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Coronavirus Pandemic

Evaluation of blood and biochemical parameters of COVID-19 patients in Suez Canal University Hospital; A retrospective study

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Abstract

Introduction: The severe acute respiratory syndrome coronavirus 2 (SARS CoV2-CoV-2) viral outbreak in Wuhan (China) caused thousands of confirmed cases and deaths around the world. Severe viral pneumonia with respiratory failure and death are the ultimate consequence of infection. Aim: This study aimed to evaluate the regularly performed standard laboratory parameters that can assist in COVID-19 case identification and establish an effective approach to help care and management of (COVID-19) patients.

Methodology: COVID-19 (n = 129) patients were hospitalized in the Suez Canal University Hospital and were retrospectively examined. Laboratory parameters were gathered from patients upon admission (n = 129) during the period from the 20th of June to 15th of August 2020. SARS-CoV-2 cases were diagnosed clinically and radiologically by chest Computed Tomography (CT) and confirmed by RT-PCR.

Results: The results showed that COVID-19 survivors exhibited lower hemoglobin (Hb) and hematocrit (HCT), while showed higher Red Cell Distribution Width (RDW), neutrophil lymphocyte ratio (NLR), and lymphocytes. Logistic regression analysis showed that age greater than 60 years old, neutrophilia and high NLR were associated with more deaths.

Conclusion: Monitoring of lymphopenia, neutrophilia and NLR may help categorizing patients who may need Intensive care.

Key words: COVID-19; blood indices; biochemical parameters; Egypt.

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Introduction

Acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the name given by the World Health Organization (WHO) to the virus that caused the outbreak of infectious pneumonia in Wuhan, China [1,2]. This virus has caused thousands of confirmed cases and deaths in China. Coronavirus disease 2019 (COVID-19), the name of the viral disease caused by SARS-CoV-2, soon spread to countries all over the world, including Korea, Japan, Singapore, Iran, Italy, and Spain [3,4]. The clinical spectrum of COVID-19 patients varies from asymptomatic infection, fever, dry cough, lethargy, diarrhea, and mild upper respiratory symptoms to severe viral pneumonia, with respiratory failure, and even death [3,4].

Management of such a pandemic requires appropriate identification and containment through strict surveillance and early diagnosis [5,6]. The gold standard diagnosis of COVID-19 is accomplished by detection of the SARS-CoV-2 using quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) or viral gene sequencing [7]. In Egypt, rapid serological tests are also used to complement the PCR diagnosis. The scant availability of resources in addition to the long turnaround time results in delaying between testing and confirmation, which leads to delay in clinical judgment. Through this waiting period, patient history, hematological, biochemical parameters, and chest CT are essential for aiding in the diagnostic decision [8]. Lymphocytes maintain immune homeostasis and modulate inflammatory reactions. Several mechanisms may lead to lymphocyte deficiency during the COVID-19 outbreak [1]. The COVID-19 virus directly infects lymphocytes leading to cellular death. Angiotensin-converting enzyme 2 (ACE-2) receptors are expressed by lymphocytes; thus these cells are a direct targets of the virus [9]. The novel coronavirus directly injures the thymus and spleen [3]. Cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-6 may promote lymphocyte apoptosis,

resulting in lymphocyte deficiency [10,4]. Hyperlactic acidemia contributes to lymphocyte inhibition and affecting proliferation [11].

Approximately 69% of COVID-19 patients had lymphopenia, and their blood profile showed few reactive lymphocytes, whereas some lymphocytes appeared as lymphoplasmacytoid [2]. Reactive lymphocytes were not found in patients in Singapore during the severe acute respiratory syndrome (SARS) outbreak that occurred in 2003 [2] and in 15.2% of the patients in Hong Kong [12].

Until now, researchers have been searching for an effective antiviral treatment. Clinically, mild COVID-19-type patients improve soon after proper clinical intervention. However, for the moderate COVID-19-type patients, particularly older patients or patients with comorbidities, can deteriorate rapidely. Literally, theycan develop acute respiratory distress syndrome (ARDS) and multi-organ failure, resulting in high mortality rates [4]. Therefore, a timely diagnosis of disease progression is crucial for appropriate management and intervention.

