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Editorial

Bridging the research-practice gap plays a pivotal role in accelerating the health and well-being targets of the sustainable development goals (SDG)

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At the time, we are halfway through the ambitious global targets of the sustainable development goals (SDG) to be achieved by 2030, which was developed benchmarking the end of the Millennium Development Goals (MDG)(1). From the seventeen goals formulated, good health and well-being (SGD 3) is one where the global nations are investing (2). All those in the driving seat are forging new ways of accelerating these targets in the context of multiple crises and massive economic pressure—a recent memory is the unprecedented COVID-19 crisis that scrambled the world (3). Despite all the stresses, there is a need to look for multiple paths to catch up with the lags in the first half and speed up during the second half. One way of transpiring this is by efficient evidence generation and translation—evidence generation implies producing evidence, whereas translation means transforming valid evidence into practices(4). The translation exercises are not as easy as producing results where the actors involved must be aware of and set a feasible mechanism where they operate. This editorial note first highlights bridging the research-to-practice divide, elaborating on the current gaps and potential drivers. And then outlines how to bridge the gaps to accelerate SDG progress, presents brief global and country-level efforts against the challenges, and postulates the future focus areas.

In 2008, Butler(5) presented the concept of death in the valley, uttering the significant loss of evidence before it reaches and meets its ultimate objective. This valley—the research-practice gap—is a prevailing challenge, and little effort has been made to mitigate the problem. With the fact that progress has been minimal, putting the topic among the urgent calls for action. The sources and extents of the problem appeared in a series of works titled 'increasing value and reducing waste.'(6, 7). This work was motivated by evidence translation to practice, mainly attributed to limitations in conceptualization, selection, generation, and reaching the end users—policymakers and practitioners. Though deep and wide in low- and middle-income nations, these problems are global. Several environmental and situational complexities exist in how and to what extent research evidence is translated into policy and practice. These complexities can be explained by factors related to researchers, decision-makers, their engagement, and the context in which they operate. Culture, climate, goals, missions, processes, and time are among a few of these factors. Altogether, these resulted in the impediment of the research investment contributions to the current health system in rendering timely and quality services (6, 8).

For decision-makers and public health actors, proper evidence would improve health outcomes, strengthen health system performance, and act as a steppingstone to achieving health-related SDGs. However, the gains obtained from the research development are minimal due to the above gaps and wastages. So, bridging the research-practice gap plays a central role in achieving the set goals, which should be the main emphasis of the next hepta years in the journey toward SDGs. (2, 4). Creating a convenient landscape for actors—the people, organizations, and networks-drives the translation of evidence. In the ecosystem of these actors, mutual communication, action, and reflection under collaborative and collective action research and praxis are needed. More importantly, decision-oriented research is one approach that requires due priority due to the dire need for such evidence during this defining moment of the SDG period. This would be more facilitated when researchers and practitioners come closer through emerging frameworks like the exchange and integrative models (9, 10). Along the same line, the recent evolution of translational disciplines with the core concept of co-designing, co-production, and facilitated interventions is a profound means of bridging these gaps to maximize the efficient generation and uptake of the resulting evidence (9).

There have been various attempts in various contexts to bridge these gaps, and they show promising prospects. Robinson and his colleagues presented how the translational centers have been established and used to bridge the

gap in the UK and Australia, indicating that the knowledge/evidence generator and end users/practitioners joint exercise improved the quality and immediate application of evidence generated (11). South Africa and a handful of African countries attempted to design different frameworks, resulting in a promising prospect of producing edible evidence (12, 13). In the Ethiopian case, experiences that can be showcased (are the current joint exercise of the Ministry of Health (MoH), Regional Health Bureaus (RHBs), and researchers through various platforms. These include the Research Advisory Council (RAC) operating at the MoH (14), the Scientific Advisory Panel (SAP) at the Oromia Health Bureau (OHB), and the Knowledge Hub activities at the Amhara Public Health Institute (APHI) supported technically and financially by the Fenot-Harvard/UBC Project. These schemes are meant for joint evidence synthesis steered towards addressing decision-makers' needs. Worth mentioning also is the regular evidence -sharing sessions (Agelgil at MoH, Gela at OHB, and Sinki at APHI) to facilitate evidence uptake by bringing researchers' work to programmers.

In conclusion, making timely and effective decisions in a complex health system takes time and energy. It requires robust and timely evidence co-produced with the end users for an instant translation, which can happen when we bridge the research-practice valley. The ambitious global goals—like the SDG - greatly benefit from bridging the wide gap, which requires packing resolutions/frameworks that facilitates evidence generation, data sharing, and knowledge translations (4, 8). It is about laying the foundation of how the evidence ecosystem must operate, which needs to be properly communicated among all actors. Creating a platform where researchers and practitioners are the subject and object of inquiries is necessary (15). The academia and research institutes—the primary reservoir for researchers and research investments—are expected to creatively steer their research activities in alignment with the global SDG targets. Along the same line, the practitioners/translators must be innovative in expanding the collaboration and tracking evidence generation for instant decisions without delay and wastage. Designing and instituting context-oriented knowledge translation platforms are urgent missions to catch up with the missed opportunities in the previous half of the SDG period.

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Original Article

Time to recovery and predictors among acute kidney injury patients on hemodialysis at the national renal transplant center in Ethiopia

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Abstract

Background: *Acute kidney injury (AKI) is defined as a sudden decline in kidney function in 48 hours. Unless diagnosed and managed early, AKI causes significant morbidity and mortality due to the associated increased risk of renal damage with every delay in recovery. There is a paucity of information on the pattern of recovery time from AKI and its contributing factors. Hence, this study aimed to estimate the median time to recovery and identify predictors among AKI patients on dialysis at the national renal transplant center in Ethiopia.*

Methods: *A retrospective chart review study was conducted among 232 AKI patients on dialysis who were managed at the center from January 2018 to June 2020. Data was summarized and compared using frequency tables, median survival times, KM survival plots and Log-rank tests. To identify predictors of time to recovery from AKI, a Cox Proportional Hazard (PH) survival model was used, where Adjusted Hazard ratio (AHR), 95% CIs for AHR, and P-values were used for interpretation of results. Data management and analysis was done using SPSS software V. 25.0.*

Results: *From the 232 AKI patients on dialysis, 127 (54.7%, 95% CI=48.7%-61.3%) achieved recovery and the median time to recovery was 25.0 days (95% CI=22.1, 27.9). On the Cox PH model, having cardiovascular disease (AHR=0.51, 95% CI=0.28,0.93, p=0.028), sepsis (AHR=0.59, 95% CI=0.37, 0.95, p=0.031) and acute glomerulonephritis (AGN) (AHR=0.31, 95% CI=0.14,0.71, p=0.005) were found to be significant predictors of time to recovery from AKI.*

Conclusions: *The median time to recovery from AKI is optimal given the high-risk nature of the studied population. However, this duration may be associated with an increased risk of both short and long-term complications from continued renal damage. Having cardiovascular disease, sepsis and AGN were found to be associated with delayed recovery from AKI. Therefore, strict monitoring of AKI patients in general, and the high-risk groups in particular, is essential for rapid recovery.*

Keywords*: Acute Kidney Injury, time to recovery, survival analysis, Cox PH model, Ethiopia*
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Introduction

Acute kidney injury (AKI) is defined as a sudden decline in kidney function in 48 hours as manifested by an increase in serum creatinine of more than 0.3 mg/dl, an increase in serum creatinine of more than 50%, or the development of oliguria (1). AKI can be caused by a variety of factors in both the community and hospital setting. Pre-renal causes account for 30-40% of these causes, which include medical illnesses (both acute and chronic) and exposure to nephrotoxic drugs. Renal causes from various glomerular diseases, as well as post-renal causes, account for a significant proportion too (2-17). Given that all of these factors are common in hospitalized patients, AKI diagnosis is a common occurrence in

hospitalized patients.
Unless diagnosed and managed early, AKI causes significant morbidity and mortality and costs the healthcare system. This indicates the significance of time in the management of AKI. Delay in recovery from AKI is associated with an increased risk of renal damage, which can result in permanent loss of function and even death (1,2) . As a result, the epidemiological understanding of AKI should not only focus on its outcomes per se, but also on the time it takes to recover. The current body of literature has primarily focused on the first one, understanding the outcome of AKI, and it has been reported that AKI is associated with a poor prognosis, particularly in developing countries where early identification and management of cases is difficult due to low healthcare seeking behavior and an underdeveloped healthcare system (3,4,18-26). This indirectly implies that most patients are subjected to a continuing renal insult, which facilitates the poor prognosis in addition to the severity of the underlying cause of the AKI. As a result, understanding the pattern of recovery time and its contributors is crucial for planning evidence-based interventions for favorable short and long-term patient outcomes. Therefore, the aim of this study was to estimate the median time to recovery and identify predictors among AKI patients on dialysis at the national renal transplant center in Ethiopia.

Materials and methods

Study Design and Setting

A retrospective chart review study, with an observation period from January 2018 to June 2020, was conducted at St Paul's Hospital Millennium Medical College (SPHMMC), a tertiary teaching hospital under the Federal Ministry of Health in Addis Ababa, Ethiopia. SPHMMC is the country's second largest governmental hospital, as well as the first governmental hospital to provide both acute and chronic hemodialysis services in collaboration with the Egyptian government, and thus serves as the primary government-owned referral center for AKI patients. The hospital currently has approximately forty hemodialysis machines for end-stage renal disease and approximately six hemodialysis machines for acute kidney injury (27).

Population, Eligibility and Sample size

During the two years and half observation period, from January 2018 to June 2020, a total of 290 AKI patients received dialysis service at the center. Hence due to the small number of the source population, we included all eligible cases. Finally, 232 eligible patients, who did not have CKD at the time of admission, and had data on major exposures and outcomes, were included in the final analysis.

Operational Definition

Recovery from AKI: Recovery is declared when a patient who is diagnosed to have AKI and kept on hemodialysis achieves clinical improvement and not further requiring dialysis.

Event: Recovery from AKI
Censoring: Includes patients who were lost to follow-up, transferred out, died or completed the follow -up period before recovery from AKI.
Time to event or censoring: time between admission to the center up to recovery or censoring (in days).

Data Collection and Quality Assurance

Data was collected from medical charts of the patients using a pretested data abstraction tool that contains questions on socio-demographics, medical illness history, obstetric and surgical history, exposure to nephrotoxic drugs, pre-renal causes, and AKI outcome. To improve data quality, training on the basics of the questionnaire and data collection tool was given for two data collectors (General practitioners) for two days. In addition, double data entry, and data cleaning through checking for inconsistencies, numerical errors and missing parameters was done. Where discrepancies are observed, data entered was verified with the primary data source. Where possible, data was validated by comparing a certain percentage of data in our database with that of another database. Data consistency and completeness was checked before an attempt was made to enter the code and analyze the data. Once data cleaning was complete, the data was exported to SPSS version 25.0 software for data management and analysis.

Statistical Analysis

Data was summarized using proportions with frequency tables, Kaplan Meier (KM) plots and median survival times. Survival experience of different groups was compared using KM survival curves and Log-rank test was used to assess the statistical significance of any observed difference between the groups.
A chi-square test was used to compare the underlying characteristics of the transferred patients and the remaining patients in order to identify the presence of a statistically significant difference in their exposure to important factors that could have made them more prone to develop one group of outcome has and in turn could have biased the overall result of the study findings.
To identify predictors of time to recovery from AKI, Cox proportional hazard (PH) survival model was used. Univariate analysis at 25% level of significance was performed to calculate crude hazard ratio (CHR)

and to screen out potentially independent variables. The selected variables were included into the final multivariable Cox PH survival model at 5% level of significance where adjusted hazard ratio (AHR), 95% CI for AHR and p-value were used to interpret the results. The basic assumption of Cox Proportional Hazard model, the proportional hazards assumption, was tested using log minus log function and the plot shows a reasonable fit to the assumption with parallel lines between groups indicating proportionality. (**Supplementary file 1**)

Results

Socio-demographic and clinical characteristics

Among the 232 AKI patients on dialysis, the majority were between the age of 30 and 49 years (40.9%) followed by those 16 to 29 years (38.4%) and 122 (52.6%) were females.

The majority (85.3%) of the patients had one or more medical illnesses upon admission. From which, chronic medical illnesses, mainly hypertension (40.9%), cardiovascular disease (15.9%), and diabetes mellitus (8.6%), constituted a larger proportion. Acute medical conditions, mainly sepsis, shock and LRTI were diagnosed in 86 (37.1%), 63 (27.2%) and 63 (27.2%), respectively. Forty-two patients (18.1%) underwent major surgery.

Exposure to nephrotoxic drugs was identified in 225 (97.0%) of the patients. Among these, the majority were on PPI (89.2%), followed by vancomycin (50.9%) and ceftriaxone (35.8%). Only 22 patients were taking ACE2 expression inhibiting drugs, particularly ACEIs/ARBs by 11 (4.7%) and NSAIDs by 11 (4.7%).

Three-fourth of all patients (77.6%) were diagnosed with a glomerular disease. From which the majority had ATN (46.1%), followed by RPGN (19.4%), AGN (11.2%), and PIGN (10.3%).

A quarter of all patients (11.2%) were diagnosed with post-renal causes of AKI, mainly ureteric stone in 19 (8.2%) patients. Thirty-four (14.7%) of patients needed an Intensive Care Unit (ICU) admission. **(Table 1)**

Censoring status and median time to recovery from AKI

From the 232 AKI patients on dialysis, 127 (54.7%, 95% CI=48.7%-61.3%) achieved recovery and the rest 105 (45.5%, 95% CI=38.7%-51.3%) were censored. Among the 105 censored observations, 33 (31.4%) developed CKD, 38 (36.2%) died and the remaining 34 (32.4%) were transferred to another hospital either for convenience of family visit or seeking private hospital care. A statistical comparison of the underlying characteristics of the 34 transferred patients and the remaining 198 patients were made to identify the presence of significant difference in their exposure to important factors that could have made them more inclined to be at high risk of recovering or not and hence has biased the overall result of the study findings. Accordingly, all comparisons showed no significant difference (p-value of all -square tests were >0.05).

The overall median time to recovery was 25.0 days (95% CI=22.1, 27.9). The comparison of the median time to recovery between groups showed that there is a statistically significant difference in the time based on cardiovascular disease and sepsis. Accordingly, a significantly delayed recovery from AKI was observed among patients with cardiovascular disease (38 Vs 22 days) and those with sepsis (28 Vs 21 days) as compared with those with no such medical illnesses. **(Table 1)**

Predictors of time to recovery from AKI

To identify predictors of time to recovery from AKI, Cox proportional hazard (PH) survival model was used. Crude analysis of each independent variable with the time to recovery was run at 25% level of significance. From univariate analysis; age group, gender, hypertension, cardiovascular disease, diabetes mellitus, sepsis, shock, LRTI, major surgery, vancomycin, PPI, ACEIs/ARBs, NSAIDs, RPGN, PIGN, AGN, and ureteric stone were found to be significant and were fed into the final multivariable regression model.

In the final model, at a 5% level of significance, cardiovascular disease, sepsis and AGN were found to be significantly associated with time to recovery from AKI.

Accordingly, after adjusting for other covariates, the rate of achieving recovery among patients with cardiovascular disease was 49% lower than patients with no cardiovascular disease (**AHR=0.51, 95% CI=0.28,0.93, p=0.028**). In addition, being in sepsis was associated with a 41.0% lower rate of achieving recovery as compared to those with no sepsis (**AHR=0.59, 95% CI=0.37, 0.95, p=0.031**). Furthermore, the rate of achieving recovery among patients with AGN was 69.0% lower than those with no AGN (**AHR=0.31, 95% CI=0.14,0.71, p=0.005**). (**Table 2**)

Table 1: Participant characteristics, censoring status, and comparison of median time to recovery between groups among AKI patients on dialysis from January 2018 to June 2020, Ethiopia (n=232)

Variable		AKI outcome		Total (%)	Median time to recovery (in days)	P-value
		Recovered (%)	Censored (%)			
Age category (in years)	16-29	48 (53.9)	41 (46.1)	89 (38.4)	25.0	0.249
	30-49	60 (63.2)	35 (36.8)	95 (40.9)	24.0	
	≥ 50	19 (39.6)	29 (60.4)	48 (20.7)	30.0	
Gender	Male	54 (49.1)	56 (50.9)	110 (47.4)	27.0	0.623
	Female	73 (59.8)	49 (40.2)	122 (52.6)	25.0	
Hypertension	No	77 (56.2)	60 (43.8)	137 (59.1)	25.0	0.535
	Yes	50 (52.6)	45 (47.4)	95 (40.9)	26.0	
Cardiovascular illness	No	113 (57.9)	82 (42.1)	195 (84.1)	22.0	**0.02***
	Yes	14 (37.8)	23 (62.2)	37 (15.9)	38.0	
Diabetes mellitus	No	118 (55.7)	94 (44.3)	212 (91.4)	25.0	0.517
	Yes	9 (45.0)	11 (55.0)	20 (8.6)	28.0	
Liver disease	No	120 (55.3)	97 (44.7)	217 (93.5)	25.0	0.570
	Yes	7 (46.5)	8 (53.5)	15 (6.5)	20.0	
Sepsis	No	89 (61.0)	57 (39.0)	146 (62.9)	21.0	**0.03***
	Yes	38 (44.2)	48 (55.8)	86 (37.1)	28.0	
Shock	No	94 (55.6)	75 (44.4)	169 (72.8)	23.0	0.102
	Yes	33 (52.4)	30 (47.6)	63 (27.2)	28.0	
LRTI	No	95 (56.2)	74 (43.8)	169 (72.8)	25.0	0.536
	Yes	32 (50.8)	31 (49.2)	63 (27.2)	24.0	
Gastroenteritis	No	121 (56.3)	94 (43.7)	215 (92.7)	25.0	0.886
	Yes	6 (35.3)	11 (64.7)	17 (7.3)	26.0	
Major surgery	No	98 (51.6)	92 (48.4)	190 (81.9)	25.0	0.520
	Yes	29 (69.0)	13 (31.0)	42 (18.1)	26.0	
Vancomycin	No	66 (57.9)	48 (42.1)	114 (49.1)	22.0	0.054
	Yes	61 (51.7)	57 (48.3)	118 (50.9)	27.0	
Ceftriaxone	No	78 (52.3)	71 (47.7)	149 (64.2)	20.0	0.063
	Yes	49 (59.0)	34 (41.0)	83 (35.8)	21.0	
ACEIs/ARBs	No	122 (55.2)	99 (44.8)	221 (95.3)	25.0	0.866
	Yes	5 (45.5)	6 (54.5)	11 (4.7)	23.0	
NSAIDs	No	121 (54.8)	100 (45.2)	221 (95.3)	25.0	0.792
	Yes	6 (54.5)	5 (45.5)	11 (4.7)	25.0	
PPI	No	12 (48.0)	13 (52.0)	25 (10.8)	26.0	0.633
	Yes	115 (55.6)	92 (44.4)	207 (89.2)	25.0	
ATN	No	59 (47.2)	66 (52.8)	125 (53.9)	26.0	0.163
	Yes	68 (63.6)	39 (36.4)	107 (46.1)	22.0	
RPGN	No	101 (54.0)	86 (46.0)	187 (80.6)	25.0	0.587
	Yes	26 (57.8)	19 (42.2)	45 (19.4)	25.0	
PIGN	No	115 (55.3)	93 (44.7)	208 (89.7)	25.0	0.683
	Yes	12 (50.0)	12 (50.0)	24 (10.3)	25.0	
AGN	No	117 (56.8)	89 (43.2)	206 (88.8)	25.0	0.074
	Yes	10 (38.5)	16 (61.5)	26 (11.2)	27.0	
Ureteric stone	No	115 (54.0)	98 (46.0)	213 (91.8)	25.0	0.536
	Yes	12 (63.2)	7 (36.8)	19 (8.2)	26.0	
ICU admission	No	112 (56.6)	86 (43.4)	198 (85.3)	24.0	0.089
	Yes	15 (44.1)	19 (55.9)	34 (14.7)	30.0	

***Note:** *statistically significant*

Kaplan Meir (KM) survival function graphs of these two groups also showed that those with cardiovascular disease and sepsis had a prolonged time to clinical recovery throughout the time as compared to those with no such medical illnesses. (**Figure 2**)

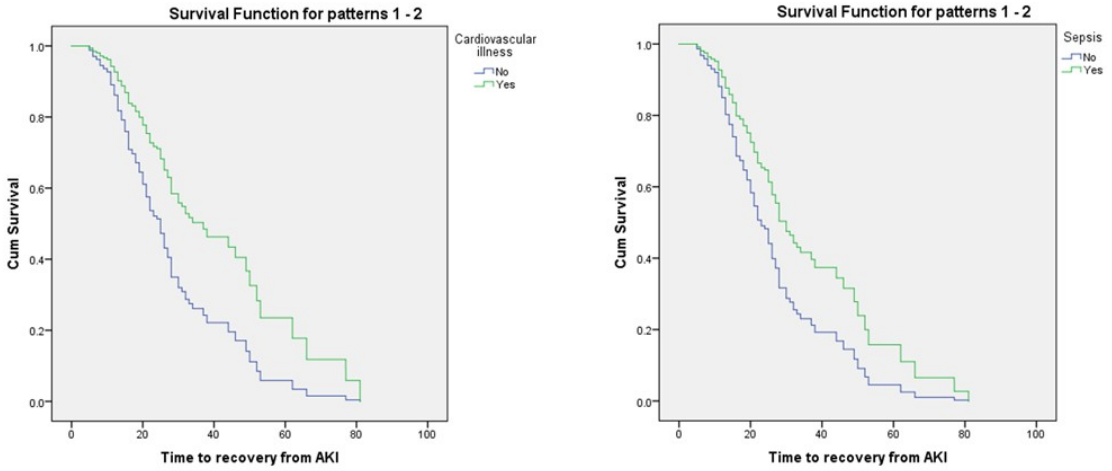

Fig 2: Kaplan-Meier survival graph of recovery time from AKI stratified by cardiovascular disease and sepsis

Table 2: Predictors of time to recovery among AKI patients on dialysis from January 2018 to June 2020, Ethiopia (n=232)

Variable	CHR (95% CI)	AHR (95% CI)	P-value
Age category (R=16-29 years)			
30-49	0.95 (0.65, 1.39)	0.94 (0.63, 1.40)	0.771
≥ 50	0.65 (0.38, 1.11)	0.65 (0.36, 1.19)	0.160
Gender (Male Vs Female)	1.09 (0.77,1.56)	1.05 (0.70,1.57)	0.823
Hypertension (Yes)	0.89 (0.63, 1.28)	0.99 (0.66, 1.48)	0.963
Cardiovascular disease (Yes)	0.53 (0.30, 0.92)	**0.51 (0.28, 0.93)**	**0.028***
Diabetes Mellitus (Yes)	0.80 (0.41, 1.58)	0.80 (0.39, 1.68)	0.559
Sepsis (Yes)	0.66 (0.45, 0.97)	**0.59 (0.37, 0.95)**	**0.031***
Shock (Yes)	0.72 (0.48, 1.08)	0.68 (0.41, 1.13)	0.137
LRTI (Yes)	1.14 (0.76, 1.71)	1.24 (0.77, 1.99)	0.384
Major surgery (Yes)	1.14 (0.75, 1.73)	1.14 (0.67, 1.96)	0.625
Vancomycin (Yes)	0.71 (0.49, 1.01)	0.85 (0.57, 1.26)	0.405
PPI (Yes)	0.87 (0.48, 1.58)	0.92 (0.48, 1.76)	0.800
ACEIs/ARBs (Yes)	1.08 (0.44, 2.65)	0.91 (0.36, 2.31)	0.836
NSAIDs (Yes)	1.12 (0.49, 2.54)	1.33 (0.56, 3.19)	0.516
RPGN (Yes)	0.89 (0.58, 1.37)	0.62 (0.38, 1.02)	0.062
PIGN (Yes)	1.13 (0.62, 2.06)	0.86 (0.43, 1.71)	0.659
AGN (Yes)	0.52 (0.25, 1.09)	**0.31 (0.14, 0.71)**	**0.005***
Ureteric stone (Yes)	1.20 (0.66, 2.19)	0.91 (0.42, 1.97)	0.814

Note: CHR, Crude Hazard ratio; AHR, Adjusted Hazard ratio; CI, Confidence interval; *statistically sig-

Discussion

The study aimed to estimate the median time to recovery and identify predictors among AKI patients on dialysis who were on follow at the national renal transplant center in Ethiopia from January 2018 to June 2020.

From the 232 AKI patients on dialysis, 127 achieved recovery and the overall median time to recovery was 25.0 days. According to studies, recovery from AKI can take a few days to weeks or even months, depending on the underlying cause of the AKI and the patients' personal risk factors. It is reported that on

average, half of AKI patients recover in 30 days, while the other half may require up to 90 days (28, 29). As a result, a median duration of 25.0 days can be considered an average duration, especially given that the majority of the studied population has an underlying risk factor that, despite their young age, could lead to additional renal damage and delayed recovery. Even if this duration can be considered optimal, it is still a long time given the increased risk of renal and systemic complications with each delay in renal recovery.

On the KM survival plot and log- rank test, a less favorable recovery experience was observed among patients with cardiovascular disease and sepsis. This was further confirmed on the final regression analysis, where having cardiovascular disease and being in sepsis were found to be associated with a 49% and 41% lower rate of achieving recovery, respectively, as compared to those with no such medical illnesses. Studies conducted in both developing and developed countries also indicated that patients with cardiovascular disease and sepsis are at high risk of complications from AKI and leading to progression to AKI and/or death implying that recovery in these groups of patients is delayed when it happens (30-32).

In addition, it was found that the rate of achieving recovery among patients with AGN was 69.0% lower than those with no AGN. As a glomerular disease, AGN causes renal injury through physical damage to the glomeruli. Since most of the time diagnosis can be delayed due to lack of symptoms among these patients, by the time AKI is developed most parts of glomeruli could be damaged. This will in turn result in delay in recovery despite provision of best care (33).

The following are the strengths and limitations of the study which should be considered when interpreting the findings. The first strength of the study is that it addressed an outcome that has received little attention, particularly in Ethiopia. The second strength is that it was conducted in a national center and included all eligible patients during the observation period, and hence it is conducted on a fairly representative sample of the population with AKI. Its limitations are, although several potential exposure variables are controlled in the study, other important exposures such as laboratory, radiologic and behavioral factors are not included due to inconsistent recording of this parameters on the charts. Furthermore, the relatively smaller sample size may have resulted in in lower study power, which may have resulted in a lower detection of other potentially significant relationships.

Conclusions

Given the high-risk nature of the studied population, the median time to recovery from AKI is optimal; however, this duration may very well be associated with an increased risk of both short and long-term complications from continued renal damage. Having cardiovascular disease, sepsis and AGN were found to be associated with delayed recovery from AKI.

As a result, strict monitoring of AKI patients in general, and the high-risk groups in particular, is pivotal for further rapid recovery. A large prospective study that takes into account all potential factors is required to reach a better conclusion.

List of Abbreviations

ACEIs/ARBs … Angiotensin-Converting Enzyme Inhibitors/ Angiotensin II Receptor Antagonists
AKI … Acute kidney injury
ATN … Acute Tubular Necrosis
AGN … Acute Glomerulonephritis
BUN … Blood Urea Nitrogen
CI …. Confidence interval
Cr … Creatinine
GFR … Glomerular filtration rate
IRB … Institutional review board
ICU … Intensive Care Unit
LRTI … Lower respiratory tract infection
NSAIDs … Non-steroidal anti-inflammatory drugs
OR …. Odds ratio
PIGN … Post-infectious Glomerulonephritis
PPI … Proton Pump Inhibitors
RPGN … Rapidly Progressive Glomerulonephritis

Declaration

Ethical Considerations

The study was conducted after securing ethical clearance from SPHMMC institutional review board (IRB) (letter no: PM.23/724). Since the study used secondary data, waiver of consent was obtained from the department of Internal medicine on behalf of the patients to be included in the study. Medical record number was used for the data collection and personal identifiers of the patient were not used in the research report. Access to the collected information was limited to the research team and confidentiality was maintained throughout the project.

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

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Author's Contribution: ATL and TWL conceived and designed the study. LHJ and TGG contributed to the conception, design of the study and interpretation of findings. ATL and TWL performed statistical analysis, and drafted the initial manuscript. All authors approved the final version of the manuscript.

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Original Article

Knowledge of alcohol consumers towards alcoholic liver disease in Afikpo, Ebonyi, Nigeria: A community-based cross-sectional study.

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Abstract

Background*: Daily alcohol consumption above recommended limits is an important cause of Alcoholic Liver Disease. Hence, this study aimed to assess the knowledge of Alcoholic Liver Disease among alcohol consumers and screen for alcohol misuse, dependence, and disorder.*

Methods*: A community-based cross-sectional survey using simple random sampling technique was conducted on residents of Afikpo age 15 and above who consume alcohol using a structured questionnaire to obtain information on alcoholic use disorder and alcohol dependence. The sample size was determined with the aid of a Raosoft sample size calculator. Data obtained was entered into an excel spreadsheet for data cleaning. The frequency, percentages and mean and Standard deviation was also obtained. Data was exported into IBM SPSS to determine the relationship between knowledge of Alcoholic Liver Disease and demographic variables using One-way ANOVA and Chi-Square where appropriate at P-value <0.05 and 5% significance level.*

Results*: The total number of study participants was 435 with a response rate of 97%. Out of which 361(80.8%) had a good knowledge of Alcoholic Liver Disease. Adults above the age of 60 had a mean audit score of 12.808 while male respondents had a mean audit score of 11.395. Adolescents had a mean CAGE test score of 1.89 while adults above 60 scored 2.48. However, participants with no education had the highest mean CAGE score of 2.27. The males had good knowledge of Alcoholic Liver Disease. (P=0.006).*

Conclusion: *The residents of Afikpo community have a good knowledge of Alcoholic Liver Disease though there is alcohol use disorder, alcohol misuse and dependence amongst residents in the community. Gender is the only demographic characteristics that influenced the knowledge of Alcoholic Liver Disease.*

Keywords*: Alcoholic liver disease; alcohol dependence; alcohol misuse; alcohol disorder; audit; cage*
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Introduction

The liver is the main organ for alcohol metabolism [1]. Alcohol is metabolized in the liver through three major pathways of which include the enzyme alcohol dehydrogenase pathway, the cytochrome P-4502E1 (CYP2E1) pathway and by mitochondrial catalase pathway. The first two pathways are of practical significance [2]. Alcohol dehydrogenase is involved in the degradation of limited quantities of alcohol, while alcohol-induced CYP2E1 pathway takes place in excessive alcohol intake [3]. Alcohol dehydrogenase is also present in the gastric mucosa; Individuals with low gastric alcohol dehydrogenase activity are more susceptible to alcoholic liver disease [4]. This may also help to explain why women who have decreased gastric alcohol dehydrogenase activity are more susceptible to developing alcoholic liver disease [5]. Alcohol dehydrogenase and cytochrome P-4502E1 convert alcohol to acetaldehyde. Acetaldehyde when accumulated, causes liver injury. Changes in lipid metabolism and in adipose tissue also enhance the process of liver injury [1]. Although most heavy drinkers do develop fatty liver, only a minority progress to liver cirrhosis; this implies that some other genetic or environmental factors are important for the disease progression [6].

Alcoholic liver disease (ALD) comprises a spectrum of disorders ranging from asymptomatic liver test derangements to severe acute hepatitis and end -stage chronic liver disease [7]. In individuals with concomitant liver diseases such as chronic viral

hepatitis, alcohol consumption promotes liver disease progression [8]. Assessing alcohol abuse in patients with ALD is essential for their treatment and prognosis. Alcoholic cirrhosis is a product of alcoholism (9). Therefore, one cannot examine alcoholic liver disease without a brief discussion of alcoholism [10]. A thorough clinical and psychological examination is crucial for alcohol abuse diagnosis. Information on the patients' clinical history, and social history can be obtained by applying some questioning skills such as a single question inquiring how often the maximum daily alcohol limit has been exceeded) [11]. Liver steatosis is the most prevalent in chronic alcohol abuse [12]. Changes associated with alcohol metabolism may subsequently trigger an inflammatory reaction, resulting in alcoholic hepatitis or chronic liver disease [4]. Simple steatosis is reversible after a number of weeks of abstinence [9]. It is regarded as a benign condition; nevertheless, given continued abuse, it could progress to fibrogenesis. However, about 20% of the patients with simple steatosis are likely to develop fibrosis or cirrhosis within a period of ten years [10].

Mortality from alcoholic liver disease closely follows per capita alcohol consumption. Malnutrition is another risk factor of ALD [13]. Heavy alcohol drinkers often times feed poorly or consume unbalanced diet.

Excessive alcohol consumption is one of the world's leading risk factors for morbidity, disability, and mortality. Approximately 3.3 million deaths (5.9% of all global deaths) and 139 million disability-adjusted life years (5.1% of the global burden of disease and injury) are attributable to alcohol use [14]. Reducing and preventing alcohol misuse and abuse is a public health concern as high rate of alcohol consumption has become a great social-health problem [15]. Alcohol-related disease results in approximately 2.5 million deaths each year and almost 4 % of all deaths worldwide are attributed to alcohol [16]. Alcohol abuse could lead to premature death, increased disease and injury; property damage from fire and motor vehicle crashes; alcohol-related crime; and lost productivity [14]. Research has also shown that the socio-economic effects associated with alcohol abuse include unemployment, violence, risky sexual behavior, and disruptions to family life and work performance [17]. Cultism may also be a big issue in some areas of the world. A popular myth in Ebonyi State, Nigeria, is that; the average Afikpo man is friendly with alcohol and loves to drink a lot, whether it is beer (5%), spirit (40%), or wine (12%). Therefore, there is need to assess the level of knowledge of ALD amongst Afikpo as the adverse effects of alcohol abuse on the liver could result in poor quality of life, low productivity, and countless deaths due to ALD that would have otherwise been avoidable.

This study aimed to assess the knowledge of ALD and screen for alcohol misuse, dependence, and disorder among alcohol consumers in Afikpo, Afikpo-North Local Government Area of Ebonyi State. Findings from this study will provide information on the extent of alcohol abuse and dependence amongst residnts of Afikpo community. It will also enable policymakers and public health multidisciplinary bodies to determine if there is a need for health promotion and education in Afikpo community so as to reduce the risk and prevalence of liver diseases related to the abuse of alcohol.

