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The Comparative Evaluation of Hospitalized Elderly Patients with COVID-19 from the Onset of the Disease to Recovery and Death in Iran

Barati Barat[1], Kaydani Masoumeh[2], Ahmadpour Fatemeh[3] Kalantar Mojtaba[4], Farhadi Birgani Fariba[1]

1. Department of Radiologic Technology, Shoushtar Faculty of Medical Sciences, Shoushtar, Iran
2. Department of occupational Health, Shoushtar Faculty of Medical Sciences, Shoushtar, Iran
3. Department of clinical biochemistry, Ahvaz university of Medical Sciences, Ahvaz, Iran
4. Department of Occupational Health, Shoushtar Faculty of Medical Sciences, Shoushtar, Iran

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Abstract

Background & Objectives: Numerous studies have shown that the risk of death is higher in elderly patients with COVID-19. In Iran, due to the growth of the elderly population and the prevalence of underlying diseases, it is necessary to pay attention to this age group of patients. In this study, clinical, radiological, PCR, and laboratory data of elderly patients with COVID-19 were collected and analyzed in two groups of recovered and dead patients.

Materials & Methods: This is a retrospective study of 196 consecutive elderly patients with COVID-19 hospitalized from March 21, 2020, to April 3, 2020, and their follow-up until April 23, 2021. Clinical characteristics, laboratory results, PCR, chest CT scans and Hounsfield Unit data were collected and analyzed in two groups of recovered and dead patients. Obtained Data were analyzed using SPSSv22.0 and MATLAB-R2017 software.

Results: The results showed that there were no specific symptoms to distinguish the death group from the recovery group. Significant differences were observed between the two groups for red blood cell counts, hemoglobin, MCHC and MCV levels, bilirubin, aminotransferase levels, CRP, white blood cells, serum BNU, creatinine and PT coagulation index. The concentrations of VBG (HCO_3) and VBG (PCO_2) in the deceased patients suggest compensated respiratory alkalosis. CT sensitivity is 100% for patients in advanced and severe stages of the disease.

Conclusion: The patients in the death group had more underlying diseases than the recovered group. COVID-19 patients are more likely to die when they have both diabetes and cardiovascular disease.

Keywords: Clinical Characteristics, Chest CT scan, COVID-19, Elderly patients, Hounsfield Unit, PCR

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Introduction

COVID-19 is a global pandemic with acute respiratory symptoms caused by the new coronavirus (SARS-CoV-2), which is highly contagious and its evolution is still unknown (1, 2). The first case of this disease was reported in Wuhan, China, which quickly spread around the world (3, 4) and at present it is a serious challenge to public health (5). A comparison between Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) with Coronavirus Disease 2019 (COVID-19) indicated that this virus is more unknown and less lethal at the same time (6). COVID-19 can cause symptoms such as fever, cough, shortness of breath, fatigue, etc.

Corresponding Author: Farhadi Birgani Fariba, Department of Radiologic Technology, Shoushtar Faculty of Medical Sciences, Shoushtar, Iran
Email:farhadi.f92@gmail.com

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In the infected patients and may lead to severe acute respiratory syndrome (SARS) and, in severe cases, it can lead to death (7-9). Existing evidence suggests that, during the incubation period, patients without symptoms can also transmit the virus to others (10, 11). Three common diagnostic methods are used to detect COVID-19 in a complementary way, including real-time fluorescence (RT-PCR), computed tomography (CT), and laboratory data (12). Chest CT scan is an important factor in identifying patients infected with COVID-19 (13-15). Common CT findings for COVID-19 include ground glass opacity (GGO) and consolidation, which have also been found in other lung infectious diseases such as SARS and MERS. In other words, there are no specific findings for COVID-19 in the CT images (16). CT scan information includes Hounsfield unit (HU) or CT numbers obtained by the following equation:

$$HU_{tissue} = \frac{\mu_{tissue} - \mu_{water}}{\mu_{water}} \times 1000, \qquad (1)$$

Where μ_{water} and μ_{tissue} are the attenuation coefficients of water and tissue, respectively. HUs range from -1000 to +1000 (-1000 is related to air and +1000 is related to dense bone and high-density materials) (17).

The risk factors for COVID-19-related mortality include old age, male gender, ethnicity and underlying diseases such as hypertension, cardiovascular disease, obesity, diabetes, tumors, immunodeficiency, liver and kidney diseases and chronic lung diseases (18, 19). Considering the growth rate of the elderly population in Iran and the high prevalence of underlying diseases (such as cardiovascular disease, hypertension, diabetes, etc.), it is necessary to pay more attention to the elderly population of Iran.

Although several vaccines have been developed to protect against COVID-19, none of them provide 100% safety. Given that we have very little knowledge of the coronavirus and high-risk groups, if we encounter another type of coronavirus in the future, we have the same problems. This study intends to comprehensively evaluate the clinical signs, laboratory data, PCR, chest CT images and Hounsfield Unit values of COVID-19 lesions in two groups of dead and recovered patients with a fourteen-month follow-up.

Material and Methods

Clinical Characteristics

The present study was approved by the Ethics Committee of Shoushtar University of Medical Sciences and Health Services (Ethical code: "IR.SHOUSHTAR.REC.1399.004"). In this retrospective study, 196 consecutive patients with COVID-19 who were hospitalized in Razi Hospital in Ahvaz and Khatam Al-Anbia Hospital in Shoushtar, Khuzestan Province, Iran were selected. The demographic characteristics, laboratory data and CT scans were collected on the admission day (two weeks: from March 21, 2020, to April 3, 2020). The patients were followed for recovery or death (14 months: March 21, 2020, to April 23, 2021).

RT-PCR

Nasopharyngeal swab specimens were collected from the patients suspected of having this infection for extracting RNASARS-COV19. Then, the specimens were placed into a collection tube containing 150 microliters of the virus storage solution, and within 2 hours, Total RNA was extracted by using the Extraction and Purification Kit (SinaClon). The sequence of primers and probe used to propagate 2 target genes were as follows: (Target 1 ORF1ab): Forward primer CCCTGTGGGTTTTACACTTAA; Reverse primerACGATTGTGCATCAGCTGA; and the probe5′-VIC CCGTCTGCGGTATGTGGAAAGGTTATGG-BHQ1-3′.

