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ORIGINAL RESEARCH

Clinical And Laboratory Features Among COVID-19 Patients At A Covid Designated Hospital In Northern Region, India

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Abstract
Introduction: World Health Organization (WHO) declared Coronavirus disease (COVID-19) as a pandemic in March 2020 and it continues to rage globally with its high infectivity, clinical severity and mortality. Studies presenting clinical and laboratory features among COVID-19 patients are mainly from China, while those from India are limited.
Aim: This study presents unique clinical and laboratory features among Indian COVID-19 patients along with a detailed review of literature.
Materials and Methods: Data from patients fulfilling case definition with positive COVID-19: RT-PCR test report from an approved laboratory in India, between April 2020 and April 2021 was collected. Data was categorized into two groups; survivors and non survivors.Statistical analysis was processed using commercial software Statistical Package for Social Science version 23. P value of < 0.05 was considered significant.
Results: Data of 507 patients admitted to COVID Management Hospital was identified among which 417 patients were survivors and 90 patients were non-survivors. Overall median age was 52 years ; 53 % were male and 47 % were females. Non-survivors were significantly older (median age, 73 years vs 44.5 years; P < .001) and were predominantly male (84% vs 47 %; P = .003). Statistically significant correlation was also noted between high values of laboratory parameters and mortality.
Conclusion:Survivors were females less than 45 years while non-survivors, were males older than 73 years. Non-survivors complained of distinct features as exaggerated dyspnea, ageusia and anosmia at presentation .Statistically significant correlation was noted between high values of fasting blood glucose,CRP, LDH, D-dimer, neutrophilia , lymphopenia and mortality
Key words: COVID-19, clinical, laboratory, co morbidity, ageusia, anosmia

Introduction

The new severe acute respiratory coronavirus 2 (SARS-CoV-2) causes Coronavirus Disease 2019 (COVID-19).Human infection with this virus was first discovered in Wuhan, China, in December 2019 [1]. The virus was formerly known as 2019 novel coronavirus (2019-nCoV), but the International Committee on Taxonomy of Viruses (ICTV) [2] renamed it SARS-CoV-2, and WHO (World Health Organization) refers to it as COVID-19.On March 11, 2020, the WHOannounced COVID-19 as a global pandemic. At the time of article submission the total

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active cases in India available at Ministry Of Health official websiteare around 23913 with a mortality of 516543.New Delhi and Mumbai , the national and financial capital respectively, alone account for 40% of the total COVID-19 deaths. The disease spreads via aerosol or droplet infection. Early diagnosis is critical for effective management and infection control. SARS-CoV-2 is currently diagnosed in the laboratory using nucleic acid amplification assays (NAAT) such as real-time reverse transcriptase (RT-PCR).

COVID-19hastaken its toll and brought great economies and healthcare systems to the edge of breakdown rapidly mainly because of it's high infectivity,variable pathogenesis , higher death rate among elderly and those with co-morbid conditions, mortality among healthcare workers, absence of effective antivirals and interrupted and staled vaccine program.Several studies have documented the clinical features of COVID-19 patientsand it is evident that laboratory investigations have a far more critical role than the etiological diagnosis, contributing directly to monitoring therapeutic intervention as well as prognostication[3][4].

Abnormal blood counts, elevated inflammatory biomarkers, coagulation parameters, and tissue-specific damage indicators are among the most common laboratory abnormalities[5]. Thesefeatures result from the complex COVID-19 pathogenesis with increased rates of acute kidney injury (AKI) resulting in renal failure (RF), acute cardiac injury (ACI) resulting in myocardial infarction (MI), keto-acidosis in euglycemic patients and disseminated intravascular coagulation (DIC) resulting in pulmonary embolism.All culminate into multiple organ failure with cytokine storm[6].Most relevant laboratory abnormalities identified in Asian COVID-19 patients arelymphopenia, along with increased values of C reactive protein (CRP), lactate dehydrogenase (LDH), erythrocyte sedimentation rate (ESR) and D-dimer [5].Other laboratory markers identified to predict the progression of COVID-19 into severe forms, includeneutrophilia, leukocytosis, lymphopenia, increased values of total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST),serumcreatinine, cardiac biomarkers, prothrombin time (PT), D-dimer, and procalcitonin [6].

