RELATIONSHIP OF RADIOLOGICAL STAGE WITH LABORATORY PARAMETERS AND MORTALITY IN COVID-19 PNEUMONIA

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ABSTRACT

Introduction*: In our study, the aim was to define the factors in the diagnosis and treatment through the examination of the relationship between computerized tomography (CT) images and other parameters in COVID-19.*

Materials and methods: *Patients receiving treatment for COVID-19 in our hospital between March 11 and April 6, 2020, had laboratory and clinical data available were included in our study. Temporal CT stages and CT severity scores were found. The effects of these stages and scores on laboratory parameters and mortality were examined.*

Results: *The change in severity scores of the patients according to the temporal CT stage was significant ($p<0.0001$). Moreover, there was a statistically significant difference in the changes of the mean values for lactic dehydrogenase (LDH), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) as compared to the temporal CT stage ($p=0.001$, $p<0.0001$, $p<0.0001$, respectively). There was a significant correlation between the CT severity score and lymphocyte count, LDH, ESR, CRP, D-dimer, and ferritin values. In our study, we sought to determine a cut-off CT severity score with a view to predicting mortality. To this aim, the optimal limit value in the ROC curve was defined as 10.5 (sensitivity 73.7%, specificity 65.1%, and AUC 0.784). Furthermore, in our study we found a significant relationship between the temporal CT stage and mortality ($p=0.017$).*

Conclusion: *In the CT of COVID-19 patients, both advanced temporal stage and a high severity score are associated with poor prognosis. Our study results can be used in developing risk scoring systems that include the parameters of imaging and biochemical tests to predict prognosis and mortality.*

Keywords: *COVID-19 radiology, mortality, prognosis, radiological stage.*

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Introduction

First defined in Wuhan, in December 2019, Coronavirus Disease 2019 (COVID-19) is a viral disease affecting the respiratory system. The disease agent was named SARS-CoV-2 because of its phylogenetic similarity with Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and Middle East Respiratory Syndrome Coronavirus (Mers-CoV)[(1)]. Unlike SARS-CoV and Mers-CoV, however, SARS-CoV-2 has a high basic reproduction number (R0) where even asymptomatic cases are infectious[(1)]. As of the publication of this study, 7,761,609 people worldwide are infected with SARS-CoV-2 and 430,241 of them lost their lives[(2)]. Despite its lower mortality rate, COVID-19 caused more deaths than SARS-CoV and MERS-CoV combined[(3)]. COVID-19 mostly shows a favorable clinical course, but where it takes a severe course, it may be accompanied by pneumonia, pulmonary edema, acute respiratory distress syndrome, or multiple organ failure leading to death[(4)]. The most important step in order to reduce the development of complications and patient mortality is the successful treatment of the cases with a severe clinical course. The most important steps to follow for a successful treat-

ment are early start of treatment agents, preventing any secondary infections, and effective organ function support. Therefore, it is imperative to take the necessary precautions by defining the factors related to a severe clinical course of[5].

The diagnosis is achieved through real-time reverse transcription polymerase chain reaction (RT-PCR). However, because of the risk of false negativity, long testing time, and the restricted availability of tests, computed tomography (CT) is used as another diagnostic tool[6]. On the other hand, the protective personal equipment (PPE) used in patient follow-up of patients, gets in the way of an effective auscultation examination. For this reason, CT has an important part to play in assessing disease severity, predicting the prognosis, and monitoring treatment response[7, 8, 9]. The aim of this study was to determine the temporal stage and severity score of CT images obtained at the time of admission and to examine their relationship with laboratory parameters and mortality.

Methods

The study was planned and conducted as a single-center, observational, and retrospective study in the xxxx Training and Research Hospital, which is a tertiary institution in xxx, functioning as a reference center in the COVID-19 pandemics. Approval was obtained for the study from the University of Health Sciences xxx Scientific Research Ethics Committee (Issue: 46418926-050.03.04, Date: 15.05.2020) and the Republic of xxxx (Application no. 2020-05-05T13_43_43). Since it was a retrospective study, there was no requirement of informed consent. There was no funding for the study.

