C-reactive protein as early markers of Bacteraemia among patients with Haematological Malignancies receiving Chemotherapy: a cross-sectional study

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ABSTRACT

Background: The immune system of patients with haematological malignancies is suppressed during chemotherapy. This renders them vulnerable to frequent infections especially of the bacterial type. Timely diagnosis of these infections is difficult, because a severe infection may be asymptomatic or manifest only in the form of fever or malaise. There is need for laboratory markers that can detect an infectious process at an early stage. This study was aimed at determining the value of using Procalcitonin (PCT) and C reactive protein (CRP), for early diagnosis of infection in patients with haematological malignancies receiving chemotherapy.

Methods: This was a cross sectional study consisting of sixty eight (68) patients with haematological malignancies. Data from each participant including sex, age, clinical and laboratory data were collected after obtaining informed consent. Blood specimens were then collected for measurement of PCT, CRP and bacteriological analysis. Patients were divided into two groups; those with a culture positive and negative result. PCT and CRP concentrations were compared between groups using t-test and non-parametric statistical tests respectively. The area under ROC curve, sensitivity, specificity, likelihood ratio, and Spearman's correlation coefficient were also calculated.

Results: A total of 14 (20.6%) microorganisms were isolated, of which 10 were gram-positive bacteria and 4 were gram-negative bacilli. The mean values of PCT which were 6.1ng/mL in the bacteraemia group and 5.1ng/mL in the non-bacteraemia group, p=0.023 and median CRP values were 24.2 (6.43-48.15) in the bacteraemia and 23.5 (6.03-75.44) in the non-bacteraemia group, p=0.832. The area under curves was 0.52 (95% CI=0.57-0.84) for CRP and 0.70 (95% CI=0.35-0.69) for PCT. PCT value of greater than 4.7 ng/mL is diagnostic for infections (sensitivity 86%, specificity 54%) while that of CRP was 21mg/mL with the sensitivity and specificity of 64% and 44% respectively. Elevated levels of PCT as well as fever were significantly associated with bacteraemia.

Conclusion: PCT was a more reliable and sensitive marker of bacteraemia among patients with

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Key words: *Procalcitonin (PCT), C reactive protein (CRP), Haematological Malignancies, Bacteraemia Marker*

haematological malignancies receiving chemotherapy than CRP.

INTRODUCTION

Although major advances in the care of patients with malignant cancers over the past several decades have resulted in improved survival, infections remain a significant cause of morbidity and mortality[1]. These Patients are immunocompromised because of both the malignancy and the treatment used to manage it[2]. This renders them susceptible to bacterial and fungal infections[3]. Early diagnosis is difficult, because a severe infection may be asymptomatic or only manifests as fever or malaise[3]. Therefore, treatment for these infections is empirical, and broad-spectrum antibiotics are recommended for patients presenting with fever[4].

Recently advances in effective Chemotherapy drugs and regimens that have improved survival rates of these patients. In spite of the obvious improvements, chemotherapy still has certain disadvantages; it induces the breakdown of mucosal barriers, usually leading to high risk of neutropenic fever, which is associated with development of severe infection and high mortality. Thus, early initiation of antimicrobial therapy[5] is vital in the management of haematological cancer patients receiving intensive chemotherapy.

Bacteraemia may cause serious complications if left untreated, while treating viral illnesses or non-infective causes of in? ammation with antibiotics is not only ineffective, but also contributes to the development of resistance, increases costs, and the risks of toxicity and hypersensitivity reactions[6] hence, the need to find indicators of bacterial infection to allow for early commencement of treatment.

Procalcitonin (PCT) is a 116 amino acid precursor of the hormone calcitonin. It has been shown, that bacterial infections are capable of triggering ubiquitous expression of the calcitonin gene(CALC-1), along with constitutive release of PCT from a number of tissues and differentiated cell types, so that a significant increase of PCT levels can be observed in patients with severe bacterial infection and/or sepsis[9] .

C - reactive protein (CRP) is an acute-phase protein that is synthesized in the liver in response to interleukin 6 and is normally found at concentrations of less than 10 mg/L in the blood. During infectious or inflammatory disease states, CRP levels rise rapidly and its levels are frequently used to aid diagnosis of infections[10]. This study aimed at evaluating the value of PCT and CRP, in early diagnosis of bacterial infections in patients with haematological malignancies on chemotherapy.

