ejpmr, 2021,8(8), 604-611.

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

A COMPARATIVE STUDY OF COVID-19 PATIENTS WITH AND WITHOUT CO-MORBIDITIES IN A RURAL TERTIARY HEALTH CARE CENTRE

[1]*Chandrashekar T. V., [2]Taseena Banu R., [3]Vasantha Kamath and [4]M. J. Jacob

[1,2]Postgraduate in General Medicine,
[3,4]Professor of General Medicine,
MVJ Medical College and Research Hospital, Hoskote, Bengaluru Rural 562114.

***Corresponding Author: Chandrashekar T. V.**

Postgraduate in General Medicine, MVJ Medical College and Research Hospital, Hoskote, Bengaluru Rural 562114.

Article Received on 10/06/2021 **Article Revised on 30/06/2021** **Article Accepted on 20/07/2021**

ABSTRACT

Background- The COVID-19 pandemic has resulted in millions of deaths worldwide, despite the numerous efforts to control spread, the disease continues to cause high morbidity and mortality worldwide. Patients with pre-existing co-morbidities were highly susceptible to severe illness and death. **Methodology-** 1754 confirmed COVID-19 patients admitted to a rural tertiary care centre from July 1st to 12th December 2020 were included in the study and were divided into 2 categories, one with pre-existing co-morbidities and another without co-morbidities. The co-morbidity distribution with respect to age, sex, clinical presentation, laboratory investigations, inflammatory marker, severity category at admission, day seven of hospital stay and final outcome were recorded for the study and compared. **Results-** Various pre-existing co-morbidities were present in 60.95% patients and 39.05% had no co-morbidities. Middle-aged and elderly patients with co-morbidities were 53.3% and those without co-morbidities were 32.56%. Among them 61.09% males and 39.91% females had pre- existing co-morbidities; 44.53% males and 55.47% females affected had no co-morbidities. Common pulmonary symptoms, extra pulmonary symptoms and rapid progression of illness was prominent in patients with co-morbidities. Fever was the most common symptom in both the categories. Diabetes was the major co-morbid condition associated with high mortality ratio and case fatality rate. NLR ratio, CRP and D-DIMER were significantly elevated in patients with co- morbidities. Highest mortality ratio was seen in patients with co-morbidities. ARDS being the most common cause of death. **Conclusion-**In this study, it was inferred that middle-aged and elderly patient with co- morbidities had severe illness with a high mortality.

KEYWORDS: COVID-19, Co-morbidities, pulmonary, Fever, Diabetes mellitus, D-DIMER.

INTRODUCTION

In December 2019, a previously unknown virus, named severe acute respiratory syndrome coronavirus was noticed in a seafood market of Wuhan, Hubei province of China.[1] WHO declared it as a pandemic on 11th March 2020.

COVID-19 patients with co-morbidities have often been associated with increased hospitalization, in-hospital complications and mortality. People with underlying medical conditions such as Diabetes mellitus, Systemic hypertension, liver, lung and kidney disease, cancer patients, smokers, transplant recipients and patients on long term steroids are at higher risk of COVID-19 infection and have shown worse prognosis.[2]

AIMS

To study and compare the clinical profile and outcome of COVID-19 patients with co- morbidities and without co-morbidities.

MATERIALS AND METHODS

This is a prospective observational study of all covid-19 positive patients tested by Rt-PCR, who were admitted in a rural tertiary care centre, Bengaluru, Karnataka, India from July 1st to 12th December 2020.

All patients were categorized as per MOHFW guidelines, as Mild i.e. patients with uncomplicated upper respiratory tract infection with SpO2: >94% at room air, respiratory rate: < 24 cycles per min with no evidence of hypoxemia or breathlessness; Moderate i.e. pneumonia with no signs of severe disease with Sp02: 90%-94% at room air, respiratory rate: 24-30 cycles per min; and Severe i.e. Severe Pneumonia with SpO2: < 90% room air with respiratory rate:
>30 cycles per min.[3]

Fever, cough, sore throat, breathlessness, arthralgia, myalgia, fatigue were considered as pulmonary symptoms and rest were considered as extra pulmonary symptoms.[4]

Co-morbidity distribution with respect to age, sex, clinical presentation, laboratory investigations, inflammatory markers, severity at admission, severity in hospital after one week and final outcome were recorded for the study and compared between the two categories (i.e., those with and without pre-existing co-morbidities).

