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Article

Frequency of Spontaneous Hemothorax, Chylothorax, Pleural, and Pericardial Effusion in Patients Who Had Thorax Tomography during Prepandemic and Pandemic Period

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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) remains a mystery in many respects. The importance of less common life-threatening diseases is still unclear. Therefore, in this study, it was attempted to determine the frequency of nontraumatic hemothorax, chylothorax, pleural, and pericardial effusion (PCE) in patients who underwent thoracic computed tomography during the pre-pandemic and pandemic period. **Materials and Methods:** This retrospective study included 147 patients over the age of 18 who were admitted to the emergency department between January 1st, 2019, and December 31st, 2020. The year 2019 was taken as the pre-pandemic period and the year 2020 was the pandemic period. Comorbidity, survival, and laboratory parameters of the patients were evaluated. **Results:** The mean age of the 147 patients included in the study was 66.41 ± 12.81 years, 54 (36.7%) were female, and the age range was 22–88 years. The mean plasma lactate dehydrogenase (LDH) level of the patients was 373.97 ± 115.77 U/L, plasma protein was 5.45 ± 1.00 gr/dL, fluid LDH was 229.37 ± 125.73 U/L, fluid/plasma LDH was 0.60 ± 0.23, fluid/plasma protein was 0.55 ± 0.29, and the amount of fluid discharged was 562.11 ± 243.01 mL. Bilateral lung involvement was present in 72 (49%) patients, and coagulation use was present in 59 (40.1%) patients. Pleural effusion (PE) was found in 43 (76.8%) of the hospitalized patients, hemothorax in 11 (19.6%) patients, and chylothorax in 4 (7.1%) patients. However, PCE was more common in the 16 (42.1%) patients admitted to the intensive care unit (ICU) ($P < 0.001$). While 38 (25.9%) of the patients were admitted to the ICU, mortality was observed in 30 (20.4%) patients. **Conclusion:** Although PE, nontraumatic hemothorax, chylothorax, and PCE are rare in COVID-19 patients, they can cause severe inflammation and poor prognosis.

Keywords: COVID-19; pleural effusion; hemothorax; chylothorax; pericardial effusion

1. Introduction

Pleural diseases are common nowadays and affect 3/1000 people [1]. Pleural fluids constitute a large part of pleural diseases. Pleural fluid develops in approximately 1.5 million patients annually in the United States

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of America (USA) [2,3]. Pleural fluid is estimated to be seen in 3–5/1000 people in Europe. Congestive heart failure, pneumonia, and malignant disease are reported as the most common causes [4]. Approximately 15%–20% of pleural fluids cannot be diagnosed [5]. The mortality rate of pleural fluids due to malignancies is high. The mortality rate of pleural fluid in the USA was generally reported as 0.3/100,000 (6). Bilateral pleural fluid is common, found in 15% of non-critical patients and 55% of intensive care patients [6,7].

Except for pleural effusion (PE) in the thorax, it is seen less frequently in hemothorax, chylothorax, and pericardial effusion (PCE). Hemothorax is the collection of blood in the pleural space [8]. The source of blood may be the chest wall, lungs, heart, or great vessels [9]. For a fluid in the pleural space to be called a hemothorax, it must contain a hematocrit value of at least 50% of the peripheral blood hematocrit [8]. Fluids containing less blood are called hemorrhagic effusions and are often associated with vascular processes, such as malignancies, tuberculosis, uremia, or pulmonary infarction [10]. Chylothorax is the leakage of the chyle into the pleural space [11]. There are many mechanisms of chylothorax, including thoracic duct trauma, malignant disease, and idiopathic. Chylothorax is suspected when milky white fluid is removed during thoracentesis [12]. PCE is an increase in the fluid between the pericardial layers. Tuberculosis, viral infections, and postoperative complications may play a role in its etiology. The frequency of PCE was evaluated as 1.3% [13].

