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TO STUDY THE PREDICTORS OF MORBIDITY & MORTALITY IN CRITICALLY ILL PATIENTS OF COVID 19 IN ICU & THEIR OUTCOMES

General Medicine

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ABSTRACT

World is now recovering from COVID-19 pandemic which started about 3 years ago in Hubei, China. Many patients were severely affected ending up in intensive care units. It is observed by clinicians that biochemical markers such as LDH, Ferritin, Interleukin-6, D-dimer, and C-reactive protein, as well as radiological parameters such as CT severity scores, can predict morbidity and mortality in COVID-19 patients. Haematological parameters such as lymphopenia , increased neutrophil to lymphocyte ratio also indicate severe disease and poor prognosis. **Materials And Methods:** This was retrospective observational study conducted in tertiary care centre in Marathwada region of Maharashtra, India. Patient's details like age, sex, symptoms, comorbidity, highest mode of ventilation and ICU stay duration were noted in the case record form (CRF) in each case. CT Chest, inflammatory biomarker and CBC for lymphocyte & Platelet were noted. **Observations And Results:** Among non-survivors, the most prevalent symptom was breathlessness, followed by cough, fever, and sore throat . Breathlessness (p value 0.003), reduced urinary output (p value 0.004), and chest pain (p value 0.0002) were statistically significant predictors of higher mortality. Comorbidities such as diabetes mellitus (, pulmonary conditions (COPD and asthma), and chronic kidney disease were also associated with higher mortality. Additionally, higher CT severity scores were correlated with increased mortality, as were elevated levels of biomarkers such as D-dimer, LDH, Ferritin, IL-6, CRP, and reduced lymphocyte and platelet counts. The study showed that ICU admission had a statistically significant impact on patient outcomes ($p<0.00001$). **Conclusion:** The study found that advanced age, co-morbidities such as diabetes mellitus, asthma, COPD, and chronic kidney disease, symptoms such as breathlessness, reduced urinary output, and chest pain, a higher CT severity score, elevated levels of biomarkers such as CRP, LDH, ferritin, IL-6, D-dimer, creatinine, and the N/L ratio, thrombocytopenia, and lymphopenia were all associated with higher mortality in critically ill COVID-19 pneumonia patients.

KEYWORDS

INTRODUCTION:

The world has just started recovering from the COVID-19 pandemic which started almost three long years back. The first cases of the virus were reported in Wuhan, Hubei, China on December 31, 2019, and it quickly spread around the world. As of January 2022, India has reported over 4.46 million confirmed cases, with the state of Maharashtra being particularly affected. [1]

COVID-19 has myriad of clinical manifestations ranging from asymptomatic to respiratory failure and death. SARS-CoV-2, the virus that causes COVID-19, can present with a wide range of clinical manifestations – ranging from asymptomatic to death. Many of these patients ended up getting admitted in intensive care units. It is observed that Geriatric and critically ill COVID-19 patients with comorbidities are at a higher risk for complications such as acute respiratory distress syndrome, sepsis, multiorgan dysfunction, and death, due to a dysregulated immune system. [23]

Many clinicians observed that biochemical markers such as LDH, Ferritin, Interleukin-6, D-dimer, and C-reactive protein, as well as radiological parameters such as CT severity scores, can predict morbidity and mortality in COVID-19 patients. Haematological parameters such as lymphopenia , increased neutrophil to lymphocyte ratio also indicate severe disease and poor prognosis.

In our study we looked into various clinical and laboratory parameters to elaborate which parameters indicate a favourable outcome and which indicate a poor prognosis.

MATERIALS AND METHODS:

Study Design:

The present study is a retrospective observational study that was conducted from July 2020 to August 2022 at MGM Medical College and Hospital, Aurangabad during the Covid pandemic. The data for the study was collected from electronic and laboratory records of patients with RTPCR or antigen positive cases of COVID-19 and HRCT showing COVID-19 pneumonia who were admitted in ICU at MGM Medical College and Hospital, Aurangabad, fulfilling inclusion and exclusion criteria. A total of 112 patients fulfilling the inclusion and exclusion criteria were enrolled in the study. Approval of institutional ethics committee was taken prior to the commencement of the present study. Patient's details like age, sex, symptoms, comorbidity, highest mode of ventilation and ICU stay duration were noted in the case record form (CRF) in each case. CT Chest, inflammatory biomarker and CBC for lymphocyte & Platelet were noted. On the basis of outcome, total 112 cases were divided into two groups: Group A (Survival) N=84, consisting of discharged patients and Group B (Non-survival) N=28 consisting of mortality cases.

