

**Association of inflammatory markers with the severity of Covid -19****Minakshi Kumari<sup>1</sup>, Sunil Kumar Verma<sup>2</sup>, Vinod Kumar<sup>3</sup>, Shashi Bala Nag<sup>4\*</sup>**<sup>1</sup>Tutor, Department of Biochemistry, SNM Medical College, Dhanbad, Jharkhand, India<sup>2</sup>Associate Professor, Department of Biochemistry, SNM Medical College, Dhanbad, Jharkhand, India<sup>3</sup>Assistant Professor, Department of Biochemistry, SNM Medical College, Dhanbad, Jharkhand, India<sup>4</sup>Assistant Professor, Department of Biochemistry, SNM Medical College, Dhanbad, Jharkhand, India

Received: 19-06-2021 / Revised: 18-07-2021 / Accepted: 21-08-2021

**Abstract**

**Background:** COVID-19 has affected the entire human population of world. It is a pandemic causing deaths of millions of people across the globe. The levels of some inflammatory markers like CRP, ferritin, LDH, TLC, D-dimer, Procalcitonin, and IL 6 are closely connected with severity of inflammation in COVID 19 patients, according to statistical analyses, and an altered level indicates a poor prognosis. There is need to evaluate the association of severity of COVID 19 with some of the important inflammatory markers like CRP, ferritin, LDH, TLC, D-dimer, Procalcitonin and IL 6. **Objective:** To evaluate the association of severity of COVID 19 with some of the important inflammatory markers like CRP, ferritin, LDH, TLC, D-dimer, Procalcitonin and IL6. **Methods and Materials:** The study was conducted in the Department of Biochemistry, S.N.M.M.C., Dhanbad from January 2021 to July 2021. A total of 150 patients with positive RT PCR were included. Serum samples taken and run on MAGLUMI series and reported for CRP, Ferritin, LDH, Procalcitonin, D-dimer, TLC and IL 6. The quantitative determination of PCT, D-DIMER, IL-6 in human serum and plasma was carried out with MAGLUMI series fully automated chemiluminescence immunoassay analyser, while C reactive (CRP) in human serum of plasma was evaluated by Latex-enhanced turbidimetric immunoassay. **Results:** There were 150 patients in total, with 59 females and 91 men. All of the parameters were evaluated on all of the patients. Males were 47.77±14.38 years old on average, while females were 42.23±17.32 years old on average. Only four of the six indicators, CRP, D-Dimer, Ferritin and IL6, achieved statistical significance in the research, with a p value of 0.01. The remaining three indicators, TLC, LDH and procalcitonin, were all non-significant. The p value for D-Dimer was 0.59, TLC p value was 0.07, procalcitonin p value was 0.32. **Conclusion:** CRP, D-Dimer, Ferritin and IL6 had significance correlation with severity of COVID 19 whereas rest three indicators like TLC, LDH & Procalcitonin had no significant correlation with severity of COVID 19.

**Keywords:** COVID -19, Inflammatory markers

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**Introduction**

COVID-19 has affected the entire human population of world. It is a pandemic causing deaths of millions of people across the globe. The majority of those infected with Covid 19 will experience mild to moderate sickness and recover without the need for hospitalisation. The following are the most prevalent symptoms: Fever, dry cough, weariness, aches and pains, sore throat, conjunctivitis, headache, loss of smell and taste, rash on skin or discolouration of fingers or toes, difficulty breathing or shortness of breath, chest pain, loss of speech or movement are all symptoms that might occur. The levels of some inflammatory markers like CRP, ferritin, LDH, TLC, D-dimer, Procalcitonin and IL 6 are closely connected with severity of inflammation in COVID 19 patients, according to statistical analyses, and an altered level indicates a poor prognosis [1].

CRP is a cytokine-induced acute phase protein that rises in concentration in response to inflammation, making it a useful early indicator of infection and inflammation. CRP has a more sensitive assay than ESR or leukocyte count, and its levels rise and return to normal faster after the sickness has passed.

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CRP levels are closely connected with severity of pulmonary inflammation in COVID 19 patients, according to statistical analyses, and an elevated CRP level indicates a poor prognosis. When a pathogen enters the body, inflammatory cytokines are overproduced to combat it, and when they become hyperactive, they can harm the lungs and other internal organs. Silent hypoxia (insufficient oxygen delivery to bodily components) results in trauma, shock, heart failure, heart attack, and multiple organ failure, which raises CRP levels [2].

When a blood clot dissolves in the body, one of the protein fragments formed is a D-dimer. It isn't found in human blood plasma regularly. D dimer tests are utilised to rule out the presence of a blood clot that isn't healthy (thrombus). Patients with Covid 19 are frequently tested for D Dimer. Autopsies performed recently on 12 patients with Covid 19 revealed deep vein thrombosis in the most severe cases, while pulmonary embolism was the predominant pathological finding in two of the cases. The clinical cause of death mentioned this explicitly. D dimer levels correlate with illness severity in SARS Cov 2 patients according to studies and are a reliable predictive predictor for in-hospital mortality in COVID 19 patients [3].

Body cannot synthesize iron of its own and it absorbs iron from diet. The majority of ingested iron is used to make RBCs, with the remainder being retained as ferritin. In all organisms, it is a significant intracellular iron store protein. When the Corona virus enters the body, the body produces an excess of cytokines to combat the infection. Internal infection and inflammation are caused by this cytokine storm, which damages internal organs. When cells are destroyed, ferritin is released into the bloodstream, resulting in hyperferritinemia. According to recently published guidelines, longitudinal monitoring of a written while hospitalisation may aid in the identification of severe patients and the prediction of Covid 19 severity in hours clinical prognosis [4].

