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RESEARCH ARTICLE

CRP, D-dimer, and Comorbidities as Potential Prognostic Factors in Critically Ill COVID-19 Patients

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ABSTRACT

Background: COVID-19, which is a serious disease caused by the SARS-CoV-2, has affected several countries worldwide. Most people make a full recovery without needing hospitalization but others with severe symptoms have developed ARDS and need an intensive care unit (ICU). During SARS-CoV-2 infection, abnormal amounts of inflammatory mediators may indicate the severity of the illness. Recognizing aberrant coagulation findings early on and keeping an eye out for coagulopathy is crucial and strongly advised to help COVID-19 patients, enhance their clinical results, and lessen serious sequelae. Monitoring for coagulopathy and abnormal coagulation results is crucial and strongly advised to support COVID-19 patients, enhance their clinical outcomes, and lessen serious consequences. **Aim**: our objective was to evaluate the levels of plasma inflammatory agents in SARS-COV-2 patients as a prognostic factor in disease severity in Egyptians. **Patients and methods:** in this study, 27 hospitalized individuals with COVID-19 confirmed diagnosis were divided into several categories; 5 mild cases, 8 moderate cases,10 severe cases, and 4 critically ill cases. Additionally, there were 5 enlisted health controls. We used the multiplex ELISA technique to assess 2 plasma inflammatory mediators in all subjects and compare disease severity. **Results:** patients with critically ill COVID-19 have much greater levels of C-reactive protein (CRP) and D-dimer than normal controls. Patients with critically ill COVID-19 severity and prognosis have higher CRP and D-dimer and showed a strong correlation ($p<0.05$) with the severity of the condition elucidating D -dimer functions as a marker for prognosis in COVID-19 patients. **Conclusion:** Present findings reveal that CRP and D-dimer levels are promising biomarkers for COVID-19 severity, suggesting that plasma inflammatory mediators could be used as warning indicators of COVID-19 severity and aid in its prognosis and treatment**.**

Keywords: Non-epithelial ovarian cancer, Malignant ovarian germ cell tumors, Sex cord-stromal tumors, Epidemiology, Prognosis; Survival

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INTRODUCTION

The COVID-19 epidemic represents a substantial challenge for governments, individuals, and societies. SARS-CoV-2 has led to approximately 5.7 million fatalities by January 22, 2022 (Lekagul et al. 2022). The name “coronavirus” is derived from the Latin word Corona, meaning “crown”, a “crown” of proteins, known as peplomers (Almeida and Tyrrell, 1967). CoVs are β-coronaviruses with the nucleocapsid's helical symmetry and its positive polarity. CoVs are RNA viruses with the largest genomes that were discovered in the 1960s. SARS-CoV-2 has a uniform linear non-segmented positive-sense RNA strand with a length of 29,903 bp and comprises a minimum of 6 open reading frames (ORFs) and a replicase protein is encoded by the first ORF while structural proteins are encoded by the other ORFs. 2 membrane and envelope proteins are arranged among the spike proteins, which directed outward from the membrane. The condensing of the RNA genome by the nucleocapsid proteins is what allows the virus to grasp the cell protein machinery during its replication cycle (Chen et al. 2020).

The s protein, which is made up of the S1 and S2 subunits, is crucial for the binding of the virus to the ACE2 receptor. S1 binds to the host cell's ACE2 receptor, and membrane fusion is caused by host transmembrane protease serine subfamily member 2 (TMPRSS2), which activates S2. Once inside the cell, SARSCoV2 uses the host's natural biological machinery to translate, replicate, and transcribe its RNA genome into different viral proteins that are needed for the encapsulation, exocytosis, and reassembling of freshly formed virions from the cell. Although SARS and COVID-19 share the same CoV-2 family member, COVID-19 is 100 times more contagious than SARS due to structural and amino acid composition variations. The order of amino acids, between SARS-CoV-1 and SARS-CoV-2 is approximately 75.5% identical (Lu et al. 2020).

The coronavirus virion particle, typically round or multi-shaped, has a concave surface with a ridge, a larger binding interface, and higher affinity with Angiotensin Converting Enzymes (ACE2), It measures 120-160 nm and includes a petal-shaped triple spike protein, which is a common feature of the coronaviruses that mediate membrane fusion. During infection and virion endocytosis, the binding of SARS-CoV-2 S protein to its cell surface receptor, (ACE2), initiates viral entry into type II pneumocytes in the human lung (Shi et al. 2020). The S protein, comprising two main domains (S1, and S2), is crucial in the initial transmission and infection of SARS-CoV-2, mediating the binding of ACE2 and promoting virus membrane fusion. Cleavage at both S protein sites is crucial for S1 binding to ACE2 and membrane fusion, promoting the entrance of SARS and SARS-CoV-2 into host cells.