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Target 2 (N): forward primer GGGGAACTTCTCCTGCTAGAAT;reverse primer CAGACATTTTGCTCTCAAGCTG; and the probe5′-FAM-TTGCTGCTGCTTGACAGATT-TAMRA-3′.

The real-time RT-PCR assay was performed to detect nucleic acid of SARS-COV19 according to the SinaClonKit protocol. The reaction mixture included 12 microliter reaction buffer, 4 microliter enzyme solution, 4 microliter Solution Probe primers, 3 µL diethyl pyrocarbonate-treated water and 2 microliter RNA template. Real-time PCR (also known as quantitative polymerase chain reaction (qPCR)) assay was performed under the following conditions: incubation for 15 min at 50°C and 5 min at 95°C, 40 cycles of denaturation for 15 s at 94°C, and extending and collecting fluorescence signal at for 45 s 55°C. Ct-value 40 or more is defined as a negative result, and Ct-value less than 37 is defined as a positive result. A medium load, as a Ct-value of 37 or less than 40, requires confirmation through re-testing.

Chest CT scan

HRCT images were obtained by the Siemens SOMATOM Sensation 64 CT scanner. Scanning parameters include 120 kVp; 100–200 mAs; pitch, 1; slice thickness, 1.5 mm; matrix size, 512 × 512; and pixel size, 0.5–0.7 mm, taken in deep breath mode with WW, 1290 and WL, 420. Regions of interest (ROI) with a diameter of 1 to 3 mm were drawn on COVID-19 lesions in different stages, and average Hounsfield unit values were recorded.

Data Analysis

SPSS Statistics 22.0 software IBM was used for statistical analysis. Categorical variables were expressed as frequency and percentage and were analyzed by Chi-square test. Continuous variables were described as median and interquartile range (IQR) and were analyzed using Kolmogorov-Smirnov and Mann-Whitney U tests. A significance level of 0.05 was considered. Also, chest CT image histograms were drawn using MATLAB R2017a software.

Results

Clinical Manifestations

Clinical information including age, gender, symptoms, the intensive care unit (ICU), and underlying disease was compared in two groups of death and recovery. The results are shown in Table 1. In men, recovery was 9% lower and death was 23.4% higher than in women. The most common symptoms in both groups included shortness of breath, cough, and fever, which did not differ significantly. The onset of symptoms until recovery and death was 4 to 11 and 10 to 21 days, respectively. Of the 47 patients who died, 19 (40.4%) were hospitalized in the ICU.

Table 1. Summary of Patient Characteristics

	% (No.)			
Parameter	Total (N=196)	Recovered (n=149)	Death (n=47)	p-value
Onset of symptom to recovery/death, median (IQR), d	9 (3-14)	6 (4-11)	15 (10-21)	0.808
Age, median (IQR), y	62 (57-94)	61 (57-77)	68 (60.7-94)	0.006
Gender				
Male	49.5 (97)	45.6 (68)	61.7 (29)	0.055

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	Female	50.5 (99)	54.4 (81)	38.3 (18)	
Symptoms					
	Shortness of breath	55.1 (108)	57.0 (85)	48.9 (23)	0.307
	cough	54.6 (107)	57.7 (86)	44.7 (21)	0.088
	Fever	50.5 (99)	51.7 (77)	46.8 (22)	0.533
	Fatigue	27.6 (54)	28.2 (42)	25.5 (12)	0.704
	Anorexia	22.4 (44)	17.4 (26)	38.3 (18)	0.603
	Myalgia	19.4 (38)	18.1 (27)	23.4 (11)	0.436
	chills	12.2 (24)	14.7 (22)	4.3 (2)	0.063
	Nausea	9.2 (18)	8.7 (13)	10.6 (5)	0.680
	Chest pain	8.2 (16)	9.4 (14)	4.3 (2)	0.043
	Headache	8.2 (16)	10.1 (15)	2.1 (1)	0.080
	Dizziness	7.7 (15)	8.1 (12)	6.4 (3)	0.212
	vomiting	7.1 (14)	7.4 (11)	6.4 (3)	0.516
	Sputum	6.1 (12)	4.0 (6)	12.8 (6)	0.028
	Diarrhea	5.1 (10)	4.7 (7)	6.4 (3)	0.662
	Sore throat	3.6 (7)	2.7 (4)	6.4 (3)	0.155
	hypotension	3.1 (6)	4.0 (6)	0.0 (0)	0.702
	Lose taste	3.1 (6)	3.4 (5)	2.1 (1)	0.071
	Loss smell	2.0 (4)	2.7 (4)	0.0 (0)	0.332
	eye redness	2.0 (4)	2.7 (4)	0.0 (0)	0.332
	Nasal congestion	1.0 (2)	1.3 (2)	0.0 (0)	0.423
	blood Vomiting	1.0 (2)	1.3 (2)	0.0 (0)	0.423
	Abdominal pain	0.5 (1)	0.7 (1)	0.0 (0)	0.677
	ICU	13.3 (26)	4.7 (7)	40.4 (19)	0.000
	Underlying diseases	61.2 (120)	55.1 (82)	80.8 (38)	0.011

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Table 2 lists the underlying diseases for both death and recovery groups. In the death group, 23% had no underlying disease and were in the age range 59.6. Most deaths were in patients with cardiovascular and diabetic problems together.

Table 2. Underlying diseases

	% (No.)
Recovery (n=82)	Cardiovascular disease 17.1 (14), diabetes 15.9 (13), renal 14.6 (12) lung infection 12.2 (10), hyperlipidemia 8.5 (7), cardiovascular disease and diabetes 6.1 (5), liver disease 4.8 (4), brain tumor surgery 3.7 (3), myocardial infarction 3.7 (3), rheumatoid arthritis 3.7 (3), migraine 3.7 (3), prostatitis 2.4 (2), Alzheimer's 2.4 (2), gout 1.2 (1)
Death (n=38)	Cardiovascular disease and diabetes 44.7 (17), cardiovascular disease 26.3 (10), Diabetes 21.1 (8), liver disease 2.6 (1), brain tumor surgery 2.6 (1), pemphigus 2.6 (1)

