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Refocusing on what matters: Equity in access to quality healthcare services

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The use of recycled tissue expander in soft-tissue reconstruction: Our experience in a resource-constrained setting

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Extra – Anatomic bypass for abdominal aortic disease in era of endovascular: A case series

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January 2023

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Editorial

Refocusing on what matters: Equity in access to quality healthcare services

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Health equity has become a priority agenda for the Sustainable Development Goals (SDGs) across all countries (1). However, as research focused on examining inequalities in coverage of health services, not much is known about inequalities in access to quality health services (2). In part, this could be due to the difficulty of measuring the quality of care because it is complex and requires examining its multidimensional constructs. It could also be because many countries are not providing sufficient health services, and when coverage is lacking, quality is often not a priority. Many countries have dealt with the coverage problem over the years, not 100% still, but the availability of health services has significantly improved. Disparities in access to healthcare services persist across low- and middle-income countries (LMICs), despite significant advances in healthcare coverage over the last few decades (3). In some countries, coverage has increased significantly while the quality of care has remained low, whereas, in others, both coverage and quality of care remain problematic.

Many people often understand health equity as the ease with which one can access healthcare services. However, access alone is not enough. Studies have shown that even when everyone has equal access to care, the poor, racial and ethnic minority groups, and people with disabilities tend to get lower-quality care (3, 4). This demonstrates how, even with increased and equitable access to services, health improvements can be elusive unless those services are of sufficient quality. This also implies that quality improvement initiatives that focus solely on the general population without addressing racial and ethnic differences may result in unequal quality.

According to a recent study, poor quality healthcare kills 5.7 million people each year in LMICs, making it a greater barrier to lowering mortality rates than lack of access to healthcare, which kills 2.9 million people each year (2). This means that each year, 8.6 million individuals living in LMICs die due to poor-quality healthcare systems. Poor care exposes patients to risk, provides misleading data about healthcare system improvements, and may encourage corrupt and fraudulent behaviour by healthcare stakeholders.

Taking maternal and child health services as an example, coverage expansion in LMICs did not result in the expected progress in maternal and newborn health impact indicators (5). It is widely acknowledged that global measures of maternal and newborn health indicators often capture only contacts with the health system, with little information about the quality of care people received. However, increasing the coverage of contact-based interventions alone is insufficient to reduce maternal, newborn, and child mortality. Increased service coverage accompanied by standard service contents would significantly contribute to the elimination of preventable causes of maternal and child mortality.

Recent studies in Ethiopia and other sub-Saharan African countries have also shown that low-quality care is the only kind of care the majority of people receive. For example, in Ethiopia, studies have found low-quality antenatal care and family planning services (6, 7). The quality of care is even worse for marginalised communities, such as the less educated and those living in rural areas. As such, existing service delivery modalities require rethinking and restructuring to address the quality gap and reach vulnerable populations.

Expanding healthcare coverage without ensuring quality care serves no purpose for those in need other than damaging their trust in the healthcare system. As a result, health systems in LMICs should focus on producing positive impacts by ensuring equitable access to quality health services, adhering to standard care processes, and ensuring a positive user experience. Therefore, health systems should focus on monitoring and addressing gaps in the quality of care by identifying what matters most to people. These include implementing effective coverage as a primary strategy to bridge the quality gap. Effective coverage requires that performance be measured not only by the number of people the health system is able to reach but also by incorporating indicators to monitor the content of care

people receive (2). Moreover, quality improvement initiatives should primarily start in areas with poor access to healthcare services and directly consider the needs and experiences of poor and vulnerable populations.

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Original Article

Incidence and factors associated with pulmonary embolism among RT-PCR confirmed Covid-19 patients with upfront CT pulmonary angiography in Ethiopia: A nested case-control study

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Abstract

Introduction: *Pulmonary embolism is one of the complications of COVID-19, with reported incidence ranging from 3 to 33 % in non-ICU patients to as high as 40% among ICU patients. Since the clinical presentations of COVID-19 and Pulmonary embolism overlap, it is difficult to differentiate between these cases. This study aimed to assess the incidence of pulmonary embolism and associated factors among confirmed Covid-19 Patients in Ethiopia.*

Methods: *A nested case control study was conducted among 131 patients with COVID-19 (40 COVID-19 patients with Pulmonary embolism and 91 COVID-19 patients with no PE) who were on follow up from May, 2021 to May, 2022. Data was summarized using frequencies with percentages. A chi-square test/ Fisher's exact test was run to determine the presence of a significant difference between the exposure variables and the development of PE. To identify factors associated with the development of Pulmonary embolism, a multivariable Binary Logistic Regression model with sensitivity analysis was run.*

Results: *The incidence of PE was 30.5% (95% CI, 22.9% - 37.4%) in the cohort of patients for whom upfront CTPA was performed. The Chi-square/ Fisher's exact test results showed a significantly higher proportion of patients with PE tend to present with shortness of breath, chest pain and anosmia/ageusia than those with no PE. However, in a subsequent regression analysis, only chest pain was found to be significantly associated with the development of PE in COVID-19 patients (AOR= 3.24, 95% CI= 1.10, 9.54, p-value=0.033).*

Conclusion: *The incidence of PE among COVID-19 patients was found to be relatively lower than reports from other countries. Having chest pain was found to be a significant factor that indicates the development of PE, implying that in a setting where performing upfront CTPA is not practical, detailed symptom inquiry could serve as an important clinical criteria.*

Keywords*: COVID-19, CT Pulmonary Angiography, Pulmonary Embolism, nested case control, Ethiopia*
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Introduction

Coronavirus disease 2019 or (COVID-19) was a mere novelty and reached the odd newspaper headline prior to its identification as a global pandemic by the World Health Organization in the second week of March 2020 [1]. It causes a respiratory illness, and is transmitted mainly through respiratory droplet and direct contact [2]. As of August 18, 2022, there have been more than 590 million COVID cases globally that resulted in over 6.4 million deaths [3]. In Ethiopia, so far, a total of 492,848 cases were confirmed with over 7,571 deaths [4].

COVID presentation can vary from asymptomatic to severe and fatal cases. Previous reports demonstrated that most patients with SARS-CoV-2 infec-

tion are asymptomatic or develop mild COVID-19, approximately 14% develop severe COVID-19 that requires hospitalization and oxygen support, and 5% require admission to an intensive care unit [5-8]. In severe cases, COVID-19 can be complicated by Acute respiratory distress syndrome, sepsis and septic shock, and multi-organ failure, including acute kidney injury and cardiac injury [9].

Several risk factors like age, comorbidity and different laboratory indexes were associated with disease severity [10-14]. Asymptomatic persons seem to account for approximately 40% to 45% of SARS-CoV-2 infections, and they can transmit the virus to others for an extended period, perhaps longer than 14 days [15-17].

Pulmonary embolism is one of the complications of COVID; and is reported to occur in out-patients, non-ICU ward patients and ICU patients, with incidence ranging from 3 to 33 % in non ICU patients up to 40% in ICU patients, indicating that we should have a high index of suspicion for PE in ward and outpatient settings too [18-22]. Studies from France and Spain reported that COVID-19 has significantly increased the incidence of PE when compared with previous years, suggesting that SARS-CoV-2 by itself may be associated with significant increment in the risk of PE [23-24]. Obesity, severe parenchymal involvement, elevated white blood cell counts are some reported risk factors for the development of PE in COVID-19 patients [25].

Clinical presentations of COVID-19 and respiratory complications overlap with PE presentations. This makes distinguishing between ARDS, progression of pneumonia and/or PE in patients with COVID-19 poses a diagnostic challenge with important therapeutic implications. This diagnostic delay is especially worse in patients presenting with a major complaint other than dyspnea [26]. Fever and chest pain have been reported to have strong associations in some studies suggesting that clinical presentation in COVID related PEs might not always have dyspnea as a prominent symptom [24]. Another diagnostic challenge in COVID related PE is that the risk factors for PE in COVID patients were reported to be different from non-COVID patients, COVID related PEs have fewer risk factors, patients complained less frequently of leg swelling/pain, exhibited a more discrete rise in D-dimers, and thrombi affected smaller pulmonary arteries [24, 25]. Current guidelines recommend the use of non-contrast chest CT for severity assessment and monitoring of disease [27].

Therefore, this study aims to assess the incidence of pulmonary embolism and associated factors among RT-PCR Confirmed Covid-19 Patients with Upfront CT Pulmonary Angiography and managed at a private specialty clinic in Ethiopia.

Methodology

Study Design, Population and Sample size

The study used a case control design nested in a retrospective cohort study of COVID-19 patients admitted to MuluG health Services, a primary Internal Medicine, Gynecology and pediatric specialty center, which gives both outpatient and non-ICU in-patient services.

The cohort was planned to study treatment outcomes. The cohort population was composed of adult COVID-19 patients admitted to the hospital from May, 2021 to May, 2022 with a clinically suspected or laboratory confirmed COVID-19 pneumonia. During this period a total of 280 patients were seen in the hospital. Patients were admitted to the medical ward and referred to a set up with ICU care if they require > 5L of oxygen. From the original cohort, patients with RT-PCR COVID pneumonia for whom upfront CT pulmonary angiography was done were identified to build the nested case control in a ratio of 1 case to 2 controls where cases are patients with CT-finding of Pulmonary Thromboembolism and controls are those with no CT-finding of Pulmonary Thromboembolism. Eligible patients for whom the relevant exposure and outcomes variables are missing from the medical charts were further excluded.

Finally, a total of 131 patients were included in the study (40 COVID-19 patients with PE and 91 COVID-19 patients with no PE). (Figure 1)

Operational Definition

Pulmonary Thromboembolism*:* A clot in the pulmonary artery or one of its branches confirmed by CT-Angiography [28].

Data Collection and Quality Assurance

A pretested data abstraction tool was used to collect the patient data on the outcome variable (PE in COVID-19) and the exposure variables (socio-demographic, comorbid illness, symptoms, laboratory and radiologic characteristics).

Data was collected by four trained General Practitioners. To improve data quality, double data entry, and data cleaning through checking for inconsistencies, numerical errors and missing parameters was done. The patients' charts were referred to verify the collected data whenever discrepancies were observed. Once data cleaning was complete, data was exported to SPSS version 25.0 software for analysis.

Statistical Analysis

The exposure variables were summarized using frequencies with percentages. A chi-square test was run to determine the presence of a significant difference between the exposure variables and the development of PE among COVID-19 patients. Where the assumptions of the chi-square test failed, Fisher's exact test

was used. A statistically significant difference was detected for variables with a P-value of ≤ 0.05.

To identify factors associated with the development of PE among COVID-19 patients, a multivariable Binary Logistic Regression model with sensitivity analysis was run. Univariate analysis was done at a 25% level of significance to screen out independent variables to be fitted in the final model. The adequacy of the final model was assessed using the Hosmer and Lemeshow goodness of fit test and the final model fitted the data well ($x^2_{(7)}$ =4.752 and p-value = 0.690). For the Binary Logistic regression, a 95% confidence interval for AOR was calculated and variables with p-value ≤ 0.05 were considered as statistically associated with the development of PE among COVID-19 patients.

RESULT

Incidence of PE and Disease outcome among COVID-19 patients

The incidence of PE was 30.5% (95% CI, 22.9% - 37.4%) in the cohort of patients for whom upfront CTPA was performed. In terms of outcome,128 patients were discharged improved (39 COVID-19 patents with PE and 89 COVID-19 patients with no PE), of which 8 required ICU admission (2 COVID-19 patents with PE and 6 COVID-19 patients with no PE). The remaining three died (1 COVID-19 patient with PE and 2 COVID-19 patients with no PE). (**Figure 1**)

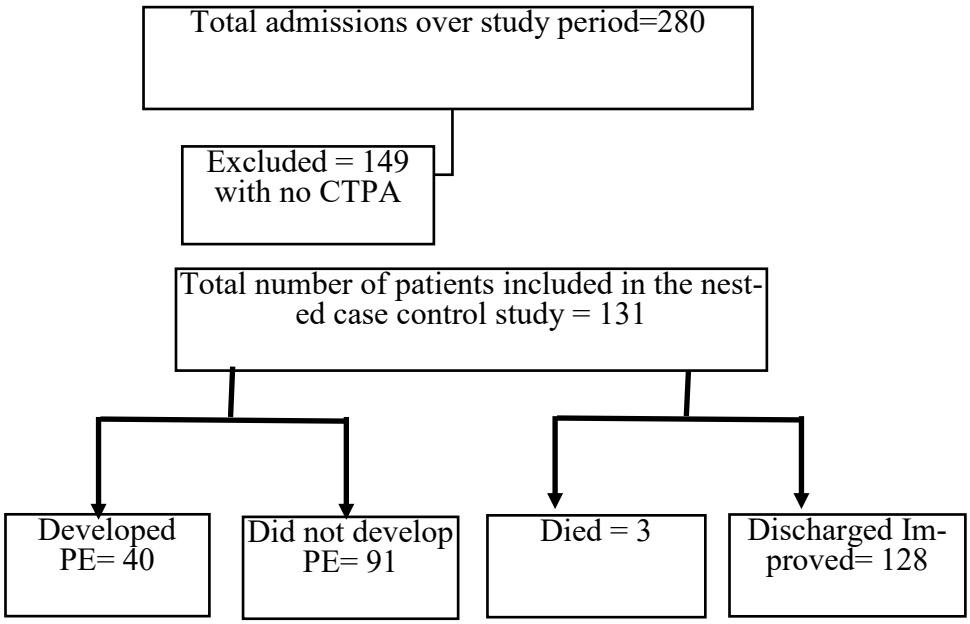

Figure 1: Flow chart showing the disposition of study participants in the final analysis, Addis Ababa, Ethiopia, 2022

Characteristics of socio-demographics, vaccination, and co-morbid illness

More than half of the participants (54.2%) were 60 years or older, and 56.5% were men. Forty-four (33.6%) of the participants had been vaccinated. Sixty nine (52.7%) participants had one or more comorbid illnesses. The most common illnesses were type II diabetes mellitus (30.5%), hypertension (30.5%) and cardiac illness (4.6%). On admission, the majority (82.4%) were diagnosed to have severe disease and the remaining 23 (17.6%) were moderate cases.

The results of the chi-square/Fisher's exact test revealed that none of these characteristics differed significantly between patients who developed PE and those who did not. (**Table 1**)

Table 1: Comparison of socio-demographic, vaccination, and co-morbid illness characteristics between COVID-19 patients with and without PE, Addis Ababa, Ethiopia, 2022 (n=131)

Table 1: Comparison of socio-demographic, vaccination, and co-morbid illness characteristics between COVID-19 patients with and without PE, Addis Ababa, Ethiopia, 2022 (n=131)

Variable	COVID-19 (%) (n=91)	COVID-19 + PE (%) (n=40)	Total (%) (n=131)	P-value
Age group (in years)				
< 60	42 (46.2)	18 (45.0)	60 (45.8)	0.903
>= 60	49 (53.8)	22 (55.0)	71 (54.2)	
Sex				
Female	41 (45.1)	16 (40.0)	57 (43.5)	0.591
Male	50 (54.9)	24 (60.0)	74 (56.5)	
Vaccination status				
Not Vaccinated	62 (68.1)	25 (62.5)	87 (66.4)	0.530
Vaccinated	29 (31.9)	15 (37.5)	44 (33.6)	
Comorbidity			69 (52.7%)	
Diabetes	24 (26.4)	16 (40.0)	40 (30.5)	0.119
Hypertension	26 (28.6)	14 (35.0)	40 (30.5)	0.462
Cardiac illness	3 (3.3)	3 (7.5)	6 (4.6)	0.369
Asthma	2 (2.2)	1 (2.5)	3 (2.3)	1.000
COVID-19 Severity				
Moderate	16 (17.6)	7 (17.5)	23 (17.6)	0.991
Severe	75 (82.4)	33 (82.5)	108 (82.4)	

Presenting symptoms characteristics

More than two-thirds of the participants (70.2%) had symptoms for no longer than a week prior to admission. The most frequent symptom was cough which was reported by 123 (93.9%) of the participants. Anorexia (77.1%), fatigue (72.5%), myalgia (51.9%), and arthralgia (51.1%) followed. Moreover, nearly half of the participants (48.1%) suffered from anosmia/ageusia. (**Figure 2**)

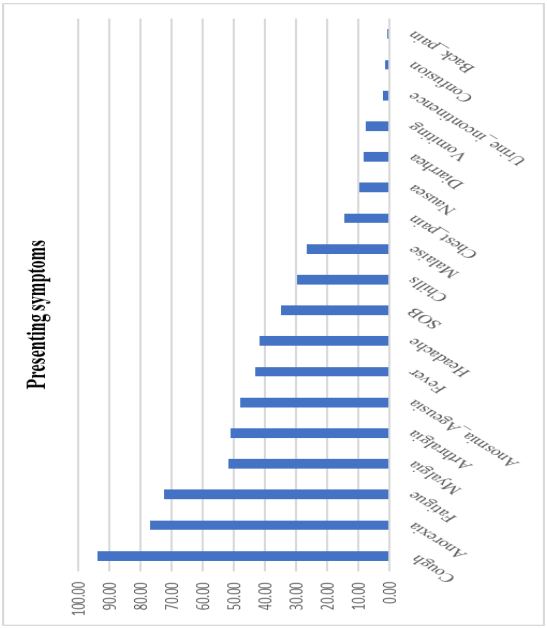

Figure 2: Presenting symptoms of participants with frequency, Addis Ababa, Ethiopia, 2022

Based on the result of the Chi-square/ Fisher's exact test, a significant difference in the symptom presentation was observed between groups with PE and those without PE in terms of the shortness of breath, chest pain and anosmia/ageusia. As a result, when compared to COVID-19 patients who did not develop PE, a significantly higher proportion of COVID-19 patients who developed PE presented with shortness of breath (29.7% Vs 47.5%, p=0.049), chest pain (8.8% Vs 27.5%, p=0.005) and anosmia/ageusia (41.8% Vs 62.5%, p=0.029). (**Table 2**)

Table 2: Comparison of presenting symptoms characteristics between COVID-19 patients with and without PE, Addis Ababa, Ethiopia, 2022 (n=131)

Variable	COVID-19 (%) (n=91)	COVID-19 + PE (%) (n=40)	P-value
Symptom duration			
≤7 days	64 (70.3)	28 (70.0)	0.970
>7 days	27 (29.7)	12 (30.0)	
Cough	84 (92.3)	39 (97.5)	0.434
SOB	27 (29.7)	19 (47.5)	**0.049***
Chest pain	8 (8.8)	11 (27.5)	**0.005***
Fever	32 (35.2)	13 (32.5)	0.767
Chills	23 (25.3)	16 (40.0)	0.090
Headache	38 (41.8)	17 (42.5)	0.937
Malaise	22 (24.2)	13 (32.5)	0.321
Fatigue	65 (71.4)	30 (75.0)	0.673
Arthralgia	42 (46.2)	25 (62.5)	0.085
Myalgia	43 (47.3)	25 (62.5)	0.108
Loss of appetite	68 (74.7)	33 (82.5)	0.329
Anosmia/ Ageusia	38 (41.8)	25 (62.5)	**0.029***
Diarrhea	8 (8.8)	3 (7.5)	1.000
Vomiting	6 (6.6)	4 (10.0)	0.493
Nausea	9 (9.9)	4 (10.0)	1.000

Baseline vital sign and laboratory biomarkers

Few patients presented with tachycardia, raised SBP and DBP, accounting for 32.8%, 22.1% and 14.5%, of the study population, respectively. On the other hand, the majority of patients had low oxygen saturation of less than 93% on room air (80.9%) and were hypothermic (72.5%).

The laboratory biomarkers report revealed that over two-third (70.2%) of the patients had a raised Neutrophil-to-Lymphocyte ratio (NLR), with 30 (22.9%) exceeding a ratio of 9. Polycythemia and thrombocytopenia/thrombocytosis were observed in 56.5% and 28.2% of the participants respectively. Furthermore, the renal panel test showed that 31 (23.7%) and 40 (30.5%) of the participants have raised BUN and creatinine, respectively.

According to the chi-square/Fisher's exact test result, none of these characteristics differed significantly between patients who developed PE and those who did not. (**Table 3**)

Variable		COVID-19 (%) (n=91)	COVID-19 + PE (%) (n=40)	Total (%) (n=131)	P-value
PR	<100	61 (67.0)	27 (67.5)	88 (67.2)	0.958
	≥ 100	30 (33.0)	13 (32.8)	43 (32.8)	
SBP	<140	71 (78.0)	31 (77.5)	102 (77.9)	0.947
	≥ 140	20 (22.0)	9 (22.5)	29 (22.1)	
DBP	<90	79 (86.8)	33 (82.5)	112 (85.5)	0.519
	≥ 90	12 (13.2)	7 (17.5)	19 (14.5)	
Sao2	≥ 93	14 (15.4)	11 (27.5)	25 (19.1)	0.104
	<93	77 (84.6)	29 (72.5)	106 (80.9)	
Temperature	<36.5	65 (71.4)	30 (75.0)	95 (72.5)	0.804
	36.5 – 37.5	20 (22.0)	7 (17.5)	27 (20.6)	
	>37.5	6 (6.6)	3 (7.5)	9 (6.9)	
NLR	≤ 3	27 (29.7)	12 (30.0)	39 (29.8)	0.431
	3-6	22 (24.2)	14 (35.0)	36 (27.5)	
	6-9	18 (19.8)	8 (20.0)	26 (19.8)	
	≥9	24 (26.4)	6 (15.0)	30 (22.9)	
HCT	≤ 45	44 (48.4)	13 (32.5)	57 (43.5)	0.092
	>45	47 (51.6)	27 (67.5)	74 (56.5)	
PLT	150-450	65 (71.4)	29 (72.5)	94 (71.8)	0.900
	<150, >450	26 (28.6)	11 (27.5)	37 (28.2)	
BUN	<20	66 (72.5)	34 (85.0)	100 (76.3)	0.122
	≥20	25 (27.5)	6 (15.0)	31 (23.7)	
Cr	<1.1	64 (70.3)	27 (67.5)	91 (69.5)	0.746
	≥ 1.1	27 (29.7)	13 (32.5)	40 (30.5)	

Factors associated with development of PE among COVID-19 patients

Univariate binary logistic regression was run at 25% level of significance to select variables to be included in the final multivariable binary logistic regression model and the following variables were found to be significant; age group, sex, vaccination status, symptom duration, shortness of breath, chest pain, anosmia/ageusia, cardiac illness, oxygen saturation and hematocrit level.

The final multivariable binary logistic regression model showed that only chest pain was significantly associated with the development of PE among COVID-19 patients at 5% level of significance.

Accordingly, after adjusting for other covariates included in the final regression model, the odds of developing PE among COVID-19 patients who presented with chest pain was 3.24 times higher than those who did not present with such symptom (AOR= 3.24, 95% CI= 1.10, 9.54, p-value=0.033). (**Table 4**)

Table 4: Factors associated with development of PE among COVID-19 patients, Addis Ababa, Ethiopia, 2022 (n=131)

Variable	COR (95% CI)	AOR (95% CI)	P-value
Age group (≥60 years)	1.05 (0.49, 2.21)	0.89 (0.39, 2.07)	0.794
Sex (Male)	1.23 (0.58, 2.62)	0.98 (0.42, 2.29)	0.962
Vaccination status (Yes**)**	1.33 (0.60, 2.92)	1.46 (0.62, 3.46)	0.387
Symptom duration (>7 days)	1.02 (0.45, 2.29)	1.15 (0.46, 2.92)	0.764
SOB (yes)	2.15 (0.99, 4.62)	1.63 (0.68, 3.92)	0.275
Chest pain (yes)	3.94 (1.44, 10.74)	3.24 (1.10, 9.54)	**0.033***
Anosmia/ Ageusia (yes)	2.33 (1.08, 4.99)	1.78 (0.77, 4.12)	0.179
Cardiac illness (yes)	2.38 (0.46, 12.33)	2.22 (0.37, 13.17)	0.380
Sao2 (<93%)	0.48 (0.19, 1.18)	0.66 (0.23, 1.89)	0.442
Hct (>45%)	1.94 (0.83, 4.24)	1.82 (0.77, 4.29)	0.173

Note: COR, Crude Odds ratio; AOR, Adjusted Odds ratio; CI, Confidence interval; *Statistically significant

DISCUSSION

The current study has assessed incidence of PE among hospitalized RT-PCR confirmed Covid-19 Patients with upfront CT Pulmonary Angiography in Ethiopia.

The majority of the study participants were older men with at least one comorbid illness and who presented with respiratory symptoms, particularly cough. The characteristics of the patients are consistent with the pattern of admission observed thus far. According to studies, these population groups are the most susceptible to developing symptomatic disease, more severe disease categories and, as a result, admission [10,17]. Additionally, it has been observed that COVID-19 infection is more likely to cause complications and poor treatment outcomes in these population groups [6,11]. Although the reports differed by location, nearly half of the participants (48.1%) claimed to have anosmia and/or ageusia, symptoms that were classified as atypical at the beginning of the pandemic. The high reported number could be due to an evolving disease presentation pattern, better patient reporting, or more thorough symptom inquiry.

The incidence of PE was found to be 30.5% (95% CI, 22.9% - 37.4%). This finding is relatively lower when compared to findings from countries like Egypt, Italy, Spain, and the United Arab Emirates, where incidence as high as 41.7% have been reported [29-34]. Furthermore, according to a meta-analysis report of 19 international studies involving a total of 2520 patients, the pooled prevalence of PE was 33% [35]. This relatively lower incidence could be explained by the relatively less severe disease pattern observed in Ethiopia and Africa in general, as reported by various studies. In terms of disease course and outcome, there was no discernible difference between groups with PE and those who do not have PE.

The commonest complaints of the study participants with PE, cough, anorexia, fatigue, myalgia and arthralgia, are atypical as compared with the common symptoms seen in PE patients during the pre COVID-19 era. Though these symptoms did not show significant association with PE, taking into account unusual presentations of PE in COVID will help reduce diagnostic delays [26].

According to the Chi-square/exact Fisher's test results, a significant difference in the symptom presentation between groups with PE and those without PE in terms of the shortness of breath, chest pain and anosmia/ageusia, indicating that patients with PE tend to present with these symptoms at a higher proportion than those with no PE. However, in a subsequent regression analysis, only chest pain was found to be significantly associated with the development of PE in COVID-19 patients. The odds of developing PE among COVID-19 patients who presented with chest pain was 3.24 times higher than those who did not present with such symptom. This suggests that, although COVID-19 infection typically manifests as respiratory symptoms that can be confused for PE, experiencing chest pain in particular could be an indication that the patient has developed PE. Chest pain was also found to be a significant predictor in a study conducted in Egypt [30].

The study's findings must be interpreted in light of the following strengths and limitations. Its strength is that this is the first study among Ethiopian patients.

Given the existing disparity in evidence, understanding the situation in our setup is crucial. In addition, the fact that upfront CTPA is not a standard diagnostic method used for COVID-19 patient assessment as it is not a cost-effective strategy, particularly in a resource-constrained setting, has made it challenging to conduct these types of studies. This has forced many studies to be conducted with a small number of patients, as few as 60 in some studies, but our study has included a relatively large number of patients which was sufficient to meet the objective of the research. The limitations of the study include that D-dimer, which has been reported to be a significant factor in a number of studies, was not assessed in our study. Furthermore, while is currently used as a standard test and is recommended for use in many settings, it is not the gold standard method modality for the diagnosis of PE because it may miss small and peripheral clots in small vessels and fails to differentiate between old and new clots. Moreover, the study did not involve multiple radiologists to confirm the consistency of the CT results.

Conclusion

The incidence of PE among COVID-19 patients was found to be relatively lower than reports from other countries. Having chest pain was found to be a significant factor that indicates the development of PE, necessitating careful evaluation and assessment of patients who exhibit this symptom. In a setting where performing upfront CTPA is not practical, detailed symptom inquiry could serve as an important clinical criteria to suspect PE and thus proceed to further confirmatory investigation.

List of Abbreviations

AARHB IRB…….Addis Ababa Regional Health Bureau Institutional Review Board
ARDS…….. Acute Respiratory Distress Syndrome
BUN……. Blood Urea Nitrogen
CI…… Confidence Interval
COVID-19……Coronavirus Disease 2019
CT…… Computed Tomography
CTPA ……. CT Pulmonary Angiography
DBP……. Diastolic Blood Pressure
HCT……..Hematocrit
ICU……..Intensive Care Unit
OR ……... Odds Ratio
PE …….. Pulmonary Embolism
PLT…… Platelet
PR…… Pulse Rate
RT-PCR……..Real Time Polymerase Chain Reaction
SARS-COV-2…… Severe Acute Respiratory Syndrome Coronavirus 2
SBP…….. Systolic Blood Pressure
Spo2…….. Oxygen Saturation
WHO…….. World Health Organization

Declaration

Ethics approval and consent to participate

The study was conducted after obtaining ethical clearance from AARHB IRB. Written informed consent was obtained from the medical director of the hospital to waive the consent of the participants. Anonymity of the participants was maintained by use of Medical record number in the research report. No other personal identifiers of the patients were used in the research report. Access to the collected information was limited to the investigators and confidentiality was maintained throughout the project.

Availability of data and materials: All relevant data are available upon reasonable request.

Competing interests: The authors declare that they have no Known competing interests

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Authors' Contribution: EKB conceived the study, prepared a data extraction sheet, collected and supervised data collection. TWL contributed to the conception, designed the study, performed statistical analysis and drafted the manuscript. TKT and EST contributed to the conception, collected and supervised data collection. EEM and KWG assisted in statistical analysis and drafting of the manuscript. MMA, AGA, YMG and MAN contributed to the conception of the study and collected data. All authors revised and approved the final manuscript. YFM contributed to the conception and proposal write up of the research.

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Original Article

The use of recycled tissue expander in soft-tissue reconstruction: our experience in a resource-constrained setting.

