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PREDICTABILITY OF COVID-19 INFECTION AND SEVERITY USING LABORATORY FINDINGS BIOMARKERS IN HOSPITALIZED AND NON-HOSPITALIZED PATIENTS

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ABSTRACT

Background*:** patients infected with SARS-CoV-2 develop potentially life-threatening pathologies involving hyper inflammation, cytokine storm, septic shock complications, coagulation dysfunction, and multiple organ failure. Laboratory biomarkers are effectively used for detecting disease severity and distinguishing between severe and non-severe COVID-19 cases to guide for best therapeutic options. ***Aim: to predict the incidence and severity of COVID-19 infection through the hematological, inflammatory and coagulation biomarkers in hospitalized and non-hospitalized patients. ***Materials and Method:*** in this retrospective cohort study, 114 patients with age ranging between 30-80 years who were diagnosed with COVID-19 positive were selected from Alnaser Isolation Center, Azawia/ Libya. Patients were classified into 49 severe or critically ill patients who admitted to the isolation center, and 65 non-sever group with or without regular symptoms. ***Results*:** among hospitalized COVID-19 patients, the levels of WBCs, NEU, CRP, ESR were increased significantly and lymphocytes were decreased significantly ($P<0.001$) in comparison to their levels in non-hospitalized patients. 10.8 % of non-hospitalized had high D-dimer level whereas, 67.3% of hospitalized patients their D-dimer level was abnormal and increased significantly ($P<0.001$). Regarding the age groups, only elderly patients (50-79 and ≥ 80 years age groups) showed a significant increase in CRP, ESR and D-dimer levels in both patient groups ($P<0.05$). Although, the mortality rate among all patients was 20.2%, this percentage increased in hospitalized patients and reached 42.9%. Non-survivors COVID-19 patients developed leukocytosis, neutrophilia and lymphopenia, along with abnormal values of D-dimer, CRP and ESR levels. ***Conclusion:*** an elevated serum WBC, NUE, ESR and CRP were associated with start of infection and severity COVID-19 with clearly low level of lymphocyte. Coagulation biomarkers play a crucial role in identifying COVID-19 infection severity and mortality.

KEYWORDS: COVID-19 infection; Severity; Laboratory Biomarkers; Hospitalization; Morality; Survivors and Non-survivors.

1. INTRODUCTION

Coronaviruses (CoVs) are positive-sense, single-stranded ribonucleic acid (RNA) viruses with a linear, non-segmented viral genome. It is a respiratory disease identified in Wuhan, China and caused by the severe acute respiratory syndrome corona virus2 (SARS-CoV-2) virus. SARS-CoV-2 is one of the corona viruses that belong to the family of Coronaviridae which is large group of viruses infecting animals and humans (Zhang *et al*., 2020). The World Health Organization (WHO) on 11 March 2020 declared COVID-19 as a pandemic due to its rapid spread worldwide. Recently, more than 226 billons of people have been infected with the virus, causing more than 4.6 million deaths in all countries throughout the world (WHO 2021). This outbreak leads to important increases in the demand for hospital beds and shortage of medical equipment, while medical staff themselves can also become infected (Ortiz-Prado *et al*., 2020). Several regions are experiencing second and third waves and are facing the limits in their test capacity, hospital resources and healthcare staff (Wynants *et al*., 2020).

Studies from China, Europe and USA show that clinical manifestation of COVID-19 ranges from asymptomatic or mild upper respiratory illness to moderate and sever disease, rapidly progressive pneumonitis, respiratory failure, acute respiratory distress syndrome, organs

failure with fatal outcomes (Melenotte *et al*., 2020). The majority of COVID-19 cases are asymptomatic, mild or ordinary, whereas one-fifth of cases are severe or critically ill cases. The estimated overall mortality rate is 2-3% in China, but half of the critically ill patients in Wuhan finally died due to life-threatening complications (Yu et al 2020). Melenotte *et al*., (2020) stated that the direct cytotoxic effects, coagulopathy and exacerbated immune responses of SARS CoV-2 play critical roles in the progression from asymptomatic toward critical or severe illness.

It has stated that the main mechanism for SARS-CoV-2 infection is the binding of the SARS-CoV-2 spike (S) protein, which is the major determinant of the virulence to the angiotensin-converting enzyme 2 cell surface receptor ACE2 on host cells and the internalization of complex by the host cell. Upon virus entry, the host immune system will respond through stimulating the immune response to eliminate the corona virus. The attachment of SARS-CoV-2 spike glycoprotein with ACE2 triggers complex molecular events that lead to hyper-inflammation and burst of cytokine storm, which is known as a hallmark of COVID-19 infection (Mahmudpour *et al*., 2020). It reported that COVID-19 cytokine storm leads to over-activation of white blood cells, which release too-great amounts of cytokines inflammation-stimulating molecules such as interleukin-6 (IL-6), tumor necrosis factor alpha (TNFα) and interleukin-8 (IL-8) into the blood (Mahmudpour *et al*., 2020; Xie *et al*., 2020).

As a result, approximately 20% of patients infected with COVID-19 develop potentially life-threatening pathologies involving hematological abnormalities, hyper inflammation, septic shock complications, coagulation dysfunction, and multiple organ failure (Potempa *et al*., 2020). Preliminary studies pointed out that the diagnosis of COVID–19 disease is challenging in the early stages due to non–obvious manifestations, therefore, hematological and other biological signs and symptoms provide clues to aid diagnosis and reduce the severity of the this disease (Słomka *et al*., 2020). It is found that COVID-19 was prone to cause hematological changes, therefore; routine hematological tests have been reported to be useful in the prognostication of diagnosed patients with coronavirus disease (Thompson *et al*., 2020).

The monitoring of hematological parameters is essential in the identification of patients who will need to be admitted in the hospital in intensive care unit (ICU) (Duarte *et al*., 2020). Furthermore, a good understanding of COVID-19 pathophysiology, in particular hematological disorders, will help to choose appropriate treatment strategies (Debuc and Smadja 2021). According to Sun *et al*., (2020) analysis of clinical characteristics of 1099 patients with COVID-19 showed abnormal parameters of leukocytes, lymphocytes and platelets in peripheral blood of some patients. Mild and common COVID-19 patients have milder symptoms and good prognosis, but severe and critically ill patients are difficult to treat and have a high mortality rate.

Blood level of the hepatically synthesized prototypic acute phase reactant, C-reactive protein (CRP) is released in response to interleukin-6 (IL-6) stimulation. CRP an inflammatory biomarker is a widely used as a diagnostic marker to assess ongoing inflammation (Wang 2020). It is notable that CRP level is effective way to assess covid-19 disease severity where it is markedly elevated in patients with COVID-19, which is unfortunately correlated with poor prognosis for survival (Potempa *et al*., 2020). It appears in blood within 6–10 hours of any tissue damaging event (Wang 2020). Therefore in hospitalized COVID-19 patients trending CRP is a simple and accessible strategy for predicting inflammation and respiratory deterioration (Mueller *et al*., 2020).

Many studies reported that there is a correlation between high levels of CRP and mortality rate in COVID-19 patients. Ullah *et al*., (2020) found that elevated CRP levels were significantly associated with a high mortality risk in 375 patients with confirmed SARS-CoV-2 infection. Simultaneously, Zhang *et al*., (2020) reported in 140 hospitalized COVID-19 patients with confirmed SARSCoV-2 infection, CRP levels varied from 28.7μg/mL in non-severe disease to 47.6μg/mL in severe disease. In another study conducted to evaluate fatal outcomes among COVID-19 patients, 187 patients from China were included among whom 43 died, and results revealed that high levels of CRP was significantly associated with mortality (Ahmeidi *et al*., 2020). Lippi and Plebani (2020) proved that the most frequent laboratories abnormalities among patients with non-severe COVID-19 infection were increased values of CRP, erythrocyte sedimentation rate (ESR) and D-dimer.