Patient population

Patients who received treatment for COVID-19 pneumonia in our hospital between March 11 and April 6, 2020, and who were 18+ were examined through a retrospective screening. Patients diagnosed with COVID-19 pneumonia were included in the study as a result of comprehensive evaluation of the epidemiological exposure history, symptoms, laboratory tests, thorax CT images, and PCR analyses.

Data collection

Age, gender, and chronic disease information of all patients included in the study, as well as their symptoms at admission, CT images and laboratory tests (neutrophil count, lymphocyte count, lactate dehydrogenase [LDH], erythrocyte sedimentation rate [ESR], C-reactive protein [CRP], D-dimer and ferritin value), RT-PCR results, follow-up clinics and their outcome were recorded in Microsoft Office Excel 2013.

Obtaining CT images

All CT scans were performed during inspiration with the patient in the supine position without using any intravenous contrast medium. For the scanning, 16-slice CT scanners (Toshiba Aquilion Lightning, Toshiba American Medical Systems Inc., Tustin, CA, USA) were used.

Scanning was performed from the upper thorax entry level to the lower level of the costophrenic angle. Each acquisition was acquired with 100 kV and 100 mAs, a 5 mm slice width. Obtained images were transferred to picture archiving and communication systems (PACS).

Interpreting images

The images of the patients included in the study were analyzed by two radiologists (C.S. with 10 years' experience and M.Y. with 3 years' experience in interpreting chest CT images).

All PACS images from CT studies were examined before accessing clinical or laboratory findings. CT characteristics were evaluated independently.

Following individual evaluations, disputes were resolved through debate which concluded in consensus.

Images were classified on two criteria

Based on time (temporal CT stages)[10]:

• Early stage (stage 1) (0-4 days): Ground-glass opacities, lower lobe and frequently bilateral involvement

• Progression stage (stage 2) (5-8 days): Rapid progression, bilateral multilobar ground-glass opacities

• Peak stage (stage 3) (9-13 days): Intense consolidations with slow progression in the areas of involvement

• Resolution stage (stage 4) (from day 14): With the infection under control, a decrease of radiological densities extending until day 26

Based on severity (CT Severity Scores)[10]:

• Each of the five lobes of the lung was evaluated and scored as follows: 0=no involvement; 1=<5%;

• 2=5-25%; 3=25-49%; 4=50-75% and 5= >75%.

The total CT severity score was the sum of individual lobar scores, ranging from 0 (no involvement) to 25 (maximum involvement).

Statistical analysis

Patient data collected within the scope of the study were analyzed using the IBM Statistical Package for the Social Sciences (SPSS) for Windows 21.0 software package. Frequency and percentage were used for discrete data, whereas mean ± standard deviation, median, minimum and maximum descriptive values were used for continuous data. ANOVA Test was used in the comparison of mean values for more than 2 groups.

Continuous variables were compared using the Pearson Correlation Analysis and categorical variables were compared with Chi-Square Test. The limit value calculation for mortality severity score was performed with the ROC Analysis. Statistical significance was defined at $p<0.05$ threshold.

Results

A retrospective screening was performed on 295 patients who were admitted to our hospital upon a diagnosis of COVID-19 pneumonia from March 11, 2020, the date the first case of COVID-19 was identified in Turkey, to April 6, 2020. A total of 257 cases whose CT images at admission were available were included in the study.

The mean age of the patients included in the study was 52±14.62 years (min=19 years, max=89 years) and 142 (55.3%) were male. The mean duration of complaints of the patients who were admitted for COVID-19 pneumonia was 6±4.621 days. Most common complaints were fever (n=136, 52.9%) and cough (n=146, 56.8%). Other complaints were related to digestive system and included dyspnea, sore throat, vomiting, and diarrhea (Table 1).