LDH is an enzyme that can be present in almost every living cell. As it converts NAD+ and NADH, LDH catalyses the conversion of lactate to pyruvate and back. A dehydrogenase is a molecule-to-molecule hydride transfer enzyme. Because it is released after this damage, LDH is widely expressed in bodily tissues such as blood cells and heart muscle, and it serves as a marker for common injuries and disorders such as heart failure. Because LDH is found in lung tissue (isoenzyme 3), patients with severe Covid-19 infections can expect to release more LDH into the bloodstream, resulting in a severe form of interstitial pneumonia that commonly progresses to acute respiratory distress syndrome. The contribution of distinct LDH isoenzymes to the LDH rise seen in COVID-19, on the other hand, has yet to be determined [5]. Thyroid parafollicular C cells ordinarily manufacture and release PCT, a 116-amino-acid precursor of the hormone calcitonin. During bacterial infection, however, it can be generated in numerous extrathyroid organs, which is mediated by elevated levels of tumour necrosis factor alpha (TNF alpha) and interleukin 6 [6].

IL-6 is an important pro-inflammatory cytokine and has been associated with more rapid disease progression and a higher complication rate in COVID-19 cases. Accumulated evidence so far has demonstrated cytokine storm syndrome is associated more severe disease and complications [7]. On the other hand, COVID-19 anosmia cases have milder disease. Based on these observations, we aimed to investigate the relationship between IL-6 levels and presence of COVID-19 related anosmia. We aimed to provide overview of association of inflammatory markers with severity of Covid 19.

**Methods and materials**

The study was conducted in the Department of Biochemistry, S.N.M.M.C., Dhanbad from January 2021 to July 2021. Ethical clearance was obtained from the ethical committee of the institution. A total of 150 patients with positive RT PCR were included. A written informed consent was obtained from each patient. Serum samples taken and run on MAGLUMI series and reported for CRP, FERRITIN, LDH, Procalcitonin, D-dimer, TLC and IL 6. The quantitative determination of PCT, D-DIMER, IL-6 in human serum and plasma was carried out with MAGLUMI series fully automated chemiluminescence immunoassay analyser, while C reactive (CRP) in

human serum of plasma was evaluated by Latex -enhanced turbidimetric immunoassay.

**Inclusion Criteria**

- i) Patients with positive RT PCR were included
- ii) Patients who had CRP, FERRITIN, LDH, Procalcitonin, D-dimer, TLC and IL 6 in the serum at the time of admission to the hospital were included in the study.
- iii) Patients who gave their informed written consent were included.

**Exclusion Criteria**

- i) Pediatric and pregnant patients were excluded
- ii) Patients with history of head trauma, preexisting smell and taste alterations for any other reason were excluded
- iii) Patients with allergic rhinitis and chronic rhinosinusitis based on clinical history and CT findings were excluded.

**Statistical Analysis**

All statistical analysis was performed with NCSS (Number Cruncher Statistical System, 2007, Kaysville, Utah, USA). Descriptive statistics were expressed as number and percentage for categorical variables and as mean, standard deviation, median, minimum, and maximum for numerical variables. Shapiro-Wilk test was used to determine whether the data showed normal distribution. Student-t-test and Mann-Whitney U test were used for parametric and nonparametric data, respectively. For categorical variables, chi-square, Fisher's exact and Fisher-Freeman-Halton exact-tests were used. Spearman test was used for correlation.

**Statistically Significant Criteria**

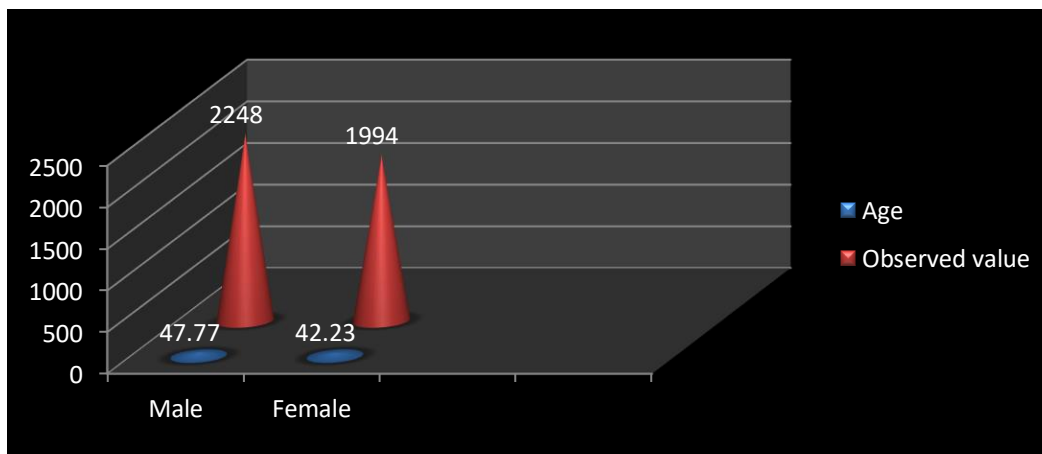
p value <0.05 was considered as statistically significant.

**Results**

There were 150 patients in total, with 59 females and 91 men. All of the parameters were evaluated on all of the patients. Males were 47.77±14.38 years old on average, while females were 42.23± 17.32 years old on average. Only four of the seven indicators, CRP, D-Dimer, Ferritin and IL6, achieved statistical significance in the research, with a p value <0.05. The remaining three indicators, TLC, LDH, and procalcitonin, were all non-significant. The p value for LDH was 0.59. TLC p value was 0.07, procalcitonin p value was 0.32. As a result, these measures were not significant inflammatory markers in COVID 19 individuals in this investigation.