Statistical methods- The required data was collected. The quantitative, qualitative and categorical variables were analysed using suitable statistical methods. The results were expressed in percentages with appropriate tables and charts. Institute Ethical committee approval was obtained before starting the study.

Inclusion criteria

Hospitalized patients who tested COVID-19 positive by Rt-PCR test and those aged more than 18 years were included in the study.

Exclusion criteria

Clinical and radiological COVID-19 suspects, who tested negative by Rt-PCR were excluded from the study.

RESULTS

From July 1st to 12th December 2020, 1754 COVID-19 positive patients were admitted to a rural tertiary care hospital, Bengaluru, Karnataka, India.

Out of these 1754 patients, 1069(60.95%) had various co-morbidities and 685(39.05%) had no co-morbidities.

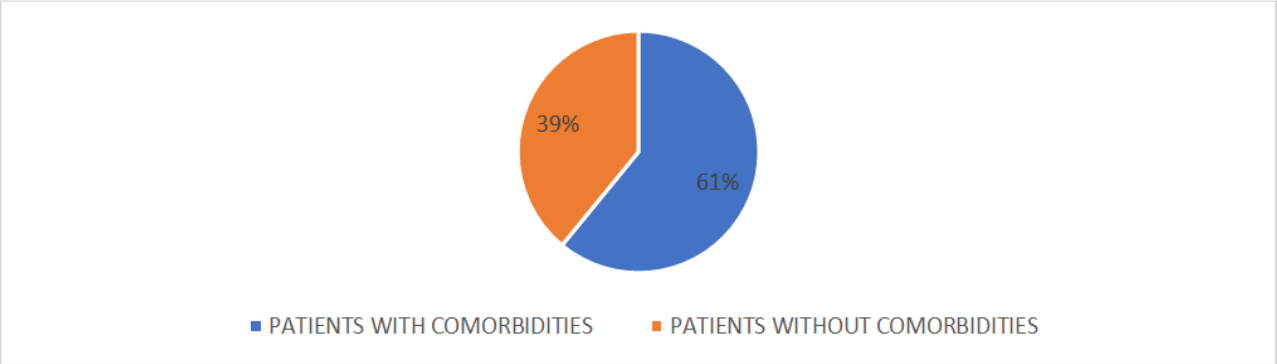

Chart-1: Showing distribution of co-morbidities in COVID-19 patients at admissions.

Table 1: Showing distribution of age, sex, and clinical presentation of COVID-19 patients.

Category	Age (In years)			Sex		Symptomatic Presentation	Asymptomatic Presentation	Pulmonary Symptoms	Extra pulmonary Symptoms
	<40	40-60	>60	M	F				
Patients With co-morbidities. n=1069	134	446	489	653	416	995(93.1%)	74(6.9%)	762 (71.2%)	233 (21.8%)
Patients Without co- morbidities. n=685	114	260	311	305	380	587(85.7%)	98(14.3%)	470 (68.6%)	117 (17.1%)

Majority of patients with pre-existing comorbidities were middle-aged and elderly (53.3%) and it was statistically significant compared to younger age group, with p value of 0.016.

The male to female ratio among co-morbidities was 3:2, and male to female ratio among no co- morbidities was 6:7. Comparative analysis among male and females with co-morbidities was statistically significant with p value of <0.00001.

93.1% patients with pre-existing comorbidities were symptomatic, 85.7% patients without pre- existing comorbidities were symptomatic, which was statistically significant with p value of <0.00001.

Among patients with co-morbidities 71.2% showed pulmonary symptoms, 21.8% showed extra pulmonary symptoms and 6.9% were asymptomatic.

68.6% patients showed pulmonary symptoms, 17.1% showed extra pulmonary symptoms and 14.3% asymptomatic, in patients without pre-existing co-morbidities category. Therefore extra pulmonary symptoms were more in patients with co-morbidities as compared to patients without co-morbidities.

Table 2: Shows pulmonary & extra pulmonary symptoms in COVID-19 patients.

