Duration of Supplemental Oxygen Requirement and Predictors in Severe COVID-19 Patients in Ethiopia: A Survival Analysis

Tigist W. Leulseged[1*], Ishmael S. Hassen[1], Mesay G. Edo[1], Daniel S. Abebe[1], Endalkachew H. Maru[1], Wuletaw C. Zewde[1], Nigat W. Chamesew[1], Tariku B. Jagema[2]

[1-3]Millennium COVID-19 Care Center, St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia

[1*]Corresponding author: Tigist W. Leulseged,

Research development office, Millennium COVID-19 Care Center, Addis Ababa, Ethiopia
Department of Internal Medicine, St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia
Phone: +251 911 45 02 53
Email address: tigdolly@gmail.com

ABSTRACT

Aim: To estimate time to getting off supplemental oxygen therapy and identify predictors among COVID-19 patients admitted to Millennium COVID-19 Care Center in Addis Ababa, Ethiopia.

Methods: A prospective observational study was conducted among 244 consecutively admitted COVID-19 patients from July to September, 2020. Frequency tables, KM plots, median survival times and Log-rank test were used to describe the data and compare survival distribution between groups. Cox proportional hazard survival model was used to assess the presence of a statistically significant association between time to getting off supplemental oxygen therapy and the independent variables, where hazard ratio, P-value and 95% CI for hazard ratio were used for testing significance and interpretation of results.

Results: Median time to getting off supplemental oxygen therapy among the studied population was 6 days. Factors that affect time to getting off supplemental oxygen therapy were age group (HR= 0.522, 95% CI= 0.323, 0.844, p-value=0.008 for ≥ 70 years) and shortness of breath (HR= 0.705, 95% CI= 0.519, 0.959, p-value=0.026).

Conclusions: Average duration of supplemental oxygen therapy requirement among COVID-19 patients was 6 days and being 70 years and older and having shortness of breath were found to be associated with prolonged duration of supplemental oxygen therapy requirement. This result can be used as a guide in planning institutional resource allocation and patient management to provide a well equipped care to prevent complications and death from the disease.

Key words: COVID-19, supplemental oxygen duration, predictors, prospective cohort, survival analysis, Cox PH model, Ethiopia

INTRODUCTION

The 2019 corona virus disease was first identified in China on December 2019 and later spread to the entire world and declared to be a pandemic by world health organization on March 11, 2020[1]. In Ethiopia the first case was identified on March 13, 2020, two days after the pandemic was declared. According to the national report, as of October 5, 2020, 79,437 cases were identified with 34,016 recovered and 1230 deaths. Since the disease transmission dynamic shifted to a community transmission, the number of new cases, those who need critical care and daily deaths are increasing, with 292 cases on critical care at different treatment centers in the country on the same day [2]. Considering the countries over burdened health care system, providing adequate care for COVID-19 patients who need hospitalization and especially supplemental oxygen therapy might be challenging if the pandemic continues.

To halt the transmission of the dynamics and because of limited knowledge on the disease progression and outcome, at first every patient who tested positive for SARS-COV-2 used to be quarantined and observed till recovery (declared by two consecutive negative RT-PCR results which are done 24 hours apart). But eventually as the number of case increases the admission and discharge criteria changed in order to accommodate the service to those who needs it most, this was also applied in our country [3,4].

Assessing the resources needed for admitted patients can be guided by the length of hospital stay or time needed to get biochemically or clinically improved. Assessing the later provides better detail about the disease effect on the patient and its burden on the health care system compared to assessing the length of stay per se as it also tells us the associated resource requirement during the hospital stay. In other words, a patient staying at a mild ward with no need of oxygen therapy or expensive antibiotics and someone on intensive care doesn't cost the same to the institution. This implies that, hospital length of stay could be influenced by not only the clinical condition of the patient but also because of the existing policies that differ with time and place that is set to control the pandemic better. Therefore, using length of stay as a clinical parameter may be biased and should not be used as an end point to assess clinical improvement from the disease.

