Original Article

DOI: 10.7860/JCDR/2021/48792.15163

Impact of Co-morbidities on Outcome of COVID-19 Patients: An Observational Study among Patients Admitted to Intensive Care Unit

Internal Medicine Section

HEMANT KUMAR[1], SUMEET DIXIT[2], NIKHIL GUPTA[3], PREETI GUPTA[4], MANOJ KUMAR PANDEY[5], SHOBHIT SHAKYA[6], AMIYA KUMAR PANDEY[7]

ABSTRACT

Introduction: Coronavirus Disease-2019 (COVID-19) has been a major cause of apprehension, morbidity, and mortality in 2020. It had been postulated that associated co-morbid conditions in COVID-19 patients increase the severity of COVID-19 which leads to six times more chances of hospitalisation than patients without co-morbid condition. Mortality is also 12 times higher in such patients.

Aim: To find out the association between co-morbidities and mortalities due to COVID-19 pneumonia.

Materials and Methods: A prospective, observational study was conducted in a tertiary teaching institute of North India which was designated Level 3 (L-3) facility for treatment of COVID-19 patients. All 109 COVID-19 patients confirmed by Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR), admitted in Intensive Care Unit (ICU) from 1st July 2020 to 30th November 2020 formed the sample of the study. Data was taken regarding past history, clinical histories and examinations and ICU care and treatments. Based on their final outcome at the end of ICU care, patients were divided into two groups-group 1 (Non-survivor or Expired) and group 2 (Survived) and intergroup differences were studied.

Results: COVID-19 infection was about three times more common in males. Severe category of COVID-19 patients had higher mortality (59.2% of severe category expired during hospital course, 1.7% patients expired in moderate category group). Most common co-morbidities were hypertension (n=51, 46.8%) and diabetes (n=48, 44%). Multivariate analysis showed that co-morbidities in the form of chronic liver disease (OR -0.127 (0.024-0.681, p-value 0.016)) and post tubercular sequel (OR 0.036 (0.003-0.442, p-value 0.009)) were less likely to occur in COVID-19 patients who survived, thus making these co-morbidities significant contributor to the adverse outcomes in COVID-19 patients. More number of co-morbidities in a patient were associated with higher chance of mortality and this trend was significant statistically (p-value <0.001).

Conclusion: Patients with multiple co-morbidities, chronic liver disease and post tubercular sequel were associated with higher mortality in COVID-19 patients.

Keywords: Chronic liver disease, Coronavirus disease-2019, Mortality, Pneumonia, Severe acute respiratory syndrome coronavirus-2

INTRODUCTION

COVID-19 has been a major cause of morbidity and mortality in 2020. It was first detected in December 2019 as clusters of unexplained pneumonia with similar clinical characteristics in Wuhan, a city in the Hubei Province of China. COVID-19 infection remains asymptomatic in 40-45% patients but these asymptomatic patients can transmit infections to other persons [1]. Around 55-60% patients are symptomatic, among them approximately 80% are mild, 15% severe and 5% are critical who have respiratory failure, sepsis, multiorgan failure etc. Case Fatality Rate (CFR) due to COVID-19 is different in different sub-groups. Case fatality in COVID-19 patients increases with increase in severity; it is as high as 50% in critical patients. Mortality is also high in patients who have co-morbidities like diabetes, hypertension, Chronic Kidney Disease (CKD), hypothyroidism etc., [2].