Methods

Study settings

Eleven autonomous communities in Afikpo North LGA Afikpo.[18]. The study was conducted in Afikpo autonomous community, formerly known as Ehugbo land. The community is settled at two localities: the upper undulating settlers (due to the basement rock) and the lower land settlers (the settlement that is close to the Cross-river floodplain's lower shore). The people of Afikpo are mostly known for subsistent farming, and they also engage in trading. The Afikpo clan is called Ehugbo people, and their famous greeting is 'Jookwa', which means good day or well done. The total population as at the last census held in 2006 was 156 611 with a projected population of 233,300 as at 2022[19]. Afikpo has a land mass of 204 square kilometers [18]. The community is the second largest urban area in Ebonyi State, Nigeria. It is the headquarters of the Afikpo North LGA. It is situated in the southern part of Ebonyi State. It is bordered to the north by the town of Akpoha, to the south by Unwana town, to the southwest by Edda, a community in Afikpo South LGA, to the east by Cross River State and the west by the town of Amasiri [18].

Study design: A community based cross-sectional study using simple random sampling technique was employed.

Study population: The respondents in this study are made up of a sample of Nigerians resident in Afikpo community who are 15 years and above and who consume alcohol. The respondents were grouped into three categories of the age range – Adolescents aged between 15 to 19 years, Adults aged 20 to 60 years, and the elderly aged 60 and above in correspondence with the criteria for a positive screening test [20].

Sample size: The sample size was calculated with the aid of a sample size calculator Raosoft (www.raosoft.com/samplesize) to be approximately 384, for a population size of 233,300[19] at a 95% confidence level, with a margin of error of 5% and a standard deviation of 50%. To account for non-responses, 450 questionnaires were distributed for this survey.

Inclusion and Exclusion Criteria
Every member of Afikpo community who resides in Afikpo, aged 15years or above and who consume alcohol is eligible for this study. Pregnant women and individuals less than 15years of age were excluded from this study.

Sampling instrument: The data collection instrument used for this study was a structured questionnaire which was developed after extensive literature review and with expert opinion. The questionnaire was face validated by three experts. Reliability analysis was conducted to check the reliability of the questionnaire using Cronbach Alpha.

The questionnaire is four sectioned with 29-item questions. Section A is to obtain information of respondents' demographics such as age, gender, education, and occupation. Section B is to assess respondents' knowledge about ALD. Respondents' whose response was 'Yes' to seven (7) out of the ten (10) questions in section B; have good knowledge, while respondents whose response was 'No' to seven (7) out of the ten (10) questions in section B have poor knowledge.

Section C uses the AUDIT model [20] to screen for alcohol use disorder. The WHO developed a simple ten-question test to determine if a person's alcohol consumption may be harmful. In this section the questions are anchored on a 5-point likert scale as 'Never' which is scored '0', 'Monthly or less' which is scored '1', '2-4 times a month' which is scored '2', '2-3 times a week' which is scored '3', '4 or more times a week' which is scored '4'. A total of ≥ 8 for men up to age 60 or ≥ 4 for women, adolescents, or men over age 60 is considered positive test [14] and indicates a strong likelihood of hazardous or harmful alcohol consumption, which could result to a negative effect on the liver. A score of 20 or more suggests alcohol dependence [21], but that is outside the scope of this present study. The AUDIT screening thresholds for the detection of alcohol abuse are ≥ 4 points for men (sensitivity 86%, specificity 89%) and ≥ 3 points for women (sensitivity 73%, specificity 91%) [20].

Section D employs the CAGE questionnaire, developed in 1968 by Ewing. The acronym CAGE represents the questions; 'Cut down', 'Annoyed', 'Guilty', 'Eye-Opener' ". Hence the questions; Have you ever felt that you ought to Cut down on your drinking? Have people annoyed you by criticizing your drinking? Have you ever felt bad or Guilty about your drinking? Have you ever had a drink first thing in the morning to steady your nerves or to get rid of a hangover (Eye-opener)?"

Individual item responses are scored 0 if the person answers "No" and 1 if the person answers "Yes". The total score can range from 0 to 4. The recommended cutoff for CAGE is ≥ 2 to screen for alcohol misuse and dependence [22]. The CAGE questionnaire has a sensitivity of more than 70% and a specificity of more than 90%. The CAGE and AUDIT questionnaires may be helpful tools to screen for maladaptive alcohol use, which could indicate an underlying ALD [20]. The questionnaire was given out to 50 persons who are not part of the study population and it was found to be easily understood and was able to obtain the required information.

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Sampling Procedure
Popular sites, including P. Noble Hotel, Ndibe beach hotel, Focus hotel, and beer parlors and bars within Afikpo, where people converge in mass during the weekends, were visited for data collection. Hospitals within Afikpo, including Mater Misericordiae hospital Afikpo and Romec hospital was also visited. The respondents were approached and given the questionnaire while seated at the bar or while waiting to see the doctor after verbal consent was obtained from the respondents and/or from their guardians (for the adolescents). They were given 5 minutes to read and respond to the questions after which the questionnaire was retrieved from them. The respondents who had difficulty reading had a trained data collector who understood the local language (Ehugbo) to assist in interpreting and recording responses. Two data collectors were trained and employed for this survey.

Data Analysis
Data obtained was codded and entered into an excel spread sheet for data cleaning. The frequencies, percentages, standard deviation were also obtained. The data was then exported into the software IBM SPSS Statistics for Windows Version 21.0 (IBM Corp, Version 21.0, Armonk, NY, USA) to determine the relationship between knowledge and the demographic variables using One-way ANOVA and Chi-square where appropriate with the statistical significance set as $P < 0.05$.

Results

Characteristics of the study participants
The reliability analysis of the questionnaire scored approximately 0.8. A total of 435 responses were retrieved and found usable giving a response rate of approximately 97%. Of the 450 respondents. 73.1% were males, while 48.8% had some form of tertiary education or currently have some form of tertiary education. About 62.7% of the respondents were aged between 20 to 60 years, while 20.8% were adolescents. Most of the participants were students (28.4%), 24.4% were self-employed, and 9.1% were farmers (Table 1).

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Table 1: Demographic characteristics of residents of Afikpo community in Ebonyi State Nigeria, 2020

Variables	Frequency (n)	Percentage (%)
Gender		
Male	318	73.1
Female	117	26.9
Age		
15-19	93	20.8
20-60	281	62.7
>60	74	16.4
Educational Level		
Nil	104	23.61
Primary	17	3.91
Secondary	105	23.8
Tertiary	215	48.8
Occupation		
Private Sector	42	9.3
Civil Servant	85	18.9
Farmers	41	9.1
Students	128	28.4
Self-employed	110	24.4
Others	44	9.8

Knowledge about Alcoholic Liver Disease

Of the 450 respondents, 361(80.8%) had a good knowledge of ALD while 86 (19.2%) had poor knowledge of ALD **(**Figure 1).

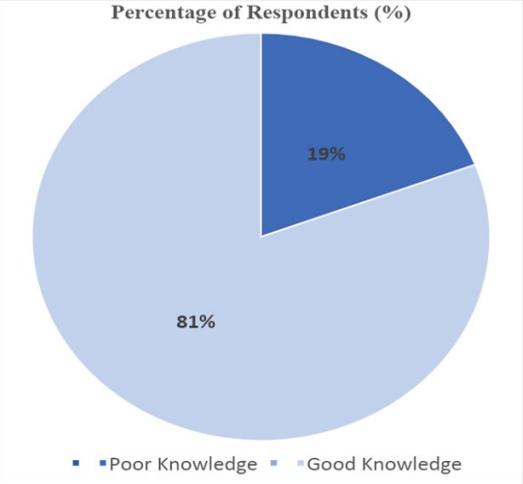

Figure 1: Pie chart showing knowledge about alcoholic liver disease among residents of Afikpo community in Ebonyi State Nigeria, 2020.

Relationship between Knowledge of Alcoholic Liver Disease and Demographic Variables.

About 221(61.4%) of respondent aged 20 to 60 years, had good knowledge of ALD, while 11.8 (10%) of respondents aged >60 years had poor knowledge of ALD. Though not at significant level.

The relationship between gender and knowledge of ALD was very significant. About 225(73.1%) males had good knowledge of ALD, while 22 (26.5%) females had poor knowledge of ALD. Findings also shows that 175(49.7%) respondents with tertiary level of education had good knowledge of ALD. However, a higher percentage of those who do not have any form of education 75(21.3%), had good knowledge of ALD compared to those with primary level of education . In comparison, 88(25.0%) with good knowledge of ALD had attained only secondary education.

Most students 107(29.6%) who participated in this study had good knowledge of ALD compared to the civil servants75(25.8%). Although occupation was not associated with knowledge of ALD **(**Table 2).

Table 2: Relationship between knowledge of Alcoholic liver disease and demographic variables of residents of Afikpo community in Ebonyi State Nigeria in 2020.

Variables	Poor knowledge n (%)	Good Knowledge n (%)	Chi-Square	df
Age				
15-19	17(20.0)	76(21.1)		
20-60	58(68.2)	221(61.4)	1.934	2
>60	10(11.8)	63(17.5)		
Gender				
Male	61(73.5)	225(73.1)	0.006	1
Female	22(26.5)	94(26.9)		
Education				
Primary	3(3.5)	14(4.0)		
Secondary	16(18.6)	88(25.0)		
Tertiary	39(45.3)	175(49.7)	5.223	3
Nil	28(32.6)	75(21.3)		
Occupation				
Private sector	6(7.0)	36(10.0)		
Civil servant	10(11.6)	75(20.8)		
Farmer	6(7.00	35(9.7)		
Student	21(24.4)	107(29.6)	14.493	5
Self-employed	28(32.6)	79(21.9)		
Others	15(17.4)	29(8.0)		

Alcoholic-use disorder identification screening test

Alcohol use disorder was evaluated using the alcohol use disorder identification test (AUDIT). Adolescents aged 15 to 19 had a mean audit score of 10.774, while respondents between the ages of 20 and 60 had a mean audit score of 11.266. Adults above the age of 60 had a mean audit score of 12.808. Male respondents in the study had a mean audit score of 11.395, and female respondents had a mean score of 11.139 (Table 3).

Table 3: Mean score of alcoholic use disorder identification test across age and gender variables of residents of Afikpo community in Ebonyi State Nigeria, 2020.

Variables	Mean(±S.D)
Gender	
Male	11.39±7.82
Female	11.14±7.50
Age (years)	
15-19	10.77±7.61
20-60	11.27±7.69
>60	12.81±7.71

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Screening of alcohol misuse and dependence

Result shows that the adolescents had the lowest mean CAGE test score of 1.89 while adults above 60 had a score of 2.48, which was the highest recorded value. Male subjects in the study had a mean score of 2.17, while the females had a score of 2.10. Respondents with primary education had a mean CAGE score of 2.06, while participants with no education had the highest mean CAGE score of 2.27. The civil servants had a score of 2.39, the farmers had a mean CAGE score of 2.47 while the student had the lowest mean CAGE score of 1.94 **(Table 4).**

Table 4: CAGE test showing alcohol misuse and dependence of residents of Afikpo community in Ebonyi State Nigeria, in 2020.

Variables	Mean (S.D)
Gender	
Male	2.17±133
Female	2.10±1.31
Age (yrs)	
15-19	1.89±1.22
20-60	2.15±1.36
>60	2.48±1.25
Educational Level	
Nil	2.27±1.28
Primary	2.06±1.24
Secondary	2.14±1.34
Tertiary	2.09±1.34
Occupation	
Private Sector	2.18±1.36
Civil Servant	2.39±1.28
Farmers	2.47±1.33
Student	1.94±1.38
Self-employed	2.13±1.32
Others	1.95±1.15

DISCUSSION

Alcohol consumption is a social lifestyle for the residents of Afikpo community. The residents enjoy spending their evenings and weekends in beer parlors. Every neighborhood in the community has at least one beer parlor, and some could have two or more. This study reveals that majority (80.8%) of the respondents demonstrated a good knowledge of ALD. Which implies that they are knowledgeable of the risks involved with excessive alcohol consumption on the liver although there is alcohol use disorder amongst the residents. This reveals a poor attitude toward the risks involved with chronic alcohol consumption.

Findings from this study reveals that there was a high level of alcohol misuse and dependence across all age except the adolescents. This could be because the adolescents and the students are dependent on their parents and their guardian, they do not earn an income so they do not consume alcohol as they desire due to inadequate finance. Although similar study revealed that there is high level of risky alcohol use amongst adolescents [23] which disagrees with the findings of this study.

In all societies, a positive correlation exists between average per capita consumption of alcohol and the frequency of cirrhosis. The amount ingested and the duration of intake correlate with the incidence of alcohol related liver disease, hence, deaths due to cirrhosis are closely tied to per capita alcohol intake [16].

Majority of the males who are within the age of 20-60 had higher level of dependence and misuse. There was an association between gender and knowledge of ALD. This could be as a result of societal influence. Often times the society frowns at a female who takes alcohol. Most females will not want to be seen consuming alcohol and will not want to admit that they consume alcohol nor to admit that they take several bottles in a day. In addition, most females usually prefer to spend their money on other things such as make-up, hair-do etc. which they consider more important than spending on alcohol. The males and the young adult tend to have high risk seeking behavior which includes risky and excessive alcohol drinking [24,25]. Previous studies agree with findings from this study which states that alcohol abuse and dependence rates are higher in men (18%) than in women (10%) and in Caucasians than in black persons; however, the black population is more prone to develop a progression of liver disease to cirrhosis [12]. In addition, men spend a lot of time at work compared to women and may spend several nights a week socializing with work colleagues after work in "drinking meetings," which are usually accompanied with by excessive consumption of alcohol [26].

Findings from this study reveals that all the respondents who are employed had alcohol disorder. This could be because they have an income unlike the students, hence have more disposable cash to finance excessive purchase of alcohol [27]. Respondents in this study had alcohol misuse and disorder, irrespective of the occupation of the respondents. This could be due to the fact that safe and high-quality varieties of nearly every kind of alcoholic beverage are available at relatively low prices in Afikpo community. In addition, work-related networking which promotes social drinking could also be a possible explanation to alcohol misuse amongst the working-class respondent. Drinking is often an integral part of social life, especially in the working environments and amongst middle-aged men who are part of the working population.[28]
However, famers appear to have the highest level of dependence. This could be attributed to their low level of education. Going to pubs often and being able to afford several bottles of alcohol seems to be their criteria to measure success and to show-off wealth. Previous studies have shown that alcohol related health issues were more amongst unskilled workers and self-employed and lowest amongst executives and farmers, blue-collar workers and laborers have the highest alcohol misuse and dependence [29]. This could be due to availability of alcohol at work, social pressure to drink while at work, separation from loved ones and lack of supervision. Hence, accessibility and affordability to alcohol and social peer -pressure seems to be a major contributory factor to alcohol misuse and dependence [29].

The respondents who do not have any form of education had the highest level of alcohol misuse and dependence although there was no association between educational level and alcohol misuse and dependence. This implies that excessive alcohol consumption is a part of the town's social fabric. The residents indulge in binge and excessive alcohol use irrespective of their educational level. Alcohol consumption seems to be a cultural practice in Afikpo. A study conducted in Japan agreed that respondents with lower education had significantly higher risks of both non-problematic heavy drinking and problem drinking. This fact is in contrast with the findings of this study [28]. Often times, lower education was significantly associated with increased risks of both non-problematic heavy drinking and problem drinking [30,31,32]. Education increases individual's awareness of healthy behaviors and practices and to acquire skills that affect health-promoting decisions [33,34,35]. Hence, education may increase individual's understanding of the negative effects of heavy drinking and may build individual's capacity to manage drinking by stopping or keeping consumption low [36,37]. Education also shapes cultural behaviors and practices [38] in the form of health-related values.
There is need for a public health campaign designed to address the threat of chronic and excessive alcohol consumption and ALD so as to reduce the risk and prevalence of liver diseases related to the abuse of alcohol in Afikpo. It would therefore be beneficial to improve knowledge and awareness of health hazards of excessive alcohol consumption as well as cultural practices and social networks promote healthy behaviors.

Limitations of study

The respondent used for this study were only those who agreed to participate as some of the respondents did not give consent, therefore the result obtained may not represent the general population.

Conclusion

The residents of Afikpo community have a good knowledge of ALD though there is alcohol use disorder, alcohol misuse and dependence in the community. Gender is the only demographic characteristics that influenced the knowledge of ALD.

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Authors contribution

Research design: Chinelo Nneka Aguiyi-Ikeanyi, Chiagoziem Urom Urom-Ndubisi and Maxwell Adibe. Data Collection: Chiagoziem Urom Urom-Ndubisi and Owoichoche Moses Agene. Data Analysis: Chinelo Nneka Aguiyi-Ikeanyi and Maxwell Adibe. Supervisors: Chinelo Nneka Aguiyi-Ikeanyi and Maxwell Adibe. Manuscript Preparation: Chinelo Nneka Aguiyi-Ikeanyi and Chiagoziem Urom Urom-Ndubisi.

Conflict of interests

There is no conflict of interest

Ethical Consideration
Ethical approval was obtained from the Research and Ethical committee of the Faculty of Pharmaceutical sciences of the University of Nigeria, Nsukka, Enugu State with the reference number FPSRE/ UNN/20/0011. Verbal Consent was obtained from every respondent before administering the questionnaire to him/her.

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Original Article
Compliance and perception towards COVID-19 preventive protocols among hospital staff in a tertiary health facility, Southwest Nigeria.

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Abstract

Background: *The COVID-19 outbreak response in Nigeria was challenged by the existing weak health sector and the frontline health workers for COVID-19 pandemic response are exposed to the pathogen. One militating factor undermining the control and prevention of COVID-19 in Nigeria was poor compliance to preventive measures. This study assessed the compliance with COVID-19 prevention protocols among healthcare workers in Federal Teaching Hospital, Ido-Ekiti, Ekiti State, Nigeria.*

Methods: *A cross sectional study and subjects were selected through a multi-stage sampling technique. Data collection was done using interviewer-administered semi-structured questionnaire over a period of five months (June-October, 2021). Data was analyzed using IBM, Statistical Package for Social Sciences (SPSS) version 27.0 and p value was set at <0.05 as the threshold for statistical significance.*

Results: *Majority (60.1%), of the respondents got information on COVID-19 protocols through seminars and workshops. However, more than a quarter (28.8%) of the respondents said the use of available PPE was suboptimal. More than one-third, (35.8%), of respondents believe the protocols are too strict. There is, however, good perception (93.3%), but relatively lower compliance (58.7%) of COVID-19 protocols among the staff. Age, marital status and sex were associated with compliance towards COVID-19 protocols in this study (P<0.05). Identified significant predictors (p<0.05) of compliance include age (AOR=1.944), female sex (AOR=7.829).*

Conclusion: *Most respondents had good knowledge of availability, perception of effectiveness, but relatively lower compliance with the COVID-19 protocols in this facility. The government or hospital authority make sure that necessary steps to further boost compliance are taken.*

Keywords: *Compliance, COVID-19 protocols, Hospital staff, Nigeria*
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Introduction

Coronaviruses (CoV) represent a family of viruses causing illnesses ranging from the common cold to more severe diseases such as Middle East Respiratory Syndrome (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS-CoV). The virus causing COVID-19 is, however, a novel coronavirus (nCoV) not previously identified in humans [1]. They are zoonotic, (transmitted between animals and people) spread through droplets (generated through coughing or sneezing, talking or breathing), that may land in any of the facial orifices of people who are nearby, or get inhaled into their lungs; hence its rapid transmission [1].

The index case was reported in December 2019 from Wuhan, Hubei province, China and has since spread globally [2]. Declared as a pandemic by WHO on March 11, 2020, the impact of COVID-19 cuts across the whole world and has profoundly impacted humanity and global economy. COVID-19 also exposed the poor state of health infrastructure in Nigeria with poor emergency preparedness as evidenced by lack of preventive protocols, ill-equipped and non-existing isolation wards, thereby exposing health workers to the deadly disease [3].

Protocols for COVID-19 control and prevention for health workers includes all standard precautions for infectious disease prevention and control as applied: hand washing (with soap and water or alcohol based hand sanitizers), use of personal protective equipment (gloves, masks, eye-wear), res-

piratory hygiene/cough etiquette, cleaning and disinfection of environmental surfaces, injection and sharps safety, sterile instruments and devices; quarantine of exposed patients and isolation and careful handling of infected patients including their samples [2].

Studies showed that quarantine, contact tracing, screening and isolation in different setting were of great benefits [4, 5]. However, compliance with and proper use of some of these precautionary methods were not properly observed even by health workers in Nigeria. Poor understanding of and compliance with the disease preventive protocols can lead to delay in instituting necessary intervention leading to transmission of infections. Despite the numerous guidelines for healthcare workers and window of online refresher courses developed by WHO, CDC, and various governmental organizations in various countries to boost the knowledge and prevention strategies, one of the major challenges which militate against the control and prevention of COVID-19 in Nigeria was the issue of poor compliance and attitude [4]. Healthcare institutions' preparedness to manage any outbreak of public health significance is dependent on several factors like adequate space for isolation of infected patients, clinical staff capacity, training exposure on biosafety issues, facility diagnostic capacity, and availability of personal protective equipment (PPE), and health care worker motivation among others [4].

The underutilization of PPE was reported by Wu *et al* and the National Hospital Infection Management and Quality Control Center as the trigger for a large-scale infection of HCWs from the Hubei province in China [6, 7]. Similarly, the Henry Ford Health System also had 46.6% of its workers infected with SARS-CoV-2 [8].These reports result into fear among HCWs giving the absence of a definitive treatment or a vaccine for SARS-CoV-2 [6, 8]. This necessitates critical assessment of compliance with preventive protocols and workplace safety among healthcare workers during the COVID-19 pandemic and beyond.

Of 529 participants in a cross-sectional study done by obtaining responses from health workers globally in March 2020, 63.6% of health workers had a positive perception of COVID-19 preventive measures [9]. Majority of the health care workers in Pakistan marked N-95 mask as essential during the collection of nasopharyngeal samples and conduct of other aerosol-generating procedures (88%), and direct care of COVID-19 patient (82%) [9]. In South Africa, about half (55.6%) of health workers had received infection prevention and control training, and they were willing to comply. However, some had no access to medical masks (11.8%) and gloves (9.9%) in their departments but were definitely willing to make use of any available resources in fighting against the infection [10].

A web-based cross-sectional study among Nigerians found that knowledge is a predictor of adherence to precautionary measures among the respondents [11].A study among health workers in South-South, Nigeria showed that majority of the participants 183 (61%) felt at risk of being infected by the virus. Most of the participants 186 (62%) agreed to inadequate work place safety and the lack of social insurance policy for healthcare workers was also seen as an obstacle to effective service delivery especially in this period of the pandemic [12]. All the participants 300 (100%) agreed to the provision of personal protective equipment (PPE) to all healthcare workers [12].

A research done on Nigerian dental students showed that most respondents (95.1%) had good perception to infection control practices in preventing the spread of COVID-19 in their clinics and training schools [13]. These responses included the perception that the current infection control measures standard in their dental schools was effective in preventing the spread of COVID-19 (24.5%). Majority (95.1%) agreed that aerosol-generating procedures in dentistry carried a high risk of spreading COVID-19 [13].

Generally, compliance with infection control behaviours can be difficult among the population. However, the thrust for compliance in the general population appears to be perceived susceptibility, perceived severity and perceived benefits of compliance in addition to accurate knowledge about the disease and the recommended behaviours. However, the major barriers include discomfort, embarrassment and practical issues [11].Despite, the efforts at curtailing the pandemic, cases are still being recorded which might be a pointer to a gap in compliance with COVID-19 prevention protocols among hospital workers. Though, studies have been done on this subject, there is paucity of data on compliance with COVID-19 prevention among healthcare workers in our local setting. Thus, the objective this study was to assess compliance with and perception of COVID-19 protocols and identify its associated factors and predictors in order to scale up efforts at addressing identified gaps.

Methods

Ekiti State, one of the six states constituting the south -western region of Nigeria, is located between longitudes 4° 45° and 5° 45° East of the Greenwich meridian and latitudes 7° 15° and 8° 15° North of the equator. With three senatorial districts (Ekiti South, Ekiti central and Ekiti North) and 16 Local Government Areas, the indigenous people of Ekiti state are mainly Yoruba (and speak the Ekiti dialect) with some non-indigenes, and other ethnic groups are also living in the state. Most of the people are Christians with some Muslims and few traditional worshippers.

The Federal Teaching Hospital, Ido-Ekiti is a 270-bedded tertiary health care facility and clinical training institution in Nigeria. It is the only tertiary insti-

tution in Ido-Ekiti, and trains medical and non-medical students from Afe Babalola University, Ado-Ekiti, alongside post graduate training via its residency programs in numerous subspecialties e.g. Obstetrics and Gynecology, Community medicine, Psychiatry, Internal Medicine, Surgery, Pediatrics and Family Medicine, etc. The hospital is one of the treatment centers for COVID-19 patients in Ekiti State, and has managed several cases. It has a holding area for suspected cases and an isolation/treatment ward for confirmed cases with designated staff like Doctors, Nurses, Health Assistants, Environmental Health Officers working in these areas with possible risk of exposure and transmission within the hospital.

Study design, eligibility criteria

This is a cross-sectional survey of COVID-19 protocol perception and compliance amongst healthcare workers in Federal Teaching Hospital, Ido-Ekiti. The total population of healthcare workers (clinical and non-clinical staff) in the hospital was about 2732. All consenting healthcare workers were recruited, while those who were working in the COVID-19 holding and isolation ward were excluded to prevent subject/selection bias. They were excluded because they were likely going to skew the knowledge and compliance assessment because of training and exposure to and usage of these measures.

Sample size Calculation

Using the Leslie Fischer's formula for population >10,000, the sample size was determined as follows: $n=Z^2pq/e^2$ [14],Where n = minimum sample size; Z = Standard normal deviate = 1.96; p = Compliance with COVID-19 protocols = 55.6% = 0.556 [11]; q = 1-p = 0.444; e = level of desired accuracy = 0.05

$$n = \frac{(1.96)^2 \text{ x}0.556\text{x } 0.444}{(0.05)^2}$$

n = 380 (approximately)

Since population size was <10,000; $n_{corrected} = n/1+n-1/N$ Where, n= Sample size = 380 N = population size, N = 2732; n= 333. Non response rate of 10%, which gives 33, was added and the total sample size now becomes 366 (333+33).

Sampling Technique

A multistage sampling technique was used to select respondents.

Stage I: Stratified sampling technique was used to group the healthcare workers into 2 strata (clinical and non-clinical staff). Clinical staffs were further stratified based on cadre. Proportionate allocation was used to allocate the number of participants to be selected from each category.

Stage II: Using the sampling frame for each category, simple random sampling using computer-generated table of random numbers was used to select willing participants till the allocated sample size for each was attained and till the overall sample size of 366 was reached.

Operational definitions

For the purpose of this study, the term hospital staff refers to clinical staffs who were involved in patient care. Secondly, compliance in this study refers to a deliberate effort at following the preventive measures, while perception is used here to refer to feeling or thinking about the preventive protocols.

Research instrument and data collection and analysis

A semi-structured questionnaire was designed by the authors and used for data collection. The questionnaire was divided into four sections (socio-demographic, knowledge of COVID-19 protocols, perception and factors affecting compliance with COVID-19 protocols).Some of the questions was adapted from previous related studies. The questionnaire was pre-tested among healthcare workers in Afe Babalola University Multisystem Hospital, Ado-Ekiti, a distance of about 43km from the study site. For reliability, test-retest was done and reliability co-efficient of, r=0.7 was obtained which showed the tool is reliable [15].Participants were informed about the study with clear instructions on how to fill the questionnaire in order to make the data valid, reliable and useful. The data obtained from the questionnaires were analyzed with IBM, Statistical Package for Social Sciences (SPSS) version 27.0. The perception and compliance on COVID-19 protocols were scored and graded into poor (<70%) and good (≥70%). This dichotomy was arrived by the authors using the mean and the spread of the scores.

Ethical Consideration

An ethical clearance with protocol number ERC/2021/06/11/558B and dated 16/06/2021 was obtained from the Ethical Committee of the Federal Teaching Hospital, Ido-Ekiti before the study was carried out. Informed verbal consent was obtained from every respondent prior to participation in this study after explaining the purpose, content, and implication of the research. Participation was voluntary; anonymity and confidentiality of the information provided was assured. Respondents who did not give consent to participate in this study were exempted.

Results

Three hundred and sixty-six (366) questionnaires were administered among healthcare workers. Three hundred and fifty-eight (358) of these questionnaires were returned completely filled and analyzed, giving a response rate of 97.8% percent.

Most of the respondents were within the age range of 20-39 years (57.3%), majority were

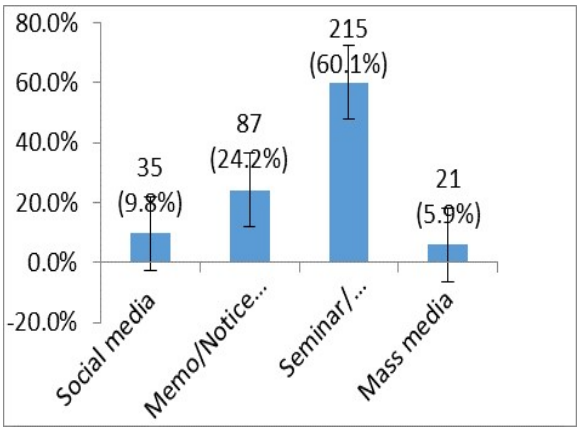
males (52.0%), had ever been married (76.3%), had tertiary education (64.0%), were doctors at different levels in their career training; Consultants (12.8%), Senior registrars (10.9%), Junior registrars (22.9%), Nurses (24.9%) and provided direct health care to patients (79.9%) (Table 1).

Table 1: Socio-demographic characteristics of respondents.

Variable	Frequency N = 358	Percentage (%)
Age group (in years)		
20 – 39	205	57.3
40 – 59	153	42.7
Sex		
Male	186	52.0
Female	172	48.0
Marital status		
Never married	85	23.7
Ever married	273	76.3
Educational attainment		
Secondary education	22	6.1
Tertiary education	229	64.0
Master's degree	57	15.9
Fellowship/Ph.D.	50	14.0
Status in health care facility		
Consultant	46	12.8
Senior registrar	39	10.9
Junior registrar	82	22.9
Nurse	89	24.9
Health assistant	57	15.9
Department/Unit		
Medicine	63	17.6
Surgery	61	17.0
Pediatric	66	18.4
Infectious disease unit	12	18.4
Obstetrics and gynecology	79	22.1
Others	77	21.5
Provide direct health care to patients		
Yes	286	79.9
No	72	20.1
Number of children living in the home		
None	110	30.7
1 – 2	120	33.5
≥ 3	128	35.8
Number of elderly living in the home		
None	272	76.0
1 – 2	63	17.6
≥ 3	23	6.4

The majority of the information (60.1%) were obtained from Seminars/Workshops and least being from mass media (5.9%) (Figure 1).

Figure 1: Sources of information on COVID-19 protocols among hospital staff in federal teaching



hospital, Ido-Ekiti.

Majority (84.3%) knew that hand hygiene facilities/stands are available and were in use by the staff. Similarly, (83.5%) and (93.3%) of them knew that hand soap and running water available and made use of them, respectively. Out of the respondents, 299 (83.5%) knew that there were dedicated isolated facilities for suspected/ confirmed COVID-19 patients. (Table 2)

Table 2: Knowledge of availability and use of COVID-19 protocols among respondents in federal teaching hospital, Ido-Ekiti. (N=358)

Variables	Available in use (%)	not in use (%)	Not available (%)
COVID-19 preventive measures			
Hand hygiene	302 (84.3)	31 (8.7)	25 (7.0)
Face masks	352 (98.3)	6 (1.7)	0 (0.0)
Disposable aprons	280 (78.2)	65 (18.2)	13 (3.6)
Protective gloves	333 (93.0)	6 (1.7)	19 (5.3)
PPE	240 (67.0)	103 (28.8)	15 (4.2)
Eye protection	243 (67.9)	59 (16.5)	56 (15.6)
Hand sanitizer	314 (87.7)	16 (4.5)	28 (7.8)
Hand soap	299 (83.5)	4 (1.1)	55 (15.4)
Running water	334 (93.3)	14 (3.9)	10 (2.8)
Isolation centre/ward	299 (83.5)	-	59 (16.5)

Table 3: Respondents' perception towards COVID-19 protocols

Perception	Yes N = 358	Per-centage (%)
Think the protocols are too strict and unattainable	128	35.8
People who have contact with COVID-19 infected person to isolate in a proper place.	353	98.6
Washing hands with soap and water frequently for at least 20 seconds and using alcohol-based sanitizers is important in prevention of COVID -19.	356	99.4
Putting on masks when moving about in the hospital to prevent infection with COVID-19.	355	99.2
COVID-19 virus spreads via respiratory droplets of infected individuals during sneezing or coughing by an infected person.	349	97.5
Staying 6 feet apart during conversations help limit the spread of COVID-19.	343	95.8
Touching or shaking hands of an infected person would result in the infection by COVID-19 virus.	290	81.0
COVID-19 will be severe among elderly, those with chronic illnesses, and the immunosuppressed	316	88.3
COVID-19 has a 100% mortality rate.	127	35.5

More than one-third, (35.8%), of respondents believe the protocols were too strict and unattainable, while (99.4%) of respondents expressed the importance of washing of hands with soap and water (Table 3)

PPE was always worn by about a third of 20.7% of the respondents who participated in this study. Face shields were worn by (39.9%) of the respondents. Majority always make use of face masks (81.3%), alcohol based sanitizers (81.0%), regular hand washing (80.2%), and use of protective hand gloves (81.3%) (Table 4). However, just about half (58.7%) of them demonstrated compliance with the protocols with 148 (41.3%) having poor compliance with COVID-19 protocols. (Table 5). More than three quarters, 334 (93.3%) of them had good perception of COVID-19 protocols in this

facility (Table 5).

