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Original Article

Evaluation of Pleural Complications Affecting Mortality in COVID-19 Patients

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ABSTRACT

Objective: This study aimed to retrospectively evaluate pleural complications in patients who were polymerase chain reaction (PCR)-positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and admitted to the hospital with COVID-19 pneumonia.

Methods: A total of 164 patients who applied to our hospital between March 2020 and May 2021 with PCR-positive for SARS-CoV-2 were retrospectively evaluated and were followed up and treated in the service or intensive care unit. Pleural complications were detected during the treatment of COVID-19 pneumonia. In the current study, mortality was taken as the death of the patients in the first 30 days after hospitalization. Pleural complications occurring during treatment were classified into two groups: the pneumothorax (PNX) group and the pneumomediastinum (PMN) group.

Results: Of the patients, 69 (52.3%) had isolated PNX and 14 (43.7%) had isolated PMN. PNX and subcutaneous emphysema were determined in 50 (37.9%) patients, PMN and subcutaneous emphysema were determined in 13 (40.6%), PMN, PNX, and subcutaneous emphysema were determined in 3 (9.4%), and PMN and PNX were determined in 2 (6.3%) patients. Hydro-PNX was determined in 12 (9.1%) patients, and PNX and empyema were determined in 1 (0.7%) patient. When the relationship between pleural complications occurring during treatment due to COVID-19 pneumonia and mortality was examined, mortality was observed in 14 (43.8%) of the PMN patients and 104 (78.8%) of the PNX patients ($p<0.001$). When the relationship between gender and mortality was examined, mortality was observed in 75 (65.8%) of the male patients and in 43 (86%) of the female patients ($p=0.008$).

Conclusion: As a result, it was found that PNX after positive pressure ventilation increased mortality more than other pleural complications and worsened the prognosis. We think this issue will contribute to the literature in the COVID-19 pandemic and in pandemic diseases that may occur later and cause pleural involvement.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), also known as coronavirus disease 19 (COVID-19), is a disease that is characterized by pathologies that reduce the respiratory capacity of patients. The first case in Turkey was seen on March 11, 2020, which was the same date that it was declared a pandemic by the World Health Organization.[1] The respiratory capacity of patients infected with COVID-19, who required hospitalization, and common ground-glass areas detected on thorax computed tomography (CT) imaging decreased over time. In patients with reduced respiratory capacity, the process starts with oxygenation with a nasal cannula; after the exacerbation of the decrease in the respiratory capacity of the patient, the need for high flow nasal cannula, noninvasive mechanical ventilation, and then invasive mechanical ventilation is common. Pleural complications may occur with the application of higher pressure oxygenation to the patient over time and the increase in the severity of fibrosis. These pleural complications vary, such as pneumomediastinum (PMN), pleural effusion, subcutaneous emphysema, pneumothorax (PNX), hydro-PNX, and empyema. This study aimed to retrospectively evaluate pleural complications, such as PMN, pleural effusion, subcutaneous emphysema, PNX, hydro-PNX, and empyema, in patients who were polymerase chain reaction (PCR)-positive for SARS-CoV-2 and admitted to the hospital with COVID-19 pneumonia.

MATERIALS AND METHODS

A total of 164 patients who applied to our hospital between March 2020 and May 2021, who were found to be PCR-positive for SARS-CoV-2, were retrospectively eval-

uated and were followed up and treated in the service or intensive care unit (ICU), where pleural complications were detected during the treatment of COVID-19 pneumonia. The data of the patients were obtained through the hospital information management system. The pleural complications seen in the patients were determined by examining their thorax CT or posteroanterior (PA) chest radiographs. Between March 11, 2020, which was the date of the first case of COVID-19 in Turkey, and May 31, 2021, a total of 11 800 COVID-19-infected patients were admitted to the ICU of our hospital and 3441 patients died in the ICU. Mortality due to COVID-19 was found to be 29.16% in our ICU.

In the current study, mortality was taken as the death of the patients in the first 30 days after hospitalization. Patients were classified prognostically according to the oxygenation method applied while lying down due to COVID-19 pneumonia. The prognosis of patients who became stable when oxygenated by nasal oxygen mask was mild; the prognosis of those who became stable when oxygenated with high flow nasal cannula was moderate; and when the partial oxygen pressure was <50 mmHg and the partial carbon dioxide pressure was >50 mmHg and the patients required the use of an invasive mechanical ventilator, the prognosis was classified as severe.