The laboratory examinations after COVID-19 patient's admission showed a mildly abnormal increase of erythrocyte sedimentation rate (ESR) (Pu *et al*., 2020). ESR determination may contribute to the management of COVID-19 patients and provide additional information on disease progression (Lapić *et al*., 2020). Although ESR is considered as the least specific laboratory inflammatory biomarker in COVID-19 infection because it can to be affected by other numerous pathophysiological conditions (Lapić *et al*., 2020), it still used for distinguishing between severe from non-severe COVID-19 cases (Lapić *et al*., 2020). Zhang *et al*., (2020) pointed out that ESR and CRP levels depend on the differences in immune system of the COVID-19 patients and they can be used as a reference to predict the disease progression.

Valerio *et al*., (2021) highlighted that in addition to inflammatory biomarkers, the coagulation abnormality particularly D-dimer has positively associated with the COVID-19 severity. D-dimer is the principal breakdown

fragment of fibrin and is used as a biomarker of fibrin formation and degradation. During thrombus formation, plasmin degrades cross-linked fibrin polymers, resulting in the formation of a number of soluble crosslinked fibrin degradation products of various molecular weights. The smallest and most well characterized of these products is D-dimer (Moresco *et al*., 2003). Any process that involves in the production and breakdown of fibrin in covid-19 patients causes an elevation in D-dimer levels (Ullah *et al*., 2020). The most common initial hemostatic abnormalities observed in severe COVID-19 patients are mild thrombocytopenia, increased fibrinogen and D-dimer (Ghahramani *et al*., 2020).

Numerous studies have shown that healthy individuals have low levels of circulating D-dimer, whereas elevated levels are found in conditions associated with thrombosis (Weitz, Fredenburgh and Eikelboom 2017). D-dimer is a marker of fibrinolysis and has been used as a diagnostic and prognostic marker in venous thromboembolic events (VTE), which has been seen frequently in sever hospitalized covid19 patients (Creel-Bulos *et al*., 2020). Thus, D-dimer level is higher in the COVID-19 subjects who are critically ill or those who expire and is associated with death in patients with COVID-19 rather than non-sever patients (Berger *et al*., 2020).

Therefore, it really crucial to identify the clinical laboratory significance in particular hematological, inflammatory and coagulation parameters to predict the COVID-19 infection progression and avoid the patient's condition deteriorates (Sun *et al*., 2020). The main laboratory changes encompass an array of increased inflammatory biomarkers, derangement of coagulation parameters, pathological values of non-specific tissue injury indicators and alterations of the complete blood count with or without leukocytosis, but with lymphopenia, the latter being particularly unusual for viral infections (Lapić *et al*., 2020). Thus, the aim of this research is to predict the infection and severity of COVID-19 infection through the hematological, inflammatory and coagulation biomarkers in hospitalized and non-hospitalized COVID-19 patients.

2. MATERIAL AND METHODS

2.1Study design and participants

In this retrospective cohort study, 114 patients with age ranging between 30-80 years who were diagnosed with Covid-19 positive were selected to carry out this research during the period from September 2020 to June 2021. All the confirmed cases with COVID-19 was defined as a positive result to real-time reverse-transcriptase polymerase-chain-reaction (RT-PCR) assay using nasal and pharyngeal swab specimens.

COVID-19 patients were classified based on the severity into two groups (severe and non-severe). Forty nine covid-19 patients were severe or critically ill patients. The medical records were retrospectively reviewed, and hospitalization patient data were compiled from Alnaser Isolation Center, Azawia/ Libya, which were designated center by the government for hospitalizing COVID-19 patients in Zawia. Clinical characteristics and laboratory parameters were collected upon admission and during hospitalization. Sever or critically ill patients were defined as those admitted with severe symptoms such as shortness of breath, peripheral blood oxygen saturation is less than 75% and those admitted to the intensive care unit (ICU) at the isolation center who required mechanical ventilation or had a fraction of inspired oxygen.

The other 65 covid-19 patients were non-sever group (non-hospitalized) classified as the non-sever group with or without regular symptoms (fever, respiratory symptoms, and radiographic evidence of pneumonia) they did not require an admission to the isolation center.

2.2. Data collection

All data including age and laboratory test results including hematological biomarkers results (complete blood count), inflammatory biomarkers results (C-reactive protein and erythrocyte sedimentation rates) and coagulation biomarkers results (D-Dimer) were obtained from the available electronic medical records in the isolation center. Blood samples from non-sever or non-hospitalized patients were taken and collected from all patients and this blood were analyzed by using hematology analyzer (sysmex ks21) to obtain the complete blood count results (CBC). CRP and D-Dimer were tested on an I-CHROMA analyzer. ESR was measured by using Westrengate method. Final laboratory test results before discharge or death were also collected. Clinical outcomes were followed until discharge or death.

3. Statistical analysis

All data obtained were calculated and analyzed by using Microsoft Office Excel 2010 and the SPSS 19.0 software (statistical package for statistical analysis). Descriptive analysis was performed on all the variables. Categorical variables were described as counts and percentages, continuous variables were expressed as mean ± SD and qualitative variables were expressed as frequency and percentage. Differences between the two groups (non-severe and sever groups) were determined using the independent sample t-test analysis. Statistical significance was defined as $P < 0.05$ and $P < 0.001$.

4. RESULTS

In this study a total of 114 COVID-19 patients of age ranging between 30-80 years were participated. 65 of COVID-19 patients were non-severe condition and they did not need to be hospitalized in the isolation center (non-hospitalized patients), while 45 of COVID-19 patient were in severe or critical ill condition and required to be admitted in hospital (hospitalized patients). Hematological, inflammatory and coagulation routine blood tests were conducted for non-hospitalized patients following confirmed positive for COVID-19

with RT-PCR test and the hospitalized patients after admission to the Alnaser Isolation Centre.

4.1 The overall frequencies (as percentages) of Clinical laboratories biomarkers of hospitalized and non-hospitalized COVID-19 patients

4.1.1 Frequencies and percentages of hematological biomarkers in hospitalized and non- hospitalized COVID-19 patients

Blood routine tests were conducted for all patients after admission to the centre. The abnormal values of white blood cell (WBC) were much higher in hospitalized patients 36 of 49 was abnormal than non-hospitalized patients 25 of 65 was abnormal with percentage 73.3% and 38.5% respectively. Nearly all hospitalized covid-19 patients 46 out of 49 had low lymphocytes with percentage 93.9%, while approximately half of non-hospitalized covid-19 patients 35 out of 65 exhibit low count of lymphocytes with percentage 53.8%.

Abnormal elevation count of neutrophils was seen in all covid-19 patients, this elevation was more in hospitalized patients 41 out of 49 patients than non-hospitalized patients 35 out of 65 patients with percentage 83.7% and 53.8% respectively. Most of RBCs count and hemoglobin levels were within the normal range except that only 36.7% of hospitalized and 32.3 of non-hospitalized patients their blood hemoglobin was lower than the normal range. Almost all non- hospitalized patients their platelets count was normal, while 24.5% of hospitalized covid-19 patients showed low platelet count (Table 1).

Table 1: Shows frequencies and percentage of hematological biomarkers in hospitalized and non- hospitalized COVID-19 patients.

Hematological parameters	Reference Range	Frequencies in comparison to reference range	Non-hospitalized patients (n=65)	Non-hospitalized patients (%)	Hospitalized patients (n=49)	Hospitalized patients (%)
WBCs	3900-10900 x10^6/L	Normal	34	52.3 %	13	26.5%
		High	25	38.5%	36	73.5%
		Low	6	9.2%	0	0
Lymphocytes	1.2-3.3 x10^6/L	Normal	29	44.6%	3	6.1%
		High	1	1.5%	0	0
		Low	35	53.8%	46	93.9%
Neutrophils	1.5-8 x10^6/L	Normal	29	44.6%	8	16.3%
		High	35	53.8%	41	83.7%
		Low	1	1.5 %	0	0
Hemoglobin	12.5--16.5g/dl	Normal	43	66.2%	28	57.1%
		High	1	1.5%	3	6.1%
		Low	21	32.3%	18	36.7%
RBCs	3.8—5.8 x10^6/L	Normal	57	87.8%	40	81.6%
		High	4	6.2%	5	10.2%
		Low	4	6.2%	4	8.2%
Platelets	150—400 x10^6/L	Normal	60	92.3%	28	57.1%
		High	1	1.5%	9	18.4%
		Low	4	6.2%	12	24.5%

4.1.2 Frequencies and percentages of inflammatory and coagulation biomarkers in hospitalized and non-hospitalized COVID-19 patients

The inflammatory biomarkers in all patients were really high in hospital and non-hospitalized COVID-19 patients. Only few covid-19 patients displayed high CRP and ESR levels in non-hospitalized patients. On the contrary, nearly all hospitalized patients had high CRP and ESR levels with percentage reached 89.8% for both. Regarding the coagulation biomarkers D-dimer, 33 of 49 hospitalized covid-19 patients had abnormal high of D-dimer level with percentage 67.3%, and only 7 of 65 non-hospitalized patients their D-dimer level was high with percentage 10.8 % (Table 2).

