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Original Article

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

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Abstract

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

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

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

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

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

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

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

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

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

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

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

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

Methodology

Study Design, Population and Sample size

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

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

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

Operational Definition

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

Data Collection and Quality Assurance

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

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

Statistical Analysis

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

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

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

RESULT

Incidence of PE and Disease outcome among COVID-19 patients

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

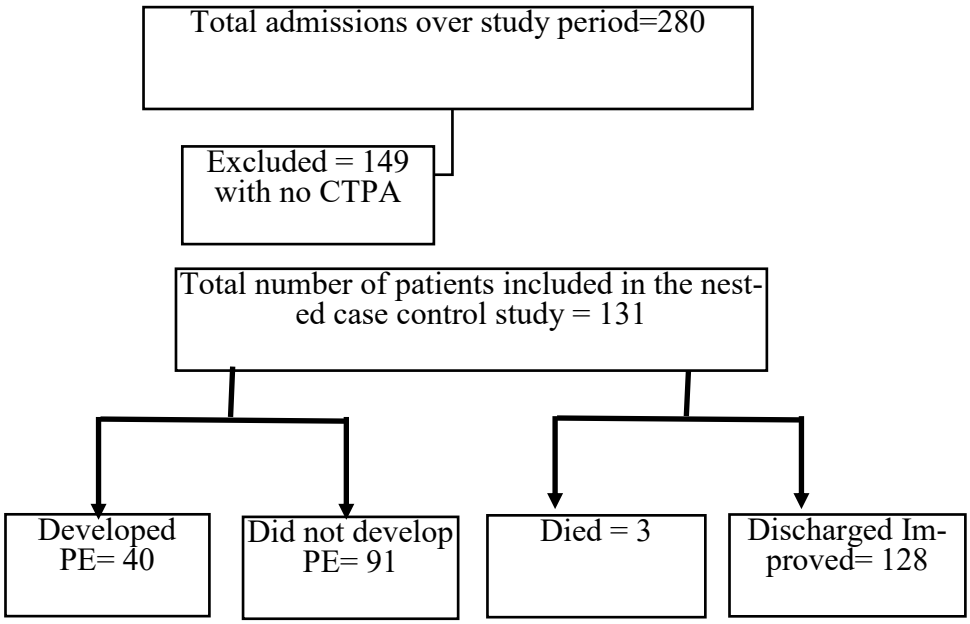

Figure 1: Flow chart showing the disposition of study participants in the final analysis, Addis Ababa, Ethiopia, 2022

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

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

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

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

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

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

Presenting symptoms characteristics

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

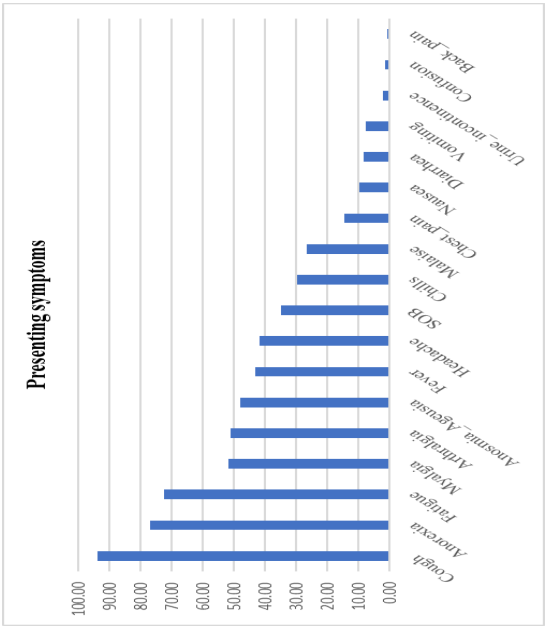

Figure 2: Presenting symptoms of participants with frequency, Addis Ababa, Ethiopia, 2022

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

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

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

Baseline vital sign and laboratory biomarkers

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

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

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

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

Factors associated with development of PE among COVID-19 patients

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

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

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

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

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

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

DISCUSSION

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

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

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

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

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

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

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

Conclusion

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

List of Abbreviations

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

Declaration

Ethics approval and consent to participate

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

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

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

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

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