Symptoms	n	%
Fever	136	52.9
Cough	146	56.8
Throat ache	28	10.9
Dyspnea	41	16.0
Gastrointestinal symptoms	19	7.4

Table 1: Application symptoms of COVID-19 pneumonia cases (N: 257).

In 107 patients (41.6%), an accompanying chronic disease was present, the most common being hypertension (n=71, 27.6%) (Table 2).

Chronic diseases	n	%
Asthma	14	5.4
COPD	10	3.9
CHF	15	5.8
HT	71	27.6
DM	42	16.3
CRF	7	2.7
Malignancy	11	4.3

Table 2: Chronic diseases of COVID-19 pneumonia cases (N: 257).
COPD: Chronic Obstructive Pulmonary Disease, CHF: Chronic Heart Failure, CRF: chronic renal failure, DM: Diabetes Mellitus, HT: Hypertension.

The number of patients who needed oxygen at admission was 53 (20.6%). During follow-up, 24 patients (9.4%) developed the need for intensive care. It was found that 19 patients (7.4%) died.

While 148 (57.6%) of the cases were PCR-positive, 109 (42.4%) had no PCR positivity despite clinical and CT findings compatible with COVID-19.

Lymphopenia was present in 165 (64%) of 256 patients whose lymphocyte counts were accessible. The increase in erythrocyte sedimentation rate (ESR) was found in 188 (82%) of 228 cases and an increase in CRP value in 176 (74%) of 239 cases. Other laboratory values at the time of admission are provided in Table 3.

	Patients N (%)	Mean value ± SD	Median (max-min)
Neutrophil (× 10^9 per L; normal range 1.5–6.6)	256 (100)	4.3±2.8	3.5 (0.3-24.3)
Increased	39 (14)	9.5±2.8	8.3 (6.6-24.3)
Lymphocytes (× 10^9 per L; normal range 1.5–3.5)	256 (100)	1.4±0.7	1.3 (0.3-4.39)
Decreased	165 (64)	1.1±0.3	1.0 (0.3-1.4)
LDH ((U/L; normal range 200-450)	256 (100)	502±249	432 (36-1905)
Increased	120 (47)	676±264	604 (453-1905)
ESR (mm/h; normal range 0-20)	228 (100)	47±26.92	44 (3-140)
Increased	188 (82)	55±23	49 (21-140)
CRP (mg/L; normal range 0–8)	239 (100)	49±59.3	24 (0-277)
Increased	176 (74)	66±61	44 (9-277)
D-dimer (µg/L; normal range 0–500)	204 (100)	899±2154	368 (110-27000)
Increased	82 (40)	1846±3177	941 (502-27000)
Serum ferritin (ng/mL; normal range 22-275)	178 (100)	527±1007	239 (6-9055)
Increased	86 (48)	990 ±1335	546 (278-955)

Table 3: Laboratory values of COVID-19 pneumonia cases at admission.
CRP: C - reactive protein, ESR: Erythrocyte sedimentation rate, LDH: Lactic dehydrogenase, SD: Standard deviation.

An assessment of the distribution of study patients based on their temporal CT stages showed that most patients (n=117, 45.5%) were in stage 2. In stage 1 and stage 3, there were 38 (14.8%) and 102 (39.7%) patients, respectively. No patient was found at the temporal CT stage 4 (Table 4).

The mean CT severity score of the patients was 8.8±5.155 (min=1, max=22). There was a statistically significant difference between severity scores based on the temporal CT stages (p<0.0001). Post-hoc analysis showed that this difference was found between stages 1 and 2 and between stages 2 and 3. Stage 3 had the highest CT severity score, while the lowest severity score was found in stage 1 (Table 4).