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Abstract

Background: *Reconstruction of scar excision defects with expanded flaps is a veritable option in reconstruction but unaffordable to patients in resource-poor settings. The recycling of the expanders is avoided for fear of infection. The study presents our preliminary experience with recycled tissue expanders in a resource-constrained setting.*

Patients/Methods: *This is a retrospective study of all patients who had tissue expansion using recycled expanders. The expanders were sterilized by boiling intermittently in sterile water over 12 hours and washed with ceftriazone just before surgery.*

Results: *A total of 14 expanders were used in all female patients with mean age of 25 years. About 71% of cases had successful expansion while 29% had implant extrusion of which only 7% was severe and had termination of expansion.*

Conclusion: *The success with recycled tissue expanders presents an opportunity to offer a reconstructive care to resource-constrained patients and improve the volume of patients undergoing expansion.*

Keywords: Recycled expanders, Resource-poor settings, Scar defect reconstruction
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Introduction

Scars arising from various forms of soft tissue injuries affect forms or function of different parts of the body and constitute a major reconstruction challenge to the reconstructive plastic surgeon. They are usually as a result of poorly managed wounds. These wound burdens are themselves a form of neglected epidemics in the developing nations.[1] A major factor that contributes to poor wound management and eventual development of unsightly scars is the paucity of work force especially in the specialty of reconstructive and aesthetic plastic surgery in Nigeria who are routinely faced with this daunting task [2]. The impact of function limiting scars on the work force remains disturbing in the resource poor nations where the affected persons are mainly in the active age group.[3]

The reconstruction of wounds and defects caused by excision of these scars is currently done with several options with their respective merits and demerits. These include direct closure, split thickness and full thickness skin grafting techniques, pedicled and free flaps, and the use tissue expansion techniques, which make up the reconstructive tool box.[4] The use of split-thickness skin graft though the commonest reconstruction modality employed by the plastic surgeons especially in the developing countries has limitations in which the need for a flap reconstruction often arises.[5,6] The use of flap option in reconstruction on the other hand is a highly preferred modality where applicable due to provision of sensate, stable cover, with aesthetic superiority.[7] Many flap options exist in the armamentarium of the reconstructive plastic surgeon for managing these defects. The common types are broadly classified as pedicled and free flaps respectively. Both free and pedicled flaps could be raised as expanded flaps exist which is produced by tissue expansion technique to achieve adequate size for complete coverage.[8]

Tissue expansion is a technique that expands soft

tissues to attain an optimal aesthetic and functional size required to achieve coverage of defects when direct closure is not feasible.[8] This modality in addition to providing sensate, stable and aesthetically stable flaps, also ensures contour and colour match. [9] The expanded flaps also have vascular superiority over the non-expanded immediate flap counterparts, and are thinner and more pliable. It was first introduced by Neumann and later popularized by Charles Radovan.[9,10] It has found application in different soft tissue defect reconstruction of the craniofacial, truncal regions and the breast. It is also used in upper extremities but very rarely in the lower extremities. [9]

Tissue expanders are a form of implant with their attendant complications.[10] Of these complications, infections are major disaster that should always be prevented. It is one reason they have been employed in a non-reusable manner. However, the cost of procuring the tissue expanders is relatively high and unaffordable to the majority of the patients in the resource-poor setting.[11] They are therefore not readily available even when their needs are obvious. This therefore creates a need for an affordable and readily available alternative. We therefore resorted to recycling of the tissue expanders to obviate the constraint placed by cost. The aim of this was to compare the infection profile in the application of the recycled tissue expanders with the single use tissue expanders. We therefore wish to share our experience and challenges in using recycled tissue expanders in achieving soft tissue coverage of defects in a resource poor setting. The idea of reusing tissue expanders have been advocated for developing nations by researchers and practitioners in other climes who have also practiced the concept. [12,13]. It was also advocated that used expanders be therefore sent the developing countries to ease the financial challenges in procuring new ones.[13]

Patients and Method

The study is a three year retrospective survey of patients who had tissue expansion using recycled tissue expansion from January 2010 to December 2012. Patients' folders were retrieved from the medical records department of the hospital. All single use expanders were excluded from the study. Data from the case notes were extracted using a proforma designed for the study. Expanders were of varied sizes ranging from 70cc to 500cc chosen to match the patient and the size of the defect preoperatively. All expanders were textured with remote filling ports. They had not been used on patients with chronic infections like hepatitis B or C viruses, or retroviral disease. The expanders were boiled intermittently in water at 100^0C for about 10 minutes and allowed to cool for about 1 hour and the cycled repeated continually over a period of 12hour. This method was adapted by the researchers as a modification of Tyndallization to reduce number of days and duration of heating viz-a-viz the effect of heating on the expander[14]. On the day of surgery the expanders were washed ceftriazone constituted with sterile water at 1gm of the drug per expander. A preliminary microbiological study showed negative growth on the inner and outer parts of the expanders.

All procedures were done under general anesthesia with endotracheal tubes. Strict aseptic cleaning and draping were carried out. Strict asepsis was observed throughout the procedures. Prophylactic parenteral antibiotics were given at the induction of anesthesia. Incisions were made in the vicinity of the defect and pockets created with blunt dissection with incremental sizes of Hegar's dilators. The pockets were all located in the subcutaneous plane[7,9]. Haemostasis was ensured and the pockets washed with antibiotic solutions. The expanders were inflated to 10-20%of their volume. Wounds were closed in two layers with simple interrupted technique. All procedures were carried out by the most senior consultant of the unit.

Post-operative antibiotics were given for 7-10 days. Wound inspection was done on the post-operative day 4. Patients were discharged home if there was no wound complications and given 2 weeks appointment for removal of stitches and subsequent expansion. Wounds with any form of complication necessitated continuing in-patient care till properly managed. Wound dressings were subsequently changed on alternate day basis. Expansion was commenced after wounds have healed. Complications observed were managed accordingly with procedure continuing in minor cases but aborted in the major cases.

Ethical Considerations

Ethical clearance was obtained from the Research and Ethics Committee of National Orthopaedic Hospital Enugu to conduct the study and report on these cases. The selected patients had given informed consent for the procedure, for clinical photography and eventual publication without disclosing their identity.

Results

A total eight patients had tissue expansion with recycled expander over the period. Records of two were missing and could not be included in the study. Six patients managed with a total of 14 expanders were analyzed all of whom were females with age range of 24 years to 28 years and the mean age of 25 years. Indications were mainly due to abnormal scars resulting either from burns or road traffic accident. One was due plexiform neurofibroma excision scar.(Table 1) The upper limb had the highest number of expanders while the trunk had the least.(Table 2) The length of stay and the mean duration of commencement of expansion was similar for other parts of the body except the head which is about half the duration for others.(Table 3)

Table 1: Indications

S/No	Indications	Frequency	Percentage
1	Post-burn Scars	3	50%
2	Hypertrophic Scars following Road traffic Accident	2	33%
3	Facial plexiform neurofibroma excision scars	1	17%
4	Total	6	100%

Table 2: Expander distribution at various sites

Region of the body	No of expanders	Percentage
Scalp	4	29
Neck	2	14
Upper trunk	2	14
Uper limb	6	43
	14	100

Table 3: post-operative hospital stay and average period of commencement of out-patient expansion

Site of expander	Average hospital post-operative stay	Average time of commencement of out-patient expansion post surgery
Head	3.5 days	8 days
Neck	14 days	15.5 days
Upper trunk	8 days	15 days
Upper limb	10 days	15 days

Minor complications observed were expander migration(33%), hematoma(33%), valve leaks (16%), swelling(16%), and epidermal necrosis (16%).(Table 4) There was expander extrusion in 4 out of 14 implants used necessitating premature termination of expansion and outright removal of the expander. In one of the four, there was severe infection. Another patient who had the procedure done in the upper limb developed a wrist drop, necessitating termination of further tissue expansion. However the already expanded flap was adequate for the reconstruction.

Successful reconstruction was achieved in 10 out of the 14 expanders (71.4%) involving 4 out of the 6 patients (66.7%). Patients were all satisfied with the successful outcome and the reduced cost of care.

Discussion

Unsightly scars may affect either form or function. The growing interest in appearance has necessitated revision of most socially visible scars. All the patients in the study were females. This is not unconnected to their higher aesthetic concerns. It is similar to indications found in other published re-

ports.[11,15] The average age was 25 years which is a time of image consciousness. And also it is a time of excellent wound healing potentials.

The use of tissue expansion to resurface scar excision defect is one of the modalities currently applied in scar revision procedures. This among other factors might have contributed to the relative increase in both the demand and the cost of procuring tissue expanders making it more difficult for economically constrained patients to benefit in the procedure. This notwithstanding, tissue expansion remains a highly sought option of scar reconstruction partly because of its advantages in providing a cover with color and contour match as well as its ease of use in setting where free tissue transfer skills are not readily available.[7] Our environment is therefore one that could benefit maximally from tissue expansion option soft tissue reconstruction. Yet the practice has been limited by both cost and consequently, the availability of the tissue expanders. Our choice of recycled tissue expanders was to obviate the challenges of the cost of procuring the expanders though not without the fears of infective complications.

Generally, complications in tissue expansion varies from 13-40%[10]. The complications in this study affected 28.5% of tissue expanders which is similar to the rate observed in another study [10]. They all had implant extrusion which led to the outright termination of the process according to the tradition [7]. The implant extrusion might be related to the pressure necrosis and the poorer blood supply in the subcutaneous layer compared to the sub-fascial plane. The resultant ulceration exposed the implants. The extrusion might have been mitigated if the implants had been placed sub-fascially as against subcutaneous placement used in this study.[16]

There was only one case that had a major infective complication in the study. This low infective complication is very similar to the rate of infective complications in other studies [7,17]. In the sub-saharan Africa one might expect higher infection rate being a tropical sub-region with high temperature and humidity that support faster bacterial colonization.[18] There was however paucity of literature to show any peculiar pattern of infective complication in the sub-region. The use of recycled tissue expanders was not documented in the sub-region either. More so, the financial backwardness of the region and absence of adequate health insurance coverage endears this option which evades this financial demand.[19]

To further reduce the likelihood of infection in recycled tissue expanders, the option of extended antibiotics may be used. This protocol has been recommended in another published work.[20] When infections are not significantly different from the single use practice, the recycling may be encouraged in the economically constrained settings.

This study however is limited by the sample size as well as by being a single centre and a retrospective study. Multicenter, large volume, prospective studies are therefore recommended to establish the value or otherwise of the use of recycled tissue expanders in reconstruction in resource poor settings.

Conclusion

The success with recycled tissue expanders which are sourced at relatively no added cost to the patient presents an opportunity to offer reconstructive services to the resource constrained patients who are usually not covered by health insurance services in developing countries. This would improve the practice of tissue expansion in the sub-region while not putting added cost on the patients.

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Conflict of interest

We declare that there was no conflict of interest affecting this study.

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Original Article

Prevalence and drug susceptibility pattern of urinary tract infections among war disabled patients of Denden Hospital, Asmara, Eritrea

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Abstract

Background: *Urinary Tract Infections (UTIs) are the most common bacterial infections. The objective of the study was to assess UTI prevalence, common bacterial pathogens responsible for UTI, and the drug susceptibility pattern of bacteria towards commonly used drugs for UTI treatment among war-disabled patients admitted to Denden Military Hospital, Asmara, Eritrea.*

Methods: *A prospective cross-sectional study was conducted among 236 war veterans who were disabled during the war and took treatment at Denden Military Hospital.Midstream urine samples were collected in culture bottles. All collected urine samples were then cultured on different bacteria culture media. Biochemical tests were performed on posi-tive urine cultures based on significant bacteriuria as per the Kass count (>10^5 organisms/mL). Antimicrobial susceptibility tests were performed to analyze the resistance/ susceptibility pattern. Statistical Package for Social Services, version 20.1 was used for data entry and analysis.*

Results: *The overall prevalence of UTI was 81.7% (193/236). The common isolates were Escherichia coli (E.coli) 73(36.8%) followed by Staphylococcus aureus (S. aureus)38(19.1%). Usage of catheters with culture positivity was 22 (95.6%), 58 (95%), and 38(90.4%) for suprapubic, Condom, and Urethral Catheters, respectively. The antibiogram showed 62(84.9%) isolates of E.coli were resistant to Nitrofurantoin, while Staphylococcus aureus was found resistant to Tetracycline 25 (65.7%).*

Conclusion: *The results showed that most of the disabled patients included in the study were infected with UTI, and the most common pathogen isolated was E. coli followed by S. aureus. Based on the antimicrobial susceptibility test, the drug of choice for Gram-negative bacteria can be Amikacin, Gentamycin, and Cefalexin. While for Gram-positive bacteria it can be Ampicillin.*

Keywords: *Eritrea, War Disabled, Asmara, Urinary Tract infection. Antimicrobial Susceptibility pattern, Denden Hospital.*

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Introduction

Urinary Tract Infections (UTIs) are the most common bacterial infections, as they contribute toone-third of all nosocomial infections.[1]Implications of UTIs are severe as they impose great morbidity, mortality, and serious economic consequences on public health.[2] The magnitude of UTI severity ranges from self-limiting infection to death-causing systemic disease. Globally, millions of people have UTI each year, and the same number of people are at risk of acquiring this infection.[1] Diabetes mellitus, advanced age, urinary tract obstruction, immune suppression, and neurological disorders are the risk factors that make people susceptible to UTIs. Diverse microorganisms are adduced with UTIs, the most prevalent are Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Enterococcus faecalis, Staphylococcus aureus, and Staphylococcus saprophyticus.[3] There are many published reports in the last decades which drew a conclusion of increased drug-resistant bacteria in UTIs worldwide. In earlier studies, it is also concluded that the microorganism responsible for UTIs and its drug sensitivity pattern can be changed based on the geographic and biological status of the subjects.[4] Antimicrobial re-

sistance is always a major concern for many life-threatening infections. In the case of UTIs self-medication and poor diagnostic and culture facilities are the major factors considered for antimicrobial resistance in many developing countries.[5] Therefore, in a developing country like Eritrea, antibiotic treatment for Urinary Tract Infections must rely on the institutional susceptibility profile of the bacteria. Numerous published studies state that those people who are unable to empty the bladder due to neurological conditions like stroke, multiple sclerosis, and spinal cord injuries often require catheters.[6]There are reports which manifest a strong relationship between catheter usage and UTIs.[7,8]Urinary Tract infected patients are generally catheterized for their safety and prevention of further complications, but extended catheter usage increases the risk of morbidity among hospital and nursing home admitted UTI patients.[9]

Catheter-related infections are widespread if the use of catheters is not properly directed.An earlier study reported that around 12% to 16% of total hospitalized patients are catheterized, and the majority of them don't have proper direction and knowledge about catheter usage and its impact on the health of hospitalized patients. A report from The American National Healthcare Safety Network (NHSN) mentioned that almost 75% of UTI-infected patients in the hospital are related to extended usage of a catheter, and it is considered a high-risk factor for developing Catheter-Associated Urinary Tract Infection (CAUTI).[10,11]

Long-term health consequences are widespread in any armed conflict, even in fighters who return to civilian life.[12]Many government and Non-government organizations (NGOs) participate actively in the treatment and compensation of war-disabled people, as it is a major and long commitment.[13] Any armed conflict causes a serious impact on the physical and mental health of combatants, the same issues were noticed by many Eritreans after the Ethio- Eritrean war. After independence, the Eritrean government released many war-disabled veterans from active duty, which helped them lead civilian life and become productive members of the society.[14]The present study was conducted in Denden Military Hospital of Asmara, Eritrea. The main responsibility of Denden hospital is to provide medical services to patriots and to the late youngsters who participated actively and physically disabled during the war for securing independence from Ethiopia.[15] Therefore, assessing the prevalence of UTIs and determining the common etiologic agents along with their susceptibility profiles among war-disabled patients of Denden Hospital is important in planning for any intervention to control the infection among the patients. Furthermore, the information obtained from the current study may be used in a wider sense to understand the drug resistance of encountered isolates in association with catheter usage and provide reference data for further studies. As the study was targeted at disabled patients, the findings can be used as a reference to compare the prevalence and etiologic agents with those of physically normal patients. The identification of resistant organisms to antibiotics will provide a base to revise the existing treatment guideline.

Materials and methods:

Study Design

This was a prospective cross-sectional study conducted to investigate the prevalence, identification of common etiological agents, and the drug resistance pattern of etiological agents identified among war-disabled patients suffering from UTI at Denden Military Hospital, Asmara, Eritrea.The study was conducted from April - December 2021.

Sample Size

The sample size determination was done using a formula for a small population with an assumption of 50% prevalence, since no previous study was done in the area. 95% CI, 5% margin of error and 5% of non-respondent rate gave a final sample size of 236.[16]

Sampling Technique

In this study, 236 war-disabled patients who were taking treatment in Denden Military Hospital for different disabilities were selected using a simple random sampling method. Urinalysis, culture, and antimicrobial sensitivity patterns were performed. The results obtained were analized with a statistical package and printed as a hard copy. The results will be used as a reference for decreasing the prevalence of UTI in the hospital and modifying any necessary practices that would decrease the rate of infection.

Reagent Preparation

The analytical part of the study started with preparing the required materials, reagents, and equipment before the collection of samples, and transporting them to the site of analysis. The culture media were allowed to come to room temperature to prevent thermal shock, the media were, therefore, left in open air in the laboratory before inoculating the samples. Each sample was labeled with a series of numbers that contains the date of collection and the sample code.

Sampling Criteria

The study subjects to be sampled were primarily selected based on whether they have taken any antibiotics within the previous two weeks; those individuals who had been treated within two weeks with antibiotics were not allowed to participate in the study. Catheterized patients were asked to change their catheters before sampling because contaminating organisms may arise due to the long-time stay of the catheter.

Sample Collection

A sterile cup labeled with number codes and a questionnaire was provided for each eligible subject. The non-catheterized and condom catheterized subjects were asked to clean their genital area with clean water before they collect their midstream clean-catch urine. The catheter was changed for all

catheterized subjects before the collection of urine. The samples were transported to the site of analysis within one hour of collection in tightly capped cups using a sample transport box.

Urine Analysis, Cytology, and Sediment gram

A chemical indicator-impregnated test strip was dipped into a standard urine test tube containing 12-15ml of urine. The chemical strip develops a color change as the indicator is exposed to the chemical constituents of the urine. The urine in the test tube was then subjected to centrifugation at 2500rpm for five minutes.Decant, the supernatant,and sediment were suspended, and a drop was put on a slide with a coverslip and examined for pus cells, Red Blood Cells (RBC), bacteria, and casts. An examination is done initially at a low-power (10X) and then at a high -power (40X) field. Based on the presence of cells by microscopy, the samples were categorized as "Full, much, moderate, and none".

Inoculation of a Urine Sample

Cysteine-lactose-electrolyte-deficient agar, Mac-Conkey agar, Mannitol salt agar, Eosin methylene blue, and 5% Blood agar plates (Oxoid, Ltd, UK) were used for culturing each collected urine sample. Approximately 0.002 ml of urine was used with the help of a calibrated wire loop and streaked on a freshly prepared differential and selective culture media. The streaked plates were incubated at 37°C, overnight,the incubation was extended up to 48 hours for slow-growing strains. After the completion of incubation, the plates were inspected for growth and colony characteristics. If a single bacterium was recovered at a concentration $\geq 10^5$ colony-forming units per milliliter of urine, the culture was considered significant for UTI. Different biochemical tests like Gram's reaction, Indole test, Methyl red, Voges–Proskauer, Citrate utilization, Tryptophan deaminase reaction (TDA) Oxidase, Catalase, Triple Sugar Iron test (TSI), Fermentation of carbohydrates (such as glucose, sucrose, mannitol,) and utilization of Amino acids (such as Lysine, Ornithine, Arginine), was done with the bacterial colonies differing in size, shape, and color for further characterization and identification of bacteria at the species level.[17-26]All Biochemical reagents were obtained from (Oxoid, Ltd, UK).

Antimicrobial Susceptibility Test

The antibiotic sensitivity profile of each isolate was done by the Kirby-Bauer disc diffusion method using Mueller Hinton Agar **(**Himedia®,Mumbai, Maharashtra, India**).**[27] Eleven commercially available antibiotic discs for Gram-negative and seven for Gram-positive (Himedia®, Mumbai, Maharashtra, India) were used for the identification of antibiotic susceptibility. The isolates were recorded as "sensitive, intermediate, or resistant" based on the Clinical Laboratory Standards Institute (CLSI 2019) criteria.[28]

Quality Control of Materials and Reagents

To maintain the quality of the specimen and to come up with the required viability of the microorganisms, urine which had not stayed greater than an hour was inoculated. Along with this, to signify the quality of media, the powder form of different types of agar was checked for the expiration date. After preparation, all culture media were incubated in an incubator at the beginning (100%) and following (10%) to control growth and predict the degree of contamination. The quality control of all solid and liquid media for different tests was done by inoculating known standard organisms like (American Type Culture Collection) ATCC 29213 for *S.aureus* and ATCC 25922 for *E.coli*.

Ethical Consideration

Since Denden Military Hospital is a resident of war-disabled patients, it encompasses high ethical issues. The research got ethical clearance from the ethical committee of Asmara College of Health Sciences and the Ministry of Health, Asmara, Eritrea (ACHS/ SAHP/ 03/2019). Personal consent was taken from each participant after explaining the purpose and procedure of the study. The patients' results in this study were kept confidential. The overall study results were given to the administrators of the hospital to use as a base for further intervention in the control and prevention of UTIs, which can help the patients get better treatment and care.

Data Analysis

Data were analyzed using SPSS version 20.1. The UTI status was recorded as present or not present as our primary outcome, and if the number of bacteria is $>10^5$/mL in the urine, it implies the presence of UTI. The total prevalence of UTI was calculated by dividing the number of participants by the total number of study subjects who took the culture test with the presence of $>10^5$/mL of bacteria in their urine. To descriptively summarize the categorical characteristics of the study participants,frequencies and percentages were used. For testing the difference in proportions of UTI across categorical variables, Pearson Chi -square/Fisher Exact Test was used. The P-value of ≤ 0.05 was considered significant in analyzing the relationship between variables. The odds ratio and 95% Confidence Interval (CI) were also calculated to identify statistical significance.

Results

Description and clinical information of the study subjects

The participants of this study were 236 war veterans who were disabled during the war and taking treatment at Denden Military Hospital. Those patients who gave consent and complied with the designed criteria of selection were selected for the study. Out of the 236 participants involved in the study, 226 (95.7%) were males. The mean age of the subjects

was 46.7 years with a standard deviation of 7.9 and ranged from 27 to 70 years. No demographic and socioeconomic status of the study participants were collected for the study. From a total of 236 participants who had not taken any antibiotics within the last two weeks, 208(88.1%) had at least one complaint of UTI. While the remaining 28(11.8%) did not have any complaint of UTI during their disabled period of life. Out of the 208 participants who had at least one complaint of UTI, 150 (72.1%) were experiencing a recurrent infection and the rest 58(27.8%) just had a history of UTI infection without recurrence. The subjects of the study had different statuses of catheterization ranging from non-catheterized 110 (46.6%) to Condom catheterized 61 (25.8%), Urethral catheterized 42 (17.7%), and Supra-pubic 23 (9.7%).

Urine Culture Results of War-Disabled Patients in Denden Hospital

Urine culture was carried out on all 236 participants, where urine samples were inoculated into different culture media. The outcome of the culture result indicated 193(81.7%) with positive growth, and the remaining 43(18.2%) showed no growth on any of the media inoculated. Among the 193 participants who showed significant growth, 65(33.6%) were with more than one isolate, while the remaining 128 (66.3%) showed a single isolate. In total, 198 isolates with 21 different species were recovered from 19 growth-positive participants. Based on the findings, *E. coli,* a Gram-negative bacterium, with the greatest percentage and frequency 73(36.8%), followed by *Staphylococcus aureus* 38(19.1%) the only Gram-positive bacteria found in this study.*P. aeruginosa* and *P. mirabilis,*the other Gram-negative bacteria together were 30 (15.1%), while the rest were made 57 (28.7%). Different types of biochemical tests and Gram staining were done to differentiate bacteria at the species level. (**Figure 1)**

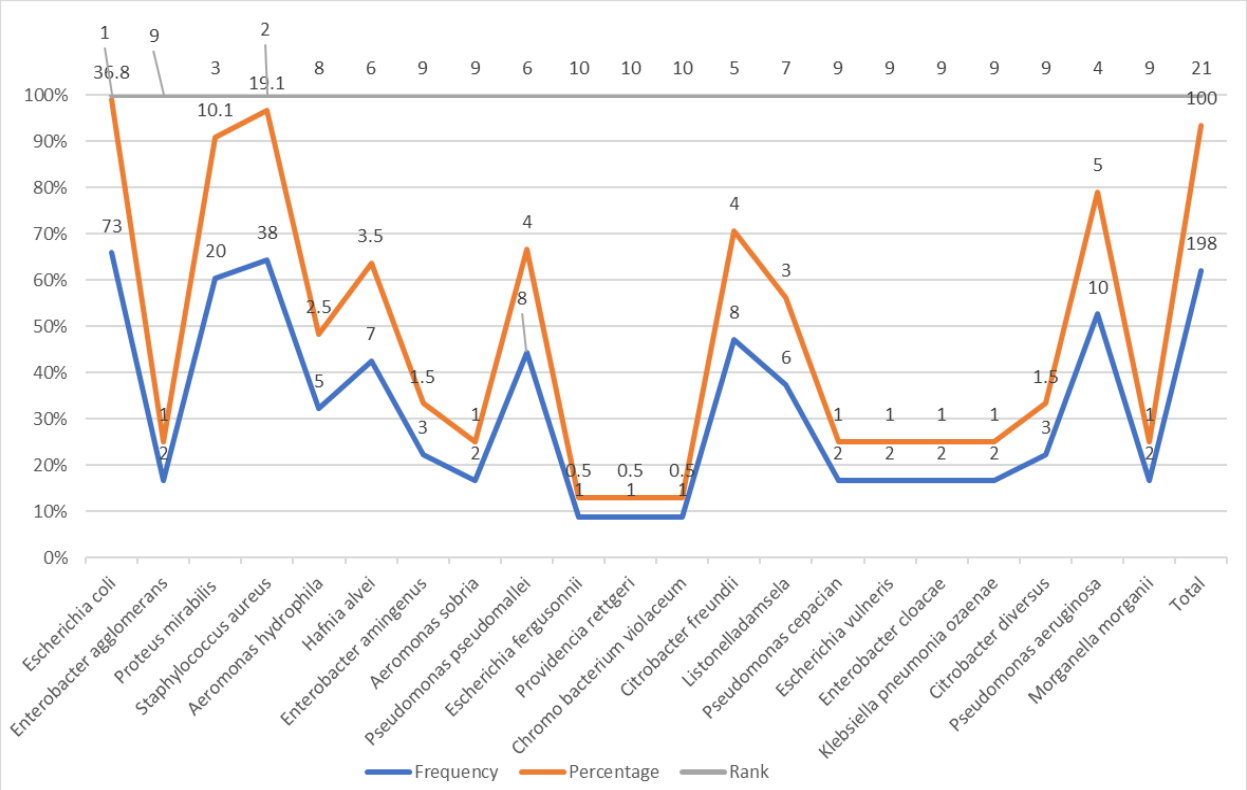

Figure-1: Type and Frequency of Organisms Isolated from Urine Specimen of Disabled Patients in Denden Military Hospital, Asmara, Eritrea

Relationship of Urine Chemical and Sedimentation Tests with Culture results of Disabled Patients in Denden Hospital

Routine microscopic and chemical tests were performed on all 236 urine samples for different types of diagnostic parameters like Red Blood Cells, pus cells, bacteria, chemical tests for leukocytes, and blood nitrate test. The detailed results are shown in **Table 1** Logistic regression of variables was also done to identify a significant or nonsignificant relationship between diagnostic parameters and the growth of bacteria in urine samples of War Disabled Patients **(Table 2).**

Table 1: Urine Chemical and Sedimentation test results of Disabled Patients in Denden Hospital, Asmara, Eritrea

Diagnostic Parameters	Grade Total (236)	Growth of Bacteria (193)	Chi (c2), P-value
Chemical Leukocyte Test	Neg (n=62)	47(75.8%)	c2=5.08
	+1 (n=25)	18 (72%)	P Value <0.044
	+2 (n=36)	32 (88.8%)	
	+3 (n=113)	96(84.9%)	
Chemical Blood Test	Neg (n=86)	57 (66.2%)	c2=34.22
	+1 (n=30)	21 (70%)	P Value <0.001
	+2 (n=40)	40 (100%)	
	+3 (n=25)	25 (100%)	
	+4 (n=55)	50 (90.9%)	
Chemical Nitrite Test	Positive (n=98)	92(93.8%)	c2=16.46
	Negative (n= 138)	101(73.1%)	P Value <0.001
Pus cell Microscopy	Full of (n=125)	118 (94.4%)	c2=60.19
	Many (n=16)	14 (87.5%)	P Value <0.001
	Moderate (n=12)	12 (100%)	
	Few (n=36)	28 (77.7%)	
	None (n=47)	21 (44.6%)	
RBC Microscopy	Full of (n=28)	28 (100%)	c2=23.90
	Many (n=32)	31 (96.8%)	P Value <0.001
	Moderate (n=9)	9 (100%)	
	Few (n=62)	52 (83.8%)	
	None (n=105)	73 (69.5%)	
Bacteria Microscopy	Full field (n=14)	12 (85.7%)	c2=26.61
	Moderate (n=30)	30 (100%)	P Value <0.001
	Few (n=46)	46 (100%)	
	None (n=146)	105 (71.9%)	

Table 2: Logistic regression of variables about different Diagnostic Parameters

Diagnostic parameters	Grade Total (236)	Growth of Bacteria (193)	Odds Ratio	95% CI	P-value
Chemical Leukocyte Test	Neg (n=62)	47(75.8%)	-	-	-
Chemical Leukocyte Test	+1 (n=25)	18 (72%)	1.219	0.427-3.478	0.712
	+2 (n=36)	32 (88.8%)	0.392	0.119-1.289	0.123
	+3 (n=113)	96(84.9%)	0.555	0.255-1.207	0.137
	+3 (n=25)	25 (100%)	-	-	-
	+4 (n=55)	50 (90.9%)	0.197	0.071-0.546	0.002
Chemical Nitrite Test	Positive(n=98)	92(93.8%)	0.178	0.072-0.441	<0.001
	Negative (n= 138)	101(73.1%)	-	-	-
Pus cell Microscopy	Full of (n=125)	118 (94.4%)	0.048	0.018-0.125	<0.001
	Many (n=16)	14 (87.5%)	0.115	0.024-0.565	0.008
	Moderate (n=12)	12 (100%)	-	-	-
	Few (n=36)	28 (77.7%)	0.231	0.087-0.611	0.003
	None (n=47)	21 (44.6%)	-	-	-
RBC Microscopy	Full of (n=28)	28 (100%)	-	-	-
	Many (n=32)	31 (96.8%)	0.074	0.010-0.563	0.012
	Moderate (n=9)	9 (100%)	-	-	-
	Few (n=62)	52 (83.8%)	0.439	0.198-0.971	0.042
	None (n=105)	73 (69.5%)			
Bacteria Microscopy	Full field (n=14)	12 (85.7%)	0.427	0.092-1.991	0.279
	Moderate (n=30)	30 (100%)	-	-	-
	Few (n=46)	46 (100%)	-	-	-
	None(n=146)	105 (71.9%)	-	-	-

Relationship of Catheter usage with Culture Results and Development of Infection

In our study, out of a total of 236 participants, 126 (53.3%) were catheterized with different types of catheters and the rest 110(46.6%) were non-catheterized. Urinary tract infection was high in catheterized participants compared to non-catheterized 118 (93.6%) (Chi c2=25.57, P value<0.001). In our study, we found 208 participants out of 236 had at least one complaint of UTI during the disability period. The analysis of results concerning catheters are shown in **Tables 3 and 4.**

Table 3-: Association of Catheter Usage and Culture Growth Pattern

Type of catheter		Growth (n=193),	No Growth (n=43),	Chi (c2), P-value
Catheter	Supra pubic (n=23)	22 (95.6%)	1(4.3%)	c2=1.08 P>0.50
	Urethral (n=42)	38 (90.4%)	4 (9.5%)	
	Condom (n=61)	58 (95%)	3 (4.9%)	
Sub total	(n=126)	118(93.6%)	8 (6.3%)	c2=25.57 P value<0.001
No catheter	(n=110)	75 (68.1%)	35 (31.8%)	

Table 4: Logistic regression of variables to establish an association of Catheter Usage and Bacterial Culture Growth Pattern in War Disabled Patients

Type of catheter		Growth	No Growth	Odds Ra-	95% CI	P-value
Catheter	Supra pubic	22 (95.6%)	1(4.3%)	0.879	0.0871-8.905	0.913
	Urethral (n=42)	38 (90.4%)	4 (9.5%)	2.035	0.431-9.606	0.369
	Condom (n=61)	58 (95%)	3 (4.9%)	-	-	-
Sub total	(n=126)	118(93.6%)	8 (6.3%)	0.145	0.064-0.330	
No catheter	(n=110)	75 (68.1%)	35 (31.8%)	-	-	-

