Clinical features and risk predictor markers in COVID-19 patients in correlation with disease severity and comorbidities - A data-based retrospective study

Renuka Suvarna 1, Monalisa Biswas 2, Vijetha Shenoy Belle 3, Vishal Shanbhag 4

1 Division of Ayurveda, Centre for Integrative Medicine and Research, Manipal Academy of Higher Education, Manipal, India

2, 3 Department of Biochemistry, Kasturba Medical College, Manipal, Manipal Academy of Higher Education, Manipal, India

4 Department of Critical Care, Kasturba Medical College, Manipal, Manipal Academy of Higher Education, Manipal, India

Corresponding author:
Dr. Vijetha Shenoy Belle
Associate Professor
Department of Biochemistry,
Kasturba Medical College, Manipal,
Manipal Academy of Higher Education, Manipal, India 576104
Email: vijetha.shenoy@manipal.edu

Abstract:

Background: COVID-19 infection displays a highly heterogeneous spectrum of severities. Laboratory findings are pivotal cues to assess disease severity and aid in retarding/reversing disease progression. This study aims to identify the haematological, biochemical, and immunological specifics of COVID-19 patients with varying severity and associated comorbidities.

Methods: This retrospective study recruited a total of 192 RT PCR confirmed COVID-19 patients. Data on laboratory findings, clinical characteristics, treatment, and hospital stay were obtained and analysed.

Results: The patients were grouped into mild, moderate, and severe categories based on disease severity. 96 patients had mild disease, 31 were classified as having moderate COVID-19, and 67 patients had severe COVID-19.

39.58% of the patients were females. The overall death rate among admitted COVID-19 patients is observed to be 19.02%, sepsis and multi-organ failure as the most common cause.

The variation in laboratory variables and comorbidities as CAD, CKD, HTN, DM strongly correlate with the severity and increases with the age factor. Pre-existing chronic liver disease emerged to be a comorbidity of significance for acquiring severe COVID-19.

Conclusion: Presence of comorbidities, advanced age and male sex emerged as important...
risk factors while derangements in thrombo-inflammatory markers and haematological indices might be crucial predictors of disease progression. Thromboembolism or superinfection induced sepsis, and multi-organ failure emerged as leading contributors to mortality. High-risk patterns in thrombo-inflammatory and immunohematological markers allow for early detection of the disease progression and aid in the institution of personalized intensive therapeutic interventions and monitoring to avoid further deaths.

**Keywords:** COVID-19, risk factors, inflammation, mortality, multiorgan failure

**INTRODUCTION**

The coronavirus disease outbreak and transmission in 2019 have posed significant problems to worldwide public health [1]. The infection has been identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which can spread via respiratory droplets, person to person, or aerosol. COVID-19 has already spread over the world, and according to WHO data, with over 163,869,893 cases diagnosed in over 210 countries, resulting in around 3,398,302 deaths as of May 20, 2021 [2]. COVID-19 is a disease presenting several clinical symptoms of cough, anosmia, dysgeusia, dyspnea, and fever, which leads to a critical condition in some cases entailing the unique management at the intensive care unit. Acute respiratory distress syndrome, which includes pneumonia and septic shock-induced multi-organ failure, can cause death in critically ill patients [3]. Therefore, it is critical to identify virus carriers as soon as possible to avoid their transmission and control disease progression.

The role of antibodies in viral clearance and disease severity regulation and the long-term durability of these responses following primary infection is currently limited or controversial [4]. Antibody responses to SARS-CoV-2 tend to be higher in COVID-19 patients with severe disease than in asymptomatic or mildly ill individuals, raising questions about the efficacy of SARS-CoV-2 antibody responses. The prognosis is poor in patients who are older and have co-morbid conditions.

Furthermore, in COVID-19, several hematological and biochemical parameters have emerged as possible biomarkers for predicting severe disease and mortality. Health practitioners have struggled to determine a symptom-based diagnosis and prediction of progression to severe disease; however, evidence reiterates that symptom-based prediction/screening might not be a feasible or accurate indicator to determine the probability of COVID-19 risk, infection, or severity [5]. The complexities that underpin these health inequalities are unknown, but they almost certainly involve a combination of social, economic, and behavioral variables [6].

Numerous studies have aimed to investigate the role of biochemical and hematological parameters in COVID-19 and its correlation with disease severity and comorbidities to arrive at an effective algorithm that could predict poor prognosis and enable prioritizing allocation of intensive care units (ICU), ventilation/ extracorporeal membrane oxygenation (ECMO) resources, early intensive intervention and monitoring of such patients [7]. However, consensus regarding the same is yet to be achieved, and researches need to focus on the regional profile of the biomarkers in COVID-19. Therefore, this study describes
hematological, biochemical, and immunological specifics in COVID-19 patients and helps distinguish the parameters with disease severity and comorbidities.

METHODS

Study design and participants

This retrospective study was done from June 2020 to July 2020 in patients with confirmed COVID-19 admitted to Kasturba Hospital, Manipal. Patients with COVID-19 <18 years of age and patients having other influenza-like illnesses but a negative RT-PCR report were excluded from the study.

The classification of disease severity is as follows: (1) mild group – minor symptoms no involvement of pneumonia (2) moderate group – fever, respiratory symptoms, and (3) severe group – ICU admission, severe respiratory distress. The Institutional Ethical Committee approved the study. (IEC 592 – 2020)

Data collection

The clinical history, biochemical, haematological, and immunological characteristics were extracted from electronic medical records. In addition, hematological data (Complete Blood Counts), glycaemic parameters (glycated hemoglobin - HbA1c), Renal function test (Urea, Creatinine, sodium, potassium), liver function test (Total protein, T-Bil, DB, AST, ALT, ALP), calcium, phosphorous, C-Reactive Protein (CRP), D-dimer, ferritin, lactate dehydrogenase, troponin – T, creatine phosphokinase, and N-Terminal pro Brain Natriuretic Peptide (NT pro BNP), were collected from Laboratory information system.

Statistical analysis

Categorical variables are presented as percentages; continuous variables were defined using median and interquartile ranges (IQR). Mann-Whitney U test was used to identify group differences between the variable. Spearman correlation coefficient was used to determine a correlation between variables and disease severity. Statistical analyses were performed using EZR statistical software.

RESULTS:

Out of 192 COVID-positive patients included in our study, 96 patients had mild COVID, 31 were classified as having moderate COVID-19, and 67 patients had severe COVID-19.

