Differential diagnosis of COVID-19 pneumonia from acute heart failure in pandemic: Importance of radiological and laboratory findings

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ABSTRACT
Differential diagnosis of COVID-19 pneumonia from acute heart failure in pandemic: Importance of radiological and laboratory findings

Introduction: COVID-19 pneumonia typically presents with high fever, cough, and shortness of breath and on thorax computed tomography (CT) peripheral ground glass opacities help the diagnosis. Although typical imaging findings for COVID-19 pneumonia are specified in thorax CT, these findings can be
INTRODUCTION

The first cases of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), causing pneumonia were reported in China, in December 2019. Shortly after, cases of the novel coronavirus disease 2019 (COVID-19) has become a global public health problem as a result of the rapid increase in the number of cases, worldwide (1-3).

The clinical findings of COVID-19 range from mild symptoms such as asymptomatic disease and mild upper respiratory tract infection to severe viral pneumonia accompanied by respiratory failure and multiple organ dysfunction, which can result in death. Clinically, COVID-19 pneumonia typically presents with high fever, cough, and shortness of breath, and on thorax computed tomography (CT) the images of peripheral ground glass densities help diagnosis (4-8).

Although typical imaging findings for COVID-19 pneumonia are specified on thorax CT, these findings can be confused with several diseases (9). One of this clinical entity is acute heart failure (AHF), which is a clinical entity characterized by fluid accumulation in the interstitial space and alveolar space as a result of...
the increase in hydrostatic pressure in the pulmonary capillaries, and it is another common cause of GGO observed on thorax CT. Therefore, clinicians may have difficulties in the differential diagnosis of AHF and COVID-19 pneumonia, especially during the COVID-19 pandemic process (10-12).

The fact that pulmonary edema caused by acute heart failure can mimic several diseases in thorax CT, may lead to delays in the diagnosis and treatment of these patients. Therefore, in the present study, we aimed to investigate the roles of radiological findings and inflammatory markers in the differential diagnosis of COVID-19 pneumonia and AHF in cases who admit to the emergency department (ED) with complaints of respiratory distress, during the pandemic process.

MATERIALS and METHODS

Study Design

This study was conducted as a retrospective cohort study on patients who admitted to the Emergency Department of Malatya Training and Research Hospital and hospitalized in the intensive care unit (ICU) with the diagnosis of acute respiratory failure, between May 15, 2020 and July 30, 2020. A total of 74 adult patients (aged ≥18 years) consisting of 39 patients who were diagnosed with COVID-19 pneumonia and 35 patients who were diagnosed with AHF after excluding COVID-19 pneumonia, were included in the study. The patients were divided into two groups, namely COVID-19 pneumonia group and AHF group. Laboratory and radiological findings of COVID-19 pneumonia and AHF cases were compared.

Data Collection and Definitions

The COVID-19 cases were confirmed by real-time reverse transcription polymerase chain reaction (RT-PCR) test from upper respiratory sample (nasopharyngeal and/or oropharyngeal swab) or lower respiratory tract sample (tracheal aspirate), in patients with clinical suspect of positive SARS-CoV-2. In addition, COVID-19 pneumonia cases were defined as symptomatic depending on typical positive thorax CT findings (13). The diagnosis of AHF was based on acute and chronic heart failure guidelines of the European Society of Cardiology (ESC) and at least two consecutive negative COVID-19 RT-PCR tests (14).

The demographic data, vital signs, complaints, comorbidities, biochemistry results, complete blood count results, coagulation parameters (D-dimer, fibrinogen), inflammatory markers (C-reactive protein (CRP), procalcitonin (PCT), ferritin, albumin, and cardiac enzyme values of the patients, at the time of admission, were recorded. The data were obtained by scanning the hospital medical record system and picture archive and communication system (PACS), retrospectively.