Different studies are conducted that assessed the length of hospital stay of COVID-19 patients with a wide difference in reported values[5-12]. A systematic review that analyzed 45 studies conducted in different countries shows that the median length of hospital stay ranges from 4-53 days in China and 4-21 days outside China [13]. As explained above, these studies are influenced by the above changing criteria in admission and discharge that results in a different implication of length of hospital stay at different time of the pandemic and at different countries, one might imply duration from getting diagnosed to getting negative and another might imply from time of becoming symptomatic to a week or two after getting symptom free.

In addition, studies concerning biochemical recovery are conducted measuring the time from getting positive up to negative viral shedding as declared by two consecutive laboratory result of a RT-PCR that is done at least 24 hours apart[14-18]. Such kind of studies can provide an input in terms of understanding the viral shedding pattern so that decision about quarantine and self isolation can be made so that infection transmission can be minimized. Because of the change in the practice, being positive by itself is no more a criteria to guide patient admission and discharge. Thereby, its current cost implication to the health care system is minimal.

Since the current hospitalization policy focused on those who are symptomatic and need medication or supplemental oxygen therapy, understanding the oxygen requirement of severe COVID-19 patients and what predicts it is important. Knowing average duration of supplemental oxygen requirement helps not only in identifying who is at most risk and should be protected but it also assists in deciding on building hospitals capacity in terms of oxygen facility arrangement and organizing ICU and wards with inbuilt supplemental oxygen system. To the best of our knowledge, there is no such study conducted yet in both Ethiopia and outside.

Therefore, in this study we aimed to assess severe COVID-19 patients' clinical improvement by measuring the time needed from admission and being on supplemental oxygen therapy to getting off supplemental oxygen therapy and its predictors among patients admitted to Millennium COVID-19 Care Center in Ethiopia.

METHODS AND MATERIALS

Study setting and period

The study was conducted at Millennium COVID-19 Care Center (MCCC), a makeshift hospital in Addis Ababa, the capital city of Ethiopia.

Study Design

The study design was hospital based prospective observational design. The observation was made from July to September, 2020.

Source and Study Population

The source population was all severe cases of COVID-19 admitted at MCCC with a confirmed diagnosis of COVID-19 using RT-PCR, as reported by a laboratory given mandate to test such patients by the Ministry of Health and who were on follow up from July to September, 2020 [3].

During this interval a total of 244 COVID-19 patients were admitted to the Center. All the 244 patients were studied.

Sample size Determination and Sampling Technique

All consecutively admitted Severe COVID-19 patients during the follow up period were included in the study.

Eligibility criteria

All Severe COVID-19 patients who were on treatment and follow up at the MCCC from July to September, 2020 were included.

Operational Definitions

Event: Getting off supplemental oxygen therapy

Censoring: Includes patients lost to follow-up, transferred out, died or completed the follow-up period before getting off supplemental oxygen therapy.
Time to event or censoring: time between initiations of supplemental oxygen therapy to getting off oxygen supplement (in days).

Data Collection Procedures and Quality Assurance

An interviewer administered pretested questionnaire that consists of the variables of interest was developed from the patient registration and follow up form and used to collect the necessary data from the patients and their medical charts.

Training on the basics of the questionnaire and data collection tool 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 difference among survival distributions of groups for equality.

Univariate analysis was performed to calculate an unadjusted hazard ratio (HR) and to screen out potentially significant independent variables at 25% level of significance. Association between the most relevant independent variables and the time to getting off supplemental oxygen therapy was assesses using multivariable Cox proportional hazard survival model. Adjusted HR, P-value and 95% CI for HR were used to test significance and interpretation of results. Variables with p-value ≤ 0.05 were considered as statistically associated with time to getting off supplemental oxygen therapy in days. The basic assumptions of Cox Proportional Hazard model was tested using log minus log function.

