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Original Article

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

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Abstract

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

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

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

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

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

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Introduction

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

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

Among the characteristics of the disease, viral

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

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

Methods and materials

Study setting and design

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

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

Population and eligibility

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

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

Sample size Determination and Sampling Technique

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

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

Operational Definitions

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

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

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

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

Event: Achieving viral clearance from Covid-19 infection.

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

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

Data Collection Procedures and Quality Assurance

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

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

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

Data Management and Data Analysis

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

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

Result

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

Characteristics of the Study participants

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

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

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

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

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

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

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

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

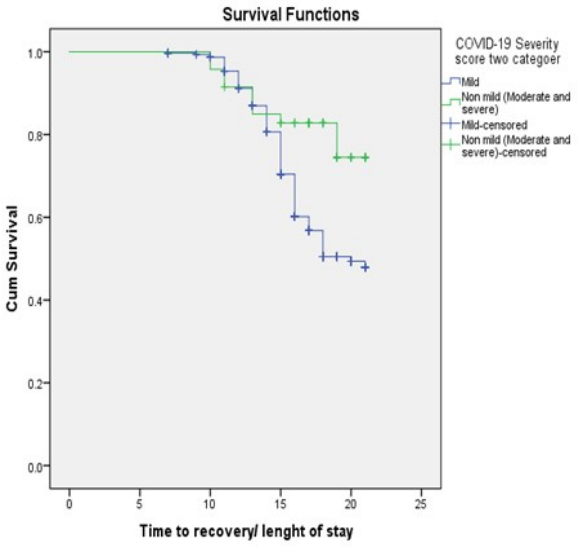
Variable	Censoring status		Total (%)
	No of censored (%)	No of event (%)	
Sex			
Female	107 (67.3)	52 (32.7)	159 (44.2)
Male	121 (60.2)	80 (39.8)	201(55.8)
Place of residence			
Outside Addis Ababa	11 (47.8)	12 (52.2)	23 (6.4)
Addis Ababa	217 (64.4)	120 (35.6)	337 (93.6)
Health care worker			
No	218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

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

Comparison of survival experience

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

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



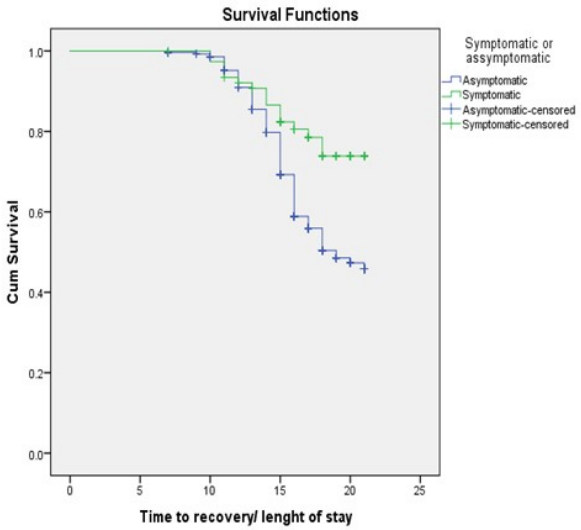


Figure a: Survival functions of COVID-19 severity score and presence of symptom by time

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

Results of Multivariable Cox Proportional Hazard Model

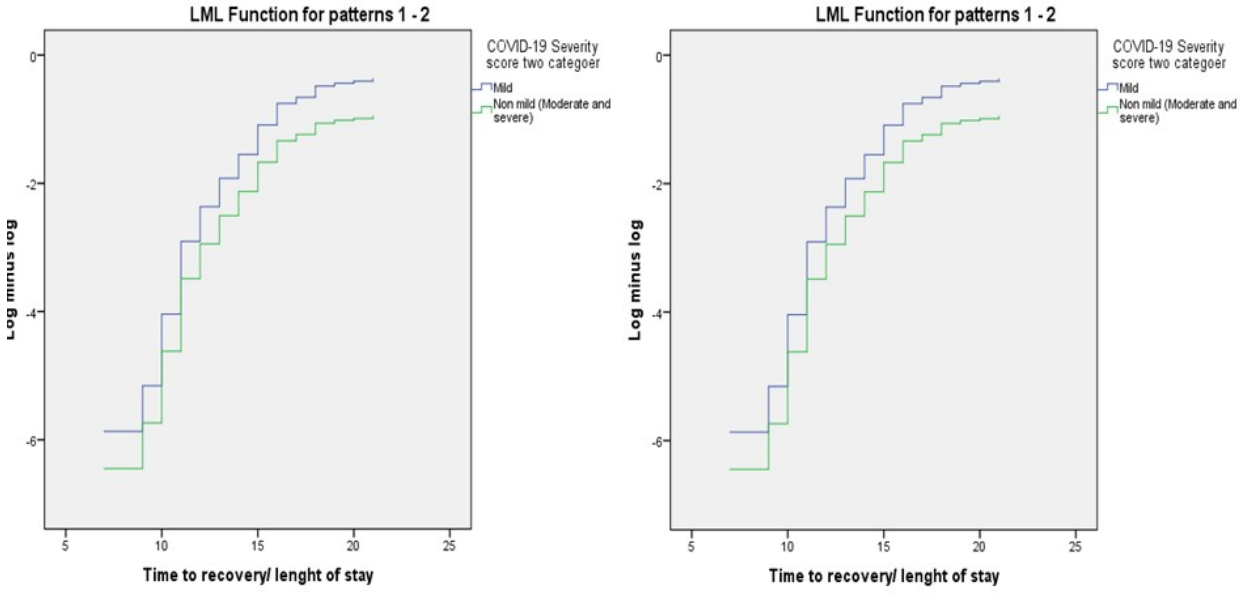
The fundamental assumption of Cox Proportional Hazard model, which is proportional hazards assumption, was tested using Log minus Log function on SPSS version 23 software. Parallel lines between groups indicate proportionality [30]. **Figures b** reveals that the survival curves seem parallel throughout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

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

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

Note:*Statistically significant

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



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

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

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

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

Discussion

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

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

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

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

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

Conclusion

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

Declaration

Ethics approval and consent to participate

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

Competing interests

The authors declare that they have no known competing interests

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

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

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

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

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