A Study of Severity of COVID With Respect To Age, Gender and Inflammatory Markers in Patients Admitted At a Tertiary Care Hospital

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ABSTRACT
Background: COVID-19 has become a health concern and has a high mortality rate. Hence, this study was performed to study the severity of COVID with respect to age, gender, comorbidity and inflammatory markers.
Methods: This was a retrospective cohort study. 100 COVID positive patients diagnosed by RT PCR were included. Patients were categorized on the basis of gender, age, severity and comorbidities for comparison of epidemiologic characteristics, laboratory values and outcome.
Results: Pulse rate and respiratory rate were significantly elevated in patients with severe disease as compared to patients with moderate disease. Mean neutrophil count, lymphocyte count and NLR ratio, CRP, S.Ferritin and D-Dimer were significantly elevated in patients > 40 years compared to patients < 40 years in age and in patients with comorbidities than those without. Severity was found to be significantly higher in males, patients with co morbidities and those with higher ESR and CRP.
Conclusion: Tachycardia and tachypnoea may be markers of conversion of moderate disease to severe course and NLR, ESR, CRP, Ferritin and D Dimer may be the markers of more severe disease and higher mortality. Thus, COVID 19 patients with comorbidities, age more than 40 years, elevated NLR, ESR, CRP, Ferritin and D Dimer should be treated more aggressively. An RCT may help to develop a severity scoring system based on these factors to clearly identify the patients who may be managed at home and aid in conservation of medical resources for those who actually need them.

Keywords: COVID 19; severity, inflammatory markers, comorbidity

INTRODUCTION

Corona virus disease was first reported in December 2019 in Wuhan, China. Later named COVID-19, it was declared a global pandemic by WHO (World Health Organization) on 11th March 2020. Since then it has spread rapidly, reaching over 2 million confirmed cases globally[1].

The pathogen is a highly contagious novel enveloped RNA betacoronavirus and may cause various symptoms such as pneumonia, fever, breathing difficulty and lung infection[2]. The illness ranges in severity from asymptomatic to severe. It has been reported that 6% of cases develop critical illness[1]. Mortality rate among diagnosed cases has a variable range. The WHO estimated the global mortality rate to be about 3% of confirmed cases but it may vary regionally[3].

The disease has now spread to all of the world including all regions of India. It's significant mortality poses a need for collecting and disseminating information regarding clinical profile of the diagnosed cases to aid in formulating treatment protocols and to make required changes in the

protocol from time to time. Hence, we performed this study to describe the clinical profiles of COVID positive patients admitted in our hospital, a tertiary care centre in rural area on western coast of Gujarat.

METHODOLOGY:

The study was a retrospective cohort study carried out after obtaining approval from Institutional Ethics Committee. 100 consecutive patients with confirmed Covid-19 infection admitted to our hospital were included.

All patients coming to our hospital who were suspected to have COVID 19 were admitted to suspected COVID area. COVID 19 was diagnosed if RT PCR test for COVID 19 came positive. All COVID 19 positive patients were subjected to CBC, Urine RM, RBS, RFT, S. electrolytes, LFT, ABG (arterial blood gas), ESR, CRP, S. Ferritin, D Dimer, S. LDH, ECG and Chest X ray. HRCT Chest was done if indicated. Other investigations like USG abdomen and 2DECHO were also done whenever indicated. All the patients were treated according to the standard COVID 19 treatment protocol.

The medical records of these patients were retrieved from the records section and analyzed by the research team of the Department of Medicine. Epidemiological, clinical, laboratory, and radiological characteristics, treatment and outcome data was obtained from the medical records. The patients were categorised as mild, moderate and severe based on ABG criteria for comparison of epidemiologic characteristics, laboratory values and outcome. They were also categorised by gender and age (< 40 years or > 40 years) for comparison. The data so collected was analysed on Microsoft Excel Datapak to describe the frequency of presenting symptoms, trends of lab reports, frequency of severe illness, morbidity and outcome of the patients. The results are presented as mean ± SD or proportion.

