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Association of Comorbidities & Disease Outcome in COVID-19 Patients in A tertiary Care Medical College in India

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ABSTRACT

Background: Severe acute respiratory syndrome corona virus-2 [SARS CoV2], the virus that cause the COVID-19 pandemic remained a persistent challenge worldwide. India emerged as the second most affected nation after the United States. Many previous studies confirmed the association of comorbidities like diabetes, hypertension, etc. as associated with adverse outcomes in COVID-19.

Aim of the work: The current study aimed to ascertain the association of comorbidities like diabetes, hypertension, and CAD with adverse disease outcomes in COVID-19 pneumonia.

Patients and Methods: A retrospective observational study was conducted with the data retrieved from medical records of patients admitted with a reverse transcription-polymerase chain reaction [RT-PCR] positive COVID-19 in the intensive care unit [ICU] of a tertiary medical college. We analyzed 467 RT-PCR confirmed COVID19 cases with respect to the association with adverse and critical disease states. Criticality was defined as any one of: a] use of ventilation, b] death or c] Radiographic assessment of lung edema [RALE] Score >24.

Results: Of the total cases among critical cases, 52% [95% CI 46%-59%] has comorbidity and non-critical cases 41% had comorbidity [95% CI 34%-48%]. The prevalence of diabetes among critical cases was 43% [95% CI 37%-49%] while in non-critical cases it was 28% [95%CI 21%-34%]. Hypertension was prevalent in 30% [95% CI 24%-37%] in non-critical cases while it was prevalent in 33 % [95% CI 27%-38%] in critical cases. We also examined the association of comorbidities in the ICU admitted cohort and found that there is a significant association of diabetes [p-<0.01] and hypertension [p-<0.01], Obesity [p<0.05], and CAD [p<0.05] with adverse disease outcome.

Conclusion: Three most common comorbidities, diabetes, hypertension, and obesity have statistically significant associations with adverse outcomes in COVID 19. There was also a statistically significant association seen with CAD, probably due to the thrombogenic potential of COVID-19.

Keywords: COronaVIrus Disease; SARS CoV2; Comorbidity; Indian; Southeast Asian

INTRODUCTION

COrona VIrus Disease [COVID-19] pandemic has been a persistent threat to the worldwide population; India has emerged as the second most affected country after the United States. COVID-19's pathogen has been identified as severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2], which is related to SARS-like coronavirus [1].

SARS-CoV-2 was found to be a member of the -coronavirus 2b lineage in the phylogenetic tree. The whole genome of SARS-CoV-2 was examined, and it was discovered that this unique virus shares 87.99 percent homologous sequences with SARS-like coronaviruses [2]. SARS-CoV-2, like SARS-CoV, has been found to infect human cells expressing angiotensin-converting enzyme 2 [ACE2]. SARS-CoV-2 is thought to be the third zoonotic human coronavirus in this century, based on current information [3].

COVID-19 is SARS-like atypical pneumonia that can be transferred from person to person, primarily through respiratory droplets, but also through contact with eye mucosa, according to early findings from Wuhan. Although the virus has been found in feces, the virus transmission through the digestive tract has yet to be established. In most cases, the incubation period is 2–14 days. Fever, muscle soreness, weariness, and a dry cough characterize mild cases. Several patients complained of neurological and gastric issues. Dyspnea can develop after a week in severe cases. Acute respiratory distress syndrome, septic shock, and metabolic acidosis develop in severe cases, making them difficult to care for [4-6].

The basic reproduction number [R0] of SARS-CoV-2 was predicted to be around 2.2 and even greater in early epidemiological studies [ranging from 1.4 to 6.5]. COVID-19 has a low death rate and a high morbidity rate, making it difficult to control virus spread [7, 8].

Many studies [8-10] have found an association of comorbidities like diabetes, hypertension, coronary artery disease [CAD], a respiratory disease with COVID-19 and its adverse outcomes [11, 12]. We as tertiary care teaching medical colleges in central India are managing COVID-19 cases, most of which are referral cases.

THE AIM OF THE WORK

The aim of this study was to ascertain the association of comorbidities like diabetes, hypertension, and CAD with adverse disease outcome in COVID19 pneumonia

PATIENTS AND METHODS

Study design: A retrospective observational study was conducted with the data retrieved from medical records of patients admitted with Reverse Transcription–Polymerase Chain Reaction [RT-PCR] positive COVID-19 in the Intensive Care Unit [ICU] of CR Gardi Hospital, RD Gardi Medical College, Ujjain Madhya Pradesh. In this study, we analyzed 467 RT-PCR confirmed COVID-19 cases with respect to the association with adverse and critical disease states. Critical disease was defined as any one of a] use of ventilation, b] death or c] Radiographic assessment of lung edema [RALE] Score >24 [17].

