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Study of D-dimer & CRP in 2 nd wave of Covid 19

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Abstract :
Objective: *we aimed to provide correlation of D-dimer & CRP with severity of disease in 2 nd wave of covid 19.*
Methods*: 100 patients admitted in Shri Mahant Indresh Hospital Covid Ward with positive RT PCR. Serum samples taken and run on VITROS 5600/7600 and reported for D-dimer & CRP.*
Results*: with 100 patients 34 were females & rest 66 were males. Out of which both parameters run on all patients. Mean age of CRP for males 58.92 ±15.63 & Mean age for females 55.23±15.60. Observed value for CRP 55.40±64.98 for males 47.46±57.00 for females & observed value for D-dimer is 2736± 2948 for males & for females 3968± 4912. In this study D-dimer was significant as compared to Crp.*

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I. Covid-19 Pandemic In India

First case of Covid 19 infection reported in Kerala, India on January 30 2020, a 20 year old female presented that she had returned to Kerala from Wuhan ,China on January 23rd. India currently has the largest number of confirmed cases in Asia and has the second highest number of confirmed cases in the world after United States with more than 9,000,000 reported cases of COVID-19 infection and more than 100,000 death per day. Cases hit mid September in India with over 90,000 case reported per day and have since come down below 40,000 in December.

By mid may 2020 around half of all reported cases in the country Mumbai, Delhi, Ahmedabad, Chennai, Pune, Kolkata as of 10 September 2020 lakshadweep is the only region which has not reported a case on 10 June India's recoveries exceeded active cases for the first time infection rate started to drop significantly in September and the number of daily new cases and active cases starts to decline rapidly.

Signs and Symptoms of Covid 19

Covid 19 effects different people in different ways most infected people will develop mild to moderate illness and recover without hospitalization most common symptoms:
Fever,dry cough,tiredness,aches & pains, sore throat, conjunctivitis,headache,loss of smell &taste,rash on skin or discoloration of fingers or toes, difficulty breathing or shortness of breath, chest pain, loss of speech or movement.

Important parameters are :

CRP

CRP a cytokine induced acute phase protein that increases in concentration as a result of inflammation, hence it is used as early marker or indicator of infection and inflammation.
The assay of CRP is more sensitive than ESR and leukocyte count, their levels rise and return to reference range more rapidly after the disease has subsided.
Why CRP test is important in Covid 19 prognosis?
Statistical studies among Covid 19 patients shows that CRP levels are highly correlated with the inflammation in the lungs and an increased CRP level is suggestive of poor prognosis. When a pathogen enters in body, inflammatory cytokines will be overproduced to fight against it and when it hyperactivates it can damage lungs and other internal organs. CRP levels are elevated in silent hypoxia (insufficient oxygen supply to body parts) results in trauma, shock, heart failure, heart attack and multiple organ failure .

During infectious or inflammatory disease states-
CRP levels rise rapidly within the first 6 to 8 hours.
Peak at is at up to 300 to 350mg/L after 48 hours .

CRP is raised by up to 50,000 times in acute inflammation.

CRP is one of the markers to evaluate the security of infection prognosis and therapeutic monitoring CRP is tested together with other clinical parameters for initial evaluation and follow up of Corona virus infection

D-DIMER

D-dimer is a fibrin degradation product that is often used to measure and assess clot formation. Amid the COVID-19 pandemic, elevated D-dimer levels have been associated with disease severity & mortality trends.

The liver produces several important proteins involved in the coagulation process, one of which is made up of three pairs of different polypeptide chains which include a,b & g.

Each of the interwined polypeptide chains that comprise a single fibrinogen molecule is held together by disulfide bonds.

The formation of fibrin begins with cleaving of the a and b polypeptide chains of the fibrinogen molecule, which is achieved by thrombin. This cleaving event causes the fibrin monomers to spontaneously polymerize which results in formation of double stranded fibrin protofibrils.

To strengthen normally weak network that exists between the fibrin monomers and the protofibrils a transglutaminase enzyme known as factor XII a is activated.

If an injury occurs the fibrinolytic system will activate to limit the size of the clot. This system begins with the release of plasminogen activator from the vascular endothelial cells to allow this molecule to bind to the fibrin surface of plasmin.

Fibrin bound plasmin will then degrade the fibrin network into several soluble fragments of which will include the D-dimer .

The presence of D-dimer in blood plasma which is half life of roughly 8 hours until kidney clearance occurs is often used as a clinical biomarker to identify thrombotic activity and therefore diagnose conditions like pulmonary embolism , deep vein thrombosis, venous thromboembolism, & disseminated intravascular coagulation.

D- Dimer is a product of fibrin degradation that in health circulates in blood plasma at low blood concentration. Since activated blood coagulation and consequent fibrinolysis is associated with increased plasma D-dimer concentration, D-dimer has proven a clinically useful marker of thrombotic disease.

