Hematological changes associated with COVID-19 infection

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Abstract

Background: The unresolved COVID-19 pandemic considerably impacts the health services in Iraq and worldwide. Consecutive waves of mutated virus increased virus spread and further constrained health systems. Although molecular identification of the virus by polymerase chain reaction is the only recommended method in diagnosing COVID-19 infection, radiological, biochemical, and hematological studies are substantially important in risk stratification, patient follow-up, and outcome prediction.

Aim: This narrative review summarized the hematological changes including the blood indices, coagulative indicators, and other associated biochemical laboratory markers in different stages of COVID-19 infection, highlighting the diagnostic and prognostic significance.

Methods: Literature search was conducted for multiple combinations of different hematological tests and manifestations with novel COVID-19 using the following key words: “hematological,” “complete blood count,” “lymphopenia,” “blood indices,” “markers,” “platelet” OR “thrombocytopenia” AND “COVID-19,” “coronavirus2019,” “2019-nCoV,” OR “SARS-CoV-2.” Articles written in the English language and conducted on human samples between December 2019 and January 2021 were included.

Results: Hematological changes are not reported in asymptomatic or presymptomatic COVID-19 patients. In nonsevere cases, hematological changes are subtle, included mainly lymphocytopenia (80.4%). In severe, critically ill patients and those with cytokine storm, neutrophilia, lymphocytopenia, elevated D-dimer, prolonged PT, and reduced fibrinogen are predictors of disease progression and adverse outcome.

Conclusion: Monitoring hematological changes in patients with COVID-19 can predict patients needing additional care and stratify the risk for severe course of the disease. More studies are required in Iraq to reflect the hematological changes in COVID-19 as compared to global data.

KEYWORDS
CBC, coagulopathy, COVID-19, hematology
INTRODUCTION

The highly contagious novel coronavirus, also known as COVID-19 and SARS-CoV-2, was first reported in Wuhan, China, in December 2019. 1-2 It has spread worldwide over 110 countries affecting over 118,000 cases in a short period of less than 4 months raising a global concern. Hence, World Health Organization (WHO) declared COVID-19 a pandemic on March 11.

During 2020, two waves of COVID-19 hit Europe. 3 The first spike was in April which has been managed with general restrictions and lockdown in the absence of curative treatment and vaccine, followed by the second wave with a soaring number of cases recorded in November. By contrast, the number of the new cases in the United States and Asia continued to increase relatively steadily to peak in November. In Iraq, the first reported case was in February, 4 then the cases slowly increasing until June 20, when the number of new cases first crossed the 1000 mark contrasting the pattern of the neighboring countries such as SA, UAE, Jordan, and Iran which had significant decline in their cases by June. Regression in the reported numbers was noticed until 10th Feb 2021 when numbers escalated again, yet the Ministry of health has not confirmed European mutated strain in Iraq. 5

Novel COVID-19 is a single-stranded RNA from Coronaviridae family. It is an enveloped human β-coronavirus which shares 80% of human SARS-CoV-1 genetic sequence and 96.2% of bat coronavirus RaTG13. 6 Virus envelop is coated by spike (S) glycoprotein consisting of S1 and S2 subunits. S1 mediates virus entry by binding host angiotensin-converting enzyme 2 (ACE2), sialic acid, 7 and CD147. 8 Several strains of COVID-19 appeared since it was first reported. Phylogenetic tree analysis identified various Asian strains (L, S, V, O) and European strains (G, GH, GR). 9 GR strain has exposed to several mutations in S1 subunit, of which G614 variant linked to increased virus infectivity and transmissibility rather than severity of the illness compared to the original D614 form 9,10 via promoting viral replication in human lung epithelial cells and primary human airway tissues. 11

The clinical manifestations of novel COVID-19 vary from asymptomatic to acute respiratory distress, depending on virus rout of entry, virus load, host immunity, and comorbidity human. 12 Common clinical presentation is summarized in Table 1. Respiratory and gastrointestinal infection represent the bulk of the COVID-19-positive patient presentation, yet, asymptomatic/ presymptomatic infection is estimated to be 40% of all cases. 13 Many extrapulmonary neurological, dermatological, and cardiovascular manifestations have been frequently reported 14 concomitant with, after, or less frequently independent of respiratory infection (Table 1). Acute respiratory distress and subsequent respiratory failure are the leading cause of death in COVID-19-positive patients. 15,16

Although molecular identification of the virus by polymerase chain reaction (PCR) is the only recommended method in diagnosing COVID-19 infection 17,18 radiological, biochemical, biomarkers, and hematological studies are substantially important in risk stratification, patient follow-up, and outcome prediction. 19-21 Hematological tests including complete blood picture and coagulation studies in PCR-positive patients depict variable degree of changes according to the patient immune response and infection severity. 22 Many physicians consider early hematological changes as a clue for COVID-19 infection when the presenting sign and symptoms are unusual particularly when there is constrain of molecular testing. 23 On the other hand, hematological changes provide help when the symptomatic patient receives a negative molecular test, fishing for patients who require PCR test repeat. Taking into consideration the marked heterogeneity of the reference ranges of complete blood cell counts and leukocyte differential cell counts in different racial, ethnic group, 24 in this review, we summarized the hematological changes in different stage of COVID-19 infection highlighting the diagnostic and prognostic significance.