Several theories have been given to explain mechanism of severity and mortality. There is an increase in expression of Angiotensin-Converting Enzyme 2 (ACE-2) receptors on target organs including the cardiovascular system, kidneys, lungs and brain [3] especially in co-morbid conditions. Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), which causes COVID-19, attaches to these receptors and downregulate it which leads to vasoconstriction, tissue ischaemia and regulate and renal remodelling. This is also one of reason that patients died with multiorgan failure in COVID-19 [4]. Other mechanism of complication is release of pro-inflammatory cytokines especially in immunocompromised individuals like diabetics, CKD patients etc., which increase inflammation in various organs like plaque rupture in coronary artery, Acute Respiratory Distress Syndrome (ARDS) in lungs, generalised hypercoagulability which leads to micro thrombi, ischaemia and tissue necrosis [5]. Diabetes is one of most common non communicable disease all over world. Diabetes causes excessive inflammation and also release tissue injury related enzymes which causes excessive morbidity and mortality in COVID-19 [6]. Chronic liver diseases like chronic viral hepatitis, liver cirrhosis, non-alcoholic fatty liver disease are not associated with an increased risk of acquiring COVID-19 infection in the absence of immunosuppressive therapy but these patients have high risk to get severe illness from COVID-19 [7]. Associated co-morbid conditions increase severity of COVID-19 which leads to six times more chances of hospitalisation than patients without comorbid condition. Mortality is also 12 times higher in such patients [8]. Multiple co-morbidities in patients with COVID-19 increases immunosuppression which leads to increased viral replication hence causes severe pneumonia which leads to a higher mortality rate in these patients as compared to patients with no or lesser number of co-morbidities [9].

As prevalence of non-communicable diseases like diabetes, hypertension, cardiac diseases, liver diseases, chronic pulmonary diseases are increasing worldwide so this study was planned to see association of co-morbidities with mortality in COVID-19 patients.

MATERIALS AND METHODS

This prospective, observational study was conducted at Dr. Ram Manohar Lohia Institute of Medical Sciences (Dr. RMLIMS), a tertiary teaching institute of Lucknow, Uttar Pradesh, India which was a designated L-3 facility for treatment of COVID-19 patients from 1st July 2020-30th November 2020. Ethical approval was taken from the Institutional Ethics Committee (IEC No.63/20). Informed consent was taken from the patients/family members.

Inclusion criteria: All the patients with moderate to severe COVID-19 pneumonia who were admitted to ICU facility of COVID-19 hospital of the present study, during the study time period were included in the study after obtaining informed consent from patients/family members.

Exclusion criteria: Patients aged <18 years, suffering from other ailments and also non-COVID-19 patients where cause death of patient is different and pregnant females were excluded from the study.

COVID-19 pneumonia was classified according to respiratory rate and oxygen saturation as mild pneumonia (RR <24/min and SpO_2 >94%), moderate pneumonia (RR 24-30/min, SpO_2 90-94%) and severe pneumonia (RR >30/min, SpO_2 <90%) [10]. Total 130 patients, who were in the ICU during the study duration, were screened for study but 21 patients were excluded due to unavailability of complete data. A 109 patients were included and analysed in this study. All patients were given appropriate treatment according to ICU protocol. Detailed data was collected including present condition, past history and other relevant clinical history. Detailed data regarding comorbidities were also collected.

Based on their final outcome at the end of ICU care, patients were divided into two groups.

Group 1 (Non-survivor or Expired): This group included those patients who died during hospital stay.

Group 2 (Survived): This group included all those patients who survived during hospital stay and were discharged after recovery.

All demographic, clinical and co-morbidity data were compared between survivor and non-survivor groups.

STATISTICAL ANALYSIS

Discrete data were analysed by cross-tables using descriptive method. Univariate and multivariate logistic regression was applied to see the impact of co-morbidities on adverse outcomes in COVID-19 patients. The p-value <0.05 was considered as statistically significant association.

RESULTS

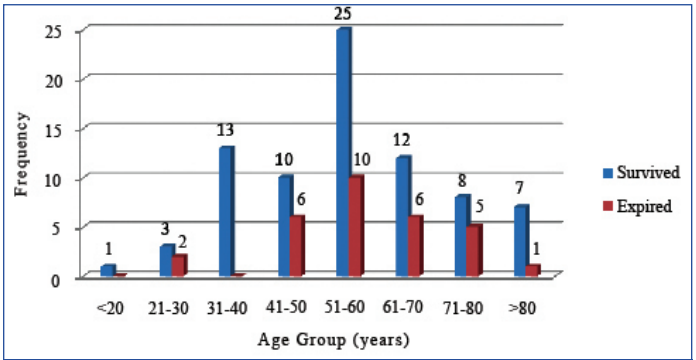
A total of 109 COVID-19 patients admitted in ICU were analysed. Out of 109 patients, 79 survived and were discharged successfully while 30 patients expired during hospital stay. Co-morbidities were analysed in all 109 patients and compared in both groups.