Laboratory Results

The median and interquartile range of laboratory parameters are shown in Table 3. The results suggested that there was a significant relationship between the death and recovery groups for the following factors: WBC, RBC, Hb, MCV, MCHC, PT, AST, ALT, direct bilirubin, total bilirubin, BUN, Creatinine, LDH, serum albumin, VpO_2, $VFIO_2$, $VHCO_3$, BE and BB. Compared to the recovered group, the values of white blood cells in the death group showed a significant increase in comparison with normal range. The percentage of hematocrit was decreased in patients of the death group. There was no significant difference in the reduction of hematocrit percentage between the death group and the recovered group. The Prothrombin Time (PT) in the death group increased significantly compared to the recovery group and the normal value. The ESR value in both groups were significantly higher than the normal values. The AST enzyme level in the death group was higher than the normal values. The ALT enzyme level in the death and recovery group was almost normal, but the difference was meaningful between the death group and the recovery group. BNU level in the death group was higher than in the recovered group and the normal range, and this difference was also significant in both studied groups. LDH level in the death and recovery group was higher than the normal value (M: 235-470 and F: 230-460), and there was a significant difference between the two groups.

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Table 3. Laboratory results of Patients Infected with covid-19

		Median (IQR)			
factor	Normal range	Total (N=196)	Recovered (n=149)	Dead (n=47)	p-value
WBC, $10^3/\mu L$	4-10	7.7 (5.7-11.3)	7.2 (5.5-9.9)	10.6 (6.9-13.9)	0.000
RBC, $10^6/\mu L$	4.5-5.9	4.1 (3.7-4.5)	4.2 (3.8-4.5)	3.8 (3.3-4.2)	0.002
Hb, g/dL	12-16	11.8 (10.4-13.1)	11.9 (10.6-13.4)	11 (9.9-12.6)	0.011
Hct, %	42-48	33.7 (30.2-37.8)	33.9 (30.8-38)	33.1 (28.6-36.6)	0.087
MCV, fL	80-98	83 (78.4-86.5)	82.5 (77-86.2)	84.7 (80.6-90.7)	0.022
MCH, pg	27-32	28.9 (27.1-30.5)	28.9 (27.2-30.4)	29.4 (26.8-31.8)	0.451
MCHC, g/dL	31.5-36	34.7 (33.8-35.6)	34.8 (34-35.7)	34.3 (33.4-35.2)	0.016
MPV, fl	7.5-11.5	8.7 (8.1-9.1)	8.6 (8-9.2)	8.9 (8.3-9.6)	0.083
PT, Seconds	12	13 (12-14)	12.9 (12-13)	14 (12-17)	0.000
ESR, mm/h	1-15	41 (25-65)	40 (23.5-65)	51.5 (25.7-73.7)	0.336
AST	5-40	39.5 (27-65.7)	38 (24.5-56)	64 (32.7-93.2)	0.001
ALT	0-40	20.5 (13-39.7)	20 (12-35.5)	30.5 (16-62)	0.013
Direct bilirubin	0.1-0.4	0.2 (0.2-0.4)	0.2 (0.2-0.3)	0.3 (0.2-0.7)	0.000
Total Bilirubin	0.4-1.2	1 (0.8-1.4)	1 (0.7-1.3)	1.4 (0.9-2)	0.000
BUN, mg/dL	6-21	19 (13-33)	17 (12-26)	35 (22-49.5)	0.000
Creatinine, mg/dL	0.6-1.5	1.1 (0.8-1.5)	1 (0.8-1.3)	1.4 (1-1.9)	0.000
LDH	230-470	588 (439-772)	547 (431-699.5)	732 (573-1005)	0.000
Creatine Phosphokinase (CPK)	M: UP TO 195 F: UP TO 170	94 (50-217.7)	89 (50-176.5)	143.5 (53.5-513.2)	0.141
BS, mg/dL	70-120	122.5(98-180)	117.5 (96.5-171.2)	158 (109.5-190.7)	0.064
Serum Albumin, g/dL	3.5-5	3.7 (3.1-4.2)	4 (3.6-4.5)	3 (2.7-3.7)	0.001

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VGB					
PCO_2, mmHg	40-50	42.7 (36.9-48.2)	43.1 (36.9-48.5)	40.5 (33.4-46.9)	0.083
PO_2, mmHg	30 - 50 80-100	29.6 (21.6-44.1)	28.3 (20.7-38.1)	37.1 (22.8-68.2)	0.010
FIO_2, %		21 (21-21)	21 (21-21)	21(21-21)	0.015
HCO_3-act, meq/L	22 – 27	25.1 (21.4-29.3)	25.5 (22.6-29.3)	23.05 (18.05-28.2)	0.027
HCO_3-std, meq/L	22 – 27	23.5 (21.4-26.5)	23.8 (21.9-(-26.5))	21.4(19.4-26)	0.028
BE meq/L	(-2) – (+2)	0.2 ((-2.2) -3.9)	0.6 ((-1.5)-3.9)	-4.3((-6.8)-2.4)	0.019
BB, Mmol/ L	42	48.2 (45.8-51.9)	48.6 (46.5-52.1)	43.5 (40.9-48.9)	0.011
Temperature, C		37 (37-37)	37 (37-37)	37 (37-37)	0.590
PH, IU/L	7.3-7.4	7.3 (7.3-7.4)	7.4 (7.4-7.4)	7.3 (7.3-7.4)	0.094

PCR and CT findings

To compare CT and PCR diagnostic methods, their sensitivity was obtained. As can be seen in Table 4, 67of the 196 patients studied had a false-negative PCR, 15 of whom were in the death group and 52 in the recovered group. Among all patients, 8 had false-negative CTs, of whom 2 were in the death group and 6 in the recovery group, who had no symptoms in the CT and their CT was normal. For both groups, the sensitivity of chest CT scan was higher than PCR.

Table 4. The Comparison of CT and PCR

		Total (N=196)	Recovery (n=149)	Death (n=47)
PCR				
	False negative % (No.)	34.2 (67)	34.9 (52)	31.9 (15)
	sensitivity	65.8%	65.1%	68.1%
CT				
	False negative % (No.)	4.1 (8)	4.1 (6)	4.3 (2)
	sensitivity	95.9%	96%	95.7%

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To evaluate and compare CT scan manifestations in the two death and recovered groups, the findings were divided into three stages (Figure 1).

