Evaluation of Hematological Changes During COVID-19: A Systematic Review

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ABSTRACT

Objectives: COVID-19 pandemic has affected more than 6 million people globally. Most of the affected patients presents with fever, cough, nausea, vomiting, fatigue and dyspnea. Molecular testing by PCR is gold standard test to diagnose COVID-19 infection but if unavailable, hematological profile of COVID-19 patients is a good prognostic marker for COVID-19 disease. The aim of our review is to summarize the recently available literature regarding hematological alterations in COVID-19 patients along with their trend in the disease course and their prognostic implications in terms of severe disease.

Design: Systematic review.

Methods: Literature published between 2020 to 2022 on Google Scholar was included in our review by following PRISMA guidelines. Articles were shortlisted on the basis of inclusion and exclusion criteria.

Results: Total 139 articles were initially identified. After removal of duplicates and screening on basis of present exclusion and inclusion criteria 17 articles were found. Out of these 17 articles, there were 10 retrospective studies, 3 prospective studies, 2 case control studies and 2 cross sectional studies.

Conclusion: Hematological markers predicts the outcome of COVID in patients irrespective of their age, gender and co-morbidities. There is a positive relationship between disease severity and blood count of neutrophils, leukocytes, NLR, MDW, thrombocytopenia, lymphocytopenia, IL-6 and CRP.

Keywords: Hematological changes, Complete blood count, Immunological markers, Lymphopenia, Lymphocytosis, Thrombocytopenia, COVID-19, Corona Virus

INTRODUCTION

Corona virus, also known as COVID-19, is a highly contagious virus that was initially discovered in China in the end days of December 2019[1]. Till now, almost 541 million cases have been diagnosed with COVID-19 of which almost 6 million patients have died[2]. COVID-19 was declared as a pandemic by World Health Organization on 11th March 2020[3]. Till now, various strains of COVID-19 have hit the world and the virus is still changing strains everyday[4]. COVID-19 belongs to a family of SARS-Cov-2, known as Beta coronavirus, that is genetically identical to (MERS-CoV) (Middle East Respiratory Syndrome coronavirus) and (SARS-CoV) Severe Acute Respiratory Syndrome Virus[5]. Almost 80% of patients who suffer from COVID-19 remain asymptomatic or have mild symptoms that recover either spontaneously or by supportive therapy without development of any complication and need for hospitalization[6]. Most of the patients who have confirmed COVID-19 disease presents clinically with fever, cough, nausea, vomiting, fatigue and dyspnea but according to some studies, fever is less common in SARS-CoV-2 as compared to SARS-CoV and MERS-CoV[7]. The most frequently encountered gastrointestinal symptoms were nausea, vomiting, abdominal pain and diarrhea that was often associated with headache and myalgias. Moreover, sudden loss of olfactory sensation has also been reported by many studies even in asymptomatic patients[8]. The diagnosis of SARA-CoV-2 is made on detection of virus in nasopharyngeal and oropharyngeal secretions but it is evident from literature that the virus is also present in tears, breast milk and semen of COVID-19 infected patients hence these body secretions can be used as an alternative sample for diagnosis of COVID-19 via molecular testing[9]. Researches that have done so far on infectivity of COVID-19 have shown that children aged less than 14 are less susceptible to acquiring COVID-19 infection than adults (aged between 15 to 64 years) while on the other hand, people greater than 65 years of age are more prone to acquire COVID-19 in comparison to adults[9].

