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Evaluation of Computed Tomography Images Compatible With COVID-19 in Cases of Viral Pneumonia Undiagnosed Prepandemic

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Abstract

Objective: COVID-19 has a wide clinical spectrum, from cases with mild symptoms to cases with severe lung involvement. After the first cases appeared in Wuhan, the virus spread rapidly without understanding its transmission routes and clinical significance. The aim of the study is to show that SARS-CoV-2 caused undiagnosed COVID-19 pneumonia cases in Turkey with the effect of increased transportation facilities and rapid viral spread in the pre-pandemic period.

Methods: Study was designed observational cross-sectional study. In this study were retrospectively analyzed 350 patients, who were conducted computed tomography after pre-diagnosis of pneumonia in the radiology department of our hospital before March 1, 2020. Radiologically, the severity of pneumonic involvement was measured and scored. Demographic characteristics, laboratory findings and symptoms of the patients were examined. The relationship between the clinical course of the patients and radiology involvement was examined. SPSS 23.0 package program was used for statistical analysis and $p < 0.05$ was considered statistically significant.

Results: The average age of the twelve patients was 70,3±17,3. Patients male/female ratio was 3/9. Symptomatology and co-morbidities were similar. There was no statistically significant difference in laboratory data between the died and surviving patient groups. When the radiological pneumonia involvement patterns of the deceased and surviving patients were compared, it was seen that the right middle, right lower, left middle lobe involvement and total radiological scores were statistically significantly higher in the deceased group than in the surviving patients ($p<0.05$).

Conclusion: The cases reported before the pandemic in various parts of the world show that the virus spread between countries has reached a size that makes it impossible to detect the cases and that the epidemic is striking than expected. Tomography is an important diagnostic tool for detecting cases that cannot be detected by serological and molecular tests and taking precautions by monitoring the outbreak.

Keywords: COVID-19, Prepandemic, Contagiousness, Tomographic Images, Early Findings

Introduction

In December 2019, in Wuhan, China, pneumonia cases related to the wholesale seafood market with unknown causes were reported (1). COVID-19 pneumonia (Corona Virus Disease) caused by SARS-CoV-2 spread through the entire world and has been declared as a pandemic by World Health Organization on March 11, 2020 (2). As of November 26, 2021, there are approximately 260 million cases and 5 million fatalities globally, and Turkey accounting for 8 million cases and 75000 deaths (3). For nasopharynx samples, diagnosis is the detection of the virus via real-time reverse-transcriptase-polymerase reaction (RT-PCR) (4), its sensitivity is variable as it depends on the duration of symptoms, viral load, the rate of viral replication in the upper respiratory tract, and quality of the test sample, and has a reported pooled sensitivity of 64.8% (95% confidence interval (CI) (54.5–74.0) in clinical practice (5) Computed tomography (CT) examination plays an important role in pandemic areas in the diagnosis of COVID-19 because of its high sensitivity (6). Neutrophil Lymphocyte Ratio (NLR) and Platelet Lymphocyte Ratio (PLR), which are inflammation markers, have prognostic significance in COVID-19 (7). Sars CoV-2 was detected in wastewater samples of Italy and in respiratory tract samples of intensive care units in France on December 2, 2019 (8-10). In Turkey, the first case was reported on March 9, 2020 (11). In our study, we retrospectively scanned computed tomography of 12 patients admitted to our hospital before March 2020, based on viral pneumonia with unidentified causes and we have found that the symptoms were coherent with SARS-CoV-2 pulmonary involvement.

Material and Method

Clinical Study Design

This clinical trial was designed as a retrospective analysis of data obtained from patient files and level of evidence was determined as 3 according to the Scottish Intercollegiate Guidelines Network (SIGN100) (12).

Patients, data dollection and setting

After the approval of the Ethics committee (2021/49-09), 350 patients, who were conducted CT after pre-diagnosis of pneumonia in Radiodiagnostic Department of …….University Hospital between the dates of November 1, 2019, and March 1, 2020, were retrospectively analyzed. Evaluation of their clinical findings and laboratory data, 12 patients were detected to have positive findings of viral pneumonia and COVID-19 positive computed tomography.

