

## CASE REPORT

# A CASE OF BILATERAL RECURRENT EXUDATIVE PLEURAL EFFUSION IN A POST COVID PATIENT

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### Abstract:

COVID-19-related pleural effusions are frequently described during the ongoing pandemic. Pleural effusions result from the accumulation of fluid in the pleural space surrounding the lungs. The most common causes of bilateral pleural effusions are due to congestive cardiac failure, nephrotic syndrome, anasarca due to any protein deficiency state or fluid overload, hypothyroidism. Few exudative causes of bilateral pleural effusion also like tuberculosis, primary and metastatic pleural malignancy, bronchogenic Ca, lymphomas, Immunological diseases: Mixed connective tissue disease, long standing cardiac failure or liver failure (on diuretics). Exudative causes of bilateral turbid pleural effusion with recurrent accumulation are very rare without any other associated pathology. The significance of pleural effusions in COVID-19 pneumonia has not been well assessed due to the rarity of the disease limited to case reports/series. A 72-year-old male patient comes to emergency with the complaints increasing shortness of breath for 3 days, Dry cough for same duration, H/O of COVID pneumonia 2 months back with no other comorbidity. A chest computer tomography (CT) radiograph revealed a bilateral pleural effusion, which was further assessed as exudative type. Pleural fluid study reveals exudative hemorrhagic turbid fluid with ADA 71.5 U/L with neutrophilic leukocytosis. Pleural fluid culture reveals moderate growth of pseudomonas species with scanty growth of Candida species. The patient was diagnosed as a case of bilateral complicated recurrent parapneumonic effusion and treated with antibiotic as culture sensitivity with steroids. After 4 times aspiration paracentesis patient was discharged with minimal bilateral pleural effusion. The patient has been followed for 4 months and now he is doing well.

**Key words:** Pleural Effusion, COVID-19, ADA, IL-6, HRCT

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### Introduction:

A transudative pleural effusion occurs when pleural fluid accumulates because of an imbalance between the hydrostatic and oncotic pressures. The leading causes of transudative pleural effusions are congestive heart failure, cirrhosis, and pulmonary embolism. In contrast, an exudative pleural effusion occurs when the local factors influencing the accumulation of pleural fluid are altered. The leading causes of exudative effusions are pneumonia, cancer, and pulmonary embolism.<sup>1</sup>

Pleural effusions result from the accumulation of fluid in the pleural space surrounding the lungs. More than 1.3 million cases occur each year in the United States. The cause of bilateral pleural effusions is generally thought to be due to congestive heart failure (CHF), renal or liver failure.<sup>2</sup>

Pleural effusions had been associated as an independent predictor for poor outcome in critically ill

patients with ARDS from infectious and non-infectious etiologies. A large observational study of 476 COVID-19 patients by Feng et al. reported that although the overall incidence of pleural effusions was 5.7%, the incidence of pleural effusions was 18% in critically ill patients versus 3.1% ( $p < 0.001$ ) in non-critically ill patients. Para pneumonic effusions together with empyema thoracis accounted for 20.4% of all our cases. It is estimated that about 40% of patients with pneumonia develop a concomitant pleural effusion although some studies show the incidence of this complication of pneumonia to be less than 20%.<sup>33</sup> In one series,<sup>4</sup> Para pneumonic effusion together with empyema's accounted for 14% of all cases of pleural effusions, both transudate and exudative.<sup>3</sup>

### Case Report:

A 72-year-old man nonsmoker, on diabetic normotensive was admitted to high dependency unit

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(HDU) due to increased shortness of breath for 3 days, dry cough for same duration, fall of oxygen saturation for 12 hours, H/O of Covid Pneumonia 2 months back with CT Severity score 15/35. Patient was well alert with occasional exertional shortness of breath after discharged from hospital 2 months back. He complaining of shortness of breath for last 3 days which increased on exertion but no orthopnea. He also noticed fall of oxygen saturation to 75 % and comes to emergency for better management. On physical examination reveals pulse 120 b/min, BP 130 /70 mm Hg, Temp 98.6F,R, Rate 30 breaths/min, Spo2 75 % with room air. There was no pallor, clubbing, pedal edema, jaundice or lymphadenopathy. Breath sound diminished on both lower chests with dullness on percussion note. There was no added sound on both sides of chest.