Initial hematological picture of COVID-19 virus as depicted by laboratory analysis have shown an increased neutrophil level (greater than 0.70×10^3 per μL), decreased lymphocyte count (less than 0.8×10^3 per μL), increased level of CRP (greater than 4.75 mg/dl) and increased LDH levels (greater than 593 u/l). All these laboratory parameters were considered as predictors of mortality in the initial course of disease[10]. Lymphopenia is a common hematological finding in COVID-19 (in which there is reduced levels of CD4 and CD8 cells) along with thrombocytopenia and leukopenia[11]. CD4 and CD8 T-lymphocytes are basic element of body immunity and helps the individual to fight against virus and eliminate it from body and are thus useful markers of severity of disease as well as prognostic markers to assess the clinical outcomes of disease[12]. According to Li et al, increased serum Amyloid levels is also significant marker of severity in COVID-19 disease and should be correlated clinically with other laboratory parameters[13]. Complicated COVID-19 infection presents with acute renal failure, myocardial infarction, muscle injury and gastrointestinal bleeding along with some superadded secondary infections (both bacterial and fungal)[14].

Although diagnosis of COVID-19 is made on molecular testing via polymerase chain reaction (PCR), the role of hematological,

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radiological and biochemical markers is important in determining the severity of disease, its clinical outcome and prognosis of disease[15]. Hematological changes of COVID-19 are observed basically in two hematological test, Complete blood count and coagulation profile. Several physicians have identified hematological changes in COVID-19 as an indicator COVID-19 disease in situation where clinical picture of patient is contradictory and molecular testing is not available[16-18]. The aim of our review is to summarize the recently available literature regarding hematological alterations in COVID-19 patients along with their trend in the disease course and their prognostic implications in terms of severe disease.

METHODS

Search Strategy: We searched the literature from 20th May, 2022 to 26th May,2022 by using Google Scholar databases. "Hematological changes", "Complete blood count", "Immunological markers", "lymphopenia", "lymphocytosis", "thrombocytopenia", "COVID-19" and "Corona Virus." were used as keywords. Only articles published in English language were recruited. Duplicates were removed from data manually.

Studies which explained the hematological changes in COVID-19 disease were included. Meanwhile, studies which have:

- Duplicate publications
- Full articles not available
- Publications in languages other than English and
- Review Articles
- Articles discussing hematological changes of COVID-19 in children, pregnant ladies and persons with any underlying autoimmune diseases.

Search strategy is summarized in figure 1.

Data Extraction and Analysis: To conduct this study the author's name, type of research, hematological parameter studied and findings were reviewed.

RESULTS

Total 139 articles were initially identified. After removal of duplicates and screening on basis of preset exclusion and inclusion criteria 17 articles were found. Out of these 17 articles, there were 10 retrospective studies, 3 prospective studies, 2 case control studies and 2 cross sectional studies. The included articles are summarized below.

DISCUSSION

Hematological and Immunological Variation : In July 2020 a study done in Wuhan, China comparing immunological and haematological variations among survivors and non-survivors of COVID-19, which clearly showed that early in disease there was decreased count of lymphocytes, eosinophils and platelets while increase count in neutrophils, leukocyte, increase neutrophil to lymphocyte ratio (NLR) and interleukin-6 (IL-6). The counts reversed in survivors and remained same among non-survivors serving a reliable marker of recovery[19]. According to a study by Usul E et al. the cut-off point for platelet values was found to be <210. The cut-off value for NLR was observed to be a little less than 2. The cut-off point for leukocyte values was found to be <8. The limit point for neutrophil values was found to be approximately 4. The cut-off point for hemoglobin was found to be >14. The cut-off point for SII values was found to be ≤480 among COVID-19 positive patients[20].