39.58% of the patients were females. Figure 1 shows the gender distribution among patients in the three groups.
Table 1 summarizes age, duration of hospital stay, and the duration of ICU stay in the three groups.

**Table 1: Comparison of age and hospital/ICU stay**

<table>
<thead>
<tr>
<th>Test parameter (Unit)</th>
<th>Mild N = 96 Median (Q1, Q3)</th>
<th>Moderate N = 31 Median (Q1, Q3)</th>
<th>Severe N = 67 Median (Q1, Q3)</th>
<th>P-value *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>44 (32, 59)</td>
<td>60 (47.5, 73)</td>
<td>62 (50, 70)</td>
<td>0.0000064</td>
</tr>
<tr>
<td>Duration of hospital stay</td>
<td>9 (7, 11)</td>
<td>16 (10.5, 21)</td>
<td>19 (12, 24)</td>
<td>5.082e-12</td>
</tr>
<tr>
<td>Duration of ICU stay</td>
<td>0.0 (0.0, 0.0)</td>
<td>0.0 (0.0, 14.25)</td>
<td>11.5 (5, 18.0)</td>
<td>&lt; 2.2e-16</td>
</tr>
</tbody>
</table>

Table 2 shows the hematological profile of patients among the three groups.

**Table 2: Comparison of hematological parameters**

<table>
<thead>
<tr>
<th>Test parameter (Unit)</th>
<th>Mild N = 96 Median (Q1, Q3)</th>
<th>Moderate N = 31 Median (Q1, Q3)</th>
<th>Severe N = 67 Median (Q1, Q3)</th>
<th>P-value *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (g/dL)</td>
<td>12.4 (10.6, 13.6)</td>
<td>11.8 (10.15, 13.6)</td>
<td>11.6 (9.5, 13.6)</td>
<td>0.4845</td>
</tr>
<tr>
<td>WBC (10³/µL)</td>
<td>6.8 (5.1, 10.1)</td>
<td>7.0 (5.2, 11.17)</td>
<td>9.0 (6.25, 14.6)</td>
<td>0.013</td>
</tr>
<tr>
<td><strong>Platelets (10³/µL)</strong></td>
<td>220 (175.2, 271.5)</td>
<td>190 (141, 239)</td>
<td>200 (128, 307)</td>
<td><strong>0.2355</strong></td>
</tr>
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</tr>
<tr>
<td><strong>PDW</strong></td>
<td>16.8 (16.4, 17.2)</td>
<td>17.2 (16.9, 17.55)</td>
<td>17.3 (16.8, 17.9)</td>
<td><strong>0.0001068</strong></td>
</tr>
<tr>
<td><strong>Neutrophils (%)</strong></td>
<td>66.4 (52.4, 79.3)</td>
<td>77.1 (60.7, 81.87)</td>
<td>80.2 (69.5, 88.3)</td>
<td><strong>0.00000397</strong></td>
</tr>
<tr>
<td><strong>Lymphocytes (%)</strong></td>
<td>20.5 (12.2, 34)</td>
<td>14.1 (9, 22)</td>
<td>9 (5.82, 15)</td>
<td><strong>0.000000010</strong></td>
</tr>
<tr>
<td><strong>Monocytes (%)</strong></td>
<td>9.0 (6.55, 11.6)</td>
<td>8.0 (5.0, 11.6)</td>
<td>6.0 (93.9, 8.3)</td>
<td><strong>0.00008633</strong></td>
</tr>
<tr>
<td><strong>Basophils (%)</strong></td>
<td>0.4 (0.3, 0.5)</td>
<td>0.4 (0.2, 0.5)</td>
<td>0.3 (0.2, 0.7)</td>
<td><strong>0.7436</strong></td>
</tr>
<tr>
<td><strong>Eosinophils (%)</strong></td>
<td>0.7 (0.2, 1.75)</td>
<td>0.1 (0.1, 1.0)</td>
<td>0.75 (0.1, 18.0)</td>
<td><strong>0.000558</strong></td>
</tr>
<tr>
<td><strong>NLR</strong></td>
<td>3.1 (1.57, 6.1)</td>
<td>5.47 (2.77, 8.48)</td>
<td>8.27 (4.6, 15.0)</td>
<td><strong>0.000000042</strong></td>
</tr>
<tr>
<td><strong>PLR</strong></td>
<td>9.35 (3.28, 17.75)</td>
<td>14.37 (5.59, 20.69)</td>
<td>21.40 (99.57, 44.7)</td>
<td><strong>0.0007412</strong></td>
</tr>
<tr>
<td><strong>LMR</strong></td>
<td>2.43 (1.61, 3.65)</td>
<td>1.79 (1.03, 2.54)</td>
<td>1.36 (0.93, 2.51)</td>
<td><strong>0.001877</strong></td>
</tr>
<tr>
<td><strong>Absolute lymphocyte count (10³/µL)</strong></td>
<td>1.44 (1.06, 1.98)</td>
<td>0.99 (0.7, 1.4)</td>
<td>0.82 (0.52, 1.18)</td>
<td><strong>0.000000066</strong></td>
</tr>
<tr>
<td><strong>Absolute neutrophil count (10³/µL)</strong></td>
<td>4.28 (2.6, 7.4)</td>
<td>5.23 (3.49, 8.51)</td>
<td>7.72 (4.53, 10.97)</td>
<td><strong>0.0003255</strong></td>
</tr>
<tr>
<td><strong>Absolute eosinophil count (10³/µL)</strong></td>
<td>0.05 (0.015, 0.1)</td>
<td>0.01 (0.0, 0.08)</td>
<td>0.02 (0.0, 0.04)</td>
<td><strong>0.0544</strong></td>
</tr>
<tr>
<td><strong>SII</strong></td>
<td>643.91 (307.8, 1302.1)</td>
<td>1071 (317.5, 1717.95)</td>
<td>1623.53 (718, 3705.9)</td>
<td><strong>0.000195</strong></td>
</tr>
</tbody>
</table>

Table 3 summarizes the differences in circulating levels of biochemical markers among the three groups.
Table 3: Comparison of biochemical parameters

