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Comparison of D-dimer & CRP for wave 1st & 2nd of COVID 19

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Abstract:
Objective: *we aimed to provide comparison of D-dimer & CRP with wave 1st & 2 nd with severity of disease.*
Methods*: 100 patients admitted in Shri Mahant Indresh Hospital Covid Ward with positive RT PCR for wave 1 & wave 2. Serum samples taken and run on VITROS 5600/7600 which is dry chemistry and reported for D-dimer & CRP.*
Results*: with 100 patients data was collected for wave 1 & wave 2 for Covid 19. D- dimer- Mean± SD - 2161±2679 & CRP 29.85±25.36 wave1 &*
D-dimer- Mean±SD - 3106±4286 & CRP 53.02±62.52 wave 2 both are significant.
D-dimer is significant for both wave1 & wave 2 of Covid 19.
In wave 2 D-dimer was more significant than CRP.
D-dimer in wave 1 & wave 2 in males & females were 2375±2737 & 1714±2578 in wave1 & 2736±2948 & 3968±4912.
CRP in wave 1 & wave 2 in males & females were 55.40±64.98 &47.46±57.00 in wave 1 & 22.43±23.41 & 33.93±25.56
In comparison both CRP & D-dimer were valuable parameter to anticipate the possibility of aggravation of nonsevere Covid 19.

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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.

Parameters are :

CRP

C-Reactive Protein is an annular pentameric protein found in blood plasma, whose circulating concentrations rise in response to inflammation. It is an acute phase protein of hepatic origin that increases following interleukin 6 secretion by macrophages and T cells.Its physiological role is to bind to lysophosphatidylcholine expressed on the surface of dead or dying cellsin order to activate the complement system via Clq (1)

CRP is synthesized by liver(2) in response to factors released by macrophages & fat cells (adipocytes)(3). It is a member of pentraxin family of proteins (2).

. It is not related to C-peptide (insulin) or protein C (blood coagulation). C reactive protein was first pattern recognition receptor (RRR) to be identified(4).

Discovered by Tillet and Francis in 1930(5), it was initially thought that CRP might be a pathogenic secretion since it was elevated in a variety of illnesses, including cancer(2). The later discovery of hepatic synthesis demonstrated that it is a native protein(6-8).

Initially CRP was measured using quelling reaction which gave a positive or negative result. Now a days dynamic light scattering after reaction with CRP – specific antibodies(9).

The CRP gene is located on chromosome 1 (1q23.2)(10). It is a member of small pentraxins family. The monomer has 224 aminoacids(11) with molecular mass 25,106 Da. The complete protein composed of five monomers has a total mass of approximately 120000 Da.

CRP binds to phosphocholine expressed on the surface of dead or dying cells and some bacteria. This activates the complement system, promoting phagocytosis by macrophages which clears necrotic and apoptotic cells and bacteria(9). This so called acute phase response occurs as a result of increasing concentrations of IL-6 which is produced by macrophages as well as adipocytes in response to a wide range of acute & chronic inflammatory conditions such as bacterial, viral, or fungal infections, rheumatic & other inflammatory diseases, malignancy, other tissue injury and necrosis. These conditions cause release of interleukins-6 and other cytokines that trigger the synthesis of CRP & fibrinogen by the liver.

CRP binds to phosphocholine on microorganisms, it is thought to assist in complement binding to foreign and damaged cells and enhances phagocytosis by macrophage which express a receptor for CRP. It plays a role in innate immunity as an early defence system against infections(9).

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 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:

100 patients were taken from 1st wave & 100 patients from 2nd wave and D-dimer & CRP were done on all.

D- dimer- Mean± SD - 2161±2679 & CRP 29.85±25.36 wave1 &

D-dimer- Mean±SD - 3106±4286 & CRP 53.02±62.52 wave 2 both are significant.

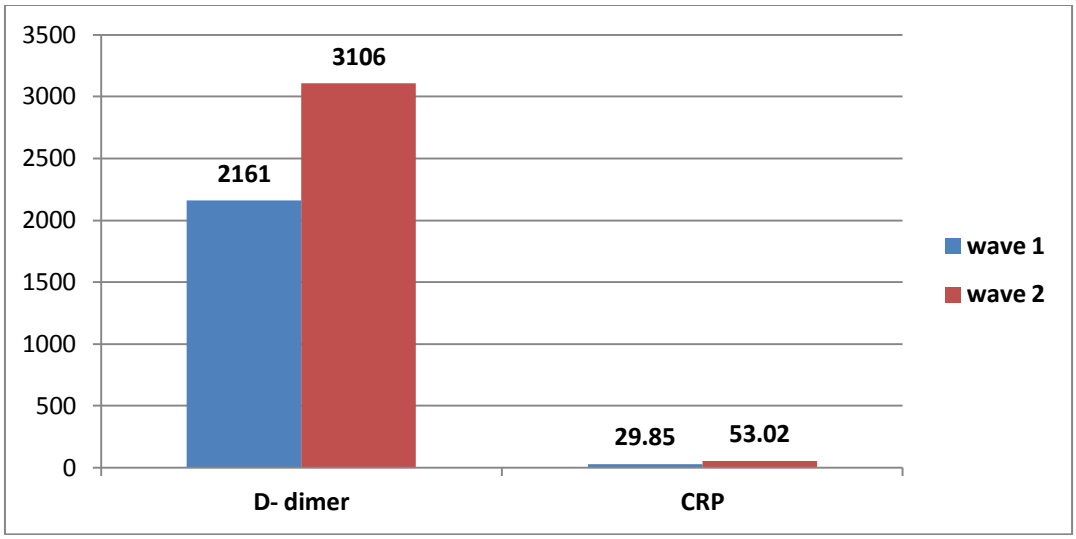
D-dimer is significant for both wave1 & wave 2 of Covid 19.