According to another study materialized in Pakistan, White blood cells were tested in 475 individuals, and therefore the Positive group's leukocytosis was significantly higher than the Control groups. Also, Platelet to lymphocyte ration and neutrophil to lymphocyte ratio vary considerably. Both patients and controls showed low lymphocyte count (p 0.001). Not all the biochemical indicators were examined in healthy controls due to an absence of resources. Between critically ill and non-critically ill patients, there was a significant difference in serum levels of inflammatory markers like ferritin, D-Dimer and CRP, procalcitonin and LDH levels along with some interleukins like IL-6. Levels of liver enzymes like ALT, AST was also deranged and clotting profile of patients including PT and APTT was abnormal[21]. A study revealed that COVID-19 positive with critical condition had more immature granulocyte than patients with mild disease. Also, neutrophils in covid positive patients had hypo granulated neutrophils and fewer number of reactive lymphocytes[22]. In his study concluded that the critical group had pointedly greater WBC, NLR, immature granulocyte% and CRP levels. Neutrophil dysplasia, including chromatin abnormalities APHA and degranulation was detected in about 71% of patients with severe disease and around 55% of patients with mild disease. In COVID- 19 patients, the deadly changes %, Döhle body, vacuole count and no. of giant neutrophils there have been considerably higher. The severe group had higher percentages than in mild group ($P < .01$) reflecting that this infection induces systemic inflammatory response[23]. Results from 555 patients—236 female and 319 males—were compared to those from 532 patients—226 female and 306 males—in the non-ICU group and 23 patients—10 female and 13 males—in the ICU group. As compared to individuals hospitalized for non-urgent ailments, ICU patients had a greater average age. When the ICU admitted, patients were equated to the non-ICU group, the lymphocyte (except for > 7 days) RBC, haemoglobin, creatine kinase, LMR, eGFR were reduced. Values of the lymphocytes, neutrophils, P-LCR, and total bilirubin were discovered to be relevant electing to consult an ICU. Patients with atypical findings on Xray had a prolonged Partial thromboplastin time.

Those who had abnormal picture of x-ray had a really high levels of K^+ in blood[24].

A study by Hasan A et al. stated that out of 121 COVID-19 patients in our ICU, 85 died and 36 recovered. WBC, total neutrophil count, neutrophil to lymphocyte ratio (NLR), CRP, D-dimer and ferritin level were all elevated from normal values among 85 expired patients, while lymphocyte and platelet count were lowered in 56.79% and 67.06% of cases, respectively. The typical levels of the biomarkers CRP, ferritin, D-dimer, WBC, absolute neutrophil, and neutrophil to lymphocyte ratio (NLR) are much greater in patients who have gave up the ghost than in people who are treated. Conversely, individuals who have kicked the bucket had lower levels of haemoglobin (Hb), absolute lymphocyte, absolute eosinophil, lymphocyte to C-reactive protein ratio (LCR), and platelet count. Serum levels of various electrolytes were also varying among patients of COVID-19[25]. According to a study situated in Nepal, out of 100 participants, 96% had WBC count above 12,000/ cmm. 25 you look after them has leukocyte count above 24,000/ cmm. the best increase in TLC was seen in an exceedingly 46-year-old male, reaching 51.000/cmm. only 1 case (1%) of leucopenia revealed a decrease in total leucocyte count, while five (5%) patients had normal total leucocyte counts. 49 (49%) of the patients had neutrophil differential counts that were over 90% of all WBCs. Above 85 % showed significantly low count o lymphocytes. Eosinophilia and monocytopenia was also observed in quite a majority[26]. A study situated in Dhaka stated that out of 92 covid positive cases, ICU patients had a lower haemoglobin level (Hb <13gm/dl, 64% vs 34% in ICU and non-ICU cases respectively, p value=.028)[27].

Variations in Enzymes: A study by Ali ET et al. revealed significant statistical differences between the group containing healthy people