Antimicrobial Susceptibility Pattern of Isolates

A total of 173 common isolates obtained after urine culture were tested against several drugs to assess their antibiotic susceptibility patterns. Eleven different antibiotics were used for 135-Gram-negative bacteria, and 7 antibiotics were tested against 38 *Staphylococcus aureus* isolates. The selection of antibiotics was based on the treatment guidelines of the country for treating different bacterial infections.[29,30].Gram-negative bacteria were found sensitive to Amikacin (76%), Gentamycin (72.5%), and Cefalexin (69%), and resistant to Nitrofurantoin (78%), Ampicillin (69.3%), Co-trimoxazole (71.2%), and Nalidixic acid (68%). Of Gram-negative isolates, *E.coli* showed higher sensitivity to Amikacin (79.4%) and Gentamycin (75.3%), while it was resistant to Nitrofurantoin (84.9%) and Ampicillin (75.3%). *Pseudomonas spp*. showed higher sensitivity to Cefalexin (77.7%) and Gentamycin (77.7%), but showed resistance to Nitrofurantoin (55.5%) and Nalidixic acid (61%). *Proteus* spp. showed higher sensitivity to Amikacin (85%), and Gentamycin (85%), but were resistant to Ampicillin (100%), Nitrofurantoin (100%), and Co-trimoxazole (100%).**Table 5** Only one type of Gram -positive bacteria was isolated and it showed a higher level of sensitivity to Amikacin (92.1%) followed by Ciprofloxacin (71%) but was found resistant to Tetracycline (65.7%).**Table 6**

Table 5: Antibiotic Sensitivity Pattern of Selected Gram-negative organisms to standard antibiotics among UTI patients of Denden hospital, Asmara, Eritrea

			Amikac	**Ampicill**	**Ceftazi**	**Cefalex**	**Ciproflo**	**Genta**	**Chlorom**	**Nalidix**	**Cotrimo**	**Nitrofur**	**Tetracy**
E.coli	73	Sensitive	58	12	49	49	34	55	32	15	18	9	20
			79.40%	16.40%	67.10%	67.10%	46.50%	75.30%	43.8%	20.50%	24.60%	12.30%	27.30%
		Intermediate	0	6	1	9	2	3	9	3	4	2	3
			0%	8.20%	1.30%	12.30%	2.70%	4.10%	12.30%	4.10%	5.40%	2.70%	4.10%
		Resistant	15	55	23	15	37	15	32	55	51	62	50
			20.50%	75.30%	31.50%	20.50%	50.60%	20.50%	43.80%	75.30%	69.80%	84.90%	68.40%
Pseudomonas spp	18	Sensitive	11	7	7	14	10	14	10	7	8	8	11
			61.10%	38.80%	38.80%	77.70%	55.50%	77.70%	55.50%	38.80%	44.40%	44.40%	61.10%
		Intermediate	0	4	3	1	3	1	3	0	0	0	0
			0%	22.20%	16.60%	5.50%	16.60%	5.50%	16.60%	0%	0%	0%	0%
		Resistant	7	7	8	3	5	3	5	11	10	10	7
			38.80%	38.80%	44.40%	16.60%	27.70%	16.60%	27.70%	61.11%	55.50%	55.50%	38.80%
Proteus mirabilis	20	Sensitive	17	0	17	9	20	17	0	3	0	0	3
			85%	0%	85%	45%	100%	85%	0%	15%	0%	0%	15%
		Intermediate	3	0	0	11	0	0	0	0	0	0	0
			15%	0%	0%	55%	0%	0%	0%	0%	0%	0%	0%
		Resistant	0	20	3	0	0	3	20	17	20	20	17
			0%	100%	15%	0%	0%	15%	100%	85%	100%	100%	85%
Citrobacter spp	8	Sensitive	6	2	7	6	5	5	3	2	2	2	1
			75%	25%	87.50%	75%	62.50%	62.50%	37.50%	25%	25%	25%	12.50%
		Intermediate	0	0	0	2	0	0	1	1	0	0	0

			Ami-kac	Am-picill	Ceftazi	Ce-falex	Ciproflo	Gen-ta	Chlorom	Na-lidix	Co-trimo	Ni-trofur	Tetra-cy
			0%	0%	0%	25%	0%	0%	12.50 %	12.50 %	0%	0%	0%
		Re-sistant	2	6	1	0	3	3	4	5	6	6	7
			25%	75%	12.50 %	0%	37.50 %	37.50 %	50%	62.50 %	75%	75%	87.50 %
Aeromonas spp	7	Sen-sitive	7	1	4	5	3	4	3	2	2	0	2
			100 %	14.20 %	57.10 %	71.40 %	42.80 %	57.10 %	42.80 %	28.50 %	28.50 %	0%	28.50 %
		Inter-mediate	0	1	0	0	0	0	0	1	0	1	1
			0%	14.20 %	0%	0%	0%	0%	0%	14.20 %	0%	14.20 %	14.20 %
		Re-sistant	0	5	3	2	4	3	4	4	5	6	4
			0%	71.40 %	42.80 %	28.50 %	57.10 %	42.80 %	57.10 %	57.10 %	71.40 %	85.70 %	57.10 %
			0%	71.40 %	42.80 %	28.50 %	57.10 %	42.80 %	57.10 %	57.10 %	71.40 %	85.70 %	57.10 %
Enterobacter spp	9	Sen-sitive	5	4	5	7	7	7	5	3	3	3	3
			55.50 %	44.40 %	55.50 %	77.70 %	77.70 %	77.70 %	55.50 %	33.30 %	33.30 %	33.30 %	33.30 %
		Inter-mediate	0	0	1	1	0	1	0	0	1	0	1
			0%	0%	11.10 %	11.10 %	0%	11.10 %	0%	0%	11.10 %	0%	11.10 %
		Re-sistant	4	5	3	1	2	1	4	6	5	6	5
			44.40 %	55.50 %	33.30 %	11.10 %	22.20 %	11.10 %	44.40 %	66.60 %	55.50 %	66.60 %	55.50 %

Amikac-Amikacin Ampicill- Ampicillin Ceftazi-Ceftazidime Cefalex- Cefalexin Ciproflo-Ciprofoxacin Genta-Gentamycin Chlorom-Chloramphenicol Nalidixic acid Cotrimo- Cotrimoxazole Nitrofur-Nitrofurantoin Tetracy-Tetracycline

Table 6: Antibiotic Sensitivity Pattern of selected Gram-positive organisms to standard antibiotics among UTI patients of Denden hospital, Asmara, Eritrea

	Erythro	Ampi	Vanco	Cipro	Genta	Chloram	Tetracy
Sensitive	19	35	24	27	20	25	10
	50%	92.10%	63.10%	71%	52.60%	65.70%	26.30%
Intermediate	8	-	3	3	5	5	3
	21%	-	7.80%	7.80%	13.10%	13.10%	7.80%
Resistant	11	3	11	8	13	8	25
	28.90%	7.80%	28.90%	21%	34.20%	21%	65.70%

Erythro-Erythromycin Ampi-Ampicillin Vanco-Vancomycin Tetra-Tetracycline
Cipro-Ciprofloxacin Genta-Gentamycin Chlorom-Chloramphenicol

Discussion

To our knowledge, the current study is the first to determine the Prevalence, common Etiologic agents, and Antimicrobial Susceptibility Patterns of UTI among war Disabled Patients in Asmara, Eritrea.

The government of Eritrea within its limited resources always took a maximum attempt to help and assist people who were with war disabilities, to gain maximum potential, and to minimize the suffering that the war veterans experienced during the conflict. Along with Eritrean government efforts, the people of Eritrea also have great respect for the war-disabled veterans, and there is always an honor for the great service and sacrifices which they rendered for their liberty and security. The Eritrean government along with the people also recognizes the rights of war-disabled veterans, the right to be treated with respect and dignity.[14]

A planned and well-organized assessment should be a priority regarding identifying health issues and solving those issues in special groups like war-disabled veterans.[31]

Agha *et al*. in their study mentioned a disparity between the resource allocation and health status of the general population and war veterans.[32] Armed conflicts lead to battlefield injuries, and these injuries can be long-term physical or mental, and can severely affect their response to treatment.[33,34]Therefore, healthcare planning and resource allocation to veterans should be different and more special than the non-veteran patient population.[32]

Battlefield injuries can cause different types of disabilities. The most common and accepted disabilities among war veterans are eye and ear disorders, musculoskeletal disorders, and mental health disabilities.[35] The mortality rate among war veterans with lower extremity amputations is higher than the normal population in a 24-year follow-up study.[36]While another study conducted among war veterans reported that kidney and urinary tract diseases are one of the most prevalent illnesses.[37]

Here in our study, we have taken war veterans from Denden Military Hospital which is treating patients with all forms of disability. The prevalence of UTI among our patients is (81.7%), which is comparatively similar to combatants of world war I, as approximately (80%) of them died due to pyelonephritis.[38,39]At the same time, any war disability requires short or long term hospitalization, and 40% of nosocomial infections are urinary tract infections.[40]In our study, all war disabled patients were taking treatment in Denden Military Hospital.

Structural,physiological and behavioral disorders as well as demography are generally considered risk factors for UTI, among which, structural and physiological disorders are the most commonly accepted risk factors.[41]Amputations,urogenital, urethral, and spinal cord war injuries can lead to long-term disability, and these injuries can also be risk factors for

UTI.[42-44] In our study, we have not taken any account on the type of war injuries, instead,we focused only on war disabled veterans.

Catheter usage has a great impact on the risk of UTI. [41]Out of 236 war-disabled patients, 126 (53.3%) were using different types of catheters for bladder drainage.Those subjects who were using catheters showed a high prevalence of UTI compared to those who were not using any catheter**.** Previous studies showed that patients with genitourinary, urethral, and spinal cord war injuries often require catheteres for bladder drainage, and some cases of war amputation also need a catheter for UTI management.[41,42,44,45] Bacteremia is another health issue associated with catheters among UTI patients,the case fatality rate is three times higher in comparison to non-bacteriuric patients.[46-49]

In the present study, catheterized participants were using different types of catheters, which include suprapubic, urethral, and condom, and all of them showed a high presence of bacteria in their urine culture. Earlier studies done on Spinal cord injury patients reported that bacteriuria is less common with intermittent catheterization (70%) compared to indwelling catheters (98%).[41]

The results of our study on catheterized participants are validated by the previous reports, which showed that the usage of either suprapubic or urethral catheters can lead to serious UTIs compared to non-catheterized participants. Earlier studies suggested that the usage of condom catheters lowers the incidence of bacteriuria, and they are more comfortable [50]. At last, the usage of chronic indwelling catheters must be based on prolonged comfort for the patient and the mindset of a physician,which allows them to manage challenges related to catheters.[51]

In our study, there were 110 non-catheterized participants, and the prevalence of UTI among them was (68%). As mentioned earlier, the behavior of disabled people can also be a risk factor for UTI.Therefore, failing to adjust to disability and having poor personal hygiene can be contributing factors to the high prevalence of UTI in non-catheterized war-disabled patients.[41]

Battlefield injuries can lead to serious complications of infections which can result in amputation, loss of function, or death. Thus, the characterization of the bacteria could influence the selection of empiric antimicrobial agents used to prevent infection. In our study, the prevalence of Gram-negative bacteria especially *E.coli* was high compared to other Gram-negative bacteria. *Staphylococcus aureus*is the only Gram-positive bacteria reported in the present study.

In earlier studies done on combat-related genitourinary trauma, extremity injuries, burn injuries,and spinal cord injuries concerning UTIs, the most frequent bacteria reported were E.coli, Pseudomonas aeruginosa, Klebsiella pneumoniae, Coagulase-negative staphylococcus, and Staphylococcus aureus.[52-56]

In our study (100%), patients are living in Denden War disabled veterans'/military hospital. There are previous reports that state that Urinary Tract infections are widespread in long–term–care facility residents, and the most frequent pathogens isolated were *E. coli,*Coagulase -negative *Staphylococcus,*and *Streptococcus.*[57]

In the present study, the presence of pus cells, and white blood cells are proof that these cells failed in fighting the infection of the body, which causes a significant growth of bacteria in the body. Pyuria, which is the presence of pus cells in the urine, is a warning of microbial infection in the body.[58]While in those patients where there is only microbial growth (bacteriuria) without pyuria, it is a sign of diabetes, enteric fever, bacterial endocarditis, or contaminants from the perineum,[59] as well as it might be a urinary tract infection caused by apathogenic microorganism such as *E. coli*, *Klebsiella*, and Proteus.[59] In the same way, a positive nitrite test was associated with significant bacterial growth in the urine samples of War Disabled Veterans. Pathogens such as *E.coli, Proteus species*, and *Klebsiella species* when present in sufficient concentration in the urine, can reduce nitrate to nitrites, and this sufficient presence of nitrite in urine indicates UTI. [59] Similarly, a high count of RBCs in the urine with nitrite and pus cells also indicates an infection.[59]

Military conflicts increase the risk of acquiring new multidrug-resistant strains of bacteria and their distribution and spreading.[54] There is a great possibility of the inflow of multidrug-resistant bacteria by soldiers on deployment. As the soldiers are repatriated due to appalling diseases or injuries during deployment, they can easily transfer those multidrug-resistant bacteria into the hospitals where they are getting treated in the home country.[54]In our study Gram-negative bacilli, especially *E. coli,* exhibited a wide spectrum of resistance to Ampicillin, Nalidixic acid, and Nitrofurantoin, reducing their empirical usages. Apart from *E. coli*, other Gram-negative bacilli such as *K. pneumonia*, *Proteus spp*, *Citrobacter spp,Aeromonas spp*, and *Enterobacter spp* also exhibited resistance to similar antibiotics in varying degrees. As there is a high level of resistance exhibited by Gram-negative bacteria against routinely used antibacterial drugs such as ampicillin, nitrofurantoin, nalidixic acid and Co-trimoxazole,which is a major upset for the effective care of UTI in war-disabled people. A study conducted in Denden Hospital, Asmara, Eritrea also showed a lower level of sensitivity to Ampicillin, Nalidixic acid, and Co-trimoxazole against a variety of Gram-negative bacteria.[15]While in the current study, only Gram-positive bacteria showed an elevated level of resistance to tetracycline.

Conclusion and recommendation:

The results of our study showed that urinary infection is an important clinical problem among the military trauma population. Our results also displayed that UTI is also a widespread problem among long-term–hospital residents. The current study demonstrated that *S.aureus* and *E.coli* are

common pathogens isolated from war-disabled patients and taking treatment in Denden Military Hospital, Asmara, Eritrea. This study also found that the presence of bacteria in urine is high in catheterized patients, in comparison to non-catheterized disabled patients. Catheterized patients were using different types of catheters, and all types of catheter usage demonstrated a high presence of bacteriuria. The current study also tried to identify the AST pattern of isolated bacteria to drugs that are in clinical practice in the country for the treatment of UTI. Here, we found that most isolated bacteria were resistant to antibiotics. Healthcare professionals and policymakers of the hospital must consider this resistance pattern in their clinical practice as well as in the policy-making process. Based on the results of antimicrobial susceptibility tests, it is recommended to continue with drugs like Amikacin, Gentamycin, Ciprofloxacin, and Ampicillin for the management of both Gram-negative and positive uropathogens respectively. Most importantly, the current AST data can be used to understand the trends of antibiotic susceptibility, this can assist clinicians in prescribing the correct antimicrobial therapy to prevent indiscriminate use of antibacterial drugs and resistance emergence.

Conflict of Interest: No Conflict of Interest

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Original Article

Validation of HIV risk screening tool to identify infected adults and adolescents greater than 14 years at community level in Tanzania and Zambia

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Abstract

Introduction: *There are several risk factors being used to identify undiagnosed HIV-infected adults. As the number of undiagnosed people gets less and less, it is important to know if existing risk factors and risk assessment tools are valid for use.*

Methods: *Data from the Tanzania and Zambia Population-Based HIV Impact Assessment (PHIA) household surveys which were conducted during 2016 was used. We first included 12 risk factors (being divorced, separated or widowed; having an HIV+ spouse; having one of the following within 12-months of the survey: paid work, slept away from home for ≥1-month, having multiple sexual partners, clients of sex workers, sexually transmitted infection, being tuberculosis suspect, being very sick for ≥3-months; ever sold sex; diagnosed with cervical cancer; and had TB disease into a risk assessment tool and assessed its validity by comparing it against HIV test result. Sensitivity, specificity and predictive value of the tool were assessed. Receiver Operating Characteristic (ROC) curve comparison statistics was also used to determine which risk assessment tool was better.*

Results: *HIV prevalence was 2.3% (2.0%-2.6%) (n=14,820). For the tool containing all risk factors, HIV prevalence was 1.0% when none of the risk factors were present (Score 0) compared to 3.2% when at least one factor (Score ≥1) was present and 8.0% when ≥4 risk factors were present. Sensitivity, specificity, PPV, and NPV were 82.3% (78.6%-85.9%), 41.9%(41.1%-42.7%), 3.2%(2.8%-3.6%), and 99.0%(98.8%-99.3%), respectively. The use of a tool containing conventional risk factors (all except those related with working and sleeping away) was found to have higher AUC (0.65 vs 0.61) compared to the use of all risk factors (p value <0.001).*

Conclusions: *The use of a screening tool containing conventional risk factors improved HIV testing yield compared to doing universal testing. Prioritizing people who fulfill multiple risk factors should be explored further to improve HIV testing yield.*

Keywords*: Adult HIV risk assessment tool; Undiagnosed HIV; Never tested for HIV; HIV testing yield, Tanzania, Zambia*

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Introduction

HIV testing is the gateway for case finding, care, and treatment, as well as prevention services for high-risk individuals (1-3). Over the years, remarkable progress has been made in diagnosing infected people and putting them on treatment. To date, Eastern and Southern African countries have coverage of 87% (77%-95%) compared to the 90% UNAID's target of diagnosing 90% of all estimated HIV infected people by 2020, while the coverage is 68% (54%-87%) for Central and Western African countries (4). This correlates with the high uptake of HIV testing across these countries. Prior HIV testing among surveyed men and women 15-49 years was 62% and 74%, respectively for Eastern, Southern, and Central African countries, respectively, from 2015-2018. It was much lower for Western African countries at 31% for women and 16% for men (5, 6).

Maintaining such high testing coverage or conducting door-to-door testing in high-risk communities is not feasible because of the limited funding available for HIV programs considering the flattening of global support for HIV programs, especially that of PEPFAR over the past 10 years (7, 8). As a result of that, a strategic shift has been made to implement targeted HIV testing with the aim of getting high testing yield per dollar spent on HIV test kit in many country HIV programs, including high-burden countries to put as many infected people on treatment and reduce new infection and mortality

in the process (9).

A number of HIV risk factors have been identified and in use to effect targeted HIV testing of at-risk people. The World Health Organization (WHO) recommends HIV testing for clients having sexually transmitted infection (STI), viral hepatitis, tuberculosis (TB); key populations including commercial sex workers, men having sex with men, and IV drug users; clients with symptoms or medical conditions that could indicate HIV infection, including presumed and confirmed TB cases (1, 2). Other factors known to increase the risk of HIV infection include having multiple sexual partners (10, 11), being divorced, separated or widowed (DSW) (12), history of being a client of a sex worker (13), having cervical Cancer (14), being partners with known infected person (15).

A number of HIV risk assessment tools were validated in different settings in an effort to determine best options to identify HIV infected adults (10, 16,17). These tools often don't include risk factors recommended by the WHO and in use in high prevalence countries. Knowing the performance and limitation of a risk screening tool containing all common HIV risk factors is crucial to determine case finding strategies that better fit routine implementation setting and assess quality of testing services both in clinical and community settings. This study aims to:

1. determine the performance of a hypothetical HIV risk assessment tool that contains conventional HIV risk factors to identify undiagnosed HIV+ adults and adolescents >14 years,
2. determine the performance of a hypothetical HIV risk assessment tool that contains all potential HIV risk factors to identify undiagnosed HIV+ adults and adolescents >14 years,
3. determine the performance of a hypothetical HIV risk assessment tool that contains only statistically significant HIV risk factors to identify undiagnosed HIV positive adults and adolescents >14 years
4. determine which of the above three tools is better in terms of overall performance to identify undiagnosed HIV positive adults and adolescents >14 years
5. determine if the presence of multiple HIV risk factors in one person improves performance of risk assessment tool to identify undiagnosed HIV positive adults and adolescents >14 years.

Materials and Methods

Study setting and design: This is a cross-sectional study based on secondary analysis of data from two community-based household surveys that were conducted in Zambia (2016) and Tanzania (2016-2017). These surveys were Population-Based HIV Impact Assessment (PHIA) studies conducted with PEPFAR support. These study countries are high burden countries providing donor driven (PEPFAR and Global Fund) HIV program. HIV response is mostly facility based where diagnostic and treatment services are provided with community component mainly focusing on prevention and care aspect. PHIA surveys are cross-sectional nationally representative, household-based surveys. The main objectives of the surveys are to measure national HIV prevalence and viral suppression, nationally and sub-nationally, to assess the impact of HIV treatment and prevention programs in each country. Participants were selected using two-stage, stratified cluster sampling. Participants who provided written consent undergo interview based on a structured questionnaire and a biomarker for HIV testing (18, 19).

Inclusion criteria: adolescents and adults >14 years who had matching interview and biomarker datasets (HIV testing result) and who had never tested for HIV prior the survey was included.

Sample size: was calculated to allow comparison between areas under receiver operating characteristic (ROC) curves between two different risk assessment tools. Sample size was calculated to be 1,363 assuming AUC1=0.65, AUC2=0.6, alpha=0.05, power= 80%, correlation in positive group=0.4, and correlation in negative group=0.4 (21).

HIV risk factors: the following variables were considered in different HIV risk assessment tools to generate a tool with better sensitivity, specificity, and positive predictive value (PPV+): being divorced, separated or widowed (DSW) (12), having an HIV+ spouse (15), having paid work within 12 months of the survey, slept away from home for at least a month within 12 months of the survey, having multiple sexual partners (10, 11)within 12 months of the survey, had ever sold sex (13),clients of sex workers within 12 months of the survey, had sexually transmitted infection (STI) within 12 months of the survey(1, 2), diagnosed with cervical cancer (14), being a tuberculosis (TB) suspect within 12 months of the survey which meant having any of the following symptoms: cough, fever, night sweats or weight loss, had TB disease, past or present, and being very sick for at least 3 months within 12 months of the survey, that is being too sick to work or do normal activities (1, 2).

HIV risk assessment tools examined:

Four different hypothetical tools were considered in the validation:

- Tool 1: A tool that contained all conventional and any newly identified statistically significant risk factors that predicted HIV infection status in individuals never tested for HIV,
- Tool 2: A tool that contained only statistically significant risk factors associated HIV infection,
- Tool 3: A tool that contained conventional

risk factors only, and

Tool 4: A tool that contained conventional risk factors and a combination of newly identified risk factors.

HIV testing: was offered for everyone in the survey and performed for all consenting adults and adolescents >14 years during the survey. Known HIV+ status was further confirmed through the use of antiretroviral markers within the blood. Those with antiretroviral markers were excluded from the study.

Data analysis

Data were obtained from the public domain of PHIA website (22) and analyzed using Stata 14.0 statistical software. First, risk factors that had association with HIV infection among those who never tested for HIV were identified using Chi Square test. To develop scores for a risk assessment tool, appropriate screening items were selected and coded one when the risk factor was present and zero when it was not and the total score calculated for each individual as the sum of the numerical values of the screening items included within a tool. For instance, for the first screening tool where all risk factors were included, the minimum score was 0 while the potential maximum was 12.Chi Square test was also done to examine if having risk screening score of ≥1, ≥2, ≥3, or ≥4 was associated with HIV infection. Sampling weights were used to adjust statistical values taking into account complex sampling design used in PHIA surveys (20).

To determine the optimal cut-off for the screening tool that will enable identification of people at risk of HIV infection, a receiver operating characteristic (ROC) curve was plotted. The area under the ROC (Receiver Operating Characteristic) curve, Area Under the Curve (AUC) and corresponding sensitivity, specificity, positive predictive (PPV) and negative predictive values (NPV) using the screening tool at different levels of scores were determined. ROC comparison statistics was used to statistically test equality between AUC of the different scores. For the score selected to be having the best combination of sensitivity, specificity, PPV, NPV and AUC, similar analysis was conducted to see if age, gender, and residence affected AUC. This was done by doing stratified analysis of AUC using the stated variables.

Finally, to compare and select between the different risk assessment tools, test of quality of AUC was done. Number needed to test to identify one HIV infected person (NNT+) was also calculated to see if risk assessment tools reduced this number compared to universal testing. To select appropriate variables for the second tool, logistic regression was used. Variables with p- value <0.25 during bi-variable analysis were included in the final model. Variables with p-value <0.05 in the final model were included in the making of Tool 2.

Ethical considerations: Both PHIA surveys had written informed consent, both for interview and blood collection for all participating adults. Parents consented for adolescents. All datasets don't have individual identifiers like names or addresses that can be used to identify people. In addition, the study got a non-human subject determination from the Office of International Research Ethics of Family Health International (FHI360).

Results

Selection of study participants

Of 68,564 adults and adolescents >14 years included in the Tanzania and Zambia PHIA studies, 55,340 had a matching interview and biomarker (including HIV testing) datasets. Of these, 39,103 (70.7%), had previously been tested for HIV and 181 (0.3%) had missing previous HIV testing data, and hence excluded from the analysis. Of the remaining 16,056, 15160 (94.4%) were tested for HIV. Excluding those who didn't have sampling weights, the final study sample was 14,820. (Figure 1)

Compared to individuals who were eligible for inclusion in this study but had missing HIV testing result, those who were tested for HIV during the survey were likely to be older, male, from urban area. They were also less likely to have multiple sexual partners or sexually transmitted infection in the past 12 months. (Table 1)

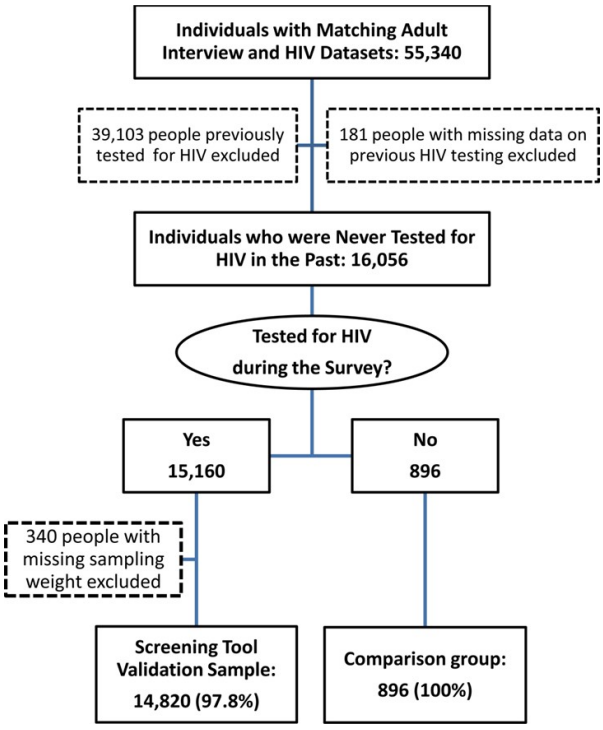

Figure 1. Selection of Study Sample

Table 1. Comparison between Study Participants and non-Participants based on Socio-demographic Characteristics and HIV Risk Factors

Variable	Response	Total, n	Study Participants (Tested for HIV during survey), n (%)	Non-participants (Not tested for HIV during Survey), n (%)	P value
Age	15-24	8,297	7868 (53.1%)	429 (47.9%)	<0.001
	25-49	3,789	3507 (23.7%)	282 (31.5%)	
	50+	3,630	3445 (23.2%)	185 (20.6%)	
Gender	Male	8,488	7945 (53.6%)	543 (60.6%)	<0.001
	Female	7,228	6875 (46.4%)	353 (39.4%)	
Residence	Urban	4,817	4461 (30.1%)	356 (39.7%)	<0.001
	Rural	10,899	10359 (69.9%)	540 (60.3%)	
Education	No education	2,887	2753 (18.6%)	134 (15.0%)	<0.001
	Primary	8,243	7792 (52.6%)	451 (50.3%)	
	Secondary	4,372	4096 (27.6%)	276 (30.8%)	
	Tertiary	214	179 (1.2%)	35 (3.9%)	
Wealth Quintile	Lowest	3,785	3587 (24.2%)	198 (22.1%)	<0.001
	Secondary	3,613	3442 (23.2%)	171 (19.1%)	
	Middle	3,336	3168 (21.4%)	168 (18.8%)	
	Fourth	2,460	2291 (15.5%)	169 (18.9%)	
	Highest	2,522	2332 (15.7%)	190 (21.2%)	
Marital status	Single, Married	13,772	12981 (87.6%)	791 (88.3%)	0.542
	DSW[$]	1,944	1839 (12.4%)	105 (11.7%)	
Spouse is Known to have HIV	No	15,673	14777 (99.7%)	896 (100.0%)	0.106
	Yes	43	43 (0.3%)	0 (0.0%)	
Having Paid Work*	No	10,842	10212 (68.9%)	630 (70.3%)	0.377
	Yes	4,874	4608 (31.1%)	266 (29.7%)	
Slept Away from Home for >1 month*	No	13,708	12916 (87.2%)	792 (88.4%)	0.280
	Yes	2,008	1904 (12.8%)	104 (11.6%)	
Multiple Sexual Partners*	No	14,125	13292 (89.7%)	833 (93.0%)	0.002
	Yes	1,591	1528 (10.3%)	63 (7.0%)	
Ever Sold Sex	No	14,125	13292 (89.7%)	833 (93%)	0.428
	Yes	1,591	1528 (10.3%)	63 (7.0%)	
Clients of Sex Workers*	No	14,962	14107 (95.2%)	855 (95.4%)	0.749
	Yes	754	713 (4.8%)	41 (4.6%)	

Characteristics of study participants

Variable	Response	Total, n	Study Participants (Tested for HIV during survey), n (%)	Non-participants (Not tested for HIV during Survey), n (%)	P value
Sexually transmitted infection*	No	14,382	13522 (91.2%)	860 (96.0%)	**<0.001**
	Yes	1,334	1298 (8.8%)	36 (4.0%)	
Has Cervical Cancer	No	15,632	14741 (99.5%)	891 (99.4%)	0.921
	Yes	84	79 (0.5%)	5 (0.6%)	
Presumptive TB[#]*	No	15,356	14479 (97.7%)	877 (97.9%)	0.726
	Yes	360	341 (2.3%)	19 (2.1%)	
TB disease, current or past	No	15,547	14657 (98.9%)	890 (99.3%)	0.225
	Yes	169	163 (1.1%)	6 (0.7%)	
Sick for the past 3 months*	No	15,073	14214 (95.9%)	859 (95.9%)	0.953
	Yes	643	606 (4.1%)	37 (4.1%)	
Total		15,716	896 (100%)	14,820 (100%)	

[$]Divorced, Separated, or Widowed, *within the last 12 months of the survey,
[#]Cough, fever, night sweats, or weight loss

Characteristics of study participants

Of 14,820 study participants, 57.8% were men, and had a median age of 30 (IQR: 21-24). HIV prevalence was 2.3% (95% (CI): 2.0-2.6). HIV prevalence was higher for the age category 25-49, among women, and in urban settings, while it was lowest for those with secondary education and those in the highest wealth quintile. (Table 2)

Table 2 Socio-demographic Factors Associated with HIV Infection among adults and adolescents >14 years who were never tested for HIV before PHIA Surveys conducted in Zambia (2016) and Tanzania (2016-2017)

Variable	Response	Total, n	HIV+, n (%)	P value
Age	15-24	8,114	49 (0.6%)	**<0.001**
	25-49	3,443	196 (5.7%)	
	50+	3,263	95 (2.9%)	
Gender	Male	8,567	162 (1.9%)	**0.002**
	Female	6,253	176 (2.8%)	
Residence	Urban	4,707	130 (2.8%)	**0.026**
	Rural	10,113	207 (2.1%)	
Education	No education	2,647	82 (3.1%)	**0.001**
	Primary	8,182	197 (2.4%)	
	Secondary	3,859	55 (1.4%)	
	Tertiary	132	4 (3.1%)	
Wealth Quintile	Lowest	3,398	73 (2.1%)	**0.038**
	Secondary	3,412	70 (2.0%)	
	Middle	3,081	73 (2.4%)	
	Fourth	2,432	79 (3.2%)	
	Highest	2,496	43 (1.7%)	
Total		14,820	338 (2.3%)	

[$]Divorced, Separated, or Widowed; *within the last 12 months of the survey, [#]Cough, fever, night sweats, or weight loss

Statistically significant predictors of HIV infection

Table 3 summarizes predictors of HIV infection by including only factors being examined in the development of factors included in the development of risk assessment tool. Accordingly, all factors were predictors of infection except for the following variables: Presumptive TB, TB disease, and being sick in the past 3 months.

