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ETHIOPIAN MEDICAL JOURNAL
APRIL, 2022

EDITORIAL

ORIGINAL ARTICLES

CASE REPORTS

BRIF COMMUNICATION

LITERATURE REVIEW

Anteneh Asefa[1], Mirkuzie Woldie[2] ,. Ethiop Med J, 2022 Vol. 60, No. 2

EDITORIAL

PROMOTING RESPECTFUL MATERNITY CARE IN LOW- AND MIDDLE-INCOME COUNTRIES: WHAT DO WE NEED TO ACCELERATE PROGRESS TO MATERNAL HEALTH TARGETS OF THE SUSTAINABLE DEVELOPMENT GOALS ?

Anteneh Asefa[1]*, Mirkuzie Woldie[2]

More than 800 women die each day due to preventable conditions that emerge in the course of pregnancy and childbirth, despite remarkable declines in maternal mortality in the past decades [1]. According to the World Health Organization's (WHO's) estimates, 295,000 maternal deaths occurred in 2017 [1]. Low uptake of maternal health care services, especially skilled birth attendance, remains a key challenge to reducing maternal mortality in low- and middle-income countries (LMICs) [2]. A significant portion of the low uptake of services is attributable to poor quality of care which spans both clinical and non-clinical aspects of care during childbirth, which includes the mistreatment of women [3].

The mistreatment of women during facility-based childbirth—an issue that is gaining international scrutiny—is a violation of women's human rights and a significant deterrent to the utilisation of skilled birth services [4]. Mistreatment also jeopardises women's right to a safe, satisfying, and positive childbirth experience, and could even lead to poor mental health [3]. Despite the deep-rooted existence and normalisation of mistreatment, focused mitigative measures are minimal, predominantly due to the lack of evidence in the field. Mistreatment takes various forms including verbal abuse, physical abuse, sexual abuse, stigma and discrimination, detention, neglect and abandonment, non-confidential care, non-consented care, and poor health system conditions and constraints [4]. Several studies from sub-Saharan Africa, including Ethiopia, and other LMICs reported high levels and diverse manifestations of the mistreatment of women during facility-based childbirth [4-7].

With the aim of meeting the maternal mortality targets of the Sustainable Development Goals (SDGs), strategies for ending preventable maternal mortality were introduced in 2015. The strategy calls for health systems not to neglect respectful maternity care (RMC) while endeavouring to deliver effective clinical interventions [8]. WHO's framework for quality maternal and newborn health care reinforces the important role of RMC, and identifies respect and preservation of dignity as one of the eight domains of quality of care [9]. Addressing both the health system bottlenecks that drive disrespectful behaviour among service providers, and the health system constraints that limit RMC require evidence-driven actions [10]. However, there is a research gap on the barriers to the promotion of RMC and the effectiveness of RMC interventions in mitigating the mistreatment of women, especially in LMICs. Additionally, "research on maternal health services—including RMC—is meagre and largely masterminded by international researchers, local researchers often playing ancillary roles when involved" [10]. It is therefore imperative to embed research on RMC into maternal health quality improvement initiatives, build local research and implementation capacity on RMC in LMICs, test and integrate RMC into pre-service training curriculum of healthcare professions education, and explore and document strategies to strengthen the engagement of key stakeholders in RMC agenda.

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ORIGINAL ARTICLE

EFFECT OF THERMAL INACTIVATION OF BIOLOGICAL SPECIMENS ON THE LIMIT OF DETECTION OF RT-PCR IN THE DIAGNOSIS OF SARS COV-2

Fekadu Alemu, MSc.[1$], Getachew Tesfaye Beyene, PhD.[1$*], Eyerus Selomon, BSc[1], Zewudu Selomon, BSc[1], Sinknesh Wolde, MSc[1], Desalegn Abeje Tefera, BSc[1], Dawit Hailu Alemayehu, MSc[1], Adane Mihret, PhD[1], Alemseged Abdissa, PhD[1], Andargachew Mulu, PhD[1]

ABSTRACT

Background: *Coronavirus disease 2019 (COVID-19) is characterized as a global pandemic by World Health Organization. For the safety of medical laboratory personnel and the environment, thermal inactivation of clinical samples is a common practice performed by most laboratories before nucleic acid extraction. However, there are conflicting reports in the literature regarding the effect of thermal inactivation on the analytical sensitivity of molecular assays.*

Objective*: To test the impact of thermal inactivation using alternative methods on the analytical sensitivity of respiratory samples.*

Method: *We compared the impact of thermal inactivation of biological samples after adding lysis buffer at 72^0C for 10 minutes by dry heat block and water bath on analytical sensitivity of severe acute respiratory syndrome coronavirus 2 (SARS-CoV2). Furthermore, we tested the effect of the thermal inactivation method at 56^0C using a water bath on the detection rate of SARS-CoV2.*

Result: *All samples tested positive in dry heat block was also tested positive in the water bath. We observed a similar viral detection rate of viral RNA at 56^0C for 15 min and 30 min, whereas inactivating samples at 56^0C on the water bath for 45 minutes drastically reduces the virus detection rate by 20%.*

Conclusion*: Water bath is not inferior to dry heat block to treat samples with lysis buffer, and can be used instead of dry heat block in district laboratories. However, the inactivation of samples at 56^0C over 30 minutes drastically reduces the virus detection rate. Hence, samples shall not be heat-treated before nucleic acid extraction.*

Keywords: *SARS-CoV2, COVID-19, heat inactivation, heat block, water bath*

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) is the virus responsible for the coronavirus disease 2019 (COVID-19) pandemic [1]. The World Health Organization (WHO) on March 11, 2020, has declared the COVID-19 outbreak a global pandemic [2], and then the demand for laboratory equipment, chemicals, and personal protective equipment has soared. In resources limited countries like Ethiopia, the availability of the right and properly functioning laboratory equipment is scarce. Given that the expansion of the pandemic to different regional states in the country is rapid, it is very difficult for district laboratories to avail all the necessary and standard equipment used for SARS-CoV2 diagnosis in this emergency time. Hence, the shortage of laboratory equipment and consumables needed for the extraction and detection of SARS-CoV-2 RNA in respiratory samples has forced many laboratories to find alternative approaches for sample preparation [3]. To protect medical laboratory personnel from infection, most laboratories inactivate the virus, causing COVID-19 in clinical samples before nucleic acid extraction and testing by applying high temperatures [4]. However, the outcome of applying different methods of heat inactivation on the detection of the viral RNA is not well explored and findings are controversial.

Therefore, this study aims to explore the impact of heat inactivation of the nasopharyngeal swab on the water bath and compare with heat treatment of samples after adding lysis buffer using dry heat [heat block] and moist heat [water bath] on reverse transcription-polymerase chain reaction (RT-PCR).

METHODS

We performed two experimental designs to show the impact of temperature on the test result of nasopharyngeal swab (NPS) samples that were known positive for SARS-CoV2 RNA. In the first experiment, we compared the impact of dry heat block with water bath heat inactivation of samples after lysis buffer is applied to the samples. Briefly, in a standard Da An Gene Nucleic Acid extraction protocol next to the addition of proteinase K, we apply lysis buffer into the samples followed by a dry heat block at 72^0C for 10 minutes. However, in most of our district laboratories, there is a huge shortage of dry heat blocks, hence we wanted to test if water bath inactivation (moist heating) at 72^0C for 10 minutes can be used instead of dry heat block to facilitate viral RNA extraction. For this purpose, randomly 20 NPS samples sent to AHRI's SARS-CoV2

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laboratory for routine diagnosis that were confirmed positive for SARS-CoV-2 RNA were included.

We aimed the second experimental design to assess the impact of water bath heat inactivation at 56^0C directly on NPS samples over time before initiation of nucleic acid extraction. Here we took 15 NPS samples randomly that were confirmed positive for SARS-CoV-2 RNA from the samples AHRI received for routine COVID-19 diagnosis. The samples were heat-treated by a water bath at 56^0C for 15 minutes, 30 minutes, and 45 minutes.

RNA extraction
Viral nucleic acid (NA) was extracted from 200 µL respiratory samples (NPS and oropharyngeal swabs in viral transport medium using the NA extraction and purification reagent, Dn An Gene Co., Ltd, as recommended by the manufacturer (Da An Gene Co., Ltd, of Sun Yat-sen University, China). Briefly, 50 µL proteinase K and 200 µL lysis buffer were mixed with 200 µL NP and/or Nasal swab samples. Then, the lysed samples were heat-inactivated parallelly on a dry heat block and in a water bath at 72^0C for 10 minutes, followed by the addition of inhibitor remover and subsequent washing. Finally, the NA was eluted in 50 µL molecular grade water preheated at 72^0C.

RT-PCR for the detection of viral RNA
In the experiments, the careGENETM COVID-19 RT-PCR kit was used to detect SARS-CoV2 RNA. The kit has the following combination of detection targets and fluorescent reporters; nucleocapsid (N) gene reported by FAM, RNA-dependent RNA polymerase (RdRP) gene by CY5, and the internal control (IC) by ROX. Regardless of the RT-PCR system, the kit has the limit of detection10copies/ µL of viral RNA. The analytical sensitivity (cut-off value) of the careGENETM for positive tests is a cycle threshold of ≤ 43, and any reading above 43 is a negative test. Finally, the amplification reaction mixes for both experiments were run on Agilent Technologies Stratagene, Max3005P RT-PCR system according to the protocol provided by the manufacturers.

Ethics: The study is approved by the Armauer Hansen Research Institute/ALERT Ethics Review Committee.

RESULT

The first experiment where we have compared the use of dry heat block and water bath at a temperature of 72^0C for 10 minutes after the addition of lysis buffer during RNA extraction shows that all the 20 samples that were positive in dry heat block turned out to be all positive in the water bath. The Ct values of the samples tested by dry heat block and water bath were nearly similar (P-value = 0.00023). Interestingly, the overall average of the change in the Ct value (ΔCt) for the N gene (in the FAM Chanelle) of the samples processed by water bath demonstrated a 2.79 lower Ct value than the sample treated by heat block. We observed a similar result for RdRP gene (in the CY5 channel) that is, samples inactivated by water bath had a 2.63 lower Ct value than the sample treated by dry heat block (Table 1).

In the experiment where we tested the impact of heat inactivation by the use of water bath directly on NPS samples at 56^0C over time, we observed that the N-gene which is reported by HEX channel showed similar analytical sensitivity (detection level) when samples were treated at 56^0C for 15 min and 30 min. That is, out of the 15 samples that were confirmed positive before heat treatment, 6.67% of the specimens were detected negative for the N-gene; whereas 13.3% of the samples were turned negative for the RdRP gene when they were heated 56^0C for 15 min and 20 min. When the time of inactivation increased to 45 min, 20% of the samples turned negative for both N gene and RdRP gene (Table 2).

DISCUSSION

Heat treatment of virus inactivation rate depends on ways of applying heat [5]. Concerning the modes of transmission of SARS-CoV-2 inactivation rate under heat treatment at 70^0C can vary by almost two orders of magnitude depending on the treatment procedure [6]. Here, we tested the impact of different sources of heat on the analytical sensitivity or the limit of detection of SARS-CoV-2 RNA. The study shows that all the samples that were positive when treated by dry heat block during lysis nearly all turned positive when heat treated by a water bath. This suggests that the water bath is not inferior in its use for virus inactivation during lysis for RNA extraction, and can be used in place of a dry heat block in district laboratories where there is a shortage. The United States Centre for Disease Control and Prevention advised moist heat as the method for virus inactivation [7]. Interestingly, in line with this, our data shows samples heat treated with water bath during lysis have a higher viral load, on average a difference of Ct value greater than 2.5 for both N and RdRP genes, showing that SARS-CoV2 inactivation by water bath during lysis is advantageous over dry heat block because it lowers the limit of detection of the viral RNA.

Studies suggest that heat-inactivated biological

Table 1: A comparison of the Ct values of the targets, N and RdRP genes reported by FAM and CY5, respectively of the NP samples treated at 72^0C for 10 minutes using dry heat block and water bath for RNA extraction. ROX channel is the reporter for internal control.

Samples ID	***Dry heat block***			***Water bath***			***Change in Ct values (†ΔCt)***	
	ROX	FAM	CY5	ROX	FAM	CY5	‡FAM_{Dry}-FAM_{Wet}	§$CY5_{Dry}$-$CY5_{Wet}$
AHRI-16584	18.64	13.77	16.50	17.65	12.13	15.29	1.64	1.20
AHRI-16063	17.04	14.48	16.60	16.51	14.13	16.14	0.35	0.47
AHRI-16055	16.93	13.86	17.10	16.76	12.83	14.98	1.03	2.09
AHRI-16283	16.48	18.11	20.80	14.94	16.46	19.01	1.65	1.77
AHRI-16307	23.03	23.17	24.20	21.78	21.97	23.31	1.20	0.89
AHRI-16442	16.25	29.49	29.60	16.18	28.71	29.17	0.78	0.43
AHRI-16281	15.16	30.65	29.70	15.45	29.49	28.85	1.16	0.81
AHRI-16448	16.86	28.98	29.10	16.02	24.93	24.80	4.05	4.30
AHRI-16392	14.82	33.72	32.80	14.29	29.23	29.12	4.49	3.67
AHRI-16441	16.84	30.17	30.50	16.58	29.15	30.58	1.02	-0.08
AHRI-16417	17.91	32.73	32.30	17.50	31.05	30.71	1.68	1.55
AHRI-16447	16.05	31.51	31.90	16.20	29.96	30.31	1.55	1.56
AHRI-16404	16.82	33.27	33.30	15.78	31.07	31.83	2.20	1.47
AHRI-16437	16.55	35.6	34.10	15.14	31.40	32.46	4.20	1.60
AHRI-16447	16.05	31.51	31.90	16.20	29.96	30.31	1.55	1.56
AHRI-16439	19.37	43	29.60	16.66	33.07	NCt	11.40	NCt
AHRI-16478	14.61	31.75	32.8	15.46	29.99	31.43	1.76	1.36
AHRI-16403	19.42	29.2	41.4	17.44	NCt	28.9	NCt	12.46
AHRI-16435	19.65	36.54	41.7	19.67	36.56	31.58	0.2	10.14
AHRI-16466	15.36	44.63	NCt	15.65	33.38	32.46	11.3	NCt

† Refers to change in Ct value
‡ Refers to subtraction of Ct value in FAM channel reading of the water bath from a FAM channel reading in the dry heat block
§ Refers to subtraction of Ct value in Cy5 channel reading of the water bath from a Cy5 channel reading of dry heat block
NCt: No cycle threshold

Table 2: Positive detection rates of SARS-CoV2 NP samples for N- and RdRP-genes after direct heat inactivation using water bath at 56^0C over time.

Total number of samples	No treatment (Zero time)	Heat treatment at 56^0C					
		15 min		30 min		45 min	
		N-gene	RdRP gene	N-gene	RdRP gene	N-gene	RdRP gene
15	100%	93.3%	86.7%	93.3%	86.7%	80%	80%

samples may not be suitable for proper detection of viral RNA as there is a possible reduction in the sensitivity and increase in the limit of detection of viral RNA resulting in a significant number of false-negative results [6,8]. In this context, in our second experiment, we tested the impact of water bath heat inactivation methods over time on the detection rate of SARS-CoV2. Our data show a similar detection rate of the viral RNA when applying heat of 56^0C for 15 min and 30 min while heating the NPS samples for 45 minutes [which is the standard temperature-time combination to inactivate viruses] drastically reduces the virus detection rate that is, 20% (3/15) positive samples turned to negative. This implies that the standard temperature-time combination to inactivate viruses has a negative impact on the RT-PCR-based diagnosis. This agrees with a study that reported after heat inactivation treatment 13% (6/46) of positive samples turned negative [4] and is in line with WHO recommendation. We have also observed that there is a difference in the detection rate of the virus regarding the two target genes, N gene has a higher detection rate where 6.67% of positive samples turned in to negative whereas 13.3% of positive samples turned to negative for RdRP gene. An earlier study also reported that the Ct value for RdRP gene was 1.2 times larger than that of the N gene [9], suggesting that primer sets for detecting the SARS-CoV2 N gene might be the choice for highly sensitive detection of the virus.

In conclusion, the water bath is not inferior to dry heat block for virus inactivation for detecting SARS-CoV2 RNA and can substitute dry heat block in district laboratories where there is a shortage. However, the inactivation of NPS samples at 56^0C over 30 minutes drastically reduces the virus detection rate and increases false negativity, and thus sample should not be heat-treated before nucleic acid extraction.

Conflict of interest

The authors have declared that no competing interests exist

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Authors' contribution

FA: Formal analysis, Methodology, Writing - review & editing
GTB: Conceptualization, Formal analysis, Methodology, Writing - review & editing
ES: Investigation, Methodology, review & editing
ZS: Investigation, Methodology, review & editing
SW: Investigation, Methodology, review & editing
DAT: Investigation, Methodology, review & editing
DHA: Formal analysis, Methodology, Writing - review & editing
AM: Investigation, Methodology, review & editing
AA: Investigation, Methodology, Supervision, Writing - review & editing
AnM: Conceptualization, Formal analysis, Methodology, Writing - review & editing

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ORIGINAL ARTICLE

CLINICAL ASSESSMENT OF ABSENCE OF THE PALMARIS LONGUS MUSCLE IN AFRICAN ANTIGUAN POPULATION.

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ABSTRACT

Background: *The knowledge of the prevalence of the palmaris longus (PL) tendon according to gender and ethnicity is important for surgeons planning to use its tendon for transfer and transplant. Unfortunately, there is no information related to the prevalence of PL agenesis in the African Antiguan population. This study aimed to determine the prevalence of PL agenesis and its association with gender, body side and hand dominance in the African Antiguan population by using the Chi-square test.*

Methods: *In this random cross-sectional study, six hundred African Antiguan subjects (300- males and 300- females; age range 18-62 years) were tested for the absence of PL tendon, using Schaffer's test. In subjects with negative Schaffer's test, Thompson's test, Mishra's test I, Mishra's test II, and Pushpakumar's "two-finger sign" method were used to confirm its absence.*

Results*: Overall agenesis of PL in the present study reached 12.8%, unilateral agenesis (7%) was more common than bilateral absence (5.8%). The PL agenesis was found significantly greater (p=0.037) in females (15.6%) than the males (10%). The muscle agenesis was significantly more often on the left side than the right (p=0.02). In both right-hand (p>0.05) and left-hand (p<0.05) dominant subjects, the left-sided agenesis was greater.*

Conclusions: *This study reaffirms the existence of ethnic differences in the prevalence of PL agenesis. The prevalence of PL agenesis in the African Antiguan population is lesser than the reported incidence of 15% in standard textbooks, and much higher than the black and Asian population. The PM tendon is prevalent in vast majority (87.2%) of African Antiguans, and it is not diminishing rapidly like in middle eastern populations. Hence the surgeons can still harvest the tendon for various reconstructive and tendon graft surgery in African Antiguans.*

Key words*: Palmaris longus; Agenesis; Hand dominance; Variation.*

INTRODUCTION

Palmaris longus (PL) is a phylogenetically retrogressive muscle having a short fusiform belly and a long slender tendon. It arises from the medial epicondyle of the humerus, with additional origin from intermuscular septa and the antebrachial fascia this myotendinous flexor continues distally with palmar aponeurosis [1]. The PL muscle exhibits numerous variations due to functional evolutionary influence; it may be agenesis, either unilaterally or bilaterally, split, incomplete, double, digastric, or anomalous insertion [2]. In addition, it has been noted that some of the PL anomalies lead to various clinical conditions, for instance, entrapment of the ulnar nerve and artery in the tunnel of Guyon, and compression of the median nerve in the carpal tunnel [3]. Palmaris longus contributes to the strength of thumb abduction and it anchors the skin and fascia of the hand to resist the horizontal shear force in the distal direction, as in holding a cricket bat [1,4]. The cognizant of the prevalence of PL in association with ethnicity, sex, and limb side is important for surgeons for its use as a tendon graft in various cosmetic and reconstructive hand surgeries.

Most surgeons consider the PL as an ideal choice of tendon grafts for secondary tendon reconstruction, tendon transfers, and other reconstructive efforts because it accomplishes the necessary criteria of0020length, thickness, and availability. Since it is superficial in the position it can be harvested without resulting in any maneuvering disability [5]. For several decades, anatomists and clinicians have documented variations in the rate of absence of PL across races, ranging from 0.6% in the Korean population to 63.9% in the Turkish population [6,7]. Studies have been done on agenesis of PL in various ethnic groups of African [8-15]. However, there are no reports available on the prevalence of PL in African Antiguan populations. Therefore, this study was undertaken to determine the prevalence of unilateral/bilateral PL absences and its association with body side, sex, and hand dominance in African Antiguan populations.

MATERIALS AND METHODS

Study design

This analytical cross-sectional study was conducted to determine the prevalence of PL agenesis in the African Antiguan community and,

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secondly, to evaluate its association with gender, side of the limb, and hand dominance using a battery of clinical tests.

Subjects: Six hundred African Antiguan subjects (300- males and 300- females; age range 18-62 years) were examined for the presence or absence of PL tendon, using the clinical tests. The study was approved by Institutional Review Board of American University of Antigua (AUA IRB). The procedure was explained, and informed consent was obtained from the subjects. The subjects filled the questionnaire format that included age, gender, hand dominance, and ethnicity. The study excluded the people with a history of injury, surgery, scars on the wrist area, or any physical disabilities of their upper limbs. The sample size was determined using the approximate population size of 64,000 Antiguans age group between 18-62 years (Male-30000, Female-34000) using a confidence interval of 95% and a margin of error of 5% and the sample size was calculated as 600 (Male -300, Female-300). The normal male and female subjects were recruited randomly from the hospital, university sector and those who attended the community health fairs (year 2015-2017) organized by the American University of Antigua, Antigua.

Clinical tests and data collection: The presence of the PL tendon was assessed on both sides of the wrist using five clinical tests. We primarily asked the subjects to perform a standard test (Schaeffer's test): opposition of the thumb to the little finger and then flex the wrist (Fig. 1A).

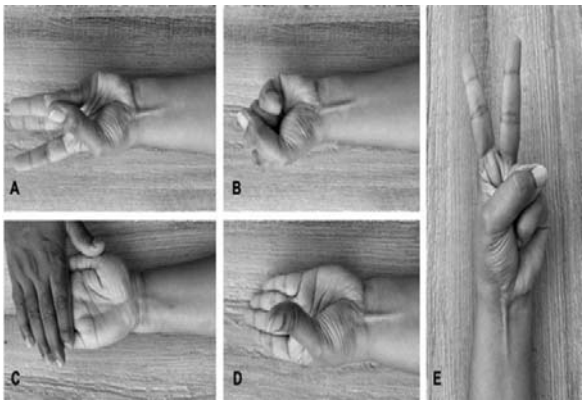

Figure 1. Presence of the Palmaris longus tendon. A. Standard test (Schaeffer's test); B. Thompson's test; C. Mishra's test I; D. Mishra's test II; E. Pushpakumar's "two-finger sign" test

If the tendon was visible as a raised ridge on both sides of the wrist, then the PL tendon was declared as bilaterally present. If the tendon is not visible and palpable, then the subjects performed four additional tests to confirm its absence (Fig. 2).

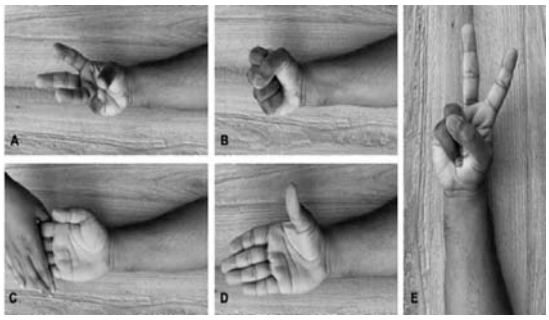

Figure 2. Absence of the Palmaris longus tendon. A. Standard test (Schaeffer's test); B. Thompson's test; C. Mishra's test I; D. Mishra's test II; E. Pushpakumar's "two-finger sign" test

The four tests were Thompson's test: The subject was asked to make a fist, then flex the wrist, and finally, the thumb was opposed and flexed over the fingers (Fig. 1B). Mishra's test I: The metacarpophalangeal joints of all fingers were passively hyperextended by the examiner and the subject was asked to actively flex the wrist (Fig. 1C). Mishra's test II: The subject was asked to abduct the thumb against resistance with the wrist in slight palmar flexion (Fig. 1D). Pushpakumar's "two-finger sign" test: The subject was asked to fully extend the index and middle finger; the wrist and other fingers were flexed and finally the thumb was fully opposed and flexed (Fig. 1E). The data was entered in the following parameter. Bilateral absence: Absence of the PL tendon on both sides. Symmetry of palmaris longus in relation to body side: If the absence was only on one side, either in right or left hand, then it was recorded as unilateral absence on the corresponding side and the dominant hand of the subjects was also noted. For accuracy, all the tests were performed thrice and the principal investigator who investigated the agenesis of PL tendon is a clinician as well as the subject expert.

Data analysis: The data were presented in percentage values and the palmaris longus absence was analyzed statistically using SPSS software (version 11.5). The prevalence of PL tendon agenesis and its association with gender, limb laterality, and hand dominance were analyzed statistically by the Chi-square test. Statistical significance was set at $P < 0.05$.

RESULTS

The overall PL absence was found in 77 (12.8%) subjects, the absence was significantly (P=0.037) greater in females (15.6%) than in the males (10%). The palmaris longus muscle was absent bilaterally in 35 (5.8%) subjects and

unilateral absence was found in 42 (7%) subjects with no statistically significant sex difference. The bilateral (female-7%, male-4.6%) and unilateral (female-8.6%,male-5.3%) absence of PL were greater in females than the male, with no significant difference. Unilateral absence of the PL was significantly higher (P = 0.01) in the left hand [23 (10.8%)] than in the right hand [9 (7.0%)]. The PL absence in the left hand was significantly (P=0.02) greater in females [23 (7.6%)] than the male subjects [10 (3.3%)], while in the right hand the PL absence was greater in males [6 (2%)] than the female subjects [3 (1%)] with no significant sex differences (Table.1).

We noted that 554 (92.33%) subjects had right-hand dominance and 46 (7.66%) subjects had left -hand dominance. The left-hand dominant had a significantly higher (P=0.02) absence of Palmaris Lon-gus (23.9%) when compared with right-hand dominant (11.94%) (Table.2).

In right-hand dominant subjects, PL was absent on the left side in 23 (4.15%) and on the right side in eight (1.4%) subjects with significant difference (P=0.006). In left-handed dominant subjects, it was absent on the right side in one (2.17%) and on the left side in 10 (21.73%) subjects with significant difference (P=0.003). Therefore, the left-sided absence was greater in both left-hand and right-hand dominant subjects, but a significant difference was found only in the left-hand dominant subjects (P<0.001) (Table.3).

Table 1. Gender wise distribution of Palmaris longus agenesis and its lateralization

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Gender	PLP n(%)	PLA n(%)	ULA n(%)	BLA n(%)	PLP n(%)	ULA n(%)	PLP n(%)	BLA n(%)	Right Hand n(%)		Left Hand n(%)	
									Present	Absent	Present	Absent
Male (n=300)	270 90%	30 10%	16 5.3%	14 4.6%	270 90%	16 5.3%	270 90%	14 4.6%	294 98%	6 2%	290 90%	10 3.3%
Female (n=300)	253 84.3%	47 15.6%	26 8.6%	21 7%	253 84.3%	26 8.6%	253 84.3%	21 7%	297 99%	3 1%	277 92.4%	23 7.6%
overall (n=600)	523 87.2%	77 12.8%	42 7%	35 5.8%	523 87.2%	42 7%	523 87.2%	35 5.8%	591 98.5%	9 1.5%	567 94.5%	33 5.5%
Chi-square	4.305		0.0291		2.847		1.773		1.015		5.419	
p-value	0.037*		0.864		0.091		0.183		0.314		0.02*	

PLP- Palmaris longus present; PLA- Palmaris longus Agenesis; ULA-Unilateral Agenesis; BLA-Bilateral Agenesis
*Significantly different.

Table 2. Association between palmaris longus agenesis and hand dominance

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PL	Hand dominance		Chi - square	p-value
	Right n(%)	Left n(%)		
Present	488 (88.06%)	35 (76.08%)		
Absent	66 (11.94%)	11 (23.9%)	5.467	0.02*
Overall	554 (92.33%)	46 (7.66%)		

PL– Palmaris longus; * Significantly different

Table 3. Association between laterality of palmaris longus agenesis and hand dominance

Palmaris longus	Hand dominance		Chi - square	p-value
	Right n(%)	Left n(%)		
Right absent	8 (1.4)	1 (2.17)	0.153	0.695
Left absent	23 (4.15)	10 (21.73)	25.27	0.001*
Chi -square	7.46	8.36		
p-Value	0.006*	0.003*		

* Significantly different

DISCUSSION

Palmaris longus muscle is well developed in arboreal mammals like orangutans. Other primates like humans, chimpanzees, and gorillas are less arboreal; hence PL gradually undergoes degeneration due to non-adaptive evolution in the Homininae [16]. Standard textbooks of hand surgery state that the rate of absence of PL is 15% in the global population [17]; this statement differs markedly when the present study data were compared with the results of other ethnic groups (Table.4). Overall agenesis of PL in the African Antiguan population was 12.8%. This value is comparable to the very low prevalence of PL agenesis in the black populations, Ghana [8,9], East Africa [10], Nigerian population [11] and the lowest was recorded in Zimbabwe (1.5%) [12]. However, South African [13] and Ethiopian populations [15] exhibited a slightly greater prevalence of PL agenesis. The reason for less degeneration of PL in the African population could be explained by the high pervasiveness of manual labor which requires a tensed palmar fascia for a strong grip [10].In the South and Southeast Asian population, the agenesis of PL was very low in Koreans and Chinese, but in Indians, Malays, Nepalese, and Filipinos the rate of absence was moderate [18-23].In the two multiethnic studies done on the Malaysian and Indonesian population, the overall absence of PL was 9.3% and 10.4% respectively [24,25]. Among the Middle Eastern population, very high percentages of PL agenesis were observed in Bahrain; Iran, and Egypt populations [26-28]. The highest prevalence of PL agenesis was recorded by Ceyhan and Mavt in Turkey (63.9%) [7]. Solanti et al. in a multiethnic study on the USA population reported that the prevalence of PL tendon agenesis is greater in whites (14.9%) than the African Americans (4.5%) and Asians (2.9%) [29]. Eric et al. in Serbian [30] and Thompson et al. in the Caucasian population [16] reported the greater absence rate of PL. In the South American population, also the agenesis of PL was slightly higher in the Chilean and Brazilian populations [31,32].

Apart from ethnic variations in the PL agenesis, various studies proposed that its absence is more common in women, bilateral absence is more common than unilateral, and unilateral absence occurs more frequently on the left side. This type of distribution in the prevalence pattern doesn't fit completely with the results of our study. In agreement, the overall prevalence of PL agenesis in the African Antiguan population was significantly greater in females than the males. Numerous studies have indicated that the agenesis of PL is more common in females than males [8,9,12,14,15,21-24,26-29,31-33]. In accordance, with our study, significant sex difference was observed in Malay [21], Iran [27], Egyptian [28], Brazilian [32], and Turkey populations [33]. This could be explained by that female has low expressivity of the gene of the presence of PL comparedto males [34]. In contrast, few studies reported that PL absence is more common in males [10,11,13,16,18,19,20,30].

In our study unilateral absence was greater than the bilateral absence with no significant difference. In concurrence with our study, other African populations also reported unilateral agenesis was more common [8,10-13,14,15]. Furthermore, other studies done on Caucasians [16], Chinese [19], Indian [20], Malays [21], Nepalese [22], Filipino [23] Serbian [30] and Chilean [31] also reported in favorable to our study. Mbaka et al. [11] in Nigerian, Yong et al. [21] in Malays and Eric et al. [30] in the Serbian population found unilateral absence is significantly more common than the bilateral absence. The bilateral absence was greater than the unilateral absence among most of the Middle Eastern population [7, 26-28,33], but the significant difference was reported by Ceyhan et al., Kose et al. and Hiz et al. [7,33,35] in Turkey and Rouf et al in Egyptian population [28]. In the present study, both unilateral and bilateral absence of PL was greater in females than the males. However, no significant sex difference was found. In contrast, Mkaba et al. [11] in the Yoruba Nigerian population reported a significantly higher bilateral agenesis rate in

Table 4. Compilation of palmaris longus agenesis prevalence reported in various population

Authors	Population	PL absence						Total (%)
		Unilateral		Bilateral		Overall		
		M (%)	F (%)	M (%)	F (%)	M (%)	F (%)	
Gangata et al., 2009	Zimbabwe	0.33	0.56	0.22	0.33	0.56	0.9	1.46
Offei et al., 2014	Ghana	2.1	4.7	0.7	1.6	2.7	6.3	3.8
Kigera et al., 2011	An East African Study	3.6	3	1.3	1	4.9	3.9	4.4
Mbaka et al., 2009	Nigerian	5.4	6	1.5	0.4	6.9	6.4	6.7
Berhe et al., 2014	Ethiopian	6.9	7.7	7.4	10.1	14.3	17.8	15.3
Ndou et al., 2010	Mixed South African	1.5	4.5	1.5	4	3	8.5	11.5
Osonuga et al., 2012	Ghanaian	1.3	1.36	0	0.44	1.3	1.8	3.1
Venter et al., 2014	South African	7.7	6.8	6.5	5.4	14.2	12.2	24.4
Sater et al., 2010	Bahrain	17.8	17.9	16.2	21.3	34	39.2	36.8
Raouf et al., 2013	Egypt	21.9	19.7	26.8	32.8	41	54.74	50.8
Kose et al., 2009	Turkey	9.03	13.62	11.7	18.37	20.74	32.44	26.59
Karimi-Jashni et al., 2014	Iran	9.1	13.2	13.5	25.4	22.7	38.6	30.7
Ceyhan and Mavt., 1997	Turkey	19.5	22.9	42.1	45.3	61.6	68.3	63.91
Kyung et al., 2012	South Korea	1.3	2.5	3.3	0.8	4.7	3.3	4.1
Sebastin et al., 2006	Singaporean China	3.8	2.5	1	1.7	8.3	2.4	4.6
Roohi et al., 2007	Malaysia	5.8	7.1	1.3	4.4	7.1	11.5	9.3
Yong et al., 2017	Malay	6.08	9.77	3.04	4.4	9.1	14.2	11.7
Lamichhane et al., 2017	Filipino	12.94	15.3	0.4	2.58	4.77	12.72	17.5
Sharma et al., 2019	Nepalese	11.2	11	3.2	4.1	14.4	15.2	14.8
Kapoor et al., 2008	Indian	12.71	6.06	5.08	10.06	17.8	16.67	17.2
Hadi & Masri., 2015	Indonesian	6.43	6.51	3.71	4.14	10.2	10.7	10.4
Thompson et al., 2001	Caucasian	19.3	13.3	10	7.3	29.3	20.6	25
Alves et al., 2011	Chilean	10.46	11.4	6.97	10.52	17.44	21.93	20
Morais et al., 2012	Brazilian	10.3	16.7	13.1	10.7	21.1	29.7	26.5
Eric et al., 2010	Serbia	18.5	22.25	18.5	13.3	39.5	35.5	37.5
Solanti et al., 2012	Multiethnic USA	7.6	10.1	6.6	8.8	14.2	18.9	16.3
Present study	African Antiguan	5.3	8.6	4.6	7	10	15.6	12.58

PL- Palmaris Longus Muscle; M- Male, F-Female

males. Kapoor et al. [20] in Indian, Sater et al. [26] in Bahrain, and Karimi et al. [27] in the Iranian population found significantly greater bilateral absence in females.

Our study in the African Antiguan population confirmed that the overall prevalence of unilateral agenesis on the left side is significantly more common in women. This is consistent with studies done on Indians, Bahrain, Iranian, Serbian, and Turkish populations [20,26,27,30,33], but no significant sex difference was observed in the Nigerian and Chinese populations [11,19]. Alternatively, Abledu et al. in the Ghana population observed that unilateral right-side agenesis was significantly more common in females [8]. While in Malays, the left-side agenesis was significantly higher in males [21], no significant sex difference was observed in studies done on East African [10] and Nepalese populations [22].

In both right and left-hand dominant subjects, the PL genesis was significantly more common on the left side. This result is consistent with Morais et al study on the Brazilian population [34]. In Caucasian [36], Ghana [8], East Africans [10], Zimbabwe [12], Ethiopian [15], and Malay [21] populations the absence was more common on the non-dominant. In another study on the Brazilian population, the left-handed subjects showed higher PL agenesis on the left side, and in right-handed subjects, the agenesis was similar on both sides [32]. The limitation of this study is that the clinical test may rarely lead to the fallacy of a normal muscle as a pathological finding or agenesis. Ultrasonography or MRI would confirm the variations of PL, but like the clinical test, they cannot be applied for documenting the prevalence of PL tendon in large-scale population studies because it is neither cost-effective nor time-saving [33].

Among the clinical test, the Schaeffer test was not always reliable because it showed negative results in subjects with feebly developed PL. In such cases, Mishra's second test which involves resisted abduction of the thumb demonstrated the PL tendon more prominently.

