Original Research Article

COMPARATIVE STUDY OF SERUM FERRITIN WITH C- REACTIVE PROTEIN SERUM ADENOSINE DEAMINASE, AND OTHER BIOCHEMICAL PARAMETERS IN COVID-19 PATIENTS

ABSTRACT: - In COVID-19 pandemic clinical assessment is indispensable, but laboratory markers, or biomarkers, can provide additional, objective information which can significantly impact these components of patient care. COVID-19 is not a localized respiratory infection but a multisystem disease caused by a diffuse systemic process involving a complex interplay of the immunological, inflammatory and coagulative cascades. The understanding of what the virus does to the body and how the body reacts to it has uncovered a gamut of potential biomarkers. Our study demonstrates the different classes of biomarkers – immunological, inflammatory, cardiac, biochemical in terms of their pathophysiological basis. The correlation of serum ferritin with CRP, ADA and biochemical parameters predicting cardiac injury, liver injury and renal injury were evaluated. Serum ferritin and CRP was found to be significantly elevated with the disease severity. Serum ADA levels were also significantly different in group with high ferritin, which demonstrate that increased ADA leads to low adenosine, which is further responsible for exaggeration of inflammatory response in Covid-19. This suggest the protective role of adenosine in COVID 19. CKMB and LDH also serves as important biomarkers for cardiac injury and was found to be significantly different in groups with high ferritin which also suggestive of myocardial damage. Hepatic and renal bio parameters were also significantly different in groups with high ferritin levels, which is also suggestive hepatic and renal damage.

KEYWORDS:- Serum ferritin, CRP,ADA, biochemical markers, Covid-19

INTRODUCTION:

Coronavirus disease 2019 (COVID-19) is a global pandemic caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), it is now being recognized as a multisystem disease which may cause even death. Hence timely diagnosis and proper intervention is needed for better prognosis. Accordingly, COVID-19 has focused attention not only on mechanisms by which the disease-causing coronavirus enters and infects the host but also on new treatment strategies.

Several laboratory investigations have been associated with worse outcomes in patients with COVID-19, of them acute phase reactants or inflammatory biomarkers have important role such as Ferritin and C-Reactive Protein (CRP). Moreover, identification of laboratory parameters capable of discriminating between severe and non-severe cases, or those at high or low risk of mortality, will allow for improved clinical situational awareness.

"The massive release of pro-inflammatory mediators and the aberrant activation of the immune and coagulation systems, resembles the so-called cytokine release syndrome, a group of conditions sharing the same pathogenic mechanism, although with a different aetiology""[1].

"This cytokine storm accounts for the two main causes of mortality in COVID-19, ARDS and secondary haemophagocytic lymphohistiocytosis, the latter occurring in a small subset of patients"[2]. "Furthermore, since increased levels of ferritin along with a cytokine storm have been described in patients with severe COVID-19" [3], "it has been speculated that COVID-19 may be included in the spectrum of the hyperferritinemic syndromes"[2].

Adenosine deaminase (ADA) in humans is involved in the development and maintenance of the immune system. However, ADA association has also been observed with epithelial cell differentiation, neurotransmission, and gestation maintenance[4]. It has also been proposed that ADA, in addition to adenosine breakdown, stimulates release of excitatory amino acids and is necessary to the coupling of A1 adenosine receptors and heterotrimeric G proteins.[5] Adenosine deaminase deficiency leads to pulmonary fibrosis,[6] suggesting that chronic exposure to high levels of adenosine can exacerbate inflammation responses rather than suppressing them. The augmented activity of ADA in viral pneumonia further supports the role of this enzyme as a marker of stimulated cell-mediated response. ADA activity has been shown to be especially high in T cells and macrophages, and an increased activity of serum ADA has been associated with conditions involving lymphocyte proliferation and macrophage activation, i.e. a stimulated cell- mediated immune response [7,8]. In viral infections, the first line of defence in the lower respiratory tract is the pulmonary macrophage. At the mucosal level, the immune response involves natural killer cells and T lymphocytes. At later stages, viral infections may transiently suppress the alveolar macrophage phagocytic system.