Table 3. Predictors of HIV Infection among adults and adolescents >14 years who were never tested for HIV before PHIA Surveys conducted in Zambia (2016) and Tanzania (2016-2017)

Variable	Response	Total, n	HIV+, n (%)	Crude Odds Ratio	P value	Adjusted Odds Ratio	P value
Marital status	Single, Married	13,045	230 (1.8%)	1		1	
	DSW[$]	1,775	108 (6.1%)	3.6 (2.7-4.8)	<0.001	3.7 (2.7-5)	<0.001
Spouse is Known to have HIV	No	14,777	333 (2.3%)	1		1	
	Yes	43	5 (11.0%)	5.3 (1.8-15.6)	0.004	5.7 (1.8-18.2)	0.005
Having Paid Work*	No	9,692	172 (1.8%)	1		1	
	Yes	5,128	166 (3.2%)	1.8 (1.4-2.4)	<0.001	1.7 (1.3-2.2)	0.001
Slept Away from Home for >1 month*	No	12,939	273 (2.1%)	1		1	
	Yes	1,881	65 (3.5%)	1.7 (1.1-2.5)	0.016	1.4 (0.9-2.2)	0.089
Multiple Sexual Partners*	No	12,970	282 (2.2%)	1		1	
	Yes	1,850	58 (3.1%)	1.4 (1.0-2.0)	0.042	1 (0.6-1.5)	0.889
Ever Sold Sex	No	14,786	333 (2.3%)	1		1	
	Yes	34	5 (13.5%)	6.8 (3.2-14.5)	<0.001	6.8 (3.1-14.9)	<0.001
Clients of Sex Workers*	No	14,100	304 (2.2%)	1		1	
	Yes	720	36 (4.9%)	2.3 (1.5-3.5)	<0.001	1.5 (0.9-2.5)	0.127
Sexually transmitted infection*	No	13,385	274 (2.0%)	1		1	
	Yes	1,435	65 (4.5%)	2.3 (1.6-3.2)	<0.001	1.9 (1.3-2.9)	0.004
Has Cervical Cancer	No	14,755	335 (2.3%)	1		1	
	Yes	65	4 (5.5%)	2.6 (1.1-5.9)	0.029	2 (0.8-5.1)	0.152
Presumptive TB[#]*	No	14,460	326 (2.3%)	1		1	
	Yes	360	12 (3.3%)	1.5 (0.8-2.8)	0.231	0.7 (0.2-2.6)	0.616
TB disease, current or past	No	14,639	330 (2.3%)	1		1	
	Yes	181	8 (4.4%)	2.0 (0.9-4.2)	0.07	2.2 (0.5-9.1)	0.264

Variable	Response	Total, n	HIV+, n (%)	Crude Odds Ratio	P value	Adjusted Odds Ratio	P value
Sick for the past 3 months*	No	14,242	317 (2.2%)	1		1	
	Yes	578	22 (3.8%)	1.7 (0.9-3.1)	0.086	1.4 (0.7-2.6)	0.347
Total		14,820	338 (2.3%)				

[$]Divorced, Separated, or Widowed; *within the last 12 months of the survey, [#]Cough, fever, night sweats, or weight loss

HIV Prevalence by Risk Factors

Figure 2 summarizes HIV prevalence by risk factor. The highest was recorded for people who sold sex (13.5%), followed by spouses of HIV-infected adults (11%) and those who were divorced, separated, or widowed (6.1%). The presence of other risk factors had HIV testing yield ranging from 3.1%-5.5%. TB in the past 10 years had a testing yield of 33.3% for Zambia compared to 3.7% for those without TB in the past 10 years, p value <0.001 (data not shown).

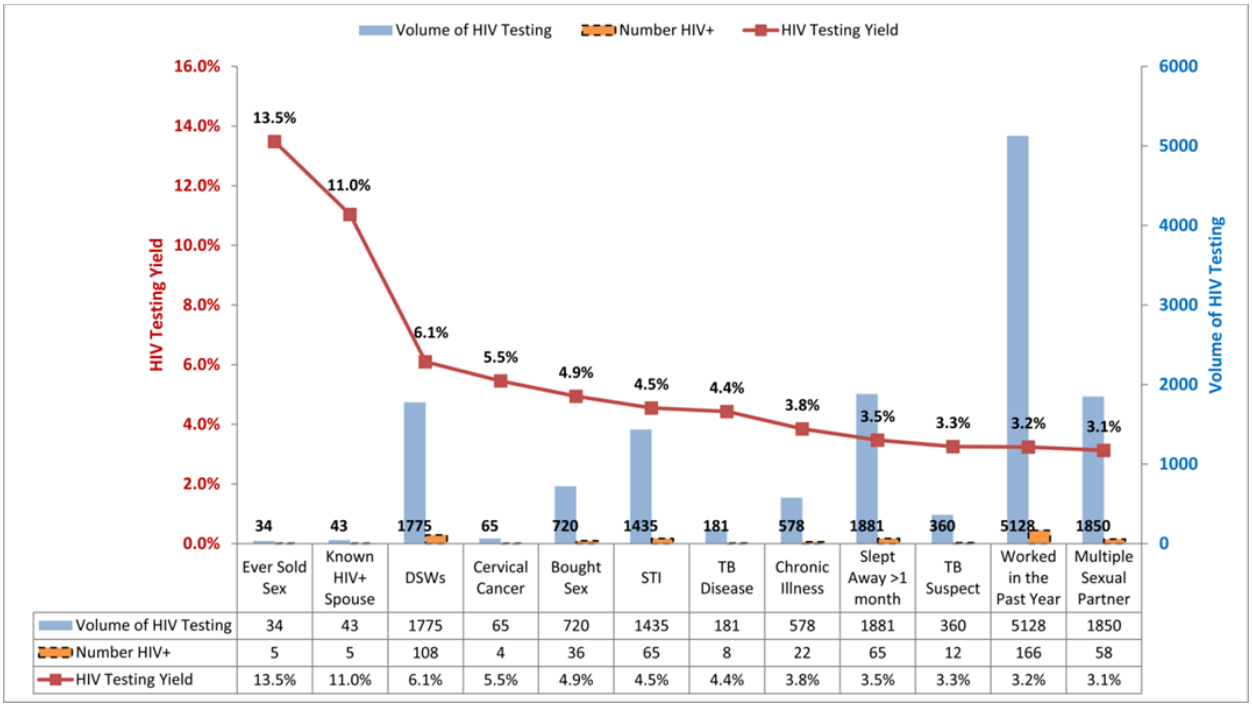

Figure 2. HIV Testing Yield by Risk Factors among Adults and Adolescents >14 years who were never tested

Determining cut off (risk score) for risk assessment tools

Looking at the performance of Tool 1 at different risk score levels, those individuals having one or more risk factors were found to have an HIV prevalence of 3.2% which increased with increasing cut-off: 4.4%, 5.6%, 7.9% HIV prevalence for two, three, and four cut-off scores respectively (Table 4). Area under the curve (AUC) can be seen to reduce as the risk assessment cut-off increases. A score of ≥1 was found to have the highest sensitivity at 82.3% (95% CI: 78.6% -85.9%) with the next score of ≥2 having nearly half the sensitivity at 46.8% (42.0%-51.6%). The specificity was higher for a higher cut-off. Positive predictive value was higher for a higher cut-off point while negative predictive value was comparable between all cut-off scores (Figure 3).

Table 4. Association of HIV Risk Scores with HIV Infection using a tool that contains all HIV Risk Factors for Adults and Adolescents >14 years who were never tested for HIV before PHIA Surveys conducted in Zambia (2016) and Tanzania (2016-2017)

Risk Score	Response	Total, n	HIV+, n (%)	P value
Score≥1	No	6,122	59 (1.0%)	**<0.001**
	Yes	8,698	279 (3.2%)	
Score≥2	No	11,238	179 (1.6%)	**<0.001**
	Yes	3,582	159 (4.4%)	
Score≥3	No	13,556	267 (2.0%)	**<0.001**
	Yes	1,264	71 (5.6%)	
Score≥4	No	14,445	308 (2.1%)	**<0.001**
	Yes	375	30 (7.9%)	

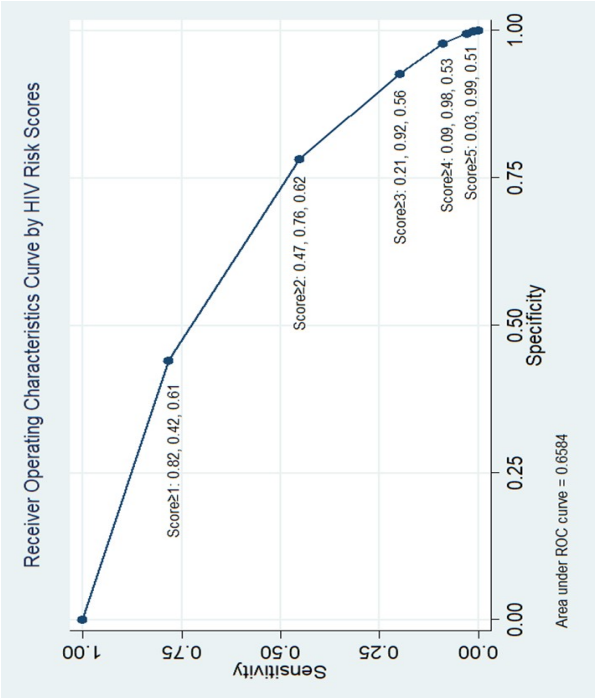

Figure 3. Receiver Operating Characteristics Curve by HIV Risk Scores for Adults and Adolescents >14 years who were never tested for HIV before PHIA Surveys conducted in Zambia (2016) and Tanzania (2016-2017).

The sensitivity, specificity, and area under the curve are indicated for each cut-off. Compared to a cut-off score of ≥1, AUC was comparable with a cut-off score of ≥2, while it was lower for those with higher cut-off scores (p value <0.001). (Table 5) The AUC was comparable by age, gender, and residence. (Table 6)

Table 5. Sensitivity, Specificity, Positive Predictive Value (PPV+), and Negative Predictive Value (NPV-) for HIV Risk Screening Tool Containing Various Combinations of All Risk Factors
* Score≥1 means an individual who has one or more risk factors for HIV; ** AUC= Area under the Curve of a Receiver Operating Curve;

Screening Tool Score*	Sensitivity	Specificity	PPV	NPV	AUC **	P Value ***
Score≥1	82.3% (78.6%-85.9%)	41.9% (41.1%-42.7%)	3.2% (2.8%-3.6%)	99.0% (98.8%-99.3%)	0.612	
Score≥2	46.8% (42.0%-51.6%)	76.4% (75.7%-77.1%)	4.4% (3.7%-5.1%)	98.4% (98.2%-98.6%)	0.615	0.7137
Score≥3	21.0% (17.1%-24.9%)	91.8% (91.3%-92.2%)	5.6% (4.3%-7.0%)	98.0% (97.8%-98.3%)	0.560	<0.001
Score≥4	8.9% (6.2%-11.6%)	97.6% (97.4%-97.9%)	8.0% (5.1%-10.9%)	97.9% (97.6%-98.1%)	0.533	<0.001

*** P value compares AUC for a given score with the reference Score≥1

Table 6. Comparison of Receiver Operating Characteristics Curve for HIV Risk Screening Tool (Score≥1) by Age, Gender, and Residence for Adults and Adolescents > 14 years who were never tested for HIV before PHIA Surveys conducted in Zambia (2016) and Tanzania (2016-2017)

Variable	Response	Observation	Area Under ROC Curve	P value
Age	15-24	7,868	0.5756	0.6033
	25-49	3,507	0.5705	
	50+	3,445	0.5478	
Gender	Male	7,945	0.6119	0.6448
	Female	6,875	0.6212	
Residence	Urban	4,461	0.6070	0.7531
	Rural	10,359	0.6137	

Figure 4 summarizes relationship between eligibility, sensitivity, and PPV or HIV testing yield. Eligibility for HIV test decreased with increasing risk score cut-offs: 56% would be eligible with a cut-off score of ≥1, while it was 2% for a cut-off score of ≥4. HIV testing positivity (PPV) and sensitivity or eligibility was negatively correlated with both going down with increasing cut-off score, while PPV increased.

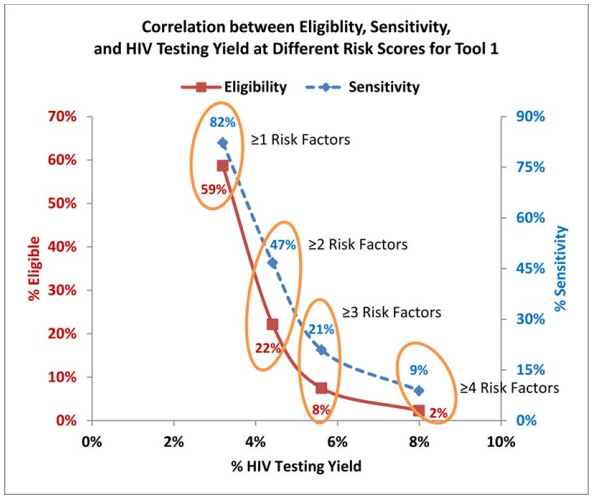

Figure 4. Relationship between Eligibility, Sensitivity, and HIV Testing Yield for a Risk Assessment Tool that contains all Risk Factors for Adults and Adolescents > 14 years who were never tested for HIV before PHIA Surveys conducted in Zambia (2016) and Tanzania (2016-2017)

In the tool that contained only statistically significant risk factors from the final logistic regression model (Table 3) (Tool 2), being DSW (odds ratio (OR): 3.9 (95% CI: 2.9-5.2); being spouse of a known HIV+ person (OR: 6.1 (95% CI:2.0-19.1)); having history of selling sex for money (OR: 7.7 (95% CI:3.6-16.3)); having sexually transmitted infections in the past 12 months (OR: 2.1 (95% CI:1.4-3)), and having a paid work in the past 12 months (OR: 2.1 (95% CI:1.4-3)); were included in the final model. Tool 4 which contained customized risk factors, the combination of risk factors having paid work in the past year and sleeping away from home for more than a month in the past 12 months were combined as predictors in addition to conventional risk factors. Having a paid work and sleeping away from home were statistically significant predictors of undiagnosed HIV infection (OR: 1.8 (95% CI: 1.1-3.0)).

Comparison of risk assessment tools

Looking at the different risk assessment tools, all were statistically significant predictors of HIV infection with p-value <0.001. For all tools, if none of the risk factors was present, HIV prevalence would be low in the range of 1.0-1.3%. (Table 7) Sensitivity was better for Tool 1 but the corresponding specificity was the lowest. AUC was better for all other tools as compared to this tool, and the difference was much higher for Tools 3 and 4 (p-value<0.001). (Table 8) PPV or HIV testing yield was highest for Tools 3 and 4 at 4.2% and 4.0%, respectively, if at least one risk factor was present. Tool 3 had the lowest proportion of people eligible for testing at 34%the highest being for tool 1 at 59%. (Table 7) Number needed to test (NNT+) was 24 for Tool 3, while it was 43 if universal testing was used.

Table 7. of Risk Scores with HIV Infection using a tool that contains all HIV Risk Factors for Adults and Adolescents >14 years who were never tested for HIV before PHIA Surveys conducted in Zambia (2016) and Tanzania (2016-2017)

Risk Assessment Tool	Response	Total, n	HIV+, n (%)	P value
Tool 1: All Risk Factors: Score≥1	No	6,122	59 (1.0%)	**<0.001**
	Yes	8,698	279 (3.2%)	
Tool 2: Statistically Significant Risk Factors in final model: Score≥1[#]	No	7,850	90 (1.2%)	**<0.001**
	Yes	6,970	247 (3.6%)	
Tool 3: Conventional Risk Factors: Score≥1	No	9,717	123 (1.3%)	**<0.001**
	Yes	5,103	215 (4.2%)	
Tool 4: Customized Tool: Score≥1*	No	9,294	117 (1.3%)	**<0.001**
	Yes	5,526	221 (4.0%)	

[#]Only those included in the final model were considered; *Customized tool=Conventional risk factors + Working for a payment in the past 12 months and sleeping away from home for at least 1 month in the past 12 months of the survey.

Table 8. Sensitivity, Specificity, Positive Predictive Value (PPV+), and Negative Predictive Value (NPV-) for each potential HIV Risk Screening Tool for Adults and Adolescents >14 years who were never tested for HIV before PHIA Surveys conducted in Zambia (2016) and Tanzania (2016-2017)

Risk Factor Selection Strategy	Sensitivity	Specificity	PPV	NPV	AUC**	P value***
Tool 1: All risk factors	82.3% (78.6%-85.9%)	41.9% (41.1%-42.7%)	3.2% (2.8%-3.6%)	99.0% (98.8%-99.3%)	0.6116	
Tool 2: Statistically significant only[#]	73.4% (69.1%-77.6%)	53.6% (52.8%-54.4%)	3.6% (3.1%-4.0%)	98.9% (98.6%-99.1%)	0.6267	0.035
Tool 3: Conventional risk factors	63.5% (58.9%-68.1%)	66.2% (65.5%-67.0%)	4.2% (3.6%-4.8%)	98.7% (98.5%-98.9%)	0.6469	<0.001
Tool 4: Customized tool*	65.5% (61.0%-70.1%)	63.4% (62.6%-64.2%)	4.0% (3.5%-4.5%)	98.7% (98.5%-99.0%)	0.6412	<0.001

[#]Only those included in the final model were considered; *Customized tool=Conventional risk factors + Working for a payment in the past 12 months and sleeping away from home for at least 1 month in the past 12 months of the survey. **AUC= Area under the Curve of a Receiver Operating Curve;
*** P value compares AUC for a given risk assessment tool with the reference tool that contains all risk factors.

Discussion

We set out to validate HIV risk assessment tool used for adults. In this process, we tried various combinations of risk factors in different tools for best possible

outcome. The final tool we recommend for use contains conventional risk factors. This screening tool showed a moderate sensitivity and specificity for identifying infected adults at household level. Using this screening tool, the number needed to test to diagnose one HIV infected adult would be 24 down from 43 if universal testing was used.

Looking at individual risk factors, the prevalence of HIV in those who never tested for HIV remained to be high compared to those without risk factors except for TB related risk factors and chronic illness. Two risk factors that stood out with having testing yield of >10% were selling sex for money and having an HIV+ spouse. This is comparable to reported prevalence of 12-20% among FSWs in the study countries (23). ICT for spouses records even higher testing yield at 32% in program settings (24). Marital status is an important risk factor. Being divorced widowed or separated was found to be the third highest risk factor with a yield of 6.1%. DSWs are easily identifiable at community level and can be used to identify at risk people at community or facility level. It is already a risk factor in many countries (25, 26).Cervical cancer is an important risk factor since Human Papiloma Virus, which is a sexually transmitted viral infection, is the causative agent (27). Co-infection with HIV was 5.5% in this study. Having multiple sexual partners was found to have a relatively lower prevalence at 3.1%. This may be due to the higher condom use during casual sex with a non-regular partner (28, 29).

Lifetime TB disease was not statistically significant at the 0.05 cut-off. This should not be misinterpreted as TB not being a risk factor. Data on year of TB diagnosis were present only for Zambia and when we did analysis comparing TB diagnosed in the past 10 years to those who never had TB, or who had TB before 10 years, TB prevalence was much higher at 33.3% prevalence. This should be used in practice instead of lifetime TB disease.

Presumptive TB was not predictor of HIV infection because probably it was defined broadly especially for cough. A definition of cough > 2 weeks may make improve the positivity. In studies where the later definition was used, the positivity was found to be higher (30, 31).

Adults having multiple risk factors were found to have high testing yield and were a small fraction of the total assessed. This should be explored to further identify additional risk factors. A very good example in current use by different case finding and prevention programs is being long distance truck driver, who are likely to sleep away from home, and have multiple sexual partners including sex workers (32, 33).

This study also provides some form of reference for the percentage of people who are potentially eligible for HIV testing fulfilling at least one of the conventional risk factors among those who never tested for HIV. In this study, 34.4% adults who never tested for HIV would be eligible for testing. That is around 9.1% of the initial number of adults interviewed. This provides a reference value with which to compare community HIV case finding interventions when such risk factors are used. However, it would not be advisable to test this much adults as it wouldn't be cost effective. A more targeted approach focusing on sex workers and their clients, partners of known HIV+ index cases, DSWs, and TB cases would be important starting points (2).

Eliciting some of the risk factors especially those related to sexual history may need some experience especially when implementing the risk assessment tool at community level. The use of health extension workers or community health workers who formally do health interventions may help. At facility level where these risk factors are often used maintaining quality of counselling needs to be ensured through ongoing training and on job coaching. Some of the risk factors are treated in speciality clinics like TB in TB clinic, or STI and cervical cancer in gynaecology clinics for women. This will make it easier to implement universal testing for these groups by providing integrated testing services.

The large number of study participants was one of the strengths of the study. Missing data was minimal and was not related to the risk factors being studied. The performance of the final tool was found to be independent of age, gender, and residence making the use of the tool applicable in different scenarios. Some of the risk factors were captured a little different from what is used in actual settings. All parameters of screening tool are likely to improve if the presence of the following risk factors was determined for the past 10 years just like what we did with TB instead of just the past 12 months: multiple sexual partners, STI, and clients of sex workers.

Conclusion

Use of a screening tool containing conventional risk factors improved HIV testing yield compared to doing universal testing. The use of multiple risk factors to improve HIV testing yield should be explored further.

Declarations

Consent for publication

Not applicable

Conflict of interest

The authors declare that they have no competing interests.

Author contribution

KDY originated the research idea, and collected and analyzed the data; KDY & JM contributed to data analysis and writing the manuscript; All authors read and approved the final manuscript.

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Original Article
Dialysis Prescription: Determinants and relationship with intradialytic complications and the dialysis dose. A prospective study.

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Abstract

Introduction: *Dialysis still remains the most common modality for the treatment of end stage kidney disease and it could be maneuvered to augment its dose, minimize complications and improve outcome. Dialysis prescription is a brief of how dialysis is to be given and involves adjustments in patients' characteristics, disease or dialytic procedure. This study aimed to assess the determinants of the prescribed dialysis and its relationship with intradialytic complications and the dialysis dose.*

Methods*: A prospective study in which 1248 sessions for 232 consented participants with end stage kidney disease on maintenance hemodialysis were studied from 2017-2020. Biodata was taken, participants were examined and blood samples were taken to determine electrolytes, urea/creatinine and hematocrit. Pearson's correlation was used to determine the strength of association between dialysis dose and some variables.*

Results*: Determinants of the prescribed dose were dialysis frequency (P<0.001), and predialysis systolic blood pressure (P<0.001) and packed cell volume (P<0.001). Dialysis sessions without significant intradialytic blood pressure changes were most likely to be completed, as sessions with intra-dialysis hypotension were most likely to be terminated. Participants dialyzed with high flux dialyzers, via an arterovenous fistula, higher blood flow and ultrafiltration rates had higher dialysis doses (P<0.001 in all instances).*

Conclusion*: Higher dialysis doses were achieved with higher blood flow and ultrafiltration rates. Intradialytic hypotension was common with dialysis termination, higher blood flow and ultrafiltration rates. Intradialytic hypertension was common with low flux dialyzers. An optimized dialysis prescription is needed to deliver an adequate dialysis dose and minimize complications.*

Keywords*: End stage kidney disease, intra-dialysis hypotension, intra-dialysis hypertension, prescribed dialysis*
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Introduction

Despite advances in dialysis modalities, optimal dialysis delivery is still largely unattainable particularly, in low income nations (LINs). Agaba et al reported a urea reduction ratio (URR) of 45.3 ± 8.6% in Nigeria and attributed this low dose to socioeconomic factors and frequent breakdown of dialysis machines.[2] Amini et al in Iran, a developing nation, found a URR of 61.0 ± 11.8% and solute clearance (Kt/V) of 1.2 ± 0.4 and found similar limitations to effective dialysis delivery in LINs.[3] However Rafik et al in Morocco reported that increasing the blood flow rate (BFR) from 250 ml/min to 350 ml/min increased the mean URR from 75.41 ± 5.60 to 83.51 ± 6.12 and mean single pool Kt/V from 1.28 ± 0.25 to 1.55 ± 0.15.[4] Dialysis delivery is reported to be better in the developed nations due to better socioeconomic standards, government financing, reliable energy supply and a more enlightened population.[5] Suboptimal dialysis contribute to increased morbidity and mortality, more so in LINs. The dialysis prescription appears to be the final attempt at addressing these shortcomings, particularly in LINs.

The delivered dose is defined as adequate when the assessment measures, Kt/v or URR is at least 1.2 or 65% respectively. It is dependent on patients' prevailing clinical and laboratory parameters, the prescribed dose, dialysis facilities and personnel, and energy supply and is directly related to the blood pressure control and fluid balance. Adequate dialysis increases appetite and is associated with higher serum albumin and hematocrit. Inflammation in dialysis patients is partly attenuated with an adequate dialysis dose. [3-5].

Literature is scanty concerning the place of prescribed dialysis in improving treatment outcome in LINs. We studied the prescribed dialysis dose, its determinants, and its relationship with intradialytic complications and dialysis dose.

Methods

Study Design

This was a two-center hospital based prospective study conducted at the Federal Medical Centre, Abeokuta (FMCA) from January to December 2017 and Babcock University Teaching Hospital (BUTH), Ilishan-Remo, from August 2018 to December 2020, both cities in Southwestern, Nigeria, about 30 kilometers apart.

Study setting and population

Two hundred and thirty two participants with chronic kidney disease (CKD) in end stage according to the KDOQI 2012 criteria, ≥16 years, met the inclusion criteria and gave informed consent had 1248 sessions[6].Patients with kidney transplant, infections, and sessions less frequent than once weekly were excluded

Study Objectives

To assess the prescribed dose, its determinants and its relationship with intradialytic complications and the delivered dose.

Sample size estimation

Using a previous study's prevalence of 6.1% for patients on maintenance hemodialysis (MHD) for less than a year and on twice weekly treatment[7] (a common regimen in LINs). This gave an estimated sample size of 232 (after an attrition of 10%).

Data collection procedures

Retrieved were age, etiology of CKD, erythropoietin and dialysis frequency, intradialytic hypotension (IDH), intradialytic hypertension (IDHT) and dialysis termination. Unfractionated heparin 5,000 IU was used, alterations were documented. Dialysate buffer was bicarbonate based, where sodium profiling was done, it was documented.

Height and weight were measure bare-footed, on light clothing and without cap or head gear. After 5 minutes rest, vitals participants were examined to determine the oxygen saturation (SPO_2), temperature, pulse rate (PR) and blood pressure (BP), and dialysis was prescribed. These vitals were repeated half hourly throughout dialysis. Predialysis samples were taken, patient were connected, other pre-dialysis protocols were observed and dialysis was commenced.

Where the blood flow rate (BFR) or dialysate flow rate (DFR) was altered, the average was documented. At dialysis time zero, the dialysate flow was stopped, BFR was reduced to 100ml/min, five minutes later, blood flow was stopped and sample was taken from the arterial portal first for renal biochemistry, then for hematocrit.[8]

Dialysis dose was calculated using Daugirdas second generation logarithmic formula:

$Kt/V = -In(R - 0.008 \times t) + (4.35 \times R) \times UF/W$ [9].

The URR was calculated from the formula:

(differrence in urea/pre dialysis urea) X 100.

The URR and Kt/V were related by the equation,

Kt/V = In (1-URR), where In is natural log

The Ion Selective Electrode method was used to analyze the serum electrolytes. Serum albumin was analyzed using the bromocresol green method[9]. Hematocrit was determined using a hematocrit centrifuge. With increased risk of bleeding (deranged clotting profile), heparin dose was either reduced or withheld.

Study Definitions

Intra dialytic hypotension (IDH) was defined as ≥20 mmHg drop in systolic BP.[10]

Intra dialytic hypertension (IDHT) was defined as ≥10 mmHg rise in systolic blood pressure.[10]

Data processing and analysis

Data was entered into a data collection form, exported into SPSS 22 for cleaning, coding and analysis. Continuous variables were compared using t-test, categorical variables were compared using Chi square test or fisher's exact test. The P-value <0.05 was considered statistically significant. A multivariate logistic regression analysis was used to determine independent associates of the dialysis dose.

Ethical consideration

The Ethics Committees of the FMCA (FMCA/470/HREC/03/2017, NHREC/08/10-2015) and BUTH (BUHREC/723/19, NHREC/24/01/2018) have approved this study. The study protocol was read to participants, clarifications were given for enquiries and written informed consent were obtained. The research followed the tenets of the Declaration of Helsinki.[11]

Results

The mean age of the participant was 49.9 ± 4.6 years. Ninety (38.8%) of the participants had hypertension, all received antihypertensive drugs (**Table 1**). The overweight and obese made up 52.6% of the cohorts, had 56.6% of the sessions, but had 60.0% of sessions with Kt/V ≥1.2.

Table 1: Socio-demographic and clinical characteristics of participants

Variables	Frequency N=232 (%)	Dialysis session N=1248 (%)
Sex		
Males	143 (61.5)	818 (65.5)
Females	89 (38.5)	430 (34.5)
Age, years		
Less than 50	110 (47.4)	479 (38.4)
50 and above	122 (52.6)	769 (61.6)
Etiology of CKD		
Hypertension	90 (38.8)	585 (46.9)
Chronic glomerulonephritis	88 (38.0)	362 (29.0)
Diabetes	27 (11.6)	162 (13.0)
Others	27 (11.6)	139 (11.1)
Body mass index, m^2/kg	110 (47.4)	542 43.4)
<25.0	122(52.6)	706 (56.6)
≥25.0		
Predialysis Systolic BP, mmHg		
<140	45 (19.4)	201 (16.1)
≥140	187 (80.6)	1047 (83.9)
Predialysis Diastolic BP, mmHg		
<90	27 (11.6)	167 (13.4)
≥90	205 (88.4)	1081 (86.6)
Predialysis Oxygen saturation, %		
<95	207 (89.2)	1156 (92.6)
>95	25 (10.8)	92 (7.4)

Mean pre dialysis sodium was lower than the post dialysis (**Table 2**). The mean pre dialysis albumin was 34.7 ± 5.2 g/dl, it was higher in males (36.1 ± 4.4 g/dl versus 31.8 ± 3.7 g/dl).

Table 2: Laboratory results of participants

Variables	Pre-dialysis	Post-dialysis	t-test	P-value
Sodium	126.7 ± 4.7	134.24 ± 3.6	1.5	0.01
Potassium	5.76 ± 1.2	4.1 ± 1.1	5.5	0.001
Chloride	96.8 ± 7.6	102.4 ± 8.3	5.2	0.001
Bicarbonate	18.1 ± 4.4	20.1 ± 5.9	5.3	0.001
Urea	17.3 ± 2.7	8.1 ± 4.4	7.5	<0.001
Creatinine, u mol/l	526.6 ± 11.8	322.9 ± 11.4	7.9	<0.001
Glomerular filtration rate	5.2 ± 1.2	9.1 ± 1.6	5.8	<0.001
Hematocrit, %	23.5 ± 3.3	24.2 ± 4.8	1.1	0.