Coronavirus genomes contain three structural proteins: Membrane (M), Envelope (E), and Nucleocapsid (N), In addition to the characteristic S protein, each (M), (E) promotes virulence and (N) facilitates genomic RNA folding into the nucleocapsid (Alanagreh et al. 2020). People first classed as asymptomatic or presymptomatic are those who test positive for SARS-COV-2 by molecular diagnostics, such as reverse transcriptase polymerase chain reaction (RT-PCR). Moreover, fever, cough, dyspnea, myalgia, or fatigue are frequently associated with Covid-19 symptomatology (Yang et al.2020). Minor symptoms include diarrhea, hemoptysis, migraines, and sputum production. The characteristics of a serious illness are infectious pneumonia, which can lead to acute respiratory distress syndrome (ARDS), sudden cardiac damage, and secondary infections disease's symptomatology determines how severe it is. The mean incubation period for COVID-19 was approximately 7 days on the Chinese mainland, compared to 6 days worldwide. Numerous studies have shown that pro-inflammatory cytokines were more prevalent in the blood of Covid-19 patients.

Sometimes, during the quick progression of COVID-19, a cytokine storm occurs, which modifies the immune system by reducing the number of lymphocytes, especially T cells (Tufa et al. 2020). When the immune system is damaged overall, immune cells release a huge amount of pro-inflammatory cytokines and chemokines, which worsens the cytokine storm. The main cause of death for COVID-19 patients is virally induced hyperinflammation, which is strongly associated with disease severity (Soy et al., 2020; Salem et al., 2023). Sepsis and multiple organ dysfunction are also hallmarks of Covid-19, especially in critical and severe cases, which are caused by an incorrect immune response.

Although chemokines are crucial inflammatory mediators that aid in the immune system's res ponse to infections, hyperinflammation is most ly caused by their overproduction (Khalil et al. 2020). COVID-19 cases have progressively increased in Egypt, the number of cases in Egypt is 516,023, Number of deaths is 24.613. The number of recoveries is 442,182 (WHO, 2022). To better understand how circulating inflammatory mediators may aid in the diagnos is and monitoring ofdisease severity, this study set out to measure the levels of these mediator s in severely ill COVID-19 patients who were hospitalized in Egypt.

PATIENTS AND METHODS

Ethical statement

The present study was carried out according to the guidelines for good clinical practice and approved by the institutional ethical committee of the Faculty of Medicine, Tanta University,

Egypt with approval ID (34929/9/21). Moreover, informed written consents were taken from all subjects under investigation.

Study Subjects

Twenty-seven COVID-19 patients and five healthy control volunteers were recruited. Confirmed COVID-19 patients were enrolled from the inpatient wards and the ICU Department of Tanta University Quarantine Hospital, Tanta, Egypt, between April 2020 and September 2020, upon informed consent under a protocol approved by the Ethical Committee Review (34929/9/21), Faculty of Medicine, Tanta University, Egypt in the period between May 2020 to June 2022. Exclusion criteria included any Pregnant or lactating women, children and subjects aged <18 years. Inclusion criteria were clients aged >18 years with PCR or antigen test confirmation of COVID-19 diagnosis.

Blood sampling

Venous blood was withdrawn from each subject and all blood samples were collected into tubes with anticoagulant (EDTA). After incubating samples for 10-20 min at room temperature, blood samples were centrifuged for 20 min at 2000-3000 rpm to get clear supernatant plasma carefully. if precipitates appeared during reservation, the sample was centrifuged again to get clear plasma, and stored at -20 º c until laboratory analysis and further measurements. However, the sample size for healthy controls and COVID-19 cases was determined based on the sample collection feasibility at the time of conducting the study.

Methods and techniques

EDTA mixed blood samples were used to detect C-reactive protein (CRP), and D -dimer were carried out in separated sera using Cobas 6000 (c501 modules) auto analyzer, Roche diagnostics, Germany, according to manufacturer instructions for each parameter.

Statistical analysis

Data were analyzed statistically using 22.0 (IBM/SPSS Inc., Chicago, IL). Normally distributed quantitative data were expressed as means ± standard deviations (SD). One-way analysis of variance (ANOVA) followed by t-tests were done, respectively. The p-value < 0.05 threshold was deemed significant in statical terms when appropriate. Sometimes, Chi-square test was employed to gauge the relationship between the qualitative variables. However, values less than 0.05 were deemed significant in all applicable tests, while p value less than 0.01 were deemed highly significant.