RESULT

Censoring status and median time to getting off oxygen

Among the 244 patients, 191 (78.3%) of the patients achieved the event (getting off supplemental oxygen therapy) while 53 (21.7%) were censored.

The median time to getting off supplemental oxygen therapy was 6 days and it ranges from 2 to 35 days.

Socio-demographic, Co-morbid illness and drug use history, censoring status and survival experience

Equal proportions (21.7%) of patients were included in the study in the age groups; below 40 years, 60 to 69 years and ≥ 70 years. A smaller proportion was in 50 to 59 years. Two third (67.6%) of the patients were males. More than half (56.9%) had a history of one or more co-morbid illness. The greater proportion of the study participants were hypertensive (33.6%), followed by diabetes mellitus (28.7%), cardiac illness (11.9%) and asthma (6.1%). Thirty three (13.5%) had a history of ACEIs and/or ARBs and/or NSAID use within 14 days of admission to the center.

In all of the variable categories, the number of event achieved is greater than the censored observation. The proportion of censored observation is relatively larger as age increases, for males, for those patients with one or more pre-existing comorbid illness history and Khat chewers. On the other, those with a history of drug use had a relatively less censored observation than those with no drug use history.

The log rank test result shows that, there was a significant difference in the survival time among the patients based on age group, history of pre-existing co-morbid illness, hypertension and diabetes mellitus. Accordingly, the median duration of oxygen requirement is significantly longer for those patients ≥ 70 years (22 days) followed by 50 to 69 years (8 days) and then < 50 years (6 days) ($X^2_{(4)}$= 15.162, P-value= 0.004). Having a history of one or more pre-existing comorbid illness (7 Vs 8 days, $X^2_{(4)}$= 4.449, P-value= 0.035), hypertension (7 Vs 9 days, $X^2_{(1)}$= 5.204, P-value= 0.023) and diabetes mellitus (7 Vs 8 days, $X^2_{(1)}$= 6.773, P-value= 0.009) resulted in a prolonged oxygen therapy requirement compared to those with no such illness.

On the other hand, the survival time did not show statistically significant difference among the patients based on sex, history of cardiac illness, asthma, khat chewing and drug use history (all p-values >0.05). (**Table 1**)

Table 1: *Socio–demographic, co-morbid illness and drug use history related variables censoring status and survival experience among COVID-19 patients (n=244)*

Variable	**Censoring status**		**Total (%)**	**Median survival time (days)**	**P-vlaue**
	No of event (%)	**No of censored (%)**			
Age					
< 40	47 (88.7)	6 (11.3)	53 (21.7)	6	**0.004***
40-49	36 (81.8)	8 (18.2)	44 (18.0)	6	
50-59	33 (80.5)	8 (19.5)	41 (16.8)	8	
60-69	41 (77.4)	12 (22.6)	53 (21.7)	8	
≥ 70	34 (64.2)	19 (35.8)	53 (21.7)	22	
Sex					
Female	64 (81.0)	15 (19.0)	79 (32.4)	9	0.091
Male	127 (77.0)	38 (23.0)	165 (67.6)	6	
Preexisting Co-morbid illness					
No	92 (87.6)	13 (12.4)	105 (43.0)	7	**0.035***
Yes	99 (71.2)	40 (28.8)	139 (56.9)	8	
Cardiac					
No	173 (80.5)	42 (19.5)	215 (88.1)	8	0.076
Yes	18 (62.1)	11 (37.9)	29 (11.9)	20	
Hypertension					
No	134 (82.7)	28 (17.3)	162 (66.4)	7	**0.023***
Yes	57 (69.5)	25 (30.5)	82 (33.6)	9	
DM					
No	147 (84.5)	27 (15.5)	174 (71.3)	7	**0.009***
Yes	44 (62.9)	26 (37.1)	70 (28.7)	8	
Asthma					
No	180 (78.6)	49 (21.4)	229 (93.8)	8	0.312
Yes	11 (73.3)	4 (26.7)	15 (6.1)	22	
Medication use history within 14 days of admission (ACEIs, ARBs and NSAIDs)					
No	165 (78.2)	46 (21.8)	211 (86.5)	7	0.211
Yes	26 (78.8)	7 (21.2)	33 (13.5)	20	