Patients with severe COVID-19 appear to have more frequent signs of liver dysfunction than those with milder disease. An increase in alanine aminotransferase (ALT), aspartate aminotransferase (AST) and total bilirubin levels has been observed among many ICU patients.[9] Infection of liver cells with SARS-CoV-2 cannot be excluded as 2–10% of patients with COVID-19 have diarrhoea and viral RNA has been detected in both stool and blood samples, which implies the possibility of hepatic virus presence.[10] It is also likely that any immune-mediated inflammation, in particular cytokine storm, but also pneumonia-associated hypoxia, may lead to liver damage in critically ill COVID-19 patients.[9] C-reactive protein (CRP) levels are increased in COVID-19 patients and it has been shown that survivors had median CRP values of approximately 40 mg/L, while non-survivors had median values of 125 mg/L, indicating a strong correlation with disease severity and prognosis.[3]

AIMS AND OBJECTIVES:-

The objective of this study is to see

1) association of serum ferritin levels of hospitalised COVID 19 patients with severity of COVID 19
2) We also aim to see the association of serum ferritin levels with CRP, ADA and other biochemical parameters.
3) We also aim to study whether serum ferritin or serum adenosine deaminase is better in predicting the severity of Covid 19.

STUDY DESIGN AND PARTICIPANTS: -

This retrospective cohort study included two cohorts of adult patients(≥18years old) public sector government hospital in India. All adult patients who were diagnosed with COVID-19 according to WHO interim guidance were screened, and those who died or were discharged between June 2020), and July, 2020, were included in our study. Since the hospitals were the designated hospitals for transfer of patients with COVID-19. Our study enrolled all adult patients who were hospitalised for COVID-19 and had a definite outcome (dead or discharged) at the early stage of the outbreak.

We studied serum ferritin levels in all study subjects and corelated it with serum C- reactive protein, adenosine deaminase (ADA)and other biochemical parameters like SGOT, SGPT, Alkaline phosphatase, Total protein, serum Albumin, serum total bilirubin and Direct bilirubin, blood urea and serum creatinine with respect to the severity of the disease.

METHODS:-

All the biochemical parameters were done on auto analyser Serum ferritin was estimated by turbidometry immunoassay, ADA was estimated by PNP- XOD/ Kinetic method , CRP by immunoturbidometric assay, SGOT, SGPT by IFCC without pyridoxal phosphate, Alkaline phosphatase by AMP method, Total protein by Biuret method, serum Albumin by BCG method, serum total bilirubin and Direct bilirubin by Diazo method, Blood urea by Urease and Serum Creatinine by Modified Jaffe's Method.

STATISTICAL ANALYSIS: -
Data was entered into computer database using Microsoft excel spread sheet. The quantitative variables were expressed in terms of mean and standard deviation. The means of two groups were compared by using unpaired t-test. The means of more than two groups were compared by using One wat ANOVA test followed by post hoc Bonferroni test. P value less than 0.05 was considered as significant. The analysis was done by using the Statistical Software SPSS version 21
OBSERVATIONS AND RESULTS: -

Table no. 1

FERRITIN DISTRIBUTION :-

PARAMETER	<=200	200-500	500-1000	>1000
SERUM FERRITIN	104	48	36	26
PERCENTAGE	48.60	22.43	16.82	12.15

Table no. 2 AGE AND GENDER WISE DISTRIBUTION OF CASES

Age in years	Male	Female	Total
<=15	2	6	8
15-25	7	11	18
25-45	36	47	83

45-60	41	28	69
>60	21	15	36
Total	107	107	214

Table no. 3
GENDER WISE DISTRIBUTION OF PATIENTS ACCORDING TO SERUM FERRITIN LEVEL

Serum Ferritin	Male	Female	Total
<=200	33	71	104
200-500	34	14	48
500-1000	26	10	36
>1000	14	12	26
TOTAL	107	107	214

