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ORIGINAL RESEARCH

Role of D-dimer, ferritin and interleukin- 6 as a biochemical marker for severity of disease in COVID-19 patients admitted in a tertiary care hospital of Northern India- A retrospective study

Zarrin Afroz[1],Ritu Agarwal[2],Faisal Nasim Gilani[3]

[1]Associate Professor, Department of Microbiology, G.S Medical College and HospitalPilkhuwa – 245304. District – Hapur, Uttar Pradesh, Email id – zafroz36@gmail.com
[2]Professor& HOD, Department of Microbiology, G.S Medical College and Hospital Pilkhuwa – 245304, District – Hapur, Uttar Pradesh.
[3]Associate professor, Department of Forensic medicine and toxicology, G.S Medical College and HospitalPilkhuwa – 245304, District – Hapur, Uttar Pradesh.

Corresponding author: Dr.Zarrin Afroz,Associate Professor, Department of Microbiology, G.S Medical College and HospitalPilkhuwa – 245304. District – Hapur, Uttar Pradesh, Email id – zafroz36@gmail.com

ABSTRACT

BACKGROUND

Since the end 2019,a novel coronavirus infection COVID-19, caused by SARS-Cov 2 ,which begun as an outbreak of severe viral pneumonia in Wuhan, a central city in China ,has evolved into a global health emergency.Various biomarkers like D-dimer, IL-6 and ferritin are elevated in a significant manner in patients with severe disease.The activation of Coagulation cascade leading to elevated D-dimer concentration is a feature of disseminated intravascular coagulation and adverse clinical outcomes in COVID-19 patients. Elevated IL-6 levels in COVID patients leads to development of hypoxemia and respiratory failure. Ferritin is a key mediator of dysregulation of immune system and hyperferritinemia contributes to cytokine storm in COVID-19 patients leading to severity of disease. Identification of the severity and progression of disease with the help of biomarkers like D-dimer , ferritin and Interleukin -6 is needed for vigorous management and early treatment of patients .This might reduce morbidity and mortality related to COVID-19.

OBJECTIVES

1. To determine the role of biochemical markers like D- dimer, ferritin and IL-6 for the assessment of disease severity in confirmed positive COVID -19 cases .
2. By assessing the severity of disease help the clinicians regarding proper management and early treatment of cases.

MATERIALS AND METHODS

It was a retrospective conducted in department of microbiology for a period of 6 months from July 2020 to December 2020 on 240 confirmed COVID-19 positive cases admitted in isolation ward and ICU of G.S medical college and hospital ,Pilkhuwa . Data regarding demographic characteristics and microbiological evidence was collected from microbiology department while clinical data, lab parameters (biochemical markers like D- dimer , IL-6 and ferritin) and prognosis was collected retrospectively from MRD department. All confirmed positive cases were initially kept in isolation ward and those who didn't respond to treatment and found with progression of the disease were shifted to ICU.

RESULTS

In the present study among 240 COVID -19 positive patients 25(10.41%) patients who had severe type of disease were admitted in Intensive care unit (ICU). Majority of severely ill patients were in age group 60-65 years. Out of 206 patients with elevated D-dimer concentration 21(10.14%) patients with severe disease had D-dimer concentration ≥ 2 mg/lt. Out of 224 patients with elevated IL-6 levels 25 (11.16%) patients with severe form of the disease had IL-6 value ≥88pg/ml. Out of

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180 patients with elevated ferritin level ,24 (13.33%) patients with severe type of the disease had serum ferritin values ≥450ng/ml.

CONCLUSION

The findings in the study show that in the current situation with overcrowded intensive care units and emergency rooms , correct triage of patients in need of intensive care is necessary. Biochemical markers like D-dimer, Interleukin-6 and ferritin which can identify the severity and progression of disease should be monitored at the earliest.