**Table 1: Age and Observed value in male and female regarding D-Dimer**

D-dimer Parameter	Male Mean±SD	Female Mean±SD	T value	P value	Significant
Age	47.77±14.38	42.23±17.32	2.4703	0.02167	S(P<0.05)
Observed value	2248±2561	1994±2948	0.8121	0.0471	S(P<0.05)



**Fig 1: Age and Observed value in male and female regarding D-Dimer**  
**Table 2: Age and Observed value in male and female regarding Procalcitonin**

Procalcitonin	Male	Female			
Parameter	Mean±SD	Mean±SD	T value	P value	Significant
Age	47.77±14.38	42.23±17.32	2.4703	0.02167	S(P<0.05)
Observed value	0.318±1.212	0.683±2.6504	1.2865	0.3221	NS(P>0.05)

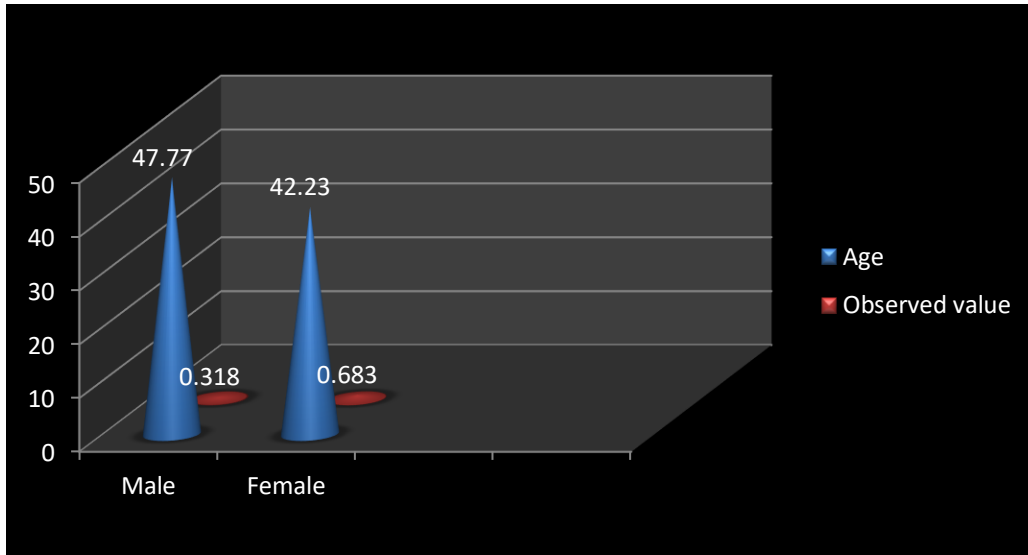


Fig 2: Age and Observed value in male and female regarding Procalcitonin

Table 3: Age and Observed value in male and female regarding TLC

TLC	Male	Female			
Parameter	Mean±SD	Mean±SD	T value	P value	Significant
Age	47.77±14.38	42.23±17.32	2.4703	0.02167	S(P<0.05)
Observed value	9173±5549	7998±3731	1.8382	0.07667	NS(P>0.05)

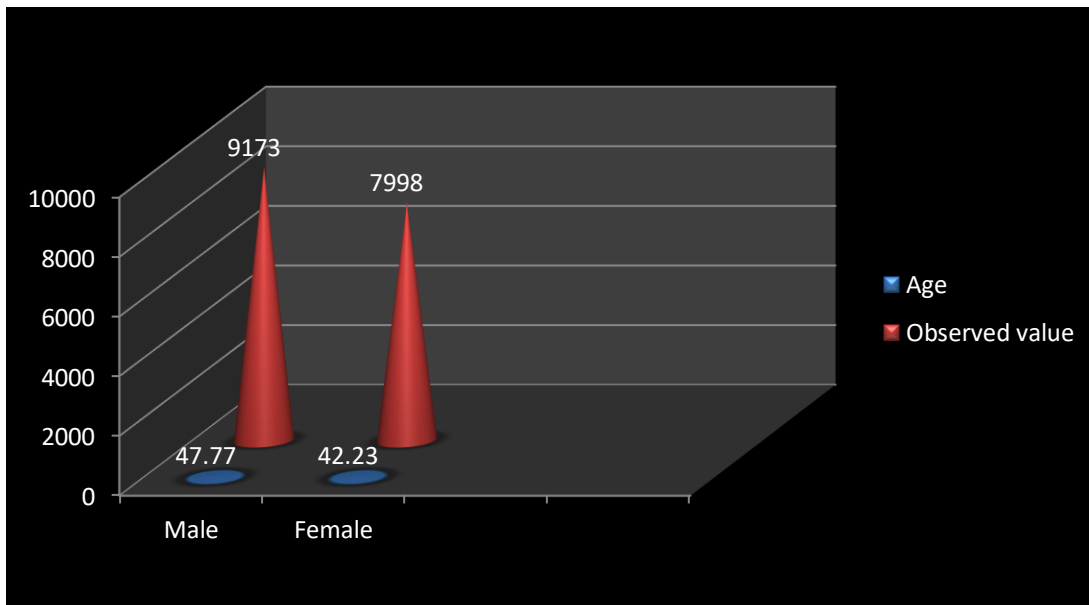
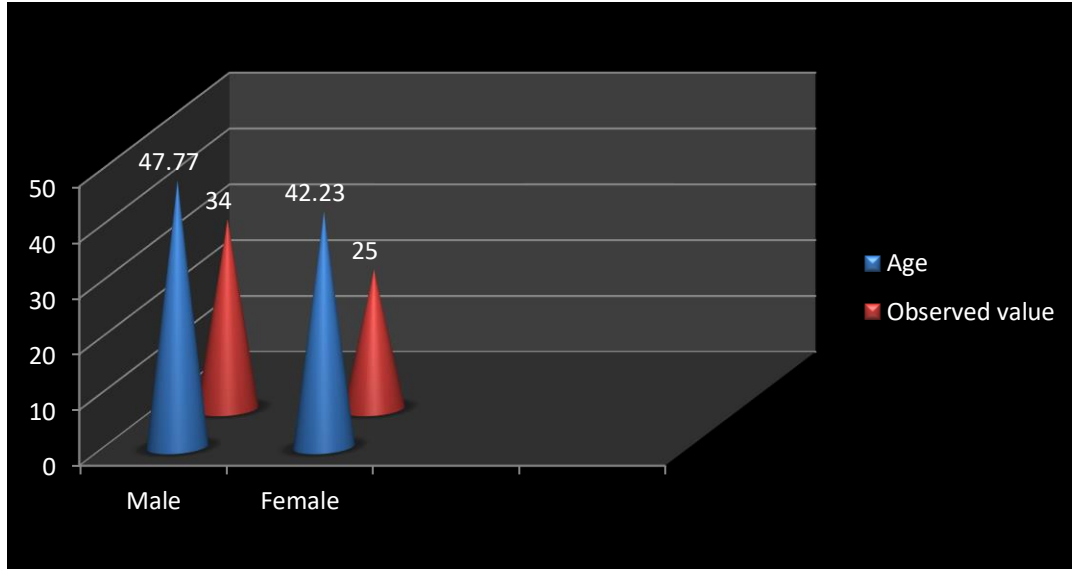


