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Internal Medicine

ANALYSIS OF FACTORS AFFECTING ICU STAY IN COVID-19 PATIENTS WITH PULMONARY AND VASCULAR MANIFESTATIONS

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ABSTRACT
Background: Pulmonary involvement and coagulopathy are common abnormalities in critically ill COVID-19 patients despite prophylactic anticoagulation. We sought to study the effect of severity of pulmonary and vascular manifestations, and other factors at the time of presentation in COVID-19 patients and their association with ICU stay duration, patient morbidity and mortality. **Patients and methods:** A retrospective cohort study performed over 219 patients admitted to COVID ICU in a tertiary care hospital over a period of 3 months. Diagnosis and severity grading of pulmonary and/or vascular manifestation was demonstrated using radiological imaging modalities such as x-ray, USG, CT and/or MRI. **Results:** The effect of the severity of pulmonary manifestations (p-value-0.000) was statistically significant on the length of ICU stay and increased mortality of the patient. Out of 219 patients, 9 patients had cerebral Infarcts and 3 patients developed ICH, venous and arterial thrombosis each respectively. However, the presence of vascular manifestation in COVID-19 patients showed higher morbidity ,mortality and ICU stay with non significant effect size (p-value-0.651).**Conclusion:** Our study provides evidence for guiding the rationality of resource directions for the needs of a large number of severe patients and may help to triage the severe patients in the early preparation for the subsequent wave of COVID-19 cases.

INTRODUCTION:

In December 2019, China reported deaths attributed to the flu-like syndrome Covid-19 [1]. By July 2020 there were over 14M patients diagnosed with Covid-19 and 600,000 deaths worldwide, with over 3.9M diagnosed and 142,000 deaths in the United States [2]

The objective of this study was to analyze the effect of vascular manifestations and other risk factors on ICU admission or death. Although some authors have described predictors of critical care needs[3], it has not been validated in various populations at different medical centers. Some authors have published on various predictors of critical illness. Liang et al. described variables that were independent factors predicting a serious illness: chest radiographic abnormality, age, hemoptysis, dyspnea, unconsciousness, number of comorbidities, cancer history, neutrophil-to-lymphocyte ratio, lactate dehydrogenase, and direct bilirubin[3]. Garg et al. concluded that underlying medical comorbidities, older age, diabetes, obesity, and male sex identified biological vulnerabilities for more severe Covid-19 outcomes[4]. Zhou et al. showed increased odds of in-hospital death associated with older age, higher Sequential Organ Failure Assessment (SOFA) score, and d-dimer greater than 1 µg/mL on admission[5]. Few studies have reported high rates of thromboembolic events in critically ill patients with COVID-19 (17–22%) despite their having received prophylactic anticoagulation. [6]

We sought to study the effect of pulmonary and vascular manifestations, and other factors at the time of presentation in COVID-19 patients that are associated with ICU admissions or death. Early identification of patients at risk for developing critical illness can aid in triage and may improve outcomes in patients with Covid-19.

Materials & Methods:

Study Design: Hospital-based retrospective cohort study.
Study period: 3 months (June 15th – September 15th, 2020).
Study Area: Tertiary care Hospital.
Sample size: with the convenient sampling method
Patients Selection: On admission, the patients were triaged clinically according to the signs , symptoms and various comorbidities into category A to F. These are as follows-
Stage 1: Mild (Early Infection) - Groups A, B & C

    Group   A: Asymptomatic but positive for COVID-19
    Group   B: Symptomatic/URTI without comorbidity
    Group   C: Symptomatic/URTI with comorbidities like obesity,>60Yrs,

DM, HTN/IHD, COPD/Immunocompromised State, and CKD.

Stage IIa: Moderate (Pulmonary Involvement Without Hypoxia) - Group D
Stage IIb: Moderate (Pulmonary Involvement with Hypoxia) - Group E
Stage III: Severe (Systemic Hyper inflammation with Cytokine Storm)- Group F

Severity of pulmonary and/or vascular involvement was assessed using x-ray, USG, CT and/or MRI.

This severity score was adapted from the one proposed by Feng et al. (7) for patients with pneumonia secondary to avian influenza virus infection and was calculated as follows: each lung was divided craniocaudally into three main zones. The upper zone included the parenchymal region above the carina, the middle zone included the parenchyma below the carina and above the inferior pulmonary vein, and the lower zone involved the parenchyma below the inferior pulmonary vein; given their anatomical extent, the middle and lower zones were further divided into a lateral and a medial area (i.e. five regions per lung for a total of ten regions). A maximum of 10% of parenchymal involvement was assigned for each area. If an area was partly spared, a score of 5% was considered. The scores of each lung were summed up to provide the final severity score. A score of 0 was defined as a total lung involvement of 0%, whereas a score of 1, 2, 3, and 4 indicated a total lung involvement in the range of 1-25%, 26-50%, 51-75%, and 76-100%, respectively.