KEYWORDS- Biochemical markers, D-dimer, Interleukin-6, Ferritin,Severity of COVID-19 infection

Introduction

As the December sun rose on Chinese horizon , the world woke up with a start and witnessed the emergence of corona virus disease 2019(COVID- 19). The causative agent of the unusual pneumonia has been identified as a novel coronavirus .SARS-CoV 2 identified through deep sequencing and investigations carried by 5 independent states of China. [1]

The illness varies from asymptomatic or mild infection to severe respiratory tract infections in humans . In previous studies coagulopathy was observed and D-dimer elevations were seen in 3.75-68 % of COVID -19 patients. D- dimer > 1 µg/ml is one of the risk factors for mortality in adult inpatients affected with COVID-19[2]. D-dimers are fibrin degradation products which have been shown to be useful clinically for ruling out pulmonary embolism., highlighting its role as a useful biomarker[3] .It has been found that one of the possible mechanisms under lying rapid progression of disease is cytokine storm .Previous retrospective studies indicate that an elevated level of interleukin -6 (IL-6) was associated with increased case fatality of COVID -19 infection.[4] In a sudy conducted earlier it has been shown that patients with IL-6 levels > 80pg/ml needed mechanical ventilation.[5] Ferritin is a key mediator of dysregulation of immune system especially under extreme hyperferritinemia , via direct immune suppressive action and pro inflammatory effects , contributing to cytokine storm thus leading to disease severity.[6] In previous studies it was found that average ferritin concentration was > 800µg / L for patients with severe disease.[7]

A careful consideration may be needed for conventional anticogulation , as there is increased risk of bleeding with COVID -19. Biomarkers which can identify formation of thrombus at earlier stages , might be used to evaluate thrombus formation and response to treatment.[3] So, the study was conducted to identify the severity and progression of disease with the help of biomarkers like D-dimer , ferritin and Interleukin -6 for vigorous management and early treatment of patients.This might morbidity and mortality related to COVID-19.

Material and methods

It was a retrospective conducted in department of microbiology for a period of 6 months from July 2020 to December 2020 on 240 confirmed COVID-19 positive cases admitted in isolation ward and ICU of G.S medical college and hospital ,Pilkhuwa . Confirmed cases were identified as those with epidemiological history, consistent with clinical manifestations and microbiological evidence (respiratory specimens positive for SARS-COV-2 by truenat and RT-PCR)[2]. Data regarding demographic characteristics and microbiological evidence was collected from microbiology department while clinical data, lab parameters (biochemical markers like D- dimer , IL-6 and ferritin) and prognosis was collected retrospectively from MRD department. All confirmed positive cases were initially kept in isolation ward and those who didn't respond to treatment and found with progression of the disease were shifted to ICU.

Inclusion criteria

1. All confirmed positive cases with with D- dimer, IL-6 and ferritin testing on admission in isolation ward.
2. Patients not responding to treatment in isolation ward and shifted to ICU.

Exclusion criteria

1.Confirmed positive cases with pregnancy , chronic liver disease , cancer ,acute coronary syndrome and history of surgery or trauma within 30 days.

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2.All confirmed positive cases without D- dimer, IL6 and ferritin testing on admission in isolation ward.

Data collection

From microbiology and MRD department.

Data was analysed by diagrammatic presentation in the form of pie charts.

Results and discussion

In the present study among 240 COVID -19 positive patients 25(10.41%) patients who had severe disease were admitted in Intensive care unit (ICU).Significantly increased concentration of serum D-dimer, interleukin -6 and ferritin were found in such patients . The percentage of severely affected patients has been shown in Fig 1.