Table no. 4
GENDER WISE DISTRIBUTION

Serum Ferritin	Male	Female	Total	P value
<= 500	67 (62.61%)	85(79.44%)	152	0.006
>500	40 (37.39%)	22(20.56%)	62	
Total	107	107		

Table no. 5
MEAN SERUM FERRITIN LEVEL IN MALES AND FEMALES

GENDER	Mean ferritin	P- value
FEMALE	532.24+- 1508.20	0.786
MALE	580.33+- 1029.47	Not significant

Table no. 6

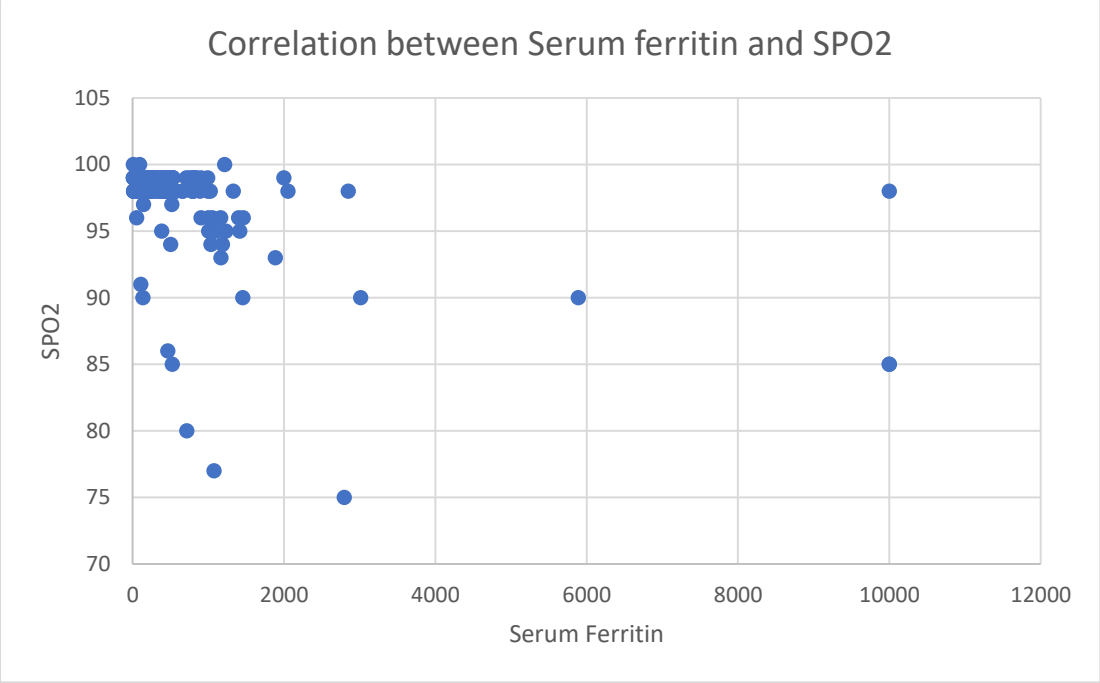
CORRELATION SERUM FERRITIN LEVELS WITH OTHER BIOCHEMICAL PARAMETERS

Parameters	Serum ferritin	Number	Mean	Std. Deviation	P value	Remark
CRP (0-5)	< = 200	104	17.5191	32.15430	0.000	CRP values for serum ferritin
	200- 500	48	15.4046	21.29573		