RESULTS

Demographic and clinical profile of Covid-19 patients

The study included 46 patients with COVID-19 with a mean age of 50,43 years, the majority were male (63%, n=29) compared to female (37%, n=17). Age had a significant effect on the disease severity that increased with age while gender didn't have a significant effect. The males were more susceptible to infection even after vaccination. In the total Covid-19 patient groups,13.26% were smokers versus 33.72% non-smokers. Additionally, 14 vaccinated COVID-19 patients were evaluated. Factors affecting post-vaccination infection were male gender (51.1%), middle-aged (mean 44,64 years), and non-smoking status (64.3%). The symptoms severity ranged from mild to critical illness (requiring mechanical ventilation and ICU admission for organ failure).

In addition to the clinical and biochemical analysis, Table 1 shows the factors (gender, age, and smoking) affecting the disease severity and classification. It was noted that gender has little effect on the disease severity where there is no significant relationship between male and female patients among groups, but the males were more susceptible to infection and complications even after vaccination. Collectively, in all Covid-19 patients, the male percentage was 29.63% versus 17.37% for females.

In turn, age has a significant effect on the disease incidence and severity in both male and female COVID-19 patients; as the patients become older, the incidence and severity of the disease increase toward the elderly. Smoking had a noticeable effect on the disease incidence and severity despite the data being insignificant where the susceptibility to Covid-19 infection was the least at first then increased to about 50% during severe and critical illness.

Nevertheless, the smoker's percentage was about 13.26% but the non-smokers was 33,72%. However, the chance of infection with COVID-19 after vaccine administration was dependent upon the gender, age, and smoking in an order of males more susceptible (57.1 %), middle-aged persons (44.64%), and non-smokers more challenged (64.3%). It can be concluded that the age of patients is a more effective factor in the incidence and severity of Covid-19. on the other hand, both Gender and smoking have insignificant effects on the disease incidence and severity.

Role of vaccination and comorbidities in COVID-19 patients

Both vaccination status and underlying comorbid conditions demonstrated a significant impact on the Covid-19 course. Vaccinated breakthrough case patients showed a profile of lower average age (44.64%) years vs 50.43 years in a cohort, higher nonsmoking rates (64.3% vs 33.72%), and reduced frequency of chronic illnesses as compared to unvaccinated groups suggesting some preservative effect against severe comorbidities and illness despite infection. Conversely, analysis of comorbidity patterns pointed to substantially increased rates of conditions like hypertension (12.5-20%) in mild/moderate, over 20% in severe/critical) in advancing COVID-19 severity categories, corresponding with a peak of 25% of severe/critical patients affected. These trends point to vaccines guarding against complicated diseases and comorbidities correlating with worsened progression and outcomes. The data collectively indicates the public health approaches to expand vaccination coverage plus clinical management of high-risk patient's comorbidities could each improve COVID-19 prognosis by limiting initial infection severity as well as deterring escalation events leading to critical illness respiratory decline or mortality in those infected patients. Tackling both vaccination and chronic disease, control remains paramount.

As shown in Table 2, comorbidities related to the incidence of COVID-19 were studied based on the Charleson S classification. Separated hypertension (HT) and Diabetes mellitus (DM) were common in mild and moderate groups with a percentage ranging from (12.5-20%) for each comorbidity. These comorbidities were combined in moderate COVID-19 patients with 12.5% groups. In severe and critical groups, COVID-19 patients became worse where other chronic diseases besides HT and DM were prominent. The percentages of these comorbidities ranged from 10-25% with or without HT but usually with DM. Unfortunately, some comorbidities particularly (HT & DM) still existed in the vaccinated patients. As the Covid-19 severity of COVID-19 increases, the percentage of comorbidities absence decreases toward severity of the Covid-19. The non-subjects have 30.65% HT at 6.13%, DM at 4,9 %, ILD at 1.2%, and HT+DM at 3.7% COPD at 2,4%. COPD+HT at 2,4%.

Correlation between Covid-19 and patient outcomes

The study found a clear correlation between COVID-19 severity and measurable patient outcomes especially mild cases that experienced 100% recovery without no identified lung fibrosis or mortality. Similarly, moderate cases saw 100% recovery without complications. However, in severe cases, the recovery rate dropped to 60% with new cases of lung fibrosis (20%) of patients and mortality also occurring in 20%.