| TABLE 1 | Clinical manifestations of patients with COVID-19 |
|----------|--------------------------------------------------|
| Clinical manifestations | % |
| Nonspecific 14 | Fever |
| | Malaise |
| | Fatigue |
| | Anorexia |
| | Myalgia |
| | Shivering |
| Flu-like illness 14 | Sneezing |
| | Sore throat |
| | Rhinitis |
| | Rhinorrhea |
| | Nasal congestion |
| Respiratory 14 | Dry cough |
| | Sputum |
| | Dyspnea |
| | Hemoptysis |
| Cardiac 14 | Chest pain palpitation |
| Gastrointestinal 14 | Nausea and/or Vomiting |
| | Diarrhea |
| | Abdominal pain |
| Dermatological 101 | Viral exanthem-like |
| | maculopapular rash |
| | Vesicular |
| | Urticarial |
| | Acral lesions |
| | Chilblain like |
| Neurological 102 | Thrombotic/ischemic |
| | Dizziness |
| | Confusion |
| | Headache |
| | Ageusia |
| | Anosmia |
| | Stroke |
| | Ataxia |

METHODS

Literature search was conducted for multiple combinations of different hematological tests and manifestations with novel COVID-19 using the following key words: “hematological,” “complete blood
count," "lymphopenia," "blood indices," "markers" "platelet" OR "thrombocytopenia" AND "COVID-19," "coronavirus2019," "2019-nCoV" OR "SARS-CoV-2." Articles written in the English language and conducted on human samples between December 2019 and February 2021 were included. The initial search results were scanned by title and abstract for relevance, then complete texts of the related articles were reviewed. We further included directly relevant studies from reference lists of appropriate records. Non-English articles were excluded from the study.

3 | SEVERITY DEFINITION

According to NIH guidelines reviewed in October 2020, COVID-19 patients are grouped into five severity categories with slight overlap. 1- **Asymptomatic or presymptomatic Infection:** those are PCR confirmed COVID-19 patients but exhibiting no symptoms. 2-**Mild Illness:** patients signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, and loss of taste and smell) with no shortness of breath, dyspnea, or abnormal chest imaging. 3-**Moderate Illness:** when lower respiratory disease is evident clinically or radiologically but have saturation of oxygen (SpO₂) ≥94%. 4-**Severe Illness:** respiratory rate exceeds 30 breaths/min, SpO₂ <94%, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO₂/FIO₂) <300 mmHg, or pulmonary involvement >50%. 5-**Critical Illness:** when there is respiratory failure, septic shock, and/or multiple organ dysfunction.

Most of the hematological changes reported early in the beginning of the pandemic were based on hospital admitted patients. Moreover, severity definition was not consistent in the literature; some studies considered all patient not requiring intensive care unit (ICU) admission as mild cases. Subsequent population-based clinical and laboratory studies increased our understanding of the role of hematological changes in disease prognosis and outcome. In this review, we summarized the hematological changes according to the severity of the presentation. We grouped the asymptomatic, mild, and moderate cases with PaO₂ >94% as none severe conditions, and patients with severe or critical condition who required assisted ventilation or ICU care as severe conditions. We also reviewed the hematological changes in special groups including children and pregnant women.

4 | HEMATOLOGICAL CHANGES IN NONE SEVERE CONDITIONS

4.1 | Changes in WBC count and morphology

The majority of early published laboratory findings of none severe COVID-19 infection are collected from hospital admitted patients at a single time point which limits our understanding of the dynamic hematological changes during the course of the disease. Asymptomatic patients constitute at least 20% of the cases, however, available literature is more concerned with the prevalence and transmission risk they carry and overlooking hematological changes. This probably because those patients were sent for self-isolation and further investigation was not recommended particularly with the overwhelmed health systems.

Studies which have looked into the WBC changes in hospitalized COVID-19 patients with none severe symptoms reported a total WBC count range of 3.1–7.6 × 10⁹/L with a mean of 4.3–5.7 × 10⁹/L. Lymphocytopenia was reported in 80.4% of none severe patients; however, mean lymphocyte counts was more 1.0 × 10⁹/L in most of the cases. Leukopenia reported in 28.1% of this category with mean neutrophil count reported by different studies to be 0.4–6.6 × 10⁹/L. It is worth noting that both lymphocytopenia and neutropenia in this group of patients were less prominent than those seen in severe cases.

A case–control study comparing the complete blood count (CBC) of symptomatic COVID-19 confirmed patients with those of symptomatic COVID-19 negative proposed eosinopenia as a potential predicting parameter of COVID-19 rather than lymphopenia and leukopenia.

4.2 | Changes in RBC indices

Hemoglobin and to less extent hematocrit are the only RBC indices reported in COVID-19 studies. Available literature showed no significant alteration in hemoglobin of those with a mild/moderate disease.

4.3 | Changes in coagulation indices

Early studies in Wuhan and Germany showed no significant differences in the platelet count of none severe compared with severe COVID-19 patients. A larger study included 926 none severe cases reported a mean platelet count of 172,000 (139,000–212,000), which was significantly higher than that reported in severely ill patients. There was no significant changes in the levels of other blood coagulation parameters in none severe illness.