From an embryological point of view, the PL develops as a skeletal muscle from the somatic mesoderm of the myotomes. The premyogenic cells migrate, proliferate, and differentiate into muscle tissue, this process is regulated by the intrinsic factor and environmental signals. The absence of these signals and muscle regulatory factors during embryogenesis causes premature differentiation of myogenic cells, resulting in the agenesis or incomplete genesis of the corresponding muscles [37,38].

CONCLUSION

Our study concludes the existence of ethnic differences in the prevalence of PL agenesis. The prevalence
of PL agenesis in the African Antiguan population is lesser than the reported incidence of 15% in standard textbooks and much higher than the black and Asian populations. The PL agenesis was more common in females and on the left side. In both dominant hands, the left-sided agenesis was more common. The PL tendon is prevalent in the vast majority (87.2%) of African Antiguans, and it is not diminishing rapidly like in the middle eastern population. Hence the surgeons can still harvest the tendon for various reconstructive and tendon graft surgery in African Antiguans.

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ORIGINAL ARTICLE

PREVALENCE OF INTESTINAL HELMINTHS AND ITS ASSOCIATED RISK FACTORS AMONG PRIMARY SCHOOL CHILDREN IN GEDEO ZONE, SOUTHERN ETHIOPIA

Feven Wudneh[1]*, Yabibal Gebeyehu[2]

ABSTRACT

***Background**: Intestinal helminths infection mainly occurs in the tropics and sub-tropics, and affects many school age children by causing anemia, malnutrition and restricting physical and cognitive development. This study aimed to assess the prevalence of intestinal helminths and its associated risk factors among primary school children in Gedeo Zone, Southern Ethiopia.*

***Methods**: A cross-sectional study was conducted from February to April 2020. Primary school children aged 5 to 16 years, and given written consent by their parents/guardians were included in the study. Stool samples were collected, processed and examined using Wet Mount (WM) and Formol-Ether Concentration (FEC) techniques. Descriptive statistics including frequency, percentage, mean, range, and standard deviation (SD) was calculated to describe relevant variables. The Chi-square(X2) test, bivariate and multivariate logistic regression were also done to determine the association between the risk factors and intestinal helminths.*

***Result**: A total of 413 school children participated in the study. The mean age ± SD was 10.7±2.64 years. The prevalence of intestinal helminths was 114 (27.6%). Ascaris lumbricoid was the most prevalent intestinal helminth 77(18.6%) followed by Hookworm 15 (3.6%) and Trichuris trichiuria 9 (2.1%). Poor hand washing practice before meal (AOR=3.72; 95% CI: 0.211-3.9; P= 0.002), drinking water from river (AOR=2.9; 95% CI: 0.56-3.51; P=0.000), living in rural area (AOR=1.81; 95% CI: 0.43-2.33; P=0.008) and improper toilet use (AOR=2.16; 95% CI: 0.39-3.36; P= 0.000) were factors associated with intestinal helminths infections.*

***Conclusions:** The prevalence of intestinal helminths infection was high in primary school children in the Gedeo zone. Therefore, intervention works including periodic school-based deworming programs is needed to avoid helminth infection in primary school children.*

***Keywords**: Intestinal helminths, Risk factors, Primary school children, Ethiopia*

INTRODUCTION

Intestinal helminths infections are major health problem that affect the health of pre-school and school age children (1, 2). According to the 2020 WHO report, more than 1.5 billion people (24% of the world's population) are infected by helminths worldwide (3).Over 267 million preschool-age and 568 million school-age children live in areas where helminths infections are highly prevalent (3, 4).Soil transmitted helminths (STH), are the major causes of parasitic infections worldwide. 819 million individuals are infected with *Ascaris lumbricoides*, 465 million with *Trichuris trichiura*, and 439 million with hookworms (5). *Strongyloides stercoralis, Hymenolepis nana* and *Schistosoma mansoni* are also intestinal helminths that affect the health status (6, 7).

Intestinal helminths infections are common in the tropical and subtropical areas of Africa (8-10). The main reasons for their high prevalence is associated with increasing population density, poverty, contaminated food, unhygienic environment, inadequate health service, poor deworming practice and inadequate health education on mechanisms of transmission, inadequate toilet facilities, inadequacy and lack of safe water supply (11, 12).

Intestinal helminths infection is linked to intestinal bleeding, abdominal pain, intestinal obstruction, malabsorption, nutrient deficiency, malnutrition, anemia and school absenteeism(13-15) resulting in restrictions in physical and cognitive development among school children (16, 17).

In Ethiopia, infections with intestinal parasites are top in the morbidity list in different health facilities. *A. lumbricoides*, *T. trichiura, H. nana, histolytica/dispar,* and *S. mansoni* are commonly seen in the country (15).Intestinal helminths infections are common in Gedeo Zone, some of the factors identified were lack of knowledge about home sanitation and hygiene, poor toilet facilities and eating uncooked vegetables (31).

Even if many studies have been conducted on the prevalence of intestinal helminths infection and associated factors among school children in different parts of Ethiopia (1, 4, 5, 6), adequate data are lacking in Gedeo Zone, South Ethiopia. The outcome of this study helps health officials to plan intervention programs in order to minimize the burden of the disease by identifying the risk factors and to design periodic mass-deworming

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Programs. Therefore, this study aimed to determine the prevalence and associated risk factors of intestinal helminths among school children in Gedeo Zone, South Ethiopia.

Materials and Methods

Study design, period and area

A school-based cross-sectional study was conducted from February to April 2020 in selected Dilla town and Dilla Zuria woreda primary schools in Gedeo Zone, South Ethiopia. Dilla is located 360 Km South of Addis Ababa. The Zone had a projected population of 1,139,429 in 2017 and has eight districts/woredas (Figure 1). Cash crop is the predominant means of income for the residents.

Study Population

All primary school children aged 5 to 16 years available during the period of data collection were the study population.

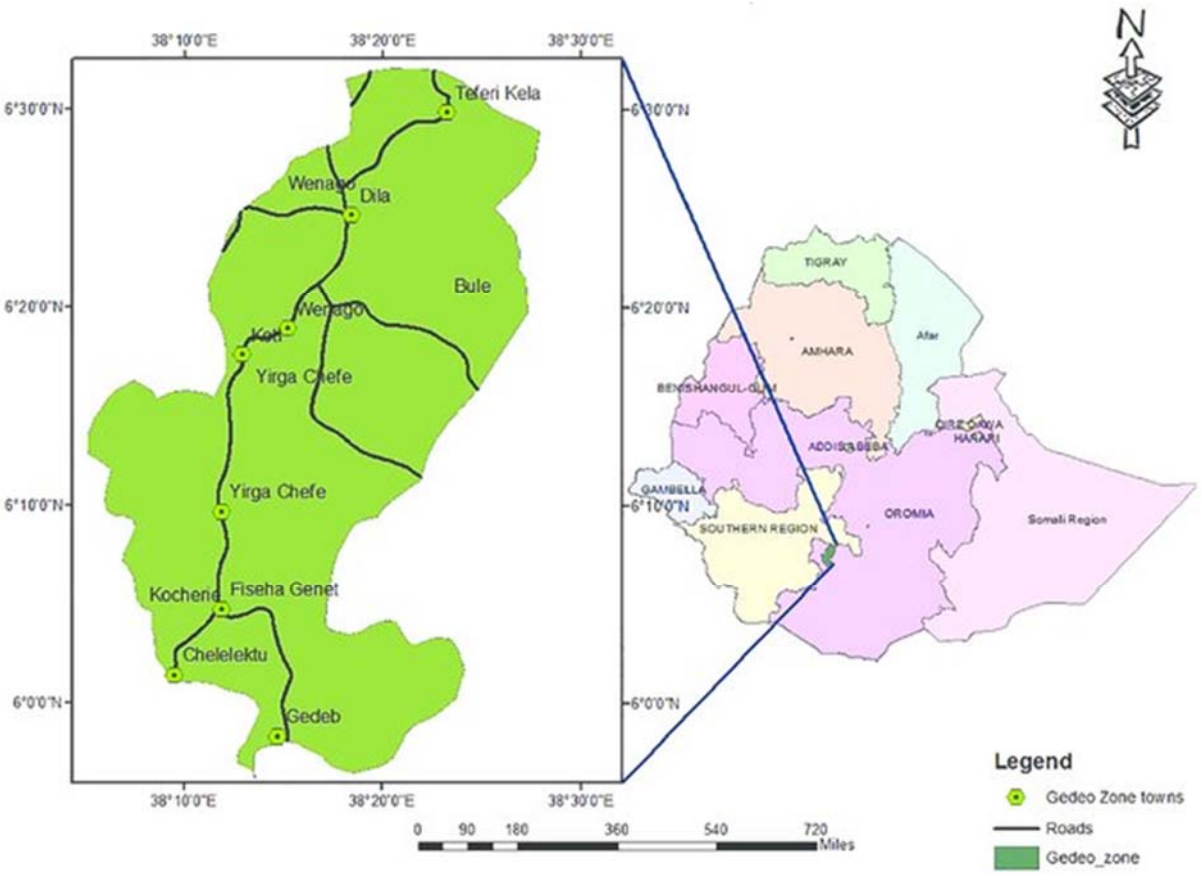
Inclusion Criteria

Participants whose parents/guardians gave written consent, willing to give stool samples, and did not take anti-helminths medication two weeks prior to the commencement of this study were included in the study.

Sampling techniques and sample size

Total of six primary schools were selected , three primary schools from Dilla (Kirinchaf, Dawit, Kofe,) and other three from Dilla zuria woredas (Sisota, Aroresa, and Chichu) by simple random sampling techniques.

Figure 1. Map of Gedeo Zone



To select the study participants, the primary school children were first stratified into six strata according to their educational levels (Grade 1 to 6) in the selected schools. The actual numbers of the study population from each class were selected using a systematic sampling technique by using the class rosters as the sample frame.

The sample size was calculated using the single population proportion formula, $n=Z^2P(1-P)/d2$, by taking a prevalence of 56% (18) (31) from a previous similar study conducted in Southern Ethiopia, 95% confidence interval, 5% margin of error and 10% non-response rate. So, the total sample size of the study participants was 417.

Data collection and processing

The data was collected using a structured questionnaire written in local languages (Gede'offa and Amharic). Data on socio-demographic characteristics and risk factors (Age, Sex, Hand wash after toilet, Toilet Use, Took anti-helminths medications, Eat raw meat, Hand washes before meal, Source of drinking water, Shoe wearing habit) were collected.

All participating children were given a labelled clean and leak-proof container with an applicator stick to collect about 2g stool. The collected sample was emulsified in 10% formalin and transported to Dilla university referral hospital laboratory. Finally, the samples were processed and examined with direct wet mount (WM) and formol-ether concentration (FEC) techniques (19-21).

Data Quality Control

On-site training was given for data collectors. A pre-test was done on 5% (21) of school children before conducting the research to check the quality of questionnaires, reagents, and instruments. Three slides were prepared for each participant and examined by an experienced medical parasitologist to avoid observation bias. Discrepancies were resolved by a senior Microscopist of Dilla university referral hospital.

Data analysis

The data were double entered into Epi Data version 3.1software and exported to SPSS version 20 software for analysis. Descriptive statistics including frequency, percentage, mean, range, and standard deviation (SD) was calculated to describe relevant variables. The Chi-square(X^2) test, bivariate and multivariate logistic regression were also done to determine the association between the associated factors and intestinal helminths.

The crude and adjusted odds ratio (OR) and 95% confidence interval was calculated. P-value less < than 0.05 was considered statistically significant. The data were expressed by text, figures, and tables.

Ethical Consideration

Ethical clearance was obtained from the research and ethical review committee of Dilla University. The objective of the study including procedure followed, benefits, potential risks, and discomforts was explained to the participants, parents, and the school community. Written informed consent was obtained from parents or the legal guardians. Children infected with any of the parasites were referred to a nearby health institution for treatment. All the information obtained from the study participants was coded to keep confidentiality.

RESULTS

Socio-demographic characteristics

The mean age ± SD of the study participants was 10.7±2.64 years. 78% of the study participants were between 10-15 years. 227(55%) participants were males. About 207 (50.1%) of them live in urban areas (Table 1).

Prevalence of intestinal helminths

Among a total of 413 children, 114 (27.6%) were infected with helminths. The most prevalent helminths were *Ascaris lumbricoid* 77 (18.6%) followed by Hookworm 15 (3.6%), *Hymenolopsis nana* 12 (2.9%), *Tricuris tricuria* 9 (2.2%), and Taenia spp 1 (0.2%). Helminths infection was more commonly seen among the age group of 5-9 years, 86 (20.8%). 60(14.6%) of the infected students were males (Table 1). A higher prevalence of helminths infection was observed in students who lived in rural areas, 60 (14.4%) (Table 2).

Associated factors of intestinal helminths infection

About 368 (89.1%) school children washed their hands after toilet use. Participants who wore shoes always and sometimes were 305(73.8%) and 108 (26.2%), respectively. The source of drinking water was 317(76.8%) pipe, 89(21.5%) well and 7(1.7%) river.

Hand washing practice before meal (AOR=3.72; 95% CI: 0.211-3.9; P= 0.002), drinking water from river (AOR=2.9; 95%: CI 0.56-3.51; P=0.000), living in rural area (AOR=1.81; 95% CI: 0.43-2.33; P= 0.008) and poor toilet use habit (AOR=2.16; 95% CI: 0.39-3.36; P= 0.000) were significantly associated with helminths infection (Table 3).

DISCUSSION

We have conducted a cross-sectional study to assess the prevalence of intestinal helminths infection and its associated risk factors among primary school children in South Ethiopia.

The prevalence of intestinal helminths was 114 (27.6%). This finding is higher than those of the studies conducted in Gondar 16.7% (4), North Western Tigray 12.7% (5), Gurage zone 9.5% (22), and Ghana 17.3% (23) and lower than those of studies conducted in Alaba Kulito 55.7% (18), Jimma 53.3% (24). The variation of the result might be due to the level of environmental sanitation, source of drinking water, personal hygiene, and prevention and control measures.

Ascaris lumbricoide was the predominant intestinal helminths (18.6%), this is higher than studies conducted in Gondar 9% (4), Gurage Zone 3% (22) and Birbir town 3.3% (14). The variation might be linked with climatic difference, difference in mass deworming programs, source of drinking water or insufficient latrine facilities (23). The most affected age group was 5-9 with a prevalence of 20 (32.7%) similar to those of studies conducted in Gurage zone (22) and Mizan-Aman town (27).

Factors significantly associated with intestinal helminths infection were improper toilet use, those who used toilets had a protective effect from helminths than those who did not use the toilets (defecate on the open field). This finding is in line with those of other studies conducted in Ethiopia (15), North Western Tigray (15) and Jawi town (28).

Those who didn't wash their hand before meals were more likely to be infected with helminths, as compared with those who wash their hands. This finding is supported by a study conducted in Gurage Zone (22), northern Ethiopia (16). Those who drunk water from the river were more likely to be infected with helminths as compared to those who drunk water from wells and pipes. This is in agreement with other studies conducted in the Democratic Republic of Korea (29) and Argentina (30).

Living in rural areas had an increased chance of acquiring helminths infection than those who live in urban areas. The finding was consistent with a study conducted in Gedeo Zone (31) and Kenya (32). In rural areas, there is a scarcity of pipe water, toilet, low personal and environmental hygiene practice.

The prevalence of intestinal helminths was high in the study area. Poor hand washing practice before the meal, living in rural areas, drinking water from rivers and inappropriate toilet use were factors significantly associated with intestinal helminths. Therefore, Interventions such as avoiding open defecation, construction of latrine, periodic mass deworming programs, and health education on various personal and environmental hygienic practices should be done routinely to prevent and control intestinal helminths.

Tables and Figures

Table 1: Socio-demographic characteristics of primary school children in Gedeo Zone, Southern Ethiopia

Variables	Category	Freq.	Percent (%)
Age	5-9	61	14.8
	10-14	322	78
	>15	30	7.3
Sex	M	227	55
	F	186	45
Residence	Urban	207	50.1
	Rural	206	49.9
Religion	Christian	380	92
	Muslim	33	8

Table 2. Prevalence of intestinal helminths by sex and residence among primary school children in Gedeo Zone, Southern Ethiopia

Intestinal parasite species	Sex n (%)		Residence n (%)	
	Male	Female	Urban	Rural
Ascaris lumbricoides	41(9.9)	36(8.7)	29(7)	41(9.9)
Trichuris trichiura	5(1.2)	4(0.9)	3(0.73)	2(0.48)
Hookworm	6(1.45)	9(2.2)	1(0.24)	12(2.9)
Hymenolepis nana	7(1.7)	5(1.2)	7(1.7)	4(0.9)
Taenia spp	1(0.4)	0	0(0)	1(0.24)
Total	60(14.6)	54(13)	40(9.7)	60(14.4)

Table 3: Risk Factors associated with intestinal helminths infection among primary school children in Gedeo Zone, Southern Ethiopia

Risk factors	Category	No.	COR(95% CI)	P-value	AOR(95% CI)	P-value
Age	5-10	61	0.75 (0.283-1.966)	0.55		
10-15	322	0.998(0.428-2.325)	0.99			
≥15	30	1				
Sex	M	227	1.14(0.739-1.755)	0.56		
	F	186	1			
Eat raw meat	No	229	1			
	Yes	184	0.897(0.582-1.384)	0.624		
Hand wash before meal	Yes	365	1			
	No	48	3.27(0.14-3.98)	0.000	3.72 (0.211-3.9)	0.002
Source of drinking water	Pipe	317	1			
	Well	89	1.79(0.213-15.152)	0.591		
	River	7	1.01(0.04-2.6)	0.000	2.9 (0.56-3.51)	0.000
Wear shoe	Some-times	108	1.077(0.662-1.753)	0.766		
	Always	305	1			
Residence	Urban	217	1			
	Rural	196	1.62(0.391-2.023)	0.050	1.81 (0.43-2.328)	0.008
Hand wash after toilet	Yes	368	1			
	No	45	0.43(0.228-0.808)	0.09	0.79(0.386-1.615)	0.517
Trimmed nail	Trimmed	214	1			
	Not trimmed	199	0.949(0.617-1.462)	0.814		
Toilet use	Yes	31	1			
	No	382	2.01(0.11-3.51)	0.000	2.16 (0.39-3.36)	0.000

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Abbreviations

HW: Hook Worm; TT: *Tricuris Tricuria;* STH: Soil -Transmitted Helminthes; WHO: World Health Organization.

Declaration

Ethical Consideration
Ethical clearance was received from the research and ethical review committee of Dilla University. The objective of the study including procedure followed, benefits, potential risks, and discomforts was explained to the participants, parents, and the school community. Written informed consent was obtained from partners or the legal guardians. Children infected with any of the parasites were referred to a nearby health institution for treatment.
All the information obtained from the study participants were coded to keep confidentiality.

Availability of data and materials
All relevant data are within the manuscript.

Competing interest
The authors declare that they have no competing interests.

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Authors' contributions
FW and YG conceived the study, participated in data collection, data analysis, drafted and finalized the manuscript for publication. Authors read and approved the final manuscript.

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ORIGINAL ARTICLE

ASSESSMENT OF PHYSICIAN ADHERENCE TO GUIDELINE RECOMMENDED MEDICATION IN HEART FAILURE WITH REDUCED EJECTION FRACTION AT OUTPATIENT CARDIAC CLINIC; RETROSPECTIVE CROSS- SECTIONAL STUDY AT TIKUR ANBESSA SPECIALIZED HOSPITAL

Rodas Temesgen[1,] Senbeta Guteta[2] Sintayehu Abebe[2]

ABSTRACT

Background*-Heart failure (HF) is a burden for the healthcare system. There is clear evidence from landmark studies that optimal uses of Angiotensin-converting-enzyme inhibitors (ACEI), Angiotensin receptor blockers (ARBs), Beta-blockers (BB), and Mineralocorticoid receptor antagonists (MRAs) to achieve target dose used in RCTs improves survival and reduce morbidity in patients with HF with reduced ejection fraction (EF).*
The objective of this study is to evaluate physicians' adherence to guideline-recommended medications for treatment of heart failure with reduced ejection fraction (HFrEF)
Method*-Retrospective cross-sectional study was conducted and the medical record of 364 patients with HFrEF treated at TASH from 2012 to 2018 was reviewed. Global class adherence score (GCA) was used to evaluate the use of ACEI, BB, ARB, and MRAs according to the international guideline by physicians. SPSS 20 software was used for data entry and analysis.*
Result*-GCA score among physicians was good in 36%, moderate in 47%, poor in 17% of the study patients. Class adherence for the individual drug was 67% for ACEI, 48.7% for MRA, and 73.6% for Beta-blockers. The proportion of patients at target dose (100%) was 7.6% for ACEI, 0.8% for Beta-blockers, and 1% for MRA. Use of more than 50% target dose was 36.7 % for ACEI, 6.6% for beta-blocker, 49% for MRA. Duration of heart failure > 5 years was associated with a good GCA (P=0.003). Diabetic patients were prescribed higher doses of ACEI, compared to non-diabetics (p=0.001).*
Conclusion *In this study use of all indicated medication as per guideline by physicians was low (36%) and the majority of patients received less than 50% target dose, especially for beta-blocker and ACEIs.*
Keywords*: Global class adherence (GCA), physician guideline adherence, Heart failure with reduced ejection fraction (HFrEF), Target dose,*

INTRODUCTION

Heart failure (HF) is a complex clinical syndrome that results from structural or functional impairment of ventricular filling or ejection of blood. It is a major public health problem affecting more than 20 million people worldwide (1). Heart failure has been classified into three subtypes, namely HF with reduced ejection fraction, HF with preserved ejection fraction, HF with mid-range ejection fraction.(2) ACEIs, ARBs, Beta-blockers & MRAs constitute the cornerstone of pharmacotherapy for HFrEF . These drugs are known to slow and retard the progress of heart failure by addressing the deleterious effect of neurohormonal stimulation.(5) International guidelines recommend the use of these classes of drugs intending to achieve target doses used in the RCTs (2).

There is clear evidence from landmark studies of disease-modulating and survival-promoting benefits of ACEI/ARB, BB, and MRA for HFrEF (6).

Optimal uses of these drugs in patients with HFrEF reduce mortality and morbidity in clinical practice. (5,6). Despite this, data from large observational studies suggest that these drugs are under prescribed in HFrEF patients. (7)

Putting guideline recommendations into practice is not optimally practiced in most of clinical practice, and surveys suggest that the implementation of guidelines remains suboptimal, particularly regarding use of beta-blockers and their dosage (8).

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Global surveys like QUALIFY survey(7) MAHLER survey,(9), HART trial(10) as well as SUGAR survey from Korea(11), USA(12), Indonesia (13), Nigeria (14), South Africa (15) shows moderate to poor adherence of physician to this international guidelines. Several reasons have been associated with the suboptimal implementation of this guideline: patient-related factors, like age, and co-morbidities leading to intolerance or contraindications; physician-related factors, including lack of awareness of treatment goals, reluctance to use newly recommended drugs or multiple therapies, focus on symptom relief rather than reduction of mortality, and fear of adverse effects; non-medical factors, including affordability such as cost of medications and inadequate access to healthcare systems, were attributed to poor adherence to the international guidelines. (7)

What is already known about this subject?

The last decades have witnessed interest in physician adherence to evidence-based guidelines directed at the management of heart failure. This has led to several publications from Europe, the USA (12), Japan (16), Nigeria (14), and South Africa (15). These international studies have shown several differences in the degree of adherence and perceived barrier to adherence. Real-life physician adherence studies are scanty in Africa. A study from Nigeria shows physician-adherence to evidence-based Heart failure drugs was variable (14) and another study from South Africa (15,17) reports comparable adherence from other countries, with a low rate of beta-blockers and MRAs prescription. The Sub- Saharan Africa survey of heart failure also showed most patients were treated with renin-angiotensin-aldosterone system blockers but not with B-blockers at discharge (18).

What does this study add?

Even though, Ethiopia has a comparable cardiovascular disease burden as other developing countries, a study on the practice of this international guideline adherence is limited. The prevalence of HFrEF is increasing with the aging of the population and the rise of multiple comorbidities. Therefore, it is necessary to reassess physicians' adherence to the latest guidelines.

How might this impact clinical practice?

This study assesses the practice of physicians in adhering to evidence-based international guideline recommendations, in prescribing these life-saving medications in a patient with HFrEF. This lays a foundation to further study the perceived barrier in practicing evidence-based HF treatment in our setup and encourages clinicians to work on the gap identified, which benefits patients.

The objective of this study is to evaluate physicians' adherence to guideline-recommended medications for treatment of Heart failure with reduced ejection fraction (HFrEF).

METHODS

Study design

This is a retrospective cross-sectional study; medical records of patients with HFrEF treated at Tikur Anbessa specialized hospital from 2012- 2018 were reviewed.

Study area /setting

Tikur Anbessa specialized Hospital is a tertiary-level, teaching public hospital. It is located in the capital city of Ethiopia, Addis Ababa. It is the largest Hospital in Ethiopia. The hospital serves as a top referral hospital for patients coming from all over the country. The cardiology unit in the department of internal medicine is staffed with cardiologists, cardiology fellows, internists, and internal medicine residents. It is currently serving more than 6000 patients with different cardiac conditions on an outpatient base.

The source population for this study was all patients who are diagnosed to have heart failure with reduced ejection fraction and on follow-up at the outpatient cardiac clinic.

The study populations were patients who were diagnosed to have HFrEF fulfilling the inclusion criteria and included in this study

Inclusion criteria:

- Patients > 18 years old,
- Patient who had at least 4 regular follow-ups at the outpatient cardiac clinic,
- Patients with impaired left ventricular function with an ejection fraction of < 40 % in recent echo done at least within the last 2 years
- Heart Failure (HF) medication prescription ordered by physicians.

Exclusion criteria;

- Unavailable echocardiography results for classifying the type of HF as reduced ejection fraction versus preserved ejection fraction.

Sample size and sampling technique

Sample size determination:

According to previous year's recordings, it is anticipated that over the study period a total of 4500 patients are seen at the cardiac follow-up clinic. A sample size of 383 patients was calculated based on a previous study: Janet *et .al* a retrospective study from Nigeria, on physician adherence to pharmacotherapy guidelines for chronic heart failure, where ACEIs/ARBs were prescribed in 83% of patients, beta-blockers were used in 48% and aldosterone antagonists in 41% of patients. Confidence interval of 95% and degree of freedom of 0.05 was used.

Data collection procedures
Data were collected from the medical records of patients using a checklist. To keep the data quality, data collectors were trained. The investigators supervised the data collection process.

Data Quality control
Data were checked for completeness and consistency before data entry by the principal investigator and entered into EPI info version 3.5.1 and exported into SPSS for data analysis. After data entry, data cleaning was made by running frequencies of each variable to check for accuracy, outliers, and consistencies.

Statistical analysis
The data were analysed using SPSS statics version 20. Continuous parameters were recorded as means ± SD. Descriptive data were given in percentages & table. A Chi-square test was done to see the association between categorical variables. P-values of less than 0.05 and a confidence level of 95% by the two-sided test were considered to indicate statistical significance.

OPERATIONAL DEFINITIONS

Global Guideline Adherence Score
Global class adherence score was defined as a performance measure on basis of the three pharmacologic class, ACEIs/ ARBs, beta-blockers, and MRAs to evaluate physician guideline adherence.
A global guideline adherence score was constructed based on physicians' adherence to guidelines regarding the following three classes of medications; ACEIs/ ARBs, beta-blockers, & MRAs.
The adherence score was the ratio of the treatment prescribed to the treatment that should theoretically have been prescribed. The theoretical treatment score was calculated for every patient, taking into account treatment eligibility criteria and the existence of contraindications to drugs or treatments based on international guidelines on the management of HFrEF.
The score was calculated for each patient by summing the points attributed as follows: one point for non-prescription in the absence of specified indications and one point each for the use of ACEIs or ARBs, beta-blockers, MRAs (if indicated),. Non-administration of recommended drugs because of specific contraindications or intolerance was scored as adherence to guidelines.

The score ranges from 0 (poor) to 1(excellent), and three levels of adherence were defined:

- **GOOD ADHERENCE (**use of all indicated medications in eligible patients; score=1); I.e. Based on the ratio of the treatment prescribed to the treatments that should have been prescribed, E.g.: 3:3=1
- **MODERATE ADHERENCE** (use of more than half of **indicated** medications in eligible patients; score>0.5−<1); and
- **POOR ADHERENCE** (use of ≤50% of indicated **medications** in eligible patients; score ≤0.5).
- **ADHERENCE-** relates solely to physicians following guidelines and not to patient compliance to drugs.
- **TARGET DOSE:** -Recommended maximal tolerable drug dose in HFrEF according to previous landmark trials.
- **ACEIs Target dose**: -lisinopril, enalapril, and fosinopril 20 mg/day, captopril1 50-100 mg/ day and ramipril 10 mg/day
- **ARBs Target dose:** - Valsartan 320 mg/day, losartan100 mg/day and Candesartan 32 mg/ day
- **Beta-blockers Target dose**- Metoprolol 200 mg/day, carvedilol 50 mg/day, carvedilol phosphate extended-release 80 mg/day, bisoprolol 10 mg/day, Atenolol 100 mg
- **MRA Target dose**- Spironolactone 50 mg/ day

STUDY VARIABLES

Dependent variables:
- Physician Guideline Adherence (Global class adherence)

Independent variable
- Residence, Sex, Age, Marital Status, Educational Status, Occupation
- Comorbidity, duration of heart failure, time since the last hospitalization

.Research checklist

We used the STROBE reporting guidelines. Cuschieri, Sarah (2019). The STROBE guideline, Saudi Journal of Anaesthesia. 13. 31. 10.4103/sja.SJA_543_18.

RESULT

Description of the study participants
A total of 364 patient's charts were reviewed. The baseline characteristics of the study participants are described in *Table 1*. The mean age of the patients was 48.7. Majority of the patients were male (60.4 %). For those who had previous hospitalization, the mean time since the last hospitalization was 8.5 months. The majority of patients, 64.6% were in New York Heart Association (NYHA) class II, and 23.6% of patients were NYHA class III in their most recent outpatient visit.

Table 1: Socio-demographic characteristics of heart failure patients with reduced ejection fraction in Tikur Anbessa Hospital, Addis Ababa, Ethiopia 2012-2018 (n=364)'

Variable	Response category	Frequency	Percent
Sex(%)	Male	220	60.4
	Female	144	39
Residency (%)	Urban	222	60.9
	Rural	142	39.1
Mean Age(year)+/- SD	Mean	48.7 year +/- 14.07	
	Medical History		
Smoking status	Current smoker	11	3
	Ex-smoker	84	23.1
	Non-smoker	269	73.9
Duration of Heart failure	Less than 5 years	308	84.6
	Greater than 5 years	56	15.4
Mean time since Hospitalization	Less than 6 month	78	21.4
	6 month to 1 year	126	34.6
	Greater than 6 month	140	38.5
	Never hospitalized	20	5.5
Co-morbidities	Atrial fibrillation	40	11
	Stroke	9	2
	DM	84	23.1
	Dyslipdemia	40	11
	Hypertension	143	39.3
	Asthma	8	2.2
	AKI/CKD	8	2.2
	Other	32	8.8
Average SBP(MMHG)	Mean	122.37	
Resting heart rate (BPM)		81.55 (Average)	
NYHA class	1.Class I	38	10.4
	2.Class II	235	64.6
	3.Class III	86	23.6
	4.Class IV	5	1.4
Left ventricular Ejection fraction	EF= 30-40%	43.3%	
	EF=15-30%	51.7%	
	EF<15%	5%	
Etiology of Heart failure	Ischemic Heart disease	53.6%	
	Cardiomyopathy	35.7%	
	Valvular heart disease	10%	
	Other	1%	

Comorbidities frequently seen include; Hypertension (39.3%) diabetes mellitus (23.1%) atrial fibrillation (11%) CKD (2.2), Asthma/COPD, (2.2%) & stroke (2%). Mean heart rate of the patients was 81.55 .b.p.m. and 89 % of the patients were in sinus rhythm. Among patients in sinus rhythm 87%.had a heart rate ≥70 b.p.m.

ACEIs (Angiotensin-converting enzyme inhibitors)

Among patients who have indication for ACEI, 70.6 % of patients were on ACEI. Among non-prescribed patients, 9.3 % were on ARBs and 20.3 % of patients were not on ACEIs/ARBs when indicated. Enalapril was the most commonly prescribed ACEIs (69.8%). The mean dose of ACEIs (enalapril) prescribed was 8.14 mg. Thirty-six patients had contraindication for ACEIs due to AKI, Hyperkalaemia, and ACEIs induced Cough. Those with ACEIs induced cough (32 patients) were put on ARBs. A total of 33 patients were on ARBs. Among these patients, all of them were in less than 50% target dose. Physician class adherence to ACEIs alone was 67.6%.

BETA-BLOCKER

Among the 97% of patients who had an indication for beta-blockers, 79.4 % of the patients used beta blockers, the most common reasons for not prescribing beta -blockers were intolerance and hypotension. Among patients who were on Beta-blocker, 57 % were on Metoprolol followed by Atenolol (31%). The rest were on carvedilol & bisoprolol.

Among patients on Beta-blocker, the majority (45.05%) were on less than 25% of the target dose and two-third of patients was on less than 50% of the target dose. Only 7 % of patients were prescribed above 50% of the target dose. Eleven patients had contraindication for beta-blocker; all of them were due to hypotension and intolerance.

Among patients for whom metoprolol was prescribed, 37% were on Metoprolol succinate and 14% on Metoprolol Tartrate. The type of metoprolol prescribed for the remaining 49% was not documented. Physician class adherence to Beta-blockers was 73.6%.

MINERALOCORTICOID RECEPTOR ANTAGONISTS

Among the 95% of patients who had an indication for MRAs, 49.18% were on mineralocorticoid receptor antagonists (spironolactone). The mean dose of Spironolactone used was 24.9 mg /dl. Among those who were not on MRAs, 12(3.3%) patients had contraindication (Hyperkalaemia and Acute renal failure) and few patients were on class I heart failure with no strong indication for MRAs.

Among patients on MRAs, 87% were on 50 % target dose. Physician class adherence to MRAs alone was 48.7%.

Table 2: Physician Class Adherence for individual drugs used

Drugs	Physician class adherence		Target dose used			
			<25%	25-50%	50-75%	100%
			N (%)			
ACEI/ARB	N	%				
Yes	290	79.8	27.3	8.2	36.7	7.6
No	74	20.3				
Beta blockers						
Yes	289	79.4	50.9	21.1	6.6	0.8
No	75	20.6				
MRA						
Yes	179	49.3	0	0	48.3	1
No	185	50.7				

ACEI-Angiotensin-converting enzyme inhibitors, ARB- angiotensin II receptor blockers, MRA-mineralocorticoid receptor antagonists.

FACTORS ASSOCIATED WITH PHYSICIAN GUIDELINE ADHERENCE

Longer duration of heart failure was associated with good guideline adherence (P=0.003), whereas longer duration since the last hospitalization for heart failure was not associated with good guideline adherence (P value=0.157). Patients with diabetes were prescribed a higher dose of ACEIs compared to non-diabetics (*P* =0.000). There was no association between having multiple cardiometabolic comorbidities and good guideline adherence (P value=0.422).

According to underlying heart failure, dilated cardiomyopathy followed by ischemic heart disease was associated with better use of all indicated medications (51.5% vs. 35.9 %) (P = 0.001). Guideline adherence was low in those with valvular heart disease (26.2%), (P=0.001)

Most patients received diuretic agents (88.0%) and the majority were on antiplatelet agents (54%), statins (64.4%), digoxin (25.7%), and nitrates (6.8%). Few patients were also on HAART, anti-coagulant, oral hypoglycaemic agents & insulin.

Table 3- Factors associated with physician guideline adherence

Variable	N(%) (Prescribed all indicated medications)		P- Value
Duration since last hospitalization for heart failure	Greater than 6 month	37.8%	0.157
	Less than 6 month	30.8%	
Duration of heart failure	Greater than 5 years	53%	0.003
	1-5 years	33.1%	
	Less than 1 year	33.3%	
Multiple Comorbidity	Yes	36.9%	0.422
	NO	36.3%	
Underlying causes of heart failure	Dilated cardiomyopathy	51.5%	0.001
	Ischemic heart disease	35.9%	
	Valvular heart diseases	21%	

Global Class Adherence

Good adherence, as defined as the use of all 3 indicated drugs, was seen only in 36.2% of the patients. Adherence class was moderate in 46.9 % of patients, use of 2 of the indicated medication. In 16.7 % of the time physicians, guideline adherence was poor (only 1 or none of the indicated medication was used)

Not using a specific medication when it was not indicated/ when there was a contraindication was scored as guideline adherence for the individual drug. Class Adherence for individual drug use despite dosage used was 48.7% for MRA, 73.6% for Beta-blocker, 67.6 for ACEI.

The proportion of patients at target dose (100%) and >50% of target dose was low for most drugs (7.6% and 36.7% for ACEI,) (0.8% and 6.6% for Beta Blocker) and (0.3 % and 49 % for MRA), respectively.

