Original Investigations

Clinical and radiologic characteristics of symptomatic pregnant women with COVID-19 pneumonia

Kuzan et al. Pregnancy and COVID-19 pneumonia

Taha Yusuf Kuzan[1], Kübra Murzoğlu Altıntoprak[1], Hatice Özge Çiftçi[1], Beyza Nur Kuzan[2], Murat Yassa[3], Niyazi Tuğ[3], Nuri Çagatay Çimşit[2]

[1]Clinic of Radiology, Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital, İstanbul, Turkey
[2]Department of Radiology, Marmara University Faculty of Medicine, İstanbul, Turkey
[3]Clinic of Obstetrics and Gynecology, Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital, İstanbul, Turkey

Address for Correspondence: Taha Yusuf Kuzan
Phone: +90 216 606 33 00 e-mail: tykuzan@gmail.com ORCID: orcid.org/0000-0002-5420-8507

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Abstract

Objective: To describe the radiological features, diagnostic accuracy and features of imaging studies and their relation with clinical course of coronavirus disease 2019 (COVID-19) pneumonia in pregnant women.

Material and Methods: The clinical, laboratory and radiological features of symptomatic pregnant women suspected for COVID-19 were retrospectively reviewed. Chest radiography (CXR) and chest CT findings of COVID-19 in pregnant women were identified.

Results: Fifty-five of eighty-one pregnant women were included in the final analysis. The most common admission symptoms were dry cough (45.4%), fever (29.1%) and dyspnea (34.5%). Radiological imaging studies were performed to 34 (61.8%) patients. Fourteen (66.7%) of the laboratory-confirmed COVID-19 patients had parenchymal abnormalities in CXR, and most common abnormalities were airspace opacities (61.9%) and prominent bronchovascular shadows (28.6%). Seventeen (85.0%) of the patients had parenchymal abnormalities consistent with COVID-19 in their chest CT. Chest CT most commonly showed bilateral (88.2%), multilobe (100%) involvement; peripheral and central distribution (70.6%); patchy-shape (94.1%) and ground-glass opacity (94.1%). The

sensitivity of CXR and chest CT was calculated as 66.7% and 83.3%, respectively. Preterm birth rate was 41.2% (n = 7/17). Five (9.1%) of the 55 pregnant women admitted to the intensive care unit, three of those developed acute respiratory distress syndrome (ARDS) and one of them died.
Conclusion: This study describes the main radiological features of symptomatic pregnant women infected with COVID-19. The refusal rate among pregnant women for the imaging modalities involving ionizing radiation was high. The preterm birth and cesarean section rates were observed as remarkably increased.
Keywords: COVID-19, pregnancy, computed tomography, chest radiography, radiology

Introduction

Pregnancy is known to cause significant anatomical and physiological changes in respiratory functions; these changes can increase susceptibility to respiratory tract infections and can quickly lead to respiratory failure [1]. In addition, the change of immune system during pregnancy leaves pregnant women vulnerable to viral infections, which may lead to even more severe symptoms [2]. Previous studies have also shown that Severe Acute Respiratory Syndrome (SARS) / Middle East Respiratory Syndrome (MERS) infections were associated with serious maternal diseases, maternal deaths, and spontaneous abortions [3–5]. Pregnant women are at increased risk for severe illness from COVID-19 compared to non-pregnant people [6,7]. Additionally, there may be an increased risk of adverse pregnancy outcomes, such as preterm birth, among pregnant people with COVID-19 [8,9]. Moreover, the high refusal rate of modalities involving ionizing radiation during pregnancy and the risks to fetuses present as a limiting factor in the diagnosis and treatment of pregnant women, making the diagnostic process more difficult when compared to the non-pregnant population [10]. Therefore, pregnant women constitute a vulnerable group that requires special attention in the diagnosis and treatment of COVID-19.

The most commonly used reference standard in the diagnosis of COVID-19 is the reverse transcription polymerase chain reaction (RT-PCR) test. However, due to the technical limitations of the test and its relatively higher false negative rates, radiological imaging including chest CT and chest radiography (CXR) play an important role in the diagnosis and evaluation of pregnant women suspected with COVID-19 infection [11,12]. Chest CT has been reported to be more sensitive than other modalities in the diagnosis of COVID-19 pneumonia [13].