In the face of rapidly modifyingand frequent addendums, the list of disease predictors seems never ending .Clinical and laboratory features may show unique demographicpatterns that may play key role in identifying variations and the abnormalities may correlate well with disease severity. Also a combination of deranged parameters may help identify patients likely to be COVID-19 positive.Although Chinese researchers have published extensively in this regard, to the best of our knowledgethere are limited such studies from India.

Aim

This study presents the unique clinical and laboratory features among Indian COVID-19 patients along with a detailed review of literature.

Materials and Methods

Study design

Data related to patients with confirmed COVID-19 admitted to COVID-19 Management Hospital Level II from April 2020 untilApril 2021, was collected. Keeping compliance to contactless safety measures during pandemic oral consent was recorded from patients or patients' families,for the use of their anonymously gathered data forthis retrospective observational study. The study was carried out in conformity with the Helsinki Declaration, the terms of local legislation and was approved by the institutional ethics committee.

Inclusion criteria

Data of patients fulfilling WHO-COVID-19 case and surveillance definition [7] and having positive COVID-19 RT-PCRtest report referred from a regional ICMR (Indian Council Of Medical Research)approved COVID-19 laboratory, was included.

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Exclusion criteria

Data of patients with common bacterial or Non COVID-19 virus associated community-acquired pneumonia, negative RT -PCR testwas excluded.

Data Collection

Data was obtained from the Laboratory and Hospital Information Systems (LIS/ HIS) which provided information on the age, gender, location of each patient, laboratory parameters performed , information on vitals etcVitals for patients were recorded on multi-parameter patient monitors directly connected to patient e- files in HIS. Data was reverified from medical records in case of discrepancy.All laboratory investigations were performed at a containment laboratory fulfilling the requirements for a COVID-19 biosafety facility as prescribed by Center for Disease Control and Prevention 2020c.Laboratorystaff were well trained for appropriate sample collection, storage, packaging,spill management and transport. Samples collected for laboratory investigations were flagged as potentially infectious and laboratory staff involved in collection, handling or transportation of bloodsamples adhered rigorously to infection prevention and control guidelines for biosafety issued periodically by ICMR for COVID-19.

The Berlin definition of acute respiratory distress syndrome (ARDS) was used [8]. AKI was defined in accordance with Kidney Disease: Improving Global Outcomes definition, as one of the following:(1) a serum creatinine increase ≥0.3 mg/dL (≥26.5 μmol/L) within 48 hours, (2) a serum creatinine increase to ≥1.5 times baseline within the previous 7 days; or (3) a urine volume ≤0.5 mL/kg/h for 6 hours [9]. ACI was defined as blood levels of cardiac biomarkers (e.g., troponin I) exceeding the upper reference limit by the 99th percentile or appearance of new abnormalities in electro or echocardiograph. Time interval between onset of signs and symptoms to hospital admission,dyspnea, ARDS, ICU (intensive care unit) admission, and hospital discharge were recorded.Patient data was categorized into two groups;survivors and non survivors.The date of disease onset was defined as the day on which the first symptom was recognized.The end-point of this study was a composite measure consisting of invasive ventilation or death.

Haematological testing, including haemoglobin (Hb) concentration, white blood cell (WBC), platelets (PLT), neutrophil, and lymphocyte counts, were performed on blood samples anticoagulated with ethylenediamine tetra-acetic acid (EDTA) using Sysmex XS 800i Japan instrumentation and proprietary reagents (Sysmex Corporation, Kobe, Japan). Coagulation assays,includingprothrombin time/international normalized ratio (PT/INR) and D-dimer were performed on plasma collected into 3.2% buffered sodium citrate blood tubes using Sysmex CA 600 Series Japan instrumentation and proprietary reagents.Clinical chemistry testing were performed on plasma and serum collected in plain (clot activator vacutainers),Sodium fluoride and EDTA vacutainersusing automated analyzers EM 360 ,TransAsia, India and Vitros 5600;Ortho Clinical Diagnostic ,USA. These tests included measurement of serum glucose, urea, creatinine, sodium, potassium, AST, ALT, LDH, total bilirubin, serum creatinine,albumin, ferritin, CRP and cardiac troponin I (TnI). Throughout the study period , the same set of analyzers was employed. Internal quality control (IQC) processes and participation in an External Quality Assessment Scheme (EQAS)were used to validate the quality of test results.