Table 4: Compliance with COVID-19 protocols among respondents (N=358)

Variables	Compliance			
	Always	**Sometimes**	**Rarely**	**Never**
	n (%)	**n (%)**	**n (%)**	**n (%)**
Face mask	291 (81.3)	63 (17.6)	4 (1.1)	0 (0.0)
Face shield	143 (39.9)	130 (36.3)	59 (16.5)	26 (7.3)
Alcohol-based hand sanitizer	290 (81.0)	36 (10.0)	30 (8.4)	2 (0.6)
*PPE	123 (34.4)	108 (30.2)	53 (14.8)	74 (20.6)
Social/Physical distance	162 (45.3)	133 (37.2)	36 (10.0)	27 (7.5)
Avoiding handshakes	174 (48.6)	120 (33.5)	48 (13.4)	16 (4.5)
Observing cough etiquettes	248 (69.3)	95 (26.5)	8 (2.2)	7 (2.0)
Regular hand washing	287 (80.2)	67 (18.7)	4 (1.1)	0 (0.0)
Protective hand gloves	291 (81.3)	54 (15.0)	6 (1.7)	7 (2.0)

Table 5: Perception and compliance scoring among respondents

Variable	Frequency	Percentage (%)
Perception of COVID-19 protocols		
Good (≥70%)	334	93.3
Poor (<70%)	24	6.7
Mean score± SD	87.6±11.8	
Range	22.2-87.6	
Compliance with COVID-19 protocols		
Good (≥70%)	210	58.7
Poor (<70%)	148	41.3
Mean score± SD	82.7±14.8	
Range	36.8-100.0	

There was significant association between the marital status, age, sex, department/unit, provision of direct health care of the respondent and their compliance with COVID-19 protocols. (Table 6)

Female respondents were about eight times more compliant with COVID-19 protocols than the male respondents ($p<0.001$). Also, health workers in the infectious disease unit were three times more compliant than other categories of health workers. ($p=0.002$) (Table 7)

Table 6: Factors associated with compliance towards COVID-19 protocols among respondents

Variable	Compliance with COVID-19 protocols		
	Good n (%)	Poor n (%)	p-value
Age group (in years)			
20 – 39	107 (52.2)	98 (47.8)	0.004
40 – 59	103 (67.3)	50 (32.7)	
Sex			
Male	97 (52.2)	89 (47.8)	0.009
Female	113 (65.7)	59 (34.3)	
Marital Status			
Never married	32 (37.6)	53 (62.4)	<0.001
Ever Married	178 (65.2)	95 (34.8)	
Educational Attainment			
Secondary Education	7 (31.8)	15 (68.2)	<0.001
Tertiary Education	126 (55.0)	103 (45.0)	
Master's Degree	32 (56.1)	25 (43.9)	
Fellowship/Ph.D.	45 (90.0)	5 (10.0)	
Status in Health Care Facility			
Consultant	43 (93.5)	3 (6.5)	<0.001
Senior Registrar	32 (82.1)	7 (17.9)	
Junior Registrar	47 (57.3)	35 (42.7)	
Nurse	52 (58.4)	37 (41.6)	
Health Assistant	23 (40.4)	34 (59.6)	
Other Health Worker	13 (28.9)	32 (71.1)	
Department/Unit			
Medicine	50 (79.4)	13 (20.6)	<0.001
Surgery	42 (68.9)	19 (31.1)	
Pediatrics	21 (31.8)	45 (68.2)	
Infectious Disease unit	11 (91.7)	1 (8.3)	
Obstetrics and Gynaecology	63 (79.7)	16 (20.3)	
Others	23 (29.9)	54 (70.1)	
Provide direct health care to patients			
Yes	191 (66.8)	95 (33.2)	<0.001
No	19 (26.4)	53 (73.6)	
Knowledge of COVID-19 protocols			
Good	204 (61.1)	130 (38.9)	
Poor	6 (25.0)	18 (75.0)	

Discussion

In this study, 358 respondents were sampled with the doctors being more which was similar to other studies conducted in Nigeria and Latin America [16, 17]. This might be due to the nature of the research which borders on safety and compliance with protocols. In addition, doctors are directly involved in patient care, and therefore are at a higher risk of exposure to COVID-19 which may serve as the impetus behind the participation.

The most common source of information was seminars/workshops (60.1%), followed by memo/notice boards (24.2%) and least was mass media (5.9% which served as media to improve the knowledge of the health workers.. This finding agreed with that of a similar study conducted in India where healthcare workers had inadequate knowledge about COVID-19 pandemic [9]. The sample size and geographical variations of our studies could explain the differences in our findings.

Table 7: Predictors of good compliance with COVID-19 protocols in federal teaching hospital, Ido-Ekiti.

Variable		AOR	95% CI		p-value
Age group (in years)					
	20 – 39[(ref)]	1.000			
	40 – 59	1.944	0.806	4.689	0.139
Sex					
	Male[(ref)]	1.000			
	Female	7.829	3.203	19.135	<0.001
Marital status					
	Never married[(ref)]	1.000			
	Ever married	1.684	0.543	5.221	0.366
Educational attainment					
	Secondary education[(ref)]	1.000			
	Tertiary education	2.002	0.351	11.406	0.434
	Master's degree	1.172	0.161	8.558	0.876
	Fellowship/Ph.D.	4.155	1.454	37.996	0.027
Status in health care facility					
	Consultant	65.100	3.130	1353.836	0.007
	Senior registrar	43.754	69.855	691.855	0.007
	Junior registrar	12.450	1.141	135.831	0.039
	Nurse	7.206	0.883	58.771	0.065
	Health assistant	2.667	0.306	23.253	0.375
	Other health worker[(ref)]	1.000			
Department/Unit					
	Medicine	2.011	0.448	9.025	0.362
	Surgery	1.470	0.098	3.259	0.346
	Pediatrics	1.081	0.017	2.389	0.057
	Infectious disease unit	3.325	1.240	46.041	0.002
	Obstetrics and gynaecology	1.658	0.140	3.083	0.595
	Others[(ref)]	1.000			
Provide direct care to patients					
	Yes	2.981	1.007	8.828	0.049
	No[(ref)]	1.000			

Generally, most of the participants (91.6%) had a positive perception about the preventive and control measures of COVID-19. About a third (35.5%) had poor perception on the mortality rate of COVID-19 as 100%. These responses on perception among healthcare workers could have negative consequences on patient care and also on the dynamics of potential COVID-19 outbreaks. This could lead to delays in the implementation of necessary preventive measures, which may increase the burden of COVID-19. Healthcare workers with negative perception could also spread infection to coworkers, their families and the general public [12], thereby increasing the burden of the disease both in terms of reproduction number, morbidity and mortality.

In this study, most respondents had good practice of preventive measures of COVID-19 for this was conducted among homogenous group of hospital workers. This helps reduce the risk of spread of the disease and transmission of the infection by health care workers to their families. This was also obtained in a study among nurses in a selected tertiary hospital in south-south Nigeria, where majority reported practicing the preventive measures of COVID-19 [18].

The study was also among healthcare workers in a tertiary setting just like the present study; hence, the finding was similar. Similar findings were reported by studies conducted in Saudi Arabia and among Chinese residents [19, 20]. In these studies, health care workers were willing and ready to apply infection control measures since the onset of MERS-CoV. However, almost two thirds of their respondents were not aware of protocols for the care of patients with MERS-CoV infection during the peak of COVID-19 infection [19, 20].

This study also showed significant association between marital status, sex and compliance with COVID-19 preventive measures. Good compliance was reported more among married healthcare workers (65.2%), and the female respondents and older respondents had a better compliance than those who were younger. Female hospital staff were almost eight times more compliant than their male counterparts, and older respondents were almost twice (AOR=1.944; 95%CI= 0.806-4.689) more compliant than the younger ones. Older respondents with possible co-morbidities are more likely to be cautions compared with the younger who feel they are agile and healthy with no compelling reason for observing the preventive measures. There was a downward trend in the odds of compliance with COVID-19 protocols in the cadre and qualifications of the hospital staff as the Consultant were found to be sixty-five times more compliant than other hospital staff. Similarly, those with Fellowship/Ph.D. were four times more compliant. This could be due to the fact that knowledge and degree of exposure towards the virus also follow this trend presumably. Majority of the participants also strongly agreed that there was high possibility of getting the infection in the hospitals. These findings are in agreement with those of similar studies where sex, level of education, years of experience and unit of practice were determinants of compliance with preventive measures of COVID-19 [18, 21].

Conclusion

Majority of the respondents were aware of the COVID-19 prevention protocols with seminar / workshop being the most common source of information. The hospital staff demonstrated good perception, but relatively lower compliance with COVID-19 preventive protocols. The predictive factors of compliance with COVID-19 protocols include older age, female sex, higher cadre and qualifications.

Recommendations

The Management of the Hospital needs to put monitoring measures in place to scale up compliance with the COVID-19 preventive protocols particularly targeting younger workers, male staff and those in lower cadre in the hospital.

There is a need for the Hospital Management to also scale-up training on the use of COVID-19 prevention protocols among the staff of the Hospital. The Government should also assist the Hospitals in ensuring steady supplies and provision of these preventive gadgets to prevent stock-out.

Conflict of interest declaration

The authors declare no conflict of interest, and the study was financed by the authors.

Author contributions

KAD- Conceptualization of research title, study design, data analysis and presentation and manuscript preparation; MOA- Review of manuscript and methodology; TTA- Field work, data collection and data analysis; EBI-Manuscript write-up and data collection; OA-Literature review and data collection; POA-Literature review; EME-Field work and data collection; SAA-Literature review; CCC-Design of research tool and data collection; ENE-Field work, data analysis; IEA-Design of research tool and data collection; AGN- Literature review; KJO- Design of research tool and data collection; OO-Manuscript preparation and editing; HY-Field work and data collection.

Implications of the study

This study found that compliance with COVID -19 protocols among the study population of hospital staff was below average. With this poor compliance, the control and transmission of COVID-19 within and outside the hospital environment might be difficult to achieve. It also showed a gap in the control efforts geared towards the disease in this locality.

Study limitations

This is a cross-sectional study design, and the statistical associations or inferences obtained may not be causal. Being cross-sectional, it may also be prone to recall bias and due to the fact that the study assessed compliance and perception to a desirable practice, it might also be faced with social desirability bias.

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Original Article

Magnitude and factors associated with seizure-related injury among patients with epilepsy at Amanuel Specialized Mental Hospital, Addis Ababa, Ethiopia

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Abstract
Background: *Seizure-related injuries (SRI) constitute one of the major areas of concern in managing people with epilepsy. Of those, the ones with generalized tonic-clonic seizures and drop attacks, are prone to sustain motor vehicle accidents, falls, burns, drowning, fractures, soft tissue and head injuries. Hence, this study aimed to assess the magnitude and associated factors of SRI among patients seen at Amanuel Specialized Mental Hospital, Ethiopia.*
Methods: *A cross-sectional study was conducted at a regular seizure follow up clinic. A total of 298 patients above 15 years of age were included in this study. Patients' socio-demographic and clinical data were collected based on interview and record review. Descriptive statistics were done and multivariable logistic regression was used to determine independent predictors of SRI with adjusted odds ratio and corresponding confidence interval. A p-value <0.05 was considered as statistically significant.*
Results: *A total of 298 patients were included in this study. Of these, 34.9% were reported to have SRI. Lacerations (54.2%), burn (19.8%) and dental-loss (15.8%) were the most common type of injuries. There was a 2.2-fold increase in the odds of SRI among those in grades 1-6 educational levels (AOR=2.19, 95% CI (1.04-4.54)), and a lower risk of SRI was found among those who could read and write (AOR=0.11, 95% CI (0.13-0.86)).*
Conclusions: *The study documented significant level of SRI among the study population with varied levels of severity. To minimize SRI ,it is essential to target the above predictors through proper surveillance system in the follow-up clinics with continuous advocacy work to the family and working environment.*

Keywords*: Seizure-related injuries, Epilepsy, Trauma*
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Introduction

Epilepsy is one of the most common acquired chronic neurologic disorders with a prevalence of approximately 0.8% [1]. Epileptic patients often have seizures with impairment of consciousness and abnormal uncontrolled movements [2]. In addition, they may have antiepileptic drug related side effects such as drowsiness, ataxia, blurred vision, and diplopia [3]. It seems intuitive that any condition involving a fall or impairment of consciousness has the potential to cause injuries and that curtailment of certain physical activities may reduce the risk of injury [4]. Even in the absence of obvious clinical seizure activity, paroxysmal (EEG) discharges have been shown to affect alertness and mental speed [4].

Epilepsy is also known to be associated with a number of co-morbid conditions which may also play an additional role in increasing the risk of injury. Attention deficit disorder is much more common in children with epilepsy (37% compared to 5% in healthy controls) [5], and has clearly been associated with an increased risk of accidental injury [6, 7]. Additionally, about a third of epileptic patients are shown to have some degree of cognitive impairment which may interfere with the awareness and alertness towards sensing and reacting to potentially dangerous situation. Some also suffer from co-morbid conditions like cerebral palsy that can interfere with motor response.

Several epilepsy-specific variables have been cor-

related with higher risks of injury. Seizure type has been a factor in most studies [8]. In a study done to assess the clinical risk factors for Seizure related injury (SRI) in adult People With Epilepsy(PWE) and analyzed to develop a predictive model done by Somsak Tiamkao and colleagues showed that Generalized Tonic–cloniuc Seizure (GTC) seizure type, having history of seizure attacks at least 12 times per year, and day time seizure were significant risk factors of having SRI. Based on this they developed the predictive model for having SRI in PWE and it gave 90.3% sensitivity and 46.7% specificity on the occurrence of SRI. They concluded that the significant predictive factors for SRI in PWE were the occurrence of GTCs, seizures at least 12 times per year or day time seizures [9].

An aspect of seizures most concerning to persons with epilepsy and to those who care for them is the potential for seizure-related injuries. Driving accidents, falls, drowning, suffocation, and other injuries are frequent concerns. Indeed, laws and rules concerning epilepsy are generally intended to protect the person with seizures from injuries as well as the public from the consequences of that person's seizures, especially with respect to driving a vehicle, piloting a plane, and operating other types of machinery [10]. Although taking preventive measures is to be encouraged, at times this concern may lead to unnecessary interventions that can potentially limit the privacy of patients and their right to participate in certain activities and will become an additional cause of stigma. Hence, identifying potential predicting factors and applying individualized preventive measures is an invaluable means to improve the qualityof the health of patients. This will subsequently be a relief to the care takers, the public and the country as a whole. Patients with epilepsy can sustain any type of injury related to the seizure.A study conducted in Ethiopia showed that generalized seizures occurred in 69% of the cases, partial seizures in 20% and unclassifiable seizures in 11% [11].

To the best of our knowledge, there was no study done in Ethiopia which assessed SRI'S and associated factors so far. Hence, this study is aimed to assess the magnitude and associated factors for SRI among patients with epilepsy in Amanuel Specialized Mental Hospital. This study may benefit the health system to tailor necessary measures to mitigate the occurrence of the injuries and their complications thereby improving the health-related quality of life among patients with epilepsy and contributes its part in minimizing the loss of productivity and expenses that significantly compromise the country's economy. Importantly, the study may provide insight into the magnitude and types of SRI, and socio demographic factors associated with SRI. This would further enable health care programs to use the data for planning and policy formulation like developing and implementing preventive measures to help patients with epilepsy.

Methods

Study design and area: Institutional based cross sectional study was conducted from September 1-14, 2014 at Amanuel Mental Specialized Hospital (AMSH). AMSH is the oldest mental health hospital in the country established in 1930 and is situated in Addis Ababa, the capital city of Ethiopia. It currently has a total of 300 beds of which 277 are for inpatients and 23 for Emergency room, serving people from all corners of the country. There is also a large outpatient service, having more than 100,000 visiting patients each year. The hospital is known for treating PWE in a time when there were no neurologists in the country,- and that tradition is still continuing.

Study population: The study participants were recruited from regular seizure follow up clinic in the hospital during the study period. All patients with epilepsy, aged of above or equal to 15 years old diagnosed by unequivocal clinical and/or EEG diagnosis of epilepsy (≥2unprovoked seizures) were enrolled.

Sample size and sampling technique: A total of 298 patients who had a follow up at the clinics were enrolled in order of their arrival to the AMSH regular seizure clinic during the study period.

Study tool and data collection: Data was collected on patients socio demographic (Age, gender, race, occupation), seizure related information (nature, circumstance, severity, and consequence), Epilepsy (aura, prodromal, ictal and post-ictal phenomena description), were assessed using pre-tested structured questioner and a check list on review of information from the patient's record. Specific clinical data was gathered & organized using the diagnostic scheme for the classification of seizures and epilepsy by ILAE, 1981 (to determine the epileptic seizure type), & Seizure Frequency Scoring Scale as modified from *E.L. So et al*.1997(12). Data was collected by two medical professionals based on interview, physical examination and review of the patient's record. And SRI history is collected as long as they remember.

Data analysis: The data was entered and analyzed using the statistical package for social sciences (SPSS) version 16 statistical Software. The descriptive information was determined using the frequency, proportion, mean, and standard deviations. Odds ratios (OR) and their 95% confidence intervals (CI) were estimated using bivariate and multivariable logistic regression analysis to identify possible explanatory variables associated with seizure related injury. P-value of less than 0.05 was used to chose variables which have association in the bivariate model to mul-

tivariable model analysis. The result at p-value <0.05 was considered statistically significant in the final model.

Operational definitions

Epilepsy; two or more unprovoked seizures

SRI; any physical trauma or injury that resulted as a direct consequence of the seizure

Status epileptics; a single seizure episode lasting for at least 30 minutes, or two or more episodes occurring one after the other before the patient regains full consciousness in between the attacks.

Results

Socio-demographic characteristics of study participants.

A total of 298 patients were included in the study with a response rate of 100%. The majority of patients included in the study were younger 192(64.4%), males 174(58.4%), Christians 239 (80.2%), single 189(63.4%), Right-handed 288(96.6%), educated 222(74.5%), unemployed 133 (44.4%), and 216(72.5%) were living with their parents or siblings **(**Table 1).

Type of seizure related injuries

A total of 114 (34.9%) patients reported to have SRI due to active seizure (Figure 1). Out of these 10 (8.8%) reported multiple types of injuries while the rest had single type of injury. Most common types of injuries sustained were lacerations (54.2%), burn (19.8%) and dental-loss (15.8%). Additional reported injuries included fractures, joint dislocation, contusion and head injury **(**Table 2).

Clinical characteristics of epileptic patients during presentation

Of those patients included in the study 162 (54.4%) had seizure for more than 10 years. All the rest reported to have their seizure onset within the last 10 years. Among these participants 120 (40.3%) had seizure attacks usually during the nighttime while 83 (27.9%) had seizure during the day time. Seizure related injury happened mostly at home 61 (53.5%) followed by work place 21 (18.4%), in the street19 (16.7%) and school 11 (9.6%) **(**Figure 1).

Table1. The socio demographic characteristics of study population seen at regular seizure follow up clinics of Amanuel Specialized Mental Hospital, 2015. (n=298)

Characteristics	Frequency	Percentage
Age groups		
15-30	192	64.4
31-65	106	35.6
Mean age(+SD)	30.6(12.5)	
Gender		
Male	174	58.4
Female	124	41.6
Marital status		
Single	189	63.4
Married	87	29.2
Divorced/Separated	8	2.6
Widowed	14	4.7
Handedness		
Right-handed	288	96.6
Left-handed	10	3.4
Educational level		
Unable to read and write	76	25.5
Able to read and write only	21	7.0
Grade 1-6	61	20.5
Grade 7-12	92	30.9
Grade 12+	48	16.1
Living situations		
Alone	18	6.0
With parents and /or siblings	216	72.5
With spouse	52	17.4
Other	12	4.0
Occupational status		
Self	101	34.0
Government	57	19.2
NGO	7	2.4
Unemployed	133	44.4

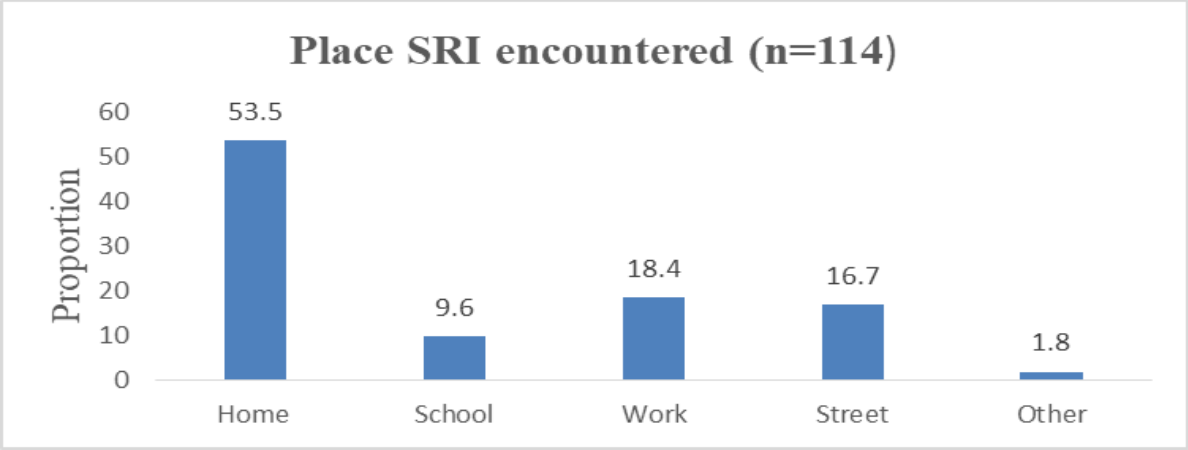

Figure 1. The place where SRI encountered among epileptic patients at regular seizure follow-up clinics of Amanuel Specialized Mental Hospital, 2015.

Table 2. The magnitude, type and severity of active seizure related injuries among Epileptic Patients seen at regular seizure follow up clinics of Amanuel Specialized Mental Hospital, Addis Ababa, 2015.

Type of injury	**Number (%)**	**Degree of Severity**		
		Mild No(%)	Moderate No(%)	Severe No(%)
Fracture	6 (6.3)	6 (100)	--	--
Joint dislocation	6 (6.3)	2 (33.3)	2(33.3)	2(33.3)
Laceration	52 (54.2)	45 (92.7)	6 (6.3)	1 (1.0)
Contusion	6 (6.3)	6 (100)	--	--
Sprain	2 (2.1)	2 (100)	--	--
Burn	19 (19.8)	10 (52.6)	6 (31.6)	3 (15.8)
Head injury	5 (5.2)	5 (100)	--	--
Dental injury	18(15.8)	--	--	--
Multiple injuries	10			
Total	114*	76	12	6

**104 active injuries (cases) 10 were multiple injuries.*

The rest 95(31.9%) had seizure attacks both during the day and the night time. The majority 283 (94.9%) of the participants reported GTC seizure during attack. Among them only three patients were ever diagnosed with status epileptics. Most reported 237(79.5%) a seizure time ranging from 5-30 minutes during attack (Table 3). A total of 87 (29.2%) participants reported to have pre-seizure symptoms or aura whereas the majority 231(77.5%) reported to have post-seizure symptoms of some kind.

The most frequently reported post-seizure symptoms were headache 70(23.5%) and deep sleep 65(21.8%). The majority of participants 255(85.1%) had delays in starting treatment after onset of seizure. Among these 111(35.1%) delayed for less than one year, 91 (31.6%) for 1 to 5 years and the rest 53(18.4%) for more than five years (Table 3).

Table 3. The clinical characteristics of epileptic patients during presentation at regular seizure follow up clinics of Amanuel Specialized Mental Hospital, Addis Ababa 2015.

Clinical characteristics (n=298)	**Frequency**	**Percentage**
Onset of epilepsy symptoms		
Last 1 year	10	3.4
Last 1-5 years	62	20.8
Last 5-10 years	64	21.5
Before 10 years	162	54.4
Signs and symptoms that come before the actual seizure		
Headache	12	13.8
Blurring of vision	30	34.5
Shocking sensation	8	9.2
Dizziness	10	11.5
Fearfulness	13	14.9
Palpitation	4	4.6
Other	10	11.5
People tell you about what actually happens during the seizure		
GTC	283	94.9
Focal	13	4.4
Absence	2	0.7
The duration of the actual seizure in most of the attacks		
< 5 min	58	19.5
5-30 min	237	79.5
> 30 min	3	1.0
What happens after the actual seizure stops		
Nothing	67	22.5
Headache	70	23.5
Deep sleep	65	21.8
Confusion/disorientation	17	5.7
Headache and Deep sleep	60	20.1
Headache and confusion	5	1.7
Both (headache +deep sleep +confusion)	6	2.0
	8	2.7
Ever been diagnosed with status epileptics		
Yes	3	1.0
No	295	99
The time gap between the onset of the symptoms and the start of antiepileptic drug treatment		
Immediately	43	14.9
< 1 year	111	35.1
1-5 years	91	31.6
> 5 years	53	18.4
Last time you had a seizure		
Last 24 hrs.	16	5.4
Last 1 week	36	12.1
Last 1 month	51	17.1
Last 1-6 months	65	21.8
Last 6-12 months	63	21.1
Before 2 years	67	22.5
Timing of the occurrence of most seizure attacks		
Night time when asleep	120	40.3
Day time when awake	83	27.9
Day time or night time	95	31.9

Continued….

Seizure frequency score		
Seizure free, off AED	**19**	**6.4**
Seizure free, need for AED unknown	**27**	**9.1**
Seizure free, on AED	**54**	**18.1**
Simple partial seizure only	**6**	**2.0**
Nocturnal seizure only	**15**	**5.0**
1-3/yr.	**34**	**11.4**
4-11/yr.	**20**	**6.7**
1-3/mo.	**97**	**32.6**
1-6/wk.	**22**	**7.4**
1-3/d	**2**	**0.7**
4-10/d	**2**	**0.7**

Associated factors of SRI

A multivariate logistic regression result depicted that; The odds of SRI increased by 2.2 times (AOR=2.19, 95% CI (1.04-4.54) among those who were in grade 1 -6 education levels, and a lower risk of SRI was reported among those who able to read and write (AOR=0.11, 95% CI (0.13-0.86)**(Table 4).**

Discussion

Patients with epilepsy can sustain any type of injury

Table 4. The Socio demographic factors associated with active seizure related injuries among epileptic patients at regular seizure follow up clinics of Amanuel Specialized Mental Hospital, 2015.

Variables	**Active injury (SRI)**		**COR 95% CI**	**AOR 95% CI**
	Yes No (%)	No(%)		
Age groups				
15-30	68(65.4)	124(63.9)	1.00	1.00
31-65	36(34.6)	70(36.1)	0.57(0.57-1.55)	1.19 (0.65 - 2.21)
Gender				
Male	54(51.9)	120(61.9)	1.00	1.00
Female	50(48.1)	74(38.1)	1.5(0.93-2.43)	1.49 (0.86 - 2.59)
Marital status				
Single	72(69.2)	117(60.3)	1.00	1.00
Married	24(23.1)	63(32.5)	0.62(0.36-1.08)	0.98 (0.42 -2.29)
Divorced	3(2.9)	5(2.6)	0.98(0.23-4.20)	0.58 (0.12 - 2.89)
Widowed	5(4.8)	9(4.6)	0.90(0.29-2.80)	0.65 (0.16 -2. 61)
Educational level				
Unable to read and write	24(23.1)	52(26.8)	1.00	1.00
Able to read and write only	1(1.0)	20(10.3)	0.11(0.01-0.85)	0.11 (0.01 -0.86) *
Grade 1-6	28(26.9)	33(17.0)	1.84(0.92-3.70)	2.19 (1.04 -4.58) *
Grade 7-12	31(29.8)	61(31.4)	1.10(0.58-2.11)	1.17 (0.58 -2.33)
Above grade 12	20(19.2)	28(14.4)	1.55(0.73-3.28)	1.59 (0.70-3.65)
Occupational status				
Self	29(27.9)	72(37.1)	1.00	1.00
Government	20(19.2)	37(19.1)	1.34(0.67-2.69)	1.14 (0.53 -2.42)
NGO	2(1.9)	5(2.5)	0.99(0.18-5.41)	0.98 (0.17 -5.79)
Unemployed	53(51.0)	80(41.2)	1.65(0.95-2.86)	1.82 (0.96 -3.46)
Living situations				
With parents /siblings	78(75.0)	138(71.1)	1.00	1.00
Alone	8(7.7)	10(5.2)	1.42(0.54-3.74)	2.07 (0.71 -6.05)
With spouse	12(11.5)	40(20.6)	0.53(0.26-1.07)	0.62 (0.24 -1.63)
Other	6(5.8)	6(2.6)	1.77(0.55-5.67)	2.66 (0.70 -10.12)

NB=p<0.05, COR=Crud Odds Ratio, AOR=Adjusted Odds Ratio*

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related to their seizure. And this study tries to give an overall description of SRIs with their associated factors. In our study the prevalence of SRIs among PWE found to be 34.9% which is apparently more than that reported by the European cohort study (21%) [9] but less than some other reports like the one by Asadi-Pooya et al (53%) [3].

The most common types of injuries reported were lacerations (54.2%), burn (19.8%) and dental-loss (15.8%) followed by fractures, joint dislocation, contusion and head injury. There were no reports of submersion injury or injury to the eye. This is more or less consistent with other studies. There was higher prevalence of reported dental injuries (about 4.5% in other studies) [15] when we come to SRHIs (Seizure related Head Injuries) while it is common in other studies (78%) ,it was 5.2% in our case [13]. One possible explanation for this variation may be that most patients who sustained severe head injuries may not have survived to report it or some might have trivialized mild to moderate head injuries.

In this study the majority of patients reported to have seizure for more than 10 years (54.4%),while the rest had it in the last 10 years. Most had seizure attacks usually during the night (40.3%), while 27.9% had seizure during the day. The rest (31.9%) had seizure attacks both during the day and night. It is intuitive to assume that seizures that occur exclusively at night, in the safety of one's bed, probably also lead to less risk of injury than those occurring predominantly during the day.
Only three types of seizures were reported: Generalized tonic clonic-seizures (94.9%), focal seizures (4.4%) and absence seizures (0.7). Other types of seizures were not reported or detected probably as result of limited capacity and inadequate effort to look into the various seizure types by physicians and reporting errors on the patient's side. However our finding is consistent with other studies in a sense that most seizures are generalized in nature.

The duration of active seizure reported by the majority was 5-30 minutes. However we should keep in mind that much of the convulsive fit results in the attendants' panic there by making tracking of time somewhat unreliable. Moreover, we have noted that many of them count the post-ictal phenomenon including sleep time as part of the convulsion, and therefore we suspect the actual duration of the active convulsion might be less than 5 minutes as noted elsewhere in other studies.
A total of 29.2% reported to have pre-seizure symptoms or aura. Presence of a warning aura with every seizure is shown to be protective from accidents [14]. Most patients had delays in starting treatment after one set of seizure. In earlier studies this were highly associated with SRI by way of more frequent &/or longer attacks [14]. The places of the seizure also have great relevance in terms of the risks for SRI. Most seizure related injury happened mostly at home followed by work place, the street and the school. Though home is relatively safe injury depends on the circumstances and these calls for precautions even at home.

Socio demographic factors such as age, sex, religion, marital status, occupation, and living situations were not found to be statistically associated with SRI in this study, while a higher prevalence of SRI during active seizure was associated with a low educational status.Patients with a lower education status were having 2.2 times more chance of SRI compared to those who are unable to read and write. And those who have no further education ,other than able to read and write only were found to have a lower chance of exposure to SRI (AOR=0.11, 95% CI (0.13 -0.86).
This study has its own limitation which includes its retrospective nature, difficulties in retrieving relevant information from poorly documented patient charts, difficulties in differentiating single versus multiple SRI among patients, recall bias related to the different aspects of SRIs and challenges in diagnosing comorbid disorders that may be linked to SRIs.

Conclusion and recommendations

The study documented significant levels of SRI among the study population with varied levels of severity. Soft tissue injuries and burn were the most common types of injuries detected. The only sociodemographic factor associated with SRI was a lower educational status. However, further large scale epidemiologic studies are highly recommended. Availing awareness raising mechanism for epileptic patients, their care givers and professionals in Ethiopia on SRI is highly important to mitigate the problem to our understanding. Besides Surveillance and monitoring of SRIs, advocacy work on behalf of epileptic patients for a safer home and work environment is very essential.

Authors contribution

SY, YM, AA: conceptualized and designed the study. **SY:** Wrote the research proposal, conducted the research, analyzed the data and write a draft manuscript. YM, SG, and AA: Involved in the write up of the proposal, data analysis and write up of the manuscript. All co-authors contributed to its improvement and critically reviewed the manuscript development. All authors approved the final version of manuscript.

Ethical approval: Ethical clearance was obtained from the Ethical review committee of the Department of Neurology reference number SM/ NEURO/065/2007. Informed consent was obtained from all patients or caregivers involved in the study after explaining the nature of the study in the language they understand and those who were diagnosed with the SRI were linked to the appropriate facility, if they were in need of further evaluation or treatment.
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Conflict of Interest: The authors have declared that no competing interests
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In Memory of : Dr.samson Yaregal the PI of this study and our colleague ,whom we lost 2022 and saddened by his passing at a younger age.

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Original Article

Association between angiotensinogen M235T gene polymorphism and risk of hypertension: A case control study among Ethiopian patients

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Abstract

Background*: Hypertension is a major public health problem in both developing and developed nations because it is highly prevalent and is associated with complications. Numerous environmental and genetic variables are linked to the occurrence of the disease. It may be influenced by the renin-angiotensin-aldosterone system, which preserves bodily homeostasis. The angiotensinogen gene M235T polymorphisms that has an effect on the activity of the renin-angiotensin-aldosterone system are related to the high hypertension risk. The aim of this study was to find out the association between angiotensinogen M235T gene polymorphism and the risk of developing hypertension.*

Methods: *A total of 306 samples - 153 patients with hypertension and 153 age- and sex-matched healthy controls were selected using a simple random sampling technique. Clinical and biochemical variables were measured to assess the associated risk factors. Blood samples from the patients and matched controls were used to isolate deoxyribonucleic acid. The AGT M235T genotypes were identified using polymerase chain reaction and analyzed by agarose gel electrophoresis. Logistic regression with a 95% confidence interval (CI) was employed to assess the risk correlations of AGT gene M235T polymorphisms with hypertension.*

Results*: Our analysis showed that the AGT-TT genotype (odds ratio [OR] = 3.11, 95% CL = 1.67–5.79, P< 0.001) and T allele (OR = 2.18, 95% CL = 1.56–3.04, P< 0.001) are considerably higher in hypertensive patients than in healthy controls. Our study also identified the clinical risk factors for hypertension, such as, total cholesterol, triglycerol, low density lipoprotein-cholesterol, and high density lipoprotein-cholesterol levels, which were significantly higher in patients compared to controls (P< 0.001).*

Conclusion*: The AGT M235T genes of the TT genotype and the T allele are associated with an increased risk of hypertension among the Ethiopian patients. A population-based epidemiological study is needed corroborate the association between AGT and HTN.*

Keywords : *Angiotensinogen; Blood Pressure; Genotypes; Renin-Angiotensin-Aldosterone System; Risk Factor*
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Introduction

Hypertension (HTN) is a common disease manifested primarily by elevated blood pressure and remains one of the leading causes of death from cardiovascular disease [1]. With accelerated population aging, the prevalence of HTN shows an increasing trend in both developed and developing countries [2]. It is a multifactorial and complex disorder that is influenced not only by several susceptible genes but also by environmental stimuli and lifestyle [3]. As with most difficult conditions, blood pressure fluctuations are thought to be influenced by age, gender, and ethnicity as well as clinical factors such as obesity, insulin resistance, and dyslipidemia [4]. There are more than 150 potential genes associated with the control of blood pressure that are connected to several pathways; the renin-angiotensin-aldosterone

system (RAAS) is one of these pathways that has received more attention. [5].