The dialysis dose (Kt/V) was adequate in 9.2% of the sessions and with URR, 13.8%. The mean Kt/V for all sessions was 1.02 ± 0.4, higher in males (1.10 ± 0.7 versus 0.94 ± 0.3), P=0.002 (**Table 3**). The mean URR was 55.8 ± 4.0 %. Participants on weekly, twice weekly and thrice weekly sessions, and erythropoietin had 264 (21.2%), 784 (62.8%) and 200 (16.0%), and 14.2%, 53.5% and 403 32.3% respectively.

The mean dialysis duration was 3.8 ± 0.6 hours, it was higher in males (3.8 ± 0.8 hours versus 3.8 ± 0.2 hours). Sessions with high flux dialyzers, AV fistula, higher BFR and UFV had higher dialysis doses (P<0.001 in all instances). The mean BFR and UFV were 306.8 ± 13.2 ml/min and 1.3 ± 1.0 L respectively. More men than women used the IJV access, P=0.8.

Table 3: Relationship between determinants and content of prescribed dialysis, and dialysis dose

Variables	Frequency N=1248 (%)	Kt/V <1.2 N=1133 (%)	Kt/V >1.2 115 (%)	X^2	P-value
Gender					
Males	818 (85.5)	736 (65.0)	82 (71.3)	3.4	0.002
Females	430 (34.5)	397 (35.0)	33 (28.7)		
Age, years					
Less than 50	479 (38.4)	443 (39.1)	36 (31.3)	5.4	<0.001
50 and above	769 (61.6)	690 (60.9)	79 (68.7)		
Etiology of CKD					
Hypertension	585 (46.9)	521 (46.0)	64 (55.6)	4.1	0.001
Chronic glomerulonephritis	362 (29.0)	333 (29.4)	29 (25.2)		
Diabetes	162 (13.0)	151 (13.3)	11 (9.6)		
Others	139 (11.1)	128 (11.3)	11 (9.6)		
Body mass index, kg/m^2					
Less than 25.0	541 (43.3)	495 (44.6)	46 (40.0)	3.9	0.002
25.0 and above	707 (56.7)	638 (55.4)	69 (60.0)		
Systolic BP, mmHg					
Less than 140	139 (11.1)	101 (8.9)	38 (33.0)	8.8	<0.001
140 and above	1109 (88.9)	1032 (91.1)	77 (67.0)		
Oxygen saturation, %					
Less than 95	864 (69.2)	897 (71.2)	57 (49.6)	8.2	<0.001
95 and above	384 (30.8)	326 (28.8)	58 (50.4)		
Erythropoietin/week					
1	434 (34.8)	417 (36.8)	17 (14.8)	7.9	<0.001
More than once	814 (65.2)	716 (63.2)	98 (85.2)		
Hematocrit, %					
Less than 33	865 (69.3)	844 (74.5)	21 (18.3)	10.3	<0.001
33 and above	383 (30.7))	289 (25.5)	94 (81.7)		
Albumin, g/dl					
Less than 35	1096 (87.8)	1063(93.8)	33 (28.7)	10.1	<0.001
35 and above	152 (12.2)	70 (6.2)	82 (71.3)		
Creatinine, umol/l					
Less than 130	33 (2.6)	2 (9.2)	31 (27.0)	7.1	<0.001
130 and above	1215 (97.4)	1131 (99.8)	84 (73.0)		

Variables	Frequency N=1248 (%)	Kt/V <1.2 N=1133 (%)	Kt/V >1.2 115 (%)	X^2	P-value
Dialysis frequency/week					
1	389(31.2)	380 (33.5)	9 (7.8)	9.1	<0.001
2 and above	859 (68.8)	753 (66.5)	106 (92.2)		
Vascular access					
Femoral	426 (34.1)	399 (35.2)	27 (23.5)	6.5	<0.001
Tunneled internal jugular	757 (60.7)	677 (59.8)	80 (69.6)		
Arterovenous fistula	65 (5.2)	57 (5.0)	8 (6.9)		
Dialysis duration, hours					
Less than 4	170 (13.6)	164 (14.5)	6 (5.2)	6.9	<0.001
4 or more	1078 (86.4)	969 (85.5)	109 (94.8)		
Blood flow rate, ml/min					
Less than 300	307 (24.6)	296 (26.1)	109 (9.6)	8.9	<0.001
300 and above	941 (75.4)	837 (73.9)	104 (90.4)		
Dialyzer area, m^2					
Low flux, 1.3/1.4	33 (2.6)	33 (2.9)	0 (0.0)	10.8	<0.001*
High flux 1.7/1.8	1215 (97.4)	1100 (97.1)	115 (100.0)		
Ultrafiltration volume, litres					
Less than 3	630 (50.5)	588 (51.9)	42 (36.5)	7.1	<0.001
3 and above	618 (49.5)	545 (48.1)	73 (63.5)		

IDHT was more common with AV fistulas as IDH was more common with TIJV catheters, P<0.001 (**Table 4**). Dialysis sessions without significant intra-dialytic BP changes were most likely to complete their treatment, sessions with IDH were more likely to be terminated.

IDHT were more common in males as IDH was in females 207 (67.9%) versus 145 (59.9%). The mean time for the detection of IDH was 64 ± 3.8 minutes while it was 146 ±7.1 minutes for IDHT. Dialysis was terminated in 8 (3.3%) of the sessions with IDH but in 1 (0.3%) session with IDHT, and intradialytic death.

Table 4: Relationship between the content of prescribed dialysis and intradialytic complications

Variables	All sessions N=1248 (%)	IDH 242 (%)	IDHT N=305 (%)		X^2	P-value
Access						
Femoral	426 (34.1)	72 (29.8)	132 (43.3)	7.6	<0.001	
Tunneled internal jugular	757 (60.7)	157 (64.9)	120 (39.3)			
Arterovenous fistula	65 (5.2)	13 (5.3)	53 (17.4)			
Dialysis duration, hour						
Less than 4	170 (3.6)	44 (18.2)	34 (11.1)		6.7	<0.001
4 and above	1178 (96.4)	198 (81.8)	271 (88.9)			
Blood flow rate, ml/min						
Less than 300	307 (24.6)	41 (17.0)	109 (35.7)		9.3	<0.001
300 and above	941 (75.4)	201 (83.0)	196 (64.3)			
Dialyzer area, m^2						
Low flux, 1.3/1.4	33 (2.6)	4 (1.7)	14 (4.6)	2.8	0.002	
High flux 1.7/1.8	1215 (97.4)	238 (98.3)	291 (95.4)			
Ultrafiltration volume, litres						
Less than 3	630 (50.5)	93 (38.4)	196 (64.3)		7.2	<0.001
3 and above	618 (49.5)	149 (61.6)	109 (35.7)			

From Pearson' correlation (**Table 5**), albumin and dialysis duration were very strongly positive and strongly positively correlated with dialysis dose.

Table 5: Pearson's correlation: Strength of association between dialysis dose and some variables

Variables	r	CI	P-value	Correlations
Age	0.12	0.10-0.20	0.06	Weakly positive
Males	0.09	0.06-0.11	0.08	Weakly negative
Body mass index	0.02	0.01-0.43	0.06	Weakly positive
Diabetes	0.09	0.05-0.12	0.06	Weakly negative
Systolic blood pressure	0.16	0.07-0.12	0.04	Strongly positive
Oxygen saturation	0.36	0.26-0.93	<0.001	Very strongly positive
Serum Albumin	0.34	0.26-0.81	<0.001	Very strongly positive
Hematocrit	0.11	0.09-0.19	0.05	Weakly positive
Arterovenous fistula	0.27	0.20-0.56	0.001	Strongly positive
Dialysis duration	0.20	0.11-0.39	0.003	Strongly positive
Blood flow rate	0.44	0.07-0.72	<0.001	Very strongly positive
Dialyzer surface area	0.18	0.13-0.51	0.04	Strongly positive
Ultrafiltration volume	0.34	024-0.72	<0.001	Very strongly positive

Multivariate regression analysis showed SPO_2 (OR-1.23, CI-0.55-3.73, P=0.002), catheter site (OR-2.04, 1.30-3.52, P=0.001), dialysis duration (OR-1.08, CI-1.01-2.84, P=0.04), albumin (OR-2.72, CI-2.12-5.94, P<0.001), BFR (OR-3.66, CI-2.46-8.84, P<0.001), UFV (OR-2.44, CI-1.07-6.38,P=0.001) predialysis creatinine (OR-1.14, CI-0.31-1.75, P=0.02) as predictors of the dialysis dose.

Discussion

We found the major predictors of dialysis dose to be patient's hemodynamics, CKD etiology, UFV, IDH, IDHT, and comorbidities. Males received higher doses than females, similar to findings in Egypt.[12]. Women, the malnourished and children, by virtue of their lesser weight have lower urea distribution volume (UDV), which has an inverse relationship with the dialysis dose, women should therefore have higher doses as reported by Somiji et al.[13] We attribute our findings to the combined effect of higher BFR, higher albumin levels, more frequent dialysis and EPO use in males, mitigating the relationship between weight and UDV.

The positive relationship between dialysis doses and BMI disagrees with previous findings that showed an inverse relationship between the BMI and dialysis dose. [14] A very large proportion of participants had relatively higher albumin level. Many of the dialysis patients were relatives of (or retired workers) of multinational organizations who had frequent dialysis and erythropoietin treatment. We infer that this pattern is behind the higher doses found in the aged who had hypertensive nephropathy, unlike chronic glomerulonephritis, which was more common in the young.[15] Infectious causes of kidney disease are common in the young in SSA.[15] Our findings agree with findings in the United States that found higher doses with advancing age, better living standard and access to medicare, common in these two groups most probably accounted for these findings.[16]

Diabetics had lower dose compared to those with hypertension and glomerulonephritis. We attribute this to the greater degree of atherosclerosis, autonomic neuropathy, cardiac systolic dysfunction in them.[17] Higher BP were associated with lower doses, similar to findings by Raikou et al[18] that hypertension was an impediment to dialysis adequacy. The positive relationship between bicarbonate and dialysis dose agrees with a previous study. Acidosis induces vasodilatation, peripheral pooling, thereby increasing the risk of IDH, however, bicarbonate buffers often minimizes the incidence and severity of IDH.[19]

Albumin was positively related to the dialysis dose. Normal serum albumin reflects dialysis adequacy, good nutritional balance, less edema and absence of protein energy malnutrition (PEM).[20] Lower pre dialysis creatinine gave higher dialysis dose. Narrow intradialysis osmotic gradient prevents excessive fluid shift hence lesser episodes of IDH, greater contribution of solute clearance to dialysis dose, and less ultrafiltration based solute removal.[21]

The positive relationship between the hematocrit and dialysis dose mirrors findings by El Shehkl et al.[12] Anemia frequently coexist with hypoalbuminemia, higher plasma volume and decreased effective oxygen transport, factors which separately and in combination lead to low dialysis dose and poor treatment outcome.

The AV fistula and the tunneled jugular access gave higher dialysis doses compared with the femoral access. The point of needle placement into the AV fistula can impact the dialysis dose and the recirculation time, which when high, leads to overestimation of dialysis dose commonly seen in low weight individuals. Tunneling with lesser intravascular fibrous tissue prevents luminal narrowing over time. Moreover, infections are more common in femoral than in tunneled access and AV fistula.[22]

Terminated sessions produced lower doses than completed ones. Higher ultrafiltration rates are seen within the first 2 intradialysis hours, followed by increased solute clearance. Removal of most middle and larger molecules is directly related to dialysis duration.[23] The significance of this is better appreciated knowing that middle and large molecules are largely responsible for most of the uremia symptomatology.[24] Ultrafiltration reduces the urea content of ultra-filtrate and urea generated intradialysis.[24]

Features of excessive UFV are made worse in the presence of a high BFR, high flux dialyzers, fever, excessive inter dialytic weight gain coupled with poor cardiac reserve associated with poor adrenegic response to fluid loss.[25] Recurrent UFV of up to 4 liters could be associated with IDH, myocardial stunning and increased mortality.[26]

The nephrologist's ultimate target in prescribing dialysis, is to give an optimal dose, with very few/no peridialytic events, improve QOL and prolong life. Rich et al[27] reported that death was common after the seventh day of stopping maintenance hemodialysis. The nephrologist would therefore prefer higher BFR, longer duration, high flux dialyzers, higher UFV, a tunneled access or an AVF. However, this "blinded" prescription often heightens the risk for IDH particularly with background dysautonomia.[26] When this blinded prescription becomes recurrent, despite good clinical and laboratory performance, it would often be associated with dialysis cachexia and PEM secondary to excessive intradialytic protein loss from high flux dialyzers.[27]

This study showed that lower BFR, low flux dialyzers, shorter dialysis duration and lower UFV, led to lower doses, a prescription pattern commonly given when the nephrologist anticipate possible intradialysis hemodynamic instability. Unfortunately, this prescription pattern could ultimately give lower doses associated with dialyzer blood clotting induced by stasis. When recurrent, it could lead to poor BP control, arrhythmias, acute and chronic coronary syndromes, reduced QOL, higher morbidity and mortali-

ty rates.[28] The nephrologist would therefore find a 'mid-point' prescription in which hemodynamic instability are minimized while attempting to give relatively higher doses.

It is worth noting that the dialysate fluid composition is also an important consideration for the nephrologist. Sodium profiling could be needed in conditions of IDH and IDHT as the case may be.[29] Water purification and delivery is also a priority to the nephrologist as infections cause vasodilatation and lower doses. Though the concentration of dialysate fluid was not altered in this study, it is worth stating that in patients with poor blood pressure control, high dialysate calcium could be detrimental as it could heighten the risk of tissue calcification, cardiovascular events and intra dialytic death.[30] While optimal doses are targets for nephrologists, often times, many prescriptions are given to reflect a balanced-point between the aggressive and cautious prescription patterns.

An implication of this study for clinical practice, is to emphasize the possibility of delivery an adequate dose while not subjecting patients to undue peridialytic stress.

We encountered some limitations. The contribution of the residual renal function to the delivered dose was not determined. The presence of some comorbidities that could be confounders could not be effectively ruled out. There were some irregularities with dialysis intervals and inability to control the choice of parameters for dialysis. The blood PH, the most reliable marker of MA, was not assessed on account of cost. The dry weight of participants could not be effectively assessed. Larger population studies are needed to formulate a comprehensive dialysis delivery program that will be applicable to all population groups.

The study is strengthened by its two center design and its relatively large sample size.

Conclusion: Despite efforts to improve dialysis delivery over the past decades, inadequate dialysis is still a very common finding in many LINs including Nigeria. Patient related factors, disease condition, socioeconomic deprivation and state of dialysis facilities play various roles in treatment outcome. The use of the AV fistula, tunneled jugular catheters, higher BFR and UFV, high flux dialyzers and longer dialysis duration were found to produce higher dialysis doses. Dialysis termination was more common with IDH than with IDHT.

We recommend that the content of the prescribed dialysis should therefore be carefully and intelligently individualized, and maneuvered to give dialysis patients an effective and optimal dose with minimal adverse consequences.

Authors' contribution

Conceptualization and design of paper: PKU.
Collection of data: PKU.
Implementation of research: PKU, SK
Data analysis and interpretation: PKU, SK
Preparation of manuscript: PKU, SK
The authors checked and approved the final manuscript before submission.

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Consent for publication
Not applicable

Availability of data and material
The datasets supporting the conclusions of this article are included within the article. Additional material can be obtained upon reasonable request.

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The authors have no conflict of interest to declare.

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Original Article

Determinants of time to viral clearance among SARS-CoV-2 infected individuals at Millennium COVID-19 care center in Ethiopia: A prospective observational study

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Abstract

Background*: Understanding the COVID-19 disease course in terms of viral shedding is important to assist in providing a tailored isolation and treatment practice. Therefore, the current study aimed to estimate time to viral clearance and identify determinants among SARS-CoV-2 infected individuals admitted to Millennium COVID-19 Care Center in Ethiopia.*

Methods: *A Prospective observational study was conducted among 360 randomly selected SARS-CoV-2 infected individuals who were on follow up from 2nd June to 5th July 2020. Kaplan Meier plots, median survival times, and Log-rank test were used to describe the data and compare survival distribution between groups. Association between time to viral clearance and determinants was assessed using the Cox proportional hazard survival model, where hazard ratio, P-value, and 95% CI for hazard ratio were used for testing significance*

Results*: The Median time to viral clearance was 16 days. The log-rank test shows that having moderate and severe disease, one or more symptoms at presentation, and presenting with respiratory and constitutional symptoms seems to extend the time needed to achieve viral clearance. The Final Cox regression result shows that the rate of achieving viral clearance among symptomatic patients was 44% lower than patients who were asymptomatic (AHR=0.560, 95% CI=0.322-0.975, p-value=0.040).*

Conclusions*: Presence of symptoms was found to be associated with delayed viral clearance implying that symptomatic patients are more likely to be infectious and therefore, attention should be paid to the practices regarding isolation and treatment of COVID-19 patients.*

Key words: *SARS-Cov-2, COVID-19, Viral clearance, prospective cohort, survival analysis, Cox PH model, Ethiopia*

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Introduction

With an increasing number of new cases, the Coronavirus Infectious Disease 2019 (COVID-19) caused by the Severe Acute Respiratory Syndrome Coronavirus Type 2 (SARS-CoV-2) has remained a global problem. According to the World Health Organization (WHO) weekly update, the total global cases as of July 25 2021 were over 193 million, of which over 4.7 million in Africa [1]. At the same time, there have been 277,318 cases and 4,349 COVID-19-related deaths in Ethiopia since the first case was confirmed on March 13, 2020 [2].

At the beginning of the pandemic, little was known about the characteristics of the disease. As research continues, knowledge about the clinical, epidemiologic, laboratory, and radiologic characteristics of the disease grows, and it appears to vary from place to place, as well as from person to person based on sex, age, and other factors reflecting the contribution of patients' background characteristics to the clinical presentation, severity, and outcome of the disease [3-22].

Among the characteristics of the disease, viral

shedding duration has vital importance since it determines a person's infectivity and the propagation of the infection, and thus the community level of infection. Therefore, understanding viral shedding pattern of the disease will guide the quarantine and isolation practices in order to halt the transmission of the disease. So far, studies on viral shedding are limited and are from outside Africa. The studies revealed that the median duration from diagnosis up to negative viral shedding varies from place to place and could range from 14 to 48 days, and the major identified determinants were age, sex, temperature at admission, time from symptom onset to admission, hospital length of stay, having symptomatic infection, fever, chest tightness, pneumonia, invasive mechanical ventilation and and lower lymphocyte count [23-27].

Given the limited well-established knowledge about the disease, documented disparities in its features and the practical significance of understanding viral shedding pattern, it is crucial to investigate the disease in the local setting. Therefore, the objective of this study was to estimate time to viral clearance and identify determinants among SARS-CoV- 2 infected patients admitted to Millennium COVID-19 Care Center in Ethiopia.

Methods and materials

Study setting and design

The study was conducted at Millennium COVID-19 Care Center (MCCC), a makeshift hospital in Addis Ababa, the capital city of Ethiopia. The center is remodeled from the previous Millennium hall/ Addis park which was a multipurpose recreational, meeting and exhibition center. The center had 1000 beds including 40 ICU beds. In the first few months of the pandemic in the Country, COVID-19 centres were designed to serve both as a quarantine and treatment centre in order to halt the transmission of the disease. Therefore, anyone who tested positive for SARS-Cov -2 gets admitted to COVID-19 Centres despite their risk status till viral clearance is declared by accredited laboratory.

The study design was hospital based prospective observational design. The follow up was made from June 2 to July 5, 2020.

Population and eligibility

The source population was all individuals admitted to MCCC with a confirmed diagnosis of COVID-19 using RT-PCR (real-time reverse transcription polymerase chain reaction) from referral centers and who were on follow up from June 2 to July 5, 2020. During this period a total of 768 SARS-CoV-2 infected individuals were seen at the Center.

The study population was all selected SARS-CoV-2 infected individuals who were on treatment and follow up at MCCC from June 2 to July 5, 2020 who fullfilled the eligibility criteria of being on treatment and follow up at the center during the observation period,had clear chart documentation and consented to participate.

Sample size Determination and Sampling Technique

Sample size was determined using sample size calculation formula of the survival method for one population group (Freedman 1982) by considering the following statistical assumptions: 95% Confidence Interval (CI), power of 90%, survival probability of 0.5, 5% marginal error10% non-response rate and with finite population correction (since the total source population was 774). The final sample size estimated for this study was 366.

To select the study participants from the sampling frame, simple random sampling method using computer based table of random numbers was employed.

Operational Definitions

Asymptomatic patient: any patient who has tested positive for COVID-19 but does not have any symptoms. These patients are detected after isolation and contact tracing as done by the Ethiopian Public Health Institute (EPHI) [28].

COVID-19 severity: was determined based on the WHO classification as follows [29].

- **Mild Disease:** Characterized by fever, malaise, cough, upper respiratory symptoms, and/or less common features of COVID-19 (headache, loss of taste or smell etc.)
- **Moderate Disease:** Patients with lower respiratory symptom/s. They may have infiltrates on chest X-ray. These patients are able to maintain oxygenation with room air.
- **Severe Disease:** These patients have developed complications. The following features can define severe illness.
  - Hypoxia: SPO2 (Oxygen saturation) ≤ 93% on atmospheric air or PaO2:FiO2 < 300mmHg (SF ratio < 315)
  - Tachypnea: in respiratory distress or RR (respiratory rate)>30 breaths/minutes
  - More than 50% involvement seen on chest imaging

Viral clearance: Viral clearance from Covid-19 infection as evidenced by two negative RT-PCR tests done on nasopharyngeal swab specimen at least 24 hours apart. The second negative test date was taken as the date of viral clearance.

Event: Achieving viral clearance from Covid-19 infection.

Censoring: Patients lost to follow-up, transferred out, died or completed the follow-up period without achieving the event.

Time to event or censoring: Time between date of laboratory sample taken which confirmed Covid-19 infection to viral clearance from Covid-19 infection or censoring (in days).

Data Collection Procedures and Quality Assurance

A pretested interviewer administered checklist was developed from the patient registration and follow up form, which is based on the WHO CRF, and used to collect the necessary data from the patients and their medical charts prospectively from admission till time of viral clearance, June 2 to July 5, 2020.

Training on the basics of the checklist was given for ten data collectors (BSc nurses and General practitioners) and two supervisors (General practitioner and public health specialist) for one day.

Data consistency and completeness was checked before an attempt was made to enter the code and analyze the data.

Data Management and Data Analysis

The collected data was coded and entered into Epi-Info version 7.2.1.0, cleaned and stored and exported into SPSS version 23 for analysis. Frequency tables, Kaplan Meier (KM) plots and median survival times were used to describe the data. Survival experience of different groups was compared using KM survival curves. Log-rank test was used to assess significant differences among survival distributions of groups for equality. Association between time to viral clearance and determinants was assessed using Cox proportional hazard survival model, where hazard ratio, P-value and 95% CI for hazard ratio were used for testing significance and interpretation of results.

Univariate analysis was performed to calculate crude hazard ratio (CHR) and to screen out potentially significant independent variables at 25% level of significance. Association between the most relevant independent variables and the time to viral clearance from COVID-19 infection was assessed using multivariable Cox proportional hazard survival model. Adjusted Hazard Ratio (AHR), P-value and 95% CI for AHR were used to test significance and interpretation of results. Variables with p-value ≤ 0.05 were considered statistically associated with time to viral clearance from COVID-19 infection in days. The basic assumptions of Cox Proportional Hazard model was tested using log minus log function.

Result

Information was obtained from 360 participants among the 366 samples selected, making the response rate 98.4%. All selected patients consented to participate. Six participants were excluded because they had incomplete data on outcome status and other relevant explanatory variables.

Characteristics of the Study participants

The median age of the participants was 30.0 years (IQR, 24.0 - 40.0 years). The minimum and the maximum age of the participants were 1 and 75 years, respectively. Majority of the participants (55.8 %) were males and the rest (44.2 %) were females, and 337 of them (93.6 %) were from Addis Ababa. Only 11 (3.1%) of the patients were health care workers. There were three pregnant women, two at first trimester and one at the third.

Close to two third of the participants (70.8%) acquired the disease through community transmission, and the rest (29.2%) were through a known contact or travel history. Forty one (11.4%) had a history of pre-existing co-morbid illness. The commonest co-morbid illness was hypertension (5%) followed by type 2 diabetes mellitus (2.2%), HIV (1.9%), bronchial asthma (1.1%), seizure disorder (0.6%), chronic liver disease (0.3%) and tuberculosis (0.3%). Five of the participants (1.4%) had a history of substance abuse including cigarette and shisha smoking and khat chewing. Regarding drug used within 14 days of admission, ACEIs, ARBs and NSAIDs were reported by one (0.3%), one (0.3%) and five (1.4%) of the patients, respectively.

More than two third (78.6%) of the participants were asymptomatic at presentation and the rest (21.4%) were symptomatic. The commonest presenting symptoms were respiratory symptoms (18.3 %) followed by constitutional (12.8%), gastrointestinal (1.9%) and neurologic (0.8%) symptoms. Majority of the patients (86.9 %) had mild COVID-19 at admission and the rest had moderate (12.2%) and severe (0.8%) disease. (**Table 1**)

Censoring status, incidence rate of viral clearance and median time to viral clearance

Among the 360 participants, 132 (36.7%, 95% CI=32.2%-41.4%) achieved viral clearance, while 228 (63.3%, 95% CI=58.6%-67.8%) were censored. The censored observations were due to transfer to another facility (37) and the end of the observation period (191), there was no loss to follow up or death.

The incidence rate of viral clearance among the study population during the observation period was 4.03 per 100 person-day of observation (95% CI=3.54, 4.58).

The median time to viral clearance was 16 days, and it ranges from 7 to 21 days.

Table 1: Characteristics of the study participants and censoring status (n=360)

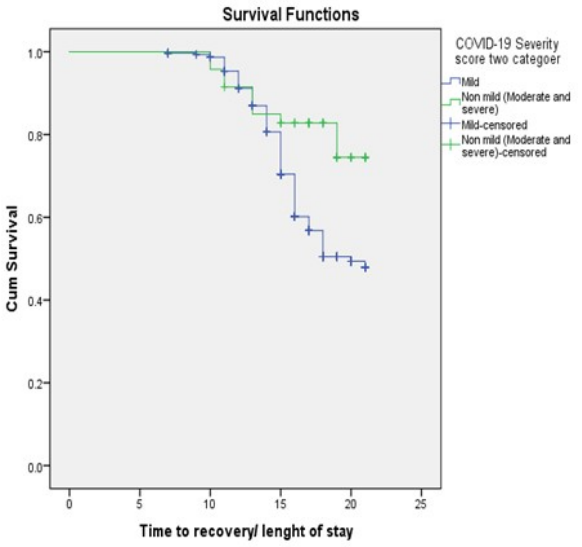
Variable	Censoring status		Total (%)
	No of censored (%)	No of event (%)	
Sex			
Female	107 (67.3)	52 (32.7)	159 (44.2)
Male	121 (60.2)	80 (39.8)	201(55.8)
Place of residence			
Outside Addis Ababa	11 (47.8)	12 (52.2)	23 (6.4)
Addis Ababa	217 (64.4)	120 (35.6)	337 (93.6)
Health care worker			
No	218 (62.5)	131(37.5)	349 (96.9)
Yes	10 (90.9)	1 (9.1)	11 (3.1)
Pregnancy status			
No	32 (20.5)	124 (79.5)	156 (99.2)
Yes	3 (100)	0	3 (0.8)
How patient contracted the disease			
Non community transmission *	74 (70.5)	31(29.5)	105 (29.2)
Community transmission	154 (60.4)	101(39.6)	255 (70.8)
Pre-existing co-morbid illness			
No	198 (62.1)	121(37.9)	319 (88.6)
Yes	30 (73.2)	11(26.8)	41 (11.4)
Substance use*			
No	223 (62.8)	132(37.2)	355 (98.6)
Yes	5 (100)	0	5 (1.4)
Drug use in 14 days (ACEIs, ARBs and NSAIDs)			
No	222 (62.7)	132 (37.3)	354 (98.3)
Yes	6 (100)	0	6 (1.7)
Presence of symptoms			
No	168 (59.4)	115 (40.6)	283 (78.6)
Yes	60 (77.9)	17 (22.1)	77 (21.4)
Respiratory symptoms*			
No	175 (59.5)	119 (40.5)	294 (81.7)
Yes	53 (80.3)	13 (19.7)	66 (18.3)
Constitutional symptoms*			
No	192 (61.1)	122 (38.9)	314 (87.2)
Yes	36 (78.3)	10 (21.7)	46 (12.8)
Neurologic symptoms*			
No	227 (63.6)	130 (36.4)	357 (99.2)
Yes	1 (33.3)	2 (66.7)	3 (0.8)
Gastro intestinal symptoms*			
No	224 (63.5)	129 (36.5)	353 (98.1)
Yes	4 (57.1)	3 (42.9)	7 (1.9)
COVID-19 Severity			
Mild	191 (61)	122 (39.0)	313 (86.9)
Moderate	34 (77.3)	10 (22.7)	44 (12.2)
Severe	3 (100)	0	3 (0.8)

Non community transmission*: includes contact with a diagnosed person, working in a center caring for COVID-19 patients, history of travel outside of Ethiopia and contact with a traveler
Substance abuse*: includes cigarette smoking, shisha smoking and khat chewing.
Respiratory symptoms*: includes dry cough (13.6%), cough with sputum production (5.6%), sore throat (6.1%), runny nose (3.1%), chest pain (3.9%) and shortness of breath (1.9%).
Constitutional symptoms*: includes fever (6.4%), myalgia (2.8%), arthralgia (2.2%), malaise (4.7%) and head-ache (6.4%).
Neurologic symptoms*: includes altered consciousness (0.3%) and seizure (0.6%).
Gastrointestinal symptoms*: includes abdominal pain (0.6%), vomiting/ nausea (1.1%) and diarrhea (0.8%).

Comparison of survival experience

A log rank test was used to assess differences in the survival distribution among groups. Accordingly, the survival time was significantly different among the different groups in COVID-19 severity, presence of symptom, and respiratory and constitutional symptoms (p-values < 0.05). Having non mild (moderate and severe) disease and having one or more symptoms at presentation seems to extend the time needed to achieve viral clearance. The time needed to achieve viral clearance was longer among participants with moderate and severe disease (19.3 days) compared to those with mild disease (17.9 days) ($X^2_{(1)}$= 7.841, P-value= 0.005). The survival time showed that those participants who presented with one or more symptoms achieved viral clearance in a relatively longer time (19.2 days) than those who had no symptom at presentation (17.8 days). As shown in **Figure a** the KM survival function graph also showed that those with mild disease and those with no symptom at presentation have a favorable survival (time to achievement of viral clearance) experience. The right panel of the figures shows that the instantaneous chance of achieving viral clearance increases for both COVID-19 severity groups and presenting symptom groups as the duration of treatment increases.

Similarly, the time needed to achieve viral clearance was longer among participants who presented with respiratory symptoms (19.3 days) and constitutional symptoms (19.4 days) compared with those who didn't have respiratory symptoms (17.9 days) and those who didn't have constitutional symptoms (17.9 days), respectively.