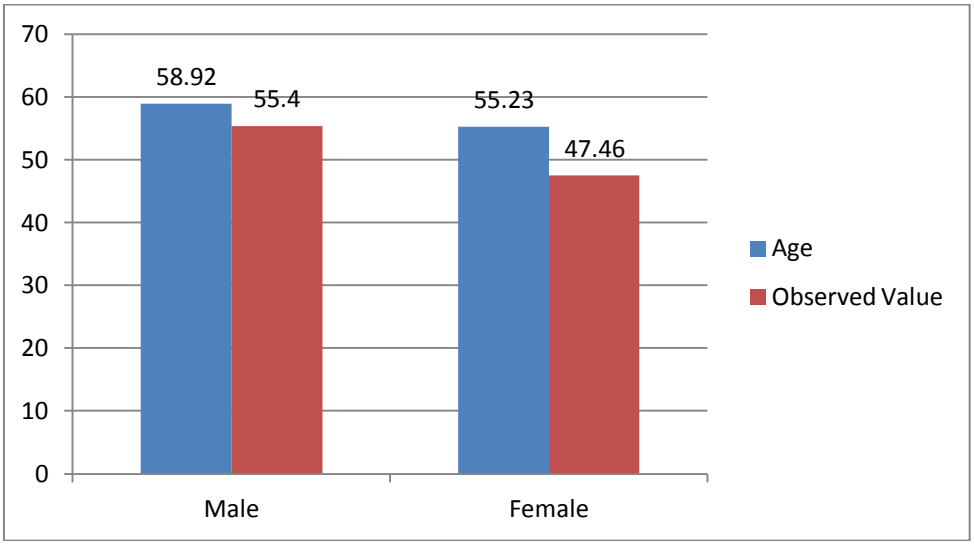
Covid 19 the pandemic disease caused by infection with novel virus , SARS-Cov-2 can now be added to already extensive conditions that may be associated with elevated D-dimer.

The discovery that D-dimer may be elevated in Covid 19 was first reported by physicians in Wuhan, China where the epidemic started. A study of 191 patients with Covid 19 who were hospitalized in Wuhan during January 2020 at the outset of the pandemic, revealed that D-dimer was elevated in many of these patients .

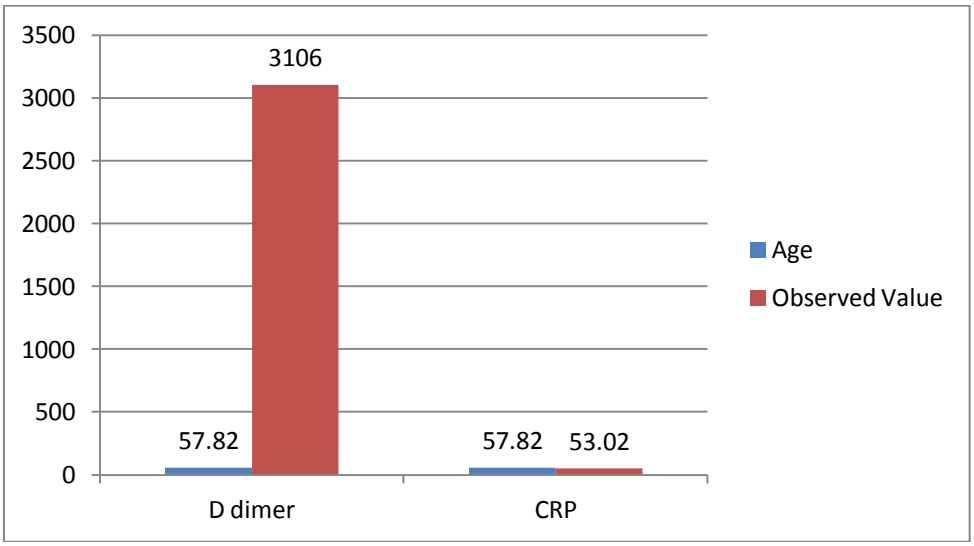
II. Results:

With 100 patients 30 were females & rest 60 were males. Out of which 2 parameters run on all patients. Mean age for males 58.92±15.63 & Mean age for female 55.23±15.60. Observed value for CRP 55.40±64.98 for males 47.46±57.00 for females & observed value for D-dimer is 2736± 2948 for males & for females 3968± 4912. D-dimer was significant in this study with p value 0.00001.