Pulmonary symptoms	No. of patients With co-morbidities	No. of patients Without co-morbidities
Fever	657(61.46%)	382(55.77%)
Cough	434(40.6%)	211(30.80%)
Breathlessness	379(35.45%)	184(26.86%)
Sore throat	241(22.5%)	103(15.04%)
Rhinorrhoea	189(17.7%)	87(12.7%)
Myalgia	235(21.98%)	136(19.85%)
Arthralgia	156(14.59%)	73(10.66%)
Fatigue	263(24.6%)	155(22.63%)
Extra pulmonary symptoms		
➢ **Neurological**		
Headache	88(8.23%)	20(2.92%)
Anosmia	67(6.27%)	17(2.48%)
CVA	9(0.84%)	3(0.44%)
Seizures	5(0.47%)	2(0.29%)
Altered sensorium	6(0.56%)	2(0.29%)
➢ **Gastrointestinal**		
Diarrhoea	31(2.9%)	15(2.19%)
Pain abdomen	23(2.15%)	10(1.46%)
Anorexia	12(1.12%)	6(0.87%)
Nausea	11(1.02%)	6(0.87%)
Vomiting	9(0.84%)	3(0.44%)
➢ **Cardiovascular**		
Chest pain	4(0.37%)	3(0.44%)
Palpitation	2(0.18%)	1(0.14%)
➢ **Cutaneous**		
Maculopapular rash	3(0.28%)	1(0.14%)
Petechiae	2(0.18%)	1(0.14%)
Painful acral red purple papules	1(0.09%)	0(0%)
➢ **Haemoptysis**	3(0.28%)	1(0.14%)

Fever was the most common presenting symptom in both the categories, 61% in those with co- morbidities and 55% in those with no co-morbidities, followed by cough 40.6% in co- morbidities and 30.8% in no co-morbidities patients.

Apart from pulmonary symptoms, neurological symptoms were more common in both categories, followed by gastrointestinal symptoms.

At admission patient's spo2, respiratory rate, other vitals were noted and categorized into mild, moderate and severe according to the standard guidelines set by the MOHFW. Patients were treated for COVID-19 and co-morbidities, and severity recorded after 1 week.

Table 3: Showing severity-categorization of COVID-19 patients at admission, severity in hospital after 1 week and death.

Category	No. Of patients With Co-morbidities (1069)			No. Of patients without Co-morbidities (685)		
	At admission	**After 1 week**	**Deaths n=63**	**At admission**	**After 1 week**	**Deaths n=12**
Mild	378(35.36%)	317(29.65%)	5(7.94%)	394(57.5%)	384(56.35%)	1(8.33%)
Moderate	408(38.16%)	356(33.3%)	19(30.06%)	205(29.9%)	203(29.63%)	4(33.3%)
Severe	283(26.47%)	396(37.04%)	39(61.9%)	86(12.5%)	96(14.01%)	7(58.3%)

283(26.47%) patients with pre-existing co-morbidities were severe-category at admission, after 1 week of hospital follow up the number of severe cases increased to 396(37.04%), 113 (10.57%) patients with co-morbidities progressed from mild-moderate category to severe category during 1 week of hospital stay.

86(12.5%) patients without pre-existing co-morbidities were severe-category at admission, after 1 week of hospital follow up 96(14.01%) progressed to severe category, only 10(1.46%) patients with no co-morbidities progressed from mild-moderate to severe category during 1 week of hospital stay.

Hence more number of COVID-19 patients with co-morbidities were severe at admission and showed rapid progression of illness as compared to patients without co-morbidities.

Co-morbid conditions were evaluated and managed as per standard guidelines along with COVID-19 treatment.

Table 4: Showing co-morbidities and death distribution among COVID-19 admissions.

Co-morbid condition	No. Of patients (1069)	% among co-morbidities.	% among total admissions.	No. of death	% death among co- morbidities (63)	% among total deaths (75)
Diabetes mellitus	406	37.97	23.14	42	66.66	56
Systemic Hypertension	387	36.2	22.06	38	60.31	50.6
Diabetes+ Hypertension	188	17.58	10.71	21	33.33	28
COPD	123	11.51	7.01	17	26.98	22.66
Obesity	111	10.38	6.32	12	19.04	16
Ischemic heart disease (CVD)	83	7.76	4.73	6	9.52	8
Chronic liver disease	64	5.99	3.65	4	6.3	5.33
Chronic kidney disease	47	4.39	2.67	12	19.04	16
Bronchial asthma	38	3.55	2.16	9	14.28	12
Cerebrovascular accident	38	3.55	2.16	9	14.28	12
Hypothyroidism	29	2.71	1.65	4	6.3	5.33
Malignancy	17	1.59	0.96	2	3.17	2.66

Diabetes mellitus was the most common co-morbidity, which accounts for about 23.14% of total COVID-19 admissions and 37.97% among various co-morbidities.