<table>
<thead>
<tr>
<th>Test parameter (Unit)</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 96</td>
<td>N = 31</td>
<td>N = 67</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median (Q1, Q3)</td>
<td>Median (Q1, Q3)</td>
<td>Median (Q1, Q3)</td>
<td></td>
</tr>
<tr>
<td><strong>Inflammatory Markers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP</td>
<td>5.72 (2.05, 20.45)</td>
<td>69.78 (15.85, 157.06)</td>
<td>80.61 (39.96, 174.44)</td>
<td>4.945e-11</td>
</tr>
<tr>
<td>D Dimer</td>
<td>0.4 (0.2, 1.1)</td>
<td>0.9 (0.4, 7.97)</td>
<td>1.6 (0.3, 4.2)</td>
<td>0.008087</td>
</tr>
<tr>
<td>Ferritin</td>
<td>121.2 (42.05, 284.02)</td>
<td>410.8 (192.1, 1030)</td>
<td>633.9 (304.3, 1237)</td>
<td>0.00000009</td>
</tr>
<tr>
<td>LDH</td>
<td>258 (211, 321)</td>
<td>345 (267, 408)</td>
<td>455 (370.5, 621)</td>
<td>8.633e-10</td>
</tr>
<tr>
<td><strong>Average Glucose &amp; Renal Function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1c</td>
<td>5.6 (5.3, 7.27)</td>
<td>5.8 (5.6, 6.9)</td>
<td>6.9 (5.8, 8.3)</td>
<td>0.2355</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.79 (0.65, 0.99)</td>
<td>1.05 (0.93, 1.57)</td>
<td>1.13 (0.76, 1.55)</td>
<td>0.00007809</td>
</tr>
<tr>
<td><strong>Liver Function Test</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Total Bilirubin</td>
<td>0.41 (0.31, 0.59)</td>
<td>0.57 (0.38, 0.88)</td>
<td>0.55 (0.38, 1.02)</td>
<td>0.01463</td>
</tr>
<tr>
<td>Direct Bilirubin</td>
<td>0.15 (0.09, 0.22)</td>
<td>0.27 (0.16, 0.38)</td>
<td>0.26 (0.14, 0.53)</td>
<td>0.000045</td>
</tr>
<tr>
<td>AST</td>
<td>26 (19, 41)</td>
<td>47 (26, 65)</td>
<td>39 (23.5, 62)</td>
<td>0.01833</td>
</tr>
<tr>
<td>ALT</td>
<td>20 (13, 35.3)</td>
<td>31 (19, 44)</td>
<td>27 (20, 44)</td>
<td>0.02696</td>
</tr>
<tr>
<td>ALP</td>
<td>72 (56, 96)</td>
<td>88 (67, 126)</td>
<td>90 (63.5, 123.5)</td>
<td>0.04635</td>
</tr>
<tr>
<td>Total Protein</td>
<td>6.95 (6.4, 7.3)</td>
<td>6.95 (6.2, 7.5)</td>
<td>6.7 (6.0, 7.1)</td>
<td>0.03514</td>
</tr>
</tbody>
</table>
Cardiac Markers

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>Troponin T</strong></td>
<td>0.01 (0.006, 0.17)</td>
<td>0.017 (0.015, 0.072)</td>
<td>0.026 (0.014, 0.098)</td>
<td>0.85</td>
</tr>
<tr>
<td><strong>NT pro BNP</strong></td>
<td>481 (250, 1484)</td>
<td>698 (332, 4679)</td>
<td>2216 (611, 9873)</td>
<td>0.026</td>
</tr>
<tr>
<td><strong>CPK</strong></td>
<td>188 (74, 348)</td>
<td>252.5 (170.25, 334.75)</td>
<td>83 (75.25, 106.25)</td>
<td>0.3965</td>
</tr>
</tbody>
</table>

Electrolytes

<p>| | | | | |</p>
<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Sodium</strong></td>
<td>137 (134, 139)</td>
<td>134 (132, 137)</td>
<td>133 (130, 137.2)</td>
<td>0.001618</td>
</tr>
<tr>
<td><strong>Potassium</strong></td>
<td>4.25 (3.92, 4.65)</td>
<td>4.4 (4.0, 4.75)</td>
<td>4.25 (3.9, 4.8)</td>
<td>0.9046</td>
</tr>
<tr>
<td><strong>Calcium</strong></td>
<td>9.1 (7.85, 9.35)</td>
<td>8.5 (8.3, 8.7)</td>
<td>8.1 (7.95, 8.4)</td>
<td>0.2056</td>
</tr>
</tbody>
</table>

Figure 2 shows the proportion of patients with a known history of hypertension, diabetes mellitus, chronic kidney diseases, and coronary artery disease prior to COVID-19 infection.

**Figure 2: Proportion of patients with major comorbidities**
Table 4 outlines the correlation of the four major comorbidities with the severity of COVID-19 as observed among the patients.

**Table 4: Correlation of age & comorbidities with the severity of COVID-19 infection**

<table>
<thead>
<tr>
<th>Test parameter</th>
<th>R</th>
<th>P-value *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.33</td>
<td>0.0000032</td>
</tr>
<tr>
<td>CAD</td>
<td>0.197</td>
<td>0.00668</td>
</tr>
<tr>
<td>CKD</td>
<td>0.159</td>
<td>0.0298</td>
</tr>
<tr>
<td>HTN</td>
<td>0.291</td>
<td>0.0000495</td>
</tr>
<tr>
<td>DM</td>
<td>0.301</td>
<td>0.0000243</td>
</tr>
</tbody>
</table>

*Spearman correlation

Table 5 summarises the correlation of inflammatory markers with the severity of COVID-19 infection.

**Table 5: Correlation of biomarkers with the severity of COVID-19 infection**

<table>
<thead>
<tr>
<th>Test parameter</th>
<th>R</th>
<th>P-value *</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP</td>
<td>0.464</td>
<td>0.00000000251</td>
</tr>
<tr>
<td>Ferritin</td>
<td>0.418</td>
<td>0.0000005</td>
</tr>
<tr>
<td>D dimer</td>
<td>0.248</td>
<td>0.0265</td>
</tr>
<tr>
<td>LDH</td>
<td>0.506</td>
<td>1.54e-10</td>
</tr>
<tr>
<td>NLR</td>
<td>0.402</td>
<td>0.000000226</td>
</tr>
<tr>
<td>PLR</td>
<td>0.27</td>
<td>0.00025</td>
</tr>
<tr>
<td>SII</td>
<td>0.29</td>
<td>0.0000779</td>
</tr>
</tbody>
</table>

*Spearman correlation
Figure 3 shows the treatment modalities adopted for our patients categorized into three groups.