METHODS

Study area and population

The study was conducted at the University Teaching Hospital (UTH) and Cancer Diseases Hospital (CDH) Lusaka, Zambia from February to July, 2016. Our study population included Patients with a haematological malignancy receiving chemotherapy whether presenting with fever or not. Patients between the ages of 3 to 70 years were recruited. Paediatric patientsseen from the paediatric oncology ward were included in the study, while adult patients were recruited from the Department of Medicine at the University Teaching Hospital. Other adult patients those with lymphomas were seen within the various wards of the Cancer Diseases Hospital.This study was approved by the Zambia Biomedical Research Ethics Committee.

Study design, algorithm and data collection

This was a cross sectional study involving sixty eight(68) patients. Patients were evaluated for clinical evidence of infection, and samples collected for processing. Prior to specimen collection the body temperature was taken and recorded by an attending nurse or clinician. Fever was defined as a sustained single oral temperature reading higher than 38.0°C. Neutropenia was defined as leukocyte count less than 1.0×109/L for adults and 1.5×109/L for paediatric patients. Patients referred to as “with bacteraemia” were those with a positive blood culture while “patients without bacteraemia” were

those with no bacteriological or clinical signs of infection, and did not receive antibiotics for at least one month.

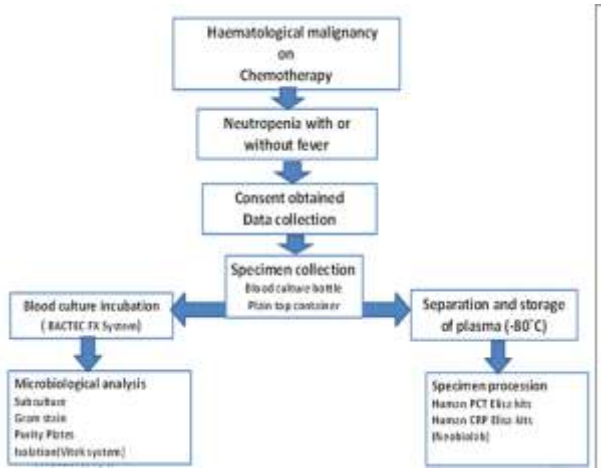

Figure 1: shows the process that was followed from participant recruitment, to specimen collection and processing

Demographic and clinical data were collected from patients and their files. The medical history data included the specific type of malignancy a patient has, whether or not they were chemotherapy, any other medication they had taken and the presence of medical conditions that may confound the research findings; included here were any major surgeries, burns, myocardial infarction and so on.

Specimen collection

Blood cultures were collected first using a 10 ml 21G syringe for adults and a 5 ml syringe for children. About 8mls of adult blood was then transferred into the blood culture bottle for adults and 1 to 3ml of blood into the paediatric blood culture bottles. The remaining 2mls of blood was transferred into plain containers and labelled appropriately. The blood specimens were transported to the laboratory within 1 hour after collection for preparation and storage. Blood culture bottles were incubated in the BACTEC™ FX blood culture system immediately upon arrival in the laboratory.

Before collection of blood, the skin was cleaned vigorously over the veni-puncture site in a circle approximately 5cm in diameter with an alcohol swab for about 30 seconds. Starting from the centre of the circle, 10% povidine iodine (betadine) was applied in ever widening circle until the entire circle was saturated with iodine, then left to dry for about 30 to 40 seconds. When collection was complete the iodine was removed from the skin with an alcohol swab. The cap was then removed and the septum disinfected with an alcohol swab and allowed to air dry.

Specimen analysis

The Human procalcitonin and C-reactive protein ELISA (Enzyme-Linked Immuno-sorbent Assay), a quantitative competitive immunoassay was used for measurement of PCT and CRP. It's manufactured and supplied by Neo-scientific group, United States of America. For bacteriological analysis specimens were incubated in the BACTEC™ FX blood culture system and Subculture unto Blood Agar, Chocolate Agar and Mac Conkey Agar and used the VITEK system for identification of microorganisms and their species.

