ORIGINAL RESEARCH PAPER
Volume - 9 | Issue - 9 | September - 2020 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

HEMATOLOGICAL FINDINGS AND COMPLICATIONS IN COVID 19 PATIENTS: A REVIEW.

Pathology

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ABSTRACT

COVID-19 is a systemic infection with a significant impact on the hematopoietic system and hemostasis. Lymphopenia may be considered as a cardinal laboratory finding, with prognostic potential. Neutrophil/lymphocyte ratio and peak platelet/lymphocyte ratio may also have prognostic value in determining severe cases. During the disease course, longitudinal evaluation of lymphocyte count dynamics and inflammatory indices, including LDH, CRP and IL-6 may help to identify cases with dismal prognosis and prompt intervention in order to improve outcomes. Biomarkers, such high serum procalcitonin and ferritin have also emerged as poor prognostic factors. Furthermore, blood hypercoagulability is common among hospitalized COVID-19 patients. Elevated D-Dimer levels are consistently reported, whereas their gradual increase during disease course is particularly associated with disease worsening. Other coagulation abnormalities such as PT and aPTT prolongation, fibrin degradation products increase, with severe thrombocytopenia lead to life-threatening Disseminated intravascular coagulation (DIC) which necessitates continuous vigilance and prompt intervention. COVID-19 infected patients whatever hospitalized or ambulatory are at high risk for VTE and an early and prolonged pharmacological thromboprophylaxis with low molecular weight heparin is highly recommended. Last but not least, the need for assuring blood donations during the pandemic is also of indispensable value.

KEYWORDS

Coagulation; Coronavirus; COVID-19; Lymphocytes; SARS-CoV-2.

INTRODUCTION

In December 2019, many patients with pneumonia of unknown aetiology were reported by the health organisations in Wuhan, Hubei Province, China [1]. By the end of early January 2020, the causative agent of this pneumonia of unknown aetiology was identified as a novel coronavirus by many independent laboratories in China. The World Health Organization (WHO) has named this causative virus as novel coronavirus 2019 (2019-nCoV) [2]. Humans can be infected by six coronaviruses that (HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1, SARS-CoV, and MERS-CoV). The first four viruses mainly cause the common cold, whereas the SARS-CoV and MERS-CoV viruses cause severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), respectively [3].

According to the WHO, till now there are 45,25,420 confirmed cases and 303341 estimated deaths in world by 15th may, 2020. The 2019-nCoV, SARS-CoV and MERS-CoV have several common clinical presentations, which vary from asymptomatic infection to severe diseases and severe acute respiratory syndrome [4, 5]. Various haematological and biochemistry findings in COVID-19 patients may provide clues for ongoing and future research projects concerning the investigations of the2019-nCoV. In this review, we have tried to apply current understanding of the haematological and biochemistry findings in COVID-19 patients for the characterization of 2019-nCoV.

COVID-19 is a systemic infection with a significant findings like lymphopenia , altered Neutrophil/lymphocyte ratio, peak platelet/ lymphocyte ratio, blood hypercoagulability, elevated D-Dimer levels, PT, aPTT prolongation, increase in fibrin degradation products, severe thrombocytopenia and Disseminated intravascular coagulation (DIC). Inflammatory indices, including LDH, CRP, IL-6, high serum procalcitonin and ferritin have also emerged as poor prognostic factors [6].

Review Of Literature

Guan et al provided data on the clinical characteristics of 1,099 COVID-19 cases with laboratory confirmation during the first two months of the epidemic in China. It was observed that the vast majority of patients presented with lymphocytopenia (83.2%), whereas 36.2% had thrombocytopenia and 33.7% showed leukopenia. These haematological abnormalities were more prominently seen among severe versus non-severe cases (96.1% versus 80.4% for lymphocytopenia, 57.7% versus 31.6% for thrombocytopenia and 61.1% versus 28.1% for leukopenia). These results were also found to be consistent with four other descriptive studies that were conducted during the same period in China and included 41, 99, 138 and 201 confirmed cases with COVID-19, respectively [7].