Laboratory results revealed the following values: white blood cell (WBC) count:  $3.3 \times 10^3$ /all (59% neutrophils, 37% lymphocytes, 4.10% monocytes, 3.3% eosinophils and 0.3% basophils); Hemoglobin: 8.10g/dL; platelet count:  $120 \times 10^3$ /iL; total protein: 7.1 g/dL (normal range: 6.0 to 8.3 g/dL); Albumin: 3.8 g/dL (normal range: 3.5 to 5.5 g/dL); Uric acid 608 imol/L (normal range: 90 to 420 imol/L); Erythrocyte sedimentation rate (ESR): 90 mm/h; CA-19.9- 30 U/ml: (normal range: <34 U/mL); CEA -3.08 ng/ml (normal range <5) Ferritin: 1120 ng/mL (normal range: 10 to 300 ng/mL); Interleukin 6-613.3 pg./ml (normal up to 7.0). D Dimer 3.04 mg/L (normal range <.55 FEU. CRP <5 mg/L, SGPT-58 U/L, Troponin I-<0.012 ng/ml, Procalcitonin .04ng/ml (Normal <0.046), NT -pro BNP-164.8 pg./ml, LDH-485 U/L (Normal 120-246). S. Creatinine-.4 mg/dl. Na-123 mmol/L. K-4.2 mmol/L, TSH-2.47 i IU/ml. Echocardiogram-color Doppler shows normal study with PASP 36 mm of Hg. His previous HRCT Chest reveals bilateral pleural effusion with pneumonia on resolution 11/2 months back.

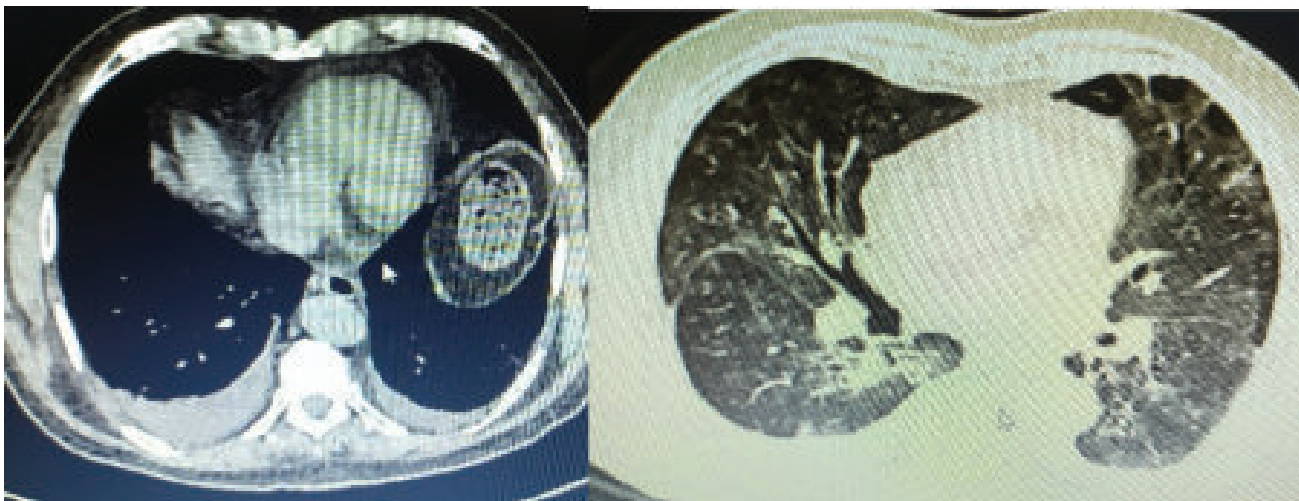
This time HRCT of Chest reveals bilateral pleural effusion more on left side (Fig.-1). On 3<sup>rd</sup> day of admission about 1000 cc purulent color fluid was

drawn from left side and send for investigation. Analysis of the left sided pleural fluid revealed an exudative type. The pleural fluid contained WBC 21485 cell/mm (55% neutrophils, 43% lymphocytes, 2% macrophages, mesothelial cell 2%) RBC 8946c/mm, total protein 3100 mg/dL, LDH 3160 U/Sugar 91.8 mg/dl and ADA 71.5 U/L (normal range: <25 U/L). Pleural fluid culture was sterile and Gene expert for TB PCR negative. And pleural fluid for cytology shows no malignant cell. The right side pleural fluid about 800 cc on next day showed the similar exudative type.