The robust data about radiological and clinical features of pregnant women with COVID-19 pneumonia is scarce in the literature. This study aimed to identify the demographic characteristics and evaluate the clinical, laboratory, and radiological findings of symptomatic pregnant women with COVID-19 pneumonia.

Materials and Methods

Patient population and study design

This retrospective study was yielded at two tertiary health care centers dedicated for SARS-CoV-2 pandemic between March 15th and September 1th, 2020. Symptomatic pregnant women suspected with COVID-19 infection were included to the study. Patients who were tested for SARS-CoV-2 infection for universal screening purposes were not included in the study [14]. Patients who refused chest CT or CXR with negative PCR test result were excluded. Those patients were managed according to the national guidelines [15]. Pregnant women with COVID-19 infection confirmed either with PCR-testing or imaging studies were included to the final analysis (Figure 1). The disease was classified as mild, moderate and severe according to its clinical severity [15].

The demographic characteristics, clinical signs and symptoms, and laboratory results of the patients were obtained from the patients' electronic health records. Clinical symptoms, including fever (≥ 37.3°C), cough, dyspnea, sore throat, and fatigue, were assessed in terms of COVID-19. RT-PCR tests were performed on the combined swab samples taken from the oropharynx and the nasopharynx of the patients were used to confirm SARS-CoV-2 infection. The radiological

examinations (CT and/or CXR) of the pregnant women were re-evaluated independent from the initial report. The study was approved by the local Ethical Committee (protocol no: 2020.4/07-312) and the national health authorities.

Radiologic imaging

Low-dose imaging protocol was followed. Radiological imaging criteria were met if at least 2 of the following symptoms were present: a fever above 38.3 °C, a respiratory rate of 22 breaths/minute and above, saturation of peripheral oxygen (SpO_2) below 93%, or severe dyspnea. The possible effects of radiation exposure on the fetus were explained in detail and written consent was obtained from each patient. The choice of imaging method (CXR and/or CT) was decided together with the patient, considering diagnostic performance of imaging methods, the pregnancy trimester and the clinical condition of the patient.
Chest radiography was performed using a digital X-ray machine (DRGEM Radiography System, South Korea). The CXR parameters are as follows: 75-110 kVp, 4-8 mAs, and detector size 35 cm x 43 cm with grid. During the examination, the abdomen and pelvis were protected with a lead sheath. The effective dose for CXR images was not exceed 0.07 mSv (millisieverts).
Chest computed tomography was performed on all patients using a 16 or 128-slice CT scanners (Optima 520 CT, GE company or Ingenuity Core 128, Philips Healthcare). CT images were obtained with the patient in the supine position at full inspiration and without contrast medium. For the pregnant participants, 80 kV tube voltage, 50 mAs automatic tube current modulation, 5 mm slice thickness, 5 mm slice interval, a noise index of 16, 36.0 DFOV, and 512 x 512 matrix were used. The thyroid, abdomen, and pelvis were protected by the lead sheath. The dose-length product (DLP) was 25-100 mGy.

Image analysis

The reconstructed images were transmitted to the workstation and picture archiving and communication systems (PACS) for multiplanar reconstruction post-processing. The chest radiographs and chest CT images of the cases were evaluated by three radiologists, blinded to RT-PCR results, at the radiology workstation. In the cases where the three radiologists evaluated differently, the result was reached by consensus.
The CXR findings were classified as typical, indeterminate, atypical, and negative for COVID-19 [16]. For statistical evaluation, typical and indeterminate groups were considered COVID-19 positive, and atypical and negative groups were accepted as COVID-19 negative. An example of chest CXR findings is shown in Figure 2.
CT findings were categorized as non-COVID-19, indeterminate COVID-19, probable COVID-19, and classic COVID-19 according to the COVID-19 infection version 2 of the British Society of Thoracic Imaging (BSTI) [17]. For statistical evaluation, non-COVID-19 cases were categorized as CT negative group, while indeterminate COVID-19, probable COVID-19 and classic COVID-19 cases were categorized as CT positive group.
The distribution in the lung, shape, location, appearance, and size of the largest lesion were recorded. In addition, vascular enlargement, intralobular / interlobular septal thickening, air bronchogram, subpleural curvilinear lines, parenchyma findings such as bronchial wall thickening, fibrous bands, halo sign, reversed halo sign noted. Extrapulmonary findings such as pleural effusion, pleural thickening, and enlarged lymph nodes were also included. In the chest CT positive cases, CT severity index according to the degree of lesion distribution was calculated as described previously [18].

