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ORIGINAL: Investigating the Outcomes of COVID-19 Paraclinical Parameters among Hospitalized Patients

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ABSTRACT

Introduction: Introduction: COVID-19 has been a global pandemic since the end of 2019, and it is important to determine the complications and mortality of patients according to their paraclinics. Due to the numerous statistical gaps between different studies, in this study, the consequences of COVID-19 were examined according to paraclinical cases in inpatients admitted to Valiasr Hospital in Qaemshahr in 2019-2020.

Material and Methods: This research is in the form of a descriptive-cross-sectional. Blood tests at the time of admission of definite patients with COVID-19 were the basis of the study of patients in the ordinary and special care departments of Valiasr Hospital, Qaemshahr. After obtaining permissions and determining the entry and exit criteria of patients' files, the researcher made a checklist based on the goals of the study variables provided, the information was completed and analyzed by SPSS version 26.

Results: Generally, 67. 1% of patients were hospitalized in ordinary wards and the rest were hospitalized in special care wards. 53.3% of all patients were men. The age group of 71-80 years had the highest frequency. 100% of patients had lung involvement in chest imaging. The results showed that 47% of patients had leukopenia and 34.6% of patients had lymphopenia. The results for PMN showed that only 1.3% of patients had neutropenia, while 12.9% of them were in the normal range. Thrombocytopenia disorder was observed in 6.9% of patients.

Conclusion: Male sex and old age had the most cases of disease and mortality. An increase in the level of CRP, liver enzymes, neutrophilia, leukopenia, lymphopenia, leukocytosis, and thrombocytopenia was among the most important and common paraclinical consequences of COVID-19. Neutropenia, thrombocytosis, and lymphocytosis were not associated with mortality, which requires further studies.

Introduction

Members of the coronavirus family play a role in causing respiratory diseases, including severe diseases. There are dozens of coronaviruses in the world that cause disease in animals. However, only two strains of this family were known to cause disease in humans in the 20th century, including 229E (HCoV-229E) and

OC43 (HCoV-OC43). The SARS-CoV-2 outbreak demonstrated for the first time that animal coronaviruses have the potential to be transmitted from other species to humans and have devastating effects (1). The SARS-CoV pandemic (2002-2003) affected more than 8,000 cases and led to a mortality rate of nearly 10%. In 2019, the SARS-CoV-2, or COVID-19 virus appeared during an outbreak in Wuhan, China, which spread throughout the world and caused a severe pandemic (2). In July 2020, a more infectious viral variant with a G614 amino acid variant replaced the original D614 strain in the S protein as the dominant form in the pandemic. Different viral variants of this strain were observed all over the world, and such strains emerged independently in different geographical areas and then spread widely. Some of these strains showed a higher potential to be transmitted from one person to another or to cause severe illness or death in infected people (3).

The clinical spectrum of the COVID-19 disease is very wide, ranging from asymptomatic infection to mild, moderate, or severe disease requiring hospitalization, oxygen therapy, intensive care, and mechanical ventilation. The symptoms usually appear within 4-5 days of exposure and almost always within 14 days. Symptoms include cough, fever, myalgia, headache, shortness of breath, sore throat, and gastrointestinal symptoms such as nausea, vomiting, and diarrhea (4). Sudden onset of dysgeusia and anosmia (loss of taste and smell) occurs in a significant number of cases and usually disappears within weeks to months. Age is the strongest risk factor for severe COVID-19 outcomes (characterized by the need for hospitalization, intensive care, and mechanical ventilation) (5). Covid-19 deaths occur in people over 45 years of age in more than 95% of cases, and more than 80% of deaths occur in people over 65 years of age. The risk of severe COVID-19 disease increases significantly with increasing body mass index. Moreover, patients with underlying diseases such as cardiovascular diseases, diabetes, hypertension pressure, organ transplant, asthma, etc., are at a high risk of death in case of contracting Covid-19 (6, 7).

Various studies investigated the frequency of paraclinical parameters in Covid-19 inpatients. In a review study of 28 articles (n=4663 patients) in China in May 2020, Zhang et al. (2020) found that the mean age of onset was 48.4 years and 53.3% of patients were male. Also, leukopenia, lymphopenia, thrombocytopenia, elevated C-reactive protein (CRP), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were reported in 24%, 47.9%, 12.6%, 73.6% 21.9% and 22.5% of cases, respectively (8). In another review study of 55 articles (n=8697) in China from January 1 to March 16, 2020, Zhu et al. (2020) found that 53.3% of patients were male. Also, normal leukocytes, leukocytosis, leukopenia, lymphopenia, elevated CRP, and liver dysfunction were reported were reported in 64.7%, 9.9%, 23.5%, 47.6%, 65.9%, and 26.4% of cases, respectively (9).

