ORIGINAL RESEARCH PAPER

Cardiology

ROLE OF VARIOUS INTRAVASCULAR AND INFLAMMATORY MARKERS IN PREDICTING MORTALITY IN COVID 19 PATIENTS

KEY WORDS:

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ABSTRACT

Introduction: A novel virus, named severe acute respiratory syndrome coronavirus 2 (SARS-Co-2) is the cause of current pandemic .In covid infection various biomarkers are elevated which are helpful in predicting mortality and hospital stay of patient. Cytokine strorm is associated with high inflammatory mediators. Commonly studied markers are D dimer ,serum ferritin and IL-6. Increase mount of cytokines was associated with severe pulmonary damage. Similarly comorbities in patients like diabetes and hypertension affect the prognosis of patient. **Method:** This is an observational study conducted in tertiary care hospital. D Dimer,serum ferritin and platlet count were measured during the study .All this parameters was measured at admission. Various comorbity was studied and the prevalence of it in mortality was measured.**Sample size:** 50 **Result:** We studied 50 patient who succumbed their life due to covid 19 at our center.In our study it was found that serum ferritin and D Dimer was significantly high in patient who expired. Measurement was done on the day of admission. Platelet count were studied in all patient and it was found that as per severity there was significant decrease in platelet count. Among this patient who suffered majority of them were diabetic (26) and hypertensive (23) .Both Diabetes and hypertension together were present in 16 cases. Average platelet count was 1.63 lac in our study. Average D Dimer and Ferritin was 1690 and 562 respectively in study group **Conclusion:** Measurement of various inflammatory and vascular biomarkers usually predict the severity and prognosis of the patient. Patient with Diabetes and hypertension should be considered as high risk situation when it comes to covid 19 patients mortality risk. Patient with this risk factor shound be treated vigorously and the measurement of D Dimer ferritin and platelet should be considered frontline investigations in all patient considering the mortality risk.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARSCoV-2) is the cause of the current pandemic coronavirus disease 2019 (COVID-19). As of feb, 2021, there have been 97,945,912 confirmed cases, including 2,118,808 deaths, Worldwide. SARS-CoV-2 has genetic relation with two members of Betacoronavirus, severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV). COVID-19 has rapidly spread to more than hundred countries across the world . A retrospective review of lung injury caused by COVID-19 found that there were varying degrees of changes in laboratory cardiac markers [1]. Therefore, there is a great deal of attention as to whether it causes myocardial injury. Covid 19 infection induces a profound inflammatory response which triggers the coagulation cascade [2]. Activation of the coagulation cascade in COVID-19 patients is associated with a hypercoagulable state and adverse clinical outcomes including death. Occurrence of dysfunctional coagulation in COVID-19 patients emphasizes the crucial need for a hemostasis-focused laboratory monitoring and therapeutic management [3]. Currently, the best available laboratory diagnostic marker for COVID- 19–associated hemostatic abnormalities is considered to be D-dimer [4].

Hyperferritinemia caused by the excessive inflammation due to the infection is associated with the admission to the intensive care unit and high mortality, and represents an indication to recognize high-risk patients to guide the therapeutic intervention to control inflammation[5-7]. Serum ferritin, a feature of hemophagocytic lymphohistiocytosis, which is a known complication of viral infection, is closely related to poor recovery of COVID-19 patients, and those with impaired lung lesion are more likely to have increased ferritin level .we briefly review evidence supporting the hypothesis that ferritin levels might be a crucial factor influencing the severity of COVID-19

Viral infection and inflammation result in lung damage. Damaged lung tissues and pulmonary endothelial cells may activate platelets in the lungs, resulting in aggregation and formation of microthrombi, which increases platelet consumption. Most patients with COVID-19 who have thrombocytopenia have elevated D-dimer levels Cytokines fight against the pathogen but when the system hyperactivates, it can damage lung tissue. CRP production is induced by cytokines – and by tissue destruction [8-10].Serum C-reactive protein (CRP) has been found as an important marker that changes significantly in severe patients with COVID-19.[11] CRP is a type of protein produced by the liver that serves as an early marker of infection and inflammation.6 In blood, the normal concentration of CRP is less than 10mg/L; however, it rises rapidly within 6 to 8 hours and gives the highest peak in 48 hours from the disease onset.[12] Its half-life is about 19 hour. its concentration decreases when the inflammatory stages end and the patient is healing