Most critically and fortunately, critical COVID-19 cases have a 0% recovery rate with no survivals but mortality reached 100%. Cross categories, as severity increased, recovery declined sharply from 100% to 60% to 0% while negative outcomes of lung damage and death rose from 0% to 20% to 100% between mild, severe, and critical patients. The data highlights COVID-19's special ability to quickly spiral into life-threatening and unrecoverable conditions as severity escalates. Mild cases retain chances of full recovery, pointing to the importance of early supportive care to halt clinical deterioration and improve outcomes overall.

As shown in Table 3, the percentages of cure in both mild and moderate patients' groups were 100% but in the severe group, the cure was about 60% and there was no cure in critically ill patients. COVID-19 patients in both mild and moderate critical ill groups were devoid of lung fibrosis with no death. The severe group had a

2% of lung fibrosis and 2% of death. Unfortunately, no cure, no lung fibrosis, and all patients were dead with a percentage reaching 100%.

Mechanical ventilation mechanisms in COVID-19 patients.

As shown in Figure 1, the percentage of ventilation technique in invasive patients was 5,19%, noninvasive patients 20,74%, and oxygen reservoir was 2,7%. Patients with COVID-19 may experience respiratory failure; as a result, they require intense ventilation (IV) to breathe support. Guidelines for the care and treatment of COVID-19 patients state that a good outcome depends on limiting the amount of hypoxia. However, the IV mechanism is used in patients with severe symptoms who need critical care unit. In the early stages of illness, the NIV technique may be beneficial as oxygen delivery to avoid silent hypoxia, and potential Covid-19 consequences. It is possible to reduce the strain on the health care system by quickly implanting patients who are asymptomatic or only mildly ill without compromising the safety or efficacy by using an O2 reservoir.

Inflammatory and coagulopathy mediators

Figures 1, and 2 summarize the concentrations of circulating inflammatory biomarkers in study samples and controls compared to critically ill, patients with Covid-19 had higher circulating concentrations of the inflammatory mediator (CRP), and D-dimer as a clot or coagulation marker.

DISCUSSION

Understanding the pathophysiology of the disease, especially in severe and critically ill cases, is crucial to the proper assessment of the need for any relevant intervention and the prediction of prognosis. For the role of age in disease characteristics (e.g., infectivity, severity) and outcomes (e.g., mortality, cure) of COVID-19 patients, our current results showed that the mean ages of patients are 51,9 ± 14.92, which ranged from 28-84 years. and the mean age of severe patients is over 49.5 ± 18.78. The case fatality rate of severe patients is (20%), the

case fatality rate of critical patients is (100%), the case fatality rate of patients under 60 (20%), and the case fatality rate of patients with 60-70 years is (80%). This means the death rate is higher in patients with ages ranging from (60-70) years in line with the study by Song et al. (2020), which showed the same pattern for mean age, and the mean age of severe Covid-19 patients is over 70 and the case fatality rate of patients over 60 is 4.5%, which is significantly higher than that of patients under 60 (1.4%).

This present study revealed that elderly people are more susceptible to severe Covid-19 and this observation agrees with Zhang et al. (2022) who showed that aging makes people more susceptible to chronic diseases and infections. Additionally, the death rate from COVID-19 increases exponentially with age, and older people are at greater risk of contracting Covid-19, most infections with critically ill patients are elderly about 50% are over 60 years old. Therefore, the elderly is more susceptible to SARS-CoV-2 infections than the younger due to age, which seems to be one of the important factors affecting SARS-COV-2, where the primary risk factor for unfavorable results was thought to be age.

The process and links of pathogenesis are the same for all people, including virus exposure, entry into the body, replication, and a series of symptoms and diseases, but the incidence and severity of the disease are related to the body's immune function. Based on the body's immunity, SARS-CoV-2 infection is contagious, i.e., the outcome will be different for older and younger people due to immune differences. In turn, the initial alarm signals in older people are slowly released when the virus attacks the body, leading to more viral replication, so the virus will enter the body faster and more cells become infected (Dhama et al., 2020). Regarding the role of gender in COVID-19, our present results show that the males are 29.63% and females 17.37%. Formerly, several authors have suggested that men are more likely to be infected with Covid-19, especially after 50 years of age. These differences are usually attributed to three determinants: differences in immune function, the effects of sex hormones, and gender-related behavior (Ciarambino et al., 2021).

