"A Systematic Review on Clinical Characteristics and Co Morbidities of Covid 19 Patients"

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ABSTRACT:

Rationale of the study: Novel corona virus disease outbreak occurred in 2019 presenting as a respiratory illness. This infection spread to the whole world and caused significant mortality and morbidity. Clinical presentation and complications of COVID 19 are still obscure which needs to be explored.

Aim of the study: This article aims at exploring the role and contributions of comorbidities in patients with COVID 19 infection.

Materials and methods: A meta-analysis from 12 published articles obtained from electronic literature search was performed using PubMed, Scopus, Web of Science, google scholar and MedLine Plus. Full text articles published from 2020-2022 which were written in English were selected.

Results: In this meta-analysis the total sample size was 7708, of which the median age of presentation was 57yrs. There was a predominance of males with the M:F ratio being 1.2:1. The most common symptom noted was fever (75.18%) and loss of smell (74.90%), the least common symptom was vomiting (4.76%). The most common co morbidity seen associated with Covid 19 patients was hypertension (34.54%) and diabetes (20.99%) and the least common was malignancy (2.02%) and the p value noted was >0.05.

Conclusion: Covid 19 infection presents with acute respiratory distress syndrome and its clinical progression and prognosis is impacted by the presence of comorbidities especially hypertension and diabetes. This may help in proper identification of patients in risk category and prompt to take necessary precautions while treating the patients..

INTRODUCTION

In 2019 cases of pneumonia of unknown etiology were identified in Wuhan China as severe acute respiratory syndrome coronavirus 2 SARS CoV 2. This viral infection soon became pandemic involving people of both gender and all age group. The virus has now spread rapidly to involve 180 countries and is a currently considered a pandemic.[1] Corona virus is an enveloped virus with a central core of single stranded RNA which encodes for structural and non-structural proteins. These viruses have spike like projections made up of glycoprotein on their surface which gives crown like appearance when observed under electron microscope, hence called corona virus. [2] The clinical features seen in this infection may range from common cold to severe manifestations like bronchitis, pneumonia, severe acute respiratory distress

syndrome (ARDS), multi organ failure leading to even death. The main cause of death in COVID 19 infections are ARDS, renal and cardiac failure. Global mortality rate of patients with COVID 19 infections is estimated to be around 2.2%.[3] However limited literature available suggests that underlying pre-existing condition and age may exacerbate the infection and worsen the symptoms and prognosis.[4] Available literature has suggested that patients with diabetes, lung disease and cardiovascular diseases, hypertension, liver and kidney diseases, cancer patients on chemotherapy, smokers are at increased risk of COVID 19 infection.[5] This article aims at exploring the role and contributions of comorbidities on patients with COVID 19 infection.

METHODS:

This systematic review was done based on recommendations from the Cochrane guidelines for systemic reviews of intervention and was written according to Preferred Reporting Items for Systematic Reviews and Meta analyses (PRISMA).[6] Articles were read and evaluated by two authors. They screened article titles and abstracts independently. Third author checked the screening results. Eligible Full text articles were selected and reviewed for further assessment. Data such as name of author, year, sample size, gender, co morbidity, clinical features were entered into excel sheet for further evaluation. The medical term

"Malignancy" included "Malignant tumor, Malignancy, Cancer, Carcinoma". The term "COPD" included "COPD", "Chronic obstructive pulmonary disease", "Chronic Lung Disease". The term "Cerebrovascular diseases, Cerebral infraction" were considered under the title of "Cerebrovascular diseases.