	500-1000	36	31.1869	30.11805		>1000 was significantly different from<= 200,200-500 and 500-1000
	>1000	26	59.9792	25.434777		
ADA	< = 200	104	13.1332	6.21567	0.000	ADA values for serum ferritin>1000 was significantly different from<= 200,200-500 and 500-1000
	200- 500	48	16.1629	6.20561		
	500-1000	36	16.4842	6.64242		
	>1000	26	23.3062	17.99416		
LDH	< = 200	104	402.837	122.5039	0.000	No significant difference was found between serum ferritin <= 200& 200-500 and 500-1000 & >1000
	200- 500	48	559.854	443.2383		
	500-1000	36	822.222	653.6104		
	>1000	26	733.654	520.6285		
SGOT	< = 200	104	32.038	26.2290	0.000	Significant between < = 200 and >1000 And 200-500 and >1000
	200- 500	48	40.667	18.6757		
	500-1000	36	45.944	30.3314		
	>1000	26	62.462	63.8763		
SGPT	< = 200	104	22.806	14.1602	0.000	Significant between < = 200 and 200-500 and < = 200>1000
	200- 500	48	39.688	32.8460		
	500-1000	36	34.167	20.5197		
	>1000	26	49.269	62.4862		
ALKALINE PHOSPHATASE (ALP)	< = 200	104	91.385	44.2972	0.009	Significant between < = 200 and >1000 And 200-500 and >1000
	200- 500	48	95.833	42.1721		
	500-1000	36	106.139	64.9787		
	>1000	26	180.346	320.2162		
TOTAL PROTEIN	< = 200	104	7.441	6.5354	0.170 NS	
	200- 500	48	10.308	14.4952		
	500-1000	36	7.808	9.0106		
	>1000	26	5.812	0.9167		
ALBUMIN	< = 200	104	4.104	0.6503	0.022	significant between <=200 and
	200- 500	48	3.902	0.4724		
	500-	36	4.300	4.4617		

	1000					>1000 and 500-1000 and >1000
	>1000	26	2.896	.7660		
TOTAL BILIRUBIN	< = 200	104	0.5009	0.33160	0.000	>1000 significantly difference with <=200, 200-500 and 500-1000
	200- 500	48	0.7563	0.95448		
	500-1000	36	0.8944	0.5132		
	>1000	26	1.7308	2.15940		
SERUM CREATININE	< = 200	104	0.882	0.3180	0.000	>1000 significantly differ with <=200,200-500 and 500-1000
	200- 500	48	1.104	.3826		
	500-1000	36	1.022	.2799		
	>1000	26	1.808	1.5197		
BLOOD UREA	< = 200	104	24.587	11.2764	0.000	Significant difference except <=200 and 200-500
	200- 500	48	29.104	13.7690		
	500-1000	36	41.750	22.1222		
	>1000	26	63.308	41.3142		
CK-MB	< = 200	104	16.4725	10.46267	0.015	Significant difference between <=200 and 500-1000
	200- 500	48	16.3781	9.24443		
	500-1000	36	25.6147	39.33128		
	>1000	26	25.4231	7.99852		
SPO2	< = 200	104	98.394	1.2651	0.000	SPO2 values for serum ferritin> 1000 was significantly different from<= 200,200-500 and 500-1000
	200- 500	48	98.208	1.9347		
	500-1000	36	97.306	3.8383		
	>1000	26	93.038	6.3213		

Scatter diagram showing correlation of serum ferritin with SPO2



i) We also tried to establish the correlation in between ferritin and SPO2, and it was found to be -0.457. This indicates that higher values of SPO2 are associated with lower values of ferritin and the result is statistically significant(P=0.000<0.05)

ii) CORRELATION BETWEEN SER. FERRITIN AND SPO2 in females and males. We found females is -0.552 and in males it is -0.393. Both are significant .This indicates that in males as well as females, more is the SPO2 less is serum ferritin value or less is the SPO2 more is the ferritin. By converting correlation to z score and comparing them, it was found that difference between two correlations is not significant (p>0.05). This indicates that magnitude of severity in males and females is same.