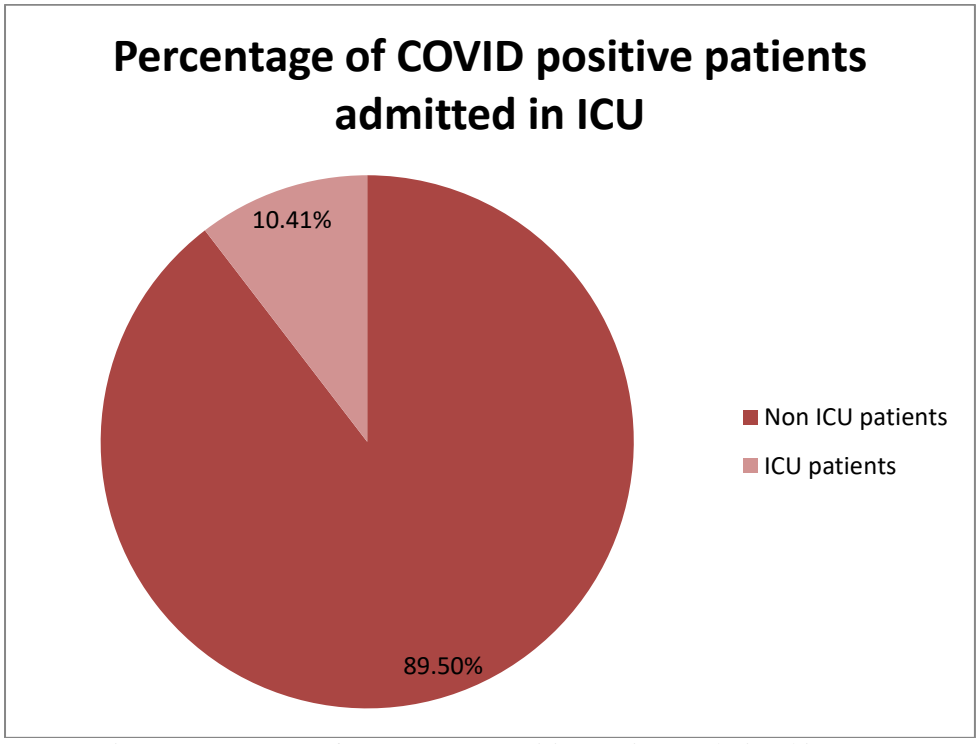

Fig 1 : Percentage of COVID -19 positive patients admitted in ICU

Majority of severely ill patients were in age group 60-65 years. Our findings are similar to the study conducted by Bilian Yu*et al*[3]where the most common age group of severely ill patients was >65 years . Another report by Aurora J *et al*[8] states that the most common age group of severe COVID disease was > 75 years . Our data is in contrast with the study conducted by Farghaly S *et al*[9] where the most common age group affected with severe disease was 40-49 years. Due to ageing frequencies for comorbidities such as hypertension and diabetes are very high . It has been found that adaptive immunity is disabled by SARS-CoV- 2. This feature is referred to as immunity exhausted.This exhaustion may be coupled with ineffective and detrimental innate response. [8]

In the present study among 240 COVID-19 positive patients 34 (14.16%)patients had normal D-dimer levels and in 206 (85.84%)patients D-dimer was found to be elevated .The percentage of patients in which D-dimer level was elevated is shown in fig2.

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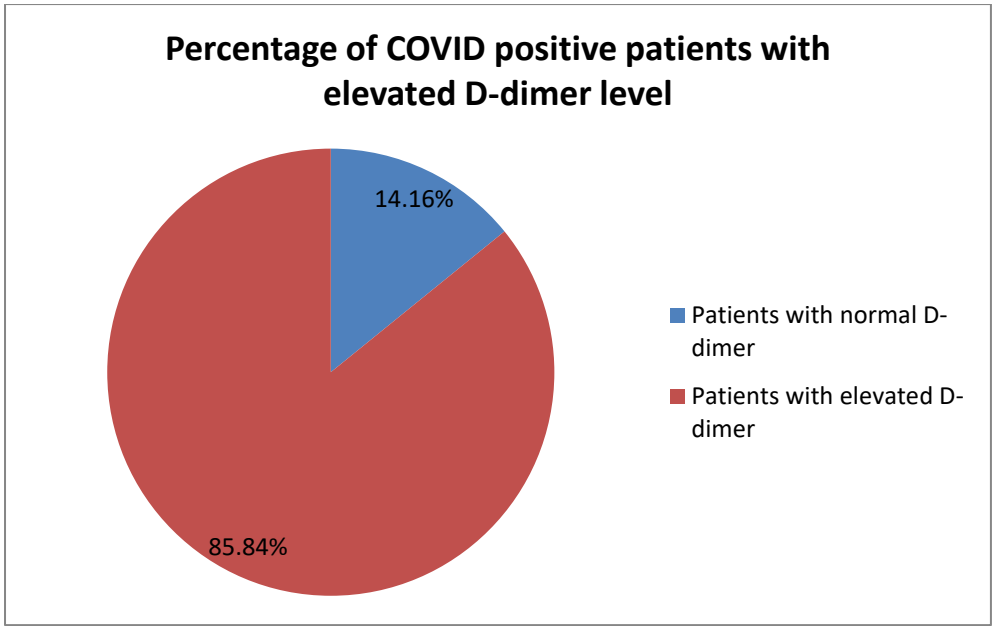