5 | HEMATOLOGICAL CHANGES IN SEVERE CONDITIONS

5.1 | Changes in WBC count and morphology

There are consistent data indicating that lymphocytopenia and neutrophilia are features of severe COVID-19 illness (Table 2). Longitudinal assessment of laboratory parameters of 13 patients with severe illness showed significant and sustained lymphocytopenia [0.6(0.6–0.8)] and neutrophilia [4.7(3.6–5.8)]. Another study of 69 patients reported that severely ill patients developed
| Author            | Year  | No. of studies | Pooled number of patients | Outcome          | Hematological parameter | Results | 95%CI    | p         | Cut-off |
|-------------------|-------|----------------|----------------------------|------------------|--------------------------|---------|----------|-----------|---------|
| Huang et al.      | Jan-20| 25             | 5350                       | IUC or death     | ↑CRP                     | RR =1.84| 1.45, 2.33| <0.001   | ≥10     |
|                   |       |                |                             |                  | ↑D-dimer                 | RR =2.93| 2.14, 4.01| <0.001   | ≥0.5    |
| Lagunas-Rangel et al. | Apr-20| 6              | 828                        | Severity         | ↑CRP, ↑D-dimer           | SMD =2.404| 0.98, 3.82| 0.000    |         |
|                   |       |                |                             |                  | ↓CRP                     | SMD = -0.912| -1.27, -0.55| 0.005    |         |
| Xu et al.         | June-20| 20             | 4062                       | Severity         | ↑WBC, ↑Lyc, ↑CRP         | WMD =1.76| 0.31, 3.22| Not specified |         |
| Henry et al.      | June-20| 18             | 2984                       | Severity         | ↑WBC, ↑LYC, ↑CRP, ↑D-dimer | WMD =0.41| 0.16, 0.66| 0.00     |         |
|                   |       |                |                             |                  | ↑NP                      | WMD =1.73| 1.57, 1.85| 0.00     |         |
|                   |       |                |                             |                  | ↑LYC                     | WMD = -0.28| -0.3, -0.25| 0.00     |         |
|                   |       |                |                             |                  | ↑CD4                     | WMD = -3.94| -8.02, 0.13| 0.12     |         |
|                   |       |                |                             |                  | ↑CD8                     | WMD = -2.22| -5.01, 0.57| 0.41     |         |
|                   |       |                |                             |                  | ↑Monocyte                | WMD = -0.03| 0.07, -0.01| 0.82     |         |
|                   |       |                |                             |                  | ↑Eosinophil              | WMD = -0.01| -0.02, -0.01| 0.01     |         |
|                   |       |                |                             |                  | ↑PLC                     | WMD = -2.34| -30.8, -15.9| 0.02     |         |
|                   |       |                |                             |                  | ↑Hb                      | WMD = -6.52| -9.2, -3.85| 0.80     |         |
|                   |       |                |                             |                  | ↑aPTT                    | WMD = -1.11| -2.33, 0.10| 0.72     |         |
|                   |       |                |                             |                  | ↑LYC                     | WMD =0.42 | -0.52, -0.33| 0.12     |         |
|                   |       |                |                             |                  | ↑CRP                     | WMD =2.11 | 0.72, 3.51 | 0.005    |         |
|                   |       |                |                             |                  | ↑D-dimer                 | WMD =0.67 | 0.02, 1.32 |          |         |
| Xiong et al.      | Jun-20| 9              | 1105                       | Severity         | ↑PT, ↑D-dimer, ↑PLT, ↑aPTT| WMD =4.15| 3.15, 5.15| 0.53     |         |
|                   |       |                |                             |                  | ↑LYC                     | WMD = -0.44| -0.54, -0.35| 0.00     |         |
|                   |       |                |                             |                  | ↑PLC                     | WMD = -48.3| -57.7, -38.9| 0.00     |         |
|                   |       |                |                             |                  | ↑Hb                      | WMD = -1.34| -4.85, 2.1| 0.64     |         |
| Lima et al.       | Jul-20| 3              | 648                        | Mortality        | ↑D-dimer                 | 11-fold higher | 11-fold higher | -       |         |
| Lippi et al.      | Jul-20| 9              | 1779                       | Severity         | ↑PLC                     | WMD = -31 | -35, 29   | <0.001   |         |
|                   |       |                |                             |                  | OR =5.1                  | 1.8, 14.6 |            | 0.00     |         |
| Lapić et al.      | Jul-20| 3              | 819                        | Mortality        | ↑ESR                     | SMD 0.82 | 0.16–1.47| <0.000   |         |
| Shi et al.        | Jul-20| 10             | 1845                       | Mortality        | ↑NP                      | SMD =0.93 | 0.63–1.24| <0.001   |         |
| Soraya et al.     | Aug-20| 7              | 393                        | IUC              | ↑WBC, ↑LYC, ↑PLC, ↑D-dimer | WMD = -0.56| -0.71, 0.40| <0.000   | 0.83    |
|                   |       |                |                             |                  | ↑NP                      | SMD = -0.32| -0.49, 0.15| 0.0002   | 170.8   |
|                   |       |                |                             |                  | ↑D-dimer                 | SMD =0.44 | 0.24, 0.64| <0.000   | 3.65    |
|                   |       |                |                             |                  | SMD =0.53,               | 0.31, 0.75| <0.000   |          |         |