Fig 3: Age and Observed value in male and female regarding TLC

**Table 4: Age and Observed value in male and female regarding CRP**

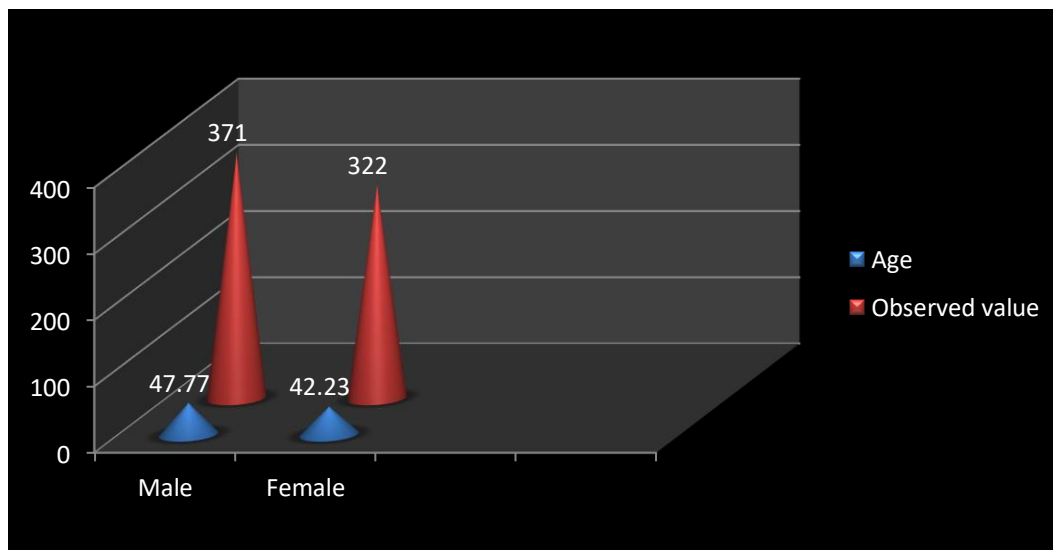
CRP	Male	Female			
Parameter	Mean±SD	Mean±SD	T value	P value	Significant
Age	47.77±14.38	42.23±17.32	2.4703	0.02167	S(P<0.05)
Observed value	34.76±26.30	25.78±23.44	2.4631	0.02867	S(P<0.05)



**Fig 4: Age and Observed value in male and female regarding CRP**

**Table 5: Age and Observed value in male and female regarding LDH**

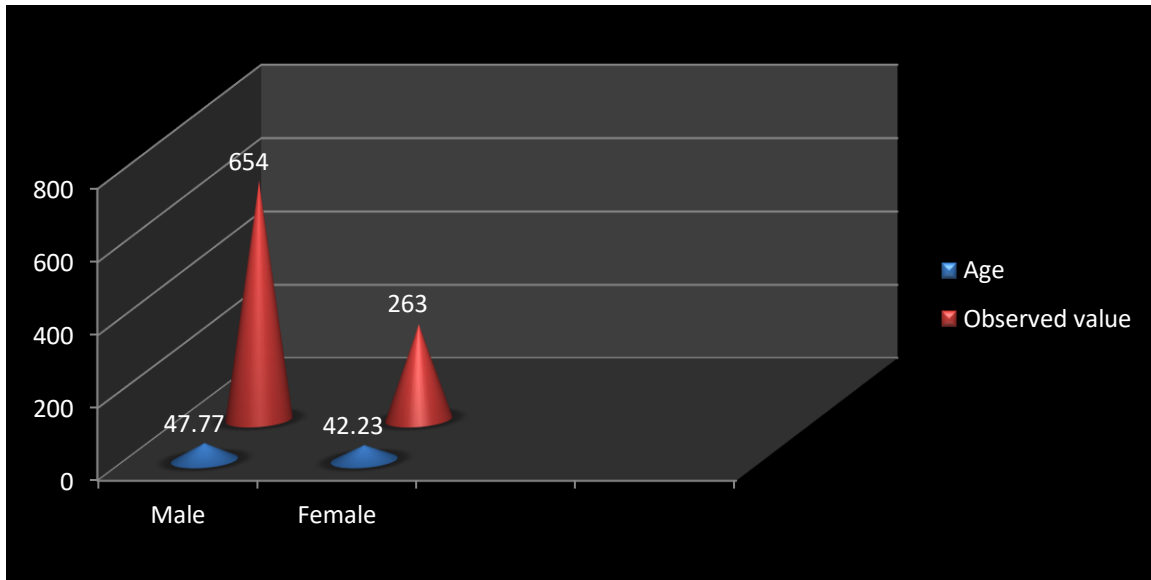
LDH	Male	Female			
Parameter	Mean±SD	Mean±SD	T value	P value	Significant
Age	47.77±14.38	42.23±17.32	2.4703	0.02167	S(P<0.05)
Observed value	371.0±188.7	322.2±165.4	2.4662	0.12178	NS(P>0.05)