Radiological scoring

To semi-quantitatively evaluate pneumonic involvement intensity, a scoring was conducted based on CT scan images of patients using the parameters below (Table 1). The two radiologists evaluated the tomography findings independently. While performing the evaluation, peripheric bilateral focus screen appearance, multi-focal rounded focus screen areas, and typical COVID-19 CT findings with a reverse halo in Table 1 were assumed to be positive in addition to partially meaningful peripheric, multi-focal, diffused focus screen opacities (13). To measure the involvement intensity, the method developed by Ooi et al which divides each lung into three

zones; top-mid-bottom, amounting to a total of 6 zones. Scoring was conducted for the involvement volume of each area. Involvement scoring was 1 point for 0-25 percent, 2 points for 50-75 percent, and 4 points for 75-100 percent for each zone. Total scoring of all 6 zones meant mild involvement for 1-5 points, medium involvement for 6-11 points, and intense involvement for 12 points and above (Table 2) (14). Our evaluation was based on 1.5 mm wide and gapless sections acquired with low dosage radiation (mAs: 50, Kvp: 120) using (Siemens Somatom Scope (Germany) 16 section CT device. We showed examples of radiology involvement and scores in figure (Figure 1).

Table 1. Typical And Atypical Computed Tomography Findings Sars-CoV-2 Pneumonia

Typical findings	• Peripheral, bilateral ground glass view • (Crazy-paving) • Multifocal “rounded” glass ground • Reverse halo	* 1
Partially Meaningful	Lack of typical findings, and • Multifocal, diffuse, perihilar, or unilateral ground glass opacities that are not peripheral and "rounded" • Few and very small areas of ground glass that are peripheral and not "rounded"	2
Atypical findings	Lack of typical findings, and • Isolated lobar or segmental consolidation areas (not ground glass) • Tree-in-bud view and small nodules • Moderate thickening of interlobular septa and pleural effusion	3
Negative	No findings of pneumonia	4

***Computed Tomographic Findings Description in Table 1*.

1. Findings were initially evaluated as COVID-19 pneumonia. In addition, other viral pneumonia and organized pneumonia might be assumed in the diagnosis.
2. Findings are positive for viral pneumonia (including COVID-19). In addition, other infectous and non-infectous processes must be evaluated for the differential diagnosis.
3. Findings are not typical for COVID-19. It might be considered for the differential diagnosis. Viral pneumonia must be excluded with laboratory and clinical studies.
4. There are no pneumonia findings

Table 2. Computed tomography score tables of acute respiratory disstress syndrome

Involvement ratio (%)	**Score**	**Total point***	**Involvement levels**
0-25	1	1-5	Mild
25-50	2	6-11	Moderate
50-75	3	≥ 12	Severe
75-100	4	*(Maximum 6x4=24 score)	