<=25% involvement - Mild (score-1)
25-50% involvement - Moderate(score-2)
>50% involvement - Severe/ARDS (score-3, 4)

Vascular manifestations such as cerebral Infarct, ICH, vein and arterial thrombosis were diagnosed using CT, MRI and USG Doppler studies if clinically and biochemically indicated.

Inclusion criteria:

1. All patients with RTPCR positive confirmed COVID 19 infection admitted to the ICU who were imaged as part of the normal treatment and follow-up protocol.
2. Patients clinically classified as category D or above in the ICU.
3. Adult patients over the age of 18 years.
4. Patients who were diagnosed for vascular coagulopathy using radiological imaging.

Exclusion criteria:
1. Patients not admitted to the ICU.
2. Patients with RTPCR test negative.
3. Patients clinically classified as category A, B, and C.
4. Patients in whom imaging data was not available/ performed.
5. Patients with the old history of stroke.
6. Paediatric patients and patients below 18 years of age.

Data collection: Manual search method from the hospital medical records, Hospital patient database (PALASH software), and radiology information system (PACS) was done.

Statistics:
SPSS version 20 version was used for analysis. Descriptive statistics were performed. Ordinal and nominal variables were expressed in terms of percentages with 95% confidence interval (CI) while continuous variables were expressed in terms of the median with range. A p-value of 0.05 or below was considered statistically significant while an effect size of 0.5 or above was considered clinically significant. The data was censored for analysis on 15th September 2020.

RESULTS
Our study was conducted in a tertiary care hospital over a period of 3 months with 219 patients admitted to the COVID ICU who were imaged as part of the normal treatment and follow-up protocol.

Baseline characteristics and their effect on the ICU stay and mortality are demonstrated in Table 1. The various vascular complications affecting the ICU stay (Table 1) and mortality (Figure 1) are depicted.

Table 1:- Analysis of ICU Stay based on the Covid-19 vascular manifestation

| Variable	Event (Death)	Mean ICU stay (in days)	Confidence Interval	p-value (Log-rank)
Absent(n-201)	61	26	16.74-35.21	0.651
Present(n-18)	7	18	13.10-22.91	
Cerebral Infarct(n-9)	3	14	9.80-17.68	0.207
Intracranial Hemorrhage (n-3)	2	17	-	
Vein Thrombosis (n-3)	2	12	3.87-19.12	
Arterial Thrombosis (n-3)	0	16	5.79-27.54	
Overall (n-219)	68	28	19.12-36.58	
Comorbidities Diabetes (n-90)	35	26	14.45-37.13	0.380
Hypertension (n-98)	38	14	12.34-15.44	0.048
COPD (n-09)	01	16	13.57-19.31	0.101
IHD (n-16)	07	14	09.69-18.85	0.408
Anemia (n-05)	00	--	--	0.139
CVA (n-01)	00	--	--	0.310
Malignancy (n-02)	00	--	--	0.457
Psychiatric (n-01)	01	05	--	0.013
CKD (n-17)	13	12	07.45-15.94	0.010
CLD (n- 03)	01	10	05.84-14.15	0.771
None (n-61)	09	23	16.20-29.44	0.054
Multiple (n-73)	34	13	11.56-15.01	0.007
Age Less than 65 (n-138)	28	21	16.62-24.71	0.001
More than 65 (n-81)	40	22	12.31-31.66	
Sex Male (n-147)	42	17	13.99-20.03	0.898
Female (n-72)	26	33	22.92-43.93	
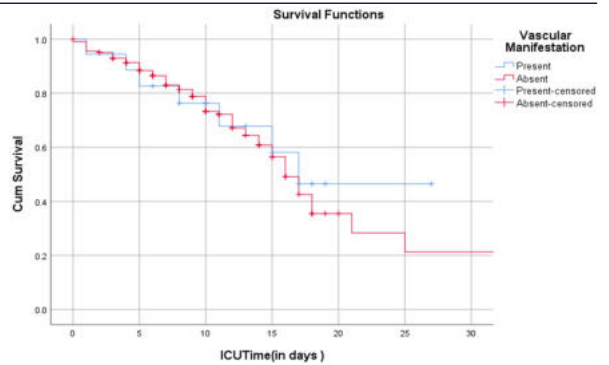
Figure 1:- Analysis of survival based on the presence of vascular manifestations