56% of mortality cases were Diabetic; 66.66% deaths with pre-existing co-morbidities had Diabetes, with case fatality rate of 10.34%, and mean HbA1c was 9.1 in deaths.

Hypertension was the second commonest co-morbidity. Among the fatal cases 50.6% were hypertensive. 60.31% of deaths with co-morbidities had hypertension, and case fatality rate was 9.8%. Multiple co-morbidities were seen in majority of severe COVID-19 cases.

Table 5: Showing laboratory investigations and inflammatory markers in COVID-19 patients.

Laboratory parameters	Patients With Co-morbidities	Patients Without Co-morbidities
Increased NLR	713(66.7%)	426(62.2%)
Normal NLR	356(33.3%)	643(37.8%)
Platelets		
<1.5 lakh/ml	354(33.1%)	252(36.8%)
>1.5 lakh/ml	715(66.9%)	433(63.2%)
LFT		
Hyperbilirubinaemia	121(11.32%)	47(6.86%)
Transaminitis	442(41.35%)	224(32.7%)
Hypoalbuminaemia	146(13.66%)	67(9.78%)
RFT		
Increased urea	186(17.34%)	73(10.66%)
Increased creatinine	243(22.73%)	121(17.66%)
Increased Inflammatory markers		
ESR	673(62.96%)	384(56.06%)
CRP	801(74.9%)	420(61.31%)
SERUM FERRITIN	654(61.12%)	312(45.55%)
SERUM LDH	678(63.42%)	219(31.97%)
D-DIMER	795(74.37%)	451(65.84%)
Abnormal chest X-ray (pneumonic patch)	956(89.43%)	549(80.12%)

Increased NLR was seen in 66.7% of co-morbidities patients and 62.2% of no co-morbidities patients, which was statistically significant with p value <0.00001.

CRP was elevated in 74.9% of patients with co-morbidities and 61.3% of patients without co-morbidities. D-DIMER was elevated in 74.37% co-morbidities patients and 65.84% no co- morbidities patients, which was statistically significant with p value <0.00001.

Out of 1754 patients there were 75 (4.28%) deaths of which 63(84%) had various pre-existing co-morbidities and 12(16%) had no co-morbidities.

1679(95.72%) patients improved with treatment and discharged from the hospital, average duration of hospital stay was prolonged (22 days) in those with co-morbidities and was 14 days in those without co-morbidities.

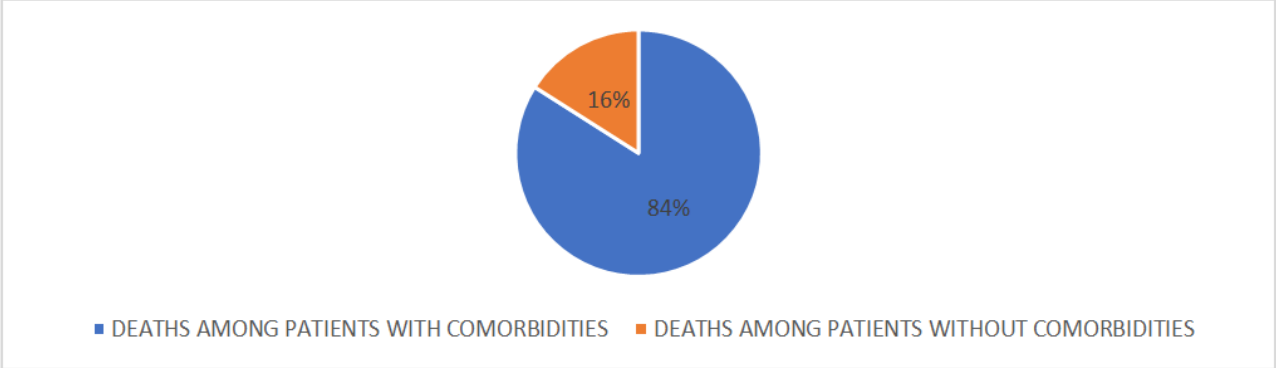

Chart- 2 showing death among COVID-19 patients with co-morbidities & without co- morbidities.

Among 75 deaths, 6(8%) were initially admitted under mild category, out of which 5 had co- morbidities and 1 had no co-morbidity. 23(30.6%) deaths were noted in patients initially admitted under moderate category in which 19 had co-morbidities and 4 with no co-morbidities. 46(61.3%) deaths were noted in patients admitted under severe category in which 39 had co-morbidities and 7 had no co-morbidities. [Table 3].