Computed Tomography Image Acquisition and Radiological Interpretation

All thorax CT scans were collected at the end of inspiration with patients in the supine position without injection of contrast agent. 128-slice multi detector CT device (Philips Ingenuity, Philips Systems, Cleveland, OH, USA) was used for all thorax CT examination. The thorax CT scanning range included the whole chest from the level of the upper thoracic inlet to the diaphragm. Thorax CT images were evaluated with mediastinal (width, 350 HU; level, 40 HU) and parenchymal (width, 1500 HU; level, −700 HU) windows settings. The scanning parameters were as follows: 140 kV, 20-665 mA, 0.625 mm slice collimation, reconstruction matrix of 512 × 512, slice thickness of (helical mode) 0.67-5 mm, slice thickness of (axial mode) 0.625-12.5 mm.

Patients that underwent thorax CT evaluation at the time of hospital admission were included in the study. Thorax CT images of the patients were evaluated blindly by a radiologist experienced in chest radiology. The presence or absence of the thorax CT findings including ground-glass opacities (GGO), consolidation, crazy paving pattern, air broncho-gram, distribution of lesions, pleural effusion, involvement of lobes, and cardiomegaly were recorded.

Statistical Analysis

In the study, normally distributed data were expressed as mean value ± standard deviation and data without normal distribution were expressed as median (min-max) values, numbers, and percentages. The distribution of variables was tested by Skewness & Kurtosis. In the comparisons of two independent groups, the independent variables were compared by using t test for the analysis of the parametric data. The Mann Whitney U test was used for the analysis of the non-parametric data and the Chi-Squared test was used for the analysis of the categorical data. SPSS version
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23.0 was used for all analyzes. The results were evaluated at 95% confidence interval and a value of p<0.05 was accepted statistically significant.

The study protocol was approved by Turkish Ministry of Health and Clinical Ethics Committee of Inonu University (protocol code: 2020/125). Since the study was conducted retrospectively, written informed consent form was not obtained from the patients.

RESULTS

Demographical Characteristics

A total of 74 patients were enrolled in the study. The patients were divided into two groups as confirmed COVID-19 pneumonia patients (n= 39) and AHF (n= 35). Of all the patients, the mean age 68.41 ± 12.14 years, and 30 (40.5%) female and 44 (59.5%) were males. COVID-19 exposure history was found significantly higher in the COVID-19 pneumonia patients’ group (p< 0.001). Chronic kidney disease and chronic heart failure respectively were found significantly higher in the AHF patients’ group (p= 0.002, p< 0.001). There was no difference in age, gender between two groups. The baseline demographic characteristics of the two groups are summarized in Table 1.

The most common complaints of the patients at the hospital admission were shortness of breath in 71 (95.9%) patients, cough in 37 (50%) patients, and fever in 29 (39.2%) patients. We found that the fever, cough, and fatigue were significantly higher in the COVID-19 pneumonia patients’ group (p< 0.001) (Table 2).

Comparison of Radiological and Laboratory Findings

We found that there were too many radiological differences between the two groups. There was significant difference of lesions distribution between the two groups, centrally distributed lesions were found significantly higher in AHF patients (85.8% vs. 23%, p< 0.001) (Figure 1). There were also differences between the two groups for ground-glass opacity, consolidation, crazy paving patterns respectively (p= 0.016, p= 0.004, p= 0.001). Pleural effusion and cardiomegaly were found significantly higher in AHF patients (p< 0.001, p< 0.001) (Figure 2). The comparison of thorax CT imaging findings were summarized in Table 3.

On the emergency department admission, counts of the white blood cells and lymphocytes were found significantly lower in COVID-19 pneumonia patients (10.07 ± 4.89 x 10⁹/L vs 14.22 ± 6.60 x 10⁹/L, p= 0.003, 0.74 x 10⁹/L (0.26-2.35) vs 1.68 x 10⁹/L (0.24-10.23), p=