**Figure 3: Treatment modalities in the study population**

![Treatment Modalities Chart]

Figure 4 outlines the treatment combinations adopted for our patients.

**Figure 4: Combination of treatment used in study groups**

![Treatment Combinations Chart]

The overall death rate among admitted COVID-19 patients is observed to be 19.02%. The death of a 75-year-old male patient is reported in the mild category. He had a pre-existing history of hypertension, diabetes mellitus, and stage 5 chronic kidney disease. At presentation, he also showed dengue-associated thrombocytopenia, bilateral klebsiella infection, and metabolic encephalopathy. In the moderate category, there were no deaths reported among the 31 cases. However, two patients were discharged against medical advice,
and the family was counselled about their poor prognosis (a 39-year-old male with diffuse chronic liver disease with portal hypertension, streptococcal cellulitis, cardiomegaly, and septic shock and a 23-year-old male with mesenteric ischemia with extensive small bowel gangrene). 53.73% (n=36) of the patients with severe COVID-19 expired during their hospital stay. 78.37% (n=29) of the deaths were attributed to sepsis and multi-organ dysfunction syndrome, majorly due to E Coli or Klebsiella bacteraemia. 13.7 % (n=4) of these cases had been documented to have ventilator-associated pneumonia, while 6.8% (n=2) were recorded to have candida sepsis. One patient progressing to septic shock had a history of pulmonary thromboembolism and post TB bronchiectasis, while another patient in septic shock manifested diabetic ketoacidosis. 18.91% (n=7) of the expired patients had a history of pre-existing cancers (multiple myeloma, pancreatic cancer, pancreatic neuroectodermal tumour, papillary thyroid carcinoma, cancer of rectum, AML). 14.28% (n=5) of the patients had a history of chronic liver disease and associated encephalopathy, with alcoholic liver disease being the most common etiology. Pre-existing history of COPD and bronchial asthma was found in one patient each. Among infectious diseases, 5.4% (n=2) of the cases had active leptospirosis, one documented case each of HIV, dengue, and melioidosis. One patient showed seropositivity for Hepatitis B and C. Two patients had a history of pre-existing autoimmune conditions (autoimmune encephalitis and myasthenia gravis). 5.4% (n=2) of the expired patients presented at admission with NSTEMI, another 5.4% (n=2) had conduction heart ailments, while 13.5% of the cases showed features of heart failure. Two patients were known cases of old CVA, and 18.9% (n=7) of the patients had a known history of hypothyroidism. It is unfortunate that a 68-year-old patient had nil pre morbidities but spontaneously progressed to Type I respiratory failure associated with ARDS and expired.

**DISCUSSION:**

COVID-19 illness is categorized from mild to severe based on age, associated comorbidities, oxygen saturation, and vitals. COVID-19 severity stratification guides health care professionals to prioritize treatment for severe manifestations and reduce mortality. As the novel coronavirus SARS-CoV-2 continues to pose a dilemma with its heterogeneous presentations and trajectories, a one rule fits all standard and effective therapeutic regimen remains elusive. Various therapeutic regimes, including a cocktail of antiviral, anti-inflammatory, anticoagulant, and fibrinolytic approaches, continue to emerge, with therapies gaining and losing validity as more evidence continues to unfold. An observed spectrum of five patient phenotypes in SARS-CoV-2 infections calls for a rapid shift to personalized, tailored therapies and the application of phenotype-based precision medicine [8]. Phenotype 1, the most benign and common form, represents a cluster where symptomatic therapy suffices to achieve relief and resolution. Phenotype 2 represents 80% of hospitalized patients who typically manifest hyper-inflammation and remain hypovolemic mildly to moderately hypoxic with or without small opacities on chest radiographs. Phenotype 3 presents with moderate to severe desaturation and high respiratory rates. Patients with phenotype 4 present with severe hypoxia, hypoxic vasoconstriction, multiple ground glass opacities, micro embolic lesions, and BB coalescent lines in most zones (indicative of interstitial injury) lower
lobe edema and require immediate intubation. Patients with phenotype 5 (rare) manifest an advanced stage with coinfection or acute lung injury [8]. Demographic profile and biochemical, haematological, and immunological markers guide the treating physician for a better prognosis. This study investigates hematological, biochemical, and immunological specifics in COVID-19 patients of varying disease severity.

A total of 192 RT-PCR confirmed COVID-19 patients were enrolled for the study. 96 patients had mild COVID-19, 31 were having moderate COVID-19, and 67 patients had severe COVID-19. The patient population represented 60.42% of males and 39.58% of females (Fig 1). Out of 192 COVID-19 patients, 73 (38%) patients required ICU admission. The duration of hospital stays and ICU stay correlated with infection severity and associated comorbidities (Table 1). The major and common comorbidities recorded in our study participants were diabetes mellitus, chronic kidney disease, and coronary artery disease, with more prevalence of comorbidities in severe COVID 19 infections. All four major comorbidities showed a statistically significant but weak positive correlation with severity of COVID 19 except age and diabetes mellitus, which showed a moderate positive correlation. Diabetes mellitus was the most prevalent premorbid condition observed in our patient population. Our study observed significant leukocytosis, neutrophilia, lymphocytopenia, elevated NLR, elevated PLR, elevated SII, decreased monocytes, and decreased LMR with increase in the severity of COVID 19. The median SII was elevated above the normal threshold even in mild COVID 19 and showed marked elevations across the three groups. Acute-phase inflammatory mediators like CRP, ferritin, cardiac and hypoxia markers such as LDH and NT pro-BNP, and thrombotic marker D Dimer showed statistically significant elevations with increasing severity of Covid infections. A significant decrease in sodium ion level and a significant increase in creatinine level were observed between the three groups, even though the overall median creatine and sodium did not cross the critical cut-off. Anticoagulation followed by steroid therapy were the most frequently opted intervention regimes used in our patient population apart from first-line symptomatic treatment and prophylactic antibiotics. Multi-organ dysfunction and septic shock emerged as the major cause of mortality among our patients, with pre-existing liver disease being the most frequent additional premorbid factor in expired patients, followed by hypothyroidism.

