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Platelets, D-dimer and Lactate Dehydrogenase (LDH) as Cost Effective Biomarkers for the detection of COVID-19-Associated Coagulopathy (CAC)

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ABSTRACT

We highlighted the role of D-dimers, platelet count and LDH (lactate dehydrogenase) as primary biomarkers in diagnosing the COVID-19-associated coagulopathy (CAC) in severe and critical cases. 141 COVID-19 patients of severe and critical categories, were enrolled from an epicenter tertiary care hospital. The mean values of platelets were found normal, whereas, the mean values of LDH were found elevated in both severe and critical cases. There was no patient with low value of LDH in both groups. 87% patients were having high values of LDH in severe cases, whereas, 98% patients were having high values of LDH in critical cases. Majority patients were having normal value of platelet counts. 43% critically infected patients were having raised D-dimers, whereas, 38% raised D-dimers were found in severely infected patients. According to t-test, severe and critical cases were not found significantly different in platelet counts and LDH values. In developing countries, LDH along with platelet count and D-dimers can make a cost effective trio for an earliest detection of COVID-19-associated coagulopathy (CAC). Regular monitoring of these biomarkers can prompt early detection and timely management of CAC.

Keywords: COVID-19-associated coagulopathy (CAC), D-dimers, Lactate dehydrogenase (LDH), Platelets, Biomarkers

INTRODUCTION

COVID-19 can cause multi-organ dysfunction particularly acute lung injury, cardiac injury, kidney injury and disseminated intravascular coagulopathy (Cucinotta & Vanelli, 2020; Ackermann et al., 2020; Zhu et al., 2020). The primary cause of death from COVID-19 is an acute lung injury due to progressive respiratory failure. The virus causes alveolar damage initially, mediated by endothelial injury, immune cells recruitment, and coagulation system activation. (Noris et al., 2020). The COVID-19-associated coagulopathy (CAC) can be differentiated from bacterial sepsis induced coagulopathy (SIC) and disseminated intravascular coagulation (DIC). The CAC usually presents with prominent elevation of D-dimers and fibrinogen degradation products with minimal changes in the platelet count and pro-thrombin time (PT) (Connors & Levy, 2020). It is more likely to occur in severe and critical COVID-19 patients, and D-dimers and PT can be used as predictors for the mortality in COVID-19 (Connors & Levy, 2020; Long et al., 2020). Similarly, lactate dehydrogenase (LDH) is also identified as a potential predictor for an early recognition of lung injury, respiratory failure and disease severity in COVID-19 (Han et al., 2020; Erika et al., 2020). Venous thromboembolism (VTE) and arterial thrombosis are more recurrent in CAC as compared to SIC or DIC probably due to widespread inflammation, hypoxia and diffuse intravascular coagulation (Iba et al., 2020). There is a high incidence of VTE (27%, 25%) and arterial thrombosis (3.7%) in COVID-19 patients admitted in the intensive care (Klok et al., 2020).

There is a dire need of the hour to identify the cost-effective primary biomarkers for the diagnosis of the disease severity in COVID-19, so

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that a comprehensive treatment can be offered earlier in the management algorithm. This study was aimed at identifying a potential role of cost-effective trio of D-dimers, platelet count and LDH as primary biomarkers in the diagnosis of COVID-19-associated coagulopathy (CAC) in the severe and critical cases reported in an epicenter tertiary care hospital of Pakistan.

MATERIALS AND METHODS

Study Design & Setting

This observational study was carried out in the intensive care units (ICUs) of King Edward Medical University (KEMU)/ Mayo Hospital, Lahore, Pakistan from 15 May to 14 July 2020. We included a total of 141 patients of severe and critical categories. The severity of COVID-19 was defined according to World Health Organization (WHO) clinical management guidelines for COVID-19 (WHO, 2020). The study was conducted after getting the ethical approval from the Institutional Review Board (No. 356/RC/KEMU).

Inclusion & Exclusion Criteria

Severe and critical patients of COVID-19 of either gender, aged between 18-80 years with a positive real-time reverse transcriptase polymerase-chain-reaction (rRT-PCR) assay for SARS-CoV-2 were included upon informed consent.

Laboratory Testing

Blood samples were drawn for D-dimers, LDH and platelet counts in light blue-top, red-top and lavender-top BD Vacutainer tubes respectively upon admission and were sent to the pathology laboratory of King Edward Medical University/ Mayo Hospital. D-dimers were detected using Diazyme D-dimer Assay with reference range of 0-0.50 µg/ml. LDH was measured by Beckman Coulter AU Analyzer with reference range of 100-250 U/L and platelet count was measured by Sysmex Hematology Analyzer with reference range of 150-400 10^9/L.

Data Analysis

The frequencies and descriptive statistics were calculated for all variables in SPSS version 23. The data of platelets and LDH was found normalized ($p<0.050$) according to Shapiro-Wilk test. Therefore, the independent samples t-test was applied to find if two groups (i.e., severe and critical patients) were significantly different. The p values of less than 0.050 were considered significant.

RESULTS AND DISCUSSION

Background Information

Mean patient age was 48 years. There were total 24.8% female and 75.2% male patients. There were 12(19.4%) female and 50(80.6%) were male patients in critical cases. There were 23(29.1%) female and 56(70.9%) male patients in severe cases.