Furthermore, other related studies have been conducted by Arntz (10), Zhang (11), Li (12), Liu (13), Wang (14), Chen (15), Guan (16).

In addition to damaging businesses and the economy of the affected communities, COVID-19 has led to many psychological harms such as anxiety, depression, isolation, suicide, etc., and has affected the rules and order of people's daily lives due to self-quarantining (17). People with an underlying disease have experienced an exacerbation of the disease symptoms or even died. Although several currently used drugs do not have the proven and approved specific effect on treating COVID-19 symptoms, they have helped reduce the disease complications and improve the general condition of patients, especially the drugs that were proposed for "SARS" and "MERS" in the past. Therefore, an effort has been made to increase information about this virus by determining the frequency of paraclinical risk parameters of COVID-19 outcomes in hospitalized patients.

Methods

This is a descriptive-cross-sectional study that

was conducted on COVID-19 patients admitted to Valiasr Hospital in Qaemshahr. All the medical files of COVID-19 patients admitted to Valiasr Hospital of Qaemshahr from March 5, 2020, to November 5, 2020, were reviewed. Inclusion criteria included a confirmed COVID-19 and a complete medical file. Exclusion criteria also included being diagnosed with a disease other than COVID-19 and incomplete medical file.

Paraclinical tests upon admission have been the basis for investigating the prevalence of paraclinical parameters and prognosis of patients in the general and ICU wards of Valiasr Hospital in Qaemshahr. After obtaining permission and determining the inclusion and exclusion criteria of related patient files, the data were completed by preparing a researcher-made checklist based on the objectives of the study. The aforementioned checklist was prepared based on the review of previous similar studies in different countries and the opinions of respected supervisors and advisors. All the relevant variables were evaluated in this checklist. Therefore, the prognosis of inpatients could be accurately measured based on the paraclinical parameters upon admission. This checklist consists of 12 items and is not against scientific and ethical principles. Then the collected data were entered in the checklist and analyzed using SPSS ver. 26.

Results

Demographic features of the patients are demonstrated in ***Table1***. The results showed that 46.7% of patients were women. In addition, most of the people infected with COVID-19 were in the age range of 71-80. Most of the patients were hospitalized in the ordinary ward and only one patient was in the CCU. People with BMI=25-29.9 had the highest frequency.

Table 1. Demographic features of the patients

Variables		Frequency	Percent (%)
Gender	Female	112	46.7
	Male	128	53.3
Age	0-10	2	0.8
	11-20	1	0.4
	21-30	4	1.7
	31-40	21	8.8
	41-50	29	12.1
	51-60	44	18.3
	61-70	48	20
	71-80	60	25
	81-90	26	10.8
	91-100	5	2.1
Ward	CCU	1	0.4
	ICU	78	32.5
	Ordinary	161	67.1
BMI	<18.4	4	1.7
	18.5-24.9	45	18.8
	25-29.9	59	24.6
	>30	57	23.8
	ND*	75	31.3

* Not mentioned

Clinical results of patients are shown in ***Table2***. The results showed that 47% of patients had leukopenia and 7% had leukocytosis. In addition, 34.6% of patients had lymphopenia. The results for PMN showed that only 1.3% of patients had neutropenia, while 12.9% of them were in the normal range. Thrombocytopenia disorder was observed in 6.9% of patients.

Table 2. Clinical results of patients

Variables			Frequency	Percent (%)
WBC (×1000/µL)	First	0-3.9	34	14.2
		4-11	158	65.8
		>11	44	18.3
		ND	4	1.7
	Last	0-3.9	7	2.9
		4-11	64	26.7
		>11	47	19.6
		ND	122	50.8
Lymphocyte (%)	First	0-24%	153	63.7
		25-45%	75	31.3
		>46%	9	3.8
		ND	3	1.3
	Last	0-24%	83	34.6
		25-45%	29	12.1
		>46%	3	1.3
		ND	125	52.1