Coronavirus disease 2019 (COVID-19) spread first in China and then to the whole world [14-16]. The diagnosis of COVID-19 was made based on contact history, clinical features, imaging findings, and the results of reverse transcription-polymerase chain reaction (RT-PCR) tests [17]. COVID-19 infection causes prothrombotic, hyperinflammation, vasculopathy, and cytokine storm. These phenomena are secondary to endothelial damage due to thrombosis [18]. There was an increased incidence of lymph node enlargement, PCE, and PE in severe and critical patients. This suggests that extrapulmonary lesions may indicate severe inflammation [19]. Although chylothorax is rare in COVID-19 patients, there have been reports of it. Thrombus formation at the source of the chylothorax may result in impaired lymphatic drainage [20]. There are reports of the unusual first manifestation of this deadly infection, such as hemoptysis, pneumothorax, hemothorax, and pneumomediastinum [21].

The importance of life-threatening and less frequent diseases during the pre-pandemic and pandemic period is not known. Therefore, it was attempted to determine the frequency of nontraumatic hemothorax, chylothorax, PE, and PCE in patients who underwent thorax computed tomography (TCT) during the pre-pandemic and pandemic period.

2. Materials and Methods

Study design and population: This retrospective study included 147 patients over the age of 18 who were admitted to the emergency department between January 1st, 2019, and December 31st, 2020. Patients in 2019

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constituted the pre-pandemic period group. The images of 12,437 non-traumatic patients who were admitted to the emergency department and had TCT were scanned from the hospital registry system. Patients who were admitted to the emergency department in 2020 were regarded as the pandemic period group. TCTs of these patients were carried out for diagnosis, and 6744 non-traumatic patients was screened. When considering the patients in the pandemic period, patients who were diagnosed with COVID-19 or who were positive for RT-PCR were selected. Out of a total of 147 patients, 54 (36.7%) were pre-pandemic patients and 93 (63.3%) were pandemic patients.

Inclusion criteria: Non-traumatic patients older than 18 years of age who underwent TCT and had their hemogram and biochemistry done in the emergency department were included in the study.

Exclusion criteria: At the time of admission, patients younger than 18 years of age, with a low coma score, cerebrovascular disease, patients taking psychiatric drugs, patients with acute liver failure, dialysis patients due to acute renal failure, infectious patients, such as meningitis, encephalitis, and acute tuberculosis, pregnant women, patients whose hemogram and biochemistry blood results were not evaluated at admission, patients with bleeding diathesis, patients with an International Normalized Ratio (INR) value above 1.5, and patients who did not undergo TCT were excluded from the study. The study was performed by the Declaration of Helsinki after approval was obtained from the local ethics committee.

The patients were formed into two groups in terms of coagulation, fluid color, microbiology, serology, PE, hemothorax, chylothorax, and PCE. Four groups were determined according to lung findings on the right, left, bilateral, and absence of involvement. According to the survival of the patients, four groups were formed, the outpatient follow-up, hospitalization, intensive care unit (ICU), and deceased groups.

Laboratory design: Hemogram and biochemical blood samples of the patients were taken at the time of admission to the emergency department. The hemogram blood was analyzed using a Sysmex DI-60 CBC analyzer (Istanbul, Turkey). The biochemistry blood was analyzed with a Beckman Coulter Automated AU-680 (Beckman Coulter, Inc., Fullerton, CA, USA). The hemogram and biochemistry results were examined in 45–60 min.

Thoracentesis [22] ultrasonography and pericardiocentesis [23] of the patients were performed with echocardiography and appropriate methods according to the literature. The fluid samples taken were delivered to the biochemistry, microbiology, and serology laboratories as soon as possible. Thus, using Light's criteria [24], transudate-exudate differentiation, and microbiological and serological negative and positive conditions were determined. Informed consent was obtained from the patients and their relatives for the thoracentesis, pericardiocentesis, and subsequent therapeutic fluid drainage.