**Fig 5: Age and Observed value in male and female regarding LDH**

**Table 6: Age and Observed value in male and female regarding Ferritin**

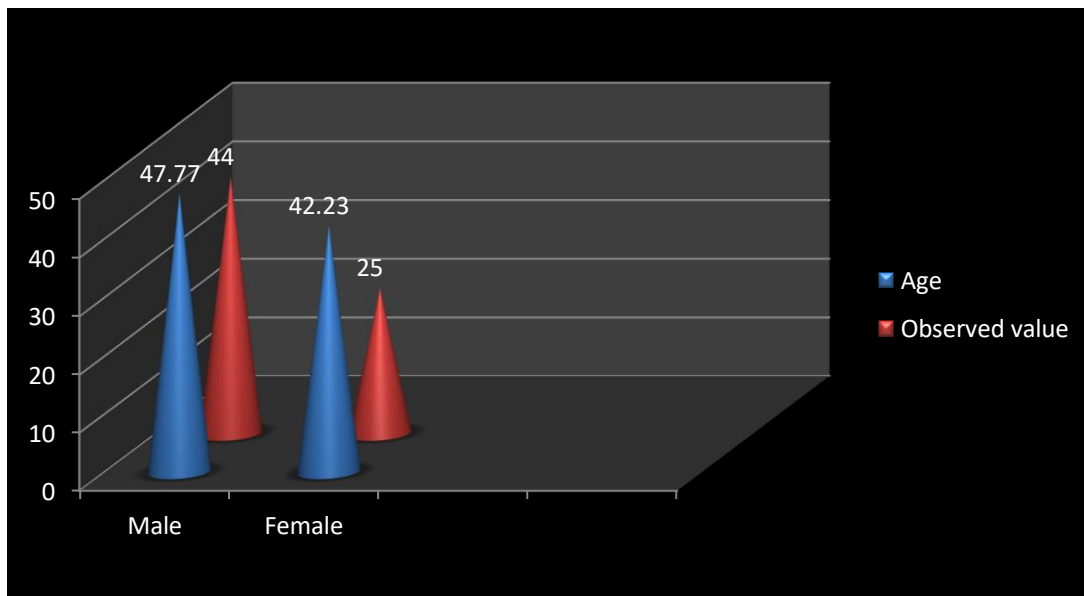
Ferritin	Male	Female			
Parameter	Mean±SD	Mean±SD	T value	P value	Significant
Age	47.77±14.38	42.23±17.32	2.4703	0.02167	S(P<0.05)
Observed value	654.6±830.4	263.8±250.1	4.4173	0.0001	S(P<0.05)



**Fig 6: Age and Observed value in male and female regarding Ferritin**

**Table 7: Age and Observed value in male and female regarding IL 6**

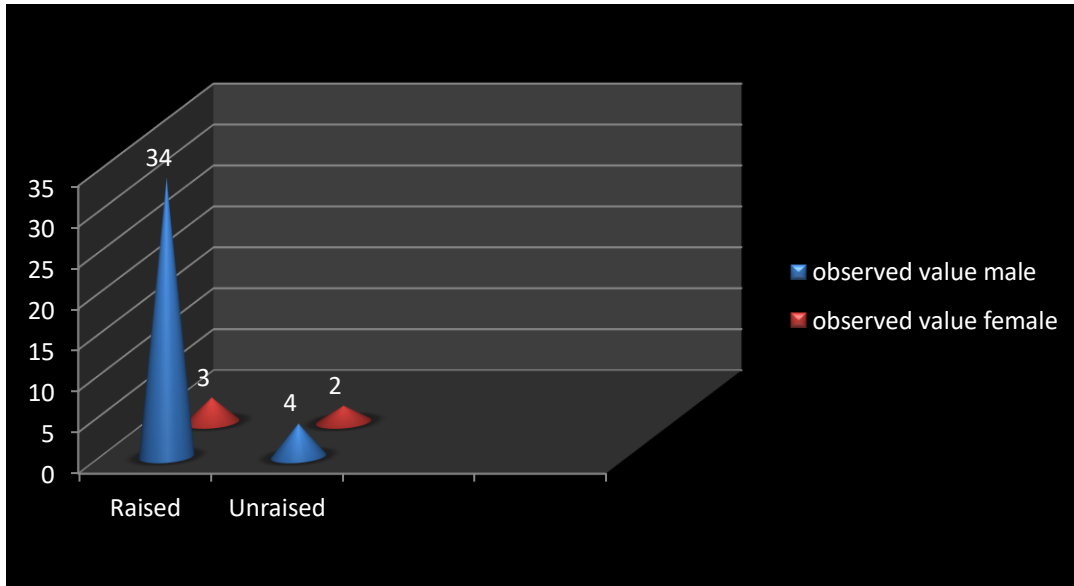
IL 6	Male	Female			
Parameter	Mean±SD	Mean±SD	T value	P value	Significant
Age	47.77±14.38	42.23±17.32	2.4703	0.02167	S(P<0.05)
Observed value	44.76±26.30	25.78±23.44	2.4631	0.02867	S(P<0.05)



**Fig 7: Age and Observed value in male and female regarding IL 6**

**Table 8: Raised and Unraised value in male and female regarding CRP**

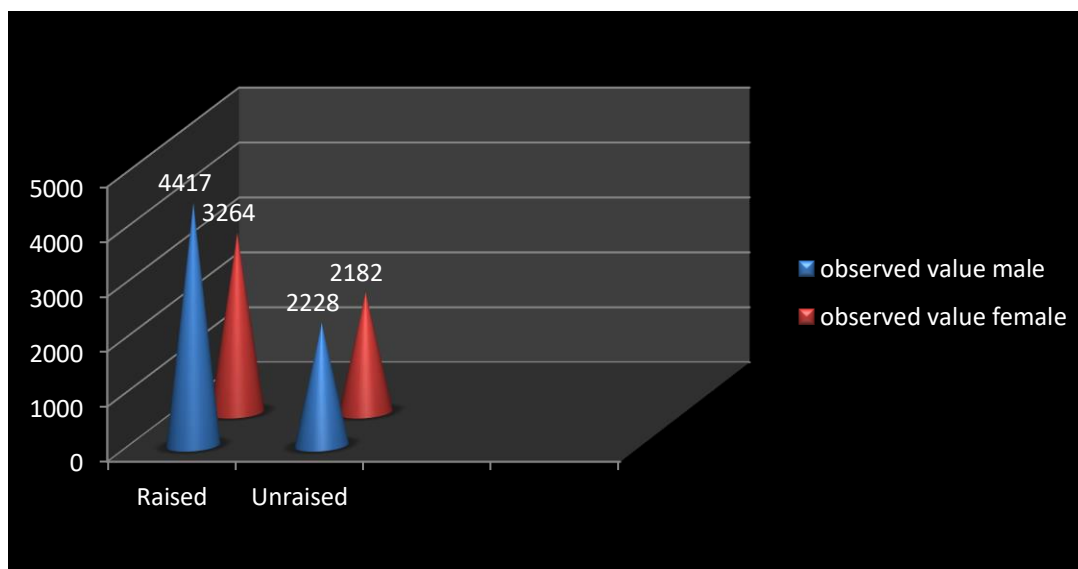
CRP	Raised	Unraised	T Value	P Value	Significant
Observed value male	34.89±25.90	4.537±1.227	13.248	0.0001	S(P<0.05)
Observed value female	3.333±2.386	2.847±1.247	0.1144	0.8003	NS(P>0.05)