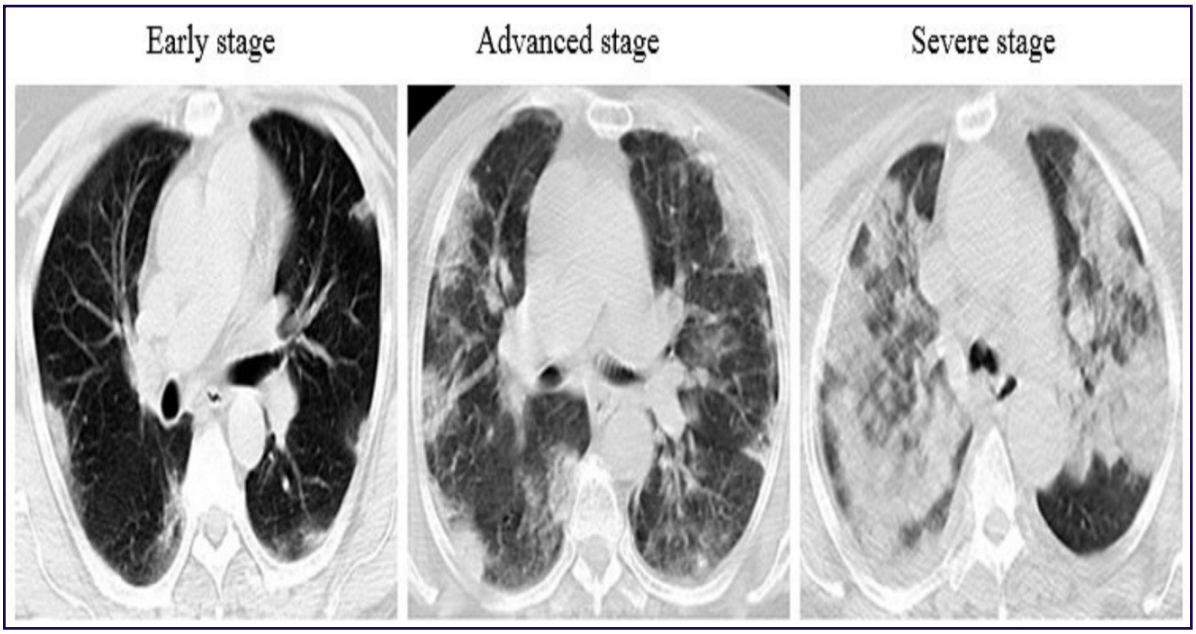

Figure 1. The stages of COVID-19

As shown in Table 5, early stage, single or multiple ground glass is mostly seen as peripheral and bilateral. Sometimes, due to the thickening of the septa, crazy paving appears in the ground glass opacity background. In advanced stage, lesions of previous stage become wider and denser, and condensation occurs. In some cases, the air bronchogram is observed in the background of condensation. In severe stage, the disease progresses further and diffuse consolidation occurs, which can cover most of the lung and appear as white-out lung. A meaningful relationship was reported between the death group and the recovered group in the three stages. The median time from the first CT scan to recovery and death was 3 to 8 days and 1 to 14 days, respectively, although in rare cases, this interval lasted 1 to 3 months.

Table 5. CT findings in initial chest CT scan

	% (No.)			
	Death (n=47)	Recovery (n=149)	Total (N=196)	P-value
stage				
Early stage (single/multiple GGO septal thickening crazy paving peripheral distribution)	42.3 (83)	54.4 (81)	4.3 (2)	0.000

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Advanced stage (GGO with consolidation Air bronchogram)	35.2 (69)	41.6 (62)	14.9 (7)	0.012
Sever stage (Diffuse consolidation Whited out lung)	18.4 (36)	0.0 (0)	76.6 (36)	0.000
Without findings	4.1 (8)	4.1 (6)		0.701
First CT scan to recovery/death, median (IQR), d	4 (2-11)	4 (3-8)	4.3 (2)	0.677

Hounsfield unit values

The results of Hounsfield unit values of ROIs are listed in Table 6. The intensity histogram results showed the intensity range of 30 to 120, 70 to 170 and 150 to 220 for early, advanced and severe stages, respectively.

Table 6. The Hounsfield unit value of COVID-19 stages

		HU: Median(IQR)
normal		-934 (-1024 t0 -830)
suspect		-810 (-856 to -786)
Stages		
	early	-625 (-795 to -413)
	advanced	-317 (-523 to -226)
	severe	-180 (-274 to -49)
Findings		
	GGO	-554 (-790 to -485)
	Consolidation	32 (-183 to 132)

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For instance, Figure 2 shows CT images and intensity histograms of a patient who had two CT scans taken at one-week interval. As can be seen, in this special case, it took one week for the disease to progress from suspected stage to severe stage. For early and severe stages, the median (IQR) values of HU related to ROIs were -712.8 ± 117.2 and -177.1 ± -107.6, and the intensity histogram range was 50 to 100 and 150 to 200, respectively.