Statistical analysis

The study analyzed the medical history, underlying comorbidities, clinical presentation , duration of hospital stay , vitals and investigations performed. The data was processed in an electronic format to delete duplications .Continuous variables were represented using mean and median values, whereas categorical variables were expressed using frequencies and

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percentages. The Mann-Whitney test for independent samples was employed to compare laboratory parameters between COVID-19 survivors and non-survivors because normal distribution could not be proven. The chi-squared χ 2 test was used to compare proportions for categorical variables, which were reported as counts and percentages. When the data was sparse, Fisher's exact test was utilized. A p value of less than 0.05 was significant. Relationship between patient outcome and laboratory parameters at hospital admission in order to identify possible predictors of hospital deaths was analyzed using multiple regression. Statistical analysis was processed using commercial software Statistical Package for Social Science (IBM SPSS Statistics, Version 23.0. Armonk, NY: IBM Corp).Linear regression analysis was performed using data regarding independent variablesto measure the strength of association with mortality.Coefficientof determination R2 was adjusted for multiple variables. This enabled us to separately measure the potential predictors of adverse outcome related to prognostic impact.

Results

As per data from medical records byApril 2021, 507 RT-PCR positive COVID -19 patients were admitted to COVID-19 Management Hospital Level II among which 417 patients were discharged(survivors) and 90 patients succumbed to death (non-survivors) indicating that overall 17.8% patients reached the composite endpoint during the study period. The basic characteristics of all patients are presented in *Table 1.*

The overall median age was 52 years; 53 % were male and 47 % were females. Notably there was no patient belonging to pediatric age group.The median period from onset ofinitial symptom to hospital admission, dyspnea, and ARDS were 3days, 5 days and 7 days, respectively. The average length of stay in the hospital was 12 days. Diabetes (24%) was the most prevalent co-morbidity, followed by hypertension (12%) and cardiovascular disease (10%). Fever (97%), fatigue (64 %), dry cough (62%), dyspnea (32 %), ageusia and anosmia (both 33 %), myalgia (33%), and pharyngalgia(32 %) were the most common clinical features at the onset of infection among both groups together.

The 90 non-survivors, were much older (median age, 73 years versus 44.5 years; P<.001) predominantly male (84% versus47 %; P = .003). Ninety percent of them had tachypnoea. They were more likely to have a comorbid condition of uncontrolled diabetes (44.4% versus 20%; P = .001) than hypertension (31% versus 8%; P = .002) and cardiovascular diseases(24% versus 7%; P=.002) .About 20% patients among non-survivors had more than one co-morbid condition. Non-survivors complained of exaggerateddyspnea (94% versus 19%; P < .001),ageusia (92% versus 19%; P < .001) and anosmia (94% versus 19 % P < .001) at presentation. At hospital admission, mean pulse and respiratory rate was higher among non- survivors than in survivors (PR 85 versus 82 ; RR 24 versus 20 P = .003). Similarly, the MAP and mean Sp O2 on room air was lower in non-survivors than in survivors (55 mmHg versus 82 mmHg; P = .001) and (72 versus 95, P = .001). Statistically significant correlation was noted between high values of laboratory parameters such as fasting blood glucose ,CRP, LDH, D-dimer, ferritin serum creatinine, urea , hypoalbuminemiaand mortality .Adjusted coefficient of determination “R2” was 0.979 denoting positive strength of association. Among the hematological parameters studied neutrophilia and lymphopenia correlated with mortality. Mild thrombocytopenia was also noted among the non-survivors. Survivors were predominantly females less than 45 years who had controlled diabetes as comorbidity, presenting mainly with fever, fatigue,dry cough, paryngalgia and SpO2 within normal limits .Survivors had deranged LFT,KFT and coagulation parameters which progressively returned to normal .The detailed comparison of laboratory features in both groups are presented in *Table 2*.

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Table 1:Clinical features of COVID-19 disease survivors and non-survivors.