Table 2: Shows frequencies and percentage of inflammatory and coagulation biomarkers in hospitalized and non- hospitalized COVID-19 patients.

Inflammatory and coagulation biomarkers	Reference Range	Frequencies in comparison to reference range	Non-hospitalized patients (n=65)	Non-hospitalized patients (%)	Hospitalized patients (n=49)	Hospitalized patients (%)
CRP	0—10 mg/dl	Normal	19	29.2%	5	10.2%
		High	46	70.8%	44	89.8%
ESR	0—20 mm/1h	Normal	28	43.1%	5	10.2%
		High	37	56.9%	44	89.8%
D-dimer	0—500 mg/dl	Normal	58	89.2%	16	32.7%
		High	7	10.8%	33	67.3%

4.2 The variation in the mean values of hematological biomarkers in hospitalized and non-hospitalized COVID-19 patients.

The variation in the mean values of most hematological parameters showed a significant increase in hospitalized COVID-19 patients in comparison to their mean values in non-hospitalized patients, except lymphocytes which showed a significant decrease, where the p-value was significant in most hematological values (P<0.001).

The mean counts of WBCs was 14.90±6.01 in patients with COVID-19 in hospitals which was significantly higher than in non-hospitalized patients 10.61±5.94, where P-value = 0.000. Also, mean counts of neutrophil were significantly elevated in COVID-19 patients who admitted in hospitals 12.50±4.63 than in non-hospitalized COVID-19 patients 8.73±5.03, the P value = 0.000. Similarly, The mean values of lymphocytes were normal in non-hospitalized COVID-19 patients (1.24±0.61), while the mean values this cells was absolutely lower than the normal value in hospitalized COVID-19 patients 0.70±0.31, this variation was significant where P-value = 0.000. However, there was no significant difference in the mean values of RBCs, platelets and hemoglobin for non-hospitalized and hospitalized COVID-19 patients, where the P value > 0.05 (Table 3 & Figure 1).

Table 2: shows the mean values of haematological biomarkers in hospitalized and non- hospitalized COVID-19 patients (P-value <0.001).**

Hematological parameters	Non- hospitalized patients Mean±SD	Hospitalized patients Mean±SD	*P value*
WBCs	10.61±5.94	14.90±6.01	0.000**
Lymphocytes	1.24±0.61	0.70±0.31	0.000**
Neutrophils	8.73±5.03	12.50±4.63	0.000**
Hemoglobin, g/L	13.06±1.27	13.17±1.89	0.739
RBCs	4.77±1.27	4.96±0.80	0.372
Platelets	231.90±9.96	277±22.06	0.063

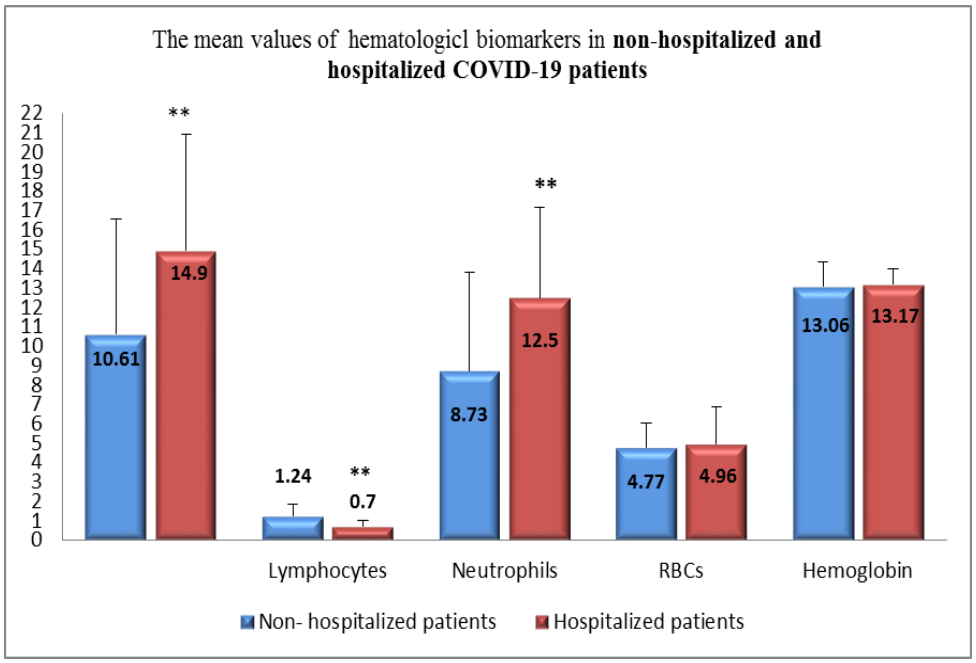

Figure 1: shows the mean values of hematologicl biomarkers in non-hospitalized and hospitalized COVID-19 patients.

4.3 The variation in the mean values of inflammatory and coagulation biomarkers in hospitalized and non-hospitalized COVID-19 patients.

Although the levels of inflammatory biomarkers: CRP and ESR were increased in both hospitalized and non-hospitalized COVID-19 patients, these increased levels of CRP 123.47±10.85 and ESR 60.59±4.20 in COVID-19 patients who were admitted in hospital was significantly higher than in COVID-19 patients who were non-hospitalized 53.82±7.38 and 28.96±2.29 respectively (P<0.001). Regarding the level of coagulation biomarkers: D-dimer level was normal in non-hospitalized COVID-19 patients 499.92±152.33; however, in hospitalized patients the D-dimer level was abnormal and absolutely elevated 4355±622.15, this increase was significant (P-value <0.001) (Table 4 & figure 2).

Table 3: shows the mean values of inflammatory and coagulation biomarkers in hospitalized and non-hospitalized COVID-19 patients (P-value <0.001).**

Inflammatory and coagulation biomarkers	Non- hospitalized patients Mean±SD	Hospitalized patients Mean±SD	*P value*
CRP	53.82±7.38	123.47±10.85	0.000**
ESR	28.96±2.29	60.59±4.20	0.000**
D-dimer	499.92±152.33	4355±622.15	0.000**

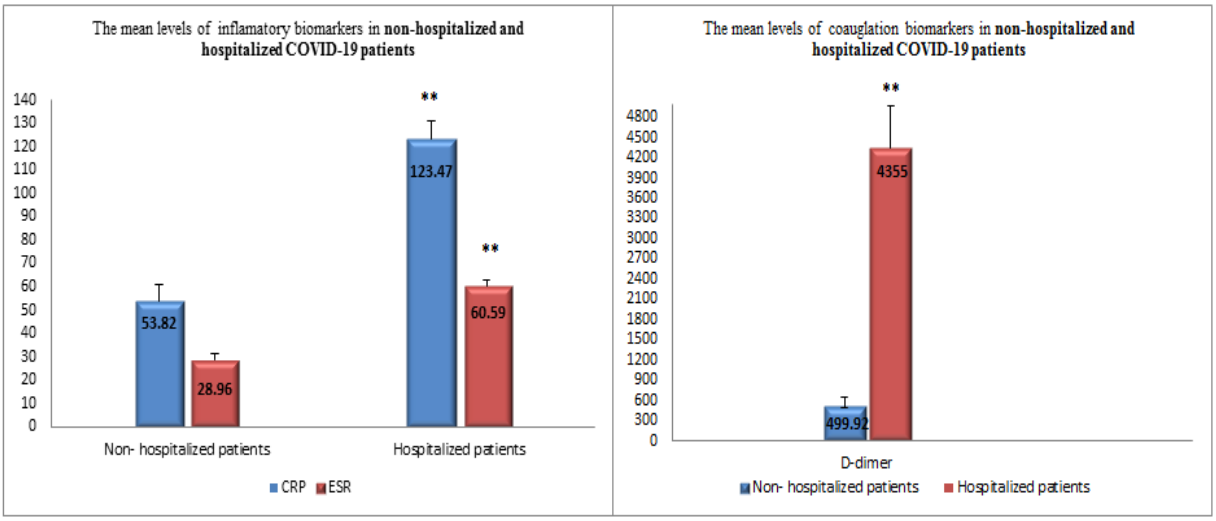

Figure 2: shows the mean values of inflammatory and coagulation biomarkers in non-hospitalized and hospitalized COVID-19 patients.