Pleural complications occurring during treatment were classified into two groups: PNX and PMN groups. Other pleural complications, such as subcutaneous emphysema, pleural effusion, and empyema accompanied by PNX or PMN, were evaluated together in these two groups. The modified Charlson comorbidity index (CCI) was used to evaluate the comorbidity status of the patients and examine its effects on mortality.

Statistical analyses

Statistical analyses were performed using IBM SPSS Statistics for Windows 22.0 (IBM Corp., Armonk, NY, USA). Numerical variables were expressed as mean±standard deviation and median (min–max), and the categorical variables were expressed as numbers and percentages. Parametric test assumptions (normality and homogeneity of variances) were checked before the groups were compared in terms of the numerical variables. The differences between the groups were examined using the t-test in the dependent groups. Categorical values were analyzed with Fisher's exact test. The Mann–Whitney U and the Kruskal–Wallis tests were used to compare the continuous variables. A value of $p<0.05$ was accepted to be statistically significant for all of the analyses.

RESULTS

This study included 164 patients, 114 (69.5%) of whom were males and 50 (30.5%) were females. The mean age of the patients was 62.4±14.8 years. While the mean age in the PNM group was 54.9±18.4 years, the mean age in the PNX group was 64.3±13.2 years (p=0.014) (Table 1).

Of the patients, 69 (52.3%) had isolated PNX and 14 (43.7%) had isolated PMN. PNX and subcutaneous emphysema were determined in 50 (37.9%), PMN and subcutaneous emphysema were determined in 13 (40.6%), PMN, PNX, and subcutaneous emphysema were determined in 3 (9.4%), and PMN and PNX were determined in 2 (6.3%) patients. Hydro-PNX was determined in 12 (9.1%) patients, and PNX and empyema were determined in 1 (0.7%) patient. Table 1 shows the demographic infor-

Table 1. Demographic characteristics of the patients

Variable		Pneumomediastinum		Pneumothorax		p
		n	%	n	%	
Gender	Male	25	78.1	89	67.4	0.238
	Female	7	21.9	43	32.6	
Age (years), (Mean±SD)		54.9±18.4		64.3±13.2		0.014
Age (years)	≤65	22	68.8	67	50.8	0.067
	>65	10	31.3	65	49.2	
Pleural situations	Isolated	14	43.7	69	52.3	
	Subcutaneous emphysema	13	40.6	50	37.9	
	Pneumothorax + subcutaneous emphysema	3	9.4	0	0	
	Pneumothorax	2	6.3	0	0	
	Pleural effusion	0	0	12	9.1	
	Empyema	0	0	1	0.7	
CCI	0–3	20	62.5	60	45.5	0.084
	>3	12	37..5	72	54.5	
WBC	Median	8.7		11.4		0.112
NLR	Median	9.2		16		0.051
CRP	Median	76.4		102.5		0.107

SD: Standard deviation; n: Number; CCI: Charlson comorbidity index; WBC: White blood cell; NLR: Neutrophil–lymphocyte ratio; CRP: C-reactive protein.

mation of the patients. The mean hospitalization period of the patients was 22.7±16.9 days (Table 1).

The patients were divided into three groups according to their prognosis: mild, moderate, and severe. Of the ICU patients, 103 (62.8%) were determined to have a severe prognosis due to the need for the use of an invasive mechanical ventilator, 39 (23.8%) were determined to have a moderate prognosis due to the need to be connected to a noninvasive mechanical ventilator, and 22 (13.4%) were determined to have a mild prognosis which required the application of oxygenation with a nasal cannula (Table 2).

The patients were divided into two groups according to their age, comprising those ≤65 years of age and those >65 years of age. In the comparison between the age groups and the prognoses of the patients, it was determined that the prognosis was more severe in patients >65 years of age when compared with those who were ≤65 years of age (p=0.014) (Table 2).

When the patients were compared in terms of prognosis with pleural complications occurring during the treatment of COVID-19 pneumonia, 11 (34.4%) of the PMN patients had a mild prognosis, 8 (25%) had a moderate prognosis, and 13 (40.6%) had a severe prognosis, while for the PNX patients, 11 (8.3%) had a mild prognosis, 31 (23.5%) had a moderate prognosis, and 90 (68.2%) had a severe prognosis (p<0.001). It was observed that subcutaneous emphysema occurring in the patients with PMN and PNX did not have a significant effect on their prognosis (p=0.018) (Table 2).