Statistical analysis

Data was analysed with Statistical Package for Social Sciences (SPSS) version 21 and STATA version 12, results were summarised on to tables and graphs. All statistical tests were performed at 5% significance level or 95% confidence interval with p-value of less than 0.05 to determine statistical significance. Patients were grouped as blood culture positive (bacteraemia group) and blood culture negative (non-bacteraemia group) then compared with demographic and clinical characteristics as well as the levels of PCT and CRP in both groups. Descriptive statistics were reported in terms of absolute frequencies and percentages. Distributions of CRP data were described in terms of median values and range, because of its non-normal distribution. Comparison between groups was performed using the nonparametric Mann–Whitney U test for CRP. Procalcitonin values were normally distributed and were described in terms of mean

values. Comparisons between groups were performed using an independent t-test. Data was calculated for sensitivity and specificity, derived from receiver operating characteristics (ROC) curve with blood culture as a reference. Performance indicators of PCT and CRP for various cut-off values were also analysed.

RESULTS

Study participant characteristics

As shown in table 1, a total of 68 participants were enrolled in the study, of which 36 (52.9%) were males and 32 (47.1%) were females.The median (range) age was **14 (4-43)** years in the group with bacteraemia and **16 (4-70)**in the group without bacteraemia. Twenty two (22) of the participants presented with fever and neutropenia while 46 of them only had neutropenia. Bacteraemia was detected in 14 (20.6%) of the 68 patients using blood culture. All patients were suffering from a haematological malignancy and were receiving chemotherapy. Amongst the diagnoses were acute leukaemia (26.5%), Chronic leukaemia (16.2%), Hodgkin's Lymphoma (13.2%), Non-Hodgkin Lymphoma (36.8%), Multiple myeloma (4.4%), Langerhan histiocytosis (2.9%).

*Table 04, shows the organisms isolated in patients with haematological malignancies. Fourteen (*14) blood cultures were positive out of the total sixty eight (68) patients enrolled in the study among patients with haematological malignancies and gram-positive organisms were the most frequent isolated agents responsible for 71% (10) of positive cultures, with gram-negative representing 29% (4). The most frequent microbial agents isolated were *staphylococcus spp, bacillus spp, Corynebacteria spp* and *E.coli*

Table 1: *Comparison of study participant characteristics between patients with and without bacterial infection*

Characteristic	All	Bacteraemia Present	No Bacteraemia present	P-Value
Number (%)	68	14 (20.6)	54 (79.4)	
Age (Median, range)	4-70	14 (4-43)	16 (4-70)	0.169[m]
Sex				
Males	36	7 (50%)	29 (53.7%)	0.805[c]
Females	32	7 (50%)	25 (46.3%)	
Underlying malignancy				
Leukaemia	29	8(57.1%)	21(39.6%)	0.554[f]
Lymphoma	34	6(42.9%)	28(52.8%)	
Multiple myeloma	3	0(0%)	3(5.7%)	
Langerhan histiocytosis	2	0(0%)	2(1.9%)	
Fever (≥38.0˚C)				
No	46	5 (35.7%)	41 (75.9%)	0.004[c]
Yes	22	9 (64.3%)	13 (24.1%)	
Biomarker				
CRP (median, range)		23.5 (6.03-75.44)mg/ml	24.2 (6.43-48.15)mg/ml	0.832[m]
PCT(Mean, SD)		6.1 ± 1.3ng/ml	5.1 ± 1.7ng/ml	0.023[t]

m = mann-whitney test used; c= chi-square; t= independent t test; f= fishers exact test reported r=range

As shown in the table above, all characteristics were not associated with bacteraemia except for PCT levels and presence of fever.

The distribution of PCT and CRP level between groups

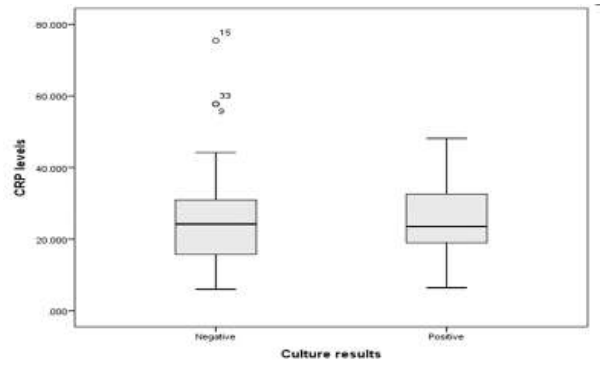

Figure 2: *The box plot showing distribution CRP levels for patients with bacteraemia and those without bacteraemia.*

As shown in figure 02, the median CRP concentrations for the bacteraemia group and non-bacteraemia group being 23.5 (6.03-75.44) mg/ml and 24.2 (6.43-48.15) mg/ml respectively were not

significantly different (p=0.832) among patients with haematological malignancies.