Inclusion And Exclusion Criteria:

Inclusion Criteria:

1) Patients above 18 years of age
2) Moderate cases with dyspnoea, hypoxia and spo2 < 94% on room air, respiratory rate more than or equal to 24 breaths per minute.
3) Severe cases of pneumonia with respiratory rate > 30 breaths per minute, severe respiratory distress with spo2 < 90% on room air
4) WHO ordinal scale score > 4.

Exclusion Criteria:

1) Patients on immunosuppressive drugs
2) Patients who died within 48 hours of admission.

Statistical Analysis:

Data was entered in MS Excel and analysed using SPSS software, with chi-square test and odds ratio used to test proportions, p-value <0.05 considered significant, and results presented in visual forms like bar and pie diagrams.

OBSERVATIONS AND RESULTS:

Table 1. Age Distribution Of Patients

Sr. No.	Age group (Years)	Group A N (%)	Group B N (%)	Total N (%)
1	19 to 30	12 (11 %)	6 (5 %)	18 (16 %)
2	31 to 50	42 (38 %)	17 (15 %)	59 (53 %)
3	51 to 70	23 (21 %)	4 (4 %)	27 (25 %)
4	> 70	7 (6 %)	1 (1 %)	8 (7 %)
Total		84 (25 %)	28 (25 %)	112 (100 %)

Above table shows distribution of Cases according to Age. Majority of cases i.e. 59 (53 %) were from age group 31 to 50 years followed by 27 (25 %) cases from age group 51 to 70 years.

Table 2: Distribution Of Cases According To Sex

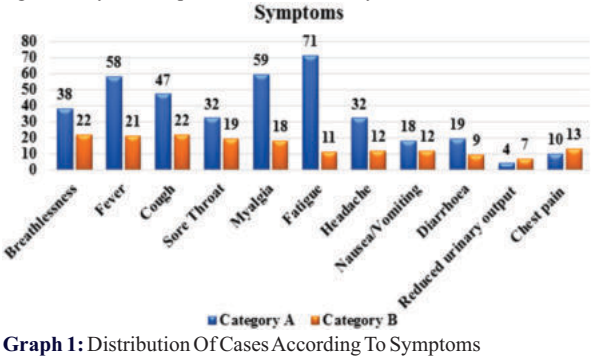
Sr. No.	Sex	Group A N (%)	Group B N (%)	Total N (%)
1	Male	57 (51 %)	18 (16 %)	75 (67 %)
2	Female	27 (24 %)	10 (9 %)	37 (33 %)
Total		84 (25 %)	28 (25 %)	112 (100 %)

This shows distribution of Cases according to Sex. Males were 75 (67 %) and females were 37 (33 %). Male to female ratio was 2:1

Table 3: Distribution Of Cases According To Symptoms

Sr. No.	Symptoms	Group A Present N (%)	Group B Present N (%)	Total Present N (%)	P Value
1	Breathlessness	38 (34 %)	22 (20 %)	60 (54 %)	0.003
2	Fever	58 (52 %)	21 (19 %)	79 (71 %)	0.55
3	Cough	47 (42 %)	22 (20 %)	69 (62 %)	0.37
4	Sore Throat	32 (29 %)	19 (17 %)	51 (46 %)	0.67
5	Myalgia	59 (53 %)	18 (16 %)	77 (69 %)	0.55
6	Fatigue	71 (63 %)	11 (10 %)	82 (73 %)	0.1
7	Headache	32 (29 %)	12 (11 %)	44 (40 %)	0.655
8	Nausea/Vomiting	18 (16 %)	12 (11 %)	30 (27 %)	0.20
9	Diarrhoea	19 (17 %)	9 (8 %)	28 (25 %)	0.31
10	Reduced urinary output	4 (4 %)	7 (6 %)	11 (10 %)	0.004
11	Chest pain	10 (9 %)	13 (12 %)	23 (21 %)	0.0002

Above table shows distribution of cases according to symptoms at time of presentation. Presentation with breathlessness (p value 0.003) , reduced urinary output (0.004) and chest pain (0.0002) was significantly more in patients who eventually succumbed.