Similar to any other pathogenic infection, SARS-CoV-2 triggers both the innate and adaptive arms of the human immune system [9]. However, hyper trigger stimulates excessive pro-inflammatory responses, which lead to widespread tissue damage [10]. The systemic uncontrolled immune dysregulation stimulates astronomical amounts of inflammatory cytokines, typically referred to as the “cytokine storm” [11].

CD4+ and CD8+ T cells (80% of the total infiltrative inflammatory cells) are dedicated to phagocytosing infected host cells. In contrast, the CD4+ T cells activate the cell-mediated humoral response responsible for the generation of virus-specific antibodies. An imbalance favouring naïve T cell activity against regulatory T cells contributes to hyperinflammation through a massive, coordinated cytokine release [10]. Further, the complement system's pro-inflammatory C3a and C5a components trigger massive inflammation by recruiting inflammatory cells and neutrophil activation. Cytokine storm evolves through several
pathways leading to interleukin-6 (IL-6) release, which further activates several cells through positive feedback stimulating acute-phase reactants like CRP and ferritin [11].

Thus, immune cells, inflammatory mediators, and acute phase reactants are indispensable facilitators of Covid-19 disease trajectories and hence the importance of these hematological and inflammatory markers in Covid-19. A healthy vascular endothelium plays a crucial role in vasomotor, hemostatic, angiogenic, inflammatory processes, immunology regulation, and homeostasis. It is characterized by vasodilatory, antithrombotic, anti-aggregation fibrinolytic, and anti-inflammatory properties [12,13].

COVID-19 pathophysiology seems to alter the essential characteristics of vascular endothelium, triggering a storm of inflammatory and thrombotic cascade [14]. Severe endothelial dysfunction caused by dual pathways of viral burst and dysregulated astronomical cytokine production induces a hypercoagulable state, similar to what is seen in DIC, thus increasing the risk of macro and microvascular thrombosis. This explains the pathophysiology of the observed multi-organ dysfunctions and MOF-induced deaths in severe COVID-19 patients [15,16]. COVID-19 patients have shown an increased incidence of thrombotic complications such as pulmonary embolism, deep vein thrombosis, and myocardial infarction [8].

**Leukocytosis:**

Our study showed WBCs to be significantly elevated in severe COVID-19. Taj S et al. demonstrated that leukocytosis, neutrophilia, and increased NLR have a significant association with the disease severity and revealed that leukocytosis on the admission of COVID-19 patients was associated with increased risk of death in hospital, also showed that patients who had fatal outcomes had significant leukocytosis compared to survivors. [17].

**Neutrophilia:**

Neutrophilia has been a unanimous finding in COVID-19 infections and a predictor of disease severity, and our study observed the same. The systemic inflammatory response in Covid-19 activates neutrophils via virus-induced inflammatory mediators such as IL-6, IL-8, GCSF, IFN-γ, TNF-α, etc. [18]. Neutrophils recruited to growing thrombi form neutrophil extracellular traps (NET), the organized extrusion of the chromatin of mature neutrophils. NETs are antibacterial and prothrombotic [11].

**Lymphocytopenia:**

We observed a significant decrease in lymphocyte counts across the three groups, with the median lymphocyte count in the severe group below the lower recommended cut-off. Lymphocytopenia has been correlated to disease severity and mortality and is shown to be a reliable and effective biomarker for the severity of COVID-19 disease [19]. Lymphopenia on admission is associated with a three-fold risk of poor outcomes in younger patients. Several studies identified lymphopenia as a reliable marker of disease progression and severity with magnitude higher in dead and ICU patients than non-severe or "survivor" patients. After a week of symptom onset, the appearance of significant lymphopenia is shown to coincide with worsening clinical status and induction of "cytokine storm."[11]
It has also been indicated as an important prognostic tool among COVID-19 patients. Decreased lymphocyte count has been attributed to viral invasion and lysis, interleukin stimulated lymphocyte apoptosis, decreased lymphocyte turnover due to the "cytokine storm" induced atrophy of lymphoid organs, and reduced lymphocyte proliferation due to lactic acidosis [11]. Impaired myelopoiesis and lymphohematopoietic system involvement have been observed within a hyper inflammation status in SARS-COV-2-infected patients [9].

However, few studies have shown non-significant alterations in lymphocyte counts among groups such as Yang et al., who reported an insignificant difference in lymphopenia between non-severe and severe patients [20].

NLR:

Considering lymphopenia to be a nonspecific or rather a non-absolute indicator of COVID-19 severity, the predictive capacity of lymphopenia can be significantly improved if combined with neutrophilia to generate a neutrophil-lymphocyte ratio (NLR). A study demonstrated a 3-to-4-fold increase in NLR in severe and critical COVID-19 patients compared to moderate patients [19]. Liao D et al. reported elevated NLR as a valuable predictor of disease severity and associated mortality [21]. Further, Yang AP et al. concluded that high NLR and older age are the independent factors indicating the poor clinical outcome of covid-19 patients [22]. NLR revealed a similar trend with IL-6 at hospitalization, ICU admission, and mortality [23]. Temporally rising NLR has also been suggested as a prognostic marker for predicting poor outcomes [24]. As COVID-19 causes a systemic inflammatory response, neutrophils are activated by virus-induced inflammatory markers IL-6 and IL-8, GCSF, IFN-ϒ, TNF-α formed by lymphoid and endothelial cells. Conversely, the immune response is considerably depressed, notably in the helper T lymphocytes [25]. NLR, a ratio reflecting two arms of hyper inflammation response, is thus a strong predictor of disease severity and progression.

Monocytes:

Our study found a statistically significant decrease in monocyte counts across the increasing severity of COVID 19. Scientific evidence has shown that monocytes are decreased in Covid 19 and correlate with disease progression [26]. Activated monocytes and damage-associated molecular patterns from injured tissues produce inflammatory cytokines and chemokines, stimulating neutrophils, lymphocytes, platelets, vascular endothelial cells, and monocytes to express tissue factor and phosphatidylserine and trigger coagulation [11]. Increased monocyte consumption hence accounts for decreased monocyte counts in circulation.