In the review articles on Covid 19 published in various national and international journals between the Jan 2020 to Dec 2022 was used. The search was conducted using keywords "corona virus or Covid 19", "Covid 19 and clinical features" in PubMed, EMBASE, and Web of Science databases on online platforms. We concentrated on article on Covid 19 with information on age, gender, clinical features, prevalence of risk factors and co morbid diseases. In the present study the retrieved articles were fully evaluated for document type, scientific source, country and indexed keywords. The analyzed articles which were openly accessible and written in English only. The article analyzed widely ranged from original articles, reviews, case reports, meta analysis. Inclusion criteria: Studies with > 100 sample size, articles written in English, Full articles with information and data on comorbidities and individuals diagnosed with COVID-19, patient dataset with COVID-19, and major comorbidities like CVD, HTN, Diabetes, COPD. Articles with only abstracts and articles which were written in any other language other than English and sample size <100 were excluded from the study. (Fig 1)
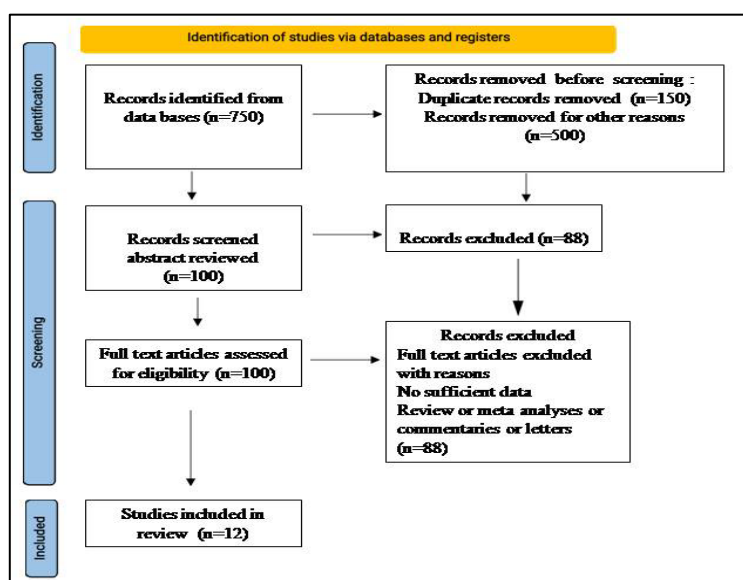

Fig 1 Showing PRISMA flow chart diagram showing the number of records identified in the search to the number of studies included in the review

The details were entered into excel sheet and Statistical analysis was carried out using Statistical Package for the Social Sciences (SPSS) version 23.0 and Microsoft Excel 2016. Continuous variables were expressed as medians and interquartile ranges or simple ranges, as appropriate. Categorical variables were summarized as counts and percentages.

We assessed whether the prevalance of co morbidities had any significant difference in the severe and non severe covid patients and p value was determined using t test. P value of <0.05 was considered to be statistically significant.

RESULTS

The current study was a systematic review and the prevalence of comorbidities noted in summarized in Table.

No	Author	HT	DM	CVD	COPD	CereVD	Malignancy	CKD	CLD	Imm. sup	Hepatitis	Psychiatric	Asthma	Obesity	Thyroid
1.	Liu K	13	14	10	2	0	2	7	7						
2.	Wang D	43	14	20	1	1	1	1		1	2				
3.	Guan et al	164	81	27	121	15	9	7		2	23				
4.	Feng X et al	78	49	39	3	7	12	7	5			3			
5.	Soni SL et al	19	17	2	2			3	1				42	1	6
6.	Lv Z et al	125	72	51	17		2	20	16	2			12		
7.	Zhang Q et al	32	30	13	6	99		1	6	1					
8.	Zhang X et al	712	338	223	21	82	43	58	121						
9	Boscolo-Rizzo, P	56	20		28		12	18	16	13				30	
10.	Albangali M et al	294	368		54			6					26		

No	Author														
11.	Rai DK et al	268	245	50	0			36							
12.	Farhana A et al	859	370	69	83			9					117		
	Total	2663	1618	504	239	204	81	173	172	19	25	3	197	31	6

Table 1 showing the prevalence of co morbidities in the current systematic review