RESULTS:

Total 100 patients were included in study. 68 % were male (mean age 46.85 ± 14.72 years) and 32 % were female (mean age 49.16 ± 17.18 years). 67 patients were < 40 years of age and 33 patients were > 40 years. 61 % patients had mild disease (categorized on the basis of arterial blood gas analysis), 18 % patient had moderate disease and 21 % patients had severe disease. Co morbidity was present in 46% patients out of which 29 (63.04%) patients had hypertension, 13 (28.26%) had diabetes, 7 (15.21%) had ischemic heart disease,6 (13.04%) had hypothyroidism, 2 (4.34%) had asthma and 1(2.17%) each had gout and ovarian carcinoma.

Fever, cough and breathlessness were the most common symptoms. 56% patients had fever, 54 % had cough and 53 % had breathlessness. 83% patients had at least one of them. 20% patients had wheezing and 14% had expectoration. There was no significant difference in presenting symptoms between males and females, in patients < 40 years of age as compared to those > 40 years and also between patients with and without co morbidity. Cough was more common in patients with moderate disease as compared to patients with severe disease (83.33% v/s 57.14%). Breathlessness was more common in patients having severe as compared to patients with moderate disease (83.33 v/s 95.23%), however none reached statistical significance. (Table 1)

There was no significant difference in spo2, pulse rate and respiratory rate based on gender, age or comorbidity. spO2 was lower in patients with severe disease as compared to those with moderate disease (90.19 ± 7.02 v/s 93.11 ± 9.13, p = 0.152), but the difference was not statistically significant. Both pulse rate (beats/min) and respiratory rate (breaths/min) were significantly elevated in patients with severe disease as compared to patients with moderate disease (97.90 ± 20.45 v/s 83.56 ± 12.35, p = 0.011) and (33.71 ± 7.08 v/s 27 ± 6.05 p = 0.003) (Table 1).

The mean values of hemoglobin, total leucocytes count, platelet count, blood urea, serum creatinine, SGPT and SGOT of the study population were within normal limits. Also, there was no significant difference in above mentioned parameters in male and female, moderate and severe disease, age less than 40 years and more than 40 years and in patients with and without co morbidities.

There was no statistically significant difference in neutrophil count, lymphocyte count and neutrophils to lymphocyte ratio in males and females and in patients with moderate and severe disease. However, there was significant difference in mean neutrophil count and mean lymphocyte count in patients > 40 year in age as compared to those < 40 years (neutropil count 75.21 ± 10.87 v/s 64.91 ± 11.9, p = 0.001; lymphocyte count 18.93 ± 10.58 v/s 28.52 ±

11.82 , p = 0.001). NLR ratio was also significantly elevated in patients > 40 years of age compared to patients < 40 years of age (6.79 ± 6.57 v/s 3.36 ± 3.93, p = 0.002). Similarly mean neutrohil count and mean lymphocyte count were significantly different between patients with comorbidities and without any comorbidities (76.24 ± 10.35 v/s 68.04 ± 12.39, p = 0.001) and (17.28 ± 9.85 v/s 26.19 ± 11.94, p = 0.001). The NLR was also significantly elevated in patients with co morbidities compared to those without co morbidities (7.07 ± 6.27 v/s 4.46 ± 5.62, p = 0.033). (Table 2)

Among the inflammatory markers, only CRP (mg/dl) showed statistically significant difference between male and female patients (61.85 ± 63.80 v/s 38.15 ± 42.37, p = 0.030). S.Ferritn (ng/ml), ESR(mm/hr), D-Dimer (ng/ml) and S.LDH(U/l) showed no significant difference. Similarly no significant difference in levels of inflammatory markers was seen between moderate and severe disease.

On comparing > 40 years with < 40 years age group, CRP, ESR and D-Dimer were found to be significantly elevated in patients > 40 years as compared to those < 40 years in age 67.02 ± 65.63(mg/dl) v/s 28.39 ± 27.03(mg/dl), p = 0.00; 64.64 ± 33.19 v/s 48.06 ± 30.33, p = 0.015 and 970.04 ± 992.74 v/s 612.64 ±450.65, p = 0.015 respectively). S. Ferritin was also significantly elevated in > 40 years age group (p=0.045). However, there was no significant difference in S.LDH between the two age groups.