Table 2 Continue

PMN (%)	First	0-46%	9	3.8
		47-76%	109	45.4
		77-100%	119	49.6
		ND	3	1.3
	Last	0-46%	3	1.3
		47-76%	31	12.9
		77-100%	77	32.1
		ND	129	53.8
Platelet (×1000/µL)	First	1-139	37	15.4
		140-450	197	82.1
		>450	3	1.3
		ND	3	1.3
	Last	1-139	23	9.6
		140-450	86	35.8
		>450	7	2.9
		ND	124	51.7
CRP (mg/L)	First	0-6	24	10
		> 7	194	80.8
		ND	22	9.2
	Last	0-6	7	2.9
		> 7	17	7.1
		ND	216	90
LDH	First	<259	1	4
		260-500	9	3.8
		>501	21	8.8
		ND	209	87.1
	Last	<259	-	-
		260-500	-	-
		>501	1	0.4
		ND	239	99.6
AST (U/L)	First	<31	60	25
		>31	54	22.5
		ND	126	52.5
	Last	<31	16	6.7
		>31	23	9.6
		ND	201	83.8
ALT (IU/L)	First	<32	75	31.3
		>32	39	16.3
		ND	126	52.5
	Last	<32	19	7.9
		>32	19	7.9
		ND	202	84.2

* Not mentioned

Discussion

A total of 249 patients were initially included in the study, of whom 9 were excluded due to incomplete medical files. Therefore, the results of this study, which was conducted on 240 COVID-19 patients admitted to Valiasr Hospital in Qaemshahr in 2019-2020, showed that 32.5% and 67.1% of the patients were admitted to ICU and general wards were male. A total of 53.3% of all patients were men and the rest were women. The highest and lowest number of patients belonged to 71-80 and below 20-year-age groups, respectively. Besides, 65.41% of the patients were admitted to the general wards, and the rest were admitted to ICUs, and also 100% of the COVID-19 patients had pulmonary involvement in chest imaging.

The prevalence of thrombocytosis in all patients of the present study was 9.6%. While thrombocytosis prevalence was 63% in a study by Pourmohammad (18). However, the same prevalence rate was equal to 4.5%, 5.37%, and 4.5% in studies by Mousavi (19), Yang (20), and Zhang (8), which was more than the present study. Platelets as acute-phase reactants may explain thrombocytosis cases in COVID-19 patients. Further studies are needed in this field. In this study, thrombocytopenia was reported in 16.56% and 19.27% of the COVID-19 patients admitted to the general and ICU wards. In total, thrombocytopenia was reported in 9.6%

of all patients admitted to all wards. The thrombocytopenia prevalence was reported to be 51.9% and 36.2% in studies by Mousavi (19) and Guan (16), which indicates the higher prevalence of thrombocytopenia in these studies compared to the present study. However, thrombocytopenia prevalence was 13%, 13.42%, 12.6%, 17%, 5%, 12%, 17%, 22.5%, and 17.6% in the studies by Pourmohammad (18), Yang (20), Zhang (11), Wan (21), Houng (22), Chen (15), Li (12), Zhang (11), respectively. The results of these studies showed that the prevalence of thrombocytopenia was close to or less than our study.

The presence of thrombocytopenia in COVID-19 patients is justified as follows: Following a viral infection, a cytokine storm causes damage to bone marrow progenitor cells and leads to a decrease in the production of platelets. Also, damage to the pulmonary capillary networks leads to megakaryocyte rupture, which in turn affects the release of platelets in the pulmonary circulation and indirectly reduces the synthesis of platelets in the systemic circulation. Also, COVID-19 increases the level of autoantibodies and immune complexes, which leads to the specific destruction of platelets by the immune system. These immune complexes are deposited on the surfaces of platelets and are recognized by the reticuloendothelial system, and, therefore, platelets are destroyed as a target tissue. Antibodies produced during viral infection may bind specifically to antigens on platelets through molecular mimicry and lead to increased destruction of platelets. Also, the increased pulmonary platelet accumulation leads to the microthrombosis and consumption of platelets. Further studies are needed in this field (23, 24).

