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D- DIMER AS A BIOMARKER FOR DISEASE OUTCOME IN GERIATRIC COVID-19 PATIENTS: A CASE CONTROL STUDY

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ABSTRACT The COVID 19 pandemic has infected more than 19.4 crore persons in the world and 3 crores in India. It has killed more than 41 lakhs in the world and 4 lakhs in India (as on 24/7/2021).

SARS COV-2 RNA virus (of beta genera) is mainly transmitted by droplets and aerosols and infects others by inhalation through the nose and mouth. The spike protein of the virus gets attached to ACE 2 receptors in the nasal mucosa and oral cavity and in about 20% cases may reach the lungs. Cytokine storm and vascular thrombosis are the main pathogenic mechanisms, which cause serious illness.

The endothelium is inflamed and damaged either directly by the virus or by host immune mechanism. This endothelial dysfunction causes a pro-coagulant state.

D dimer is a fibrin degradation product. Studies have shown that serious cases of COVID have significantly raised D dimer levels. The values vary a little from laboratory to laboratory and the normal cut-off level of a given laboratory should be considered.

This study was aimed to correlate the levels of D dimer with outcomes (survival or death). The clinical feature and laboratory parameters of 300 (150 survivors and 150 deaths) confirmed COVID 19 cases were studied, and chi square test was applied to the levels of D dimer with the outcomes. It is observed that levels of D dimer at admission that were above 350 nanograms per ml (0.35 micrograms per ml) were significantly associated with poor outcomes.

KEYWORDS : COVID 19, D-Dimer, FDP, Endothelitis, Prothrombotic states

INTRODUCTION:

Covid 19 has so far infected more than 9.4 crore persons globally and 3 crores in India.

It has killed more than 41lakhs worldwide and 4 lakhs in India (as on 24/7/2021).

The virus is transmitted as droplets and aerosol from the nose and mouth of an infected person to others mainly through the nasal and oral mucosal epithelium which has ACE 2 receptors. (1)

Mechanism of SARS-CoV-2 invasion into host cells:

Coronaviruses are enveloped, single-stranded RNA viruses and belong to the beta genera. Once viruses bind to host receptors (attachment), they enter host cells through endocytosis or membrane fusion (penetration). When viral contents are released inside the host cells, viral RNA enters the nucleus for replication and is used to make viral proteins (biosynthesis). Now new viral particles are made (maturation) and released. Coronaviruses consist of four structural proteins; Spike (S), membrane (M), envelop (E) and nucleocapsid (N). Spike comprises two functional subunits; S1 subunit is responsible for binding to the host cell receptor and S2 subunit fuses the viral and cellular membranes. (1)

Like SARS-COV, structural and functional analysis has shown that the spike for SARS-CoV-2 also binds to ACE2 receptors. ACE2 expression is high in nasal mucosa, lung epithelial cells, heart, ileum, kidney and bladder.

After SARS-CoV-2 binds to the host protein, the spike protein undergoes protease cleavage 1) at the S1/S2 cleavage site for priming and 2) for activation of the spike for membrane fusion at the S 2 site. The characteristic unique to SARS-CoV-2 among coronaviruses is the existence of furin cleavage site ("RPPA" sequence) at the S1/S2 site. Although the S1/S2 site is also subjected to cleavage by other proteases such as transmembrane protease serine 2 (TMPRSS2) and cathepsin L, the expression of furin makes this virus very pathogenic.(1)

Endothelial injury as a cause of increased thrombotic tendency-

The acute problems in serious SARS-CoV2 infection are

1) Cytokine storm
2) Increased propensity of vascular thrombosis.

Besides severe pulmonary involvement, thrombosis and pulmonary embolism with elevated d-dimer and fibrinogen levels were observed in severe diseases.

Endothelial cells also express ACE2 and comprise one third of lung cells.

The functions of the endothelium are promotion of vasodilation, fibrinolysis and preventing aggregation of

platelets. Since the endothelium plays a significant role in thrombotic regulation, the hypercoagulable profiles that are seen in severe disease indicate significant endothelial injury.