Statistical analysis

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Data obtained in the study were analyzed using IBM SPSS Statistics for Windows 20.0 (IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test was used to analyze the normal distribution of the variables. The student t-test was used for the variables with normal distribution, and the Mann-Whitney U test was used when examining the differences between the groups for those with non-normal distribution. Chi-square analysis was performed to examine the relationships between the nominal variable groups. Correlation analysis was performed with variables of the pre-pandemic and pandemic periods. In addition, univariate regression Cox analysis was applied with all of the variables in the pre-pandemic and pandemic periods. Predictive values were determined by multivariate regression Cox analysis for the parameters that were significant in the univariate analysis. Receiver operating characteristic (ROC) curve analysis was performed for the sensitivity and specificity values of mortality. When interpreting the results, $P < 0.05$ was considered statistically significant.

3. Results

The mean age of the patients was 66.41 ± 12.81 years, 54 patients (36.7%) were female, and the age range was 22–88 years. The age distribution of the pre-pandemic and pandemic groups was very close to each other and no statistically significant difference was found. In addition, no significant difference was found between the groups in terms of gender. The mean values of the patients in the analyses were as follows: blood glucose: 157.52 ± 83.67 mg/dL, plasma lactate dehydrogenase (LDH): 373.97 ± 115.77 U/L, plasma protein: 5.45 ± 1.00 g/dL, liquid: LDH 229.37 ± 125.73 U/L, liquid/plasma: LDH 0.60 ± 0.23, fluid/plasma protein: 0.55 ± 0.29, D-dimer: 471.54 ± 164.29 ugFEU/mL, sedimentation: 38.70 ± 20.57 mm/h, C-reactive protein (CRP): 86.37 ± 48.07 mg/dL, white blood cell count (WBC): 17.80 ± 5.15 ×10^3/UL, neutrophil: 8.44 ± 2.39 ×10^3/UL, lymphocyte: 2.15 ± 0.64 ×10^3/UL, platelet: 241.36 ± 94.16 ×103/µL, and the amount of fluid discharged: 562.11 ± 243.01 mL. While the parameters were statistically significant between the groups, the fluid/plasma LDH ratio was not significant (**Table 1).**

Table 1. Comparison of Baseline Characteristics and Laboratory Findings in the Pre-Pandemic and Pandemic Period

	All patients n:147(%) mean±SD	*Pre-pandemic n:54(%) mean±SD*	*Pandemic n:93(%) mean±SD*	*P-Value*
Baseline characteristics				
Age (Year)	66.41±12.81	66.26±15.66	66.50±10.93	0.676
Gender (Female/Male)	54(36.7)/93(63.3)	18(33.3)/36(66.7)	30(32.3)/63(67.7)	0.893*
Laboratory Findings				
Blood Sugar, mg/dL	157.52±83.67	132.30±38.06	172.16±98.41	**0.019**
Plasma LDH, U/L	373.97±115.77	285.80±90.26	425.17±96.76	**<0.001**
Plasma Protein, g/dL	5.45±1.00	6.09±0.74	5.08±0.95	**<0.001**
Liquid LDH, U/L	229.37±125.73	174.65±102.62	261.14±127.45	**<0.001**
Liquid/Plasma LDH	0.60±0.23	0.59±0.22	0.61±0.23	0.856
Liquid/Plasma Protein	0.55±0.29	0.61±0.37	0.52±0.22	**0.035**
D-Dimer, ugFEU/mL	471.54±164.29	413.69±162.88	505.14±156.35	**0.001**

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Sedimentation, mm/h	38.70±20.57	32.81±15.08	42.12±22.55	**0.012**
C- Reactive Protein, mg/dL	86.37±48.07	60.62±30.14	101.32±50.28	**<0.001**
White Blood Cell, 10^3/UL	17.80±5.15	16.62±4.77	18.49±5.27	**0.026**
Neutrophil, 10^3/UL	8.44±2.39	7.56±1.66	8.95±2.60	**0.002**
Lymphocyte, 10^3/UL	2.15±0.64	2.49±0.71	1.96±0.50	**<0.001**
Platelet, x $10^3/\mu L$	241.36±94.16	291.92±89.66	212.0±84.07	**<0.001**
Amount of Fluid Discharged, mL	562.11±243.01	524.44±172.26	583.98±274.42	**0.001**