DISCUSSION: -

Though most patients with COVID- 19 have suffered from mild symptoms without pneumonia, a large proportion of patients developed respiratory distress leading to death. The majority of patients was found between the age group of 25-45years and 45-60 years, whereas there were only 6 patients below 15 years. COVID-19 shows an increased number of cases and a greater risk of severe disease with increasing age.[11,12] Age-varying susceptibility to infection by SARS-CoV-2, where children are less susceptible than adults to becoming infected on contact with an infectious person, would reduce cases among children. Decreased susceptibility could result from immune cross-protection from other coronaviruses.[13,14,15] Age distribution was almost same in both the gender. We also found the prevalence of disease was same in both the gender.[16] The previous reports,[17,18,19] older patients (≥65 years old), were more likely to have a *Severe* type of COVID-19. Men tended to develop more severity than women. We found 40 men were having ferritin levels more than 500 whereas there were only 22 females having ferritin levels above 500, and difference is statistically significant (p =0.006). This indicates that the number of males exceeds in severity as compared to females. Which indicates the high risk for men with COVID-19 for severe outcomes and death.[16]

This has led the researchers to explore effective predictors of disease severity that can help in assessing the severity of disease. In our study we found 104 cases of hospitalized Covid 19 were having serum ferritin within normal range. These 104 cases were having mean SPO2 98.394, which also suggest that ferritin level is not increased in non-severe Covid 19 patients, whereas in 26 patients with serum ferritin level more than 1000 the mean SPO2 was found to be 93.038 which suggest that hyperferritinemia occurs with the disease severity, or hyperferrintenemia may be responsible for the worsening of disease. So, there is strong association of ferritin levels with the severity of the disease[20]. The CRP values were significantly high in patients with ferritin >1000 i.e. 59.97 where the mean SPO2 was 93.038 indicating a strong association of CRP with the severity and the prognosis of the disease.[3] "In the systemic hyperinflammation phase of COVID-19 proposed by Siddiqi and Mehra"[21], "there is a significant elevation of inflammatory cytokines and biomarkers, such as interleukin (IL)-2, IL-6, IL-7, granulocyte-colony stimulating factor, macrophage inflammatory protein 1-α, tumour necrosis factor-α (TNF-α), CRP, ferritin, PCT, and D-dimer. This stage consists of the most severe manifestation of the cytokine storm, in which excessive hyperinflammation may lead to cardiopulmonary collapse and multi-organ failure".[21,22] Both CRP and ferritin are significant crucial markers in predicting the severity of the disease as well as the prognosis of the disease.[23,24,25]

ADA values in patients with serum ferritin>1000 were significantly high from the patients with serum ferritin <= 200,200-500 and 500-1000 which suggest the role ADA in immunomodulation. High ADA levels may cause low adenosine which is further responsible for inflammation. The role of adenosine in attenuating and modulating an excessive inflammatory response is emerging. In experimental ischemia/reperfusion models, adenosine and its agonists have been shown to block infiltration, trafficking, activation of PMNs and production of superoxides, with mitigation of reperfusion damage.[26] "By the adenosine signaling, platelets, endothelial cells, macrophages, T cells, and mast cells are also modulated for an anti-inflammatory action".[27] "Given these properties, adenosine could be used to treat acute lung injury (ALI) and ARDS".[28,29] "In fact, the response of PMNs to adenosine and the presence of receptors for it on the human lung reinforce this hypothesis".[30] "In many animal models of ALI and ARDS, adenosine or specific agonists have shown the ability to reduce inflammation, regulate endothelial integrity, and balance lung fluids".[30,31,32,] „Serum ADA reflects lymphocyte activation as part of the immune response. Although the pathophysiology of COVID-19 remains largely enigmatic, recent studies identified similarities with Middle East Respiratory Syndrome CoronaVirus (MERS-CoV) and SARS-CoV" .[33] Adenosine and the key adenosine regulators adenosine deaminase (ADA), adenosine kinase (ADK), and equilibrative nucleoside transporter 1 may play a role in COVID-19 pathogenesis. Researches have highlighted 1) the non-enzymatic role of ADA by which it might out-compete the virus (SARS-CoV-2) for binding to the CD26 receptor, 2) the enzymatic roles of ADK and ADA to increase adenosine levels and ameliorate Advanced Respiratory Distress Syndrome, and 3) inhibition of adenosine transporters to reduce platelet activation, thrombosis and improve COVID-19 outcomes. Depending on the stage of exposure to and infection by SARS-CoV-2, enhancing adenosine levels by targeting key adenosine regulator like ADA and monitoring its levels might be of prognostic and therapeutic use against COVID-19. "A crucial role of ADA is in the development and function of the immune system. In particular, it has been observed that this catabolic enzyme, regulating extracellular adenosine levels, takes a significant part in the regulation of adenosine receptor activation by endogenous adenosine, with a deep impact in the tuning of immune cell responses under adverse conditions".[34] A number of ADA inhibitors have been designed and synthesized, classified as ground-state