2. Materials & methods

2.1. Study design and participan

A single-center, prospective, observational study was conducted among COVID-19 positive patients at a tertiary care hospital from (8 months). All the patients included in the

study were real-time polymerase chain reaction (RT-PCR) positive and had typical Computed tomography (CT) radiological features suggestive of COVID-19. All positive patients included in the study and written informed consent was obtained from all the study participants and confidentiality of information was assured to them. This study was approved by the Institutional Ethical Committee of the JJ Hospital.

Data on the patients with confirmed COVID-19, admitted to our tertiary care hospital, april 2020 to dec 2020, was retrospectively collected through an electronic records system (EMS) and was analyzed. The information included demographic details, laboratory findings, and clinical details including co-morbidities and disease outcomes. Patient's details were kept confidential.

Patients with a positive result of the nucleic acid test of SARS-CoV-2 by real-time fluorescence RT-PCR as per World Health Organization guidelines were considered as confirmed COVID-19 cases. Criteria for admission to the hospital was moderate to severe disease where the respiratory rate was more than 24/min or SpO2 was less than 95%. The patients who were still admitted to the hospital and the patients discharged against medical advice during this study period were excluded from the study.

2.2. Data collection

D-dimer values within 24 h of admission and the highest values during hospital stay were extracted for all the patients included in the study. On admission Routine investigation were done and checked repeatedly.CRP and serum ferritin value was checked and measured subsequently needed.

2.3. Laboratory investigations

Coagulation parameters were analyzed using a coagulation analyzer . D-dimer testing was performed using a latex-enhanced photometric immunoassay . The laboratory reference interval was 0–0.5 μg/ml FEU. ferritin level was measured in term of ng/ml. complete hemogram was measured and platlet value was specifically focused on.

2.4. Statistical analysis

Continuous and categorical variables were presented as mean ± standard deviation or median (interquartile range [IQR]), as appropriate. Categorical variables were presented as n (%). Event frequencies were compared between non-survivor groups wherever necessary with a chi-squared test calculator (P-value). The optimal D-dimer cutoff point and C-statistic of routine tests both on admission and during hospital stay were evaluated by receiver operator characteristic (ROC) curve. Age-adjusted D-dimer cutoff for patients aged over 50 was used to generate the ROC to evaluate the impact of false positives. The outcomes were compared by Kaplan-Meier survival analysis. Hazard ratio (HR) and 95% confidential interval (95% CI) were calculated by log-rank tests. Kaplan-Meier survival analysis was done in non-survivors in patients with co-morbidities. A value of $P < 0.05$ was accepted as statistically significant.

3. Results

3.1. Baseline characteristics and establishing optimum cutoff value for D-Dimer

The data of 50 patients with COVID-19 were analyzed in the study, according to our inclusion and exclusion criteria. All the COVID-19 patients requiring admission were given prophylactic low molecular weight heparin (LMWH). The median age of the patients was 61 years, ranging from 28 years to 84 years. Of the 50 patients, all were adults (28-84 years) . Majority of the patients were male 66% (33), as compared to the female patients 34% (17). The basic clinical characteristics of the patients, including age, gender, comorbidities, and D-dimer values are presented in Table1 . All non survived 50 deaths were recorded amongst these admitted patients.

