ORIGINAL RESEARCH PAPER

Pathology

A STUDY ON VARIATIONS IN INFLAMMATORY MARKERS PROFILE OF COVID-19 PATIENTS AND ITS CORRELATION WITH SEVERITY OF DISEASE.

KEY WORDS: Covid-19, Inflammatory Markers.

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ABSTRACT

Background: Since covid has emerged as the most dreadful global health crisis and data on diagnostic profile and morbidity mortality indicators in it is still limited, we propose to study the correlation of morbidity and mortality with values of Inflammatory markers in these patients. **Aim:** To STUDY variations in INFLAMMATORY MARKERS IN COVID-19 PATIENTS and correlating it with severity of disease. **Materials and Methods:** using CLIA technique, four inflammatory markers (TROPONIN -I , ferritin, procalcitonin, IL -6) were studied among 400 patients. This was correlated with severity of the disease outcome among the patients. **Results:** Among the inflammatory markers we studied IL-6 ,Ferritin,Troponin -I ,Procalcitonin. Raised values of IL-6 and raised ferritin levels were associated with severity. Troponin I (91%) ,Ferritin(70.8%) ,Calcitonin (78.5%) were increased but showed no association with mortality. However only IL-6 seems to be associated with increased mortality among Covid patients. **Conclusion:** On the basis of findings in this study Inflammatory markers particularly IL -6 and ferritin can be concluded as important predictors of disease severity and outcome.These parameters can be used to identify high-risk patients at resource-limited settings.

INTRODUCTION

Severe acute respiratory syndrome-coronavirus-2, a coronavirus, initiated an outbreak of pneumonia from Wuhan in China, which then spread all over the world resulting in more than 6 million deaths worldwide as of March 2022 and emerged as the most dreadful global health crisis since the era of the influenza pandemic of 1918. After the first cases ,SARS-CoV-2 rapidly spread across the world in a short period of time and the World Health Organisation (WHO) declared it as a worldwide pandemic on March 11, 2020. Since being declared a global pandemic, COVID-19 has spread to many countries worldwide and has overwhelmed many healthcare systems. The pandemic has also resulted in the loss of livelihoods due to prolonged shutdowns, which have had a bad effect on the global economy. Even though substantial progress in clinical research has led to a better understanding of SARS-CoV-2 and the management of COVID-19, continuous spread of this virus and its variants has become an issue of increasing concern.SARS-CoV-2 continues to create fear across the world, with many countries going through a second or third wave due to the emergence of mutant variants of the virus.

The clinical characteristics of the disease range from asymptomatic cases or mild nonspecific symptoms such as fever, cough, sore throat, headache, and nasal congestion to severe cases such as pneumonia, respiratory failure which require mechanical ventilation to multi-organ failure, sepsis, and death. As the transmission rate is high, we require an effective diagnostic and therapeutic strategy in order to contain the infection and prevent community transmission. The COVID-19 pandemic in India was first observed on 30 January 2020.which later progressed to having the largest number of confirmed cases in Asia. In India, from 3 January 2020 to 2 September 2022, there have been 4,44,42,507 confirmed cases of COVID-19 with 5,27,932 deaths, reported to WHO. In Madhya Pradesh , 10.5% confirmed cases were reported during this period.

Severe COVID-19 is commonly complicated with inflammatory markers that were associated with poor prognosis in severe COVID-19. Severe pneumonia can lead to abnormal coagulation.Systemic vasculitis and cytokine mediated coagulation disorders are the principal factors causing multi organ failure in patients with severe COVID-19 complications.

SARS-CoV-2 activates the innate immune system to kill the virus however, excessive immune responses can lead to inflammatory storms, damage microcirculation, activate the blood coagulation system, and lead to disseminated intravascular coagulation (DIC).However since covid is newly emerged and data on diagnostic profile and morbidity mortality indicators in it is still limited. Hence we propose to study the correlation of morbidity and mortality with inflammatory: IL-6, FERRITIN, TROPONIN-I, CALCITONIN.