Mean age of patients in survived group and expired group was 56.1 years and 58.9 years, respectively. Higher mortality was seen in elderly as they had more comorbidities and lower immunity. COVID-19 infection was about three times more common in male population as compared to female population. This trend may be because males do outside work more frequently than females hence more chance of exposure. Severe category of COVID-19 patients had higher mortality. Around 59.2% of severe category patients expired during hospital course while only 1.7% patients expired in moderate category group. Most common presenting symptoms were fever, breathlessness and cough. These three symptoms constituted >60% of all COVID-19 patients' symptoms. Clinical signs like respiratory rate were higher (>30/ min) in expired group as compared to survived group (<30/min). Blood pressure was almost same in both the groups. Oxygen saturation was lower (<90%) in expired group while it was >90% in survived group [Table/Fig-1].

Variables studied		Number of patients (n)	Survived N (%)	Expired N (%)
Total patients (%)		109 (100%)	79 (72.48%)	30 (27.52%)
Age (Years), mean±SD			56.10±16.567	58.90±13.200
Sex	Male	81	63 (77.8%)	18 (22.2%)
	Female	28	16 (57%)	12 (43%)
Severity	Moderate	60	59 (98.3%)	1 (1.7%)
	Severe	49	20 (40.8%)	29 (59.2%)
Symptoms	Fever	69	48 (69.6%)	21 (30.4%)
	Cough	51	42 (82.3%)	9 (17.7%)
	Breathlessness	63	43 (68.3%)	20 (31.7%)
	Nausea/Vomiting	11	5 (45.5%)	6 (54.5%)
	Myalgia	27	18 (66.7%)	9 (33.3%)
	Common cold	6	6 (100%)	0
	*CNS symptoms	6	3 (50%)	3 (50%)
Respiratory Rate (per Min), mean±SD		109	25.5±6.67	31.5±7.4
Systolic BP (mmHg), mean±SD		109	134.94±20.7	132±20.9
Diastolic BP (mmHg), mean±SD		109	78.97±12	78.6±11.33
SPO_2 (%), mean±SD		109	90.5±9.86	86.1±7.75

[Table/Fig-1]: Clinico-demographic data of all COVID-19 patients.
*Giddiness, Drowsiness, Loss of consciousness; CNS: Central nervous system; BP: Blood pressure; SPO_2: Serum pressure of oxygen

Maximum COVID-19 patients were in the age group of 51-60 years. This is the age group in which people have high mobility along with comorbidities. So, this age group is more vulnerable for severe disease and ICU admission. [Table/Fig-2].



[Table/Fig-2]: Age wise distribution of COVID-19 Patients.

Most common co-morbidity was hypertension (46.8%) in this study. It was there in 60% in expired group while 41.8% in survived group. This difference was not significant (p=0.088). Diabetes was the second most common co-morbidity present in COVID-19 patients. It was present in 45.57% of survived group and in 40% of expired patients group. Other co-morbidities were less common but more frequent in expired group as compared to survived group.

By univariate analysis, among all co-morbidities post tubercular sequel was seen significantly associated (p=0.014) with adverse outcome in COVID-19 patients. On multivariate analysis significant association was observed between chronic liver disease (p=0.016) and post tubercular sequel (p=0.009) with adverse outcome in COVID-19 Patients. [Table/Fig-3].

Number of co-morbidities per patient was higher in expired group. One, two and three or more co-morbidities were present in 20%, 23.33% and 43.33% in expired group respectively while in survived group 32.9%, 31.6% and 8.8% patients had one, two and three or more co-morbidities. Higher number of co-morbidities in a patient were associated with higher chance of mortality and this trend was significant statistically (p-value <0.001). [Table/Fig-4].