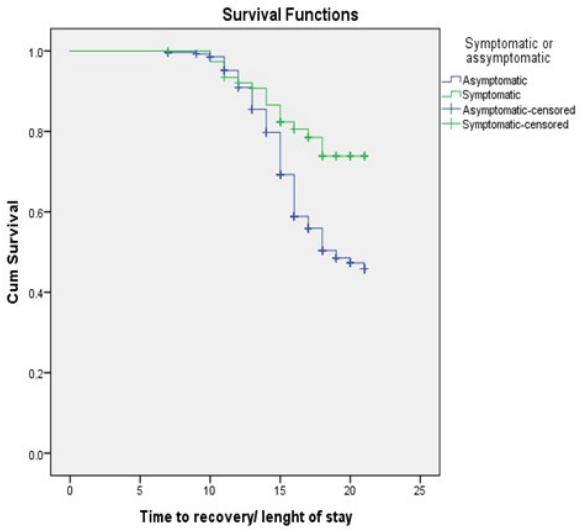


Figure a: Survival functions of COVID-19 severity score and presence of symptom by time

On the other hand, the survival time did not show statistically significant difference among the different groups classified by sex, place of residence, health care worker, how patient contracted the disease and pre-existing co-morbid illness (all p-values >0.05). **(Table 2)**

Results of Multivariable Cox Proportional Hazard Model

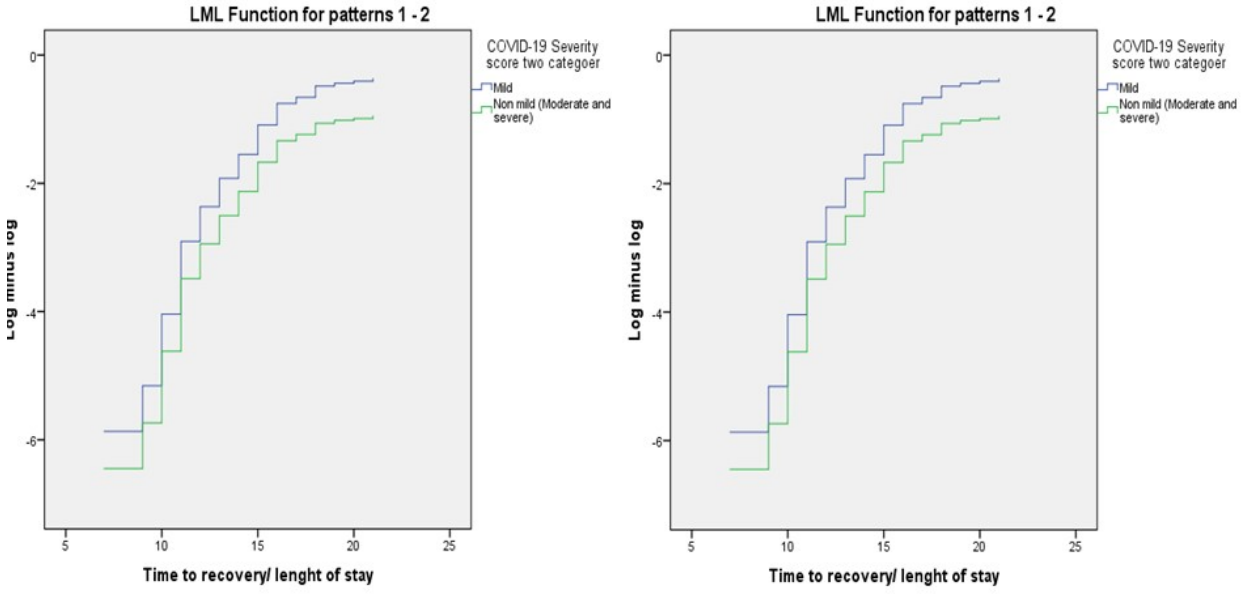
The fundamental assumption of Cox Proportional Hazard model, which is proportional hazards assumption, was tested using Log minus Log function on SPSS version 23 software. Parallel lines between groups indicate proportionality [30]. **Figures b** reveals that the survival curves seem parallel throughout the study time. These plots show reasonable fit to the proportional hazard assumption

Table 2: Comparison of viral clearance from COVID-19 among participants (n=360)

Variable	Category	Test of equality over groups	
		Mean survival time (days)	Log rank (mantel cox) (p-value)
Sex	Female	18.1	0.810
	Male	18.1	
Place of residence	Outside Addis Ababa	17.1	0.162
	Addis Ababa	18.2	
Health care worker	No	18.1	0.621
	Yes	17.4	
How patient contracted the disease	Non-community trans-mission	18.6	0.143
	Community transmission	17.9	
Preexisting co-morbid illness	No	18.1	0.441
	Yes	18.5	
Presence of symptoms	Asymptomatic	17.8	0.001*
	Symptomatic	19.2	
Respiratory symptom	No	17.9	0.002*
	Yes	19.3	
Constitutional symptom	No	17.9	0.014*
	Yes	19.4	
COVID-19 Severity Score	Mild	17.9	0.005*
	Non mild	19.3	

Note:*Statistically significant

Figure b: Log minus Log function for presence of symptom and COVID-19 severity score



Based on the result of the Univariate analysis at 25% level of significance and the significant variables identified from literatures, the following variables were included in the final regression model; age, sex, pre-existing co-morbid illness/s, presence of symptom and COVID-19 severity.
However; only presence of symptoms at presentation was found to be significantly associated with time to viral clearance in the multivariable Cox proportional hazard model at 5% level of significance.
Accordingly, after adjusting for other covariates, the rate of achieving viral clearance among symptomatic participants was 44% lower than participants who were asymptomatic at presentation (HR= 0.560, 95% CI= 0.322-0.975, p-value=0.040). (**Table 3**)

Table 3: Results for the final Cox proportional hazard model among participants (n=360)

Variables	CHR (95% CI)	AHR	95.0% CI for AHR	P-value
Age	0.999 (0.986, 1.012)	1.002	(0.988, 1.016)	0.796
Sex				
Female		1		
Male	1.042 (0.735, 1.478)	1.077	(0.758, 1.532)	0.678
Preexisting Co-morbid illness				
No		1		
Yes	0.762 (0.411, 1.413)	0.852	(0.449, 1.616)	0.623
Presence of Symptom				
Asymptomatic		1		
Symptomatic	0.458 (0.275, 0.763)	0.560	**(0.322, 0.975)**	**0.040***
COVID-19 Severity				
Mild		1		
Non mild	0.422 (0.221,0.805)	0.560	(0.272, 1.154)	0.116

Note: CHR, Crude Hazard ratio; AHR, Adjusted Hazard ratio; CI, Confidence interval; *Statistically significant

Discussion

In this study we assessed the determinants of time to viral clearance among 360 RT-PCR confirmed SARS -CoV-2 infected individuals who were admitted to Millennium COVID-19 Care Center in Ethiopia from 2nd June to 5th July, 2020. Among the 360 participants, 132 (36.7%, 95% CI=32.2%-41.4%) achieved viral clearance, and the median time to viral clearance was 16 days, ranging from 7 to 21 days. This finding is comparable with results from other studies that reported a median duration of 14, 15, and 17 days in different countries and different age groups [23-26]. This shows that irrespective of the presenting symptom and disease severity, the one infected with the virus could remain to be a threat to others due to the possibility of long duration of viral shedding especially among those who are not in isolation and are in contact with the community.

Survival distribution between groups, as assessed by KM plots and log-rank test, shows that having moderate and severe disease, having one or more symptoms at presentation, and presenting with respiratory and constitutional symptoms seem to extend the time needed to achieve viral clearance. This implies that having a more severe disease category and developing symptomatic disease are associated with prolonged viral shedding leading to an extended infectiousness period which puts close contact at risk. But on further regression analysis, only presence of symptoms at presentation was found to be a significant factor that determines the time to viral clearance. Accordingly, the rate of achieving viral clearance among sympto-

matic patients was 44% lower than patients who were asymptomatic after being adjusted for other variables. This implies that symptomatic patients have a relatively delayed viral clearance duration compared to asymptomatic patients. This could be because most of the symptomatic patients in the current study had respiratory tract symptoms that could have increased the likelihood of detecting the virus in the upper respiratory tract sample. This finding is also in accordance with a study conducted in Wuhan where having symptom was found to be a significant predictor of duration of viral shedding, with a prolonged viral shedding among patients who present with symptomatic infection [26].

On the other hand, factors that are identified to be significant determinants of viral clearance like age, sex, presence of co-morbid illness, and disease severity didn't show any significant association with time to viral clearance.

In this study, the majority of the participants (63.3%) were censored due to referral to other centers, and due to the relatively short study period. The upper limit of the observation period is chosen because of the change in the patient discharge criteria which focused on a clinical decision in addition to the RT-PCR result per se which made us unable to get two consecutive negative RT-PCR results for each patient. This might have resulted in underestimation of the median viral shedding duration obtained from the study. Therefore, the result has to be interpreted with this limitation in mind.

Conclusion

The median time to viral clearance among SARS-CoV-2 infected individuals admitted to Millennium COVID-19 Care Center was found to be 16 days. Presence of symptoms was found to be associated with delayed viral clearance. This implies that symptomatic patients are more likely to be infectious because of the prolonged viral shedding in addition to the presence of more concentrated virus in the upper respiratory tract that enhances the transmission. Therefore, attention should be given in the isolation and treatment practice of SARS-CoV-2 infected individuals with regard to the presence of symptoms. Furthermore, to guide the local practice with better evidence, further multicenter and/or community based study with prolonged observation is recommended.

Declaration

Ethics approval and consent to participate

The study was conducted after obtaining ethical clearance from St. Paul's Hospital Millennium Medical College Institutional Review Board (Ref No: pm 23/23).0020Written informed consent was obtained from the participants. The study had no risk/negative consequence on those who participated in the study. Medical record numbers were used for data collection and personal identifiers were not used in the research report. Access to the collected information was limited to the principal investigator and confidentiality was maintained throughout the project.

Competing interests

The authors declare that they have no known competing interests

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Authors Contribution: TWL conceived and designed the study, revised data extraction sheet, performed statistical analysis, and drafted the initial manuscript.

KTY, ABB and TBJ: contributed to the conception, designed data extraction sheet, undertook review and interpretation of the data, revised the manuscript and approved the final version

ISH, EHM, WCZ, NWC, TTA, MGE, EKG, MDH, EYM, FMA, MBT and SSA: contributed to the conception, obtained patient data, undertook review and interpretation of the data, revised the manuscript and approved the final version

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Availability of data and materials: All relevant data are available upon reasonable request.

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Original Article

Value of baseline radiograph for COVID-19 infected patients

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Abstract

Introduction: *A cluster of pneumonia cases of unknown origin was first reported in Wuhan China then the causative pathogen was identified and named severe acute respiratory syndrome coronavirus 2 (SARS-Cov2) and the associated disease was named coronavirus disease 2019 (COVID-19). Chest radiograph has lower sensitivity for the detection of lung abnormalities but it has a role in disease progression and also in the late stages of COVID-19. This study aims to evaluate the value of baseline radiographs in COVID-19-infected patients.*

Method: *This is a retrospective study of COVID-19 patients with RT-PCR confirmation who were admitted to Eka Kotebe General Hospital and had baseline chest x-ray between April and May 2020. Baseline chest x-ray of all patients who have confirmed COVID-19 infection was reviewed and analyzed.*

Result: *The study included 355 patients, 224 (63.1%) were male and 131 (36.9%) were female. Patient age ranged from 4 - 82 years with a mean age of 35. Two hundred twelve patients were symptomatic; the rest 143 were asymptomatic. Of the 355 baseline CXR, only 60 (16.9%) had abnormal radiographs and the rest 295 (83.1%) had normal radiographs. A combination of interstitial changes and GGO were the predominant descriptive finding accounting for 33.3% .*

Conclusion: *Even if chest radiographs are important in the workup of patients with COVID-19 infection, the use of baseline radiographs in COVID-19 infection should not be a routine practice. Disease severity and timing of imaging appear to impact the rates of normal baseline imaging.*

Keywords: Baseline, COVID-19, Chest Radiograph
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Introduction

Coronavirus is enveloped RNA virus belonging to the family of coronaviruses and is broadly distributed among humans and other mammals and causes respiratory, enteric, hepatic, and neurologic disease(1) . The two beta coronaviruses, severe acute respiratory syndrome (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) have caused more than 10,000 cumulative cases in the past two decades with mortality rates of 10% for SARS-CoV and 37% for MERS-CoV (2).

A cluster of pneumonia cases of unknown origin was first reported in Wuhan city china on 31 December 2019 and on January 7, 2020, the causative pathogen was identified as a novel coronavirus(3). This virus was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) and the associated disease was named coronavirus disease 2019 (COVID-19). Since December 2019, COVID-19 has rapidly spread from Wuhan to other parts of China and throughout the world, and on March 11, 2020 COVID-19 was declared a pandemic by WHO(4).

On March 13, 2020, the first COVID-19-infected person in Ethiopia was confirmed (5). The most common symptoms associated with COVID-19 infection are fever (accounting for 98% of the symptoms), myalgia or fatigue, and shortness of breath. Less common symptoms include sputum production, headache, haemoptysis, sore throat, chest pain, and diarrhea(2). The severity of the disease can range from asymptomatic and mild cases to acute respiratory distress syndrome and death (6).

According to Fleischner society, a multinational consensus statement, imaging is indicated for patients with COVID-19 with evidence of worsening of respiratory status and for patients with moderate to severe features of COVID-19 regardless of the COVID-19 test result. Imaging is not indicated for patients with mild features

of COVID-19 unless they are at risk for disease progression and it is not indicated as a screening test for COVID-19 in asymptomatic individuals (6). COVID-19 primarily affects lung parenchyma and it has a high rate of human-to-human transmission and the number of confirmed cases is increasing exponentially.

The diagnosis of the COVID-19 is confirmed by a positive reverse transcriptase-polymerase chain reaction (RT PCR) nasopharyngeal or oropharyngeal swab test. This test is highly specific however, the sensitivity is reportedly as low as 60-70%. The high rate of false-negative results particularly early in disease time courses and inconsistent availability of testing means that a systematic approach to diagnosis must be employed including radiological imaging (7). Baseline chest X-ray has lower sensitivity compared to initial RT-PCR but because of inconsistent availability of RT-PCR and long turnaround time, CXR can aid in the diagnosis of COVID-19.

The most common radiographic features in confirmed COVID-19 patients are peripheral rounded ground-glass opacity, consolidation and pulmonary nodules. The distribution of the lung changes was more common in lower zones and bilateral (8). The chest x-ray findings in these patients frequently showed bilateral lower zone consolidation which peaked at 10-12 days from onset (8)

Disease severity and timing of imaging appear to impact the rates of normal baseline imaging. In a non -severe disease, up to 18% of patients have a normal initial CXR or CT but only 3% in severe disease (9)

CT has higher sensitivity reaching about 97% especially in detecting early disease and most studies regarding the characteristics pattern of imaging findings have focused predominantly on the use of CT imaging(10).

Although chest radiograph is not considered to be sensitive for the detection of lung abnormalities especially in the early stage of the disease, it has a role in the disease progression and also in the late stages of COVID-19(11).

Chest X-ray is a relatively inexpensive and widely available diagnostic modality and in addition to the clinical findings, appearance on chest X-ray can aid in assessing the severity of illness and also guide in management. In the institution where this study was conducted, routine CXR was the routine practice for all patients who have proved COVID-19 pneumonia irrespective of the clinical stages of the disease. So, we would like to evaluate the value of routine CXR for COVID-19 patients. This study will evaluate the value of baseline radiograph in patients with COVID-19 infection.

Methodology

Research setting

This study was conducted at Eka Kotebe general hospital, which is under the auspices of St. Amanuel Mental Hospital and has been inaugurated in October 2019. Since March 2020 this hospital has been assigned as the first treatment centre for COVID-19 patients in Addis Ababa, Ethiopia. During the initial phases of COVID-19 infection in Ethiopia, when this data was collected, all patients who are positive for RT-PCR were admitted to this hospital irrespective of their clinical condition.

Study design and study population

This study is an institutional-based retrospective cross-sectional study done on chest radiographic images of all RT-PCR confirmed COVID-19 infected patients who were hospitalized in Eka Kotebe general hospital in the period from April to May 2020. All COVID-19 confirmed patients who fulfill the inclusion criteria and have chest radiographic imaging done at the Eka Kotebe general hospital during the stated study period were included in this study.

Sampling size determination

The sample size was calculated using Daniel's formula for a cross sectional study, where P=30% (from previous similar studies (12)); d=5% (margin of error); and Z=standard score, corresponding to 1.96, with a 95% confidence interval. This would give a sample size of 323. To compensate for non-response and incompleteness, 10% was added, giving a total of 355 study participants.

$N= Z^2 P (1-P)/ d^2$

Where:

N = total number of subjects required in the population

Z = a standardized normal deviate value that corresponds to a 95% level of confidence equal to 1.96

P = estimate of the prevalence of CXR abnormalities, 30 %

d = margin of error, which corresponds to the level of precision of results desired

$$N = \frac{(1.96)^2 \times 0.3x(1-0.3)}{(0.05)^2} = 322.69$$

Non-response rate = 10% of N = 10/100 (323) = 32.3. Total sample size = 323 + 32.3 = 355

Data collection procedure

Data was collected using a structured questionnaire developed which contains patient age and sex, initial clinical evaluation during patient admission to the institution, and the first CXR taken on admission. The radiographs then were reviewed by three consultant radiologists who have more than ten years of experience and imaging data were filled separately and images that had differences in the findings were again reviewed with the radiologists together and a consensus was made on the findings and questionnaire were filled accordingly.

All COVID-19 confirmed patients in Eka Kotebe general hospital during the stated study period are eligible for this study. All COVID-19 confirmed patients who had chest radiographic images in Eka Ko-

tebe general hospital during the stated study period are included in this study. Patients with confirmed COVID-19 infection in Eka Kotebe general hospital who don't have chest radiographic images were automatically excluded from the study.

Data processing and analysis

The data was checked for clarity and completeness. Data were analysed using nonparametric statistical methods with the help of the SPSS software package. Then summarization and comparison of data were done.

To evaluate the clarity of the questionnaire, validity of the instruments, and after the pre-test, the findings and observations obtained were used to modify the questionnaire and the data collection process accordingly.

Operational Definitions

Clinical severity scoring

Asymptomatic or pre-symptomatic infection: Individuals who test positive for SARS-CoV-2 using a virologic test but who have no symptoms that are consistent with COVID-19.

Mild illness: Individuals who have any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but who do not have shortness of breath, dyspnoea, or abnormal chest imaging.

Moderate illness: Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have an oxygen saturation measured by pulse oximetry (SpO2) ≥94% on room air at sea level.

Severe illness: Individuals who have SpO2 <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 mm Hg, a respiratory rate >30 breaths/min, or lung infiltrates >50%.

Critical illness: Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.

Chest X-ray severity scoring system

Each lung is divided into three zones. Upper level: above the inferior wall of the aortic arch, middle level: below the inferior wall of the aortic arch and above the inferior wall of the right inferior pulmonary vein (hilar structures) and the lower level is below the inferior wall of the right inferior pulmonary vein (lung bases) then score (from 0-3 points) is assigned to each zone based on the detected lung abnormalities. 0- no lung abnormalities, 1- interstitial infiltrates, 2- interstitial and alveolar infiltrates (interstitial predominance) and 3- interstitial and alveolar infiltrates (alveolar predominance). The overall score is the sum of points from all the zones which ranges from 0-18 points and chest findings were reviewed accordingly and severity categorized as mild, moderate and severe based on sum of scores.

Linear (interstitial) opacities: described as horizontal white lines or reticular changes (15).

Ground glass opacities: described when lung markings are partially obscured by increased whiteness (15).

Consolidation: described when the lung markings are completely lost due to whiteness

Ethical considerations

No patient identifiers were used in data collection or analysis and imaging data were collected from the image store. Any piece of information was kept confidential by keeping the anonymity of the study subjects. Permission was given from the institution and ethical clearance was obtained from the department research and ethics committee.

Result

The study included 355 patients; among them, 224 (63.1%) were male and 131 (36.9%) were female. The mean age was 35 ± 16 years with the age range of 4 to 82 years old (Figure 1).

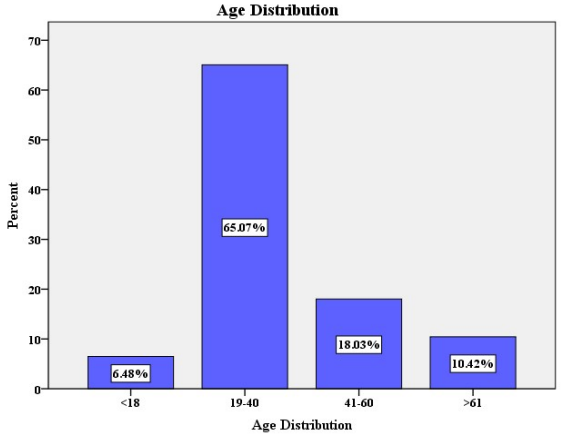

Figure 1: Age distribution of patients with COVID-19, Eka Kotebe, General Hospital, Ethiopia , 2020

Among the total of 355 patients, 143 (40.3%) were asymptomatic and 212 (59.7%) were symptomatic. From 212 patients who were symptomatic 191 (90.1%) had mild symptoms, 6 (2.8%) had moderate symptoms and 15 (7.1%) showed severe symptoms.

Among 212 symptomatic patients 43 (20.3%) had abnormal chest X-rays. Among the 191 patients with mild clinical symptoms 30 (15.7%) had abnormal radiograph but from the 15 patients with severe clinical symptoms 12 (80%) had abnormal radiograph. From the 143 asymptomatic patients 17 (11.9%) had abnormal chest X-rays. (figure 2)

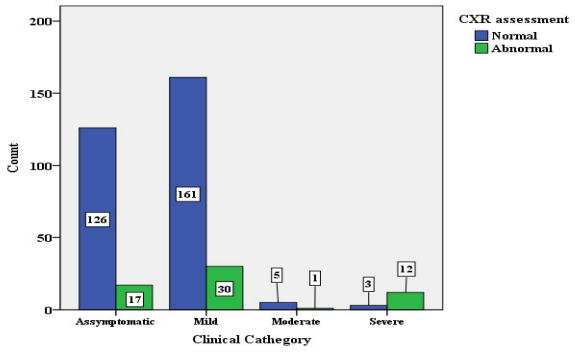

Figure 2: Clinical category based on chest radiographic assessment, Eka Kotebe, General Hospital, Ethiopia 2020

Of 355 patients only 60 (16.9%) showed abnormal chest radiograph and the rest 295 (83.1%) had normal chest radiograph. From 60 patients who showed chest x-ray abnormality; 40 (66.7%) showed a mild abnormality, 8 (13.3%) showed moderate abnormality and 12 (20%) showed severe abnormality.

As shown from figure [3] below, from the 40 patients who showed mild severity on chest radiograph, the majority of patients are in the age range of 41 and 60 years, while from 12 patients who showed severe chest radiograph abnormality the majority of the patients are above 61 years old.

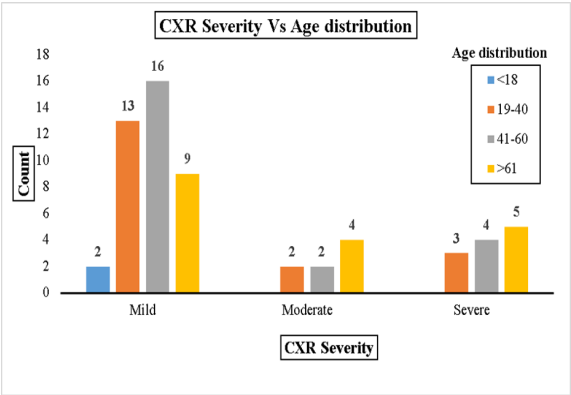

Figure 3: CXR severity with age distribution, Eka Kotebe, General Hospital, Ethiopia 2020

Out of 40 patients who showed a mild radiographic abnormality, 27 (67.5%) patients had a severity score range of 0-5 and 13 (32.5%) patients had a severity score range of 6-11. From 8 patients who showed a moderate abnormality, 6 (75%) patients had a severity score range of 6-11, and 2 (25%) patients had a severity score of ≥ 12. From the total of 12 patients who showed severe chest x-ray abnormalities, 1 (8.3%) patient had a severity score range of 6-11 while the rest 11 (91.7%) patients had a severity score of ≥ 12.

A combination of linear interstitial changes and GGO were the predominant radiographic finding accounting for 20 (33.3%), followed by an interstitial change which accounts for 11 (18.3%) of the total 60 patients with abnormal chest X-ray. Ground glass opacity alone accounts for 10 (16.7%) and consolidation alone was the least predominant finding accounting for 3 (5%) of the total 60 patients with abnormal chest X-rays. (figure 4)

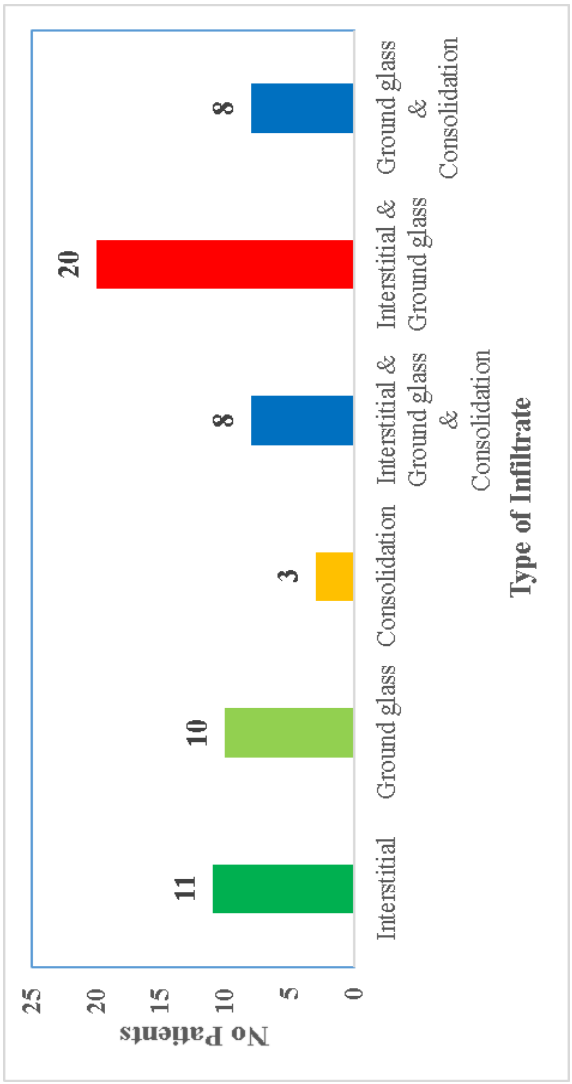

Figure 4 :Frequency of patients for types of infiltrate, Eka Kotebe, General Hospital, Ethiopia

A combination of lower and middle lung location is the predominant chest radiograph location account ing for 22/60 patients (36.7%). Which are multifocal in 86.7% and bilateral in 83.3%. (Table 1)

Table 1: patterns of CXR findings in COVID-19 patients, Eka Kotebe, General Hospital, Ethiopia , 2020

Radiologic Properties	Categories	Frequency	Percent
Location abnormality	Lower	16	26.7
	Middle	3	5.0
	Diffuse	15	25.0
	Lower & Middle	22	36.7
	Middle & Upper	3	5.0
	Lower & Upper	1	1.7
Focality of findings	Unifocal	8	13.3
	Multifocal	52	86.7
Laterality of findings	Unilateral	10	16.7
	Bilateral	50	83.3
Centrality if findings	Peripheral	45	75
	Central	3	5
	Both	12	20
Other associated findings	None	346	97.5
	Effusion	1	0.3
	Mediastinal abnormality	2	0.6
	Dilated main pulmonary artery	1	0.3
	Basal atelectasis bilateral	2	0.6
	Left lower sub segmental atelectasis	1	0.3
	Left basal atelectasis and elevated left hemi diaphragm	1	0.3
	Effusion & mediastinal abnormality	1	0.3

Discussion

This research describes the common radiographic features of 355 COVID-19 infected patients. From the baseline radiographs of these patients, only 60 (16.9%) patients showed abnormal chest radiographs and the rest 295 (83.1%) had normal radiographs. The majority of patients 212/355 (59.7%) were symptomatic presenting mainly with mild symptoms (90.1%), the rest 143/355 (40.3%) were asymptomatic. The major radiographic abnormalities were interstitial and ground-glass opacity which were mainly located in the middle and lower lobe and also predominantly bilateral and peripheral.

Unlike other similar studies which showed the rate of normal chest radiographs ranging from 5.6% to 58.3% (8, 12), our study showed the great majority of baseline radiographs (83.1%) to be normal. The reason can be explained by the fact that most patients were asymptomatic and among those symptomatic cases, most patients (90.1%) had mild symptoms. Another explanation could be that during the period when this data was collected, all patients who were positive for RT-PCR for COVID-19 were admitted to the hospital irrespective of their clinical status. The rate of abnormal chest radiographs is higher in those who have severe clinical symptoms as shown in our study which revealed 80% of radiographs with severe clinical symptoms were abnormal. Even if radiographs are important in the diagnosis of COVID-19 pneumonia and evaluate other mimickers of pneumonia, it should not be used as a screening for COVID-19 infection, and baseline radiographs have no value in asymptomatic patients' and for those having mild and moderate clinical symptoms. The findings of normal chest radiograph at baseline imaging are not a guarantee for subsequent development of abnormalities on follow-up imaging because chest radiograph severity scores will change over time (9). So, follow-up chest radiographs in patients who have normal baseline radiographs can be done if there is clinical disease progression (6).

In the initial phase of the pandemic, including the scenario in our study setting, chest radiographs were routinely used in patients presented with ambulatory care settings but more than half of the radiographs were found to be normal and only 5% of abnormal radiographs showed severe disease(13, 14). Due to the low sensitivity of radiographs for patients with COVID-19 infection (14), clinical evaluation and screening for patients with COVID-19 infection is important to avoid unnecessary radiographs.

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Despite the variable radiographic features described in the literature, the predominant radiographic findings reported and also shown in this study are interstitial changes and ground-glass opacities either alone or in combinations. Bilateralism of the findings which are predominantly in the lower lobes and peripheral lung shown in this study was also features reported in most literature. (8, 13-15). Consolidations were the least radiographic findings in our study which is also consistent with findings in other works of literature (15).

The frequency and severity of radiographic findings also depend on the clinical severity score (8). In our study, out of 40 patients who showed mild chest radiographic majority (67.5%) had a severity score range of 0 – 5, and out of a total of 12 patients who showed severe chest radiographic abnormality , 91.7% had severity scores of greater than 12.

Conclusion and Recommendation

Even if chest radiographs are important in the workup of patients with COVID-19 infection, the use of baseline radiographs in COVID-19 infection should not be a routine practice. The most common radiographic findings of COVID-19 infection are interstitial findings and ground glass lesions predominantly at bilateral lower lobes in the peripheral lungs.

Limitation

This is a retrospective single centred study.