Platelets:

Our study did not observe significant differences in platelet counts across the three groups, contrasting to many existing studies that report thrombocytopenia as a marker of disease severity. Literature evidence emphasizes that thrombocytopenia aggravates proportional to disease severity, with the lowest platelet count recorded in patients with the critical disease. Taj S et al. showed a significant association of platelet count and MPV with disease severity. At the same time, Liao D et al. found significantly lower platelet count in patients with critical and severe disease [17, 21]. Thrombocytopenia was shown to correlate with other
coagulation parameters and increased risk of mortality. The mechanism behind the observed thrombocytopenia is postulated to be related to thrombin generation, immunological destruction of platelets, impaired megakaryopoiesis, and inappropriate platelet consumption [27]. Platelets, once activated, recruit more platelets and crosslink with them via fibrinogen, secrete pro-inflammatory cytokines, proangiogenic factors, and promote leukocyte activation and extravasation. Primary hemostasis begins with platelet activation [11]. Therefore, thrombocytopenia might be a valuable indicator for disease progression and coagulopathy.

**Systemic immune inflammation index (SII):**

Systemic immune inflammation index (SII) is a novel comprehensive index of inflammatory, immunoregulatory (innate-adaptive, stimulatory-regulatory), and thrombotic arms encompassing neutrophil, platelet, and lymphocyte counts implicated in a myriad of inflammatory syndromes like cancer, stroke, venous sinus thrombosis as well as COVID 19 [28]. A retrospective study by Muhammad S proposed SII as a potent predictor of disease severity, ventilation requirement, and poor clinical outcome in COVID patients. A letter to the editor by Wijeratne T recommends SSIIi measurement in prognostication of COVID 19 patients based on their observation that SSIIi clinically correlated with a neurological or thromboembolic event well-studied case and the shared pathology between stroke and COVID-19 associated neurological/thromboembolic complications [29].

**Indices:**

Our study reports a positive clinical utility of NLR, PLR, LMR, and SII in risk stratification of COVID 19. A significant association of hematological indices like NLR, LMR, and PLR has been reported in Covid 19 disease and its severity. Previous investigations have also reported NLR and PLR as significant prognostic factors for disease progression [30, 31]. A study reported the highest median PLR of 1.63 in patients with moderate Covid disease with the lowest PLR in the mild group [17].

Leukocyte, neutrophil, platelet count, NLR, and SII values can be used to diagnose COVID-19. NLR, PLR, and SIII are parameters that can be used to predict severity and hospital outcome in patients with COVID-19-associated pneumonia. Secondarily, they can detect a severe inflammatory process and immune system homeostasis loss, which entails severe clinical pictures and poor prognosis [32].

**CRP:**

Our study showed circulating CRP to be statistically significant between the three groups, and CRP was positively correlated with disease severity. CRP is an exquisitely sensitive systemic marker of acute-phase response in inflammation, infection, and tissue damage, which could be used to indicate inflammation [33]. Numerous studies have reported CRP to be positively associated with COVID 19 severity and elevated CRP as a predictor of poor prognosis [11, 34]. However, Chen et al. reported higher mean CRP in the severe group when compared to mild/moderate, though the difference was not statistically significant [35].
**Ferritin:**

Ferritin, a positive acute phase reactant, differed significantly among the three study groups and showed a moderate positive correlation with disease severity. Retrospective studies have reported the role of ferritin in predicting disease severity, ICU admission, and the need for ventilation and failure in predicting mortality [9, 17]. A meta-analysis reported that ferritin levels could predict severe disease and mortality [36].

**Cardiac Biomarkers:**

We observed a statistically significant and remarkable elevation of NT pro-BNP with increasing severity of COVID-19. Cardiac injury secondary to viral infection and inflammatory cascade-mediated damage plays a vital role in disease progression and outcome. Cardiac complications in Covid-19 infections have been attributed to intracellular viral replication-induced cardiomyocyte degeneration leading to cardiac dysfunction, arrhythmia, and cytokine storm mediated to microcirculation defects and tissue ischemia, which can also exacerbate atherosclerosis progression susceptibility to acute myocardial infarction [37]. Creatine phosphokinase, cardiac troponins, and natriuretic peptides have been used to assess cardiac risk and Covid-19 diseases severity in patients with higher levels found to be associated with higher mortality [38]. Hence, troponin and natriuretic peptides have been recommended for risk stratification and aid decision-making about the rational use of cardiac imaging, initiation of invasive and aggressive interventions, and prognostication [11].

**LDH:**

LDH, a potent marker of tissue hypoxia, has shown a significant and moderate to high positive correlation with severity in our study. Our findings are consistent with existing scientific literature, which recommends using this marker to assess tissue perfusion and hypoxia in COVID-19. Elevated LDH has been associated with a higher risk of ARDS, need for intensive care, and mortality [39, 40].

**D dimer:**

We observe a statistically significant difference and a moderate positive correlation of D Dimer with disease severity. D Dimer also seems to be a crucial pathophysiological marker of the disease as most of our patients benefit from anticoagulation treatment, and no anticoagulation-induced adverse events were reported.

Studies have shown higher D dimer and fibrinogen levels in patients with severe COVID-19 and fatal outcomes. Increased D-dimer levels have been associated with a worse prognosis in patients with COVID-19, including an increased risk of ICU admission, mechanical ventilation, and death [41]. A study reports that 81% of the ICU patients show elevated D-dimer indicating micro thrombosis as the main presentation of hypercoagulable state [40]. Increased D-dimer levels might be indicative of pulmonary intravascular coagulopathy. Macrophages, recruited to fibrin thrombi, generate plasmin, through which fibrin is degraded to D-dimers. Autopsy analyses have revealed fibrin-rich thrombi containing neutrophils in the alveolar capillaries and increased lung megakaryocytes producing young platelets, which are more thrombogenic. Owing to the high fibrinolytic capacity of lungs, vigorous fibrinolysis...
leads to the production of D-dimers, which spill into the blood [11]. Patients showed higher levels of D-dimer and higher levels of CRP and creatinine, probably due to increased vascular permeability, kidney, or liver disease.

However, D-dimer levels need to be interpreted with caution in COVID-19 infected patients as it is often elevated with advanced age, in females, active malignancy, surgery, pregnancy, immobility, connective tissue disorders, end-stage renal disease, prior thromboembolic disease, and it reflects a later stage in the hemostatic process. It is released when the fibrinolytic processes degrade a clot. Finally, D-dimer levels do not capture the dynamic effects of functional interactions among platelets, endothelium, and fibrinolytic processes [42].