DISCUSSION

This hospital-based cross-sectional study done in Ethiopia included 364 participants' to evaluate physicians' adherence to guideline-recommended medications for the treatment of chronic heart failure (CHF) with reduced ejection fraction adherence to the four classes of medication recommended for HFrEF according to international guidelines like ESC. Overall physician adherence to international guidelines when treating heart failure patients with low EF was low. Physicians used all indicated medications 36% of the time with Good global class adherence, used half of all the indicated medication with moderate GCA 46.8% of the time and global class adherence was poor in 16.76% of the time (only one or none of the indicated medication used).

Compared to guideline adherence study from Nigeria, where good guideline adherence was seen, 51 % of the time, finding from this study showed guideline adherence was low (14). In another multicentre study from Europe, MAHLER study; good GCA was seen in 63% of the physician. Compared to our study where guideline adherence was assessed for residents, internists, cardiology fellows, and Cardiologists, the MAHLER study was done only among cardiologists which probably contributed to the improved guideline adherence. (15)

Class Adherence for individual drug use despite dosage used was 48.7% for MRA, 73.6% for Beta-blocker, 67.6% for ACEI which is comparable to adherence study from Nigeria (14) and South Africa (15). Proportion of patients at target dose and >50% of target dose was low for most drugs (7.6% and 36.7% for ACEI, 0.8% &6.6% for Beta Blocker, and 0.3 % and 49 % for MRA, respectively.

Compared to other studies on international guideline adherence like QUALIFY-HF in which ACEIs were used in 73.2%, Beta-blockers used 84.6% of the time and MRA used - 78.9% of the time, guideline adherence in this study was low for individual drugs(9).

Especially the mean dose of beta-blockers used was very low (34.4 mg/dl for metoprolol). In addition to the use of a low dose of beta-blockers, a significant proportion of the patients were on metoprolol tartrate which has limited data from studies on its benefit on HF patients. The mean dose of ACEIs used in this study (8.2 mg/dl) was relatively lower than what was seen in many adherence studies. The use of MRA was lower but the average dose used was (24.4 mg/dl), which approached 50% of the recommended dose for MRA (Spironolactone). The reason behind the lower target dose use for all individual drugs class may be physician-related, patient-related, or system-related which were not addressed in this study.

Duration of Heart failure greater than five years was associated with a good global class adherence (p-value -0.03), those with a duration of heart failure greater than 5 years were more likely to be prescribed all the indicated medication than those with shorter duration since diagnosis of heart failure. Among those with heart failure diagnosed more than 5 years ago, in 53% of the patient all indicated medication was used. Even though having co-morbidity (DM, HTN) in comparison with those with no comorbidity or co-morbidity with little cardio-metabolic risk was associated with better guideline adherence in the QUALIFY-HF study, this is not seen in this study(P =0.422) (7). Longer duration since the last hospitalization (greater than 6 months) was not associated with a better /good global class adherence.(P-value 0.157). According to underlying causes of heart failure, patients with dilated cardiomyopathy are more likely to be prescribed all the indicated drugs; good global class adherence was seen in 51.7 % of the patients (P-value =0.001) followed by the patient with Coronary artery disease. Patients with valvular heart disease were more likely not to be in all indicated medications with lower guideline adherence. Only 21 % of patient with valvular heart disease was prescribed all indicated medication, P= 0.001
The presence of DM was associated with a higher dose of ACEIs use (15-20 mg Enalapril) with P-value (0.001). Majority of patients with DM were prescribed above 50% target dose of ACEIs. This is due to the indication of ACEIs in DM patients to prevent and delay the progress of diabetic nephropathy in addition to its cardiovascular use.

In this study, physician adherence to the international guideline for treatments of heart failure with reduced ejection fraction was low. In addition, physicians were less likely to use target doses of these indicated drugs. A longer duration of heart failure was associated with better physician guideline adherence but longer duration since the last hospitalization, having multiple comorbidities was not associated with better guideline adherence.

CONCLUSION AND RECOMMENDATION

In this study use of all indicated medications as per international guideline recommendation for HFrEF was low. Only 36% of patients were prescribed all the indicated drugs. The dose used for individual drug class was sub-optimal, and less than 50 % of the target dose. Especially, the beta-blockers dose was very sub-optimal.
This finding emphasizes the importance of physician adherence to international guidelines when treating patients with HFrEF. A HFrEF patient has to be on all indicated medications as per guidelines, and their dosage has to be optimized on their follow-up with the aim of achieving target dose as per recommendation by guidelines.
Further research is recommended to investigate the common factors behind physician failure to adhere to guideline recommendations. Whether patient, physician, or system-related factors are the reason behind low adherence has to be studied. In addition, quality improvement programs aiming at improving the care of heart failure patient both in inpatient and outpatient setup need to be worked on, including improving physician adherence to guideline-recommended medication. In long run, Physician adherence to international guideline when treating HFrEF patients will improve survival and minimize recurrent hospitalization.

LIMITATION

This is a single hospital-based study and the reason for physicians' non-adherence to guidelines was not studied. Because of the nature of the study, most of the information is collected from secondary data, information inconsistency and incompleteness may be there.

GENERALIZABILITY

This study sample is representative of the population. In this study physician adherence to guideline -recommended medication was low. Since Tikur Anbessa specialized hospital is among fewer hospitals equipped with cardiologists & Internists in Ethiopia we can safely speculate physician guideline adherence can even be lower in the hospitals where there are no cardiologists & fewer internists which is the case in the majority of Ethiopian hospitals.

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CONTRIBUTORSHIP

Authors were involved in planning, conducting, and reporting this work. There is no additional contributor to this work.

ETHICAL CLEARANCE

This research was conducted after passing through ethical clearance from Addis Ababa university institutional ethical review board. As the study is conducted by reviewing individual patient documents, data were collected anonymously and kept confidential. No personal identifiers were used on the data collection form. Collected data were only accessed by the investigators. We claim that this research was conducted following the declaration of Helsinki.

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ORIGINAL ARTICLE

OPERATING ROOM EFFICIENCY IN A TERTIARY CENTER IN ETHIOPIA

Abraham Genetu [1], Yonas Ademe[1], Tsegazeab Leake[2], Habtamu Aderaw [3], Abebe Bekele[4,5]

ABSTRACT

Background: *Operating room (OR) efficiency is a measure of how well time and resources are used for their intended purposes in the operating room. Commonly used parameters are cancelation rate, first case start-time, turnover time, and utilization rate. While previous similar study from our hospital showed inefficient OR utilization, the difference in performance among available ORs has not been described.*

Methods: *A cross sectional study was done at Tikur Anbessa Specialized Hospital, 550 bed tertiary teaching hospital, from November 2, 2020, till Jan 22, 2021. Out of total 9 operating rooms, four, i.e., Gastrointestinal, Gynecology, Pediatric Surgery and Endourology operating rooms were studied for efficiency parameters .*

Results: *Out of the 570 patients listed for surgery,404 were operated. The average cancellation rate was 27.3%,the highest being for Gynecology OR (41.5%) and lowest for Pediatric Surgery OR (18.2%). Average start time was 8:43am (SD = ± 25min). Start time was delayed by 43 minutes from the agreed 8:00 am. Only 2.5% of OR days were started within agreed time. Mean turnover time for all ORs was 25.2 minutes, the highest being for Gynecology OR(35min) and lowest for Pediatric Surgery OR(14min). Average OR utilization was 6hrs 30 min, which was 72% of the daily allocated 8hrs time.*

Conclusion: *Our operating rooms have a high cancellation rate and delayed start time. Turn over time and OR utilization were in general acceptable. There were significant differences in efficiency parameters across the four ORs. The OR manager in collaboration with all teams should work on improving start time and cancellation rates, and also identify why some ORs performed better than others while in the same institution.*

Keywords*: Operating Room, Efficiency, Cancellation Rate, Turn over time, OR Utilization, Start time, Surgical Volume*

INTRODUCTION

Operating room (OR) is one of the most resource-intensive service areas in hospitals which can represent up to 40 - 60% of total hospital supply expenditure (1). Having efficient ORs can have implications in reducing surgical waiting lists, improving the hospital's financial status, and overall patient satisfaction (3). An efficient OR is one that starts early, finishes on time, uses minimal time in between the cases, and has a low cancellation rate (2).

Different metrics have been suggested to measure OR efficiency. The commonly used efficiency assessment parameters include cancelation rates, first case start-time, turnover time (the time between two consequent cases), turnover time, prediction bias, post-anesthesia care unit delays, OR utilization time, and excess staffing cost. Improving some of these efficiency metrics is one of the strategic pillars of the Ethiopian Save Lives through Safe Surgery Initiative (4).

So far, there is no validated list of efficiency parameters that can be replicated in different setups. A scoring system utilizing some of these parameters to assess the quality of OR suite functioning from the hospital's perspective was suggested by Macarino (5). It utilizes the above-mentioned parameters with score points given to each. However, the scoring system has not been reproduced and validated by other studies.

Except for the cancellation rate, assessment of other efficiency parameters remains uncharted territory in the literature (6–8). The majority of studies from Ethiopia also focused on cancellation rate only (6,9,10). The first study that used five efficiency parameters was from Tikur Anbessa Specialized Hospital by Negash et al(2). While they studied all the elective operating rooms in the hospital and reported compiled findings, the possible efficiency difference in each operating surgical unit was not described. In the current study, we described the efficiency of four of the nine ORs which can be helpful for future quality improvement programs.

The objectives of this study were to use four efficiency indicators in selected ORs and assess differences in efficiency among them. This study can also be an addition to the growing list of studies focusing on the efficiency of OR, so that eventually a comprehensive list of efficiency assessment tool can be developed.

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METHODS

Study setup:
This study was done at Tikur Anbessa Specialized Hospital, which is a 550-bed tertiary teaching hospital in Addis Ababa, Ethiopia. The hospital has 9 operating rooms for elective surgery. Each room is assigned to a specific surgical unit or department. Data were collected for a period of three months from November 2, 2020, till Jan 22, 2021 (199 OR days), from four of the nine operating rooms; Gynecology, Gastrointestinal Surgery, Pediatric Surgery, and Endourology.

Study design
A cross-sectional descriptive study design was used.

Sampling:
Among the nine ORs, 4 were taken by a draw because of the limited resources available to study all the nine ORs.

Operational Definitions
For this study, we utilized first-case start time, turn over time, OR utilization time and cancellation rate as indicators of efficiency.

- ***Start time*** – is the time first cased entered into OR. The hospital's agreed start time is 8:00 am for patient entry. Delayed start time is defined as first case entry into OR after 8:15am.
- **Turnover time** – is the time it takes from the previous patient out till the next patient comes into OR. We used a turnover time of <25 minutes to show good performance (5) .
- **Operating Room utilization** - the proportion of time within the working hours in which a patient was in the operating room (does not include turnover time). We used 70 - 80% OR time utilization as efficient utilization(11). This was calculated as used OR time during the day divided by the hospital's working hour (8hrs).
- **Cancelation rate** – is the proportion of cases canceled from those scheduled to be operated on each day. We used a rate of <2 - 5% to consider efficient OR utilization. Cancellation data were collected daily by OR coordinators.

Data collection, quality and analysis
Data collection format was developed by authors and pretested. Data collection was made by assigned nurses and monitored by the operating rooms coordinator. Authors had performed weekly random cross checking for correctness and reliability. First case entry, first case incision time, first case out of OR time, next case(s) entry time and out of OR time, last case out of OR time and cancellations of the day were collected for each OR. Data were entered and analyzed using SPSS version 22. Descriptive statistics was applied to show the results of different efficiency parameters.

Ethical considerations
Ethical approval was obtained from the department of surgery research committee.

RESULTS

3.1 Overall OR Performance and Cancellation Rate
Data were collected from Nov 2, 2020 till Jan 29, 2021. There were a total of 89 days, out of which 24 were weekends and 3 were public holidays leaving 62 working days. This equates to 248 OR days for the four ORs studied. Among these, 199 OR days (80.2%) had patients scheduled, and at least one patient operated on, while 49 OR days (19.8%) were missed. 14 OR days were missed by Gynecology OR because no patient was scheduled. Twenty one and eight OR days were missed by Gynecology and GI teams, respectively because all patients were cancelled, and no other patient was replaced for surgery on the day of surgery. Maximum number of cases operated per day was four. {table 3.1}
During the study period, out of the 570 patients listed for surgery, 404 were operated on 199 OR days making the overall cancellation rate 27.3%. Cancellation rate was the highest with Gynecology OR at 41.5% and lowest with Pediatric surgery OR at 18.2%. (figure 3.1)

Table 3.1. Operating room performance during the study period among four operating units

	Gastrointestinal OR	Gynecology OR	Pediatric Surgery OR	Endourology OR
Average number of cases per day	1.4	1.2	2.8	2.3
Number of Operated cases	73	35	152	144
Cancelled cases	34	29	29	45
Cancellation percentage	38.1	41.5	18.2	23.8

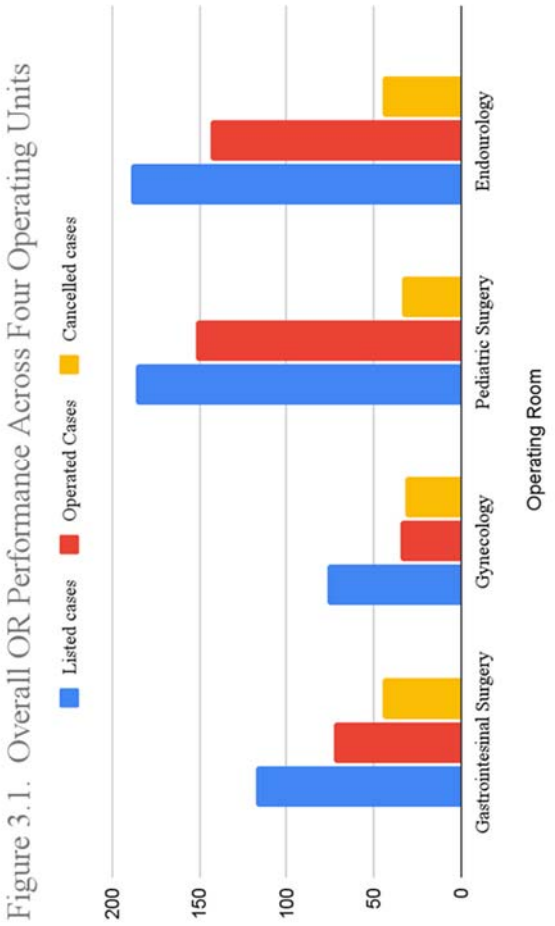

Figure 3.1. Overall OR Performance Across Four Operating Units

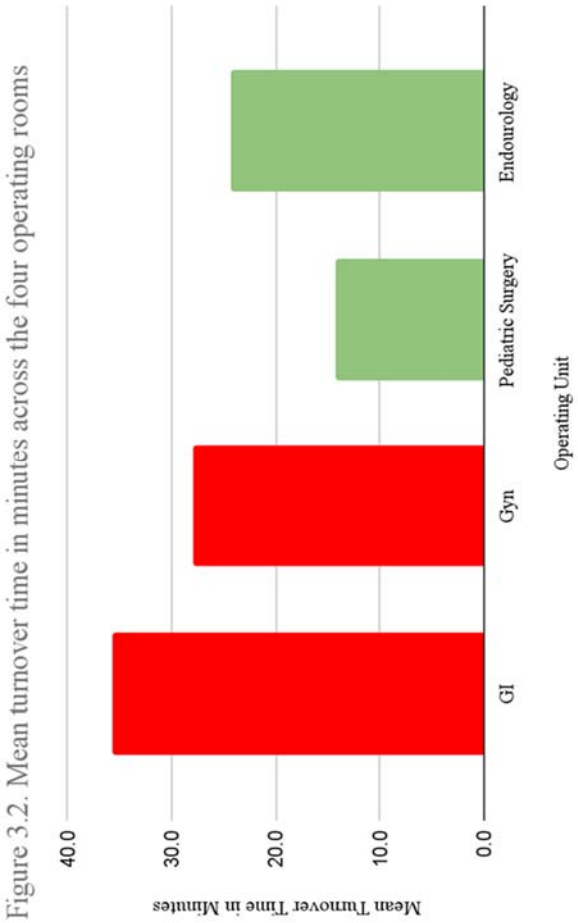

Figure 3.2. Mean turnover time in minutes across the four operating rooms

3.2. Start time

In this study, the average time across the four operating rooms patients entered theatres was 8:43am (*SD* = ± 25min). Start time, as defined by first case entry into OR, is delayed on average by about 43 minutes from agreed 8:00 am. Segregated by operating theatre, the start time for the four operating units (GI Surgery, Gynecologic surgery, Pediatric Surgery and Endourology) were 8:51am, 9:13, 8:37, and 8:36 am, respectively. Start time was within 15 minutes of agreed time in only 2.5% of OR days, and the difference between start times was statistically significant (ANOVA p = 0.001).

3.3. Turn over time

From the 199 OR days, 131(65.8%) had more than one case, and hence turn over time was calculated. Mean turnover times for Gastrointestinal, Gynecology, Pediatric surgery and Endourology units were 35min, 28min, 14 min and 24 minutes, respectively. Total mean turnover time for all ORs was 25.2 ± 31 minutes. An ANOVA test showed a significant difference between ORs (p-value of 0.048). {*Figure 3.2.*}

3.4. OR Utilization

Mean OR utilization time for Gastrointestinal, Gynecology, Pediatric surgery, and Endourology units was 6hrs 31min ±91min, 6hrs 46min ±109min, 7hrs ±14min and 5hrs 48min ±46min respectively. Average OR utilization was 6hrs 30 min ±83min, which is 72% of the daily allocated 8hrs time. Lowest utilization rate was 15.6% by Gynecology OR and the highest utilization rate was 133.2% by Pediatric Surgery OR.

DISCUSSIONS

Cancellation causes anxiety, stress, and disruption of life for patients and families in addition to the obvious impact on the overall efficiency of the ORs and wastage of resources(7,12). In our study the cancellation rate was 27.3%, which was lower than findings from previous studies (33.9%, 35.8%)(2,10). This could be explained by the fact that we excluded OR days on which all patients were canceled.

The striking finding in our study was that the cancellation rate varied from 18.2% to 41.5% in between different OR tables in the same institution. While the hospital should work on reducing the cancellation rate to the recommended level (2 - 5%), it is worth noting that any improvement projects should consider the variable efficiency of the different OR tables and address the reason for the issue (5,13,14).

Different institutions define start time differently. Some use the time first case when given anesthesia medications, and others first case incision time, but the most widely accepted definition of start time is the time of first case entry into OR(15). Starting on time reduces wastage of scheduled theatre time, associated overtime costs, unplanned cancellations and increases the capacity to have more elective surgery (13)**.** There are two ways of assessing start time tardiness, one is calculating average start time and comparing the time of delay from the agreed start time for the OR assessed, and the second is to calculate the percentage of OR days when start time was delayed from agreed start time. Macario suggested a definition of late start time when OR starts at least 45 minutes, others allow only up to 15 minutes of grace time(5,13). In our study, only 2.5% of OR days started within 15 minutes of the agreed start time, which is comparable to a previous study (6.6%)(2). Meantime of start time was also 8:43 am, which is 28 minutes late beyond the grace period. Assessing the reasons for delay could be important to improve start time.

While up to 25 min of turnover time is recommended for cleaning of the OR and preparation for the next patient, prolonged turnover time can be a significant source of delay and overall theatre inefficiency (16). The average turnover time of our ORs was found to be 25.2 minutes which is similar to that of the previous study from the same institution(2). This is an acceptable finding, but there is still a statistically significant difference between different OR tables turnover time that requires further study to identify the reasons.

Start time and turn over time show how early the OR was started to be used, and how quickly subsequent patients were wheeled into OR, respectively, however, they fail to describe for how long during the day the OR was in service. For this reason, the addition of OR utilization as another parameter can help fill this information gap. Acceptable OR utilization by most institutions is 75 – 80% and American Hospital Association has set a value of 75%(13,15). Overall OR utilization in our study was 72% but ranges from 15.6% to 133.2%. A previous study from the same hospital also reported a wide range from 10.5%—174% (2).

Even though the average OR utilization of 72% is acceptable according to international recommendations that suggest 70 - 80 % utilization as efficient, our findings show that there were underutilization and overutilization whose average could deceive as a good utilization rate (3,5). Both underutilization and overutilization should be discouraged. OR utilization should also be interpreted along with other parameters to have a better picture. For example, a delayed start time with good OR utilization could mean that staff are working after the normal working hours to finish the already started or scheduled cases. For this reason, the addition of another parameter, the ‘last case out of OR time’, could help differentiate whether the OR utilization is within or beyond the normal working hours.

CONCLUSION

Our operating rooms have a high cancellation rate and delayed start time. Turn over time and OR utilization were acceptable. There were significant differences in efficiency parameters across the four ORs. The OR manager in collaboration with all teams should work on improving start time and cancellation rates, and also identify why some ORs in same institution performed better than others. While OR is a complex environment to assess its efficiency completely, continuous monitoring using at least few of the available parameters could have a positive impact on overall performance. Future studies should also focus on development of easily reproducible and scorable OR efficiency assessment tools.

LIMITATION

The data analysis included only if at least one patient was operated at the selected OR during the day. However, during data collection we noticed that there were days when no patient was listed or when no patient was operated on because all listed patients were cancelled. Excluding these data may undermine the actual efficiency metrics like cancellation rate. Above all, literature in evaluating OR efficiency is not robust. Utilized efficiency metrics are not yet validated.

CONFLICTS OF INTEREST

Authors declare no conflict of interest.

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ORIGINAL ARTICLE

FACILITATORS AND BARRIERS OF MATERNAL HEALTH SERVICE DELIVERY PERFORMANCE IN NORTH-WEST ETHIOPIA: EXPERIENCES OF CAPACITY-BUILDING PROGRAM PARTICIPANTS

Yeshambel Agumas Ambelie[1], Getu Degu Alene[2] and Damen Hailemariam Gebrekiros[3]

ABSTRACT

Background: *Achieving incredible performance is a function of the way in which the health system organizes the six key building blocks. Particularly, strengthening leadership and governance supports understanding the proximate facilitators and barriers of maternal health delivery performance. This study aimed at exploring facilitators and barriers of maternal health performance with special reference on institutional delivery performance in North-West Ethiopia.*

Methods: *Phenomenological study was conducted from October to November 2018 at health centers located in North-West Ethiopia. Data were collected, until information saturation, from eleven purposively selected key-informant interviews. Using open code software, data were analyzed thematically. Data were transcribed, coded, categorized and thematized.*

Results: *Strong management system, enhanced work environment, ambulance, integrated maternal waiting home, and quality maternal service emerged as core dimensions for improved institutional delivery performance. Strong management system was characterized by the involvement of key stakeholders, strong ambulatory health team, functional health development army, and regular pregnant women's conference. Enhanced work environment was explained by staff morale and ethics, improved staff motivation and commitment and strong health center -health post linkage. The ambulance service was described in terms of ownership, and whether the ambulance was used to transport women home after giving birth. Integrated maternal waiting home was linked to basic services (food, water, and bathroom), cultural ceremonies. Quality maternal service was defined with staff empathy, improved pregnant women counseling, enhanced communication, strong referral linkage, and enhanced customer satisfaction.*

Conclusions: *Strong management system, enhanced work environment, ambulance, integrated maternal waiting home, and quality service facilitate the institutional delivery performance. Applied research could be conducted to test the practicability of these facilitators.*

Keywords: *Facilitators and barriers, Institutional delivery, Experiences, Capacity-building, Ethiopia*

INTRODUCTION

Achieving incredible performance is a function of the way in which the health system organizes the key building blocks: service delivery, health workforce, medical products, health information systems, healthcare financing, and leadership and governance (1). Particularly, strengthening leadership and governance supports understanding the proximate facilitators and barriers of the health system performance including institutional delivery. Ethiopia has put improved institutional delivery performance as one of the key performance indicators in reducing maternal mortality rate from 353 to less than 70 per 100,000 live births by 2030 (2).

To maximize the benefits of leadership and governance in improving and sustaining health system results, the Management Sciences for Health (MSH), a non-governmental organization, developed a leadership development program that currently centers integrated leading, managing and governing for results model (3). This model comprises three logically related elements: people and teams empowered to lead and manage and govern the health delivery system, improved health system performance, and better outcomes and impacts aligned with the national and international health goals. In turn, three dimensions such as enhanced work environment, strong management system, and responsiveness characterize improved health system performance. The improvement of these dimensions thereby increases service access, expands service availability, brings better quality and ensures lower cost.

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Regarding this, enhanced knowledge, increased demand and access, adequate finance and supply and transportation were reported as important characteristics of improved health system performance (4-8). Focus on community health needs, teamwork, financial limpidity, amplified use of research evidence, and monitoring and evaluation were also identified as characteristics of improved health system performance (9-12). In turn, improved health system performance contributes for health service results improvement (4, 13, 14).

Therefore, constructing facilitators and barriers of maternal health performance with special reference to institutional delivery performance is important (15, 16). This could highlight the scientific and empirical underpinning of facilitators and barriers affecting such performance in a specific society.

METHODS

Study design and participants

A phenomenological study was conducted from October to November 2018 in Northwest Ethiopia. Eleven key-informants were selected from seven health facilities purposively. These key-informants were among the intervention group who took integrated leadership, management and governance capacity building. This capacity building was implemented to examine its effect on institutional delivery performance among health facility teams. To grant informative data: age, sex, qualification, profession, service year and responsibility of the participants were taken into consideration in the sampling process.

Data collection

Data were collected using unstructured key-informant interview guide, which was developed by an expert panel. Five area experts participated. Audiotape records were used to collect the data. The principal investigator conducted all the interviews. A strong attention was given to initial contact with participants, sequencing of questions, probing of information, control of conversations, and creating an atmosphere in which participants can willingly explain their views and opinions.

The interview continued until saturation of information was obtained. Probing was used to explore adequate data on the field. Average interviewing time was 50 minutes per participant. A unique code was given to each participant. Each key-informant was interviewed in her/his own facility. The focus areas of the interview were indicated in **Table 1**.

Table 1: Topic guide for exploring participants' experiences, North-West Ethiopia, 2018

Questions	Prompts
How important is the leadership development program in improving institutional delivery performance?	Would you elaborate?
How was your facility's institutional delivery performance in the last six months?	Improved/not improved
What factors affect institutional delivery performance?	Would you list?
Is /are there any indigenous knowledge that support to improve institutional delivery performance?	Would you express?

Trustworthiness

The credibility of data was enhanced through three fold of data triangulation techniques. The first technique was translating the data collection guide to the local language, Amharic. The second technique was linking with diversified data sources using age, sex, qualification, profession, service year and responsibility as diversification parameters. The last technique was linking to physical back-checks of participants prior to interview dates.

Data analysis

In analyzing the data using open code software, five critical principles were considered. These included recognize and account for own perspective, understand the context in identifying the views, know that theory guides approach to analyze, comprehend that attention to deviant cases yield new insights, and be thoughtful that data analysis is iterative or nonlinearly process.

Bearing these principles in mind, data were analyzed using the thematic analysis technique that allowed for a variety of ontological and epistemological viewpoints. It was done by distilling the information into meaningful themes.

Overall, five interrelated stages were followed in analyzing the data:

a) The interview records were transcribed verbatim. The transcriptions were read and re-read to familiarize the data, which led to data immersion. This enables to examine patterns such as relationships or contradictory responses. At this level, the transcribed data were translated to English.

b) The data were coded into exhaustive, mutually exclusive and clearly specified categories to identify the emerging themes. The MSH integrated leading, managing and governing for results framework elements were used as a priori codes, and then elaborated new codes underneath these.

c) Data of a topic was displayed by reviewing the coded data, to examine each important theme in developing a hypothesis and extract meaning.

d) Data reduction, getting the big picture by looking for patterns across themes, was done to filter the most essential concepts and relationships.

e) Data interpretation was done by searching core meanings of the participants' thoughts, feelings and behaviors described but with wider social and theoretical relevance. The overall interpretation was made by identifying how themes related to each other, explained how study questions were answered, and what the findings mean beyond the context of the study.

In addition, the most important quotations were presented to illustrate the main ideas. Moreover, dependability, confirmability and transferability of attributed meanings and lessons were evaluated. Dependability was assessed by the replicability of the meanings by multiple analysts. Confirmability of the meanings were ensured through audit trial, i.e., permit external review of analysis decision. Transferability of the lessons from one context to another was explained by proposing a model (put in the results section).

Ethical consideration

Ethical approval was secured from the institutional review board of Bahir Dar University with a protocol record 090/18-04. Additionally, permission letter was obtained from Amhara Public Health Institute with a protocol record number 1/780. Moreover, written consent was obtained from each participant. Furthermore, data were stored with a locked cabinet.

RESULTS

Basic characteristics of the study participants

The total participants were eleven. Their age ranges from 25 to 30 years. Sixty five percent of them were male. Their average service year was 5.6 years, which ranged from 3 to 10 years. Nine of them had BSc degree (**Table 2**).

Table 2: Basic characteristics of the participants, North-West Ethiopia, 2018 (n=11)

Code	Age (years)	Sex	Qualification	Profession	Service year	Responsibility
A	26	M	BSc	Health officer	3	Head of the facility
B	28	M	BSc	Health officer	8	Head of the facility
C	30	F	BSc	Midwife	7	Maternal service owner
D	29	M	BSc	Nurse	7	Health extension program coordinator
E	26	F	BSc	Midwife	3	Maternal service owner
F	30	M	BSc	Health officer	10	Head of the facility
G	30	F	BSc	Nurse	9	Health extension program coordinator
H	25	M	Diploma	Nurse	3	Health extension program coordinator
I	27	M	Diploma	Midwife	3	Maternal service owner
J	29	M	BSc	Health officer	4	Head of the facility
K	30	F	BSc	Midwife	5	Maternal service owner

Facilitators and barriers of institutional delivery performance

Strong management system, Enhanced work environment, Ambulance, Integrated maternal waiting home, and Quality maternal service were emerged as facilitators and barriers of institutional delivery performance **(Table 3).**

Table 3: Facilitators and barriers of institutional delivery performance, North-West Ethiopia, 2018

Dimensions	Dimensions description	Participants involved
Strong management system	Involvement of key stakeholders	A,B,C,E,H,I,J,K
	Strong ambulatory health team	A,B
	Functional health development army	A,C,D,F,G,H
	Regular pregnant women's conference	A,B,D,G,H,I
Enhanced work environment	Improved staff morale and ethics	A,B,E,G,I
	Improved staff motivation	A,B,E,I,J
	Improved staff commitment	A,B,C,D,E,F,G,I,J,K
	Strong health center-health post linkage	B,C,E,G,I,J
	Empowered staff that enjoy personal life	E,G,J
Ambulance	Facility ownership	A,B,C,D,E,G,H,I,K
	Back the delivery mother to home	A,B,D,F,I,J
Integrated maternal waiting home	Basic services (food, water, bathrooms)	A, B,E,F,G,H,J,K
	Porridge ceremony	A,B,C,D,F,G,H
	Coffee ceremony	A,B,C,D,E,F,G,H,I,K
Quality maternal service	Compassionate, respecting and caring staff	B,C,F
	Improved pregnant women counseling	A,B,C,D,H,I,J
	Improved communication	B,H,I,J
	Strong referral linkage	A,B,C,D,H,K
	Enhanced customer satisfaction	A,B,E,G,K

Note: *Key stakeholders refer to husband, in-law, father confessor, traditional birth attendants and organizations working on maternal health.*

Strong management system

Majority of the participants (n=8) stated that involving key stakeholders such as husband, in-law, father confessor and traditional birth attendants influenced institutional delivery performance (**Table 3**). Particularly, they explained that involving the father confessors and traditional birth attendants who were highly listened by the community exceedingly strengthened the performance. These people, when they believed in the issues, had the power to excommunicate traditional beliefs towards institutional delivery, and to support nurturing institutional delivery.

> *"[…]. While we started working closely with the father confessors and traditional birth attendants, many pregnant mothers give birth in our facility."* B, 28-years old male health officer.

Besides, identifying and functioning closely with organizations working on maternal health improved institutional delivery performance. In collaboration with such organizations, the health facilities prepared a community-based data for decision-making map that shows the relationship between the father confessor, traditional birth attendant, developmental army leader, and the pregnant women. They also prepared a Gospel check with the key message that is thank you for giving birth in your facility.

Indirectly, the health centers and the health posts communicated through this Gospel check that comprised Name of the health center, Name of the mother, Kebele, Got, Name of the developmental army leader, House number, Delivery date, Newborn's weight, any complex problem, Health services offered, and Date in that the Gospel check was given.

"Working with the Pathfinder, […] we prepared a Gospel check with the key message that is thank you for giving birth in your facility." A, 26-years old male health officer.

The other element that influenced institutional delivery performance within the strong management system was the ambulatory health team. This had three-fold responsibilities. First, it empowered the leaders of the health development army to advocate for the institutional delivery service. The health developmental army supported to function responsibilities in an integrated way and to benchmark lessons is an important indigenous platform.

Thus, by strengthening 1 to 5 networks, the women can be saved from death while giving birth. Second, it supported these people to explore the home-based challenges of the pregnant women that made them not to give birth at the facility. Last, it brought a change of idea or breakthrough initiative with key stakeholders to overcome the challenges.

"… The ambulatory health team is responsible to design indigenous change ideas. It does so with a field checklist that contains elements such as number of developmental army leaders educated, number of households visited, number of pregnant women and key stakeholders contacted, problem they raised, the problem-based cases developed and shared breakthrough initiatives set." G, 30-years old female nurse.

Regular pregnant women's conference was also reported as an influencing element of institutional delivery performance. People involved, skills of the facilitators, contents, methodology, and timing, influenced conference outcomes. From the participants point of view, unlike the previous pregnant women's conferences that involved only pregnant women, the current pregnant women's conferences included the husbands, in-laws, father confessors, traditional birth attendants, leaders of the development army, and members of organizations working on maternal health. In fact, this brought a remarkable improvement on institutional delivery.

"[…]. The presentation of the stage drama entitled, Tutelage my mother from suffering and death to the conference participants supports to improve the institutional delivery performance." K, 30-years old female midwife

Enhanced work environment

As indicated in Table 3, five participants reported that the presence of morally and ethically sound staff was among the characteristics of an enhanced work environment. Such a staff was empowered to face actual pregnant women's challenges regarding institutional delivery and achieve better results. The complexity of the challenges encouraged the staff to strengthen the existed health system that is the health center-health post linkage overseeing the developmental army. Oftentimes, committed staff is ready to sacrifice something in creating a conducive environment for mothers to give birth at the facility. Such staff always has exemplary deeds to scale up in improving institutional delivery.

"Morally speaking, our deeds towards institutional delivery before participating in the leadership development program were empty promises. But, when we committed to strengthening the health center-health post linkage that oversees the developmental army; we get the institutional delivery performance improved." I, a 27-year male midwife

Ambulance

All the study participants pointed out that the ambulance service influenced the institutional delivery performance in a greater way (**Table 3**). They characterized it by both the facility's ownership of the ambulance and the transport service it gave in taking the mothers back to their homes after giving birth.

However, most of the participants expressed that the ownership of the ambulance was to the district health office. They also noted that the ambulance only brought the pregnant mother to the health facility. This remained a challenge to the families to back the mothers and newborns to home. Concerning this, some facilities improved institutional delivery performance by taking mothers back home after delivery, using the ambulance.

"You know! Pregnant women are more than bridegrooms are. In our locality, the groom used special mule, horse, or car to bring the brides from the nuptial house and use some better thing to back, perhaps, with special gifts to the family. Here, the bride might give … virginity, but the pregnant women provide baby or life that ensures the continuity of the human race." E, 26-year female midwife.

Integrated maternal waiting home

Integrated maternal waiting home is a temporary residence built near a health facility where women stayed in their final weeks of pregnancy to bridge the geographical gap with obstetric care. It is an equity-based strategy and low-cost solution to increase institutional delivery. It is characterized by the availability of basic services such as food, water, rest and bathrooms; porridge and coffee ceremonies; counseling and health education; recreation platforms like television (**Table 3**).

This modality was important because of three main reasons, i.e., the far-apartness between the households and the health facility; the absence of vehicle roads in most of the villages; the tradition that the pregnant women functioned routine tasks fighting with labor pain. The integrated waiting home, launched with the full participation of the community, encouraged the women to come early to the health facility. Additionally, to improve the community's ownership, the supplies of the waiting home-like food, coffee, and porridge cereals were mobilized from them.

"…Six months ago, only 1-2 pregnant women a month stayed at the waiting home, but now it is 1-2 women a day." K, 30-year female midwife

Quality of maternal service

Quality maternal service emerged as the last core dimensions that explain the institutional delivery performance (**Table 3**). Empathy (compassion, respect and caring) was expressed among elements that affected quality maternal service. The formal service to the pregnant women started at a time she got the ambulance team that was responsible to bring the pregnant women to the health facility. Serving the pregnant women with compassion, respect and care from this point satisfied both the woman and whole family, alongside applying science and technology in facilitating the labor.

"…. You can imagine *that they will talk about it for years."* C, 30-year female midwife

While the pregnant women arrived at the health facility, the staff counseled and communicated both the pregnant women and family members with great empathy to reduce their disturbance. This created trust and family hood between the staff and pregnant women including the whole family.