Fig 2: Percentage of COVID-19 positive patients with elevation in D-dimer level

Out of 206 patients with elevated D-dimer concentration 21(10.14%) patients with severe type of the disease had D-dimer concentration ≥ 2 mg/lt. Serum D-dimer concentration in patients with severe form of the disease was significantly higher than compared to those with milder forms. Percentage of patients with severe form of disease due to elevated D-dimer level is shown in Fig 3.

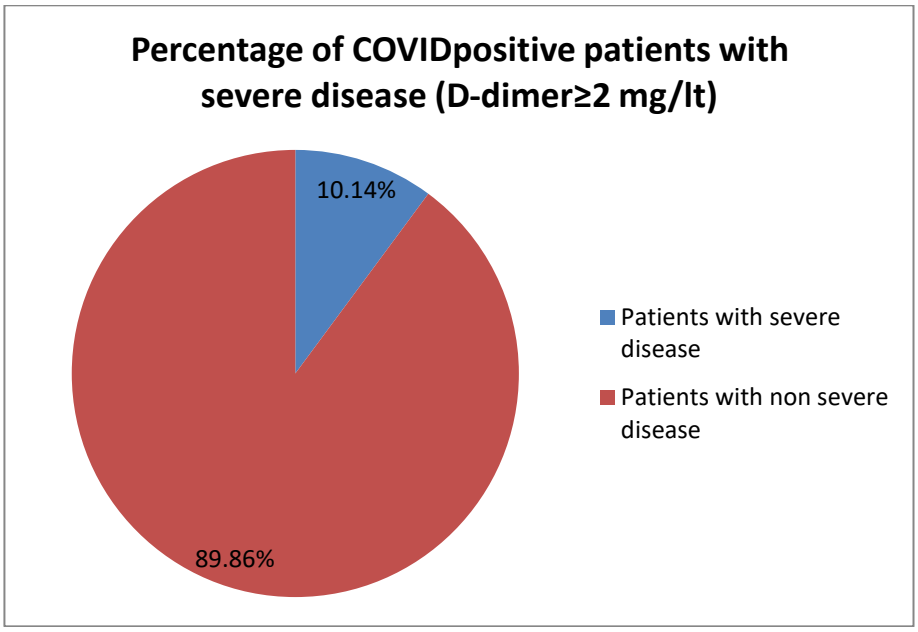

Fig 3: Percentage of COVID -19 patients with severe disease due to elevated D-dimerlevel(≥2mg/lt)

This is in consistence with the study conducted by Yao Y *et al*[2] where D-dimer >2mg/lt at admission was the only criteria associated with increased mortality in COVID-19 patients. Another study by Yu Hai-Han *et al*[10] report that D-dimer > 0.5 mg/lt is associated with severity of infection in patients with COVID -19.Abnormal D-dimer level is associated with poor prognosis due to formation of thrombus leading to embolism.Careful consideration should be made over conventional anticoagulation as there is increased risk of bleeding in patients with COVID -19.[3]

In the present study among 240 COVID-19 positive patients interleukin -6 (IL-6) level was found to be normal in 16 (6.66%) and in 224 (93.3%) patients it was found to be elevated. Percentage of patients with elevated IL-6 is shown in fig 4.