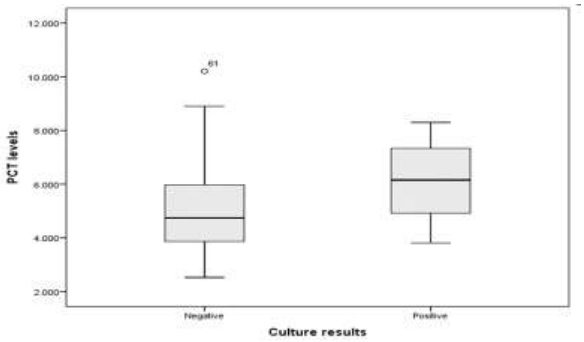

Figure 3: A box plot showing the distribution of PCT levels for patients with and without bacteraemia.

As shown in figure 03, the mean PCT concentrations for the group with bacteraemia and those without were 6.1 ± 1.3ng/ml and 5.1 ± 1.7ng/ml respectively. The bacteraemia group had higher mean PCT levels than those without bacteraemia (p=0.023).

Area under ROC curve for PCT and CRP

ROC Curves were used to determine the diagnostic value of using CRP and PCT to predict an infection in patients with haematological malignancies. As shown in **table 2** below, the area under curve (AUCs) was 0.702 (95% CI =0.35 - 0.69) for PCT and 0.519 (95% CI=0.57 – 0.84) for CRP. Area under curves values for each marker PCT (0.702) demonstrate greater discriminatory ability than CRP (0.52) to differentiate infections, suggesting that PCT is superior to CRP in detecting bacteraemia. The results also showed that the AUC for PCT (0.702) was statistically significant in discriminating bacteraemia (p=0.021), compared with CRP (p=0.832)

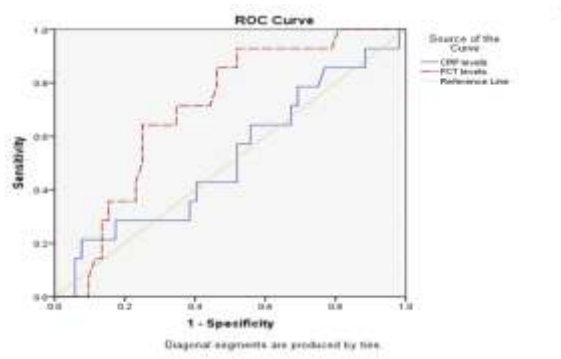

Figure 4: *Receiver operating characteristic curves for procalcitonin and C-reactive protein levels*

Table 2, *the table shows the areas under the ROC curves of PCT and CRP (70% and 52%, respectively), and the Confidence intervals (CI).*

Biomarker	AREA	Standard error	95% CI	P-Value
PCT	0.702	0.069	**0.345 – 0.693**	**0.021**
CRP	0.519	0.089	0.566 – 0.838	0.832

As can be seen from the table, the AUC for PCT (p=0.021) was significant compared with CRP in predicting a bacterial infection.

Performance indicators at different Cut-off values

From Table 3, Cut offs for PCT that we used were 4.7ng/ml, 5.0ng/ml, 5.1ng/ml. These cut-off values were chosen based on the best sensitivity and specificity obtained from ROC curve analysis and according to the literature. The cut offs for CRP were not satisfactory as both the sensitivity and specificity were low but a cut off of 21mg/ml gave us the sensitivity and specificity of 64% and 44% respectively.

Table 3: *Sensitivity, Specificity, positive and negative likelihood ratios for PCT and CRP at different cut offs.*

Markers	Cut offs	Sensitivity (%)	Specificity (%)	LR+	LR-
PCT	5.0	71.	61.5	1.85	0.47
	5.1	71.4	65.4	2.06	0.44
	4.7	86	54	1.87	0.26
CRP	20.88	64.3	42.3	1.11	0 .84
	21.0	64.3	44.2	1.15	0.64
	23.5	50	48	0.96	1.04

Legend: Positive likelihood ratio (LR+), negative likelihood ratio (LR-)

Correlations of PCT and CRP in patients with haematological malignancies

There was a positive correlation between levels of PCT and CRP, as can be seen in figure 05, in both groups with and without bacteraemia. This shows a close relationship between the two biomarkers. Spearman Correlation Coefficient indicated statistical significance r = 0.39 ($p < 0.001$).