On comparing patients with and without comorbidities, ESR was found to be significantly elevated in patients with co morbidities compared to patients without any co morbidities (67.50 ± 37.37 v/s 53.06 ± 26.55, p = 0.032). For S.Ferritin and D-Dimer also the difference reached significance level (p=0.05), however, there was no significant difference in CRP and S.LDH. (Table 3)

Sixteen patients died. Mortality was significantly higher in > 40 years age group as compared to < 40 years age group (p = 0.017) and also in those with comorbidity as compared to those without comorbidity (p = 0.011). However, there was no statistically significant difference in mortality between males and females or patients with moderate and severe disease.

DISCUSSION:

Originally named severe acute respiratory syndrome coronavirus[3] (SARS-CoV- 2), it was later named COVID 19 by the WHO to refer to a coronavirus that caused peumonia in Wuhan, China on 29 December 2019[4,5,6].It is thought that the primary source were bats (as it is closely similar to bat coronaviruses), while it spread to humans via transmission from wild animals illegally sold in the Huanan Seafood Wholesale Market[7]. From there it spread rapidly causing massive loss of life and property all over the world to be declared a pandemic in March 2020. However, true overall mortality rate is uncertain as the total number of cases (including undiagnosed persons with milder illness) is unknown[8].

The COVID-19 pandemic has set challenges for health services rarely seen at times other than wars. Hence, this study was performed to identify likely symptoms and clinical trajectories that may allow prognostication and effective management of COVID 19 patients and also help in effective communication with patients and families.

In the previous studies fever,[9,10,11]. cough, breathlessness and fatigue were reported to be the most prevalent symptoms.[9,12,13,14, 15] Leucocytosis, lymphopenia, elevated CRP and D-dimer[16]and elevated blood urea were also noted. Acute respiratory distress leading to respiratory failure and acute cardiac injury leading to myocardial failure were reported as the most common causes and modes of death.[9,12,13,17] They also observed that the patients who expired were more likely to have age>45 years, comorbidities,[12,13,15,16] significantly lower spO_2 and elevated SGOT, SGPT at presentation as compared to recovered patients.[12,13] However, most of these studies were done in China.

We found that most common symptoms were cough, breathlessness and fever which were proportionately more common in severe cases although the difference was not statistically significant. Pulse rate and respiratory rate both were significantly higher in those with severe disease as compared to those with moderate disease. Hence, pulse and respiratory rate may be used to differentiate between moderate and severe cases.

We observed significant differences in > 40 years and < 40 years age groups. Neutrophilia and lymphopenia

were significantly more prominent, neutrophil lymphocyte ratio (NLR) was also significantly higher and ESR, CRP, Ferritin and D- Dimer were significantly more elevated in >40 years age group as compared to < 40 years age group and those with comorbidity as compared to those < 40 years age and those without comorbidity respectively. Similarly, neutrophilia and lymphopenia were significantly more prominent, ratio of neutrophils to lymphocyte count was also significantly higher and ESR, CRP, Ferritin and D- Dimer were significantly more elevated in those with comorbidity as compared to those without comorbidity. We also found that mortality was significantly higher in > 40 years age group and the patients with comorbties. These findings point towards the possibility that elevated NLR, ESR, CRP, Ferritin and D Dimer may be the markers of more severe disease and higher mortality.

Thus, this study confirms the previous findings of fever, cough and breathlessness being most common symptoms, higher age and presence of comorbidities being risk factors for more severe course of illness and higher mortality. This study also adds that cough, fever and breathlessness are more commonly present in severe cases, that tachycardia and tachypnoea may be markers of conversion of moderate disease to severe course and that NLR, ESR, CRP, Ferritin and D Dimer are the markers of more severe disease and higher mortality.

COVID 19 has become a public health and medical emergency in almost all countries and patient protection and treatment have become the primary concern for services and clinicians. Given the evident rapidity of the terminal phase, understanding the symptoms in the cohort unlikely to survive and their susceptibility to pharmacological (or other) measures will allow clinicians to direct appropriate management.

CONCLUSION: Although an adequately designed RCT is required to give more specific answers, COVID 19 patients with comorbidities, age more than 40 years, elevated NLR, ESR, CRP, Ferritin and D Dimer should be treated more aggressively to reduce morbidity and mortality. An RCT may help to develop a severity scoring system based on these factors to clearly identify the patients who may be managed at home and those who need hospitalization and special care. In view of the scale of affected population, this will definitely aid in conservation of medical resources for those who actually need them.

