Diagnostic role of laboratory findings and clinical symptoms in detecting the severity of COVID-19 disease

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Abstract. – OBJECTIVE: The novel coronavirus (COVID-19) pandemic poses a monumental challenge to healthcare systems worldwide. Clinical features and data-driven decisions could differentiate the virus's early stages.

This study aims to provide valuable diagnostic data that can help determine the severity of COVID-19 infection and allow for early detection.

PATIENTS AND METHODS: A sample of 214 patients was collected to validate our approach. The data were grouped into ordinary (126 cases) or severe (88 cases) groups. The information they provided included age, gender, creatinine levels, blood pressure, glucose levels, creatine phosphokinase (CPK), alanine transaminase (ALT), cough, fever, expectoration, myalgia, headache, dyspnea, abdominal discomfort, and chest pain. Statistically, the Mann-Whitney U, T, and Chi-square tests were utilized to determine the significant differences in collected data between two groups of patients and the severity of those differences between categorical variables.

RESULTS: The patients' age range was 21 to 84 years. The male gender was predominant (56%), particularly in the severe group (63.6%). The results summarized that the mortality rate for COVID-19 patients is high (4.7%). Symptomatic patients with abnormal creatinine levels, blood pressure, glucose level, CPK, ALT, cough, expectoration, dyspnea, and chest pain were significantly linked with both COVID-19 patient groups ($p < 0.05$). Compared to the ordinary group, patients in the severe group had abnormal creatinine levels (77.8%), high blood pressure (87.5%), diabetes mellitus (55.3%), high CPK level (85.7%), high ALT value (88.2%), cough (44.4%), expectoration (86.7%), dyspnea (81.0%), and chest pain (80.0%).

CONCLUSIONS: Patients with abnormal creatinine levels, blood pressure, glucose levels, CPK, ALT, cough, dyspnea, and chest pain are at high risk for severe COVID-19 infection.

Key Words:
COVID-19 disease, Clinical symptoms, Laboratory findings, COVID-19 severity.

Introduction

This study documents several key contributions to the field of Coronavirus disease (hereafter COVID-19). Due to its high transmission capability, mobility, and mortality, COVID-19 changed

the course of the world. In 2020, the World Health Organization (WHO) described COVID-19 as a pandemic that contaminated millions of people globally. The WHO also indicated that COVID-19 inflicted dramatic economic hardship on many communities. Similarly, it prohibited people from moving willingly inside countries and provinces[1,2]. Generally, patients' arrivals at the emergency unit in a hospital are subject to necessary tests, such as blood pressure measurement, temperature measurement, stethoscope, oxygen saturation, a complete blood count (CBC), and sometimes electrocardiograms (ECG). Physicians who suspect COVID-19 often request different laboratory examinations to evaluate diseases associated with COVID-19 infection, such as kidney disease, diabetes mellitus, heart disease, liver disease, and coagulation.

A series of recently published reports[3-5] and available data has indicated the high incidence of kidney function in COVID-19 patients, indicating the importance of measuring the creatinine level of the infected patients. The literature review shows that 35% of admitted COVID-19 patients had elevated ALT levels. In comparison, 46% of patients had elevated plasma aspartate aminotransferase (AST) levels[6]. In addition, lab testing revealed a marked elevation of CPK for COVID-19 patients[7-9].

Many investigations[10-13] have shown that most COVID-19 variants and other infectious lung disorders have similar symptoms, such as fever, cough, weariness, myalgia, arthralgia, anosmia, pharyngitis, and dysgeusia. Furthermore, pneumonia cases are high during the winter season when other pathogen infections cause respiratory ailments, making it even more difficult for public health and clinicians to detect infected individuals[14,15]. Thereupon, earlier detection of potentially severe COVID-19 patients based on regular clinical and laboratory results would save their lives and decrease the otherwise huge healthcare cost. On the other hand, prior research[16-18] found that computed tomography (CT) imaging improved the speed and reliability of quick triage for COVID-19 patients.

Based on the short preview above, this study seeks to provide significant contributions to the field of the study. These contributions are based on clinical indications, symptoms, and laboratory test findings that may lead to an accurate diagnosis of COVID-19 infection and early prediction of its severity.

Patients and Methods

A total number of 239 patients with positive results for real-time reverse transcription polymerase chain reaction test (RT-PCR) were collected from Prince Hamza Hospital. The collected data has been completed in cooperation with Hakeem System for Electronic Health Solutions in Amman, Jordan. The researchers consider this study a case study because the completed data set was collected from Prince Hamza Hospital.