(Continues)
| Author | Year | No. of studies | Pooled number of patients | Outcome | Hematological parameter | Results | 95%CI | p          | Cut-off |
|--------|------|----------------|---------------------------|---------|-------------------------|---------|------|-----------|---------|
| Zheng et al. | Aug–20 | 13      | 3027                      | Mortality | ↑D-dimer | OR =43.24 | 9.92,188.49 | 0.0001 | <4 x 10^9/L > 0.5 mg/L |
|          |      | 4       | 1286                      |          | ↑WBC       | OR =0.30  | 0.17,0.51  |         |         |
|          |      |         |                           | Severity | ↑WBC       | OR =0.30  | 0.17,0.51  |         |         |
|          |      |         |                           |         | ↑D-dimer   | OR =43.24 | 9.92,188.5  |         |         |
| Ghahramani et al. | Aug–20 | 17     | 1099                      | Severity | ↓LYC      | WMD =-0.43 | -0.56,0.30 | <0.001 |         |
|          |      |         |                           |         | ↓Monocyte | WMD =-0.06 | -0.12,0.0  | 0.032  |         |
|          |      |         |                           |         | ↓Eosinophil | WMD =-0.03 | -0.05,0.001 | 0.037  |         |
|          |      |         |                           |         | ↓Hb       | WMD =-5.94 | -8.23,-3.64 | 0.001  |         |
|          |      |         |                           |         | ↑PLC      | WMD =-27.97 | -39.6,-16.4 | 0.001  |         |
|          |      |         |                           |         | ↑NP       | WMD =-0.74  | -1.00,5.43 | 0.001  |         |
| Elshazli et al. | Aug–20 | 16     | 6320                      | Severity | ↑WBC      | OR =1.75  | 1.21,2.54  | 0.000  |         |
|          |      |         |                           |         | ↑NP       | OR =2.62  | 1.72,3.97  | 0.000  |         |
|          |      |         |                           |         | ↓LYC      | OR =0.30  | 0.19,0.47  | 0.000  |         |
|          |      |         |                           |         | ↓Monocyte | OR =-0.56 | 0.42,0.74  | 0.000  |         |
|          |      |         |                           |         | ↓NP       | OR =3.97  | 2.62,6.02  | 0.000  |         |
|          |      |         |                           |         | ↑D-dimer  | OR =1.82  | 1.00,3.33  | 0.047  |         |
|          |      |         |                           |         | ↑Fibrinogen | OR =3.14  | 1.64,6.00  | 0.001  |         |
|          |      | 11      | IUC                       |         | ↑WBC      | OR =5.21  | 3.00,9.05  | 0.000  |         |
|          |      |         |                           |         | ↑NP       | OR =6.25  | 3.00,9.05  | 0.001  |         |
|          |      |         |                           |         | ↓LYC      | OR =0.21  | 0.10,0.47  | 0.000  |         |
|          |      |         |                           |         | ↓Monocyte | OR =0.43  | 0.28,0.68  | 0.000  |         |
|          |      |         |                           |         | ↓NP       | OR =4.19  | 4.72,8.58  | 0.000  |         |
|          |      |         |                           |         | ↑PT       | OR =2.18  | 1.58,6.47  | 0.001  |         |
| Figliozzi et al. | Aug–20 | 49 | 587,790                   | Mortality | ↑LYP      | OR =2.86  | 1.09,7.6  | 0.037  |         |
|          |      |         |                           |         | ↑D-dimer  | OR =4.4  | 1.10,17.58 | 0.04  |         |
| Bashash et al. | Sep–20 | 13 | 3383                      | Severity | ↑PLC      | WMD = -21.5 | 31.57,-11.43 | <0.001 |         |
| Alnor et al. | Sep–20 | 21 | 1099                      | Severity | ↑WBC      | MD =-1.28 | 0.37,2.20  | <0.001 |         |
|          |      |         |                           |         | ↑NP       | MD =-1.49 | 0.64,2.35  | <0.001 |         |
|          |      |         |                           |         | ↓LYC      | MD =0.32  | -0.42,0.21 | <0.001 |         |
|          |      |         |                           |         | ↓Monocyte | MD =-22.4 | -35.3,-9.5 | <0.001 |         |
|          |      |         |                           |         | ↓NP       | MD =-4.1  | -6.42,-1.78 | <0.001 |         |
|          |      |         |                           |         | ↑CRP      | MD =49.2  | 31.2,67.1  | <0.001 |         |
|          |      |         |                           |         | ↑D-dimer  | SMD =0.58 | 0.37,0.78  | <0.001 |         |
| Wu et al. | Oct–20 | 4 | 31100                     | Infection | ABO group | OR =1.249 | 1.114,1.440 | <0.001 |         |
|          |      |         |                           |         | A         | OR =0.699 | 0.634,0.770 | <0.001 |         |
|          |      |         |                           |         | B         | OR =2.422 | 0.94,6.29  | 0.069  |         |
|          |      |         |                           |         | O         | OR =0.748 | 0.56,1.01  | 0.056  |         |
|          |      |         |                           |         | AB        | OR =1.271 | 0.89,1.81  | 0.181  |         |
|          |      |         |                           |         | O         | OR =35.89 | 0.001  |         |
|          |      |         |                           |         | B         | OR =1.250 | 0.001  |         |
| Author          | Year  | No. of studies | Pooled number of patients | Outcome     | Hematological parameter | Results  | 95%CI      | p       | Cut-off |
|-----------------|-------|----------------|---------------------------|-------------|-------------------------|----------|------------|---------|---------|
| Zhang et al.    | Oct-20| 7              | 4663                      | Severity    | ↓LYC                   | OR = 4.5 | 3.3–6.0   | 0.686   | >9.5    |
|                 |       |                |                           |             | ↑CRP                   | OR = 3.0 | 2.1–4.4   | 0.356   |         |
| Del Sole et al. | Oct-20| 12             | 2794                      | Severity    | ↑D-dimer               | OR: 5.67 | 1.45–22.16 | 0.001   |         |
