Critical cases of COVID-19 patients can be predicted by the biomarkers of complete blood count

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Abstract

Background: The confirmatory test for COVID-19 relies on the virus levels in the patients and sampling methods. Besides, there is no definitive description of the role of diagnostic lab parameters in the analysis of positive cases yet. Objective: To investigate the positive COVID-19 cases by screening out hematological biomarker for detection of disease severity and progression. Methods: Data of 110 confirmed COVID-19 cases at King Abdulaziz hospital were analyzed, 42 (38.2%) of the cases were treated in ICU. All variables' means and variances were compared between two groups (non-severe patients and severe) using statistical analysis. Results: ICU and non-ICU positive cases rates were 38.2% and 61.8% respectively. Out of COVID-19 patients, 60% showed lymphopenia and neutrophilia (P < 0.025) and Eosinopenia (60.9%). Furthermore, low levels of MCH and hemoglobin were observed in 96.4% and 90%, respectively. At a significance level of 5%, statistical tests showed a statistically significant difference between groups under investigation in both the mean value and variance for lymphocyte, neutrophils, platelet, and WBCs variables. Conclusions: The analysed variables can be used for predicting patients with positive COVID-19 cases. Lymphocytes and neutrophils were much helpful in monitoring disease severity and infection progression. Moreover, these results encourage considering data as a useful, rapid, and easy way to arrive at a decision of disease severity.

Keywords: CBC; Laboratory biomarker; COVID-19; Lymphopenia; Eosinopenia
1 Introduction

Two highly pathogenic human coronaviruses had been triggered major epidemics over the last 20 years, Severe Acute Respiratory Syndrome (SARS, 2003), and Middle East Respiratory Syndrome (MERS, 2014) \(^1\). Many unexplained cases of pneumonia by the newly identified SARS-CoV-2 were recorded in Wuhan, China on 31 December 2019 \(^2\). It expands and reaches all over the world creating a global health crisis. There is clear heterogeneity in the pathogenic severity of COVID-19 from asymptomatic to serious cases according to WHO 2020 \(^3\). Peripheral white cell differential may be a systemic inflammatory response predictor and is commonly examined as useful indicator of viral pneumonia patients \(^4\). As such biomarkers are required to identify patients’ severity, recent studies have shown correlations between COVID-19 disease and different hematological test results \(^5,6\). These studies have shown that biomarkers in the standard CBC parameters can estimate the development of that infectious disease \(^7–9\).

COVID-19 clinical diagnoses are principally relying on the identification of nucleic acid of the viruses in the laboratory, which are influenced by the virus levels in patients and by methods of sampling. There are also false-negative observations \(^10,11\). Several recent articles have shown the clinical and epidemiologic features of COVID-19 patients, but there is minimal laboratory evidence for contaminated patients. Our research aimed to study different hematological parameters of positive RT-PCR cases for COVID-19 to provide a basis to use these parameters for diagnosis and as a prognostic indicator for patients’ severity.

2 Methods

2.1 Study design

Our retrospective study on laboratory CBC parameters comprised one hundred and ten positive COVID-19 cases and were divided into ICU and non-ICU patients’ groups. All were confirmed using reverse transcription-polymerase chain reaction (RT-PCR Abbott company, USA) in king Abdulaziz hospital. The study was approved by the hospital’s Ethics Committee (Reference NO. 301020). Demographic parameters (age, gender, ethnicity, mortality) and laboratory assessments of complete blood count of the patients were obtained exclusively from the Laboratory Information System (phoneix) in King Abdulaziz hospital. Patients with complete data, including 68 non-severe and 42 critical cases (ICU group), were randomly selected. The patients grouped into severe and non-severe COVID-19 according to the interim guidance of the World Health Organization \(^12\). Whole venous blood samples have been collected on BD EDTA tube and CBC profile analysis has been performed on Sysmex xn-10 and Sysmex xn-20 analyzer (JAPAN).

2.2 Statistical analysis

The statistical analysis, reporting, and graphical representation were done using the following packages: pandas 1.0.5, numpy 1.18.5, hypothesis 5.18.3, IPython 7.16.1, pandas_datareader, scipy 1.5.0, and matplotlib 3.2.2. The data-processing environment was Jupyter 2.1.5 with python 3.7.7.final.0 64-bit on an Intel Core i7-4710HQ. Operating system Microsoft Windows 10 64-bit. A significance level \((\alpha)\) of 5% was used as a maximum accepted p-value to reject the null hypothesis. And as we are measuring the difference in both directions (positive and negative) p-value is compared to 2.5%.