Gender and Age:

We report older age as a risk factor of severe COVID infection, with males more susceptible to COVID 19. A study by Taj S et al. reported that Covid 19 affected males more than females, and older age was a risk predictor of critical/extensive lung involvement and increased oxygen requirement [17]. Literature evidence shows that older age of COVID-19 patients was associated with up to 2.5 times increased odds of developing leukocytosis and neutrophilia [19]. A study conducted by Jin JM et al. also reported that a greater percentage of men acquire severe Covid infection than women. Terpos E et al. described older age and male gender as risk factors for severe disease and death in patients with COVID-19. A study reported that female patients had significantly lower odds of developing neutrophilia than males [19]. The higher preponderance to male sex is probably due to the biological differences in males’ and females’ immune systems that affect the ability to fight against COVID-19 infection. Females are generally more resistant to infections than males; this may be mediated by several variables such as lifestyle, sex hormones, and high expression of Angiotensin-Converting Enzyme 2 (ACE 2) in males [43]. However, contrasting evidence by some studies also reported no association of COVID-19 severity with gender.

Comorbidities:

Our study reports diabetes mellitus, hypertension, CKD, CAD, cancer, chronic liver disease, and hypothyroidism as major comorbidities in patients with severe COVID 19 and poor outcomes. In addition, hypertension, diabetes, heart disease, COPD, and asthma have been reported in different studies as predictors for severe COVID-19. Reinforcing the views of COVID-19 being a thrombo-inflammatory syndrome, patients with severe disease and fatal outcomes have been observed to manifest features suggestive of endothelial dysfunction, widespread coagulopathy, and complement-induced thrombosis resulting in systemic microangiopathy and thromboembolism. Endothelial dysfunction and hyper inflammation results in diffuse alveolar damage and quickly progresses to pulmonary intravascular coagulopathy, a specific form of DIC. Evidence reiterates that a substantial proportion of patients with severe COVID-19 have a preexisting history of hypertension, diabetes, chronic kidney disease, and cardiac/cerebrovascular disease [42].

Coronaviruses have a unique affinity to the host angiotensin-converting enzyme 2 receptors (expressed in vascular endothelium). Thus, a preexisting enhanced endothelial dysfunction
among these premorbid patients is likely to promote the likelihood of a cytokine storm leading to adverse clinical outcomes and death [42, 44].

Our study emphasizes the increased risk of severe COVID-19 infections in individuals with chronic liver diseases (alcoholic liver disease and nonalcoholic fatty liver disease, also known as metabolic associated fatty liver disease). Unfortunately, though, the effect of liver diseases in the severity of COVID-19 infection has been explored to a limited extent. A meta-analysis reported that preexisting liver diseases or acute liver injury play a vital role in predicting mortality in COVID-19 infection [45].

Dysregulated hepatic immune responses and a chronic low-grade inflammatory environment may trigger a high-grade cytokine storm [40]. Another study attributed coagulopathy as an underlying mechanism of liver injury and elevated transaminases due to the observation of extensive vascular portal and sinusoidal thrombosis [46]. Patients with metabolic dysfunction-associated fatty liver (MAFLD) had shown a 4–6-fold increase in severity of COVID-19, and its severity and mortality increased in patients with higher fibrosis scores. A study concluded cirrhosis as an independent predictor of severity of COVID-19 with increased hospitalization and mortality [47]. In addition, the patients with MAFLD had a higher risk of disease progression, a higher likelihood of abnormal liver function from admission to discharge, and longer viral shedding time compared to patients without NAFLD [48]. Gao F et al. concluded that in nondiabetic patients with COVID-19, the presence of MAFLD was associated with a 4-fold increased risk of severe COVID-19 [49].

A similar study by Zhou et al. concluded that younger patients (less than 60 years) with MAFLD manifested severe disease than patients more than 60 years; thus, MAFLD is an independent risk factor for severe COVID-19 [50, 51].

**Treatment modalities:**

Most of our patients received and benefitted from anticoagulation therapy, a combination of anticoagulation and corticosteroid regimen was the second standard treatment modality. Remdesivir was used majorly in patients (about 60%) with severe Covid 19. Evaluating the levels of IL-6 early in disease onset can stratify patients at higher risk to develop a more severe form of the disease. Viseslav Popadic et al. reported no differences in mortality between the groups with Tocilizumab use. Tocilizumab administration caused elevation of IL-6 levels after usage due to disrupted clearance after drug saturation of the receptors. The levels of IL-6 and TNF-α in patients with COVID-19 were reported to be sustained during days or even weeks, which makes the decision for administering the anti-cytokine treatment more complex [52].

Further, the potential benefit of immunomodulatory agents in phenotype 5 Covid patients may result in the emergence of severe adverse events which complicate management, such as systemic superinfections (viremia by cytomegalovirus and bacterial sepsis) [8]. Although the anticoagulant therapy in COVID-19 patients has become almost mandatory in treatment protocols, a significant decrease in the overall mortality of critically ill patients has not been noted yet, speaking in favor of multiple pathophysiological mechanisms responsible for poor prognosis clinical outcomes [52]. D-dimer levels have been recommended as a part of the
risk stratification criteria to decide anticoagulation [11]. Many patients manifest hypercoagulability, increasing the risk of deep venous thrombosis, pulmonary thromboembolism, myocardial infarction, ischemic stroke, etc. Thus, all hospitalized patients are believed to benefit from prophylactic anticoagulation unless they have severe thrombocytopenia or active bleeding. Heparin usage is associated with reduced D dimer levels, fibrin degradation products, and IL-6 and significantly reduced 28-day mortality rates [8].

The positive effects of recommended antiviral agents like remdesivir and favipiravir, as presented by Beigel et al., are limited to evidence of shorter time to recovery [53]. It is postulated that these antiviral agents promote rapid viral clearance, shorten the disease course, and reduce oxygen requirement. However, the supportive data on lower rates of respiratory failure, ICU admissions, or all-cause mortality is missing [54].

Considering the effects on outcomes, WHO recently recommended against the use of remdesivir, as evidence suggested no effects on mortality, need for mechanical ventilation, and other outcomes. WHO Solidarity Trial Consortium, “Repurposed antiviral drugs for COVID-19 - interim WHO Solidarity trial results,” The New England Journal of Medicine, vol. 384, no. 6, pp. 497–511, 2020. As we encounter the entire spectrum of presentations, thrombo-inflammatory biomarkers continue to hold a pivotal place in risk stratification, prognostication, and assessment of the severity of COVID-19 infection. Comorbidities conferring higher risk coupled with critical to high-risk concentration of circulating biomarkers might assist the development of risk prediction models and potentially aid in tailoring personalized/ phenotypic therapeutic strategies, which could improve clinical outcomes [42].

