Blood Cells Indices are Determinants of the COVID-19 Outcome: A Cross-Sectional Study from Kurdistan Region-Iraq

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Citation: Al-Nimer MSM, Merza TA, Mohammed KYMY, Mohammed HA. Blood Cells Indices are Determinants of the COVID-19 Outcome: A Cross-Sectional Study from Kurdistan Region-Iraq. Electron J Gen Med. 2021;18(5):em304. https://doi.org/10.29333/ejgm/11013

ARTICLE INFO

INTRODUCTION

COVID-19 is a pandemic viral disease caused by a coronavirus (CoV), presented with respiratory and extra-respiratory signs and symptoms. Polymerase chain replication technology is the definite laboratory tool for the diagnosis of CoV infections. The hematological indices are also useful in the diagnosis and assessment of COVID-19. Lymphocytes and monocytes are part of immune system, which specifically determine the immune response to the foreign substances and microorganisms, while the main function of the neutrophils is protecting the humans from bacterial infections. Lymphocytopenia is commonly reported in COVID-19 patients [1,2], and other studies found that lymphocytopenia is a prognostic marker as 35-75% of patients who had lymphocytopenia did not survive [3]. Also, another study reported that patients who were admitted to the intensive care unit had a cutoff value of lymphocyte count < 0.6x109/L [4]. Lymphocytopenia observed in severe COVID-19 disease is significantly characterized by a lower number of CD4+ and CD8+, and usually associated with a significant increase of C-reactive protein, D-dimer and interleukins (including IL-2R, IL-6, IL-10) and tumor necrosis factor-α [5].

A small percentage of patients with severe illness showed a leukocyte count > 10,000/mm3 which is due to a higher number of lymphocytes or neutrophils or both [1]. A significant high neutrophil count is an indication of the bacterial superinfection, cytokine storm, and hyperinflammatory state that accompanied CoV infections [6-8]. Moreover, the neutrophil-to-lymphocyte ratio (NLR) is significantly increased in severe COVID-19 compared with those with mild-illness [8]. The majority of patients showed significant low platelet count and linked with severe infection and hypoxia [9-11]. Mean platelet volume (MPV) was found to be increased in COVID-19 with unfavorable outcomes (death or venous thrombosis) compared with patients who survived without thrombosis complication [12]. Another retrospective study, including 85
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COVID-19 patients, found that patients with severe pneumonia had a significant MPV-to-platelet count ratio, which can be considered as an independent risk factor for severe pneumonia [13]. The rationale of this study is that the hematological indices can give a typical pattern of viral infection, specifically for CoV infections. Also, it can be applied to discriminate and predict the survivals of COVID-19 patients. This cross-sectional study aimed to investigate the clinical importance of determining the hematological indices as diagnostic and prognostic markers in a small sample of the Kurdistan population taking into consideration the concomitant diseases and the outcome events.

MATERIALS AND METHODS

Design and Setting

This cross-sectional study included adult patients of both sexes hospitalized in the West Erbil Emergency Hospital, Kurdistan region, Erbil-Iraq, between August 10 and November 19, 2020. The West Erbil Emergency Hospital was established for quarantine and management of COVID-19 in the Kurdistan region, with 102 beds, thirty-four physicians, ten pharmacists, 224 nurses, specialized laboratories and radiological departments for diagnosis of CoV infections, and the facilities of artificial ventilation.

The diagnosis of COVID-19 was confirmed by polymerase chain reaction (PCR) assays on the swabs obtained from the nasopharynx. The Ethical and Scientific Board at the Ministry of the Heath in the Erbil approved this study, and exempt the need for consent.

Sample Size

The sample size was calculated using α-coefficient (type II error) = 0.05, β-coefficient (type I error) = 0.2, and power = 85%). The patients were randomly recruited from the hospital using a random numbers table according to the number of admission sheet records.