Indicators that determine the severity of disease, therapeutic response, and disease outcome are needed. A complete profile of blood indices may be a useful indicator to direct rational medication and care that might significantly reduce the mortality rate of severe cases. In the present study, we evaluated common COVID-19 laboratory parameters that can assist in diagnosis and provide an effective approach to care and manage COVID-19 patients.

Table 1. Sociodemographic characters of patients.

Characteristics	n (%)
Gender	
Male	75 (58.14)
Female	54 (41.86)
Job	
No work	63 (48.84)
Governmental work	14 (10.85)
Private work	8 (6.20)
Medical team	21 (16.28)
Missing	23 (17.83)
Address	
Urban	40 (31.01)
Rural	65 (50.39)
Missing	24 (18.60)
Age groups	
< 40 Year	27 (20.93)
40 Year	29 (22.48)
60 Year	45 (34.88)
80-87 Year	4 (3.10)
Missing	24 (18.60)
Mean ± SD	52.35 ± 17.17
Fate	
Improvement	112 (86.82)
Death	17 (13.18)

Methodology

Confirmed COVID-19 patients, which were hospitalized in the Suez Canal University Hospital, were retrospectively examined. Laboratory parameters were collected from June 20 to August 15, 2020. During this period, the Suez Canal University isolation ward had 129 confirmed cases of COVID-19 infection. SARS-CoV-2 was confirmed by an RT-PCR assay, which performed on nasopharyngeal swabs (sent to the Egyptian health ministry). A clinically confirmed diagnosis was also achieved by chest CT. All patients received treatment in the Suez Canal University isolation ward.

For each patient, Demographic data, clinical history, and laboratory results during hospitalization were collected. Patients The parameters collected upon admission regardless their levels included a complete blood profile in addition to measurements of C-reactive protein (CRP), procalcitonin (PCT), ferritin, lactate dehydrogenase (LDH), prothrombin time (PT), partial prothrombin time (PTT), electrolytes (Na, K, Mg, and Ca), liver function, albumin, kidney function, and D-dimer levels.

According to the fate of patients derived from hospitalization records, they were divided into survivors and non-survivors in accordance with Egyptian guidelines [13]. Clinical improvement was defined as the resolution of fever for ≥ 48 h and the suspension of oxygen supplementation. We present a detailed analysis of the hematological and biochemical parameters of the confirmed COVID-19 patients at the Suez Canal University isolation ward. We also analyzed the hematological indices of all COVID-19-infected patients, including an assessment of blood cell counts (hemoglobin (Hb), red blood cells, white blood cells, and platelet counts), red cell indices (PCV hematocrit, mean cell volume (MCV), mean corpuscular hemoglobin (MCH), red blood cell distribution width (RDW)), and platelet count using a Sysmex XP200 (Tukang, Singapore). The biochemical parameters ferritin, LDH, Na, K, Mg, Ca, SGPT, SGOT, UREA, Mg, and albumin were measured using a BT 1500 Chemistry Analyzer (Licenza, Rome). These measurements were done using a colorimetric assay (endpoint and kinetic assays) according to standardized techniques. A POCT (Nanjing, China) analyzer was used to measure CRP, PCT, and D-dimer.

Statistical analysis

All statistical analyses were performed using the Statistical Package for Social Science Program (SPSS version 22 for windows). Continuous data are presented as the mean along with a standard deviation. For the analytical data, the chi-square test was used to determine differences between the qualitative data. Statistical significance was considered at p-values ≤ 0.05.

Results

This study included 129 patients admitted to the Suez Canal University isolation ward from June 20 to August 15, 2020. They all tested positive by the PCR assay. Most of them were males (58%). Of these, 48.84% of the patients were not working, and 16.28% were from the medical team. Approximately 34.88% were in an age range from 60 to less than 80 years old (Table 1).

Hematological parameters included the mean ± SD of Hb, total mean leucocyte count, lymphocytes, lymphocyte percentage, and neutrophil/lymphocyte ratio (NLR), which were 12.42 ± 2.10 g/dL, 8.67 ± 5.62×10^9/µL, 1.96×10^3 ± 0.961, 27.35 ± 15.12, and 4.54 ± 5.52, respectively.