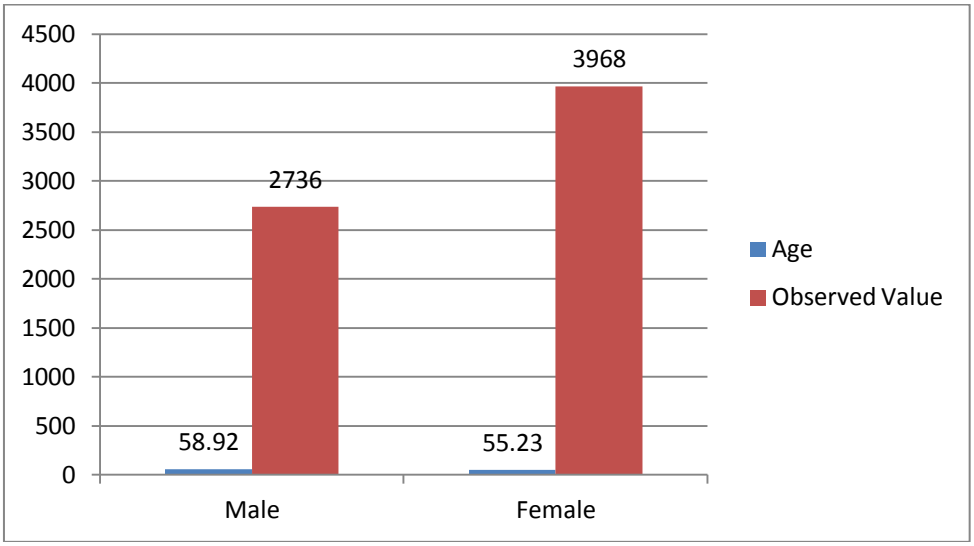
Parameter CRP	Male	Female	T value	P value	Significant
	Mean±SD	Mean±SD			
AGE	58.92±15.63	55.23±15.60	0.0199	0.9841	NS(P≥0.05)
Observed value	55.40±64.98	47.46±57.00	0.0747	0.9406	NS(P≥0.05)



	D Dimer	CRP			
Parameter	Mean±SD	Mean±SD	T value	P value	significant
Age	57.82±15.63	57.82±15.63	0.0	1.0	NS(P≥0.05)
Observed Value	3106±4286	53.02±62.52	7.122	0.00001	S(P≤0.05)



	D dimer (Male)	Female			
Parameter	Mean±SD	Mean±SD	T value	P value	Significant
Age	58.92±15.63	55.23±15.60	1.0825	0.2817	NS(P≥0.05)
Observed Value	2736±2948	3968±4912	1.5505	0.1242	NS(P≥0.05)



III. Discussion:

Covid 19 is hypothesized to be caused by cytokine release syndrome (CRS), an inflammatory immune response leading to organ failure(1-2). Severe Covid 19 & CRS have been linked to elevated levels of interleukin (IL) 6(3-5) which stimulates the liver to produce C- reactive protein(CRP) &fibrogen(6) . in addition to CRP & fibrinogen, LDH & ferritin correlate with plasma IL-6levels(7-8).

Clinical studies demonstrated that altered levels of some blood markers might be linked with the degree of severity and mortality of patients with Covid 19. Of these clinical parameter serum CRP has been found as an important marker that changes significantly in severe patients with Covid 19. CRP is a type of protein produced by liver that serves as an early marker for infection & inflammation. In blood the normal concentration of CRP is less than 10 mg/L it rises rapidly within 6-8 hours & gives its peak in 48 hours from disease onset. Its half life is about 19 hours & its concentration decreases when inflammatory stages end and patient is healing. CRP preferably binds to phosphocholine expressed highly on the surface of damaged cells. This binding makes active classical complement pathway of the immune system and modulates the phagocytic activity to clear microbes & damaged cells from organism. When inflammation resolves CRP concentration falls making it a useful marker for monitoring disease severity.

Significant increase of CRP was found with levels average 30-50 mg/L in patients with Covid 19. For example a study reported with more severe symptoms had an average CRP concentration of 39.4mg/L & patients with mild symptoms CRP concentration of 18.8mg/L(9). Another study mean conc. Of CRP was significantly higher in severe patients 46mg/L than non severe 23mg/L(10).

Several studies have looked to measure D-dimer levels in hospitalized Covid-19 patients to determine whether this biomarker could be useful in predicting patient outcome. In one study conducted in China between January 31 & February 12,2020 the biological characteristics of total 274 Covid 19 patients median age of 62 were analyzed. Of the 113 patients who did not survive it was reported that their D-dimer levels were higher at median of 4.6microgm/ml whereas the surviving 161 patients had D-dimer levels hat averaged at 0.6 microgram/ml. Similar results were reported in another study conducted in China between January 1 & February 2020.

For all those serious adverse clinical outcomes those with elevated D-dimer at admission were more likely to be affected than those with normal D-dimer.

High D-dimer blood levels might be features of both Covid 19 infection & Pulmonary Embolism. Previous reports focussed on different threshold of D-dimer blood levels upon admission to predict Pc in Covid 19 patients(11-13).

Both D-dimer & CRP blood levels are increased during early stages of Covid 19 infection due to systemic inflammation (14). However over time one would expect D-dimer & CRP levels to gradually decrease together as Covid 19 infection resolves. Hence one should measure the blood levels of both biomarker over time and if there is discrepancy with an increase in D-dimer blood levels and decrease in CRP blood levels then VTE & PE should be suspected since this is phenomenon may represent resolution of Covid-19 infection, but also ongoing and possibly worsening VTE in the absence of full-dose anticoagulation theraphy.

IV. Conclusion

In this study D-dimer is significant as compared to CRP as in 2nd wave of Covid 19 most of the patient had raised- D- dimer for which all patients were given blood thinners as most common complication causing death for 2 nd wave was pulmonary embolism. For each patient blood thinner was important mode of treatment for 2nd wave of Covid 19. We found D-dimer was best laboratory marker in our study. And D-dimer values in initial stage of disease helped to save thousand of cases to develop pulmonary embolism.

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