In this study, 32.5% and 67.1% of COVID-19 patients admitted to ICU and general ward had lymphopenia. In total, lymphopenia was reported in 34.6% of all patients admitted to all wards. The prevalence of lymphopenia in studies by Yang, Chen, and Sao was 35.57%, 35%, and 8.9%, respectively, which was less than the present study. But the prevalence of lymphopenia in studies by Pourmohammad (18), Mousavi (19), Zhang (8), Zhou (9), Wan (21), Guan (16), Wang (14), Liu (13), Li (12), and Arntz (10) was 57. 5%, 52.7%, 47.9%, 47.6%, 64.5%, 50%, 63%, 83.2%, 3.70%, 72.3%, 69%, 69.9%, 67%, respectively, which indicates heterogeneous reports of the lymphopenia prevalence in different studies. This elevated lymphopenia rate (especially the decrease in the population of T cells) may be due to Inflammatory cytokine storms such as TNF-α and IL-6 as well as Fas-FasL interactions that are closely related to lymphopenia, and treatment with tocilizumab, an IL-6 receptor antagonist, increased number of circulating lymphocytes. Also, COVID-19 infection can lead to T-cell exhaustion by increasing the expression of cell exhaustion markers (such as PD-1, Tim-3, and NKG2A) and decreasing the expression of activation markers (such as CD107a and IFN-γ). Also, the SARS-CoV-2 virus may directly infect and involve T cells and interfere with the expansion of T cells in such a way that the expression of some genes involved in the activation and function of T cells, such as MAP2K7 and SOS1, decreases in T cells of patients with severe covid-19 (25, 26). Further studies are needed in this regard.

In this study, 1.3% of COVID-19 patients admitted to ICU and general wards had lymphocytosis, and in total, lymphocytosis was reported in 3.75% of patients. The lymphocytosis prevalence was 37.5% in Cao's study, which was more than the present study; however, in other reviewed studies, there was no report of lymphocytosis despite reporting changes in other blood cells. The cause of this phenomenon requires further studies (27).

In this study, 6.02% of COVID-19 patients admitted to ICU and general wards had neutropenia, and the total neutropenia rate was 1.3%. The neutropenia prevalence in studies by Mousavi et al. and Zhang was 21.4% and 17.6%, respectively, which was more than the present study. However, in other reviewed studies, there was no report of neutropenia despite changes in other blood cells (11, 19). In this study, 99.6% of COVID-19 patients

admitted to ICU and general wards had neutrophilia, and the total rate was 50.83%. The neutrophilia prevalence was 4%, 2.6%, and 19% in studies by Yang et al (20), Zhang et al (8), and Cao et al (27), respectively, which was different from our study. However, the neutrophilia prevalence in Chen et al.'s study (12) was 38%, which was similar to the present study. The cause of neutrophilia in SARS-CoV-2 infection is due to the increased number of neutrophils in the epithelium of the nasopharynx and subsequently in the more distal areas of the lung, which may be attributed to changes in gene expression in these cells (28-30).

The results of the present study showed that 14.64% and 15.66% of COVID-19 patients admitted to ICU and general wards had leukopenia, respectively, and the total rate was 15%. The leukopenia prevalence was 9%, 15.5%, and 20.7% in studies by Chen, Sao, and Wan, respectively, which was similar to the present study. But the leukopenia prevalence was reported to be 28%,24.16, 58%, 24%, 23.5%, 29.4%, 25%, 33.7%, 37.2%, and 27% in studies by Pourmohamad (18), Yang (20), Li (12), Zhang (8), Zhu (9), Hong (22), Guan (16), Liu (13) and Zhang (11), respectively, which was not consistent with the results of the present study. Leukopenia can be caused by components of leukocyte count with predominance of lymphopenia or predominance of neutropenia.

The results of the present study showed that 21.01% and 16.86% of COVID-19 patients admitted to ICU and general wards had leukocytosis, respectively and the total prevalence was 19.58%. The leukocytosis prevalence was 18.3%, 24%, 19%, and 21% in studies by Pourmohammad (18), Chen (15), and Liu (13), respectively, which is similar to the present study. The leukocytosis prevalence was reported to be 1.34%, 9.9%, 6.6%, 5.9%, 12.1%, 10.4%, and 30% in studies by Yang (20), Zhu (9), Wan (21), Guan (16), Zhang (8), Cao (27), and Hong (22), respectively, which indicates heterogeneous reports of the prevalence of leukocytosis in covid-19 patients. Leukocytosis can be caused by components of the leukocyte count, including lymphocyte predominance or neutrophil predominance.

The results of the present study showed that 91.71% and 81.92% of COVID-19 patients admitted to ICU and general wards had elevated CRP, respectively. The prevalence of elevated CRP in the studies by Yang, Zhou, Li, and Guan was 55.03%, 65.9%, 44.3%, and 60.7%, respectively, which was not consistent with the results of the present study. But the same prevalence was 79%, 90%, 73.6%, 86%, 83.9%, 93%, 88% and 78.4% in the studies by Pourmohammad (18), Mousavi (19), Zhang (11), Chen (12), Liu (13), Zhang (8) and Cao (27), respectively, which was similar to the present study (12-7, 15, 16, 18-20, 22). The elevated CRP seems to be due to higher production of inflammatory cytokines and lung tissue damage in COVID-19 patients. In severe COVID-19, where the lung tissue is more damaged and the arterial blood oxygen saturation level drops below 90, the CRP value is higher than in other milder forms of COVID-19 (31, 32). Further studies are warranted in this field.