Table 1. The classification of COVID-19 patients based on clinical and biochemical analysis and the effect of Gender, age, and smoking on the disease severity

Covid-19 groups	Gender		Age	Smoking	
	Male (n= 29)	Female (n=17)	Years (X ± SD)	-Ve (n= 33)	+Ve (n=13)
Control (n=5)	2 (40%)	3 (60%)	26.2 ± 9.15b	5 (100%)	0 (0)
Mild (n=5)	4 (80%)	1 (20%)	44.8 ± 10.76 a, b	4 (80%)	1 (20%)
Moderate (n=8)	5 (62.5%)	3 (37.5%)	51.75 ± 17.09a	7 (12.5%)	1 (87.5%)
Severe (n=10)	7 (70%)	3 (30%)	49.5 ± 18.78 a, b	6 (60%)	4 (40%)
Critical (n=4)	3 (75%)	1 (25%)	61.5 ± 13.08a	2 (50%)	2 (50%)
Vaccinated (n=14)	8 (57.1%)	6 (42.9%)	44.64 ± 12.99 a, b	9 (64.3%)	5 (35.7%)
Statistical test	Chi-Square		One way ANOVA	Chi-Square	
	X2 = 2.44 p-value = 0.832 n. s.		3.057 0.02 *	X2 = 4.825 p-value = 0. 435 n. s.	

Data are expressed as means (X ± SD) and n is pointing to the number of clients. Means with letters a or b is significantly different at $p \leq 0.05$, while means without a or b are not significantly different.

Table 2. Comorbidities associated with COVID-19 and their percentages

Subject's groups	Comorbidities					
	NO	HTN	DM	ILD	HTN, DM	HTN, COPD
Control cases (n=5)	5 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Mild cases (n=5)	3 (60%)	1 (20%)	1 (20%)	0 (0%)	0 (0%)	0 (0%)
Moderate cases (n=8)	6 (75%)	1 (12.5%)	0 (0%)	0 (0%)	1 (12.5%)	0 (0%)
Severe cases (n=10)	4 (40%)	2 (20%)	1 (10%)	0 (0%)	1 (10%)	2 (20%)
Critical cases (n=4)	1 (25%)	0 (0%)	1 (25%)	1 (25%)	1 (25%)	0 (0%)
Vaccinated (n=14)	11 (78.6%)	2 (14.3%)	1 (7.1%)	0 (0%)	0 (0%)	0 (0%)
Statistical test	Chi-Square Tests (Fisher- Exact Test) χ^2 = 24.704 p-values = 0.294 n.s.					

Data are expressed as percentages. HTN means Hypertension, DM is Diabetes mellitus, ILD is interstitial lung disease and COPD is a chronic obstructive pulmonary disease.

Table 3. Ultimate outcomes in different COVID-19 patients' groups.

Covid-19 groups	Cured	lung fibrosis	death
Mild cases (n=5)	5 (100%) a	0 (0%) a	0 (0%) a
Moderate cases (n=8)	8 (100%) a	0 (0%) a	0 (0%) a
Severe cases (n=10)	6 (60%) a	2 (20%) a	2 (20%) a
Critical cases (n=4)	0 (0%) a	0 (0%) a	4 (100%) b
Statistical test	Chi-Square Tests (Fisher- Exact Test)		
	$\chi^2 = 15.796$ p-value <0.001		

A similar study by Lakbar et al. (2020) showed that SARS-CoV-2 may also affect men and women differently. It therefore remains unclear if the disease characteristics and outcomes of patients with SARS-CoV-2 infection differ between the genders. Many studies debated about the role of gender in the disease development and severity, out of them, Bwire (2020) reported that the incidence of Covid-19 in men was almost 4 times higher than in women (4.4% vs 1.2%) suggesting that men may have a higher risk of developing severe Covid-19 and associated death rates than women, which agree with the current study the number of severe patients is 10 patients, 7 of them are males and 3 are females and the number of critical patients is 4 patients, 3 patients of them are male and 1 is female. the number of moderate patients is 8 patients, 3 of them are females and 5 are males. but in the mild group, one is female and 4 are males confirming these authors' opinions that males are more infected with SARS-COV-2 than females.