Statistical Analysis

Descriptive analyses were performed for the characteristics of the patients. The normally distributed continuous random variables were expressed as the mean ± SD and categorical variables are expressed as percentages. Fisher's exact test was used to compare the severity of the disease between trimesters and the one-way ANOVA test was used to compare the severity of pneumonia involvement (CT severity index). The sensitivity of CXR and chest CT was calculated for the diagnosis of COVID-19 disease, using RT-PCR as reference. SPSS 17.0 was used for the statistical analyses.

Results

Eighty-one pregnant women suspected with COVID-19 infection were enrolled. Forty-seven patients (58.0%) refused chest CT and CXR due to the possible effects of ionizing radiation. Out of these, 26 patients who had negative RT-PCR-testing were excluded. Fifty-five pregnant women with COVID-19 infection confirmed either with RT-PCR-testing or imaging studies were included to the final analysis. With RT-PCR testing alone 29, imaging studies alone 2, and both, 24 pregnant women were confirmed to have COVID-19 infection. Radiological imaging studies were performed to 34 (61.8%) patients. The positivity rate in PCR-testing among patients with abnormal imaging was 92.3% (n = 24/26).

Demographic, clinical and laboratory characteristics of pregnant women were given in Table 1. The first, second, and third trimester distribution of pregnant women at the time of application were 8 (14.6%), 24 (43.6%), and 23 (41.8%), respectively. The patients' clinical condition was mild in 8 (100%) pregnant women in the first trimester. In the second trimester, 20 (83.3%) cases were mild, 3 (12.5%) cases were moderate, 1 (4.2%) case severe, in the third trimester 18 (78.3%) cases were mild, 2 (8.7%) cases were moderate, 3 (13.0%) cases were severe. Although mild and severe cases were more frequent in the third trimester, the difference between trimesters was not statistically significant ($P = 0.672$). CT severity index of pregnant women in first, second, and third trimesters was 3.7, 7.5, and 6.3, respectively. Although pneumonia involvement (CT severity index) was higher in the second and third trimester, the difference between trimesters did not reach a statistically significant level ($P = 0.697$). During the study period, 12 cases gave birth by cesarean (C/S), and 5 cases had a normal spontaneous vaginal delivery (NSVD), for a total of 17 cases delivered (7 preterm, 10 term), and 1 case of missed abortus (7 weeks). The remaining 37 were still pregnant during the study.

Five of 55 patients (9.1%) were admitted to the intensive care unit (ICU). One patient and the fetus died in her 22nd weeks of gestation due to acute respiratory distress syndrome (ARDS). CXR detail of that patient was common airspace opacities more prominent in the lower lobes, compatible with ARDS (Fig. 2). Repeated RT-PCR testing was performed to 9 of 34 (26.5%) patients whose first RT-PCR test was negative. Second RT-PCR test increased the COVID-19 positivity rate from (47/81) 58.0% to (53/81) 65.4%. There was no vertical transmission.

The radiological classification of imaging studies was summarized in Table 2. Twenty-one of 34 patients underwent CXR and 20 of them underwent low-dose chest CT. In 7 patients, both CXR and chest CT were performed. The sensitivity of CXR and chest CT was calculated as 66.7% (95% CI 43.0 to 85.4%) and 83.3% (95% CI 58.6 to 96.4%), respectively, using RT-PCR as reference. Fourteen of the 21 COVID-19 patients (66.7%) had parenchymal abnormalities in CXR. 12 had bilateral and 1 had unilateral airspace opacities (consolidation or ground-glass opacity) and, 1 had prominent bronchovascular shadows alone. The distribution of the airspace opacities was central and peripheral in 5 cases, central in 4 cases, and peripheral in 5 cases. Prominent bronchovascular shadows were observed in 6 cases, 5 of which were bilateral. The radiological findings of abnormal chest CT were given in Table 3.

Discussion

This study defined the clinical presentation, laboratory and radiological features of symptomatic pregnant women diagnosed with SARS-CoV-2 infection either by RT-PCR testing or imaging studies.