"… Though pregnancy is not a disease, it is among the potential killing health-*related issues … thus caring the women closely, and counseling and communicating their family is important".* A, 26-year male health officer

The other element that influenced the institutional delivery performance within quality maternal service was the strong referral linkage between the health post and health center that oversaw the developmental army. This army was structured in 1 to 5 and 1 to 30 networks. The 1 to 5 network had a daily meeting, and the 1 to 30 network had a weekly meeting. After the meeting, each of the 1 to 5 networks reported the pregnant mothers who were at term to the 1 to 30 network leaders. By aggregating the reports, the 1 to 30 network leaders reported to the health extension workers. In turn, the health extension workers communicated the mothers and the family to be ready for institutional delivery. These workers stressed on referral to the health center for integrated maternal waiting home services. This improved quality service and thereby contributed to improving institutional delivery performance.

"…We have established an uninterrupted reporting system between the 1 to 5 and 1 to 30 networks, the health posts and the *health center. It avoids unnecessary delay among pregnant women, which consequently enable us to provide quality institutional delivery service that satisfied both the pregnant women and families."* D, 29-year male nurse.

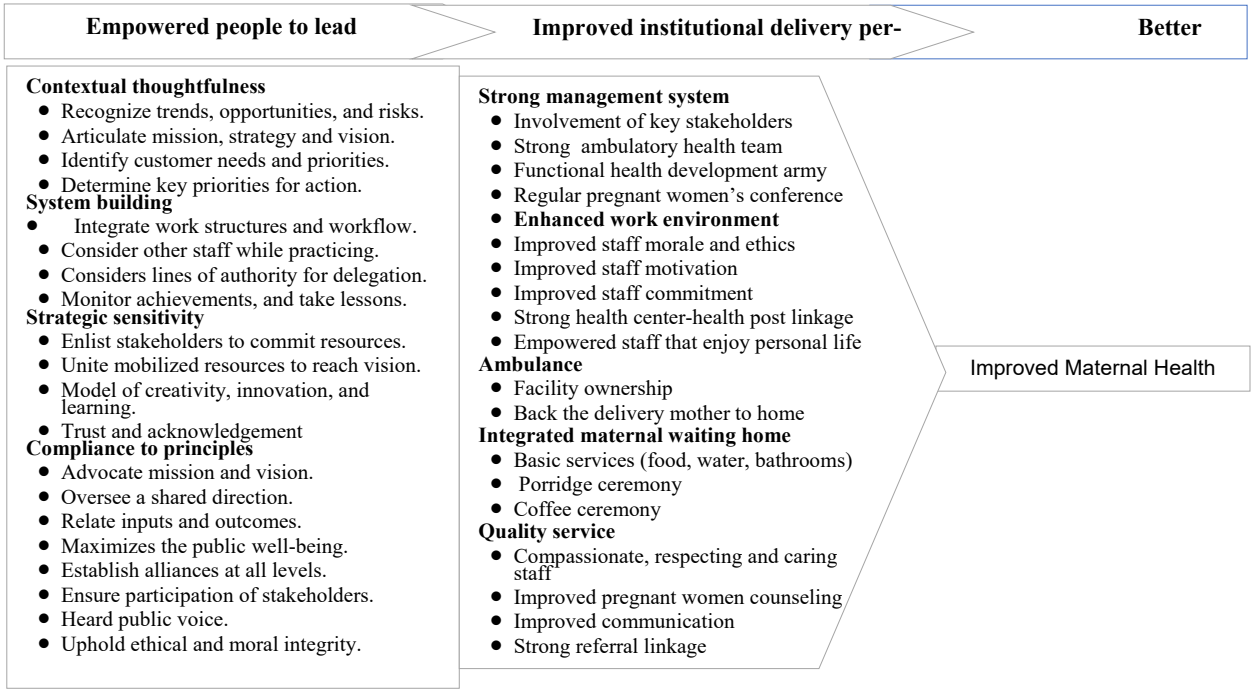

Figure 1. Leadership for better health outcomes framework, Northwest Ethiopia, 2018

Figure 1 displays the facilitators and barriers of maternal health service delivery performance. The elements clustered within empowered people to lead the health delivery system in the figure were the latent factors extracted elsewhere (17).

DISCUSSION

This study provides five core dimensions that facilitate institutional delivery performance to improve the maternal health outcomes. These were strong management system, enhanced work environment, ambulance, integrated maternal waiting home, and quality maternal service.

A *strong management system* is related to the involvement of key stakeholders, strong ambulatory health team, functional health development army, and regular pregnant women's conference. The ambulatory health team is responsible to design and benchmark indigenous change of ideas, educate leaders of the developmental army, visit households to contact pregnant women and key stakeholders, identify local problems related to institutional delivery service, and develop problem-based cases to present in the pregnant women's conference and set a shared breakthrough initiative.

Empowering the health developmental army simplifies the task of the ambulatory health team in executing responsibilities to the household level. These findings are consistent with results of other studies that reported increased community awareness, development army, cultural tradition and rituals and knowledge regarding pregnancy danger signs as predictors of institutional delivery (18, 19). The similarity of the settings for the studies might be a potential reason for such dependability.

Enhanced work environment is characterized by sound staff morale and ethics, improved staff motivation and commitment, strong health center-health post linkage and employee empowerment to enjoy personal life. Other studies indicated that enhanced work environment mediated between transformational leadership and employee creativity and performance (20-22). Enhanced work environment is also reported as an enabler of creating conditions for effective and efficient work, boosting morale, and reducing turnover and attrition (23). This shows that how creating enhanced work environment is important across different settings.

Ambulance service has a remarkable association with improved institutional delivery performance. Particularly, some facilities improved institutional delivery performance by taking mothers back home after delivery, using the ambulance. These finding is supported by other studies that reported freely available transport predicted utilization of institutional delivery (24-26). This illustrates that lack of transportation infrastructure is a common barrier for improved institutional delivery.

Integrated maternal waiting home has also notable consequence to improve institutional delivery performance. Its consequence is more visible, particularly, in areas that pregnant women travel long distance fighting with hilly street and river overflow to give birth at a health facility. Thus, establishing the integrated waiting home can also highly influence the pregnant mothers to love giving birth at the health facility, though no other study has reported it to the best of our knowledge.

The last core dimension *is quality maternal service.* It is described by the presence of compassionate, respectful and caring staff; improved pregnant women counseling; improved communication; strong referral linkage and enhanced customer satisfaction. These findings are supported by previous studies that reported lack of quality care, abominable behavior of staff, and frequent referrals to higher centers as reasons for underutilization of public health facilities for delivery services (21, 27). The importance of quality service to address client expectations and achieve the highest possible service outcomes with the resources available is also reported by other studies (28, 29). This manner of service delivery might encourage pregnant women to win all the challenges they faced and give birth at the facility. Additionally, both the women and the families might promote the service for their lifetime.

Generally, the current factors affecting institutional delivery performance, which are assembled in the leadership for better maternal health outcomes framework could be transferable across time and similar settings.

Away from all the implications, the social desirability bias is the major limitation that twists the current findings.

CONCLUSION

Strong management system, enhanced work environment, ambulance, integrated maternal waiting home, and quality service facilitate the institutional delivery performance. Applied research could be conducted to test the practicability of these facilitators and barriers.

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CONFLICT OF INTERESTS

All the authors declare that they have no both financial and non-financial competing interests.

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ORIGION ARTICLE

HOSPITALS PREPAREDNESS FOR COVID-19 PANDEMIC RESPONSE IN SOUTH-EAST ETHIOPIA

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ABSTRACT

Background: Healthcare facilities play a critical role within the health system in providing essential medical care to the community, particularly in a crisis or pandemic. Evidence regarding hospital preparedness during Corona Virus (COVID-19) pandemic is scarce in Ethiopia. Therefore, this study aimed to assess the level of hospital preparedness for the COVID-19 Response in Southeast Ethiopia.

Methods: A facility-based cross-section study was conducted in the health facilities of Bale, East Bale, and West Arsi zone from June 15-30, 2020. A total of ten hospitals were included in this study. Data were collected using a structured questionnaire. EpiData version 3.1 was used for data entry and SPSS version 20 was used for analysis. The results were described using tables and texts.

Results: None of the included hospitals started the COVID-19 testing service during the study period. Six hospitals have intensive care (ICU) units for adults, however, the maximum bed capacity per hospital was five. Only four hospitals incorporated COVID-19 disaster planning into their planning. Most (90%) of the hospital established multidisciplinary teams to address COVID-19. Nine hospitals prepared information materials on COVID-19 to communicate to patients and their families.

Conclusion: Hospital preparedness for the management and response to the COVID-19 pandemic was not practiced according to the standard set by the World Health Organization and Ministry of Health. Capacity-building activities are strongly recommended to fulfill the required supplies and skilled manpower.

Key Words: Health facility, preparedness, COVID-19, Health professionals, Ethiopia

INTRODUCTION

Coronavirus disease 2019 is an emerging respiratory disease that is caused by a novel coronavirus and was first detected in December 2019 in Wuhan, China (1-3). On January 30, 2020, the World Health Organization (WHO) declared the outbreak a Public Health Emergency of International Concern (4-7).

The infectious agent responsible for causing COVID-19 is transmitted via respiratory droplets from infected individuals and remains viable on non-living objects under appropriate atmospheric conditions for several days (8). The symptoms of COVID-19 may range from a mild to a severe presentation, causing acute respiratory distress syndrome (ARDS), thereby requiring mechanical ventilation (9).

Healthcare facilities play a critical role within the health system in providing essential medical care to the community, particularly in a crisis or pandemic. Prolonged and combined outbreaks can lead to the progressive spread of disease with rapidly increasing service demands that can potentially overwhelm the capacity of hospitals and the health system at large (10).

In developing countries, especially sub-Saharan African countries, there are concerns with their ability to adequately deal with COVID-19. Given the fragile health systems in most sub-Saharan African countries, new and re-emerging disease outbreaks such as the current COVID-19 epidemic can potentially paralyze health systems at the expense of primary healthcare requirements. Effective outbreak responses and preparedness during emergencies of such magnitude are challenging across African and other lower-middle-income countries (11).

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In Ethiopia, the first COVID-19 case was reported on 13 March 2020. As of September 13, 2020, Ethiopia reported a total of 64,301 COVID-19 cases and 1,013 deaths (12). A range of strategies was implemented by the government to reduce the spread of the pandemic: including quarantine of people coming from abroad at least for 14 days, closure of schools, suspending of public gatherings, and temporary closure of churches and mosques.

Planning for a community outbreak of COVID-19 is critical for maintaining healthcare services during a response. All public health facilities in the study area should be prepared for the possible arrival of patients with COVID-19. According to World Health Organization, all public health facilities should ensure their staff is trained, equipped, and capable of delivering the needed services. To enhance the readiness of the health facilities to cope with the challenges of the outbreak, a pandemic, or any other emergency or disaster, hospital managers need to ensure the initiation of relevant generic priority action (10, 13). Without appropriate emergency planning, local health systems can easily become overwhelmed in attempting to provide care during a critical event. Limited resources, a surge in demand for medical services, and the disruption of communication and supply lines create a significant barrier to the provision of health care. To the best of our knowledge, there is no previous evidence showing the level of hospital preparedness for the COVID-19 pandemic in Ethiopia. Therefore, this study aimed to assess the preparedness of public hospitals for the reception and care of COVID-19 infected patients in Bale, East Bale, and West Arsi zones of southeast Ethiopia.

METHODS

Study setup, design, population, and sampling

An institution-based cross-sectional study was conducted in all government-owned hospitals in West Arsi, Bale, and East Bale Zones from June 15 to 30, 2020. All government Hospitals found in the three zones were included in the study to assess their preparedness for COVID-19 response. A total of ten hospitals were found in the three zones namely, Goba referral hospital, Robe general hospital, Madda Walabu hospital, Dellomena hospital, Ginnir hospital, Kokosa hospital, Arsi Negele hospital Shahshemene referral hospital, Dodola hospital, and Melkaoda hospital. Out of the ten hospitals, three of them were primary hospitals, six general hospitals, and one specialized hospital. Those ten hospitals serve a total of 3, 642,023 populations in their catchment, according to the 2007 census.

Data collection tools

The data were collected by using a structured checklist adopted from WHO and CDC (10, 13). It was modified to our context according to the Ethiopian Public Health Institute protocol for health facility preparedness and response (14). The core area of the checklist are (1) Prevent the spread of COVID-19 within the facility; (2) Promptly identify and isolate patients with possible COVID-19 and inform the correct facility staff and public health authorities; (3) Care for a limited number of patients with confirmed or suspected COVID-19 as part of routine operations; (4) Potentially care for a larger number of patients in the context of an escalating outbreak while maintaining adequate care for other patients; (5) Monitor and manage any healthcare personnel that might be exposed to COVID-19; and (6) Communicate effectively within the facility and plan for appropriate external communication related to COVID-19.

Study Variables

The study assessed the aspect of the health facilities including physical infrastructure for COVID-19 patient's reception and care, the structural arrangement of the facility, equipment supplies, drugs, presence of plan for covid-19, the existence of indicators of success, human resource training, availability of human resource, triage system, and laboratory service, the capacity of adequate provision of emergency care; in terms of adequate provision of drugs, equipment and supplies, referral plan, suspect handling, and screening process, provision of conducive environment, waste management system, adequately trained personnel, appropriate triaging of patients to the right zone for medical attention, communication system.

Data Collection Procedures and quality controls

Data were collected by trained data collectors through face-to-face interviews with Hospital managers and an interview was supported with observations wherever applicable as per the guidelines. Data collectors and interviewees' were provided with a facemask and instructed to have acceptable social distancing before the interview to prevent the risk of COVID-19 transmission. During the data collection procedures, all the collected data were reviewed and checked on daily bases. The questionnaire was pretested and modified before the actual data collection process.

Data Analysis procedures
The collected data were entered using EpiData version 3.1, cleaned, and analyzed using SPSS V.20. The results of the study were organized and presented descriptively using frequency tables and text narration.

Ethical Considerations
Ethical clearance was obtained from Madda Walabu University's research ethics committee. Letter of ethical clearance and support letters were submitted to the clinical director of respective hospitals. Permission to conduct the study was sought from Each department head. All collected data were kept confidential and analyzed in aggregate and were used only for the study.

RESULTS

Basic description of the study hospitals

A total of ten hospitals were included in this study. Four hospitals were from the Bale zone, one hospital from the East Bale and five hospitals were from the West Arsi zone.

Interview regarding the hospitals' preparedness plan was conducted with Medical directors, chief executive directors, and hospital managers. Among the hospitals, six hospitals were general hospitals, three hospitals were primary/district hospitals, and one hospital was a specialized hospital. Regarding bed capacities of the hospitals, it ranges from 47 to 230 beds. Among the total included hospitals, two hospitals were working as a COVID-19 treatment center and others were providing routine hospitals services during the data collection period. None of the hospitals have a COVID-19 testing service during the study period. Six hospitals have intensive care (ICU) units for adults. Only one hospital has an ICU bed for pediatrics. Six hospitals have ICU beds for neonates. Out of all hospitals, only five hospitals have a mechanical ventilator. Nine hospitals trained health professionals on how to take nasopharyngeal swab sample taking for COVID-19 testing (**Table 1**).

Development of written COVID-19 plan

Out of ten hospitals included in the study, only four hospitals incorporated COVID-19 disaster planning into their planning. Most (90%) of the hospital established multidisciplinary teams to address COVID-19. All of the study hospitals designated patient isolation centers (**Table 2**).

Elements of COVID-19 plan

Health facilities' plan regarding their preparedness and response in containing covid-19 has been assessed. Accordingly, fifty percent of health institutions completed planning for protecting patients, healthcare personnel, and visitors from COVID-19, and written protocol for identifying, monitoring, and reporting covid-19 among staff, hospitalized patients, attendants, and volunteers. Only 30% developed a written protocol for monitoring and tracking covid-19 related staff absence. In 50% of the institutions, the incident management team for covid-19 response has been completed. An incentive mechanism is also in place for staff working on direct care for COVID-19 management or prevention in half of the health institutions (**Table3**).

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Facility Communication plan for COVID-19

Ninety percent of the health institutions had developed policies and information materials on covid-19 for communicating information on COVID-19 to patients and their families. A person taking responsibility for communication with public health authorities was also assigned in 90% and the rest 10% were in progress.

Consumables and durable medical equipment and supplies

Twenty percent of health institutions completed estimating the quantities of essential patient care materials and equipment that would be needed for at least eight weeks of the outbreak. The stock was also prepared with a checklist for disaster response supplies and to address a likely shortage in 40%.

Table 1: Descriptive characteristics of included hospitals

Items	**Response**	**Frequency (%)**
Hospitals included by zone	Bale zone	4 (40)
	East Bale zone	1 (10)
	West Arsi zone	5 (50)
Level of the included hospitals	Primary hospital	3 (30)
	General hospital Specialized/ Ref. hospital	6 (60)
		1 (10)
Bed capacity of included hospitals	Arsi Negele hospital	62
	Dellomena hospital	53
	Ginnir hospital	127
	Gobba referral hospital Kokosa hospital	178
		47
	Madda Walabu hospital Shahshemene hospital Robe hospital	51
		230
		80
	Dodola hospital	85
	Melkaoda hospital	114
Does the hospital have ICU bed for adults?	Yes	6 (60)
	No	4 (40)
Hospitals bed capacity for adult ICU	<5 bed	8 (80)
	5 bed	2 (20)
Does the hospital have ICU beds for pediatrics?	Yes	1 (10)
	No	9 (90)
Does the hospital have ICU beds for neonates?	Yes	6 (60)
	No	4 (40)
Hospitals bed capacity for neonatal ICU	6-10 beds	3 (50)
	11-30 beds	3 (50)
Does the hospital have a mechanical ventilator?	Yes	5 (50)
	No	5 (50)
Number of mechanical ventilators	<5 ventilators	3 (60)
	5 ventilators	2 (40)
Does the hospital have a microbiology laboratory that has culture testing?	Yes	2 (20)
	No	8 (80)
Does the hospital train health professionals on how to take a nasopharyngeal swab for COVID-19 testing?	Yes	9 (90)
	No	1 (10)
Does the facility start the COVID-19 test by PCR?	In progress Not started	1 (10)
		9 (90)
Does your facility currently work as a COVID -19 treatment center?	Yes	2 (20)
	No	8 (80)

Table 2: Development of written COVID-19 plan in hospitals

Items	Response	Frequency %
COVID-19 planning has been incorporated into disaster planning and exercises	Completed / observed Completed / but not observed	4 (40)
	In progress	3 (30)
	Not started yet	2 (20)
		1 (10)
A multidisciplinary planning committee or team has been created specifically to address COVID-19	Completed / observed	8 (80)
	Completed / but not observed	1 (10)
	In progress	1 (10)
The facility designated a patient isolation center	Completed	10 (100)
The facility trained staff for the development of the COVID-19 treatment center	Completed	6 (60)
	In progress	1 (10)
	Not started yet	3 (30)
A facility collaborate with respective leadership for the decision to allocate potential resource for COVID-19 response	Completed	8 (80)
	In progress	2 (20)
A copy of the hospital COVID-19 preparedness plan is available at the facility	Completed	4 (40)
	In progress	4 (40)
	Not started	2 (20)
A copy of the hospital COVID-19 preparedness plan is accessible by staff	Completed/observed	2 (20)
	In progress	5 (50)
	Not started	3 (30)
The plan identifies the person(s) and the organizational structure authorized to implement the plan	Completed	4 (40)
	In progress	4 (40)
	Not started	2 (20)
Responsibilities of key personnel and departments within the facility related to executing the plan have been described	Completed	4 (40)
	In progress	4 (40)
	Not started	2 (20)

Table 3: Elements of COVID-19 plan preparedness and response plan

Items	Response	Frequency (%)
A plan/action is in place for protecting patients, healthcare personnel, and visitors from COVID-19	Completed In progress Not started	5(50) 4(40) 1(10)
A written protocol has been developed for identifying, monitoring, and reporting COVID-19 among staff.	Completed In progress Not started	5(50) 2(20) 3(30)
A written protocol has been developed for identifying, monitoring, and reporting COVID-19 among hospitalized patients, attendants, and volunteers	Completed In progress Not started	5(50) 1(10) 4(40)
A plan to monitor and track COVID-19 related staff absences has been developed	Completed In progress Not started	3(30) 4(40) 3(30)
Incident management team for COVID-19 response has been established	Completed/observed Completed/not observed In progress	5(50) 4(40) 1(10)
Incentive mechanism in place for staff working on direct care for COVID-19 management or prevention	Completed In progress Not started	5(50) 4(40) 1(10)

A process of ensuring the provision of supplies and material recommended in infection prevention and control measures is in place and the process is completed in 30% of health institutions (**Table 4**).

Table 4: Status of consumables and durable medical equipment and supplies

Items	Response	Frequency%
Estimates have been made of the quantities of essential patient care materials and equipment that would be needed for at least an eight-weeks of the outbreak (e.g., PPE, intravenous pumps and ventilators, pharmaceuticals)	Completed In progress Not started	2(20) 6(60) 2(20)
Prepared stock with a checklist for disaster response supplies	Completed/observed In progress	4(40) 6(60)
A plan has been developed to address likely supply shortages (e.g., personal protective equipment), including strategies for using normal and alternative channels.	Completed In progress	4(40) 6(60)
A process is in place to ensure that the facility provides supplies and materials necessary to adhere to recommended infection prevention and control practices (e.g. hand, respiratory hygiene, etc)	Completed In progress	3(30) 7(70)

Identification and management of ill patients
Fifty percent of hospitals prepared pre triage areas as per protocol. Designation of location for covid-19 screening and case management is completed in 50 and 40% respectively. All of the health institutions completed the designation of location for hand washing. Half of the institutions did not establish alternatives to face-to-face triage, and40% have no policy to test COVID-19 for any laboring mother, patient with cough and/or fever, and patients in the ICU and thirty percent have a policy (**Table 5**).

Visitor's access and movement within the facility
Reviewing and updating a plan for the covid-19 pandemic for visitor access and movement within the facility has been completed in 20% of the health facility. Half of the health institutions have plans and materials developed to post signs at the entrances to the facility instructing visitors not to visit if they have fever or symptoms of a respiratory infection.

Table 5: Identification and management of ill patients

Items	Response	Frequency
The facility prepared pre triage area as per protocol	Completed	5(50)
	In progress	4(40)
	Not started	1(10)
Determined how suspected cases will be isolated from other waiting patients during emergency department care	Completed	7(70)
	In progress	2(20)
	Not started	1(10)
Specifically-trained healthcare personnel has been assigned responsibility for overseeing the triage process.	Completed	7(70)
	In progress	1(10)
	Not started	2(20)
A facility designated a location for COVID-19 screening	Completed/ observed	5(50)
	In progress	4(40)
	Not started yet	1(10)
A facility designated a location for COVID-19 screening isolation	Completed/ observed	5(50)
	Completed/not observed	1(10)
	In progress	3(30)
	Not started yet	1(10)
A facility designated a location for case management	Completed/ observed	4(40)
	Completed/ not observed	1(10)
	In progress	2(20)
	Not started yet	3(30)
A facility designated a location for a hand washing area.	Completed/ observed	10(100)
Alternatives to face-to-face triage have been established. Ex. a telephone triage system for prioritizing patients who require a medical evaluation.	Completed	3(30)
	In progress	2(20)
	Not started	5(50)
A facility has the policy to test COVID-19 for any laboring mother, patient with cough and/or fever, and patients in the ICU	Completed	3(30)
	In progress	3(30)
	Not started yet	4(40)

Fifty percent of the hospital has criteria and protocols for limiting or restricting visitors from the facility or into rooms of suspected patients or patients confirmed of COVID-19. Around one-third of the facility didn't start developing criteria for limiting / restricting visitors. Eighty percent has assigned a crowd controller to reduce patient and attendant crowding.

Occupational health

In this study, half 5(50%) of the hospitals observed have employee sick leave that is none punitive, flexible, and consistent with the public health policy to stay at home. The process of identifying and managing health care providers with fever and symptoms of COVID-19 was found in 7 (70%) of the hospitals observed. A plan for monitoring and assigning work restrictions for ill and exposed health care providers was found completed in 5 (50%) of the hospitals. Four (40%) of the hospitals have a guideline for auditing adherence to the recommended personal protective equipment use by health care providers, similarly, a process of auditing adherence to recommended handwashing practice was present in 3(%) of the observed hospitals.

Education and training

Regarding education and training provision preparedness on COVId-19 for staff five (50%) of the hospitals have a complete plan to provide education for patients and family members of patients on prevention and control of COVID-19. And 7(70%) of the observed hospitals have the plan to provide training to health care professionals. Six (60%) of the facilities have provided training on infection prevention and control for supportive staff (guards, janitors, food service, and staff working in morgue) having closer contact with patients and monitoring their practices. Seven (70%) of the facilities also have designated a person or a team with responsibility for coordinating education and training on COVID-19

Health care/ Surge Capacity

Regarding increased health care/ surge capacity, a plan to allow expanded service hours (shifting plan) was completed in 3 (30%) of the facilities. Strategies for maintaining the hospital routine and continuing care for patients with chronic disease, women giving birth, emergency service, and other none COVID-19 case was found completed in 7 (70%) of the facilities observed. Facilities space for expanding service need of inpatients beds was identified by only 2 (20%) of the hospitals. Criteria have been developed for determining when to cancel elective admission/ non-emergency service and surgeries have been completed in 4 (40%) of the observed facilities. Plan for shifting care service away from the hospital was completed for 4 (40%) of the observed facilities. It is only 1 (10%) of the hospitals that have a plan for initiating and expanding the use of call centers and telemedicine to serve patients without face-to-face contact. Ethical issues concerning how decisions will be made in the event healthcare services must be prioritized and allocated (e.g., decisions based on probability of survival) have been discussed were found completed in 1(10%) of the hospitals observed (**Table 6**).

Table 6: Health care/ Surge capacity preparedness of hospitals to prevent and manage COVID-19

Item	Response	Frequency (%)
Developed staffing plan to allow for expanded service hours when needed	Completed In progress Not started yet	3 (30) 4 (40) 3 (30)
Plans include strategies for maintaining the hospital's routine and continuing to care for patients with chronic diseases, women giving birth, emergency services, and other non-COVID-19 care	Completed In progress	7 (70) 3 (30)
Facility space has been identified that could be adapted for use as expanded inpatient beds. (E.g. convalescent homes, hotels, schools, community centers, etc...)	Completed In progress Not started yet	2 (20) 4 (40) 4 (40)
Criteria have been developed for determining when to cancel elective admissions/ non-emergency services and surgeries.	Completed In progress Not started yet	4 (40) 3 (30) 3 (30)
Plans for shifting healthcare services away from the hospital, e.g., to home care or pre-designated alternative care facilities have been discussed.	Completed In progress Not started yet	4 (40) 3 (30) 3 (30)
Created "fast-track" or another method for rapid evaluation and prescribing for minor illnesses	Completed In progress Not started yet	5 (50) 3 (30) 2 (20)
Developed a referral plan for non-COVI-19 patients that do not need emergency care	Completed In progress Not started yet Missing value	3 (33.3) 2 (22.2) 4 (44.4) 1
Plans for initiating and expanding the use of call centers and telemedicine to be able to serve patients without face-to-face contact.	Completed In progress Not started yet	1 (10) 2 (20) 7 (70)
Developed a care plan that reduces the number of staff caring for suspected/ confirmed cases until transferred	Completed In progress Not started yet	7 (70) 2 (20) 1 (10)
Maintaining two meters distance between beds in normal emergency department care in case COVID-19 increases	Completed In progress Not started yet	2 (20) 4 (40) 4 (40)
Developed risk communication and transportation plan for suspected cases	Completed In progress Not started yet	8 (80) 1 (10) 1 (10)
COVID-19 center dedicated treatment center for non-COVID-19 health problems e.g. *surgery, oby/gyne*	Completed Not started yet	4 (40) 6 (60)
Ethical issues concerning how decisions will be made in the event healthcare services must be prioritized and allocated (e.g., decisions based on probability of survival) have been discussed.	Completed In progress Not started yet	1 (10) 4 (40) 5 (50)
A procedure has been developed for communicating changes in hospital status to health authorities and the public.	Completed In progress Not started yet	5 (50) 4 (40) 1 (10)
Legal counsel and ministry of health contacts have been consulted to determine the applicability of declaring a facility "staffing crisis" and appropriate emergency staffing alternatives.	Completed In progress Not started yet	5 (50) 1 (10) 4 (40)
An ethical and morgue management team has been established	Completed In progress Not started yet	3 (30) 2 (20) 5 (50)
An area in the facility that could be used as a temporary morgue and expanding morgue capacity has been identified.	Completed In progress Not started yet	2 (20) 2 (20) 6 (60)

DISCUSSION

Globally, hospitals are currently facing an enormous challenge in delivering routine health services and increased patients surges due to the coronavirus disease (COVID-19) pandemic. Hospitals are required to prepare all the necessary resources to handle the increased patient flow as well as the increased consumption of scarce health care resources (1). This study aimed to assess hospitals' preparedness for COVID-19 prevention and control in Bale, East Bale, and West Arsi hospitals.

In this study, the ten hospitals have a total bed capacity of 1,027. The minimum bed capacity among the included hospitals was 47 beds and the maximum was 230 beds. The bed capacities of the hospitals might be inadequate to effectively respond to the pandemic. In terms of Intensive Care Unit (ICU) capacities of the hospitals, of the ten hospitals, six hospitals had an adult ICU. The number of adult ICU beds per hospital was very low, the minimum was one, and the maximum was 5 beds. From the ten hospitals in the three zones, only five hospitals have mechanical ventilators. Among the five hospitals, two hospitals have five mechanical ventilators and the rest have less than five which is very low compared to the population size and the number of expected cases of COVID-19.

The data from China suggest that 15–20% of COVID-19 cases require hospitalization, with about 15% of cases presenting with severe symptoms and 5% requiring intensive care (15). In Italy and Spain, 40–55% of COVID-19 positive cases have been hospitalized, with 7–12% requiring admission to intensive care units (16). Estimates from China also suggest that patients in intensive care units (ICUs) require approximately 13 days of respiratory support, (17) while data from Italy show that 10–25% of patients will require ventilation and some patients will need ventilation for several weeks (18). This trend of hospitalization indicates that business-as-usual service delivery approaches are not sufficient to respond once a cluster of cases or widespread community transmission is registered and surge capacity will be needed. Modeling studies suggest non-pharmaceutical interventions such as physical distancing, school, and university closures, banning of mass gatherings, and remaining indoors, on spreading the number of cases over a longer period to give health systems the opportunities they need to cope with caseloads (19-21).

Half of the health institutions in the study area did not have a plan for protecting patients, healthcare personnel, and visitors from COVID-19 19, and also did not have a written protocol for identifying, monitoring, and reporting COVID-19 among staff. Fifty percent of the institutions didn't have an incident management team for COVID-19 response and incentive mechanism for staff working on direct care for COVID-19 management or prevention. This indicates health facilities are not well prepared to combat the COVID-19 pandemic and insight of this COVID-19 will easily infect and spread to people receiving service from those hospitals.

The finding of this study revealed that 90% of health institutions assigned a person which is responsible for communication with external partners and developed informational materials on COVID-19 and relevant policies for their patients and families. In contrast, 10% didn't assign a person yet, although the Ethiopian Ministry of Health recommends that information should be provided to the family and their patients in a language easiest for them to understand (22).

Availability of personnel and medical supply must be ensured for the prevention of COVID-19 (23, 24), though only 20% of health institutions in the study area have made estimates of the quantities of essential patient care materials and equipment that would be needed for at least an eight-weeks of an outbreak. This indicates that health facilities are not well prepared to fight this pandemic and shows many activities are still to be done by these health institutions. Twenty percent have never made the estimates of quantities of necessary equipment and materials important for patient care when the disease is already spread throughout all the parts of the country.

Although World Health Organization (WHO) has designed a tool for forecasting/estimating supplies (25), 60% of health institutions did not make an estimate yet and were in the progress of estimating the necessary materials needed for at least the coming eight months. The first case of coronavirus was detected in Ethiopia on March 13, 2020 (22) and only 20% completed the estimation of materials needed and this is very late when compared to the work done with the time elapsed. WHO recommends that minimum standards should be in place to ensure the protection of health care workers, patients, and visitors from COVID-19 (26) even if only less than one-third of the facility completed the provision of supplies and materials necessary to adhere to recommended infection prevention and control practices.

Although Ethiopian Ministry of Health guidelines orders health care facilities to prepare pre-triage areas and determine ways of isolating suspected cases from others (22), only fifty percent of health facilities in the study area prepared pre-triage areas. Seventy percent (70%) completed determining how to isolate suspected cases from others. This is higher than the study conducted in Ukraine in which 33% of the facility screened COVID-19 suspected persons before entering the facility (27). This may be due to differences in the time of the study because the screening capacity of health facilities will increase over time. For identification and management of ill patients 70% assigned specifically-trained healthcare personnel to bear responsibility for overseeing the triage process, whereas only half of the health facilities completed designation of location and isolation for COVID-19 screening. A facility that has alternatives to face-to-face triage and that has the policy to test COVID-19 for any laboring mother, patient with cough and/or fever, and patients in the ICU is only 30%.

Health facilities preparedness in terms of limiting visitors' access and movement within the facility, limiting visitors not to enter the facility if they have symptoms of respiratory infections, and restricting the visitor's number entering the room of patients suspected of coronavirus is found incomplete. This shows that extra effort is needed from the respective hospitals to review and update a plan for visitors' access and movement within the facility, and also a plan for the visitors when to enter and not to enter the facility should be prepared and posted for the visitors.

Occupational health preparedness is a crucial activity to respond to and manage the COVID-19 pandemic. In this regard, having employee sick leave that is none punitive, flexible, and consistent with public policy; plan for monitoring and assigning work restrictions for ill and exposed health care providers; having a guideline for adherence to the recommended PPE for HCP and having auditing adherence to recommended handwashing practice were expected from each hospital (28).

The Ethiopian Public Health Institute standard for COVID-19 preparedness requires all hospitals to have employee sick-leave policies that are none punitive, flexible, and consistent with public policy (14). In the current study, only 4 (4%) of the observed hospitals have implemented this. All hospitals are expected to have a process to identify and manage HCP with fever and symptoms of COVID-19, in the current study 7 (70%) were found to have implemented this. .

Hospitals are expected to have a plan for monitoring and assigning work restrictions for ill and exposed Health Care Providers this is observed in only half 5(50%) of the observed hospitals. A guideline for auditing adherence to recommended PPE use by HCP and a process for auditing adherence to recommended hand hygiene practices by HCP was observed in 4(40%) and 3 (30%) of the observed hospitals respectively. In the study, it was found that still there are gaps in fulfilling the requirements for COVID-19 prevention as to the standard set by WHO, CDC, and Ministry of Health (10, 13, 14). Even if there were efforts made to practice as per the standard. The European Center for Disease Control has also stated that hospitals are required to provide a minimum composition of PPE to manage suspected or confirmed cases of COVI-19 (13, 14).

To respond and manage COVID-19 hospitals are responsible to provide education and training, providing training for their staff, training on infection prevention for support staff, and have designated a person of a team with responsibility for coordinating education and training on COVID-19 (29). In the current study Seven (70%) of the observed hospitals have the plan to provide training to health care professionals. Six (60%) of the facilities have provided training on infection prevention and control for supportive staff (guards, janitors, food service, and staff working in morgue) having closer contact with patients and monitoring their practices. And seven (70%) of the facilities also have designated a person or a team with responsibility for coordinating education and training on COVID-19. This indicates that almost all of the studied hospitals did not completely implement the standard for the staff education and training preparedness as set by Ethiopian Public Health Institution, World Health Organization, and Center for Disease Control (10, 13, 14).

The study has also tried to assess the health care/ surge capacity preparedness of hospitals to prevent and manage COVID-19 in the hospitals found in the three zones. In this regard in most of the facilities, we have found the preparation to be less than fifty percent. Even if staffing plan is crucial in responding to COVID-19 (10, 14). In this study; only 3 (30%) of the hospitals have developed staffing plans to allow for expanded service hours when needed. Three 30% of the hospitals have not completed a plan that includes strategies for maintaining the hospital's routine and continuing to care for patients with chronic diseases, women giving birth, emergency services, and other non-COVID-19 care.

This may result in increased morbidity and mortality of people with conditions that could be managed otherwise. Eighty percent of the hospitals did not completely plan for facility space that could be adapted for use as expanded inpatient beds such as convalescent homes, hotels, schools, community centers, etc. And less than half 4(40%) of the hospitals have developed criteria for determining when to cancel elective admissions/ non-emergency services and surgeries and have completed a plan for shifting healthcare services away from the hospital, e.g., to home care or pre-designated alternative care facilities have been discussed.

Hospitals are expected to have referral plans and to have the plan to initiate alternative service approaches for clients (10, 14). Developed a referral plan for non-COVI-19 patients that do not need emergency care was found completed in 3 (30%) of the facilities assessed. And a completed plan for initiating and expanding the use of call centers and telemedicine to be able to serve patients without face-to-face contact was found only in one (10%).

Reducing the number of staff caring for suspected/ confirmed cases until transferred and maintaining two meters distance between beds in normal emergency department care in case COVID-19 increases is an important component of COVID-19 prevention preparedness and management (14); in our observation, we noted that 7(70%) and 2 (20%) of the observed hospitals respectively have a complete plan for these actions.