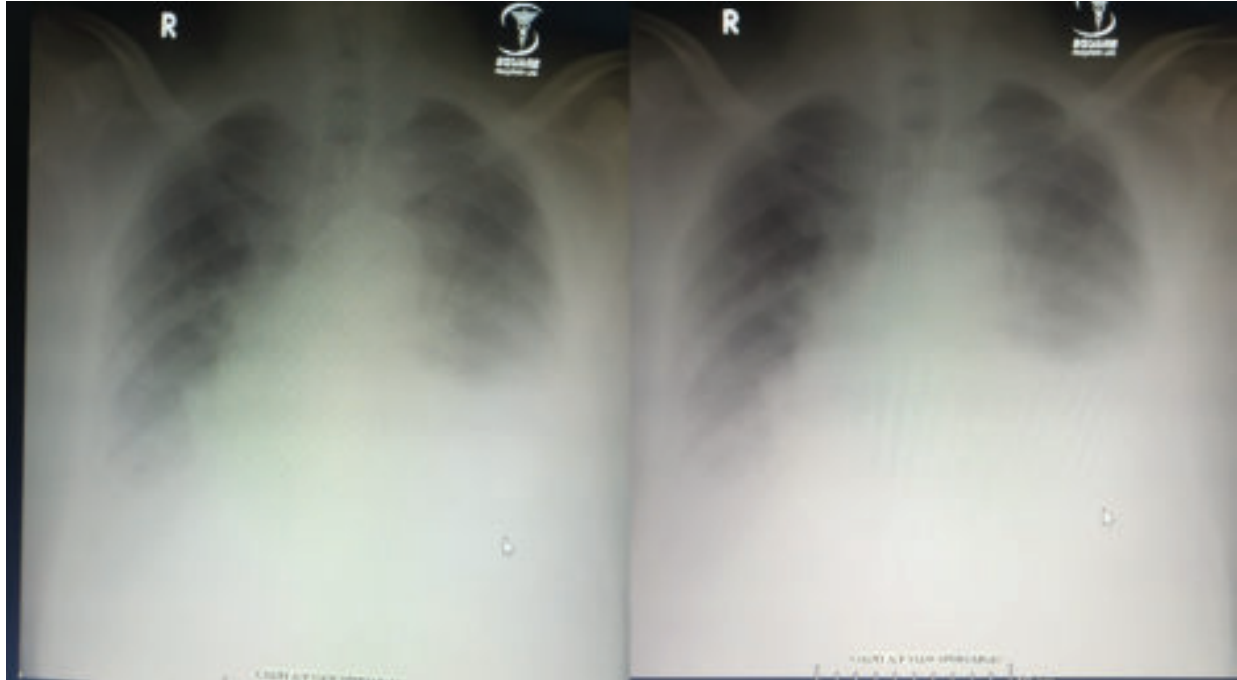
After 2 days 'patient's oxygen demand decreased to 1 liter and moved to cabin. USG of chest revealed again bilateral pleural effusion about 440 cc on rt side and 23 cc on left side. Chest X-ray also revealed rt sided effusion (Fig-2). USG of whole abdomen after 2 days revealed bilateral pleural effusion on right about 500 cc and on left about 110 cc, Fatty change in liver grade 1, bilateral renal cortical cysts. Again 10th day after admission USG guided aspiration of fluid from right side done, revealed purulent color of fluid and send for investigation again. The pleural fluid again was turbid and study reveals WBC 4233 cell/mm (73% neutrophils, 25% lymphocytes, 2% macrophages, 2% mesothelial cell), RBC 10230 cell/cmm, total protein 3300 mg/dL, LDH 3230 U/Sugar 55.8 mg/dl and ADA 41.2 U/L (normal range: <25 U/L). Gene expert for TB PCR was Negative and pleural fluid for cytology shows no malignant cell. Culture of fluid revealed growth of pseudomonas species. This time pts IL -6 was increased to 1340 pg./ml.

Moderate growth, candida species (non albicans-scanty growth which is carbapenem resistant (CRE+). Antibiotics were rescheduled accordingly.