Imaging features of COVID-19 infection in pregnant women, as in the non-pregnant population, are predominantly peripheral and bilateral patchy ground glass opacities with or without consolidation [12,19–21]. In this study, the radiological features were commonly seen in both central and peripheral. This

difference might be related to the phase of the disease or the diseases might progress rapidly in pregnant women [20]. The other imaging features of COVID-19 were similar with previous studies [12,20,21] .

Three of every five pregnant women did not give consent for imaging studies involving ionizing radiation in this study. To the best of our knowledge, this finding was not previously reported. Royal College of Obstetricians and Gynecologists guidelines state that maternal health is more important than fetal health in pregnant patients: therefore, radiological examination can be performed in pregnant women in accordance with the as low as reasonably achievable [2]. In routine chest CT, the radiation dose is approximately 4-7 mGy, and the radiation dose of a CXR or low-dose chest CT is far below the accepted limit for a fetus [22]. Radiation exposure of less than 100 mGy in-utero after implantation has no proven deterministic effect on the fetus. However, stochastic effects of cancer induction are known to exist, albeit slightly, and increase in proportion to dose [23]. The use of radiological examinations in the diagnosis of COVID-19 pneumonia in pregnant patients requires special attention due to the risk of fetal teratogenicity caused by radiation exposure. The lung ultrasound may provide a good solution for patients who refuse chest CT or CRX [14,24].

The diagnostic performance of chest radiography in detecting COVID-19 pneumonia is lower than that of CT, and the sensitivity was reported to be 33–69% in studies involving few non-pregnant cases [25]. Chest CT sensitivity was reported as high as 94% in a meta-analysis [26]. Similarly, the sensitivity of CXR in detecting COVID-19 pneumonia was found to be 66.7% in this study, whereas chest CT sensitivity was 86.6%. Authors postulate that CXR can be used as the initial radiological examination for symptomatic pregnant patients with COVID-19 considering its relatively lower radiation dose and moderate sensitivity. However, a normal CXR can not rule out COVID-19. In this study, ARDS development was detected on the CXR in one case and on the chest CT in two cases and, one of these cases involved concomitant pneumothorax and pneumomediastinum (Figure 3). This severe patient was treated in the intensive care unit and required mechanical ventilation. Although spontaneous pneumomediastinum is a rare complication of COVID-19, the mechanism of pneumomediastinum is not clear [27].

Those individual cases led us the importance of radiologic imaging not only in diagnosing COVID-19 pneumonia but also in detecting accompanying complications of the disease.

The most common admission symptoms of the patients included in the study were dry cough, fever, and dyspnea, which were similar with those in the non-pregnant population. Laboratory findings showed a normal leukocyte count, lymphopenia, and increased CRP and LDH concentrations, which were similar to the findings in non-pregnant population [28,29].

In our study group, 6 of the 9 pregnant women whose first RT-PCR test was negative, had a positive result on the second RT-PCR test. Although the RT-PCR test is accepted as a reference in the diagnosis of COVID-19, the sensitivity of the test is low. The positivity rate of the first test is 60–71%, and the positivity rate increases with subsequent tests [30]. Thus, a diagnosis of COVID-19 should not be ruled out in pregnant patients with a single negative RT-PCR test result. Considering the method used to obtain the sample, and low sensitivity due to technical reasons, repetition of the test should not be avoided in cases where the first test is negative if clinical, laboratory, or radiological findings are consistent.

It is shown that COVID-19 in pregnancy was associated with maternal morbidity and preterm birth and required high (8%) intensive care admission [6,9]. Similarly, in this study 54.3% of all births were performed with cesarean section and the preterm birth rate was found as 58.8%. In addition, 9.1% of the pregnant patients included in the study admitted to the ICU, 3 of those developed ARDS and one of them died. Some of the studies conducted at the beginning of the pandemic claim that the course of COVID-19 during pregnancy is not different than non-pregnant [31,32]. Contrary to these studies, our preliminary results suggest that clinical course of the COVID-19 in pregnancy seems more severe, similar to more recent studies [7,33]. Similar to our study results, the trimester of pregnancy has been shown to affect the clinical severity of COVID-19 [34]. However, in our study, although there is a percentage difference

between trimesters, the reason for not having a statistically significant relationship may be the relatively small number of patients. RT-PCR test positivity was not observed in any of the delivered fetuses, which supports the notion that the disease has no vertical transmission [35,36].