As shown in **Figures 1** the KM survival function graph also showed that patients in the younger age group have a favorable survival experience compared to those who are in the immediate older age group. Similarly, both the survival and hazard function graphs showed that a favorable survival experience is observed among patients with no history of pre-existing co-morbid illness compared to those with one or more co-morbid illness/s.

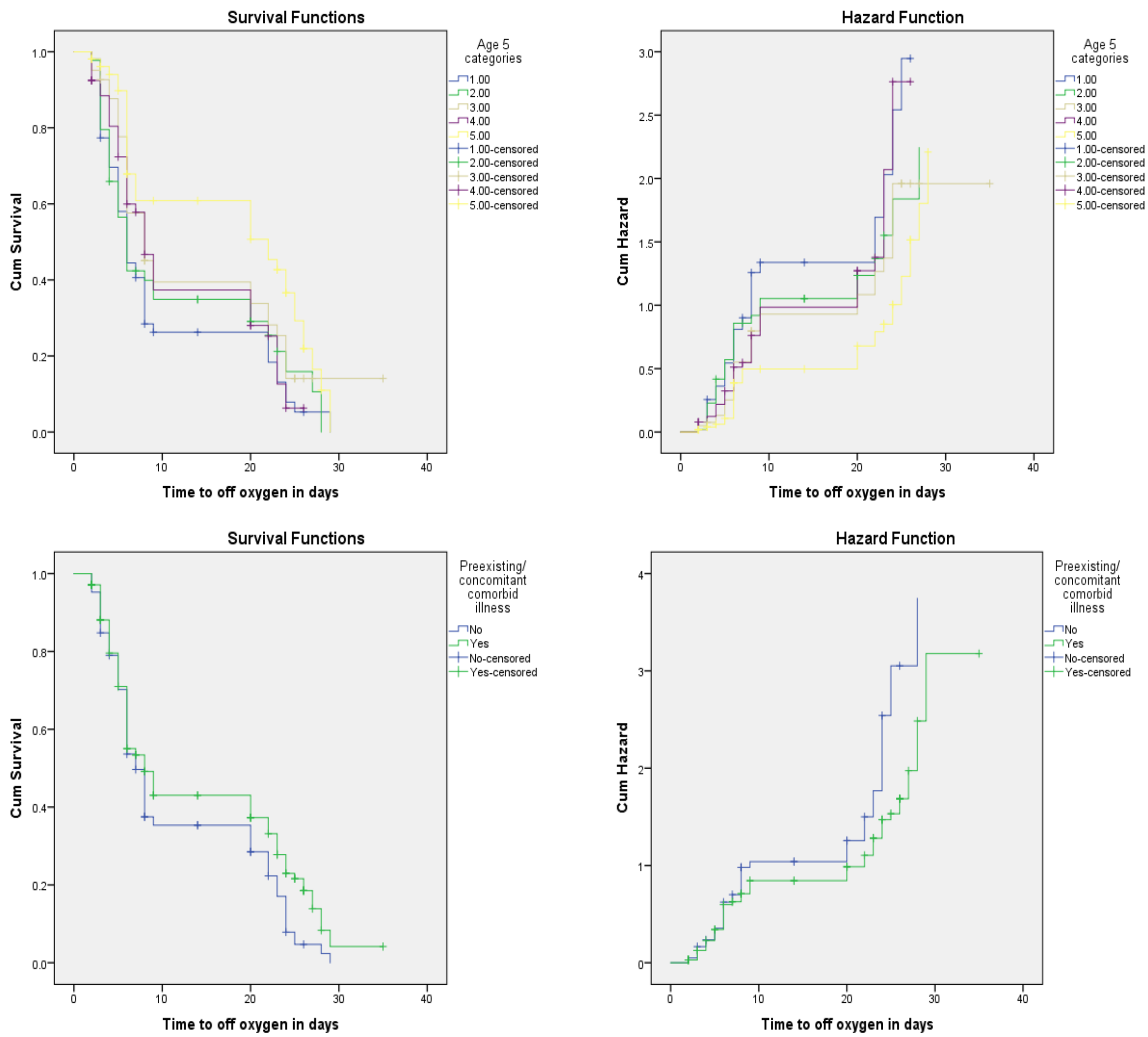

Figure 1: *Survival and Hazard functions for age group and pre-existing co-morbid illness by time*

Presenting symptom related variables, censoring status and survival experience

Two hundred thirty two (95.1%) of the patients were symptomatic at presentation. The most frequent complaint was cough (80.7%) followed by Shortness of breath (64.3%), Cough with sputum (47.5%), Fatigue (47.5%), Fever (34.8%), Chest pain (34.1%), Headache (24.6%), Arthralgia (19.7%), Myagia (16.8%), Sore throat (16.4%), Nausea/ vomiting (7.8%) and Diarrhea (5.7%).

The proportion of patients who achieved the event was greater than the censored observation in all of the patients with the above symptom categories.

According to the log rank test result, a significantly longer duration of oxygen therapy was needed among patients with a complaint of shortness of breath (8 days) compared to those with no such complaint (6 days) ($X^2_{(4)}$= 4.494, P-value= 0.034). On the contrary, the log rank test didn't show any significant difference in the survival time among the other symptom groups (all p-values >0.05). (**Table 2**)