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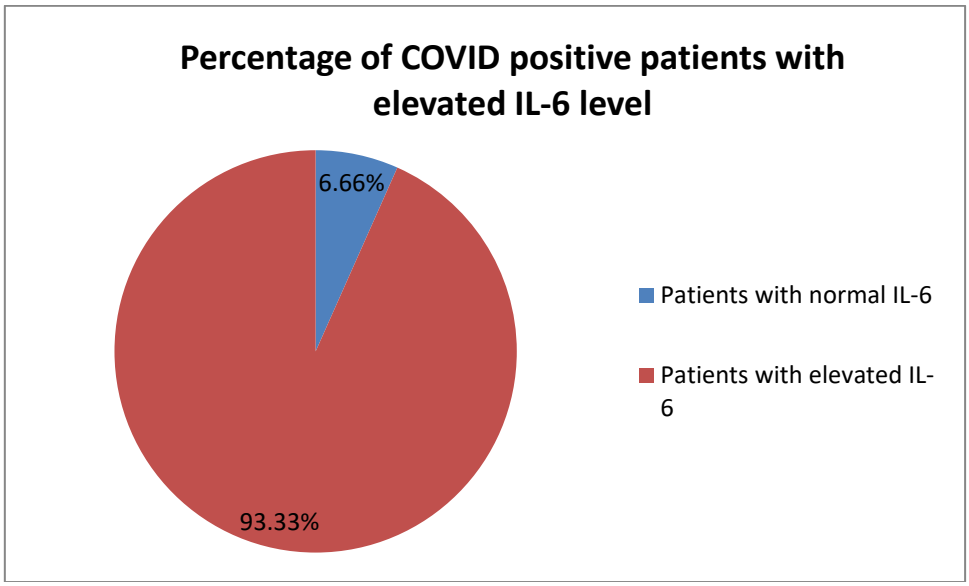

Fig 4: Percentage of COVID-19 positive patients with elevation in IL-6 level

Out of 224 patients with elevation in IL-6 levels 25 (11.16%) patients with severe form of the disease had IL-6 value ≥88pg/ml. IL-6 was higher as severity of the infection increased. The percentage of patients with severe form of disease due to elevated IL-6 level is shown in fig 5.

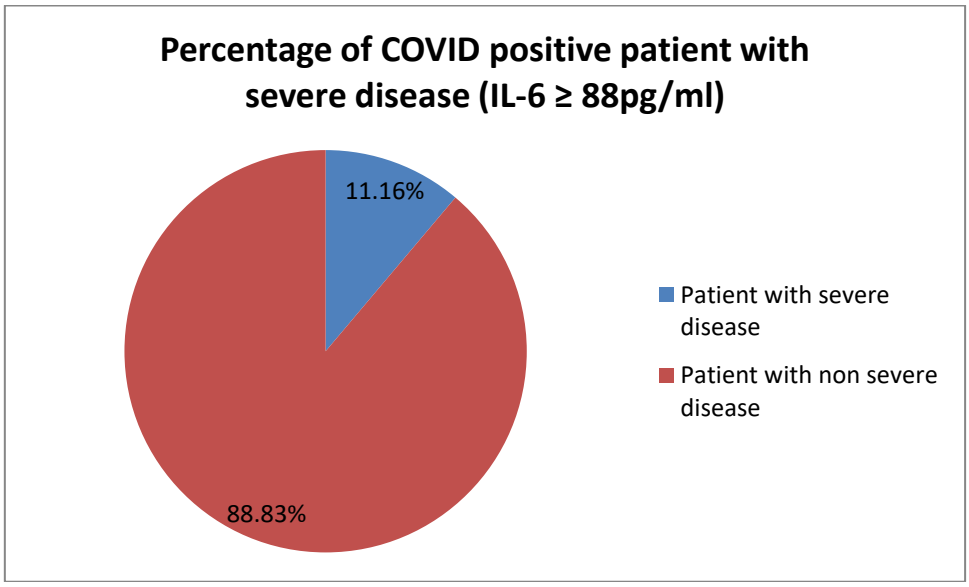

Fig 5: Percentage of COVID-19 patients with severe disease due to elevated IL-6 level(≥88 pg/ml)