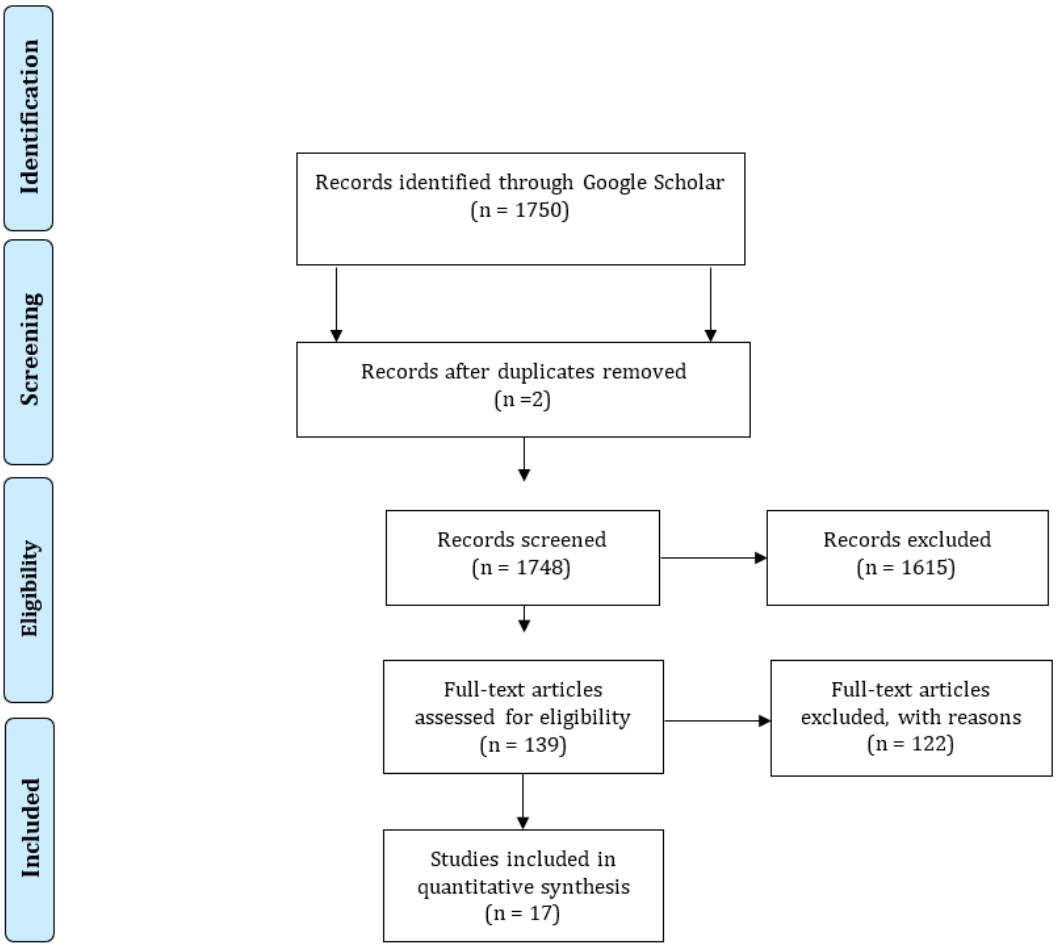

Figure 1: Search strategy

and group with mildly or severely ill patients. and mild groups were found within the data analysis accustomed evaluate the haematological parameters of the groups ($p > 0.05$). in comparison to the moderate and healthy groups, the severe group's mean RBC values revealed a substantial reduction. When comparing the complete severe group with every other group, the analysis of biochemical data showed that LDH (Lactate dehydrogenases), ferritin, ALT (Alanine Transaminases), and AST (Aspartate Transaminases) all had significant differences. D-dimer and APTT didn't significantly change, and Trop-T (Troponin T) was negative in each group[28]. Routine blood values were accustomed predict the mortality and treatment response in patients of COVID-19 including higher pre-post values of alkaline phosphate along with increases in serum values of creatine kinase myocardial band (CK-MB), aspartate aminotransferase, Total bilirubin, Conjugated bilirubin, creatinine kinase, lactate dehydrogenase (LDH), glucose, serum levels of creatine, urea and acid within the deceased group while total protein and albumin were lesser through this group. The before and after levels of alanine amino-transaminase, estimated glomerular filtration rate and albumin were lesser within the deceased group. Additionally, to those, the hematological parameters in non-survivors presented to us with deranged values of serum inflammatory markers including C-reactive protein (CRP), serum levels of D-dimer, ferritin and procalcitonin. Further, estimated Sedimentation rate of patients (ESR), was also increased along with deranged clotting profile of patients including INR, PT and APTT. Hematological profile showed increase in TLC count with more neutrophils, increased RBC and platelet count. Similarly, Reticular Distribution Width was also disturbed in these patients with the figures being >12 × 109/L, >15%, >10 × 109/L, >149 × 109/L, and < 3 × 1012/L for mortality, respectively. Reduced immunity and various comorbidities were seen to affect the prognosis negatively[29].