Measurements indicated a C-reactive protein (CRP) concentration of 23.45 ±3 4.98 mg/L and a ferritin concentration of 534.70 ± 519 ng/mL (Table 2). We observed that survivors had higher hemoglobin (Hb), hematocrit (HCT), and normal red cell distribution width (RDW) values (12.65 ± 1.87, 37.21 ± 4.8, and 14.16 ± 1.91, respectively) compared with non-survivors (10.91 ± 2.85, 32 ± 8.4, and 16.29 ± 3.94, respectively). In addition, survivors had statistically significant higher ages compared with non-survivors (49.5 ± 17.44 and 64.5 ± 11.72, respectively) (Table 3).

We also found that the survivors exhibited higher levels of lymphocytes, neutrophil count (2056.20 ± 940.65, 5285 ± 4313.9, respectively compared to non-survivors (1385.70 ± 912.47, 11690 ± 9888.92, respectively). The results showed that 14.3% and 52.5% of survivors and non survivors showed high leukocytic count while 78.5% and 47.1% of survivors and non survivors showed normal total WBCs count respectively, 29.5% and 58.8 % from survivors and non survivors respectively had lymphopenia, 17% and 64.75% of survivors and non survivors showed neutrophilia respectively, while 29.5% and 70.6 % of survivors and non survivors had high NLR respectively (Table 4).

Table 2. Biochemical parameters of the studied sample.

Title	Mean	SD
CRP (mg/L)	23.45	34.98
Ferritin (ng/ml)	534.70	519.21
LDH (U/L)	489.35	182.78
Na+	141.75	13.52
K+	4.04	0.78
Ca++	4.45	0.37
INR	1.10	0.13
Prothrombin Time(s)	14.34	1.82
SGOT	40.09	19.82
SGPT	41.55	31.95
hs CRP (mg/L)	7.83	4.29
Urea	50.63	15.05
Mg	2.15	0.35
Control time PTT(s)	28.51	6.12
PTT	40.38	6.27
Albumin	3.83	0.77
D-dimer (ug/mL)	0.84	1.17

The stepwise logistic regression analysis showed that patients' fate (improvement and death) as dependent variable and job, total leukocytic count, neutrophils lymphocytes, NLR and age as independent variables, the results showed that among COVID- 19 patients; the absence of a job increased risk of death by four folds compared with non-working patients with a non-significant difference ($p > 0.05$), while increased NLR and neutrophils associated with more deaths among COVID-19 patients (OR: 1.78 and .70 respectively) which was statistically significant ($p < 0.05$), lymphocytes and total leukocytic count had a non- significant effect on the fate of COVID-19 patients ($p > 0.05$), increase age was associated with more

Table 3. Red Blood indices and platelets according to cases fate.

Title	Survivors		Non-Survivors		*p*-value
	Mean	SD	Mean	SD	
Hemoglobin	12.65	1.87	10.91	2.85	0.03*
Age	49.5	17.44	64.5	11.72	0.001*#
Haematocrit PCV	37.21	4.84	32.48	8.40	0.04*
MCH	27.84	2.67	27.84	4.20	0.99
MCHC	33.92	1.46	33.59	1.32	0.36
MCV	81.96	5.86	82.65	10.47	0.79
Red Cell	4.57	0.68	4.03	1.25	0.10
RDW	14.16	1.91	16.29	3.94	0.04*
Platelet	271.5	1.142	271.2	1.132	0.99

Student *t*-test was used; * Statistically significant at 95% level of confidence.

Table 4. Leucocytes and cases fate.

Title	Details	Survivors				Non-Survivors				*p*-value
		No.	%	Mean	SD	No.	%	Mean	SD	
WBCs	Low	8	7.1	7.92	4.20	0	0.0	13.61	10.02	0.03*# 0.00*ǂ
	Normal	88	78.6			8	47.1			
	High	16	14.3			9	52.9			
Lymphocytes	Low	33	29.5	2.05	0.9	10	58.8	1.3	0.9	0.01*# 0.03*ǂ
	Normal	79	70.5			7	41.2			
Neutrophils	Low	11	9.8	5.285	4.3	0	0.0	11.69	9.8	0.03*# 0.00*ǂ
	Normal	68	60.7			3	17.6			
	High	19	17.0			11	64.7			
	Missed	14	12.5			3	17.6			
NLR	Normal	64	57.1	3.62	4.05	2	11.8	10.91	9.33	0.01*# 0.00*ǂ
	High	33	29.5			12	70.6			
	Missed	15	13.4			3	17.6			

* Statistically significant at 95% level of confidence; # Mann-Whitney test was used; ǂ Chi-Square test was used.

deaths which was statistically significant ($p < 0.05$). Age greater than 60 years old was associated with more deaths (age entered as more than 60 years old and less than 60 years old) (Table 5).