AIMS AND OBJECTIVES

- To study inflammatory markers - Interleukin 6, Procalcitonin, Ferritin, Troponin- I, C- Reactive Protein in these patients
- To correlate morbidity and mortality of COVID-19 patients with above findings
- To determine the effect of above mentioned parameters on the prognosis of a patient.

MATERIALS AND METHODS : Study Design :

In this retrospective study we studied 400 confirmed COVID 19 positive patients aged 18 years and above admitted in Gajra Raja Medical College, Gwalior upto 31st June 2022 for a period of One and a half year. Ethical clearance was obtained from ethical committee of Gajra Raja Medical College, Gwalior .

Inclusion Criteria :

Cases confirmed with covid by RT-PCR were included in this study.

Exclusion Criteria :

COVID suspect and Non COVID home quarantine patients were excluded from the study.

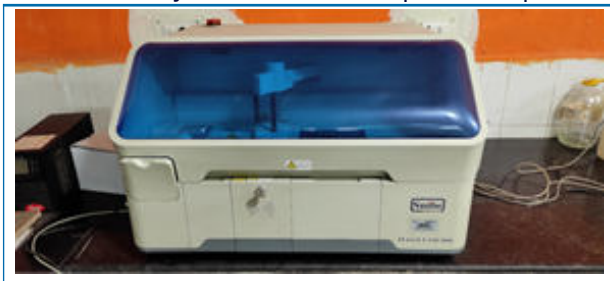

Figure: Snibe Meglumi 800 for IL-6, Ferritin, TROPONINI, PROCALCITONIN

For this we used the kit which is an In vitro chemilu minescence Immunoassay for the quantitative determination of PCT in human serum and plasma with the MAGLUMI 800 Fully-auto chemiluminescence immunoassay .

Specimen Collection And Preparation

Standard sampling tubes or tubes containing separating gel are used.Blood is collected aseptically following the universal precautions for venipuncture.

For plasma samples, the anticoagulant iEDTA-2K has been used. We ensure that complete clot formation in serum and plasma specimens has taken place prior to centrifugation. Some serum specimens, especially those from patients receiving anticoagulant or thrombolytic therapy, may exhibit increased clotting time.

If the serum and plasma specimen is centrifuged before a complete clotting, the presence of fibrin may cause erroneous results. Serum and plasma samples must be free of fibrin and other particulate matter.

For serum and plasma, do not use hemolyzed or grossly lipemic specimens as well as specimens containing particulate matter or exhibiting obvious microbial contamination.

Centrifuged serum and plasma specimens with a lipid layer on the top must be transferred to a sample cup or a secondary tube. Transfer only the clarified specimen without the lipemic material. Test all samples (patient specimens and controls) within 3 hours in MAGLUMI 800 System.

RESULTS

- Among our study population, 66% were males whereas 34% were females.
- Among 400 covid-19 patients, we observed the highest number of patients in the age group of 31-40 years (32.5%) whereas the least number were observed in the age group of >70 years (0.5%).
- 98% of patients had increased values of IL-6.
- 91 % patients had Troponin-I values above the range.
- 70.8% patients had increased level of Ferritin.
- 78.5% of patients had abnormal(increased) levels of Procalcitonin

Following parameters were significantly associated with severity :

- Mean ferritin of severe patients was highly significant (p=<0.0001).
- Mean age of severe patients was highly significant (p=<0.0001).
- Mean IL-6 of severe patients was highly significant (p=<0.0001).

We observed 8.8%(35/400) mortality among our study population.

Mortality :

8.75% mortality was observed among our study population. Out of 8.75% mortality patients, highest mortality observed in the age group of 31-40 years whereas least percentage of mortality observed in the age group of 21-30 years. It was associated significantly with raised ferritin levels.