4.4 The variation in the hematological biomarkers in hospitalized and non-hospitalized COVID-19 patients based on the different age groups

It is notable that in hospitalized and non-hospitalized COVID-19 patients the mean counts of WBCs and NEU increased significantly (P<0.05) in age dependent manner, where the highest values were seen in the elderly groups (≥ 80 years). Unless in hospitalized patients particularly in 50-79 years the mean values of NEU were lower than other age groups. However, only lymphocytes decreased significantly (P<0.05) with increasing the age in both COVID-19 patient groups. Regarding the RBCs, hemoglobin and PLT in hospitalized and non-hospitalized patients the result did not show any significant variation between the age groups (Table 5 & Figure3).

Table 4: shows the variation in the hematological biomarkers in hospitalized and non-hospitalized COVID-19 patients based on the different age groups and p-value, (* P-value <0.05).

Age groups	Hematological biomarkers	Non-hospitalized patients Mean ± SD	Hospitalized patients Mean ± SD	P-Value
20-49 years	WBC x10^6/UL	9.57 ± 1.30	14.91 ± 1.37	0.021*
	LYM x10^6/UL	1.28 ± 0.72	0.81 ± 0.43	0.009*
	NEU x10^6/UL	6.94 ± 0.86	13.22 ± 1.24	0.011*
	Hb mg/dl	13.33 ± 2.0	13.97 ± 1.73	0.354
	RBC x10^6/UL	5.09 ± 1.42	5.71 ± 0.70	0.186
	PLT x10^6/UL	235.11 ± 11.05	332.40 ± 64.98	0.172
50-79 years	WBC x10^6/UL	11.07 ± 0.89	14.55 ± 1.20	0.024*
	LYM x10^6/UL	1.24 ± 0.54	0.70 ± 0.28	0.001**
	NEU x10^6/UL	10.00 ± 0.90	11.84 ± 0.83	0.141
	Hb mg/dl	12.95 ± 1.49	12.77 ±1.97	0.697
	RBC x10^6/UL	4.61 ± 0.21	4.71 ± 0.13	0.690
	PLT x10^6/UL	234.65 ± 16.68	283.00 ± 24.91	0.113
≥ 80 years	WBC x10^6/UL	12.89 ± 2.57	16.27 ± 1.84	0.031*
	LYM x10^6/UL	1.03 ± 0.21	0.56 ± 0.62	0.007*
	NEU x10^6/UL	9.96 ± 2.07	14.17 ± 1.92	0.016*
	Hb mg/dl	12.41 ± 2.08	13.72 ± 1.49	0.226
	RBC x10^6/UL	4.16 ± 0.22	4.94 ± 0.19	0.124
	PLT x10^6/UL	202.83 ± 38.79	186.37 ± 40.02	0.773

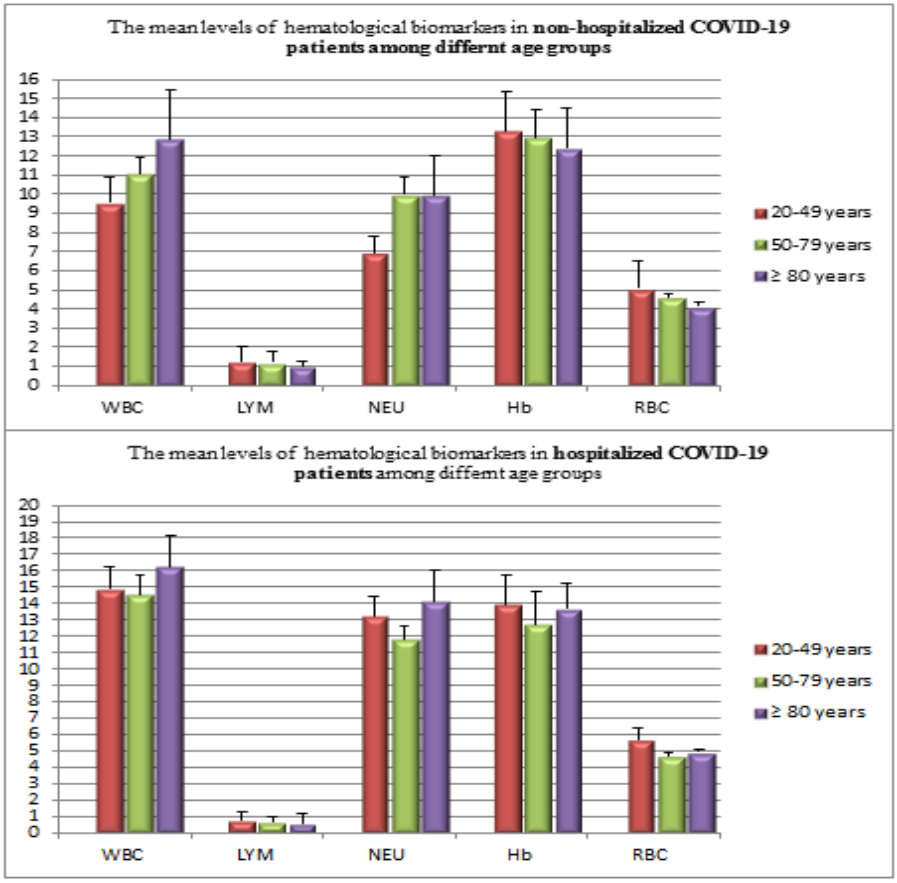

Figure 2: shows the mean values of hematologicl biomarkers in non-hospitalized and hospitalized COVID-19 patients based on the different age groups.

4.5 The variation in the coagulation and inflammatory biomarkers in hospitalized and non-hospitalized COVID-19 patients based on the different age groups

Generally, there was an increase in the mean levels of coagulation and inflammatory biomarkers (D-dimer, CRP and ESR) with increasing the age among all age groups in hospitalized and non-hospitalized COVID-19 patients even though this increase was much higher in patients who were in hospital. However, only older patient groups (50-79 years and ≥ 80 years) showed a significant result in the levels of CRP, ESR and D-dimer among hospitalized and non-hospitalized patients ($P<0.05$ & $P<0.001$). In the middle age groups (20-49 years), there was also differences in the level of CRP, ESR and D-dimer, but did not reach the significant (P value >0.05) (Table 6, figure 4&5).