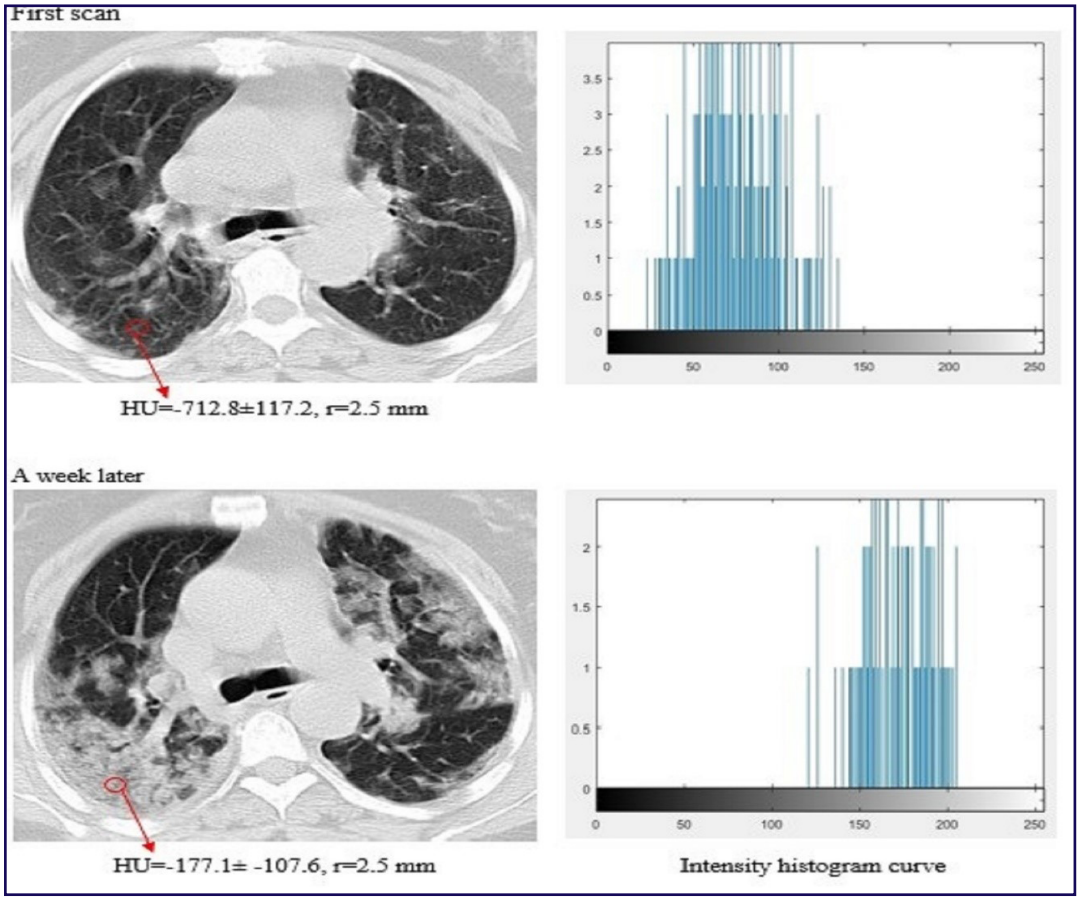

Figure 2. A 74-year-old female patient with symptoms including fever above 38 degrees and cough. In the initial scan, the disease was in suspected stage, and a week later, the disease progressed to severe stage. A ROI with a diameter of 2.5 mm is drawn on the area involved in both images and the Hounsfield unit values are displayed. Also, an intensity histogram related to the ROIs is presented.

Re-infecting patients

Of the 196 patients studied, 12 were re-infected with COVID-19 About four to six months after the first infection. 3 of them were admitted to the ICU and died and 9 recovered. All re-infected patients had headaches. In the CT images of the recovered patients, only GGO was observed and in two cases there were no manifestations. All three deceased patients had cardiovascular disease. The time interval from onset of the disease to recovery or death in the re-infection were shorter than in the first infection cases (about a week).

Discussion

Clinical Manifestations

The death group was in a higher age range than the recovered group, and there was a significant difference between these two groups. In a study, Zhang and colleagues (2020) showed that people over 60 years old have a higher risk of receiving treatment methods such as admission to the ICU and ventilator and death (18). The comparison between the

two groups indicates that the patients in the death group had more underlying diseases than the recovered group, and there is a significant difference between the two groups. In a study by Deng and colleagues (2020), most of the individuals who died had an underlying disease, and underlying diseases such as high blood pressure and heart disease were the most common among the patients who deceased, which is consistent with the findings of the present study (19).

Laboratory Result

In this study, a significant reduction in red blood cell counts, hemoglobin, MCHC and MCV levels was observed in the patients who died compared to the recovered patients. In a meta-analysis study, Mark S. Lensney et al (2020) indicated that the decrease in hemoglobin was significantly associated with the severity of COVID-19. On the other hand, a decreased RBC count in critically ill patients may be due to the lysis of RBC by the virus (20, 21). Also, the results showed that bilirubin and aminotransferase levels in COVID-19 patients who deceased were significantly higher than recovered. Other studies have shown that even some critically ill patients had twice as many aminotransferases and bilirubin compared to the patients who recovered. The first suggestion is liver damage, although no severe liver damage has been observed in clinical trials in the studies, and this may be due to the high expiratory, positive pressure and biliary obstruction caused by right hepatic arterial pressure or it may be due to drug-induced liver damage. Several studies have shown that high levels of creatinine kinase and lactate dehydrogenase are strongly associated with illness severity.

According to our study, in patients who died, LDH and creatinine kinase were significantly increased and were higher compared to the recovered patients. Hence, even an increase in aminotransferases may not be limited to the liver and, like other severe influenza infections, can be caused by myositis (22). According to the present study, the levels of CRP and white blood cells in died patients is significantly higher than in recovered patients. According to Shaboshi et al (2020), inflammatory response markers, i.e. CRP, procalcitonin and leukocytes were significantly higher in patients suffering from heart damage, and it can be due to increased release of necrotizing inflammatory cytokines and death of heart cells (23). According to our study, serum BNU and creatinine levels and PT coagulation index in the deceased patients are significantly higher than in the recovered patients. According to Yichm Cheng et al (2020), renal disorders, including high BUN level, protein excretion, hematuria and high urinary creatinine, age over 65 years old, disease severity, leukocyte count above 4×10^9 /L and low lymphocyte count are directly related to mortality (24). Multiple organ involvement, including the liver, gastrointestinal tract, and kidney, was observed during the course of SARS in 2003 and COVID-19 in 2020 (25). Multiple organ involvement is also seen in our study. Based on a cohort study, approximately 10,000 adults with a high ratio of albumin to creatinine are associated with a higher risk of death (26) in such a way that even patients with renal disorders have a higher risk of death than patients with lung infection and pneumonia (27). Studies show that the level of virus accumulation in kidney cells than the lungs is higher due to the higher expression level of the receptor level of this virus, i.e. ACE2 levels, (28). Another possible cause may be due to the effect of cytokines induced by the virus, hypoxia, shock, or rhabdomyolysis on the kidney and its damage. There is also a marked increase in creatinine kinase levels in COVID19 patients, which confirms muscle damage (29), as can be seen in the present study. According to the results of our study, the concentrations of VBG (HCO_3) and VBG (PCO_2) in the deceased patients suggest compensated respiratory alkalosis, which can indicate

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hyperpnoea, increased respiration, decreased blood CO_2 and, for compensating it, decreased concentration of HCO_3, in the deceased patients.

