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The Impact of Metabolic Syndrome on Clinical Outcome of COVID-19 Patients: A Retrospective Study

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ABSTRACT

Background and aim: The COVID-19 disease has a very high infectivity rate, and the spectrum of the disease symptoms varies from asymptomatic to severe cases of respiratory failure. Metabolic syndrome has been identified as an independent risk factor for severe COVID-19. We studied the relationship between hypertension, diabetes, and obesity, individually and together as a metabolic syndrome, with COVID-19 patients admitted to our hospital.

Materials and methods: We conducted a retrospective observational study involving 204 hospitalized patients with COVID-19 at our tertiary care center. COVID-19 patients were divided into two cohorts, metabolic syndrome and non-metabolic syndrome, according to modified World Health Organization criteria. The outcomes of the analyses were hospital mortality, length of stay in the hospital, need for intensive care unit, invasive mechanical ventilation, and hospital readmissions.

Results: The main finding of our study is that metabolic syndrome patients had significantly greater odds of having hospital mortality (OR=6.59 (2.98-14.55), p=0.025) and hospital readmission (OR=8.17 (1.572-42.51), p=0.013) respectively as compared to non-metabolic syndrome patients. Both hospital mortality and readmissions were regarded as predictors of the severity of COVID-19 disease.

Conclusion: The COVID-19 patients with metabolic syndrome are more prone to hospital mortality and readmission than those with non-metabolic syndrome.

1. Introduction

Coronavirus (SARS-CoV-2) originated in Wuhan city, China, and spread like wildfire worldwide, resulting in over a million deaths, thereby becoming a public health problem of global interest.^[1] The Coronavirus disease 2019 (COVID-19) has a very high infection rate and spreads across borders, reaching pandemic proportions.^[2] The spectrum of the disease symptoms varies from asymptomatic to severe cases of respiratory failure, which can lead to mortality.^[3] Studies conducted worldwide have identified body mass index (BMI) and metabolic syndrome as strong independent risk factors for severe COVID-19.^[4] The known risk factors for Metabolic syndrome (MetS) include abdominal obesity, atherogenic dyslipidemia, raised blood pressure & insulin resistance, that further lead to developing conditions such as Coronary artery disease and Diabetes mellitus.^[5] As per WHO (World Health Organisation), Metabolic syndromes are characterized by a minimum of three of the following five factors: 1,) Pre-diabetes (HbA1c > 5.7%) or confirmed

history of diabetes or under treatment for diabetes, 2) Obesity (BMI \geq 30 kg/m²), 3) History of hypertension or under antihypertensive treatment, 4) Triglyceride (TG) \geq 150 mg/dL, and 5) High-density Lipoprotein (HDL) < 50 mg/dL for women and, 40 mg/dL for men or use of a cholesterol-lowering medication with confirmed/ documented history of hypercholesterolemia.^[5] Coronaviruses have been demonstrated to have an affinity for and bind to target cells via angiotensin-converting enzyme 2 (ACE2). These enzymes are released by epithelial cells of the lung, kidneys, intestines, and blood vessels.^[6] The ACE release is more in people under treatment with ACE inhibitors and angiotensin II receptor blockers (ARBs), used for treating hypertension in metabolic syndrome. Increased cellular binding and infection of SARS-CoV-2 are possible due to the enhanced expression of ACE2 in the lung, kidney, heart, and pancreas, as observed in rodent models of DM. Other anti-diabetic medications with similar ACE expression include thiazolidinediones (pioglitazone).^[7] Circulating levels of furin, a cellular

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protease involved in facilitating coronavirus entry by cleaving the S1 and S2 domain of the spike protein, are elevated in patients with DM.^[8] Additionally, Chronic inflammation and oxidative stress, hypercytokinemia, immune dysregulation, endothelial dysfunction, and cardiovascular abnormalities are all possible mechanisms through which the excess in adipose tissue could lead to the acute hyperinflammatory state that characterizes severe SARS-CoV-2 infections and is responsible for its complications.^[9] This study attempts to determine the association between MetS and outcomes of severe COVID-19 infection, emphasizing mortality, the need for mechanical ventilation, intensive care unit (ICU) admissions, and re-admissions. Furthermore, we have also explored the relationship between age, gender, hypertension, diabetes, and obesity, individually and together as Metabolic Syndrome with clinical outcome of COVID-19 and its implications for the management of metabolic syndrome in patients admitted in our hospital during the first wave of COVID-19 pandemic in India (from 1st April 2020 to 30th November 2020). The findings of our study can help provide direction for future studies and aid in the development of a high-risk score for effective and timely management of severe clinical outcomes in COVID-19 patients.