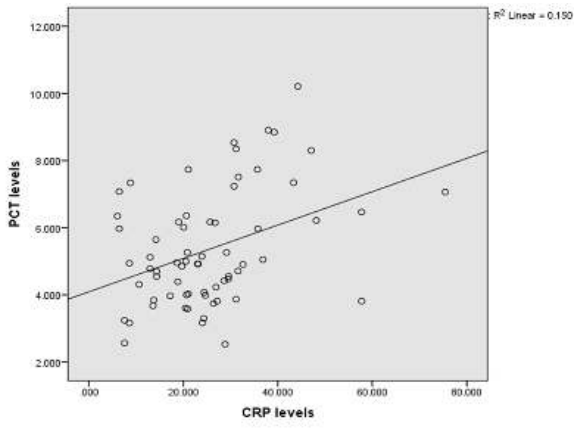

Figure 5: *Correlation between the serum concentrations of C-reactive protein (CRP) and procalcitonin (PCT)*

Bacterial infections isolated

Fourteen (14) blood cultures were positive out of the total sixty eight (68) patients enrolled in the study among patients with haematological malignancies and gram-positive organisms were the most frequent isolated agents responsible for 71% (10) of positive cultures, with gram-negative representing 29% (4), as shown in **table 4**.

Table 4: Bacterial infections isolated from patients with haematological malignancies

ORGANISM		NO. OF ISOLATED
Gram Positive Bacteria (GPB)		
Coagulase Negative Staphylococcus	*-Staphylococcus hominis*	04
	-Staphylococcus epidermidis x2	
	-Staphylococcus capitis	
Staphylococcus aureus		02
Corynebacteria jeikeium		02
Bacillus spp		02
Gram Negative Bacteria (GNB)		
Klebsiela pneumonia		01
Escherichia coli		02
Enterobacter cloacae		01
TOTAL		**14**

As can be seen from the table, a higher distribution of gram positive bacteria has been noted in this study.

DISCUSSION

The value of the inflammatory biomarkers such as PCT and CRP, in the diagnosis and assessment of infection in non-neutropenic patients has been well established in clinical studies during the past decade[14]. Although it has been shown that PCT can also be produced by leukocytes[15], Carnino *et al*[16] reported that PCT and CRP react more, in deeply neutropenic patients their study done in Italy.

Ruokonen, Sauer and Kim in their separate studies involving immunocompromised patients recently demonstrated that these patients are also capable of producing high PCT serum levels in severe systemic bacterial or fungal infections[17-19]. Our results in which PCT levels were elevated in patients with bacteraemia in patients with neutropenia support these findings, despite there are concerns that these markers may be produced in low concentration in patients with neutropenia[20].

In our study PCT levels increased significantly in the presence of bacteraemia. The mean PCT levels were

statistically different in patients with bacteraemia and the group (p=0.023), with PCT being more elevated among patients with bacteraemia. This was not observed with CRP levels between the two groups as there was no significant differences between the two groups (p=0.832). These findings were similar to a study done by Marshal *et al*, where they found that PCT levels were higher (p< 0.01) in bacteraemia[21] but CRP showed no statistical significance (p=0.79) among HIV patients.

In this study the area under ROC curve for PCT was found to be 0.702 in contrast to 0.519 for CRP for discriminating between patients with bacteraemia and those without bacteraemia. It can be seen from these findings that CRP had poor discriminatory power and hence cannot be reliably used as a diagnostic marker of bacteraemia in patients with haematological malignancies receiving chemotherapy. In contrast PCT performed well in discriminating bacteraemia in these patients.

The cut offs for CRP were not satisfactory as both the sensitivity and specificity were low. The best cut off for PCT was 4.7ng/ml which corresponds to the sensitivity and specificity of 86% and 54% respectively with relatively favourable likelihood ratios as compared to other cut off values. In the clinical and Laboratory sense, these results imply that PCT is a marker that might help clinicians to detect bacteraemia early in patients with haematological malignancies on chemotherapy. A similar cut off for PCT reported in our study was also by suggested by Massaro *et al* where they reported that PCT concentrations of between 1ng/ml to 5ng/mL were strongly suggestive of bacteraemia[17]. However, PCT is better at detecting bacteria in blood but not necessarily its absence, since the specificity is not high enough. Therefore, we suggest that the use of this marker should always be followed up with standard microbiological analysis.