The natural substrate of RAAS, angiotensinogen (AGT), is produed in the liver and released into the bloodstream. It interacts with renin to form angiotensin I, a precursor to angiotensin II, and is crucial for maintaining fluid homeostasis and controlling blood pressure [6]. AGT is a 12 kb long gene on chromosome 1 (1q42–q43) that belongs to the serpin gene superfamily and has 5 exons and 4 introns. The AGT gene's M235T polymorphism refers to the substitution of the amino acid threonine (T) for methionine (M) at position 235, giving rise to three genotypes: MM, MT, and TT [7]. When compared to those with the MM genotype, those with the TT genotype have greater blood pressure and plasma AGT levels because of the AGT-M235T polymorphism [8].

Studies on hypertensive and normotensive individuals have shown an association between the chromosomal region containing the AGT M235T gene and blood pressure. This led to the hypothesis that AGT M235T may be a candidate gene for essential HTN in humans and that the TT genotype of the AGT gene is correlated with HTN in different ethnic populations [9]. However, there are conflicting results on the effect of the AGT M235T gene polymorphism on HTN. This discrepancy is emphasized in certain studies that established a link between these polymorphisms and HTN, while others did not [10]. Thus, the purpose of this study was to identify the association of AGT M235T gene polymorphisms with risk of HTN and to determine the effect of clinical parameters in predicting the occurrence of HTN among the Ethiopian population.

Patients and Methods

Study Design and Participants

From May to August 2022, a hospital-based matched case control study was conducted at Debre Tabor Referral Hospital. The hospital has a follow-up medical referral clinic (MRC) for chronic illnesses, including HTN where treatment and follow-up services are provided for patients with HTN take place. All patients who visited MRC were the source population, and patients who were under follow-up for HTN were the cases. Age and sex-matched normotensive patients managed at the facility during the study period served as controls.

Inclusion and Exclusion Criteria

The study included patients who were diagnosed to have hypertension and were receiving treatment and follow-up care at MRC for at least one year. The controls were age- and sex-matched healthy individuals with normal blood pressure results from the same geographical location and social status. Patients who were diagnosed to have renal disease, secondary HTN, or a chronic bacterial or viral infection were excluded. Patients who were unable to respond or are not willing to give informed consent were excluded from this study.

Sample Size Determination

The sample size was determined using analytical study sample size calculation by taking confidence level of 95%, a power of 80% with a double population proportion formula.

$$\text{Sample size} = \frac{r+1}{r}\frac{(p^*)(1-p^*)(Z_\beta + Z_{\alpha/2})^2}{(p_1 - p_2)^2}$$

Since similar studies are not done in the Ethiopian population, the sample size was determined by assuming expected proportions of 0.35 associations among the hypertensive case group and 0.20 among the normotensive control group [11]. The final sample size after adding the 10% non-response rate was 306 (153 cases and 153 controls) of both sexes. Participants were selected by simple random sampling methods, using a table of random numbers (TRN), from all the registered patients.

Data Collection Methods

The socio-demographic characteristics of both patients and healthy control subjects were assessed using a semi-structured questionnaire. Portable digital scales and portable stadiometers were used to determine body weight and height, respectively. Body mass index (BMI) was computed by dividing weight (in kilograms) by height (in meters squared). Participants were classified as underweight (BMI < 18.5 kg/m^2), healthy (18.5 - 25 kg/m^2), overweight (25.0–29.9 kg/m^2) or obese (≥ 30 kg/m^2) based on their BMI [12]. A digital instrument was used to measure blood pressure in the sitting stance after 5 minutes of rest, and the average of three readings was to determine and record the SBP and DBP. Participants were categorized as hypertensive if their mean SBP ≥ 140mmHg and mean DBP ≥90mmHg or if they used antihypertensive medication; pre-hypertension, SBP 120–139 mmHg or DBP 80–89 mmHg; normal blood pressure, SBP <120 mmHg and DBP <80 mmHg [13].

Sample Collection and Laboratory Methods

All participants, including patients and healthy controls had a blood sample of five milliliters taken from the median cubital vein by laboratory staff following quality control and safety procedures. From the 5 ml sample, 3 ml was retained in the test tube without anticoagulants to allow the blood to clot. The tubes were then centrifuged to extract the serum, which was then collected into new tubes for biochemical tests. Enzymatic analyses of TC, TG, LDL, HDL, creatinine, and glucose were performed on each test in the Debre Tabor Referral Hospital diagnostic laboratory using the Dimension EXL 200 fully automated analyzer. Results were then scored by an investigator blinded to the sample withdrawal condition

and experimental groups. diabetes mellitus has been identified if the fasting plasma glucose level is greater than 110 mg/dl [14]. Dyslipidemia can be defined if TC, TG, and LDL levels are above 200 mg/dl, 150 mg/dl, and 130 mg/dl, respectively, and the HDL level is below 60 mg/dl [12]. Kidney disease was diagnosed if the blood creatinine concentration was >1.3 mg/dl [15].

In the molecular biology laboratory at the University of Gondar, genomic deoxyribonucleic acid (DNA) was extracted from the remaining 2 ml of samples collected in EDTA-containing tubes from each participant. The non-enzymatic salting-out approach [16] was used to isolate DNA from ethylenediaminetetraacetic acid (EDTA) anticoagulated blood from both patients and controls. The blood was then put into a clean 1.5 ml Eppendorf tube. By lysing and eliminating them with a buffer solution, red blood cells were removed. To lyse white blood cells, a nuclear lysis buffer solution was used. Then, to precipitate and remove proteins, 6 M, highly concentrated sodium chloride (NaCl) was applied. After freezing with isopropanol and washing with 70% ice-cold ethanol, the DNA was precipitated. Then, Tris-EDTA (TE) buffer was used to dissolve genomic DNA. The quality of isolated genomic DNA was verified utilizing 1% agarose gel electrophoresis (Figure 1), and the sample was kept at -20 °C until it was needed [17].

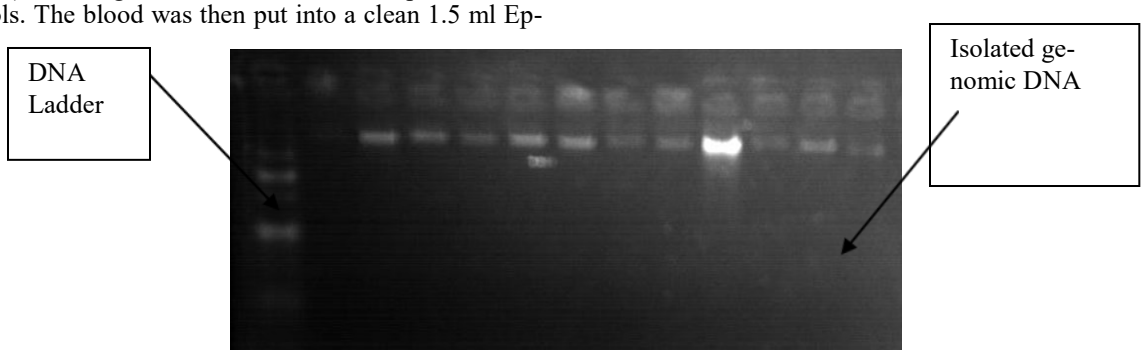

Figure 1: 1% agarose gel electrophoresis showing the quality of isolated genomic DNA

The AGT M235T genotypes were identified using the forward primer, 5'CAG GGT GCT GTC CAC ACT GGA CCC C-3' and the reverse primer, 5'-CCG TTT GTG CAG GGC CTG GCT CTC T-3'. Amplification was performed in a 25 µl reaction mixture using 12.5 µl of master mix (constituting of MgCl2, dNTPs, PCR buffer, and Taq polymerase), 1 µl forward primer, 1 µl reverse primer, 2 µl of each sample, and 8.5 µl PCR grade water added to complete the total volume . The initial denaturation stage of the amplification was set at 10 min at 95 °C, and it was then followed by 35 cycles of amplification with denaturation stages of 10 s at 94 °C, primer hybridization stages of 30 s at 64 ° C, elongation stages of 20 s at 72 °C, and a final elongation stage of 5 min at 72 °C. In a 10 µl mixture containing 5 U of the particular restriction enzyme Tth111I, the amplified fragment of 165 bp was exposed to enzymatic digestion for 3 h at 65 °C. The mutant T235 allele splits into two pieces that are 141 and 24 bp, but the normal M235 allele is not digested [18]. Finally, AGT M235T genotypes 165 bp band (MM), 141 bp band (TT), and both 165 and 141 bp band (MT) PCR products were separated electrophoretically for 50 minutes at 120 V on a 2% agarose gel (Figure 2).

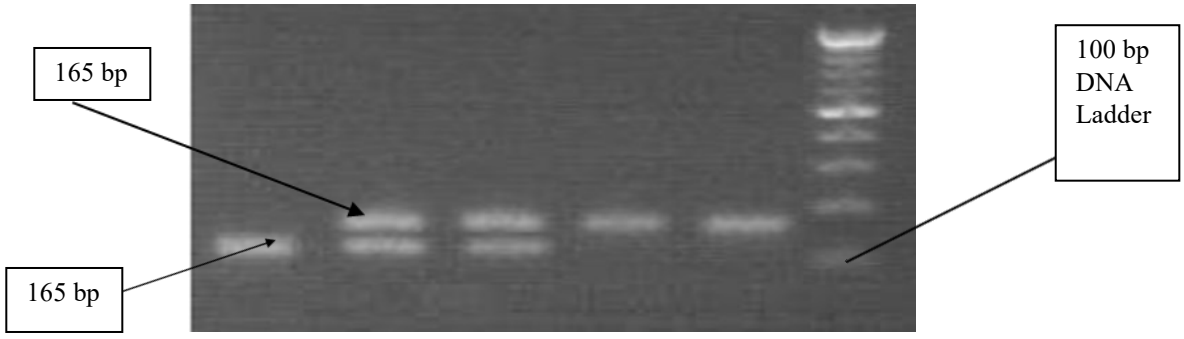

Figure 1: 1% agarose gel electrophoresis showing the quality of isolated genomic DNA

Statistical Analysis

The data were analyzed using STATA version 14. Mean and standard deviation (x+s) were used to summarize the quantitative data, and the t-test for independent samples was applied to test statistical differences in continuous variable measures among the cases and controls. The chi-square test was used to determine the level of significance the differences in genotype and allele frequencies in the two groups. Logistic regression with a 95% confidence interval (CI) was employed to assess the risk correlations of AGT gene M235T polymorphisms with HTN. A one-way analysis of variance (ANOVA) was used to compare the association between AGT genotypes and clinical explanatory factors. Statistical significance was defined as a p-value less than 0.05.

Results

Socio-Demographic and Clinical Characteristics

Of the total 153 patients with HTN, 80 (52.3%) were male and 73 (47.7%) were female. Among the 153 healthy control groups, 77 (50.3%) were male and 76 (49.7%) were female. The mean age of the study group was 58.7 ± 12.8 and 57.5 ± 6.9 for cases and controls, respectively. The clinical risk factors of HTN such as total cholesterol (TC), triglycerol (TG), LDL-cholesterol, and HDL-cholesterol levels are significantly higher in patients when compared to controls (P< 0.001). However, there were no significant differences in body mass index (BMI), fasting blood glucose (FBG), or blood creatinine level between the two

Table 1: Demographic and clinical characteristics of the study participants in Debre Tabor Referral Hospital, Northwest Ethiopia, 2022

Variables	HTN (n=153)	Control (n=153)	P-value
BMI (Kg/m^2)	23.9±3.9	23.2±3.5	0.0965
FBG (mg/dl)	93.8±19.1	91.1±8.6	0.1020
Creatinine (mg/dl)	0.82±0.14	0.80±0.12	0.1448
Total Cholesterol (mg/dl)	192.8±60.5	147.5±51.2	< 0.001*
Triglyceride (mg/dl)	142.6±67.5	104.9±37.0	< 0.001*
LDL-Cholesterol (mg/dl)	96.2±35.6	73.3±27.7	< 0.001*
HDL-Cholesterol (mg/dl)	43.4±10.2	51.6±10.0	< 0.001*
Family history of HTN (%)	54.2 %	55.5 %	0.8183

Note: *P-value <0.05 is considered statistically significant. **Abbreviations:** HTN, Hypertension; BMI, Body Mass Index;; FBG, Fasting Blood Glucose; LDL, Low Density Lipoprotein; HDL, High Density Lipoprotein.

Distribution of AGT Genotypes and Allele Frequencies

The frequencies of the TT, MT, and MM genotypes among the patient group were 56.2%, 28.1%, and 15.7%, respectively, whereas in the control group the same were found to be 30.1%, 43.8%, and 26.1%, respectively (Figure 3). A significant difference is observed in the distribution of AGT genotype polymorphism between the two groups. Furthermore, the frequency of homozygous TT genotype in patients was three times higher than in the control group (OR=3.11; 95% CI: 1.67-5.79; P< 0.001). The allelic frequencies showed high significance between the two groups, in which the T allele was two times higher than the M allele in hypertensive patients (OR:=2.18; 95% CI: 1.56-3.04; P< 0.001) compared to healthy controls. However, AGT genotypes MT and MM were less frequent in hypertensive patients in comparison to healthy controls (Table 2).

Table 2: Distribution of AGT genotypes and allele frequencies of the study participants in Debre Tabor Referral Hospital, Northwest Ethiopia, 2022

Genotype	HTN (n=153)	Control (n=153)	OR (95% CL)	p-value
TT	86 (56.2 %)	46 (30.1 %)	3.11 (1.67-5.79)	< 0.001*
MT	43 (28.1 %)	67 (43.8 %)	1.06 (0.56-2.01)	0.835
MM	24 (15.7 %)	40 (26.1 %)	Ref	
Allele Frequency				
T	215 (70.2 %)	159 (51.9 %)	2.18 (1.56-3.04)	< 0.001*
M	91 (29.8 %)	147 (48.1 %)	Ref	

Note: *P-value <0.05 is considered statistically significant.

Abbreviations: Ref, Reference; CL, Confidence Level; OR, Odds Ratio.

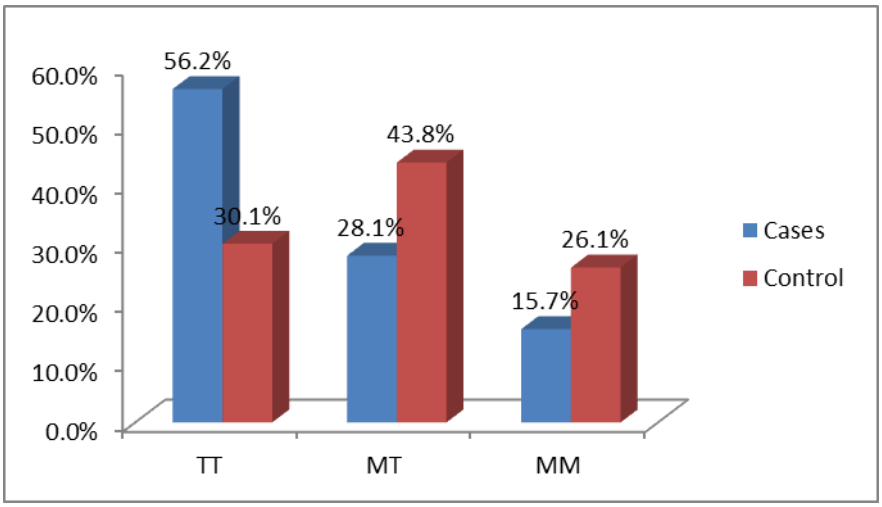

Figure 3: Distribution of the AGT M235T genotype in cases and controls

Association between AGT Genotypes and Clinical Parameters

Table 3 lists the clinical parameters of patients with HTN and normotensive controls in relation to the AGT M235T genotype. The AGT genotypes (TT, MT, and MM) in the study groups were assessed with fasting blood glucose, blood pressure, and lipid profiles. Blood pressure was more strongly correlated with the AGT-TT genotype than the MT and MM genotypes for SBP, Mean (SD) 138.1±17.2 Vs 127.0±13.7 and 125.3±13.4; *P*< 0.001), and DBP (86.8±9.2 Vs 81.4±7.2 and 80.5±7.2; *P*< 0.001), respectively. The other clinical variables were not found to be significant with the genotypes in the study groups (P> 0.05).

Table 3: Association of AGT M235T genotype with clinical characteristics in Debre Tabor Referral Hospital, Northwest Ethiopia, 2022

	Genotypes			
Variables	TT (N=132)	MT (N=110)	MM (N=37)	p-value
	Mean (SD)			
BMI (Kg/m^2)	23.5±3.8	23.6±3.1	23.5±3.4	0.1680
SBP (mmHg)	138.1±17.2	127.0±13.7	125.3±13.4	< 0.001*
DBP (mmHg)	86.8±9.2	81.4±7.2	80.5±7.2	<0.001*
FBG (mg/dl)	94.8±17.8	90.2±8.6	91.4±16.2	0.4157
TC (mg/dl)	167.8±56.6	170.3±58.4	174.8±71.0	0.1436
TG (mg/dl)	125.6±57.6	118.7±51.4	128.9±67.0	0.1578
LDL-C (mg/dl)	87.5±33.6	84.4±35.3	79.5±31.5	0.6981
HDL-C (mg/dl)	46.8±10.6	47.1±10.8	49.6±11.6	0.3027
Creatinine (mg/dl)	0.81±0.13	0.81±0.15	0.80±0.13	0.3530

Note: *P-value <0.05 is considered statistically significant.

Discussion

Although contradictory results have been reported, the AGT gene M235T polymorphism has been found to be highly related to a higher prevalence of HTN in populations from different ethnic groups [19]. In our investigation, patients with HTN had much greater rates of the T allele of the AGT M235T variation than did controls, and they also had significantly higher rates of AGT 235T homozygosity than did the healthy control subjects, as shown in Table 2. This finding is in agreement with a meta-analysis conducted in Indonesia, including 41 studies, which found that patients with the T allele were more likely to develop HTN compared to the carriers of the M allele (OR =1.15; 95%CI = 1.00–1.32; P <0.05) [20]. A case-control study with positive results was conducted in the Egyptian population, including 83 hypertensive cases and 60 age- and gender-matched normotensive controls. The study found that patients with the TT genotype (OR= 36.217, P <0.001) and T allele (OR= 7.267, P < 0.001) were significantly associated with a high risk of developing HTN [21]. Similarly, other studies conducted in populations from Greece [22] Malaysia [23], South India [19], and China [24] showed that the AGT gene TT genotype and 235T allele were associated with a high incidence of HTN.

The exact mechanism by which the M235T mutation in the AGT gene increases the risk of HTN is unknown. The AGT 235T variation features a guanine-to-adenosine transition at -6 bp upstream of the transcription initiation site and has been determined to be in full linkage disequilibrium. [25]. This nucleotide substitution affects the basal transcription rate of this gene in different cell lines, resulting in the AGT T235 variant and higher plasma AGT levels, which may contribute to the elevation of blood pressure [23]. AGT M235T-TT carriers have a higher level of angiotensin II than non-carriers, which affects the function of endothelial cells in a number of ways, including by promoting endothelial cell apoptosis, raising vascular endothelial growth factor, and impairing the production of nitric oxide. This results in a higher risk of HTN and its associated complications [26].

On the other hand, the findings of this study disagree with the case-control study conducted in Sudan, which included 96 patients with essential hypertension and 79 apparently healthy controls. The study showed no correlation between the AGT M235T gene polymorphism and hypertension [27]. In addition, other studies conducted in populations of Nigeria [25], Mongolia [28], and Thailand [29] contrasted with the findings of the current study, as they were unable to detect any significant association between 235T homozygosity and the risk of HTN. Conflicting results regarding the involvement of AGT gene M235T polymorphisms in HTN are likely due to ethnic differences, population heterogeneity, geographic differences, sampling biases, and possibly other ecological factors. Additionally, a number of environmental variables, including nutrition and exercise, are connected to alterations in the epigenetic state [30].

There are some limitations to this study. First, the relatively small sample size may lead to a

bias in identifying the AGT M235T genotype in hypertension patients. Second, there are no measurements of plasma angiotensinogen levels or other genes of RAAS that correlate directly with the genetic polymorphisms investigated in this study. Its strength is that this is the first investigation into the relationship between genetic variations of AGT and hypertension in the Ethiopian population. This study also examined the risk of hypertension associated with clinical and biomedical characteristics to underline the crucial importance of the link with the disease. The findings of this study will serve as a baseline for these locations, but further research must be done to find other gene polymorphisms that could be reliable indicators of hypertension in this population..

Conclusion

The present study indicated that the AGT M235T gene of the TT genotype and the T allele have been associated with a high risk of hypertension. As a result, the AGT gene M235T polymorphism may be used as a biomarker for early hypertension diagnosis as well as to manipulate antihypertensive medication therapeutic strategies. In future studies, a population-based study should be needed for further clarification of the association between AGT and hypertension.

Abbreviations: AGT: Angiotensinogen; BMI: Body Mass Index; DNA: Deoxyribonucleic Acid; DBP: Diastolic Blood Pressure; EDTA: Ethylenediaminetetraacetic Acid; FBG: Fasting Blood Glucose; HDL: High Density Lipoprotein; HTN: Hypertension; LDL: Low Density Lipoprotein; PCR: Polymerase Chain Reaction; RAAS: Renin-Angiotensin-Aldosterone System; SBP: Systolic Blood Pressure; TC: Total Cholesterol; TG: Triglycerol.

Declarations

Ethics approval and consent to participate: The study protocol was approved by the University of Gondar institutional review board (Ref. VP/RTT/05/1016/2022). Study participants were recruited only after informed written consent was obtained from each of them. All the data were obtained anonymously and treated confidentially.

Consent to Publish: Not applicable

Availability of data: The data used and/or analyzed in the current study can be provided by the corresponding author upon request.

Competing interests: The authors claim to have no conflicts of interest.

Authors' contribution

All authors made a significant contribution to the work reported, whether that was in the conception, study design, execution, acquisition of data, analysis, or interpretation. A.M. prepared the final draft of the manuscript. M.A. and N.B. critically reviewed the article and gave final approval of the version to be published. All authors agreed on the journal to which the article has been submitted.

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Original Article
The accuracy of widal test for typhoid fever diagnosis in Ethiopia: Systematic review and meta-analysis

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Abstract

Introduction: *Widal agglutination test is a serologic investigation that is used to diagnose typhoid fever. This is an easy, fairly inexpensive, and readily available test with questionable reliability. The test performance differs from setting to setting depending on the technique used and other factors. The accuracy of this test in Ethiopia is poorly understood. So, the aim of this scientific work was to analyze the accuracy of Widal agglutination in diagnosing typhoid fever in Ethiopia.*

Methods: *We performed a systematic review and meta-analysis. Two electronic databases (PubMed/Medline and Google scholar) were searched using preset search strategy to find relevant studies. The methodological quality of the studies included was evaluated with a QUADAS-2. We extracted important variables from the eligible articles. Statistical analysis was conducted using STATA version 14. The protocol of our systematic review and meta-analysis is registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the record number CRD42020194252.*

Results: *The electronic quests yielded 42 papers of which 8 were eligible for analysis. The quality of these studies was rated to be moderate based on the QUADAS-2. The pooled sensitivity, specificity, and negative, and positive predictive values of the Widal test were 80.8%, 53.0%, 98.5%, and 2.1% respectively.*

Conclusion: *The widal agglutination test has average specificity, very good negative predictive value, and very poor positive predictive value for the diagnosis of typhoid fever. Depending on Widal to diagnose typhoid fever may lead to over-diagnosis of typhoid fever and related complications including inappropriate use of antibiotics. There is an urgent need for quick and dependable tests for diagnosing typhoid fever, particularly in settings like Ethiopia where doing timely culture is not feasible.*

Keywords*: Widal test, Accuracy, Typhoid fever, Systematic review, Meta-analysis, Ethiopia*
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Introduction

Typhoid fever is an important community health problem that affects nearly 21.6 million people and kills around 200,000 people each year globally (1).The illness is mainly acquired by ingesting of food or water contaminated by the stool and seldom by urine or vomitus of patients and carriers (2). Africa has an intermediate to high burden of the disease, 10-725 cases per 100 000 population per year (1,3).

It is common in low-resource countries including Ethiopia (4,5). It is commonly considered as one of the differential diagnoses in a patient presenting with short onset fever. However, as the symptoms are non-specific and similar with other acute febrile illnesses, clinical diagnosis is not straight forward (6). Microbiologic culture (bone marrow aspirate, blood, stool, and urine) that will enable one to isolate the etiologic agents (*S. Typhi and/or S. Paratyphi*) is the gold standard in the diagnosis of typhoid fever. Nevertheless, microbiologic culture is not readily available, takes 2-7 days for the result to be ready, and is more expensive. Getting a rapid, accurate, and affordable test(s) is of paramount importance.

Different rapid diagnostic methods are available to diagnose typhoid fever (7,8). Among the Rapid diagnostic methods, Widal, TUBEX, Typhidot, and TPTest are to be mentioned. The commonly available and utilized rapid diagnostic method in Ethiopia is Widal agglutination. Though, Widal agglutination test is commonly available and used to diagnose typhoid fever, it has questionable reliability.

Widal agglutination is a serologic diagnostic test that is used to diagnose typhoid fever. It detects the presence of agglutinin (antibody) in the serum of an infected person with *salmonella typhi*. The reaction between the agglutinin in the serum of the infected patient and the *salmonella typhi (S. Typhi)* antigens will result in agglutination. The antigens used to demonstrate agglutination are H (flagellar) and O (somatic) antigens of *S.typhi* (9). The Immunoglobulin M (IgM) somatic O antibody of S.typhi appears initially and represents the first serologic response in acute typhoid fever, while immunoglobulin G (IgG) flagellar H antibody usually develops more slowly and persists for longer (10,11).

After 100 years of its introduction as a serologic way of typhoid fever diagnosis, the Widal test still remains to be associated with controversies related to the quality of the antigens used and interpretation of the result, especially in endemic regions (9). Widal test is a simple, non-expensive and fairly non-invasive test with debatable reliability (12). Widal test has a reportedly high sensitivity and better specificity though variable. Similarly it has very good negative predictive value but has poor positive predictive value (13-15). Nevertheless; Widal agglutination test could remain reactive during convalescent time and has cross-reactivity with other microorganisms resulting in false positivity. These conditions will result in over-diagnosis of typhoid fever (16). Additionally, overreliance on this test combined with poor clinical judgment may result in over prescription of antibiotics and associated antibiotics resistance.

The test performance differs from setting to setting depending on the technique used and other factors. Single slide agglutination test is widely practiced point of care test in Ethiopia. The serial tube titration method is rarely used in clinical settings. There are multiple cross sectional studies done in Ethiopia to address the use of widal test in the diagnosis of typhoid fever. Most of the studies conducted revealed conflicting results on the accuracy of widal test in the diagnosis of typhoid fever in Ethiopia. There are studies in other settings that stated widal test is less accurate and no more recommended for the diagnosis of typhoid fever. In spite of this, widal test is widely used across Ethiopia. So, summarizing studies on the diagnostic accuracy of Widal test will help to inform decision makers to prepare diagnostic algorithms on the use of Widal tests, other rapid diagnostic tests and culture. Therefore, we set out to do systematic review and meta-analysis of the accuracy of Widal test in Ethiopia.

Methods of the Review

We conducted the study in accordance with the guideline of the PRISMA group (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (17). We used the PRISMA check list (18) to safeguard the inclusion of all pertinent information.

Search strategy. The review focused on resources that described and explicate issues that are related to Widal test and its performance as compared to culture. Databases that were searched for resources included MEDLINE (Pub Med) and Google scholar, and reference lists of relevant papers. The search terms included "Widal" ,"Widal tests" , "typhoid"," typhoid fever", "Ethiopia" in all fields of the databases to establish previous literature on Widal tests for diagnosing typhoid fever. All relevant articles with no restriction on the time of publication were included in this study. The search terms used included but not limited to 'Widal' AND/OR 'Typhoid' AND 'Ethiopia', 'Widal tests' AND/OR 'typhoid fever' AND 'Ethiopia', and 'Widal tests' AND/OR 'typhoid' AND 'Ethiopia'.

Using the above mentioned search terms we searched for eligible articles. References for the applicable citations and reviews were manually searched for applicable citations and professionals in the field were consulted to enrich the search. The titles and abstracts of all recovered studies were independently evaluated by two authors (OA and SG). The same reviewers judged the full texts of the retained studies. At each step disagreements were resolved by discussion with the presence of a third reviewer (KS). The last search was conducted on September 11, 2020.

Inclusion and exclusion criteria

Inclusion criteria; All human studies that have compared Widal agglutination test with culture in Ethiopia.

Exclusion criteria; Studies with sample size less 50, studies that did not publish full articles or the full article not available, and studies done on asymptomatic participants were excluded.

Risk of bias in individual studies

Two reviewers (OA, SG) independently evaluated the risk of bias in the studies using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool. Disagreements were resolved by a third reviewer (KS). The results of the risk of bias assessment were described as part of the narrative synthesis.

Data Extraction

Each study was subjected to the following search: study author, year of publication, place of study, index test (Widal), study design, sample size, and the characteristics of the sample population. Comprehensive data about the Widal test was extracted from the studies that were included: the test brand, country and name of the manufacturer, the procedure of the Widal test. Similarly, we took the true positive (TP), false positive (FP), false negative (FN), and true negative (TN) of the Widal agglutination as compared to culture. Other important variables were also extracted.

Data synthesis process

We have used the two by two table variables; true positives, false negatives, false negatives and true negatives for producing pooled sensitivity, specificity, negative predictive value and positive predictive value. We extracted these important variables in Microsoft excel. The quantitative synthesis was performed using STATA version 14. For estimating the accuracy we used bivariate model to calculate sensitivity & specificity, positive & negative predictive vales along with 95 percent confidence intervals (CIs). These measures were pooled using the random effects model. Sensitivity (true positive rate) was defined as the probability that a test result will be positive when the disease exists and calculated as = TP/ (TP+FN). Similarly, specificity (true negative rate) was defined as the probability that a test result will be negative when the disease is not present and calculated as = TN/ (TN+FP). Heterogeneity (differences in reported estimates among studies) was evaluated by a Q test statistic (Chi square value with p values) and I^2values.

Quality Assessment

The studies quality assessment was conducted using Quality Assessment of Diagnostic Accuracy Studies) tool (QUADAS-2)(19). The QUADAS-2 tool was completed by following stepwise guidelines to judge risk of bias (four domains) and concerns about applicability (three domains) for each study.

Results

Search results

The electronic searches yielded 42 articles. Thirty-four of these papers were excluded from this review and meta-analysis (eleven of the studies were excluded because of duplication, 11 were excluded due to non-relevance after reviewing their titles, 9 articles excluded because they were done on asymptomatic participants, two of the articles were not accessed (these articles required fee and the authors could not afford), and one article was done on non-human participants). The details of the article inclusion and exclusion are shown in figure 1 below.

We included 8 cross-sectional studies in this systematic review and meta-analysis (20-27). All eight of the included studies were used in the qualitative synthesis while 6 of them were utilized for the quantitative synthesis (20-25). The studies used for quantitative synthesis had a total sample size of 1727 participants. The studies were conducted in six regions of the country, Addis Ababa (21,22), Oromia (25,26), South nations and nationalities (24), Tigray (20), Amhara (23), and Somali(27). No study was retrieved regarding the Widal study from the remaining regions of the country (Harar, Benishangl-Gumuz, Gambella, Afar, and Dire Dawa)(**Table 1).**

Table 1. Characteristics the included studies

Author, year	Region of the country	Sample/ participants	Widal test* positivity n (%)	Culture positivity n (%)	Remark
A.G. Wasihun et al, 2015	Tigray	502	343 (68.4)	8 (1.6)	
Andualem et al, 2014	Addis Ababa	270	88 (32.6)	11 (4.1)	
Legesse Garedew et al, 2018	Addis Ababa	288	148 (51.4)	1 (0.68)	66% of the Widal reactive patients were prescribed antibiotics
Meseret Birhanie et al, 2014	Amhara	200	38 (19)	1 (0.5)	
Deksissa and Gebremedhin , 2019	Oromia	372	209 (56.2)	10 (2.7)	
Ameya et al, 2017	SNNPR^^	95	65 (68.4)	19 (20)	
Dawit et al, 2019	Somali	203	N/A^	22 (11)	
Habte et al, 2018	Oromia	421	N/A^	21 (5)	

^ N/A- not available, ^^ SNNPR- Southern Nations, Nationalities and Peoples Region

*The numbers presented here regarding Widal test are for the Sliding agglutination technique.

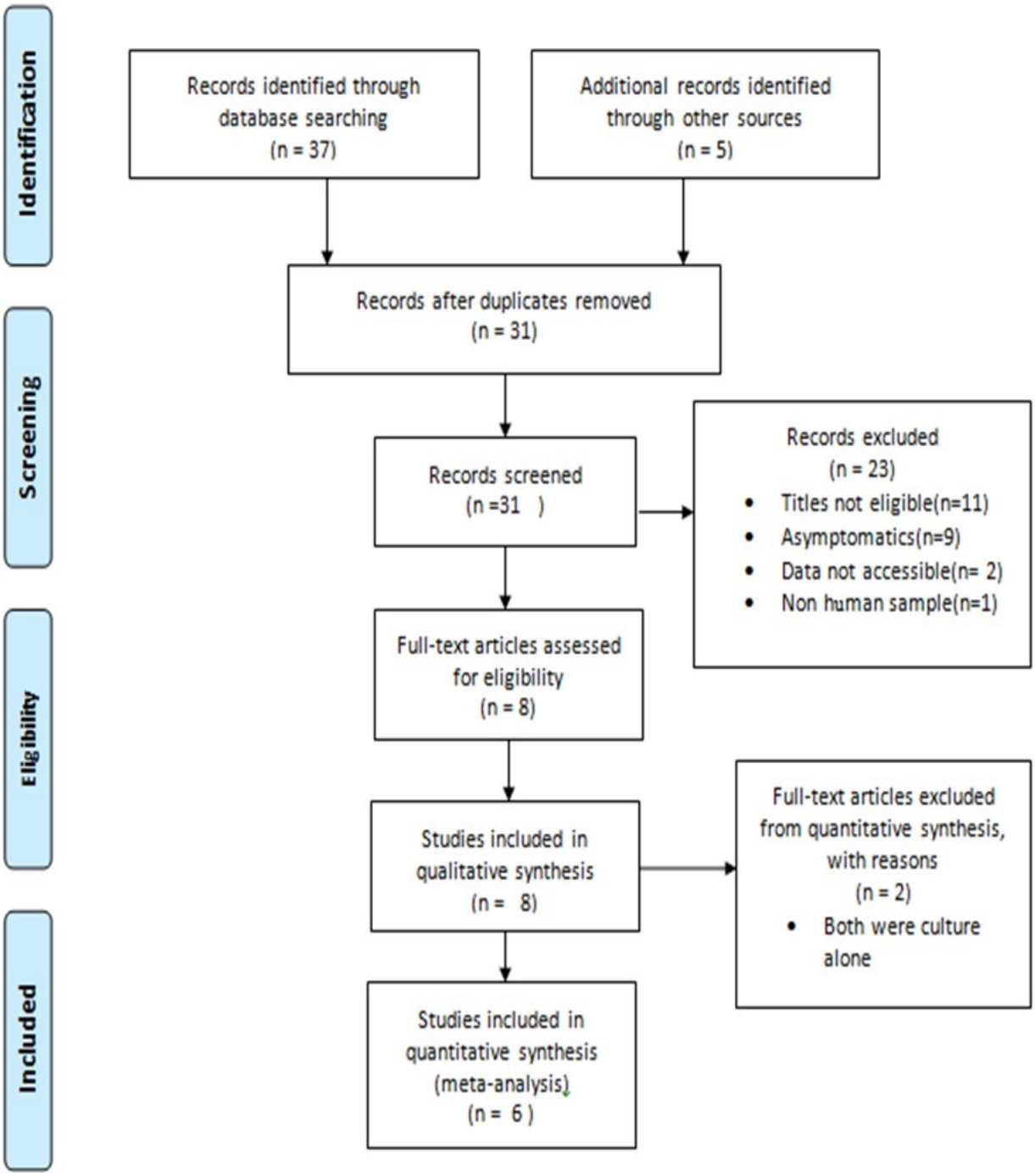

Figure 1 A flow diagram of the selection of eligible studies

Table 2 Summary of the quality assessment of the included studies

Study	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
A.G. Wasihun et al	Φ	Φ	Φ	Φ	Φ	Φ	Φ
Andualem et al	♣	♣	*	♣	♣	♣	♣
Legesse Garedew et al	Φ	Φ	Φ	Φ	Φ	Φ	Φ
Meseret Birhanie et al	Φ	Φ	*	Φ	Φ	Φ	*
Deksissa and Gebremedhin	*	♣	♣	♣	*	♣	♣
Ameya et al	*	♣	♣	*	*	♣	♣

♣ *Low risk;* Φ*High risk;* * *Unclear risk*

Qualitative synthesis

All the studies included in this review have analyzed febrile individuals with a clinical suspicion of typhoid fever. Among the 8 studies contained within in this review, 6 of them have compared the index Widal agglutination test to a reference blood (20-23) or stool (24,25) culture. On the other hand, two of the studies (26,27) just did blood culture alone. The sensitivity, specificity, negative predictive value, and positive predictive vales of the Widal test ranged from 71.2-100%, 0.68-68.4%, 90-100%, and 2.6-48.8%, respectively. The culture positivity rate ranged from 0.35%- 20%.