Study Limitation

The limitations of our study are the absence of multiple RT-PCR tests in some pregnant women and the relatively low number of patients included in the study.

Conclusion

This study describes main radiological features of symptomatic pregnant women infected with COVID-19. The refusal rate among pregnant women for the imaging modalities involving ionizing radiation was high. The preterm birth and cesarean section rates were observed as remarkably increased.

Ethics Committee Approval: The study was approved by the local Ethical Committee (protocol no: 2020.4/07-312) and the national health authorities.
Informed Consent: Written consent was obtained from each patient.
Conflict of Interest: No conflict of interest is declared by the authors.
Financial Disclosure: The authors declared that this study received no financial support.

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Table 1. Demographic, clinical and laboratory characteristics of pregnant women at admission (n=55)	
Patient demographics	
Age (mean ± SD)	29.7 ± 6.4 (19 - 53)
RT-PCR positivity	53/81 (65.4%)
Presenting findings	
Fever (> 37.3°C)	16 (29.1%)

Dry Cough		25 (45.4%)
Dyspnea		19 (34.5%)
Fatigue		11 (20.0%)
Sore Throat		17 (30.9%)
Anosmia		5 (9.1%)
Suspicious contact		26 (47.3%)
Laboratory tests		
WBC	Low	1 (1.8%)
	Normal	43 (78.2%)
	High	11 (20.0%)
Lymphocyte	Low	23 (41.8%)
	Normal	32 (58.2%)
	High	0 (0%)
CRP (n=52)	Normal	18 (34.6%)
	High	34 (65.4%)
LDH (n=43)	Normal	26 (60.5%)
	High	17 (39.5%)
SD: Standard deviation; RT-PCR: reverse transcription polymerase chain reaction WBC: White Blood Cell; CRP: C-reactive protein; LDH: Lactate dehydrogenase		

Table 2. Radiologic imaging of patients (N= 34)	
Chest radiography classification (n=21)	
Negative	6 (28.6%)
Atypical	1 (4.7%)
Indeterminate	9 (42.9%)

Typical	5 (23.8%)
Chest CT classification (n=20)	
Normal	3 (15.0%)
Non-COVID-19	0 (0.0%)
Indeterminate COVID-19	2 (10.0%)
Probable COVID-19	1 (5.0%)
Classic COVID-19	14 (70.0%)

Table 3. Case-based chest CT findings of pregnant women with COVID-19

case	**1**	**2**	***3***	***4***	***5***	***6***	***7***	***8***	***9***	***10***	***11***	***12***	***13***	***14***	***15***	***16***	***17***
RT-PCR	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-
CT classification Classic COVID-19 Probable COVID-19 Indeterminate COVID-19 Non- COVID-19	Classic	Classic	Classic	Classic	Classic	Classic	Classic	Classic	Classic	Classic	Indeter-minate	Classic	Classic	Classic	Classic	Indeter-minate	Probable
Lung Involment Bilateral (B/L)	B/L	B/L	B/L	B/L	B/L	B/L	B/L	B/L	B/L	Right	B/L	B/L	B/L	B/L	B/L	B/L	Right

Right Left																	
Number of lobes involved (1-5)	5	5	5	5	4	5	5	5	5	2	2	4	5	3	5	2	2
Max diameter of lession (cm)	2.1	5.5	3.5	6.7	4.7	3.7	6.6	2.2	2.3	5.1	4.7	3.4	8	4.3	9.2	3.1	1.0
CT Severty Index Mild (≤ 5) Moderate (6-11) Severe (≥ 12)	Severe (18)	Moderate (7)	Severe (12)	Moderate (6)	Moderate (6)	Moderate (10)	Moderate (7)	Moderate (7)	Mild (5)	Mild (4)	Mild (2)	Mild (4)	Modarete (6)	Mild (3)	Severe (22)	Mild (2)	Mild (2)
Distrubition of Lesions Peripheral(P) Central (C) Peripheral and central (P&C)	P&C	P&C	P&C	P&C	P&C	P&C	P&C	P&C	P&C	P	P	P	P&C	P	P&C	P	P&C
Shape of lesions Patchy Diffuse	Patchy	Patchy	Patchy	Patchy	Patchy	Diffuse	Patchy	Patchy	Patchy	Patchy	Patchy	Patchy	Patchy	Patchy	Patchy	Diffuse	Patchy	Patchy
Appeareance of Lesions Ground glass opacity (GGO) Consolidation (c) GGO and consolidation (GGO&C)	GGO&C	GGO&C	GGO	GGO&C	GGO&C	GGO&C	GGO&C	GGO	GGO	GGO	C	GGO&C	GGO	GGO	GGO&C	GGO	GGO&C
CT Paranchimal findings																	