Laboratory Findings

Table I shows the minimum, maximum and mean values of platelet count and LDH in both severe and critical cases. The mean values of platelets were found normal, whereas, the mean values of LDH was found elevated in both severe and critical cases.

Table. I: Minimum, Maximum and Mean Values of Platelet Counts and Lactate Dehydrogenase (LDH) in Severe & Critical Patients

Groups	**Platelets** Normal Range: 150-400 10^9/L			**LDH** Normal Range: 100-250 U/L		
	Min.	Max.	Mean	Min.	Max.	Mean
Severe (n=79)	25	547	250.56±103.491	135	2219	643.06±391.48
Critical (n=62)	106	526	257.06±92.69	225	2865	724.25±420.43

Table II shows the frequency distribution of low, high and normal values in severe and critical cases. There was no patient with low value of LDH in both groups. 87% patients were having high values of LDH in severe cases, whereas, 98% patients were having high values of LDH in critical cases.

Majority (72-77%) of the patients (severe-critical) were having normal values of platelet counts in both groups. 43% critically infected patients were having raised D-dimers, whereas, 38% severely infected patients were having raised D-dimers.

Table II. Prevalent frequencies (high, low, normal) of Platelet Counts, Lactate Dehydrogenase (LDH) and D-dimers in Severe & Critical Patients

Groups	Platelets			LDH			D-dimers		
	High (%)	Low n(%)	Normal n(%)	High n(%)	Low (%)	Normal n(%)	High n(%)	Low (%)	Normal n(%)
Severe (n=79)	(7.6%)	16(20.3 %)	57(72.2 %)	69(87.3 %)		10(12.7 %)	30(38%)		49(62%)
Critical (n=62)	(6.5%)	10(16.1 %)	48(77.4 %)	61(98.4 %)		1(1.6%)	27(43.5 %)		35(56.5 %)

Statistical Analysis

According to the t-test, the patient groups: severe and critical were not found statistically significantly different in both continuous variables, i.e., platelet counts [p value: 0.34965; t-value: -0.38707] and LDH [p value: 0.119372; t-value: -1.18322].

DISCUSSION

This study was aimed to find out the primary role of these biomarkers (D-dimers, platelet count and LDH) in interpreting the COVID-19-associated coagulopathy (CAC) in severe and critical cases. We found that although, the majority of the patients were having almost normal values of platelets in both severe and critical categories, but many of them were having raised LDH values. Moreover, the 38-43% patients in severe and critical cases were having raised D-dimers. The severe and critical groups of patients were not found statistically significantly different. In our study, the effect of this virus on the platelets is quite unusual with the most common observation being a mild decrease or no change in majority of the patients. The drop in the platelet count is attributed to the endothelial activation and the consumption of platelets in the formation of micro thrombi at various places in the body (Connors & Levy, 2020).

Elevated D-dimers (>0.5 µg/ml) in the blood of COVID-19 patients has been observed in a large number of patients admitted in the intensive care units and were found an independent predictor for mortality (Schutgens, 2020; Yu et al., 2020). D-dimers were found four times higher in severely affected patients compared to mild-moderate cases (Tang et al., 2020). A poor prognosis has been reported in such severely infected patients (Long et al., 2020; Yu et al., 2020). In a Chinese study, the elevated D-dimers (>0.5 µg/ml) were found in 46.4% patients, raised LDH (≥250 U/L) was found in 41% patients and thrombocytopenia was found in 36.2% patients (Guan et al., 2020). Raised LDH levels were also linked with an increased disease severity and mortality in patients with COVID-19 (Henry et al., 2020). Risk factors associated with lung injury (Liu et al., 2020), acute respiratory distress syndrome (ARDS) and mortality includes elevated levels of both LDH and D-dimers (Wu et al., 2020).

Thrombocytopenia, prolonged PT (pro-thrombin time), and elevated D-dimers are suggestive of DIC. Whereas, in SIC, thrombocytopenia is usually more profound with no or modest elevation of the D-dimers. Therefore, CAC is a distinct entity which includes a prominent elevation of D-dimers with minimal abnormalities in the platelet count and PT (Connors & Levy, 2020). Along with D-dimer elevation and platelet count reduction, the considerable increase of LDH is a hallmark of hemolysis and endothelial damage hence pointing towards hemolytic implications (Liu et al., 2020; Shi et al., 2020).

The interim guidelines for COVID-19 management recommend regular monitoring of D-dimers, pro-thrombin time (PT), and platelet counts in all symptomatic COVID-19 patients for earlier detection of CAC in order to commence the prophylactic use of anti-coagulation i.e. low molecular weight heparin (LMWH) (Levi et al., 2020; Lancet Hematology, 2020). Lactic

dehydrogenase (LDH) is elevated in intravascular hemolysis and can be used as a surrogate marker for hemolysis which greatly contributes towards coagulopathy as per Virchow's triad.

LIMITATIONS

The present study has a couple of limitations; firstly, large sample size would certainly improve the precision of results; secondly, growing evidence regarding various preliminary biomarkers of the disease severity is keeping the medical experts on their toes since beginning of the pandemic.

CONCLUSION

In the developing countries like Pakistan, LDH along with platelet counts and D-dimers can make a cost effective trio for an earliest detection of COVID-19-associated coagulopathy (CAC) and subsequent commencement of prophylactic anticoagulation. However, further studies are needed for the formation of of meticulous clinical practice guidelines.

Authors report no conflict of interest.

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