Quantitative synthesis

The main outcomes of concern were the sensitivity, specificity, negative predictive and positive values predictive values of Widal agglutination as compared to the reference test (culture in this case).

The pooled sensitivity of Widal agglutination test in the diagnosis 80.8% (95% CI, 68.6-92.9%). Similarly, the pooled specificity of Widal test was determined to be 53.0% (95% CI, 52.8-55.2%). The pooled negative and positive predictive values of the Widal test were 98.5% (95% CI, 97.2-99.7%) and 2.1% (95% CI, 1.1-3.0%) respectively. The pooled Widal and culture positivity in our study was 35.0% (95% CI, 33.2-36.6%) and 1.2% (95% CI, 0.8-1.7%). The forest plots of the pooled negative and positive predictive values are depicted below (Figure 2 and 3).

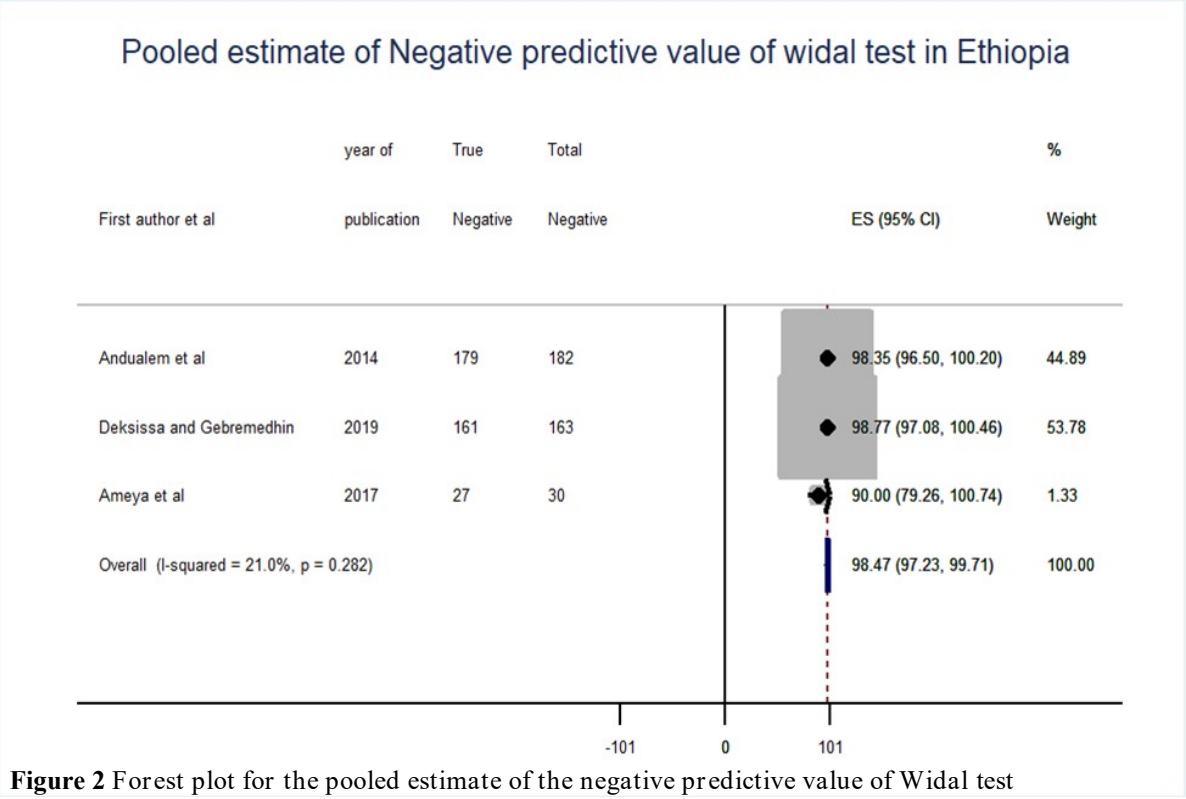

Figure 2 Forest plot for the pooled estimate of the negative predictive value of Widal test

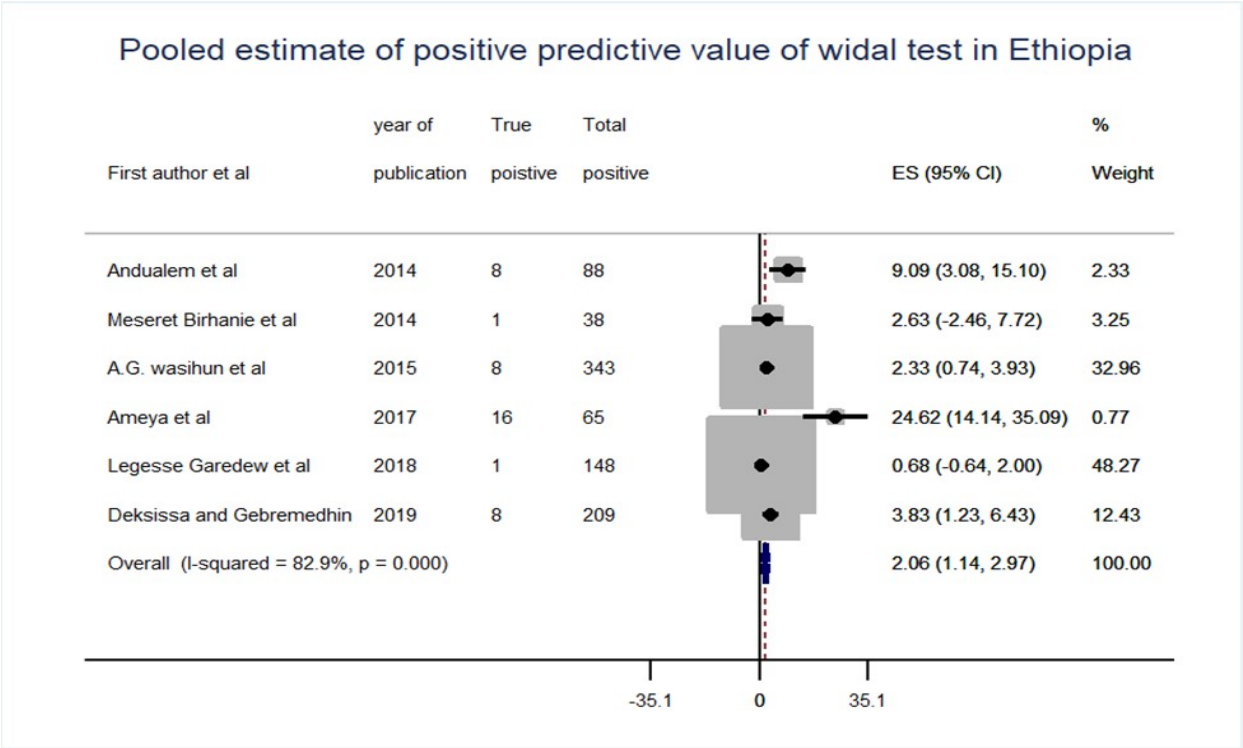

Figure 3 Forest plot for the pooled estimate of positive predictive value of the Widal test

Discussion

In our review, we have pooled the sensitivity, specificity, negative and positive predictive value of sliding Widal agglutination test using culture as a reference test. The pooled estimate from this review has revealed that the sliding Widal agglutination test has good sensitivity and excellent negative predictive value. However, it has a low specificity (53.0%) and positive predictive value (2.1%).

The pooled sensitivity of Sliding Widal agglutination test in this study was 80.8% (95%CI, 68.6-92.9%) and the negative predictive value was 98.5 %(95% CI, 97.2-99.7%). The sensitivity was comparable to a review conducted by Mengist and Tilahun (SN=73.5%) (28) and R. Bundalian et al (SN=32-95%) (29) while the negative predictive value of our study (98.6%) was much higher as compared to that reported by Mengist and Tilahun (NPV=60%) (28) and Begum et al (NPV=62.9%) (30). The NPV of our study was comparable to that reported by Taiwo et al (98.3%) (31) and Ley et al(100%) (13).

The pooled specificity and positive predictive value of Widal test in this study were 53.0% and 2.1% respectively. This positive predictive value is extremely low as compared to different other studies (15,30,32-34). One of the reasons may be the lower cuts –off for the O (1:80) and H(1:160) antibodies used in our study in contrary to that by Willke et al (1:200) (15). The other reason might be the lower culture positivity rate of our study.

The serologic (sliding agglutination Widal) diagnosis of typhoid fever occurred in up to a third of the study participants (35.0%) in this study. On the other hand, the culture confirmed typhoid fever was observed in 1.2% of the participants in our study. There is similar report of serologic diagnosis rate in Nigeria (35) and a higher rate (81%) in Tanzania (36). The culture proven diagnosis rate of typhoid fever was comparable to that of Congo (2.4%) (37) but lower as compared to that in Nigeria (22.1%) and Tanzania (11%) (35,36).

As mentioned earlier this study has shown a very low PPV (2.1%). Positive predictive value is the probability that subjects with a positive screening test truly have the disease. Thus, sliding Widal agglutination test is poorly reliable in identifying those truly diseased by typhoid fever. Nevertheless, this test has high NPV (98.5%) that means a subject with a negative Sliding Widal agglutination test is highly likely not to have Typhoid fever.

The strengths of our study include the relatively larger total sample size as compared to previous studies done in Ethiopia and the assessment of an important research question. Among the limitations of this study are our use of a reference test (blood and stool) that has lower sensitivity and the studies retrieved covered only some portion of Ethiopia.

Conclusion and recommendations

Our study is the first systematic review and meta-analysis to evaluate the accuracy of Widal test in Ethiopia. Widal agglutination test has average specificity, very good negative predictive value and very poor positive predictive value for the diagnosis of typhoid fever. Relying on Widal for the diagnosis of typhoid fever may lead to over-diagnosis of typhoid fever and related complications including inappropriate use of antibiotics. There is an urgent need of rapid and reliable tests for the diagnosis of typhoid fever particularly in settings like Ethiopia where doing timely culture is not feasible.

Declarations

Ethics consideration

This study is a systematic review and meta-analysis and obtaining an ethical approval was not necessary.

Availability of data and materials

All data generated or analyzed during this study are included in the manuscript. However, the raw data are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This study received no funding from any source.

Authors' contributions

OAM and SG carried out this study, drafted the manuscript and coordinated the study. KS participated in the design of the study and performed the statistical analysis and edited critically the manuscript. OAM and SG suggested the title of the research. All the authors read and approved the final manuscript for submission to EMJ.

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Systematic Review

Comparative efficacy and safety of anti-infective drugs for patients with mild to severe COVID-19: A systematic review and network meta-analysis of randomized controlled trials

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Abstract

Background: *Different anti-infective drugs have been proposed for the treatment of patients with COVID-19. We carried out a network meta-analysis to assess their relative efficacy and safety.*

Methods*: We searched relevant databases for all randomized controlled trials that reported the efficacy and or safety of any anti-infective drugs published up to April 30, 2022 for different outcomes. We did both pairwise and network meta-analysis with 95% confidence intervals using a fixed-effect model. We assessed studies for quality of evidence using an extension of the standard Grading of Recommendations, Assessment, Development and Evaluation approach considering P<0.05 to be statistically significant.*

Results*: We included 68 RCTs for 27,680 participants on 22 anti-infective drugs. For clinical recovery at 14 days Ivermectin (OR= 3.00, 95%CI: [1.82; 4.96]; p < 0.0001; moderate certainty evidence), Baricitinib plus Remdesivir (OR= 2.20, 95%CI: [1.35; 3.53]; p = 0.005; low certainty evidence), and Favipiravir (OR= 2.16, 95%CI: [1.27; 3.68]; p = 0.004; moderate certainty evidence) were statistically effective than standard of care. There was no statistically significant difference between treatments for the viral clearance at 14 days outcome and standard of care. In terms of death outcome, only combined therapy of Baricitinib and Remdesivir showed statistically significant risks of ratio (RR= 0.47, 95%CI: [0.23; 0.99]; p = 0.03). Arbidol (RR= 0.46, 95% CI: [0.23; 0.95]; p = 0.04) was statistically safe drug than standard of care.*

Conclusion*: This Network Meta-analysis suggests that Baricitinib plus Remdesivir is more effective than the other anti-infective drugs in treating patients with COVID-19 in terms of clinical recovery at 14 days, mortality and adverse events outcomes.*

Keywords*: COVID-19, SARS-CoV-2, treatment, network meta-analysis, systematic review, randomized controlled trials.*

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Introduction

COVID-19 is a respiratory illness caused by a novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS CoV-2)(1) and it was labeled a pandemic of international concern by the World Health Organization on March 11, 2020(2). Its major mode of transmission is from human to human through respiratory droplets(3-5) and its clinical presentations can be from subclinical with mild to severe infections(6-9). As of 16 July 2021, there were 189,749,287 confirmed cases and 4,083,256 (2.15%) deaths globally(10). Currently, many anti-infective drugs are being repurposed for patients with COVID-19 including remdesivir (used to treat Ebola virus disease and Marburg virus infections (11), lopinavir and ritonavir (used to treat HIV/ AIDS (12), chloroquine phosphate or hydroxychloroquine (used to treat malaria (13), tocilizumab (used to treat rheumatoid arthritis (14), corticosteroids, stem cells, among others.

Anti-infective drugs act on SARS-CoV-2 by inhibiting its replication(15). Their effect is higher in the early stages of the disease because of active replication of the virus in the early courses of infection(16). Remdesivir, a broad-spectrum antiviral medication of nucleotide prodrug adenosine analog, inhibits viral replication by binding to the viral RNA-dependent RNA polymerase and terminating RNA transcription (17). Chloroquine and hydroxychloroquine inhibiting the fusion of SARS-CoV-2 and the host cell membranes by increasing the endosomal pH.(18) Both have immunomodulatory effects which are potential mechanisms of action for the treatment.(19) Lopinavir/ritonavir, a protease inhibitor that may inhibit the action of 3CLpro, leads to disruption of SARS-CoV-2 replication and appears to be highly conserved (20). Ivermectin, a well-known anti-helminthic agent from the late-1970s, eliminate SARS-CoV-2 by inhibiting importin α/β1 mediated transport of viral proteins in and out of the nucleus(21).

Several randomized clinical trials are underway and currently, there are about 2868 trials registered worldwide for the treatment of COVID-19(22). Yet, the only US Food and Drug Administration (FDA)-approved anti-infective drug is Remdesivir. It has been approved for the treatment of hospitalized patients (aged ≥12 years and weighing ≥40 kg)(23). Its administration was associated with clinical improvements(24) and significantly lower serious adverse drug reactions (ADRs) when compared to control groups(25). Mortality was decreased in hospitalized COVID-19 patients treated with only hydroxychloroquine combined with azithromycin(26). Remdesivir, hydroxychloroquine, and lopinavir regimens had little or no effect on hospitalized patients with COVID-19 in decreasing overall mortality(27). Recent studies showed that Ivermectin had beneficial effects in COVID-19 by reduction of mortality, higher negativity rate, and higher symptoms alleviations rate(28). One network meta-analysis done by mixing observational and RCT studies revealed that anti-inflammatory agents and remdesivir were associated with improved outcomes of hospitalized COVID-19 patients(29).

There have been efforts underway to identify effective drugs for the treatment of COVID-19 there were a couple of systematic reviews combined with meta-analysis and/or network meta-analysis carried out to systematically synthesis the efficacy and safety of such drugs. However, currently available reviews did not recommend the best drugs in terms of clinical recovery, viral clearance, and tolerability; besides, some are already outdated as new findings are emerging. There were two such potential reviews. One was published in April 2021 that reviewed 33 articles published up to February 2021(30), and the second was a living review published in May 2021 that included articles published up to December 2020(31).

Therefore, our systematic review and network meta-analysis aimed to compare the efficacy and safety of anti-infective drugs for patients with mild to severe COVID-19.

Methods

The systematic review and network meta-analysis was conducted and reported following the Preferred Reporting Items for Systematic Reviews and Meta-analyses Extension for network meta-analysis (PRISMA-NMA)(32) (Supplementary material 2). The protocol was prospectively registered with PROSPERO2021 (ID: CRD42021230919)(33).

Eligibility

The PICOS (participants, interventions, comparison, outcomes, and study designs) description model was used to set eligibility criteria of the study

- Participants: patients with mild, moderate and severe COVID 19, confirmed by laboratory RT-PCR or imaging (chest CT scan or chest x-ray).
- Intervention: any anti-infective drug tested to evaluate its efficacy or safety in patients diagnosed with COVID-19. Different dosages and durations of anti-infective drugs were taken as individual treatments but separately evaluated for subgroup analysis.
- Comparator: standard of care or placebo.
- Outcomes: Primary outcomes were time to clinical recovery and treatment-emergent serious adverse events. Secondary outcomes were rate of viral clearance, all-cause mortality, and adverse events.
- Study design: RCTs, published in the English language.

Search strategy and study selection

We searched PubMed, Cochrane Central Register of Controlled Trials, COVID-evidence, Cochrane COVID-19 Study Register, Embase, and clinical trial registration sites in the US (ClinicalTrials.gov), Europe (clinicaltrialsregister.eu), and China (chictr.org.cn) up to 30 April 2022 for all RCTs that evaluated the efficacy or safety of any anti-infective drugs. For the PubMed database, we used the MeSH terms “Antiviral Agents” OR “specific drugs” AND “COVID-19” OR “SARS-COV-2” limited to human studies and published in English languages**.** Paper was included if it is RCT investigating anti-infective drug treatment and clinical outcomes in confirmed COVID-19 disease with at least one of the outcomes. Additional potential papers were considered from reference lists of included articles and other relevant

systematic reviews. The title/abstract was initially as well as full text screened by two independent reviewers and disagreements were resolved by third authors.

Table 1: Summary characteristics of studies included in the systematic review and network meta-analysis

SN	Authors/ year	Setting/ Country; registration number	Study design; sample size; arms	Mean age years; sex ratio (M to F)	Intervention (name, dose, frequency, route etc.)	Comparator (name, dose, frequency, route etc.)	Outcomes (primary; secondary)
1	Chen L,2020	Single center/ China; ChiCTR2000030054	RCT; 67; 3 (2:2:1)	45.22/45.67/51.33; 39/44/58	1.Hydroxychloroquine 200mg orally BID for 10 days 2. Chloroquine 1000mg orally QD for the first day, then 500 mg QD for additional 9 days	Standard of care	time to clinical recovery (TTCR); time to SARS-CoV-2 RNA negativity, 2. length of hospital stay 3. Changes on chest CT scan; 4. duration (days) of supplemental oxygenation; 5. frequency of adverse events; 6. clinical status; 7. all-cause mortality;
2	Abd-Elsalam S,2020	Multicenter/Egypt; NCT04353336	RCT; 194; 2 (1:1)	40.35/41.09; 57.7/59.8	HCQ 400 mg BID in day 1 followed by 200 mg BID for 15 days	Standard of care	1.recovery within 28 days 2. need for mechanical ventilation, 3. death;
3	Abd-Elsalam S2,2020	multicenter/Egypt; NCT04447534	RCT; 191; 2 (1:1)	43.48/43.64; 54.2/67.4	Hydroxychloroquine 400 mg BID on day 1, then 200 mg BID for 5 days PLUS zinc sulfate 220 mg BID	Hydroxychloroquine 400 mg BID on day 1, then 200 mg BID for 5 days	1.recovery within 28 days, 2.the need for mechanical ventilation, and 3. death
4	Babalola OE,2020	Nigerian; ISRCT-N40302986	RCT; 62; 3 (1:1:1)	48.3/39.7/44.8; 71.4/66.7/70	1.Ivermectin 6mg twice a week. 2. Ivermectin 12mg twice a week for 2 weeks	lopinavir / ritonavir daily for 2 weeks	time to SARS-CoV-2 negativity;
5	Beigel J,2020	Multicenter/ multi-county; NCT04280705	RCT; 1062; 2(1:1)	58.6/59.2; 65.1/63.7	Remdesivir 200 mg loading dose on day 1, followed by 100 mg daily for up to 9 days	Placebo	Time to recovery; clinical status at day 15, time to discharge, days of hospitalization, mortality at 14 and 28 days
6	Cao B,2020	China; ChiCTR2000029308	RCT; 199; 2 (1:1)	58/58*; 61.6/59	lopinavir–ritonavir 400 mg-100 mg orally BID for 14 days	Standard of care	time to clinical improvement; Mortality at 28 days, adverse events, the duration of mechanical ventilation, the duration of hospitalization

7	**Cavalcanti A,2020**	**Multicenter/ Brazil; NCT04322123**	**RCT; 665; 3 (1:1:1)**	**49.6/51.3/49.9; 56.7/64.3/54.2**	**1.hydroxychloroquine 400mg BID plus azithromycin 500 mg daily for 7 days. 2.hydroxychloroquine 400 mg BID for 7 days**	**Standard of care**	**Clinical status at 15 days; clinical status at 7 days, duration of hospital stays, hospital death**
8	Doi Y,2020	Japan; jRCTs041190120	RCT; 88; 2 (1:1)	48.0/51.0*; 52.3/70.5	Favipiravir 1,800mg orally BID at least 4 h apart on the first day, followed by 800mg BID for a total of up to 19 doses over 10 days	Favipiravir 1,800mg orally BID at least 4 h apart on the six day, followed by 800mg orally BID for a total of up to 19 doses over 10 days	Time to SARS-CoV-2 clearance; SARS-CoV-2 clearance by day 10, death
9	Furtado R,2020	Brazil; NCT04321278	RCT; 447; 2 (1:1)	59·4 /60·2*; 65/67	Azithromycin 500 mg orally, nasogastric, or intravenous administration once daily for 10 days	Standard of care	clinical status at day 15; mortality at 29 days, length of hospital stays
10	Goldman J,2020	Multi-county; NCT04292899	RCT; 397; 2 (1:1)	61/62*; 60/68	Remdesivir 200 mg on day 1, followed by 100 mg of Remdesivir once daily for the subsequent 4 days.	Remdesivir 200 mg on day 1, followed by 100 mg of Remdesivir once daily for the subsequent 9 days	clinical status on day 14; adverse events, time to clinical improvement, time to recovery, time to modified recovery, death
11	Horby P and Landray M,2020	Multicenter/UK; ISRCTN50189673, NCT04381936	RCT; 5040; 2(1:2)	66/66.4; 60/61	lopinavir–ritonavir 400 mg-100 mg orally for 10 days	Standard of care	28-day all-cause mortality; time to discharge
12	Horby P,2020	Multicenter/UK; SRCTN50189673; NCT04381936	RCT; 4716; 2(1:2)	65.2/65.4; 61.5/62.6	hydroxychloroquine sulfate 800 mg at baseline and at 6 hours, followed by 400 mg starting at 12 hours after the initial dose and then every 12 hours for the next 9 days	Standard of care	28-day mortality; time until discharge, initiation of invasive mechanical ventilation
13	Hung I,2020	multicenter/Hong Kong; NCT04276688	RCT; 127; 2 (2:1)	51·0/52·0*; 52/56	lopinavir 400 mg/ ritonavir 100 mg every 12 h PLUS ribavirin 400 mg every 12 h PLUS three doses of 8 million international units of interferon beta-1b on alternate days for 14 days	lopinavir 400 mg/ ritonavir 100 mg every 12 h for 14days	time to a nasopharyngeal swab negative; time to resolution of symptoms, length of hospital stays; and 30-day mortality

14	Ivashchenko A,2020	Multicenter/ Russia; NCT04434248	RCT; 60; 3 (1:1:1)	Comparable	1.AVIFAVIR 1600 mg BID on Day 1, followed by 600 mg BID on Days 2–14 (1600/600 mg). 2. AVIFAVIR 1800 mg BID on Day 1, followed by 800 mg BID on Days 2–14 (1800/800 mg)	Standard of care	Elimination of SARS-CoV-2 by Day 10; rate of viral clearance by Day 5, time to normalization of clinical symptoms, adverse events
15	Kamran M,2020	Single center / Pakistan; NCT04491994	RCT; 500; 2 (2:1)		HCQ 400 orally BID for day one followed by 200 mg BID for next 5 days	Standard of care	disease progression within 5 days; viral clearance
16	Kasgari H,2020	single center/ Iran; IRCT20200328046886N1	RCT; 48; 2 (1:1)	45/60*; 46/29	400mg sofosbuvir, 60mg daclatasvir and 1200mg ribavirin	Standard of care	length of hospital stays; frequency of ICU admission, invasive mechanical ventilation, duration of ICU admission, mechanical ventilation, frequency and
17	Khamisa F,2020	single/ Oman; NCT04385095	RCT; 89; 2 (1:1)	56/54; 53/64	Favipiravir 1600 mg on day 1 followed by 600 mg BID for a maximum of 10 days, and interferon beta-1b at a dose of 8 million IU (0.25 mg) BID for 5 days	HCQ 400 mg BID on day 1, then 200mg BID for 7 days	time to clinical recovery; intensive care unit (ICU) admission rate, mortality within 14 days
18	Nojomi M,2020	single/ Iran; IRCT20180725040596N2	RCT; 100; 2 (1:1)	56.6/56.2; 66/54	hydroxychloroquine (400mg on first day) followed by 400 mg KALETRA (Lopinavir/ ritonavir)	Hydroxychloroquine (400 mg BD on first day) followed by ARB (200mg TDS) 7 to 14 days	hospitalization duration and clinical improvement 7 days; death during the 30 days of treatment, duration of hospitalization, need for invasive mechanical ventilation
19	Ruzhentsova T,2020	multicenter/ Russia; NCT04501783	RCT; 168; 2 (2:1)	41·7/42.0; 43.8/53·6	Favipiravir 1800 mg BID on day 1, followed by 800 mg BID for up to 9 days	Standard of care	time to clinical improvement and the time to viral clearance; rate of clinical improvement at Day 7 and the rate of viral clearance at Day 5
20	Sadeghi A,2020	multicenter/Iran; IRCT20200128046294N2	RCT; 66; 2 (1:1)	58/62*; 61/42	400mg sofosbuvir and 60mg daclatasvir daily for 14days	Standard of care	clinical recovery within 14days; all-cause mortality, requirement for mechanical ventilation, duration of hospital stay and time to hospital discharge
21	Sekhavati E,2020	Single center/ Iran	RCT; 111; 2 (1:1)	54.38/59.89; 50/41	Oral AZM 500 mg daily, oral LPV/r 40 0/100 mg twice daily and oral HCQ 400 mg daily for 5 days	oral LPV/r 400/ 100 mg twice daily and oral HCQ 400 mg daily for 5 days	mortality, duration of hospitalization and need for intensive care unit (ICU) admission

23	Spinner C,2020	multicenter/United States, Europe, and Asia; NCT04292730	RCT;584;3 (1:1:1)	56/58/57*; 61/60/63	Remdesivir 200mg intravenously on day 1, followed by 100mg once daily for the subsequent days, infused over 30 to 60 minutes (5 and 10 days)	Standard of care	clinical status on day 11; adverse events, time to recovery, time to clinical improvement, all-cause mortality
24	Tang W,2020	multicenter/ China; ChiCTR2000029868	RCT; 150; 2 (1:1)	48.0/44.1; 42/40	Hydroxychloroquine loading dose of 1200 mg daily for three days followed by a maintenance dose of 800 mg daily (total treatment duration: two or three weeks	Standard of care	Negative conversion by 28 days; all cause death
25	Udwadia Z,2020	multicenter/ India; CTRI/2020/05/025114	RCT; 147; 2 (1:1)	43.6/43.0; 51/57	oral favipiravir (1800 mg BID loading dose on day 1; 800 mg BID maintenance dose thereafter) for 14 days	Standard of care	time to the cessation of oral shedding of the SARS-CoV-2 virus, hospital discharge; time to clinical cure, ventilation (noninvasive or mechanical), time to hospital discharge
26	Wang Y,2020	multicenter/China; NCT04257656	RCT; 237; 2 (2:1)	66·0/64.0*; 56/65	intravenous Remdesivir (200 mg on day 1 followed by 100 mg on days 2–10 in single daily infusions)	Placebo	time to clinical improvement; all-cause mortality at day 28, frequency of invasive mechanical ventilation, duration of hospital admission
27	Yueping L,2020	single-center/ Guangzhou, China; NCT04252885	RCT; 86; 3 (2:2:1)	50.7/50.5/44.3*; 50/45.7/41.2	lopinavir (200mg)/ ritonavir (50mg) orally BID, 500 mg, each time for 7-14 days), arbidol (100mg) (orally TID, 200mg daily for7-14 days)	Standard of care	rate of positive-to-negative to day 21; rate of positive-to-negative to day 14
28	Ahmeda S,2021	Single center/ Bangladesh	RCT; 72; 3 (1:1:1)	42; 46	1.oral ivermectin12 mg once daily for 5 days. 2. oral ivermectin plus doxycycline (12 mg ivermectin single dose and 200 mg doxycycline on day 1, followed by 100 mg every 12 h	Placebo	time required for virological clearance, remission of fever (37.5 C) and cough within 7 days; duration of hospitalization, all-cause mortality, Drug safety
29	Dabbous H,2020	multicenter/ Egypt; NCT04351295	RCT; 96; 2 (1:1)	36.15/34.86; 52.1/45.5	chloroquine 600 mg tablets twice daily for 10 days;	1600 mg of favipiravir twice a day on the first day and 600 mg twice a day from the 2 to 10 day	Death, hospitalization, need mechanical ventilation
30	Ader F, 2021	multicenter/ France; unpublished/ NCT04315948	RCT; 583; 5 (1:1:1:1:1)	65/63/62*; 71.7/73.1/70.9	1.lopinavir/ritonavir (400 mg lopinavir and 100 mg ritonavir every 12h for 14 days). 2.hydroxychloroquine (400 mg twice on day 1 then 400 mg once daily for 9 days)	Standard of care	clinical status at day 15; SARS-CoV-2 quantification in respiratory specimens, safety analyses

31	Beltran G. J,2021	unpublished/ NCT04391127	RCT; 106; 3 (1:1:1)	48.9/56/53.8; 66.6/58.3/62.1	1.Hydroxychloroquine, 400 mg BID on the first day and subsequently, 200 mg BID for 4 days. 2.ivermectin, 12 mg or 18 mg	Placebo	duration of hospitalization, the total duration of hospitalization, and the safety
32	Brown S,2021	NCT04329832	RCT; 85; 2 (1:1)	51/58; 44/33	hydroxychloroquine 400mg BID on the first day, followed by 200 mg BID for the following 4 days (total dose,2.4 gm	Azithromycin loading dose of 500 mg on the first day, followed by 250 mg daily for the next 4 days (total dose, 1.5 gm)	Day 14 COVID ordinal outcomes scale; hospital-free, ventilator-free, and intensive care unit (ICU)–free days
33	Dabbous HM,2021	Egypt; NCT04349241	RCT; 100; 2 (1:1)	36.3/36.4; 50/50	favipiravir 3200mg at day1 followed by 600mg twice (day2-day10)	hydroxychloroquine 800mg at day1 followed by 200mg twice (day2- 10) and oral oseltamivir 75mg/12hour/day for 10 days	SARS-CoV-2 viral clearance on days 3, 7, and 14; clinical outcomes on days 3, 7 and 14
34	Dubée V,2020	multicenter/ France; unpublished/ NCT04325893	RCT; 250; 2 (1:1)	76/78*; 52/44.8	800mg hydroxychloroquine on Day 0 followed by 400mg per day for 8 days	Placebo	death or tracheal intubation within 14 days; mortality and clinical evolution at Day 14 and 28, viral shedding at Day 5 and 10
35	Elgazzar A,2020	multicenter/ Egypt; unpublished/ NCT04668469	RCT; 600; 2 (1:1)	57.45/56.7; 70/70.5	Ivermectin 0.4mg/kg body weight maximum 4 tablets (6mg /tablet) once daily dose	hydroxychloroquine (400 mg every 12 hours for one day followed by 200 mg every 12 hours for 5 days)	clinical, laboratory improvement; adverse events
36	Galan L ,2021	Brazil	RCT; 168; 3 (1:1:1)	54.8/51.9/53.2; 56.8/57/8/60.7	1.CQ diphosphate (450 mg, BID on day 0, and once daily from day 1 to day 4, total dose 2.7 g). 2.HCQ sulfate (400 mg twice on day 0, and once daily from day 1 to day 4, total dose 2.4 g)	ivermectin (14 mg once at day 0 + 1 placebo tablet at day 0, and once daily from day 1 to day 2, + 1 placebo tablet daily from day 3 to 4, total dose 42 mg)	need of supplemental O2, invasive ventilation, admission in ICU, death
37	Hernandez-Cardenas C, 2021	Mexico; Unpublished/ NCT04315896	RCT; 214; 2 (1:2)	50/49; 82/68	HCQ orally or by nasogastric tube, 200 mg BID for 10 days	Placebo	Mortality; days of mechanical ventilation, days of hospitalization and cumulative incidence of serious adverse events

38	Horby P and Land-ray M,2021	Multi-center/ UK; NCT04381936/ ISRCT-N501896	RCT; 7763; 2 (1:2)	65·4/65.2; 62/62	Azithromycin 500 mg daily by mouth or intravenously for 10 days or until dis-charge	Standard of care	28-day all-cause mortality
39	Huang Y-Q,2020	single-center/ China; ChiCTR2000029387	RCT; 101; 3 (1:1:1)	40.3/43.3/43.8; 55/53/28	1.RBV loading dose of 2g, followed by oral doses of 400–600mg TID depending on patients' body weight, for 14 days. 2. LPV/r orally at a dose of 400 mg/100 mg per dose BID for 14 days	RBV plus LPV/r	median interval to SARS-CoV-2 nu-cleic acid negativi-ty, the proportion of patients with SARS-CoV-2 nu-cleic acid negativity at day 14, the mor-tality at day 28, the proportion of pa-tients re-classified as severe cases, and adverse events
40	Kalil A,2021	Multi-county; NCT04401579	RCT; 1033; 2 (1:1)	55.8/55; 64.3/61.9	Remdesivir intravenously 200-mg loading dose on day 1, followed by a 100-mg maintenance dose ad-ministered daily on days 2 through 10	Baricitinib 4-mg daily dose (either orally [two 2-mg tablets] or through a nasogastric tube) for 14 day	time to recovery; clinical status at day 15
41	Lou Y,2020	China; ChiCTR2000029544	RCT;29; 3 (1:1:1)	53.5/58/52.5; 70/77/70	1. Baloxavir marboxil 80 mg once a day orally on Day 1 and Day 4; for pa-tients who are still positive in virological test, they can be given again on Day 7. 2. Favipiravir 1600 mg or 2200mg orally, followed by 600 mg each time, three times a day, and the dura-tion of administration was not more than 14 days	Standard of care	percentage of sub-jects with viral negative by Day 14 and the time from randomization to clinical improve-ment; adverse events, death
42	Medina E,2021	single center/ Colom-bia; NCT04405843	RCT;400; 2 (1:1)	37/37*; 39/44.9	Ivermectin 300 μg/kg per day for 5 days	Placebo	time to resolution of symptoms within a 21-day; adverse event

Data extraction

Data extraction was performed by two independent reviewers and disagreements were resolved by third authors. The data collection format was adapted from the Cochrane data extraction tool(34). Extracted information was included the first author's name and year of publication, setting, country, study design, follow-up duration, age (mean/median), the proportion of male participants, treatment characteristics (name, dose, route, frequency, duration), sample size, study funder, type of statistical analysis, proportion or number of participants with clinical improvement, proportion or number of participants with viral clearance, death, and adverse events

Data synthesis and analysis

We summarized the included articles with a descriptive table. We did direct pairwise meta-analyses using standard inverse-variance fixed-effect by meta command of RStudio Version 1.2.5019 for studies reported in head-to-head comparisons for all supposed primary outcomes. We computed the odds ratio (OR) and risks ratio (RR) and its 95%confidence interval (CI) for the dichotomous variables and mean difference (MD) for continuous outcomes. We tested between-study heterogeneity in each pairwise using I^2 statistics (35).