Tube thoracostomy was performed in 126 (76.8%) patients, consisting of 88 (53.7%) on the right, 30 (18.3%) on the left, and 8 (4.9%) bilaterally. Tube thoracostomy was not performed in 38 (23.1%) patients. While the prognosis of 86 (69.4%) patients who underwent tube thoracostomy was severe, 17 (44.7%) patients who did not undergo tube thoracostomy showed a severe prognosis (p=0.01) (Table 2).

The patients were evaluated in two groups according to the modified CCI: CCI=0–3 and CCI >3. There were 80 (48.8%) patients with CCI between 0 and 3. The prognosis of 43 (53.8%) of these patients was severe. There were 84 (51.2%) patients with CCI >3. The prognosis of 60 (71.4%) of these patients was severe (p=0.01) (Table 2).

There was no statistically significant difference between the median values of the C-reactive protein (CRP), neutrophil–lymphocyte ratio (NLR), and white blood cell (WBC) and the prognosis of the patients (p=0.274, p=0.219, and p=0.076, respectively). Table 2 shows the conditions that affected the prognosis (Table 2).

Mortality was observed in 118 (71.9%) patients. When the relationship between pleural complications occurring during treatment due to COVID-19 pneumonia and mortality was examined, mortality was observed in 14 (43.8%) of the PMN patients and in 104 (78.8%) of the PNX patients (p<0.001) (Table 3).

Statistically, PNX is more mortal than PMN in COVID-19 patients. Subcutaneous emphysema accompanying PMN and PNX had no effect on mortality (p=0.216) (Table 3).

When the relationship between gender and mortality was examined, mortality was observed in 75 (65.8%) of the male patients and 43 (86%) of the female patients (p=0.008) (Table 3).

Table 2. Factors affecting the prognosis of the patients

Variable		Mild		Moderate		Severe		p
		n	%	n	%	n	%	
Gender	Male	19	16.7	31	27.2	64	56.1	0.024
	Female	3	6	8	16	39	78	
Age	≤65	16	17.8	26	28.9	48	52.8	0.014
	>65	6	8.1	13	17.6	56	74.7	
Pleural situations	Pneumomediastinum	11	34.4	8	25	13	40.6	<0.001
	Pneumothorax	11	8.3	31	23.5	90	68.2	
Subcutaneous emphysema	Yes	6	9.1	23	34.8	37	56,1	0.018
	No	16	16.3	16	16.3	66	67.4	
Tube thoracostomy	Yes	10	7.9	30	23.8	86	68.3	0.001
	No	12	31.6	9	23.7	17	44.7	
Tube thoracostomy side	Right	9	10.2	25	28.4	54	61.4	0.118
	Left	1	3.3	3	10	26	87.7	
	Bilateral	0	0	2	25	6	75	
CCI	0–3	17	21	20	24.7	43	53.8	0.010
	>3	5	6	19	22.9	60	71.4	
CRP (g/L)	Median	35.2		86.9		104.0		0.274
NLR	Median	7.6		14.8		17.1		0.219
WBC (10^9 L^{-1})	Median	8.7		11.4		11.2		0.076

n: Number; CCI: Charlson comorbidity index; WBC: White blood cell; NLR: Neutrophil–lymphocyte ratio; CRP: C-reactive protein.

Table 3. Factors affecting mortality

Variable		No mortality		Yes mortality		p
		n	%	n	%	
Pleural situations	Pneumomediastinum	18	56.2	14	43.8	<0.001
	Pneumothorax	28	21.2	104	78.8	
Subcutaneous emphysema	Yes	22	33.3	44	66.7	0.216
	No	24	24.5	74	75.5	
Gender	Male	39	34.2	75	65.8	0.008
	Female	7	14	43	86	
Age (years)	≤65	35	39.3	54	60.7	<0.001
	>65	11	14.7	64	85.3	
Age (years)	Mean±SD	53.3±18.5		66.0±11.6		<0.001
Tube thoracostomy	Yes	25	19.8	101	80.2	<0.001
	No	21	55.3	17	44.7	
CCI	0–3	34	42.5	46	57.5	<0.001
	>3	12	14.3	72	85.7	
NLR	Median	8.3		17.9		<0.001
WBC (10^9 L^{-1})	Median	9.9		11.4		0.022
CRP (g/L)	Median	57.1		109.2		0.001
Prognosis	Mild	22	100	0	0	<0.001
	Mid	16	32.7	23	59	
	Severe	8	7.8	95	92.2	

SD: Standard deviation; n: Number; CCI: Charlson comorbidity index; WBC: White blood cell; NLR: Neutrophil–lymphocyte ratio; CRP: C-reactive protein.