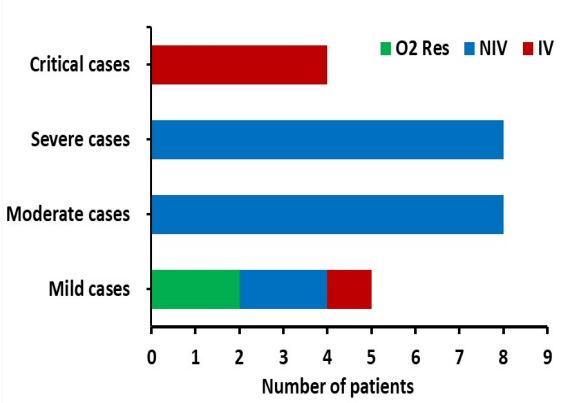

Figure 1. Mechanical ventilation mechanisms in Covid-19 patients' groups

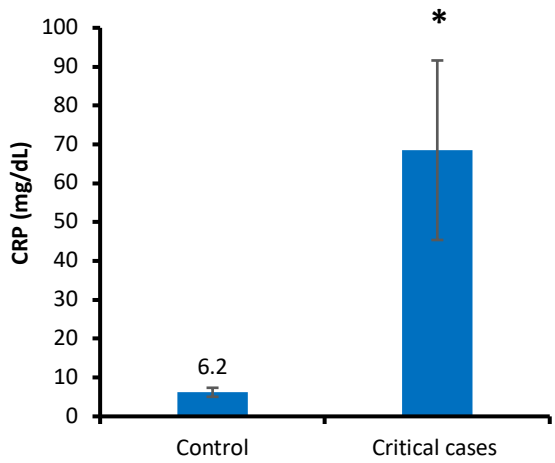

Figure 2. The concentration of C-reactive protein (CRP) in COVID-19 patients. Columns with letters a or b are significantly different at $p \leq 0.05$, while means without a or b are not significantly different.

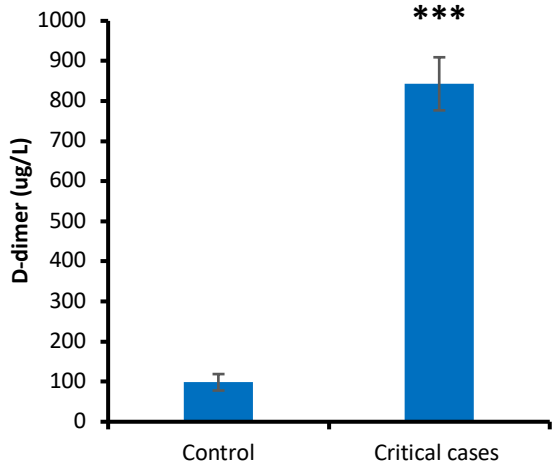

Figure 3. The influence of D -dimer on different groups of COVID-19 patients. Columns with letters a or b are significantly different at $p \leq 0.05$, while means without a or b are not significantly different.

On the contrary, Lakbar et al. (2020) demonstrated that men and women react to the infection directly when both are subjected to the infection with SARS-COV-2. Compared to men, women have additional immunological traits that give them an advantage when expos ed to viral infections. For instance, Toll-like receptor 7 (TLR7), which is known to detect viral RNA, is expressed more frequently in women. Additionally, they generate more interferon-α, which is linked to lung tissue defense (Liu et al., 2023). Concerning how smoking affects the severity of COVID-19, smoking tobacco is the primary cause of disease, disability, and death. Research by Brake et al. (2020) showed that smoking increases the expression of the SARS-CoV-2 receptor, ACE2 in the lungs, which increases the possible sites of viral entry men have higher rates of smoking than women. Furthermore, there exist some social norms that discourage men from seeking treatment or physician consultation. As a result, men often delay seeking treatment, which can increase the probability of adverse outcomes after Covid-19 infection.

First intracellular entry by interactions with glycoproteins spiked by the virus, further research has verified that human lungs show increased ACE2 expression. It is, therefore, plausible that smokers are exposed to higher SARS-CoV-2 loads because of increased expression of ACE-2, which may provide a mechanistic explanation for the increased risk of severe disease and mortality associated with smoking in COVID-19 patients.

A study by Reddy et al. (2021) found that current smokers have an increased risk of presenting to the hospital with severe COVID-19 and are approximately twice as likely to experience severe or critical COVID-19 as former or never-smokers. Principally, in Covid-19 patients, smoking is linked to higher severity of the disease. In our results, smoking had a noticeable effect on the disease incidence and severity despite data being insignificant where the susceptibility to Covid-19 infection was the least at first then increased to about 50% during severe and critical phases. Nevertheless, the smoker's percentage was about 13.26% but the non-smokers was 33,72%.