The characteristics of CRP, such as its insufficient specificity, and vulnerability to immuno-suppressant, are probably reflected by these results. It is also known to be a sensitive marker of inflammation caused by high tumour load, malignant cell lyses, or drug administration as well as infection[23]. This could have contributed to it being a poor marker of bacteraemia given our patient population. A study conducted in Italy by Dipalo *et al* demonstrated that bacterial infections are capable of triggering ubiquitous expression of the calcitonin gene (CALC-1) and release of PCT from many cell types. Fleischhack, Schüttrumpf and Sandri in separate studies that were done in German and Italy reported the specificity of PCT to bacterial than other causes of infections or inflammation[14, 23, 25.] This probably explains the superiority of PCT compared to CRP, in the diagnosis of bacteraemia which has been demonstrated in our study.

We further explored the relationship between PCT and CRP and found that there was positive correlation(r=0.39, p<0.001). These findings indicate a linkbetween the two markers. That is, the variations in PCT concentration were concomitant with the variations in CRP concentrations. Further, studies are required to determine the value of constructing combinations between PCT and CRP, this might give a higher diagnostic value than examine them individually.

From studies by Gencer, Perola and Rintalareported the incidence of bloodstream bacterial infections of between 7.7% and 37% in patients with neutropenic fever[19-21]. In this study we found the prevalence of bacterial infection in patient with haematological malignancies with neutropenia to be 20.6% (14) out of 68 patients.

In our study, Gram positive bacteria were the most commonly isolated organisms in comparison to Gram negative bacteria. This finding was in line with a study by Ramphal that indicated a shift in the cause of bacteraemia in cancer patients from predominance of gram-negative rods to gram-positive cocci[22]. The most common infective agent that we isolated is *Coagulase-negative staphylococci*, mainly *Staphylococcus epidermidis* similarly found by Hämäläinen[2]. The reasons for the

increase in gram positive organisms have not been clearly identified but this could suggest; indwelling intravascular devices, high dose chemotherapy inducing mucositis, more importantly prolonged neutropenia[2, 22, 23]. There is inherent risk of infection that some low-virulence gram positive organisms pose in immunocompromised patients[24].

Although, a shift in favour of gram positive organisms infection has been noted among patients with neutropenia, gram negative organisms are still important and are associated with high mortality[23].

CONCLUSION

Procalcitonin was a more reliable and sensitive marker of bacteraemia than CRP. Its measurement could be useful in the early diagnosis of bacterial infections in these patients. In contrast, the sensitivity and specificity for CRP are too low to safely rely on it as a marker of bacteraemia in patients with haematological malignancy; this is in spite of CRP being used routinely in clinical practice as an indicator of bacterial infections.

LIST OF ABBREVIATIONS

PCT, Procalcitonin; CRP, C-reactive protein; UTH,University Teaching Hospital; CDH,Cancer Diseases Hospital; ELISA, Enzyme-Linked Immuno-sorbent Assay; ROC,receiver operating characteristics; GPB,Gram Positive Bacteria;GNB, Gram negative Bacteria.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Zambia Biomedical Research Ethics Committee (UNZA BREC) ASSURANCE NO. FWA00000338 IRB00001131 of IORG0000774 (REF No.005-11-15) and permission to conduct the study was obtained from the UTH and CDH management. The study participants were provided with an information sheet and given a thorough explanation of intent and rationale of the research after which the patient gave written informed consent without duress, thus ensuring a true meeting of minds between the researcher and the patient. All this was done on a private one to one basis to avoid undue influence that may affect or substitute the patient's will for others.

ACKNOWLEDGEMENTS

We would like to thank those who have been of help over the course of this research, the Department of Pathology and Microbiology, Microbiology laboratory, the Tropical Enterology and Nutrition Group (TROPGAN) laboratory, Paediatric Oncology ward, the Department of medicine at the University Teaching Hospital (UTH) and the Cancer Diseases Hospital (CDH) in Lusaka and many departments around the University of Zambia.

FUNDING

The study was funded in part through the Moses Sinkala award

AVAILABILITY OF DATA AND MATERIALS

All data analysed in this study can be accessed on request to the corresponding author.

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

KMK, FSK & TK conceived the study. KMK performed data collection sample. KMK, FSK, TK, SKM, BMH, SM, MS, JN and SMCcontributed to data analysis and interpretation. All authors read and approved the final manuscript.

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