In wave 2 D-dimer was more significant than CRP.

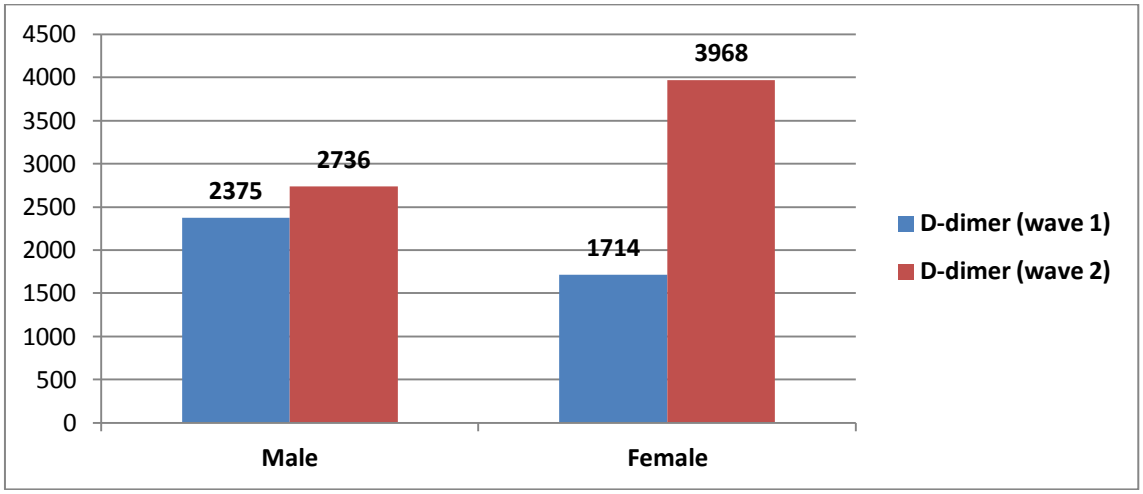
D-dimer in wave 1 & wave 2 in males & females were 2375±2737 & 1714±2578 in wave1 & 2736±2948 & 3968±4912.

CRP in wave 1 & wave 2 in males & females were 55.40±64.98 &47.46±57.00 in wave 1 & 22.43±23.41 & 33.93±25.56.

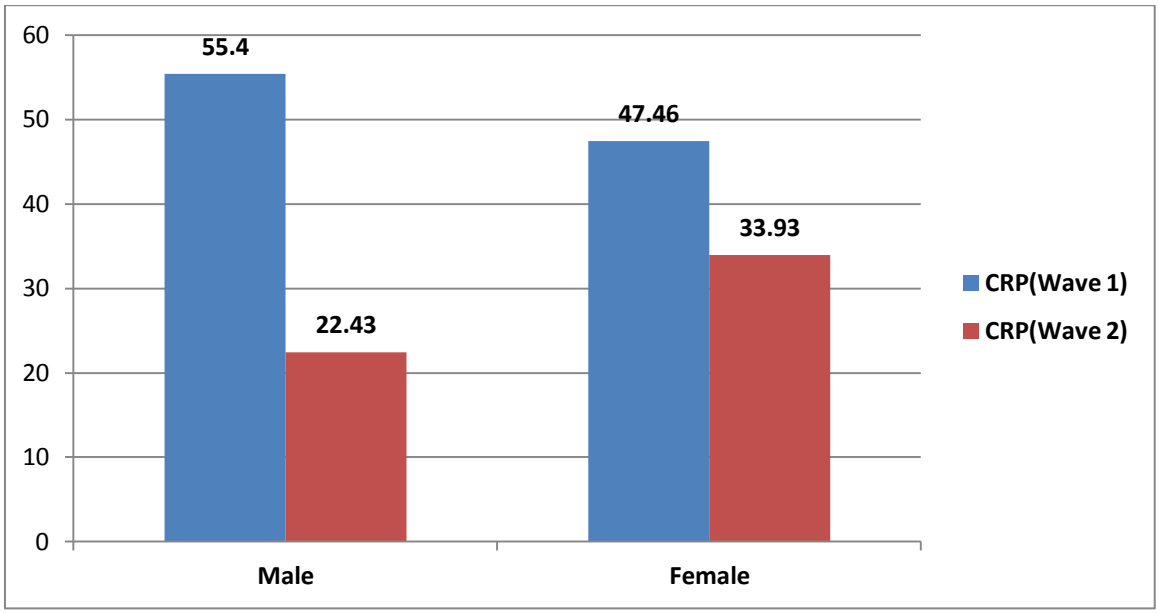
	D- dimer	CRP			
Parameter	**Mean±SD**	**Mean±SD**	**T Value**	**P Value**	**Significant**
wave 1	2161±2679	29.85±25.36	7.9547	0.00001	S(P≤0.05)
wave 2	3106±4286	53.02±62.52	7.1224	0.00001	S(P≤0.05)