In this systematic review a total of 12 publications over the years of 2020- 2022 summarized in (Table 2)

No	Author & Year	Title of article	Journal & Year	N	Age		Gender	
					Range	Median or Mean ±SD	M	F
1	Liu K December 30, 2019 to January 24, 2020	Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province. Chin Med J (Engl)	Chin Med J (Engl) (2020)133: 1025-1031.	137	20-83	57	61	76
2	Guan et al December 11, 2019 to January 29, 2020	Clinical characteristics of Coronavirus disease 2019 in China	The New England Journal of Medicine (2020);382 :1708-1720	1099	35-58	47	639	460
3	Wang D January 1 to January 28, 2020	Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus - infected pneumonia in Wuhan, China	JAMA (2020) ;323:1061-1069.	138	22-92	56	75	63
4	Boscolo -Rizzo, P January 17, 2022, to February 4, 2022	Coronavirus disease 2019 (COVID-19)–related smell and taste impairment with widespread diffusion of severe acute respiratory syndrome–coronavirus-2 (SARS-CoV-2) Omicron variant	Int. Forum Allergy Rhinol.2022;12:1273-1281.	338	34-59	46	155	183

5	Feng X et al January 23, 2020 to February 22,2020	Clinical characteristics and short term outcomes of severe patients with Covid-19 in Wuhan, China	Front Med (2020);7:doi=10.3389/fmed.202.00491	114	50-77	63.96± 13.41	71	43
6	Zhang Q et al January 2020 and February 2020	Clinical features and prognostic factors of patients with COVID-19 in Henan Province, China	Human Cell 2021;34:419-435	172	16-98	47.9 ± 18.	92	80
7	Lv Z et al February 2020 to March 2020	Clinical characteristics and analysis of risk factors for disease progression of COVID-19: A retrospective Cohort Study	International Journal of Biological Sciences 2021;17:1-7	409	38-62	50.47± 12.43	188	221
8	Zhang X et al February 12 and April 10, 2020	Symptoms and health out-comes among survivors of COVID-19 infection 1 year afterdischarge from hospitals in Wuhan, China.	JAMA Network Open2021; 4:e2127403	2433	49-68	60	1205	1228
9	Soni SL et al April 1 to May 25, 2020	Demographic & clinical profile of patients with COVID-19 at a tertiary care hospital in north India	IJMR 2021;153:115-125.	114	13-79	33.5	66	48
10	Albangali M et al April 2020 to August 2020	Clinical Characteristics and Treatment Outcomes of Mild to Moderate COVID-19 Patients at Tertiary Care Hospital, Al Baha, Saudi Arabia: A Single Centre Study	Journal of Infection and Public Health 2022;15:331-337	811	14-66		403	408

11	Rai DK et al	Clinical characteristics, treatment outcomes and factors associated with severe illness in 813 COVID-19 patients admitted in a tertiary care hospital of eastern India	Adv Respir Med 2022;90:193-201	813	35-65	50.96 ± 15.3	639	174
12	Farhana A et al	Clinical characteristics among patients with COVID-19: A single-center retrospective study	Biomedical Reports 2022;17:94	1096	41-58	49.89		

Table 2 showing list of articles used in this systematic review from Jan 2020 to Dec 2022 with age and gender distribution

The total number of Covid 19 patients in this systematic review was 7708. It was observed that the median age of presentation was 57yrs and age ranged from 16-98yrs. Males comprised of 69.31% in patients with non severe covid and remaining 30.69% in patients with severe covid. Females comprised of 74% in patients with non severe covid and remaining 26% in patients with severe covid and the p value was 0.281. (Table 2)

Gender	Non severe (n=4547)	%	Severe (n=1832)	%	Total (n)	P value
Male	2565	69.3	1136	30.69	3701	
Female	1982	74	696	26	2678	0.281435

Table 3 showing p value of t test of severe and non severe COVID infection in males and females