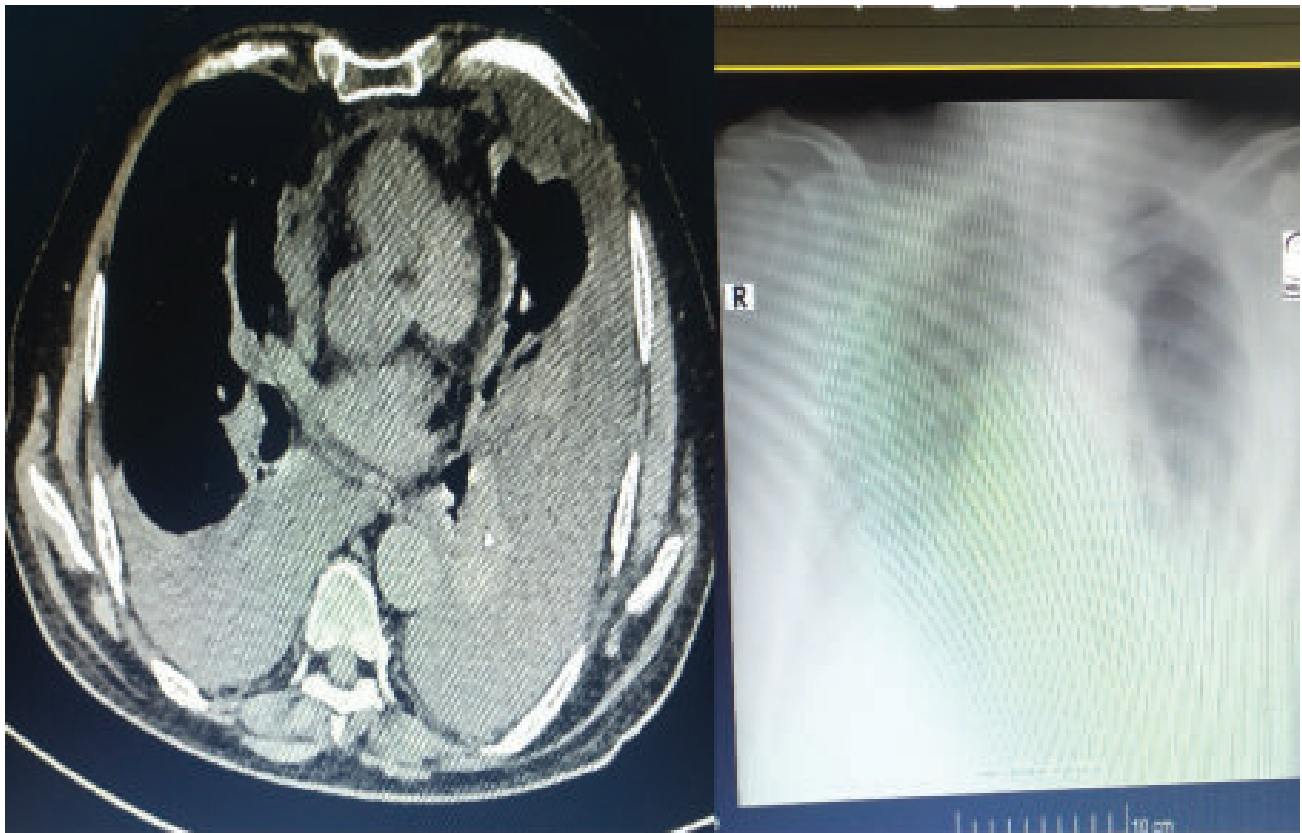
On 12 th day of admission patients developed chest tightness and CT Chest revealed bilateral pleural effusion more on right side (Fig.-3). Bedside aspiration of turbid pleural fluid of about 300 cc was drawn again from right side.



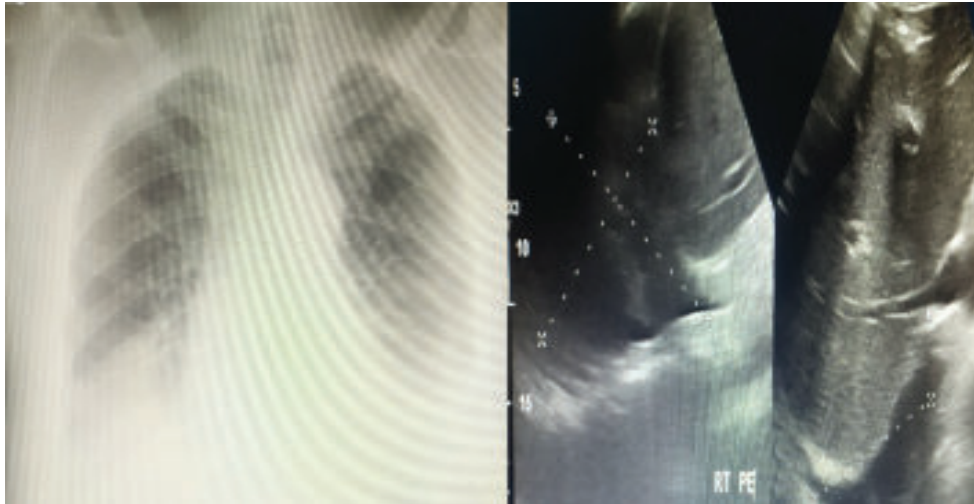
**Fig.-1:** HRCT chest showing bilateral pleural effusion with bilateral consolidation (during admission with covid-19)