CT stage	N (%)	Mean Value*	SD	Median (IQR)	*p* value
1. Stage	38 (14.8)	2.84	1.653	2.0 (1.8-4.0)	
2. Stage	117 (45.5)	8.84	4.226	8.0 (6.0-12.0)	<0.0001
3. Stage	102 (39.7)	11.19	5.172	8.0 (11.0-15.0)	
Total	257 (100)	8.88	5.155	9.0 (5.0-12.0)	

Table 4: Temporal CT stage and CT severity score relationship of COVID-19 pneumonia cases.
**CT Severity score mean value. IQR: Inter quantile range, SD: Standard deviation.*

The change in the mean values of LDH, ESR, and CRP according to the stages the study subjects went through was statistically significant (p=0.001, p<0.0001, p<0.0001, respectively) (Table 5). In post-hoc analysis, the change between stage 1 and stage 2 was significant for LDH and sediment values, but the change between stage 2 and stage 3 was not found to be significant. For the CRP value, there was a significant difference between all three stages.

In the correlation analysis between CT severity score and laboratory parameters, the correlation between the values for lymphocyte, LDH, ESR, CRP, D-dimer, and ferritin was found to be statistically significant (p<0.0001). Accordingly, a weak correlation was found between CT severity score and lymphocyte count. There was a weak positive correlation between LDH, ESR, D-dimer and ferritin values and the severity score, while a moderately positive correlation was found with CRP (Table 6).

The ROC analysis showed that the optimal limit value for the CT severity score was 10.5 for predicting mortality. The sensitivity for this value was 73.7%, and the specificity was 65.1%. The area under the curve (AUC) was 0.784 (Figure 1).

		Simple size	Mean value ± SD	*p* value	N (%)*	Mean value ± SD
Neutrophils	1. Stage	37	4.0±2.1		5 (14)	6.7±5.6
	2. Stage	117	4.2±3.3	*0.677*	16 (14)	7.4±6.4
	3. Stage	102	4.5±2.5		18 (18)	7.8±3.4
	Total	256	4.3±2.8		39 (14)	9.5±2.8
Lymphocytes	1. Stage	37	1.5±0.8		24 (65)	1.2±0.8
	2. Stage	117	1.5±0.7	*0.072*	69 (59)	1.2±0.7
	3. Stage	102	1.3±0.6		72 (71)	0.9±0.3
	Total	256	1.4±0.7		165 (64)	1.1±0.3
LDH	1. Stage	37	375.62±141.74		6 (16)	647±130
	2. Stage	117	502.14±241.86	*0.001*	56 (48)	659±263
	3. Stage	102	547.06±273.43		58 (57)	697±277
	Total	256	501.75±249.38		120 (47)	676±264
ESR	1. Stage	28	27.50±19.17		15 (54)	42±14
	2. Stage	106	45.98±25.9	*<0.0001*	90 (85)	52±23
	3. Stage	94	54.18±27.16		83 (88)	60±24
	Total	228	47.09±26.92		188 (82)	55±23
CRP	1. Stage	33	9.97±11.78		13 (39)	22±10
	2. Stage	109	43.75±56.57	*<0.0001*	76 (70)	61±60
	3. Stage	97	69.12±64.27		87 (90)	78±63
	Total	239	49.38±59.387		176 (74)	67±61
D-dimer	1. Stage	22	586.55±737.21		7 (32)	1417±837
	2. Stage	97	757.01±1066.93	*0.378*	37 (38)	1567 ± 1389
	3. Stage	85	1140.81±3110.08		38 (45)	2198±4458
	Total	204	898.54±2154.46		82 (40)	1847±3177
Ferritin	1. Stage	19	216.05±356.66		4 (21)	528±623.425
	2. Stage	86	435.23±538.76	*0.088*	39 (45)	770±625.98
	3. Stage	80	698.79±1400.35		43 (54)	1135±1752.99
	Total	185	526.69±1007.58		86 (48)	937±1317.31

Table 5: Evaluation of laboratory parameters according to temporal CT stage of COVID-19 pneumonia cases.
**Number of patients with abnormal value. Abnormal value: Values below the reference range for lymphocytes and values above others. CRP: C - reactive protein, ESR: Erythrocyte sedimentation rate, LDH: Lactic dehydrogenase, SD: Standard deviation.*