*SD; Stanndard Deviation, LDH: Lactate Dehydrogenase *:Chi-square test, Mann-Whitney U test was used for other variables*

There was no significant difference between the groups in terms of gender, but the excess of males in the pandemic group was remarkable (P = 0.893). In addition, 44 (47.3%) of 59 patients using coagulation were observed to be in the pandemic group (P = 0.024). Bilateral lung involvement was observed in 72 (49%) patients (P = 0.001). Of the discharged fluids, 110 (74.8%) were serious and 37 (25.2%) were serosanguineous (P = 0.010). Microbiology positivity was observed in 20 (13.6%) patients, and serology positivity was observed in 39 (26.5%) patients. In addition, 119 (81%) patients had PE, 23 (15.6%) spontaneous hemothorax, 5 (3.4%) chylothorax, 29 (19.7%) PCE. Of all patients, 38 (25.9%) were hospitalized in the ICU, and mortality occurred in 30 (20.4%) patients. Despite having the same characteristics, the excess of patients in the pandemic group was remarkable (**Table 2**).

Table 2. Pre-pandemic and Pandemic Period Comparison of Variables

		Pre-pandemic n:54(%)	*Pandemic n:93(%)*	*Total (%)*	*P-value**
Gender	Female	18(33.3)	30(32.3)	48(32.7)	0.893
	Male	36(66.7)	63(67.7)	99(67.3)	
Coagulation Use	No	39(72.2)	49(52.7)	88(59.9)	**0.024**
	Yes	15(27.8)	44(47.3)	59(40.1)	
Lung Involvement	No	5(9.3)	8(8.8)	13(8.8)	**0.001**
	Right	19(35.2)	16(17.2)	35(23.8)	
	Left	15(27.8)	12(12.9)	27(18.4)	
	Bilateral	15(27.8)	57(61.7)	72(49)	
Liquid Color	Serous	47(87)	63(67.7)	110(74.8)	**0.010**
	Serosanguineous	7(13)	30(32.3)	37(25.2)	
Microbiology	Negative	52(96.2)	75(80.6)	127(86.4)	**0.006**
	Positive	2(3.8)	18(19.4)	20(13.6)	
Serology	Negative	46(85.2)	62(66.7)	108(73.5)	**0.019**
	Positive	8(14.8)	31(33.3)	39(26.5)	
Pleural Effusion	No	15(27.8)	13(14)	28(19)	**0.040**
	Yes	39(72.2)	80(86)	119(81)	
Hemothorax	No	48(88.9)	76(81.7)	124(84.4)	0.347
	Yes	6(11.1)	17(18.3)	23(15.6)	
Chylottax	No	52(96.3)	90(96.8)	146(96.6)	0.878
	Yes	2(3.7)	3(3.2)	5(3.4)	
Pericardial Effusion	No	48(88.9)	69(74.2)	117(89.6)	**0.027**
	Yes	6(11.1)	24(25.8)	30(20.4)	
Survival	Follow-up	24(44.4)	5(5.4)	29(19.7)	**<0.001**
	Hospitalization	14(25.9)	42(45.2)	56(38.1)	
	Intensive Care Unit	11(20.4)	27(29)	38(25.9)	
	Dead	5(9.3)	19(20.4)	25(16.3)	

Total		54(36.7)	93(63.3)	147(100)

**:Chi-square test*

In the analysis of the survival group with the variables, no statistically significant correlation was found with gender (P = 0.184). Coagulation use was observed the least in outpatients with 4 (13.8%) cases. In addition, coagulation use was found in 22 (39.3%) of those hospitalized, 17 (44.7%) of those admitted to the ICU, and 16 (66.7%) of those with mortality (P = 0.001). Lung involvement was bilateral in 29 (51.8%) hospitalized patients (P < 0.001). The color of the collected fluid was serous in 40 (71.4%) patients (P = 0.014). Microbiological positivity was higher in the hospitalized group with 9 (16.1%) cases (P = 0.012). Serological positivity was higher in the mortality group with 15 (62.5%) cases (P < 0.001). PE was more common in 43 (76.8%), hemothorax in 11 (19.6%), and chylothorax in 4 (7.1%) patients in the hospitalized group. However, PCE was more common in 16 (42.1%) patients admitted to the ICU (P < 0.001, **Table 3**).