When the relationship between age and mortality was examined, mortality was observed in 54 (60.7%) patients who were ≤65 years of age and in 64 (85.3%) who were >65 years of age (p<0.001). The mean age of the patients with mortality was 66±11.6 years and that of those without mortality was 53.3±18.5 years (p<0.001) (Table 3).

Mortality was observed in 101 (80.2%) patients who underwent tube thoracostomy and in 17 (44.7%) patients who did not undergo tube thoracostomy (Table 3).

Mortality was observed in 46 (57.5%) patients with a CCI between 0 and 3 and in 72 (85.7%) patients with CCI > 3 (p<0.001) (Table 3).

When the median NLR, WBC, and CRP values of the patients with mortality were compared with the median NLR, WBC, and CRP values of those without mortality, statistical significance was found for all three parameters (p<0.001, p=0.022, and p=0.001, respectively) (Table 3).

When the relationship between the prognosis of the patients and mortality was examined, no mortality was observed in any of the patients with a mild prognosis. Mortality was observed in 23 (59%) patients with a moderate prognosis and in 95 (92.2%) patients with a severe course (p<0.001). Table 3 shows the conditions affecting mortality (Table 3).

DISCUSSION

Coronavirus (SARS-CoV-2), which emerged in 2019, causes rare pleural complications, such as PMN, PNX, and subcutaneous emphysema. As a result of diffuse fibrosis in the lung parenchyma in patients with COVID-19 pneumonia, spontaneous or iatrogenic pleural complications may occur and result in the need for the use of mechanical ventilation. Adequate data on the incidence of PNX and PMN occurring after COVID-19 pneumonia are not yet available in the literature. This study aimed to evaluate the cases of PNX, PMN caused by COVID-19 pneumonia, and other pleural complications (subcutaneous emphysema, empyema, and pleural effusion) accompanying these cases. In a study of 6574 COVID-19 patients conducted in 16 centers in England, it was reported that PNX was determined in 60 (0.91%) patients.[2] In the current study, 121 (1.02%) PNX cases and 21 (0.18%) PMN cases were detected among 11 800 patients with COVID-19 PCR positivity who were hospitalized in the ICU for a 1-year period. In addition, 11 PNX and 11 PMN cases were detected among patients with COVID-19 PCR positivity who were hospitalized in pandemic wards. When the literature was examined, it was seen that the current study was one of the largest series performed with the coexistence of pleural complications and COVID-19 pneumonia.

PNX due to COVID-19 is three times more common in men than in women. In this study, the data obtained were similar to those reported in the literature.

PMN occurs when the free air that emerges due to the rupture of the alveoli, as a result of increased intrathoracic pressure for any reason, spreads to the mediastinum. Air resulting from alveolar rupture may spread from the retropharyngeal and submandibular areas to the neck, as

well as from the paraaortic or periesophageal areas to the diaphragm and retroperitoneal area.[3] PMN can be classified as spontaneous, iatrogenic, and traumatic. In patients with COVID-19 pneumonia, iatrogenic PMN can be seen as a result of alveolar rupture due to high pressure as a result of the use of a mechanical ventilator, and spontaneous PMN can also be seen rarely without any reason.[3] Spontaneous PMN is mostly a self-limiting disease[4] and can cause serious circulatory and respiratory pathology. Therefore, spontaneous PMN formation in COVID-19 patients should be considered an indicator of the poor prognosis of the disease. In this study, iatrogenic PMN was observed in 13 (40.6%) of 32 PMN patients during mechanical ventilator application and 8 (25%) during high flow nasal cannula or continuous positive airway pressure (CPAP) application (Fig. 1). Spontaneous PMN was observed in 11 (34.4%) patients without any iatrogenic cause while they were being oxygenated by nasal cannula or while they were lying in the pandemic ward (Fig. 2). No mortality was observed in the patients with spontaneous PMN. However, 14 (66.6%) of the 21 (65.6%) patients with PMN due to the use of a mechanical ventilator (invasive, noninvasive, and high flow) died.