Our data suggest that even moderately elevated IL-6 levels of about 88pg/ml are sufficient to cause respiratory failure in COVID-19 patients. This is also proved in the study conducted by Herold T *etal*[5] where the patients with IL6 levels ≥80pg/ml had high risk of respiratory failure compared to patients with low IL-6 levels. This is in contrast with the study conducted by Sabaka P *et al*[11] where the concentration of IL-6 > 24pg/ml denoted the development of disease severity like pneumonia leading to ARDS (acute respiratory distress syndrome) which causes acute hypoxemia leading to respiratory failure. According to previous studies IL-6 is superior to all inflammatory markers for the prediction of respiratory failure in COVID-19 and plays an important role in immune dysregulation and ARDS in COVID-19.[11]

In the present study among 240 COVID-19 positive patients ferritin level was found to be normal in 60(25%) and in 180 (75%)patients it was seen to be elevated . The percentage of patients with elevated ferritin level is shown in fig 6.

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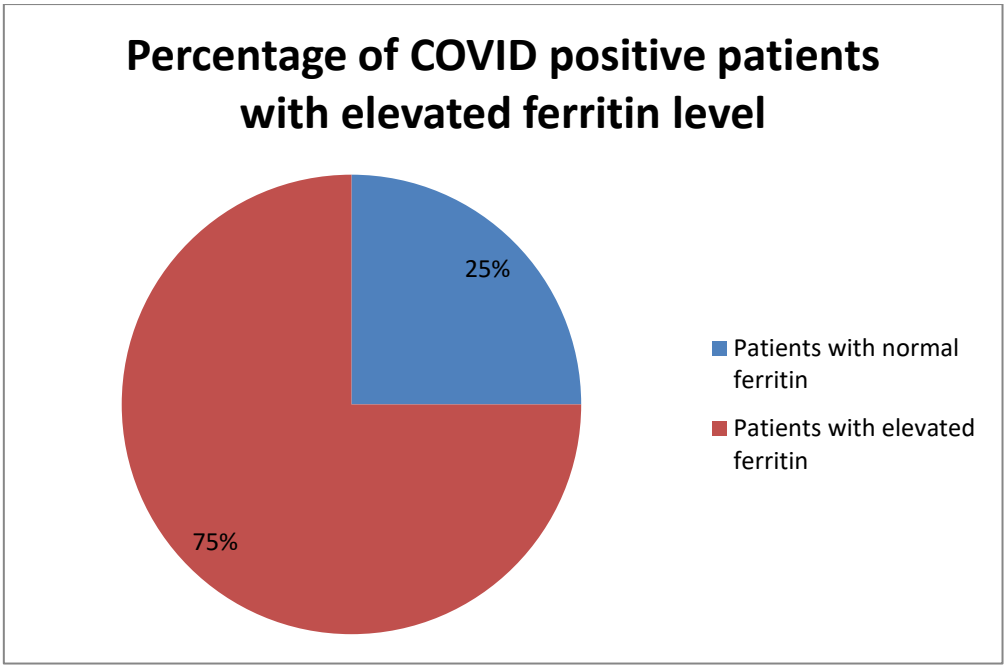

Fig 6:Percentage of COVID-19 positive patients with elevated ferritin level

Out of 180 patients with elevated ferritin level ,24 (13.33%) patients with severe type of the disease had serum ferritin values ≥450ng/ml.Percentage of patients with severe disease due to elevated ferritin level is shown in fig7.