Participants

A total number of 204 patients were allocated from single-center (128 males and 76 females, with a mean age of 58.3 years). Current illnesses were reported in 19 (9.3%) patients with diabetes mellitus; 45 (22.1%) patients with hypertension; 80 (39.2%) patients with hypertension and diabetes mellitus; and 4 (2%) patients with blood disorders. We categorized the patients into four categories according to their outcomes (Figure 1):

- Group A: patients who recovered from illness and discharged from the hospital.
- Group B: patients who were discharged from the hospital with minor clinical features (dry cough, fatigue, etc.) without any evidence of clinical and radiological investigations that indicate the presence of any complications).
- Group C: Patients with clinical features of COVID-19 and required quarantine in the hospitals to avoid future complications. Some of these patients required oxygen therapy.
- Group D: Patients who died (non-survivors) in the intensive care unit. Most patients admitted to the intensive care unit (ICU) required oxygen therapy and ventilator support.

Group A represented the survivors while Group D represented non-survivor patients.

Determination of Clinical Variables

On admission, samples of the blood obtained from patients under careful precautions and sent to the laboratories of the hospital to determine the hematological indices (blood samples with EDTA as an anticoagulant), and quantitative serum C-reactive protein (separated serum from a blood sample without EDTA). Neutrophil-to-lymphocyte (NLR) and platelet-to-lymphocyte (PLR) ratios were simply calculated by...

Figure 1. Distribution of COVID-19 according to the outcomes
The number of male patients was non-significantly different. The mean age of the patients with concomitant diseases was higher than the mean age of the patients without concomitant diseases. Concomitant diseases such as hypertension and diabetes were present in a significant proportion of patients. The distribution of hematological indices and ratios according to the presence of concomitant diseases is shown in Table 1.

### Results

#### Statistical Analysis

The results are expressed as a number and mean (standard error). The statistical analysis was performed using ANOVA (Levene’s statistics) to test for homogeneity of variance. The mean values of hematological indices and ratios were compared using the Student’s t-test. A p-value of 0.05 was considered significant.

#### RESULTS

**Distribution of Hematological Indices and Ratios According to the Presence of Concomitant Diseases**

A total number of 204 patients were included in this study. The number of male patients was non-significantly different (χ²=0.837, P=.382) higher than the corresponding female patients, and the mean age of the patients with concomitant diseases was higher than patients without concomitant diseases. There is no significant difference in the red cell indices in patients with or without concomitant diseases. The red cell indices were within the normal range. The mean values of the blood platelet indices are within normal limits, and the platelet count was higher than the lower limit of normal platelet count (150,000/mm³). Moreover, the data showed homogeneity in the distribution of hematological indices and ratios. The outcomes of patients according to the concomitant illnesses are shown in Table 2.