Eligibility Criteria: All RT-PCR confirmed COVID-19 cases admitted to ICU of our hospital, age 15 years onward were included in the study. Those patients/legal guardians denying consent for the study were excluded.

Participants: From the medical record section of our institute, records of 467 eligible patients admitted in COVID-19 dedicated ICU from June 2020 to January 2021 were analyzed for the study.

Variables: Data were retrieved from the medical record section, following information was noted [i] demographic parameters [age, sex] of the patients; [ii] presenting symptoms and duration of symptoms; [iii] presence of any comorbid illness [hypertension, diabetes, coronary artery disease, cerebrovascular disease, Chronic Kidney Diseases [CKDs], [iv] available investigations [complete blood count, liver and kidney function tests, electrolytes, chest X-ray, etc.], [v] outcome [vi] disease course and ventilatory requirement status. Diabetes was defined as per the American diabetic association's definition of diabetes as HBA1c > 6.5%, fasting blood glucose [FBG] >126mg/dl, or random blood sugar [RBS] > 200 mg/dl multiple times during the stay of the patient [13] or a known case of diabetes under treatment. Hypertension was defined as blood pressure [BP] >140/90 mmHg on multiple measurements during the course of the stay or known case of hypertension under treatment [14]. Coronary artery disease [CAD] was defined as a known case of CAD on treatment or case of CAD found by us based on ECG [Electrocardiography] changes or two-dimensional echocardiography post-admission or those who developed an acute coronary event post-admission. Obesity was defined as having body mass index [BMI] >30 kg/m^2. [15]

Age Groups: Cohort was divided into three age groups. Relatively young patient's age group <35 years of age, middle age group 36–55-year age group and elderly age group >55 years.

Critical illness: Another indicator, critical disease was developed, and defined as the presence of any of the following factors during the course of disease a] death as disease outcome b] use of ventilators during disease course [both invasive and non-invasive] c] Radiographic Assessment of Lung Edema [RALE] score >24 in any of chest skiagram during the disease course [16].

RALE Score: The score was calculated, after dividing each radiograph into four quadrants and giving each quadrant a consolidation score ranging from 0-4 to quantify the extent of alveolar opacities, a density score based on a percentage of opacification, ranging from 1-3 [1=hazy, 2=moderate, 3=dense]. The final RALES score is calculated as the product of consolidation score and density score for each quadrant and summing all four [17].

Statistical Analysis: We used SPSS 23 package for analysis. For analysis of proportion Pearson's Chi-Square test was used with an estimation of risk by Odds Ratio [OR] estimate and Fisher's exact test for calculating 2-sided p-values. For analysis of continuous string, variables mean, a one-sample t-test was used.

Ethical aspects: This study was approved by Institutional Ethics Committee; reference number 28/2021 dated June 21, 2021. Informed consent was obtained from all the participants included in the study.

RESULTS

a] Descriptive Data: In the cohort of 467 cases, the mean age was 54 years [age range 15-92 years]. There were 297[63%] males and 170 [37%] females. Age distribution indicates age as being a risk factor for ICU admissions. The mean age was 54.5 years. Both median [58 years] and mode [60 years] lie in the elderly age group. A one-sample t-test, testing the age group of the ICU admitted patients against the mean 60 years indicated the test to be significant with a p-value <0.001. Among 467 cases, cases cured and discharged were 359 and a fatality of 108 was reported. Overall, ICU case fatality was 23%.

b] Distribution according to age groups: Out of total 467 ICU admissions, 19% [n=91] was from age group <35, 23% [n=123] was from age group 36-55, while 54% [n=251] were from age group greater than 55 [Table 1].

c] **Comorbidities distribution among critical cases:** Among 467 cases admitted in ICU, 52.5% has no co-morbidity, 26.1% has single co-morbidity and 21.4% has multiple co-morbidities [Table 2].

A total of 280 [59.9 %] cases landed in severe disease as per our criteria of critical cases whereas, 187 [40.01%] cases were non-critical. Of the total cases among critical cases, 52% [95% CI 46%-59%] has comorbidity and in non-critical cases, 41% had comorbidity [95% CI 34%-48%]. The prevalence of diabetes among critical cases was 43% [95% CI 37%-49%] while in non-critical cases it was 28% [95% CI 21%-34%]. Hypertension was prevalent in 30% [95% CI 24%-37%] in non-critical cases while it was prevalent in 33% [95% CI 27%-38%] in critical cases. [Table 5]