Table 2: *Presenting symptom related variables censoring status and survival experience among COVID-19 patients (n=244)*

Variables	Censoring status		Total (%)	Median survival time (days)	P-vlaue
	No of event (%)	No of censored (%)			
Presence of symptom					
Asymptomatic	11 (91.7)	1 (8.3)	12 (4.9)	6	0.662
Symptomatic	180 (77.6)	52 (22.4)	232 (95.1)	8	
Fever					
No	118 (74.2)	41 (25.8)	159 (65.2)	8	0.360
Yes	73 (85.9)	12 (14.1)	85 (34.8)	7	
Cough					
No	35 (74.5)	12 (25.5)	47 (19.3)	8	0.465
Yes	156 (79.2)	41 (20.8)	197 (80.7)	8	
Cough with sputum					
No	102 (79.7)	26 (20.3)	128 (52.5)	7	0.603
Yes	89 (76.7)	27 (23.3)	116 (47.5)	8	
Sore throat					
No	156 (76.5)	48 (23.5)	204 (83.6)	8	0.887
Yes	35 (87.5)	5 (12.5)	40 (16.4)	8	
Chest pain					
No	121 (75.2)	40 (24.8)	161 (65.9)	8	0.230
Yes	70 (84.3)	13 (15.7)	83 (34.1)	8	
Myalgia					
No	157 (77.3)	46 (22.7)	203 (83.2)	8	0.193
Yes	34 (82.9)	7 (17.1)	41 (16.8)	6	
Arthralgia					
No	153 (78.1)	43 (21.9)	196 (80.3)	8	0.482

Yes	38 (79.2)	10 (20.8)	48 (19.7)	6	
Fatigue					
No	102 (79.7)	26 (20.3)	128 (52.5)	8	0.466
Yes	89 (76.7)	27 (23.3)	116 (47.5)	8	
SOB					
No	73 (83.9)	14 (16.1)	87 (35.7)	6	**0.034***
Yes	118 (75.2)	39 (24.8)	157 (64.3)	8	
Headache					
No	143 (77.7)	41 (22.3)	184 (75.4)	8	0.949
Yes	48 (80.0)	12 (20.0)	60 (24.6)	8	
Nausea/ vomiting					
No	176 (78.2)	49 (21.8)	225 (92.2)	8	0.638
Yes	15 (78.9)	4 (21.1)	19 (7.8)	7	
Diarrhea					
No	182 (79.1)	48 (20.9)	230 (94.3)	8	0.398
Yes	9 (64.3)	5 (35.7)	14 (5.7)	20	