|                 |       |                |                           |             | ↓PLC                   | OR: 3.61 | 2.62–4.97 | 0.001   |         |
| Kiss et al.     | Nov-20| 93             | 25901                     | Mortality   | ↑WBC                   | OR = 3.7 | 1.72, 7.69 | 0.001   | >9.5    |
|                 |       |                |                           |             | ↑WBC                   | OR = 6.25 | 2.86, 14.29 | 0.000   | >10.0   |
|                 |       |                |                           |             | ↓LYC                   | OR = 0.38 | 0.20, 0.72 | 0.001   | <4.0    |
|                 |       |                |                           |             | ↑NP                    | OR = 3.74 | 1.77, 7.92 | 0.001   | <0.8    |
|                 |       |                |                           |             | ↑D-dimer               | OR = 2.32 | 1.23, 4.37 | 0.009   | >6.3    |
|                 |       |                |                           |             | ↑D-dimer               | OR = 4.30 | 1.55, 11.98 | 0.005   | >0.50   |
|                 |       |                |                           |             | ↓D-dimer               | OR = 6.63 | 3.62, 12.14 | 0.000   | >1.0    |
|                 |       |                |                           |             | ↓IUC                   | OR = 4.52 | 1.95, 10.52 | 0.000   | >9.5    |
|                 |       |                |                           |             | ↑WBC                   | OR = 3.64 | 1.22, 5.71  | 0.014   | >10.0   |
|                 |       |                |                           |             | ↑PLC                   | OR = 4.54 | 2.58, 7.95  | <1.0    |         |
|                 |       |                |                           |             | ↑WBC                   | OR = 3.68 | 0.31–0.56   | <0.001  | 263.5   |
|                 |       |                |                           |             | ↑CRP                   | OR = 36.88 | 29.10–44.65 | <0.001  | 0.635   |
| Haryanto et al. | Dec-20| 23             | 4848                      | Severity    | ↑D-dimer               | MD = 0.43 | 0.31–0.56 | <0.001  | >0.5    |
|                 |       |                |                           |             | ↑CRP                   | MD = 36.88 | 29.10–44.65 | <0.001  |         |
| Zong et al.     | Jan-21| 24             | 5637                      | Mortality   | ↑PLC                   | OR: 7.37  | 2.08–26.14 | 0.001   |         |
| Gungor et al.   | Jan-21| 39             | 7813                      | Severity    | ↑D-dimer               | WMD: 0.45 | 0.3–0.56   | <0.001  | >0.5    |
|                 |       |                |                           |             | ↑WBC                   | RR = 1.58 | 1.25–2.00  | <0.001  |         |
|                 |       |                |                           |             | ↓NP                    | WMD: 0.19 | 0.5–1.54   | <0.001  |         |
|                 |       |                |                           |             | ↓D-dimer               | WMD: 0.51 | 0.33–0.69  | <0.001  |         |
|                 |       |                |                           |             | ↑D-dimer               | WMD: 0.81 | 0.44–0.86  | <0.001  |         |
|                 |       |                |                           |             | ↑D-dimer               | WMD: 6.58 | 3.59–9.57  | <0.001  |         |
|                 |       |                |                           |             | ↑PT                    | WMD: 1.27 | 0.49–2.06  | <0.001  |         |
|                 |       |                |                           |             | ↑PLC                   | WMD: 1.82 | 1.4–2.37   | <0.001  |         |
| Zhu et al.      | Feb-21| 34             | 6492                      | Severity    | ↑PLC                   | WMD = −16.29 | 25.34–7.23 | <0.001  |         |
|                 |       |                |                           |             | ↑aPTT                  | WMD = −0.81 | −1.94–0.33 | <0.001  |         |
|                 |       |                |                           |             | ↑D-dimer               | WMD = 0.44 | 0.29–0.58  | <0.001  |         |
|                 |       |                |                           |             | ↑Fibrinogen            | WMD = 0.51 | 0.33–0.69  | <0.001  |         |
|                 |       |                |                           |             | ↑PT                    | WMD = 0.65 | 0.44–0.86  | <0.001  |         |
|                 |       |                |                           |             | ↑D-dimer               | WMD: 6.58 | 3.59–9.57  | <0.001  |         |
|                 |       |                |                           |             | ↑PT                    | WMD: 1.27 | 0.49–2.06  | <0.001  |         |
|                 |       |                |                           |             | ↑PLC                   | WMD: −39.73 | −61.99–17.5 | <0.001  |         |
| Lin et al.      | Feb-21| 13             | 1341                      | Severity    | ↑PLC                   | WMD = −24.83 | −34.12–15.54 | <0.001  |         |
|                 |       |                |                           |             | ↑D-dimer               | WMD = 0.19 | 0.09–0.29  | <0.001  |         |
|                 |       |                |                           |             | ↑Fibrinogen            | WMD = 1.02 | 0.5–1.54   | <0.001  |         |
|                 |       |                |                           |             | ↑aPTT                  | WMD = 0.19 | −0.13–0.51 | 0.243   |         |
neutrophilia during hospitalization with a median peak absolute neutrophil count of $11.6 \times 10^9/L$.\textsuperscript{39} A retrospective study on 201 Wuhan patients, looked into risk factors associating with acute respiratory distress syndrome (ARDS) development and death, concluded that increased neutrophils ($p < 0.001$) and decreased lymphocytes ($p < 0.001$) were risk factors for ARDS, and increased neutrophils ($p = 0.03$) was associated with higher risk of death.\textsuperscript{50,41}