**Fig 8: Raised and Unraised value in male and female regarding CRP**

**Table 9: Raised and Unraised value in male and female regarding D-Dimer**

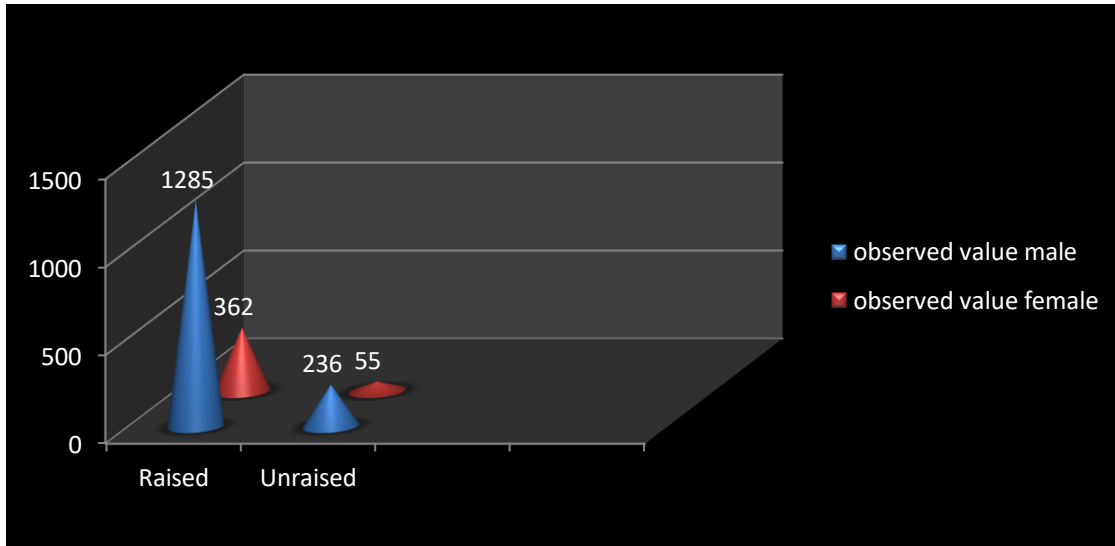
D- Dimer	Raised	Unraised	T Value	P value	Significant
Observed value male	4417.4±165.8	2228.3±282.4	7.6778	0.73	NS(P>0.05)
Observed value female	3264.6±17.98	2182.6±45.67	11.3437	0.65	NS(P>0.05)



**Fig 9 : Raised and Unraised value in male and female regarding D-Dimer**

**Table 10: Raised and Unraised value in male and female regarding Ferritin**

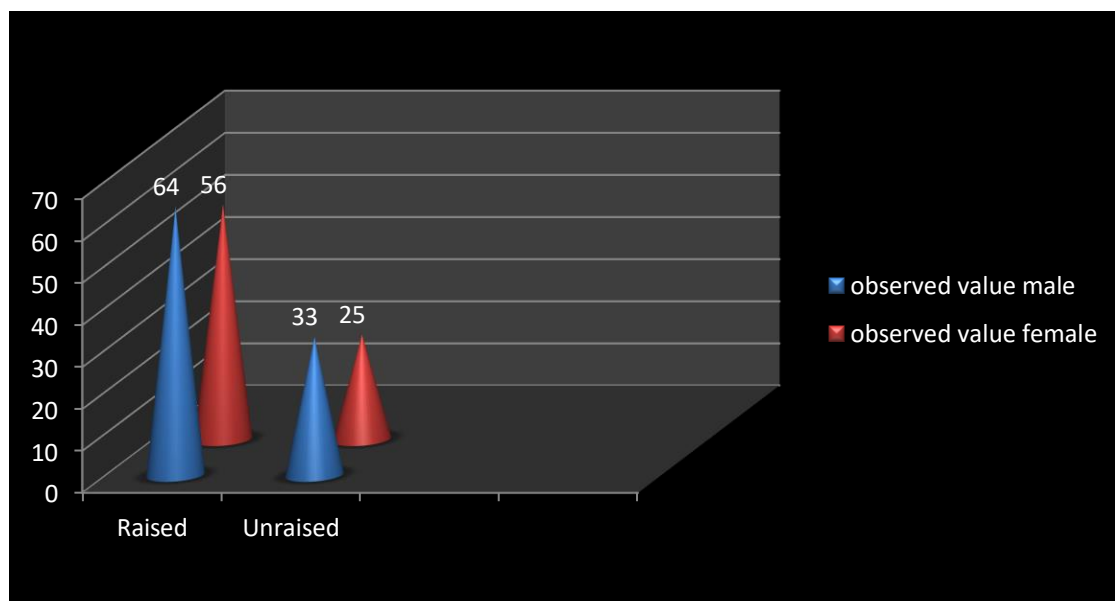
Ferritin	Raised	Unraised	T value	P Value	Significant
Observed value male	1285±1518	236.1±12457	7.6386	0.001	S(P<0.05)
Observed value female	362.1±259.6	55.45±3.907	13.8156	0.0001	S(P<0.05)