Characteristics	Total (n = 507)	Survivors (n =417)	Non-survivors (n =90)	Significant P value
Age groups				
< 45	218	209	9	
45–59	118	115	5	
60–75	109	75	33	
> 75	62	18	44	0.0001*
Gender				
Male	271	194	76	0.003*
Female	236	223	14	0.002*
Comorbidity				
DM	123	83	40	
HT	62	34	28	
CVD	52	30	22	
CLD	28	27	1	
CBVD	28	27	1	
CKD	29	28	1	
Symptoms and signs				
Fever	492	473	19	
Fatigue	326	312	14	
Dry cough	317	280	37	
Dyspnea	164	80	84	0.0001*
Ageusia (Loss of taste)	165	82	83	0.0001*
Anosmia (Loss of smell)	165	80	85	00.001*
Myalgia	167	161	6	
Pharyngalgia	166	160	6	
Headache	33	32	1	
Dizziness	33	32	1	
Vitals				
BT More than 37◦C	255	240	15	
BT Less than 37◦C	252	177	75	0.002*
PR(bpm)	83	82	85	0.003*
RR	22	20	24	0.001*
MAP(mmHg)	83	88	55	0.001*
SpO2/HFNC	90	95	72	0.001*
Onset of symptoms to				
admission (days)	3	4	2	
dyspnea (days)	5	7	4	
ARDS (days)	7	7	7	
Length of hospital stay (days)	12	10	14	

Data are n (%). P values indicate differences between survivors and non-survivors. Body temp(BT) , respiratory rate (RR), and Mean arterial pressure (MAP) , high flow nasal cannula (HFNC), beats per minute (bpm),acute respiratory distress syndrome(ARDS) ,diabetes mellitus (DM),Hypertension (HT),Cardiovascular disease (CVD);Chronic liver disease (CLD),Cerebrovascular disease(CBVD),Chronic kidney disease (CKD)

Table 2: Comparison of laboratory features between COVID-19 disease survivors and non- survivors

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Characteristics	Levels among Survivors (n =417)	Levels among Non-survivors (n =90)	Significant P value
Fasting blood glucose, mg/dl	100	140	0.001*
Albumin g/dl	3.4	3.2	
ALT U/L	30	55	0.001*
AST U/L	40	65	0.001*
Total Bilirubin µmol/L	0.6	0.7	
LDH, U/L	310	517	0.001*
Potassium, mmol/L	4	3.4	
Sodium, mmol/L	134	136	
Urea, mg/dl	234	432	0.001*
Creatinine, mg/dl	5.3	7.1	0.001*
TnI, ng/ml	0.006	0.048	0.001*
PT/INR	1.01	1.12	0.001*
D-Dimer µ/ml	820	2000	0.001*
Ferritin ng/mL	702	1485	0.001*
CRP mg/L	50	100	0.001*
Hb, g/dl	13	11	
WBC x 10^9/L	4.7	6.7	
Neutrophils x 10^9/L	4.1	7.6	0.001*
Lymphocytes x 10^9/L	1.05	0.2	0.001*
Platelets x 10^9/L	189	156	
Aspartate aminotransferase (AST); Alanine aminotransferase (ALT);C reactive protein (CRP); Hemoglobin (Hb); Cardiac troponin I (TnI); Lactate dehydrogenase (LDH); Prothrombin time/international normalized ratio (PT/INR); White blood cells (WBC).			

Discussion

Increasing burden of high risk COVID-19 patient management has overwhelmed the vulnerable healthcare systems in developing countriescomplicated by the false optimism that the disease can be easily controlled by such fragile systems. The obvious and hidden toll of the pandemic cannot be underestimated and therefore,it is compulsory to manage resources judiciouslyregardless of being a developed or developing country. Thismakes characterization of high and low risk patients essential. The current study serves to highlight the leading clinical and laboratory features that could help in identification of a fraction of COVID-19 patients with a higher risk of mortality.To the best of our knowledge only few studies have been published so far with regard to clinical and/or laboratory features in COVID -19among Indian population[10][11][12][13].

Significant pattern of clinical features among COVID-19 Indiannon- survivors observed was elderly age group, male predilection, high risk comorbidityofdiabetes, along with characteristic presentation of exaggerateddyspnea,ageusia and anosmia.An interesting findingin our study was that 9 young male patients between 35-45 years showed a steep decline in SpO2, slipping into ARDS and necessitating ventilator support, ultimately culminating in mortality. Rest of patients requiringventilator support were above 60 years of age with co-morbidity ofdiabetes. Our results are consistent with a large Chinesestudy of72 314 cases,reporting an increased case-fatality rate of 14·8% in individuals aged 80 years and older[14]. A study from Northern India reported that most of the COVID-19 patients

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reporting to their hospital were young and asymptomatic [14]. This could be partlyexplained by the variation in patient referral from nearby areas to our and their center.