Morphological picture of cells

WBCs

Some neutrophils showed clumped chromatin with toxic granules and heavily cytoplasmic vacuoles. The shape of the nucleus varied with C-shaped and peculiar nuclear projections. Some neutrophils showed bilobed, trilobed, and a hypo-segmented nucleus (Figure 1). Lymphocytes appeared as large granular lymphocytes (LGL) with round to indented nuclei, condensed chromatin, some with many prominent nucleoli, along with an abundant, pale blue cytoplasm with distinct variably sized azurophilic granules (Figure 2).

Platelets

Platelets were adequate with a few giant forms and some giant platelets with vacuolations. Some platelets showed protruding pseudopodia (Figure 2).

Monocytes

Peripheral blood films revealed activated monocytes with prominent cytoplasmic vacuoles and a few granules. The nuclei were large with fine chromatin and nuclear blebbing. Nuclear overlapping by vacuoles was observed in some cells (Figure 2).

Blast cells and normoblasts

Blasts were observed in some blood films with blasts showing a bizarre shape and an increased nucleocytoplasmic ratio. Late normoblasts were also observed, suggesting bone marrow irritation.

Discussion

The lockdown of Wuhan, China, on February 23, 2020, caught the world's attention. SARS-CoV-2 is one of the coronaviruses and a member of the *Coronaviridae* family, identified in both avian hosts and several mammals [14]. To manage COVID-19 infection, early diagnosis, appropriate treatment, and future control measures are all essential to limit the spread of the virus. Laboratory parameters play an indispensable role in the early assessment of disease etiology, diagnosis, treatment, and follow-up.

Patients have a normal leukocytic count,later on, leukopenia or leukocytosis can occur, although leukopenia is more frequently observed [3].

Table 5. Logistic regression analysis between fate as dependent variable and job, NLR, lymphocytes, and age as independent variables.

Item	Beta	Odds ratio	*p*-value	Confidence interval	
				Lower Limit	Upper Limit
Job	-1.511	4.533	0.18	0.508	40.47
NLR	-0.132	1.876	0.04*	0.805	3.98
Neutrophils	-2.601	0.701	0.00*	0.190	0.88
Lymphocytes	0.106	1.112	0.14	1.035	1.20
Leukocytes	-0.199	0.819	0.61	0.381	1.76
Age	-0.060	1.942	0.00*	0.895	3.99

Job entered as (0 not working and 1 working), NLR (0 low, 1 high), Lymphocytes (0 low, 1 normal), neutrophils (0 normal, 1 high), leukocytes (0 normal, 1 high), age (1 more than 60 years, 0 less than 60 years) all these were independent variables, and fate (1 improvement, 0 death) as dependent variable; * Statistically significant at 95% level of confidence.

Figure 1. Peripheral blood films stained with leishman and Gimesa stains showing several neutrophils with **a:** C-shaped; **b:** V shaped; **c:** S shape; **d**: Fetal-like; **e:** hyposegmented; **f:** heavy granulations; **g:** nuclear projections; **h:** U shaped COVID nuclei. Leishman and Giemsa ×200–400.