Studies addressing peripheral blood film of a COVID-19 patient described a characteristic neutrophil nuclei with C-shaped, single-lobed nuclei, morphologic abnormalities in the granulocytic series and leukoerythroblastic reaction.\textsuperscript{42,43} Blue–green leukocyte inclusions were reported in the circulating neutrophils and/or monocytes of critically ill patients with liver impairment and lactic acidosis and proposed as a poor prognostic indicator.\textsuperscript{44} By contrast, activated monocytes were observed in clinically improved patients.\textsuperscript{32,43}

Flow cytometry performed on peripheral blood lymphocytes of ICU patients showed a significant reduction in the absolute T-cell count in most cases as well as CD45+, CD3+, CD4+, CD8+, CD19+, and CD16/56+ counts. However, unlike immunodeficiency virus (HIV) and cytomegalovirus, the CD4/CD8 ratio was not inverted in all groups of patients.\textsuperscript{39,45}

Many studies have suggested neutrophil-to-lymphocyte ratio (NLR) as an independent risk factor for mortality in severely ill patients with COVID-19 with a cut-off value varied between 3.0 and 13.\textsuperscript{46} Table 2. Pooled data from 13 studies involving 1579 patients reported NLR sensitivity of 0.78 and 0.78 specificity in predicting disease severity. Ten studies involving 2967 patients reported higher sensitivity 0.83 and specificity 0.83 in predicting mortality.\textsuperscript{47}

5.2 | Changes in RBC indices

Meta-analysis results regarding hemoglobin level in severely ill COVID-19 patients are conflicting. A meta-analysis study including 224 severely ill COVID-19 patients reported significantly lower hemoglobin than none severe cases with a weighted mean difference (WMD) of $-7.1 \, \text{g/L;}$ 95% CI, $-8.3$ to $-5.9 \, \text{g/L.}$\textsuperscript{36} Other study found the difference was not significant.\textsuperscript{48} The lowest hemoglobin level was seen in patients who reached a composite endpoint (included admission to ICU, requirement of invasive ventilation, and death).\textsuperscript{49} The reduction in Hb may indicate disease progression, however, age and comorbidities are confounding factors in this patient group and data should be interpreted cautiously.\textsuperscript{50}

Elevated red blood cell distribution width (RDW), a component of complete blood counts that reflects RBC variation in volume and size, has been shown to be associated with elevated mortality risk for patients with COVID-19.\textsuperscript{51}

5.3 | Changes in coagulation indices

Altered coagulability is a poor prognostic indicator in severely and critically ill patients with COVID-19, Table 2. The laboratory manifestations of coagulopathy are elevated D-dimer, slight decrease in platelet count, prolonged PT, and reduced fibrinogen level. Thrombotic events and bleeding often occur in subjects with weak constitutions, multiple risk factors, and comorbidities.\textsuperscript{52} A meta-analysis of 22 studies conducted in china involving 4,889 confirmed COVID-19 patients found that mean D-dimer was $0.67 \, \mu\text{g/ml;}$ (95% CI: 0.56–0.78), mean platelet $186.34 \times 10^9/L$ (95% CI: 175.84–196.85), mean PT $12.20 \, \text{s}$ (95% CI: 11.52–12.84), and mean fibrinogen $4.24 \, \text{g/L}$ (95% CI: 3.40–5.15).\textsuperscript{53} Patient with severe illness had longer PT ($MD = 0.65 \, \text{s;}$ 95% CI: 0.36–0.95, $p < 0.05$), shorter aPTT ($MD = -0.01 \, \text{s;}$ 95% CI: $-2.58$–2.56, $p = 0.99$), higher D-dimer ($MD = 0.44 \, \mu\text{g/ml;}$ 95% CI: 0.23–0.66, $p < 0.05$), and lower platelet count ($MD = -14.47 \times 10^9/L,$ 95% CI: $-33.0$–4.06, $p = 0.126$).\textsuperscript{53}