Table 3. Analysis of variables by outpatient follow-up, hospitalization, intensive care unit and mortality

Survival		**Follow-up** ***n:54(%)***	**Hospitalization** ***n:93(%)***	**ICU** ***n:(%)***	***Dead*** ***n:(%)***	***P-Value****
Gender	Female	10(34.5)	13(23.2)	17(44.7)	8(33.3)	0.184
	Male	19(65.5)	43(76.8)	21(55.3)	16(66.7)	
Coagulation Use	No	25(86.2)	34(60.7)	21(55.3)	8(33.3)	**0.001**
	Yes	4(13.8)	22(39.3)	17(44.7)	16(66.7)	
Lung Involvement	No	0	1(1.8)	11(28.9)	1(4.2)	**<0.001**
	Right	14(48.3)	15(26.8)	4(10.5)	2(8.3)	
	Left	9(31)	11(19.6)	3(7.9)	4(16.7)	
	Bilateral	6(20.7)	29(51.8)	20(52.6)	17(70.8)	
Liquid Color	Serous	27(93.1)	40(71.4)	29(76.3)	14(58.3)	**0.014**
	Serosanguineous	2(6.9)	16(28.6)	9(23.7)	10(41.7)	
Microbiology	Negative	29(100)	47(83.9)	33(86.8)	18(75)	**0.012**
	Positive	0	9 (16.1)	5(13.2)	6(25)	
Serology	Negative	28(96.6)	47(83.9)	24(63.2)	9(37.5)	**<0.001**
	Positive	1(3.4)	9 (16.1)	14(36.8)	15(62.5)	
Pleural Effusion	No	0	13(23.2)	11(28.9)	4(16.7)	**0.002**
	Yes	29(100)	43(76.8)	27(71.1)	20(83.3)	
Hemothorax	No	29 (100)	45(80.4)	31(81.6)	19(79.2)	**0.011**
	Yes	0	11(19.6)	7(18.4)	5(20.8)	
Chylottax	No	29(100)	50(92.9)	37(97.4)	23(100)	0.135
	Yes	0	4(7.1)	1(2.6)	0	
Pericardial Effusion	No	29(100)	51(98.2)	22(57.9)	11(45.8)	**<0.001**
	Yes	0	1(1.8)	16(42.1)	13(54.2)	
Total		29(19.7)	56(38.1)	38(25.9)	24(16.3)	147(100)

**:Chi-square test, ICU: Intensive Care Unit*

In the correlation analysis of the pre-pandemic and pandemic groups with the variables, a negative correlation with PE, lymphocyte, platelet, and plasma protein levels, and a positive weak, and/or moderate correlation with other parameters was found. In addition, in the univariate analysis of the pre-pandemic and pandemic groups with the variables, statistically significant parameters were found to be a predictive marker

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only for lung involvement, PE, WBC, lymphocyte, neutrophil, platelet, plasma LDH, and plasma protein values in the multivariate analysis (**Table 4**).

Table 4. Univariate-multivariate Cox regression and correlation analyses to predict patient development