Fatality was predominant in middle-aged and elderly, those who belonged to severe category and in those with pre-existing co-morbidities.

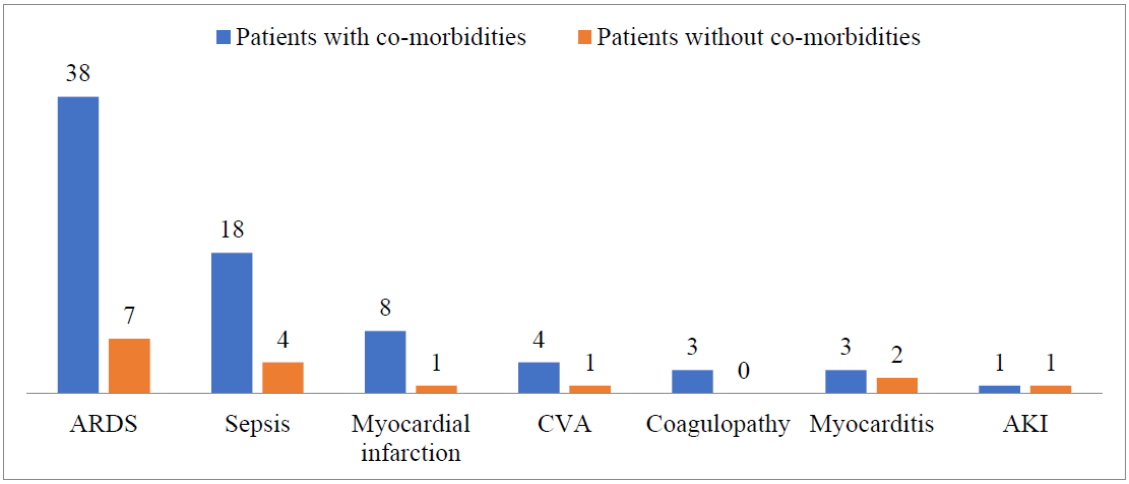

Chart-3 cause of death among COVID-19 admitted patients.

ARDS with respiratory failure was the most common cause of death in both patients with and without co-morbidities and it accounted for about 60% of the total deaths and 60.3% of deaths in co-morbidities patients.

DISCUSSION

Respiratory viruses associated with pandemics include influenza virus, severe acute respiratory syndrome (SARS), Middle East respiratory virus (MERS), H1N1influenza, and now corona virus 19.[5] Corona viruses are a large group of medium-sized enveloped positive-stranded RNA viruses that cause illness in humans and animals.[6] It has now spread to 223 countries worldwide. COVID-19 has affected more than 122,435,348 cases with 2,704,440 deaths globally.[7]

In a retrospective study done by Adekunle et al, they found that elderly population were more susceptible to this infection, with more ICU admission and higher mortality rate. The age-related changes in the old

population, changes in lung anatomy and muscle atrophy which results in changes in physiological function, reduction of lung reserve, reduction of airway clearance, and reduction of the defence barrier function.[8] Since natural immunity is reduced profoundly in patients with co-morbidities as they are taking multiple drugs concurrently, the dangerous adverse drug reactions alongside down regulation of immune function occur in these patients and may increase the risk of severe illness and death.[9] This was confirmed in our study with high infectivity and mortality in middle aged and elderly population with co-morbidities.

In a study by Bhandari et al and Wang et al which showed 66.6% and 54.3% male preponderance respectively.[10,11] We noted male preponderance with 54.62% males among total admissions, male to female ratio among co-morbid patients approximately 3:2 and male to female ratio among those without co-morbidities approximately 6:7.

This male predominance may be due to the increased time spent outside the house, for work and travel by males which is greater in comparison to their female counterpart. Co-morbidities were more in males due to multiple factors including habits, stress, occupation etc.

COVID-19 showed wide range of clinical presentations, more number of patients with co- morbidities were symptomatic (93.1%) compared to patients without co-morbidities (85.7%). Among patients with co-morbidities 71.2% showed pulmonary symptoms, 21.8% showed extra pulmonary symptoms and 6.9% were asymptomatic. Among patients without co-morbidities 68.6% showed pulmonary symptoms, 17.1% showed extra pulmonary symptoms and 14.3% asymptomatic.

In a study by Varghese et al. Fever was reported as the most common presenting symptom followed by cough.[12] In our study fever was found to be the most common presenting symptom both groups.