Having developed risk communication and transportation plan for suspected cases is a requirement for preparedness and response to curb and manage outbreaks of COVID-19 (30). In this study, 80% of hospitals have completed the plan. And only four (40%) of the observed hospitals have COVID-19 center dedicated treatment centers for non-COVID-19 health problems such as surgery, obstetrics, and gynecology.

Discussion of ethical issues concerning how decisions will be made in the event healthcare services must be prioritized and allocated (e.g., decisions based on probability of survival) is a requirement for COVID-19 care and management (14) but it only 1 (10%) of the observed hospitals have completed plan. A procedure has to be developed for communicating changes in hospital status to health authorities and the public and legal counsel and ministry of health contacts have to consult to determine the applicability of declaring a facility "staffing crisis" and appropriate emergency staffing alternatives (14) in this aspect half (50%) observed hospitals have completed plan.

Legal counsel and Ministry of Health contacts to determine the applicability of declaring a facility "staffing crisis" and appropriate emergency staffing alternatives; planning for ethical and morgue management team establishment and an area in the facility that could be used as a temporary morgue and expanding morgue capacity has to be identified (14). But in this study 5 (50%), 3 (3%), and 2 (20%) of the observed hospitals respectively have completed such plan.

CONCLUSION

Preparedness for management and response to the COVID-19 pandemic was not fully practiced according to the standard set by the world health organization and the national standard set by the Ministry of Health and Ethiopian Public Health Institute. Although there are efforts made towards the preparation and response to the pandemic, the achievements of almost all of the hospitals included in the study were below the expected standard. Capacity-building activities to fulfill the standard need in supplies and skilled human power to combat COVID -19 pandemics are mandatory. Concerned bodies including national, regional, and zonal stakeholders need to work on strengthening the capacities of hospitals to respond to COVID-19 by providing technical and materials support.

Strength and limitations of the study

Among the strength, the study has tried to assess the preparedness and response of hospitals for the prevention and management of COVID-19 using a standard checklist through direct interview and observation of the facilities. Among the limitations, as we have included only 10 hospitals found in West Arsi, Bale, and East Bale zone, the finding may not be generalized to other hospitals in Oromia and national level.

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Conflict of Interest:

Authors have no conflict of interest to declare

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ORIGINAL ARTICLE

ADHERENCE AND BARRIERS TO SECONDARY PROPHYLAXIS FOR RHEUMATIC HEART DISEASE AT TIKUR ANBESSA SPECIALIZED HOSPITAL

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ABSTRACT

Introduction: *Rheumatic heart disease (RHD) is one of the major causes of cardiovascular disease in developing countries. Secondary prophylaxis is effective for preventing recurrent acute rheumatic fever (ARF) and the progression of RHD. The purpose of the study was to assess adherence and barriers to use secondary prophylaxis for RHD at Tikur Anbessa Specialized Hospital (TASH).*
Methods: *Cross-sectional study was conducted from June 5, 2020, to September 4, 2020, at Tikur Anbessa Specialized Hospital, Ethiopia. A structured questioner was used for the data collection on awareness, adherence, and barriers for benzathine penicillin prophylaxis in adults with RHD. Data were analyzed using SPSS version 26.*
Results: *A total of 385 patients participated in this study, 305(79.6%) patients were aware about sore throat associated with heart disease, and about 288 (75.6%) patients know that benzathine penicillin prevents tonsillitis. Adherence rate was 77.9%. The main barriers for nonadherence in this study were the unavailability of medications, schedule forgetfulness, and health professionals' refusal to inject benzathine penicillin. Increased age was found to have a significant association with adherence to B. penicillin. For each one-year increase in the age of patients with RHD, the adherence decreases by 3% [AOR= 0.97; 95% CI 0.95, 0.99], P value = 0.006)*
Conclusion: *Adherence level to monthly benzathine penicillin injection was low, which is below WHO recommendation. This study has revealed major barriers that affect adherence to secondary prophylaxis for RHD that can be used to develop interventions to improve adherence.*
Key words: *Rheumatic heart disease, adherence, barriers, secondary prophylaxis.*

INTRODUCTION

Rheumatic fever (RF) and RHD remain significant causes of cardiovascular disease in the world today. They are major public health problems in many developing countries (1).
The prevalence of RHD across World Health Organization (WHO) regions remains high. Although RF and RHD have progressively declined in developed countries over the past 50 years, they continue to increase at a striking rate in developing countries. Linked to poverty and poor access to health care facilities, estimates suggest that roughly 50% of cardiac patients in less developed countries have RF and/or RHD (2).
In Ethiopia, the prevalence of Rheumatic Heart Disease is 19 per 1000 population which is much higher than the prevalence of other developing countries (3). It accounts for 34 % of all spectrums of cardiovascular diseases on follow up at major referral hospitals in Ethiopia (4).
Secondary prophylaxis through the administration of benzathine penicillin G (BPG) to patients with a previous history of RF and/or RHD is effective at preventing streptococcal pharyngitis and recurrence of rheumatic fever.
The long-term follow-up studies have proved that the early initiation of secondary prophylaxis is very effective to stop or slow down further progression of RHD (5).
This study was conducted to better understanding current adherence rate and barriers to secondary prophylaxis in patients with RHD at the largest referral hospital of the country. This study will have a significant impact to tackle these barriers.

METHODS

Study design and period

Tikur Anbessa Specialized Hospital is located in capital city Addis Ababa, Ethiopia. It is the largest specialized referral teaching hospital in the country. In addition to teaching, the hospital also provides both inpatient and outpatient services to patients referred from different parts of the country. Currently, it is the only governmental hospital where cardiac surgery is practiced in the country with a follow-up clinic for congenital and acquired heart disease in children and adults. The study period was from June 5, 2020 to September 4, 2020 GC, TASH, Addis Ababa, Ethiopia. Cross sectional study using structured questioners on adherence for the BPG prophylaxis for the last one year and barriers to use BPG prophylaxis.

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Adult patients with Rheumatic Heart Disease prescribed with monthly BPG for at least one year' on follow up at the cardiac clinic and who gave informed consent were included in the study. Sample size was calculated using single population proportion formula. Convenience sampling method was used to include all patients with RHD fulfilling the inclusion criteria.

A structured questionnaire adopted and modified from different literatures was prepared in English and translated to Amharic.. The data was collected through patient interview, and review of medical charts and injection cards. The questionnaire was pre-tested in order to check the questionnaire is clear and addressing the objective of the study. Training was given to data collectors. The data collectors were general practitioner and 4th-year medical students. The data collectors were trained and supervised by the investigators. The collected data was checked for completeness before data entry process.

Data was entered and analyzed using SPSS version 26 (IBM® SPSS®). Association was done done by chi-square test for categorical tests and considered to be statistically significant when the P value was below 0.05. Confidence interval was set at 95%.

Ethical clearance was obtained from Department of Internal Medicine research ethical committee. A written informed consent was obtained from the patients before data collection. The patients' response was fully confidential.

OPERATIONAL DEFINITION

Rheumatic Heart Disease (RHD): Refers to the major long-term sequel of acute rheumatic fever, which involves the cardiac valves leading to stenosis or regurgitation with resultant hemodynamic disturbance.

Acute rheumatic fever (ARF) is delayed, nonsuppurative sequel following group A streptococcus pharyngitis and may consist of arthritis, carditis, chorea, erythema marginatum, and subcutaneous nodules

Good adherence or adhered to prophylaxis: if the rate of adherence is covering >= 80% of prophylaxis. i.e., patient has not missed any injection or only missed three or less injections in the last one year or received prophylaxis nine or more times).

Poor adherence or not adhered to prophylaxis: if the rate adherence is <80%, i.e. patient had missed their regular injection more three times in the last one year.

RESULTS

A total of 385 patients with RHD attending adult cardiac clinic participated in the study. Among the participants, 276 (71.7%) were females and 345 (89.6%) were urban residents.

The mean age was 31 years, (SD, 10.7). Most of participants were from Addis Ababa 259 (67.3%) (Table 1).

Table 1. Socio-demographic characteristics of patients with RHD attending adult cardiac clinic at TASH, Addis Ababa, Ethiopia, 2020

Variables	No.	Percent (%)
Age category (n=385)		
<20 years	54	14.0
20-29 years	140	36.4
30-39 years	114	29.6
40-49 years	49	12.7
50-59 years	21	5.5
>=60 years	7	1.8
Sex (n=385)		
Female	276	71.7
Males	109	28.3
Residence (n=385)		
Rural	40	10.4
Urban	345	89.6
Region (n=385)		
Addis Ababa	259	67.3
Oromia	82	21.3
Amhara	21	5.5
SNNPR	20	5.2
Others	3	.8
Marital status (n=383)		
Single	147	38.4
Married	205	53.5
Divorced	23	6.0
Widowed	8	2.1
Occupation (n=383)		
Government employee	76	19.8
Non-government employee	71	18.5
Student	59	15.4
House wife	63	16.4
Farmer	17	4.4
Merchant	16	4.2
No occupation	81	21.1
Family Income (n= 378)		
> 1000 Ethiopian birr	269	71.2
< 1000 Ethiopian birr	82	21.7
No income	27	7.1
Level of Education (n= 372)		
No formal education	40	10.8
Primary school	124	33.3
Secondary school	133	35.8
Teriary	75	20.1

Among 383 participants, 219 (57.2%) had history of sore throat. However, only 148 (67.9%) of them received medical doctor or other health professional prescribed medications for the sore throat. Antibiotics were the most prescribed medications 152(69.2%). Three hundred five respondents (79.6%) were aware that sore throat is associated with heart disease, while 55(14.4) of them were not aware and 23(6%) did not have any clue about it. Three hundred two (79.5%) have heard about rheumatic heart disease before. With regard to the purpose of benzathine penicillin, 288(75.6%) believe that it prevents tonsillitis, 123 (32.2%) think it is a cure for RHD and 30(7.9%) think that it prevents worsening (Table 2).

Table 2. Awareness regarding rheumatic heart disease among patients with RHD attending adults cardiac clinic at TASH, Addis Ababa, Ethiopia, 2020.

Variables	No.	Percent (%)
History of sore throat (n=383)		
Yes	219	57.2
No	164	42.8
Treatment for sore throat (n=218)		
Antibiotics	152	69.7
Salt	16	7.3
Traditional herbs	44	20.2
Other	6	2.8
Person prescribed the medication for sore throat (n=218)		
Myself	22	10.1
Friend/Relative	44	20.2
Medical doctor/ other health professional	148	67.9
Others	4	1.8
Awreness of complications of sore throat (n=379)		
Yes	294	77.6
No	85	22.4
Sore throat associated with heart disease (n=383)		
Yes	305	79.6
No	55	14.4
No idea	23	6.0
Ever heard about rheumatic heart disease (n=380)		
Yes	302	79.5
No	78	20.5
Benzathine pencicilin prophylaxis for RHD, alleivate the symptoms (n=382)		
Yes	70	18.3
No	312	81.7
Benzathine penicillin prophylaxis for RHD, prevent worsening (n=382)		
Yes	30	7.9
No	352	92.1
Benzathine pencicilin prophylaxis for RHD, cure the disease(n=382)		
Yes	123	32.2
No	259	67.8
Benzathine pencicilin prophylaxis for RHD, prevent tonisillitis (n=381)		
Yes	288	75.6
No	93	24.4

Among 384 participants in the past 1 year, 211(54.9%) did not miss monthly injection, 37(9.6%) patients missed one injection, 51(13.3%) missed two to three injections and 85(22.1%) missed more than three injections yielding adherence rate of 77.9 %. About 85(22.1%) patients did not adhered for monthly BPG injection. Two hundred and thirsty three (61.8%) waited until next appointment when they missed injection. Seven (1.9%) took alternative medication (herbal) when they missed monthly injection. Most of patients, 287 (75.3%) never experienced adverse reaction to benzathine penicillin. Most of the patients, 230 (59.9%) in this study were diagnosed with RHD diagnosed in the past 10 years and 113(29.4%) patients were diagnosed to have RHD in the past 11-20 years (Figure 1). About 240 (62.3%) were started on benzathine penicillin prophylaxis in the past 10 years (Table 3).

Table 3. Adherence to b. penicillin prophylaxis for RHD among patients with RHD attending adult cardiac clinic at TASH, Addis Ababa, Ethiopia, 2020

Variables	No.	Percent (%)
Serious reaction (more than local swelling and pain) following a previous b. penicillin injection (n=381)		
Yes	94	24.7
No	287	75.3
Attend appointment for BPG penicillin prophylaxis (n=382)		
Alone	216	56.5
With a family member	163	42.7
With others	3	.8
Benzanthine pencillin prophylaxis card is useful (n=380)		
Yes	341	89.7
No	39	10.2
Time since BPG prophylaxis started (n=385)		
<10 years	240	62.3
11- 20 years	110	28.6
21-30 years	31	8.1
Do not know	4	1
Injections missed in the past 1 year (n=384)		
None	211	54.9
One	37	9.6
Two to three	51	13.3
More than three	85	22.1
What do you do if you miss monthly benzanthine pencillin (n=377)		
Wait until my next appointment	233	61.8
Go a few days latter	137	36.3
Take alternative medication (herbal)	7	1.9
Hospital admissions in the last 1 year (n=385)		
No admission	279	72.5
Once	45	11.7
Twice	13	3.4
Three times	20	5.2
Four and more	28	7.3
Co-morbidities (n=385)		
No	339	88.1
Hypertension	13	3.4
Diabetes mellitus	5	1.3
Ashma	3	.8
Other	25	6.5

In this study, the main reason for missing injection for most of patients, 216 (56.1%), were due to lack of medication supply followed by schedule forgetting, 167(43.4%) and health professional refusal to inject benzathine penicillin, 149(38.7%). For majority of patients, 376(97.9%), the usual waiting time at clinic during injection was less than 1 hour (Table 4).

Importance of benzathine injection prophylaxis that had been explained by doctor for majority, 346(90.1%) patients. Regarding effectiveness of the medication, 362(94%) believed that the drug is effective. For 267 (69.7%) participants, cost associated to coming to clinic (like days off work, transportation etc.) prevent coming to injection clinic. About 346(90%) agreed secondary prophylaxis card or booklet that list dates of injections is very useful. Majority, 294(76.5%), agreed analgesic mix or taking divided dose injection can increase adherence. From this study, long waiting time at clinic was not an obstacle to monthly injection, 266(69.4%) (Table 4).

Table 4. Barriers to monthly b. penicillin injection among patients with RHD attending adult's cardiac clinic at TASH, Addis Ababa, Ethiopia, 2020

A Variables		No.	Percent (%)
	Felt well and healthy	55	14.3
	Forgetting	167	43.4
	Unavailability of transport	22	5.7
	Transport cost	25	6.5
	No medication supply/ stock out	216	56.1
	Cost related to BPG injection	79	20.5
	Fear of side effect	54	14.0
	Fear of pain	28	7.3
	Health professional refuse to administer BPG	149	38.7
	Being busy	45	11.7
	Distance	11	2.9
	Other reason	4	1.0
Why health proffessionals refuse to give injection (n=379)			
	Fear of of side effects	254	67.0
	Lack of training how to inject	60	15.8
	Because they feel that it is not their responsibility	21	5.5
	Inadequate number of health professional in remote areas	26	6.9
	Other	18	4.7
Usual waiting time at clinic where you receiving prophylaxis (n=384)			
	< 1 hour	376	97.9
	1 hour and more	8	2.1
Doctor has explained what rheumatic heart disease is	Agree	347	90.4
	Neutral	8	2.1
	Disagree	29	7.6
Doctor clarified me why the injections are important			
	Agree	346	90.1
	Neutral	8	2.1
	Disagree	30	7.8
I believe that this medication is effective			
	Agree	362	94.5
	Neutral	14	3.7
	Disagree	7	1.8
Cost associated to comming to clinic (days off work, transportation, etc), prevent me from coming			
	Agree	267	69.7
	Neutral	26	6.8
	Disagree	90	23.5
Secondary prophylaxis cards or bookets that list dates of injections are very useful (Reminder)			
Agree		346	90.1
Neutral		30	7.8
Disagree		8	2.1
Taking analgesic mix or divided dose injection can increase adhrence			
	Agree	294	76.6
	Neutral	70	18.2
	Disagree	20	5.2

However, in multivariable analysis, only increased age was found to have significant association with adherence to BPG. As a result, for each one-year increase in the age of patients with RHD attending adult cardiac clinic at TASH, the adherence to BPG decreases by 3% [AOR= 0.97; 95% CI 0.95, 0.99] (Table 5)

Table 5. Bivariable and Multivariable Logistic Regression analysis results of factors associated with adherence to b. penicillin patients with RHD attending adults' cardiac clinic at TASH, Addis Ababa, Ethiopia, 2020

Explanatory Variables	**Adherence to b. penicillin**		**COR(95% CI)**	**AOR(95% CI)**	**P-value**
	Adhered	**Not adhered**			
Age in year	30.03 ± 10.4¥	34.0 ± 11.2¥	0.97(0.95, 0.99)*	0.97(0.95, 0. 99)	0.006
Time since benzathine penicillin prophylaxis started					
≤ 10 years	194 (80.8%)	46 (19.2%)	1		
11 - 20 years	83 (76.1%)	26 (23.9%)	0.76 (0.44, 1.31)		0.317
21 – 30 years	19 (61.3%)	12 (38.7%)	0.38 (0.17, 0.83)*		0.015

¥ mean ± SD * statistically

significant at p value of ≤ 0.05

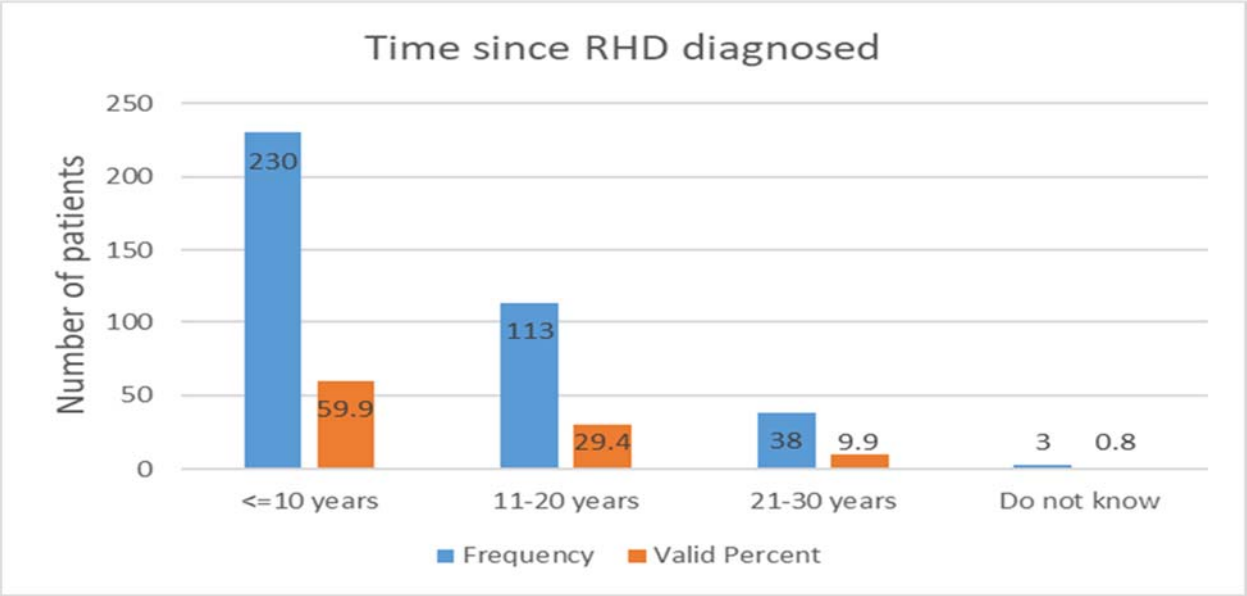

Figure 1. Time since RHD diagnosed among patients with RHD attending adult cardiac clinic at TASH, Addis Ababa, Ethiopia, 2020. **(n=384)**

DISCUSSION

Out of 385 study participants, females were 276 (71.7%), most of them were from urban area 354 (89.6%). The mean age of participants was 31 years. From the study participants, 219(57.2%) reported having had history of sore throat which is lower than the study done in Cameroon (71.1%) which is probably due to different sociodemographic background. Antibiotics were the most prescribed medications, 152(69.7%) and health professionals prescribed treatment for majority of the patients (67.9%) that is higher than Cameroon study, 45% and 35.8% respectively (6).

In this study, 305(70.6%) patients were aware that sore throat is association with heart disease which is better than the Cameroon study in which 70% participants did not know the association between sore throat and rheumatic heart disease (6). About 302(79.6%) have heard about rheumatic heart disease. With regard to knowledge of BPG prophylaxis among patients, 288(75.6%) patients responded as it prevents tonsillitis, and 30(7.9%) patents were aware that it useful to prevent worsening rheumatic heart disease.

Out of 384 participants, 211(54.9%) did not miss monthly injection, 37(9.6%) missed one injection, 51(13.3%) missed two to three injection and 85 (22.1%) missed more than three injections in the past one year. The overall adherence rate for this study was 77.9%, which is better than similar study done in Jimma, Ethiopia (adherence rate was 55.2%) (7). The better adherence rate in this study can be due to the fact that most of participants were from urban area and they have better understanding of benefit of BPG prophylaxis. However, the adherence rate in this study is lower than Indian patients (93.6%) (8) which may be due to difference in socioeconomic background as compared to our patients. Our study finding adherence rate is comparable to Pakistan study finding (73.5%) (9).

Major barriers for prophylaxis in this study was unavailability of drug 216(56.1%), forgetfulness 167(43.4%), health professional refusal to give injection 149(38.7%), cost related to BPG injection 79(20.5%) and fear of side effects 54(14%). This finding is consistent with study done on barriers to BPG prophylaxis in Jimma, Ethiopia where the main barriers were unavailability of medication and drug side effects (10).

This study finding barriers are also consistent with Indian study, the main barriers were non-availability of drug, pain and fear of injection (8). Other influencing factors for prophylaxis in different studies were, treatment schedule, distance from healthcare facility, perception that the symptoms are benign and self-limited and lack of awareness, which were not in this study finding. Poor recall system was barrier in other study, which is similar to this study finding. For majority of participants, 376 (97.9%), the usual waiting time at clinic was less than 1 hour, which is much less than Egypt study, for whom 66% patients waiting for 1 to 3 hours average 2 hours (11).

In this study, for each one-year increase in the age of patients with RHD, the adherence decreases by 3%. This could be probably better family or care giver support for young patients as compared to older patients.

LIMITATION

The limitation of this study is that it was conducted in a single tertiary care center and may not be representative of the country. The other limitation of the study, as it was done over a short period of time and the data may not be complete.

CONCLUSION

Adherence to BPG prophylaxis for RHD was low (77.9%) in patients attending the cardiac clinic at TASH. This study finding barriers might be used as input to find solutions to increase adherence. In addition, creating awareness regarding the benefit of BPG prophylaxis is essential.

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CONFLICT OF INTEREST

No conflict of interest.

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ORIGINAL ARTICLE

DISTAL OESOPHAGEAL CANCER AND ITS HISTOLOGICAL PATTERN: A FIVE YEARS RETROSPECTIVE REVIEW AT MUHIMBILI NATIONAL HOSPITAL, DAR ES SALAAM

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ABSTRACT

Background: *Esophageal carcinoma is a significant cause of morbidity and mortality among cancer patients in Tanzania. Squamous cell carcinoma is the most predominant subtype encountered. But the adenocarcinoma might also occur, especially in the distal third of the esophagus. Risk factors and treatment of these two histological subtypes vary significantly. Hence it is important to understand the true prevalence of Distal oesophageal cancer and that of adenocarcinoma. This study aimed to understand the prevalence of Distal oesophageal cancer and that of adenocarcinoma.*

Methods: *This was a retrospective chart review for patients treated with oesophageal cancer from April 2013 to April 2017 at Muhimbili National hospital. Patients with Distal oesophageal cancer were identified and their socio -demography, Takita's dysphagia grade, tumor length from the upper incisor teeth, endoscopic tumor morphology, histology and stage of the disease was abstracted. Data was analyzed using SPSS where descriptive statistics were computed. Associations were determined using chi-square test with significance set at <5%. Ethical approval was obtained from Muhimbili University Institutional Review Board.*

Results: *Distal oesophageal cancer made 34.1% of all esophageal cancers, with no variations over the five-year review. The mean age of patients with Distal oesophageal cancer was 59.7 years with female predominance at 2:1 for men. Adenocarcinoma was the most predominant histological subtype at 3:1 for squamous cell carcinoma. Low socio-economic status, alcohol drinking, smoking cigarettes and positive history suggestive of Gastro Oesophageal Reflux Disease were common among these patients. Most of the tumors are fungating with late presentation judged clinically with dysphagia as the most common presentation.*

Conclusion: *Clinicians and researchers should be aware of the higher incidence of Distal oesophageal cancer presenting with adenocarcinoma. Failure to recognize this unique entity in a region where squamous cell carcinoma is the most predominant type might result in misinterpretation of data and misallocation during treatment and prognostication.*

Keywords*: Distal oesophageal cancer; Distal esophageal cancer; esophageal adenocarcinoma; gastro esophageal cancer; esophageal cancer trend*

INTRODUCTION

Oesophageal Cancer (EC) ranks seventh globally in incidence and sixth in mortality accounting for 1 in 20 of all cancer-related mortality in 2018 (1). EC exhibits geographical variations with rates reported to be higher in Eastern Asia and Eastern Africa regions including in Tanzania (2). Two commonly encountered histological subtypes also show significant geographic variation: oesophageal Squamous Cell Carcinoma (ESCC) is predominant in many Low – and – Middle-Income settings (LMICs) and oesophageal adenocarcinoma (EAC), typically occurring in the distal oesophageal , is predominant in the High-Income Countries (HICs) settings (3).

Therefore, to properly understand EC in any region, it is important to take into consideration this histological variability as they have different risk factors to address. The synergistic effect of heavy drinking and smoking has been responsible for risk factors for ESCC in the HICs while the risk factors in LMICs are still elucidated (4). The increasing prevalence of obesity and waist circumference, GERD, and the decline in H.pylori infection due to improvements in hygiene are speculated to be responsible for the increase in EAC in the HICs (5). With rapid westernization in many LMICs, how these factors shape the histological subtype in the distal oesophageal had remained unknown.

Furthermore, the treatment classification and outcomes measures differ significantly between the two histological groups just as is their aetiology (6). In Tanzania, EC ranks 5th by contributing to 2,516 cases and is 3rd in mortality by 2,486 cancer-related deaths in 2018 alone (7). The true impact of westernization on distal oesophageal cancer, which should be predominantly EAC, has remained unknown and unattended. This has led to misclassification of patients with

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EC by grouping them as a similar entity of disease by the clinicians. Understanding distal oesophageal cancer burden and its histological subtype hence became a necessity to address the disparities in research and treatment among patients with EC in Tanzania and the region, which this study aimed to address. This study will add value to the on-going case-control studies in this region and also address outcomes among these patients.

METHODS

Study design and setting
This was a hospital-based retrospective study conducted at Muhimbili National Hospital (MNH) and Ocean Road Cancer Institute (ORCI) from April 2013 to April 2017. The two hospitals, both located in Dar es Salaam, provide comprehensive cancer management in Tanzania. MNH offers diagnostic and surgical care to EC patients, and ORCI offers chemotherapy and radiation therapy services to the same patients.

Study population
Patients who presented with dysphagia and were diagnosed to have EC during the study period were involved. Cases were included if they had histological confirmation of EC from MNH pathology laboratory, and had endoscopically detected lesions at or below 30cm from upper incisor teeth. Patients of all sexes and age groups were included.

Subjects identification
The Muhimbili National hospital histopathology registry was examined to identify all patients with a diagnosis of oesophageal cancer during the period under review. Hospital registration numbers, names and sex were collected in an excel spread sheet identifying 1200 cases. Since some patient might have reached ORCI without going through MNH histopathology registry, similar exercise was repeated by collecting all the hospital registration numbers, names and sex on a separate excel spread sheet identifying 1056 cases. The two excel spread sheets were merged to remove duplicates whereby 1000 patients with oesophageal cancer remained in the final excel spread sheet. The 1000 case notes were reviewed to identify EC patients with an endoscopic diagnosis of distal EC. The two lists were compared for similarity and where discrepancy arose, an independent abstractor was assigned to repeat the abstraction process for the individual case.

Study power
With 34.1% of patients having distal oesophageal carcinoma, the study had the power of 80% to detect the difference of less than 5% with 95% confidence interval of between 0.3116 and 0.3713.

Variables collected
Variables collected from the case notes included demography of the patients: age in years, occupation of the patient, level of education, Risk factors include: smoking, alcohol intake, reported a family history of oesophageal cancer, features of GERD. Clinical features including the modified Takita's dysphagia score, the endoscopic tumour location from the upper incisor teeth and tumour morphology, the histological tumour type, and stage of the disease.

Data analysis
Data were checked for completeness, de-identified, coded, and entered into Statistical Package for Social Scientists (SPSS) software version 26 for analysis. Categorical variables were summarized as proportions while continuous variables were summarized as means with standard deviation. Tumour location was sub-grouped as at 35cm, 35 to 36cm, and at 37cm and compared by the two histological subtypes. Significant differences in histology by the length from the upper incisor were considered when the p-value was less than 5%. Patients were grouped as young (< 40years), middle-age (40 – 60years), and elderly (> 60 years of age). The proportion of patients with the common risk factors was computed among those in whom they were reported. The trend over five years was computed by comparing the proportion of distal EC over total EC during each year and plotted on a line curve.

Ethics approval
The study protocol was reviewed and approved by the Institutional Review Board of the Muhimbili University of Health and Allied Sciences and permission to conduct the study was obtained from Muhimbili National Hospital and Ocean Road Cancer Institute administration. No direct patient identifiers were used during data analysis following the de-identification process.

RESULTS

We identified 1000 case notes of patients with a histological diagnosis of oesophageal cancer of which 341 were found by endoscopy to have a distal oesophageal cancer giving an incident rate of 34.1%. In **Table I** below, we describe the socio-demography and risk factor profile of patients with distal EC. They had a mean age of 57.9±13.7 (29 – 92) years and the majority were 40 years and older. Females were the majority with a female to male ratio of 2:1. Most patients had low socioeconomic status characterized by a primary level of education in 260 (76.3%) and peasant as occupation in 189(55.4%).

Table I: Demography, risk factor profile and year of diagnosis of patients with distal oesophageal carcinoma at MNH 2013-2017

Variable	Frequency (%)
Age groups (years)	
< 40	39 (11.4)
40 to 60	152 (44.6)
> 60	150 (44.0)
Sex	
Male	112 (32.8)
Female	227 (66.6)
Education level attained	
Primary	260 (76.3)
Secondary	68 (19.9)
Secondary and above	13 (3.8)
Occupational status	
Peasant	189 (55.4)
Employed	117 (34.3)
Not employed	35 (10.3)
Family history of EC (n=321)	
Yes	40 (12.5)
No	281 (87.5)
Alcohol (n=321)	
Yes	227 (66.6)
No	114 (33.4)
Smoking cigarette (n=273)	
Yes	132 (48.4)
No	141 (51.6)
History of GERD (n=321)	
Yes	200 (60.4)
No	131 (39.6)

Of the assessed risk factors, alcohol information was available in all the patients of which 66.6% reported having used it. Family history was positive in 12.5% of 321 cases. GERD presentation was collected in 331 with 60.4% reporting positive history. Cigarette smoking was reported in 48.4% of the 273 patients.

In Table II, we present the clinical presentation as dysphagia grade assessed by modified Takita's grading system summed in four groups with combined Grade five and six. A majority had grade three dysphagia in 163 (47.8) followed by grade II dysphagia in 123 (36.1). The most predominant endoscopic morphology was that of a Fungating tumor seen in 288(84%) of the patients followed by that of ulceration in 38(11.1%). Histologically, tumors were either adenocarcinoma or squamous cell carcinoma with the former being the most predominant type in 249(73%).

An overwhelming majority of the patients were reported to have a locally advanced disease clinically in 290 (85%).

The mean tumor location from the upper incisor for the distal adenocarcinoma was 35.7±2.8 (32 – 40) cm. We grouped tumors as below 35cm, from 35 to 36cm, and at 37cm and beyond. Adenocarcinoma was predominantly present at all intervals of the distal oesophageal when compared to oesophageal carcinoma. This dominance was significantly increasing downwards (p=0.0001). [**Fig. 1**]

Table II: Clinical presentation, endoscopic tumor morphology, histologic type and stage at diagnosis for distal oesophageal cancer at MNH 2013-2017.

Variable	Frequency (%)
Modified Takita's dysphagia grade	
Grande 2	123 (36.1)
Grande 3	163 (47.8)
Grande 4	30 (8.8)
Grade 5 and above	25 (7.3)
Tumor endoscopic morpholo-gy	
Fungating	288 (84.5)
Ulcerative	38 (11.1)
Stricturing	9 (2.6)
Infiltrative	4 (1.2)
Not documented	2 (0.6)
Histological type	
Adenocarcinoma	249 (73.0)
Squamous cell carcinoma	92 (27.0)
Stage at diagnosis	
Locally advanced	290 (85.0)
Metastatic	46 (13.5)
Not documented	5 (1.5)

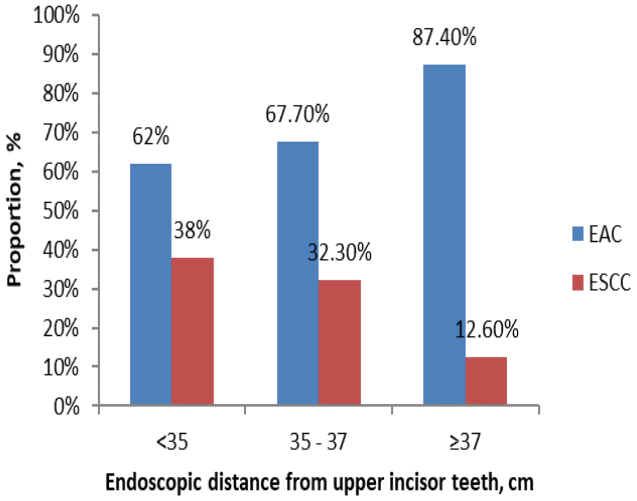

Figure 1: Columns showing three distance categories from upper incisors teeth stratified by histologic diagnosis for distal EC.

We finally evaluated to see if distal oesophageal carcinoma has been increasing over the five years. **Fig. 2** depicts a near stable pattern whereby distal oesophageal cancer constitutes about 30% of oesophageal cancer. There was an almost 9% drop in 2015 but a steady rise was seen in 2016 continuing through to 2017.

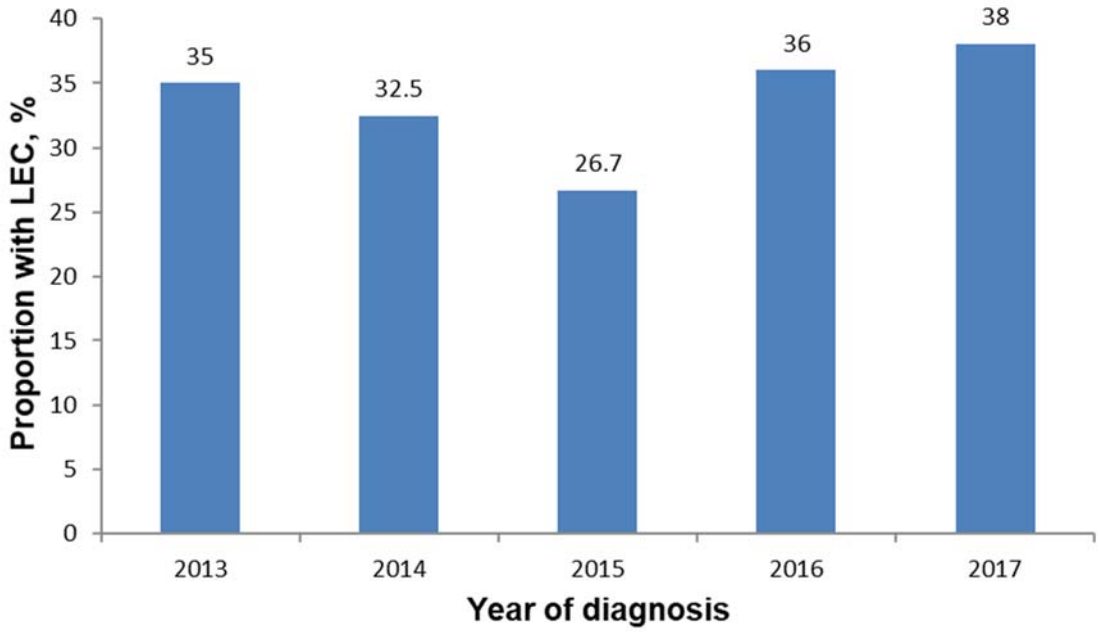

Figure 2: Bar chart showing five year trend of distal oesophageal cancer in Dar-es-Salaam from 2013 – 2017.

DISCUSSION

Incidence of distal cancer

This is the first study that looked at distal EC in a region recognized globally as a high-risk belt for EC in general.