Pre-Pandemic and Pandemic Period								
Patient	***Correlation***		***Univariate***			***Multivariate***		
	r	***p***	***HR***	***95% CI***	***p***	***HR***	***95% CI***	***p***
Lung involvement	0.245	**0.003**	1.635	1.174-2.277	**0.004**	3.196	1.715-5.955	**<0.001**
Pleural Effusion	-0.202	**0.014**	0.348	0.146-0.827	**0.017**	0.001	0.000-0.050	**0.001**
White Blood Cell	0.176	**0.033**	1.081	1.005-1.163	**0.037**	0.777	0.628-0.962	**0.020**
Lymphocyte	-0.403	**<0.001**	0.223	0.115-0.429	**<0.001**	0.101	0.028-0.359	**<0.001**
Neutrophil	0.281	**0.001**	1.338	1.123-1.593	**0.001**	1.833	1.110-3.026	**0.018**
Platelet	-0.411	**<0.001**	0.990	0.985-0.994	**<0.001**	0.990	0.982-0.998	**0.018**
Plasma LDH	0.582	**<0.001**	1.017	1.012-1.023	**<0.001**	1.025	1.003-1.047	**0.023**
Plasma Protein	-0.487	**<0.001**	0.290	0.183-0.459	**<0.001**	0.412	0.181-0.935	**0.034**
Liquid LDH	0.333	**<0.001**	1.007	1.004-1.011	**<0.001**			
D-Dimer	0.269	**0.001**	1.004	1.002-1.006	**0.002**			
Sedimentation	0.219	**0.008**	1.030	1.007-1.054	**0.011**			
C-reactive protein	0.410	**<0.001**	1.025	1.014-1.036	**<0.001**			
Coagulation use	0.192	**0.020**	2.335	1.135-4.803	**0.021**			
Microbiology	0.220	**0.007**	6.240	1.388-28.052	**0.017**			
Serology	0.202	**0.014**	2.875	1.210-6.833	**0.017**			
Survavil	0.345	**<0.001**	2.283	1.519-3.429	**<0.001**			
Blood Sugar	0.230	**0.005**	1.009	1.002-1.016	**0.011**			
Liquid Color	0.214	**0.009**	3.197	1.297-7.906	**0.012**			

All the variables from Table 4 were examined, and only those significant at a P <0.05 level are shown in univariate analysis. Multiple Cox proportional hazards model includes all the variables in univariate analysis with forward stepwise method. CI: confidence interval; HR, hazard ratio. LDH: Lactate Dehydrogenase,

The receiver operating characteristic (ROC) curve analysis graph performed to determine the mortality positivity of the pre-pandemic and pandemic groups is given in **Fig 1**. and the data are given in **Table 5**.

Figure 1. ROC curve analysis according to mortality positivity of variables

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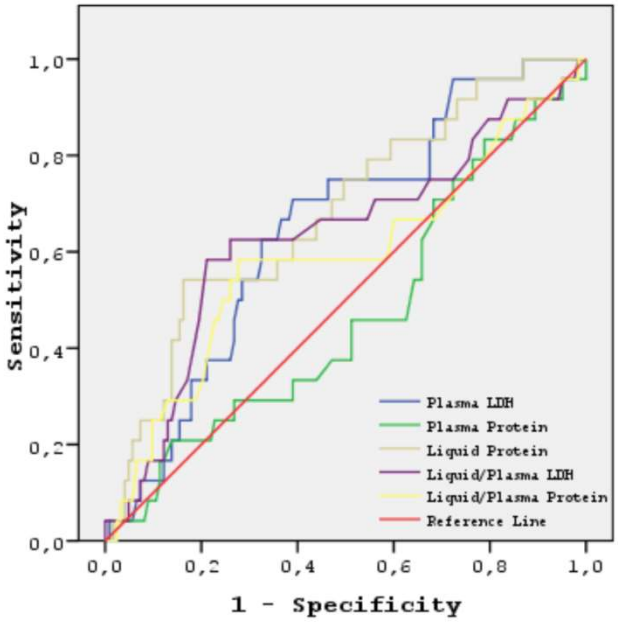

Tablo 5. ROC curve analysis according to mortality positivity of variables

Receiver Operating Characteristic (ROC)					
Mortality	**Sensitity**	**spesificity**	**AUC**	**95% CI**	**P-value**
Plasma LDH	**83.3**	**74.8**	**0.650**	**0.539-0.761**	**0.021**
Plasma Protein	37.5	34.1	0.470	0.342-0.598	0.639
Liquid LDH	**87.5**	**83.7**	**0.681**	**0.564-0.797**	**0.005**
Liquid/Plasma LDH	**70.8**	**62.8**	**0.631**	**0.499-0.764**	**0.042**
Liquid/Plasma Protein	33.3	28.5	0.587	0.448-0.725	0.180