The most common clinical symptoms of Covid 19 noted in this review and comparison with other studies was fever 75.18%, and the least common symptoms was vomiting 4.76%. (Table 3)

	Clinical symptom	Current systematic review N=7708	Paudel SS N=1786	Huang C N=41	Ashish Bindra N=323
1	Fever	75.18%	88.8%	98%	88%
2	Loss of smell	74.90%			
3	Fatigue	65.97%	33%	44%	62%
4	Sputum	56.38%	28.5%	28%	
5	Cough	54.57%	68%	76%	40%
6	Anorexia	46.17%			
7	Joint Pain	44.67%			
8	Blocked nose	44.56%			
9	SOB	42.29%	17%		
10	Tightness in chest	28.93%			
11	Myalgia	27.73%	14%		20%
12	Headache	27.10%	10.2%	8%	
13	Sore throat	25.04%	11.4%		
14	Dyspnea	17.84%		55%	15%
15	Heart palpitations	16.84%			
16	Chest Pain	16.59%	0.11%		11%

17	GI disturbances	14.06%			
18	Diarrhea	11.02%	4.4%	3%	
19	Chill	10.52%			
20	Dizziness	9.42%			
21	Nausea	6.34%			
22	Hemoptysis	5.10%		5%	
23	Vomiting	4.76%	4.1%		
24	Productive cough				
25	Rhinorrhea		3.2%		9%
26	Abdominal pain		0.16%		

Table 4 showing percentile representation of clinical presentation seen in COVID

In this study the clinical features among severe and non severe cases of COVID were compared and it was noted that among patients with severe Covid infection diarrhoea was the most common presentation whereas dry cough was the least common presentation. Among patients with non severe Covid infection dry cough was the most common clinical presentation whereas diarrhoea was the least common symptom. However, the comparison of various clinical features among severe and non severe Covid patients showed a p value of >0.05. (Table 4)

	CLINICAL FEATURE	SEVERE	%	NON SEVERE	MEAN	%	TOTAL	P VALUE
1.	Fever	902	33	1833	366.6	67	2735	0.154814
2.	Fatigue	508	42	691	138.2	58	1199	0.345708
3.	Dry cough	218	17	1032	206.4	83	1249	0.115071
4.	Anorexia	289	57	217	43.4	43	506	0.413325
5.	Myalgia	66	22	228	45.6	78	294	0.128707
6.	Dyspnea	743	57	580	116	44	1315	0.413225
7.	Expectoration	333	38	535	107	62	868	0.281098
8.	Diarrhoea	272	66	141	28.2	34	413	0.311594
9.	Nausea	53	28	134	26.8	72	187	0.190731
11.	Headache	293	63	170	34	37	463	0.335369

Table 5 showing t test p value of clinical symptoms in patients with severe and non severe COVID infection and their p value

In the current study comorbidities seen in patients with severe and non severe Covid infection showed that Hypertension and diabetes were the most common comorbidity whereas chronic kidney disease was the least common in patients with severe Covid. Among patients with non severe Covid CLD was the most common comorbidity and hypertension and diabetes were the least common comorbidity. However, the P value of all comorbidities compared among patients with severe and non severe Covid were >0.05. (Table 5)

	COMORBIDITY	SEVERE	Mean	%	NON SEVERE	Mean	%	TOTAL	P VALUE
1.	Hypertension	976	139.4	49	1005	143.5	51	1981	0.484417
2.	Diabetes	396	56.57	49	420	60	51	816	0.464828
3.	Cardiovascular disease	140	20	46	164	23.42	54	304	0.437896
4.	Cerebrovascular disease	54	7.71	47	60	8.57	53	114	0.457998
5.	COPD	70	10	48	76	10.85	52	146	0.457434
6.	CKD	30	4.28	37	51	7.28	63	81	0.312538
7.	CLD	31	4.42	23	101	14.42	77	132	0.242093