In this study, 15.92% and 30.12% of had an elevated AST level, respectively upon admission. Also, 10.82% and 22.89% of COVID-19 patients admitted to ICU and general wards had an elevated ALT level, respectively. Elevated ALT and AST were reported to be 12.08% and 18.12% in Yang's study (20), 22.5%, and 21.9% in Zhang's study (11), respectively. Wan (21) and Hong (22) reported elevated AST in 22.2% and 37% of cases, respectively. Elevated LT and AST levels were also reported in 21.3% and 22.2% of cases in Guan's study (16), 28% and 35% of cases in Chen's study (15), 17% and 24% of cases in Li's study (12),4.18% and 28.5% of cases in Zhang's study, and 10.8% and 17.4% of cases in Cao's study, respectively. Liver dysfunction was also reported in 26.4% and 38% of cases in studies by Zhu and Arntz, respectively (9, 10). The results of these studies were consistent with the present study. The causes of increased liver enzymes during COVID-19 seem to be direct damage to the liver, associated inflammatory responses, congestive hepatopathy, liver ischemia, drug-induced liver damage, and muscle destruction

(33, 34).

In this study, the most affected age group was 71-80 years old and the average age of infection was 71 years old. The results of other studies also showed that the age of infection was 47 to 70 years (18-20), which can be due to the increased elderly population in the studied areas, lifestyle and little attention to health issues in older adults, and weaker immune systems in old age. The low number of hospitalizations in age groups under age 20 may be due to the limitations in admitting pediatric patients and the referral of most of these patients to a more equipped pediatric hospital.

Also, 52.5% of all patients were male. In other studies, the percentage of male COVID-19 patients varied from 44.5 to 72% (10-12, 27). The lower prevalence of the disease in women seems to be due to the expression of a series of genes related to the body's immune system on the X chromosome, which reduces the level of viral load and inflammation rate compared to men. The lower levels of ACE2 in women compared to men the location of the ACE2 gene on the X chromosome (males being homozygous and women being heterozygous) and the effect of testosterone on ACE2 levels are effective in this regard (35, 36).

Moreover, 100% of patients had lung involvement in chest imaging. Mousavi et al (19) reported that 65.8% of patients had pulmonary involvement in chest imaging, which was consistent with the present study. However, covid-19 patients had pulmonary involvement in more than 86% of cases in the studies by Yang (20), Wan (21), Hong(22), Guan (16), Wang (14), Liu (13), Arentz (10), and Cao (27), the, which were similar to the present study. According to the practical definition, patients with lung involvement in chest imaging and positive PCR tests were selected as participants with confirmed COVID-19 in the present study. Besides, respiratory involvement was the dominant form when the patients were infected. In addition, the majority of patients had respiratory problems caused by Covid-19 when they contracted this disease. Also, the presence of pulmonary involvement in chest imaging is related to the time interval between infection and imaging.

Conclusion

Overall, since various factors can indicate the severity of the disease and the subsequent mortality, the male gender and old age account for the most cases of infections and the subsequent mortality, and develop the severe form of the disease more frequently than other people. Also, results of the laboratory tests showed that an increase in CRP, liver enzymes, neutrophilia, leukopenia, lymphopenia, leukocytosis, and thrombocytopenia are among the most important and common paraclinical outcomes of COVID-19. Neutropenia, thrombocytosis, and lymphocytosis were not associated with mortality in the present study, although this issue should be further studied in a larger statistical population. The small sample size and incomplete information in the medical files of COVID-19 inpatients are among the limitations of this study. It is suggested to perform further studies with a higher sample size and at the national and international level to compare the results between different cities of a country and different countries with each other. It is also suggested that other variables that may have an effect (such as the period between symptom onset and doctor visit, BMI, etc.), should be investigated. It is also suggested that more comprehensive studies be conducted on the prognostic value of each of the paraclinical indices studied in the present research.

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Conflicts of interest

The authors declare no conflict of interest.

Authors' contributions

All authors were involved in the conception and design, analysis and interpretation of the

data, drafting of the manuscript and revising it critically for intellectual content, approved the final version for submission, and agreed to be accountable for all aspects of the work.

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