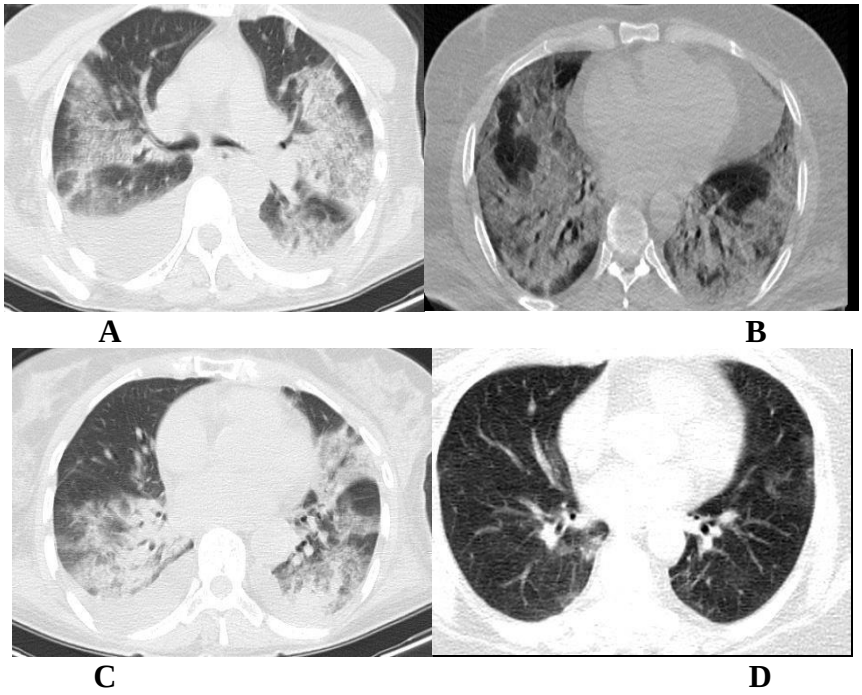

Figure 1. Radiological findings in early case **A.** Left lung upper lobe three points **B.** Bilateral lung involvement four point **C.** Right middle zone two point **D.** Left lung one point

Statistical analysis

The compliance of the data to normal distribution was examined using the Shapiro Wilk test. It was observed that the variables in Ex and Follow-up observations did not conform to the Normal distribution, and the Mann Whitney U test was used in the comparison of the two groups. As descriptive statistics, mean ± standard deviation for numerical variables, Median and Percentile 25 and 75 for categorical variables are given as numbers and% values. SPSS Windows version 23.0 package program was used for statistical analysis and $p < 0.05$ was considered statistically significant.

RESULTS

Average age of the patients was 70,3±17,3. The male/female ratio of the patients was %25 to %75. The most accompanying disease was hypertension, at a rate of 50%. The comorbidity of patients ratio is %75. Five patients were being monitored in intensive care units, four of which were general ICU and one of which was coronary ICU (Intensive Care Unit). Two patients died (Table 3).

Table 3. Demographic Characteristics of Patients

Age, mean±SD (range:min-max)	70,33±17,35 (30-93)
Gender	**n (%)**
Male	3 (25)
Female	9 (75)
Prognosis	**n (%)**
Inpatient- General ICU	5 (41,7)
Inpatient-Service	5 (41,7)
Outpatient	2 (16,7)
Result	**n (%)**
Exitus	2 (16,7)
Survivor	10 (83,3)
Symptoms	**n (%)**
Syncope	1 (8,3)
Impaired of general condition	1 (8,3)
Fatigue- diarrhea – fever	1 (8,3)
Fatigue, tiredness, dyspnoea	1 (8,3)
Dyspnoea – cough	1 (8,3)
Cough	2 (16,7)
Cough - dyspnoea	1 (8,3)
Cough - dyspnoea, sputum, fever	1 (8,3)
Cough , sputum, throat pain	1 (8,3)
Cough, chest pain, fever	1 (8,3)
Comorbidity	**n (%)**
Yes	9 (75)
No	3 (25)
Hypertension	1 (8,3)
Hypertension , demantia	1 (8,3)
Hypertension, lung neoplasm	1 (8,3)
Hypertension, bipolar disorder	1 (8,3)
Hypertension, Diabetes Mellitus	1 (8,3)
Hypertension, COPD- cirrhosis	1 (8,3)
CKD	1 (8,3)
Congestive heart failure	1 (8,3)
Non ST MI	1 (8,3)
No	1 (8,3)
Number of Comorbidity	**n(%)**
No	3 (25)
1	4 (33,3)
2	4 (33,3)
3	1 (8,3)

CKD: Chronic Kidney Disease, COPD: Chronic Obstructive Pulmonary Disease, Non ST MI: Non ST Elevated Miyocardial Infarctus.

Comparing laboratory findings of survivor and dead patients CRP, Procalcitonin, NLR, PLR, and Absolute Lymphocyte was determined no significant difference in these groups (p>0.05) (Table 4).