The researchers followed specific inclusion criteria. In the first place, COVID-19 diagnosis was determined according to positive RT-PCR and CT scan reports results. In the second place, the COVID-19 patients with laboratory exams and clinical symptoms were included. It is worth pointing out that twenty-five patients were excluded from this study for several reasons. First, there was insufficient history data and laboratory exams of 10 patients. Second, there were nine patients without CT scan information. Equally important, six died for unrelated reasons to COVID-19 infection. Another key point, all patients' demographic information was kept confidential and collected after granting Prince Hamza Hospital's ethical committee approvals.

Medical and Clinical Data

Patient information, including age, gender, medical history, clinical signs and symptoms, laboratory test results, and CT reports, were collected for 214 patients included in this study. Following their clinical respiratory function results, patients were placed in ordinary or severe groups. Patients were either placed in ordinary or severe groups. Clinically, the respiratory function becomes worse in the severe stage. Therefore, the patients were defined as severe when they had saturated oxygen (less than 93%), respiratory rate (more than 30 times/min), and/or deteriorated chest CT images[19,20].

The laboratory tests and clinical signs and symptoms were analyzed in two groups of patients, including creatinine level, blood pressure, diabetes mellitus (level of glucose in the blood), ALT level, CPK level, fever, cough, expectoration, myalgia, headache, dyspnea, abdominal pain or diarrhea, pharyngeal discomfort, and chest pain. Nevertheless, the sensitivity of RT-PCR for detecting COVID-19 is limited. Therefore, based on the literature, further radiological high-resolution CT examinations were required in case of COVID-19 suspicion[21-23].

Statistical Analysis

This study used the Statistical Package for Social Sciences (SPSS 22.0; IBM Corp., Armonk, NY, USA). The mean and standard deviation (SD) of quantitative data were used, while categorical variables were expressed as a percentage of the total. For two groups of patients, demographic variables were mainly creatinine level, blood pressure, diabetes mellitus (level of glucose in the blood), CPK level, ALT l   evel, fever, cough, expectoration, myalgia, headache, dyspnea, abdominal pain or diarrhea, pharyngeal discomfort, and chest pain. The researchers utilized the Mann-Whitney U test and *t*-test to examine the significance of differences between the two groups. Furthermore, the Chi-square test was used to determine the significance of ordinary and severity patients. Finally, the Shapiro-Wilk test was used to check if the continuous variable follows a normal distribution. *p*-value lower than 0.05 (*p*-value < 0.05) was considered statistically significant.

Results

This section summarises the findings and contributions made. This study categorized the 214 patients aged 21 to 84 years in accordance with their clinical respiratory functions into two groups, i.e., ordinary and severe. Table I shows 126 ordinary cases (64 males and 62 females) and 88 severe cases (56 males and 32 females). Generally, the results concluded that male patients (56%) are higher than female patients (46%). The results demonstrated a slight difference between infected male and female patients in the ordinary group (50.8% male to 49.2% female). In comparison, the number of infected males is dominated in the severe group (63.6% male to 36.4% female).

The table results also summarized the effective percentages of COVID-19 infection on severity and mortality rate for the patients. A further novel result is that the mortality rate for Jordanian patients infected with COVID-19 is 4.7%, higher than the worldwide average of 2.15%[24].

A total of 214 COVID-19 patients with RT-PCR and CT-positive results were assessed. According to the findings shown in Table II, symptomatic patients with creatinine level ($N_{Ordinary}$ = 8; N_{Severe} = 28; $p < 0.05$), blood pressure ($N_{Ordinary}$ = 4; N_{Severe} = 28; $p < 0.05$), glucose level ($N_{Ordinary}$ = 34; N_{Severe} = 42; $p < 0.05$), CPK ($N_{Ordinary}$ = 4; N_{Severe} = 24; $p < 0.05$), ALT level ($N_{Ordinary}$ = 4; N_{Severe} = 30; $p < 0.05$), cough ($N_{Ordinary}$ = 100; N_{Severe} = 80; $p < 0.05$), expectoration ($N_{Ordinary}$ = 4; N_{Severe} = 26; $p < 0.05$), dyspnea ($N_{Ordinary}$ = 8; N_{Severe} = 34; $p < 0.05$), and chest pain ($N_{Ordinary}$ = 6; N_{Severe} = 24; $p < 0.05$) were statistically in a significant linking with both COVID-19 patients' groups. The researchers obtained good results with this method. It is worth discussing these interesting facts revealed by the results. The results show that a significant difference could be seen between COVID-19 disease severity and these findings. Compared to ordinary patients, more patients in the severe group exhibited increasing creatinine levels (Ordinary = 22.2% to Severe = 77.8%), blood pressure (Ordinary = 11.5% to Severe = 87.5%), glucose level (Ordinary = 44.7% to Severe = 55.3%), CPK values (Ordinary = 14.3% to Severe = 85.7%), ALT levels (Ordinary = 11.8% to Severe = 88.2%), expectoration (Ordinary = 13.3% to Severe = 86.7%), dyspnea (Ordinary = 19.0% to Severe = 81.0%), chest pain (Ordinary = 20% to Severe = 80.0%).