### Table 1. Analysis of hematological indices data according to the presence of concomitant diseases

| Variables | Non-hypertensive non-diabetes (n=60) | Hypertensive (n=45) | Diabetes mellitus (n=19) | Hypertensive and diabetes (n=80) | Analysis of variance | Homogeneity of variance |
|-----------|------------------------------------|---------------------|--------------------------|---------------------------------|---------------------|-------------------------|
| Age (year) | 46.3 (1.5)                         | 58.8 (1.9)          | 55.9 (2.1)               | 67.6 (1.2)                      | F-value | P-value |
| Sex (M:F) | 40:20                              | 26:19               | 12:7                     | 50:30                           |         |         |
| RBC count (×10^12/mm³) | 4.8 (0.08) | 4.6 (0.1) | 4.6 (0.2) | 4.7 (0.1) | 0.770 | .512 |
| Hb (g/dL) | 13.5 (0.2)                         | 13.1 (0.3)          | 10.1 (0.1)               | 13.2 (0.2)                      | 1.297   | .277 |
| Hct (%)  | 40.5 (0.8)                         | 39.6 (1.1)          | 38.3 (1.3)               | 39.1 (0.6)                      | .395    | .395 |
| MCH (pg) | 28.5 (0.4)                         | 28.5 (0.4)          | 28.7 (0.7)               | 27.8 (0.3)                      | .036    | .476 |
| MCHC (g/dL) | 33.2 (0.2) | 33.1 (0.2) | 33.1 (0.4) | 33.0 (0.2) | 1.174   | .321 |
| MCV (fl) | 85.7 (1.1)                         | 86.2 (1.1)          | 84.0 (2.2)               | 84.2 (0.7)                      | .455    | .714 |
| RDW (%)  | 13.2 (0.2)                         | 13.5 (0.2)          | 12.9 (0.2)               | 13.4 (0.2)                      | .526    | .526 |
| WBC count (×10^9/mm³) | 14.8 (0.8) | 13.8 (1.0) | 15.1 (1.9) | 12.8 (0.6) | 1.299   | .276 |
| Neutrophil (%) | 8.3 (0.6) | 8.2 (0.7) | 8.1 (0.8) | 7.8 (0.5) | 0.134   | .940 |
| Lymphocyte (%) | 13.3 (0.9) | 12.8 (1.0) | 13.2 (1.8) | 13.6 (0.7) | 0.140   | .936 |
| Monocyte (%) | 5.5 (0.8) | 9.4 (1.1) | 5.0 (1.0) | 8.0 (0.9) | 3.372   | .021 |
| Eosinophil (%) | 0.8 (0.1) | 1.1 (0.2) | 1.1 (0.3) | 0.8 (0.1) | 0.941   | .422 |
| Basophil (%) | 0.1 (0.0) | 0.2 (0.0) | 0.2 (0.1) | 0.1 (0.0) | 1.222   | .303 |
| Platelet count (×10^9/mm³) | 251.5 (15.2) | 255.9 (19.0) | 247.3 (31.0) | 246.6 (15.1) | 0.056   | .983 |
| PCT (%)  | 0.2 (0.01)                         | 0.2 (0.02)          | 0.2 (0.02)               | 0.2 (0.01)                      | 0.315   | .815 |
| MPV (fl) | 8.9 (0.1)                          | 9.0 (0.1)           | 9.1 (0.2)                | 9.0 (0.1)                       | 1.109   | .347 |
| PDW (%)  | 42.7 (0.9)                         | 40.8 (1.4)          | 40.7 (2.3)               | 42.3 (0.8)                      | 1.607   | .189 |
| PLR      | 37.3 (2.9)                         | 39.3 (3.7)          | 38.6 (6.9)               | 38.6 (2.8)                      | 1.607   | .189 |

The results are expressed as number, percentage, and mean ± SE. The data were statistically analyzed using a two-tailed, one-way analysis of variance (ANOVA), homogeneity test of variance (Levene’s statistics), receiving operating characteristics, and calculating the risk odd ratios for continuous data, and Chi-square test for categorized data. P-value ≤ 0.05 is a lower significance level. SPSS-20 (IBM-compatible) was applied for statistical analysis.

### Table 2. Distribution of the patients according to their outcomes categories

| Category | Non-hypertensive non-diabetes (n=60) | Hypertensive (n=45) | Diabetes mellitus (n=19) | Hypertensive and diabetes (n=80) | Total (n=204) |
|----------|------------------------------------|---------------------|--------------------------|---------------------------------|--------------|
| A        | 22 (36.7)                          | 8 (17.8)            | 3 (15.8)                 | 12 (15.0)                       | 45 (22.1)    |
| B        | 5 (8.3)                            | 6 (13.3)            | 4 (21.1)                 | 10 (12.5)                       | 25 (12.3)    |
| C        | 18 (30.0)                          | 19 (42.2)           | 5 (26.3)                 | 28 (35.0)                       | 70 (34.3)    |
| D        | 15 (25.0)                          | 12 (26.7)           | 7 (36.8)                 | 30 (37.5)                       | 64 (31.3)    |
| Total    | 60 (100)                           | 45 (100)            | 19 (100)                 | 80 (100)                        | 204 (100)    |

The results are expressed as number (percentage). Category A: recovery, Category B: Discharge without complete recovery, Category C: quarantine in the hospital with signs and symptoms, Category D: death.
likely to have unfavorable outcomes compared with hypertensive (36.8% versus 26.7%). On admission, diabetic patients had a lower percentage of saturated oxygen compared with others (Table 3), which is significantly less than the corresponding value of non-hypertensive non-diabetic patients (76.4±3.3% versus 81.3±1.4%). During the course of COVID-19, there are no significant differences between patients with and without concomitant diseases in the erythrocyte sedimentation rate and C-reactive protein, accounting for significantly higher values compared with normal upper limits (Table 3).