As shown in **Figures 2** the KM survival function graph also showed that those with no symptom of shortness of breath at admission have a favorable survival experience (time to getting off supplemental oxygen therapy) compared to those with such symptom. The hazard function also shows that, for those patients with no shortness of breath the instantaneous chance of getting off supplemental oxygen therapy increases as the duration of treatment increases.

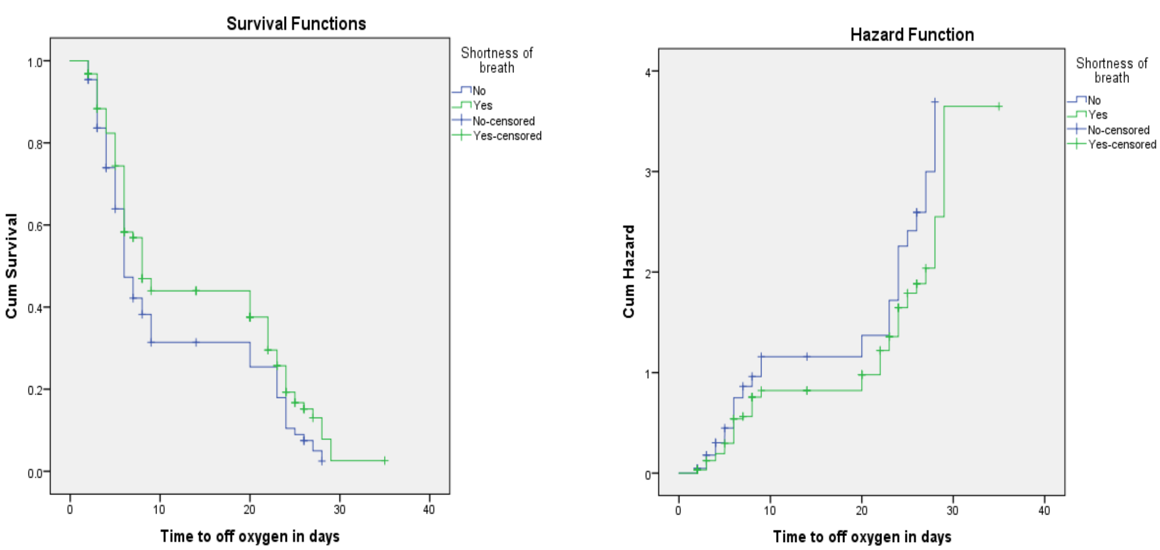

Figure 2: *Survival and Hazard functions for shortness of breath by time*

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 [19]. **Figures 3** shows that throughout the study time the survival curves seems to be parallel among the groups classified by age group and the presence of shortness of breath. Therefore, these plots show reasonable fit to the proportional hazard assumption.