| Table 1. Demographic characteristics of the patients |
|-----------------------------------------------------|
| All patients (n= 74) | Confirmed COVID-19 pneumonia (n= 39) | Acute heart failure (n= 35) | p |
|----------------------|---------------------------------------|----------------------------|---|
| Age, years (Mean ± SD) | 68.41 ± 12.14 | 69.54 ± 11.53 | 67.14 ± 12.83 | 0.400** |
| Sex | | | | |
| Female | 30 (40.5%) | 12 (30.7%) | 18 (51.4%) | 0.071* |
| Male | 44 (59.5%) | 27 (69.2%) | 17 (48.5%) | |
| COVID-19 exposure history | | | | |
| Present | 31 (41.9%) | 30 (76.9%) | 0 (0%) | < 0.001* |
| Absent | 43 (58.1%) | 9 (23.1%) | 34 (100%) | |
| Comorbidities | | | | |
| Malignancy | 4 (5.4%) | 1 (2.5%) | 3 (8.5%) | 0.254* |
| CKD | 8 (10.8%) | 0 (0%) | 8 (22.8%) | 0.002* |
| Alzheimer disease | 9 (12.2%) | 1 (2.5%) | 2 (5.7%) | 0.108* |
| Diabetes mellitus | 27 (36.5%) | 13 (33.3%) | 14 (40%) | 0.552* |
| Hypertension | 66 (89.2%) | 32 (82%) | 34 (97.1%) | |
| COPD | 25 (33.8%) | 10 (25.6%) | 15 (42.8%) | 0.037* |
| CHF | 34 (45.9%) | 10 (25.6%) | 24 (68.5%) | |< 0.001* |
| IHD | 31 (41.9%) | 16 (41%) | 15 (42.8%) | 0.673* |
| Cardiac arrhythmia | 9 (12.2%) | 6 (15.3%) | 3 (8.5%) | 0.371* |

CKD: Chronic kidney disease, COPD: Chronic obstructive pulmonary disease, CHF: Chronic heart failure, IHD: Ischemic heart disease.
* Chi-square test.
** Independent samples t test.
Compared with AHF, COVID-19 pneumonia patients had higher levels of lactate dehydrogenase (LDH), creatine kinase (CK) and ferritin (524 IU/L (242-1904) vs 363 IU/L (136-986) p= 0.002, 152 U/L (20-1416) vs 89 U/L (20-519) p= 0.013, 873.47 ± 643.96 ng/mL vs 261.53 ± 401.28 ng/mL p< 0.001).

Although patients in both groups had an increased level of CRP, COVID-19 pneumonia patients had significantly higher levels of CRP compared with AHF patients (15.33 ± 7.19 mg/dL vs 5.43 ± 6.62 mg/dL, p< 0.001). Also, the level of NT-proBNP was found significantly higher in the AHF patients’ group.

Table 2. Clinical signs and symptoms of the patients

| Onset symptoms                     | All patients (n= 74) | Confirmed COVID-19 pneumonia (n= 39) | Acute heart failure (n= 35) | p       |
|------------------------------------|---------------------|--------------------------------------|-----------------------------|---------|
| Fever                              | 29 (39.2%)          | 28 (71.7%)                           | 1 (2.8%)                    | < 0.001* |
| Cough                              | 37 (50%)            | 32 (94.8%)                           | 5 (14.2%)                   | < 0.001* |
| Dyspnea                            | 71 (95.9%)          | 36 (92.3%)                           | 35 (100%)                   | 0.094*  |
| Fatigue                            | 15 (20.3%)          | 14 (35.8%)                           | 1 (2.8%)                    | < 0.001* |
| Pretibial edema                    | 19 (25.7%)          | 0 (0%)                               | 19 (54.2%)                  | < 0.001* |
| Chest pain                         | 5 (6.8%)            | 2 (5.1%)                             | 3 (8.5%)                    | 0.556*  |
| Presence of the fever in hospital admission | 28 (37.8%)          | 28 (71.8%)                           | 0 (0%)                      | < 0.001* |

* Chi-square test.

Figure 1. Axial plane of thorax CT images in patients with COVID-19 pneumonia showing A. Bilateral subpleural patchy ground-glass opacities (GGOs), consolidations, and crazy paving patterns in right lobe. B. Bilateral subpleural patchy GGOs and consolidations. C. Bilateral subpleural consolidation and air bronchogram sign, D. Bilateral subpleural patchy GGOs and consolidations.
(3975 ± 8288 pg/mL vs 17251 ± 15233 pg/mL, p<0.001). A comparison of the laboratory data was summarized in Table 4.