Subcutaneous emphysema is the most common finding accompanying PMN.[5] Chalumeau et al.,[6] in a study conducted on PMN, found that the rate of subcutaneous emphysema was 82%. In the current study, 16 (50%) of 32 PMN patients seen after COVID-19 infection had subcutaneous emphysema. With appropriate treatment for PMN, mediastinal and subcutaneous air resorption can be achieved within 5–7 days.[7]

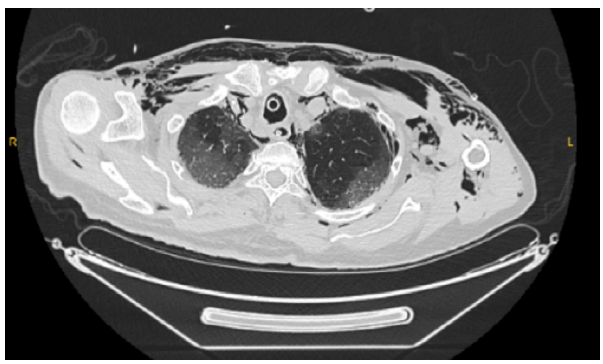

Figure 1. Coexistence of iatrogenic PMN and subcutaneous emphysema after invasive mechanical ventilation.

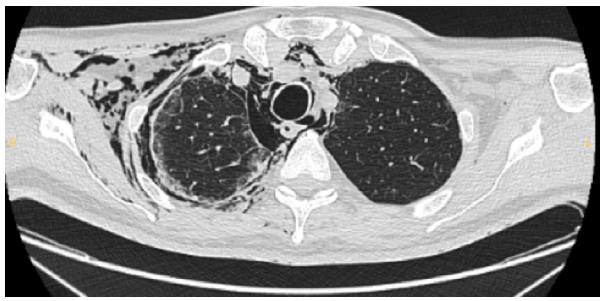

Figure 2. Spontaneous PMN and subcutaneous emphysema after COVID-19 infection.

Another major pleural complication after COVID-19 is PNX.[8] In patients infected with COVID-19 who require hospitalization, PNX can also be seen as iatrogenic PNX as a result of positive pressure air delivery with a mechanical ventilator, such as PMN. It can also be seen as a spontaneous PNX as a result of air filling. In the current study, PNX occurred in 132 (80.5%) patients. Iatrogenic PNX occurred during invasive mechanical ventilator application in 90 (68.2%) patients and during noninvasive mechanical ventilator application in 31 (23.5%) patients. Spontaneous PNX has occurred for no apparent reason.

The development of PNX after COVID-19 infection has been reported as an important prognostic factor in the literature.[9–12] In this study, it was observed that the prognosis was severe in 90 (68.2%) of 132 patients who had PNX. It was determined that the prognosis was severe in 13 (40.6%) of 32 patients with PMN. According to these data, PNX affects the prognosis worse than PMN ($p<0.001$). In addition, mortality was observed in 104 (78.8%) of 132 patients who developed PNX after being diagnosed as PCR-positive for COVID-19. Mortality was observed in 14 (43.75%) of 32 patients with PMN. According to these data, it was understood that PNX occurring after COVID-19 infection caused higher mortality in patients when compared with PMN ($p<0.001$). When the literature was examined, there were no other studies comparing the mortality caused by PNX and PMN after COVID-19 infection. In this respect, it is believed that the current study will contribute to the literature.

When the effects of PNX and PMN accompanying subcutaneous emphysema were examined on the prognosis and mortality after being diagnosed as PCR-positive for COVID-19, no statistically significant data could be obtained ($p=0.018$ and $p=0.216$).

When the studies of Yang et al.[13] and Zumla et al.[14] were examined, it was determined that inflammatory response is an important prognostic factor in COVID-19. In the current study, when the relationship between the median CRP, NLR, and WBC values and the prognosis of the patients was examined, it was found that the median value increased gradually from mild to severe, but it was not statistically significant ($p=0.274$, $p=0.219$, and $p=0.076$, respectively). However, when the relationship between the median NLR, WBC, and CRP values and mortality was examined, it was found that the median value was higher in the patients with mortality, and it was found to be statistically significant in accordance with the literature ($p<0.001$, $p=0.022$, and $p=0.001$, respectively).

Limitations of the study

The main limitations of this study were the fact that the study was retrospective, it was a single center, the number of patients was small, and statistical analysis could not be performed, which resulted in the exclusion of very few isolated pleural complications, other than PNX or PMN, from the study.