Table 6 showing comparison of comorbidities in patients with severe and non severe COVID infection and their p value

Discussion

The systematic review was based on data from 12 studies with confirmed cases of COVID-19. The average incubation period for COVID-19 is reportedly different in different studies and is approximately 5.2 days and the symptoms of COVID-19 may appear anytime from 2 to 14 days after exposure; therefore, 14-day quarantine is recommended.[7] In this study the average age of patients in this study was 57yrs. Contrary to our findings Huang 2020 and Chang 2022 found that the average age was 49yrs and 35.5 yrs respectively.[8,9]

Patients with COVID infection present with a wide clinical symptoms ranging from mild complaints to more critical cases associated with difficulty in breathing. It was noted that the top 3 clinical common symptoms were fever being the most common followed by loss of smell and fatigue and the least common symptoms were nausea, hemoptysis and vomiting and were mostly similar to work of Hyuang C, Paudel SS, Ashish Bindra, Mehta are represented in table 2.[9-12]

Model studies have estimated that 1.7 billion people globally (22% of the population) have at least one comorbidity that is associated with an increased risk of developing severe COVID-19.[13,14] It is proposed that the virus utilizes ACE- 2 receptors which are expressed in various human organs on their cell surface. SARS CoV 2 enters the host cell via ACE 2

receptors due to higher release of proprotein convertase which prevents ACE 2 from performing its normal protective function causing injury especially to the lungs and heart which leads to progression and worsening of COVID 19 disease. [15]

It was noted in this study that hypertension was the most common comorbidity among patients with severe covid than in non severe patient; however it was not statistically significant similar to findings of Lippi G 2020.[16] Hypertension causes dysregulation of the RAAS, immune response, gastrointestinal tract, and inflammation increasing the severity of COVID 19 and is a predictor of worse prognosis.[17] It has been thought that a putative upregulation of ACE 2 in hypertensive patients treated with RAS blocker might potentially contribute to advance course of COVID 19 and higher risk of SARS CoV 2 infections. Many contradict this concept and support that RAS blockers have protective role and an independent role in COVID but may be co-dependant on many underlying factors like age, obesity, diabetes, cardiovascular, cerebrovascular and chronic pulmonary diseases. [18]

A membrane bound protein named Furin is expressed in high levels in diabetic patients which activates attachment of SARS Cov 2 to the ACE 2 receptors which helps in entry of virus into the cell escaping from the human immune systems which leads to higher lung inflammation and lower insulin levels. [19,20] Impaired functions of T cell and elevated levels

of interleukin-6 (IL-6) with impaired phagocytic cell capabilities plays a decisive role in developing COVID 19 disease in diabetics.[21] Marchand 2020 1st observed an increased risk of developing type 1 Diabetes mellitus (T1DM) in patients with COVID 19.[22] Viral infections induce anti pancreatic antibodies which lead to destruction of pancreatic islets and β cells leading to T1DM. [23,24] Ketoacidosis was noted in 77% of COVID patients with T2DM. [25] 11-58% of all COVID 19 patients have diabetes and fatality rate estimated is around 8%.[26,27] The risk for ICU admissions in COVID 19 individuals with diabetic comorbidity is 14.2% higher than individuals without diabetes. [28] Though not statistically significant diabetes was the most common comorbidity among patients with severe covid and the least common in non severe covid.