Frequent association of comorbid condition of diabetescould be contributory in causing systemic hypoxia. Guan et al [15] reported a frequency 8.2% diabetes among 1590,COVID 19 Chinese. This frequency hiked to 34·6% in patients with severe COVID-19 [15].In a meta-analysis of six Chinese studies, the frequency of diabetes was 9·7% in the entire COVID-19 cohort of 1527 patients, similar to the estimated frequency of diabetes in China (10·9%) [16].Interestingly in our study hyperglycemia was also found among 166 (40%) patients who had no pre-existing diabetes. Among this category 50 (30%) were non-survivors.Existing literature is deficit to explain,how hyperglycemia is triggered in absence of pre-existing diabetes in a fraction of COVID-19 patients with worst outcomes. In the CORONADO study 11·1% of the participants had diabetes-related complications at the time of admission including 132 patients with severe hyperglycemia [17].The role of hyperglycemia, necessitates further examination as glycemic control prior to , at the time , and during hospitalization are all important considerations [17].Study from USA involving 1122 patients with COVID-19 reported mortality rate four times higher among diabetics or hyperglycemic patients (28·8%) than those with normoglycemics (6·2%) [18][19].

ACE2 (angiotensin converting enzyme 2)receptors are present in the lung, heart, liver, kidney, ileum, and brain and have anti-inflammatory function normally [19]. They are also present in pancreaticβ-cells providing easy attachments for the COVID -19 virus .This could potentially precipitate an acute loss of insulin secretion complicated by the cytokine storm causing rapid metabolic decline, leading to diabetic ketoacidosis or hyperglycemic hyperosmolar syndrome[19].The COVID-19 virus enhances angiotensin II expression, which leads to ACE2 downregulationdriven by endocytosis and activation of proteolytic cleavage and processing[20]. Alveolar wall thickening, oedema, inflammatory infiltration, and bleeding occur as a result of the lack of anti-inflammatory action in lungs. ACE 2 receptors are overexpressed, particularly in type II alveolar pneumocytes which makes lungs the most sensitive tissue in COVID-19 infections[21].International cohort study by Morales DR et al [22]could not establish a correlation between ACE inhibitors or angiotensin receptor blockers and the risk of COVID-19 hospital deaths.

Guan et al [15] in their study targeting 1590 patients,reported HT (n=269,16.9%) as the most common comorbidity followed by cardiovascular diseases (n=59,3.7%).Although severely affected COVID-19 patients have shown highfrequency of HT, still it is not clear as yet whether HT was pre-existing and undiagnosed in these patients previously which only exacerbated during COVID-19 infection. Or whether this association is confounded by factors such as age, mental status during pandemic, and other co-morbidities including obesity, DM orCKD.

Both direct myocardial injury due to viral effect on myocardial cells and effects of systemic inflammation play a role in ACI [16][23]. Shi S et al [23] reported a mortality of 51% among Chinese COVID-19 patients with ACI as compared to 4.5%among those without.The overall incidence of ACI is variable, although approximately 8% cases may develop very high cTnIlevels[16]. AChinese study reported 17% incidence of cTnI elevation among COVID-19 patients [24]. It is clear, that presence of pre-existing CVD (cardiovascular disease) or ACI has consistently been found to be a strong negative prognostic predictor[24].In our study higher level of Tn I among non-survivors with pre-existing CVDwas noted with no event of raised Tn I recorded in absence .

In concordance with the study of Wang D et al [25] the clinical features in this study showed a weekly pattern .During the first week the clinical features were predominantly fever, fatigue, dry cough, dyspnea, ageusia, anosmia suggesting side effects of viral attack and replication. Among the non-survivors too, some clinical features such as exaggerated

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dyspnea,ageusia,anosmia persisted.The body temperature reverted to normal by the end of first week due to the widespread use of antipyretics.During the second week fever, cough,dyspnea,ageusia and anosmia resolved among the survivors.Notably among the non-survivors, there was quick clinical deterioration over the second and third week of hospital stay with multiple organ dysfunction , ARDS, RF,DIC,ACI and thrombocytopenia, of varying degree.Our results were similar to those reported by other studies [10][11][12]