AUC: Area Under the Curve, 95% CI: 95% Confidence Interval

4. Discussion

It is known that before the COVID-19 pandemic, PE comorbidity was detected at certain rates depending on the situation. However, the rate of spontaneous hemothorax, chylothorax, and PCE was very low. It was determined that these cases increased significantly in the pandemic period. However, studies comparing these during the pre-pandemic and pandemic periods were not found within the scope of the literature review in the present study. There were only a few studies at the case level. It was shown that PE, hemothorax, chylothorax, and PCE were significantly increased during the pandemic period in patients who underwent TCT imaging in emergency department admissions.

In COVID-19 pneumonia, cytokine storm, macrophage activation, and secondary hemophagocytic lymphohistiocytosis cause hyperimmune dysregulation response with both local and systemic effects. Although lung involvement is prominent, organ involvement is observed due to secondary intravascular coagulation and systemic immune response [25]. A secondary cytokine storm occurs with the insufficient

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defense mechanism caused by COVID-19, an aggressive immune response, increased interleukin-6 production, and tissue damage [26]. COVID-19 adds Angiotensin-Converting Enzyme-2 (ACE-2) receptor-related local endothelial damage to the picture. Influence of ACE-2s and cytokine storm cause infected cell death. As a result, the local inflammatory response, released proinflammatories and procoagulants leak into the capillary network. This triggers alveolar structure and vascular endothelial damage. The prevalence of ACE-2 receptors in infection type II pneumocytes causes typical lung lesions to occur [27].

Various studies have shown that the radiological manifestations of PE, PCE and even ascites are highly variable. PE has many causes, including viral pleuritis, congestive heart failure, and cancer [28]. One-year mortality in non-malignant PE patients ranges from 25% to 57% [29]. It was reported that PE occurs in 10.3% of COVID-19 patients. It was found that COVID-19 patients have a higher incidence of PE than the normal population. This suggests that there is a more pronounced inflammatory response in the lung [30]. In a study using serial TCT, the incidence of PE increased from 12% to 38% on the fifth and second days after the onset of COVID-19 symptoms [31]. In the TCT findings of 153 patients with COVID-19, PE was found to be bilateral in most patients (65.36%) and PCE was found in 7.84% [32]. In addition, significantly decreased lymphocyte, and increased platelet, C-reactive protein, lactate dehydrogenase, and D-dimer levels were observed in patients with COVID-19, which showed that inflammation was severe and the disease may worsen [15,33,34]. This showed that the changes in these indicators were more pronounced in the pandemic group than in the pre-pandemic group. While the rate of PE was 26.5% in the pre-pandemic period group, this rate increased to 54.4% for the pandemic period group. In addition, the mortality rate was significantly higher in patients with PE than in patients without PE. During the pre-pandemic period, ICU admission was 7.5% and the mortality rate was 3.4%. However, during the pandemic period, ICU hospitalization increased up to 18.4% and mortality up to 12.9%. But under these circumstances, the comorbid condition of the patients with the COVID-19 should not be ignored. It is thought that patients with PE in COVID-19 have severe inflammation and poor prognosis. PE in COVID-19 patients can be used as a potential predictor of progression to severe or critical conditions.

COVID-19 may predispose patients to thrombotic disease in both venous and arterial circulation due to excessive inflammation, platelet activation, endothelial dysfunction, and stasis [35]. Most autopsy reports describe hyaline membrane changes and microvessel thrombosis in patients with COVID-19 [36]. Pulmonary bleeding is a recurrent finding in patients with COVID-19 and has been reported in 17% of severe cases receiving extracorporeal support [37]. Necrotizing pneumonia is strongly associated with the occurrence of pulmonary hemorrhage and severely elevated inflammatory markers and is associated with a poor prognosis [38,39]. It can cause deep parenchymal damage and lead to serious complications, such as spontaneous hemothorax. In systematic reviews, 22% of dissected lungs before and after death showed macroscopic