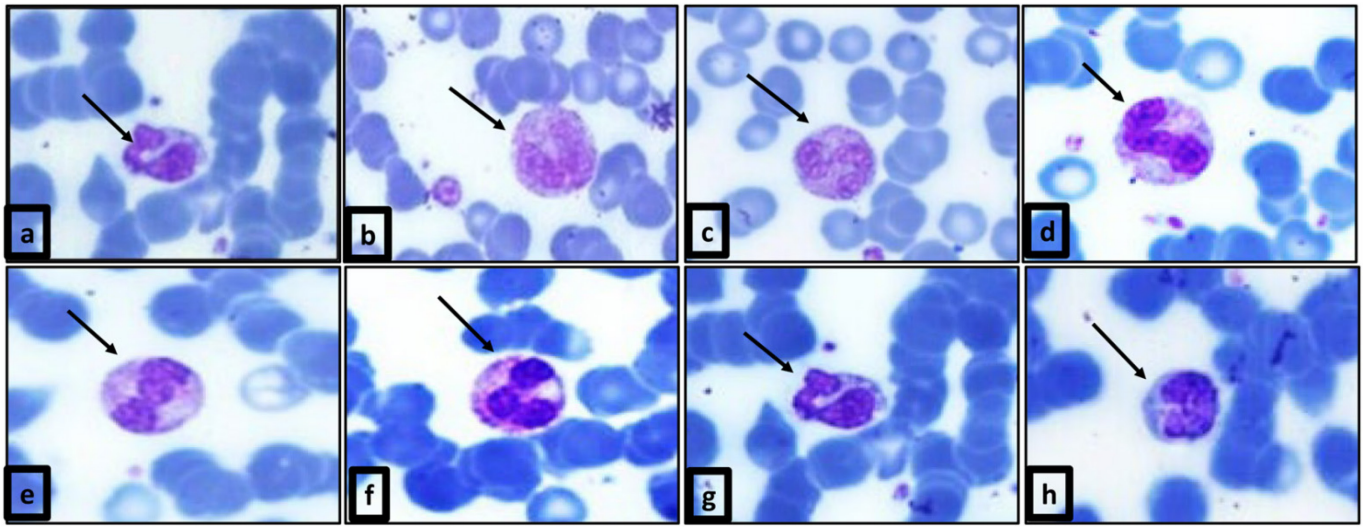
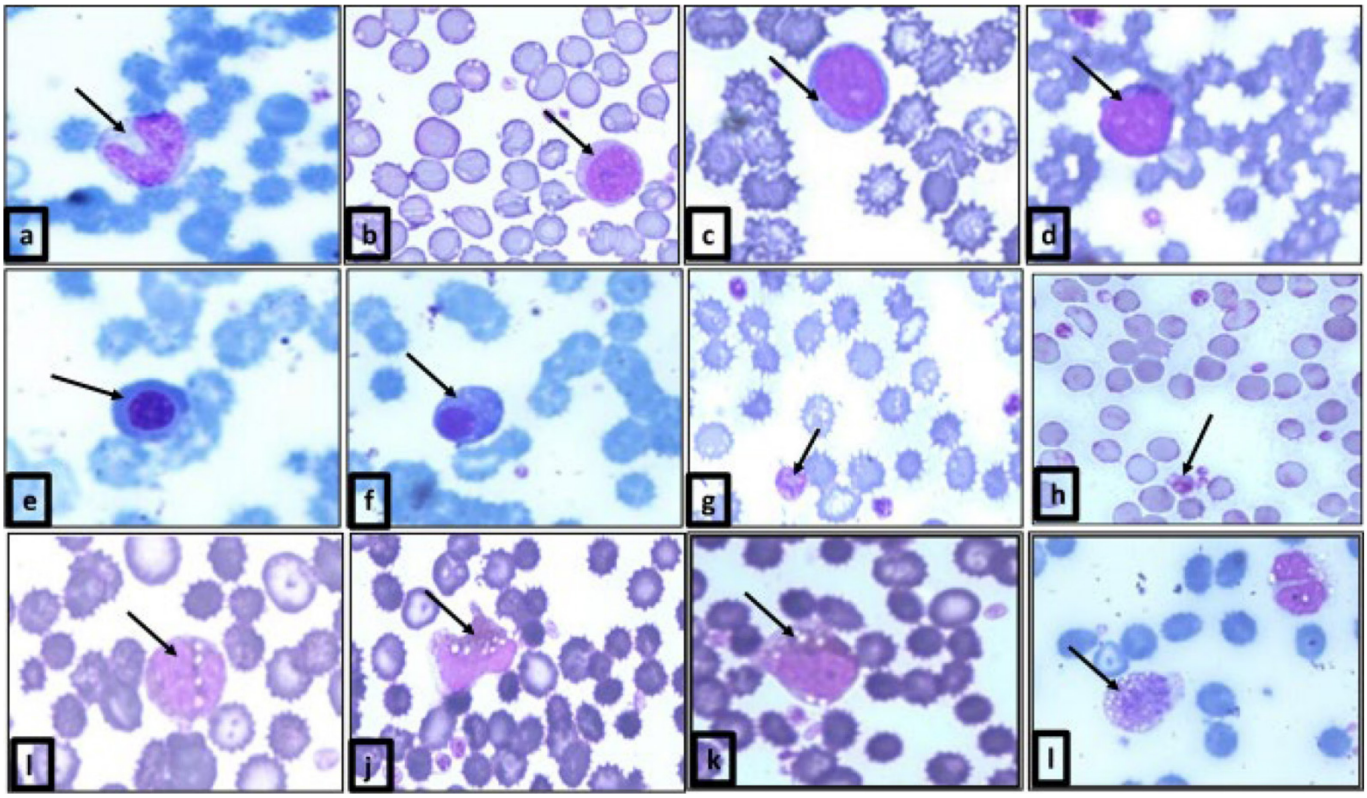