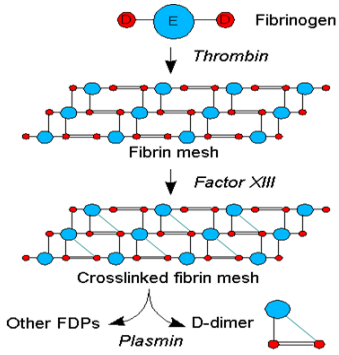
Endothelial dysfunction causes microvascular dysfunction by causing more vasoconstriction with organ ischaemia, inflammation, tissue oedema and a pro-coagulant state. (2)

Evidence of direct viral infection of the endothelial cell and diffuse endothelial inflammation was also found in autopsies. Although the virus uses ACE2 receptor expressed by pneumocytes in the epithelial alveolar lining to infect the host, the ACE2 receptor is also widely expressed on endothelial cells, which traverse through multiple organs. (2)

Extensive endothelial dysfunction along with apoptosis can occur due to direct viral infection of the endothelium or may be immune-mediated due to host cell response. Viral elements have been shown within endothelial cells with an accumulation of inflammatory cells. These findings suggest that SARS-CoV-2 infection facilitates the induction of endothelitis in several organs. This may be the reason why patients with pre-existing endothelial dysfunction, which is associated with male sex, smoking, hypertension, diabetes, obesity and established cardiovascular disease have adverse outcomes in COVID-19. (2)

D Dimer

Structure: (3)



- D-dimer is the degradation product of fibrin (by plasmin), that had been cross-linked by factor XIII. Small quantities (less than 250 ng/ml) are normally present in blood.
- Thrombin is formed upon activation of the intrinsic / extrinsic pathway of the coagulation cascade. It cleaves fibrinopeptide A and B from fibrinogen, that results in soluble fibrin monomers. These monomers associate to form fibrin polymers.
- Activated factor XIII crosslinks the D domains of these fibrin polymer. This produces an insoluble cross-linked fibrin clot.
- The fibrinolytic system normally maintains a balance between coagulation and fibrinolysis. Plasmin cleaves insoluble fibrin polymers, resulting in the production of fibrin degradation products (FDPs). If the polymers are cross-linked between two D domains of the fibrinopeptides, D-dimer is produced. The normal concentration of D-dimer is < 250 ng/mL, or < 0.25 mcg/mL.

The reference range/cut -off value for D-dimer is established by the performing laboratory and varies with methodology and manufacturers.

In case of the designated laboratory that was conducting investigations of the COVID patients of our dedicated COVID hospital, the normal levels were given as less than 500 ng/ml (0.5 mcg/ml) (4)

Interpretation:

Elevated D-dimer levels show ongoing activation of the haemostatic and thrombolytic system and is of use in the following conditions:

- Evaluation of thrombus formation-rising values may indicate worsening, in conditions with pro-thrombotic tendency, as in COVID.
- Monitoring anticoagulative treatment (a decreasing value indicates effective treatment)
- Ruling out DVT, pulmonary embolism.
- Disseminated intravascular coagulation (DIC).
- Vasculo-toxic snake venom poisoning.

The D-dimer test has a high sensitivity but low specificity. The level may be elevated in pregnancy, inflammation, malignancy, trauma, postsurgical treatment, liver and heart disease. It may be high in hospitalized patients

- A high triglyceride / elevated bilirubin level, an elevated serum rheumatoid factor level, or haemolysis may falsely increase the D-dimer values.

The D-dimer level in individuals with factor XIII deficiency remains low (zero in homozygous factor XIII deficiency), though there may be a large clot, due to the inability of crosslink formation. If these individuals develop thrombosis, they have increased fibrin degradation products but undetectable plasma D-dimer levels.