2. Materials and methods

Study design

The study was a retrospective observational study involving 204 hospitalized patients with COVID-19 disease and confirmed by the reverse transcriptase-polymerase chain reaction (RT-PCR) method at our tertiary care center from North India. Demographic & clinical data was collected via master chart review by the primary investigator from 1st April 2020 to 30th November 2020. Patients who were COVID-19 positive and diagnosed by the RT-PCR method, patients who fall under the metabolic syndrome criteria, and patients with other co-morbidities were included in the study. According to

modified WHO criteria, patients were divided into two cohorts, metabolic syndrome, and non-metabolic syndrome.^[5, 10] The outcomes of the analyses were hospital mortality, length of stay (LOS) in hospital, need for intensive care unit (ICU), invasive mechanical ventilation (IMV), and hospital readmissions.

Statistical analysis

Information collected during the study was entered into a Microsoft Excel worksheet. All the data were processed using Statistical Package for Social Sciences (SPSS) version 27 (IBM, Chicago, USA). Categorical data were expressed as a percentage (%), and Pearson's Chi-Square test & Odds Ratio (OR) were used to assess the strength of association between various categorical variables. Odds Ratio (OR) was used to measure the association between exposure and outcome. A P-value less than 0.05 (0.01) was considered significant (Highly significant).

3. Results

The data were collected from 204 hospitalized patients with confirmed COVID-19 disease (99%) were RT-PCR positive, while 1% of patients were rapid antigen test positive and were confirmed with RTPCR later. The mean age of the patients was 45.69± 19.38, and 50.5% were < 45 years of age. For this study, 45 years of age was taken as a cut-off for categorizing patients into <45 years (45 years of age). Among the 204 patients, most of them were male (62.8%) and did not have any co-morbidity (80.9%). More than two-thirds of the patients (72%) had normal BMI (≤ 25), and 66.2% of patients stayed for more than 1 week in the hospital. Nine days was the median LOS. In total, 54(26.4%) patients required ICU care. Characteristics of disease severity were a) Patients who required ICU admission at any point during hospitalization b) Patients who never required ICU admission. [Table 1].

Table 1. Baseline Characteristics and severity of disease among patient admitted with COVID-19.

Characteristics		Ward (n=150), n(%)	ICU (n=54), n(%)	Total (n=204), n(%)
Age in Years	<45	94 (46.1)	9 (4.4)	103 (50.5)
	≥ 45	56 (27.5)	45 (22.1)	101 (49.5)
	Total	150 (73.5)	54 (26.5)	204 (100)
Gender	Female	58 (28.4)	18 (8.8)	76 (37.2)
	Male	92 (45.1)	36 (17.6)	128 (62.8)
	Total	150 (73.5)	54 (26.5)	204 (100)
Obesity	BMI ≤ 25	116 (56.9)	31 (15.2)	147 (72.1)
	BMI>25	34 (16.7)	23 (11.3)	57 (27.9)
	Total	150 (73.5)	54 (26.5)	204 (100)
Selected Co-morbidities	Diabetes	27 (18)	29 (53.7)	56 (27.5)
	HTN	24 (16)	21 (38.9)	45 (22.1)
	Obesity	34 (22.7)	23 (42.6)	57 (27.9)
	COPD	3 (2)	3 (5.6)	6 (2.9)

	BA	5 (3.3)	4 (7.4)	9 (4.4)
	CAD	3 (2)	9 (16.7)	12 (5.9)
	CKD	1 (0.7)	8 (14.8)	9 (4.4)
	CLD	0 (0)	1 (1.9)	1 (0.5)
	TB	1 (0.7)	2 (3.7)	3 (1.5)
Duration of Hospital Stay	<1 week	37 (18.1)	32 (15.7)	69 (33.8)
	≥ 1 Week	113 (55.4)	22 (10.8)	135 (66.2)
	Total	150 (73.5)	54 (26.5)	204 (100)
RT-PCR	Positive	150 (73.5)	54 (26.5)	204 (100)

*Figures in parenthesis indicate percentages.