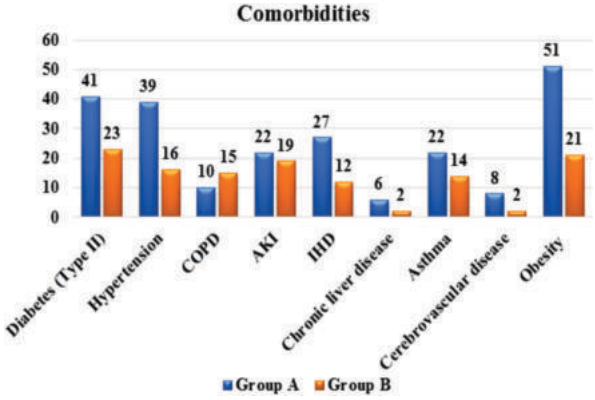


Graph 1: Distribution Of Cases According To Symptoms

Table 4: Distribution Of Cases According To Comorbidities

Sr. No.	Comorbidity	Group A Present N (%)	Group B Present N (%)	Total Present N (%)	P Value
1	Diabetes (Type II)	41 (37 %)	23 (21 %)	64 (58 %)	0.003
2	Hypertension	39 (35 %)	16 (14 %)	55 (49 %)	0.327
3	COPD	10 (9 %)	15 (13 %)	25 (22 %)	<0.0001
4	Chronic kidney disease	22 (20 %)	19 (17 %)	41 (37 %)	0.0002
5	Ischemic Heart Disease	27 (24 %)	12 (11 %)	39 (35 %)	0.304
6	Chronic liver disease	6 (5 %)	2 (2 %)	8 (7 %)	1.000
7	Asthma	22 (20 %)	14 (13 %)	36 (33 %)	0.021
8	Cerebrovascular disease	8 (7 %)	2 (2 %)	10 (9 %)	0.703
9	Obesity	51 (46 %)	21 (19 %)	72 (65 %)	0.176

Most common comorbidity was obesity (65%) though it showed only weak statistically insignificant correlation with mortality. In our study diabetes (p value 0.003), COPD (p value <0.0001) and chronic kidney disease (p value 0.0002) were significantly more in non-survivors.



Graph 2: Distribution Of Cases According To Comorbidities

Table 5: Distribution Of Cases According To Biomarker's Result

Sr. No.	Biomarkers	Group A		Group B		Total	t value	P value
		Abnormal N (%)	Mean ± SD	Abnormal N (%)	Mean ± SD	Abnormal N (%)		
1	D-dimer (mg/L)	50 (45%)	1.53 ± 1.16	22 (20%)	2.28 ± 1.27	72 (65%)	2.89	0.004
2	LDH (U/L)	34 (30%)	172.6 ± 51.39	18 (16%)	214.35 ± 54.53	52 (46%)	3.66	0.0004
3	Ferritin (µg/l)	41 (37%)	254.78 ± 117.49	21 (19%)	328.75 ± 92.08	62 (56%)	3.03	0.003
4	IL-6 (pg/ml)	43 (38%)	3.01 ± 2.6	23 (21%)	4.58 ± 2.15	66 (59%)	2.88	0.004
5	CRP (mg/L)	62 (55%)	17.07 ± 8.72	28 (25%)	24.3 ± 4.9	90 (80%)	4.16	0.0001
6	Lymphocytes (/mm^3)	33 (29%)	6025 ± 2431.7	15 (13%)	5017.86 ± 1622.54	48 (42%)	2.013	0.04
7	Platelet (lakh/mm^3)	11 (10%)	4.29 ± 1.81	13 (12%)	2.65 ± 1.68	24 (22%)	4.388	<0.0001
8	N/L Ratio	21 (19%)	3.08 ± 3.19	26 (23%)	5.61 ± 3.20	47 (42%)	4.24	0.0001
9	Serum Creatinine	10 (9%)	1.39 ± 0.38	12 (11%)	2.43 ± 1.38	22 (20%)	2.30	0.03

All parameters – D-dimer, Lactate dehydrogenase, ferritin, C reactive protein, Interleukin-6, serum creatinine-were statistically significantly raised in non-survivors. Non-survivors had statistically significant lymphopenia, thrombocytopenia and raised N/L i.e. neutrophils to lymphocyte ratio compared to survivors.