Vasculer enlargement	+	-	+	-	-	+	-	-	-	+	-	+	+	+	-	-	-
Intralobular reticular dencity	+	-	-	-	+	+	-	-	-	-	-	-	+	-	+	-	-
Bronchial wall thickening	+	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-
Subpleural curvilineer lines	+	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-
Air bronchogram	-	-	-	+	-	+	-	-	-	-	+	-	-	-	+	-	-
Fibrous band	+	-	-	+	+	-	-	-	-	-	+	-	+	-	+	-	-
Subpleural sparing	-	+	+	-	-	+	+	-	-	-	-	+	+	-	-	-	-
Halo sign	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-
Reversed halo sign	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Extrapulmonary Manifesation																	
Pleural thickening	-	-	-	-	-	-	-	-	-	+	+	+	-	-	-	-	-
Lymphadenopaty	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Pleural effusion	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-
Pneumomediastenum and Pneumothorax	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-

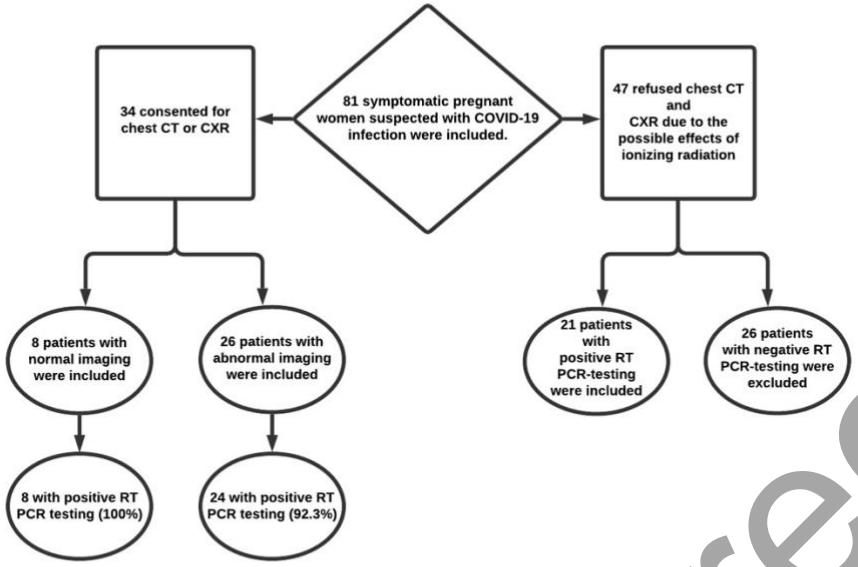
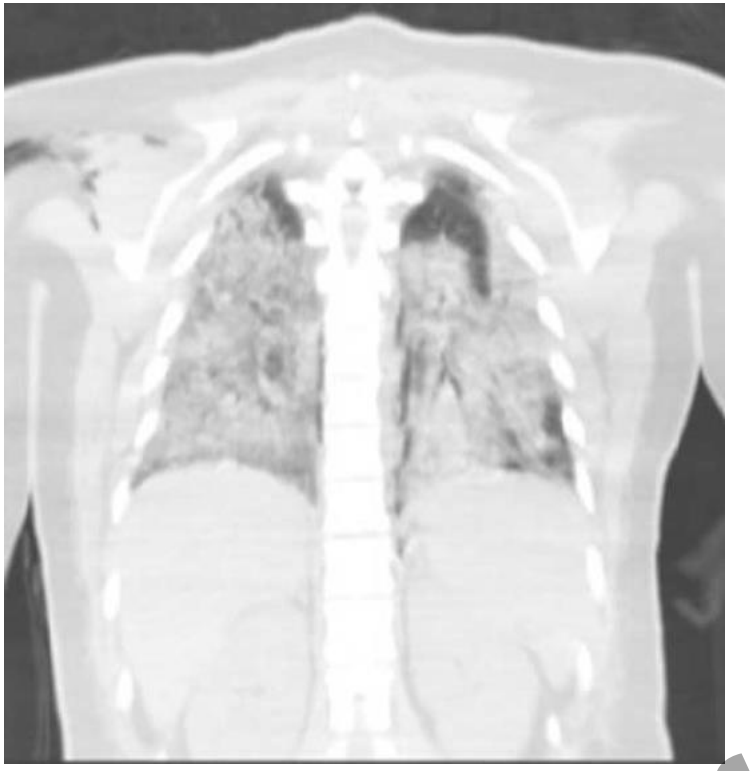