d] Risk estimates according to age group: Out of 108 deaths, 19% [n=21] belong to age group <35 years, 27.5% [n=28] belongs to age group 36-55 years and 54.7% [n= 58] belongs to age group >55 years. For age group greater than 55years [n=251] 53.7% of our patients belonged to the older age group. In this cohort, irrespective of other factors, contribution over the total death pool was 76.9% [n=83]. Hence if age greater than 55 odd ratios for death was 3.63 and [ranging 2.4-7.2 with 95% CI] and relative risk [RR] for death if age >55 was 1.7 times, p-value < 0.0001 statistically significant. [Table 3]

e] Risk estimates according to comorbidities: Patients with comorbidities were a common theme among ICU admitted patients of COVID19. If we take diabetes and hypertension as indicators, in our study, among all ICU admissions 47.5% [n=222/467] were either diabetic or hypertensive. Among them 21.4 % cases [n= 100] were both diabetic and hypertensive 26.1% [n=122] were either diabetic or hypertensive [Table 4]. A strong association with adverse disease outcomes was seen with diabetes. 37% [n=173] admitted patients were diabetic, among death pool 63 % [n=63] were diabetic with risk estimates for the adverse outcome [death] were OR 4.329 CI 95% RR 2.2 P-value-<0.01 was significant A similar strong association with adverse outcome [death] was seen with hypertension. 32% [n=149] were hypertensive, among death pool 46.3% [n=50] were hypertensive, with risk estimates for adverse outcome [death] were O.R- 2.260 CI 95% RR 1.679 P-value <0.01 was significant. There was a similar association seen with obesity. 7.3% [n=34] of total admission were obese, among death 12% [n=13] were obese, with risk estimates for adverse outcome were OR 2.202 95% CI, RR- 2.058 p<0.05 was significant.

Association with CAD was also observed. 8.8% [n=41] of total admissions were suffering from coronary artery disease before admission or suffered an acute coronary event during treatment. Among the death pool 14.8% [n=16] cases with CAD, with risk estimates for death were O.R. 2.325 95% CI, RR-2.127 p -0.01 was significant.

Table 1: ICU admissions across different age groups

	Frequency	Percent
Age Less than 35	91	19.5
Age Group 36-55	123	26.3
Age greater than 55	251	53.7
Total Cases	465	99.6
Data Missing	1	0.4

Table 2: Frequency of comorbidities

	Frequency	Percent
No comorbidity	245	52.5
Single Comorbidity	122	26.1
Two or more comorbidities	100	21.4
Total	467	100.0

Table [3]: Association of adverse outcome [death] with age groups

Total Admission n=467	% Of Total admission	Total death in Age group	% Of deaths	Odds Ratio	Relative Risk [CI-95%]	p-value [2 sided]
Age group 15-35 [n=91]	19.5% [91/467]	21	19% [21/108]	0.997	1.003	1
Age Group >55 [n=251]	53.7% [251/467]	59	54% [59/108]	1.04	1.01 [0.9-1.1]	0.9

Table [4]: Association of adverse outcome [death] with different comorbidities

Total Admission n=467	% Among Total admission	% Among death	Odds Ratio	Relative Risk [CI-95%]	p-value
Diabetic death	37%	63% [n=63/108]	4.329	2.2 [1.78-2.73]	<0.01*
Hypertensive death	32%	46.3% [n=50/108]	2.26	1.679 [1.29-2.185]	<0.01*
Obesity [BMI>30 kg/m^2]	7.3%	12% [n=13/108]	2.2	2.05 [1.06-3.97]	<0.05*
CAD	8.8.%	14.6% [n=16/108]	2.325	2.127 [1.18-3.83]	<0.05*

*Association was found statistically significant

Table [5]: Prevalence of Comorbidities [95% Confidence Interval] in Critical vs. Non-Critical cases*

Total cases 467	Any comorbidity		Hypertension		Obesity		Diabetes	
	%	CI	%	CI	%	CI	%	CI
Critical [n=280; 59.9% of Total]	52%	46%-59%	33%	27%-38%	8%	4%-11%	43%	37%-49%
Non-Critical cases [n=187; 40.04% of total]	41%	34-48%	30%	24%-37%	7%	3%-11%	28%	21%-34%

***Note: Critical cases are defined as the presence of** any one of a] use of ventilation b] death or c] RALES score >24 during the disease course.

DISCUSSION

The United States Centers for Disease Control and Prevention [CDC] has created a list of certain comorbidities, like cardiovascular disease, diabetes mellitus, hypertension, chronic lung disease, chronic kidney disease, and Obesity; that have been associated with severe COVID-19 disease [defined as infection resulting in hospitalization, admission to the ICU, intubation or mechanical ventilation, or death]. They do note that the strength of the association varies between the comorbid disease conditions [18]. Many studies found a strong association of comorbidities with COVID19 and severe disease outcomes [19-23].