	Alive (N= 365)	Median	Death(N=35)	Median	p-Value
Age	44.05±11.16	42.00	46.46±10	45.00	0.2135
IL-6	178.45±546.79	60.95	148.13±265.03	61.09	0.9172
TROPONIN-I	1.74±1.23	1.70	1.39±0.82	1.59	0.1587
FERRITIN	938.82±931.29	510.20	1494.58±865.98	1437.80	0.0002
CALCITONIN	1.90±13.26	0.19	0.5±1.14	0.19	0.9085

DISCUSSION

This was a retrospective study done by critical analysis of the information obtained from the pathology and medicine department of Gajra Raja Medical College, Gwalior (Madhya Pradesh) from 1st December 2016 to 31th June 2022. Following laboratory parameters were analysed and correlated with severity and mortality of patients:
Inflammatory Profile Analysis-IL-6, Troponine, Ferritine, Procalcitonin.

Inflammatory Profile Analysis - IL-6, Troponin, Ferritin, Procalcitonin

IL-6 :During covid 19, we observed 98% patients having abnormal levels of IL-6.Mean IL-6 had no significant association with mortality(p=0.9172) but was associated with severity . However, contradictory to our study Andre Santa Cruz et al 2021(1) suggested IL-6 levels were significantly raised in non survivors.

Troponin :During covid 19, we observed 91 % patients having abnormally increased level of Troponin-I. Gregorio Tersalvi et al ,2019(2) concluded Elevated troponin levels are frequent in patients with COVID-19 and significantly associated with fatal outcomes. Several mechanisms may explain this phenomenon like viral myocarditis, cytokine-driven myocardial damage, microangiopathy, and unmasked CAD.

Ferritin: During covid 19, we observed 70.8% patients having abnormally high levels of Ferritin. Mean ferritin of alive observed highly significant compared to dead patients of mean ferritin(p=0.0002).Mean Ferritin of Severely affected patients was high to mean Ferritin of moderately affected patients(p=<0.0001) so ferritin levels can be concluded to be associated with disease severity and mortality.Similar findings were seen in study done by Daniela Cihakova et al ,2021 (3) in which Ferritin was significantly elevated in severe cases of COVID-19[4-9]. In another study of 229 COVID-19 patients, a ferritin level >750 ng/ml was an independent predictor of death.

Procalcitonin :During covid 19, we were observed 78.5% patients having increased level of Procalcitonin.Mean procalcitonin of alive and dead patients had no significant difference between them.(p=0.9085)

However a study done on Procalcitonin levels in COVID-19 patients, Rui Hu, Xiang Chen, August 2020(10) showed that PCT can be an indicator of disease severity and may contribute to determining the severity of patients with COVID-19. Sagar S Maddani et al(11) concluded High ferritin as independent predictors of admission in critical care units.

Univariate analysis of demographic and laboratory data showed higher age, male sex,higher values of ferritin to be significant like our study .Multivariate logistic regression analysis of these significant variables showed ferritin to be the independent predictors of the requirement of admission to a critical care unit.

SUMMARY

The present study comprises the retrospective study of 400 cases of covid positive patients from 1st December 2020 to 30 th June 2022 in the department of pathology, Gajra Raja Medical College, Gwalior(M.P.)

The salient findings of present study (2022) are summarised as follows-

- Among 400 patients , 78% had severe covid and mortality was seen in 8.8 % cases.
- Most common presentation is in the 31-40 yrs age group (32.5 %) followed by the 41 -50 yrs age group (27.5%).
- Only 1% presented before 20 yrs of age.
- Higher aged patients were more severely affected .
- Males were affected more commonly with the sex ratio of 1.94 :1.
- Among the inflammatory markers we studied which included IL-6,Ferritin,Troponin -I ,Procalcitonin. Raised values of IL-6 and raised ferritin levels were associated with severity. Troponin I (91%) ,Ferritin(70.8%), Calcitonin (78.5%) ,CRP (89%) were increased but showed no association with mortality.Howe ever only IL-6 seems to be associated with increased mortality among Covid patients.

CONCLUSION

Among the inflammatory markers we studied raised values of IL-6 and ferritin were associated with severity and ferritin was also associated with mortality .

We can conclude IL-6 ,Ferritin as important predictors of disease outcome in COVID-19 patients and advice these two to be monitored for prognosis and treatment strategy .

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