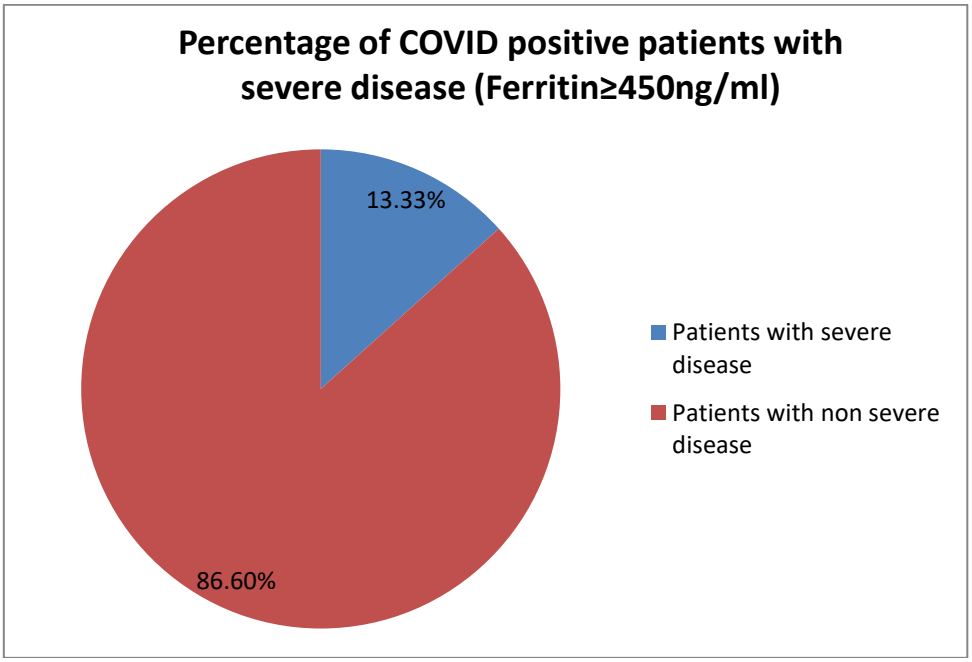

Fig 7:Percentage of COVID positive patients with severe disease (Ferritin ≥ 450 ng/ml)

The findings in present study is similar to the study conducted by Ahmed S *etal*[12]where hyperferritinemia (ferritin level > 400 ng/ml) was noted in patients with severe disease but is in contrast with the study conducted by Bozkurt TF *et al*[13] where ferritin level >264.5ng/ml was associated with severity of disease in COVID positive patients . Lab findings in patients with severe COVID-19 disease showed data congruous with cytokine storm involving inflammatory markers including ferritin , which has been found to be associated with critical and life threatening disease.[6]

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CONCLUSION

To put in a nutshell,in the current situation with overcrowded intensive care units and emergency rooms , correct triage of patients in need of intensive care is necessary. Biomarkers like D-dimer, Interleukin-6 and ferritin which can identify the severity and progression of disease should be monitored at the earliest. D-dimer levels in critically ill patients is significantly elevated .Aggressive anticoagulant therapy must be given for prophylaxis of venous thromboembolism. IL-6 is an effective biochemical marker that can predict the upcoming respiratory failure with high accuracy and help the physicians correctly apportion patients at an early stage. Ferritin concentration is also a promising predictor of mortality. Deferoxamine, a nontoxic iron chelator along with decreased dietry iron can modify serum ferritin levels and reduce worsening of COVID-19 disease , specially in individuals with morbidities cursing with elevated ferritin levels such as diabetes.Such patients with abnormal level of the above biochemical markers should be kept in intensive care unit at the earliest so as to prevent mortality from COVID-19 disease.

DECLARATION

ACKNOWLEDGEMENT

Department of microbiology. G.S medical college and Hospital, Pilkhuwa,Hapur.

CONFLICT OF INTEREST

Authors declare that there is no conflict of interest.

AUTHOR'S CONTRIBUTION

All the authors listed in this study have made a substantial and intellectual contribution to the work and approved it for publication.

ETHICS STATEMENT

Ethical clearance has been obtained by Institutional Ethical committee.

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