PCR and CT-scan

Our results showed that, CT sensitivity is 100% for patients in advanced and severe stages of the disease. Most deceased patients are in severe and advanced stages. 2 of the deceased patients showed no signs of COVID-19 in the initial CT, and the next time they got CT again and their CT findings were in severe stage. In the deceased patients the median time from emergence of symptoms to death was 10 to 21 days, so it is recommended that patients with symptoms such as shortness of breath, cough and fever, who have a positive PCR test and a normal CT scan, must be followed to prevent the disease from progressing. The patients with no underlying disease were more likely to reduce CT from advanced stage to early stage and be discharged from hospital (Figures 3 and 4). The underlying disease has a significant impact on the progression of the disease and the death of patients. In Figures 5 and 6, the CT images of two patients are shown, in which early stage was developed to advanced and severe stages in approximately 2 months and both patients died. In a study, Yang and colleagues indicated that pleural effusion occurs in severe stage (30). In addition to severe stage, we also observed plural effusion in early and advanced stages (Figure 7).

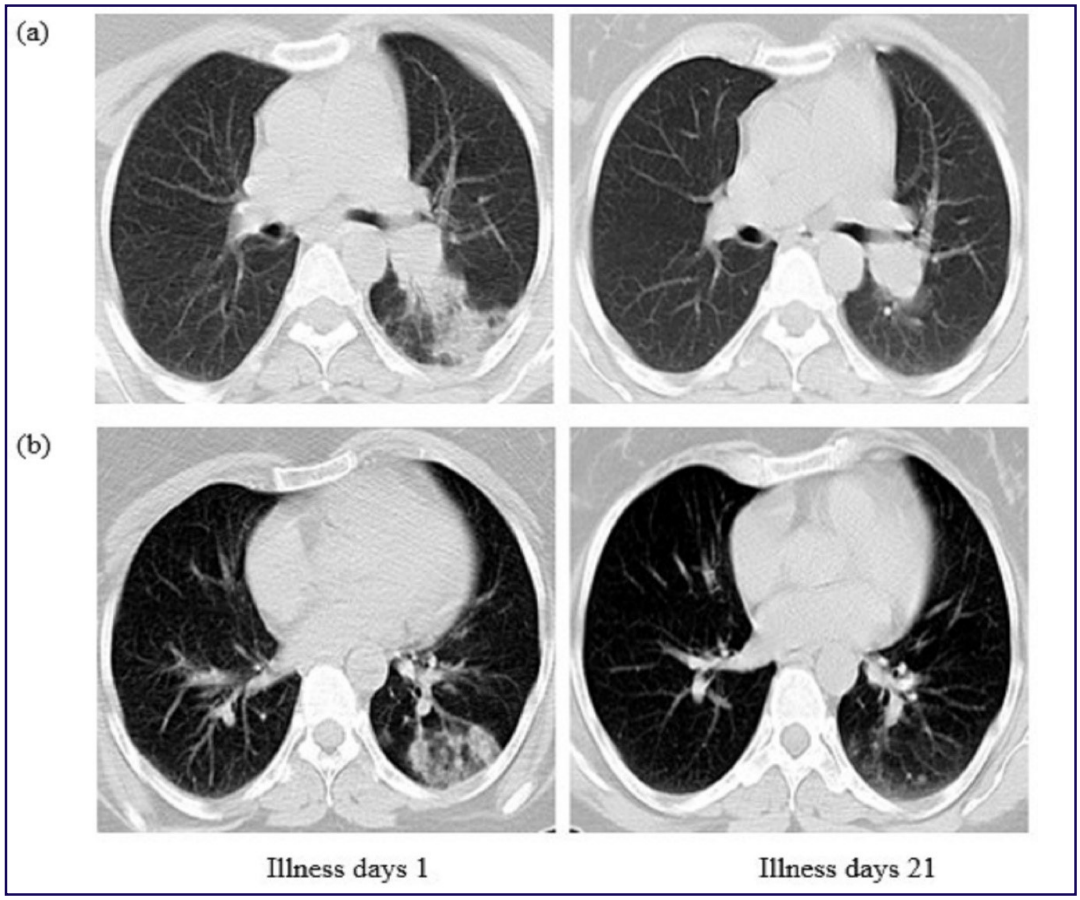

Figure 3. A 63-year-old female patient with cough and shortness of breath and a history of contact with a patient with no underlying disease. In the initial scan, ground glass and consolidation are observed in the posterior of the upper lobe of the left lung, which are lost in the next CT (21 days later). For instance, two distinct slices (a, b) of the patient's CT scans are shown.

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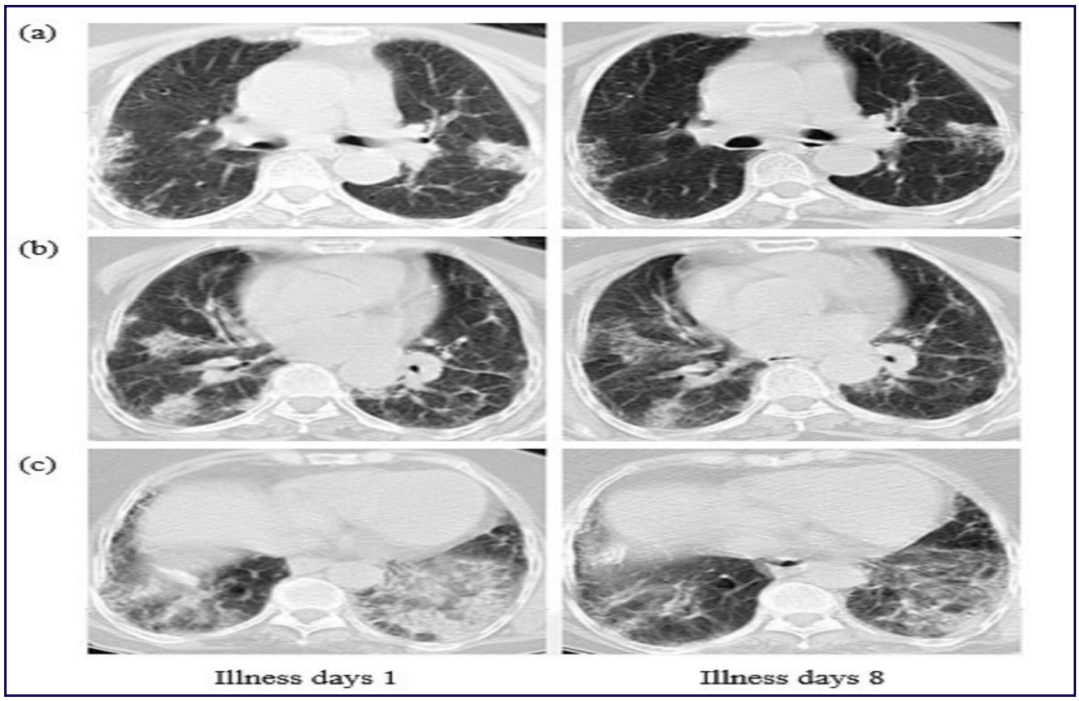