A network meta-analysis (NMA) was performed using the netmeta commands in the RStudio Version 1.2.5019 to combine all direct and indirect comparisons (36). The geometry network maps were drawn to give an overview of the relationships between each pair of treatments (37). We have checked the major assumptions: (1) similarity, (2) inconsistency (disagreement between the different sources of evidence), and (3) intransitivity (38, 39). The network forest to summarize an effect size as pooled OR and RR with a 95% confidence interval (CI) setting a p-value of less than 0.05. We used the league tables to display the relative efficacy and safety outcomes(40). Inconsistency was quantified using the global Q test and locally using the so-called node-splitting (SIDDE) (41, 42). The surface under the cumulative ranking area (SUCRA) and P-score were used to show the hierarchy of superiority among interventions(43).

Quality assessment

We used the version 2 risk of bias Cochrane assessment tool (RoB2) for evaluating each selected RCT (44) and for each outcome. The tool is structured into five domains: the randomization process; deviations from intended interventions; missing outcome data; measurement of the outcome and selection of the reported result. We assessed the quality of evidence using an extension of the standard GRADE-NMA (Grading of Recommendations, Assessment, Development and Evaluation extension to network meta-analysis) approach which is based on the contributions of the direct comparisons to the estimation in the network meta-analysis(45). We downgraded evidence based on the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) and categorized into four levels: high, moderate, low, and very low.

Sensitivity and subgroup analysis and publication bias

We performed a sensitivity analysis on the impact of high risk of bias studies. Subgroup analysis was done among different severity of disease (mild, moderate and severe COVID 19). The publication bias was assessed by a comparison-adjusted funnel plot to identify small study publication bias.

Results

Study characteristics

From the total 1,017 articles retrieved, 68 studies met the eligibility criteria, of which 16 excluded from the main analysis because of risk of bias. A total of 42 studies were included in the systematic review and network meta-analysis (Figure 1). The selected studies involved a total of 37,429 participants, with a mean age of 50.1years and 77% male. The details of study characteristics are given in (Table 1).

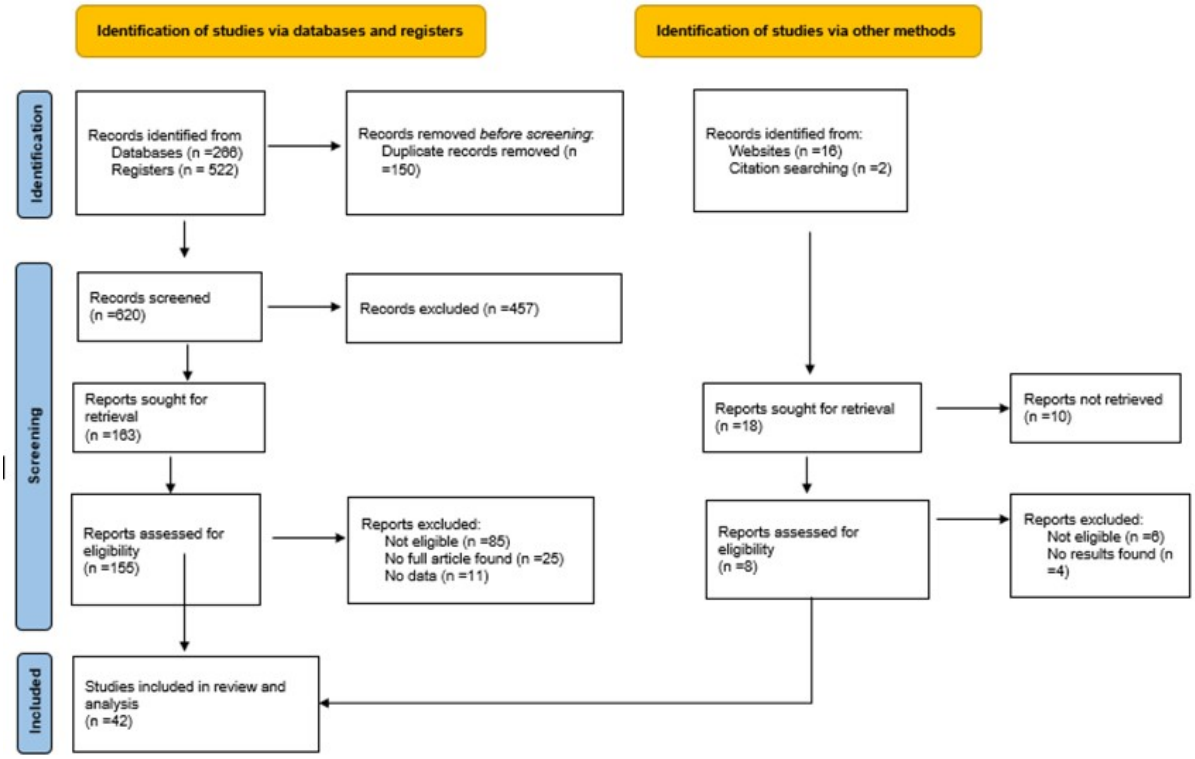

Figure 1: PRISMA flow chart of study selection for inclusion in the systematic review and network meta-analysis

The geometry network maps presentation of all treatment compaisons for each outcome is presented below **(**Figure 2**)**.

There were more than 22 different anti-infective drugs including Arbidol, Azithromycin, Baloxavir Marboxil, Baricitinib, Chloroquine, Daclatasvir, Favipiravir, Hydroxychloroquine, Ivermectin, Lopinavir–Ritonavir, Ribavirin, Sofosbuvir, Remdesivir, Placebo, Standard of care and their combinations. Standard of care treatment is selected as reference therapy for the analysis of NMA.

As per RoB2 risk of bias evaluation using the Excel tool ROB2_IRPG_beta_v7, 42 studies had some concern of risk of bias (62%). 18 studies were found to have a low risk of bias (27%), while the remaining eight studies had a high risk of bias (11%) (Figure 3).

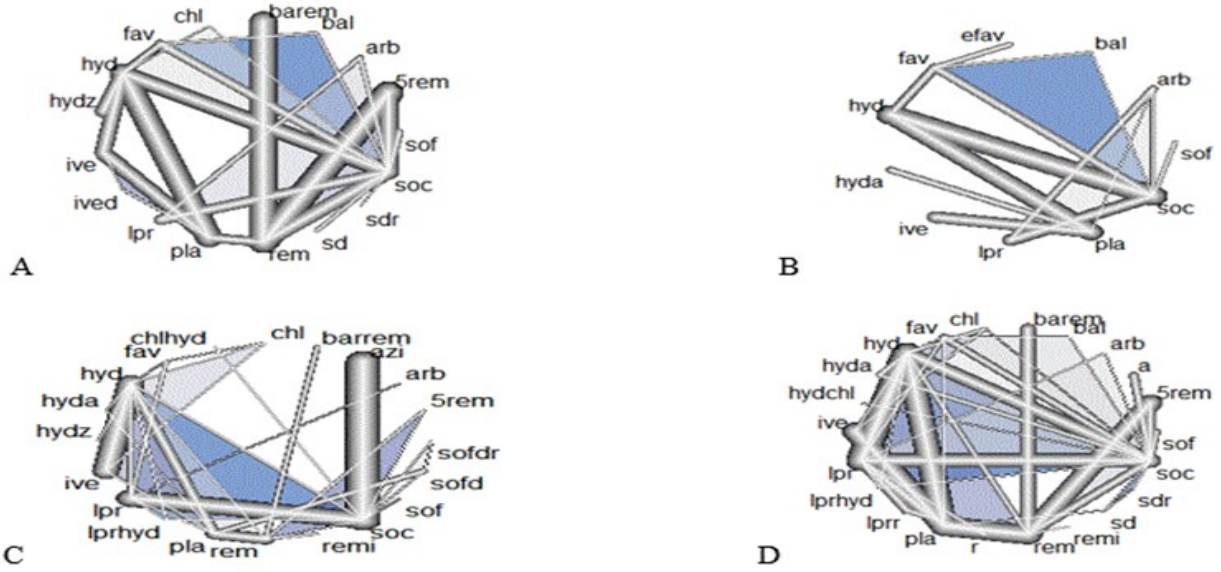

Figure 2: Network graph of eligible articles of anti-infective drugs for patients with mild to severe COVID-19. (A) Clinical recovery rate at 14 days; (B) Viral clearance rate at 14 days; (C) Mortality rate; (D) Adverse events. The thickness of the lines proportional to the number of studies evaluating each direct comparison and shaded triangle represents multi-arm trial.

5rem: remdesivir for 5 days; arb: arbidol; a: azithromycin; bal: baloxivir; barem: baricinib plus remdesivir; chl: chloroquine; fav: favipiravir; hyd: hydroxychloroquine; hydz: hydroxychloroquine plus azithromycin; ive: ivermectin; iverd: ivermectin plus doxycycline; lpr: lopinavir-ritonavir; pla: placebo; rem: remdesivir; sd: sofosbuvir plus daclatasvir; sdr; sofosbuvir/ daclatasvir/ ribavirin; soc: standard of care.

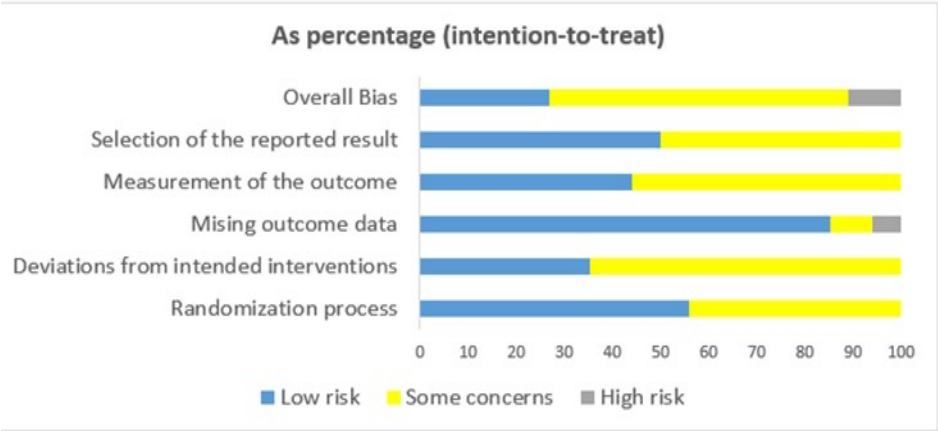

Figure 3: risks of bias diagram for all eligible studies assessed

Meta-analysis

Pairwise meta-analysis had shown higher statistically significance odds of clinical recovery rate at 14 days when Favipiravir (OR= 2.20; 95%CI: (1.22; 3.97); 4RCT) than standard of care but Hydroxychloroquine (OR= 1.28 95%CI: (0.83;1.97); 3RCTs) has low odds of clinical recovery rate at 14 days than standard of care **(**Supplementary material 3**, Table 1**). No drug had no statistically significant difference in direct comparison to the standard of care treatments for viral clearance rate at 14 days: Favipiravir (OR =1.94; 95%CI: (0.97; 3.86), 5RCTs), Hydroxychloroquine (OR= 0.86; 95%CI: (0.62; 1.20), 5RCTs) and Lopinavir/Ritonavir (OR= 1.02; 95%CI: (0.61; 1.73), 2RCTs) (Supplementary material 3**, Table 2**). Reduction in death rate due to COVID-19 was not better for Sofosbuvir plus Daclatasvir (OR= 0.36; 95%CI: (0.13; 1.04); 3RCTs) and Lopinavir/Ritonavir (OR= 1.08; 95%CI: (0.95; 1.23); 3RCTs) than standard of care (Supplementary material 3**, Table 3**). Favipiravir (OR= 1.35; 95%CI: (1.08; 1.70); 3RCTs), Lopinavir/ Ritonavir (OR= 1.15; 95%CI: (1.02; 1.29); 4RCTs), and Hydroxychloroquine (OR= 1.17; 95%CI: (1.03; 1.32); 5RCTs) were less tolerable than standard of care in treating COVID-19 (Supplementary material 3**, Table 4**).

Network meta-analysis
Clinical recovery rate at 14 days

The network meta-analysis with 35 papers investigating 17 treatment drugs in 6,228 participants identified more than five drugs statistically significant in increasing the clinical recovery at 14 days than standard of care (Supplementary material 3, Table 1). In general, network forest plot by frequentist approach has shown that Ivermectin (OR= 3.01; 95%CI: (1.82; 5.00); p-value < 0.0001, moderate certainty of evidence), Remdesivir for 5 days (OR= 1.86; 95%CI: (1.27; 2.74); p-value 0.0016, low certainty of evidence), combined Remdesivir and Baricinib for 10 days (OR= 2.20; 95%CI: 1.34; 3.53; p-value 0.002, low certainty of evidence), Favipiravir (OR= 2.20; 95%CI:(1.32; 3.60); p-value 0.002), Remdesivir for 10 days (OR= 1.50; 95%CI:(1.03; 2.20); p-value 0.03, low certainty of evidence) and Sofosbuvir plus Daclatasvir (OR 3.63; 95%CI 1.02; 12.93; p-value 0.05, low certainty of evidence) were more effective than standard of care in clinical recovery at 14 days (Figure 5). Hierarch by frequentist P-score ranked Ivermectin drug (83.3%) as the best top followed by Sofosbuvir plus Daclatasvir (80.7%), combined Remdesivir and Baricinib for 10 days (68.8%) and Favipiravir (67%) (Figure 4). The total global heterogeneity for this network overall was statistically significant low heterogeneity (I^2 = 53% (15.6%; 73.9%); p value = 0. 008). Then the node splitting method (Separate indirect from direct design evidence (SIDDE)) revealed that there was evidence of local inconsistency identified in several pair of closed loops of networks comparison in clinical recovery at 14 days outcome.

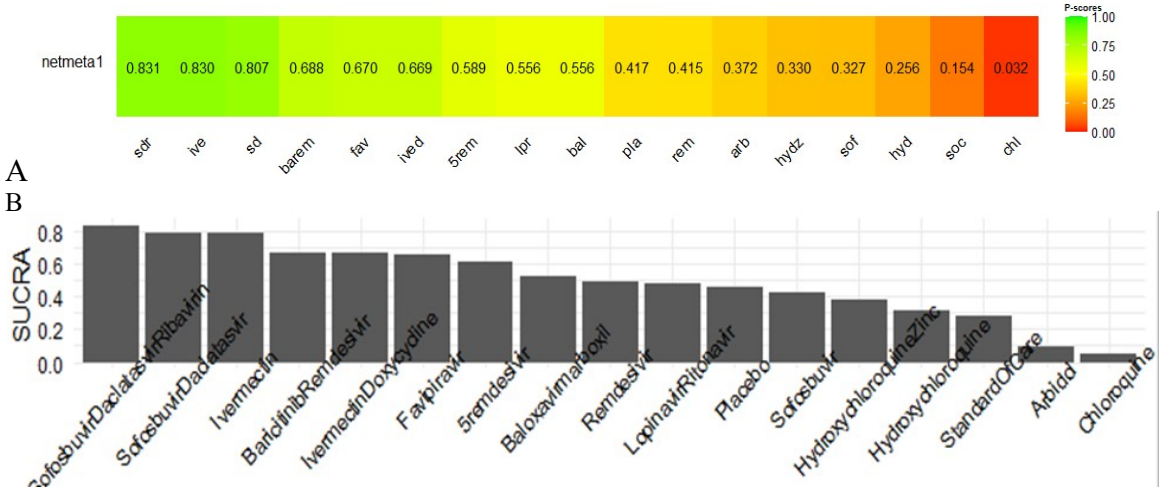

Figure 4: Hierarchy rank plot of network meta-analysis of Anti-infective drugs for clinical recovery at 14 days: P-score (A) and SUCRA (B)

5rem: remdesivir for 5 days; arb: arbidol; a: azithromycin; bal: baloxivir; barem: baricinib plus remdesivir; chl: chloroquine; fav: favipiravir; hyd: hydroxychloroquine; hydz: hydroxychloroquine plus azithromycin; ive: ivermectin; iverd: ivermectin plus doxycycline; lpr: lopinavir-ritonavir; pla: placebo; rem: remdesivir; sd: sofosbuvir plus daclatasvir; sdr; sofosbuvir/ daclatasvir/ ribavirin; soc: standard of care.

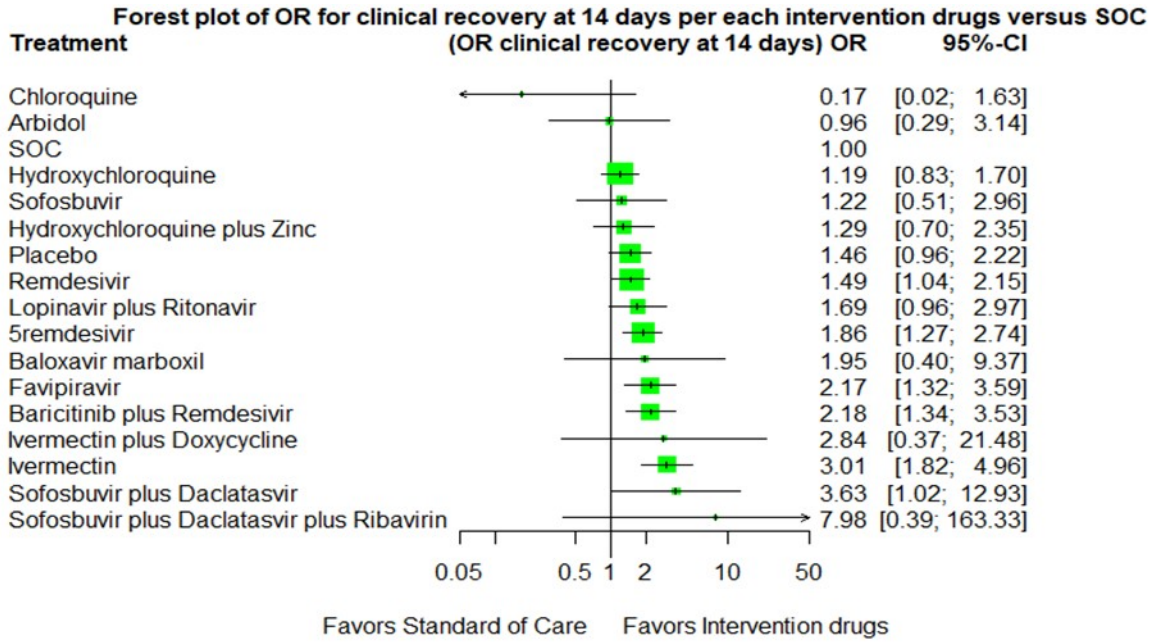

Figure 5: Forest plot. Network meta-analysis estimates of drug-level versus standard of care for the clinical recovery at 14days outcomes.

Viral clearance rate at 14 days

19 papers reporting on 11 treatment drugs involved 1,759 participants were presented by frequentist approach network graph (Figure 2) and relative estimates of effective by Netleague table (Supplementary material 3, Table 2). There was no statistically significant difference between an anti-infective drug in terms of viral clearance at 14days comparing to the standard of care: Arbidol (OR 1.55; 95%CI 0.65; 3.72), Favipiravir early treatment (OR 1.51; 95%CI 0.42; 5.49), Lopinavir/ Ritonavir (OR 1.29; 95%CI 0.68; 2.47) and Sofosbuvir (OR 1.59; 95%CI 0.37; 6.76) (Figure 6). Surface under the cumulative ranking curve (SUCRA) hierarchy ranked Arbidol best top safe drug (SUCRA = 74.2%) followed by Sofosbuvir (SUCRA = 68%) and Favipiravir (SUCRA = 67.6%) as third best drug (Figure 7). Global heterogeneity/ inconsistency was revealed with wide confidence interval (heterogeneity: I^2 = 24.7% (0.0%; 61.7%); Q = 14.6; p-value = 0.20).

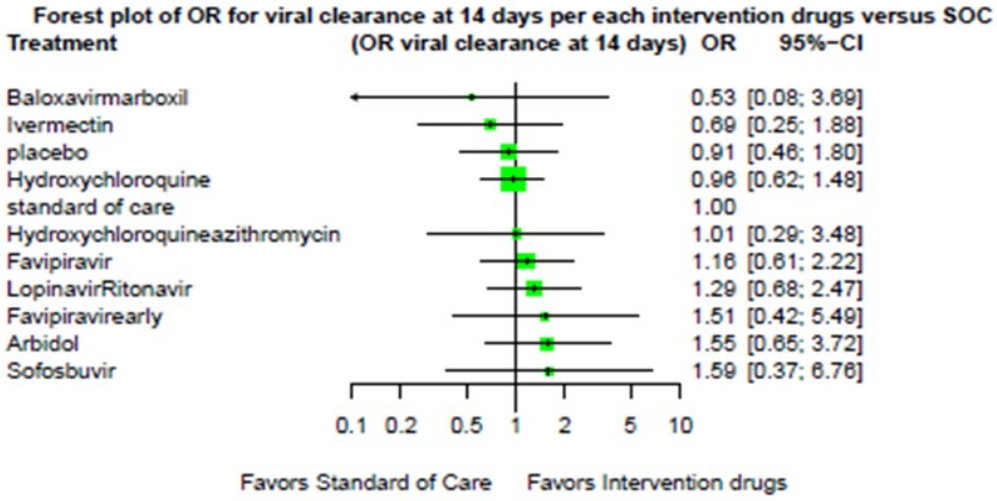

Figure 6: Forest plot. Network meta-analysis estimates of drug-level versus standard of care for the viral clearance at 14 days outcomes

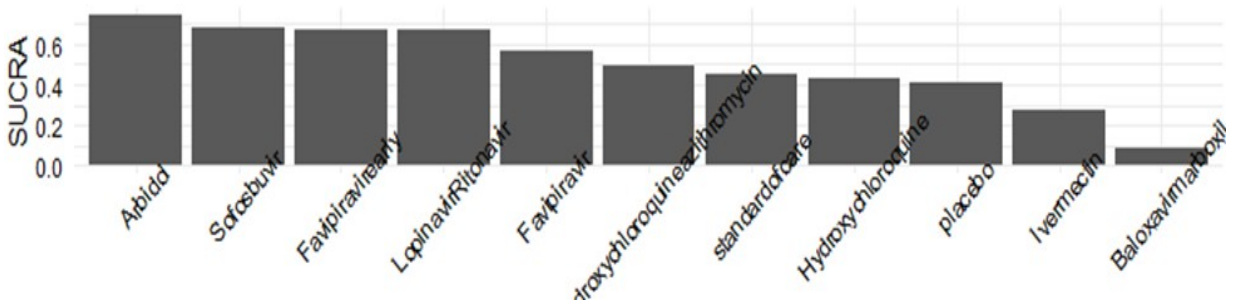

Figure 7: Sucra plot of network meta-analysis of Anti-infective drugs for viral clearance at 14

Mortality rate

The network meta-analysis of 47 studies examining 20 treatment drugs involved 34,461 participants was plotted by network graph (Figure 2) and their relationship by a league table (Supplementary material 3, Table 3). Statistically significant lower risks of mortality were shown for combined Baricitinib with Remdesivir therapy than standard of care therapy (RR= 0.47; 95%CI: (0.24; 0.94); P-value 0.03; very low certainty of evidence). Remdesivir for five days (RR= 0.53; 95%CI: (0.25; 1.13); P-value 0.10; low certainty of evidence), Ivermectin (RR= 0.75; 95% CI: (0.49; 1.14); P-value 0.18; low certainty of evidence), Remdesivir for 10 days (RR= 0.75; 95%CI: (0.47; 1.16); P-value 0.19; low certainty of evidence) and Hydroxychloroquine plus Azithromycin (RR= 0.61; 95%CI: (0.22; 1.73); P-value 0.35; very low certainty of evidence) decrease death but statistically not significant (Figure 8). Ranking analysis for mortality performed with surface under the cumulative ranking curves (SUCRA) strongly suggested that combined Baricitinib with Remdesivir therapy was the first top best (effective) treatment (SUCRA =85.4%) followed by remdesivir for 5 days second best drug (SUCRA = 79.3%), and Ivermectin third best drug (SUCRA = 68%) in decreasing mortality and P-score of frequentists also suggest similar hierarchy (Figure 9). The heterogeneity tau for this network overall was 0.10, which we considered low heterogeneity (Heterogeneity I^2 = 7.2% (0.0%; 36.5%)) and Q statistic was used to assess consistency under the assumption of a full design-by-treatment (consistency between designs) revealed no inconsistency seen with Q = 12.06 (p value 0.84).

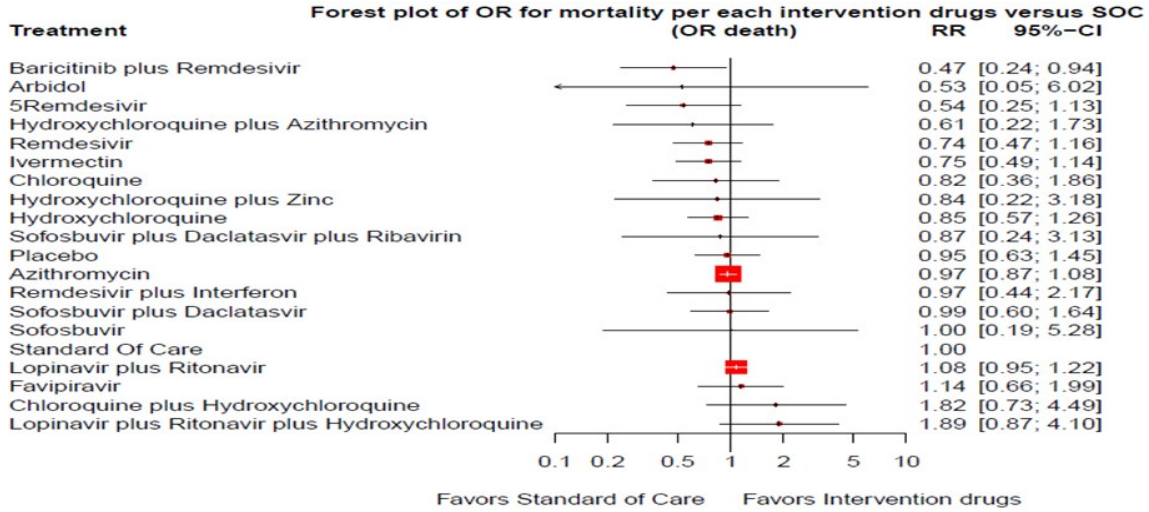

Figure 8: Forest plot. Network meta-analysis estimates of drug-level versus standard of care for the Mortality outcomes. *5Remdesivir-Remdesivir for five days; Remdesivir- Remdesivir for ten days*

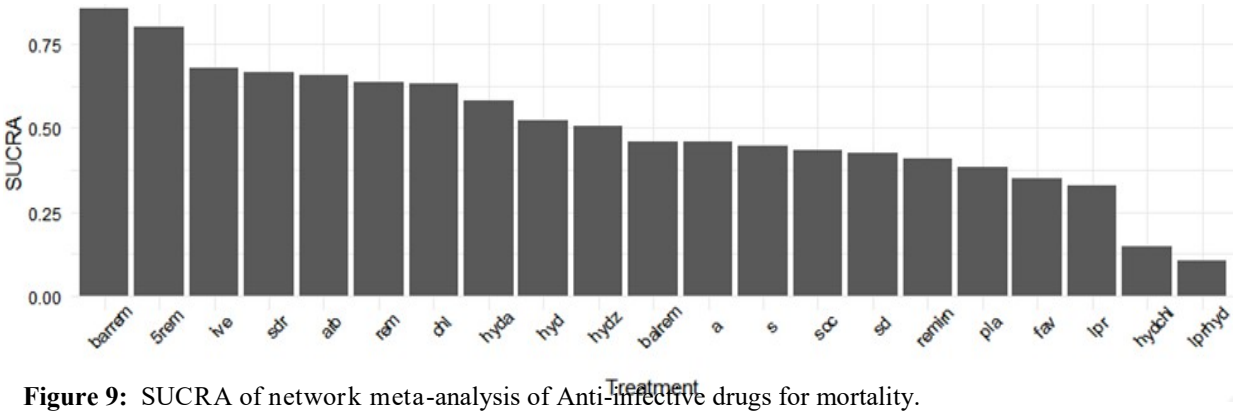

Figure 9: SUCRA of network meta-analysis of Anti-infective drugs for mortality.

Adverse events

An adverse event outcome was reported by 42 studies involving 22 treatment agents on 9,790 patients with COVID19 infection and have been shown by network geometry (Figure 2). Arbidol therapy results statistically significant low risks ratio than the standard of care therapy (RR= 0.46; 95%CI: (0.23; 0.95); p-value 0.04; very low certainty of evidence), and Sofosbuvir/Daclatasvir (RR= 0.40; 95%CI: (0.12; 1.03); p-value 0.056), but Hydroxychloroquine (OR= 1.17; 95%CI: (1.06; 1.29); p-value 0.002), lopinavir-ritonavir versus standard of care (OR= 1.26; 95%CI: (1.15; 1.38); p-value < 0.0001), and remdesivir versus standard of care (OR= 1.20; 95%CI: (1.20; 1.34); p-value 0.002) had statistically significant high risks ratio in developing adverse events Figure 10, Figure 11, Supplementary material 3). (Ranking analysis for adverse event was performed with P-Score probability strongly suggested that Sofosbuvir/Daclatasvir (P-Score = 95.4%) as top safe drug and Arbidol (P-Score = 94.1%) the second safe drug and standard of care (P-Score = 76.3%) as third safe drug in treatment of COVID-19. We quantified the heterogeneity with I^2 as moderate (heterogeneity I^2 = 61.9% (45.1%; 73.6%) and global inconsistency was found assessed by Q statistic after detaching of single designs and SIDDE approach (Cochran's Q= 60.23; p-value < 0.0001) and identified on several network loops comparison.

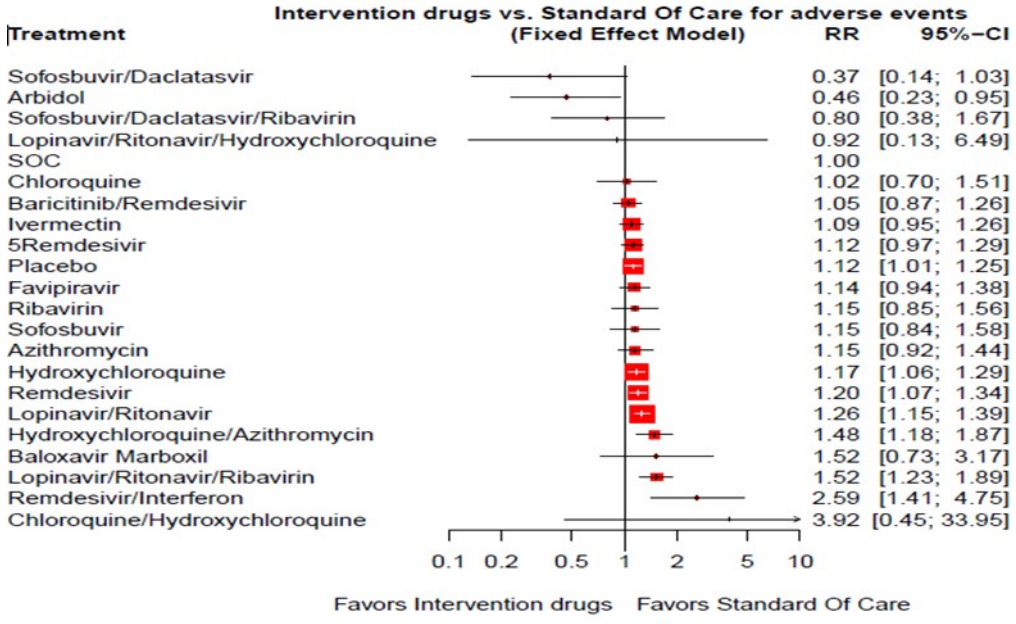

Figure 10: Forest plot. Network meta-analysis estimates of drug-level versus standard of care for the adverse event outcomes. *CI: Credible interval; SOC: standard of care; RR: Risk Ratio*

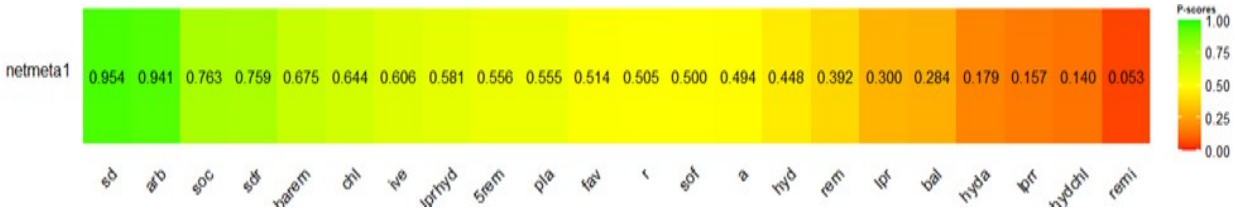

Figure 11: Netmeta P-Score hierarchy probability of network meta-analysis of Anti-infective drugs for any adverse events.