We report a predominance of adenocarcinoma (AC) in the distal oesophageal in a geographic region where the usual predominant subtype has been SCC: 1 in 3 histological subtypes identified were of EAC. However, the prevalence of SCC in the same region was still high when compared to the picture seen in Europe and the US (8, 9). Overall, SCC is still the most predominant cancer globally with EAC now constituting about 40%, up from 10% 4 decades ago (10). The predominance of distal EAC in the west has been linked to the rise of risk factors such as obesity, gastroesophageal reflux, and Barrett's oesophageal (11). The exact risk factors for EAC in this setting remain unknown, likewise that of ESCC. Current risk factor studies have focused on SCC, but with this picture of a similarly higher prevalence of EAC, there is a need to not forget that the risk factors might be different. Segregation of data based on histology cannot be avoided to get accurate data on EC risk in this region with a high incident case.

Alcohol, Smoking, and GERD

Two fifth of patients with distal EC had a positive history of smoking and 2 in 3 of the patients had reported being taking alcohol. Both cigarette smoking and alcohol intake are known to be strong risk factors for ESCC with little conclusion on their role on EAC of the oesophageal (12). The confounding effect of other factors responsible for the development of distal oesophageal malignancies needs to be further explored in this setting. The just -completed case-control study on EC in Tanzania, carried out at MNH, focused only on ESCC.

Gastroesophageal Reflux Disease (GERD) has long been known to be a predisposing factor for the development of Barrett's oesophageal (13). GERD is not properly investigated in our setting but a prolonged history of heartburn was taken as a surrogate for GERD.

However, racial differences in the occurrence of GERD were seen in the US with a distal incidence among black when compared to whites (14). This was despite other studies showing the similar prevalence of heartburn, of all severities, among races (15). But, with more than half of our patients with distal EC reporting a positive history of heartburn, the role of GERD should not be underrated. Identifying patients with GERD in society and treating them has been shown to reduce the incidence of AC of the oesophageal and oesophago-gastric junction (EGJ) in the west (16). Studying the prevalence of GERD in Tanzania and instituting medical treatment and follow up therefore has the potential to address EAC in the distal oesophageal.

Smoking and features suggestive of GERD together with obesity have long been known to be causative of distal EAC of the oesophageal (17). In Tanzania, obesity is not anticipated among people of low socio-economic status unlike in the High- Income countries (18). In Tanzania, obesity has been noted to be more prevalent among high socioeconomic status groups, especially among women (19, 20). Looking at academic status and employment status, most of the patients we reviewed here had low socioeconomic status. This makes the potential role of obesity, though not studied, doubtful but still probable in our setting. A comprehensive study, evaluating all the currently known risk factors for distal oesophageal EAC is urgently needed as there is the potential to intervene.

Gender disparities

While it is known that EC, both EAC, and ESCC, is a male predominated disease (21), our findings suggest a higher prevalence of distal EC among the female sex in the Tanzanian population. Hypothesis towards the male predominance in the West was linked to the protective role of oestrogen among females, lost as they attain menopausal status (22). Oestrogen receptors are known to induce oesophageal cell apoptosis, hence preventive for both ESCC and EAC in western populations (23). The endogenous oestrogen effect is lost following menopausal attainment. Being a retrospective study, the menopausal status of EC patients is not routinely captured hence was not studied. But it is known that African women reach menopause almost a decade or earlier compared to western counterparts (24). Women in Africa might therefore not have these oestrogen protective effects against oesophageal cancer. But this selectively higher female prevalence in the distal oesophageal needs further scrutiny.

Genetic predisposition

About 1 in 10 of our patients had a documented history of having a family relatedness that had developed EC. Genetic predisposition is unusual except with palmar and plantar keratosis (tylosis) where up to 95% of victims will develop EC by age 65 (25). It is important to study these patients further during the clinical assessment to document the presence or absence of palmar and plantar keratosis. This familial clustering, though rare, is shown to occur at a relatively young age and is associated with a poor prognosis (26). Quantifying the number of family members affected is needed among these patients to rule out the possibility of chance alone (27). The involvement of two or more first-degree family members with EC had up to 10-fold increased risk for cancer (28). There is a possibility of genetic risk that is based on the Nucleotide Excision Repair pathway which is exacerbated by ever-smoking, overweight/obesity, male sex, and ever drinkers (29). Epidemiological studies properly assigning genetics risks coupled with targeted genetic studies among younger victims of EC are needed in the African population.

Management implications

The two histological subtypes demand different management approaches hence every effort should be made to have this clear to practicing clinicians and oncologists. The recently launched Tanzania National Cancer treatment guideline did not make this distinction. Even though occurring in the same location, EAC and ESCC are staged differently (with regards to primary tumour status and tumour grade for stage I – IIIb) hence the need to pay attention to this histological difference in the distal oesophageal (30). Failure to properly stage these patients might result in misplacement in treatment category suitability. EAC in the distal stomach might be categorized as gastric cancer or EC according to Siewert-Stein classification for Gastroesophageal junction tumours.

Tumour location was only provided as the distance of the upper margin from the upper incisor teeth. This is contrary to the current requirement by the 8th edition of the AJCC staging system for all EC to be reported from the epicentre of the tumour and be assigned c (31). This is important for treatment planning and can either be obtained endoscopically if no complete obstruction or by chest computed tomography. Similarly, knowing the epicentre is more important for adenocarcinoma of the distal oesophageal as it can reclassify them as either oesophageal cancer or gastric cancer according to Siewert-Stein's classification. Distal adenocarcinomas with epicenters no more than 2cm from the gastric cardia are classified as oesophageal carcinoma while the rest are adenocarcinomas. (32)

Management of EC has significantly evolved over the years with the introduction of neoadjuvant Carboplatin and Taxol plus 41.1Gys concurrent therapy followed by surgery. This study demonstrated significant benefits for the ESCC and only marginal benefits for EAC (33). It is important to follow current evidence when managing patients with distal oesophageal cancers. This can only be realized if patients are properly assigned a proper histological diagnosis and further sub-categorization of the EAC groups into the three Siewert groups.

Conclusion

Distal oesophageal cancer is not uncommon in Tanzania, affecting 1 in 3 patients with EC. We have demonstrated a higher predominance of oesophageal adenocarcinoma over squamous cell carcinoma occurring in these patients. Failure to recognize this unique entity in a region where squamous cell carcinoma is the most predominant type had led to misinterpretation of data and misallocation during treatment and prognostication. This present study highlights the urgent need to consider this entity of patients in the case-control studies and treatment strategies. Further research is needed to fully expose the aetiology of oesophageal adenocarcinoma in Tanzania.

List of abbreviations

AJCC	America Joint Committee on Cancer
EAC	Oesophageal Adenocarcinoma
EC	Oesophageal Cancer
ESCC	Oesophageal Squamous Cell Carcinoma
GERD	Gastro oesophageal Reflux Disease
HIC	High Income Country
MNH	Muhimbili National Hospital
MUHAS	Muhimbili University of Health and Allied Sciences
LMIC	Low and Middle Income Country
SPSS	Statistical Package for Social Sciences

Declarations

Ethics approval and consent to participate

MUHAS IRB approved this study in accordance with the declaration of Helsinki and waiver of consent was provided.

Consent for publication

MUHAS IRB provided consent for publication

Availability of data and materials

Data that gave this report shall be available on fair request to the corresponding author's institution.

Competing interests

All authors have completed the ICMJE uniform disclosure form (available at: http://dx.doi.org/10.21037/aoe-2020-geja-01). The authors have no conflict of interest to declare.

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Authors' contributions

(I) Conception and design: LO Akoko, FM Sudai; (II) Administrative support: LO Akoko; (III) Provision of study materials or patients: None; (III) Collection and assembly of data: FM Sudai, NE Kivuyo; (IV) Data analysis and interpretation: LO Akoko, and R Khamis; (V) Manuscript writing: All authors; (VI) Final approval of manuscript: All authors.

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ORIGIONAL ARTICLE

DRINKING WATER ANTIMICROBIAL RESISTANCE ENTERIC BACTERIAL LOAD AND PUBLIC HEALTH RISK IN NORTHWEST, ETHIOPIA: A LABORATORY-BASED CROSS-SECTIONAL STUDY

Chalachew Yenew*[1], Melese Kebede[2], Melkamu Mulat[3]

ABSTRACT

Background: The security of the drinking water supply has been sullied by antimicrobial-resistant bacteria at the source, within the dispersion framework, and amid families dealing with, which may cause intense or incessant wellbeing issues. Therefore, this study aimed at determining the antimicrobial-resistant bacterial contamination, health risk, and associated factors of drinking water in Northwest Ethiopia.

Methods: A laboratory-based cross-sectional study was employed by taking 60 water samples collected from the household tap and drinking water storage container by following the standard microbial analysis method. Besides, a sanitary survey was conducted for the municipal water supply system from March to May 2020. Descriptive statistics and multiple linear regression models were employed.

Results: The prevalence rate of multidrug resistance *Escherichia coli* species was 80% (95% CI: 76.9-81.2 %), Salmonella species was 40% (95% CI: 38.7-45%) and Shigella species was 60% (95% CI: 56.9-65%). The overall Health risk index (HRI) of drinking water showed that 45.83%, 41.67%, and 12.5% of them were categorized as low, intermediate, and high-risk classes, respectively. The load and health risk could be strongly correlated with the low residual chlorine of drinking water.

Conclusions: The contamination of drinking water with antimicrobial-resistant waterborne bacteria in the community could indicate an occurrence of treatment failure. Hence, proper drinking water treatment and strict supervision are needed to prevent the contamination of the water and related consequences.

Keywords: Antibiotic-resistant bacteria, Drinking water, Health risk, Ethiopia

BACKGROUND

The prevalence of antimicrobial-resistant pathogens, including waterborne antibiotic-resistant bacteria, is ever increasing. The widespread emergence of AMR bacteria has become one of the grimmest challenges in low-income countries including Ethiopia resulting from irrational antibiotic consumption, prescription without susceptibility test, self-medication, and prolonged hospitalization (1). Some experimental studies and surveillance in Ethiopia showed that *E. coli, Shigella*, and *Salmonella* species developed resistance to frequently recommended antibiotics (2).

In Ethiopia, 54% of households that use an improved source of drinking water. Nine households in every ten used non-treated drinking water. Emerging risks and challenges are those that are coming into existence because of changes in the environment. Assessment of the qualities of urban water source and tap water distribution systems in Arba-Minch town showed that the distribution lines were contaminated with Waterborne Bacteria (WBB) such as *Salmonella* and *Shigella* (3).

A study conducted in North Gondar, on the other hand, showed that 50% of water samples collected from water lines contaminated with indicator WBB *E.coli* (4). Assessment of the level of AMR contamination and source identification is highly relevant for policy intervention. Therefore, This study aimed at determining the antimicrobial-resistant contamination, health risk, and associated factors of drinking water in Northwest Ethiopia.

METHODS

Study design and period

A laboratory-based cross-sectional study was carried out for a month from March to May 2020 at Debre Tabor town, Debub Gondar Zone of the Amhara Region, about 100 kilometers southeast of Gondar and 50 kilometers east of Lake Tana. This historic town has a latitude and longitude of 11°51′N 38°1′E with an elevation of 2,706 meters above sea level.

Sample size determination and sampling technique

A total of 60 water samples each from the drinking water tap and storage container of the household was taken using random sampling techniques (5).

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Water sample collection

For bacteriological analysis, drinking water samples were collected using an autoclaved bottle containing two drops of sodium thiosulfate (10% $Na_2S_2O_3$) for complete neutralization of any residual chlorine present and preserving microbial contamination. Before taking a sample from the tap, the mouth of the tap was cleaned with a clean cloth to remove any dirt if present (6). Then, the drinking water of the tap was flushed for 5 min and then sterilization of the mouth of a tap was done with a spirit of flame followed by cooling it with water to run for 1–3 min at a medium flow (7). Then the sterilized bottle was opened, filled with water, leaving a small air space, and shaked before analysis. The collected water samples from each source were labeled and kept in a cold box containing ice freezer packs (<4ºC) and transported to Felege Hiwot Referal Hospital.

Sample processing techniques of WBB isolation and susceptibility testing

Sample preparation

Every 10 ml of sample was aseptically homogenized into 90 ml of sterile peptone water in a clean 250 ml sterile jar, shaken, and 1:10 dilutions were made using Poured techniques (8). The water samples of the tap and storage container were further diluted by mixing 1ml of each homogenized sample and 9ml of sterile 0.85% physiological saline solution (NaCl) to make 10^{-5} dilutions using a vortex mixer. For the water samples collected from the household tap and storage container, homogenized samples were plated.

WBB isolation and identification technique

0.1ml of the prepared diluted sample was directly inoculated on differential and selective agar media after primary and secondary enrichment, and incubated at 37 °C for 18–24 hours. After incubation, lactose and precipitated bile salts were added for presumptive identification of *E. coli* on the selective medium MacConkey agar. Thiosulfate and Ferric Citrate were used to observe hydrogen sulfide production for presumptive identification of *Salmonella* and *Shigella* on Selective medium SS agar.

MDR profile testing

We have performed the M D R testing for all the isolated WBB species. The slanted cultures were subcultured and purified. The pure colonies were inoculated into Nutrient Broth and incubated at 37^{O}C for 18-24 hours.

After incubation, the turbidity of the culture was adjusted to 0.5 McFarland Standard to bring the cell density to approximately 10^{7}-10^{8}cfu/ml. A sterile cotton swab dipped the standardized suspension. The culture was spread evenly over the entire surface of the Muller-Hinton agar plates by swabbing in three directions at 90^{0} of each spreading. The plate allowed drying before applying antimicrobial discs. The following standard and Oxoid drug discs used: Vancomycin (VA) of 30µg; *Cotrimoxazole* (SXT) of 25µg; Ciproflaxicillin (Cip) of 5µg; *Doxycycline* (DC) of 30µg and Amoxicillin (AMX) of 2 µg, that were commonly used antibiotics in Ethiopian healthcare facilities based on the guidelines developed from Clinical and Laboratory Standards Institute of US (9).

Health risk analysis

To measure the sanitary condition and analyze the risk to health matrix,the World Health Organization (**WHO**) standards recommended to determine the degree of contamination were used(10). Besides, data on sanitary inspection of water sources were collected using the standard format described by WHO and UNICEF (11).

An observation checklist (sanitary inspection form) containing ten items and consisting of a set of questions with yes or no answers was used. A risk factor was assigned with a score of 1 for yes, while a risk factor with a score of 0 for no. A combination of the scores for each item was used to determine the sanitary risk scores, which were categorized into four categories: 0-2, 3-5, 6-8, and 9-10 for low, moderate, high, and very high risk of contamination, respectively.

Quality control

We assigned qualified, competent, and proficient laboratory personnel's for the laboratory analysis and data collection, as well as the personnel that interpreted the results and those that were involved in the monitoring of AMR. Before the actual data collection, training, and discussion with 02 supervisors, 03 data collectors, and 02 laboratory technicians were undertaken for 02 days. Triplicate and duplicate samples were collected. Information on each sampling site and identification of the sampling locations were done by *Global Positioning System* (*GPS*). To check the sterility of the prepared media, 5% of the prepared batch of media was incubated overnight and checked for microbial growth in the media, and reference strains were also used.

Data analysis

The data were coded and entered using Epi info-7 and exported to STATA version 16. then Mean prevalence of AMR bacteria, variability, and linear regression were executed by using STATA statistical software version 16. We conducted a multiple linear regression model to determine the relationship between AMR WBB in drinking water with associated factors.

Ethics Approval

Ethical clearance was obtained from the Institutional Review Board of the Jimma University and an official letter was submitted to the concerned bodies. The concerned bodies were informed to get the assurance of the study and confidentiality was maintained at all levels of the study. Informed consent was obtained from all participants and the Institutional Review Board of the Jimma University approved it with Ethical approval of Research protocol letter with its reference number IRB00010/2020.

RESULTS

We collected 60 drinking water samples each from the household tap and storage container.Households use both improved and unimproved water sources for their daily water consumption. Based on the present survey, about 112 (93.33%) and 8(6.67%) households used improved and unimproved sources of water; respectively. the Household hygienic practices for handling of drinking water, presence and concentration of *Salmonella, Shigella, TC,* and *E. coli,* MDR level and Health risks was determined. We also compared the microbiological quality results of drinking water samples from household taps and a storage container with national/WHO/EPA guidelines.

Household hygienic practices for handling and WBB analysis of drinking water

In this study, we assessed the hygiene of household taps and storage containers using sanitary inspection checklist. 63.9% of the respondents treated their drinking water, which was fetched from the tap before consumption. Out of the total respondents who treated their drinking water, 55.88% used ceramic water filters, while 23.53% added chorine and 20.58% boiled water. Among the drinking water assessed, 30.56% of the area around the tap was in an unhygienic environment. Besides, 36.11% of the drinking water storage containers had poor hygiene (Table 1).

Table 1: The hygienic status of household tap and storage containers found at Debre Tabor town, Ethiopia, 2020.

S.NO	Items	Alternative	Respondent (%)
1.	Do you use anything to make drinking water safer?	Yes	63.9
		No	36.1
2.	Methods used to make drinking water safer?	Boiling	20.58
		Adding chlorine	23.53
		Water filter	55.88
3.	Are there any flies, dust, and other contaminants around the area of the tap?	Yes	30.56
		No	69.44
4.	Are there any flies, dust, and other contaminants around the area/on the storage container?	Yes	36.11
		No	63.89

The results showed that 27 % of the drinking water samples collected from the household tap were contaminated with TC with an overall mean±SD (11.19±11.45) whereas 50% of the drinking water samples collected from a storage container were positive with TC value of 47.15±27.0. The adjusted mean±SD of *E.coli* counts for drinking water samples collected from the household tap and storage container were 3.45±1.70 and 6.32±7.61 sequentially. Besides, 23% of the drinking water samples of the Tap contaminated with *Shigella* at a rate of 3.45±1.72while 3% of drinking water samples of household containers had *Shigell*a at the rate of 2.32±1.6. Moreover, 33.33% of drinking water from the tap was also contaminated with *Salmonella* with a rate of

and 23% of the drinking water from storage containers contaminated with *Salmonella with a rate of* 3.02 ±2.71 (Table 2).

The prevalence rate of MDR *E. coli* species was *80%* (95% CI: 76.9-81.2 %) with resistance to AMX, SXT, and VA with a MIZ of 8.5mm (95% CI: 6.5-8.9mm), *Salmonella* species was 40% (95% CI: 38.7-45%) with resistance to Van, SXT, and AMX with a MIZ of 7.83mm (95% CI: 6.2-9.4mm) and *Shigella* species was 60% (95% CI: 56.9-65%) with resistance to SXT, AMX, VA, & DC with a MIZ of 7.65mm (95% CI: 6-8mm) (Table 3).

Table 2: Summary of WBB counts (% or Mean±SD in log CFU/100ml) of water samples collected from the tap and household storage containers of Debre Tabor town, Ethiopia, 2020

WBB	N	Frequency	Adjusted Mean±SD in log CFU/100ml	WHO, 2004 standard
Drinking-water of the tap				
TC	30	8 (27%)	11.19±11.45	
Shigella	30	7 (23%)	3.45±1.72	0 cfu/100ml(A)
Salmonella	30	10(33%)	2.87±2.63	0 cfu/100ml
E.coli	30	14 (46%)	3.45±1.70	0 cfu/100ml (A)
Drinking-water of the household storage container				
TC	0	15 (50%)	47.15±27.0	
Shigella	0	2 (3%)	2.32±1.61	0 cfu/100ml (A)
Salmonella	0	7 (23%)	3.02 ±2.71	0 cfu/100ml (A)
E.coli	0	10 (30%)	6.32±7.61	0 cfu/100ml(A)

Table 3: MDR level of WBB isolated from Drinking water in case of Debre Tabor Town, 2020.

WBB species	Resistance		Sensitive		MDR Rate
	Antibiotics	MIZ	Antibiotics	MIZ	
E.coli	AMX, SXT & VA	8.5mm (95% CI: 6.5-8.9mm)	CIP& DC	25.50mm (95%CI: 22, 29.45)	*80%*(95% CI: 76.9-81.2 %)
Salmonella	SXT, VA&AMX	7.83mm(95% CI: 6.2-9.4mm)	CIP& DC	27.50mm (95%CI: 23.25,30.45)	40% (95% CI: 38.7-45%)
Shigella	SXT, AMX, VA, & DC	7.65mm(95% CI: 6-8mm).	CIP	19mm (95% CI: 16.5, 23.2)	60% (95% CI: 56.9-65%)

Health risks of drinking water consumption contaminated with AMR

The overall Health risk index (HRI) of drinking water showed that 45.83%, 41.67%, and 12.5% of them were categorized as low, intermediate, and high-risk classes, respectively (Table 4).

Associated factors with AMR WBB in drinking water

According to the correlation analysis of the WBB, their growth parameters, and the level of Sanitary Risk (SI), most of the bacteriological parameters showed a significant correlation with the SI level of risk and a significant correlation with residual

Table 1: The hygienic status of household tap and storage containers found at Debre Tabor town, Ethiopia, 2020.

Sample	SI	*Total coliform*					*Fecal coliform*			
		1-10	10-100	100-000	>1000	0	1-10	10-00	100-1000	>1000
Tap	1-2	4	2	0	0	19	1	1	0	0
	3-5	8	11	0	0	7	5	0	0	0
	6-8	0	3	0	0	0	3	0	0	0
	9-10	0	0	0	0	0	0	0	0	0
HHSC*	1-2	4	18	0	0	12	3	1	0	0
	3-5	0	10	3	0	6	3	10	0	0
	6-8	0	1	0	0	0	0	1	0	0
	9-10	0	0	0	0	0	0	0	0	0
HRI			Low		45.83%					
			Intermediate		41.67%					
			High		12.5%					

***Where: HHSC: Household Storage Container, SR: Sanitary Risk**

chlorine concentration. The bacteriological parameters assessed *by TC* in the drinking water storage container showed a relative strong correlation with SI (*Correlation coefficients* (r) = 0.856**) and with residual chlorine concentration (*Correlation coefficients* (r) = 0.622**) (Table 5).

DISCUSSION

WBB of drinking water determination is a good representative of public health risk since it can be a medium for the transmission of pathogenic disease, particularly from fecal contamination. A similar study conducted in Nekemte town has shown that 37% of the drinking water was contaminated

Table 5: Correlation analysis output of WBB growth parameters, sanitary inspection risk score, *and drug use characteristics (CHXS) with AMR WBB load for each water sample at Debre Tabor town, Ethiopia, 2020.*

Growth parameters	AMR WBB					
	On Tap water			On Household storage container water		
	E.coli	*Salmonella*	*TC*	*E.coli*	*Salmonella*	*TC*
pH	0.106	0.144	0.097	-0.091	0.046	0.023
Conductivity	0.289	0.209	0.157	-0.037	0.089	0.061
Turbidity	0.164	0.084	0.207	0.001	0.008	0.116
Residual chlorine	0.674**	0.713**	0.633**	0.787**	0.620**	0.622**
Drug use CHXS	0.004	0.084	0.007	0.001	0.008	0.016
Sanitary Risk (SI)	0.711**	0.601**	0.493**	0.741**	0.562**	0.856**

**. Correlation is significant at the 0.05 level (2-tailed).

with *FC*, which was more than that of the present study(12). However, *E.coli's* finding in this study was higher than those from the studies conducted in Addis Ababa City (2.4%) (13)and Dharan, Nepal town (21.1%) (6).

This difference might be due to the difference in the safety and quality control of water through the evaluation of water sources and managing contamination of water supply. Moreover, it may associate with frequent pipe breakage, leakage, and passing of pipelines through the ditches and drainage systems.

The *E.coli* load was higher than the study conducted in Kolla diba town of Ethiopia (32.5%) (14) And lower than Babati town. Tanzania (86%) of drinking water samples contaminated with *E.coli*(15). The difference might be the treatment of drinking water and variation in climatic conditions.
According to Temesgen & Hameed (2015), there was high contamination of drinking water with AMR WBB due to improper treatment and the existence of poor sanitation (17). Assessment of the qualities of urban water source and tap water distribution systems in Arba-Minch town revealed that the distribution lines were the most contaminated with AMR WBB, such as *Salmonella* and *Shigella* (3).

The relationship between sanitary inspection scores and the bacteriological risk category is used to identify the level of risk of contamination due to AMR WBB. A study conducted by Tsega*et et al.* (2013)showed that the total sanitary risk score had a significant relationship with the level of fecal contamination(18). Moreover, a similar study conducted in Bahir Dar town showed that 45.7% and 11.4% of drinking water samples had low and very high-risk scores, respectively(19). The reason for the difference in risk score between the present study and the study conducted by Milkiyas *et al.* (2011) and Tsega et al. (2013) might be the hygiene and sanitation condition of the water storage container, awareness of the community towards water storage container and the dose of residual chlorine. The limitation of all previously conducted studies and the present study was that they used the membrane filter and culture method, not molecular analysis techniques.

CONCLUSIONS

The finding of this study has shown possible health hazards related to the consumption of drinking water. Identification of these hazards would help health officials to pay attention to safety and quality issues regarding drinking water. Moreover, it would contribute to the awareness of consumers and water sector officials about safety and quality issues related to the consumption of drinking water. It can encourage water sector officials to follow proper water treatment procedures during distribution up to consumption. The finding suggested the importance of water quality training for humans working in water sectors, implementation of water treatment, and strict follow-up of the implementation of acceptable hygienic practices might improve water quality. Besides, minimizing irrational drug use could also help to reduce AMR in drinking water and the environment.

List of Abbreviations

WBB: Waterborne Bacteria; CIs: Confidence Intervals; WHO: World Health Organization; US: United State; EPA: Environmental Protection Agency; *E. coli: Escherichia coli*; ARR: Antibiotic Resistance Rate; MIZ: Mean Inhibition Zone: MDR: Multidrug Resistance: mg/l milligram per liter, pH: negative logarithmic concentration of hydrogen, SD: Standard Deviation: SI: Sanitary Inspection, TC: Total Coliform; UNICEF: United Nations Children's Fund

Declarations

Consent to Publish
Not applicable because no person's data is in the manuscript.

Availability of Data and Materials
All data and materials are available from the corresponding author. Thereforeat a reasonable request, the corresponding author shared it via email.

Competing Interests
The authors declared that they had no any financial and nonfinancial competing interests.

Funding
No funds were obtained for this study.

Authors' Contributions
MK has been actively involved during the conception of research issues, MM is involved in the development of research proposals, and CY has been involved in conception of research issues, development of research proposals and writing of various parts of the research report and prepares the final manuscript. All authors have read and approved the final version of the manuscript. Chalachew Yenew had full access to all data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

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CASE REPORT

PROPYLTHIOURACIL-INDUCED SEROPOSITIVE VASCULITIS WITH ALVEOLAR HEMORRHAGE

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ABSTRACT

Propylthiouracil (PTU) is a commonly used anti-thyroid medication. As a rare complication, PTU can induce antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), resulting in nephritis and alveolar hemorrhage. Here we presented a 52 years old Ethiopian woman who developed AAV during her PTU therapy for toxic goiter. Her clinical, laboratory, and chest imaging were all consistent with the diagnosis. She showed marked improvement after discontinuation of the medication and the addition of corticosteroid and cyclophosphamide. Our case, the first in Ethiopia, illustrates the importance of attentiveness, early identification, and management of this rare side effect of PTU therapy.

***KEY WORDS**: Propylthiouracil, ANCA, Vasculitis, Alveolar Haemorrhage*

INTRODUCTION

Propylthiouracil (PTU) is a common medication used to treat thyroid disorders. A high percentage of patients on this medication have antineutrophil cytoplasmic antibodies (ANCA). However, only a few of these patients develop ANCA-associated vasculitis (AAV), manifesting with alveolar hemorrhage (DAH) and glomerulonephritis [1-4]. We present the first reported case in Ethiopia of a 52-year-old woman who experienced AAV during PTU therapy for a toxic goiter.

Case Presentation

A 52 years old Ethiopian woman who has been taking PTU for the past three years for toxic goiter**,** linked to our pulmonary clinic for cough and blood-tinged sputum, headaches, and easy fatigability of 2 weeks duration. Given her clinical presentation and abnormal CXR (bilateral lower lobe infiltrates), she was initially treated by her primary care physician with antibiotics (ceftriaxone and azithromycin) for pneumonia.

She failed to clinically improve and was referred to our Chest Clinic for further evaluation. Additional history revealed a PTU dose of 100 mg daily, essential hypertension on nifedipine, and previously treated hepatitis C with a sustained viral response.

On evaluation, her vital signs were as follows: BP 125/85mmHg, RR 22bpm, PR 111bpm, T 36.5^{o}C, and SO2 95% on room air at rest.

Her physical examination was significant for pale conjunctiva, anterior neck mass (nodular goiter), and bibasilar crepitation. Initial laboratories revealed a WBC count 4.7× 10^9/L [3.6-10.2×10^9/l], hemoglobin 8.1g/dl [12.5-16.3g/dl], and platelets count 382 × 10^9/L [152-348×10^3/l]; thyroid function test, electrolytes, liver function test and coagulation profile were all normal.

Additional laboratory testing suggested a moderate microcytic hypochromic anemia (mean corpuscular volume 79.2Fl (80-100Fl); serum iron 20 ug/dL(50-150ug/dl); ferritin 61.31 ng/mL(12-150ng/ml); and total iron-binding capacity 276 ug/d(250-450ug/dl). Other pertinent additional results included an elevated ESR (120mm/hr [1-10mm/hr]), elevated CRP (12mg/l [0-1mg/l], abnormal urine analysis +2 RBC/high power field and +2 protein without cast, and negative RT-PCR for COVID-19. The initial non-contrast Chest computer tomography (CT) scan revealed multifocal ground-glass opacities (GGO) in the periphery of both lungs, predominantly the right middle and both lower lobes (Figure 1). Echocardiogram was normal. She was treated with supplemental iron while awaiting further investigations.

Several days later at Chest Clinic, the patient complained of persistent blood-tinged sputum and worsening dyspnea. She was now hypoxemic on room air (O2 sat 85% at rest) with progressive bilateral crepitations.

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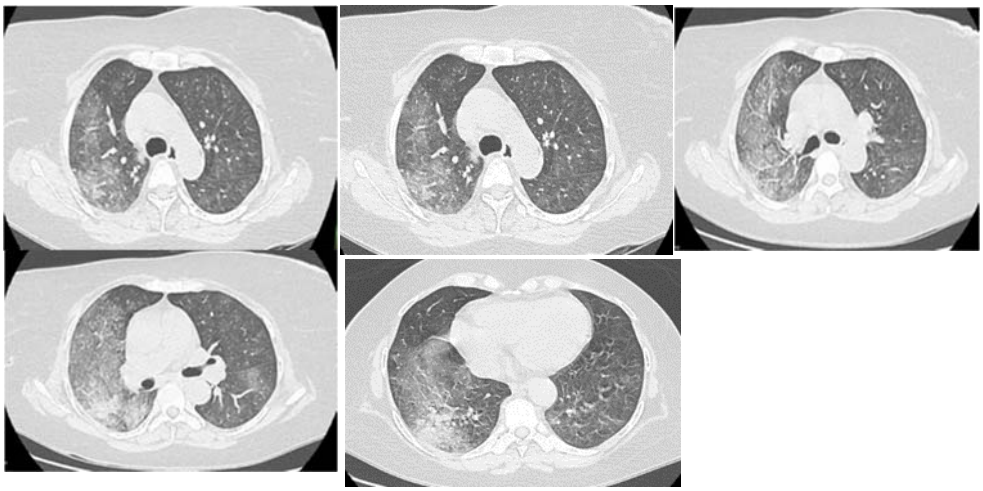

Figure 1. Axial lung windows of the high-resolution chest CT scan (was done on first clinic visit) revealed predominantly right middle and lower lung fields alveolar fillings with ground-glass opacification and some patchy area in left lung GGO.

The patient's anemia had also worsened (hemoglobin 7.5 mg/dl [12.5-16.3g/dl]) and her renal function was now impaired (BUN 36 mg/dL [3.5-9mg/dl], serum creatinine 1 mg/dL [0.6-1.3mg/dl], and a 24-hour urine protein was 1gm in 1900ml of urine). A repeat chest CT revealed more extensive GGO (Figure 2).

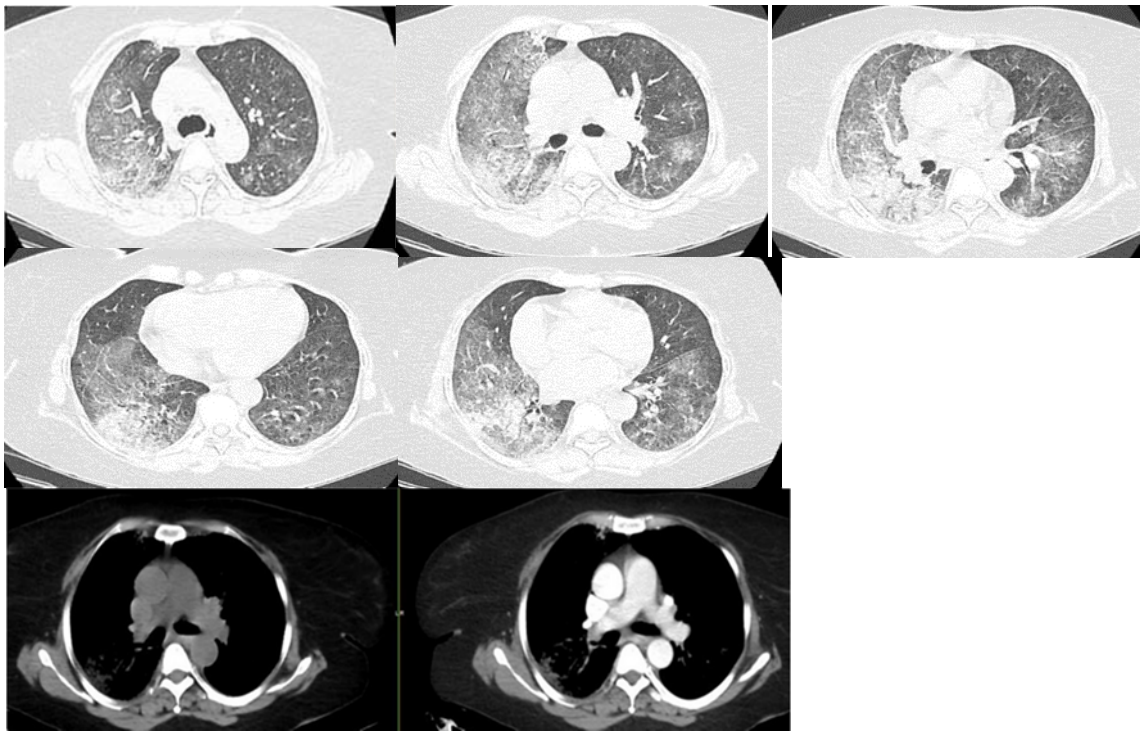

Figure 2. Axial lung and mediastinal windows of the high-resolution chest CT scan (was done at admission) showing bilateral (more diffused on the right lung and patchy on the left lung) alveolar filling and ground-glass opacification, mainly in the right lung with interval worsening from initial CT, consistent with pulmonary hemorrhage.

The patient was admitted to the medical ward with a presumptive diagnosis of PTU-induced AAV. Her PTU was stopped, and she was pulsed with methylprednisolone 1gm iv daily for 3 days and then maintained on prednisolone at 1mg/kg/day. She received 2 units of PRBC for hemoglobin of 4 mg/dl. On this treatment, her respiratory symptoms resolved and her oxygenation, renal function, and hemoglobin returned to normal.

Subsequently, cytoplasmic ANCA was positive, and both the perinuclear ANCA and antinuclear antibody (ANA) were negative, confirming the diagnosis of PTU-associated AAV. She was started on monthly IV cyclophosphamide. Currently, she is doing well; her recent chest CT showed marked clearing of her infiltrates (Figure 3). She is being evaluated for surgical management of her thyroid goiter.

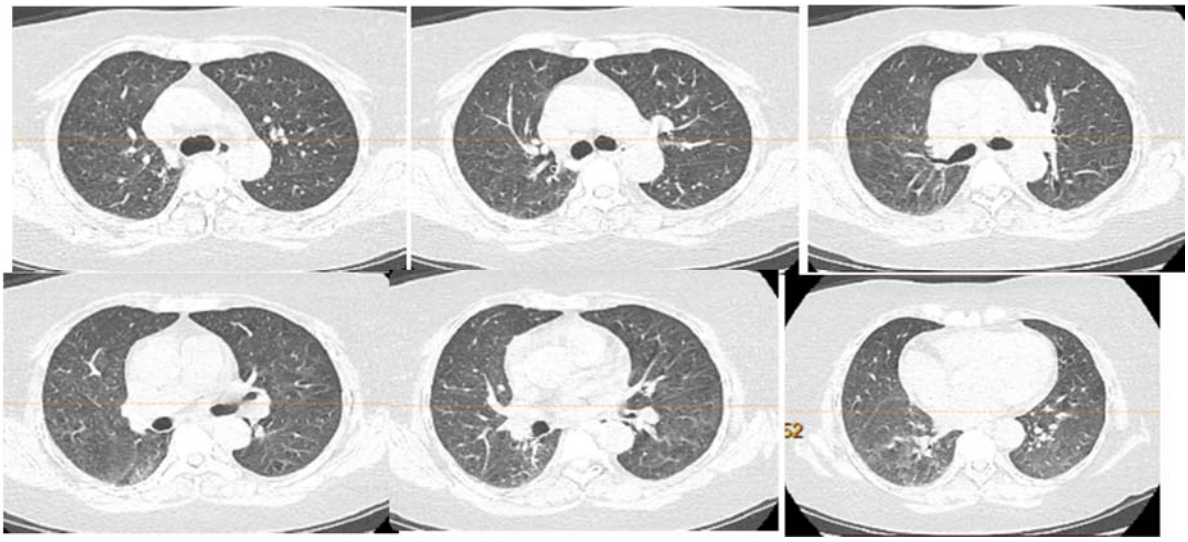

Figure 3. Axial lung windows of the high-resolution chest CT scan revealing marked resolutions of the alveolar infiltrate and ground-glass opacity after 6 weeks of PTU withdrawal, steroid, and monthly cyclophosphamide treatment, with the restoration of the lung parenchyma.