**DISCUSSION**

Acute heart failure is one of the most common cardiac emergencies. In AHF patients, the precipitating factors that require urgent intervention should be...
identified and corrected immediately. Since AHF is a life-threatening clinical condition, delays in diagnosis and treatment are associated with increased mortality and morbidity (15-17). However, in thorax CT findings, pulmonary edema caused by AHF can be confused with several exudative diseases and may cause delays in diagnosis and treatment, especially during the pandemic process (18).

Acute heart failure is a condition that heart failure symptoms and signs get worse quickly. AHF can be in the form of new-onset heart failure or more frequently as acute decompensation of chronic heart failure (14,17,19). In our study, 68.5% of AHF cases were previously treated for chronic heart failure. Although typical symptoms and signs of AHF are mostly caused by excess volume (pulmonary congestion, peripheral edema), in some cases it may be associated with hypoperfusion resulted by low cardiac output. However, due to the low sensitivity and specificity of symptoms and signs, further evaluation is required in

### Table 4. Laboratory findings of the patients

|                      | All patients (n= 74) | Confirmed COVID-19 pneumonia (n= 39) | Acute heart failure (n= 35) | p       |
|----------------------|----------------------|--------------------------------------|-----------------------------|---------|
| **Biochemical parameters** |                      |                                      |                             |         |
| Urea, mg/dL (min-max) | 57 (11-388)          | 43 (11-183)                          | 69 (29-388)                 | 0.006*  |
| Creatinin, mg/dL (min-max) | 1.08 (0.36-7.32) | 0.93 (0.36-2.09)                     | 1.46 (0.61-7.32)           | 0.003*  |
| AST, U/L (min-max)    | 43.50 (10-940)       | 51 (17-940)                          | 27.50 (10-313)             | 0.010*  |
| ALT, U/L (min-max)    | 28 (4-850)           | 29 (16-850)                          | 23 (4-296)                 | 0.120*  |
| LDH, IU/L (min-max)   | 461 (136-1904)       | 524 (242-1904)                       | 363 (136-986)              | 0.002*  |
| CK, U/L (min-max)     | 118 (20-1416)        | 152 (20-1416)                        | 89 (20-519)                | 0.013*  |
| Albumin, g/dL (min-max) | 3.20 (2.23-4.34)    | 3.10 (2.30-3.80)                     | 3.40 (2.23-4.344)          | 0.039*  |
| **Cardiac enzymes**   |                      |                                      |                             |         |
| NT-proBNP, pg/mL (Mean ± SD) | 10340 ± 13765 | 3975 ± 8288                          | 17251 ± 15233              | < 0.001** |
| Trop-I, ng/mL (min-max) | 0.10 (0.10-21.29) | 0.10 (0.10-3.53)                     | 0.12 (0.10-21.29)          | 0.112*  |
| **Coagulation parameters** |                      |                                      |                             |         |
| Fibrinojen, ng/dL (min-max) | 391 (143-1066) | 473 (200-1066)                       | 350 (143-676)              | 0.001*  |
| D-dimer, μg/mL (min-max) | 2.16 (0.19-25.20) | 2.15 (0.19-24.40)                    | 2.33 (0.19-25.20)          | 0.808*  |
| INR, (min-max)        | 1.24 (0.90-2.57)     | 1.22 (0.90-2.57)                     | 1.26 (1.04-2.52)           | 0.038*  |
| **Total blood count** |                      |                                      |                             |         |
| Wbc, 10⁹/L (Mean ± SD) | 12.03 ± 6.09        | 10.07 ± 4.89                         | 14.22 ± 6.60               | 0.003** |
| Neu, 10⁹/L (Mean ± SD) | 9.25 (3.10-3.76)    | 8.73 (1.93-20.92)                    | 10.37 (2.46-26.19)         | 0.110*  |
| Lymph, 10⁹/L (Mean ± SD) | 0.84 (0.23-10.23) | 0.74 (0.26-2.35)                     | 1.68 (0.24-10.23)          | 0.009*  |
| Hgb, g/dL (Mean ± SD) | 12.34 ± 1.91        | 12.88 ± 1.63                         | 11.74 ± 2.04               | 0.010** |
| Htc, % (Mean ± SD)    | 38.40 ± 5.83        | 38.71 ± 4.91                         | 38.06 ± 6.77               | 0.633** |
| Plt, 10⁹/L (Mean ± SD) | 237 ± 107           | 223 ± 105                            | 252 ± 109                  | 0.237** |
| **Arterial blood gas analysis** |                      |                                      |                             |         |
| pH, (Mean ± SD)       | 7.38 ± 0.11         | 7.42 ± 0.91                          | 7.33 ± 0.11                | < 0.001** |
| Po₂, mmHg (min-max)   | 67.75 (32-142)      | 54 (32-142)                          | 75.30 (46-130)             | < 0.001* |
| Pco₂, mmHg (Mean ± SD) | 39.85 ± 14.65      | 35.61 ± 9.00                         | 44.58 ± 18.06              | 0.008** |
| Hco₃, mEq/L (min-max) | 23.35 (11.40-41.00) | 23.30 (16.20-31.50)                  | 23.50 (11.40-41.00)        | 0.577*  |
| SpO₂, % (Mean ± SD)   | 88.94 ± 8.71        | 85.60 ± 9.99                         | 92.67 ± 4.92               | < 0.001** |
| Lactate, mmol/L (min-max) | 2.00 (0.50-14.00) | 1.80 (0.50-4.80)                     | 2.30 (0.50-14.00)          | 0.131*  |
| **Inflammatory parameters** |                      |                                      |                             |         |
| CRP, mg/dL (Mean ± SD) | 10.64 ± 8.49        | 15.33 ± 7.19                         | 5.43 ± 6.62                | < 0.001** |
| PCT, ng/mL (min-max)  | 0.41 (0.04-97.50)   | 0.30 (0.05-97.58)                    | 0.45 (0.04-97.50)          | 0.640*  |
| Ferritin, ng/mL       | 580.07 ± 619.60     | 873.47 ± 643.96                      | 261.53 ± 401.28            | < 0.001** |