3 Results

The characteristics of demographics and hematological laboratory findings between patients in ICU and non-ICU groups were reported in Table 1. A total of 110 adult patients (\(\geq 18\) years old) with a confirmed diagnosis of COVID-19, 69 (62.7%) were male patients while 41 (37.3%) were female patients. Percentage of Saudi Arabian ethnicity patients were 32 (29.1%), while that of the other ethnicities patients (non-Saudi) were 78 (70.9%).

| Gender | ICU patients (n= 42) (38.2%) | NON-ICU patients (n= 68) (61.8 %) | (n = 110 ) |
|--------|----------------------------|---------------------------------|---------|
|        | Male                       | Female                          | Male    | Female |
| no. of patients | 33 (78.6%) | 9 (21.4%) | 36 (52.9%) | 32 (47.1%) |
| Mortality  | 15                        | 4                               | 1       | -      | 20 (18.2%) |
| Ethnicity | Saudi Arabian             | 13                              | 2       | 3      | 14       | 32 (29.1%) |
| Others    | 20                        | 7                               | 33      | 18     | 78 (70.9%) |

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Table 1 continued

| Age  | < 39 | 40-59 | > 60 | Total |
|------|------|-------|------|-------|
| 20   | 11   | 14    | 7    | 39 (35.5%) |
| 20   | 8    | 14    | 7    | 41 (37.2%) |
| 20   | 11   | 14    | 7    | 42 (38.4%) |

Blood profile

| Hb    | Low | Normal | Total |
|-------|-----|--------|-------|
| < 32  | 3   | 1      | 4 (9.1%) |
| 32-36 | 2   | 4 (9.1%) |
| > 36  | 3   | 2      | 5 (11.8%) |

| MCH   | < 32 | 32-36 | > 36 | Total |
|-------|------|-------|------|-------|
| 150   | 28   | 29    | 20   | 77 (71.1%) |
| 150-150 | 13   | 14    | 11   | 48 (43.2%) |
| > 150 | 12   | 13    | 10   | 35 (32.7%) |

| Platelets | < 150 | 150-450 | > 450 | Total |
|-----------|-------|---------|-------|-------|
| 4         | 1     | 16      | 1     | 22 (20.3%) |
| 28        | 29    | 4 (9.1%) |
| 1         | 1     | 2 (1.8%) |

| WBCs     | < 4.5 | 4.5 - 11.5 | > 11.5 | Total |
|----------|-------|-------------|---------|-------|
| 11       | 5     | 26          | 5       | 31 (29.1%) |
| 11       | 5     | 26          | 5       | 31 (29.1%) |
| 21       | 4     | 4           | 4       | 37 (34.1%) |

| Neutrophils | < 50 | 50-70 | > 70 | Total |
|-------------|------|-------|------|-------|
| 1           | 1    | 14    | 12   | 27 (25.1%) |
| 1           | 1    | 14    | 12   | 27 (25.1%) |
| 28          | 7    | 30    | 28   | 93 (84.5%) |

| Lymphocytes | < 20 | 20-45 | > 45 | Total |
|-------------|------|-------|------|-------|
| 32          | 7    | 17    | 10   | 66 (60%) |
| 1           | 2    | 16    | 17   | 36 (32.7%) |
| 1           | 2    | 16    | 17   | 36 (32.7%) |

| Monocytes   | < 2   | 2-11 | > 11 | Total |
|-------------|------|------|------|-------|
| 4           | 1     | 1     | 1    | 6 (5.4%) |
| 28          | 7     | 30    | 28   | 93 (84.5%) |
| 1           | 1     | 1     | 1    | 6 (5.4%) |

| Eosinophils | < 1   | 1-3  | > 3  | Total |
|-------------|------|------|------|-------|
| 21          | 6     | 20    | 20   | 67 (60.9%) |
| 9           | 3     | 16    | 8    | 36 (32.7%) |
| 3           | -     | -     | 4    | 7 (6.4%) |

Note: (a) Data includes Saudi Arabian residents and non-Saudi. Non-Saudi have been included as “Others” under ethnicity.
(b) Normal range of White Blood Cell (WBC) is 4.5-11.5 K/uL, Mean Cell Hemoglobin (MCH) is 32-36 pg, platelets are 150-450 K/uL, Neutrophils % is 50-70, Lymphocytes % is 20-45, Monocytes % is 2-11 and Eosinophils % is 1-3.