		No. of. Individuals	Percentage %
Gender	Male	33	66%
	Female	17	34%
Age	25 – 35	12	24%
	36 – 44	15	30%
	45 – 50	23	46%
Co-morbidities	Only hypertension	23	46%
	Only diabetes mellitus	26	52%
	IHD	13	26%
	CVA	4	8%
Serum ferritin levels	Less than/equal to 300	10	20%
	Greater than 300	40	80%
CRP	Positive	50	100%
	Negative	0	0%
Platlet count	Less than 1.5 lakh	27	54%
	More than 1.5 lakh	23	46%
D Dimer	Less than 0.5	11	22%
	0.5-1.0	14	28%
	More than 1.0	25	50%
Symptoms	Fever	37	74%
	Cough	23	46%
	Breathlessness	38	76%
	Chest pain	4	8%

4. Discussion

D-dimer is the fibrin degradation products released upon cleavage of cross-linked fibrin by plasmin [13]. D-dimer is routinely utilized clinically in diagnosing disseminated intravascular coagulation (DIC) and those with low pretest probability for deep vein thrombosis (DVT) and pulmonary embolism (PE) [14]. D-dimer elevation has been reported to be one of the commonest laboratory findings noted in COVID-19 patients requiring hospitalization [15]. Studies have shown that rising D-dimer levels during the course of hospitalization are associated with worst long-term outcomes [16].

Elevated ferritin levels were found also in autopsies of 12 patients whose cause of death was SARS-CoV-2 infection[17]. An analysis of the peripheral blood of 69 patients with severe COVID-19 revealed elevated levels of ferritin compared with patients with non-severe disease. Therefore, it was concluded that serum ferritin levels were closely related to the severity of COVID-19[18]. Finally, laboratory findings in patients with severe COVID-19 showed data consistent with cytokine storm involving elevated inflammatory markers, including ferritin, which has been associated with critical and life-threatening illness[19].

Of all the inflammatory markers, serum ferritin levels were elevated in least proportions of patients with moderate/severe disease. Yet, serum ferritin outperformed other inflammatory markers in predicting mortality, with greatest AUC and odds ratio. High serum ferritin levels were also independently associated with poor outcomes in the patients of this study.

Three mechanisms of thrombocytopenia are hypothesized in this review:

1. Direct infection of bone marrow cells by the virus and inhibition of platelet synthesis. Following virus infection, cytokine storm destroys bone marrow progenitor cells and leads to the decrease of platelet production. Lung injury indirectly results in reduction of platelet synthesis.
2. Platelet destruction by the immune system.
3. Platelet aggregation in the lungs, resulting in microthrombi and platelet consumption

In severe patients, platelet levels were significantly lower than non-severe patients at admission, 1 week and 2 weeks after admission [20-21]. Viral infection may affect hematopoiesis [22], in which SARS-CoV-2 may potentially impact megakaryocyte maturation and platelet production. Thrombocytopenia was also reported in severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) patients [23]. The mechanism behind could be abnormal megakaryocyte maturation in severe coronavirus infection [24-25].

CRP is non-specific marker of infection, inflammation and tissue injury .Concentration tells about the severity of the illness[26-27].

The patients who died from COVID-19 had about 10 fold higher levels of CRP than the recovered patients. A significant association was observed between CRP concentrations and the aggravation of non-severe patients with COVID-19 , and the authors proposed CRP as a suitable marker for anticipating the aggravation probability of non-severe COVID-19 patients, with an optimal threshold value of 26.9 mg/L[28].

4. Conclusions

SARS-CoV-2 damages myocardial cells and induces changes of laboratory cardiac markers to varying degrees. 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. Therefore, for patients with COVID-19, it is necessary to actively prevent myocardial injury and reduce the possibility of irreversible remodeling of the myocardium with finally preventing the occurrence of congestive heart failure. Among the measured coagulation parameters, D-dimer during hospital stay had the highest C-index to predict in-hospital mortality in COVID-19 patients. D-dimer value ≥ 2.01 g/mL can effectively predict in-hospital mortality in patients with COVID-19. A significant association of increased D-dimer level has been found with diabetes mellitus and elderly age.

Thrombocytopenia in COVID-19 patients could be used as an effective biomarker to guide bone marrow damage, disease severity, possible deterioration of intravascular coagulation defect, and vascular endothelial activation during viral sepsis induced biological catastrophic cascades 29.

5. Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper

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