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hemorrhagic changes. Histopathologically, alveolar hemorrhage was observed in 33% of the cases and partial hemorrhagic necrosis was observed in 0.3% [40]. Clinically significant pulmonary hemorrhage was identified in patients with Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2)-associated pneumonia with and without therapeutic anticoagulation [41]. In the present study, the frequency of nontraumatic hemothorax was 4.1% during the pre-pandemic period, whereas this rate increased to 11.6% during the pandemic period. This situation can be explained by the mechanism of action in COVID-19 patients.

To date, few reports have been made of chylothorax in patients with COVID-19. The SARS-CoV-2 infection causes prothrombotic, hyperinflammation, cytokine storm, and involvement of the lymphatic system in the background. This may result in chylothorax as a result of further obstruction of the preexisting altered course of the superior vena cava and/or the right subclavian vein by a common prothrombotic state [18]. The frequency of chylothorax was also very low in the present study, similar to the literature. While it was 1.4% during the pre-pandemic period, it was observed as 2.04% during the pandemic period.

The primary clinical manifestation of COVID-19 is a respiratory disease, but recent reports have suggested cardiac involvement in 12% of patients. More importantly, cardiac injury has been associated with a higher risk of mortality [42]. Pathological inflammatory processes cause increased production of pericardial fluid, resulting in exudative PCE. Clinical symptoms vary according to a variety of factors, including the onset and amount of accumulation, the underlying disease, and the patient's comorbid conditions [43]. In a study conducted on 300 patients with acute pericarditis, the frequency of PCE was found as 60% and that of pericardial tamponade was 5% [44]. In the literature, five cases of cardiac tamponade requiring emergency pericardial drainage were reported in Italy [45], the USA [46], and the United Kingdom [47]. Publications on radiological data highlight rare PCE [20]. As seen in these studies, the frequency of PCE is high and the rate of pericardial tamponade is low. While the rate of PCE was 4.1% during the pre-pandemic period, it was found to increase up to 16.3% during the pandemic period. While considering this increase, the comorbid situation that occurs with COVID-19 should be kept in mind. PCE was seen in 16 (47%) of 34 patients admitted to the ICU and in 13 (54.2%) of 24 patients with mortality. Considering the age, comorbidity, and all of the COVID-19 patients in the cases of the present study, it was found that pericardiocentesis was performed in 7 (4.8%) patients.

5. Conclusions

Although PE, nontraumatic hemothorax, chylothorax, and PCE are rare in COVID-19 patients, they can cause severe inflammation and poor prognosis. It is suggested to use these four causes as a potential predictor of progression to severe or critical conditions in patients with COVID-19.

Supplementary Materials: The following supporting information can be downloaded at: www.mdpi.com/xxx/s1

Figure 1. ROC curve analysis according to mortality positivity of variables

Table 1. Comparison of Baseline Characteristics and Laboratory Findings in the Pre-Pandemic and Pandemic Period

Table 2. Pre-pandemic and Pandemic Period Comparison of Variables

Table 3. Analysis of variables by outpatient follow-up, hospitalization, intensive care unit and mortality

Table 4. Univariate-multivariate Cox regression and correlation analyses to predict patient development

Tablo 5. ROC curve analysis according to mortality positivity of variables

Author Contributions: For research articles with several authors, a short paragraph specifying their individual contributions must be provided. The following statements should be used "Conceptualization, A.C., K.A.T and F.T.T; methodology, A.C.; software, F.T.T. and K.A.T; validation, A.C., F.F.T. and K.A.T.; formal analysis, A.C.; investigation, F.T.T. and K.A.T; resources, A.C.; data curation, F.T.T.; writing-original draft preparation, A.C.; writing-review and editing, F.T.T. and K.A.T; visualization, A.C.; supervision, F.T.T.; project administration, A.C.; funding acquisition, F.T.T. All authors have read and agreed to the published version of the manuscript.

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