**Fig 10: Raised and Unraised value in male and female regarding Ferritin**

**Table 11: Raised and Unraised value in male and female regarding IL 6**

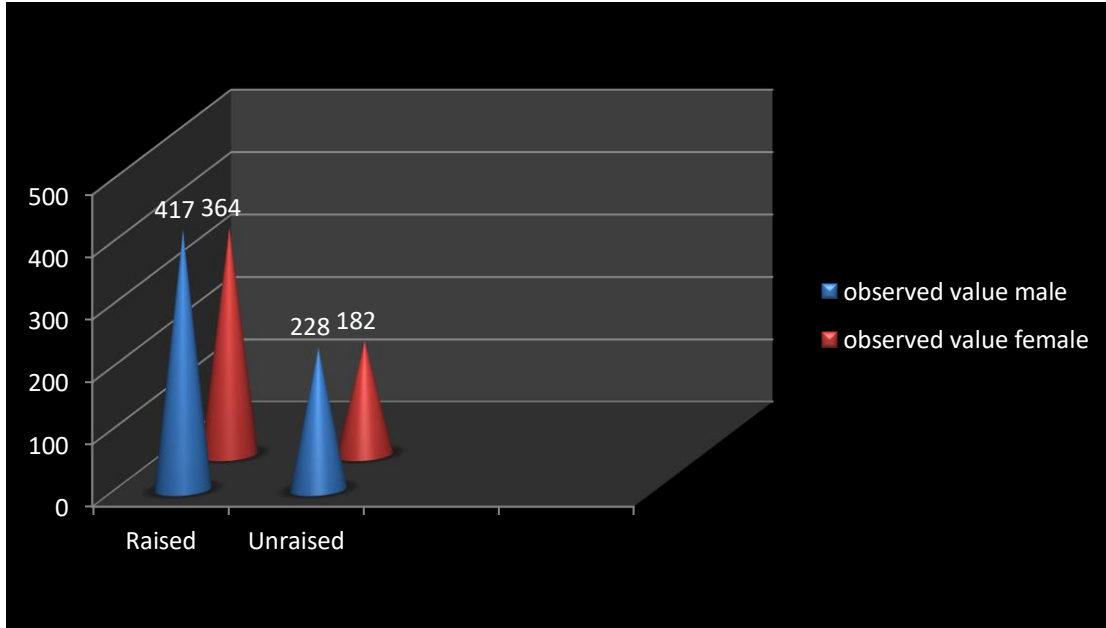
IL 6	Raised	Unraised	T value	P Value	Significant
Observed value male	64.23 ± 23.21	33.1±12457	7.6386	0.001	S(P<0.05)
Observed value female	56.1±259.6	25.45±3.907	13.8156	0.0001	S(P<0.05)



**Fig 11: Raised and Unraised value in male and female regarding IL 6**

**Table 12: Raised and Unraised value in male and female regarding LDH**

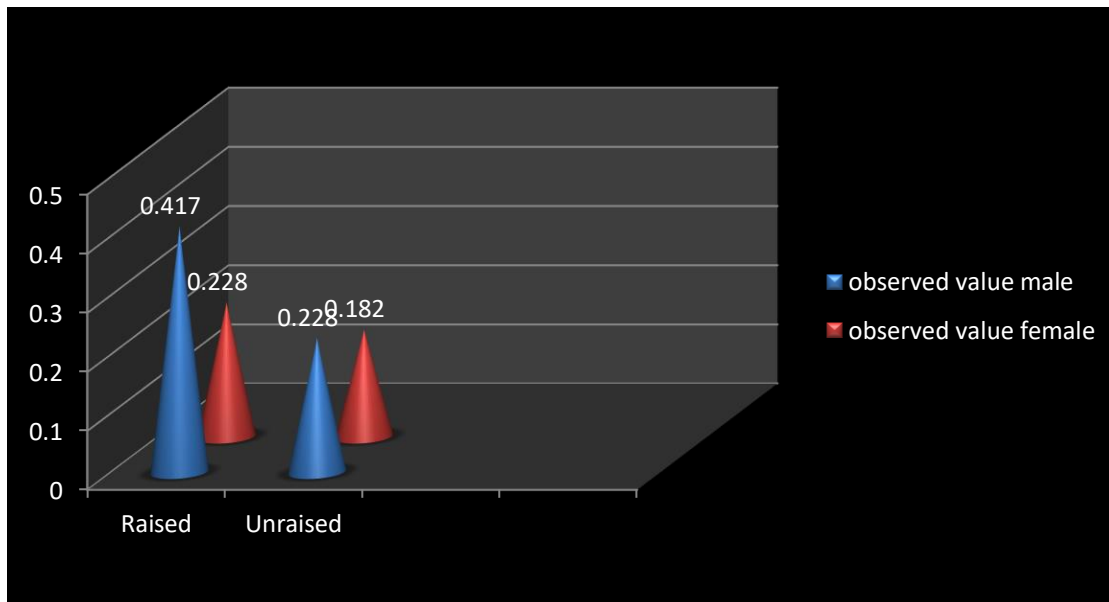
LDH	Raised	Unraised	T Value	P value	Significant
Observed value male	417.4±165.8	228.3±282.4	7.6778	0.42	NS(P>0.05)
Observed value female	364.6±17.98	182.6±45.67	11.3437	0.53	NS(P>0.05)



**Fig 12: Raised and Unraised value in male and female regarding LDH**

**Table 13: Raised and Unraised value in male and female regarding Procalcitonin**

Procalcitonin	Raised	Unraised	T Value	P value	Significant
Observed value male	0.4174±165.8	0.2283±282.4	7.6778	0.71	NS(P>0.05)
Observed value female	0.3646±17.98	0.1826±45.67	11.3437	0.61	NS(P>0.05)