DISCUSSION

We report the first Ethiopian case of AAV associated with PTU therapy. The diagnosis was based on compatible clinical features, lack of response to antibiotics, characteristic findings on Chest CT, ANCA seropositivity, and clinical improvement after withdrawal of PTU and treatment with corticosteroids and cyclophosphamide.

Numerous case reports have previously documented the association of PTU and AAV[5-7] and several closely resemble our case. The mechanism of ANCA seropositivity and vasculitis caused by PTU has not been well defined. PTU accumulates in neutrophils and binds to and alters the myeloperoxidase antigen[8,9]. This alteration could potentially lead to the formation of autoantibodies in susceptible individuals.

For those with a mild presentation like constitutional symptoms, arthralgias/arthritis, or cutaneous vasculitis discontinuation of the culprit drug (PTU) may suffice for the necessary intervention. For cases with life-threatening or more severe disease manifestations involving lung and/or kidney involvement require treatment with high doses of glucocorticoids and cyclophosphamide or rituximab[10,11].

In conclusion, our case of PTU-associated AAV illustrates the importance of attentiveness, early identification, and aggressive treatment of this medication-induced complication.

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Conflict of Interest: There isn't any conflict of interest to report.

Consent: The patient consented to the publication of this case details.

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BRIEF COMMUNICATION

DEVELOPING A BURN UNIT: OUR EXPERIENCE AT ALEX EKWUEME FEDERAL UNIVERSITY TEACHING HOSPITAL ABAKALIKI, SOUTHEAST NIGERIA

Charles Chidiebele Maduba MBBS,FWACS, Ugochukwu Uzodimma Nnadozie MBBS, FWACS, FACS, Gabriel Mmaduwuike Okorie MBBS,FWACS, Edwin Ifeanyichukwu Enyanwuma MBBS, FWACS

ABSTRACT

***Background**: The burden of burn injuries in developing countries overwhelms the few regional burn centers. Tertiary institutions are involved hugely in the management of extensive burn injuries despite the lack of specialized burn units. This necessitates setting up a burn unit in our tertiary center. We aim to share our experience to stimulate our colleagues in different tertiary institutions to commence the process of setting up a Burn Unit in their respective institutions.*

***Methods and Results**: The development of the Burn unit in Alex Ekwueme Federal University Teaching Hospital Abakaliki took approximately 7.5 years from September 2013 to March 2021. It started as a Burn Facility and smoothly developed into a Burn Unit with a distinct leadership and resulted in a more effective and smooth running of the unit with an improved capacity and a promising outcome.*

***Conclusion**: A strong commitment is required from the plastic surgeons to drive the process of setting up a Burn Unit through a rigorous transition from a burn facility smoothened by the ability to make a case for expansion of an existing unit. The argument is to ensure that Burn Unit takes its rightful place like Emergency and In-*

INTRODUCTION

Burn injuries require an urgent attention within the shortest possible time. Because of the need to give patients immediate attention it is necessary to have facilities patient would be able to access within an hour of injury to minimize metabolic response to injury of which a mode of transport most suitable is chosen[1]. In Nigeria where there are thirty-six federating states and the federal capital territory, there is a need to have burn unit in each state and the federal capital territory, and the burn centers in each of the six geopolitical zones. This would help to ensure comprehensive burn care coverage in the federation.

Burn burden is largest in the low and middle income countries where the burn care facilities and the expertise are also suboptimal [2]. In Nigeria for instance where there are about two hundred million citizens, there are less than two hundred plastic surgeons who are saddled with the responsibility of managing burn victims in the region [3]. The distribution of the plastic surgeons is also skewed such that most plastic surgeons practice in the more urbanized States and mostly in the federal government owned hospitals. The patient in rural areas of which most of the Ebonyi state regions fall under, do not have access to intra-state burn units.

Although there are no published works on the number of burn facilities/units/centers in the country, the Nigeria Burn Injury Society have documented that 22 institutions in the country provide various burn services. In the Southeast specifically where there are 10 tertiary health institutions involved in burn care, there are only 2 burn units and one regional burn centre. Others run either burn facilities or nothing and could benefit from our experience to transit to burn units.

The level of burn care provided in health institutions have been stratified into three which are Burn facilities, Burn Units and Burn Centers[4]. The Burn facilities are a level of burn care which is for management of non-complex burn injuries. It is just same as a standard plastic surgical ward. The Burn Unit is at the second tier of care. It has a separately staffed ward with distinct headship from the plastic ward. The Burn Center is a geographically distinct institution fully equipped for managing most complex burn. It is usually a referral center receiving patients from different burn units[4].

Most teaching hospitals in Nigeria manage burn victims. The major constraint to burn management in these institutions is dearth of manpower and infrastructure for burn care. However in a few tertiary institutions the manpower capacity to run either Burn Facilities or Burn Units is readily available, but the major setbacks are infrastructure and institutional support.

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A burn Unit is supposed to manage burn victims of intermediate injury usually less than 30%[4]. But in practice burn of much higher severity are managed in the tertiary institution with mostly burn facility due to capacity constraint in the Burn centers. This strongly necessitates setting up a burn unit in the tertiary hospitals which exist in each of the thirty six federating units and the federal capital territory as either university teaching hospitals or federal medical centers.

We are therefore constrained to share our experience in a federal university teaching hospital which is barely 10 years old but has evolved from running a burn facility to running an established ultra-modern Burn Unit in a resource constrained environment. It is hoped that be sharing our experience, we would stimulate our colleagues in different tertiary health institution to commence the process of setting up a Burn Unit in their respective institutions. This would reduce the pressure on the limited bed spaces and human resources in the regional Burn Centers in the developing countries[5].

Method

Alex Ekwueme Federal University Teaching Hospital Abakaliki (AEFUTHA) was established as Federal Teaching Hospital Abakaliki (FETHA) in December 2011 by Upgrade of the Federal Medical Center Abakaliki with absorption of the personnel and facilities of the Ebonyi State University Teaching hospital Abakaliki. This gifted the new hospital with two facilities which led to streamlining services in the two facilities with one running maternal and child health services with other supporting units. The other runs surgical and adult medical services. Neither of the facilities at the time of the merger had a plastic surgeon nor a Burn facility. Burn patients were largely referred to the Regional burn center at National Orthopaedic Hospital Enugu which is less than 100km away from both facilities.

In 2013, following employment of two consultant plastic surgeons a 20 bedded plastic ward was created in which burn and non-burn patients were managed without a separation. Some burnpatients were also managed in both General surgical and Orthopaedic wards due to insufficient bed space in the plastic surgery ward. In 2015 however, an 8-bedded Burn Facility was created out of the Plastic Surgery Ward leaving the latter with only a 12 bed capacity. The burn facility essentially took care of the acute burn cases while the chronic burn wounds which are burn incidents greater than 3 weeks were managed either in the Plastic ward or in the Orthopaedic and General Surgery Wards. This arrangement was utilized till March 2021 when a Burn Unit was established in the new trauma center of the hospital. The floor plan encompasses a dirty zone for changing of outdoor wears to duty scrubs. The next zone is the transition zone which accommodates the nursing station and entrances leading to the last zone, the acute zone which is divided into the intensive care section and the high dependence section, has male and female subunits respectively. The painting was done with the antibacterial paints and the unit is fully air conditioned. Hydrotherapy is achieved with overhead showers to reduce cross-infection of using burn bath. The Burn Unit comprised a 4 bedded Intensive Care Unit with a single colt, and an 8 bedded High Dependence Unit with a colt. It has a distinct headship from the Plastic Surgical Ward and runs in a multidisciplinary and interdisciplinary manner with intensivists, microbiologist, hematologist and other relevant specialties collaborating with the plastic surgeons.

Fig 1: Transition zone

Results

In the period under study the Burn and plastic division has evolved from running a 20 bedded unit of which 8 beds were dedicated to burn patients, to a 12 bedded burn unit with both intensive care and high dependence sections (Figures 1&2).

Figure 2: A bed unit in the Burn Intensive care unit showing a ventilator and a nebulizer

This increase in capacity and capability has translated to a better outcome with the few patients so far managed in the new burn unit. We have been able to achieve survival in an 85% flame burn with significant inhalation burn following gas explosion [Data for this is not included in this paper].

The human capacity has also increased from only four specialty nurses trained in Burn and Plastic Post-basic Nursing to 20 of them who now work with non-specialized nurses as assistants. There are now 6 consultant plastic surgeons and 5 senior registrars in plastic surgery involved in the running of Burn Unit. Other support staffs who work as orderlies, potters, and administrative personnel have also been employed. There has also been a huge improvement in the residency training programme with a full accreditation by both National Postgraduate medical College of Nigeria and the West African college of Surgeons.

DISCUSSION

The establishment of Burn Units in Tertiary institutions has become inevitable owing to the increasing national population and attendant parallel rise in especially flame burn events[6].Also, the available Regional Burn Center is not sufficient to handle all the victims especially when there is a major disaster. However such projects could be very challenging due to lack of adequate manpower and infrastructure, as well as poor institutional support.

As the burn burden continues to increase in especially poor resource countries, the plastic surgeon that is often saddled with the burn care task[7], is confronted with the need to work with the institution to set up a burn unit. It is often not easy to start with a burn unit due to lack budgetary allocation to fund such projects. It therefore requires, in such constraining settings, starting first with a burn facility in a plastic surgery or even a general surgical department. It is easier to start this with just a minimum upgrade of the standard ward facilities. The need to start up with a burn facility is so that the management of burn victims could be commenced and audited to have a basis for further expansion of infrastructure and upgrade of man power component of burn care. And for tertiary hospitals who already run burn facilities, it necessary to upgrade to burn unit to improve outcomes.

This is even more so since auditing burn care settings is known to independently affect outcomes.[8]

A major challenge to our progressing from the burn facility to burn unit was the failure of the key players in the different level of management to appreciate the need for a distinct burn unit without considering it an undue favour to plastic division which is a mere unit of the department of Surgery. Burn unit should be seen in the same pedestal as Accident and Emergency Unit, Intensive Care Unit and Theatre Unit. Even though it is run by the plastic surgeons due to the need to prevent and manage most of the post-burn sequalae, it is a distinct unit that is very crucial to the society at large.

Burn trauma is very devastating and requires a distinct unit with specialized personnel[9].It could be argued that having an intensive care unit may obviate the need for a burn unit. A study however has shown that when such patients are managed in the conventional intensive care unit that the outcome was not goodenough.[10]

The main responsibility the plastic surgeon in ensuring a smooth transition from burn facility to burn unit is to convince the institution of the relevance of a burn unit to the institution and the society at large. In part an audit of the Burn facility would equip the plastic surgeon with facts to make a strong case for a Burn unit[11]. Burn Awareness creation could also attract the attention of both governmental and non-governmental organizations to assist with infrastructural support and other forms of assistance[12]. Our transition was made possible by a construction of a new trauma center arguably the largest in the country by the state government which has a sufficient space for the burn unit. The second factor was the involvement of one of the consultants in the top management of the hospital. The final factor was engagement of a very senior colleague with view to obtainment of accreditation. This further facilitated the commitment of the management to ensuring the accreditation for Fellowship training was secured for the two colleges.

CONCLUSION

The will-power of the plastic surgeon drives the process of starting up a burn facility and transiting smoothly to a befitting burn unit in a tertiary health care facility. When this is tactfully done, the resultant increase in burn care capacity snowballs to an improved outcome in the burn care.

Conflict of Interest: There is no conflict of interest.

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BRIEF COMMUNICATION

LEGALISATION OF ABORTION AND MATERNAL MORTALITY IN ETHIOPIA

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ABSTRACT

It is commonly assumed that legalisation of abortion leads to reduced maternal mortality both generally, and from abortion specifically. This paper surveys the available literature on maternal mortality and its causes in Ethiopia before and after legalisation of abortion in 2005, finding that abortion mortality had already fallen to low levels before legalisation, and did not drop noticeably further after legalisation. These findings are then compared with abortion mortality in other African contexts. Explanations for these findings are offered.

INTRODUCTION

Abortion was legalised in Ethiopia in 2005 as a means of reducing maternal mortality from abortion as well as more generally. Although abortion was not legalised on demand, it was legalised on broad socio-economic grounds: the Center for Reproductive Rights place it in the same category as the UK and Finland which, while not strictly allowing abortion on demand, do allow something close to that in practice.[1] While the received wisdom is that legalising abortion contributes to these aims, examples are rare, as most countries follow the same trajectory of abortion deaths and maternal deaths as before. In some countries, such as the Netherlands [2] and Rwanda,[3] deaths from abortion even increased proportionately on legalisation. In Poland [4] and Chile,[5] deaths from abortion and maternal deaths in general fell after prohibition of abortion in 1993 and 1989. Poland now has the lowest maternal mortality ratio in the world, and Chile has the second lowest in the Americas.[6] The impact of legalisation in Ethiopia cannot be assumed on the basis of theory, therefore; we must look at the evidence.[a]

FALLING MORTALITY PRIOR TO LEGALISATION

Prior to 2005, mortality from abortion had already dramatically declined to 6-7% of maternal deaths, as shown by at least four systematic reviews, meaning it had declined in absolute terms and even relative to other causes of maternal death.[8-11] 'Abortion' in reviews of maternal mortality typically refers to both induced abortion and spontaneous abortion, so the proportion of maternal deaths due to induced abortion was smaller still.[b]

This is in line with the experience of almost all developed countries, in which deaths from abortion fell to very low levels before abortion was legalised, as a result of safer illegal methods and better post-abortion care. In the 21st century, these factors are even more salient, with the widespread availability of misoprostol, manual vacuum aspiration, and better antibiotics.

NO FURTHER REDUCTION AFTER LEGALISATION

In the decade following legalisation, the proportion of maternal deaths due to abortion did not fall beyond the prior trajectory, and arguably did not fall at all. It is even possible, in light of evidence below, that it increased. The same reviews discussed above[c] all offer figures around 6-7% for the years after 2005. Mekonnen[11] has the most complete data and cites figures between 2 and 9%, with a median of 6%. The most recent three studies gave figures of 2, 8, and 9%. Gebrehiwot specifically looked at the impact of legalisation and found no statistically significant decrease in abortion mortality or maternal mortality. He did find, however, that 'the severity of abortion complications and the case fatality rate increase during the transition of legal revision.' The case fatality more than tripled.[12]

If abortion legalisation had a significant impact on mortality, we would expect a disproportionate decrease in deaths from abortion (especially since the proportion of maternal deaths due to abortion naturally declines over time regardless of the law). The data as described above do not support this. Tessema has shown how abortion mortality decreased exactly in line with other

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[a]See Miller (forthcoming)[7] for a fuller treatment of empirical evidence relating to the legalisation of abortion and maternal deaths in other countries.

causes of maternal mortality.[13]

COMPARISON WITH OTHER COUNTRIES

We would also expect Ethiopia to have significantly fewer maternal deaths due to abortion than other comparable countries with restrictive laws. But the Ethiopian figures are about average for, or higher than, East Africa generally. The Kenyan Confidential Enquiry into Maternal Deaths recently estimated 8.3% of maternal deaths due to abortion, but only 1.7% were demonstrably induced abortions.[14] The Ugandan Ministry of Health recorded that 5% of maternal deaths were due to abortion,[15] while a study in 2013 found that abortion was responsible for 3.8% of maternal deaths and only 1.1% of non-life-threatening complications[16]. Rwandan data showed only 3% prior to legalisation in 2012 (subsequently increasing to 7% after legalisation),[17] and already twenty years ago abortion complications constituted only 6% of maternal deaths in Malawi,[18] with a more recent study suggesting 1.9-3.8%.[19] Hence, the proportion of maternal deaths attributable to abortion in Ethiopia is comparable to, if not higher than, other countries in East Africa with more restrictive laws. In North Africa, where abortion is prohibited everywhere except for Tunisia, the proportion was only 2.2%.[20] Other studies from West and Southern Africa show percentages as low as 3.5% (Burkina Faso [21] and Benin[22]), 1.9% (Sierra Leone[23]), or 1% (Angola[24]). In some cases, abortion is not even mentioned as a cause of death.[25] In all of these countries, abortion is still prohibited.

ABORTION RATES HAVE INCREASED

Part of the argument for legalisation is that prohibition of abortion does not reduce the number of abortions. This has been proven false in many different contexts, and now in Ethiopia. According to the Guttmacher Institute's own estimates,[d] the abortion rate has gone up from 22 to 28 per 1000 women between 2008 and 2014. While there has been an increase from 103,000 to 326,000 legal abortions, this has not simply been a replacement of illegal abortions. In fact, the number of abortions performed outside of facilities (an index of illegal abortions) was estimated to have also increased from 280,000 to 294,000.[26] The proportion of women presenting for post-abortion care who reported self-inducing abortions increased by 40% over the same period.[27] This increase in illegal abortions is consistent with the experience of various other countries.[7,28]

ABORTION COMPLICATIONS HAVE INCREASED

While there is somewhat conflicting evidence on increased abortion mortality after legalisation, morbidity clearly increased. Over the period of legalisation, the proportion of women with septic shock more than doubled, with the same result for organ failure.[e] The proportion admitted to intensive care nearly tripled.[12] Between 2008 and 2014, the percentage of women receiving post-abortion care who have *severe* complications increased by over 50%, from 7% to 11%. During this time, the proportion of women presenting with organ failure quadrupled, the proportion with peritonitis quintupled, and the proportion with shock nearly doubled.[27]

Overall, complications doubled between 2008 and 2014, from 53,000 to 104,000. This is despite greatly improved reproductive healthcare, increased contraception,[f] and 'major progress' in safe abortion provision. Only a small proportion of this can be attributed to population growth.[26] Notably, there was a steep drop in physician involvement during the time period.[27] Gebrehiwot summarises, 'Overall, the frequency and severity of abortion-related morbidity for which women sought care increased between 2008 and 2014'.[27]

LONGER TERM DATA

It is harder to relate longer term declines in abortion mortality to the legalisation of abortion, since the proportion of maternal deaths attributable to abortion (including miscarriage) varies dramatically over time in general,[18,29] and since the 1980s has declined over time regardless of legal change in most countries, including – as shown above – in Ethiopia prior to legalisation. While figures of 20-70% were cited not uncommonly in previous decades,[29] such estimates are virtually unheard of anywhere in the world today, almost universally being under 10% and often, as shown above, well below 5%.[20,30] The reasons why are discussed below.

Still, it is worth examining some of the more recent literature on maternal deaths and near-misses in Ethiopia. Data from 2008-2014 suggested that abortion caused 9.3% of maternal deaths.[31] Tessema et al.'s review[32] suggested that 19.6% of maternal deaths were from abortion in 2013, though this was not a primary study. Data from 2016 found abortion responsible for 1.5% of deaths.[33] Data from 2016-2017 in one hospital show 'safe abortion' being responsible for 2.5% of deaths, though with a sample size of only 40 so a wide margin of error.[34]

[b]For this reason, all mentions of 'abortion' in this article refer to both spontaneous and induced abortion. Although we can never say with much certainty what proportion of maternal deaths result from either cause specifically, we can look at the trend of both taken together.
[c]Except Gaym (2009)[8], which does not contain studies from after 2005.

Data from 2018 found that abortion was responsible for 4.9% of maternal near misses at one hospital.[35] At another hospital in 2018-2019, abortion was responsible for 12.5% of maternal deaths.[36] 2020 data from two major hospitals found that abortion was responsible for 6.5% of maternal near-misses.[37] Finally, Tariku in 2019 did not estimate abortion near-misses or maternal deaths as a percentage, but found that 'Severe acute maternal morbidity and maternal near miss related to abortion are high despite the availability of safe termination'.[38] Hence the data in more recent years are incredibly variable, and show no clear sign of an improvement from the legalisation of abortion, even if trends from 10-15 years later could be credibly attributed to the law of 2005.

EXPLANATORY FACTORS

As powerful as the empirical evidence from Ethiopia and elsewhere is,[7] a theoretical basis is needed to explain why legalisation of abortion does not lower the abortion mortality rate or the maternal mortality ratio – at least, in some countries. A few reasons can be given:

1. The abortion mortality rate was already low, reducing the opportunity for large decreases.
2. Many deaths from abortion result from spontaneous abortion, i.e., miscarriage, and hence could never be prevented by legalising abortion.[30]
3. Illegal abortion is far safer than it used to be, because of widespread safer techniques such as misoprostol and manual vacuum aspiration.[39-42] Some have suggested that even without accurate information provided, self-managed medical abortion can be relatively safe.[43]
4. While in illegal settings, women are at risk of being given the wrong dosage and instructions regarding misoprostol, the same is often true where abortion is legal.[39,44,45]
5. Abortion in legal settings is also moving towards self-managed abortions, reducing the disparity in technique between legal and illegal abortions.[42,46]
6. Quality post-abortion care is sufficient to prevent most deaths from abortion;[47-51] this is one of the major reasons developed countries almost universally had minimal abortion mortality prior to legalisation. Conversely, where emergency care is unavailable, abortions which would otherwise be safe can become unsafe.
7. Women seek illegal abortions even when abortion is legal, often at similar or even higher rates (as in this case).[7,28,52] Reasons include lack of access as well as women's preference: many women deliberately seek abortion outside the recommended facilities, often for reasons of privacy.[53-55]

One major reason there may be a compensatory increase in abortion deaths is that when abortion is legalised, more abortions occur (as in this case); this has been a virtually universal trend and can no longer be reasonably denied.[56,57] Hence, more women are liable to the risks of abortion. Even if legalisation leads to a lower case fatality rate, this may be offset by an increase in cases. But in many countries, there has been either no change in illegal abortions at all, or even an increase[7,28,52] – perhaps partly because criminal abortionists may feel emboldened by the new leniency of the law.[28]

Another reason for an increase in abortion deaths is the opportunity cost of diverting funding from emergency obstetric care to safe abortion lobbying or funding. This has been shown in the past to limit women's access to emergency obstetric care, which ironically could cause women to die from complications of both safe and unsafe abortions.[30,58,59]

There are further reasons we may expect an increase in maternal mortality in general from the legalisation of abortion:

1. Abortion is associated with a higher mortality rate than continued pregnancy.[60-62] Most of this is due to an increased risk of suicide,[63] which is not counted among post-abortion complications/deaths.
2. Abortion is likewise associated with increases in alcohol and drug misuse compared to completing an unwanted pregnancy, with their various impacts on health.[63]
3. Abortion has similarly been associated with increased mortality from homicide and accidental injuries relative to completing a pregnancy.[60-62]
4. Some have argued that abortion is associated with heart disease, perhaps relating to the psychosocial stress of abortion as well as the higher levels of alcohol and drug misuse.[61,62]
5. The legalisation of abortion has been linked with a large increase in prevalence of sexually transmitted diseases, with their various consequences, including death from cervical cancer or HIV/AIDS.[64-66]
6. The legalisation of abortion has also been linked with increased family breakdown and poverty,[67] which in turn have a variety of effects on mental and physical health outcomes, including mortality risk.[68]
7. The legalisation of abortion has likewise been linked with male delinquency and crime, which likely contribute to pregnant women's risk of being the victim of

[d]These estimates are open to challenge, since they rely on the controversial Abortion Incidence Complication Method, which has considerable shortcomings. Nevertheless, the shortcomings will likely bias the results in the same direction (upwards) in both years.
[e]Latter result not statistically significant due to small sample size.
[f]Incidentally, the proportion of unplanned pregnancies decreased only marginally and insignificantly during that time, from 42 to 38%.

homicide.[69]

8. Abortion availability may contribute to delayed childbearing, which is associated with increased maternal mortality.[60]
9. More speculatively, societies restricting abortion may place a higher value on, and invest in, maternity services, perhaps explaining Poland and Malta's anomalously low maternal mortality ratio.

Importantly, some of these ways in which maternal mortality may be increased can have intergenerational effects - for example, insofar as mental health problems, poverty and family breakdown are more prevalent among individuals who have experienced those in their families growing up.

CONCLUSION

Gebrehiwot comments: 'These results also show the difficulties that remain in eliminating unsafe abortion, even in countries where the procedure is legal… Since 1972, only Ethiopia, Ghana, Mozambique, Rwanda, South Africa and Zambia have changed their abortion laws… None of these countries has eradicated unsafe abortion, and many—like South Africa—have spent decades trying'.[27]

The evidence offered here suggests that the same is true for Ethiopia. Rather than being a silver bullet to reduce deaths from abortion, abortion legalisation has resulted in a vast increase in the number of abortions, without any appreciable decrease in abortion mortality or maternal mortality. There is some evidence mortality, and certainly morbidity, have even increased since legalisation.

Ethiopia's progress in reducing maternal deaths has been considerably less than expected,[13] especially with respect to abortion. It is possible that, as in other countries, a disproportionate focus on family planning based on inflated claims of abortion mortality has diverted resources from emergency obstetric care and thereby failed to reduce maternal mortality more significantly.[30, 58, 59]

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LITERATURE REVIEW

ADVANCES IN CANCER IMMUNOTHERAPY: A REVIEW OF THE LITERATURE

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ABSTRACT

Background*: Conventional cancer treatment includes surgery, radiation, hormonal and chemotherapy, sometimes a combination of these. Each of these has limitations and serious side effects, which led to a search for new treatment options. Understanding tumor immunobiology and the complex interactions between immune cells and cancer pave the way for the introduction of a novel treatment approach called immunotherapy, which is a method that utilizes the body's immune system to fight cancer. As the subject is emerging, the review aimed to describe the present developments in the field of cancer immunotherapy.*

Methods*: Literature published in English were non-systematically retrieved from PubMed/Medline, SCOPUS, Google Scholar, and the Google database using relevant searching terms. Articles were prioritized and considered based on their originality and possible clinical applicability.*

Results*: Big interest in the field of cancer immunotherapy was inspired by the success of the most important products that achieved durable responses in patients with lethal stages of cancer. Two of these approaches were; a) immune checkpoint inhibitors that target the PD-1/CTLA-4 axes in advanced melanoma, lung, and renal cell carcinomas and b) adoptive cell therapy with chimeric antigen receptor (CAR) T-cells to treat leukemia and lymphomas. Immunotherapy either stimulates/boosts the activities of specific components of the immune system or counteracts signals produced by cancer cells that suppress immune responses. It can eliminate large tumor masses in advanced-stage cancer and elicit immunological memory that can lead to prolonged protection. Generally, cancer immunotherapy strategies currently being used in clinical settings and that are under different levels of trial include; monoclonal antibodies, adoptive transfer of ex-vivo activated T-cells, cancer vaccines, oncolytic viruses, cytokines, and use of recombinant proteins or antibodies that either stimulate the immune system or block the system inhibitory pathways.*

Conclusion*: The concept of cancer immunotherapy provides a new perspective in oncology as it artificially boosts the immune system and is not associated with many of the drawbacks of conventional cancer therapies. However, suboptimal vaccine design, an immunosuppressive cancer microenvironment, and better delivery strategies to improve the effectiveness of immunotherapy need further research.*

Keywords*: Cancer, tumor, immunotherapy*

BACKGROUND

Cancer is a generic term for more than two hundred large groups of diseases (1) that can affect any part of the body. It is characterized by the uncontrolled growth and spread of abnormal cells (2-4) that grow beyond their natural limits, and which can then invade the nearby parts of the body and could spread to other organs, the process called metastasis, which is a major cause of death from cancer (5).

In the past few decades, big steps have been made in elucidating the molecular mechanisms involved in the development of cancer. It is now clear that the transformation process involves somatic mutations that lead to activation of genes that are usually involved in the regulation of cell division and programmed cell death, as well as the inactivation of genes involved in the protection against DNA damage or driving apoptosis (6). Cancer cells are constantly formed in the body, which the immune system is continually destroying (7). However, cancer cells most often use different strategies to evade the immune system (8, 9).

There were an estimated 19.3 million new cases and 10.0 million cancer deaths globally in 2020. By the year 2030, the worldwide cancer burden is predicted to intensify to 21.7 million new cases and 13 million deaths annually (10).

There are varieties of treatment options depending on the type of cancer and how far it grows and spreads (11). The most common forms are surgery, radiation, transplantation, hormonal and chemotherapy. However, most cancer patients need a combination of these (9, 11). Each of these options have their own benefits but also limitations and paramount side effects, which led to a search for new treatment modalities. Immunotherapy, in which the immune system is targeted to launch anti-cancer activity, is a rapidly evolving novel treatment alternative in the fight against cancer (12).

Advances in the knowledge of immunology led to an improved understanding of the interactions

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between the immune system and cancer cells, creating new interest in approaches that aim to treat cancer using this system (12). Immunotherapies either stimulate/boost the activities of specific components of the immune system or counteract signals produced by cancer cells that suppress immune responses (9). Strategies for generating a therapeutic immune response include the use of specific or monoclonal antibodies, adoptive T-cells transfer, immune checkpoint blockades, therapeutic vaccines, and other non-specific agents like cytokines. Approaches to unleash T-cells against tumors are particularly substantial, as the activities of T-cells present important features, which include specificity, memory, & diversity that are valued over other cancer therapies (6).

The field of cancer immunotherapy is flourishing and research findings are coming every day. With this context, the review aimed to describe the current developments on the principles of cancer immunotherapy and presently available cancer immunotherapeutic approaches. Professionals, especially those working in the field of oncology, could benefit from it both for their clinical and research practices.

METHOD

In this review of literature, we considered articles published in English on the subject of cancer immunotherapy. We conducted nonsystematic retrieval of papers from PubMed/Medline, SCOPUS, Google Scholar, and the Google database using relevant searching terms. Articles were prioritized and considered based on their originality and potential clinical relevance. Various algorithms including the following terms were used while searching literature: cancer, neoplasm, immunotherapy, cancer immunotherapy, types of cancer immunotherapy, checkpoint blockade, and cancer vaccines. The citations in this document were managed using EndNote X9.

RESULTS

Basics on tumor immunology

Cancer cells originate from several genetic and epigenetic events that deregulate homeostatic mechanisms controlling normal cell growth. However, the immune system, devoted to patrolling the organism against pathogenic events, can identify distorted cells, and in several cases cause their removal. It is however clear that several mechanisms encompassing both central and peripheral tolerance limit antitumor immunity, often resulting into progressive diseases. The acquired wing of the immune system is most relevant in managing the immune system, addressing intracellular infections (like viruses), and has evolved to be the most important part of the system in terms of controlling and exterminating cancer cells (1, 13, 14, 15).

Tumor immunology deals with the interaction between immune cells with cancer cells. Understanding this interaction is a milestone for the development of new approaches for cancer treatment (16). Long time evidence, first from animal models and later from studies in cancer patients, revealed that the immune system can recognize and reject transformed cells. Cancer immunology has been aimed at understanding the components of the immune system that are important for tumor immunosurveillance and tumor rejection to understand how, when, and why they fail in cases of clinical disease (1).

Cancer cells are identified and recognized by components of the immune system and their development can be stopped or controlled long-term through a process known as immunosurveillance by which altered cells with a potential to abnormally proliferating could be identified and eliminated. For this to function, cancer cells must display some new discriminating surface structure/antigen that can be recognized by the immune system (1, 17-20). These antigens could be recognized in two ways as non-self: by reacting against tumor-specific antigens or against tumor-associated antigens (fragments that are expressed by cancer cells and normal cells). Identification of tumor antigens recognized by T-cells is important for the forthcoming vaccine synthesis that marks tumors (1, 18, 21, 22).

Tumors are essentially invisible to T-cells until they are activated by antigen-presenting cells and because of cross priming by dendritic cells (DCs) that present tumor antigens. Recognition of tumor antigen and the costimulatory ligands by T-cells concurrently initiate a complex set of genetic programs that result in cytokine production, cell-cycle progression, and production of anti-apoptotic factors that result in proliferation and functional differentiation of T-cells. Consistent with the role of both antigen receptor and costimulatory signals in starting anti-tumor response, many vaccines identified for treatment nowadays integrate both antigen and DCs or agents that augment costimulatory signaling (6, 17). Once the cancer cells are recognized and the effecter cells are activated through cascaded of cytokines activations, the Cytotoxic T-lymphocytes (CTL) use different tools to eradicate tumor cells including exocytosis of granules containing the cytotoxic effector molecules perforin and granzyme and secretion of tumor necrosis

factor (TNF) and interferon-gamma (IFNg) that also have a tumoricidal effect (19).

The innate arm of the immune system has also a significant role in the fight against cancer. Macrophages, which often infiltrate a tumor mass, can destroy tumor cells in tissue culture through the copious production of reactive oxygen intermediates and TNF. Similarly, natural killer (NK) cells subserve a function as the earliest cellular effector mechanism against the dissemination of lymph and blood-borne metastases (19).

In general, understanding the basic principles that govern controlling immunity provided the rationale for the development of approaches to actively involve the immune system for cancer treatment. Approaches to unleash T-cells against tumors are particularly substantial, as the activity of these cells presents important features, which include specificity, memory, and diversity/adaptability that are advantageous over other cancer therapies (6).

Mechanism of evading the immune response

Tumors can occur among people who are not immunosuppressed. The findings from immunological studies, murine tumor models, and patients with cancer evidently showed that tumors have a number of mechanisms to escape the immune reaction (21, 23, 24) which is actually a major limiting factor in designing effective anticancer therapy (24).

During the early stages of tumor development, transformed cells can be poor stimulators, present poor targets, while at later stages; increasingly mounting tumors harm the acquired immune response by blocking the maturation and function of antigen-presenting cells (APCs) and causing changes in T-cell signal transduction and function. There is a correlation between some of these changes and an increased metastatic potential of a tumor, a diminished response to immunotherapy, and poor prognosis (23). Further, the majority of escape mechanisms from the routine surveillance are attributed to changes in the tumor cells themselves (loss of tumor antigens, loss of human leukocyte antigen molecules, loss of sensitivity to complement, or T cell or NK cell lysis), making them a poor target of an immune attack (1).

Tumor cells have also an intrinsic flaw in antigen processing or presentation as they lack co-stimulatory molecules such as the B7 (CD80 and CD86) molecules (19). There are reports indicating that CD80 is spontaneously expressed at low levels in tumor cells.

T-cell anergy occurs following antigen– major histocompatibility complex (MHC) recognition in the absence of co-stimulation. Furthermore, many tumors express reduced or absent levels of class-I MHC, which imparts resistance to Tc although presumably increasing susceptibility to NK cells. On top of these, tumors themselves may release various immunosuppressive factors such as transforming growth factor-b(TGFb), which is a potent immunosuppressive cytokine having effects on many mediators of the immune response including a potent inhibitory effect on differentiation of CTL [19]. Another immune evasion tactic is immune editing; one of the key features why tumors evade surveillance causing the tumors to lie latent in patients for years (24).

It is also stated that the incessant loading of vascular endothelial growth factor (VEGF), a factor produced by most solid tumors, inhibits the functional maturation of DCs, significantly decreases T-cell to B-cell ratios in the peripheral lymphoid organs, and causes rapid thymic atrophy among animals with tumor (21).
In general, mechanisms by which tumors evade the immune system include down-modulation of components of antigen processing and presentation machinery; employment of suppressor immune cells, such as regulatory T cells, myeloid-derived suppressor cells (MDSCs), and tumor-associated macrophages; production of soluble factors associated with immunosuppression, such as TGF-β and IL-10; and upregulation of ligands for co-inhibitory receptors such as programmed death ligand-1 (PD-L1) (1, 25).

Understanding the mechanisms used by tumor cells to evade immune system could result in new therapeutic approaches for preventing and/or reversing these immune alterations and could have the possibility of cultivating the present results of immunotherapy studies (23).

Immune function in cancer patients

In several cases, malignant progression is accompanied by profound immune suppression that interferes with effective antitumor activity and tumor elimination (1). It is often noted that there is a degree of systemic immune suppression among cancer patients (21). Approximately 60% to 70% of patients with some type of cancer can, in fact, be shown to have generalized systemic immunosuppression. While multiple factors such as stress and chemotherapeutic factors contribute to a reduced immune function, it is clear that tumor cells also directly induce suppression of immune responses by a number of strategies as stated above. These include secretion of cytokines,

which suppress or disrupt the robust antitumor effector responses, and mechanisms that make use of tumor cell surface receptors to modulate the function or kill immune cells. An additional means of immune suppression is when the tumor derives from the hematopoietic tissues and disrupts normal bone marrow function, resulting in reduced immune function (1, 25-27).