**Comparison between Category A and D Regarding Hematological Indices**

There are non-significant statistical differences between patients related to the categories A and D regarding the mean values of red distribution width (RDW), platelet distribution width (PDW), MPV, NLR, and PLR. The data of these hematological indices and ratios showed homogeneity as Levene’s statistic value was non-significant for each index and ratio (Table 4). Moreover, the RDW and the NLR ratio are significant discriminators of the unfavorable event (death) of patients with COVID-19 (Figure 2). The areas under the curve with 95% C.I. of the RDW and NLR are 0.618 (0.510-0.726) and 0.612 (0.505-0.718), respectively (Figure 2). The odd ratios of unfavorable (death) outcomes are 3.02, 2.407, and 2.407 at cutoff values of RDW (≥13.2), NLR (12.0), and PLR (36.8), respectively (Figure 3).

**DISCUSSION**

The results of this study indicate that the determination of hematological indices and ratios at the time of hospitalization can predict the outcome events of COVID-19 patients despite the presence or absence of concomitant diseases, including hypertension and/or diabetes mellitus. The characteristic hematological profile of COVID-19 is neutrophilia, lymphocytopenia, a higher monocyte percentage, and within the normal range of the blood platelet count. The results of this study are in parallel with previous studies that neutrophilia and lymphocytopenia are the characteristic features of CoV infection. Terpos et al. [14] reported that lymphocytopenia occurred after 7-14 days from the clinical presentation of the COVID-19, and considered as a prognostic factor. The causes of lymphocytopenia are due to the lysis of the lymphocyte as a result of binding the CoV to the angiotensin converting enzyme receptor 2 (ACE2) which is expressed on the lymphocyte [15], and to the inflammatory mediators that released as a part of cytokine storm syndrome, which cause lymphocyte apoptosis [16-18], and atrophy of lymphoid tissue [19]. A higher number of the leucocytes (> 10,000/mm³), is also a feature of COVID-19, and it may indicate superimposed secondary infection [20]. The percentage of monocyte is higher among hypertensive patients with/without type 2 diabetes mellitus. Merad and Martin [21] reported that dysregulation of the immune system as a result of hyperinflammation leads to an increase in the number of monocyte/macrophage in the bronchoalveolar fluid in severe COVID-19. This work demonstrates a significantly higher percentage of circulating monocyte in the peripheral blood, which is linked to hypertensive patients rather than to the severity of COVID-19. The explanation of this observation that peripheral monocytes are activated the vascular endothelium under the effect of excess production of IL-6 and deprivation of nitric oxide in hypertension [22]. It is well known that CoV cannot cause direct damage to the blood platelet because the platelets lack ACER-2 on their surfaces [14]. Thrombocytopenia is a feature of severe COVID-19, and it is usually noted in the non-survivors [23]. On the other side, COVID-19 patients who had a peak platelet count at the time of clinical presentation will have a worse prognosis [24]. Moreover, concomitant diseases are not the cause of the changes in the blood platelet indices of COVID-19 patients (Table 1). The results of hematological ratios during the course of illness explore their important values to discriminate and predict the patients who may be non-survivors. Red distribution width significantly discriminates the non-survivor from survivor COVID-19 (Figure 2), and COVID-19 patients who had an RDW ≥ 13.2% will get a poor prognosis. This observation wasn’t previously mentioned. The neutrophil-to-lymphocyte ratio is significantly higher in non-survivors compared with survivor patients, which this finding agreed

### Table 3. Assessment of saturated oxygen percentage (sPO₂), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) at the time of presentation with COVID-19

| Variables | Non-hypertensive non-diabetes (n=60) | Hypertensive (n=45) | Diabetes mellitus (n=19) | Hypertensive and diabetes (n=80) | ANOVA-test | Homogeneity |
|-----------|-------------------------------------|---------------------|-------------------------|---------------------------------|------------|-------------|
| sPO₂ (%)  | 81.3(1.4)                           | 84.8(1.5)           | 76.4(3.5)*              | 80.3(1.2)                       | 2.895      | .036        |
| ESR (mm/h)| 66.1(3.5)                           | 69.8(3.6)           | 72.1(6.6)               | 70.4(2.6)                       | 0.453      | .715        |
| CRP (mg/L)| 85.9(6.9)                           | 93.1(10.4)          | 98.9(19.5)              | 98.8(8.4)                       | 0.391      | .760        |

The results are expressed as mean (standard error). * Significant difference with hypertensive patients.