Table 6: Distribution Of Cases According To CT Severity Score

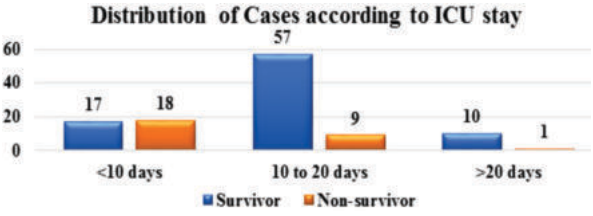
Sr. No.	CT score	Group A N (%)	Group B N (%)	Total N (%)	Chi square	P Value
1	Mild (≤ 7)	60 (54 %)	0 (0 %)	60 (54 %)	69.23	<0.00001 (S)
2	Moderate (8 to 17)	17 (15 %)	3 (3 %)	20 (18 %)		
3	Severe (≥ 18)	7 (6 %)	25 (22 %)	32 (28 %)		
Total		84 (25 %)	28 (25 %)	112 (100 %)		

Table 5 shows distribution of Cases according to CT severity score. Mild (≤ 7) score was seen in 60 (54 %) group A cases and 0 (0 %) group B cases. Moderate (8 to 17) score was seen in 17 (15 %) group A cases and 3 (3 %) group B cases. Severe (≥ 18) score was seen in 7 (6 %) group A cases and 25 (22 %) group B cases. Result showed statistical significance interpretated as more severe the lung changes on CT scan, higher the chance of mortality.

Table 7: Distribution Of Cases According To ICU Stay

No. of days of ICU stay	Survivor	Non-survivor	Total	p value =0.000072
<10	17	18	35	
10 to 20	57	9	65	
>20	10	1	11	
Total	84	28	112	

In our study survivors tended to have longer duration of stay (mean = 14.7 days) in ICU than non-survivors (mean 8.89 days). Majority of non-survivors(N=18) had shorter than 10 days of stay in ICU while only one non-survivor had more than 20 days of stay. On the other hand majority survivors had ICU stay of 10-20 days.



Graph 3: Distribution Of Cases According To ICU Stay

DISCUSSION:

In this study, the overall mean age was 46.40±14.98 years, with a mean age of 45.94 ±15.19 years in survivors and 48.78 ± 14.52 years in non-survivors. This is in line with previous studies, such as Mahendran et al [4], who found a mean age of 54.39 years (±14.99) in survivors and 60.54 years (±12.39) in non-survivors, and Gopalan et al [5] who reported a mean age of 44(33-57) years in survivors and 62 years (50-70) in non-survivors. Kokturk et al [6] also reported a mean age of 50.98±17.24 years in survivors and 71.3±15.06 years in non-survivors, and found that only 23.8% of those over the age of 65 years survived while 67.2% perished. Other studies, such as Du et al [7], have also found older age to be a statistically significant risk factor for mortality in COVID-19 patients. Our study also found that of the total of 75 males included and 37 females, 76% of males (57 patients) survived, compared to 72% survival in females (27 of 37). However, this difference in survival rate was not statistically significant (p=0.727865). Other studies have also found that males tend to have a higher mortality rate in COVID-19, although the difference was not statistically significant.

In this study, fatigue (84%) was the predominant symptom in survivors, followed by myalgia (67%), fever (69%), and cough (68%). In comparison, the predominant symptom in non-survivors was breathlessness (78%), followed by cough (78%), fever (75%), and sore throat (67%). Breathlessness (p=0.003), reduced urinary output (p=0.004), and chest pain (p=0.0002) were statistically significantly associated with higher mortality. This is consistent with other studies, such as Du et al [7], who found dyspnoea (p <0.001), fatigue (p=0.033), and headache (p=0.033) to be statistically significantly associated with higher mortality. However, findings varied across studies, such as Kokturk et al [6], who found only breathlessness to be statistically significantly associated with higher mortality (p=0.001), while Mahendran et al [4] found fever (p=0.001) and breathlessness (p=0.01) to be significantly associated with higher mortality. A study by Gopalan et al [5], which encompassed a sample of 746, found altered sensorium (p <0.001) and headache (p <0.001), breathlessness (p <0.001), anosmia (p=0.001) and myalgia (p <0.001) to be associated with higher mortality.

In this study, obesity (64%) was the most common comorbidity, followed by diabetes mellitus (49%). Diabetes mellitus (p=0.003), pulmonary comorbidities such as COPD (p=0.0001) and asthma (p=0.021), and chronic kidney disease (p=0.002) were statistically significantly related to increased mortality. This is consistent with other studies, such as Kokturk et al [6], who found hypertension (p=0.001), atherosclerosis (p=0.01), COPD (p=0.001), malignancy (p=0.001), immunosuppressed states (p=0.001), connective tissue disorders (p=0.001), and interstitial lung disease (p=0.005) to be significantly more common in the non-survivor group compared to survivors. Mahendran et al [4] also found that diabetes (p=0.016), hypertension (p=0.009), and chronic kidney disease (p=0.043) were significantly more common in non-survivors. A wider study by ICMR [5] found that diabetes mellitus, hypertension, cardiovascular disease, and kidney disease were highly associated with increased mortality (p<0.001 each) and other conditions such as bronchial asthma (p=0.055), COPD (p=0.038), obesity (p=0.004), malignancy (p=0.004), and liver disease (p=0.003) were also found to be associated.