Table 5: shows the variation in the coagulation and inflammatory biomarkers in hospitalized and non-hospitalized COVID-19 patients based on the different age groups and (*p-value <0.05), (P-value <0.001).**

Age groups	Laboratory biomarkers	Non-hospitalized patients among different age groups Mean ± SD	Hospitalized patients among different age groups Mean ± SD	P-Value
20-49 years	D-dimer mg/L	273.74 ± **27.27**	1619.50 ± **1011.4**	0.216
	ESR mm/1h	25.74 ± **3.73**	41.90 ± **9.39**	0.136
	CRP mg/L	33.74 ± **9.25**	56.67 ± **18.35**	0.284
50-79 years	D-dimer mg/L	513.36 ± **246.54**	4233.16 ± **795.29**	0.000**
	ESR mm/1h	29.21 ± **2.41**	61.51 ± **4.83**	0.000**
	CRP mg/dl	65.92 ± **10.12**	138.63 ± **12.10**	0.000**
≥ 80 years	D-dimer mg/L	1446.00 ± **942.41**	7199.87 ± **1278.28**	0.004*
	ESR mm/1h	42.16 ± **12.80**	80.37 ± **9.67**	0.039*
	CRP mg/L	79.69 ± **38.85**	148.25 ± **31.02**	0.040*

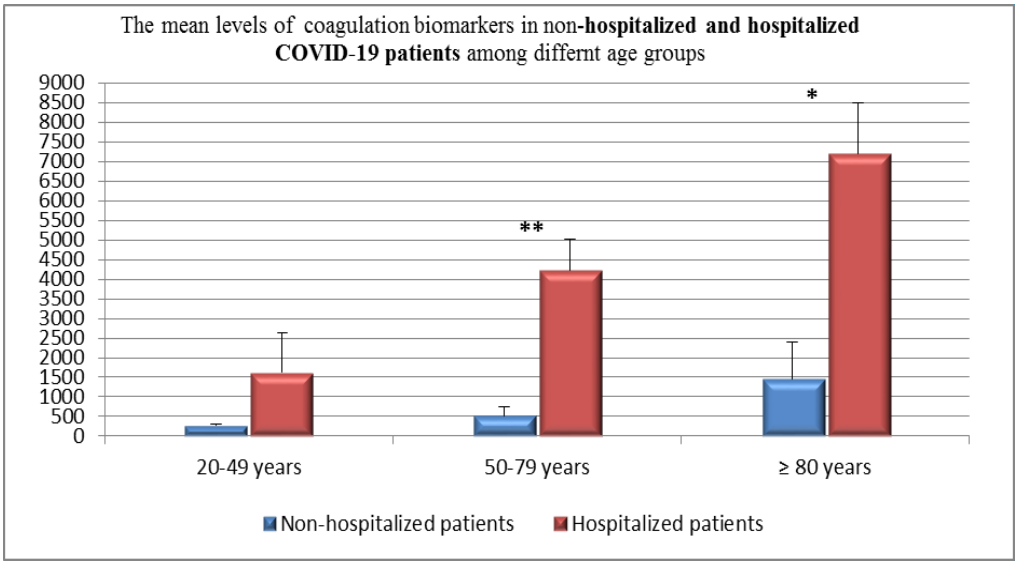

Figure 3: shows the mean values of coagulation biomarkers in non-hospitalized and hospitalized COVID-19 patients based on the different age groups.

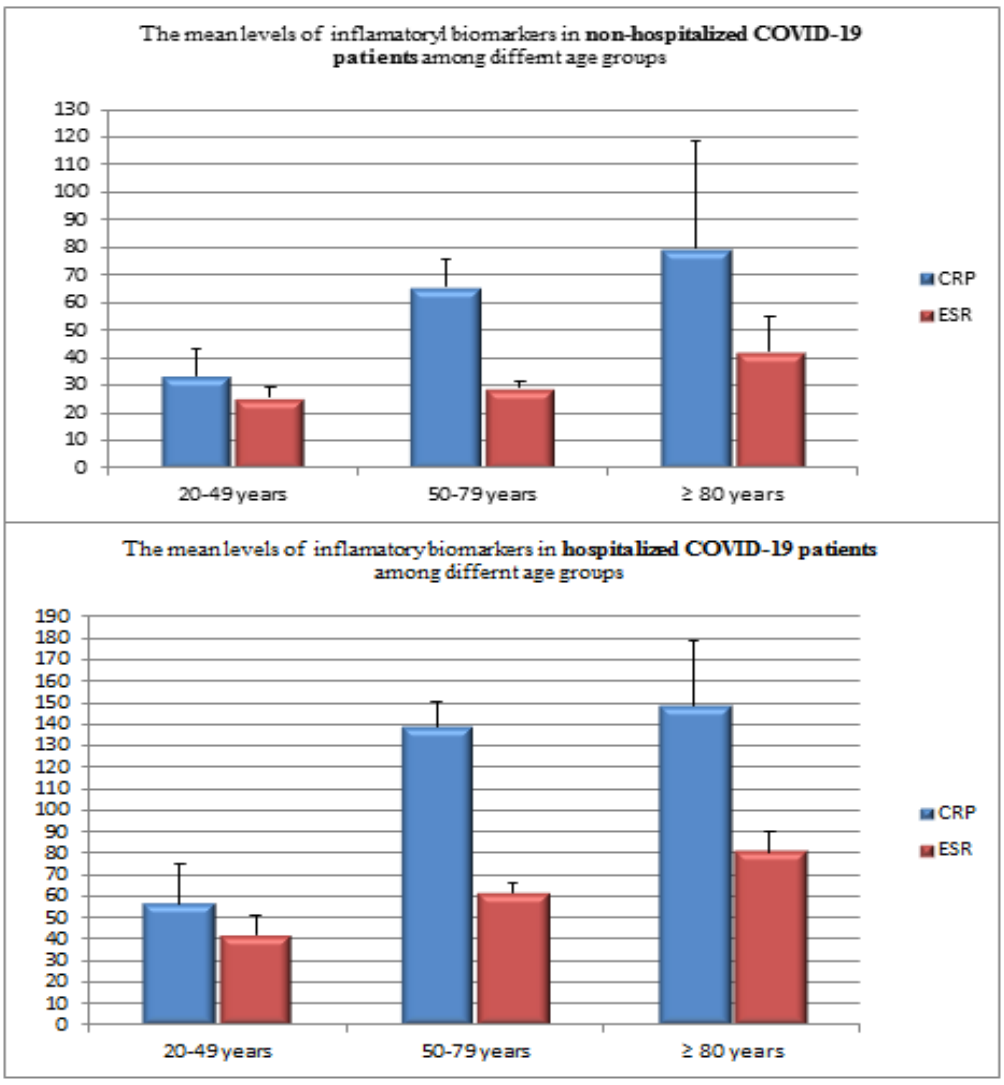

Figure 4: shows the mean values of inflammatory biomarkers in non-hospitalized and hospitalized COVID-19 patients based on the different age groups.

4.6 The mortality rate among all patients (non-hospitalized and hospitalized COVID-19 patients)

The total death number of COVID-19 patients was 23 out of 114, while ninety one patients out of 114 COVID-19 patients recovered. The highest death rate was seen in the hospitalized patients, where approximately half of the patients died (21 out of 49), and 28 stayed alive and recovered. Only 2 out of 65 COVID-19 patients who were not admitted to the hospital died 3.1%, and the majority of them (63 out of 65) recovered (Table 7).

Table 6: shows the mortality rate among all patients and in non-hospitalized and hospitalized COVID-19 patients.

COVID-19 Patients	Survival	Frequency (n=114)	Percentage (100%)
All patients	Recovery (survival)	91	79.8%
	Death (non-survival)	23	20.2%
	Total number	114	100.0%
Non- hospitalized patients	Recovery (survival)	63	96.9%
	Death (non-survival)	2	3.1%
	Total number	65	100%
Hospitalized patients	Recovery (survival)	28	57.1%
	Death(non-survival)	21	42.9%
	Total number	49	100%

The the mortality rate among all patients was 20.2%, this rate was much higher in hospitalized COVID-19 patients where 42.9% of patients dead than in non-hospitalized patients, where only 3.1% of patients dead (Figure 6).