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Table 1 Presenting symptoms and signs of the study population

Parameter	Moderate(n=18)		Severe(n= 21)		p value
Cough	15	83.33%	12	57.14%	0.077
Breathlessness	15	83.33%	20	95.23%	0.221
Fever	11	61.11%	15	71.42%	0.899
Expectoration	2	11.11%	2	9.52%	0.311
Wheezing	7	38.88%	9	42.85%	0.684
	Moderate(n=18)		Severe(n= 21)		
	Mean	SD	Mean	SD	
SpO2 (%)	93.11	9.13	90.19	7.02	0.135
Pulse Rate (/min)	83.56	12.35	97.90	20.45	**0.011**
Respiratory Rate (/min)	27.00	6.05	33.71	7.08	**0.003**

Table 2: Neutrophil count, lymphocyte count and Neutrophil to Lymphocyte ratio (NLR)

Parameter	Male (n=68)		Female (n=32)		p value
	Mean	**SD**	**Mean**	**SD**	
N (%)	72.78	11.60	69.75	13.21	0.271
L (%)	21.22	11.33	23.94	12.86	0.311
NLR	5.87	6.07	5.22	6.03	0.619
	Moderate (n= 18)		**Severe(n= 21)**		
	Mean	**SD**	**Mean**	**SD**	
N (%)	79.61	8.69	81.00	8.64	0.620
L (%)	14.66	9.72	14.11	7.68	0.844
NLR	8.29	6.30	10.10	9.15	0.236
	< 40 Years(n= 33)		**> 40 years (n= 67)**		
	Mean	**SD**	**Mean**	**SD**	
N (%)	64.91	11.84	75.21	10.87	**0.001**
L (%)	28.52	11.82	18.93	10.58	**0.001**
NLR	3.36	3.93	6.79	6.57	**0.002**
Comorbidity	**Present (n=46)**		**Absent (n=54)**		
	Mean	**SD**	**Mean**	**SD**	
N (%)	76.24	10.35	68.04	12.39	**0.001**
L (%)	17.28	9.85	26.19	11.94	**0.001**
NLR	7.07	6.27	4.46	5.62	**0.033**

Table 3: Comparison of inflammatory markers among various subsets

Parameters	Male (n=68)		Female (n=32)		P value
	Mean	**SD**	**Mean**	**SD**	
CRP (mg/dl)	61.85	63.80	38.15	42.37	**0.030**
S.ferritin (ng/ml)	418.06	336.65	285.84	311.44	0.058
ESR (mm/hr)	62.10	35.22	52.94	27.39	0.160
D-Dimer (ng/ml)	844.06	832.26	869.19	949.48	0.898
LDH (U/l)	520.01	221.89	500.16	253.19	0.705
	Moderate (n = 18)		**Severe (n = 21)**		

	Mean	SD	Mean	SD	
CRP (mg/dl)	70.22	74.85	100.70	68.85	0.202
S.ferritin (ng/ml)	599.44	362.46	645.14	356.92	0.695
ESR (mm/hr)	77.56	48.13	72.57	18.93	0.684
D-Dimer (ng/ml)	1246.61	1178.26	1334.62	1183.36	0.818
LDH (U/l)	660.56	188.41	567.90	295.78	0.245
	< 40 years (n = 33)		> 40 years (n = 67)		
	Mean	SD	Mean	SD	
CRP (mg/dl)	28.39	27.03	67.02	65.63	**0.001**
S.ferritin (ng/ml)	285.58	291.92	420.16	344.94	**0.045**
ESR (mm/hr)	48.06	30.33	64.64	33.19	**0.015**
D-Dimer (ng/ml)	612.64	450.65	970.04	992.74	**0.015**
S.LDH (U/l)	473.00	167.54	533.69	255.69	0.159
Comorbidity	**present (n = 46)**		**Absent(n = 54)**		
	Mean	SD	Mean	SD	P value
CRP (mg/dl)	66.46	64.74	44.72	51.41	0.071
S.ferritin (ng/ml)	445.59	351.22	316.26	307.58	0.055
ESR (mm/hr)	67.50	37.37	53.06	26.55	**0.032**
D-Dimer (ng/ml)	1041.54	1086.14	690.72	586.40	0.054
S.LDH (U/l)	606.87	308.75	677.63	887.60	0.585