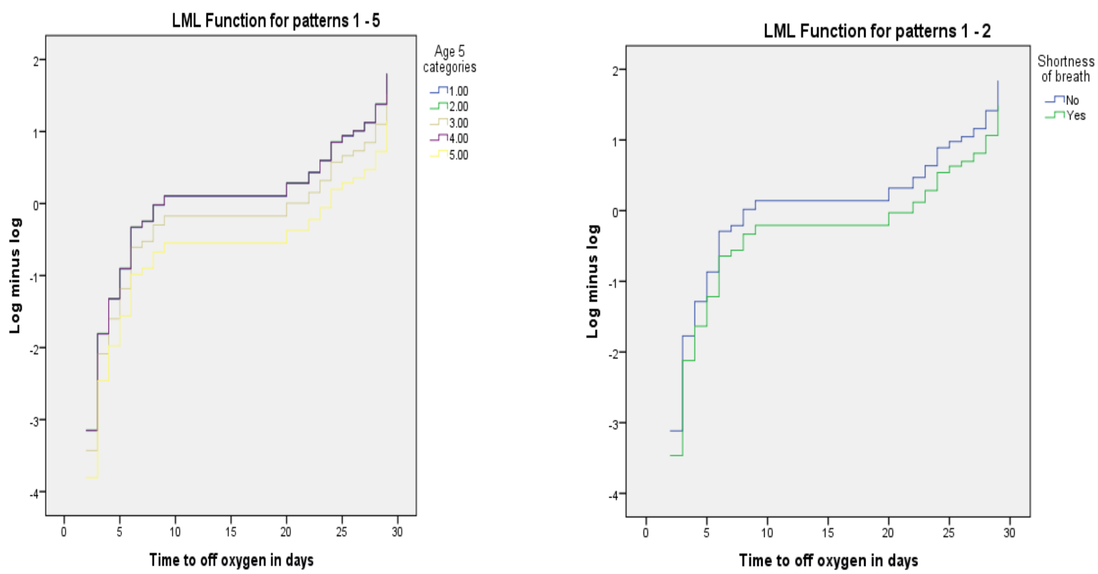

Figure 3: *Log minus Log function for age group and shortness of breath*

Univariate analysis of each independent variable with the dependent variable was run. From univariate analysis at 25% level of significance; age group, sex, cardiac illness, hypertension, diabetes and Shortness of breath were significantly associated with duration of supplemental oxygen therapy requirement among COVID-19 patients.

However; only age group and a complaint of shortness of breath were found to be significantly associated with duration of supplemental oxygen therapy requirement in the multivariable Cox proportional hazard model at 5% level of significance.

Accordingly, after adjusting for other covariates, the rate of getting off supplemental oxygen therapy among patients ≥ 70 years was 47.8% lower than patients < 40 years old (HR= 0.522, 95% CI= 0.323, 0.844, p-value=0.008). This implies that the time needed to get off supplemental oxygen therapy was significantly longer among older patients compared with the younger patients.

Having a complaint of shortness of breath at admission was associated with a 29.5% lower rate of achieving target of off oxygen therapy compared to those patients with no such complaint on admission (HR= 0.705, 95% CI= 0.519, 0.959, p-value=0.026). (**Table 3**)

Table 3: *Result of Multivariable Cox proportional hazard model among COVID-19 patients (n=244)*

Variable	CHR (95% CI)	AHR (95% CI)	P-value
Age group (in years)			
< 40	1	1	**0.034***
40-49	0.878 (0.567, 1.358)	1.009 (0.642, 1.586)	0.969
50-59	0.655 (0.419, 1.024)	0.760 (0.478, 1.209)	0.247
60-69	0.820 (0.538, 1.249)	1.005 (0.634, 1.592)	0.983
≥ 70	0.475 (0.304, 0.740)	**0.522 (0.323, 0.844)**	**0.008***
Sex			
Female	1	1	0.253
Male	1.271 (0.940,1.721)	1.226 (0.865, 1.739)	
Cardiac			
No	1	1	0.811
Yes	0.668 (0.410, 1.088)	1.937 (0.550, 1.598)	
Hypertension			
No	1	1	0.909
Yes	0.716 (0.523, 0.978)	0.978 (0.671, 1.426)	
Diabetes			
No	1		
Yes	0.660 (0.469, 0.929)	0.786 (0.540, 1.145)	0.209
SOB			
No	1	1	
Yes	0.746 (0.557, 1.001)	**0.705 (0.519, 0.959)**	**0.026***