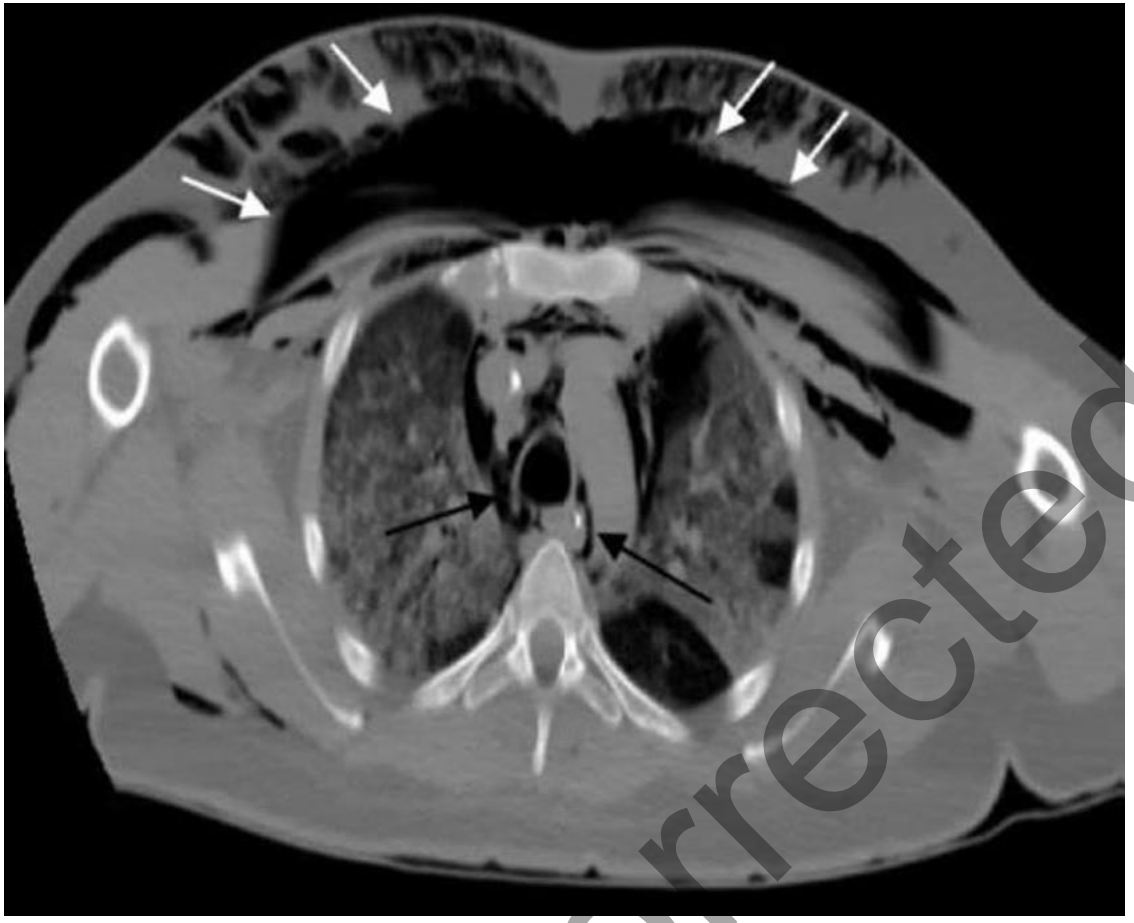
Figure 1. Flowchart of the study

Figure 2. A 35-year-old, laboratory-confirmed COVID-19, a pregnant woman with 25 weeks of pregnancy presented with fever and dyspnea. The patient developed hypoxic respiratory failure and was admitted to intensive care unit. Anteroposterior chest radiograph shows an ARDS pattern with ill-defined alveolar consolidation bilaterally in the predominantly lower zones