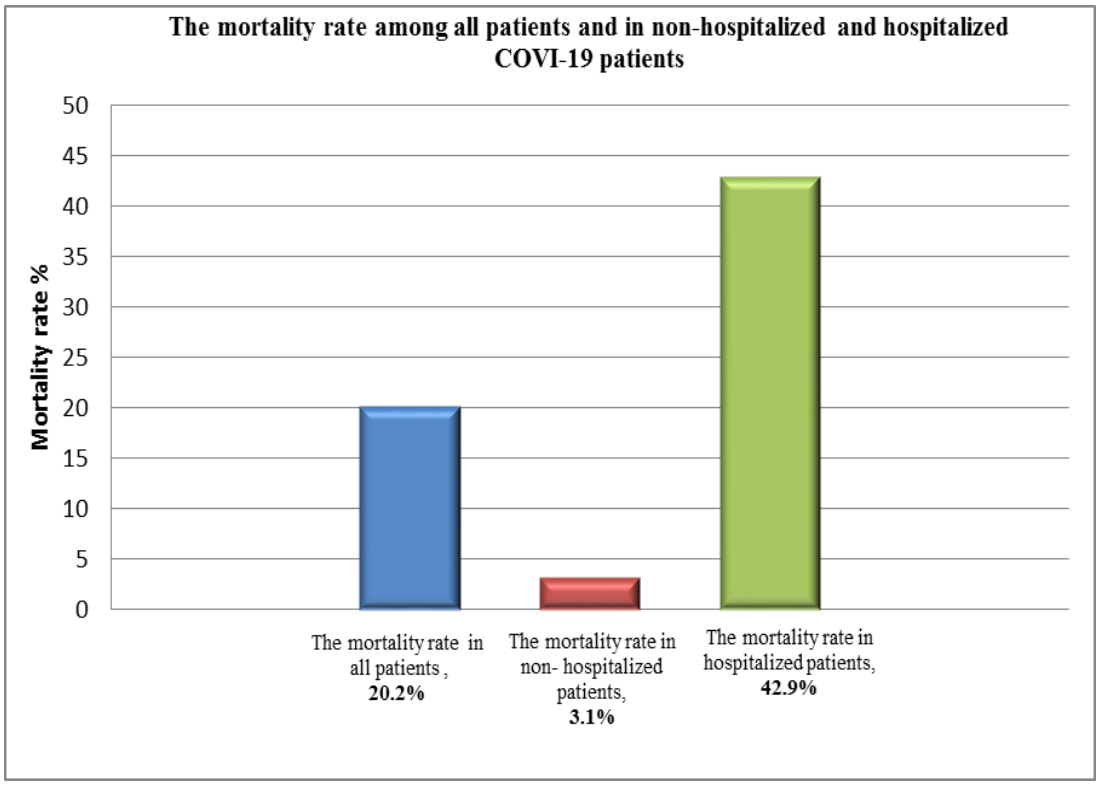

Figure 5: shows the mortality rate among all patients and in non-hospitalized and hospitalized COVID-19 patients.

4.6.1 The mortality rate and frequencies of COVID-19 among all patients based on the age groups

The mortality rate increases with increasing the COVID-19 patient's age. Most deaths was seen in elderly group patients (≥80 years years), where more than half (8 out of 14) of elderly patients died with percentage 57.1% and the recovery rate was 42.9%. The patients who were less than 80 years had less deaths rate, where 20.6% of deaths was seen in COVID-19 patients with age group 50-79 years, and only 5.4% of deaths was seen in COVID-19 patients with age group 20-49 years (Table 8 & Figure7).

Table 7: shows the mortality rate and frequencies of COVID-19 among all patients based on the age groups.

Patients age groups	Survival	Frequency (n=114)	Percentage (100%)
20-49 years	Recovery (survival)	35	94.6%
	Death (non-survival)	2	5.4%
	Total number	37	100%
50-79 years	Recovery (survival)	50	79.4%
	Death (non-survival)	13	20.6%
	Total number	63	100
≥80 years	Recovery (survival)	6	42.9%
	Death(non-survival)	8	57.1%
	Total number	14	100%

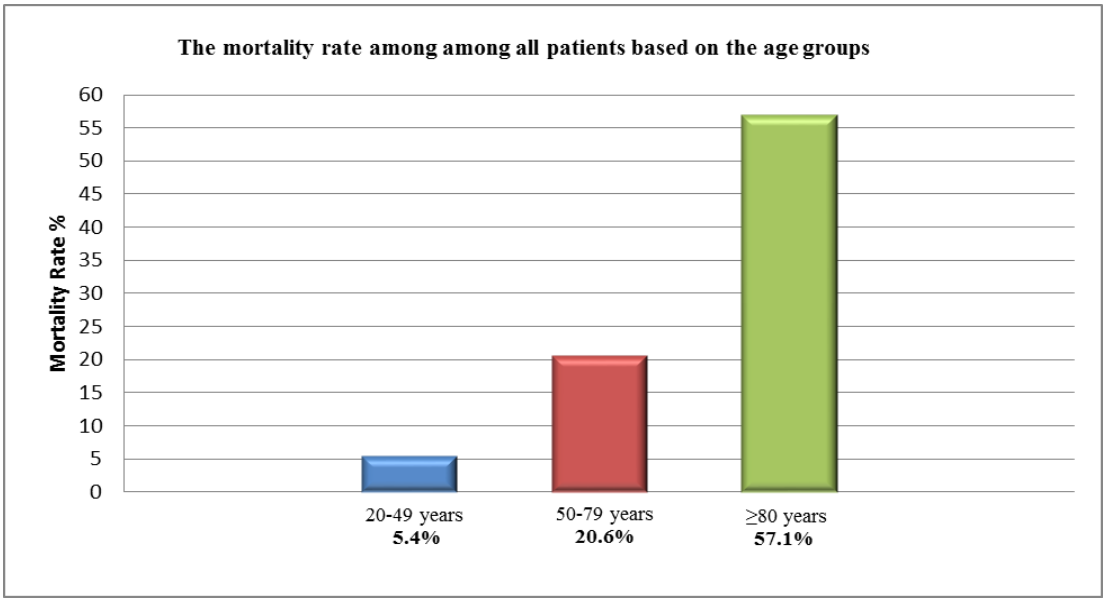

Figure 6: shows the mortality rate of COVID-19 among all patients based on the age groups.

4.7 The changes in the blood biomarkers among survival and non-survival COVID-19 patients.

Several significant differences were noted between patients who died and those who recovered from COVID-19 infection, especially encompassing higher white blood cell (WBC) count (P<0.001), higher neutrophil count (P<0.001), lower lymphocyte count (P<0.001) as well as higher levels of CRP, ESR and D-dimer levels (P<0.001) (Table 9).

Table 8: Shows the changes in the blood biomarkers among survival and non-survival COVID-19 patients.

Blood biomarkers	Survival Mean±SD	Non-Survival Mean±SD	*P-value*
WBC $x10^6$/UL	11.19±0.59	17.51±1.31	0.000
LYM $x10^6$/UL	1.11±0.61	0.60±0.05	0.000
NEU $x10^6$/UL	9.40±0.51	14.09±0.95	0.000
Hb mg/dl	13.05±1.89	13.31±1.88	0.555
RBC $x10^6$/UL	4.89±0.12	4.67±0.11	0.275
PLT $x10^6$/UL	253.12±9.49	244.69±41.60	0.845
CRP mg/dl	69.09±6.88	141.80±17.42	0.001
ESR mm/1h	33.08±2.28	80.04±4.03	0.000
D-dimer mg/L	502.62±170.01	7626.00±722.71	0.000

Non-survivors COVID-19 patients developed leukocytosis, neutrophilia and lymphopenia, along with abnormal values of D-dimer, CRP and ESR levels. In non-survivors COVID-19 patients (deaths), the levels of blood biomarkers were extremely higher than in the survivors (recovered) patients. WBCs and NEU were much higher than the normal range in the dead patients where their counts were 17.51±1.31 and 14.09±0.95 respectively. These cells were not high and very close to the normal range in the survival COVID-19 patients, where they were 11.19±0.59 for WBCs and 9.40±0.51 for NEU.

The mean value of lymphocytes was too low in the non-survivors COVID-19 patients (0.60±0.05) in comparison to its count in survival patients where it was almost within the normal range (1.11±0.61). However, there was no differences in the RBCs, PLT and hemoglobin values in the survival and non-survival COVID-19 patients, where the result of these variables was in the normal range. Also, survivors COVID-19 patients revealed a bit high levels of CRP (69.09±6.88) and ESR (33.08±2.28) in comparison to their levels 141.80±17.42 and 80.04±4.03 respectably in the non-survivors COVID-19 patients. A significantly higher value of D-dimer was seen in non-survivors COVID-19 patients 7626.00±722.71, while in survivors showed a normal level 502.62±170.01 (Table 9 & Figure 8).