Me: Mean, SD: Standard derivation, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase, CK: Creatine kinase PCT: Procalcitonin, NT-proBNP: N-terminal prohormone of brain natriuretic peptide, CRP: C-reactive protein, Lymph: lymphocyte, Wbc: White blood cell, Neu: Neutrophil, Hgb: Hemoglobin, Htc: Hematocrit, Plt: Platelets, INR: International normalized ratio, Trop-I: Troponin-I.

* Mann-Whitney U test.  
** Independent samples t test.
most cases (14,17). In our study, in line with the literature, the most common symptoms in AHF cases were shortness of breath (100%), pretibial edema (54.2%), and cough (14.2%), respectively.

The clinical manifestations of COVID-19 cases range from mild manifestations such as asymptomatic disease and mild upper respiratory tract infection to severe viral pneumonia that can lead to acute respiratory failure and death. Fever, cough, headache and weakness are the most common symptoms at the beginning of the disease. However, in 20% of the cases, pneumonia, which is the most serious and common presentation of the disease, may develop. This period is called the pulmonary phase of the disease and it is reported that shortness of breath is a common symptom on admission to the emergency department (5,8,20-25). Consistent with the literature, in our study, the most common symptoms in COVID-19 pneumonia patients were cough (94.8%), shortness of breath (92.3%), and fever (71.7%), respectively.

Pretibial edema due to the excess volume was found more frequently in AHF cases. Moreover, while fever was detected in 71.8% of COVID-19 pneumonia cases at the time of admission to the ED, it was not found in any of the AHF cases (p< 0.001). In addition, while a history of contact with a COVID-19 patient was 76.9% in COVID-19 pneumonia group, none of the AHF cases had a history of contact with a COVID-19 patient (p< 0.001). In the differential diagnosis of AHF from COVID-19 pneumonia during the pandemic pro-cess, COVID-19 contact history, symptoms and findings can provide important information to clinicians, in the first evaluation.