Among the various important factors responsible are hypertension, age > 65 years (figure 2), psychiatric illness, and multiple comorbidities. Table 2 depicts the severity of pulmonary manifestations affecting ICU stay (Figure 3) wherein the severe the acute respiratory distress is present, shorter is the stay and higher is the mortality.
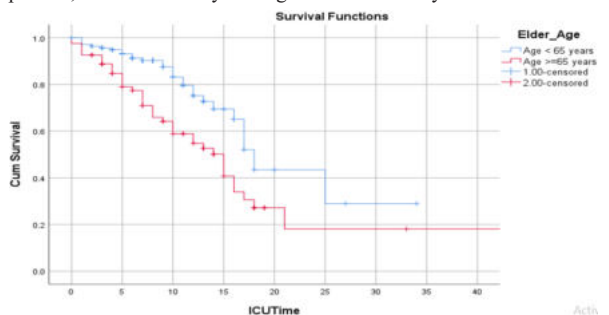

Figure 2:- Analysis of survival based on Age

Table 2:-Analysis of ICU Stay based on the severity of Covid-19 pulmonary manifestation

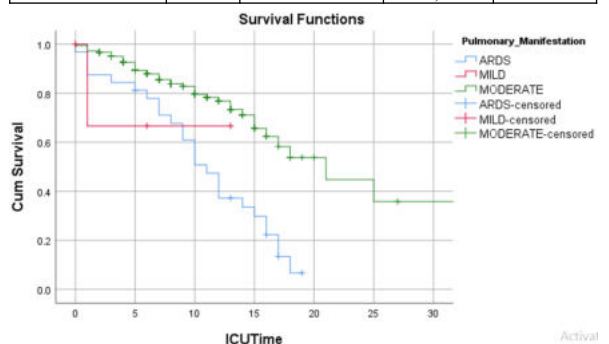| Variable	Event (Death)	Mean ICU stay (in days)	Confidence Interval	p-value
ARDS (n-32)	26	11	(8.76-12.79)	0.000 (Log rank)
Moderate (n-183)	41	35	(23.19-46.82)	
Mild (n-4)	1	9	(2.59-15.40)	
Overall (n-219)	68	28	(19.12-36.58)	

Figure 3:- Survival curves based on the severity of Covid-19 pulmonary manifestation

DISCUSSION:
In the previously reported case series of COVID-19, consistent with other previous reports [8,9], older patients (≥65 years old) were more severely affected by COVID-19. A study by Margarita Posso et al [10] in Spain revealed hypertension to be the most frequent (64.6%)comorbidity, followed by chronic kidney disease (29.3%), diabetes (28.1%), chronic respiratory disease (17.1%), heart failure (11.9%), obesity (6.6%), malignancy (5.4%), and chronic liver disease (2.3%). F.A. Kloket al [11] in the month of March and April showed a

31% incidence of thrombotic complications in ICU patients with COVID-19 infections which were remarkably high.

This study demonstrates the various important factors responsible for the length of ICU stay, morbidity, and mortality. Hypertension (p-value- **0.048)**, age > 65 years(p-value- **0.001)**, psychiatric illness(p-value- **0.013)**, and multiple comorbidities(p-value-**0.007)** showed statistically significant results. The effect of the severity of pulmonary manifestations (p-value-0.000) was statistically significant on the length of ICU stay and the increased mortality of the patient. However, the presence of vascular manifestation in COVID-19 patients leads to higher morbidity and mortality and ICU stay with non-significant effect size (p-value-0.651).

The Strengths of the study include the inclusion of consecutive patients, the follow.up duration of at least 3months, no loss to follow.up, and the radiological and objectively confirmed diagnosis of vascular events. Our study provides evidence for triaging based on comorbidities, pulmonary manifestations, and vascular manifestations in a novel manner by examining the length of hospitalization, an important but underreported indicator, and its associated factors responsible for morbidity and mortality in tertiary ICU care.

Our study was a single-center study with an underpowered sample size. Much demographic information on medical history, treatment received before admission, and the date of diagnosis and symptom onset were prone to recall bias. Finally, we also acknowledge the relatively short median follow.up duration, the number of patients still hospitalized, and the (informative) censoring of patients when discharged from the hospital in the analysis.

CONCLUSION:
In this retrospective cohort study of severe COVID-19 patients who were with vascular manifestations was associated with higher morbidity and mortality. Furthermore, comorbidities, age, and severity of pulmonary manifestation do have significant influences on the length of ICU stay, morbidity, and mortality. Our study provides evidence for guiding the rationality of resource directions for the needs of a large number of severe patients and may help to triage the severe patients in the early preparation for the subsequent wave of COVID-19 cases**.**

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