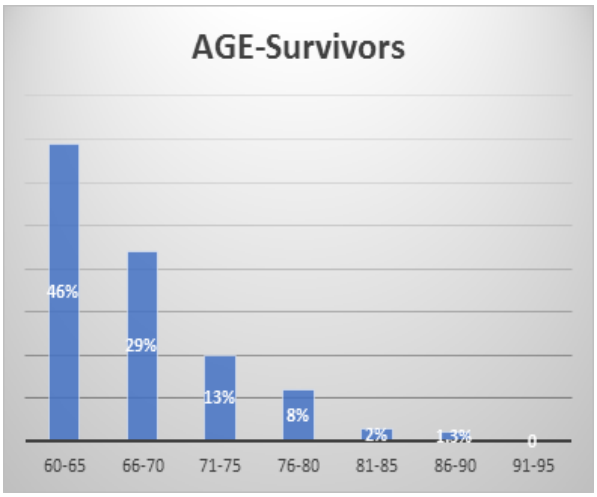
In COVID, rising titres have been shown to have predictive value and it is observed that values more than 10,000 may be seen in serious patients.

The D-dimer level increases naturally with age.
The D-dimer test has excellent negative predictive value when thrombus or pulmonary embolism is suspected. (4)

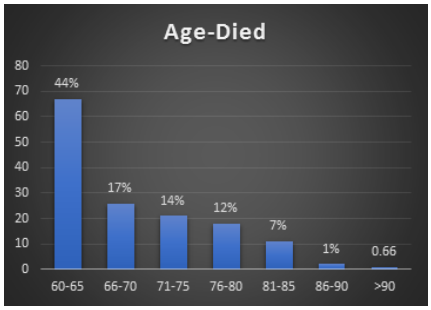
MATERIALS & METHODS:

- The data of 300 Geriatric COVID-19 patients was retrieved from the record section of the Dedicated Covid Hospital (DCH) of Government Medical College, Aurangabad.
- The data of COVID 19 positive deaths (150) and survivors (150) was entered in excel sheet and analysed. Deaths were considered as cases and survivors as control.
- Correlations of D-dimer level at entry, with disease severity and in-hospital mortality were analysed.
- Chi-square test was used (chi square =41.478, df (18), p value 0.001) to determine the optimal cut-off level for D-dimer that discriminated survivors versus non-survivors during hospitalization.

OBSERVATIONS & RESULTS:

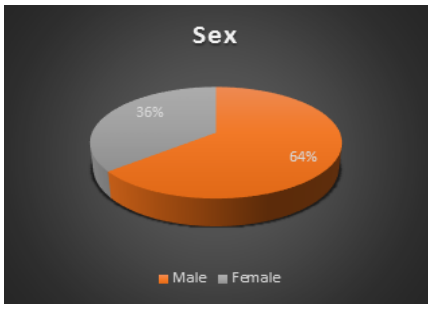


Graph 1: Age distribution of geriatric(60 years and more)survivors



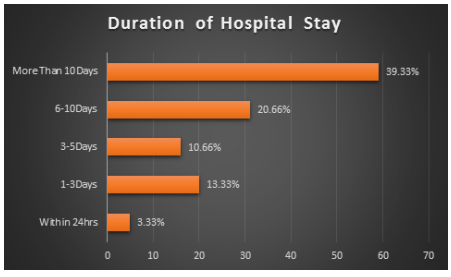
Graph 2: Age distribution of screened geriatric patients who Died

- Maximum patients belonged in both groups to the age group of 60-65 years- 46% patients survived and 44% died.



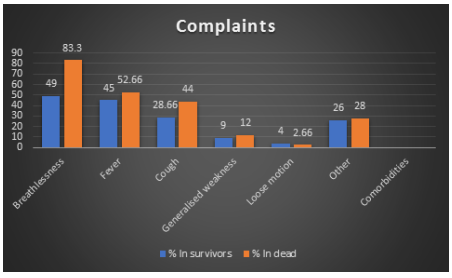
Graph 3: Sex distribution of geriatric patients who died.