Role of Inflammatory Markers in Prognosis : From a study of Ganji A et al. it is concrete that the immunologic response to the COVID infection is by over-appearance of CD8 and hyper stimulation of CTL immune responses against viruses and not by changes in ratio of CD4:CD8 and CD4 MFI (mean florescence intensity) as in other viral infections[30]. Inflammation markers like CRP, lactate dehydrogenase, ferritin, and procalcitonin showed a big direct correlation between MDW and COVID, consistent with the findings of this. Interestingly, there was no relationship between fibrinogen level and MDW or Troponin, however there was a considerable relationship between MDW and also the PT, activated partial thromboplastin time (APTT), and D-Dimer. The liver enzymes aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin all showed positive correlations with MDW. Albumen and MDW had the only negative connection ($r = -0.322$, $p = 0.001$). Patients with MDW around 25 (Q4) displayed a considerable link with Covid-related blood biomarkers that were related to poor prognosis when the assorted blood biomarkers in each MDW quartile were compared[31]. IL-6 was found to be a reliable marker for prediction the severity and mortality with discontinue value of approximately 40pg/ml and 85pg/ml correspondingly. It had been observed to be in negative co relation with lymphocyte count, positive predictor of mild diseases as tocilizumab was seen to boost the lymphocytopenia[32].

There is a considerable variance in levels of inflammatory markers including CRP and procalcitonin levels among patients who reported atypical x-ray results to those that presented with normal x-ray (all oxygen were considerably poorer among subjects with atypical x-ray results (all $P < 0.05$)[33].

Variations in Patients Taking Immunosuppressive Drugs: 49% of 151 (about seventy-four) patients who were immunocompetent with COVID were admitted and required assisted oxygenation. The proportion of this rose to 75% in immunosuppressed patients by COVID-19. Although thrombocytopenia was seen in both immunosuppressed and immunocompetent patients. In adding our study disclose that decreased platelet count was more prevalent in patients with immunosuppression than within the immunocompetent patients fighting with COVID-19. Results showed a major decrease in median value of eosinophils in patients, approaching the lower limit of zero. A considerable low monocyte count and corresponding lymphocyte count was observed in patients taking immunosuppressive drugs[34].

Variations Regarding Mortality with Relation to BMI and Comorbidity: A study situated in Saudi Arabia, reinforces this information where data from 96 COVID-19 patients were evaluated, 64 (66.7%) of whom were male and 32 (33.3%) were female. The mean age of the PA group was 64 14 years, compared to 57 16 years for the Discharged group ($P > 0.05$). Body mass index (BMI), Age, any debility (GMB, HBM, HRM) were compared between the three patient groups for this study. Discharged and passed on to the great beyond Patients within the Study Groups (DC, PA, WBC, and RBC) as compared to the deceased (PA) group, the discharged group (DC) had significantly greater red vegetative cell counts, haemoglobin (Hb), hematocrits, and platelet counts (P 0.05). Six patients (6%) had diabetes (DM), 29 (30.20%) had both HTN and DM, and 15 (15.63%) patients had hypertension (HTN)[35].

CONCLUSION

There is a significant relationship between hematological, immunological and inflammatory markers to predict the outcome of COVID in patients irrespective of their age, gender and co-morbidities. Positive relationship was seen between disease severity and blood count of neutrophils, leukocytes, NLR, MDW, thrombocytopenia, lymphocytopenia, IL-6 and CRP.

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