In our study we observed that higher number of diabetic patients had severe illness and deaths. Diabetic patients were prone to get COVID-19 infections due to impaired phagocytic cell activities. An elevated level of ACE-2 receptors found to be related to diabetes might explain the susceptibility diabetes to COVID-19.[13] Furin is a type 1 membrane-bound protease expressed in high levels in diabetic patients.[14] This pro protein convertase involved in the entry of the virus inside the host cell. The COVID-19 virus spike (S) protein attaches to the ACE-2 receptors is activated by the enormous furin levels. This pre-activation of S protein allows the viral entry into the cell and escapes from the human immune system.[15,32] Hence, deranged immune response with elevated ACE-2 receptors and furin expression may lead to higher pulmonary inflammation rate and lower insulin levels. The convenient entry of virus leads to a life- threatening situation for diabetic patients.[13,14,32] Moreover, the impaired function of T-cell and elevated levels of interleukin-6 also plays a major role in developing COVID-19 disease in diabetic patients.[15, 17,18,32]

Uncontrolled blood pressure was associated with COVID-19 infection and also with a high case fatality rate. In patients suffering from hypertension, ACE-2 inhibitors, and ARBs are frequently used for the treatment purpose. These inhibitors, when used in a high amount, upregulate ACE-2 receptor, thereby leading to increased susceptibility to COVID-19 infection.[19,20] Higher expression of ACE-2 receptor cells on the lungs makes the infection more vulnerable, and chances of severe lung injury and increased chances of respiratory failure.

The steps in controlling blood pressure should remain an essential consideration in COVID-19 patients to reduce disease burden.[21] In our study hypertension was the second major co- morbidity. The mortality ratio was 60.31% among those with co-morbidities, and 50.6% among total deaths.

COVID-19 illness can lead to the development of severe hypoxemia in 15–20% of the patients, which require ventilator support.[22] COPD and other chronic disorders were also associated with COVID-19 infections.[23] Although previous studies did not report a high number of COVID-19 cases with COPD, ACE-2 receptors were increased in this disease, contributing to the development of severe symptoms among COVID-19 individuals, including structural damage to lungs, weak immunity and increased mucous production.[24] In our study we observed that COPD was third major co-morbidity with hospitalization. Mortality ratio was 22.66% among total deaths, 26.98% among all co-morbidities deaths.

Obese people were linked with reduced oxygen saturation of blood due to reduced ventilation at the base of the lungs. Additionally, some other characteristic features of low-grade inflammation due to obesity may occur, such as the abnormal secretions of cytokines, adipokines, and interferon consequences in compromised immune response.[25,32] Obesity is one of the less highlighted co-morbidities in COVID-19 infections. Though, 47.6% of obese people get infected with COVID-19 and out of these patients, 68.6% receive ventilation in a critical situation.[26] Hence high BMI is a risk factor in COVID-19 severity. In our study we observed that obesity is the fourth major co-morbidity with hospitalization of 6.3% among total admissions. Mortality ratio was 16% among total deaths; 19.04% among co-morbidities deaths.

Patients with coronary vascular disease have a greater risk of developing acute coronary syndrome in COVID-19 due to hypercoagulable state. COVID-19 infection increases the myocardial demand, which gradually led to myocardial injury or infarction. Moreover, an increased rate of inflammatory cytokines in COVID-19 cases

mediate atherosclerosis, pro coagulant activation, and hemodynamic instability leading to ischemia and thrombosis.[27,32] In our study we observed that CVD had 7.76% hospitalization among all co-morbidities, 4.73% among total admissions. Mortality ratio was 9.52% among all co-morbidities deaths and 8% among total deaths.

Among the COVID-19 cases, 43.4% had abnormal secretion of AST, ALT, and lactic dehydrogenase.[28,32] Our study we observed that transaminitis was seen in 41.5% co-morbidities patients and 32.7% no co-morbidities patients, in our study chronic liver disease had 5.99% hospitalization among all co-morbidities, 3.6% among total admissions. Mortality ratio was 6.3% among co-morbidities, and 5.33% among total deaths.

People with asthma have delayed innate antiviral immune response and impaired secretion of IFN, which makes them more susceptible to develop severe complications.[29,32] In our study we observed that Asthma had 4.49% hospitalization among all co-morbidities, 2.73% among total admissions. Mortality ratio was 11.11% among co-morbidities, and 9.33% among total deaths.