However, the chance of infection with COVID-19 after vaccine administration was dependent upon the gender, age, and smoking in an order of males more susceptible (57.1 %), middle-aged persons (44.64%), and non-smokers more challenged (64.3%). Therefore, further studies characterizing the complex relationship between smoking and ACE-2 in COVID-19 are still warranted. For the role of comorbidities in COVID-19, diabetes is considered a dangerous factor for individuals who contract COVID-19, which requires these patients to take signifi cant precautionary measures (de Siqueira et al., 2020). In addition, SARS-CoV-2 generally increases blood glucose, which makes infection control more difficult. Diabetics were found to have greater rates of hypertension, interstitial lung disorders, and chronic obstructive pulmonary diseases (COPD). These findings may further increase the likelihood that these patients will contract Covid-19 (Chen et al., 2020). Co-morbidities associated with viral infection may lead to disease severity and illness ending, occasionally, with death. Moreover, in a survey including 7 studies by Jain and Yaun (2020).

According to suggestions, the most frequent re asons for severe illness or admission to the inte nsive care unit (ICU) are COPD, diabetes, and h ypertension, in that order. This agrees with our study, which indicates that COVID-19 patients with diabetes were 55%, those with hypertension were 48% and those with interstitial lung disease were 25%, and people with two or more comorbid diseases are more likely to develop severe diseases. For instance, hypertension with Diabetes is 47.5% and hypertension with COPD is 20%. In the mild group of patients 3, patients were devoid of any chronic diseases but only one patient with hypertension and another one with diabetes. In the moderate, 6 patients were devoid of any chronic diseases 1 patient with hypertension and another with diabetes with hypertension. In the severe group, patients with hypertension and 4 were devoid of chronic diseases,2 patients with hypertension with COPD,1 with diabetes,1 with hypertension with diabetes, and the critical group, only one was devoid of chronic disease, one with diabetes, one with hypertension with diabetes and one with interstitial lung diseases.

In our study, comorbidities related to the incidence of COVID-19 were studied based on the Charleson S classification. Separated hypertension and diabetes were common in mild and moderate groups with a percentage ranging from (12.5 to 20%) for each comorbidity. These comorbidities were combined in moderate COVID-19 patients with 12.5% groups. In severe and critical groups, COVID-19 patients became worse where other chronic diseases besides hypertension and diabetes were prominent. The percentages of these comorbidities ranged from 10-25% with or without hypertension but usually with diabetes.

There is a bidirectional relationship between Covid-19 and diabetes. On the one hand, diabetes is associated with an increased risk of severe Covid-19. On the other hand, Covid-19 may induce new-onset diabetes in healthy people. However, evidence shows that among patients with Covid-19, the risk of death from diabetes is 50% higher than those without diabetes, especially in elderly patients, additionally, there is a reciprocal association between diabetes and Covid-19. Diabetes is linked on the other hand to a higher risk of severe Covid-19. However, in healthy individuals, COVID-19 may cause diabetes to develop for the first-time evidence, however, indicates that people with COVID-19 have a 50% greater chance of dying from diabetes than from other causes particularly in older patients with T2DM (Rubino et al., 2020).

This in line with our results that there were in the critical group,2 elderly diabetic patients (59-71) ended with death. In the severe group, there was only one elderly diabetic patient (70 years) who ended with lung fibrosis during T2DM although metabolic problems can be exacerbated by inflammation, immune cell functions can also be regulated by metabolic variables. Individuals with compromised immune systems and metabolic imbalances are more vulnerable to several pathogens, including SARSCOV-2 (Daryabor et al., 2020). Comprehending the disease's pathophysiology is essential for accurately determining the

necessity of any pertinent interventions and making prognostic assessments, particularly in critically ill cases. According to the current study, individuals with COVID-19 had lower survival rates and greater requirements for mechanical ventilation when their D-dimer levels were high.

Many suggestions have been put up to explain the disease known as thrombosis in COVID-19 patients, but the mechanism by which the SARS-CoV-2 virus induces thrombosis is still not fully understood. according to one theory, endothelium damage occurs after the innate immune system is activated by viral invasion, indicating an imbalance between inflammation and coagulation. The microcoagulation cascade is activated to control this injury, resulting in an excess of thrombin and the ensuing disproportion between fibrinolysis and thrombosis. Theoretically, some inflammatory markers, including CRP, peripheral blood components including neutrophils and platelets, and a class of cytokines are crucial to this process (Sharifpour et al., 2020).