n this retrospective observational study, HRCT scans were performed on all patients admitted to the ICU with COVID-19 symptoms. The changes consistent with COVID-19 infection, such as ground glass opacity in each segment of both lungs, were assessed and a score was given to each patient, ranging from zero to twenty-five. The results showed a statistical significance with a p-value of <0.00001, indicating that a higher CT severity score was associated with a higher mortality rate. This association between higher CT scores and increased mortality was also found in other studies, such as Zhou S et al (2020) [8], Yuan M (2020) [9], and Li K et al (2020) [10], which all showed that higher CT severity scores were associated with higher mortality.

In this study, various biomarkers were examined in COVID-19 survivors and non-survivors. C-reactive protein (CRP) was found to be raised in 65 survivors with a mean value of 17.07 ± 8.72, while all non-survivors had raised CRP with a mean value of 24.3 ± 4.9. This finding is consistent with previous studies by Wang Y et al [11], Kokturk et al [6], Rong Hui-Du et al [7], and Urvi Shukla et al [12], who also observed statistically significant raised values in non-survivors. The study also found that lactate dehydrogenase (LDH) was higher in non-survivors (214.35 ± 54.53 U/L) compared to survivors (172.6 ± 51.39), which was highly statistically significant with a p-value of 0.0004, indicating an association of higher LDH with mortality. Similar results were observed in studies by Wang et al [11] , Mahendran M et al [4], and Kokturk et al [6], who reported values ranging from 407 to 866 U/L in non-survivors and a statistically significant correlation of raised LDH values with adverse clinical outcomes. Ferritin levels were also found to be higher in non-survivors (328.75 ± 92.08 µg/L) compared to survivors (254.78 ± 117.49), with similar findings observed in studies by Mahendran et al [4], Urvi Shukla et al [12], and Kokturk et al. [6] The study also found that Interleukin-6 (IL-6), a biomarker associated with cytokine storm, was raised in 43 of 84 survivors with a mean value of 3.01 ± 2.6 pg/ml and in 21% of non-survivors with a mean value of 4.58 ± 2.15 pg/ml, however the finding of raised IL-6 values did not significantly associate with higher mortality as p value was 0.385 as studied by Jiqian Xu et al [13]. Similarly, D-dimer, a biomarker associated with coagulopathy was found to be raised in 50 survivors with mean value of 1.53 ± 1.16 mg/L and in 22 of 28 non-survivors with mean value 2.28 ± 1.27 mg/L (p value 0.004) pattern of higher D-dimer values was also seen by Kokturk et al [6] and other studies. Hemogram showed that non-survivors tended to have lower values of lymphocytes (mean 5017.86 ± 1622.54/mm3) and platelets (2.65 ± 1.68 L/mm3) while the neutrophil to lymphocyte ratio was higher (13.61 ± 10.20). The finding of low platelet and lymphocyte count is seen in studies by Mahendran M et al [4], Urvi Shukla et al [12], Kokturk et al [6], and Rong Hui-Du et al [7]. Lastly, it is seen that serum creatinine was significantly raised in deceased patients (2.43 ± 1.38 mg/dl) compared to survivors (1.39 ± 0.38 mg/dl) with a statistically significant p value of 0.03, which was corroborated by multiple other studies. [4 11 6]

Our study had survivors had longer mean duration of ICU stay (mean 14.7 days), compared to non-survivors (mean 8.89 days). While most of non-survivors tended to succumb within 10 days, many survivors stayed 10-20 days in intensive care unit. Mahendra et al [4] too corroborated our findings – in their study non-survivors had lower ICU stay (3.64 ±3.04 days) compared to survivors who had longer stay (5.48 ± 3.18 days). Xu et al [13] too had similar findings. This can be explained by fact that non-survivors typically had accelerated worsening of clinical condition resulting in shorter ICU stay.

CONCLUSION:

The results of the study showed that advanced age, co-morbidities such as diabetes mellitus, asthma, COPD, and chronic kidney disease; symptoms such as breathlessness, reduced urinary output, and chest pain; a higher CT severity score, raised values of CRP, LDH, ferritin, IL-6, D-dimer, creatinine, and the N/L ratio, thrombocytopenia, and lymphopenia, were all statistically significantly associated with a higher mortality rate in critically ill COVID-19 pneumonia patients.

Conflicts Of Interest: None to declare

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