COVID-19 damage the kidneys by direct cellular injury or by secondary sepsis, leading to a cytokine storm. The kidneys are also a potential target for COVID-19.[29,32] Acute kidney injury was observed in 3–9% of the COVID-19 cases while it was reported in SARS (5%) and MERS (15%) patients with a 60%–90% mortality rate.[30,31,32] Our study 17% had AKI, and CKD had 4.39% hospitalization, with mortality ratio of 19.01%.

Patients with any malignancy are at a higher risk of developing COVID-19 infection related complications due to the weak immune response. In our study we observed that 0.96% admissions had various malignancies, which accounted 1.59% in co-morbidities, Mortality ratio was 3.17% among co-morbidities, and 2.66% among total deaths.

Hypothyroidism was also one of the observed co-morbidity among COVID-19 patients with 2.71% hospitalization among co-morbidities, 1.65% among total admissions. Mortality ratio was 6.3% among all co-morbidities deaths and 5.33% among total deaths.

In our study, majority of seriously ill and expired patients had multiple co-morbidities.

On laboratory evaluation, specific parameters like increased NLR, elevated inflammatory markers like D-dimer, and CRP was seen in both category patients of COVID-19, although significantly higher in patients with co-morbidities. This is in line with a recent study where the association of inflammatory markers with the severity of COVID-19 was highlighted and stated that measurement of inflammatory markers might assist clinicians to monitor and evaluate the severity and prognosis of COVID-19.[33]

ARDS was the most common cause of death in both group of patients with and without co- morbidities, 61% of patients with pre-existing co-morbidities and 55% of patients without co- morbidities.

CONCLUSION

Elderly and middle-aged patients with underlying pre-existing illness had severe COVID-19 and high mortality ratio when compared to patients without co-morbidities. Diabetes mellitus followed by systemic hypertension were the commonest co-morbidities associated with mortality. Hence it is necessary for timely management of these co-morbidities to prevent further morbidity and mortality in these groups. Severe category at the time of presentation, extra- pulmonary manifestations, secondary infections, elevated inflammatory markers and increased complications are implicated factors contributing to mortality in patients with co-morbid illness.

REFERENCES

1. Zayet S, Kadiane-Oussou NJ, Royer PY, Toko L, Gendrin V, Klopfenstein T. Coronavirus disease 2019: New things to know!. J Med Virol 2020: e1-2.
2. CDC. Coronavirus (COVID-19): symptoms of coronavirus. Centers for Disease Control and Prevention. 2020. [Accessed April 18, 2020, https://www.cdc.gov/coronavirus/2019- ncov/ symptoms-testing/symptoms.html].
3. Revised guidelines for Home Isolation of very mild/asymptomatic COVID-19 cases https://www.mohfw.gov.in/pdf/RevisedHomeIsolationGuidelines.pdf.
4. Philips CA, Mohan N, Ahamed R, Kumbar S, Rajesh S, George T, Mohanan M, Augustine P. One disease, many faces-typical and atypical manifestations of SARS-CoV- 2 infection-related COVID-19 disease. World J Clin Cases, 2020; 8(18): 3956-3970.
5. Wijdicks, Eelco F M. "Historical Lessons from Twentieth-Century Pandemics Due to Respiratory Viruses." Neurocritical care, 2020; 33,2: 591-596.
6. Shareef UM, Kumar V, Kamath V. What's new in COVID - 19? APIK J Int Med, 2021; 9: 29–37.
7. https://www.worldometers.info/coronavirus/#countries. [Accessed 19 March 2021].
8. Adekunle Sanyaolu, ChukuOkorie, Aleksandra Marinkovic, RishaPatidar, KokabYounis et al. Comorbidity and its impact on patients with COVID-19. SN Comprehensive clinical medicine 2020(06).
9. Mohitosh Biswas, Shawonur Rahaman, Tapash Kumar Biswas, Zahirul Haque, Baharudin Ibrahim. Association of Sex, Age, and Co-morbidities with Mortality in COVID-19 Patients: A systematic Review and Meta-Analysis. Intervirology, 2021; 64: 36- 47.
10. Bhandari S, Bhargava A, Sharma S, Keshwani P,