Wang D et al[25] reported significantly higher levels of CRP among severe than non-severe patients, suggesting that CRP may be a beneficial serum marker of disease progression in COVID-19 patients, with an optimal threshold value of 26.9 mg/L.CRP levels were strongly linked with lung lesions in the early stages of COVID-19 and represent disease severity[25].The presence of neutrophilia and high CRP among non survivors supports the principle of cytokine storm involved in the pathogenesis of COVID-19 infection .Both of these parameters imply the possibility of viremiaand bacterial co-infection, which can commonly exacerbate the clinical course of COVID-19 thus representing adverse prognostic predictors [24]. ACE2 receptors are also actively expressed by the lymphocytes [2][19][20] which increases the likelihood of lymphocyte susceptibility to injury by the virus causing steadylymphocytopenia. Tan L et al [26]and Chen N et al[3]suggested that lymphocytopenia may belinked to lymphocytic dysfunction and immunosuppression,exposing patients to an increased risk of co-infections and poor prognosis. Importantly lymphocytopenia persisted among 50% of survivors in our study even as other clinical features resolved. This is partly explained by the fact that since lymphocytes are main viral targetsthey could return to normal number only when virus is eliminated by antibodies. We also noted leukocytosis as a reflection of excessive inflammation in contrast to leukopenia.In the present study the non survivors showed a raised Neutrophil-to-lymphocyte ratio(NLR) of >4 (P = 0.046), which is similar to the observations reported by Ciccullo A et al[27].

LDH secretion is initiated by cell membrane necrosis, indicating viral infection or lung injury, such as caused by COVID -19 infection.[5][6].It is apparent that as COVID-19 primarily affects the lung, LDH enzyme is a likely marker of lung damage[5][6] .High LDH levels were accompanied with a ~6-fold increase in odds of developing severe disease and a ~16-fold increase in odds of mortality [5][6].High LDH levels were found among more than 95% of non-survivors compared to less than 60% of survivors[5][6]. Patients with severe COVID-19 infections release greater amounts of LDHisoenzyme 3 in the blood signifying severe form of interstitial pneumonia, evolving into ARDS, labelling it as a hallmark of the disease[5][6].

COVID-19 patients could be triaged into critical care based on their D-dimer levels at the time of hospital admission [24][25].ZhouFet al [24] reported that a D-dimer level >1 g/mL was the best predictor of mortality odds ratio at 18.42, 95% CI 2.64—128.55; P = 0.0033 for in hospital deaths among 191 COVID -19 patients. High D-dimer levels are related to DICdemonstrating that ahypercoagulable state may be contributing to disease severity and mortality [25].

In a prospective cohort study ,Cheng Y et al[28] reported a high prevalence of AKI among hospitalized COVID-19 patients .On admission, serum creatininewas elevated in 14.4% and blood urea nitrogen (BUN) was elevated in 13.1% of the patients.AKI occurred in 5.1% of patients throughout their stay in the hospital. Patients with elevated baseline serum creatinine (11.9 percent) had a significantly greater incidence of AKI than those with normal baseline levels (4.0 percent). Evidence of AKI at admission were associated with a higher risk of in-hospital death even after adjustment for potential confounders [28].Thecause ofAKI in patients with COVID-19 is multiplex.The finding of coronavirus PCR fragments in blood and urine of COVID-19 patients supports the hypothesis of direct viral cytopathic effects on kidney [4]. Human tissue RNA-sequencing data demonstrated thatACE2 expression in

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kidneywas ~100-fold higher than in lung.Kidney damage may result fromcoronavirus entering kidney using an ACE2-dependent pathwaywith deposition of immune complexes of viral antigen or by inducing specific immunological effector mechanisms such as specific T-cell lymphocyte or antibody . Although the incidence of AKI was 3.2%, it is an independent risk factor for in-hospital deaths and the likelihood of developing chronic renal disease in the long run[28].