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Original Article

Magnitude of chlorpromazine induced ocular toxicity among psychiatric patients at Melik and Amanuel Hospitals

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Abstract

Background: *Chlorpromazine (CPZ), a typical anti-psychotic drug, has been associated with irreversible ocular toxicity signs which are dependent on total dosage and duration where exact values varied in different studies. In Ethiopia, there is no data on chlorpromazine induced ocular toxicity.The current study aimed to determine the prevalence of Chlorpromazine induced ocular toxicity.*

Method: *All consecutive psychiatric patients taking Chlorpromazine at a dose of 100mg/d or more for more than one month were included. Then, socio-demographic data, daily dosage and duration of Chlorpromazine treatment were obtained from self-administered questionnaire as well as patients' chart review. Visual acuity of each eye was taken using Snellen's illiterate "E" chart at a distance of 6 meters. Examination was especially directed to the lids and conjunctiva for pigmentation. Complete slit lamp examination was done to look for anterior segment toxicity signs and direct ophthalmoscope for posterior segment findings.*

Result*: Out of the total 92 patients examined, 30 (32.6%) (95% CI: 22-41.8) had signs of ocular toxicity ie 8 with rosette pigments, 11 with anterior stellate cataract alone and 11 with concomitant anterior stellate cataract and corneal changes. The minimum cumulative total dose resulting in ocular toxicity was in the range between 500gm and 750gm taken more than 5 years. ALL patients having anterior stellate cataract with corneal changes had severe visual impairment.*

Conclusion: *Chlorpromazine is associated with lens and corneal toxicity at a minimum cumulative dose ranging between 500gm and 750gm taken more than 5 years. Patients with concomitant lens and corneal changes had severe visual impairment. Close and combined management of patients on Chlorpromazine between ophthalmologists and psychiatrists is recommended.*

Keywords: Chlorpromazine, Ocular toxicity, Menilik Hospital

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Introduction

Chlorpromazine (CPZ, Largactil), introduced in 1953 has been widely used in general medicine and psychiatric diseases, especially in the long term intensive therapy of schizophrenic patients. Its pharmacological properties include competitive blockage of dopamine receptor **(1).**

This drug has anticholinergic properties leading to systemic and ocular adverse effects. Ocular structures most affected are sun exposed areas such as the eyelids and conjunctiva manifesting as a purplish discolorations and pigment deposits on the cornea and lens which was first described by Greiner and berry **(2).** These changes appear after long term use due to its photosensitizing properties **(3).**

Since then, studies have shown that the incidence of ocular toxicity signs varies from 22-80 % **(4-7).**The total cumulative dosage of chlorpromazine needed for inducing toxicity signs varies in different studies betwen100g-1000 g **(8-11).** Low visual acuity associated with such ocular changes and its irreversible nature has been described **(12, 13).**

However, there has not been much interest in the recent past, possibly due to decreased use in developed countries. Also, literature in this area from developing countries is scares. As there is reappearance in use of atypical antipsychotics, it is important for clinicians to be aware of these side effects, especially in developing countries since many patients are on typical antipsychotics due to its low cost.

The magnitude of chlorpromazine-induced adnexal and ocular toxicity is unknown in Ethiopia. The aim of this study is to see the magnitude of Chlor-

promazine induced adnexal and ocular side effects and assess the minimum total cumulative dose and the minimum duration required for ocular toxicity to occur.

Subject and methods

This is a hospital based cross-sectional study conducted at Amanuel and Menelik II referral hospitals over a period of one year (July 2016-July 2017). Ammanuel and Menelik hospitals are tertiary centers in Addis Ababa for psychiatry and eye care respectively. All consecutive patients attending the psychiatry clinics of both hospitals during the study period were the source population. Psychiatric patients taking Chlorpromazine at a dose of 100mg/d or more for at least one month at the two hospitals were included. Cases that refused to be part of the study or aggressive to examine were excluded. Patients with ocular diseases which tend to decrease vision and history of trauma to the eye were also excluded.

The principal investigator identified and obtained informed (verbal) consent from patients who were taking Chlorpromazine. Then, socio-demographic data, daily dosage and duration of Chlorpromazine treatment were obtained from self-administered questionnaire as well as patients' chart review. Visual acuity of each eye was taken using Snellen's illiterate "E" chart at a distance of 6 meters. Examination was especially directed to the lids and conjunctiva for pigmentation. Complete slit lamp examination was done to look for anterior segment toxicity signs and direct ophthalmoscope for posterior segment findings.

The following operational definitions were used to evaluate the ocular toxicity of Chlorpromazine **(14)**

Eye lid toxicity:- a purplish discoloration of the lid skin

Conjunctival toxicity:- a hyper-pigmented triangle whose base is towards the limbus in the interpalpebral zone.

Corneal toxicity:- golden brown discrete deposits diffusely distributed in the epithelium, stroma or endothelium of the cornea.

Lens toxicity

Grade 1:- discrete golden brown deposits in the anterior pole of the lens.

Grade 2:- a star shaped gold brown deposits in the anterior surface of the lens (rosette opacity).

Grade 3:- dense whitish granular anterior opacity (stellate cataract)

Cumulative dose of Chlorpromazine: – dose of Chlorpromazine that has been used during the treatment period.

The collected questionnaire was checked manually for its completeness and entered in to SPSS version 20 by two data entry clerks. The collected data was entered in to and analyzed by statistical package for social science version 20. Descriptive statistics was used to describe data by using mean, frequency, percent and standard deviation. Moreover inferential statistics was used for testing association of ocular toxicity with the dose and duration of Chlorpromazine by using chi-square test and $P \leq 0.05$ was considered statistically significant.

Results

A total of 92 patients on chlorpromazine were examined. There were 62/92 (67.4%) males and 30/92 (32.6%) females as seen in **table 1**.

Table 1- Socio-demographic characteristics of patients on Chlorpromazine

Variables	Total patients	Ocular toxicity/ group (%)	Relative Risk
Sex			
Female	30	8 (26.7%)	1.0
Male	62	22 (35.5%)	1.3
Age			
<30	32	7(21.9)	1.0
>30	60	23(38.3)	1.8
Occupation			
Jobless	47	15 (31.9%)	1.1
Farmer	10	3 (30.0%)	1.0
Housewife	10	3 (30.0%)	1.0
Others*	25	9 (36.0%)	1.2

*private and government employees, students

The mean age was 36.6 (±-9.4SD) years, the range being from 16 years to 56 years. Majority of the participants 47(51.1%) were jobless. The total cumulative dosage of Chlorpromazine taken by our patients varied between 3g and 3240g. The duration that our patients took Chlorpromazine ranges from 1 month to 25 years**.**

The prevalence of Chlorpromazine induced ocular toxicity was 32.6% (95% CI: 22-41.8).The association of ocular toxicity with clinical variables like age (p=0.109), sex (p=0.398) and occupation (p=0.977) was considered but no association was found. However, the total dose and the duration of maximal dose were highly significantly associated with Chlorpromazine ocular toxicity (P=0.000).

Only 3 (3.3%) of the total patients examined had history of eye glass use and 2 of them had occasional use and had the ocular toxicity signs. The remaining one patient had a full time wear and was on Chlorpromazine at a cumulative dose in a range of 500-750g for more than 10 years but had no ocular toxicity signs.

Of the 92 patients examined, lens changes were seen in 30 (32.6%) of the cases. Eight of 30 (26.7%) patients had a grade 2 toxicity which was star shaped

lens pigmentation. The minimum total cumulative dose of chlorpromazine resulting in Lens star pigmentation was between 500-750g (**table 2)** and the minimum duration was between 5-10 years **(table 3).**

Table 2: Lenticular changes associated with cumulative total dosage of Chlorpromazine (n=92).

Total dosage of Chlorpromazine (grams)	Number of patients	Lens changes (%)	Relative Risk
0-250	35	0(0)	0
251-500	22	0(0)	0
501-750	14	10(71.4 %)	71.4
>750	21	20 (95.2)	95.2

Table 3: Lenticular changes associated with duration of Chlorpromazine intake

Total duration (years)	Number of patients	Lens changes (%)	Relative Risk
≤5	15	0	0
6-10	34	3 (8.8)	8.8
11-15	23	8 (34.7)	34.7
≥16	20	19 (95.0)	95.0

There was a significant association between lens changes and dose and duration of Chlorpromazine intake (p=0.00). All patients with this type of lenticular change alone had normal visual acuity. Only three of them complained of photophobia.

Twenty two 22/30 (73.3%) had grade 3 toxicity manifested with anterior stellate opacity. The minimum total cumulative dose of chlorpromazine resulting in stellate opacity of the lens was in the range of 500-750g and the minimum duration was 5-10 years. But, 95% of lens changes occurred at a dose above 750g taken more than 16 years.

Corneal changes were seen in 11 of 92 (12.0%) patients evaluated. All cases with corneal findings had also concomitant lenticular changes suggesting that lens changes precede corneal changes. These patients (n=11**)** had diffuse corneal pigmentation which was associated with grade three lens findings in this study. The minimum cumulative total dose of chlorpromazine resulting in corneal pigmentation was between 500-750g **(table 4)** and the minimum duration was between 10-15 years **(table 5).**

Table 4: Corneal changes associated with cumulative total dosage of Chlorpromazine (n=92).

Total dosage of Chlorpromazine (grams)	Number of patients	Corneal changes (%)	Relative Risk
0-250	35	0(0)	0
251-500	22	0(0)	0
501-750	14	2(14.3 %)	14.3
>750	21	9(42.9%)	42.9

Table 5: Corneal changes associated with duration of Chlorpromazine intake

Total duration (years)	Number of patients	Corneal changes (%)	Relative Risk
≤5yr	15	0	0
6-10yr	34	0	0
11-15	23	1 (4.3%)	4.3
≥16yrs	20	10 (50.0%)	50.0

There was a significant association between corneal findings and dose as well as duration of Chlorpromazine intake (p=0.00).

From the total 30 individuals with signs of ocular toxicity, 8 (26.7%) had normal visual acuity while 22 (73.3%) had visual impairment. All the patients with corneal findings (n=11) had visual complaints, 8/11 (72.7%) had blurring of vision and 3/11 (27.3%) had photophobia. The fact that all patients with corneal signs had concomitant lens signs resulted in severe visual impairment of these patients on visual acuity testing **(table 6).**

Table 6: Visual acuity of patients with Chlorpromazine ocular toxicity sign

Visual acuity	WHO category	Sign of ocular toxicity	Number of eyes
6/6-6/12	Normal	Rosette pigment	8(26.6%)
≤6/18-6/60	Moderate impairment	Anterior stellate cataract	11(36.7%)
<6/60-3/60	Severe impairment	Anterior stellate and corneal pigments	11(36.7%)

Discussion

The prevalence of Chlorpromazine induced ocular toxicity in this study was found to be 32.6% (95% CI: 22-41.8). Munde T et al has found the prevalence of ocular side effects for antipsychotic drugs to be 18.0% **(13).** The higher prevalence might be due to difference in study subject compositions and sun exposure due to geographic location. No obvious abnormalities were noted on external examination and no fundus changes were seen which could be attributed to Chlorpromazine.

Kinross et al have described macular pigmentation with other phenothiazine family mainly Thiorazidine and Piperidine **(15).** The fact that our patients were mostly on Chlorpromazine would explain this finding. The absence of skin pigmentation could be explained by racial differences. In addition, skin changes are said to be present only in patients with impaired glucuronide conjugation of Chlorpromazine and its metabolites.

Lens changes were the commonest (32.6%) ocular toxicity of Chlorpromazine followed by a combination of lens and corneal changes which were seen in 12.2%. Corneal changes alone were not seen which suggests that the lens changes preceded corneal changes. This goes with Barsa et al who reported lenticular changes in 27% of the cases and combined lenticular and corneal changes in 5% only **(11)**. Delong has shown that 37.0% of the cases had lens changes and 18% had corneal changes **(16).**

Malthon also found lens changes in 36.0% and corneal changes in 17.0% of the patients. On the other hand, a study done by Siddall reported lenticular involvement in 78.0% of cases **(10)**. Because of the site of the lesions in the anterior part of the lens and posterior cornea, either the drug or its metabolite in the anterior chamber might be responsible for these ocular signs. In addition, since these are exposed structures of the eye, photosensitivity may also play a role.

The minimum total cumulative dose of Chlorpromazine resulting in ocular toxicity in this study varied from 500gm to 750gm. Alexander et al found a total cumulative dose of 324gm taken for 2 years or over 2gm per/month to produce ocular toxicity while Crane et al reported that the minimum cumulative quantity of Chlorpromazine sufficient to produce eye manifestation varied from 100gm to 600 gm **(2, 17)**.

On the other hand, Buffaloe with his associates and Wetterholm et al have placed the critical cumulative dose value of Chlorpromazine at 1000g taken for a minimum duration of 5 years to produce ocular toxicity **(3, 5).** The possible explanation for this variation may be differences in metabolism, combination of other antipsychotic drugs which may have a protective effect, genetic susceptibility and sun glass use.

Half of the patients with anterior stellate cataract and

corneal changes had severe visual impairment comparable with a Spanish study which found cataract in 40.0% of cases and reduced visual acuity in 26.0% of their patients **(18).** This visual reduction is due to its effect on both the cornea and the lens.

The strength of our study is that all patients on Chlorpromazine were included without limiting dose and duration to get the minimum range of dosage and duration leading to toxicity. One of the limitations of this study was the difficulty to obtain the exact cumulative dosage and duration of Chlorpromazine for referred patients due to incomplete data. Some patients were also thought to discontinue the drug during symptom free periods for unspecified period of time while some take overdose for suicidal purposes. Some patients were kept on more than one drug which made it difficult to control its toxic effect on the eye.

In conclusion, Chlorpromazine is associated with lens and corneal toxicity at a minimum cumulative dose ranging between 500-750g taken for more than 5 years. Patients with both lens and corneal changes together had severe visual impairment. Close and combined management of patients on Chlorpromazine between ophthalmologists and psychiatrists is recommended.

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Original Article

Surveillance on pediatric bacterial meningitis in Gondar University Hospital, Ethiopia from 2012 to 2021: Retrospective analysis

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Abstract

Introduction: *Acute Bacterial meningitis is still a major cause of death in under-five children. Surveillance on Pediatric Bacterial Meningitis has been set up by the World Health Organization to generate data on vaccine preventable causes of Meningitis in under-five children. Ethiopia is one of the countries conducting the surveillance and Gondar University Hospital is one of the sentinel surveillance sites. In this study we described the epidemiological data on Bacterial meningitis in under-five children at Gondar University Hospital from 2012-2021.*

Methods: *Data were extracted directly from Gondar University Hospital surveillance database collected from under-five children admitted to the Hospital with suspected meningitis from January 1st, 2012 to December 31st, 2021. Socio-demographic and clinical characteristics were collected using standard pretested questioners. All under-five children with suspected meningitis over the 10-years period were included and descriptive statistics like frequency, percentage, mean, median and standard deviations were used for the characteristics of under-five Children with Suspected Bacterial Meningitis.*

Results: *In this study, a total of 4311 under-five admitted with suspected bacterial meningitis from 2012 to 2021 were enrolled. The majority, 71% of suspected meningitis were reported in infants. The mortality rate in suspected meningitis during the study period was 1%. The majority (92.4 %) had fever at presentation followed by seizure (62.7 %), altered consciousness (58.9 %) and bulged fontanel in 48.3 %, respectively. The commonest bacteria identified by CSF culture and Polymerase Chain Reaction was Streptococcus pneumonia (SPN). There was a reduction of confirmed meningitis cases from 2012 to 2021 (26 cases in 2012 and 6cases in 2021).*

Conclusions: *Streptococcus pneumoniae was the commonest cause of PBM. Bacterial detection by culture was low which showed that Polymerase Chain Reaction (PCR) test should be encouraged to improve bacterial detection.*

Keywords: *Under-five, Surveillance, meningitis, Gondar*

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Introduction

In under-five children bacterial meningitis is still one of the major and fatal public health problems. Despite Antibiotic therapy and updated vaccination strategies, Acute Bacterial Meningitis is persisting to be a risk to under-five children with high morbidity and mortality. Under-five children are predominantly affected by Bacterial Meningitis because of their lower immunity specially for polysaccharide containing bacteria out of which *Neisseria meningitidis, Streptococcus pneumoniae and Haemophilus influenzae* are the most common worldwide pathogens causing meningitis particularly in countries with limited resources like Ethiopia. To reduce the mortality and significant morbidity due to ABM, implementing primary prevention by routine vaccination has significant effect with lower cost especially for those with least access to health care (1, 2). In Asia and Africa even if there are reports showing in overall reduction, the three common organisms are still dominant causes of ABM for which strong surveillance system is one of the best solutions to assess vaccine efficacy and reduction of morbidity and mortality (3, 4, 5). Constraints in vaccine administration and coverage may contribute to this persistent problem in resource limited areas. To reduce such problem, continuous surveillance is mandatory which deterimines the distribution of serotypes/groups of bacteria causing Meningitis in under-five children across countries to help develop sustainable and effective vaccination programs. (6). A research done before introduction of both HIB and PCV-10 vaccines in Ethiopia reported that *S. pneumoniae* serotypes 14, 19F, 20, 1, 18 and 5 account for 76% of cases and 97% of the *H. influenzae* isolates were type b (7). Implementation of Hib and PCV-10 vaccinatin programs started in Ethiopia in 2007 and 2011, respectively. However, the impact of these vaccines on the disease epidemiology and

clinical features are investigated only in few international studies with no adequate local evidence (8).

Implementing strong Surveillance system on vaccine -preventable diseases can provide critical information for policymakers in guiding further vaccine introduction, monitoring vaccine impact, and describing changes in disease epidemiology over time (9). The objectives of Invasive Bacterial Vaccine Preventable Disease (IB-VPD) surveillance network are to describe the epidemiology and estimate the burden of invasive bacterial vaccine preventable diseases, in establishing a surveillance platform to measure vaccine impact, and characterize the circulating bacterial serotypes/serogroups in under-five children (10***).*** Gondar University Hospital has started the sentinel surveillance since 2007 in collaboration with the African Pediatric Bacterial Meningitis (PBM) surveillance network with the support of WHO and global immunization partners. We used data collected as part of PBM surveillance from 2012-2021 with the aim of describing the etiology, serotype/serogroup, epidemiology, and clinical presentations of pediatric bacterial meningitis in Gondar University Hospital. There are no reports about Pediatric Bacterial Meningitis activities in the study area and there are few reports from Ethiopia even if the surveillance has been done for more than 20years which was the main rationale of our study.

Materials and Methods

Study Design and Period

A retrospective analysis to assess the characteristics and patterns of Pediatric Bacterial meningitis was conducted at the University of Gondar Hospital from January 1st, 2012 to December 31st, 2021.

Study Area

This retrospective study was conducted at the University of Gondar Hospital, Department of Pediatrics and Child Health. The hospital is located in Gondar town 741km northwest of the capital city, Addis Ababa. Gondar University Hospital is one of the oldest Hospitals in Ethiopia. It has conducted Pediatric Bacterial Meningitis surveillance since January 2008.

Study Population

The study population of our study was all under-five children with suspected Bacterial Meningitis and admitted at Gondar University Hospital, Department of Pediatrics and Child Health from January 1st, 2012 to December 31st, 2021.

Inclusion and Exclusion Criteria

All under-five children with suspected bacterial meningitis admitted at Gondar University Hospital with analyzed CSF samples were included and children with unknown outcomes were excluded.

Case Enrollment

Active case-based Pediatric Bacterial meningitis surveillance is being conducted in Gondar University Hospital starting from January 2008 as one of the sentinel surveillance sites in Ethiopia which are being supported by WHO in the African region. Those under-five children admitted to the Hospital with suspected bacterial meningitis with CSF results were included in the surveillance.

Definition of Suspected meningitis (WHO Meningitis case definition): an illness in under-five child admitted to a hospital with sudden-onset fever (>38.5°C rectal or 38°C axillary) and one of the following signs: neck stiffness, altered consciousness with no other alternative diagnosis, or other meningeal signs; or illness in any patient under-five child who is hospitalized with a clinical diagnosis of meningitis

Data Collection process

Once enrolled, Socio-demographic data, medical history, and clinical characteristics were collected using standard pretested questioners. Bacterial identification were done using conventional microbiological methods and polymerase chain reactions (PCR) as a routine activity in the Hospital, and analysis of extracted data was performed using SPSS statistical software (Version-26).We collected the data directly from the Hospital Surveillance database by a structured data collection tool. The surveillance data has gathered important information from enrolled under-five children. Demographic data, medical history, and clinical characteristics were collected by trained clinical nurses and pediatric residents using the already prepared format by WHO at each ward of Gondar University Hospital, Pediatrics department. For each patient, standardized case investigation form nationally prepared containing information on patient demographics, clinical signs/symptoms, outcome, and laboratory results were completed. Demographic information was obtained from patient's caregiver. Pre-admission clinical history was obtained from the patients' chart, but in the event of missing or unclear information, it was obtained from the caregiver. Physical findings and other clinical Information were collected from the patient's medical record. A lumbar puncture (LP) was performed, and cerebrospinal fluid (CSF) was analyzed as a routine diagnostic test for suspected Bacterial Meningitis. Results of laboratory diagnostics were then used to classify suspected meningitis cases. Data were entered into an access data base which was prepared and distributed in collaboration with WHO and transferred on a monthly basis to Ethiopian Public Health Institute and to WHO country Support Team. CSF samples were examined for complete white blood cell count (WBC), protein and glucose concentrations, Gram stain and bacterial culture were also done on all CSF Specimens. When available, Latex Agglutination Test (LAT) specific for HIB, SPN and NM was done. Standard definitions for suspected, probable, and confirmed bacterial meningitis were used after CSF analysis in the Hospital laboratory. If the patient fulfills one of the laboratory meningitis case definitions

(Probable or suspected), the CSF was sent to the Ethiopian Public Health Institute (EPHI) for Polymerase Chain Reaction (PCR) confirmation and possible stereotyping and randomly selected samples were sent to South African regional laboratory for the purpose of quality control.

Data Processing and Analysis

Data were cleaned, coded, entered and analyzed using SPSS version-26. Descriptive statistics like frequency, percentage, mean, median and standard deviations were used for the characteristics of under-five Children with Suspected Bacterial Meningitis each year from 2102-2021. Tables and figures were used for data presentation

ETHICAL CONSIDERATION

Ethical clearance was obtained from Institutional Review Board of University of Gondar (Ref. No: VP/RTT/05/894/2022). Permission to access the collected data was secured from the University of Gondar Hospital director office. Privacy of the participants was respected and confidentiality was protected by, using codes and keeping questionnaires locked.

RESULTS

Sociodemographic Characteristics of under-five children

A total of 4311 under-five children with suspected bacterial meningitis were enrolled at the sentinel hospital from 2012 to 2021 and for all (100%) Lumbar Puncture was done and CSF samples were analyzed. Overall, 58.8% (2533/4311) of children were male and the median age was 3 months with SD 13.8. Majority (71% (3061/4311) of Suspected Bacterial Meningitis cases were reported in children aged 0–11 months. The mortality rate was found to be 1% (43/4311) (Table 1).

Table 1. Summary of Sociodemographic Characteristics of under-five children

Characteristics	Category	Number (%)
Age (in months)	0-11	3061(71%)
	12-23	490(11.4%)
	24-59	755 (17.5%)
	Unknown	5(0.1%)
Sex	Female	1726(40%)
	Male	2533 (58.8%)
	Unknown	52(1.2%)
Antibiotic before admission	Yes	83(1.9%)
	No	3244(75.2%)
	Unknown	984(22.8)
Discharge Dx	Meningitis	980(22.7%)
	Sepsis	1150 (26.7%)
	Pneumonia	862(20%)
	Unknown	1319 (30.6%)
Outcome	Discharged alive	2619(60.8%)
	Died	43(1%)
	Unknown	1649(38.2%)
Total cases with suspected Meningitis		**4311(100%)**

The clinical presentations of children at enrollment revealed that majority 92.4 %(3975/4311) has fever at presentation followed by seizure in 62.7% (2703/4311), altered consciousness in 58.9% (2539/4311) and bulged fontanel in infants with 48.3 % (2082/4311), respectively (Table 2)**.**

Table 2.Clinical signs/symptomsandClinical Characteristics of under-five children at presentation

Results of CSF Analysis and Bacterial identification

Symptom/sign at presentation	Number (%)
Fever	3975(92.4)
Bulged fontanel	2082(48.3)
Altered consciousness	2539(58.9)
Seizure	2703(62.7)
Neck stiffness	2526(58.6)

Lumbar Puncture and CSF analysis were done for all the 4311 suspected cases and majority 93.5% (4029/4311) of the CSF samples were reported to be crystal and 4.8% (203/431) were reported as turbid. Only 6.6 %(283/4311) of CSF samples were found to have cell counts above 100cells/mm^3 and 7 % (300/4311) CSF samples were reported as having protein level above 100mg/dl whereas 4.7 (201/4311) had glucose below 100mg/dl. Gram stain which was

done on 3814 (88.5%) CSF samples but positive result was reported only in 2.5 %(94/3814). Culture was done on 4144 (96.1%) CSF samples with positive result of 0.8 %(34/4144) (Table 3).

Table 3. Characteristics of Cerebrospinal Fluid in under-five children at Gondar University Hospital, from 2012-2021
HI=H.Influenzae
SPN=S.Pneumoniae

Characteristic	Number (%)
Cerebrospinal fluid appearance:	
Clear	4029(93.5%)
Turbid	203(4.8%)
Xanthrochromic	9(0.2%)
Blood stained / Trauatic	51(1.2%)
Unknown	19(0.4)
White blood cell count (cells/ mm^3):	
≤10	3375(78.3%)
10 to 100	173(4.0%)
>100	283(6.6%)
Unknown/not done	470(11%)
Protein (mg/dL) :	
<100	574(13.3%)
≥100	300(7%)
Unknown/not done	3437(79.7%)
Glucose (g/dL) :	
<40	201(4.7%)
≥40	828(19.2%)
Unknown/not done	3282(76.1%)
Latex Agglutination Test (LAT) :	
Done	121(2.8%)
Not done	4190 (97.2%)
LAT Result:	
HIB	21(17.4%)
SPN	4(3.3%)
NM	5(4.1%)
Others	1(0.8%)
Negative	90(74.4%)
Gram Stain Result:	
Gram +ve	61(1.4%)
Gram–Ve	32(0.7%)
No organism:	3721(86.3%)
Not done:	497(11.5%)
Culture Result:	
HI	7(0.2%)
SPN	24(0.6%)
NM	3(0.1%)
Others	38(0.9%)
Negative	406(94.3%)
Not done	167(3.9%)
PCR test done on 66 cases:	
HI	10(15.2%)
SPN	14(21.2)
NM	3(4.5%)
HIB+SPN	2(3.0%)
Negative	23(34.8%)
Inconclusive	14(21.2%)

NM=N.Meningitidis

Latex agglutination and Polymerase Reaction (PCR) were done and reported positive in only 24.8 % (30/121) and 41 %(27/66), respectively (fig.1). Latex agglutination and Polymerase Chain reaction tests were not routinely done for all suspected cases due to unavailability and frequent interruption of tests in the country.

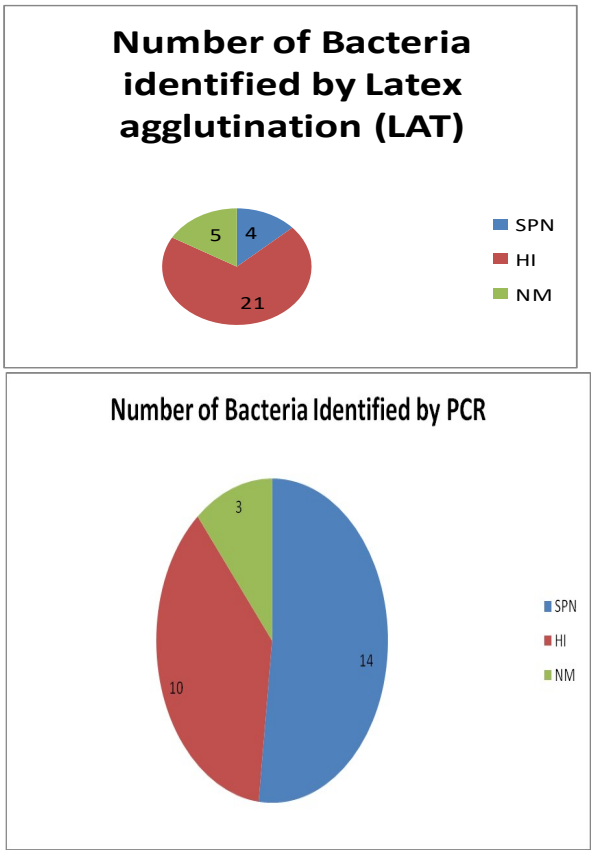
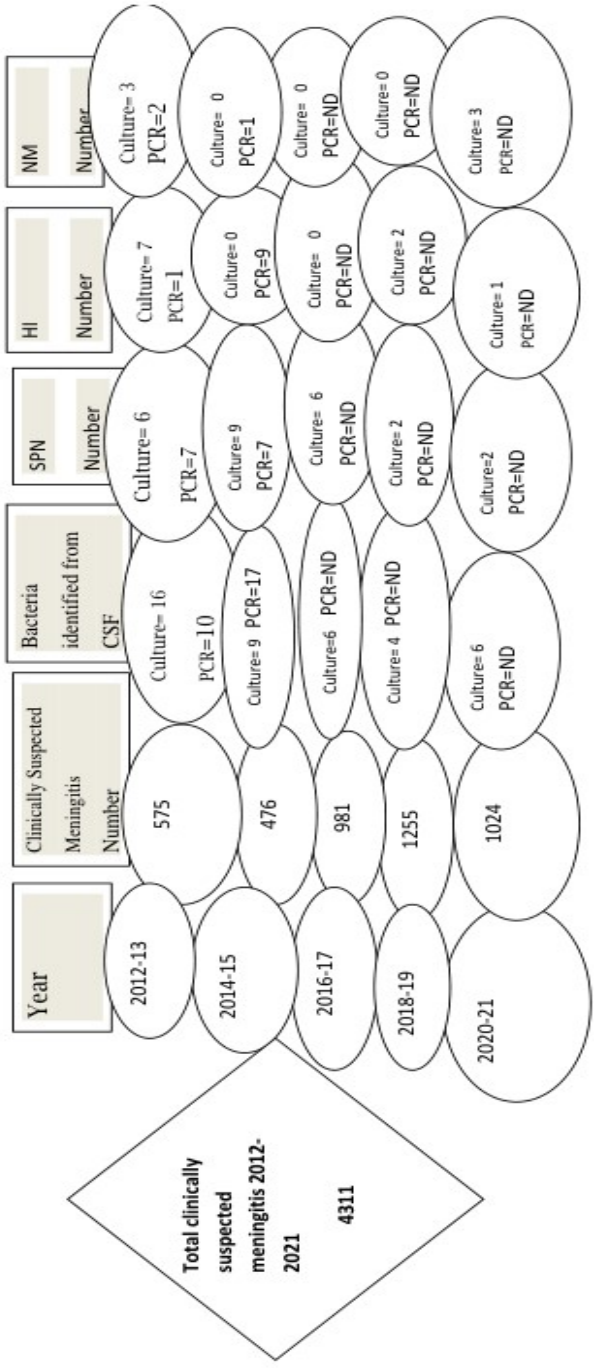


Fig.1. Bacterial detection by LAT and PCR

The number of Clinically suspected Meningitis cases in under-five children was found to be increasing (575 in 2012-13 to 1024 in 2020-2021) but the percentage of bacteria identified by CSF culture revealed a significant decreament (2.8% in 2012-13 to

0.6 in 2020-2021) (fig.2). Positive CSF culture results at Gondar University Hospital were sent to EPHI for confirmation and serotyping and reported that Stereotyping were done on 14 positive CSF samples for Pneumococcus and identified only 6 serotypes as 1, 2, 3 and 8 each and 2cases of 23F. Stereotyping performed on 8cases of *H. influenzae*– Positive CSF samples reported only 2 *HIB* isolates and *Meningococca*l serogrouping performed on 8 positive CSF samples reported only 1 case of serotype W-135.

HI=H.Influenzae ***SPN=S.Pneumoniae***



NM=N.Meningitidis **ND=Not done**

Fig.2. Year to year Distribution of Bacterial Meningitis isolates in Gondar University Hospital, 20121–2021

Discussion

Assessment of the burden of ABM, knowing major etiologic agents, and showing the changes in epidemiology are vital to establish effective and functional preventive strategies of diseases. Three sentinel sites of which Gondar University Hospital is one have been actively doing the under-five PBM surveillance in Ethiopia. A total of 4311 under-five children with suspected meningitis were enrolled at the Hospital over the last 10 years. Majority (71%) of suspected cases were infants below 12months of age; the commonest bacteria identified by CSF culture and PCR was SPN, and the overall mortality rate was 1%. These Findings support earlier evidences which revealed SPN as the leading cause of bacterial meningitis in the same Hospital ***(11),*** and also a report from Senegal found that *SPN* was the leading cause (50%) of ABM in under-five children ***(12).*** Reports from these studies showed that ABM due to HIB is decreasing perhaps due to early introduction of *HIB* vaccine in the centers. A multi-centered Hospital Surveillance done in Turkey on children below 18yrs of age identified that NM is the leading cause of ABM accounting for nearly 71% of cases which is in contrary to our study ***(13)***. This difference may be due to the difference in age difference of participants, i.e., the Turkey study included older children up to 18rs while participants in our study were only under-five children which may bring differences in bacterial etiologies of ABM. Another reason could be the difference in setups, i.e., the study in Turkey used PCV-13 vaccine which may reduce SPN cases, while we used PCV-10 vaccine. . An Indian study also reported that SPN is a leading cause (40.8%) of ABM both in children and adults which is similar with our report ***(***14).