Sharma R, Banerjee S. Clinical Profile of Covid-19Infected Patients Admitted in a Tertiary Care Hospital in North India. J Assoc Physicians India, 2020 May; 68(5): 13-17.
11. Wang D, Hu B, Hu C et al. Clinical Characteristics of138 Hospitalized patients with 2019 Novel Coronavirus infected Pneumonia in Wuhan, China. JAMA 2020.
12. Varghese GM, John R, Manesh A, Karthik R, Abraham O C. Clinical management of COVID-19. Indian J Med Res., 2020; 151: 401-10.
13. Rao S, Lau A, So HC. Exploring diseases/traits and blood proteins causally related to expression of ACE2, the putative receptor of SARS-CoV-2: a Mendelian randomization analysis highlights tentative relevance of diabetes-related traits. Diabetes Care, 2020; 2020: dc200643.
14. Fernandez C, Rysa J, Almgren P, Nilsson J, Engstrom G, Orho-Melander M, et al. Plasma levels of the proprotein convertase furin and incidence of diabetes and mortality. J Intern Med, 2018; 284(4): 377–87.
15. Shang J, Wan Y, Luo C, Ye G, Geng Q, Auerbach A, et al. Cell entry mechanisms of SARS-CoV-2. Proc Natl AcadSci U S A, 2020; 117(21): 11727–34.
16. Kulcsar KA, Coleman CM, Beck SE, Frieman MB. Comorbid diabetes results in immune dysregulation and enhanced disease severity following MERS-CoV infection. JCI Insight, 2019; 4(20): e131774.
17. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, et al. Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: a systematic review and meta-analysis. Int J Infect Dis., 2020; 94: 91–5.
18. Bhatraju PK, Ghassemieh BJ, Nichols M, Kim R, Jerome KR, Nalla AK, et al. Covid-19 in critically ill patients in the Seattle region-case series. N Engl J Med, 2020; 382: 2012– 22.
19. Chen WW, Gao RL, Liu LS, Zhu ML, Wang W, Wang YJ, et al. China cardiovascular diseases report 2018: an updated summary. J GeriatrCardiol, 2020; 17(1): 1–8.
20. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med, 2020; 8(4): e21.
21. Schiffrin EL, Flack JM, Ito S, Muntner P, Webb RC. Hypertension and COVID-19. Am J Hypertens, 2020; 33(5): 373–4.
22. Qiu H, Tong Z, Ma P, Hu M, Peng Z, Wu W, et al. Intensive care during the coronavirus epidemic. Intensive Care Med, 2020; 46: 576–8.
23. Yin Y, Wunderink RG. MERS, SARS and other coronaviruses as causes of pneumonia. Respirology, 2018; 23(2): 130–7.
24. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by the novel corona virus from Wuhan: an analysis based on decade-long structural studies of SARS corona virus. J Virol, 2020; 94(7): http://dx.doi.org/10.1128/jvi.00127-20, e00127-20.
25. Zhang X, Zheng J, Zhang L, Liu Y, Chen GP, Wang L, et al. Systemic inflammation mediates the detrimental effects of obesity on asthma control. Allergy Asthma Proc., 2018; 39(1): 43–50.
26. WHO, Geneva, Switzerland: https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)- infection-is-suspected. [Accessed 13 March 2020] Clinical management of severe acute respiratory infection when COVID-19 is suspected; 2020.
27. Bonow RO, Fonarow GC, O'Gara PT, Yancy CW. Association of coronavirus dis-ease 2019 (COVID-19) with myocardial injury and mortality. JAMA Cardiol, 2020; 5(7): 751–3.
28. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel corona virus pneumonia in Wuhan, China: a descriptive study. Lancet, 2020; 395(10223): 507–13.
29. Contoli M, Message SD, Laza SV, Edwards MR, Wark PA, Bartlett NW, et al. Roleof deficient type III interferon-lambda production in asthma exacerbations. Nat Med, 2006; 12(9): 1023–6.
30. Sun J, Zhu A, Li H, Zheng K, Zhuang Z, Chen Z, et al. Isolation of infectious SARS- CoV-2 from urine of a COVID-19 patient. Emerg Microbes Infect, 2020; 9(1): 991–3.
31. Chen YT, Shao SC, Lai EC, Hung MJ, Chen YC. Mortality rate of acute kidney injury in SARS, MERS, and COVID-19 infection: a systematic review and meta-analysis. Crit Care, 2020; 24(1): 439, http://dx.doi.org/10.1186/s13054-020-03134-8.
32. Ejaz H, et al. COVID-19 and comorbidities: Deleterious impact on infected patients. J Infect Public Health (2020).
33. F. Zeng, Y. Huang, Y. Guo, et al. Association of inflammatory markers with the severity of COVID-19: a meta-analysis. Int J Infect Dis, 2020; 96: 467-474.