Sensitivity and subgroup analysis

The result of sensitivity analysis on the low risks of bias articles found that Ivermectin (OR= 3.00; 95% CI: (1.81; 5.00); p-value < 0.0001, low certainty of evidence), Remdesivir for 5 days (OR= 1.87; 95%CI: (1.27; 2.75); p-value 0.002, low certainty of evidence), combined Remdesivir and Baricinib for 10 days (OR= 2.20; 95%CI: (1.34; 3.53); p-value 0.002, low certainty of evidence), Remdesivir for 10 days (OR= 1.50; 95%CI: (1.03; 2.20); p-value 0.03, low certainty of evidence) and Sofosbuvir plus Daclatasvir (OR= 3.63; 95%CI: 1.02; 12.93; p-value 0.05, low certainty of evidence) were more effective than standard of care in clinical recovery at 14 days (Supplementary file). Subgroup analysis found Remdesivir for 10 days caused statistically significant serious adverse events (RR= 1.43; 95%CI: (1.16; 1.75); p-value 0.0009), Lopinavir-Ritonavir (RR= 1.52; 95%CI: 1.22; 1.90); p-value 0.0002), Hydroxychloroquine (RR= 1.35; 95%CI: (1.06; 1.70); p-value 0.01), and Placebo (RR= 1.80; 95%CI: (1.40; 2.35); p-value <0.0001) (Supplementary file).

Publication bias

According to the comparison-adjusted funnel plots, there was no sign of asymmetry found in three outcomes. But, we identified publication bias for adverse events outcome which indicates that there are small-study effects in our network (p = 0.06) (Supplementary file, D).

Discussion

In this latest systematic review and network meta-analysis, we have analyzed 13anti-infective drugs pooled from 68 RCTs up to 30 April 2022. We found that our NMA showed several drugs including Ivermectin, Remdesivir, combined Remdesivir and Baricinib, Favipiravir and Sofosbuvir plus Daclatasvir are statistically significant in increasing the rate of clinical recovery at 14 days than standard of care. However, there was no statistically significant difference between assessed drugs versus standard of care interms of clinical recovery rate but there are drugs like Arbidol, Favipiravir, Lopinavir/Ritonavir and Sofosbuvir revealed high odds of increased viral clearance at 14 days. This review also found that treating with combined Baricitinib with Remdesivir, Remdesivir, Ivermectin, and Hydroxychloroquine plus Azithromycin had lower risks of ratio in terms of mortality than treating with standard of care. We revealed from this NMA Arbidol and Sofosbuvir/Daclatasvir were the highly tolerable drugs (statistically significant low risks ratio) than the standard of care therapy.

We have evaluated from our NMA that ivermectin was the best top drug in terms of increasing clinical recovery rate at 14 days, while sofosbuvir plus daclatasvir was second-best and a combination of remdesivir and baricinib was third-best compared to the standard of care therapy.

A systematic review and meta-analysis on ivermectin with random effect model revealed that ivermectin led to significant clinical improvement compared to usual therapy (OR=1.98, 95% CI: (1.11, 3.53); P=0.02) similar to a previous meta-analysis (OR= 1.38; 95%CI: (0.85, 2.24); p-value 0.187).(46) However, the meta-analysis only included three studies in the meta-analysis and all were deemed to provide low certainty evidence. A previous systematic review and meta-analysis on efficacy of remdesivir found that remdesivir did not decrease all-cause mortality (RR= 0.71, 95%CI: (0.39 to 1.28), I^2 = 43%)(47) which contradicts our result (OR= 0.61 95%C:I(0.42; 0.88); p-value 0.009; I^2= 23%). However, another meta-analysis published in June 2021 reported a significantly reduced mortality rate with the use of remdesivir (RR= 0.39; 95% CI: (0.27, 0.56); p < 0.00001).(48)

A previous systematic review and meta-analysis on favipiravir group for the treatment of patients with COVID-19 revealed significant clinical improvement on day 14 (OR 3.03; 95%CI 1.17, 7.80) but no difference for rate of viral clearance (OR= 2.19; 95%CI 0.69, 6.95), (49) and our result is in agreement (OR= 2.04; 95%CI: (1.25, 3.33); p-value 0.0042, I^2 = 0%). An updated systematic review and network meta-analysis of 25 RCTs published in January 2021 reported that remdesivir for 10-day compared to standard care were associated with a higher clinical improvement rate.(50) Our finding is similar to the previous finding in that remdesivir showed an increased clinical recovery rate by 49% (OR= 1.51; 95%CI: (1.04, 2.18); p-value 0.03). Another updated article with 196 trials enrolling 76, 767 patients reported reduces deaths with remdesivi compared with

standard care (OR= 0.90; 95%CI: (0.72,1.11); low certainty) (51), which is comparable to our finding (OR= 0.70; 95%CI: (0.35,1.38); low certainty) (Supplementary material 3).

This review may have possible limitations that would serve as an important opportunity for future reviews. Though we included more than seven databases in our search to make the meta-analysis the largest, there were still some databases that the review did not include and this may affect the comprehensiveness of the study. We included 68 articles that had sufficient evidence for analysis. The COVID-19 therapeutic options are moving very quickly and active candidates are emerging that this review may not have covered. Anti-inflammatory drugs or monoclonal antibodies are shown to have promising effects that this review did not include.

Conclusions

Baricitinib plus Remdesivir is more effective than the other 22 anti-infective drugs in the rate of clinical recovery at 14 days and mortality outcomes of patients with COVID-19, while no statistically significant difference in viral clearance at 14 days and safety outcomes. Arbidol drug is the tolerable treatment and Ivermectin had statistically significant in clinical recovery at 14 days. We recommend there will be more and multinational studies to identify the effect of Ivermectin and Arbidol on treatment of COVID-19.

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Supplementary materials
Supplementary material 1 https://bit.ly/3Zu9B3U
Supplementary material 2 https://bit.ly/3JT7AZg
Supplementary material 3 https://bit.ly/3lVKtoZ

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Review Article

Monkeypox: Scientometrics of 50 years of global scientific publications

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Abstract
Background*: Scientific publications related to epidemic diseases are crucial for controlling and treating such diseases. The present study aimed to explore and analyze international publications on monkeypox through scientometric methods.*
Methods*: This review is an applied research conducted using the scientometric method with an analytical method. All world scientific publications on monkeypox were extracted from the Web Of Science (WOS) citation database from January 1972 to May 2022 through an appropriate search strategy. Moreover, Excel and the VOS viewer Bibliometrix package of the R programming language were used for data analysis.*
Results*: In total, 1130 publications related to monkeypox were extracted from the WOS citation database. Most of the publications were original papers published in 2010. The United States, Germany, and the Congo had the most publications on monkeypox. The topic clusters of scientific publications on monkeypox have been in four topic orientations: prevention, epidemiology, treatment, and immune response.*
Conclusion*: The findings of the present investigation provided a clear picture of the publications and scientific productions of world researchers in the field of monkeypox. Accordingly, researchers and policymakers on monkeypox can better understand the scientific publications on this disease and its dimensions.*

Keywords*: Monkeypox, Scientific publications, Scientometric, Bibliometric, Topic clusters*
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Introduction

In addition to being still one of the global health challenges recently, infectious diseases are one of the leading causes of death worldwide (1). Scientists have made significant progress in recent decades in treating and preventing infectious diseases such as HIV, viral hepatitis, and tuberculosis (2). However, many other infectious diseases, such as H5N1 and H7N9 bird flu, Middle East Respiratory Syndrome, Ebola virus, Zika virus, and COVID-19, have emerged in recent years; therefore, humans are always at risk of emerging infectious diseases (3).
Monkeypox, a common disease between humans and animals, is caused by the monkeypox virus, which belongs to the Poxviridae family, the Chordopoxvirinae subfamily, and the Orthopoxvirus genus. It is closely related to the variola virus (smallpox) and leads to smallpox-like disease (4).
Monkeypox has been a rare disease native to Africa but is now spreading to western and central Africa. Confirmed cases of monkeypox have been more common since 2016 than in the last 40 years (5). the World Health Organization (WHO) reported on the monkeypox outbreak in some countries (6).

In order to control and treat the disease, diagnostic test kits, medications, vaccines, and other health measures should be developed based on a thorough understanding of the biological properties and pathogenic mechanisms of this infectious disease; therefore, extensive research is needed in this field (7). In addition, one way to respond to this disease and con-

trol its outbreak is to conduct relevant research on all its dimensions (6). Accordingly, researchers have published various studies in different scientific fields in scientific databases, especially in health, for which quantitative and qualitative evaluations are necessary (8).
Scientometrics is an effective and efficient way to assess scientific progress and identify various aspects of scientific publications (9).
These methods are used to quantify the growth of research productivity, determine the countries and institutions with high numbers of publications, develop research materials, and determine significant research gaps (10). By taking into account the statistical data of scientometric studies, it is possible to reach a general understanding of global publications in a particular field, such as the number of studies, research capacities of different countries, leading research institutes, main journals, and other research parameters, which can be used to identify the research status, dominant areas, and main gaps for strategic planning and scientific research (9).

In this respect, scientometric methods were extensively applied to evaluate the knowledge growth in research related to health science and diseases, including influenza (11), coronaviruses and COVID-19 (12, 13), brucellosis (14, 15), tuberculosis (16), and other infectious diseases (17, 18).
Mayta-Tovalino et al. (2022) (19) analyzed the trend of scientific production on monkeypox between 2018 and 2022 using bibliometric indicators. The results of this study indicated the most important journals, institutions, and authors in this field . Zeeshan et al. (2022) (20) have also used bibliometric techniques to analyze the research trend of monkeypox between 2001 and 2021. The results of this study showed the growth of documents, distribution of sources, and collaborations at the national and international levels, as well as the relationship between authors and co-authors . In another study, Lin et al. (2022) (21) demonstrated that the number of scientific publications on human-related monkeypox has increased since 2003 through analysis of scientific publications on monkeypox from 1975 to 2022. Infection, vaccine, and efficacy have been the main topics of these publications .
Given the importance of the subject, the present study has also analyzed the scientific publications on monkeypox using bibliometric and scientometric techniques.

Research questions
This study applied scientometric techniques with an analytical approach to answer the following questions:
What are the types of scientific publications in the field of monkeypox?
What is the trend of publishing scientific publications on the subject of monkeypox?
Which countries have the most scientific publications in the field of monkeypox?
What is the scientific cooperation of countries in the field of monkeypox?
In what topics have scientific publications related to monkeypox disease been published?

Methods

Search strategy and inclusion criteria

The statistical population is all the scientific publications on the subject area of monkeypox in the WOS database. The main keywords for designing the search strategy were identified using the Medical Subject Headings Database (MeSH) and consulting with specialists in the field of infectious diseases. Afterward, in the advanced search of the WOS database, publications on monkeypox disease were extracted using the following search strategy by filtering the English language on May 28, 2022.
It should be noted that the search strategy was reviewed and approved by subject matter experts who were also authors of the present study. The search operation was performed by one author and then reviewed and approved by the other authors, who were subject matter experts in the field.
The timeframe considered in the search strategy was from January 1972 until the date of extraction of the publications, and the search strategy in topic fields in all WOS databases was as follows: (Monkeypox OR Monkeypox OR monkeypox viridae OR monkeypox viridae)
Moreover, eligibility criteria for scientometrics analysis were all types of documents extracted based on the search strategy. The reason for using the WOS database was that it is the most authoritative, extensively used, and oldest citation database (22).
Considering that the objective of the present investigation was the scientometric analysis of scientific publications in the field of monkeypox; therefore, all the monkeypox scientific publications indexed in the WOS in the search strategy were included as inclusion criteria.

Data extraction and data analysis
After conducting a search in the WOS database, the results obtained were extracted in the form of a plaintext file. The excel and VOS viewer software were applied to perform scientometric analysis and visualization. The VOS viewer software is one of the most powerful and standard software for analyzing data from citation databases, which clusters the most relevant documents and their relationships (23). Moreover, this software allows drawing maps based on terms.
A term map is a two-dimensional map in which the number of term occurrences is defined by label size, and the distance between two terms can be interpreted as an indication of the relatedness of these terms based on the number of term co-occurrences in the studied corpus file (24).

The Biblioshiny graphical interface tool based on the Bibliometrix package in R programming language was employed to analyze the data. Bibliometrix is a tool for visualizing information in bibliometric analyses based on scientific productions and publications in nations and regions, journals, authors, articles, keywords, and research institutes (25). It should be noted that KeyWords Plus has been applied to draw conceptual maps in each of the publications.
The thematic map uses the Keywords Plus field. The Keywords Plus is associated with Thomson Reuters editorial experts supported by a semi-automated algorithm. Keywords Plus terms can capture an article's content with greater depth and variety (26).

Results

What are the types of scientific publications in the field of monkeypox?

A total of 1,130 scientific publications on monkeypox over the past 50 years were extracted from the WOS database. Table (1) indicates the types of scientific publications conducted on monkeypox. According to Table (1), original articles, reviews, editorials, and other publications accounted for 71.95%, 10.53%, 5.22%, and 5.22% of scientific publications on monkeypox, respectively.

Table 1. Most types of scientific publications conducted on monkeypox.

Article Type	Number of Publications	Percentage
Original Article	813	71.95%
Review Article	119	10.53%
Editorial Material	59	5.22%
Meeting Abstract	56	4.96%
Letter	31	2.74%
Book Chapter	26	2.30%
Proceeding Paper	24	2.12%
News Item	22	1.95%
Note	8	0.71%
Correction	7	0.62%

Which countries have the most scientific publications in the field of monkeypox?

Table 2. Number of publications of countries in the global publications on monkeypox 1972-2022

Countries/ Regions	Number of Publications	Percentage
USA	687	60.80%
Germany	97	8.58%
Dem Rep Congo	75	6.64%
England	59	5.22%
Switzerland	53	4.69%
Russia	48	4.25%
France	42	3.72%
Belgium	37	3.27%
Canada	36	3.19%
Nigeria	28	2.48%

According to Table (2), the United States has the most publications related to monkeypox, with 687 patients accounting for 60.80%, followed by Germany with 97 publications (8.58%), and the Republic of Congo with 59 publications (6.64%). Moreover, Figure (3) indicates the trend of publications in the ten countries with the most scientific productions on monkeypox.

Since 2000, the United States has had the highest growth rate in global scientific publications on monkeypox, as demonstrated in Figure (2). Moreover, there has been a consistent trend in scientific publications on monkeypox in Germany and the Congo. Since 2017, Nigeria has also published scientific publications on monkeypox.

What is the scientific collaboration of countries in the field of monkeypox?

Figure (3) depicts the international collaboration network of different countries in publications on monkeypox when it comes to scientific collaboration between countries.

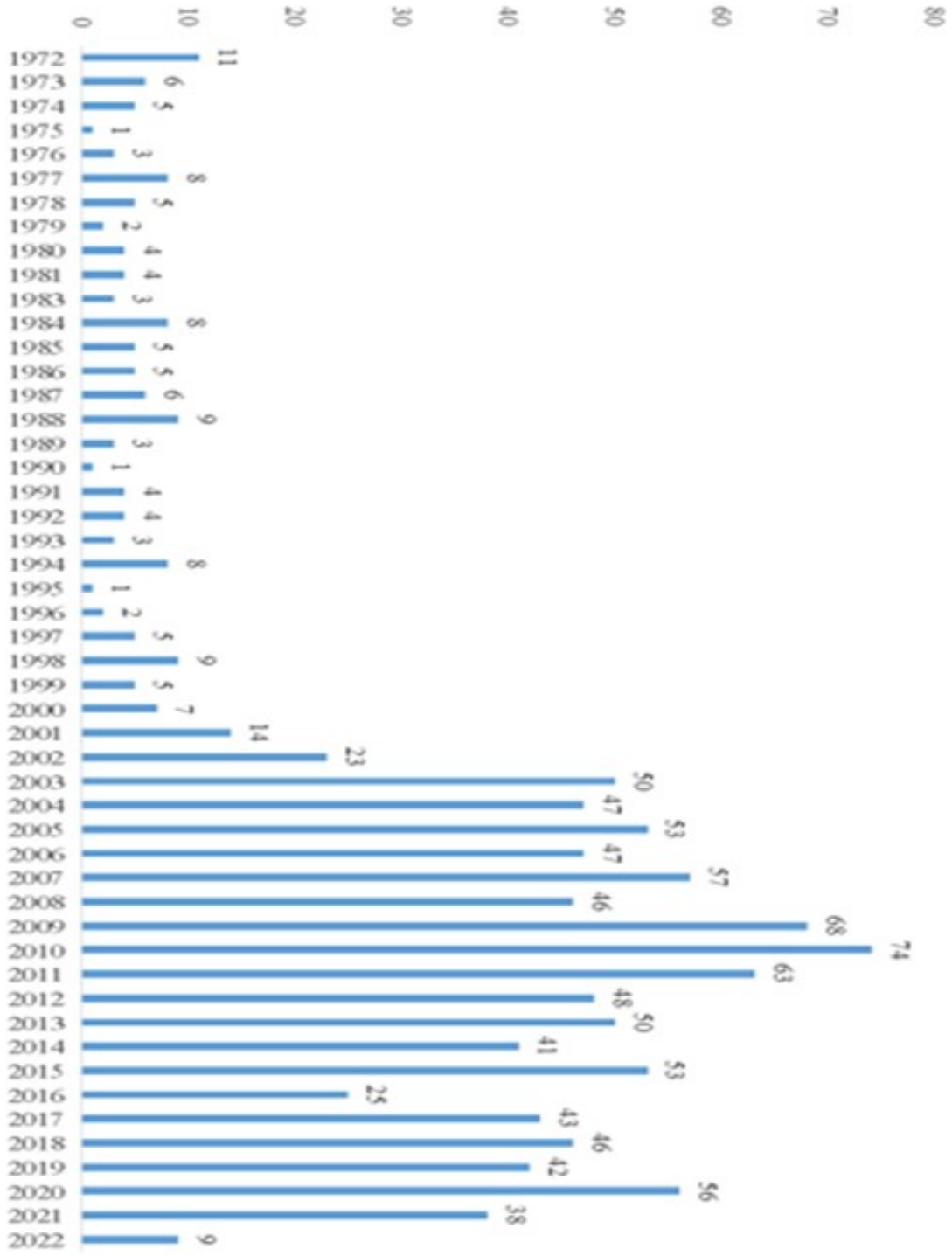

Figure 1. Trend of scientific publications on monkeypox from 1972-2022 .

Figure (1) indicates that the highest number of publications was in 2010, 2009, and 2011.

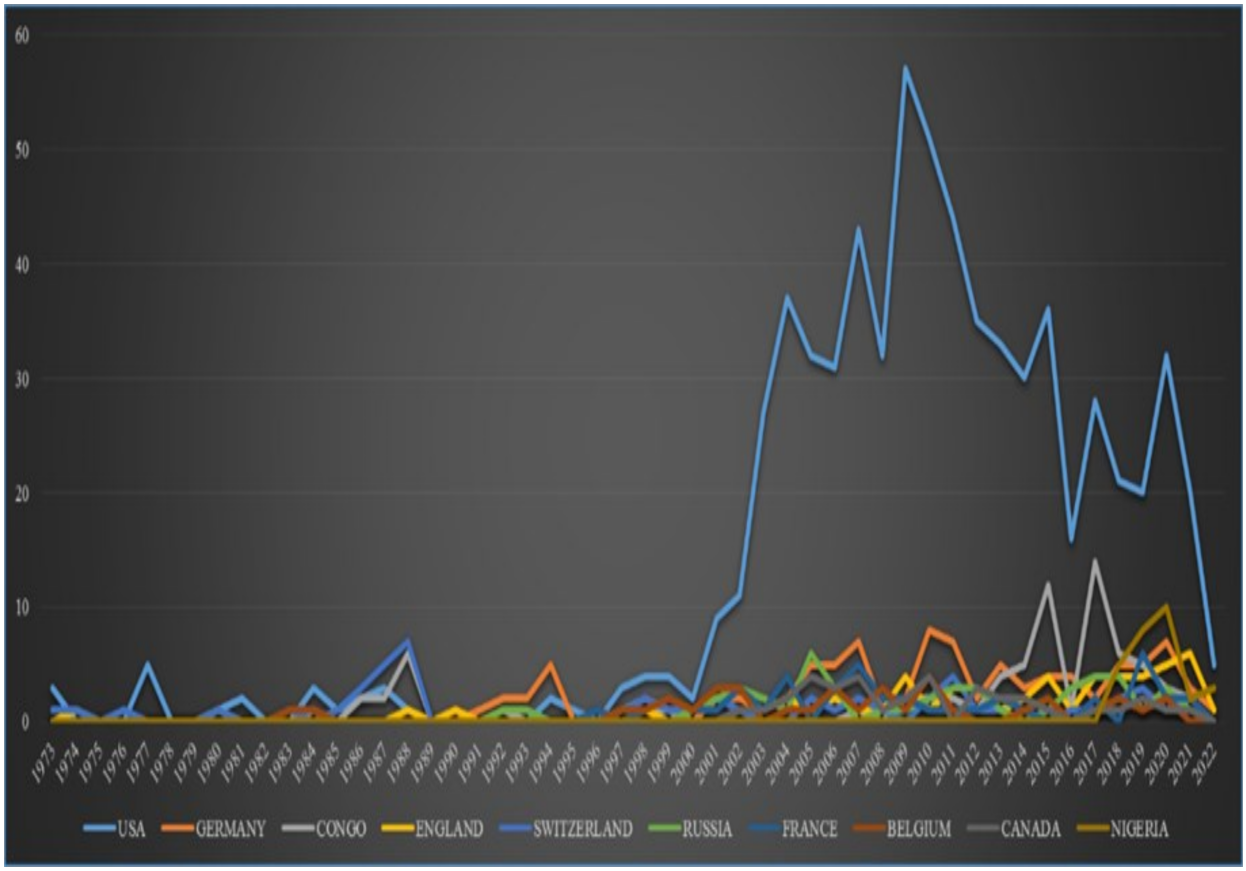

Figure 2. Trend of publications in ten countries with the most scientific productions on monkeypox from 1972-2022.

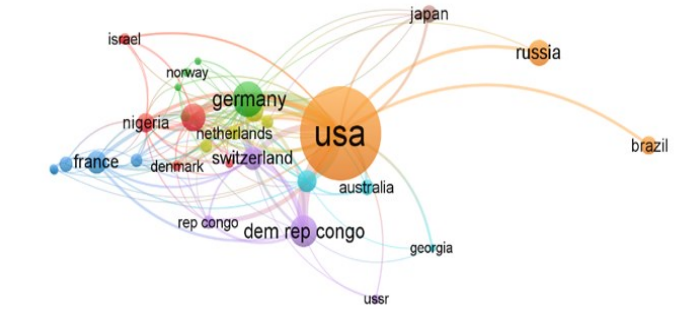

Figure 3. Collaboration of countries in the global publications on monkeypox

In what topics have scientific publications related to monkeypox disease been published?
Figure (4) shows the topic clusters of monkeypox publications based on the keyword co-occurrence.

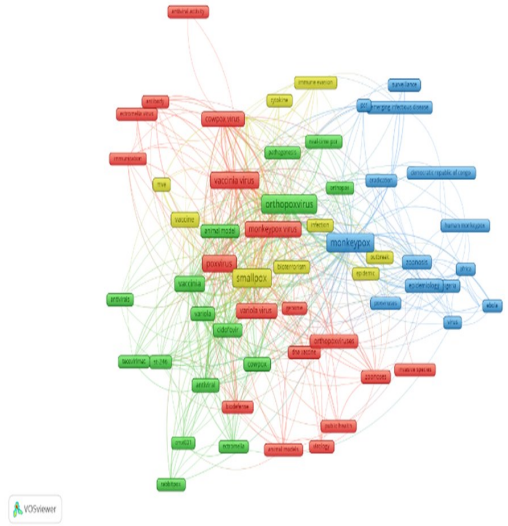

Figure 4. Network visualization based on the co-occurrence of monkeypox publications.

The frame sizes in Figure (4) represent the frequency of each keyword. Larger frames are related to higher frequencies. The frames and connections between them are depicted in four different colors in this figure. Each color represents a keyword cluster that frequently appears in monkeypox publications.

As a result, the red color denotes the subject of prevention, blue indicates the epidemiology, green implies the treatment, and yellow represents the immune response.
The density of authors' keywords in scientific publications on monkeypox is also displayed in Figure 5.

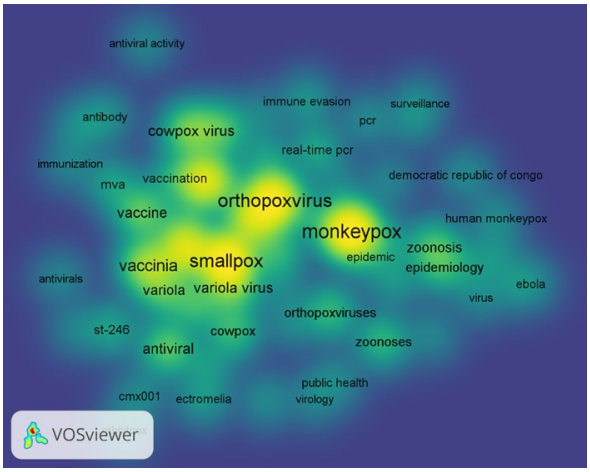

Figure 5. Density visualization based on occurrences of monkeypox publications

The density of the keyword network is depicted by the yellow-to-blue color spectrum in Figure (6). The weight density is represented by yellow, green, and blue from top to bottom. The most commonly used keywords are shown in the yellow sections. The higher the density, the more yellow the map would be. The scientific publications on smallpox had the highest co-occurrence of closely related keywords. As a result, the terms Monkeypox, Smallpox, and Orthopoxvirus were most frequently used and repeated in scientific publications regarding monkeypox.
Moreover, Figure (6) indicates the frequency of words and their co-occurrence over time. In this figure, lighter-colored frames indicate the most commonly used keywords in recent scientific publications on monkeypox, while darker-colored frames depict older keywords in monkeypox-related articles.

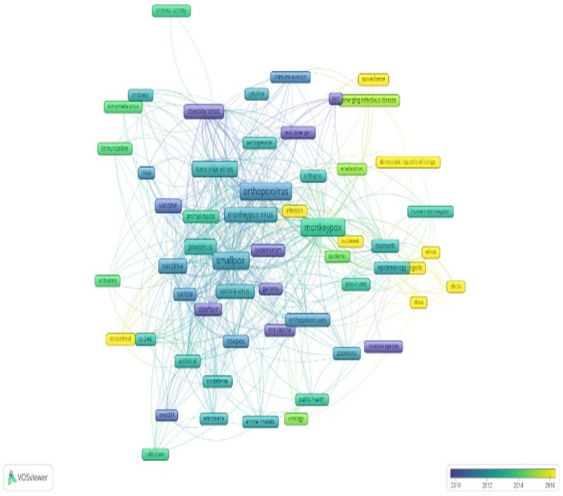

Figure 6. Overlay visualization based on the occurrences of monkeypox publications.

Therefore, "Outbreak," "Infection," "Nigeria," "Africa," and "Congo" have been the keywords in scientific publications on monkeypox in recent years and after 2016.
Moreover, Figure (8) demonstrates the thematic evolution trends in the monkeypox publications over time in four time periods, 1953-2000, 2001-2010, 2011-2020, and 2021-2022.

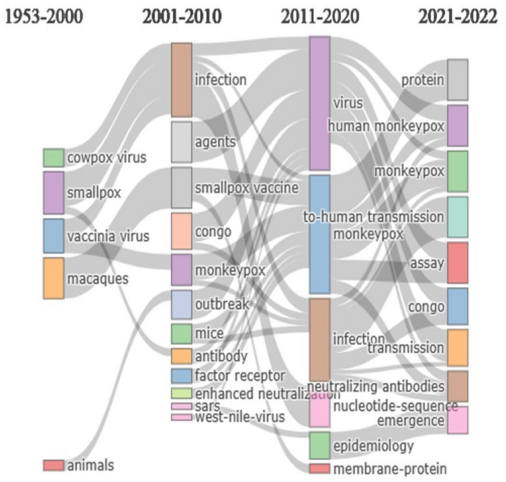

Figure 7. Thematic evolution trends in research of the monkypox publications.

Figure (7) indicates that the protein, human monkeypox, monkeypox, human transmission, assay, congo, transmission, neutralizing antibodies, and emergence were important topics in 2021-2022. Moreover, the congo has also been an important topic recently repeated in 2001-2010 and 2021-2022.

Figure (8) indicates the strategic diagram of the thematic map to demonstrate the significance and development of research topics. Moreover, it shows the thematic map based on density (y-axis) and centrality (x-axis). The centrality measures the importance of the selected theme, and density measures the development of the chosen theme.

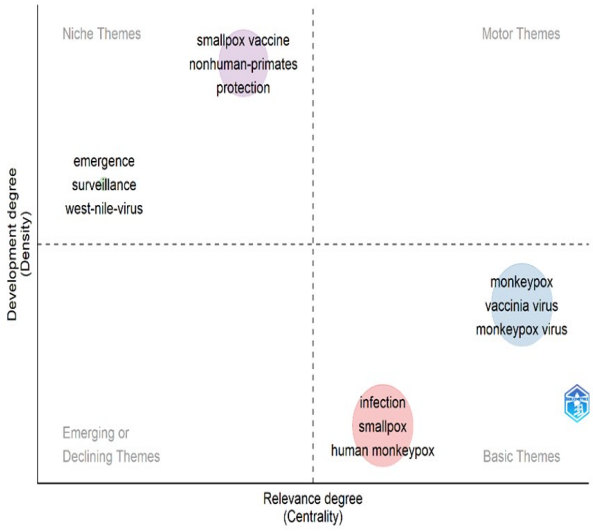

Figure 8. Thematic map based on density (y-axis) and centrality (x-axis).

In Figure (8), the upper-right quadrant indicates the motor themes. They are characterized by both high centrality and density. Moreover, there is not any topic in this quadrant. In the upper left quadrant, the niche themes are observed, which are peripheral and specific topics for the research field. "Smallpox vaccine," "nonhuman- primates," and "protection" are in this quadrant. In addition, "emergence," surveillance," and "west-nile-viruse" are in this quadrant.

The basic themes are demonstrated in the lower right quadrant. These are basic, general, and transversal themes in the research field. "monkeypox," "vaccinia virus," and "monkeypox virus" keywords are basic themes, also "infection," "smallpox," and "human monkeypox" are in this quadrant. Finally, there are emerging or declining themes in the lower left quadrant. There is not any topics in this quadrant.

Discussion

Scientometric methods are helpful in determining increased scientific activity and organizing the intellectual and scientific structure that makes up a topic area (27). This study revealed the structure of scientific publications on monkeypox using scientometric methods over the last 50 years.

According to the findings, scientific publications on monkeypox have increased significantly since 2000, with most publications occurring in 2010, 2009, and 2011. Furthermore, the majority of scientific publications were original articles. Lin et al. also showed that the increase in publications on monkeypox has been since 2003 (21).

The increase in infections in endemic areas of the disease and humans' close contact with monkeys could explain the upward trend in scientific publications on monkeypox infectious disease, a common disease between humans and animals (zoonotic disease) (28) since 2000. Consequently, studies have indicated that the monkeypox virus was first discovered in monkeys in a Danish laboratory in 1958 (29). In 1970, a 9-month-old baby boy in the Democratic Republic of the Congo was diagnosed with the disease for the first time (30). Recent studies have also indicated that the highest incidence of this disease has been in African countries, although it has been reported in other parts of the world in recent years (2, 31).

From 2009 to 2012, for three years in a row, published articles about monkeypox were higher than in past years. One of the reasons for this could be the disease's periodic outbreak and spread in endemic areas. Since 2000, the overall trend of studies has been upward. Although the outbreak of the disease has fluctuated slightly over the years, the number of studies on this virus has remained high. This problem highlights the importance of paying attention to the monkeypox disease, as a lack of attention has resulted in a steady increase in disease cases over the years. The increase in the number of publications indicates the progress of the scientific community on the subject. Moreover, the increase in the number of monkeypox publications shows the importance of the issue (20).

On the one hand, modern transportation and increased communication between different parts of the world, as well as the rapid movement of humans between countries and even continents, have resulted in the rapid and easy transmission of viruses, while on the other hand, a lack of attention to monkeypox disease in recent years and a reduced focus on the disease has resulted in the outbreak this zoonotic disease. On the contrary, since the global outbreak of the coronavirus pandemic, all of the world's attention and medical resources have been focused on this disease. Other diseases, on the other hand, have had more time to spread, and monkeypox cases have now been reported all over the world.

The United States, Germany, Congo, the United Kingdom, and Switzerland have the most publications in this field, according to the results of the present study. Furthermore, in terms of scientific publications on this disease, these countries have the highest level of scientific communication and collaboration. According to Phoobane et al. (17) on infectious diseases in Africa, the United States, the United Kingdom, South Africa, Switzerland, and Kenya have the most publications in this area. Moreover, in this field, these countries have the most international scientific collaboration. Due to the significant investment in various disease research in the United States, the study of their various aspects is at the forefront. The United States, for example, has the most global publications on tuberculosis (15, 32) and COVID-19 (33). In this regard, studies have found that a higher level of the outbreak of diseases increases researchers' interest in research and publication in those countries (34). Furthermore, country income is another reason for increased scientific publications. Accordingly, high-income countries have more scientific publications, and low-income countries have fewer scientific production (35, 36).