A retrospective single-centres case series analysed patients with COVID-19 at the Seventh Hospital of Wuhan City, China, including 187 patients with COVID-19 from another hospital in Wuhan showed that patients with high troponin-T levels (TnT) had leucocytosis ($p<0.001$), increased neutrophils ($p<0.001$) and decreased lymphocytes ($p=0.01$). The mortality during hospitalization was 7.62% (8 of 105) for patients without underlying CVD and normal TnT levels, 13.33% (4 of 30) for those with underlying CVD and normal TnT levels, 37.50% (6 of 16) for those without underlying CVD but elevated TnT levels, and 69.44% (25 of 36) for those with underlying CVD and elevated TnTs. Patients with underlying CVD were more likely to exhibit elevation of TnT levels compared with the patients without CVD (36 [54.5%] versus 16 [13.2%] [8].

Qu et al showed that among 30 hospitalized patients with COVID-19, those presenting with a peak in the platelet count during the disease course had worse outcomes. The platelet to lymphocyte ratio at the time of platelet peak emerged as an independent prognostic factor for prolonged hospitalization in the multivariate analysis. It was suggested that a high platelet to lymphocyte ratio may indicate a more pronounced cytokine storm due to enhanced platelet activation [9].

Regarding ferritin, Wu et al in their retrospective cohort study of 201 patients with confirmed COVID-19 pneumonia admitted to Wuhan Jinyintan Hospital in China showed that higher serum ferritin was associated with ARDS development in COVID patients (HR=3.53, 95%CI: 1.52-8.16, $p=0.003$); the trend of an association with survival did not reach significance (HR=5.28, 95%CI: 0.72-38.48, $p=0.10$) and concluded that older age was associated with greater risk of development of ARDS and death likely owing to less rigorous immune response. Although high fever was associated with the development of

ARDS, it was also associated with better outcomes among patients with ARDS [10].

Another emerging biomarker for COVID-19 course is interleukin-6 (IL-6). In the study by Chen et al 52% (51/99) of patients had elevated IL-6 levels at admission. Increased IL-6 levels have been associated with increased risk of death and a gradual increase during hospitalization has been reported in non-survivors [11].

Coagulation disorders are relatively frequently encountered among COVID-19 patients, especially among those with severe disease. Guan et al in a multicentre retrospective study during the first two months of the epidemic in China, found that 260 out of 560 patients (46.4%) with laboratory confirmed COVID-19 infection had elevated D-dimer (≥0.5 mg/L), whereas the elevation was more pronounced among severe cases (59.6% versus 43.2% for non-severe ones). Lymphocytopenia was also present in 83.2% of the patients, thrombocytopenia in 36.2%, and leukopenia in 33.7%. Most of the patients had elevated levels of C-reactive protein; less common were elevated levels of alanine aminotransferase, aspartate aminotransferase and creatine kinase. Patients with severe disease had more prominent laboratory abnormalities (including lymphocytopenia and leukopenia) than those with non severe disease [7].

Another retrospective study in China including 41 patients showed that D-dimer and prothrombin time (PT) levels were higher on admission among patients requiring ICU support (median D-dimer 2.4 mg/L for ICU versus 0.5 mg/L for non-ICU, p=0.0042; median PT 12.2 sec for ICU versus 10.7 sec, p=0.012) [12].

S Shi et al in their study found that patients presenting with cardiac injury in the context of COVID-19 infection are more prone to coagulation disorders compared with those without cardiac involvement (p=0.02). Complications were more common in patients with cardiac injury than those without cardiac injury and included acute respiratory distress syndrome (48 of 82 [58.5%] vs 49 of 334 [14.7%]; P<.001), acute kidney injury (7 of 82 [8.5%] vs 1 of 334 [0.3%]; P<.001), electrolyte disturbances (13 of 82 [15.9%] vs 17 of 334 [5.1%]; P=.003), hypoproteinaemia (11 of 82 [13.4%] vs 16 of 334 [4.8%]; P=.01), and coagulation disorders (6 of 82 [7.3%] vs 6 of 334 [1.8%]; P=.02). Patients with cardiac injury had higher mortality than those without cardiac injury (42 of 82 [51.2%] vs 15 of 334 [4.5%]; P<.001) [13].