**Fig.-2:** Chest X-ray A/P view showing increasing bilateral pleural effusion.



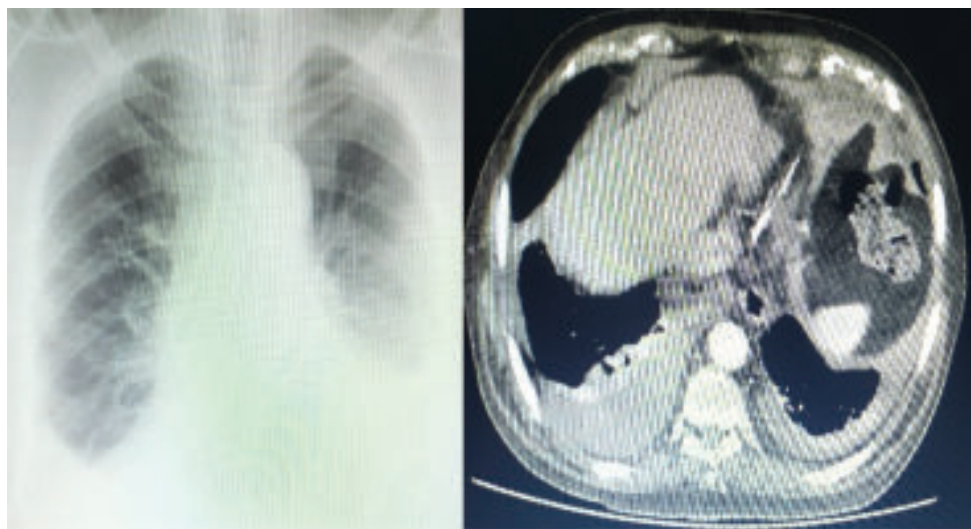
**Fig.-3:** CT Chest showing bilateral pleural effusion and chest x-ray A/P View showing bilateral minimal pleural effusion with left sided iatrogenic pneumothorax (after aspiration from left side).



**Fig.-4:** Chest X-ray A/P View showing bilateral pleural effusion more on rt side, USG Chest confirms right sided pleural effusion of about 600cc.



**Fig.-5:** Chest X-ray A/P View showing bilateral pleural effusion and CT Chest with contrast showing bilateral pleural effusion with collapse consolidation



**Fig.-6:** Chest CT Showing bilateral pleural effusion persists and X Ray Chest P/A View showing almost normal X-ray.

Patient was given 300 ml Albumin as serum albumin was 2.4 mg/dl on 19<sup>th</sup> days of admission. 07 days after 3<sup>rd</sup> aspiration patient complaints of heaviness in chest but no fever or cough. USG of chest reveals bilateral pleural effusion of about 600 cc on right side and 700 cc on left side. CXR P/A view also reveals bilateral moderate pleural effusion (Fig.-4). On 22<sup>th</sup> days of admission, aspiration of pleural fluid of about 1000 cc done from both sides done and study reveals WBC 23632 cell/cmm (90% neutrophils, 6% lymphocytes, 4% macrophages, <1% mesothelial cell), RBC 9540 cell/cmm, total protein 3500 mg/dL, LDH 3350 U/L Sugar <19.8 mg/dl and ADA 75.24 U/L (normal range: <25 U/L). Gene expert for TB PCR was negative and pleural fluid for cytology shows no malignant cell. Aerobic culture shows no growth this time. Pts IL-6 was down to 387 pg./ml.