Cancer immunotherapy

General overview

Spontaneous tumor regression may occur following bacterial, fungal, viral, and protozoal infections. This achievement inspired the development of a number of initial cancer immunotherapies, with a history spanning thousands of years. William Coley, a US bone surgeon and cancer investigator, pioneer of cancer immunotherapy, took advantage of this natural phenomenon, developing a killed bacterial vaccine for cancer in the late 1800s. He observed that inducing a fever/ and inflammation was crucial for tumor regression (25, 28).

Conventional treatments for cancer include surgery, radiation, transplantation, hormonal and chemotherapy, and sometimes combination of these, which all have limitations and detrimental side effects. However, an increasing number of clinical trials are underway to stimulate the immune system to combat cancer (24, 29-31). The first checkpoint-inhibitor, which takes the molecular brakes off T-cells to unleash them on tumors was approved by the US FDA in 2011. In 2017, the FDA also approved two chimeric antigen receptor (CAR) T-cell treatments, in which a person's immune cells are re-engineered to attack cancers (7). The notion of cancer immunotherapy offers a renewed standpoint as it is not associated with many of the drawbacks of conventional therapies. When fully activated, the immune system has immense potential as is evident from mismatched transplanted organs undergoing rapid immunological attack and rejection (31).

Working principle of immunotherapy

Instead of targeting tumors directly, the principle of cancer immunotherapy relies on the control of cancer cells through activating or reactivating the immune system (14, 29, 32, 33). Hence, the principal goal of immunotherapy is a resurrection of the patient's inefficient or suppressed immune system which would ideally result in total and permanent eradication of cancer (34). Immunotherapy works in different ways; some boost the body's immune system while others help train it to attack cancer cells (11). This approach emphasizes dual aspects; to eliminate immune-suppressing factors, and 2) to enhance tumor-killing activities (24).

In general, the goal of most approaches to cancer immunotherapy is to activate a population of effector T-cells, which can then traffic to evolving tumors and mediate the specific lysis of cancer cells (35-41).

Types of cancer immunotherapy

As it is briefly described above, over the years, researchers around the world have tried many different approaches to turn the immune system against cancer, such as cutting the brakes on immune cells, flagging cancer cells for recognition and destruction, or genetically engineering a patient's immune cells to directly target and eventually eliminate cancer cells (42). Cancer immunotherapy encompasses a variety of approaches, including the marvelous specificity of adaptive immunity as well as the diverse and potent cytotoxic arsenal of both adaptive and innate immunity (36). Cancer immunotherapy sometimes can be categorized by whether it *actively* stimulate the immune system, or *passively* alter immune system signaling or cell populations, and, the treatment is targeted at a specific, known antigenic target, or is non-specifically stimulating the entire immune system (14). The most common immunotherapeutic approaches are summarized in (Table

Table 1: Common cancer immunotherapeutic approaches currently being used in medical settings and under

Types	Working principle
Monoclonal antibodies	Target specific antigen of cancer cell
Immune checkpoint blockades	Take the 'brakes off' the immune system (unleash anti-cancer activity of T-cells) to eliminate cancer
Adoptive cell transfer	Transfusion of adoptive allogeneic or autologous T-cells into patients, tolerance to tumor antigens will be lost so that a large amount of high avidity effector T-cells will act on cancer.
Cancer vaccines	Stimulate the host immune system
Cytokines **(IL-2, IFN-α)***	Stimulate the host immune system
Oncolytic viruses	Acute tumor exposure owing to tumor cell infection and lysis and induction of systemic antitumor immunity
Combination therapy	Improves anti-cancer activity of products

*IL: Interleukin-2, IFN: Interferon-alpha

Monoclonal antibodies (mAb)

Monoclonal antibodies are used to treat different kinds of diseases, including some types of malignancies. To make a monoclonal antibody, investigators first have to identify the correct antigen to attack. For cancer, this is not constantly easy, as these cells are *self-modified* cells, and so far mAbs have proven to be more useful against some cancers than others (11). By directly targeting specific antigens expressed by cancer cells, mAbs are well-established classes of immunotherapeutic agents (1). The three most common anticancer drugs (ie, rituximab, trastuzumab, and bevacizumab) are certainly mAbs. Therapeutic levels of mAbs allow more extensive lymphocyte trafficking and activation and lysis of cancer cells (14).

Immune checkpoint inhibitors/ immune-modulating antibodies

The activity of the immune system is modulated and controlled by co-stimulatory molecules, called immune checkpoints, which are crucial for self-tolerance. The immune checkpoint pathways are normal immune signals capable of ending an immune reaction. They involve inhibitory receptors and their ligands; one is expressed by a putative target cell and the other is expressed by effector cells, like T-cells (40). When antigen recognition occurs, other molecules interact on the surface of the immune cell and the target cell to govern the balance of the interaction. If the signals are largely positive, immune cells activate and are primed to attack the antigen presented by the target cell. However, if the balance of signals is negative, then the immune cell can become deactivated, sometimes permanently, and the antigen is accepted as a self-antigen (14). Overexpression of immune checkpoint molecules by tumor cells profoundly affects tumor-specific T-cell immunity in the cancer microenvironment. This efficiently marks tumor cells as not for elimination, and can therefore reform tumor progression and eventually metastasis. Since most tumor immune escape mechanisms that use immune checkpoints block effector cell functions, antitumor immunity may be *restored by antibodies that block the inhibitory receptor-ligand interaction and thus inactivate the immune checkpoints* (40). On the basis of this immunology knowledge, antibodies capable of disrupting the ligand-receptor association for immune checkpoints and/or its functional consequences were developed. These drugs essentially take the *'brakes off'* the immune system, which benefits it recognizing and eliminating tumors (40).
Immune checkpoint treatment has led to important medical advances and provided a new firearm against cancer. This therapy has caused durable clinical responses and, in a segment of patients, long-term remissions where patients showed no clinical signs of cancer for many years (43).

Interactions between molecules on the surfaces of T cells and antigen-presenting cells (APCs) at the immune checkpoint can lead to the induction of immune tolerance. The most clinically relevant of these interactions are those between 1) Cytotoxic T lymphocyte-associated protein-4 (CTLA-4) on T cells and its ligands B7 on APC and 2) PD-1 on T cells and its main ligand PD-L1 on APC or tumor cells (44).
Immune checkpoint inhibitors that interfere either of the above interactions could lead to the activation and expansion of existing tumor-specific immune cells that are otherwise suppressed in the tumor microenvironment (TME) (22).

Ipilimumab (Yervoy), a monoclonal antibody targeting CTLA-4

In the late 1980s, French scientists who were not considering cancer at all identified a new protein on the surface of T-cells, called CTLA-4(45) also known as CD-152. It is an immune checkpoint protein receptor (46) that is expressed exclusively on T-cells, and is a critical *negative regulator* of the antitumor T-cell response (40, 47). James Allison, at the University of Texas, reported that CTLA-4 makes the *brakes on* T-cells, stopping them from launching full-out immune responses. He speculated whether blocking the blocker, i.e., the CTLA-4 molecule would make the immune system *free to eliminate cancer*. In 1996, Allison and his colleagues published a paper in *Science* showing that antibodies against CTLA-4 removed tumors in mice. In 2010, a US-based company called Bristol-Myers Squibb described patients with metastatic melanoma lived an average of ten months on the antibody, compared with six months without it. It was the first time any treatment had prolonged life in advanced melanoma in a randomized clinical trial. Nearly a quarter of participants survived at least 2 years (45).

Similarly, according to Sharma P study, tumor regression was observed in phase I/II trials using CTLA-4 antibodies in patients with a variety of tumor types, including melanoma, renal cell carcinoma, prostate cancer, urothelial carcinoma, and ovarian cancer (6, 40). In 2011, the US FDA approved Bristol-Myers Squibb's *anti–CTLA-4 antibodies*, called *Ipilimumab*, for metastatic melanoma, which marked the beginning of a new era for cancer immunotherapy (6, 25, 45, 48). The clinical achievement of anti-CTLA-4 paved a new arena termed *immune checkpoint therapy* as additional T-cell intrinsic pathways were identified and target-

for clinical development (6).

As described above, CTLA-4 mainly regulates the amplitude of early-stage T-cell activation. One of its mechanisms of action encompasses antagonism of B7-CD28–mediated co-stimulatory signals, which occur because CTLA-4 has a *much higher affinity* for B7 than CD28 does: binding of CTLA-4 to CD80/86 is 500 to 2,500 times more than that of the CD28. Signaling through CD28 promotes mRNA expression of the cytokine IL-2 and entry into the cell cycle, T-cell survival, Th-cell differentiation, and immunoglobulin isotype switching. Thus, signaling through CTLA-4 inhibits IL-2 mRNA production and inhibits cell cycle progression (40).

Anti-Programmed Death-1 (PD-1) (Nivolumab) and anti–PD-L1 antibodies

The other T-cell-intrinsic inhibitory-pathway recognized after CTLA-4 was mediated by PD-1 (***P***rogrammed ***D***eath 1) and its ligand PD-L1. PD-1 function as an immune checkpoint was not well-known until 2000 upon identification of its ligands even though it was initially cloned in 1992 in a study of molecules involved in negative selection of T-cells by programed cell death in the thymus. PD-L1 was then revealed to protect tumor cells by inducing T-cell apoptosis. Later, studies in animals assessed anti-PD-1 and anti-PD-L1 antibodies as immune checkpoint agents to treat tumors (6). Much like CTLA-4, PD-1 is expressed only in activated T-cells. However, unlike CTLA-4, PD-1 inhibits T-cell responses by interfering with T-cell receptor signaling in contrary to outcompeting CD28 for binding to B7(6, 33, 45).

PD-1 receptor is an inhibitory receptor expressed by antigen-stimulated T-cells. Interactions between PD-1 and its ligand, PD-L1, expressed in many tumors activate signaling pathways that inhibit T-cell activity and thus block the antitumor response. However, antibodies targeting PD-1 or PD-L1 block the PD-1 pathway and reactivate T-cell activity (28). As far as the past viewpoint of this drug is concerned, it was in the early 1990s that a biologist in Japan revealed a molecule expressed in dying T-cells, which he named *programmed death* 1 (PD-1) and which he recognized as the other *brake* on T cells. The first clinical trial, involving 39 participants and five different cancers, began in the year 2006. After two years, by 2008, medics were jolted by what they saw: in five of the volunteers, all of them with refractory disease, tumors were shrinking (33, 45).
According to Weinstock M *et al*. review article antibodies that block the PD-1 immune checkpoint pathway have shown encouraging antitumor activity against metastatic renal cell carcinoma in phase I and phase II trials. They have also suggested that combination approaches would be essential to enhance their efficacy (44). Similarly, according to the Carosella E *et al*. report, antibodies blocking immune check-points offer interesting and long-lasting response rates in heavily pretreated patients with advanced urologic cancers. More promising results are currently provided by - PD-1/PD-L1 inhibitors in renal cancer (40) and lung cancer (46). Nivolumab was FDA approved for patients with metastatic melanoma in 2014. Besides, nivolumab was FDA approved in 2015 for patients with previously treated advanced or metastatic non-small-cell lung cancer based on a phase III clinical trial, which reported an improvement in overall survival for patients treated with nivolumab as compared to patients treated with chemotherapy (6).

Like other cancer therapies, immune checkpoint therapies may lead to side effects and toxicities (6, 47, 49)**.** Briefly, these effects involve immune-related adverse reactions that are defined by inflammatory conditions, like dermatitis, colitis, hepatitis, pancreatitis, and pneumonitis. These side effects can be managed and usually involve administration of immunosuppressive agents such as corticosteroids, which do not appear to interfere with clinical benefit that is derived from the immune checkpoint agents. The profile of side effects that occur with both anti-CTLA-4 and anti-PD-1/PD-L1 antibodies is similar. However, the side effects appear to occur more frequently in the setting of anti-CTLA-4 therapy as compared to anti-PD-1 and anti-PD-L1 therapies (6). The future for this group of anti-cancer agents lies on a closer understanding of our immune responses in the tumor microenvironment. This will provide valuable information regarding the dynamic nature of the immune response and regulation of additional pathways that will need to be targeted through combination therapies to provide survival benefit for greater numbers of patients (43).

Adoptive cell transfer

Adoptive cellular therapy with various lymphocytes is the other groundbreaking innovation in the pillar of cancer immunotherapy, which depends on the tumor-specific T-cell (18, 50). The transfusion of adoptive allogeneic or autologous T-cells into patients is effective management for regression of cancer (51). The two main approaches in adoptive T-cell transfer in cancer immunotherapy are; 1) infusion of *ex-vivo* expanded tumor-infiltrating lymphocytes (TILs) and 2) infusion of engineered T-cells (which includes CAR-T cells and TCR-engineered T cells). So far, genetic engineering of T-cells seems a powerful tool for shaping tumor

T-cells seems a powerful tool for shaping tumor immunity (13). The approach has made a significant development on utilizing T-cells, especially in hematologic malignancies (52). Lymphocytes are firstly isolated from patients' blood, tumor-draining lymph nodes, or tumor tissue, expanded ex-vivo, and reinfused back into the patient. This strategy would, in theory, avoid the baffling duty of breaking tolerance to tumor antigens and produce a large amount of high avidity effector T cells (22, 28).

Initial tests in mice revealed that T-cells that had been cultured with leukemia cells could eliminate an established leukemia in-vivo. In patients who receive an allogeneic hematopoietic stem-cell transplant, mature T-cells in the graft mount a potent anti-leukemia response. Several groups have pursued this approach in patients with solid tumors by infusing autologous T-cells with specificity for a tumor antigen (18). According to Zhang *et al.* report, in-vitro induction and proliferation of expanded activated autologous lymphocytes is biologically safe even though it demands logistical and technical complexities (50).

In 2010, researchers published findings from chimeric antigen receptor (CAR) therapy, personalized management that involves genetically altering a patient's T-cells to make them target transformed cells. A research team in 2013 also reported that the T-cell therapy in their studies put 45 of 75 adults and children with leukemia into complete remission (33, 45). The FDA approved two CAR T-cell treatments in the year 2017. It is well described that CAR therapy and immune checkpoint inhibitors are generally different but complementary agents. In the former, patients' immune cells are genetically engineered to acquire new tumor-targeting specificity and potency while the latter leads to the activation and expansion of existing tumor-specific immune cells that are otherwise suppressed in the tumor microenvironment (22).

Cancer vaccines

Preventive vaccination against infectious diseases is considered one of the most successful health measures of all times. In addition to the successful use of preventative vaccines used in the defense against cancer causing infectious diseases like hepatitis B virus and human papillomavirus, the evidence that patients can harbor CD8+ and CD4+ T-cells capable of recognizing tumor expressed antigens hinted at the possibility of developing cancer vaccines (28). Generally, cancer vaccines activate the adaptive antitumor response largely by increased tumor antigen presentation. With the US FDA approval of the therapeutic vaccine Sipulencel-T (Provenge), cancer vaccine development is gaining huge ground. Approval of these vaccines has encouraged the concept of cancer treatment through cellular immunotherapy (53).

Age-old interest in cancer vaccines comes from the wonderful successes of prophylactic vaccines for infectious diseases. Historically, the primary approach to specifically activate host T-cells against tumor antigens (ie, active immunotherapy) has been therapeutic cancer vaccination (14). Active immunotherapy products are agents proposed to stimulate an immune response to destruct or reduce the progression of disease in patients where cancer has been diagnosed (54). However, despite impressive clinical outcomes achieved with immune checkpoint blockade and CAR therapies, the overall results of therapeutic vaccination against established tumors remain sub-optimal, as a clinical benefit for patients with cancer was largely noted as prolonged survival (25).

There are different vaccination strategies for cancer that either target the immune system in a general way (like Bacillus Calmette-Guerin (BCG)) or that directed to immune cells specifically to the cancer tissue (9). Generally, common cancer vaccination strategies include; 1)Viral vaccines; in which weakened version of herpes simplex virus (HSV) modified to produce an immune stimulating factor is being developed for melanoma and head and neck cancer. 2) Patient own tumor cells; that are extracted from the patient, irradiated to stop spreading, and engineered to produce activating growth factors. When these cells are injected back to the patient, the growth factors alert the immune system to the cancer. 3) APC like, DCs based vaccine - immature DC cells are taken from the patient, matured outside the body, loaded with tumor antigen then introduced back to the patient. Eventually the antigens will stimulate the immune cells to fight the cancer (6, 55).

Immunostimulatory cytokines

Research on the use of cytokine is currently at the front line in cancer therapy (30). Cytokines that are released in response to infection, inflammation, and immunity can function to inhibit tumor development and progression (56, 57). Immune therapy based on the use of cytokine has historically been the mainstay of immunotherapy in cancers such as melanoma and kidney cancer (52). Cytokines are groups of relatively small proteins that play a critical role in cell signaling, allowing immune cells to communicate and respond in an organized manner. They play important roles in the body's normal immune responses and in the fight against cancer. (14, 18).

As different cytokines that present in the tumor microenvironment shapes the host immune response, therapeutic manipulation of the cytokine environment constitutes one approach to stimulate protective immune responses. Indeed, William Coley's pioneering work at the end of the 19th century, in which bacterial extracts *(Streptococcus pyogenes* and *Serratia marcesens)* were administered as cancer immunotherapy (Coley's toxins) which resulted in marked alterations in cytokine levels and tumor clearance in some of the treated patients (56).

Proinflammatory cytokines can promote effector T-cell proliferation and activation. It is a promising line in cancer immunotherapy. In addition, the manipulation of cytokines can directly disrupt tumor cells, leading to apoptosis and inhibition of proliferation (18). Interferons (IFNs) and interleukins (ILs) are the common types of cytokines used in cancer immunotherapy. *IFN-α* (that enhances tumor antigen presentation and cytotoxicity) and *IL-2* (enhances NK cell and CD8+ T-cell function and increases vascular permeability) (56) were previously mainstays of treatment of metastatic renal cell carcinoma and melanoma. IFN-α was used as adjuvant therapy in resected high-risk melanoma, though the survival advantage was debatable (18). IL-2 was approved for the treatment of metastatic renal cell carcinoma and melanoma and is still used in some countries in limited highly restricted patients. Treatment requires admission in the intensive care unit because of severe systemic inflammatory responses and hypotension. A proportion of patients who took IL-2 have experienced long-term remission of their cancer (14, 18). Several additional cytokines are currently in clinical development pipeline (18).

Oncolytic viruses (OV)

OV encompasses a broad diversity of DNA and RNA viruses that are emerging as important immunotherapy to activate and redirect functional innate and adaptive immune responses towards the tumor (26, 58). They are naturally cancer-selective or can be genetically engineered (53) for optimization of tumor selectivity and enhanced immune stimulation (59) with minimal toxicity to normal tissues. They provide a diverse platform; they act as in-situ vaccines and can be armed with immune-modulatory transgenes or combined with other immunotherapies (26, 58).

Their induction of immunogenic tumor cell death and association with pro-inflammatory signals make OV promising anticancer agents. These viruses are believed to promote antitumor responses mainly through two distinct mechanisms of action: 1) acute tumor exposure owing to tumor cell infection and 2) lysis and induction of systemic antitumor immunity (22, 26). OVs selectively replicate in and kill cancer cells, and spread within the tumor. In addition to this direct oncolytic activity, they are also very effective at inducing immune responses to themselves and to the infected tumor cells (59).

The viral genome can be modified to augment anti-tumor activity and attenuate pathogenicity. Some of the abundant modifications that have been made and verified include the insertion of promoters that limit the expression of disease-causing genes to tumor cells or the deletion of pathogenic genes to limit the growth and the killing action of viruses to cancers. Additionally, oncolytic viruses can be engineered to express specific cytokines that favor immune cell recruitment and activation or to produce T-cell co-stimulatory molecules on infected tumor cells, thus facilitating the generation of T-cell activating signals (22).

Numerous viruses were tested as vectors for OV immunotherapy. Some of them are naturally non-pathogenic to humans, such as the Newcastle disease virus, a naturally oncolytic RNA virus, reovirus, and Seneca Valley virus. Others, including herpes simplex virus, measles virus, vaccinia virus, are genetically manipulated to become non-pathogenic (53, 58, 60). In 2005, an oncolytic adenovirus called H101 was approved to treat head-and-neck cancer, after evidence showed that the treatment could shrink tumors (53).

In 2015, the US FDA approved the genetically engineered oncolytic simplex virus type 1– derived **t**alimogene laherparep**vec** (T-VEC) in advanced melanoma. It becomes the first oncolytic immunotherapy against melanoma in a phase III clinical trial and is of its kind to demonstrate therapeutic benefit approved for use in Europe and the US (15, 53, 59). T-VEC is designed in such a way to selectively multiply within tumors and produce granulocyte-macrophage colony-stimulating factor (GM-CSF) to augment systemic antitumor reaction (15, 53, 58, 60).

The host anti-viral immune response is considered a major problem in achieving maximal antitumor effect by OVs. In other words, an initial host response to the virus may result in the rapid clearance of the virus before it manages to replicate and infect tumor cells at a magnitude that will ensure the initiation of an efficient vaccination response (60). Circumvention of this initial response is an active area of research (22).

Cancer vaccines

Preventive vaccination against infectious diseases is considered one of the most successful health measures of all times. In addition to the successful use of preventative vaccines used in the defense against cancer causing infectious diseases like hepatitis B virus and human papillomavirus, the evidence that patients can harbor CD8+ and CD4+ T-cells capable of recognizing tumor expressed antigens hinted at the possibility of developing cancer vaccines (28). Generally, cancer vaccines activate the adaptive antitumor response largely by increased tumor antigen presentation. With the US FDA approval of the therapeutic vaccine Sipulencel -T (Provenge), cancer vaccine development is gaining huge ground. Approval of these vaccines has encouraged the concept of cancer treatment through cellular immunotherapy (53).

Age-old interest in cancer vaccines comes from the wonderful successes of prophylactic vaccines for infectious diseases. Historically, the primary approach to specifically activate host T-cells against tumor antigens (ie, active immunotherapy) has been therapeutic cancer vaccination (14). Active immunotherapy products are agents proposed to stimulate an immune response to destruct or reduce the progression of disease in patients where cancer has been diagnosed (54). However, despite impressive clinical outcomes achieved with immune checkpoint blockade and CAR therapies, the overall results of therapeutic vaccination against established tumors remain sub-optimal, as a clinical benefit for patients with cancer was largely noted as prolonged survival (25).

There are different vaccination strategies for cancer that either target the immune system in a general way (like Bacillus Calmette-Guerin (BCG)) or that directed to immune cells specifically to the cancer tissue (9). Generally, common cancer vaccination strategies include; 1)Viral vaccines; in which weakened version of herpes simplex virus (HSV) modified to produce an immune stimulating factor is being developed for melanoma and head and neck cancer. 2) Patient own tumor cells; that are extracted from the patient, irradiated to stop spreading, and engineered to produce activating growth factors. When these cells are injected back to the patient, the growth factors alert the immune system to the cancer. 3) APC like, DCs based vaccine - immature DC cells are taken from the patient, matured outside the body, loaded with tumor antigen then introduced back to the patient. Eventually the antigens will stimulate the immune cells to fight the cancer (6, 55).

Immunostimulatory cytokines

Research on the use of cytokine is currently at the front line in cancer therapy (30). Cytokines that are released in response to infection, inflammation, and immunity can function to inhibit tumor development and progression (56, 57). Immune therapy based on the use of cytokine has historically been the mainstay of immunotherapy in cancers such as melanoma and kidney cancer (52). Cytokines are groups of relatively small proteins that play a critical role in cell signaling, allowing immune cells to communicate and respond in an organized manner. They play important roles in the body's normal immune responses and in the fight against cancer. (14, 18).

As different cytokines that present in the tumor microenvironment shapes the host immune response, therapeutic manipulation of the cytokine environment constitutes one approach to stimulate protective immune responses. Indeed, William Coley's pioneering work at the end of the 19th century, in which bacterial extracts *(Streptococcus pyogenes* and *Serratia marcesens)* were administered as cancer immunotherapy (Coley's toxins) which resulted in marked alterations in cytokine levels and tumor clearance in some of the treated patients (56).

Proinflammatory cytokines can promote effector T -cell proliferation and activation. It is a promising line in cancer immunotherapy. In addition, the manipulation of cytokines can directly disrupt tumor cells, leading to apoptosis and inhibition of proliferation (18). Interferons (IFNs) and interleukins (ILs) are the common types of cytokines used in cancer immunotherapy. *IFN-α* (that enhances tumor antigen presentation and cytotoxicity) and *IL-2* (enhances NK cell and CD8+ T-cell function and increases vascular permeability) (56) were previously mainstays of treatment of metastatic renal cell carcinoma and melanoma. IFN-α was used as adjuvant therapy in resected high-risk melanoma, though the survival advantage was debatable (18). IL-2 was approved for the treatment of metastatic renal cell carcinoma and melanoma and is still used in some countries in limited highly restricted patients. Treatment requires admission in the intensive care unit because of severe systemic inflammatory responses and hypotension. A proportion of patients who took IL-2 have experienced long-term remission of their cancer (14, 18). Several additional cytokines are currently in clinical development pipeline (18).

Oncolytic viruses (OV)

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Combination therapy

Cancer immunotherapy could be combined with conventional therapies to achieve maximal patient benefit. Fortunately, many conventional treatments for prostate and other cancers have beneficial immunological effects, making combinatorial trials an attractive area (12). Combining immune-based treatments, or pairing them with other anticancer agents like radiation or chemotherapy, scientists in the field anticipate increasing and broadening the benefits to patients (7).

In 2017, according to a report in Nature magazine, a 69 years old patient in California started to take an experimental combination of immunotherapy drugs for melanoma. The patient had a tumor growth bulging under his armpit. It was difficult to operate the tumor, and his doctor suspected that it might be spread to the patient's lungs. However, the combination of the antibodies nivolumab and ipilimumab had a remarkable outcome in which the tumor was shown destroyed (7).

Similarly, according to Antonia et al, the majority of patients with some form of cancer, like lung cancer, treated with single-agent anti–PD-1/PD-L1 do not benefit much. They stated that combination therapy with multiple immunotherapeutics was necessary to improve clinical efficacy (46). For example, because CTLA-4 and PD-1 regulate different inhibitory pathways on T-cells, combination therapy with antibodies targeting both molecules was tested and found to improve anti-tumor responses in a preclinical murine model. A phase I clinical trial with anti-CTLA-4 in combination with anti-PD-1 also demonstrated tumor regression in about 50% of treated patients with advanced melanoma, in most cases with tumor regression of 80% or higher that highlight this combination as an effective immunotherapy strategy for cancer patients (6).

Moreover, combinations of cancer vaccines with blocking monoclonal antibodies against immune checkpoint receptors such as CTLA-4 and PD-1 demonstrate dramatic synergy in murine tumor models (14). Other reports also showed that combining ipilimumab and anti–PD-1 led to tumor regression in almost a third of melanoma patients (33, 45).

Currently, there are hundreds of clinical trials on cancer combination therapies as pieces of evidence showed that two- and three-drug regimens lead to clinical benefits though do have added expenses and side effects (7, 28). Nevertheless, cancer combination therapies that include immune-based elements face specific challenges, both clinical and monetary. Some immunotherapies trigger dangerous autoimmune reactions that combination treatments can exacerbate. Besides, the cost of the drugs is much greater than that of conventional cancer treatments (7).

CONCLUSIONS

A great deal has been studied about the potential of the immune system to fight and control cancer and the range of ways that immunotherapy can improve the potential of the immune system. This knowledge has stimulated the discovery of a number of novel therapeutic options including antibodies, cell-based treatments, and cancer vaccines, which are currently being used in clinical settings, either alone or in various combinations. The clinical success by immune checkpoint therapy, using blocking antibodies to CTLA-4 and PD-1, and by CAR- T cells represents the result of efforts to harness the immune system in the eradication of cancer cells. Yet, not all patients benefited from the immunotherapeutic discovery. Efforts should now onwards focus on improving the efficacy of immunotherapy through the use of numerous combination approaches and predictive biomarkers of treatment outcome. Among possible reasons for lack of cancer eradication, suboptimal vaccine design and the presence of an immunosuppressive tumor microenvironment take the front line. Hence, unraveling the mechanisms by which cancer cells evade the immune system and developing new agents to target the relevant pathways represent the next steps in this approach for cancer treatment.

List of abbreviations

APC	Antigen-presenting cell
CAR	Chimeric antigen receptor
CD	Cluster of differentiation
CTL	Cytotoxic T-lymphocytes
CTLA-4	Cytotoxic T lymphocyte antigen 4
DC	Dendritic cells
FDA	Food and drug administration (US)
GM-CSF	Granulocyte acrophage colony-stimulating factor
HSV	Herpes simplex virus
ICAM-1	Intercellular adhesion molecule-1
IL	Interleukin
LFA-3	Lymphocyte function-associated antigen-3
mAb	monoclonal antibody
MHC	major histocompatibility complex
NK cells	Natural killer cells
OV	Oncolytic virus
PD-1	Programmed cell death 1
PD-1L	Programmed cell death 1 ligand
TME	Tumor microenvironment
TNF	tumor necrosis factor
T_{reg}	Regulatory T cells
T-VEC	Talimogene laherparepvec
WHO	World health organization

Declarations

Ethical Approval and Consent to participate: Not applicable in this section

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The Editor-in-Chief is responsible for deciding which articles submitted to the journal will be published. The decisions are made based exclusively on the manuscript's merit. They must be free from any racial, gender, sexual, religious, ethnic, or political bias. When making decisions the Editor-in-Chief is also guided by the editorial policy and legal provisions relating to defamation, copyright infringement and plagiarism. Members of the Editorial Board including the Editor-in Chief must hold no conflict of interest about the articles they consider for publication. Members who feel they might be perceived as being involved in such a conflict do not participate in the decision process for a manuscript. The information and ideas presented in submitted manuscripts shall be kept confidential. Editors and the editorial staff shall take all reasonable measures to ensure that the authors/reviewers remain anonymous during and after the evaluation process in accordance with the type of reviewing in use. The Editorial Board is obliged to assist reviewers with additional information on the manuscript, including the results of checking manuscript for plagiarism.

Responsibilities of reviewers

Reviewers are required to provide qualified and timely assessment of the scholarly merits of the manuscript. The reviewer takes special care of the real contribution and originality of the manuscript. The review must be fully objective, and the judgment of the reviewers must be clear and substantiated by arguments. The reviewers assess a manuscript for the compliance with the the profile of the journal, the relevance of the investigated topic and applied methods, the scientific relevance of information presented in the manuscript, and the presentation style. The review has a standard format. It is submitted through the online journal management system where it is stored permanently. The reviewer must not be in a conflict of interest with the authors or funders of research. If such a conflict exists, the reviewer is obliged to promptly notify the Editor-in-Chief. The reviewer shall not accept for reviewing papers beyond the field of his/her full competence. Reviewers should alert the Editor-in-Chief to any well-founded suspicions or the knowledge of possible violations of ethical standards by the authors including any duplicate submissions or publications during the review process. Reviewers should recognize relevant published works that have not been considered in the manuscript. They may recommend specific references for citation but shall not require citing papers published in the Ethiopian Medical Journal, or their own papers, unless it is justified. The reviewers are expected to improve the quality of the manuscript through their suggestions. If they recommend correction of the manuscript prior to publication, they are obliged to specify the way this can be achieved. Any manuscript received for review must be treated as confidential document.

ETHICAL CONSIDERATIONS

Researches Involving Human Participants

Manuscripts of research outputs conducted on human participants should be carried out only by or strictly supervised by, suitably qualified and experienced investigators and in accordance with a protocol that clearly states the aim of the research, the reasons for proposing that it involves human subjects, the nature and degree of any known risks to the subjects, the sources from which it is proposed to recruit subjects, and the means proposed for ensuring that subjects' consent will be adequately informed and voluntary. The protocol should be scientifically and ethically approved by one or more suitably constituted review bodies, independent of the investigators basically operating within the legal framework of each specific country or territory at which the study was conducted and operating with the internationally reputed ethical standards.

Explicitly:

- Any studies involving human participants should be approved by legally registered and accredited institutional review board (IRB) or equivalent research ethics review committee.
- Compliance with the ethical practices and its approval by the responsible IRB should be declared at submission and the review board approval document should be submitted upon request by EMJ
- How the informed consent was sought should be explained clearly with required details.
- Any clinical investigation must be conducted according to the principles expressed in ethical principles for medical research involving human subjects with the internationally reputed ethical standards specifically according to Declaration of Helsinki.
- Clinical trials should provide trial registration details, the study protocol, and trial study report guideline according to the specific study design.

Dealing with unethical behavior

Anyone may inform the Editor-in-Chief at any time of suspected unethical behavior or any type of misconduct by giving the necessary credible information/evidence to start an investigation.

- The Editor-in-Chief makes the decision regarding the initiation of an investigation.
- During an investigation, any evidence should be treated as confidential and only made available to those strictly involved in the process.
- The accused will always be given the chance to respond to any charges made against them.
- If it is judged at the end of the investigation that misconduct has occurred, then it will be classified as either minor or serious.
- Minor misconduct (with no influence on the integrity of the paper and the journal, for example, when it comes to misunderstanding or wrong application of publishing standards) will be dealt directly with authors and reviewers without involving any other parties. Outcomes include:
    - Sending a warning letter to authors and/or reviewers.-
    - Publishing correction of a paper, e.g. when sources properly quoted in the text are omitted from the reference list.
    - Publishing an erratum, e.g. if the error was made by editorial staff.
- In the case of major misconduct, the Editor-in-Chief may adopt different measures:
    - Publication of a formal announcement or editorial describing the misconduct.
    - nforming officially the author's/reviewer's affiliating institution.
    - The formal, announced retraction of publications from the journal in accordance with the Retraction Policy.
    - The formal, announced retraction of publications from the journal in accordance with the Retraction Policy.
    - A ban on submissions from an individual for a defined period.
    - Referring a case to a professional organization or legal authority for further investigation and action
    - The above actions may be taken separately or jointly. If necessary, in the process of resolving the case relevant expert organizations, bodies, or individuals may be consulted.
- When dealing with unethical behavior, the Editorial Board will rely on the guidelines and recommendations provided by the Committee on Publication Ethics (COPE).

Plagiarism prevention

The Ethiopian Medical Journal does not publish plagiarized papers. The Editorial Board has adopted the stance that plagiarism, where someone assumes another's ideas, words, or other creative expression as one's own, is a clear violation of scientific ethics. Plagiarism may also involve a violation of copyright law, punishable by legal action. Plagiarism includes the following:

- Self-plagiarism, which is using one's own previous work in another context without citing that it was used previously;
- Verbatim (word for word), or almost verbatim copying, or purposely paraphrasing portions of another author's work without clearly indicating the source or marking the copied fragment (for example, using quotation marks) in a way described under Responsibilities of authors;

* Copying equations, figures or tables from someone else's paper without properly citing the source and/or without permission from the original author or the copyright holder.

Any manuscript which shows obvious signs of plagiarism will be automatically rejected. In case plagiarism is discovered in a paper that has already been published by the journal, it will be retracted in accordance with the procedure described under Retraction policy, including blacklisting the author(s). To prevent plagiarism, submitted manuscripts will go through rigorous plagiarism detection process using standard software. The results obtained are verified by the Editorial Board in accordance with the guidelines and recommendations of the Committee on Publication Ethics (COPE).

Confidentiality

EMJ is committed to ensuring the integrity of the peer review process, in accordance with COPE guidelines. Until publication, we strictly keep confidentiality of manuscripts or materials submitted. Reviewers are also required to treat all submitted manuscripts confidentially to make the review process strictly confidential. They should not share information about the manuscript under their review with any third parties. Any breach of confidentiality during the review process will follow COPE guidelines.

Conflict of interest

According to the World Association of Medical Editors (WAME), existence of conflict of interest should be reported if there is a divergence between an individual's private interests (competing interests) and his or her responsibilities to scientific and publishing activities such that a reasonable observer might wonder if the individual's behavior or judgment was motivated by considerations of his or her competing interests. It is the responsibility of authors to disclose any financial/other interest that may have influenced the development of the manuscript. If the reviewers perceive any possible conflict of interest for manuscripts they are assigned to review, they should disclose it and they should decline the review of such manuscripts if needed. The same also applies to the editors.

Retraction policy

Legal limitations of the publisher, copyright holder or author(s), infringements of professional ethical codes, such as multiple submissions, bogus claims of authorship, plagiarism, fraudulent use of data or any major misconduct require retraction of an article according to Retraction guidelines | COPE: Committee on Publication Ethics. Occasionally, a retraction can be used to correct numerous serious errors, which cannot be covered by publishing corrections. A retraction may be published by the Editor-in-Chief, the author(s), or both parties consensually. The retraction takes the form of a separate item listed in the contents and labeled as "Retraction". The original article is retained unchanged, except for a watermark on the PDF indicating on each page that it is "retracted".

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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 Ophthalmology. 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.

General information

The Editorial Board reserves the right for final acceptance, rejection or editorial correction of papers submitted. However, authors are encouraged to write an appeal to the Editor-in-Chief for reconsideration of rejected manuscripts or any other complaints they might have.

Accepted papers are subject to Editorial revision as required and become the copy-right of the EMA Twenty-five reprints of published articles are supplied free to the first/corresponding author.

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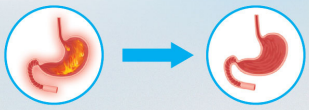

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