Co-morbidity	N (109)	Survived (79)	Expired (30)	Univariate logistic regression analysis, p-value OR (95%CI)	Multivariate logistic regression analysis, p-value OR (95%CI)
Diabetes mellitus	48 (44%)	36 (45.57%)	12 (40.0%)	1.256 (0.535-2.950) p=0.601	2.407(0.806-7.182), p=0.115
Hypertension	51 (46.8%)	33 (41.8%)	18 (60.0%)	0.478 (0.203-01.126) p=0.091	0.350(0.113-1.084) p=0.069
Chronic kidney diseases	10 (9%)	7 (8.8%)	3 (10.00%)	0.854 (0.211-03.631) p=0.854	0.746(0.150-3.703) p=0.720
Chronic liver disease	7 (6.4%)	3 (3.8%)	4 (13.33%)	0.257 (0.054- 1.223) p=0.088	0.127(0.024-0.681), **p=0.016***
Chronic cardiac disease	13 (12%)	7 (8.8%)	6 (20.00%)	0.389(0.119-1.271) p=0.118	0.508(0.126-2.045) p=0.341
Chronic Obstructive Pulmonary Disease (COPD)	4 (3.67%)	3 (3.8%)	1 (3.33%)	1.160(0.116-11.609) p=0.900	1.118(0.088-14.165) p=0.931
Post tubercular sequel	6 (5.5%)	1 (1.26%)	5 (16.67%)	0.064 (0.007-0.575) **p=0.014***	0.036(0.003-0.442), **p=0.009***
Cerebro Vascular Accident (CVA)	5 (4.58%)	3 (3.8%)	2 (06.67%)	0.568 (0.090-3.578) p=0.547	2.203(0.159-30.504) p=0.556
Hypothyroidism	7 (6.4%)	4 (5%)	3 (10.0%)	0.462 (0.097-2.204) p=0.333	0.273(0.052-1.445) p=0.127
Others#	19 (17.4%)	13 (16.45%)	6 (20%)		

[Table/Fig-3]: Univariate and multivariate analysis.
#Acute pancreatitis, Bipolar disorder, BPH, Dengue, Fournier gangrene, Gall stone, Miliary TB, OSA, Post renal transplant, Severe pancreatitis, Psoriasis

Number of Co-morbidities	Number (n)	Survived (79)	Expired (30)	p-value
0	25	21 (26.6%)	4 (13.33%)	<0.001
1	32	26 (32.9%)	6 (20%)	
2	32	25 (31.6%)	7 (23.33%)	
3 or more	20	7 (8.8%)	13 (43.33%)	

[Table/Fig-4]: Number of co-morbidities in the study participants.
*Chi- square test

DISCUSSION

Associated co-morbidities play a significant role in severity and mortality of COVID-19 patients. In the present study, a total of 109 patients admitted in ICU were analysed. 79 patients were discharged successfully from ICU and 30 patients expired during the ICU stay. Various comorbidities were analysed in both the groups. Chronic Liver Disease and Post Tubercular sequel were significant in expired group as compared to survived group. In a retrospective cohort study by Harrison SL et al., conducted in 24 centres, they found chronic pulmonary disease and diabetes as most common co-morbidities in COVID-19 patients. Cardiac disease, chronic pulmonary diseases, chronic liver diseases and renal diseases were found as significant co-morbidities, which were associated with mortality. [11]. Similar to above findings, this study also suggests post tubercular sequel and chronic liver disease as significant in expired group as compared to survived group. In the present study, cardiac disease was found more in expired group but it was not significant statistically. Docherty AB et al., analysed co-morbidities in 20133 patients in 208 hospitals of United Kingdom. Most common co-morbidities in their study were chronic cardiac disease, uncomplicated diabetes, non-asthmatic chronic pulmonary disease and CKD Chronic cardiac disease, non-asthmatic chronic pulmonary disease, CKD and chronic liver disease were found in patients who expired during hospital course [12]. This was partially similar to the present study where it was also found that chronic liver disease and past pulmonary disease were significantly associated with mortality group. Henry BM and Lippi G, did a meta-analysis of four studies with total 1389 COVID-19 patients. A 273 were classified as severe disease. They found that CKD was significantly associated with severity of the disease [13]. These findings were in contrast to the findings of this study as in this study coronary artery disease and post tubercular sequel was associated with severity of diseases.