T Guo in a retrospective single-centre case series analysed patients with COVID-19 at the Seventh Hospital of Wuhan City, China and observed the association of underlying cardiovascular disease (CVD) and myocardial injury with fatal outcomes in patients with COVID-19. Patients with high troponin-T levels may present more frequently with elevated PT (p=0.005), activated partial thromboplastin time (APTT) (p=0.003), and D-dimer (p<0.001) [8].

F Zhou et al in a multicentre retrospective cohort study from China with laboratory-confirmed COVID-19 from Jinyintan Hospital and Wuhan Pulmonary Hospital (Wuhan, China) showed that increased D-dimer levels (>1μg/mL) were significantly associated with in-hospital death in the multivariable analysis (p=0.003) [15]. In another retrospective study by Tang et al, encompassing data from 183 consecutive patients with COVID-19, non-survivors had significantly higher D-dimer (p<0.05), fibrin degradation products (FDP) levels (p<0.05), and prolonged PT (p<0.05) and APTT (p<0.05) compared with survivors at initial evaluation. By the late hospitalization, the fibrinogen and AT levels were also significantly lower in non-survivors [15].

Yang Ai-Ping et al investigated and compared neutrophil (NEU)-to-lymphocyte (LYM) ratio (NLR), lymphocyte-to-monocyte (MON) ratio, platelet-to-lymphocyte ratio (PLR), and C-reactive protein (CRP) of 93 patients with laboratory confirmed COVID-19. In their study they observed that elevated NLR and age were significantly associated with illness severity. The binary logistic analysis identified elevated NLR (hazard risk [HR] 2.46, 95% confidence interval [CI] 1.98–4.57) and age (HR 2.52, 95% CI 1.65–4.83) as independent factors for poor clinical outcome of COVID-19. NLR exhibited the largest area under the curve at 0.841, with the highest specificity (63.6%) and sensitivity (88%) [16].

Liu Yuwei retrospectively analyzed Neutrophil-to-lymphocyte ratio (NLR) as a risk factor for mortality in hospitalized patients with COVID-19 admitted to the Zhongnan Hospital of Wuhan University. 245 COVID-19 patients were included in the final analyses and the in-hospital mortality was 13.47%. Multivariate analysis demonstrated that there was 8% higher risk of in-hospital mortality for each unit increase in NLR (Odds ratio [OR]=1.08; 95% confidence interval [95% CI], 1.01 to 1.14; P=0.0147). Compared with patients in the lowest tertile, the NLR of patients in the highest tertile had a 15.04-fold higher risk of death (OR=16.04; 95% CI, 1.14 to 224.95; P=0.0395) after adjustment for potential confounders. Notably, the fully adjusted OR for mortality was 1.10 in males for each unit increase of NLR (OR=1.10; 95% CI, 1.02 to 1.19; P=0.016) and concluded NLR as an independent risk factor of the in-hospital mortality for COVID-19 patients especially for male. Assessment of NLR may help identify high risk individuals with COVID-19 [17].

Arentz Matt et al studied characteristics and outcomes of 21 critically ill patients with covid-19 in Washington stated that the mean white blood cell count was 9365/ μl at admission and 14 patients (67%) had a white blood cell count in the normal range. fourteen patients (67%) had an absolute lymphocyte count of less than 1000 cells/μl. Liver function tests were abnormal in 8 patients (38%) at admission [18].

Bhatraju et al studied Covid-19 related changes in Critically Ill Patients in the Seattle Region. On admission, lymphocytopenia was common (in 75% of the patients), with a median lymphocyte count of 720 per cubic millimetre (interquartile range, 520 to 1375). Arterial lactate was found to be 1.5 mg per decilitre or higher in 8 patients, and hepatic enzymes were 40 U per litre or higher in 9 patients. Troponin concentrations were elevated in 2 patients early in their ICU course (maximum value, 0.80 ng per decilitre) [19].

Thachil J et al studied coagulopathy associated with COVID-19. International Society on Thrombosis and Haemostasis which stated that increased d-dimers are commonly reported in patients with severe illness and may predict mortality. Prolongation in prothrombin times and degree of thrombocytopenia ($100–150\times10^9$/L) have been modest. In addition to the above parameters, fibrinogen should be monitored; non survivors with severe illness have developed disseminated intravascular coagulation around day 4; significant worsening in these parameters at days 10 and 14 was also reported [20].