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

DISCUSSION

The median time to getting off supplemental oxygen therapy among the studied population was 6 days. Previous studies that focused on length of hospital stay are conducted but there is no study that assessed duration of oxygen requirement[5-13]. Our study assessed this outcome as an indicator of clinical improvement from the disease as duration of stay is affected by national and international recommendations which varies from time to time based on admission and discharge criteria that might result in delayed discharge of patients till becoming non infectious even after clinical improvement. Knowing median duration of oxygen requirement assists in deciding on building hospitals capacity in terms of oxygen facility arrangement and organizing ICU and wards with inbuilt supplemental oxygen system so that maximum capacity can be used to provide better care to patients in the country.

On the univariate analysis, age group, sex, cardiac disease, hypertension, diabetes mellitus and shortness of breath were found to be independent predictors of duration of oxygen requirement among COVID-19 patients. But on the multivariable Cox proportional hazard model, after adjusting for other covariates, only age group and shortness of breath were found to be significant predictors of duration of supplemental oxygen requirement among COVID-19 patients.

Accordingly, after adjusting for other covariates, the rate of getting off supplemental oxygen therapy among patients 70 years and above was 47.8% lower than patients less than 40 years old. This implies that the time needed to get off supplemental oxygen therapy was significantly longer among older patients compared with the younger patients. This could be because of the increased risk of having concomitant comorbid illness and the normal aging process that diminishes body's defense mechanism. These factors result in a more severe disease progression with delayed recovery or death. Studies also support this finding showing that old age is associated with high risk of developing symptomatic disease, severe disease category and death from COVID-19 as compared to younger age group. Especially the patients 70 years and above were found to be vulnerable to much worse disease progression and outcome than other age groups[20-23].

Having a complaint of shortness of breath at admission was found to be associated with a significantly prolonged duration of supplemental oxygen requirement. The rate of getting off supplemental oxygen therapy among patients with shortness of breath was 29.5% lower compared to those patients with no such complaint on admission. Shortness of breath is a sign of lung disease. SARS-COV-2 can affect any part of the body system but the lungs are said to be more susceptible because the virus entry in to the body is made through the airways. The other reason is the abundance of angiotensin-converting enzyme 2 in the lungs that is used as a receptor by the SARS-COV-2 to enter in to the body cells. Also, if the individual develops pneumonia, it is usually going to affect both lungs compromising the lungs capacity and resulting in a drop in blood oxygen level. Because of these reasons, if the lungs got hit by the virus, it results in a more severe disease especially among those with underlying pulmonary disease resulting in a severe disease presentation and delayed recovery causing a prolonged oxygen requirement.

On the other hand, the result shows that the duration of oxygen requirement doesn't significantly differ based on sex and co-morbid illness/s history.

CONCLUSION

Average duration of supplemental oxygen therapy requirement among COVID-19 patients was 6 days. This can be used as a guide in planning institutional oxygen requirement, bed demand at Intensive care unit and wards with inbuilt oxygen supply system, and in predicting patient turn over at these units. This in turn can be used to predict institutional capacity to admit and treat patients who require oxygen therapy.

Age group of 70 years and above and having shortness of breath were found to be associated with prolonged duration of supplemental oxygen therapy requirement. This implies that, earlier identification of disease progression is advised to identify these groups of patients so that early intervention and maximum care can be provided to prevent complication from the disease and the supplemental oxygen therapy itself.

Declaration

Ethical Considerations

The study was conducted after obtaining ethical clearance from St. Paul's Hospital Millennium Medical College Institutional Review Board. Written 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

Funding source: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors Contribution: TWL and ISH conceived the study. TWL designed the study, revised data extraction sheet, performed statistical analysis, and drafted the initial manuscript. All authors contributed to the conception of the study and obtained patient data. All authors undertook review and interpretation of the data. All authors revised the manuscript and approved the final version.

Acknowledgment

The authors would like to thank St. Paul's Hospital Millennium Medical College for facilitating the research work.

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

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