Many studies from Wuhan[5][6][24][25]and a study from Italy [29] have reported serum ferritin levels in patients with severe and non-severe COVID-19 disease on hospital admission.The commonality among these studies is that all of them represent Chinese population reporting that ferritin level was 502 µg/L among survivors and as high as1435µg/L among non survivors. Levels of serum ferritinwere elevated among non-survivors throughout the clinical course, and increased with disease aggravation [24] . These studies also reported concomitant high levels of serum IL-6 on admission among patients developing severe disease. Liu T et al. [30]reported that, ferritin and IL-6 concentrations reduced as patients recovered. This suggests that ferritin synthesis in COVID-19 infection may be associated with inflammatory stimuli including cytokines, such as IL-6. Therefore, ferritin may prove to be a useful parameter to predict disease severity as well as the extent of the cytokine storm.Multiplexfeedback mechanisms between ferritin and cytokines in the regulation of pro and anti-inflammatory mediators might exist because cytokines can stimulate ferritin production and ferritin can stimulate the production of pro- and anti-inflammatory cytokines [30] .Various mechanisms have been put forth to explain high ferritin levels in COVID-19 patients .One that, ferritin being a main intracellular iron storage serves as a positive acute phase proteinthat is increased in inflammatory conditions, including acute infections and as a direct mediator of the immune system[30].Two that high ferritin levels are a characteristic feature of the Hyperferritinemic syndromes, which is a blanket term for macrophage activation syndrome, catastrophic antiphospholipid syndrome, adult onset Still's disease, and septic shock.Three that COVID- 19 infection causes protracted and progressive hypoxia as virus bindsheme groups of hemoglobin in RBCs by competing with ferritin, leaving high levels of ferritin free [30].Literature revealed conflicting reports regarding the correlation between ferritin levels and COVID-19 infection outcomes .Aretrospective analysis of 942 COVID-19 patients admitted ata multispecialty hospital in New York City Health System,USA,evaluating the predictive levels of presentation and maximum ferritin valuesreported that high levels of ferritin did not reliably indicate unfavorable prognosis including death [31].

Significantly decreased albumin level is common in severe COVID-19 with studies reporting it as an independent predictive factor for mortality [5][6][15][24] to thosereporting it to be associated with severity of ARDS [10][11][12][14] and AKI [28].In the present study too albumin levels decreased with the progression of the disease. This may help clinicians in early identification of high risk patients.Mechanisms causinghypoalbuminemia in COVID-19 have yet to be fully understood and cannot be explained only by liver dysfunction related to hepatocellular dysfunction [11][12], implying that mechanisms other than hepatocellular injury may be responsible for the severe hypoalbuminemia. Furthermore, in the current study , the median period from onset of disease to admission was just 3 days, significantly less than the half-life of serum albumin (21 days), implying that hypoalbuminemia was less likely to be either caused by impaired albumin synthesis.The mechanism may also be partially explained by the fact that in the present study a significant inter-relation was found between low albuminlevels and high inflammatory markers (CRP, Ferritin, IL-6 and NLR).Inflammation causes escape of serum albumin into interstitial space due toincreased capillary permeability.Thus, this study and literature strongly suggest that hypoalbuminemia might be due to the systemic inflammation in COVID-19.

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Limitations

This study has certain limitations and the results should be interpreted keeping them in mind**.**The small sample size in the current study , variable range of presentation and co-morbidities and age specific mortality risk limit the generalized application of these results . Being a regional study the study might have been prone to selection bias and the role of confounders might have been understated.

Conclusion

What is known

- Peak of morbidity reported is between 50-59 years with variable gender predilection.
- ARDS is a major complication among non survivors
- Leukopenia, lymphopenia, a high NLR ratio, raised D-dimer, CRP ,LDH and AST levels may help in differentiating COVID-19 from other similar illnesses

What is added

- COVID-19 non survivors were elderly males with uncontrolled diabetes as comorbidity, presenting with characteristic features of exaggerated dyspnea, ageusia, anosmia and SpO2 less than 95%.
- High values of fasting blood glucose,CRP, LDH, D-dimer, Ferritin, along withneutrophilia ,lymphopeniaand hypoalbuminemia correlated with mortality serving as powerful laboratory predictors of bad prognosis.
- Survivors were females less than 45 years with controlled diabetes as comorbidity, presenting mainly with fever, fatigue, dry cough, paryngalgia,SpO2 above 95%s and persistentlymphocytopenia on discharge.

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Conflict of interests

The authors declare that there is no conflict of interests

Authors Inclusion criteria/ contributions

All the authors contributed to the conception, design of the work and to the acquisition, analysis, and interpretation of data for the work. They also participated in the drafting and critical revisions of the manuscript for important intellectual content. All authors have accepted responsibility for the accuracy or integrity of the entire content of this manuscript and approved its submission and given their final approval of the version to be published

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