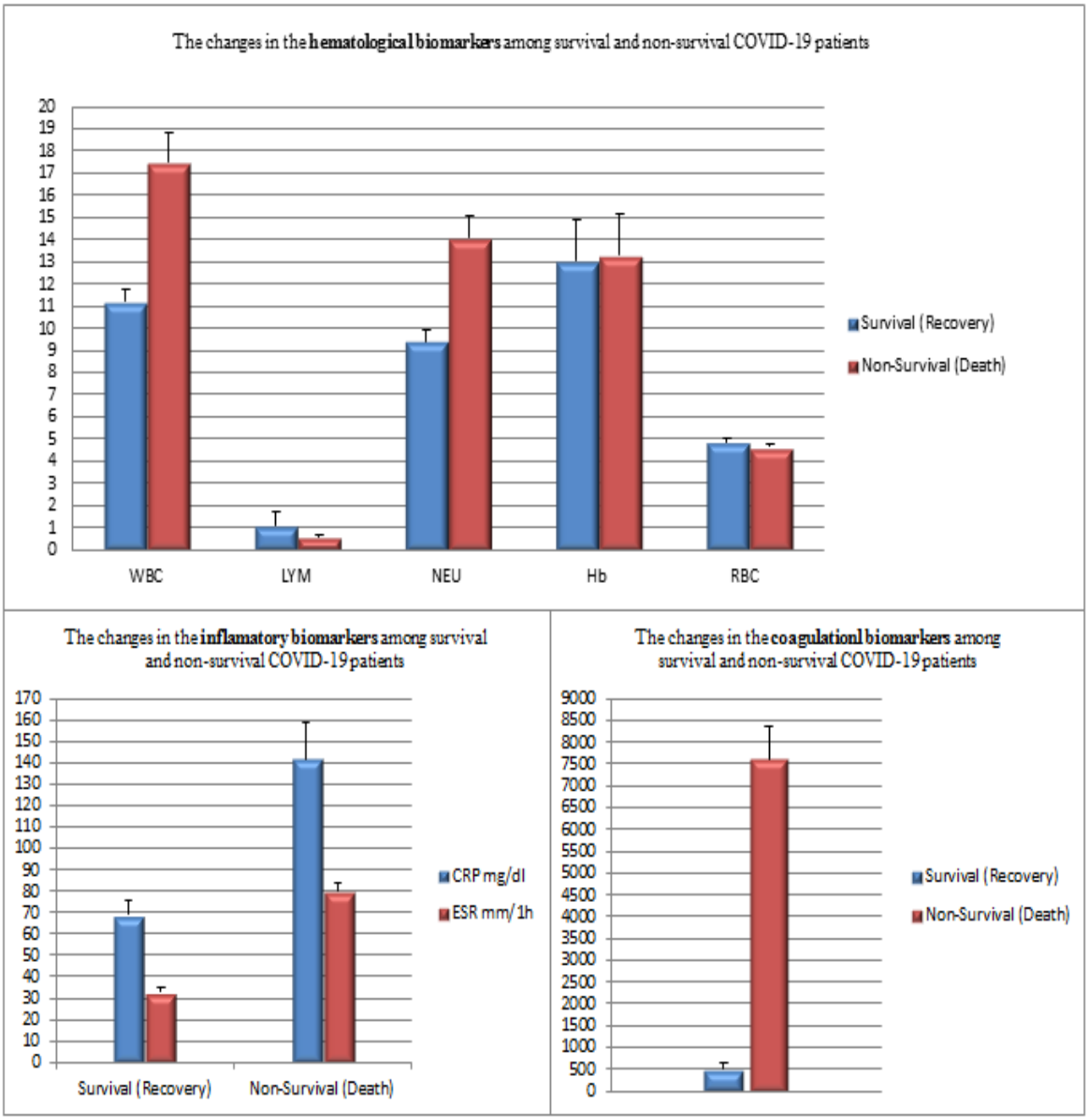

Figure 7: shows the changes in the blood biomarkers among survival and non-survival COVID-19 patients.

5. DISCUSSION

The primary aim of this study was to predict the infection and severity of COVID-19 infection through the hematological, inflammatory and coagulation biomarkers in hospitalized and non-hospitalized COVID-19 patients. In this study, obvious abnormal patterns of hematological, inflammatory and coagulation biomarkers were revealed in hospitalized and somewhat in non-hospitalized COVID-19 patients, which may allow significant discrimination, also the outcomes of this research may serve as a clinical predictor of the COVID-19 disease severity.

The values of white blood cell (WBC) were much higher in hospitalized patients than non-hospitalized patients with percentage 73.3% and 38.5% respectively. Nearly all hospitalized COVID-19 patients had low lymphocytes with percentage 93.9%, while approximately half of non-hospitalized COVID-19 patients exhibit low count of lymphocytes with percentage 53.8%. Abnormal elevation

count of neutrophils was seen more in hospitalized patients than non-hospitalized patients 83.7% and 53.8% respectively. A significant increase in WBCs and NEU among hospitalized COVID-19 patients in comparison to their mean values in non-hospitalized patients (P<0.001), except lymphocytes which showed a significant decrease (P<0.001) (Table 1 & 3 and Figure1).

This result is agreed with a study done in China by Qin *et al*., (2020) who found that severe cases tended to have significantly higher leukocyte-counts, lower lymphocyte and higher neutrophils, as well as lower percentages of monocytes, eosinophils, and basophils compared to mild cases. Similarly, Yang *et al.*, (2020) reported there was a significant decrease in lymphocytes count in hospitalized patients, where lymphopenia was seen in 80% of critically ill adult COVID-19 patients, whereas only 25% of patients with mild COVID-19 infection showed lymphopenia. These observations suggest that lymphopenia may correlate with infection severity and the inflammatory cytokines may induce profound alterations in the behaviour of hematopoietic cells, mainly neutrophils, lymphocytes and monocytes (Pujani *et al*., 2021). It also suggests that SARS-CoV-2 might mainly act on lymphocytes, especially T lymphocytes, as does SARS-CoV-2 virus particles spread through the respiratory tract and infect other cells, inducing series of immune responses, and–causing changes in number of peripheral white blood cells such as lymphocytes (Pujani *et al*., 2021).

Moreover, although there was no significant difference in the mean values of RBCs, platelets and hemoglobin for non-hospitalized and hospitalized COVID-19 patients (P>0.05), 24.5% of hospitalized covid-19 patients showed low platelet count (Table 1 & 3 and Figure1). This finding is in line with other study was conducted in Italy and pointed out that in a meta-analysis on 21 studies including 3377 COVID-19 positive patients that patients with severe and fatal disease had significantly increased WBC, and decreased lymphocyte and platelet counts compared to non-severe disease and survivors (Henry *et al*., 2020). Simultaneously, Gavriatopoulou *et al*., (2020) stated that meta-analysis of nine studies has suggested that thrombocytopenia is significantly associated with the severity of the COVID-19 disease, However, a study conducted in Libya disagreeing with the current study stated that significantly higher RBC levels were found in COVID-19 patients compared with the controls (Jaat *et al*., 2021).

The inflammatory biomarkers in all patients were really high in hospital and non-hospitalized COVID-19 patients. Nearly all hospitalized patients had high CRP and ESR levels, where their percentage was 89.8%. CRP and ESR results recorded a significant rise in hospital patients compared to non-hospitalized patients (P<0.001), suggesting that these indicators are evidence of the severity (Table2&4 and Figure2). This result is corresponding very closely to a study accomplished by Lapić *et al*., (2020) which reported that although the ESR lacks analytical and diagnostic specificity, it still used for assessment of the acute-phase reaction reflecting the inflammatory state, also for distinguishing severe from non-severe COVID-19 cases. Also, Pu *et al*., (2021) noted that COVID-19 might trigger the change of the form of erythrocytes or plasma characteristics including the immune system via an unknown mechanism to increase the ESR.