- Of the 150 deaths,64% were males and 36% were females.
- Of the total 300 cases studied (survivors and deaths), males were 57% and females 43%.



Graph 4: Distribution of hospital stay in days

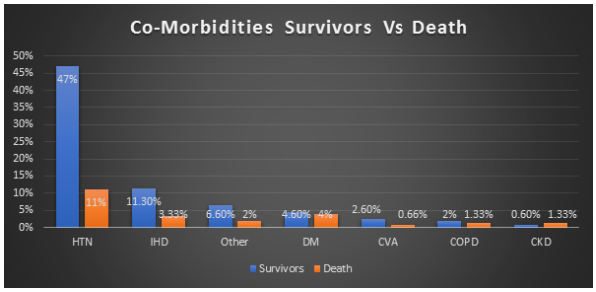
- Maximum (39.33 %) of deaths occurred after more than 10 days of hospitalization.
- Chances of cytokine storm, thrombotic episodes and secondary infection is higher in these cases



Graph 5: Complaints of Survivors Vs patients who died

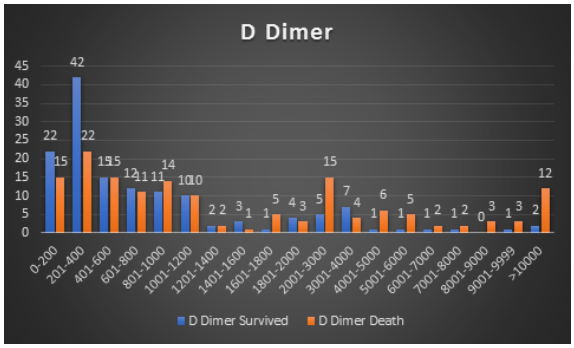
- Symptoms like breathlessness, fever, cough were more common in patients who died than those who survived

Symptoms	% In survivors	% In dead
Breathlessness	49	83.3
Fever	45	52.66
Cough	28.66	44
Generalised weakness	9	12
Loose motion	4	2.66
Other	26	28



Graph 6: Distribution of Co-morbidities in Survivors Vs Death

- Hypertension is most common comorbidity in both groups of survivors (47%) & died(11%).



Graph 7: Distribution of D-Dimer Levels of Survivors Vs Death

- D Dimer levels of patients who survived were compared with those of patients who died by applying Chi-square test, D Dimer value at admission of >350 ng/ml (0.35 mcg/ml) has been found to be statistically significant (in spite of the concerned laboratory normal cut-offvalue of < 500 ng/ml)
- D-dimer greater than 350 ng/ml (even if between 351-499 ng /ml,) could help clinicians identify patients with potentially severe illness at an earlier stage of COVID-19.

CONCLUSION:

- D-Dimer is probably the best laboratory predictor of severe illness.
- Normal laboratory levels of D-Dimer vary from laboratory to laboratory. In the one designated by state government, in which all our patients were tested, the normal D-Dimer value was given as <500 ng/ml (0.5 mcg/mL). However, in our study we found that, if at admission the D-Dimer value is >350 ng/ml (>0.35 mcg/mL), the patient should be very vigilantly observed for deterioration and it is important to do serial D-Dimer test (even daily), to see whether the level is rising, it is recommended that low molecular weight heparin (LMWH) should be started immediately in such patients and the dosage should be adjusted if values keep rising. If the values are very high for ex >2000, plain heparin may also be given for a short time followed by fractionated heparin.
- If the initial level of D-dimer is >350 ng/ml (>0.35 mcg/mL), but less than 500 ng /ml, it is technically normal. However, we found that mortality is - significantly higher in values of D-above 350. We recommend that one should start heparin in these patients too because our aim is to prevent thrombosis.

Shortcomings of the study:

1. We have only corelated D-Dimer levels statistically with outcomes and no other clinical parameters.
2. Serial estimation of D-Dimer may be a better predictor of prognosis. We have studied only initial levels of D-dimer with outcome.

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