Figure 2. Peripheral blood films showing **a:** metamyelocyte; **b:** small lymphoctes; **c:** large lymphocyte with prominent nucleoli; **d:** blast cell with prominent nucleoli; **e:** late normoblast; **f:** late normoblast; **g:** large platelet; **h:** platelet blebbing; **i:** blast cell with vacuolations; **j, k and l:** Are activated monocytes with prominent cytoplasmic vacuolations and a few granules.



In our study, the mean leukocytic count was 7.9×10^3, and the mean of the lymphocyte count was 2×10^3 for survivors, whereas the mean of the total leukocytic count increased in non-survivors to 13.61×10^3 with a decreased mean of the total lymphocytic count to 1.3×10^3 ($p = 0.034$* and 0.010*, respectively). Huang *et al.* and Xu *et al.* found that 63% of patients in Wuhan, China, and 42% of patients outside of Wuhan presented with lymphopenia [4,9].

Rodriguez *et al.* performed a meta-analysis including 511 patients, which determined that lymphopenia is present in 43.1% of COVID-19 patients [15]. In 1099 COVID-19 patients from 552 Chinese hospitals, Guan *et al.* reported that lymphopenia was detected in 82.1% and leukopenia in 33.7%, whereas leukocytosis was present in 5.9% of the patients [16].

In our study, non-survivors exhibited neutrophilia with a mean value of 11.69×10^9/L compared with 5.2×10^9/L in survivors ($p = 0.032$). The same results were observed by Fan *et al.* in a cohort of 69 COVID-19 patients. They reported that ICU patients were more likely to develop neutrophilia during their hospital stay with a median peak of absolute neutrophil count of 11.6×10^9/L compared with 3.5×10^9/L in the non-ICU group ($p < 0.001$) [17]. Superimposed bacteria may explain neutrophilia; thus, PCT is important to differentiate bacterial from viral infections in ICU patients.

In the present study, the non-surviving patients who experienced severe COVID-19 had prominent laboratory abnormalities compared with those of survivors who experienced clinical improvement. Lymphopenia is a reliable indicator of the severity and hospitalization of COVID-19 patients [18]. Wang *et al.* followed the variations in six clinical laboratory parameters from day 1 to day 19 at 2-day intervals and observed that non-survivors had an increased leukocytic count with increased neutrophils and lower lymphocyte counts compared with that in survivors [3].

A meta-analysis study revealed an increased neutrophil-to-lymphocyte ratio and decreased lymphocyte-to-C-reactive protein ratio in patients with severe COVID-19 infection compared with non-severe patients [19]. Similar results were noted in our study, including increased leukocytic counts, increased neutrophil counts, and lymphopenia in non-survivors of COVID-19 infection. In the present study, non-survivors showed higher NLR values compared with survivors, which was supported by the results of logistic regression in which neutrophilia and NLR were significant predictors of survival among COVID-19 patients. High NLR values were associated with more deaths. A recent study by Qin *et al.* was consistent with our results presented showing significantly high NLR values in patients with severe COVID-19 in a cohort of 452 hospitalized patients [20]. This reinforces the concept of a close association between the inflammatory process and COVID-19 pathogenesis.

The results of regression revealed that increased age contributes to poor survival among COVID-19 patients, which is consistent with a CDC report. The report stated that the severity of the disease increased with advanced age [21]. The nonworking population in our study showed an increased risk of poor survival compared with the working population, although this was a non-statistically significant difference. This may be due to the fact that 65.4% of nonworking subjects were over 60 years old, retired, and more susceptible to complications.