Table 4. Laboratory Examination of Patients

Parameters	Survivor (10) Median [Q1,Q3]	Exitus (2) Median [Q1,Q3]	p
CRP	91 [46 155]	104 [25 183]	0,814
Procalcitonine	1,22 [0,01 1,26]	3,16 [0,01 6,30]	0,558
Leucocyte	7730 [4570 9890]	13000 [12800 13200]	0,157
Neutrophil	6660 [3640 7000]	11400 [11200 11600]	0,099
Platelet	220000 [150000 279000]	172000 [163000 181000]	0,480
NLR	5,43 [3,06 10,4]	16,95 [12,6 21,3]	0,099
PLR	286,95 [158,82 329,68]	255,09 [196,73 313,46]	0,999
Eosinophil	40 [0 110]	5 [0 10]	0,278
MPV	10,3 [9,75 10,95]	11,05 [10,7 11,4]	0,190
PCT	0,22 [0,2 0,3]	0,20 [0,18 0,21]	0,478
Absolute Lymphocyte	680 [640 1360]	720 [520 920]	0,637

Q1: Percentile 25, Q3: Percentile 75, p value was obtained from Mann Whitney U test.
CRP: C-reactive protein PCT: Platecrit, NLR: Neutrophil Lymphocyte Ratio ,PLR: Platelet Lymphocyte Ratio, MPV:Mean Platelet Volume

Survive and dead patients' radiologic score is shown in Table 5. When exitus and surviving patients were compared, it was seen that the right middle right lower right, left middle and total scores were statistically significantly higher in the individuals in the deceased group compared to the surviving patients (p <0.05). Two patients with total scores of 15 and 19 became exitus. No statistically significant difference was found between the upper right, upper left and lower left values of the patients who had exitus and were followed up on an outpatient basis (p>0,05) (Table 5).

Table 5. Comparing Radiological Score of Patients

Parameters	Survivor (10) Median [Q1 Q3]	Exitus (2) Median [Q1 Q3]	p
Right Upper Lobe	2 [1 2]	3 [2 4]	0,273
Right Middle Lobe	1,5 [1 2]	3 [3 3]	0,030
Right Inferior Lobe	1 [1 1]	3 [2 4]	0,030
Left Upper Lobe	1 [0 1]	2 [2 2]	0,182
Left Middle Lobe	1 [1 1]	3,5 [3 4]	0,030
Left Inferior Lobe	1 [1 1]	2,5 [2 3]	0,061

Total Score	7,5 [6 9]	17 [15 19]	0,029
Q1: Percentile 25, Q3: Percentile 75, p value was obtained from Mann Whitney U test.			

DISCUSSION

The COVID-19 pandemic is spreading rapidly around the World. In some cases delay to detection of the virus in the PCR test or false negative PCR test, which is used as the key diagnostic method, may cause a delay in the diagnosis of pneumonia (15). Lung X-Ray observations are not standard and difficult to understand of disease findings. CT is used as the primary bilateral, peripheral, and basal glass opacity, consolidation, or both (16). Some SARS-CoV-2 cases may therefore have been overlooked, especially among patients with lower viral loads and often not subject to virological investigations. A clearer presentation of the radiological findings specific to COVID-19 pneumonia together with the pandemic showed us that the thoracic CT findings of some of the patients who were followed up with influenza pneumonia during the winter season before the pandemic were compatible with COVID-19 (17). Contagion of COVID-19 infection was reported in some countries before the official pandemic declaration of WHO (10, 18-20) (Table 6). Detection of SARS-CoV-2 in wastewater in some studies conducted in the same period also supports this (8,9). We first detected the patients admitted to our hospital before March 2020, the first official case of the pandemics in Turkey, based on viral pneumonia with unidentified causes and who were later admitted to the intensive care unit. Symptoms and radiological graphics of the patients were in harmony with COVID-19 pneumonia cases seen in China in December Conducted influenza tests were negative and all other tests including blood samples, tuberculosis samples, bronchoscopic evaluations and serological tests conducted as a result of gradually increasing symptoms and clinically heavy conditions also proved to be negative (21).