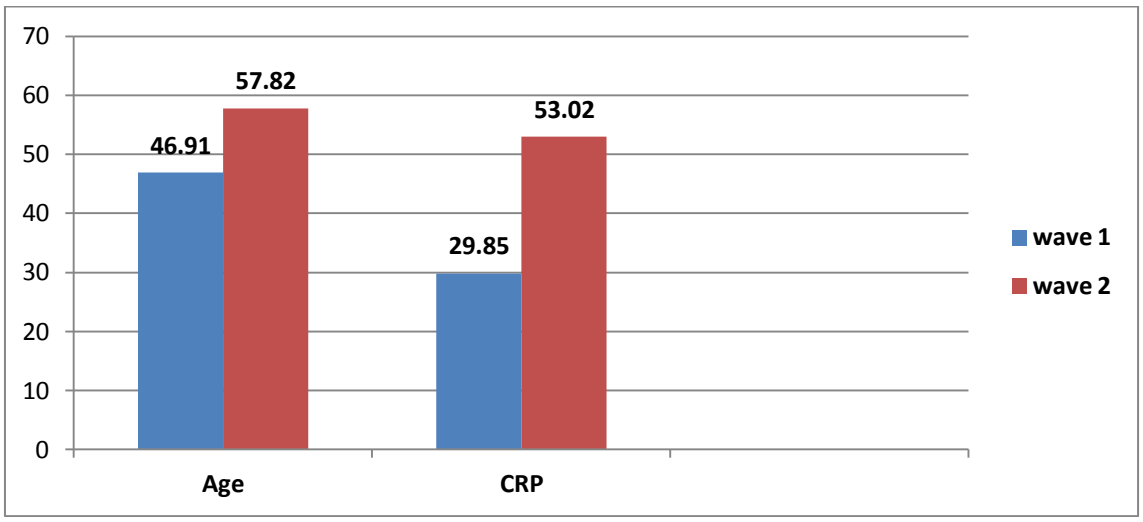
	Male	Female			
Parameter	**Mean±SD**	**Mean±SD**	**T Value**	**P Value**	**Significant**
D-dimer (wave 1)	2375±2737	1714±2578	1.758	0.0803	NS(P≥0.05)
D-dimer (wave 2)	2736±2948	3968±4912	2.1506	0..327	S(P≤0.05)



	Male	Female			
Parameter	**Mean±SD**	**Mean±SD**	**T Value**	**P Value**	**Significant**
CRP(Wave 1)	55.40±64.98	47.46±57.00	0.9186	0.3594	NS(P≥0.05)
CRP(Wave 2)	22.43±23.41	33.93±25.56	3.3179	0.0011	S(P≤0.05)



	wave 1	wave 2			
Parameter	**Mean±SD**	**Mean±SD**	**T Value**	**P Value**	**Significant**
Age	46.91±15.76	57.82±15.63	0.0698	0.9444	NS(P≥0.05)
D-dimer	2161±2679	3106±4286	1.8697	0.063	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(12-13). Severe Covid 19 & CRS have been linked to elevated levels of interleukin (IL) 6(14-16) which stimulates the liver to produce C- reactive protein(CRP) &fibrogen(17) . in addition to CRP & fibrinogen, LDH & ferritin correlate with plasma IL-6levels(18-19).

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(20). Another study mean conc. Of CRP was significantly higher in severe patients 46mg/L than non severe 23mg/L(21).

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(22-24).

Both D-dimer & CRP blood levels are increased during early stages of Covid 19 infection due to systemic inflammation (25). 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 & CRP are both significant for wave 1 & wave 2.For wave 2 Covid 19 D-dimer was more significant and was used as an important indicator for early diagnosis of Covid crisis. 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.In conclusion, elevated levels of CRP may be valuable early marker in wave 1 in predicting the possibility of disease progression in non severe patients with covid 19 which helped health workers to patients in early stage for early treatment. CRP serum levels can predict the severity and progression of illness with Covid 19. In comparison both CRP & D-dimer were valuable parameter to anticipate the possibility of aggravation of non severe Covid 19.

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