Most of the positive patients underwent blood routine examinations on admission had peripheral blood system anomalies. The rate of anemia of 90.5% of ICU patients compared to 39.7% of non-ICU patients has been observed. Moreover, 96.4% and 90% of all COVID-19 patients presented a low value of MCH and hemoglobin level, respectively regarding the reference range. The increase of neutrophils count percentage was obvious within 88.1% of ICU patients. More important, we found that 92.8% among ICU patients showed significantly decreased lymphocyte counts and 60.9% of the patients showed eosinopenia. Our study showed normal platelet counts with 95 (86.4%) among COVID-19 patients. Moreover, among ICU patients, 19 deaths had occurred, equivalent to a mortality rate of 45%.

Table 2 shows the statistical measures of the continuous variables and both p-values test. A null hypothesis Ho of no significant difference in the mean value for each continuous variable between the two groups was tested using Welch's t-Test. Another set of F-Tests was also conducted with a null hypothesis of equality invariance (Table 3 ). For the significance of mean value differences between the two groups, results show that the null hypothesis is rejected for Age, Hb, Lymphocyte, Monocyte, Neutrophils, Platelet, and WBCs. This indicates a statistically significant difference between the two groups in both the mean value and variance for Lymphocyte, Neutrophils, Platelet, and WBCs variables (Figures 1 and 2 ).
**Table 2.** Continuous variables statistical measures

|        | Mean  | S.D.  | Min  | Max  |
|--------|-------|-------|------|------|
| Age    | 52.54 | 16.94 | 19.00| 94.00|
| Eosinophils | 0.87  | 1.16  | 0.00 | 5.00 |
| Hb     | 12.05 | 2.63  | 5.50 | 17.90|
| Lymphocyte | 19.68 | 13.07 | 1.80 | 51.80|
| MCH    | 27.87 | 3.39  | 20.00| 35.20|
| Monocyte | 6.61  | 0.90  | 17.20|
| Neutrophils | 70.85 | 14.69 | 37.20| 93.30|
| Platelet | 259.15| 103.95| 105.00| 535.00|
| WBCs   | 8.98  | 5.08  | 1.68 | 25.66|

**Table 3.** The baseline characteristics variable statistical measures and tests’ results of covid-19 patients in the study subject

|                  | ICU 42 (38.18%) | None-ICU 68 (61.82%) | t-Test p-value | F-Test p-value |
|------------------|------------------|-----------------------|----------------|----------------|
| Age              | 58.048           | 49.132                | 0.0067<0.025*  | 0.4503 >0.025** |
| Eosinophils      | 0.807            | 0.913                 | 0.6473>0.025  | 0.3926 >0.025** |
| Hb               | 10.769           | 12.847                | 0.0000<0.025* | 0.4769 >0.025** |
| Lymphocyte       | 9.848            | 12.231                | 0.0003<0.025* | 0.4853 >0.025** |
| MCH              | 28.005           | 27.878                | 0.0000<0.025* | 0.0001 <0.025 |
| Monocyte         | 5.150            | 7.510                 | 0.0000<0.025* | 0.0160 <0.025 |
| Neutrophils      | 79.933           | 82.60                 | 0.0000<0.025* | 0.0014 <0.025 |
| Platelet         | 306.071          | 230.176               | 0.0006<0.025* | 0.0031 <0.025 |
| WBCs             | 13.077           | 6.453                 | 0.0000<0.025* | 0.0003 <0.025 |

Symbol (*) denote to that the difference between the means of ICU and None-ICU are statistically significance at level of significance $\alpha=0.05\%$ for all variables. Otherwise are not significant using T test.

Symbol (**) denote to that the data of ICU and None-ICU are statistically homogeneous (i.e. their variances are statistically equaling) at level of significance $\alpha=0.05\%$ for all variables. Otherwise are not homogeneous using F test.

**Fig 1.** Histogram and kernel density estimation for variables with significant statistical difference in both mean and variance
4 Discussion

Early diagnosis of COVID-19 is critical for the optimal management of infected patients to control viral spread. The standard test for COVID-19 remains RT-PCR to detect viral RNA from swap samples, although it is specific but lacks sensitivity\(^{(13-15)}\). Complete blood count (CBC) is a routine test during initial biological assessment of patients and it is well-known that the COVID-19 pandemic has significantly challenged the international laboratory hematology community\(^{(16)}\).

In the current study, male gender was estimated to be dominant among studied population which is consistent with previous literatures\(^{(17,18)}\). Moreover, it could be detected as a high-risk factor in COVID-19 infection where males were almost three times higher than females in the severity and mortality of the disease, furthermore, most of the patients are non-Saudi ethnicity.