Furthermore, the presence of the protein, human monkeypox virus, and monkeypox itself, along with the potential for human transmission, have been major focus of the research community in 2021-2022. This indicates that researchers have been working to develop improved assays for detecting the virus and neutralizing antibodies, as well as studying the emergence of monkeypox in areas such as the Congo.

The keywords "monkeypox," "vaccinia virus," and "monkeypox virus" are significant in the research field of monkeypox. Monkeypox is a rare but potentially fatal viral disease that is similar to smallpox, caused by the monkeypox virus. One of the treatments for monkeypox is the smallpox vaccine, which is based on the vaccinia virus (37,38). Smallpox vaccination using the vaccinia virus has been shown through historical data to be approximately 85% effective against monkeypox (39).

These keywords are also transversal themes, which means that they are relevant and applicable across different research fields, such as virology, epidemiology, and infectious diseases.

Conclusion

The present investigation provides a comprehensive and clear picture of monkeypox scientific publications over the last 50 years. According to the findings, scientific publications on monkeypox have increased. Furthermore, since 2000, the growth in scientific publications in this field has been at its highest rate. Monkeypox has been the subject of scientific publications in four areas of epidemiology, prevention, treatment, and immune response. Furthermore, American, African, and European countries have the highest participation in scientific publications on this disease.

Furthermore, according to the results, researchers and policymakers gain a better understanding of scientific publications on monkeypox by having access to some information such as the most important countries, authors, keywords, and topics of scientific publications.

Furthermore, by analyzing the results obtained from studies that use these keywords, researchers can gain valuable insights into the epidemiology, pathogenesis, diagnosis, treatment, and prevention of monkeypox, which can ultimately contribute to the development of effective strategies for controlling this disease.

Conflict of interest: The authors declare no conflict of interest.

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Case series

COVID-19 related multisystem inflammatory syndrome in children (MIS-C): A case series from Ethiopia

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Abstract

Background: *One in twenty of people affected by the ongoing COVID-19 pandemic have been children and adolescents. A unique complication in this age group is the Multi-inflammatory syndrome associated with COVID-19 (MIS-C). We report a single-center case series of children diagnosed with MIS-C from Addis Ababa, Ethiopia.*
Case descriptions: *This case series describes the clinical presentation and treatment outcomes of four male patients presenting at a mean age of 3 years and 11 months. All fulfilled the World Health Organization case definition criteria for the Multi-inflammatory syndrome associated with COVID-19. All were not eligible for vaccinations against severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) at the time of their diagnosis. They were treated with varying combinations of intravenous immunoglobulin, aspirin, and corticosteroids, and all recovered upon completion of their follow-up period.*
Conclusion*: Cases of Multi-inflammatory syndrome associated with COVID-19 are often misdiagnosed. This case series highlights when to consider such a diagnosis and its therapeutic options.*

Keywords*: MIS-C, Ethiopia, COVID, SARS-CoV-2, children*
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Introduction

The Multi-inflammatory syndrome associated with COVID-19 (MIS-C) is a post-infection hyper-inflammatory response primarily recognized among patients aged 18 years and less (1). It has an incidence of 316 persons per 1000000 SARS-CoV-2 infections in persons younger than 21 years (2). There is minimal data from African countries concerning severe COVID-19 infections and MIS-C among children. In a recently published retrospective cohort study from six African countries, suspected or confirmed MIS-C was diagnosed in 3.8% of children hospitalized with COVID-19 (3).

Following the reporting of the first child with MIS-C in Ethiopia in March 2021, there has been little data on further descriptions of children diagnosed with the syndrome in the country, barring a second case report in July 2022 (4,5). We report a single-center case series of four children diagnosed with MIS-C.

Case series

The parents of three children could recall their child coming into contact with a confirmed case of COVID-19 infection within the preceding 4 to 6 weeks. Their lab work-up revealed lymphopenia in one child, neutrophila and elevated creatinine in two children each and normal platelet counts, serum albumin, liver enzymes, coagulation profile, urinalysis and chest imaging in all four. Tests specific to their diagnosis and their management protocols are summarized in table 1.

None had a positive antigen or PCR test for SARS CoV-2. None of them had coronary artery dilatations or aneurysms in their echocardiography studies but two had acute mitral regurgitations and minimal pericardial effusion which resolved during follow-up studies at two and six weeks following discharge from hospital. All of them were having normal left ventricular systolic function as depicted

by normal ejection fraction and fractional shortening.

The mean duration of their hospital admission was 5.25 days. All were managed with intravenous immunoglobulin (IVIG) and aspirin and did not require admission to an intensive care unit. One child developed adverse reaction to the intravenous immunoglobulin with high grade fever, chills, rigor and his regimen was changed to a high dose (2 mg/kg/day) oral Prednisolone.

Table 1: Summary of the MIS-C specific diagnosis tests and treatment for all cases

Lab parameter	Case A	Case B	Case C	Case D
Age at presentation	4 yy 8 mo	2 yy 10 mo	4 yy 3 mo	3 yy 11 mo
Gender	Male	Male	Male	Male
Elevated C-reactive protein	Yes	Yes	Yes	Yes
Elevated SARS CoV-2 specific IgM and/or IgG	Yes (IgM and IgG)	Yes (IgG)	Yes (IgM)	Yes (IgG)
SARS CoV-2 PCR	Negative	Negative	Negative	Negative
SARS CoV-2 antigen test	Negative	Negative	Negative	Negative
Criteria met for Kawasaki disease	Yes (complete)	No	Yes (incomplete)	Yes (incomplete)
Echocardiographic abnormalities	Acute Mitral regurgitation	None	Acute Mitral regurgitation	None
Elevated troponin	Not done	Not done	Not done	Yes
Admission to intensive care unit	No	No	No	No
Vasoactive agents given	No	No	No	No
Corticosteroids given	No	No	No	Yes *
IVIG given	Yes	Yes	Yes	Yes
Aspirin given	Yes	Yes	Yes	Yes
Length of stay in hospital	5 days	2 days	10 days	4 days
Patient outcome	Improved	Improved	Improved	Improved

* Oral Prednisolone

Discussion

The diagnosis of the four cases we presented were made based on the WHO diagnostic recommendation for MIS-C for children and adolescents aged 18 years or less (6). These criteria are based on a fever of more than 3 days and two or more of suggestive dermatologic, cardiovascular or gastrointestinal features and coagulopathies. Gastrointestinal manifestations like diarrhea, abdominal pain, vomiting and mesenteric adenitis are the commonest features of MIS-C (7). This should be accompanied by elevated inflammatory markers (CRP, ESR etc), absence of alternative diagnoses, and evidence of COVID-19 infection (usually positive SARS-CoV-2 serology and a negative PCR and antigen test) or a likely contact with a patient with confirmed COVID-19.

Delayed or excess cytokine storm and an aberrant immune response mediated by non-neutralizing IgG antibodies are some of the contributing factors for MIS-C (8). The presentation of MIS-C may vary from mild disease (a less common outcome than in acute COVID-19) to features resembling Kawasaki disease with or without shock, toxic shock syndrome and macrophage activation syndrome (9). There is a slight male preponderance (55%) for MIS-C as reflected in our case series (7). A decreased systolic ventricular function is the commonest cardiologic abnormality with mild mitral regurgitation another well-described feature. Coronary aneurysms are uncommon in MIS-C (10,11). A raised CRP (94%), neutrophilia (83%) and lymphopenia are the commonest hematologic and inflammatory marker abnormalities as also evidenced in our case series (6). A recently published study has noted patients with MIS-C to be at a higher risk for coagulopathies among children and adolescents (12).

Intravenous immunoglobulin (2 g/kg over 12 hours) and aspirin with an initial anti-inflammatory dose of 30 to 50 mg/kg/day till afebrile and later a lower dose of 3 to 5 mg/kg/day for six weeks (if echocardiography is normal at follow-up at 6 weeks) or indefinitely (if coronary artery abnormalities are detected) can be used to treat children presenting with complete or incomplete Kawasaki disease (13). Alternative therapies include corticosteroids alone or intravenous immunoglobulin alone or a combination of the two (14,15).

In conclusion, we describe the multi-inflammatory syndrome associated with COVID-19 in four young

Ethiopian children. Further studies are needed to characterize this patient population and institute early recognition and therapy. As more cases are diagnosed, efforts for provision of treatment options like intravenous immunoglobulin at a wider scale in referral hospital should be emphasized.

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Review Article

History and evolution of academic publishing from the perspective of 60 years of the Ethiopian Medical Journal

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Abstract
On the occasion of the 60th Anniversary of the Ethiopian Medical Journal (EMJ), the authors briefly explore the history and current trends in academic publishing globally and in Ethiopia. Notable increases in academic publishing are recorded even though, as part of the global asymmetry in research and academic publishing, the share of Ethiopia and Africa in general remains relatively small. Challenges and opportunities and how the EMJ has handled them are assessed. The several voluntary editors over the years are commended for sustaining the quality, consistency and continuity of the journal under quite difficult circumstances which portends well for the future of the Journal and academic publishing in Ethiopia.

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Introduction

Academic Publication

A growing number of academic works is being published with the continuing expansion of higher education institutions (1), in Africa in particular (2). Academic publication based on research is important not only for the status/reputation of individuals and institutions but also for socio-economic development in general (3).

Academic publishing, a subfield of publishing which distributes academic research and promotes scholarship, is considered the primary vehicle for the advancement of scientific knowledge (4). Various definitions exist and future reviews would be expected "to take account of changing academic, social and political realities" (5). In the Ethiopian context, it has been defined by the Ministry of Science and Higher Education as ""Publication" shall mean a book, book chapter, textbook, journal article, review article, conference proceedings, teaching material or a brief, short communication or technical note that having *(sic)* been authored solely or jointly by academic/ research staff…"Academic publishing" shall mean publishing of research articles with the required level of review and editorial services as well as traceable editorial team and publication history" (6).

The first academic journal, "Journal des Sçavans", was published in France on January 5, 1665. This was followed by the publication, on March 6, 1665, of the "Philosophical Transactions of the Royal Society of London" (4,7). In Ethiopia, "The earliest known medicinal texts are the Geez "Metshafa Faws" (መጽሐፈ ፈውስ) mid-17th century and "Metshafa Medhanit" (መጽሐፈ መድሃኒት) of the early 18th century" (8). After this early start, the importance of academic journals as vehicles for research findings has grown substantially (7,9,10). Globally, there are now more than 45,ሞ000 peer-reviewed - i.e. gone through a complex and difficult quality assessment process (11) - scholarly journals, growing at approximately 6% a year (1). Most academic work was previously published in academic journals owned by nonprofit academic

societies; now more and more are owned by private 'multinational publishers'. The drive to commercialize scientific publishing has a long history but accelerated in the 1960s and 1970s when commercial publishers, mostly in the United States of America and United Kingdom, began to selectively acquire "top-quality" journals and now own almost all top publications (1).

Research and Publication

Research is recognized as important for health and development. The World Health Organization (WHO) (12) emphasizes that "All nations should become consumers and producers of research knowledge". Its importance is recognized globally (12,13), in Africa (14), and Ethiopia (6,15), including in program specific documents. Future demands for research/science and technology-based measures against major challenges such as climate change, public health emergencies/pandemics and other emerging or reemerging crisis are bound to increase.

Research is expected to be "…much more complex, multidisciplinary, collaborative, and transnational —and often occur […] at a much more rapid pace—than in the past… challenging … governments … to develop and implement policies that enable countries to benefit from the assimilation of new knowledge" (16).

Globally, the output in publications is increasing (14,16,17). However, in terms of academic publishing, there is a major asymmetry between the global North and South (10). In one example, 96% of primary data for research were collected in Low - and Middle- Income Countries (LIC & MIC) but 56% of first authors were based in High Income Countries (HIC), compared to only 8% in LIC (18). A more recent study that analyzed articles published between 2015 and 2020 across the world Bank regions (19) shows that in studies in LIC, only 43% of first authors are from LIC compared to 98% in studies in HIC being from same countries (Table 1).

Table 1: First Author Income Classification Compared with Studied Country Income Classification

Classification [a], No. (%)	**First Author WB Income Classification**				**Total (No.)**
	LIC	LMIC	UMIC	HIC	
LIC	29 (43.3)	0 (0.0)	0 (0.0)	38 (56.7)	67
LMIC	0 (0.0)	108 (69.7)	0 (0.0)	47 (30.3)	155
UMIC	0 (0.0)	0 (0.0)	98 (72.6)	37 (27.4)	135
HIC	0 (0.0)	0 (0.0)	1 (1.6)	62 (98.4)	63
Total	29	108	99	184	420

NOTE. Bold-italic numbers represent the articles with authors from the same region as the studied country.
Abbreviations: HIC, high-income country; LIC, low-income country; LMIC, lower-middle-income country; UMIC, upper-middle-income country; WB, World Bank.
[a] Includes only articles that studied a single country.
Source: adapted from 19

The pattern is repeated in specialty areas too. For emergency medicine, for example, a large proportion (45%) of studies were done in LIC or MIC but more (40.7%) of the first authors in studies from LIC were from HIC. For infectious disease research, a study showed that only 50% had either a first or last LIC-affiliated author. Among these LIC affiliated authors, 48% of first authors and 52% of last/senior authors also reported a non-LIC institutional affiliation. The asymmetry is due to several reasons, including "inequities in power and influence inherent in the research ecosystem" (10), lack of country ownership (20), entanglement in complex (USA, European Union [EU], Russia, China…) geopolitical maneuvering (21), "algorithmic logic" (22), and limited funding and high article processing charges (23).

Key to laying the ground for institutions'/teams' and researchers' level success and addressing the issue of 'decolonize' (24,25)/rectify the power asymmetry (26) is fair research contracting, which clearly addresses issues such as "1) Intellectual property rights, 2) Ownership of data and samples, 3) Capacity building and technology transfer, 4) Compensation for indirect costs, and 5) Research contracts in (legislative) context" but legal and negotiation resources in LIC are limited (27).

External resources for research in Africa have also been limited, with even the limited available tending to be skewed. For example, none of the seven institutions granted $30 million by the US President's Malaria Initiative in 2021 to help African governments improve data for decision making in malaria control and elimination were in Africa (all from US, the UK, and Australia). Overall, only 1% of research funding for malaria went to African institutions (28). It is clear that a major reform is required, including "… creating a more equal and equitable representation of researchers in LMICs in decision-making, leadership roles, authorship, and funding allocations" (29).

As for Africa in general, there is a long way to go yet. In spite of notable increases, scientific publications remain low in Africa (see below) which, in spite of having 12.5% of the world population, has only 1.1% of the world's researchers (30) and only 5% of world's scientific publications (31). Research outputs are also dominated by a few countries (32) (Fig 1), and African authors are highly underrepresented in academic publishing (33). More recently, in relation to Corona Virus Disease -2019 (COVID-19), about 20% of studies undertaken in Africa had no African author and 66% of authors on African papers were not from Africa (10,33). It is clear that 'trickle-down science' is problematic (34) and this requires reforms at all levels (35,36).

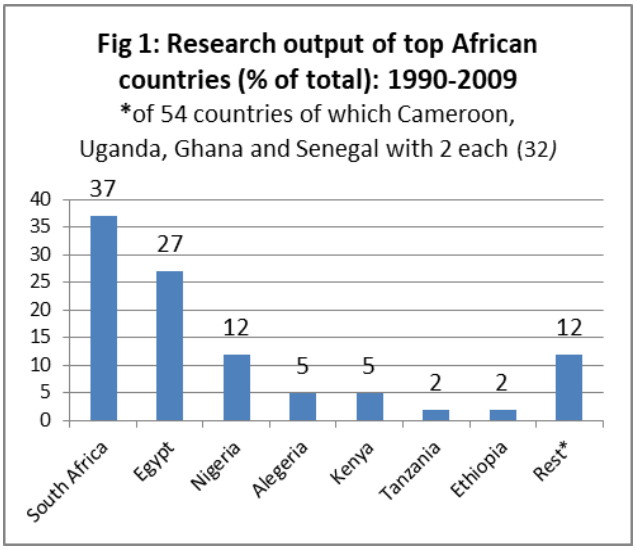

Fig 1: Research output of top African countries (%of total):1990-2009

In fact, as noted by the United Nations Conference on Trade and Development (UNCTAD) (37), "On paper, Ethiopia has most of the policies, regulations, background studies and road maps necessary to kick-start a successful process of technological learning, innovation and technological upgrading. In reality, however, there is a serious implementation gap across public institutions either because of capacity constraints or misallocation of efforts and resources".

A recent assessment (38) depicts a particular concern as there was reportedly no specific health research policy but only as part of the 2012 National Science and Technology Policy (39), the guidelines from Ethiopian Food and Drug Administration (EFDA) (40) and the National Research and Ethics Committee (41), which provide clinical trial procedures, documentation, publication, agreements for cross country studies.

There is a critical need to build bridges for health research in Ethiopia (42). Some of the gaps are attributed to overlapping mandates between the Ministry of Health (MOH) and Ministry of Science and Technology (MOST), and the lack of a coordination unit at the MOH; lack of research laws and legislation; lack of strategic documents to guide health research; and a research priority list that only addressed the research needs of some programs as opposed to sector priorities. When there is such lack of targeted coordination of health research evidence generation and use, it is not surprising that "evidence is not a major input into health-related decisions in the country" (43) even though health research intentions are voiced in major documents such as the Health Policy and the Health Sector Transformation Plan.

Publication output in Africa and Ethiopia

"There exists a big knowledge gap in Africa, which can be attributed to the lack of academic publishing by African academics" (44). Thus, Africa's research output is less than 1% of the global output of around 30000 papers a year – i.e. roughly equal to that of The Netherlands (African academics 2020). In 2005, only 29 African countries had medical journals, most only one for the country; Ethiopia had three and, the highest was Nigeria which had 26. In 2018, there were only 83 Institute for Scientific Information (ISI) indexed journals from Africa of which two were from Ethiopia (45).

As most countries, Ethiopia uses various activities/ forums to disseminate health related research outputs. These include: annual conferences of, for example, professional associations (Ethiopian Medical Association [EMA], Ethiopian Public Health Association [EPHA] etc.) or universities (Gondar, Jimma, etc.); disease based conferences e.g. Tuberculosis Research Advisory Committee (TRAC) conferences in various universities; Abstracts/ extracts of research work related to conferences or independently; digests/newsletters e.g. MOH, ARM Bulletin; Harar Bulletin of Health Sciences; Ethiopian Public Health Institute (EPHI) Newsletter; EPHA, Public Health Digest etc. However, the main forums for dissemination are academic journals and Ethiopia has, in recent years achieved a

notable increase in locally published academic journals with close to 50 additions since 2000 and a total of about 73 in 2018 (46) of which about eight are on medicine and health (Table 2).

Table 2: List of Medical/Health Journals in Ethiopia, 2018 by Year Established and Publisher

Name	Year	Publisher
Ethiopian Medical Journal[1,2]	1962	Ethiopian Medical Association
Ethiopian Journal of Health Development[1,2]	1984	School of Public Health, Addis Ababa University, & Ethiopian Public Health Association
Ethiopian Journal of Health Sciences[1,2]	1990	Jimma University
Ethiopian Journal of Pediatrics & Child Health	2005	Ethiopian Pediatrics Society
Ethiopian Journal of Reproductive Health	2006	Ethiopian Society of Obstetrics & Gynecology
Ethiopian Journal of Health & Biomedical Sciences	2008	Gondar University
Ethiopian Journal Public Health & Nutrition[2]	2016	Ethiopian Public Health Institute
Ethiopian Pharmaceutical Journal[1]	1974	Ethiopian Pharmaceutical Association

[1]Scopus Indexed [2]Referenced in the NCBI Databases

notable increase in locally published academic journals with close to 50 additions since 2000 and a total of about 73 in 2018 (46) of which about eight are on medicine and health (Table 2).

The Ethiopian Medical Journal (EMJ) could, thus be considered the first academic journal in Ethiopia.

The University College of Addis Ababa started the short lived "AAUC Bulletin" in 1961 but, as underscored by its President, it was essentially a means of communication to the public "It is leaven and ferment which enriches and enlivens the otherwise amorphous and lifeless mass around it" (47).

Academic publishing in Ethiopia: Challenges and Opportunities

There are indications that Ethiopia has a relatively high production of research literature in comparison to other sub-Saharan countries. It produced 3,514 (33 per million people) in 2018 i.e. 4.57% of Africa's and 0.11% of the global total. "According to Scimago, Ethiopia ranked 153rd out of 236 countries in terms of the number of citations per paper. International collaborations accounted for 58% of Ethiopia's research outputs in 2018, [a] decrease… from 62% in the previous year and are substantially lower than many other sub-Saharan African countries" (39).

Ethiopia, as most LICs, faces several challenges at the individual academic/researcher and organizational/institutional levels. At the individual level, the most important challenge is that not all academics publish in local journals. Factors leading to this low level of publications include lack of commitment and motivation; lack of experience and exposure to publishing; journal language, inadequate information, knowledge and skills to access accredited journals; lengthy/long publication process; heavy work overload; lack of support from the universities (45).

At the organization/institution level, several barriers have been identified. Lack of infrastructure and equipment – for example, less than 12% of the population had access to internet and there is an overall underinvestment in research infrastructure (39) – is an enduring problem (48) exacerbated by lack of coordination among institutions (49) even though they tend to concentrate in few geographical locations (37).

Authors and editors tend to agree on assessing institutional challenges but differ on individual skills as barriers (Table 3) (50). Lack of/limited funding is a barrier (38) even though there is substantial increase in recent years and with a Gross domestic Expenditure in Research and Development (GERD) of 0.6% in 2013 much higher than the average for SSA or LIC (39).

(Poor research culture, lack of national quality assurance system (51), shortage of skilled, experienced and motivated reviewers etc. compound the challenges. All these challenges tend to standout in clinical trials in LIC including Ethiopia (50).There are also a growing number of opportunities. The recognition of the importance of evidence-based decisions (52,53), supported by increase in dissemination and implementation research, including in Ethiopia (39,54). This, in the context of rapid social and economic growth – "Lions on the Move" (55) - has the potential to strengthen research capacity in LICs, including those in conflict situations (56).

The necessity of increasing the role of female researchers in increasing research productivity, a challenge globally (57) and in Ethiopia (58), is gaining recognition. There is also improvement in research ethics (59); growing recognition of academic publishing as the primary vehicle for the advancement of scientific knowledge (11) and scholarly articles as decisive in indicating societal problems and filling the gaps when, in particular, coupled with integrated knowledge translation/platform (IKT/P) initiatives (60-64). In this connection, there have been increasing calls for scientific academies and individual researchers to work harder to engage the public, "If your science doesn't affect the life of your people, nobody cares about you" (65)

.**Table 3:** Authors and editors rating of challenges in publishing articles
(Adapted from 50)

Challenge	Authors	Editors
Insufficient budget	3.90	3.48
Lack of incentive/motivation	3.68	3.60
Lengthy/long publication process	3.47	3.43
Choosing where to publish	3.16	3.10
Limited language competence in writing articles	2.67	3.75
Lack of research skills	2.55	3.73
Notes: 1=Not at all; 2=Lesser extent; 3=Uncertain; 4=Some extent; 5=Great extent;		

It has been demonstrated that local investigator-initiated studies are more likely to be implemented even though some indicate perceived preference to evidence generated by international experts (25). There are notable increases in specialization (66) and collaborative research (17,67) of the trans-disciplinary research and community-based participatory research types (68). This trend is bound to accelerate driven by continuous challenges to adapt to changes in the global and local environment - "To make global health truly global is to make global health truly local" (69-71). The importance of such collaborations looms prominently in times of crisis such as the COVID-19 pandemic (72) with some wondering "why it had to take such a gigantic human tragedy for us to work together" (73). These collaborations could be between countries – Ethiopia, for example, collaborating with over 10 countries in 2017 (74), consortia, regional organizations such as European Union (EU) and African Union (AU) or the diaspora and could, potentially, be facilitated by technological development in data handling in particular. Guidelines for rigor in design, implementation and reporting (75) and measures to reduce waste and bias (76) are also promising. There are also attempts to achieve greater accessibility, transparency and accountability for research studies designed through digital object identifiers (DOIs) and others such as the Initiative for Open Abstracts (I4OA) (77) globally and to increase the visibility of Ethiopian/African knowledge production and research outputs at the global level (78).

The potential of the rapidly increasing number of academic centers could be promising for knowledge acquisition and academic publishing. Ethiopia is a relatively late starter in the higher education 'massification' which started in the 1950s in the USA and Europe (79). Ethiopia had only two universities in 1991, increased them to 21 by 2009 and 31 by 2013 (39) and some 44 and counting by 2020 (80). 'Massification', **c**onsidered inevitable as "it allows solving the problem of knowledge generation and dissemination … [and] ... helps individuals to achieve the subjective wellbeing and professional and individual orientation, and allows a wide range of development and research projects to be handled by more qualified staff" (81). However, it could lead to major challenges in quality of research and knowledge generation (82) unless supported by expanded and increased funding support (83,84).

A number of measures, in addition to expanding and increasing funding, have been suggested to alleviate the quality problems, including the establishment of 'research universities'. It has been suggested that priority be given to collaborations with established universities that are already engaged in research, with a view to creating national role models for research production and management (44). There are also increasing calls to improve support to early-career scientists with, in particular, appropriate mentorship (85).

Contributions of the Ethiopian Medical Journal (EMJ)

EMJ has, through thick and thin, leveraging opportunities and mitigating challenges, survived – in fact thrived – for 60 years. The Ethiopian Medical Association (EMA) and its members, Addis Ababa University (AAU) and other universities, a number

of government and non-government (health) organizations have made enormous contributions.

However, the major burden was on the Editorial Board members and Editors-in-Chief. All were volunteers with heavy academic and/or service duties, contributing in their spare time without any compensation except the satisfaction of contributing to the *development* of their profession and recognition by their peers.

The Board had, on average, about 10 members with some serving for several terms. Thus, some 80 professionals from various medical and health fields have served on the Board. While most were foreigners in the first few years, Ethiopians predominated in later decades (85) (Table 4).

Table 4: EMJ, Average Number/Range of Editorial Board Members by Decade 1962-2008

Decade	Number		
	Total	Ethiopian	Foreigner
1960s	12	3	8
1970s	5-8	8	3-4
1980s	9-10	6-7	2-3
1990s	6-10	8	1-3
2000s	8-12	10	2-3

Source: Adapted from 85

The heavy burden of ensuring the relevance, quality and timeliness of the journal depended on the Editor-in-Chief. This, under any circumstances but the more so in the Ethiopian context, is a daunting task and all 15 Editor-in-Chiefs of the last 60 years (Table 5) should be appreciated for their dedication and resilience as benefactors of the development of modern medicine in Ethiopia. Special mention should be made of Dr. Oscar Barry who, not only played a major role in launching the Journal, but, as Editor-in-Chief, saw it through the difficult first years, and laid a solid basis for its recognition and development. Prof Nebiat Teferi, as the first Ethiopian and Professors Leithead and Sileshi Lulseged, the longest serving, also deserve special recognition

Conclusion

There is a clear imbalance in the research output and publications between the global north and south. The challenges faced by researchers and academics across LMICs have a complex interplay of individual and institutional level factors. Infrastructure and resource-related constraints underlie the challenges faced while individual capacity and skill fuel the difficulties faced. On the other hand, academic/research centers, science literacy, and evidence-based decision-making are increasing rapidly. The increasing number of local platforms for dissemination and advocacy of research and innovation - local medical/health journals -, an increasing number of academic training centers, improving availability of funding and other resources to support researchers, and open access to published articles are some of the positive developments fostering the growth of research and academic publishing in Ethiopia. Sustaining an academic publication by EMJ for 60 years in the complex context of Ethiopia is not a small feat. As observed over 50 years ago, “In all this flux [high turnover of editors].

Table 5: EMJ, Editor-in-Chief/Chairperson, 1962-2022

Dr B Oscar Barry	1962-1965	Dr Charles Larson	1991-1992
Prof Charles S Leithead	1966-1975	Dr Hagos Beyene	1992- 1995
Dr Craig K Wallace	1975-1977	Prof Kebede Oli	1995-2000
Prof Nebiat Tefari	1977-1978	Prof Sileshi Lulseged	2000-2007
Prof Jemal Abdulkadir	1979-1981	Dr Mesfin Araya	2008-2015
Prof Demissie Habte	1982-1985	Prof Demissie Habte	2016-2017
Prof Morten Harboe	1986	Prof Sileshi Lulseged	2018-2020
Dr Tekelemariam Ayele	1987-1988	Prof Mirkuzie Woldie	2021-Present
Dr Frances T Lester	1989-1990		

it is hard enough to build steadily and progressively, harder still to build with wisdom and foresight. Hard as it may be, however, the attempt must be made" (86). In spite of many challenges, a number of measures have been taken to increase and ensure steady growth and integrit of the publication. The role of volunteers serving as editors-in-chief, editorial board members, and peer reviewers in promoting and realizing academic publishing cannot be overstated. Enhancing EMJ's organizational/ institutional capacity, increasing its national and international recognition, and increasing the quality, frequency, accessibility, and impact of published articles will require informed attention from the next generation of editors. EMJ should prepare and strive to exploit emerging opportunities to expand and thrive proactively. Results obtained in the last 60 years in very challenging circumstances augur well for the future.

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    - The formal, announced retraction of publications from the journal in accordance with the Retraction Policy.
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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 immunodeficiency 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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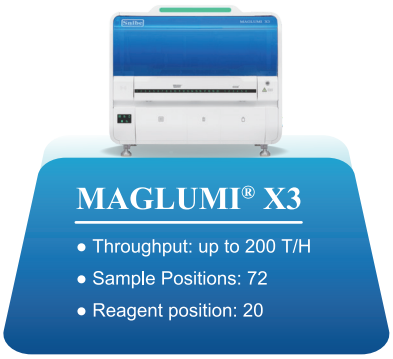

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TSH (3rd Generation)
T4
T3
FT4
FT3
Tg (Thyroglobulin)
TGA (Anti-Tg)
Anti-TPO
TRAb
TMA
Rev T3
T-Uptake

Hepatic Fibrosis
HA
PIIIP N-P
C IV
Laminin
Cholyglycine
*GP73

TORCH
Toxo IgG
Toxo IgM
Rubella IgG
Rubella IgM
CMV IgG
CMV IgM
HSV-1/2 IgG
HSV-1/2 IgM
HSV-1 IgG
HSV-2 IgG
*HSV-2 IgM
*HSV-1 IgM
*Toxo IgG Avidity
*CMV IgG Avidity

Kidney Function
β_2-MG
Albumin
*NGAL

STAT-X™
*hs-cTnI
*NT-proBNP
*Myogobin
*D-dimer
*PCT
*CRP

Fertility
FSH
LH
HCG/β-HCG
PRL (Prolactin)
Estradiol
Testosterone
free Testosterone
DHEA-S
Progesterone
free Estriol
17-OH Progesterone
AMH
SHBG
Androstenedione
PIGF
sFlt-1

Autoimmune
Anti-CCP
Anti-dsDNA IgG
ANA Screen
ENA Screen
Anti-Sm IgG
Anti-Rib-P IgG
Anti-Scl-70 IgG
Anti-Centromeres IgG
Anti-Jo-1 IgG
Anti-M2-3E IgG
Anti-Histones IgG
Anti-nRNP/Sm IgG
Anti-SS-B IgG
Anti-SS-A IgG
TGA (Anti-Tg)
Anti-TPO
TRAb
TMA
ICA
IAA (Anti Insulin)
GAD 65
Anti-IA2
*ZnT8
Anti-MPO IgG
*Anti-PR3 IgG
*Anti-GBM IgG
*Anti-Cardiolipin IgG
*Anti-Cardiolipin IgM
*Anti-Cardiolipin IgA
*Anti-Cardiolipin screen
*β2-Glycoprotein I IgG
*β2-Glycoprotein I IgM
*β2-Glycoprotein I IgA
*β2-Glycoprotein I screen
*Anti-tTG IgA
*Anti-tTG IgG
*DGP IgA
*DGP IgG

Tumor Markers
AFP
CEA
Total PSA
f-PSA
CA 125
CA 15-3
CA 19-9
PAP
CA 50
CYFRA 21-1
CA 242
CA 72-4
NSE
S-100
SCCA
TPA-snibe
ProGRP
HE4
HER-2
PIVKA-II

Infectious Disease
HBsAg
Anti-HBs
HBeAg
Anti-HBe
Anti-HBc
Anti-HBc IgM
Anti-HCV
Syphilis
Anti-HAV
HAV IgM
*HEV IgG
*HEV IgM
HIV Ab/Ag Combi
Chagas
HTLV I+II
H.pylori IgG
H.pylori IgA
H.pylori IgM
2019-nCoV IgG
2019-nCoV IgM
SARS-CoV-2 S-RBD IgG
SARS-CoV-2 Neutralizing Antibody
SARS-CoV-2 Ag
Monkeypox Virus Ag
Dengue Virus IgG
Dengue Virus NS1
*Dengue Virus IgM
*Chlamydia Pneumoniae IgG
*Chlamydia Pneumoniae IgM
*Mycoplasma Pneumoniae IgG
*Mycoplasma Pneumoniae IgM

Cardiac
CK-MB
Troponin I
Myoglobin
hs-cTnI
hs-CRP
H-FABP
NT-proBNP
BNP
D-Dimer
Lp-PLA2
MPO
*HCY
*hs-cTnI (STAT)
*NT-proBNP (STAT)
*Myogobin (STAT)
*D-dimer (STAT)

Hypertension
Direct Renin
Aldosterone
Angiotensin I
Angiotensin II
Cortisol
ACTH

Coagulation Markers
D-Dimer
*TAT
*TM
*PIC
*tPAIC

Metabolism
Pepsinogen I
Pepsinogen II
Gastrin-17
GH (hGH)
IGF-I
IGFBP-3

Prenatal Screening
AFP (Prenatal Screening)
free β-HCG
PAPP-A
free Estriol

Anemia
Vitamin B12
Ferritin
Folate (FA)
EPO
RBC Folate

Inflammation Monitoring
CRP
PCT (Procalcitonin)
IL-6 (Interleukin 6)
SAA (Serum Amyloid A)
*PCT (STAT)
*CRP (STAT)
*TNF-α

Bone Metabolism
Calcitonin
Osteocalcin
25-OH Vitamin D
Intact PTH
β-CTx
total P1NP

EBV
EBV EA IgG
EBV EA IgA
EBV VCA IgG
EBV VCA IgM
EBV VCA IgA
EBV NA IgG
EBV NA IgA

Immunoglobulins
IgM
IgA
IgE
IgG

Glyco Metabolism
C-Peptide
Insulin
GAD 65
Anti-IA2
ICA
IAA (Anti Insulin)
Proinsulin
*Glucagon
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