Previous studies have divided patients among groups to ascertain the impact of COVID-19 on the elderly age group vs. younger age groups. Erdem *et al*. divided their cohort into two age groups: >65years and <65years, and <35, 35-50, 51-65, and>65years groups [24]. Similarly, Harrison *et al*. divided the cohort into five age bands as <50, 50-59, 60-69, 70-79,>79 age groups [25].

Saluja *et al*., divided the patient's cohort into age groups of 10-29, 30-59, and >60 years [26]. Hence, we can say that age division most probably was done by local factors. In our study to ascertain the impact of advanced age on ICU admissions our cohort was divided into 3 meaningful age groups relatively young patient's age group <35 years of age, middle age group 36–55-year age group, and elderly age group >55 years.

In an Italian study about case fatality rates, authors detected age and co-morbidities as the most strongly associated factors with case fatalities and severe disease. In that report of 355 patients who died, the mean number of pre-existing co-morbidities was 2.7 per patient, and only 3 patients had no underlying condition [27].

In our study, we found that, when taking overall admissions in ICU, only 19% of cases were of younger age group [19-35 years] while 53.7% cases were of older age >55 years. A subsample of 355 patients with COVID-19 who died in Italy underwent a detailed chart review. Among these patients, the mean age was 79.5 years [SD, 8.1] and 106 [30.0%] were women. In this sample, 117 patients [30%] had ischemic heart disease, and 126 [35.5%] had diabetes [26]. In our study among the patients who died, 63% were diabetic and 46% were hypertensive while 12% were obese, and 14% were having CAD.

In this study, we have found a mortality rate of 23%, which we consider on the higher side. This may be due to the fact that our center was a tertiary care referral center, where patients with severe diseases are often referred. Similar mortality rates have been reported by Souris M *et al*. in France [28] and up to 38% overall mortality rate has been reported by Ciardullo *et al*. from Italy. [29]. In a meta-analysis of comorbidities in COVID-19 and its associations, consisting of 375,859 participants from 14 countries, the most prevalent comorbidities were diabetes, obesity, and hypertension adding up to 18.1%, 18.3%, and 21.3%, respectively. In 22 studies, independent risk factors for mortality were reported and these risk factors included obesity, renal disease, chronic obstructive pulmonary disease [COPD], diabetes, hypertension, cardiovascular disease, and neurological disease [30]. Obesity was also determined as an independent risk factor of adverse outcomes [31].

In a study published in the American heart journal, an estimated 20.5% [95% uncertainty interval, [18.9–22.1] of COVID-19 hospitalizations were attributable to diabetes mellitus, 30.2% [UI, 28.2–32.3] to total obesity, 26.2% [UI, 24.3–28.3] to hypertension, and 11.7% [UI, 9.5–14.1] to heart failure [32].

In our study, while taking overall admission in ICU, 26% of cases were having single comorbidity and 21% of cases were having two or more comorbidities. In addition, in critically ill cases, 33% had hypertension, 43% had diabetes and 8% had obesity. Similarly, in non-critically

ill patients, 30% presented with hypertension, 28% had diabetes and 7% had obesity as a comorbidity.

A known association of hypercoagulable state with these co-morbidities like diabetes, obesity, and COVID-19, may be the commonest factor between such associations. A widespread inflammation associated with these co-morbidities and COVID-19 is common between them and associated with adverse outcomes [33].

In this study to define critical disease, one of the factors used was the RALE Score. RALE score is closely associated with clinical outcomes in acute respiratory distress syndrome [ARDS] [34]. This is a scoring for quantification of involvement of the lung in the parenchyma in pneumonia as seen in chest x-ray films. The suitability of the RALE score in ARDS has been confirmed by previous studies [35-37].

The use of RALE score in the assessment of COVID 19 severity has also been used by other works as by Saluja *et al*. [38]. A severity score was produced by adopting and simplifying Warren *et al*. Radiographic Assessment of Lung Edema [RALE] score to assess the extent of infection. Each lung was given a score from 0 to 4 based on the level of consolidation or ground-glass opacity [GGO] [38]. RALE score ranges from 0 to 48. We tested the applicability of the RALE score in this scenario, the severity cut point as the RALE score ≥ 24 was analyzed by risk estimation for death as an adverse outcome. The association was significant [p value <0.002].

Conclusion:

Our study has shown that diabetes, hypertension, and obesity as the three most common co-morbidities which are significant associations with adverse outcomes in COVID-19. We also found a statistically significant association between CAD and COVID-19 adverse outcomes. More studies are warranted in this area to determine if these conditions can act as a preventable risk in susceptible groups.

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Conflicts of Interest: None.

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