In the current study CVD was associated more frequently in patients with non severe covid than in severe covid but was not statistically significant. Pre-existing CVD increases vulnerability to develop COVID 19 infection and present with more severe disease with worse clinical outcomes. The fatality rate is significantly higher in patients with hypertension, diabetes and CVD. The complication seen in CVD patients with COVID 19 infections are acute cardiac injury, acute coronary event, left ventricular systolic dysfunction, heart failure, arrhythmia with potential long-term consequences. Among these the most common complication is acute cardiac injury where there is elevation of cardiac troponin 1 above 99Th percentile upper reference limit and is a strong negative prognostic marker in patients with COVID 19.[29] Elevation of ST segment in patients with COVID 19 and CVD is reported low, whereas left ventricular systolic dysfunction, acute left ventricular failure, cardiogenic shock have not been described. [30]

COPD in this study was associated more frequently in patients with non severe covid than in severe covid however was not statistically significant. There is microbiome imbalance, weak immunity, continual mucus production, use of respiratory corticosteroids, and structural damages involved in establishing COPD.[31] COPD is a risk factor for worse clinical outcomes in COVID 19 patients like hospitalization and death.[32] Patients with COPD are more susceptible to thrombotic events which are

further worsened by COVID 19.[33] COVID 19 patients with COPD are more prone for secondary bacterial infections as alveolar macrophages show decreased bacterial phagocytosis and decreased antimicrobial peptide release which leads to secondary bacterial infection. [34]

In the current study CLD was associated more frequently in patients with non severe covid than in severe covid but was not statistically significant. The current data however suggest that liver injury in COVID 19 is mostly secondary to immune dysregulation and/or cytokine storm, development of endotheliopathy with hypoxic and/or ischemic injury, drug induced liver injury (DILI), or a combination. [35] Patients suffering from autoimmune hepatitis, cholestatic liver diseases, liver transplantation were considered at higher risk of severe COVID 19 due to co-existing immunosuppression. The mortality risk is rather influenced by comorbidities than liver transplantation status. Hence recent guidelines suggest that cessation or reduction of immunosuppressant should not be done and they should be rather prioritized for vaccination. [36,37]

CKD in the study was associated more frequently in patients with non severe covid than in severe covid but was not statistically significant. SARS CoV 2 virus was isolated successfully from the urine sample of infected patients suggesting that kidneys are potential target for SARS CoV 2. [38] Acute kidney injury (AKI) is a recognized common complication of COVID 19 and is frequently evident at hospital admission. The rate of prevalence may be as high as 45% in patients who are in ICU and require kidney replacement therapy KRT. [39] Chronic kidney disease (CKD) is a well identified risk factor for AKI in hospitalized patients and is an independent risk factor with worst outcome in COVID 19 patients. [40] High mortality seen in comorbid and elderly patient is related to decrease renal function and functioning nephron mass. [41].

The risk of developing severe COVID 19 disease associated with asthma patients is seen in smokers especially elderly.[42] The reduced expression of SARS CoV 2 receptor, ACE2 rendering asthma patients protected from COVID infection.[43] Recent data suggest that only patients with allergic asthma are

protected from COVID 19.[44] Obesity is one of the less highlighted comorbidities in COVID 19 infections. Azzolino 2020 noted 47.6% of obese people were infected with COVID 19 and out of these 68.6% were in critical condition and received ventilation.[45] Obesity is a well recognized risk factor for diabetes, hypertension and cardiovascular disease all of which are predictors of poor outcomes of COVID 19 infection. It is more challenging to treat COVID patients with obesity as it may limit medical and assistive procedure owing to the size of patient.[46] Patients suffering from any malignancy are at higher risk of developing COVID 19 infection as the immune response is weak in patients with malignancy. [47] The symptoms of COVID 19 in HIV patients are similar to those affecting general population like cough, fever etc. Age and comorbidities were the strongest predictors of severe disease and mortality and these findings are comparable with that of the general population. However the possibility of admissions to ICU and mortality rate is higher in HIV patients with COVID than general population. [48]

CONCLUSION

Males in the age range of 57yrs were commonly affected by Covid. The most common clinical symptom noted among patients with severe Covid was diarrhoea and with non severe Covid was dry cough. The most common comorbidity seen in patients with severe Covid was hypertension and diabetes. Hence identifying the relationship between comorbidities and COVID 19 and its outcomes is scientifically very important and may reveal new molecular mechanisms and opportunities for effective therapy.

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