Further, patients should be monitored (up to 12 months) after clinical cure to assess persistent hyper inflammation or hypercoagulability and consider preventive interventions [8].

**Mortality in COVID 19 (The predominance of MODS and sepsis):**

Finally, our study observed sepsis and multi-organ failure as the cause of death in 75% of our patients. Bacterial (Staphylococcus spp., Methicillin-resistant Staphylococcus aureus, Pseudomonas spp., Klebsiella spp., Escherichia coli) and fungal (Candida spp.) superinfections or a combination of these were the most documented coinfections with VAP being a recorded source of sepsis initiation. Supporting our finding of sepsis as the most significant contributor to mortality in COVID19 is evidence from numerous researchers across the world.

Viral infections cause secondary superinfections, and COVID 19 mortalities have been majorly attributed to these superinfections induced sepsis. ICU patients are known to be more prone to nosocomial pathogens, and the commonest infection observed among COVID-19 patients is ventilator-associated pneumonia (VAP), followed by bacteremia with sepsis and urinary tract infections (UTIs) [55]. Therefore, it has been recommended to assess procalcitonin at admission to aid in early risk assessment and rule out bacterial coinfection. Further, serial procalcitonin measurements have been recommended to detect secondary infections and progression to more severe diseases like sepsis / septic shock. A multicenter
study on COVID-19 patients with clinically diagnosed bacterial coinfection reported more severe illness, increased inflammatory tendency, and an increased tendency of multi-organ dysfunction [56]. Yang et al. reported bacterial coinfection as a major inducer of death [20]. Silva DL et al. also reported poorer outcomes (increased duration of hospital stay, increased mortality) in COVID-19 patients with coinfections. The study reported non-aureus Staphylococcus (catheter acquired) is associated with a higher risk of mortality. The study also reported a high prevalence of Candida spp. Candida non-albicans were associated with increased mortality, probably due to their lower sensitivity to antifungals. Patients with severe COVID-19 are more likely to undergo interventions (mechanical ventilation, broad-spectrum antibacterial, immunomodulatory therapies like tocilizumab, corticosteroids) that favor opportunistic infections [57].

Based on clinical evidence of significant bacterial and fungal superinfections, it has been recommended to strengthen investigations pertaining to secondary infections in COVID-19, enabling insights into the epidemiology, pathogens, and drug sensitivities that aid tailored therapies and prevention measures, thereby reducing mortality [58].

An editorial by Jean-Louis Vincent defines COVID-19 as sepsis (best defined as an inadequate host response to an infection) with the background that multi-organ failure accounts for most of the COVID-19 deaths. COVID-19 also displays features of systemic thrombotic endotheliopathy, which could explain the widespread organ dysfunction observed. Further, mortality rates from severe COVID-19 are similar to those observed in other forms of sepsis, and the complex immune dysfunction mimics features of other forms of sepsis. Recognizing COVID-19 as 'sepsis' can also encourage the development of therapeutic approaches that target the host response [59].

This finding is of crucial importance in the Indian setting displaying the highest prevalence of multidrug-resistant pathogens. Furthermore, the hypothesis that adverse outcomes of COVID-19 are due to coinfection induced multi-organ dysfunction syndrome and septic shock thus calls for renewed and strict infection control practices in the intensive care setting, potential antimicrobial stewardship interventions, and identification of AMR patterns [60].

**Temporal Trends in Biomarkers**

Temporal variation of biomarkers along the course of the illness rather than a single-point measurement is imperative to ascertain disease progression and therapeutic response. Time of testing and the trends are important determinants to obtain a meaningful picture [11]. A retrospective reported that WBC, neutrophil, and platelet counts progressively fell to a nadir by day 8–9 of illness but gradually recovered in the subsequent days. Hematological and immunological parameters assessed over time showed that lymphocytes, T-cell subsets, eosinophils, and platelets were markedly low at admission, especially in severe/critical disease and non-survivors. Survivors and non-survivors could be discriminated by increasing trend of eosinophils, lymphocytes, and platelets in the former compared to a significant drop in the latter. Restored levels of lymphocytes, eosinophils, and platelets could serve as predictors for recovery, whereas progressive increases in neutrophils, basophils, and IL-6 were associated with fatal outcomes [11,61].
The major findings of our study include that older age and premorbid conditions increase the risk of severe COVID 19 infections. Males seem to be more susceptible to COVID 19. Hematological markers like leukocyte counts, NLR, LMR, PLR, and SII, thrombo-inflammatory markers like D dimer, CRP, LDH, ferritin, and organ-specific markers like NT pro-BNP, creatinine, AST, and ALT differ significantly and reflect the severity and progression of COVID 19. Diabetes mellitus emerged as the most prevalent premorbidity in our patient population. The majority of our patients received prophylactic anticoagulation with a combined corticosteroid regimen being a close second, and many of the patients benefitted from this therapeutic approach. Our study reports preexisting cancer and chronic liver disease as a potential risk factor for acquiring severe COVID 19 and fatal outcomes. Multi-organ failure and sepsis (bacterial and fungal) led to mortality in the majority of our patients.

CONCLUSION:

COVID-19 is a heterogeneous disease spectrum complicated by the preexisting comorbidities, immune functioning, ethnicity, and even the age and gender of affected individuals. As we continue to update our understanding of this novel virus, its complex interaction with the human system, and strategies to effectively treat the infection and prevent mortality, biomarkers will continue to play an indispensable role in suspicion, diagnosis, monitoring, risk stratification, management of patients. Meaningful integration of laboratory variables and clinical evaluation will be paramount to guide therapeutic and intervention decisions. We suggest a serial measurement of a battery of biomarkers, careful consideration of high-risk pre morbidities, prevention and early detection of superinfections, and tailored individualized therapeutic regime could aid in effective patient management and favorable outcomes.

Limitations and future perspectives:

The study is limited by a retrospective design and the absence of data reflecting changes in serial measurements of candidate biomarkers. Follow-up of discharged patients (up to six months) could provide comprehensive data on long-term implications of COVID 19 and the extent of resolution in thrombotic and inflammatory manifestations characteristic of the COVID 19 disease.

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Conflict of interest:

The authors state that they have no conflicts of interest with regard to the present study.
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