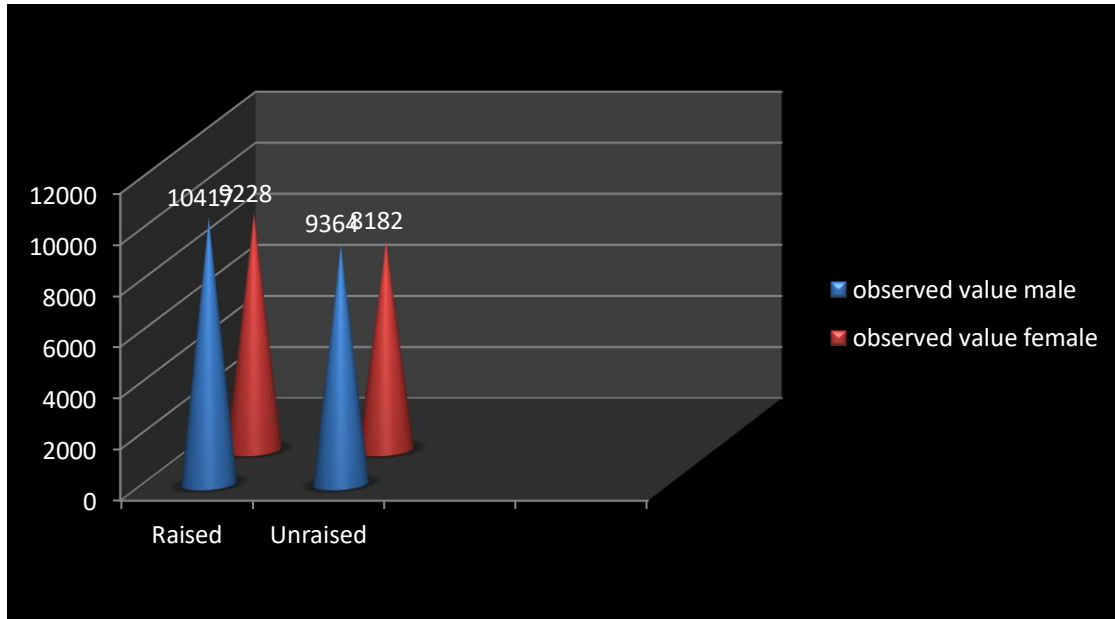


**Fig 13: Raised and Unraised value in male and female regarding Procalcitonin**



**Table 14: Raised and Unraised value in male and female regarding TLC**

TLC	Raised	Unraised	T Value	P value	Significant
Observed value male	10417.4±165.8	9228.3±282.4	7.6778	0.31	NS(P>0.05)
Observed value female	9364.6±17.98	8182.6±45.67	11.3437	0.21	NS(P>0.05)

**Fig 14: Raised and Unraised value in male and female regarding TLC****Discussion**

Cytokine release syndrome (CRS), an inflammatory immunological reaction that leads to organ failure, is thought to be the cause of Covid 19. Elevated levels of interleukin (IL) 6, which promotes the liver to create C- reactive protein (CRP) and fibrogen, have been related to severe Covid 19 and CRS. LDH and ferritin, in addition to CRP and fibrinogen, are linked to plasma IL-6 levels [8].

Clinical studies have shown that changes in the levels of various blood indicators are connected to the severity and death of Covid 19 patients. Among these clinical parameters, serum CRP has been identified as a key measure that varies considerably in severe Covid 19 patients. CRP is a protein made by the liver that acts as an early indicator of infection and inflammation. CRP has a normal value in the blood of less than 10 mg/L, rises fast within 6-8 hours, and peaks 48 hours after disease onset. It has a 19-hour half-life and its concentration falls as the inflammatory stage ends and the patient heals. CRP prefers to attach to phosphocholine, which is abundantly produced on the surface of injured cells. This binding activates the immune system's classical complement pathway and controls phagocytic activity to eliminate pathogens and damaged cells from the body. When inflammation subsides, CRP levels drop, making it a valuable marker [9]. Patients taking Covid 19 had a significant increase in CRP, with levels averaging 30-50 mg/L. Individuals with more severe symptoms had an average CRP concentration of 39.4 mg/L, while patients with minor symptoms had an average CRP concentration of 18.8 mg/L, according to one study. Another study found that the mean CRP concentration in severe patients was 46 mg/L, compared to 23 mg/L in non-severe patients [9]. Zaman et colleagues studied the efficacy of serum LDH in viral for the first time in 1988. They discovered that serum LDH levels might be used as a marker for P. Jirovecii pneumonia in patients with the human immunodeficiency virus [10]. According to Ede et al, the severity of nasopharyngeal cellular injury during viral upper respiratory tract infection was linked to acute otitis media complications, as evaluated by LDH levels in nasopharyngeal discharges. They claimed that

levels of LDH and all cytokines (interleukin-1, IL-6, and tumour necrosis factor) have a favourable connection. Serum LDH levels were shown to be higher in various investigations on severe acute respiratory syndrome (SARS) [11]. In a 2003 examination of SARS data, lymphopenia, increased LDH, AST, and creatinine kinase levels were found to be prevalent in critical cases. According to Liu et al, 58 percent of SARS patients had increased LDH levels [12]. Ferritin is a critical modulator of immunological dysregulation, especially in extreme hyperferritinemia, contributing to cytokine storm through direct immune suppressive and proinflammatory actions. It has been reported by Covid 19 that fatal results are associated by cytokine storm syndrome, implying that illness severity is dependent on cytokine storm syndrome. Many people with diabetes have high blood ferritin levels, and it's well recognised that they're more likely to develop significant covid 19 problems. In a research of 20 Covid 19 patients, it was discovered that those with severe and very severe Covid 19 had higher serum ferritin levels [13].

**Conclusion**

CRP, D-Dimer, Ferritin and IL 6 had significance correlation with severity of COVID 19 whereas rest 3 parameters TLC, LDH & Procalcitonin had no significant correlation with severity of COVID 19.

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**Conflict of Interest: Nil**

**Source of support: Nil**