Patient was gradually improved with no further complaints. After 14 days' injectable antibiotics with polymyxin B, injmoxifloxacin, injteicoplanin. Tab voriconazole with low dose steroid was added considering post covid syndrome. Patient was given discharge with exertional dyspnea but no oxygen requirement. He was being diagnosed as a case of bilateral complicated Para pneumonic effusion with post covid syndrome. After 15 days of follow up patient is exertional dyspnea persists with no H/O of weight loss. Again CT Chest with contrast done and it shows bilateral pleural effusion with no other abnormality with IL-6 230 pg./ml (Fig.-5). Patient was advised to continue deflazacort 6 mg and after 20 days of follow up he is quite ok with no exertional dyspnea. On 26<sup>th</sup> May his Chest X-ray P/A view reveals almost normal findings and his IL-6 dropped down to 30 pg./ml (Fig.-6).

#### Discussion:

Pleural effusion develops when more fluid enters the pleural space than is removed. Potential mechanisms of fluid increased interstitial fluid in the lungs secondary to increased pulmonary capillary pressure (i.e., heart failure) or permeability (i.e., pneumonia); decreased intrapleural pressure (i.e., atelectasis); decreased plasma oncotic pressure (i.e., hypoalbuminemia); increased pleural membrane permeability and obstructed lymphatic flow (e.g., pleural malignancy or infection); diaphragmatic defects (i.e., hepatic hydrothorax); and thoracic duct rupture (i.e., chylothorax). Although many different diseases may cause pleural effusion, the most common causes in adults are heart failure, malignancy, pneumonia, tuberculosis, and pulmonary embolism, whereas pneumonia is the leading etiology in children.<sup>4,5</sup>

The etiological distribution of exudative pleural effusions that is observed in a particular study depends

on the study population, whether the subjects are seen in a primary care or a tertiary referral setting, and the geographical region where the study is conducted.<sup>6</sup>

COVID-19 has been well described to present with a wide variety of respiratory complications that range from self-limiting upper respiratory tract infection to severe acute respiratory failure in the form of acute respiratory distress syndrome (ARDS) from underlying pneumonia.<sup>7,8</sup> According to eight observational studies, the location of reported pleural effusions was unilateral in 66.8% (443/663) of cases, with the remainder bilateral in 33.2% (220/663) of patients.<sup>9</sup>

Pleural diseases such as pleural effusions and pneumothoraces may also suggest a more severe clinical course in critically ill MERS patients. The presence of pleural effusion in the setting of other infections causing pneumonia (Para pneumonic effusions) has been well described among viral pathogens such as community-acquired influenza virus (A and B), adenovirus, measles, hantavirus, herpes simplex virus (HSV), Epstein-Barr virus (EBV), cytomegalovirus (CMV). Less frequently in varicella-zoster virus and human metapneumovirus.<sup>10</sup> The frequency of pleural effusions varies with age, according to a large observational study by Majidi et al. involving 552 COVID-19 patients.<sup>11</sup> In this study, although the overall rate of pleural effusions detected was 7.3%, a higher amount of COVID-19 patients age 50 years and older developed pleural effusions than those 50 years and under.

When patients with active COVID-19 infections and those with MIS present with sepsis-like illness, aggressive IV fluid will be administered, leading to a clinical state of fluid overload that may precipitate the development of diffuse bilateral lung infiltrates with pleural effusions, attributable to depressed cardiac function, overwhelming systemic inflammatory response, and third spacing of fluids.<sup>12</sup> At least 15% and more of COVID-19 patients developed either acute heart failure or kidney failure during their clinical course, increasing to more than 50% in critically ill patients.<sup>13</sup> The clinical state of fluid overload has been described as a potential etiology in SARS-related pleural effusions.

However, no study has been performed to determine the pre-existing comorbidities of congestive heart failure, hypoalbuminemia, chronic liver disease, and chronic renal failure with the risk of pleural effusions development in COVID-19 patients. The presence of SARS-CoV-2 was found in pleural effusions of 10 deceased COVID-19 patients during postmortem examination.<sup>14</sup> However, the location of pleural effusions (unilateral/bilateral), time of development,

and pleural fluid characteristics/cultures were not described. At the same time, many of the deceased COVID-19 patients had comorbidities of metastatic malignancies, cardiac, liver, and renal dysfunction, which are common etiologies of pleural effusions. The concomitant presence of co-infection such as active TB or stage IV lung malignancy has been described as predisposing factors for developing pleural effusions that are commonly lymphocytic-predominant with elevated LDH in COVID-19 patients, although limited to case reports/series.<sup>15</sup>

COVID-19-related pleural effusions were exudative in nature based on Light's criteria of pleural fluid to serum LDH ratio of 0.7 and more.<sup>16</sup> The white cell count differential in COVID-19-related pleural effusions was either lymphocytic or neutrophilic-predominant. Pleural fluid LDH was markedly elevated compared to serum LDH among several COVID-19 patients that received pleural drainage. Pleural effusions were notably hemorrhagic [pleural fluid red blood cells (RBC) > 100,000/mm<sup>3</sup>] in this case series despite systemic anticoagulation being held during pleural drainage. Pleural fluid chemistry showed an overall marked elevation in LDH level of 1550 IU/L that persisted even after excluding sanguineous appearing pleural fluid.