Coagulopathy in COVID-19 initiated by endothelial injury results in thrombin generation and fibrinolysis shut down, contributing to a hypercoagulable state, which causes a prolonged PT and aPTT. In the late stages of the DIC, PT, aPTT, fibrinogen, and platelets are decreased due to consumptive coagulopathy as observed in none survivors.\textsuperscript{54} Moreover, COVID-19 patients presenting with cardiac injury and elevated troponin-T levels were more prone to coagulation disorders compared with those without cardiac involvement.\textsuperscript{55} Studies have also detected lupus anticoagulant and antiphospholipid antibodies in COVID-19 patients, which could contribute to the hypercoagulable state.\textsuperscript{1}

Altered coagulability is complicated by venous thromboembolism in 24%, deep venous thrombosis 7%, and pulmonary embolism 19% of severely ill COVID-19 patients.\textsuperscript{56} Independent predictive parameters for thromboembolism were pneumonia, old age, spontaneous prolongation of PT $>3 \, \text{s},$ and aPTT $>5 \, \text{s.}$\textsuperscript{57} Arterial embolism in the form of acute MI, acute limb ischemia, and storks was also reported in COVID-19 patients.\textsuperscript{58,59}

The contribution of von Willebrand factor (vWF) in thrombin–flammation is well established. Several mechanisms are involved. These mechanisms starts with endothelial dysfunction.\textsuperscript{60} In severely ill COVID-19 patient, marked increase in vWF and factor VIIIc level was observed similar to that seen in severely septic non-COVID-19 ICU patients.\textsuperscript{52,61,62} With disease progression, and in the absence of anticoagulant treatment, VWF and fibrinogen levels decline with persistent high D-dimer levels and even higher P-selectin levels indicating poor prognosis.\textsuperscript{52}

5.4 | Other markers

Several biochemical tests are described as potential prognostic indicators in progressive COVID-19 infection. Serum ferritin level is elevated in 74.2% complicated viral infection.\textsuperscript{63} COVID-19 patients with elevated serum ferritin were at higher risk of developing ARDS (HR = 3.53, 95%CI: 1.52–8.16, $p = 0.003$). A meta-analysis of 18 studies concluded that the ferritin level was significantly higher in severely ill patients [WMD 397.77 (95% CI 306.51–489.02)] and non-survivors [WMD 677.17 (95% CI 391.01–963.33)]. Higher level
of ferritin was observed in patients with comorbidities such as diabetes, thrombotic complication, liver dysfunction, and cancer. Elevated C-reactive protein (CRP) was reported in 81.5%, procalcitonin in 13.7%, and LDH in 58.1% of severe COVID-19 infection and they were linked to secondary bacterial infection. Additionally, erythrocyte sedimentation rate (ESR) was reported by several studies to be significantly elevated and was considered as a predictor of infection severity.

ABO blood group was described in many studies to be associated with COVID-19. A study of pooled 31100 COVID-19 patients suggested that people with blood type A might be more susceptible to infect COVID-19 while blood type O might be less susceptible to infect COVID-19, yet no correlation between ABO blood group and severity or mortality of the infection.

### 6 | HEMATOLOGICAL CHANGES IN CYTOKINE STORM

Cytokine storm is a serious clinical state that occurs approximately 7–14 days in the course of COVID-19 infection; presented clinically as nonspecific constitutional symptoms such as persistent fever, weight loss, joint and muscle pain, fatigue, and headache. Cytokine storm characterized by a hyperinflammatory status as a consequence of proinflammatory cytokines and chemokines overproduction, resulting in pulmonary, cardio-circulatory, or combined disturbances. Extensive local edema due to vasodilatation and membrane leakage may result in multiorgan failure and uncontrollable shock. Nonsurvivor of COVID-19 as well as severe refractory patients exhibited high levels of IL-6, IL-2R, IL-8, IL-10, and TNF. Sustained high level of IL6 in particular was shown by two meta-analyses to associate with severe COVID-19 infection and high mortality.

Clinically, cytokine storm is considered when patients show clinical deterioration in the form of reduced rest oxygen saturation below 94% or tachypnea more than 30/min with at least two of three biomarker (in the absence of bacterial infection): high CRP (>100 mg/L), high serum-ferritin (>900 μg/L at one occasion, or two-fold increase in the level at admission within 48 h), and high D-Dimer level (>1,500 μg/L).

### 6.1 | Changes in WBC count and morphology

Monocytes and macrophages are activated by binding the virus via ACE2 receptors on their surface producing IL-6, IL-10, and TNF causing the nonspecific constitutional symptoms in COVID-19 patients. T-cell overactivation occurring in severe COVID-19 infection leads to the production of granulocyte-macrophage colony-stimulating factor (GM-CSF), which stimulates CD14+ CD16+ mononuclear cell to produce IL-6 and a gush of other inflammatory mediators. Markedly lower absolute lymphocyte count OR 0.41 [0.26–0.62] was observed in 169 COVID-19 patients with cytokine storm compared with those without. They also showed altered flow cytometric phenotype at the time of presentation in addition to lower eosinophils (OR 0.34 [0.20–0.57], basophils (OR 0.39 [0.20–0.74]), and monocytes (OR 0.52 [0.33–0.79]). Lymphocytopenia seen in patients with cytokine storm may be the results of direct lysis of lymphocytes by the virus as the lymphocytes do express ACE2 on its surface. Lymphocytes apoptosis could be promoted by the plethora of cytokine in this stage, which may also lead to lymphoreticular organs dysfunction impeding lymphocyte turnover.