Among the total 204 patients, 59 (28.9%) patients met the criteria for metabolic syndrome, while 145 (71.1%) patients fell under the non-metabolic syndrome category. The most common comorbid conditions were Obesity (27.9%), Diabetes (27.5%), Hypertension (22.1%). These co-morbidities were present in larger proportion than Coronary artery disease (5.9%), Bronchial Asthma (4.4%), Chronic Obstructive Pulmonary Disease (COPD) (2.9%), kidney disease (4.4%), chronic liver disease (0.5%), and Tuberculosis (1.5%). Overall, co-morbidities were present in 19.1% of cases. A total of 59

(28.9%) patients met the criteria for metabolic syndrome, and the rest 145 (71.1%) were included in the non-metabolic syndrome control group. The metabolic syndrome patients (84.7%) were significantly higher in the age of 45 years or more ($p < 0.001$). Of the 59 patients with Metabolic syndrome 40 patients were diabetic (67.8%; $p < 0.001$), 35 patients had Hypertension (59.3%; $p < 0.001$) and 40 patients (67.8%; $p < 0.001$) were obese. This study showed that patients with metabolic syndrome and each component are highly susceptible to SARS-CoV-2 infection.[Table 2].

Table 2. Characteristics and co-morbidities in Metabolic Syndrome (MetS) and Non- Metabolic Syndrome (Non-MetS) individuals.

Variables		Non-MetS (n=145)		MetS (n = 59)		Total (n=204)		P-Value
		n	%	n	%	n	%	
Age (in years)	<45	94	64.8	9	15.3	103	50.5	<0.001*
	≥45	51	35.2	50	84.7	101	49.5	
Gender	Female	51	35.2	25	42.4	76	37.3	0.335
	Male	94	64.8	34	57.6	128	62.7	
Diabetes		16	11.0	40	67.8	56	27.5	<0.001*
HT		10	6.9	35	59.3	45	22.1	<0.001*
Obesity		17	11.7	40	67.8	57	27.9	<0.001*
COPD		4	2.8	2	3.4	6	2.9	0.809
BA		5	3.4	4	6.8	9	4.4	0.293
CAD		6	4.1	6	10.2	12	5.9	0.097
CKD/AKI		4	2.8	5	8.5	9	4.4	0.071
CLD		1	0.7	0	0.0	1	0.5	0.523
TB		2	1.4	1	1.7	3	1.5	0.865

*P-Value significant at 1% level of significance.

It was observed that metabolic syndrome was more common in ≥45 years (49.5%) as compared to <45 years (8.9%) of age group ($p < 0.001$).

It was also seen that metabolic syndrome patients had significantly greater odds of having hospital mortality (OR=6.59 (2.98-14.55), $p=0.025$) and

Hospital Re-admission (OR=8.17 (1.572-42.51), $p=0.013$) respectively as compared to non-metabolic syndrome patients while LOS, ICU admission & IMV were not statistically significant (OR=0.807 (0.429-1.517), $p=0.81$;

OR=1.974 (0.586-6.652), $p=0.273$; OR=2.413 (0.818-7.116), $p=0.110$) respectively. [Table 3]

Table 3. Association between Metabolic Syndrome and severe disease outcomes (Hospital mortality, Mechanical ventilation, ICU admission, and re-admission).

Variables		Non-MetS (n = 145)	MetS (n = 59)	OR (95%CI) ^a	P-Value
LOS	<7 days	47	22	0.807 (0.429-1.517)	0.810
	≥7 days	98	37		
Hospital Mortality		12	22	6.59 (2.98-14.55)	0.025**
ICU admission		24	30	1.974 (0.586-6.652)	0.273
Hospital Re-admission		3	5	8.174 (1.572-42.51)	0.013**
IMV		13	20	2.413 (0.818-7.116)	0.110

**P Value significant at 5% level of significance.

^aOR(CI) - Odds Ratio (95% Confidence Interval).