Detecting suspicious cases as soon as possible during the COVID-19 pandemic process is the most important point in controlling the spread of the disease (18). The gold standard method in the diagnosis of COVID-19 is detection of viral nucleic acids by RT-PCR testing method. Although RT-PCR test has high specificity in diagnosis, its sensitivity is low due to its false negative results. For this reason, it has been suggested that the test is insufficient. In addition, achieving results in an average of 15 hours may cause delays in diagnosis and treatment (4,26-29).

Thorax CT has become an important tool in the diagnosis and follow-up of COVID-19 cases, thanks to the specific pathological findings in thorax CT images. In COVID-19 cases, pathological findings can be detected in thorax CT images, despite negative RT-PCR test results, and even when the patients are in the asymptomatic period. Although thorax CT is not the gold standard diagnostic test in COVID-19 cases, it can be helpful in diagnosis and differential diagnosis. In COVID-19 pneumonia, thorax CT typically shows bilateral peripheral and/or subpleural ground glass opacities, multifocal patchy consolidations, and crazy paving pattern (4,26,27,30-35). In our study, consistent with the literature, the most common thorax CT findings in COVID-19 pneumonia cases were ground-glass opacities (97.4%), consolidations (92.3%) and crazy paving pattern (28.2%) with peripheral location.

Although typical findings in thorax CT imaging for COVID-19 pneumonia are described, these findings can be confused with several diseases. AHF is another clinical condition, which is a common cause of ground glass densities observed in thorax CT images. In AHF, contrary to COVID-19 pneumonia, the ground glass densities observed predominately in the central parts, whereas peripheral parts of the lung are protected. On the other hand, in AHF, other differential findings observed in thorax CT images are pleural effusion, mediastinal lymphadenopathy, septal thickening, and enlarged pulmonary veins (9,11,18,33,36). In our study, similar to the literature, ground glass opacities (80%) and consolidations (65.7%) were predominately located in the central and lower lobes, in AHF patients. In addition, cardiomegaly in 91.4% and pleural effusion was found in 74.2% of the cases.

In our study, in COVID-19 pneumonia cases thorax CT lesions were mostly located in the peripheral parts, whereas lesions in AHF cases were mostly centrally located. In addition, pleural effusion and cardiomegaly findings were detected more frequently in AHF cases compared to COVID-19 cases. It should be noted that, the distribution of lesions on thorax CT images and the presence of pleural effusion and cardiomegaly can provide important information to clinicians in the first evaluation in the emergency department.

In COVID-19 patients, in the early period of the disease, lymphopenia is prominent in complete blood count and as the disease progresses, the lymphocyte count continues to decrease, whereas inflammatory markers increase (25,35,37,38). In our study, consistent with the literature, the mean lymphocyte count was lower in COVID-19 pneumonia group compared to the AHF group (p= 0.009). In addition, in the studies it has been shown that lymphopenia
and high serum ferritin, D-dimer, CRP, troponin, and LDH levels in COVID-19 cases were associated with poor prognosis and increased mortality (37-42). In our study, LDH, CK, CRP, and ferritin levels were increased in both groups; however mean levels of LDH, CK, CRP and ferritin were significantly higher in COVID-19 pneumonia group (p< 0.002, p= 0.013, p<0.001, p< 0.001, respectively). Similarly, although the levels NT-proBNP were increased in both groups, it was significantly higher in the AHF group (p< 0.001).

LIMITATIONS
Present study has some limitations. Firstly, this is a single center retrospective cohort study with relatively small sample size. Secondly, all thorax CT findings are reviewed by a single radiologist experienced in chest radiology.

CONCLUSION
In conclusion, we think that contact history, laboratory data and thorax CT findings can be useful in distinguishing acute heart failure from COVID-19 pneumonia in patients who admitted to the emergency department with respiratory distress during the pandemic process and can provide very important information to clinicians.

Ethical Committee Approval: The study protocol was approved by Turkish Ministry of Health and Clinical Ethics Committee of Inonu University (protocol code: 2020/125).

CONFLICT of INTEREST
The authors of this meta-analysis declare that they have no conflict of interest.

AUTHORSHIP CONTRIBUTIONS
Concept/Design: USK, AG, LAD, İP, ÖC, OK
Analysis/Interpretation: USK, AG, MY, RK, HŞ, OK
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