Singh S and Khan A, studied COVID-19 pattern in 250 pre-existing liver disease patients and compared with 2530 COVID-19 patients without pre-existing liver disease. They found that chances of hospitalisation and mortality were higher in pre-existing liver disease cohort as compared to other group [14]. These findings support the present study as chronic liver disease was associated with higher mortality in COVID-19 patients. Du RH et al., conducted a prospective cohort study to find out predictors of mortality in COVID-19 patients. They found that pre-existing cardiovascular and cerebrovascular diseases were associated with higher mortality in COVID-19 patients [15]. We also found cardiac disease and cerebrovascular diseases more in expired group but this association was not significant statistically.

Mechanism of higher mortality in pre-existing liver disease is not fully explained. Possible mechanism is that there is increased expression of ACE-2 receptors on liver cells and biliary ducts. SARS-CoV-2 virus attaches to these receptors and leads to vasoconstriction in liver micro vessels which leads to further hypoxaemic injury in pre-existing liver disease [16]. Pulmonary Tuberculosis causes destruction of lung parenchyma due to several mechanism and most common mechanism is fibrosis and bronchiectasis. SARS-CoV-2 also affects lung parenchyma primarily by attaching to ACE-2 receptors. Cytokine storm further damages lung parenchyma which leads to mortality in post tuberculosis sequel [17].

Mortality in COVID-19 also depends on numbers of co-morbidities present in one individual. In this study, 43.33% patients in expired group had three or more co-morbidities while only 8.8% patients had three or more co-morbidities in survived group. Onder G et al., analysed 355 patients who expired due to COVID-19 in Italy. They found that the mean number of co-morbidities was 2.7. 25.1% had one co-morbidity, 25.6% had two co-morbidities and 48.5% patients had three or more co-morbidities [9]. These findings are similar to the present study where we found that percentage of patients who expired with one, two and three co-morbidities were 20%, 23.33% and 43.33% respectively. This trend of multiple co-morbidities was significant statistically in expired group than that of survived group (p-value <0.001).

Limitation(s)

Firstly the number of enrolled cases with different co-morbidities was small, which might impact the power and precision of the results. Secondly, sample size of the study was small. Thirdly, the

duration and degree of control of co-morbidities in pre-covid state was not assessed.

CONCLUSION(S)

Patients with multiple co-morbidities with COVID-19 require more vigilance as they have higher chance of acquiring severe infection and higher chance of mortality. Among the co-morbidities, patients with chronic liver disease and post tubercular sequel have graver prognosis. There was only 8.8% survival rate of patients with three or more co-morbidities. thus, timely diagnosis, early isolation and intensive monitoring could be critical to reduce the mortality in patints with co-morbidities. A larger sample size study with more details of co-morbidities, their duration and degree of control in pre-covid state, is recommended in future for better precision in the results.