Planned comparisons revealed that more patients in the ordinary group exhibited cough (Ordinary = 55.6% to Severe = 44.4%). On the

Table I. Percentages and frequencies of 214 COVID-19 patients related to their infection severity, gender, and mortality.

Group		Frequency	Percentage %
Ordinary	Male	64	50.8
	Female	62	49.2
	Total	126	100.0
Severe	Male	56	63.6
	Female	32	36.4
	Total	88	100.0
Gender	Male	120	56
	Female	94	44
Mortality Rate	Alive	204	95.3
	Death	10	4.7

Table II. Chi-square test and disease-related variables and comparison between Ordinary *vs.* Severe COVID-19 patients (n=214).

			Group		Total	Chi-Square Test (χ^2)	*p*-value
			Ordinary	Severe			
Symptoms and Diseases	Creatinine	Count	8	28	36		
		% within Symptom	22.20%	77.80%	100.00%	24.02	0
		% within Group	2.30%	6.20%	4.50%		
	Blood pressure	Count	4	28	32		
		% within Symptom	12.50%	87.50%	100.00%	33.427	0
		% within Group	1.20%	6.20%	4.00%		
	Glucose level	Count	34	42	76		
		% within Symptom	44.70%	55.30%	100.00%	8.925	0
		% within Group	9.80%	9.30%	9.50%		
	CPK	Count	4	24	28		
		% within Symptom	14.30%	85.70%	100.00%	26.458	0
		% within Group	1.20%	5.30%	3.50%		
	ALT	Count	4	30	34		
		% within Symptom	11.80%	88.20%	100.00%	37.059	0
		% within Group	1.20%	6.60%	4.30%		
	Fever	Count	106	76	182		
		% within Symptom	58.20%	41.80%	100.00%	26.458	0.65
		% within Group	30.60%	16.80%	22.80%		
	Cough	Count	100	80	180		
		% within Symptom	55.60%	44.40%	100.00%	5.167	0.02
		% within Group	28.90%	17.70%	22.60%		
	Expectoration	Count	4	26	30		
		% within Symptom	13.30%	86.70%	100.00%	29.893	0
		% within Group	1.20%	5.80%	3.80%		
	Myalgia	Count	22	22	44		
		% within Symptom	50.00%	50.00%	100.00%	1.803	0.18
		% within Group	6.40%	4.90%	5.50%		
	Headache	Count	34	24	58		
		% within Symptom	58.60%	41.40%	100.00%	0.002	0.96
		% within Group	9.80%	5.30%	7.30%		
	Dyspnea	Count	8	34	42		
		% within Symptom	19.00%	81.00%	100.00%	34.241	0
		% within Group	2.30%	7.50%	5.30%		
	Abdominal pain/diarrhea	Count	6	6	12		
		% within Symptom	50.00%	50.00%	100.00%	0.414	0.52
		% within Group	1.70%	1.30%	1.50%		
	Pharyngeal discomfort	Count	4	8	12		
		% within Symptom	33.30%	66.70%	100.00%	3.426	0.06
		% within Group	1.20%	1.80%	1.50%		
	Chest pain	Count	6	24	30		
		% within Symptom	20.00%	80.00%	100.00%	21.783	0
		% within Group	1.70%	5.30%	3.80%		
Total		Count	346	452	798		
		% within Symptom	43.40%	56.60%	100.00%		
		% within Group	100.00%	100.00%	100.00%		

Creatine phosphokinase (CPK), alanine transaminase (ALT).

other side, there was no statistically significant difference between the ordinary and severe COVID-19 instances in symptomatic patients with fever ($N_{Ordinary}$ = 106; N_{Severe} = 76; p = 0.65), myalgia ($N_{Ordinary}$ = 22; N_{Severe} = 22; p = 0.18), headache ($N_{Ordinary}$ = 34; N_{Severe} = 24; p = 0.96), abdominal pain or diarrhea ($N_{Ordinary}$ = 6; N_{Severe} = 6; p = 0.52), and pharyngeal discomfort ($N_{Ordinary}$ = 4; N_{Severe} = 8; p = 0.06) indicating that there is no significant link between COVID-19 disease severity and these diseases and symptoms.