This study assessed the concentrations of CRP as inflammatory mediators and D-dimer as a clot marker in utilizing healthy comparators, researchers examined the roles of inflammatory mediators in the diagnosis and treatment of COVID-19 patients. In response to infections, the liver synthesizes significant quantities of acute phase proteins (APPs) such as CRP an acute inflammatory protein that highly sensitive biomarker for inflammation, tissue damage, and infection.

It has been shown that CRP levels are correlated with levels of inflammation. CRP levels can promote phagocytosis and activate the complement system. In other words, CRP binds to microorganisms and promotes their removal through phagocytosis. Moreover, the serum CRP levels increase during inflammatory responses. As shown previously, this biomarker may be raised by viral or bacterial infections. It is important to note that CRP levels were significantly increased in bacterial infections than in viral infections. The current study revealed significantly higher CRP levels in severe cases than in non-severe patients suggesting that the CRP level may be a biomarker of disease severity and progression in patients with COVID-19.

It was reported by Liu et al. (2020) that more severe cases infected with COVID-19 expressed significantly higher CRP levels than non-severe patients as highly sensitive biomarkers for infection, tissue injury, and inflammation is intense inflammatory protein, which makes investigators assume a correlation between CRP and inflammatory markers. Elevations of CRP can stimulate the complement system and encourage phagocytosis. The results of the current study showed that patients with severe instances had considerably higher CRP levels than patients with less severe cases, confirming previous results of Liu et al. (2020) that CRP levels may be a biomarker for the severity and course of a patient's illness. Likewise, our results demonstrated that patients with COVID-19 had significantly greater levels of D-dimer than healthy controls. Patients with critical COVID-19 had higher CRP compared to the mild or moderate group. When predicting COVID-19 severity and prognosis, CRP demonstrated high sensitivity and specificity. Therefore, there is a substantial correlation between illness severity and both age and CRP levels, and promising indicators for COVID-19 disease severity include high CRP levels.

The severe group in this study had much higher CRP levels than the other groups, which is in line with recent research that suggested CRP levels could be indicators of the severity of an illness. CRP is a nonspecific metric used to differentiate between diseases brought on by bacteria or viruses that are infectious and those that are not (Binnie et al., 2020). Another study (Chen et al., 2020) indicates that CRP is a biomarker for Covid-19 severity and that elevated levels are associated with a worse prognosis for Covid-19 suggesting that CRP may be used to predict prognosis even before the onset of the illness. It can also serve as a precursor of inflammation and infection. Both earlier and current studies have shown that elevated CRP levels during COVID-19 infection have clinical diagnostic and prognostic significance.

Concerning D-dimer as a clot marker, the D -D-dimer is a protein synthesized and released into circulation in response to the clot formation

mechanism. The normal range of D-dimer is < 50 or 500 ng/ml, which means no serious blood clot formed but if it is > 50 or 500 ng/ml there is an active blood clot formation induced by any reason (Nemec et al., 2022). Our results showed a comparison of D-dimer in Covid-19 patients. In controls with D-dimer level of 500 ng/ml and critically ill patients have D dimer levels ranging (900 -1000) ng/ml. These results show that D-dimer increased significantly in both severe and critically ill patients. This suggests that D-dimer has a serious effect on the COVID-19 severity in critical patients. It means that persons with D-dimer probably suffer from a clotting disease they have or find a clot.

Nonetheless, smoking, serious lung conditions, or a client's age greater than 60 years old may be the cause of high D-dimer levels that agree with our results. Because these data were provided for a small number of patients, likely, the differences between survivors and non-survivors were not statistically significant. Nevertheless, all these discrepancies have been extensively reported as indicators of severe disease (Abd El-Lateef et al., 2022). For example, One COVID-19 patient 65 years old suffering from COPD has a high D-dimer, and another case 55 years old is a smoker with COPD but in the critical group is a patient with interstitial lung disease have high D-dimer. Patients who passed away had higher CRP readings, high D-dimer, and associated markers with related parameters than those who survived.

In conclusion, It is essential as shown by the present study, to characterize the immune response to direct public health initiatives and actions that the severity of Covid-19 raised the levels of inflammatory mediators (CRP, D-dimer). This observation raises the possibility that these markers could be used to predict the severity and prognosis of Covid-19 patients. CRP may indicate the severity of COVID-19 when plasma inflammatory mediators signal an aberrant immune response and the start of a cytokine storm, which exacerbates the illness and may even be fatal. Briefly, CRP is an easily obtained marker that is widely accessible, reasonably priced, and correlated with both disease severity and death. In addition, our data validate the usefulness of daily CRP readings in hospitalized COVID-19 patients to aid in prognosis.

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