REFERENCES

[1] Oran DP, Topol EJ. Prevalence of asymptomatic SARS-CoV-2 infection: A narrative review. Ann Intern Med. 2020;173(5):362-67.
[2] Wu Z, McGoogan JM. Characteristics of and important lessons from the Coronavirus Disease 2019 (COVID-19) outbreak in China: Summary of a report of 72 314 cases from the Chinese Centre for Disease Control and Prevention. JAMA. 2020;323(13):1239-42.
[3] Patel VB, Zhong JC, Grant MB, Oudit GY. Role of the ACE2/angiotensin 1-7 Axis of the renin-angiotensin system in heart failure. Circ Res. 2016;118(8):1313-26.
[4] Mendoza-Torres E, Oyarzún A, Mondaca-Ruff D. ACE2 and vasoactive peptides: Novel players in cardiovascular/renal remodelling and hypertension. Ther Adv Cardiovasc Dis. 2015;9(4):217-37.
[5] Davidson JA, Warren-Gash C. Cardiovascular complications of acute respiratory infections: Current research and future directions. Expert Rev Anti Infect Ther. 2019;17(12):939-42.
[6] Guo W, Li M, Dong Y, Zhou H, Zhang Z, Tian C, et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. Diabetes Metab Res Rev. 2020:e3319. Doi: 10.1002/dmrr.3319.
[7] Zhang C, Shi L, Wang FS. Liver injury in COVID-19: Management and challenges. Lancet Gastroenterol Hepatol. 2020;5(5):428-30.
[8] Stokes EK, Zambrano LD, Anderson KN, Marder EP, Raz KM, El Burai Felix S, et al. Coronavirus Disease 2019 Case Surveillance- United States, January 22-May 30, 2020. MMWR Morb Mortal Wkly Rep. 2020;69(24):759-65.
[9] Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. JAMA. 2020;323(18):1775-76.
[10] Clinical Management Protocol for COVID19. Ministry of Health and Family welfare. (https://www.mohfw.gov.in/pdf/ClinicalManagementProtocolforCOVID19dated27062020.pdf).
[11] Harrison SL, Fazio-Eynullayeva E, Lane DA, Underhill P, Lip GYH. Comorbidities associated with mortality in 31,461 adults with COVID-19 in the United States: A federated electronic medical record analysis. PLoS Med. 2020;17(9):e1003321.
[12] Docherty AB, Harrison EM, Green CA, Hardwick HE, Pius R, Norman L, et al. Features of 20 133 UK patients in hospital with COVID-19 using the ISARIC WHO Clinical Characterisation Protocol: Prospective observational cohort study. BMJ. 2020;369:m1985. Doi: https://doi.org/10.1136/bmj.m1985.
[13] Henry BM, Lippi G. Chronic kidney disease is associated with severe coronavirus disease 2019 (COVID-19) infection. Int Urol Nephrol. 2020;52(6):1193-94.
[14] Singh S, Khan A. Clinical characteristics and outcomes of coronavirus disease 2019 among patients with pre-existing liver disease in the United States: A multicenter research network study. Gastroenterology. 2020;159(2):768-71.e3.
[15] Du RH, Liang LR, Yang CQ, Wang W, Cao TZ, Li M, et al. Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: A prospective cohort study. Eur Respir J. 2020;55(5):2000524.
[16] Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323(11):1061-69.
[17] Stochino C, Villa S, Zucchi P, Parravicini P, Gori A, Raviglione MC. Clinical characteristics of COVID-19 and active tuberculosis co-infection in an Italian reference hospital. Eur Respir J. 2020;56(1):2001708.

PARTICULARS OF CONTRIBUTORS:

1. Associate Professor, Department of Respiratory Medicine, Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, Uttar Pradesh, India.
2. Assistant Professor, Department of Community Medicine, Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, Uttar Pradesh, India.
3. Assistant Professor, Department of General Medicine, Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, Uttar Pradesh, India.
4. Assistant Professor, Department of Ophthalmology, Hind Institute of Medical Sciences, Lucknow, Uttar Pradesh, India.
5. Senior Resident, Department of Respiratory Medicine, Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, Uttar Pradesh, India.
6. Associate Professor, Department of General Medicine, Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, Uttar Pradesh, India.
7. Senior Resident, Department of Respiratory Medicine, Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, Uttar Pradesh, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Preeti Gupta,
Faculty Residential Apartments, Dr Ram Manohar Lohia Institute of Medical Sciences, Vibhutikhand, Gomti Nagar, Lucknow, Uttar Pradesh, India.
E-mail: drpreetigupta82@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]

- Plagiarism X-checker: Feb 02, 2021
- Manual Googling: May 19, 2021
- iThenticate Software: Jun 19, 2021 (10%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:

- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Jan 31, 2021**
Date of Peer Review: **Apr 20, 2021**
Date of Acceptance: **May 24, 2021**
Date of Publishing: **Jul 01, 2021**