### Table 4. Comparisons between COVID-19 patients who recovered from the disease and patients who died according to the hematological indices

| Variables | Analysis of variance | Analysis of homogeneity |
|-----------|----------------------|-------------------------|
|           | F-value | P-value | Levene statistic | P-value |
| RDW       | 15.2(0.2) | 13.7(0.2) | 3.535 | .063 | .717 | .399 |
| PDW       | 41.6(1.2) | 41.4(1.2) | 0.010 | .921 | 1.079 | .301 |
| MPV       | 8.9(0.1) | 9.190(1) | 1.042 | .310 | 3.894 | .051 |
| NLR       | 12.0(1.0) | 14.0(0.8) | 3.247 | .074 | 1.253 | .265 |
| PLR       | 36.4(3.2) | 39.6(2.5) | 0.632 | .428 | 0.083 | .773 |

The results are expressed as mean ± standard error. RDW: red distribution width, PDW: platelet width distribution, MPV: mean platelet volume, NLR: neutrophil-to-lymphocyte ratio, and PLR: platelet-to-lymphocyte ratio.
Figure 2. The area under the curve of the hematological indices in dead patients compared with recovered patients from COVID-19.

| Test Result Variable(s)                             | Area    | Standard error | p-value | 95% Confidence Interval |
|-----------------------------------------------------|---------|----------------|---------|-------------------------|
| Red distribution width (CV)                         | 0.618   | 0.055          | 0.037   | 0.510-0.720             |
| Neutrophil-to-lymphocyte ratio                     | 0.612   | 0.054          | 0.048   | 0.565-0.718             |
| Mean platelet volume                                | 0.581   | 0.055          | 0.276   | 0.454-0.669             |
| Platelet distribution width (%)                     | 0.526   | 0.055          | 0.647   | 0.417-0.634             |
| Platelet-to-lymphocyte ratio                        | 0.567   | 0.066          | 0.236   | 0.457-0.677             |

Figure 3. Odd ratios of hematological indices of unfavorable outcome (death) using cutoff median values of survival patients. Cutoff values of RDW, NLR, PLR, MPV, and PDW are: ≥13.2, 12.0, 247.3, 9.0, and 43.3. RDW: red distribution width (CV), NLR: neutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio, MPV: mean platelet volume, and PDW: platelet width distribution (%).
with previous studies [25]. This work adds two important findings that the NLR can discriminate against the non-survivors from recovered patients (Figure 2), and the NLR value of ≥12.0 during the course of illness predicts the non-survivor (odds ratio: 2.407). The PLR at a cutoff value of 36.8 can predict the non-survivors of COVID-19 patients. This observation agreed with other studies that patients with a higher PLR ratio are at risk of worse prognosis [24,25]. Mean platelet volume and platelet distribution width can predict the non-survivors as their odd ratios exceeded 1.0 but they are not discriminated against the non-survivors. This study agreed with another study that observed each one femtolitre increment of the MPV will increase the mortality rate by 1.76 [26]. Higher values of serum CRP and ESR indicate that COVID-19 patients were presented with hyperinflammation, which is prescribed in a lot of studies. Also, a low mean value of blood saturated indicates that hospitalization of the patients is absolutely indicated, and a significantly low PSO2 in diabetes patients may be due to the small sample size. Limitations of the study included the size of diabetic patients.

We conclude that the determination of hematological indices and ratios during the course of illness can serve as discriminators and predictors of patients who will get a poor prognosis. A significantly higher percentage of monocyte during the course of COVID-19 is a feature of hypertensive patients.

Author contributions: MS-AH provided the study concept and design, statistical analysis, data management, and wrote the manuscript. TAM provided the design, recruited the patients, and performed data management. KYM recruited the patients, and HWM made the applications of laboratory investigations. All authors critically reviewed the manuscript.

Funding: The Ministry of Health and Hawler Medical University in Kurdistan-Region, Iraq supported this study.

Acknowledgements: The authors express their thanks to The Ministry of Health and the Hawler Medical University at Kurdistan Region-Iraq, for giving us the facilities to do the most important study which is not provided the design, recruited the patients, and performed data management.

Declaration of interest: The authors declare that they have no competing interests.

Availability of data and material: The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

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