	N	*p* value	Correlation Coefficient
Neutrophils	256	*0.111*	1.100
Lymphocytes	256	*<0.0001*	-0.268
LDH	256	*<0.0001*	0.417
ESR	228	*<0.0001*	0.387
CRP	239	*<0.0001*	0.590
D-dimer	204	*<0.0001*	0.311
Ferritin	185	*<0.0001*	0.432

Table 6: Correlation analysis results of CT severity score and laboratory parameters in cases of COVID-19 pneumonia.
CRP: C - reactive protein, ESR: Erythrocyte sedimentation rate, LDH: Lactic dehydrogenase.

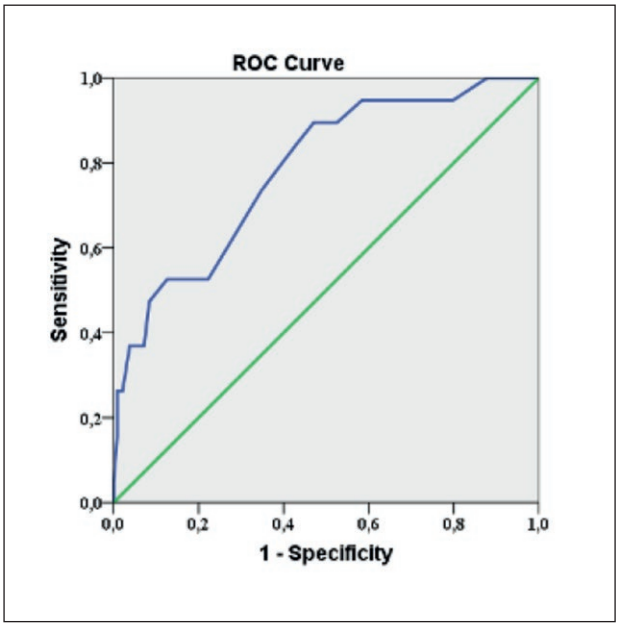

Figure 1: Roc curve for CT severity score among patients with COVID-19 for predicting mortality. The cutoff value was set 10.5. AUC under the ROC bend: 0.784, sensitivity: 73.7%, and specificity: 65.1%.

Mortality increased as the temporal CT stage progressed and this increase was statistically significant (p=0.017) (Table 7).

	Improvement N (%)	Ex N (%)	Total N (%)	*p* value
1. Stage	38 (16.0)	0	38 (14.8)	
2. Stage	111 (46.6)	6 (31.6)	117 (45.5)	*0.017*
3. Stage	89 (37.4)	13 (68.4)	102 (39.7)	
Total	238 (100)	19 (100)	257 (100)	

Table 7: Relationship between the outcome of patients and the temporal CT stage.

Discussion

As COVID-19 is a viral disease involving the respiratory tract, imaging methods play an important part in diagnosis. Thorax CT imaging is used in admission to decide about hospitalization and to plan the treatment. However, frequent CT scans cannot be performed due to the isolation measures applied at follow-up and the risks of exposure to radiation. Effective auscultation examination is also difficult because of the PPE used[11]. Consequently, the initial thorax CT images play an important part not only in diagnosis, but in predicting the severity and prognosis of the disease, as well[7]. In this study, we examined the relationship between the temporal stages and severity scores of the initial CT images and other parameters.

Past studies indicated male sex, advanced age, and accompanying chronic diseases as factors of increased risk for COVID-19 pneumonia[4, 12]. Similarly in our study population, male patients at advanced age and with accompanying chronic diseases were predominant. The most common symptoms at admission were coughing, fever, and dyspnea, as consistent with the literature[4, 13]. Unlike other coronavirus infections, symptoms of upper respiratory tract infection and gastrointestinal tract involvement were rare in COVID-19 patients[4]. In a meta-analysis involving 19 articles and 2874 patients, the most common laboratory changes in COVID-19 were identified as reduced albumin, high CRP, high LDH, increased ESR, and lymphopenia (14). Consistent with these findings, an increase in CRP, ESR, LDH, ferritin, and D-dimer values was detected in our study, while the lymphocyte count was found to decrease. As for the neutrophil count, no change was detected in our study.