Figure 4. A 71-year-old female patient with shortness of breath and a history of osteoporosis. In the first scan, the patient was in advanced stage, the ground glass patches together with the consolidation are observed, and in the second scan (8 days later), the extent and density of the consolidations are decreased. For instance, three distinct slices (a, b, c) of the patient's CT scans are shown.

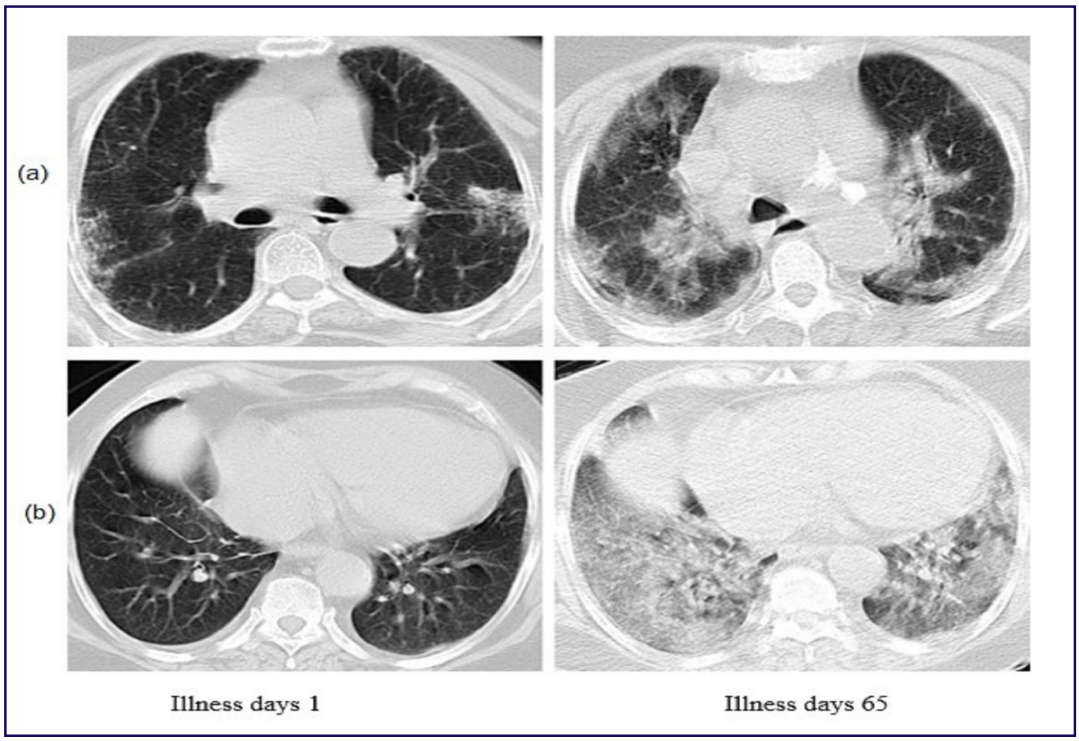

Figure 5. A 68-year-old female patient with underlying diseases, including diabetes and cardiovascular disease, symptom of shortness of breath and a history of contact with an infected person. In the patient's initial CT, ground glass opacity is observed. Increased size and density of ground glass patches in two months led to diffusion of consolidation. In the lower lobe of both lungs, the disease progressed further, and after 65 days, the consolidation spread to this area and caused a white-out lung appearance. For instance, two distinct slices (a, b) of the patient's CT scans are shown.

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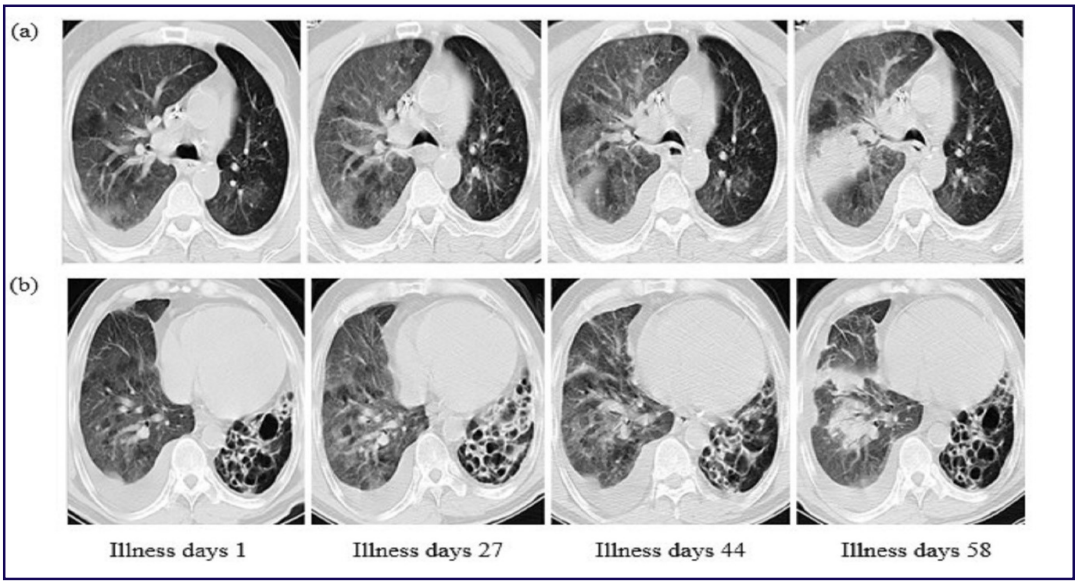

Figure 6. A 69-year-old male patient with a history of chronic kidney disease and dialysis, and a sign of cough. In the initial scan of the patient's left lung, we see bronchiectasis and decreased lung volume.