Terpos et al in their study stated that during the incubation period peripheral blood leukocyte and lymphocyte counts are normal or slightly reduced. Approximately 7 to 14 days from the onset of the initial symptoms, there is a surge in the clinical manifestations of the disease with a pronounced systemic increase of inflammatory mediators and cytokines, which may even be characterized as a “cytokine storm”. At this point, significant lymphopenia becomes evident. Although more in-depth research on the underlying aetiology is necessary, several factors may contribute to COVID-19 associated lymphopenia. Furthermore, the cytokine storm is characterized by markedly increased levels of interleukins (mostly IL-6, IL-2, IL-7, granulocyte colony stimulating factor, interferon-γ inducible protein 10, MCP-1, MIP1-a) and tumour necrosis factor (TNF)-alpha, which may promote lymphocyte apoptosis [6].

DISCUSSION

The pathological findings in this review article are representative of the various studies conducted on cases of COVID-19.

Guan et al provided data on the clinical characteristics of laboratory confirmation during the first two months of the epidemic in China. In their study it was observed that the vast majority of patients presented with lymphocytopenia whereas others showed thrombocytopenia and leukopenia. These haematological abnormalities were more prominently seen among severe cases [7]. Bhatraju et al studied Covid-19 related changes in critically ill patients in the Seattle Region. On admission, lymphocytopenia was common in patients with a median lymphocyte count of 720 per cubic millimetre. Arterial lactate was found to be 1.5 mg per decilitre or higher in 8 patients, and hepatic enzymes were 40 U per litre or higher in 9 patients. Troponin concentrations were found to be elevated in 2 patients early in their ICU course [19].

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that a high platelet to lymphocyte ratio may indicate a more pronounced cytokine storm due to enhanced platelet activation [9]. In Guan et al study, they also observed that in 260 out of 560 patients with laboratory confirmed COVID-19 infection had elevated D-dimer, whereas the elevation was more pronounced among severe cases. Lymphocytopenia was also in 83.2% of the patients, thrombocytopenia in 36.2%, and leukopenia in 33.7%. Most of the patients had elevated levels of C-reactive protein; less common were elevated levels of alanine aminotransferase, aspartate aminotransferase and creatine kinase. Patients with severe disease had more prominent laboratory abnormalities (including lymphocytopenia and leukopenia) than those with non severe disease [7]. Another retrospective study in China by Huang et al showed that D-dimer and prothrombin time (PT) levels were higher on admission among patients requiring ICU support [12]. T Guo in a retrospective single-centre case series analysed patients with COVID-19 at the Seventh Hospital of Wuhan City, China and observed the association of underlying cardiovascular disease (CVD) and myocardial injury with fatal outcomes in patients with COVID-19. Patients with high troponin-T levels may present more frequently with elevated PT, activated partial thromboplastin time (APTT) and D-dimer. F Zhou et al in a multicentre retrospective cohort study from China with laboratory-confirmed COVID-19 from Jinyintan Hospital and Wuhan Pulmonary Hospital (Wuhan, China) showed that increased D-dimer levels were significantly associated with in-hospital death in the multivariable analysis [14].

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The reason behind coagulopathy seen in severely ill COVID 19 patients could be association with the infection, inflammatory factor storm (cytokine storm), hematopoietic system damage, ischemia and hypoxia-reperfusion injury, drugs and other factors. However, further studies are required to delineate the exact cause [21].

CONCLUSION

Haematological changes are common in patients with COVID 19 which include reduced lymphocyte and platelet count, prolonged activated partial thromboplastin time and increased D- dimer levels and most patients had normal prothrombin time. Multiple studies done suggest that patients who were critically ill displayed severe virus related symptoms, were also found to have coagulation dysfunction of varying severity. In most of the cases platelet counts did not decrease to a level at which bleeding occurs. Hence, it is imperative on the part of intensivists to closely monitor haematological and coagulation parameters enabling them to take timely action and prevent mortality and morbidity due to COVID 19 infection.

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