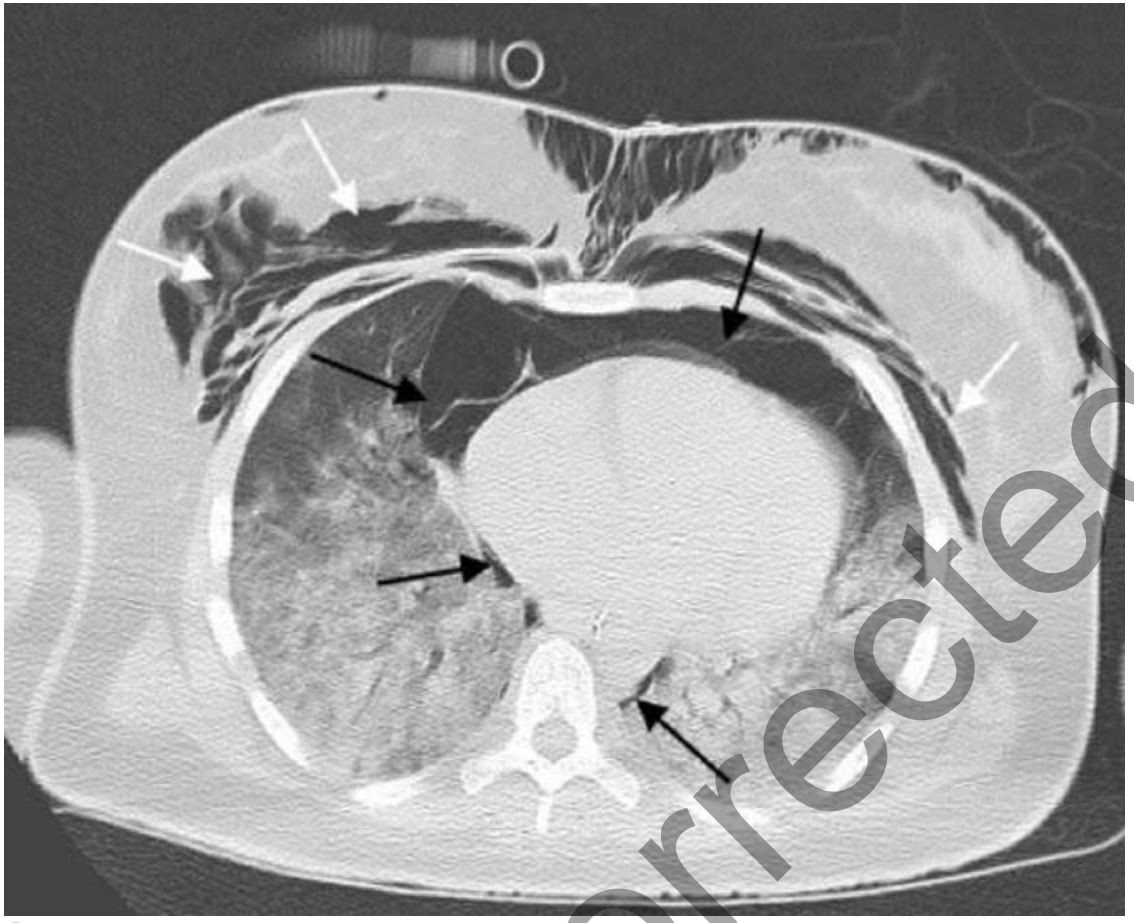


a

b



c



d

Figure 3. CT images obtained 2 hours after emergency cesarean section due to fetal distress of a 25-year-old woman with COVID-19. Coronal images (a, b) show bilateral diffuse and multiple patchy ground-glass opacities with partial consolidation. CT severity index is 22 and classified as severe. All CT images (a, b, c, d) show air in the mediastinum which is outlining mediastinal organs (black arrows). Also axial CT images (c, d) show extensive subcutaneous emphysema (white arrows) in the anterior chest wall