In fact, in this patient, ventilation was actually performed by the right lung. However, due to having COVID-19 (positive PCR), his right lung gradually became involved, and ground glass and consolidation became apparent. It took him almost two months from the onset of symptoms to his death, and during this time he underwent CT scans four times. The second scan was performed 27 days after the first scan, the third scan 44 days after the first scan, and the fourth scan 58 days after the first scan, and the patient died 3 days after the last scan. For instance, two distinct slices (a, b) of the patient's chest CT scan in the mentioned 4 times are shown. In the initial CT scan, ground glass opacity of right lung is observed. In the second and third scans, the density and size of the ground glasses have increased, and in the fourth scan, consolidation has appeared. In general, progression of the disease in this case was slow. This patient's 22-year-old daughter had symptoms of shortness of breath, a history of liver cysts, and positive PCR but no symptomatic CT, and was discharged.

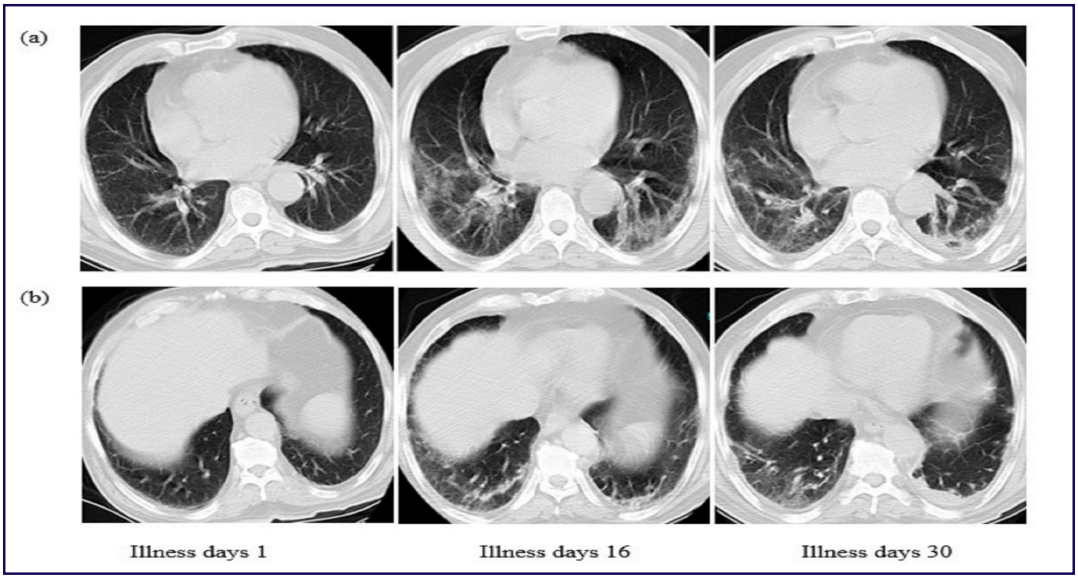

Figure 7. A 82-year-old male patient with diabetes as underlying disease, symptoms of fever and cough, and a history of contact with an infected person. No manifestations were observed in the patient's initial CT scan, but 16 days later ground glass opacity and consolidations were seen in the middle and lower lobes of both lungs, especially in the posterior and peripheral, and 30 days later, the pleural effusion appeared. For instance, two distinct slices (a, b) of the patient's CT scans are shown.

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Hounsfield unit values

All of false negative CTs are related to early stage of the disease, and the prominent feature in this stage is ground glass opacity. The results of this study suggested that, due to the slight differences in Hounsfield units of ground glass opacity and the rest of the lung parenchyma, in asymptomatic COVID-19 patients and the patients in early stage, CT images did not show any manifestations and the patient's CT was reported to be normal. The physician's experience has a great impact on the diagnosis of COVID-19. Hounsfield unit of COVID-19 suspect stage is usually between -856 to -786, meaning that it is too difficult to decide between the presence and absence of the disease and this decision-making depends on the physician's experience, skill and visual perception. In some cases, patient's COVID-19 PCR was reported to be positive and there were no clear manifestations on the CT images, but 3 to 5 days later, the disease quickly progressed to advanced stage (33). Therefore, it is very important to pay attention to ground glasses opacity that has slight difference with the lung parenchyma tissue.

Conclusions

The results of the study are summarized as follows:

1. There were no specific clinical features which could distinguish COVID-19 from other viral infections.
2. The average age of COVID-19 in the death group was higher than recovery (68 vs. 61).
3. The time interval for recovery of the disease was less than the time until death.
4. In men, recovery was less and death was higher than women.
5. Symptoms were not significantly different in the group of death and recovery (the two groups cannot be distinguished by their symptoms).
6. Most of the patients admitted to the ECU died.
7. The patients in the death group had more underlying diseases than the recovered group. COVID-19 patients are more likely to die whe they have both diabetes and cardiovascular disease.
8. A significant reduction in red blood cell counts, hemoglobin, MCHC and MCV levels was observed in the patients who deceased compared to the recovered patients.
9. Bilirubin and aminotransferase levels in COVID-19 patients who deceased were significantly higher than recovered.
10. The levels of CRP and white blood cells in patients who died is significantly higher than in recovered patients.
11. Serum BNU and creatinine levels and PT coagulation index in the deceased patients are significantly higher than in the recovered patients.
12. The concentrations of VBG (HCO_3) and VBG (PCO_2) in the deceased patients suggest compensated respiratory alkalosis.
13. CT sensitivity is 100% for patients in advanced and severe stages of the disease. Most deceased patients are in severe and advanced stages.
14. Patients with no underlying disease were more likely to reduce CT from advanced stage to early stage
15. All of false negative CTs are related to early stage of the disease, and the prominent feature in this stage is ground glass opacity.
16. Hounsfield unit of COVID-19 suspect stage is usually between -856 and -685, meaning that it is too difficult to decide between the presence and absence of the disease.
17. All of the patients who died of re-infection with COVID-19 had cardiovascular disease and complained of headaches.

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Conflict of Interests

None.

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