Our study aimed to investigate the applicable thresholds for 110 CBC profiles to identify the factors that may affect COVID-19 progression. Our study revealed that the patients in the intensive care unit for COVID-19 showed significant changes in several parameters: a high percentage of neutrophil, low count of eosinophils, and lymphopenia comparing to mild cases. This finding is primarily suggested that these factors can be considered as prognostic biomarkers to predict severe COVID-19.

The current study showed a lymphopenia in 60% of the study participants and 92.8% in ICU patients only. It is the most significant trend of the disease progression across all parameters with a critical and clear pattern and in the same line with previous reports that stated low lymphocytes and high percentage of neutrophils in most patients\(^{(8,19)}\). Also, Huang C et al. (2020) have showed that lymphopenia is a common finding in patients with COVID-19\(^{(20)}\). Similarly, Sun et al. showed lower lymphocytes, and a higher PLR in patients with COVID-19 compared to controls\(^{(21)}\). On the other hand, it was shown in different studies that COVID-19 positive patients had lymphopenia associated with the disease prognosis\(^{(21,22)}\).

Our study showed elevated neutrophils count in 60% of participants and 88.1 % in ICU patients which in consistent with the study done by Fan BE and his colleagues, 2020 that showed a significant correlation in neutrophils count among ICU patients compared with non-ICU group\(^{(21)}\).

The small part of WBCs, the eosinophils, were shown to have different functions, such as antiviral activity and immunoregulation. It has been reported in studies that eosinopenia was detected in COVID-19 patients\(^{(23-25)}\). Other study evaluated 10 COVID-19 patients showed that their eosinophil values were low on admission and changed normal after complete recovery\(^{(26)}\). In the current study, eosinopenia was detected in 60.9% which could be used as a tool in COVID-19 prognosis.

Li Q et al. (2020) have showed that there was no difference in RBC and hemoglobin levels in COVID-19 patients compared to controls\(^{(27)}\). On the reciprocal, our study showed that 90 % of the studied population were anemic, moreover mean corpuscular volume (MHC) was decreased in 96.4%. Although, it is not yet fully known whether COVID-19 affects erythrocytes or not, this finding could suggest that it may affect to some extent RBCs system.

Outcomes in the intensive care unit mortality of the study suggested unusually high ICU mortality rates (45%). The mortality rates varied significantly amongst different countries such as 17% in united states\(^{(28)}\), 25.6% in china\(^{(29)}\) and 48.8% in Italy\(^{(30)}\), this could be explained due to high aged non-Saudi ethnicity patients’ rate (70.9%) participated in our study.

Although the number of our study population (n=110) may be seemed to be inadequate, there many previous studies that comprised small number of patients on comparing with ours such as, 41 COVID-19 patients confirmed infection\(^{(31)}\),
61 COVID-19 ICU patients\(^{(17)}\), 67 COVID-19 patients from Singapore\(^{(22)}\), 75 COVID-19 mild to severe patients\(^{(32)}\) and 99 patients in a descriptive study in Wuhan\(^{(25)}\).

Based on two facts, first is the negative indications for RT-PCR testing alone as the principle way for infection controlling\(^{(33)}\), second is WHO expectation that the second wave of COVID-19 will be more severe than the first one\(^{(34)}\), our findings may play a crucial role to identify severe cases rapidly in the second wave and parameters based on CBC can be a useful tool for predicting prognosis of COVID-19. Much more, CBC tests able to be a practical and efficient method to screen large populations with low coast and less time, which may lead to enhance the management of second wave COVID-19 infection.

5 Conclusion

Based on the present study findings, older age, gender, anemia, lymphopenia, eosinopenia, and high neutrophils count could be used for predicting positive COVID-19 cases. Most important, a high incidence of lymphopenia and elevated neutrophils count were obvious and associated with ICU patients and act as a prognostic indicator for patients’ severity. Moreover, these results encourage physicians to consider CBC parameters as useful, rapid, and easy factors to predict the severity of COVID-19 patients.

Limitation

Our retrospective study was done in a single center and as a result the sample size sample was limited due to logistic problems and administrative acceptance of a large number of patients that need more processing time, so a multiple centers prospective research is recommended. Also, since this study was conducted on blood laboratory parameters, patients were not constantly tracked for all clinical manifestations. Also, unfortunately the available acceptance was limited for hematological laboratory results only.

Declaration of competing interest

The authors declared that there is no conflict of interest.

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