Li, Y. et al. conducted a study in China with 98 patients over the age 60 to examine the relationship between baseline CT findings and mortality in COVID-19 pneumonia. The patients were divided into groups according to their time of admission to the hospital. Those who applied to the hospital within 0-5 days after the onset of symptoms were classified in subgroup 1, those who applied within 6-10 days were subgroup 2, and those who applied from day 11 fell into the subgroup 3. Most patients were in the subgroup 1[11]. In our study, patients were admitted to the hospital later on, mostly in stage 2, between days 5 and 8 of illness. The reason may be relatively low public awareness on COVID-19 and an insufficient number of available tests, as our study was

performed in the first days of the pandemic. Its clinical repercussion is a higher rate of critical condition with more advanced pneumonia in our patient group.

Pan, F. et al. identified temporal CT stages and CT severity scores examining consecutive CT images of 21 patients. In their study, patients had the highest CT severity score at stage 3 and the lowest at stage 1[10]. In a systematic review of 919 patients by Salehi, S. et al., it was found that the most severe CT findings were observed approximately 10 days after the first symptoms[15]. In our study, the patients with the highest severity scores were in stage 3, as expected. An examination of the other stages showed that severity scores increased as the CT stages progressed. Moreover, diagnosis at an advanced stage was determined as a factor increasing mortality. Raising awareness in society about the disease and continuing the filiation procedures in detail may increase survival rates together with early diagnosis and treatment.

In China, Wu, J. et al. conducted a correlation analysis between lymphocyte count, monocyte count, CRP, and procalcitonin values and pulmonary inflammation index. Their findings indicated a very weak correlation with lymphocyte count, monocyte count, CRP, and procalcitonin[16]. In our study, on the other hand, a weak correlation was found between CT severity scores and lymphocyte count, LDH, ESR, D-dimer and ferritin values and a moderate correlation was found with the CRP value. This showed that, even if CT scanning could not be possible on a frequent basis, it could still contribute to the knowledge on the course of the disease by monitoring the identified laboratory parameters. In our study, it was also found that CRP, LDH, and ESR values changed according to the temporal CT stage. Consequently, laboratory parameters were related to both the severity and the temporal stage of the disease.

As frequent CT scanning and effective auscultation examination are not possible in the follow-up of patients, images obtained at admission might be useful in determining the risk of mortality. In our study, an ROC analysis was performed to find a cut-off CT severity score for mortality and this value was defined as 10.5 out of 25 (sensitivity 73.7%, specificity 65.1%, AUC 0.784). In a study Wu, J. et al., conducted on elderly patients in China, different cut-off values were defined based on the time of admission. Cut-off was defined as 14.5 (sensitivity 83.3%, specificity 77.3%) in subgroup 1 (0-5 days) and as 27.5 (sensitivity 87.5%, specificity 70.6%) in subgroup 2 (16). In this study, a different CT scoring was used with a top value of 60. Since the scoring systems in both studies are different, comparison is not possible, but the common result of both studies was that pneumonic infiltration beyond a certain level at admission was associated with a poor prognosis and mortality.

The most important limitations of our study were the retrospective design and unavailability of data on plasma cytokines and chemokines, especially IL 1 and IL 6, due to limited laboratory facilities.

In consequence, pulmonary CT imaging on admission can be beneficial especially in symptomatic patients. In the CT of COVID-19 pneumonia patients, both advanced temporal stage and a high severity score are associated with poor prognosis. Our study results can be used in developing risk scoring systems that include the parameters of imaging and biochemical tests to predict prognosis and mortality.

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