4. Discussion

This study outlines the association between MetS and outcomes of severe COVID-19 infection, with emphasis on mortality, the need for mechanical ventilation, intensive care unit (ICU) admissions, and re-admissions. The significant finding of this retrospective observational study in 204 hospitalized patients with COVID-19 is that metabolic syndrome patients had significantly greater odds of having hospital mortality (OR=6.59, $p=0.025$) and hospital re-admission (OR=8.17, $p=0.013$) respectively as compared to non-metabolic syndrome patients. Both hospital mortality and re-admissions were regarded as predictors of the severity of COVID-19 disease. Xie et al. (2020) observed that COVID-19 patients in New Orleans with metabolic syndrome had four times higher odds of fatal disease outcomes than those without the metabolic syndrome.^[11] Likewise, Ersilia Nigro et al.(2020) observed that COVID-19 disease with metabolic syndrome as a comorbid condition increases mortality risk and poor prognosis.^[12] This observation suggests that metabolic syndrome should be considered a major predictor of COVID-19 disease outcome. Also, the odds of mortality increase by the combined effects of all the individual components of metabolic syndrome.

Our study revealed that metabolic syndrome was more common in individuals > 45 years of age as compared to those <45 years of age (49.5% vs. 8.9% respectively). Similar findings were reported by Naghipour M et al. with the prevalence of metabolic syndrome 1.4 folds higher in 45-51 years old as compared to <45 years. Furthermore, the prevalence of metabolic syndrome was higher among study participants aged 45 to 69 years in a study by Mehata S et al.^[13, 14] Earlier studies^[15-18] have observed that patients with obesity are at an increased risk for severe manifestations of COVID-19 disease. Nevertheless, in our study, the hospital mortality was not significantly increased by obesity alone. In our study Diabetes Mellitus has been reported to increase the risk of ICU requirement. This finding has also been reported by Matteo Apicella et al., Santos et al. in an earlier study.^[19, 20] Zhou F et al., Richardson et al, Petrilli CM et al., Gao et al. reported hypertension as the most frequently associated co-morbidity in fatal COVID-19 outcomes, unlike our study, which suggested hypertension alone was not

associated with increased ICU requirement.^[15, 16, 21, 22] Thus, these findings suggest that an additive effect of these co-morbidities may cause the association of metabolic syndrome with COVID-19 disease's adverse outcomes. Among fatal COVID-19 cases, Obesity, Hypertension, Diabetes Mellitus, and Hyperlipidemia together as metabolic syndrome were present in higher proportions than the other co-morbidities, suggesting that metabolic syndrome predicts worse outcomes COVID-19 disease.^[13] Lastly, the effect of gender on COVID-19 disease outcomes was an important consideration of our study. In our hospitalized patients, COVID-19 disease was predominant in males (62.8%), but the hospital mortality and morbidity of patients were not affected by gender. Different results have been reported by Jian-min jin et al.(2020) in their study, which suggested male gender infected with COVID-19 is at a higher risk for adverse outcomes and death, independent of age, while a study by Xie et al. (2020) and Prince-Haywood EG et al.(2020) showed a predominance of women for COVID-19 disease.^[11, 23, 24] Thus, the gender-specific severity of COVID-19 infection needs further exploration.

5. Conclusion

In our study, patients hospitalized given COVID-19 disease, the combination of hypertension, diabetes, and obesity together as metabolic syndrome increased the odds of hospital mortality and hospital re-admissions compared with these co-morbidities individually or with no co-morbidity at all. So, working up for metabolic syndrome in COVID-19 patients is important to help physicians identify the patients at high risk for developing severe disease. Though, more research is required to understand the mechanisms behind why metabolic syndrome increases the odds for severe COVID-19 outcomes.

Conflict of Interest

The authors declared that there is no conflict of interest.

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