Lymphocytic or neutrophilic-predominant white cell count differential has been noted in other viral-related pleural effusions such as adenovirus, influenza A H5N1, and human herpesvirus.<sup>17</sup> A markedly elevated pleural fluid to serum LDH ratio of 1.3 had been suggested to support the diagnosis of COVID-19-related pleural effusions that were observed in many COVID-19 patients who received pleural drainage

Para pneumonic effusions together with empyema thoracis accounted for 20.4% of all our cases. It is estimated that about 40% of patients with pneumonia develop a concomitant pleural effusion<sup>18</sup> although some studies show the incidence of this complication of pneumonia to be less than 20%. In one series.<sup>18</sup> Para pneumonic effusion together with empyema's accounted for 14% of all cases of pleural effusions, both transudative and exudative. The percentage of positive pleural fluid cultures in our patients with empyema is surprisingly high despite the liberal prescription of antibiotics by general practitioners and primary care physicians

The ADA activity in TPE is one of the most common biomarkers used for the diagnosis and treatment decision of tuberculosis, having a high sensitivity. Adenosine deaminase (ADA) is a marker of lymphocyte activation, and has been shown to be a useful diagnostic test for PTB. ADA activity is usually measured with a colorimetric method, which is fast, inexpensive, reproducible and easy to perform. However, the predictive value of ADA activity depends on the local prevalence of TB.<sup>19</sup> Moreover, ADA activity can be increased in other diseases that present with

pleural effusion, such as lymphoma, collagen vascular diseases and bacterial empyema, and it must be used with care in countries with a low incidence of TB [19]

ADA is an enzyme that plays an important role in lymphoid cell differentiation. A pleural fluid ADA level greater than 40 U per L has a sensitivity of 90 to 100 percent and a specificity of 85 to 95 percent for the diagnosis of tuberculous pleurisy.<sup>20</sup> The specificity rises above 95 percent if only lymphocytic exudates are considered.<sup>21</sup> In areas where the prevalence of tuberculosis is low, the positive predictive value of pleural ADA declines but the negative predictive value remains high.

Bacteriological confirmation is often not achieved in tuberculous pleurisy because the mycobacterial population in tuberculous pleural effusion is generally small and cultures of the pleural fluid specimens are generally positive in only up to about 30% of cases. The presence of granulomatous inflammation on histological examination of pleural biopsy specimens is frequently used as a diagnostic criterion for pleural tuberculosis.<sup>22</sup> Malignancy, pneumonia, tuberculosis, PE, fungal infections, pancreatic pseudo cysts and intra-abdominal abscess are some of the diseases likely to produce exudative pleural effusions.<sup>23</sup> Special tests on the pleural fluid help in identifying the cause of the pleural effusion in many cases. Measurement of adenosine deaminase or  $\alpha$ -interferon helps in the diagnosis of pleural tuberculosis. If a lymphoma is suspected, flow cytometry helps in establishing the diagnosis in cases of suspected chylothorax, pleural fluid cholesterol and triglycerides help in confirming the diagnosis.<sup>24</sup>

#### **Conclusions:**

This case report will give the physicians more confident that after post covid recurrent pyogenic bilateral effusion may occur. Increased ADA does not confirm the diagnosis of TB as other findings like cell count does not support. Also empyema may also cause increased ADA which should be kept in mind. In some cases of recurrent pleural effusions with raised IL-6, long time steroid may be needed.

#### **Conflict of Interest:**

The authors stated that there is no conflict of interest in this article.

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#### **Abbreviations:**

ADA-Adenosine deaminase; TB PCR-Tuberculosis Polymerase chain reaction; HRCT-High resolution computed tomography; PPD-Purified protein derivative; WBC-White blood cell; IL-6-Interleukin-6; CRE-Carbapenem Resistant Enterobacteriaceae.

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