Neutrophilia is another sign of cytokine storm and considered as a predictor of disease severity. Neutrophils extravasate in the interstitial tissue form extracellular mesh of DNA/histones to control the infection, this exacerbate the inflammation and cause tissue damage.

Data regarding NK cells are contradicting. One study reported a reduction in the number of circulating NK cells in COVID-19 patients, whereas others showed no difference in the number of CD16+CD56+ in severe compared to none severe cases.

### 6.2 | Changes in RBC indices

Anemia is reported in some of the critically ill COVID-19 patients; however, detailed RBC indices changes in response to secondary adult hemophagocytic lymphohistiocytosis associated with this viral infection are not well characterized and require further studies.

### 6.3 | Changes in coagulation indices

During cytokine storm, immune response to infection results in overproduction of proinflammatory cytokines which activate coagulation pathway. At later stage, the tightly controlled, thrombin regulating mechanisms are impaired. Reduced anticoagulant concentrations due to reduced production and increasing consumption results in microthrombosis, disseminated intravascular coagulation, and multiorgan failure. Raised D-dimer concentrations being a poor prognostic feature and disseminated intravascular coagulation are common in nonsurvivors. A single-center study in China followed the dynamic platelet-to-lymphocyte ratio (PLR) changes during the period of hospitalization, they suggested a possible correlation between high PLR and cytokine storm associated with prolonged hospitalization days.

### 6.4 | Other markers

The cytokine profile in COVID-19-associated cytokine storm is similar to secondary hemophagocytic lymphohistiocytosis, which is commonly triggered by sepsis and viral infections. In such conditions, elevated ferritin, triglycerides, uric acid, LDH, lactate, and acute kidney injury are observed along with elevated CRP, procalcitonin, D-dimer, troponin, and alanine aminotransferase.
HEMATOLOGICAL CHANGES IN SPECIAL GROUPS

7.1 | Children

COVID-19 incidence in children is lower than that seen in adults. Recent reports from the USA Centers for Disease Control and Prevention (CDC) indicates that children younger than 19 years constituted 5% of the all cases. The course of the disease seems to be milder than adults; nonetheless, severe cases have been recorded in 3–5% and mortality 0.3%.

Four systematic reviews and meta-analyses concluded that the majority of children with COVID-19 had a normal leukocyte count. Lymphopenia was reported in relatively few number of cases (15%) and was not associated with severe course. By contrast, pooled data from 486 hospitalized children reported lymphocytosis in 22% and leukopenia in 21%. Higher incidence of lymphocytosis up to 61% was seen in neonates, yet severe cases in these neonates were relatively higher 7%. Studies rarely reported changes in hemoglobin or RBC indices and coagulative system, the available literatures showed no significant change in the Hb level in children with COVID-19 whether asymptomatic, mild, severe, or critical. The infrequent reporting of thrombotic events in children may indicate its rarity in the clinical practice.

Other laboratory findings reported in children were elevated inflammatory markers including ferritin (26% [16–40]), procalcitonin (25% [21–29]), and CRP (19% [16–22]).

7.2 | Pregnant women

The incidence and clinical manifestations of COVID-19 in pregnant women have been reported to be similar to general population with approximately 80% having mild course of the disease or asymptomatic and good perinatal outcomes. Seven cases of COVID-19 in pregnant women were reported in 15% and critical in 5%, the majority of which were associated with risk factor such as comorbidity and obesity. The mortality of pregnant women with COVID-19 was relatively low (0.43%) and close to the overall maternal mortality rate worldwide (1 in 180). Vertical transmission of the infection is an area of debate. Earlier studies showed absent placental infection and negative PCR of amniotic fluid. More recent studies identified placental infection associated with increased fibrin deposition resulting in fetal distress and subsequent premature delivery.

Hematological findings in pregnant women with COVID-19 were infrequently reported in the published studies but generally, were similar to that of nonpregnant women. A systematic review of 20 related studies included 230 pregnant or women in labor showed that 40.7% had lymphopenia, 16.7% neutropenia, and 4% thrombocytopenia. Hypercoagulability have been reported in pregnant women with severe disease. Another meta-analysis based on 11 studies with 173 severely to critically ill pregnant patients from the first trimester to the third trimester suggested that elevated D-dimer (82%), elevated neutrophil count (81%), elevated C-reactive protein (69%), and decreased lymphocyte count (59%) were the most frequent abnormalities. In a pilot study that included 21 pregnant women in the second and third trimester with COVID-19 and 48 without, a higher aPTT level, platelet count and lower fibrinogen, D-dimer levels, and antithrombin time were observed in patient COVID-19 positive pregnant women as compared to COVID-19 negative.

However, there was no difference observed in CRP and FVIII levels. Pregnancy is already a known risk for venous thromboembolism characterizing by a procoagulant imbalance. Prophylactic anticoagulant has been provided for women undergoing C sections to reduce the risk of venous thromboembolism; however, larger studies addressing the coagulopathy in this group are required.

8 | CONCLUSION

Subtle hematological changes might appear early in the course of COVID-19 infection; progressive disease associates with significant hematological changes that may lead the management plan and predict patient outcome. Research all over the world characterized the clinical, radiological, and laboratorial manifestation associated with the pandemic; however, further Iraqi studies are essential to report the clinical and hematological profile in Iraqi population over the three waves hit the country.

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