In our study, platelet counts were not significantly different between survivors and non-survivors. Guan *et al.* observed that thrombocytopenia in most patients with COVID-19 was mild (platelet counts 100–150/mm^3) [16]. Qu *et al.* showed that in severe COVID-19 infections, platelet counts had a tendency to increase early, followed by a decrease with deteriorating clinical status, thus leading to a longer hospital stay [22]. Platelet count comparison in COVID-19 ICU vs. non-ICU patients revealed that ICU patients and non-survivors had decreased thrombocyte counts [23,8]. Thrombocytopenia was identified in a meta-analysis of 9 studies consisting of 1779 COVID-19 patients. Therefore, thrombocytopenia was considered as a clinical indicator of progressing illness during hospitalization [24,25].

We noticed that there was no significance between survivors and non-survivors regarding platelet counts**.** Guan *et al*., found that thrombocytopenia in most patients with Covid-19 was mild (platelet counts 100–150/mm^3) [16]. Qu *et al.* showed that in severe Covid-19 infections, platelet counts had a tendency of early increase followed by a decrease with deteriorating clinical status, thus leading to a longer hospital stay [22].

Platelet counts comparison in COVID-19 ICU vs. non-ICU patients revealed that ICU patients and non-survivors had decreased thrombocyte counts [23,8]. Thrombocytopenia was found in a meta-analysis of nine studies of 1779 COVID-19 patients; hence thrombocytopenia was considered as a clinical indicator of progressing illness during hospitalization [24,25].

Guan *et al.* noted that in patients with COVID-19, anemia was not reported frequently [16]. Similarly, our results indicated that the mean RBC count in non-

survivors was 4.03×10^9/L compared with 4.57×10^9/L in survivors with no statistical difference. Previous studies on COVID-19 infections showed significantly lower absolute leukocyte or neutrophil counts during the early stages of the disease [26], although the mean leukocytic count in these studies did not exceed the lower limit for classification as leukopenia or neutropenia. Interestingly, we found that patients who progressed to improvement had higher HB, HCT, and normal RDW values (12.65 ± 1.87, 37.21 ± 4.8, and 14.16 ± 1.91, respectively) compared with patients who died (10.91 ± 2.85, 32 ± 8.4, and 16.29 ± 3.94, respectively).

Non-survivors had increased levels of total leukocytic count, absolute lymphopenia, absolute neutrophilia, and increased NLR compared with clinically improved patients. A retrospective study in Hong Kong and Singapore showed that lymphopenia was observed in patients who suffered from SARS-CoV in 2003 and was associated with adverse outcomes and ICU stay [25,27]. Monitoring lymphopenia may help to categorize patients who may require ICU care.

The American Society of Hematology found that in the COVID-19 hypercoagulable state with elevated D-dimer, elevated fibrinogen degradation products (FDP), elevated fibrinogen, prolonged prothrombin time (PT), and activated partial thromboplastin time (APTT) were all notable [26]. Similar findings were observed in our results. CRP, Ferritin, LDH, hsCRP, urea, PTT, and D-dimer were all elevated. Zhang *et al.* concluded that liver-related dysfunction from COVID-19 might cause the hemostatic variations, although this remains to be explored [28]. Interestingly, we found that albumin was at a lower normal level with a mean value of 3.8 (SD = 0.77), whereas SGPT and SGOT were at high mean values, which suggests that liver function is affected by COVID-19 infection.

The limitations of our study were as follows; Our study was a single-center retrospective study, this influences the generalization of data and increase the probability of selection bias; In the present study, missing data was a major limitation as laboratory examinations were not implemented daily on all patients, especially those who were minimally symptomatic in the general isolation ward. Patients who died at a given time all affected the statistical analysis.

In order to assess the specificity and reliability of COVID-19 cytopathic effects on peripheral smear blood cells, a larger population need to be evaluated in larger studies. Our objective is to describe the abnormal morphological findings of COVID-19 affected leucocytes, which would help laboratory doctors in screening, diagnosis and management of suspected COVID-19 diagnosis.

It is well-established that COVID-19 is a multiorgan infection with a noteworthy impact on the hematopoiesis and hemostatic systems. Monitoring of lymphopenia and NLR may help categorize patients who may need ICU care. It is important to identify the laboratory abnormalities early and act to prevent complications. It appears that healthcare workers will be fighting COVID-19 for a long time. Hematological parameters are still recognized as indicators for hospitalization, severe disease, and prognosis and may help doctors make appropriate clinical decisions. Further immunological, genetic studies should be conducted to manage the disease.

Authors' contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted (JIDC) and agree to be accountable for all aspects of the work.

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