Table 6. The First Early Scientific Reports Before Covid-19 Pandemic in the Current Literature

Authors	**Country**	**Date of first cases**	**Total** (M+F)	**Mean±SD** (Min-Max)	**Used diagnostic methods**	**Outcome**	
						Death	**Healing**
Deslandes A et al.[10] (June 2020)	France	27 Dec 2019	14 (6+8)	58.4±16.1 (34-92)	RT-PCR	4	10
Bernard Stoecklin S et al.[14] (February 2020)	France	16, 19 and 23 Jan 2020	3 (2+1)	36.3±8.2 (30-48)	RT-PCR	0	3
Böhmer MM et al.[15] (May 2020)	Germany	23 Jan 2020	16	-	RT-PCR	0	16
Burke RM et al.[16] (September 2020)	The US	19 Jan 2020	9	-	RT-PCR	0	9
Our Study	Turkey	29 Dec 2019	12 (3+9)	70,3±17,3 (30-93)	Thoracic CT	2	10

PCR test is important for a final diagnosis however it has low sensitivity, rough stability, and an extended timeline is required to receive the result (22). Similarly, Bhattacharjya et al. stated in their study that real-time reverse transcription-polymerase chain reaction (RT-PCR), though considered the standard testing measure, has low sensitivity and also it is time-consuming, which restricts the fast screening of individuals (23).

Patients with travel history or contact history displayed computed tomography positivity (15). RT-PCR negative patients were used for scanning and asymptotic patients with Pan et al CT positivity displayed worsening clinical conditions about two weeks after displaying symptoms (24). In the study conducted by Tao et al on 1014 patients, 601 patients were PCR positive and 888 were CT positive. 97% of PCR-positive patients were CT COVID-19 positive. This study conducted on high sensitivity CT suggests the use of CT for epidemic scanning (25). CT is important in terms of diagnosing doubtful cases and initial CT findings are diagnosed either before PCR positive results or within the first 6 days. Li et al. and Köksal et al. emphasized that radiological involvement and radiological scores are high in severe and critical patients, and both clinical laboratory and radiological evaluations predict the prognosis of patients with COVID-19. (26,27). Centers for Disease Control and Prevention (CDC) ye göre altın standart tanı testi reverse transcription-PCR (RT-PCR) (28), Moleküler yöntemlerdeki gelişmelerle birlikte Karlafti ve ark yaptğı bazı çalışmalarda daha ekonomik ve hızlı nazal antijen testinin sensitivitesinin ve spesifisitesinin yüksek olduğunu göstermişlerdir (29).In our study, 2 cases with high radiological scores and NLR values of 21.6 and 12 displayed mortality. In addition, patients treated in the intensive care unit for too long also displayed a high total score. A study similar to ours, conducted by Sensusiati et al on 111 patients, also suggested that high NLR levels, old age, and pulmonary involvement is associated with prognosis (7). In the evaluation of the last data sets obtained from passengers of Yokohama Japanese ship, 17.9 % of PCR positive tests were found to be asymptomatic and in the study conducted in Italy, 72% of patients were diagnosed be undetermined individuals (30,31). Following these results, we might assume that viral pneumonia COVID-19 cases were present in Turkey before March 2020 because there were many asymptomatic and undiagnosed heavy viral pneumonia cases in our hospital.

Limitations of the study

This study has several limitations. First, owing to the retrospective nature of the analyses, medical records were not exhaustive and some relevant information might have been missing. Second, we were unable to use virus sampling and the PCR method. The third one is that we, unfortunately, do not have data sets from all cities of Turkey and we included patients who were admitted to our hospital in Istanbul, the city in which the first case was seen and the pandemic became widespread. Finally the most important limitation is scarcity of patient number

CONCLUSION

The COVID-19 pandemic became widespread in various areas around the world before December 2019 and became a pandemic in March 2020. Although RT-PCR is assumed as a gold standard for the diagnosis of the disease, the nasal sampling method has low sensitivity

especially in cases of patients with heavy symptoms as displayed in our study. We strongly suggest using computed tomography for early diagnosis COVID-19 in suspected patients who is have clinical and laboratory findings.

Conflict of Interest

The authors report that there is no conflict of interest.

Support Resources

No financial support was used by authors during this study.

Ethical Declaration

Ethical permission was obtained from the Biruni University, Medical Faculty Clinical / Human Research Ethics Committee for this study with date 2021 and number 49-09, and Helsinki Declaration rules were followed to conduct this study.

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