Discussions

This study aims to identify laboratory and clinical features associated with severe COVID-19 disease by comparing groups of severe patients with ordinary patients. This study categorized 214 patients aged 21 to 84 years into two groups based on their clinical respiratory function (126 ordinary and 88 severe cases). The main promising result summarized that male patients are more likely to be infected by the COVID-19 virus than female patients. By the same token, the results found that the infected males dominate the severe group (63.6%). This may indicate that males are more likely to become infected with bacteria and viruses than females. In this case, females have a more robust innate and adaptive immune system[25,26]. The increasing percentage of infected males compared to females is consistent with previous studies[27-32]. These results are consistent and correlated with a meta-analysis study[33], which concluded that infected males have a higher risk of severe infection than females.

A similar pattern of results was obtained from another research[34] that found that the severity of cases among men is higher than that of women (p = 0.035). The study found that men were more likely to suffer worse outcomes and death than women. A gender-based difference in immunological responses may also be contributing to these disparities. Further, it is possible that gender differences in behaviors, such as smoking, and the prevalence of comorbidities, may contribute to the different clinical outcomes of COVID-19 infections between men and women[35]. As a result, understanding the gender sensitivity of COVID-19 infection is crucial in developing effective treatment.

The results also summarized that the mortality rate for COVID-19 patients is 4.7%. This indicates a high level of mortality rate for COVID-19 Jordanian patients compared to the general average mortality rate of the world, which was approximately 2.15% in the period from May 3, 2021, to August 6, 2021[24]. In addition, the corresponding mortality rate in China was 2.3%[36], significantly lower than our study's overall mortality rate. Expressively, the high mortality rate in our study may refer to an increase in the severity percentage of over-total infected patients, 41.1%. Increasing mortality and severity rates indicate the importance of diagnosing COVID-19 cases early to provide quick and affordable data that may help health providers decrease the possibility of risk. Therefore, to provide the best treatment for COVID-19 patients, following up on cases and early diagnosing before they become severe is a top-priority.

The findings of our study showed that abnormal creatinine levels, blood pressure, glucose level, CPK, ALT, cough, expectoration, dyspnea, and chest pain are associated with COVID-19 severity. In agreement with our study results, researchers[5,37,38] indicated that patients with severe COVID-19 are associated with abnormal creatinine levels. A large retrospective study[35] (11,291 patients admitted to intensive care units) found that elevated creatinine levels are linked with increased mortality and severity among COVID-19 patients.

The studies[5,37,38] also confirmed a link between high blood pressure levels and COVID-19 severity. Blood pressure levels associated with intensive care unit patients (49%) in Lombardy, Italy, hospitalized COVID-19 patients (56.6%) in New York, USA[39,40], and hospitalized patients (16.9 to 31.2%) in China[41-43]. Further, it was reported[30,43] that a higher prevalence of high blood pressure was a risk for progression to severity or even death in COVID-19 patients. Previous work completed by Pranata et al[44] demonstrated that high blood pressure increased the likelihood of worse outcomes, such as the severity and mortality of COVID-19 patients.

Furthermore, the findings are directly in line with previous work by other researchers. The results of this study were in line with published work which concluded that the patients with diabetes, liver injuries, and chest pain increased the severity of illness for hospitalized COVID-19 patients[45-50]. A meta-analysis study[51] of 78,874 hospitalized COVID-19 patients was performed. The study found that pre-existing diabetes patients are significantly linked with higher severity and mortality risk for admitted COVID-19 patients. This may refer to diabetic patients often suffering from comorbidities that lead to worse clinical outcomes. Therefore, it is important to pay enough

attention to diabetes COVID-19 patients to make significant progress in treatment[52].