The continued high level of ESR possibly brings a negative effect on COVID-19 patients' prognosis, since high ESR could damage the joint and thus leads to joint diseases such as osteoarthritis and may be a precursor of hepatic and renal dysfunction. Thus, COVID-19 may influence the long-term prognosis of patients (Pu *et al*., 2020). Other study agrees with the CRP result of the present study, which indicates that CRP levels increase during the period of coronavirus infection in a large number of patients this increase was significant in critical ill patients (Bajpai, Shaw and Dosi 2020). However, a study by Wang *et al*., (2020) disagree with the current study, it reported that not all COVID-19 patients experienced significant changes, and some COVID-19 patients maintained normal CRP levels throughout the course of the disease. The elevated levels of CRP might be linked to the overproduction of inflammatory cytokines in severe patients with COVID-19 (Ali *et al*., 2020)

In the current study, D-dimer was a sign of increased severity of COVID-19 patients, where its level was increased significantly in hospitalized patients (P<0.001) compared to non-hospitalized COVID-19 patients. 67.3% of hospitalized covid-19 patients had abnormal rise of D-dimer level and only 10.8 % non-hospitalized patients their D-dimer level was high (Table2&4 and Figure 2). These results are in line with study done by Terpos *et al*., (2020) who identified that in a multicenter retrospective study in China, 260 out of 560 patients (46.4%) with laboratory confirmed COVID-19 infection had elevated D-dimer (≥0.5 mg/L). This elevation was more pronounced among severe cases (59.6% vs 43.2% for non-severe ones). D-dimer dynamics can reflect the severity and their increased levels are associated with adverse outcomes ending with deaths among severe COVID-19 patients (Terpos *et al*., 2020). D-Dimer of critically ill patients with COVID-19 was significantly increased, with frequent clotting disorders and microthrombotic formation in peripheral blood vessels. (Ye *et al.*, 2020). Thus it is not possible to rely on the D-dimer level as a prognosticators diagnosis tool to predict the incidence of COVID-19 infection, but the D-dimers have greater importance in the monitoring the progression of the severity in COVID-19 patients.

The result of the present study regarding to the age groups showed that the mean counts of WBCs and NEU increased significantly (P<0.05) as soon as the patient getting older, whereas, lymphocytes decreased

significantly with increasing the age (P<0.05) (Table5 & Figure3). This is in agreement with study done in Saudia Arabia found that in a retrospective study compared the clinical features of COVID-19 in hospitalized elderly patients with young and middle-aged patients, the proportion of lymphocytes in the elderly group was significantly lower than that in the young and middle-aged group (p<0.001) (Ibrahim *et al*., 2021). In comparing hematological findings, we detected significantly higher neutrophil levels among hospitalized elderly patients compared with adult patients (Ibrahim *et al*., 2021). The elevated neutrophil counts could be explained by the fact that elderly 2019-nCoV infected patients are more susceptible to bacterial infection (Jin *et al*., 2019). However, Jin *et al*., (2019) showed that in the elderly group, the total number of leucocytes in peripheral blood was normal or decreased and there were no significant differences in white blood cell count, neutrophil, hemoglobin level, and platelet in the age groups.

In the current study levels of CRP, ESR and D-dimer increased significantly only among hospitalized older patient groups (50-79 years and ≥ 80 years) (P<0.05). This finding is in clear similarity with other studies which found that the number of patients with increased D-dimer and ESR was significantly higher in the elderly group compared with the adult group (P= 0.006) (Jin *et al*., 2019). Likewise, studies have documented that an increased D-dimer concentration is a common feature of COVID-19 infection, especially for severe patients. The elderly are more likely to develop a severe disease (Xia *et al*., 2020). However, this result is in discrepancy with other outcomes which reported that, the number of patients with increased CRP levels did not significantly differ between the elderly and adult groups (P=0.216) (Ibrahim *et al*., 2021).

In the present study, the the mortality rate among all patients (critically ill hospitalized patients and non-hospitalized patients) was 20.2% (Figure 7). This mortality rate is higher than the 3.4% reported in the literature (Guo *et al*., 2020). According to the WHO's report, the recent mortality among COVID-19 patients is about 4% (WHO 2020). Regarding hospitalized COVID-19 patients in the current study the fatality rate was (42.9%) which was much higher than in non-hospitalized patients (3.1%). The highest mortality rate was seen in hospitalized elderly patients group (≥80 years) with percentage reached 57.1% (Figure 6). This result are in line with Liua *et al*., (2020) who reported that the mortality of elderly patients with COVID-19 is higher than that of young and middle aged patients, and the proportion of hospitalized critical ill patients is significantly higher than that of non-severe patients. The elderly admitted to the intensive care unit (ICU) are more susceptible to severe illness therefore the mortality of elderly patients is higher (Liua *et al*., 2020).

In non-survivors COVID-19 patients, several significant results of higher white blood cell count (P<0.001), higher neutrophil count (P<0.001), lower lymphocyte count (P<0.05) were associated directly with the severity and mortality (Figure8). It seems that in the existing study, leukocytosis, neutrophilia and lymphopenia are implicated with increase the death rate in COVID-19 infection. This is in line with other study done in Washington, USA found that non-survivors of hospitalized COVID-19 patients demonstrated a more significant deterioration in lymphopenia and high WBCs count compared with those who survived ($P < 0.05$). It has also been reported that patients with severe disease and fatal outcomes present with a decreased lymphocyte in admission ($P < 0.001$) and during hospitalization ($P < 0.001$) compared with those who survived (Terpos *et al*., 2020).

Liu *et al*., (2020) in Zhongnan Hospital of Wuhan University identified an elevation in the neutrophil as an independent and significant predictor of mortality among 245 hospitalized COVID-19 patients, with an 8% increase in mortality with each unit increase in neutrophil (Ahmeidi *et al*., 2020). In non-survivor COVID-19 patients, RBCs, hemoglobin and platelets showed not significant difference between survival and non-survival COVID-19 patients. Thus, it is not possible to predict COVID -19 from the platelets. In contrast, this study is in discrepancy with a study found that subgroup analysis comparing patients by survival noted lower platelet count correlated with mortality. Thrombocytopenia was also associated with increased risk of severe COVID-19 illness (Al-Samkari *et al*., 2020).

In non-survivors the levels of CRP, ESR and D-dimer levels was significantly increased in comparison to survivors (P<0.001) (Figure8). This is in agreement with another study from China that included 1099 confirmed COVID-19 patients, revealed that median ESR, C-reactive protein and D-dimer levels were higher among severe cases compared to non-severe cases, demonstrating that high D-dimer and C-reactive protein levels were significantly associated with COVID-19 severity and mortality (Ahmeidi *et al.,* 2020). Zhou *et al.,* (2020) also confirm in their study that D-dimer levels exceeding 1.0 μg/mL at hospital admission correlated significantly with death among hospitalised and critical ill COVID-19 patients in China, with a p-value of less than 0.001. D-dimer has the highest C-index to predict in-hospital mortality, and patients with D-dimer levels >0.5 mg/L had a higher incidence of mortality (*P*<0.01). This suggested that D-dimer could be a potent marker to predict the mortality of COVID-19, which may be helpful for the management of patients (Huang *et al*., 2020). Contrary, Huang *et al*., (2020) reported that an elevated ESR and CRP were associated with an increased risk of severe COVID-19 need for ICU care, but not mortality.

6. Study limitations

There are several limitations of the current study that are worth mentioning. First, the sample size (only 114 COVID-19 patients) was relatively small, and may not fully reflect the characteristics of the disease for hospitalized and non-hospitalized groups. Therefore, a large sample size could give a more comprehensive understanding of 2019-nCoV. Second, the study findings might have been biased by reporting only confirmed cases in a single hospital center. Further studies that include more isolation centers, suspected and undiagnosed cases may show some differences. Finally, the study assessed only the laboratory biomarkers of COVID-19 on admission of the patients; more detailed information from other laboratory tests and clinical outcomes were unavailable at the time of analysis. Further studies are still needed.

7. CONCLUSION

This study can conclude that some routine laboratory findings could help assess disease onset, progression and manage patients who could develop critical conditions and be at risk of severity and mortality. Hematological and inflammatory biomarkers are correlated with severe prognosis or death in COVID-19 patients and can therefore be used as predictive biomarkers. Coagulation biomarkers (D-dimer) levels are commonly elevated in patients infected with SARS-CoV-2. Significantly higher levels are found in those with critical illness and may be used as a prognostic marker for infection severity and in hospital mortality. These findings should be confirmed in future studies coupled with testing other suitable clinical and laboratory indicators for evaluating disease severity and outcomes.

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