CONCLUSION

Various pleural complications occur as a result of positive pressure invasive or noninvasive mechanical ventilation applied as a result of the decreased respiratory capacity of patients due to pneumonia occurring after COVID-19. However, there are not enough studies in the literature evaluating pleural complication, mortality, and prognosis. In this study, the relationship between the pleural complications caused by COVID-19 pneumonia and prognosis and mortality were statistically evaluated to contribute to the literature at this stage. As a result, it was found that PNX after positive pressure ventilation increased mortality more than other pleural complications and worsened the prognosis. However, there was no statistically significant difference in mortality or prognosis between spontaneous PNX or other complications after oxygenation.

Ethics Committee Approval

This study approved by the Ankara City Hospital Clinical Research Ethics Committee (Date: 23.06.2021, Decision No: E1-21-1866).

Informed Consent

Retrospective study.

Peer-review

Internally peer-reviewed.

Authorship Contributions

Concept: S.A.A., A.G., M.H.; Design: S.A.A., A.G., M.H.; Supervision: S.A.A., Y.A., B.K.; Fundings: S.A.A., Y.A., D.E.; Materials: S.A.A., A.I.S., D.E.; Data: S.A.A., Y.A., B.K.; Analysis: S.A.A., A.I.S., M.H.; Literature search: A.G., M.H., A.I.S.; Writing: S.A.A., Y.A., D.E., B.K.; Critical revision: S.A.A., A.G., M.H., Y.A., A.I.S., B.K., D.E.

Conflict of Interest

None declared.

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COVID-19 Hastalarında Mortaliteye Etki Eden Plevral Komplikasyonların Değerlendirilmesi

Amaç: Bu çalışmada SARS-CoV-2 pcr pozitifliği saptanan ve COVID-19 pnömonisi ile hastaneye başvuran hastalarda meydana gelen plevral komplikasyonların geriye dönük olarak değerlendirilmesi amaçlandı.

Gereç ve Yöntem: Mart 2020–Mayıs 2021 tarihleri arasında hastanemize başvuran ve SARS-CoV-2 pcr pozitifliği saptanan ve COVID-19 pnömonisi tedavisi sırasında plevral komplikasyonların saptandığı servis veya yoğun bakımlarda takip ve tedavi edilen 164 hasta retrospektif olarak değerlendirildi. Çalışmamızda mortalite hastaların hastaneye yatış sonrası ilk 30 gündeki ölümleri olarak alındı. Tedavi sırasında meydana gelen plevral komplikasyonlar pnömotoraks ve pnömomediastinum olarak 2 grupta sınıflandırılmıştır.

Bulgular: Hastalarımızın 69'unda (%52.3) izole PNX, 14'ünde (%43.7) izole PMN mevcuttur. 50'sinde PNX ve subkutan amfizem (%37.9), 13'sınde (%40.6) PMN ve subkutan amfizem, üçünde (%9.4) PMN, PNX ve subkutan amfizem, ikisinde (%6.3) PMN ve PNX 12'sinde (%9.1) hidropnömotoraks ve birinde (%0.7) de PNX ve ampiyem birlikteliği mevcuttur. Hastalarda COVID-19 pnömonisi sebebiyle tedavi sırasında meydana gelen plevral komplikasyon ile mortalite arasındaki ilişki incelendiğinde PMN hastalarının 14'ünde (%43.8) mortalite görülmesine rağmen PNX hastalarının 104'ünde (%78.8) mortalite görülmüştür ($p<0.001$). Cinsiyet ile mortalite arasındaki ilişki incelendiğinde erkek hastaların 75'inde (%65.8) mortalite görülmüşken kadın hastaların ise 43'ünde (%86) mortalite görülmüştür ($p=0.008$).

Sonuç: Sonuç olarak pozitif basınçlı ventilasyon sonrası meydana gelen pnömotoraks durumunun meydana gelen diğer plevral komplikasyonlara göre mortaliteyi daha çok artırdığını, prognozu ise daha çok ağırlaştırdığını saptadık. COVID-19 pandemisi ile bundan sonra ortaya çıkabilecek ve plevral tutulum meydana getirebilecek pandemik hastalıklarda bu hususun literatüre katkı sağlayacağını düşünüyoruz.

Anahtar Sözcükler: Mortalite; plevral komplikasyon; pnömomediastinum; pnömotoraks.