Liver injuries have been described with COVID-19 disease. In a retrospective study[45], the authors evaluated the impact of liver injuries on clinical outcomes for 363 hospitalized COVID-19 patients. The authors found that the patients with liver injuries had a higher risk and longer stay in the hospital. The liver injury patients were independently associated with critical illness and mechanical ventilation. Another retrospective study[53] of 184 COVID-19 patients admitted to a USA hospital evaluated the effect of liver functions on clinical outcomes. The study found liver function abnormalities in more than two-thirds of the patients. Furthermore, in agreement with our study results, a systematic review and meta-analysis study[54] (12,882 COVID-19 patients) found that elevation of liver enzymes was significantly linked with COVID-19 severity (elevated AST and ALT were 41.1% and 29.1%, respectively). Thus, the elevation of liver enzyme values is considered a risk factor for an extended severity of COVID-19.

Our study results confirmed that CPK values are significantly linked with COVID-19 severity (85.70% of severe patients have abnormal CPK values). Elevation of CPK level was documented in about 20% of severe COVID-19 infections[29]. A study[55] showed that the elevation of CPK levels could be considered a factor able to predict worse clinical outcomes of COVID-19 patients. The increase in CPK levels in severe COVID-19 patients can be related to a significant and reverse correlation between the level of CPK with oxygen saturation and the severity of lung involvement in COVID-19 patients[56]. Our results indicated that increasing CPK could be a potential prognostic sign of COVID-19 severity.

Clinical features and symptoms of fever, cough, expectoration, myalgia, headache, dyspnea, abdominal pain, pharyngeal discomfort, and chest pain were evaluated in this study for ordinary and severe COVID-19 patient groups. Our study results confirmed that cough, expectoration, dyspnea, and chest pain are significantly associated with COVID-19 severity. In a study conducted to investigate the effect of clinical features on COVID-19 severity, the incidences of cough, expectoration, dyspnea, and chest pain were significantly higher in severe patients than in ordinary patients. The study summarized that the clinical features of cough, dyspnea, chest pain, and expectoration were risk factors for COVID-19 disease. Moreover, dyspnea and chest pain were the most clinical symptoms associated with severe patients. Dyspnea may result in alveoli damage, while chest pain is related to inflammatory affection of the pleura[57]. However, identifying these symptoms in clinical practice would help health providers to determine the severity of COVID-19 infection.

It can be concluded from this study that there are significant differences in laboratory findings and clinical symptoms between ordinary and severe COVID-19 patients. Severe COVID-19 infection is more likely to occur in patients with abnormal creatinine levels, blood pressure, glucose levels, CPK, ALT, cough, expectoration, dyspnea, and chest pain. These factors can be considered risk factors for an extended severity of COVID-19. Hence, health providers should consider these factors to provide the best early treatment for COVID-19 patients.

Limitations

There are several limitations to this study. First, the study population only included Amman (the capital of Jordan) patients. Second, the data of the two groups (ordinary and severe groups) were not balanced. Third, there was a lack of pediatric population. Fourth, laboratory findings and clinical symptoms were sometimes inaccurate due to treatment and medication effects.

Conclusions

Compared with ordinary COVID-19 patients, severe COVID-19 patients have a poor prognosis and high mortality. Evaluating the laboratory and clinical characteristics helps understand the mechanism of disease severity and promotes its clinical diagnosis and treatment. Diagnosing COVID-19 cases early helps health providers to decrease the severity of COVID-19 infection and provide effective treatment. By comparing groups of severe and ordinary patients, this study seeks to discover laboratory and clinical characteristics linked to severe COVID-19 disease. In this study, 214 patients ranging in age from 21 to 84 were divided into two groups based on their clinical respiratory function (126 ordinary and 88 severe cases). The majority of patients (56%) were male, especially those in the severe group (63.6%). The data showed a high mortality rate for COVID-19 patients (4.7%).

The results summarized that the patients with different mild or severe COVID-19 could be distinguished according to the evaluation of creatinine levels, blood pressure, glucose level, CPK,

ALT, cough, expectoration, dyspnea, and chest pain. These findings have a harmful effect on the patient's hospitalization and the severity of COVID-19 disease. On the other hand, the findings of fever, myalgia, headache, abdominal pain or diarrhea, and pharyngeal discomfort were not significantly associated with COVID-19 severity. Accordingly, this study advises healthcare providers to be aware of patients with abnormal creatinine levels, high blood pressure, high glucose level (diabetes mellitus), CPK, ALT, cough, expectoration, dyspnea, and chest pain where the presence of severe COVID-19 cases has a high possibility.

Informed Consent
Informed consent was obtained from all subjects involved in the study.

Data Availability
Not applicable.

Conflicts of Interest
The authors declare no conflict of interest.

Ethics Approval
Ethical approval was obtained from the Research Ethics Board of Prince Hamza Hospital (Ethical Approval number: MH/RESEARCHERS/2766).

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