and transition-state inhibitors. Drugs that affect adenosine-related mechanisms might find use against SARS-CoV-2 infection and clinical features of COVID-19.

"SARS-CoV-2 uses the ACE2 receptor to facilitate viral entry into target cells, causing multiorgan dysfunction".[35] Ischaemic reperfusion injury and cytokine storm causes secondary damage to the organs. Persistent damage to cardiomyocytes causes persistent LDH elevation. "A study showed that LDH elevation can reflect the severity of tissue injury and inflammation".[36] In our study LDH levels were increased in almost all groups, there was significant difference in between the all groups except ferritin levels 500-1000and >1000. Persistent disease progression may lead to irreversible multiorgan failure and can ultimately lead to death.CK-MB is significantly high between <=200 and 500-1000 and also significantly high which is suggestive of damage to the myocardial cells. "The mechanisms include direct infection of myocardial injury, specific binding to functional receptors on cardiomyocytes, and immune-mediated myocardial injury. These mechanisms are not independent and exist strictly in a temporal sequence, as there is a large possibility that these three injury modes simultaneously exist and act together to result in permanent cardiomyocyte loss".[37] In our study, the patients with ferritin >1000, demonstrated low levels of CKMB which may due to short half-life of CKMB. Early myocardial injury can be predicted in patients with ferritin 500-1000, and as ferritin levels increases with due time , due to the short half-life of CKMB the levels may eventually decrease. Biochemical parameters of liver injury like SGOT, SGPT, alkaline phosphatase and total bilirubin is also significantly increased in patients with ferritin >1000, which is similar to previous studies except Albumin was significantly low in ferritin >1000 and other groups and total protein was not significant. "Hypoalbuminemia in critically ill patients is multifactorial and is attributed to increased capillary permeability, decreased protein synthesis, increased turnover, decreased serum albumin total mass, increased volume of distribution, and increased expression of vascular endothelial growth factor. Although common, the exact temporal association of hypoalbuminemia is yet to be studied".[38] Parameters of kidney injury like blood urea and serum creatinine also shows same difference, which may be secondary to inflammation, ischemia and cytokine storm. Our results were similar to the previous researches.[39,40]

CONCLUSION:-

There is a crucial need to better recognize the full laboratory spectrum of COVID-19 and factors responsible for immunomodulation in COVID 19. Inflammatory markers like CRP and ferritin plays a crucial role in predicting the severity of the disease. ADA is elevated which causes low adenosine levels ,so may accentuate inflammation in COVID 19. ADA needs further attention and extensive research at various stages of COVID 19 and . With the disease severity liver and kidney are also damaged due hyperinflammation, ischemia and cytokine storm. Drugs that affect adenosine-related mechanisms might find use against SARS-CoV-2 infection and clinical features of COVID-19.

Limitations :-

1) It is a retrospective study and patients irrespective of underlying co morbidities were included in the study which may affect the biomarkers.
2) Confounding factors such as concomitant medication status and socioeconomic background and clinical history were not taken into consideration.

3) More extensive research about ADA and other biomarkers should be done according to the stage of the disease.

Ethical Approval and Consent:

The study was approved by the Institutional Research Ethics Committee and the online verbal informed consent was taken.

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