Another report from Brazil reported that using PCR for CSF sample with negative culture result showed 65% positive which indicating that using PCR can improve the speed and accuracy of acute bacterial meningitis diagnosis in a clinical setting as a complement to classical immunological and bacteriological assays in CSF. It is very useful for CSF culture-negative acute bacterial meningitis ***(15).*** Another study from Iran reported that PCR has a higher rate of bacterial detection from CSF than culture (52% vs46%) ***(16).***

The results showed that using PCR testing will have significant value in bacterial identification which is also observed in our research; even if PCR is done only on 66 CSF samples, it revealed 3 additional cases of *HIB* and 10 cases of *SPN* which were reported

to be culture negative. So, utilization of PCR test in CSF samples is recommended for clinical benefit.
Similar studiess done in Ghana and Senegal based on sentinel Surveillance revealed that suspected bacterial meningitis are decreasing and identified SPN as a major cause of ABM with serotypes 19A and 23F being major contributors*(*17,18). This is in line with our findings. Another study done in Colombia reported NM to be the commonest (75%) cause of ABM followed by SPN (19).
In this study, only a few bacterial pathogens were isolated using culture methods, likely due to high rates of antibiotic use prior to hospitalization and LP which may be an indicator to use more sensitive methods specially to detect *HIB* such as LAT which is not routinely practiced and done only in 2.8% (121/4311). In this study, LAT detected more *HIB* (17.4%) than *SPN* (3.3%) and *NM* (4.1%). A report from 5 sentinel Hospitals from Nigeria reported that nearly 2.9% of suspected cases were confirmed to have PBM with mortality rate of 15%, and the dominant pathogen was found to be SPN which is almost comparable with our study except mortality in our case was only 1%. In our study, majority (5/6) of SPN serotypes were caused by serotypes that are included in PCV-vaccine which is also the case in Nigerian study which reported that nearly half of the pneumococcal meningitis cases were due to serotypes covered by PCV-10. Our study identified 2 cases of *HIB* serotypes and a single case of serotype W of *Meningococcal* meningitis which is in agreement with other studies (20-22).

We have found that our Hospital is having very limited utilization of LAT and PCR which were done only in 2.8% and 1.5%, respectively which might have contributed to the lower pathogen detection rate.
Utilization of LAT and PCR tests showed significant improvement in detection of common organisms and also helped identify other pathogens from different countries. Studies examining bacterial meningitis in the last decade using sensitive methods such as LAT or polymerase chain reaction (PCR) have detected *HIB* in 18 to 35 per cent of likely childhood bacterial meningitis cases (23, 24, 25).
Indian Studies reported that Multiplex PCR was more sensitive than culture or antigen detection, and employing this assay can significantly increase the speed and accuracy of identification of the pathogen.
In lack of PCR, using the combination of Gram staining, culture, and LAT can increase the sensitivity and specificity close to 100%. Using Gram staining and LAT together can achieve a detection rate of nearly 85% of cases of ABM (26, 27).
So, applying Molecular techniques are more effective for establishing the etiological diagnosis of pyogenic meningitis, although they cannot completely replace conventional tests.
Studies from Central African Republic and India reported that applying PCR was able to detected bacteria missed by Culture in 20% and 10.5% of cases, respectively***(28, 29).*** Therefore PCR is a sensitive method that can be introduced in different laboratories to increase detection and help assess the performance of Surveillance and vaccinations programs.
In remote areas of Niger where proper laboratories are not available, storing CSF and applying PCR test showed significant result in identifying pathogens from CSF ***(30).*** Again recommending PCR test in resource limited areas where routine tests like Culture are not reliable due to different reasons including technicalities, using PCR will have significant impact since it can be done on small volume of CSF, it doesn't need viable bacteria, and samples can be transported easily which is one of the commonest problems of CSF culture yield.
In conclusion; our study showed that Suspected ABM cases are increasing from 2012-2021 but confirmed cases of bacterial meningitis are significantly decreasing. The increment of suspected meningitis cases in the last years is most probably due to the inclusion of neonatal ages below 1months, for whom CSF analysis is done for every neonate suspected of Sepsis to rollout meningitis with no clear evidence of meningitis unlike older children which made the lower CSF positive result in the surveillance activity of our Hospital. *Streptococcus pneumoniae* is found to be the commonest cause of community acquired bacterial meningitis. Molecular diagnosis is gaining momentum for a rapid detection of etiological agents with high sensitivity and specificity since it is unaffected by viability of the organisms. Hence, PCR should be introduced in the diagnosis to overcome the dependency on conventional methods and to improve the low detection rate of CSF culture.
The major Limitation of the study is being a retrospective one which was done on data collected at the sentinel site for the last 10years (2012-2021); some of the information was not complete: final diagnosis, outcome, squelae and only few PCR tests were done and had it been a prospective study such gaps could have been filled.

Declarations

Availability of data and materials

Data set: The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interests

The author declared that there is no conflict of interest in conducting this study.

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Authors' contribution

The author (MA) was fully involved in designing the research work, cleaning data, did the analysis and write up of the manuscript. The Author read and ap-

proved the final manuscript.

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Case Series

Extra – anatomic bypass for abdominal aortic disease in the era of endovascular: A Case Series

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Abstract

The term "extra – anatomic bypass" refers to deliberate avoidance of the natural anatomic route for vascular pathway. Common types of extra – anatomic bypass include axillofemoral and femorofemoro bypasses and their combination, being known as axillobifemoral bypass. There are 2 main purposes for doing so which are: to avoid "hostile" intra-abdominal pathology and to avoid higher risk of transabdominal reconstruction in patients with serious visceral or systemic diseases. We report our case series of extra – anatomic bypass for management of complicated abdominal aortic diseases, namely aortoiliac occlusive disease, chronic contained ruptured aneurysm, mycotic aneurysm, and lastly infected penetrating aortic ulcers. Our case series demonstrated extra – anatomic bypass as suitable operative modality for the abovementioned diseases.

Keywords: *aortoiliac disease, abdominal aortic aneurysm (AAA), chronic contained rupture (CCR), extra – anatomic bypass, mycotic aneurysm*
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Introduction

The term extra – anatomic bypass refers to deliberate avoidance of the natural anatomical vascular pathway and utilization of vascular substitutes, whose course is different from that of the arteries they are replacing (1). Axillofemoral and femorofemoral bypasses and their combination, also known as axillobifemoral bypass, are among the most usual examples of extra – anatomic bypass. Prevention of abdominal entrance in this situation was due to either to avoid "aggressive" intra – abdominal pathological conditions or to evade the increased risk of transabdominal reconstruction in those with serious visceral or systemic disease (1). There is scarce literature on usage of open extra – anatomic bypass in management of complicated abdominal aortic pathologies in the era of endovascular. We present our case series of extra – anatomic bypasses in managing such conditions.

Case Series

Case 1

A 75–year–old gentleman, with underlying ischemic heart disease, presented with intermittent claudication over left lower limb for past 3 months, worsened over past 1 month. Clinical examination revealed shinny and hairless left lower limb with dry gangrene over left 3rd and 5th toes. CT Angiography bilateral lower limb revealed bilateral peripheral vascular disease with trifurcation diseases (non–opacification of left external iliac, common femoral and left posterior tibial artery). Clinical diagnosis of left chronic limb threatening ischemia (CLTI) with left iliac artery total occlusion was made. He had undergone left axillo – unifemoral bypass, where atheromatous plaque felt over left common femoral up to superficial femoral artery.

Case 2

A 69–year–old gentleman presented with left lumbar pain for past 3 months associated with constipation, worsening for past 2 days. On examination, he had a pulsatile expansile abdominal mass which is mild tender on palpation. CT Aortogram revealed saccular aneurysm of infrarenal abdominal aorta with concealed hematoma and multiple penetrating atherosclerotic ulcers, no CT evidence of active leak. Overall features suggest impending rupture. A transperitoneal approach laparotomy revealed adhesion of infrarenal aortic aneurysm to small bowel and its mesentery was encountered

Case 3

A 66–year–old gentleman presented with fever and lower abdominal pain for a week, associated with loose stool. Clinically tender over left iliac fossa with pulsatile expansile mass. Ultrasound and CT Aortogram revealed suspicions of left common iliac artery mycotic aneurysm. He had undergone left axillo – bifemoral bypass, laparotomy, aneurysmectomy and distal aortic ligation where infected hematoma and contained leak was noted. His blood and intra operative cultures were positive for *Salmonella sp.*
(Figure 1). Decision was made for left axillo – bifemoral bypass followed by infrarenal aortic ligation.
Intra operative cultures were negative for bacteria.

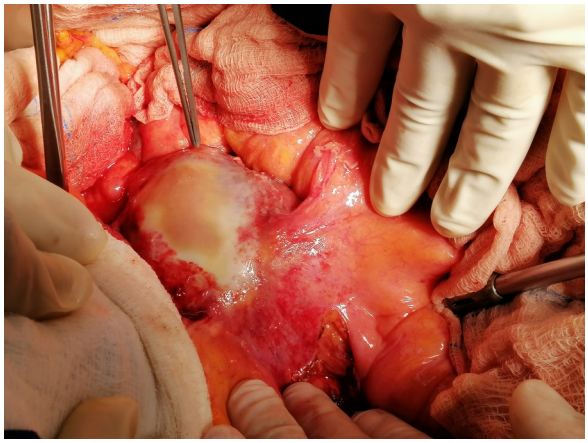

Figure 1: Proximal clamping prior to opening sac of chronic contained rupture (CCR) aneurysm, after axillo – bifemoral bypass

Case 4

A 56–year–old gentleman presented with right loin pain for 1 month, radiating to back, associated with lethargy and poor oral intake. Clinical examination revealed tender over right lumbar region with pulsatile mass. CT Aortogram revealed infrarenal abdominal aortic aneurysm with infrarenal paraaortic hematoma (could be chronic leaking) (Figure 2). Intra operative noted sealed ruptured mycotic aneurysm. He had undergone left axillo – bifemoral bypass followed by abdominal aortic aneurysm ligation and debridement of mycotic aneurysm (Figure 3). His blood culture is positive for *Salmonella sp*., intra operative culture however was negative.

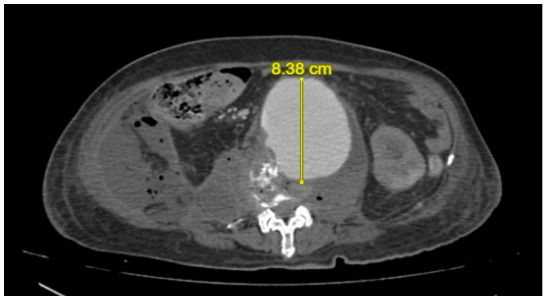

Figure 2: CT Aortogram showed infrarenal abdominal aortic aneurysm size 8.4cm (AP diameter) with surrounding paraaortic hematoma

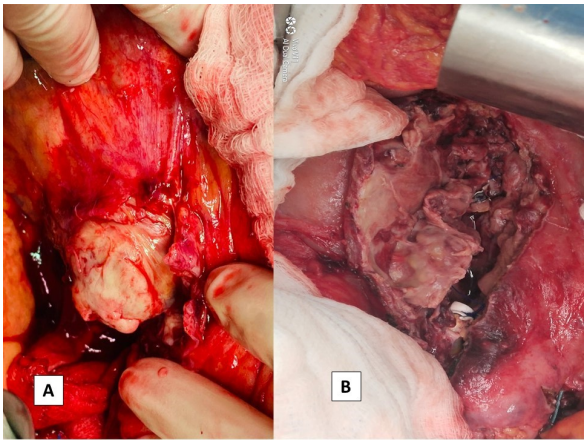

Figure 3: (A) Mycotic aneurysm with bullae seen. (B) Cut open aneurysm

Case 5

A 60–year–old gentleman presented with low back pain for 2 months radiating to suprapubic region associated with fever for 2 weeks. Clinical examination revealed tender over left iliac fossa with pulsatile mass. CT Aortogram revealed fusiform infrarenal abdominal aortic aneurysm with large penetrating atherosclerotic ulcer (Figure 4). He had undergone exploratory laparotomy + left axillo – bifemoral bypass (Figure 5) + lay open aneurysmal sac + infrarenal and inferior mesenteric artery ligation + omental plasty + bilateral common iliac artery ligation. His blood and intra operative specimens revealed positive for *Salmonella sp.*

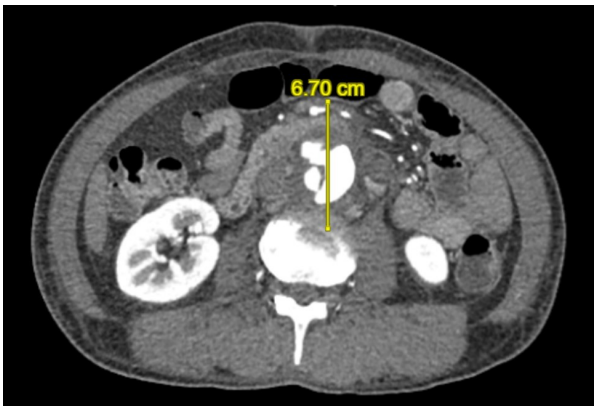

Figure 4: CT Aortogram showed infrarenal aortic

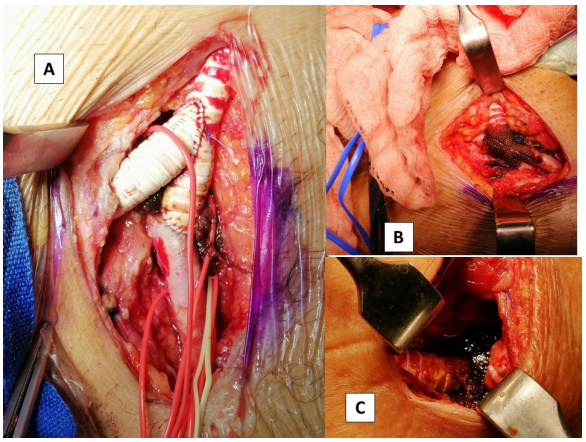

Figure 5: Construction of left axillobifemoral bypass (all using 8mm ePTFE graft with external support ring)

A) Graft to graft anastomosis external support ring (ETS) to left femoral artery
B) Right femoral artery and graft anastomosis
C) Left axillary artery and graft anastomosis

All 5 cases had extra – anatomic bypass done using ePTFE graft. There was no 30 – days postoperative mortality as well as early vascular – related complications. All 5 cases remained alive and continue to follow up in our surgical clinics (mean follow up: 14 months). There was good patency of graft for our patients with no sign of graft thrombosis till present.

Discussion

Our case series demonstrate various spectrum of complicated abdominal aortic disease, from aortoiliac occlusive disease, chronic contained ruptured aneurysm, mycotic aneurysm, and lastly infected penetrating aortic ulcer. All cases had been managed by extra anatomic bypass with certain adjunctive procedures. We would like to discuss the role of extra – anatomic bypass in management of complicated abdominal aortic diseases.

Our first patient had suffered from left CLTI secondary to left iliac artery occlusion, which is among the common sites of chronic atherosclerosis in those with symptomatic occlusive diseases of the lower extremities, besides infrarenal abdominal aorta (2). Occlusive disease in the aortoiliac segment frequently coexists with pathology below the inguinal ligament due to generalized process of arteriosclerosis (3). Management of aortoiliac disease can be classified as anatomic approach, extra anatomic bypass, or various non operative catheter – based endoluminal therapy. Aortoiliac endarterectomy, being anatomic approach has advantage of avoiding usage of prosthetic graft, had been rarely used in current vascular practice (4 – 6). Endarterectomy is useful for localized aortoiliac disease in 5 – 10% of patients (3), where vast majority of patients with extensive disease benefited from bypass graft with better patency rate (7 – 9).

Rutherford et al. found that treatment of nonocclusive disease with axillobifemoral bypass was beneficial, with 5 years primary and secondary patency rates of 91% and 100% respectively (1). Cautious avoidance of the natural anatomical route of arteries is coined with the term “extra – anatomic bypass” (1,10). Axillofemoral and femorofemoral bypass and their combination, known as axillobifemoral bypass are among common examples (1). Reasons for extra anatomic bypass include to avoid “aggressive” intra – abdominal pathologic features and to exclude patients with serious comorbidities to the high risk of trans-abdominal reconstruction (1).

A chronic contained abdominal aortic aneurysmal rupture is a well – documented subtype of abdominal aortic aneurysm (AAA) rupture in which characterized by sealed retroperitoneal hematoma (11). Absence of characteristic features of hemorrhagic shock in patients with sealed AAA rupture often possess management dilemma. (11) This group of patients often remained well for variable time frame and may only present with abdominal or back pain, like those uncomplicated AAA (11,12). Despite diagnostic modalities of choice in sealed AAA like contrasted enhanced computed tomography (CT) and magnetic resonance imaging (MRI) (11,13), we have recently dealt with unexpected chronic contained rupture of abdominal aortic aneurysm (CCR – AAA) in our second patient which results in change of operative approach. This gentleman, who had radiologically proven abdominal aortic aneurysm with concealed hematoma and focal intimal calcification discontinuity was presumed to be impending rupture in nature. These radiological findings however found to be due to contained AAA rupture with adhesion to small bowel intra – operatively (11).

Szilagyi et al. first described this phenomenon of chronic contained rupture of abdominal aortic aneurysm (14). CCR – AAA comprises of only 4% of all ruptured cases of AAA (15). To diagnose CCR – AAA, few conditions need to be fulfilled: (i) known case of AAA; (ii) previous pain symptoms that may have resolved; (iii) stable patient with normal hematocrit; (iv) a CT scan demonstrates a retroperitoneal hematoma; and (v) pathological proven organized hematoma (16).

Infected aortic aneurysm can be caused by various types of bacteria, gram – positive and gram negative. *Salmonella sp*. however remained the most common agent, accounting for up to 75% (17 – 21), which correlates with our last three patients, which yield same organism growth in either blood, intra operative specimen cultures or both.

Preliminary axillobifemoral bypass followed by aortic aneurysm resection can be useful to treat infrarenal aortic infections, which can minimize infectious graft complications, further justified by uncertainties of the magnitude of retroperitoneal infection and nature of the causative agent (22).

We had applied such principle for best interest of post operative outcome to our last three patients with diagnosis of mycotic aneurysm and infected penetrating aortic ulcers.

Conclusion

In the era of endovascular therapy, we believe that extra – anatomic bypass followed by adjunctive procedures for intra – abdominal pathologic condition especially mycotic aneurysm and chronic contained rupture aneurysm which prohibit direct entry to aneurysm sac can be considered as suitable operative modalities.

Extra – anatomic bypass often found to be more effective in managing extensive aortoiliac occlusive disease as well. Our case series had demonstrated good postoperative outcomes for abovementioned patients using extra – anatomic bypass.

Competing interests

There was no funding for the study and no conflicts of interest to disclose.

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GUIDELINES FOR AUTHORS

The *Ethiopian Medical Journal (EMJ)* is the official Journal of the Ethiopian Medical Association (EMA) devoted to the advancement and dissemination of knowledge pertaining to the broad field of medicine in Ethiopia and other developing countries. Prospective contributors to the Journal should take note of the instructions of Manuscript preparation and submission to EMJ as outlined below.

Article types acceptable by EMJ

Original Articles (*vide infra*) on experimental and observational studies with clinical relevance
Brief Communications
Case Series
Case Reports
Editorials, Review or Teaching Articles: by invitation of the Editorial Board.
Correspondences/Letters to the Editor
Monographs or set of articles on specific themes appearing in a Special Issues of the Journal
Book reviews
Perspectives,
Viewpoints
Hypothesis or discussion of an issue important to medical practice
Letter to the Editor
Commentaries
Advertisements
Obituaries

N.B. Articles are not acceptable if previously published or submitted elsewhere in print or electronic format, except in the form of abstracts in proceedings of conferences.

Content and format of articles:

Title: The title should be on a separate page. It should not have acronyms or abbreviations. The title should be descriptive and should `not exceed 20 words or 120 characters including space. The title page should include the name(s) and qualification of the author(s); the department or Institution to which the study/research is attributed and address of the corresponding Author. If the author has multiple affiliations only use the most preferred one.

1. Original Articles

2,500 words, excluding Abstracts, References, Figures and Tables. The manuscript of the Article, should appear under the following headings:

a) Abstract: The abstract of the Article is prepared on a separate paper, a maximum of 250 words; it should be structured under the titles: a) Background; b) Methods; c) Results; d) Conclusions. Briefly summarize the essential features of the article under above headings, respectively. Mention the problem being addressed in the study; how the study was conducted; the results and what the author(s) concluded from the results. Statistical method used can appear under Methods paragraph of the Abstract, but do not insert abbreviations or references in the Abstract section.

Keywords: Provide three to six key words, or short phrases at the end of abstract page. Use terms from medical subject heading of Index Medicus to assist in cross indexing the Article.

b) Introduction : Should provide a short background and context of the study and provide the rationale for doing the study. It should not be a detailed review of the subject and should not include conclusions from the paper.

c) Patients or (Materials) and Methods: should contain details to enable reproducibility of the study by others. This section must include a clear statement specifying that a free and informed consent of the subjects or their legal guardians was obtained. Corresponding author should submit a copy of institution review Board (IRB) clearance or letter of permission from the hospital or department (if IRB exempt)

with the manuscript. For manuscripts on clinical trials, a copy of ethical approval letter from the concerned body should be submitted with the Manuscript. If confidential data is being used for publication (such as student grades, medical board data, or federal ethics board data), then appropriate support/ agreement letter should be included. Photos of patients should disguise the identity or must have obtained their written consent. Reference number for ethical approval given by ethics committee should be stated. In general, the section should include only information that was available at the time the plan or protocol for the study was being written; all information obtained during the study belongs in the Results section.

d) Results: This section should present the experimental or observational data in text, tables or figures. The data in Tables and Figures should not be described extensively in the text.

e) Discussion: The first paragraph should provide a summary of key finding that will then be discussed one by one in the paragraphs to follow. The discussion should focus on the interpretation and significance of the results of the study with comments that compare and describe their relation to the work of others (with references) to the topic. Do not repeat information of Results in this section. Make sure the limitations of the study are clearly stated.

f) Tables and Figures: These should not be more than six. Tables should be typed in triplicate on separate sheets and given serial Arabic numbers. Titles should be clearly place underneath Tables and above Figures. Unnecessary and lengthy tables and figures are discouraged. Same results should not be presented in more than one form (choose either figure or table). Units should appear in parentheses in captions but not in the body of the table. Statistical procedures, if not in common use, should be detailed in the METHODS section or supported by references. Legends for figures should be typed on separate sheets, not stapled to the figures. Three dimensional histograms are discouraged. Recognizable photographs of patients should be disguised. Authors should submit editable soft versions of the tables and figures.

g) Acknowledgement: Appropriate recognition of contributors to the research, not included under Authors should be mentioned here; also add a note about source of the financial support or research funding, when applicable.

h) References:

- The titles of journals should be abbreviated according to the style used for MEDLINE (www.ncbi.nlm.nih.gov/nlmcatalog/journals).
- References should be numbered consecutively in the order in which they are first mentioned in the text and identify references in text, tables, and legends by Arabic numerals in parentheses.
- Type the References on a separate sheet, double spaced and keyed to the text.
- Personal communications should be placed NOT in the list of references but in the text in parentheses, giving name, date and place where the information was gathered or the work carried out (e.g. personal communication, Alasebu Berhanu, MD, 1984, Gondar College of Medical Sciences). Unpublished data should also be referred to in the text.
- References with six or less authors should all be listed. If more than six names, list the first three, followed by et al.
- Listing of a reference to a journal should be according to the guidelines of the International Committee of Medical Journal Editors ("Vancouver Style') and should include authors' name(s) and initial(s) separated by commas, full title of the article, correctly abbreviated name of the journal, year, volume number and first and last page numbers.
- Reference to a book should contain author's or authors' name(s) and initials, title of chapter, names of editors, title or book, city and name of publisher, year, first and last page numbers.

The following examples demonstrate the acceptable reference styles.

Articles:

- Gilbert C, Foster A. Childhood blindness in the context of Vision 2020: the right to sight. *Bull World Health Org 2001;79:227-32*
- Teklu B. Disease patterns amongst civil servants in Addis Ababa: an analysis of outpatient visits to a Bank employee's clinic. *Ethiop Med J 1980;18:1-6*

- Tsega E, Mengesha B, Nordenfelt E, Hansen B-G; Lindberg J. Serological survey of human immuno-deficiency virus infection in Ethiopia. *Ethiop Med J 1988; 26(4): 179-84*
- Laird M, Deen M, Brooks S, et al. Telemedicine diagnosis of diabetic retinopathy and glaucoma by direct ophthalmoscopy (Abstract). *Invest Ophthalmol Vis Sci 1996; 37:104-5*

Books and chapters from books:

- Henderson JW. Orbital Tumors, 3rd ed. Raven Press New York, 1994. Pp 125-136.
- Clipard JP. Dry Eye disorders. In Albert DM, Jakobiec FA (Eds). Principles and Practice of Ophthal-mology. W.B Saunders: Philadelphia, PA 1994 pp257-76.

Website:

- David K Lynch; laser History: Masers and lasers. http://home.achilles.net/jtalbot/history/massers.htmAccessed 19/04/2001

2. Brief Communication

Short versions of Research and Applications articles, often describing focused approaches to solve a health problem, or prelnary evaluation of a novel system or methodology

- Word count: up to 2000 words
- Abstract up to 200 words; excluding: Abstract, Title, Tables/Figures and References
- Tables and Figures up to 5
- References (vide supra – Original Article)

3. Case Series

Minimum of three and maximum of 20 cases

- Up to 1,000 words; excluding: Abstract, Title, Tables/Figures and References
- Abstract of up to 200 words; structured; (vide supra)
- Statistical statements here are expressed as 5/8 (62.5%)
- Tables and Figures: no more than three
- References: maximum of 20

4. Case Report

Report on a rare case or uncommon manifestation of a disease of academic or practical significance

- Up to 750 words; excluding: Abstract, Title, Tables/Figures and References
- Abstract of up to 100 words; unstructured;
- Tables and Figures: no more than three
- References: maximum of 10

5. Systematic review

Review of the literature on topics of broad scientific interest and relevant to EMJ readers

- Abstract structured with headings as for an Original Article (*vide supra*)
- Text should follow the same format as what is required of an Original Article
- Word count: up to 8,000 words, excluding abstract, tables/Figures and references
- Structured abstract up to 250 words
- Tables and Figures up to 8

6. Teaching Article

A comprehensive treatise of a specific topic/subject, considered as relevant to clinical medicine and public health targeting EMJ readers

- By invitation of the Editorial Board; but an outline of proposal can be submitted
- Word limit of 8,000; excluding abstract, tables/Figures and references
- Unstructured Abstract up to 250 words

7. Editorial

- By invitation of the Editorial Board, but an editorial topic can be proposed and submitted
- Word limit of 1,000 words: excluding references and title; no Abstract
- References up to 15.

8. Perspectives

- By invitation of the Editorial board, but a topic can be proposed and submitted
- Word limit of 1,500
- References up to six

9. Obituaries

- By invitation of the Editorial board, but readers are welcome to suggest individuals (members of the EMA) to be featured.

Preparation of manuscripts

- Manuscripts must be prepared in English, the official language of the Journal.
- On a single separate sheet, there must be the title of the paper, with key words for indexing if required, and each author's full name and professional degrees, department where work was done, present address of any author if different from that where work was done, the name and full mailing address of the corresponding author, including email, and word count of the manuscript (excluding title page, abstract, references, figures and tables). Each table/figures/boxes or other illustrations, complete with title and footnotes, should be on a separate page.
- All pages should be numbered consecutively in the following order: Title page; Abstract and keywords page; main manuscript text pages; References pages; acknowledgment page; Figure-legends and Tables
- The Metric system of weights and measures must be used; temperature is indicated in degrees Centigrade.
- Generic names should be used for drugs, followed by propriety brand name; the manufacturer name in parenthesis, e.g. diazepam (Valium, Roche UK)
- Statistical estimates e.g. mean, median proportions and percentages should be given to one decimal place; standard deviations, odds ratios or relative risks and confidence intervals to two decimal places.
- Acronyms/Abbreviations should be used sparingly and must be given in full, at first mention in the text and at the head of Tables/foot of Figure, if used in tables/figures.eg. Blood Urea Nitrogen (BUN). Interstitial lung disease (ILD).
- Use the binomial nomenclature, reference to a bacterium must be given in full and underlined - underlining in typescript becomes italics in print (e.g. *Hemophilus influenzae)*, and later reference may show a capitalised initial for the genus (e.g. *H. influenzae)*
- In the text of an article, the first reference to any medical phrase must be given in full, with the initials following in parentheses, e.g., blood urea nitrogen (BUN); in later references, the initials may be used.
- Manuscripts for submission should be prepared in Microsoft Word document file format

Submission of manuscripts

- As part of the submission process, authors are required to check off their submission's compliance with journals requirements
- All manuscripts must be submitted to the Editor-in-Chief of the Journal with a statement signed by each author that the paper has not been published elsewhere in whole or in part and is not submitted elsewhere while offered to the *Ethiopian Medical Journal*. This does not refer to abstracts of oral communications at conferences/symposia or other proceedings.
- It is the author's responsibility to proof-read the typescript or off-print before submitting or resubmitting it to the Journal, and to ensure that the spelling and numerals in the text and tables are accurate.
- Authors should submit their work through the Ethiopian Medical Journal website; ema.emj@telecom.net.et.

Conflict of interest

Authors should disclose at the time of submission of manuscripts any conflict of interest, which refers to situations in which financial or other personal considerations may compromise, or have the appearance of compromising their professional judgment in conducting or reporting the research results They should declare that there is no conflict of interest to declare if there is none,

Manuscripts review procedures

The procedures for manuscripts review include:

- Within one week of receipt of a manuscript, the Editorial Board will review it in reference to (i) conformity with the Journal's "guidelines to authors (revised version available in all issues starting January 2020)", (ii) relevance of the article to the objectives of the *EMJ*, (iii) clarity of presentation, and (iv) plagiarism by using appropriate software
- The Editorial Board has three options: accept manuscripts for external review, return it to author for revision, or reject it. A manuscript not accepted by a board member is blindly reviewed by another board member. If not accepted by both, the manuscript is rejected by the Editorial Board. Decision will be made by the suggestion of a third Editorial Board member if the decisions of first two do not concur.
- Once accepted for external review, the Editorial Board identifies one (for brief communication, case reports, and teaching articles) or two (for original articles) reviewers with appropriate expertise. The reviewers will be asked to review and return manuscripts with their comments online within two weeks of their receipt. Reviewers have four options; accept, accept with major revision, accept with minor revision, or reject.
- A Manuscript accepted subject revision as suggested by reviewers will be returned to the corresponding author. Author(s) will be given four weeks to respond to reviewers' comments, make necessary changes, and return the manuscript to the Editorial Board. A Manuscript not returned within the specified time will be considered withdrawn by the author(s).
- Manuscripts with minor revisions will be cleared by the Editorial Board and accepted for publication. Those with major revisions will be returned to external reviewers and follow the procedures as outlined for the initial review.

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