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Original Article

Early Period Results in Patients Developing Pneumothorax and Pneumomediastinum Due to COVID-19 Pneumonia: Single-Center Clinical Experience on 47 Cases

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ABSTRACT

Objective: Pneumothorax (PNX) and/or pneumomediastinum (PNM) is an entity that can occur as late findings in COVID-19 patients with mechanical ventilator support. The purpose of this study was to determine the parameters that influence morbidity and mortality associated with PNX and/or PNM secondary to COVID-19 infection.

Methods: The study was performed on patients from March 2020 to December 2020. Demographic data, comorbidities, positive end-expiratory pressure (PEEP) values, and fraction of inspired oxygen (FiO_2) percentage were analyzed. Mortality in the first 48 h, between 48 h and 7 days, and after 7 days was assayed.

Results: A total of 47 patients, only 2 of whom (4%) were in 20–40 years of age, were studied. The result was statistically significant ($p<0.03$). Bilateral PNX was seen in 5 patients (11%). Tube thoracostomy was performed in 40 patients (85%). The isolated PM was detected as a single finding in 11 patients (23%). The mean age was 62 years. The mean mechanical ventilator PEEP and the FiO_2 values were 11 cmH_2O and 84%, respectively. When the mortality of the first 48 h and the first 7 days was compared, no statistically significant difference was found. However, a significant difference in the mortality observed after the 7th day, which is consistent with the literature, and the presence of diffuse subcutaneous emphysema was detected ($p<0.05$).

Conclusion: Tube thoracostomy is a highly effective method for treating PNX in all patients. Due to the elevated risk of PNX associated with the development of PNM in patients receiving mechanical ventilation, we suggest that more sensitive and earlier lung-protective breathing methods should be used.

INTRODUCTION

The first case of pneumonia associated with coronavirus was published in Wuhan, China, in December 2019 and was later seen in other countries and then in Türkiye. The first case in Türkiye was reported on March 11, 2020.[1] Symptoms seen in patients with COVID-19 include fever, cough, decreased sense of taste, and, more seriously, pneumonia and acute respiratory distress syndrome (ARDS). Typical radiological findings are bilateral peripheral of ground-glass opacities, lobar, segmental consolidation, and air bronchograms on high-resolution computed tomography (CT).[2] Pneumothorax (PNX) and pneumomediastinum (PNM) are late findings that can be seen in patients with COVID-19 who developed ARDS in the intensive care unit and on mechanical ventilator (MV) support.[3]

PNX is defined as lung collapse due to free air collecting in the intrapleural space, either primary or secondary.[4] On the other hand, PNM, which is usually a rare entity, is the diffusion of air through the bronchovascular sheath toward the mediastinum after alveolar rupture due to increased intrathoracic pressure.[5] Subcutaneous emphysema is usually associated with PNX and is the advancement of air through the subcutaneous tissues.[5]

PNX has been reported as a complication of ARDS in SARS-CoV-1 infection, and its incidence was defined as 1.7%.[3] PNX and PNM in the patients with COVID-19 have been usually published as case reports in the literature. A multicenter retrospective study conducted by Martinelli et al.[6] examined 71 patients from 16 centers and reported that PNX was a complication depending on COVID-19, but was not seen as an independent poor prognosis criterion.

In our study, we retrospectively analyzed patients with COVID-19 who were identified to have PNX and/or PNM were followed up and treated in our clinic and in the intensive care unit, emergency services, and pandemic services in different centers in our region. It was investigated whether the presence of PNX and PNM increased mortality and to what extent they affected the prognosis in these patients.

MATERIALS AND METHODS

In this study, a total of 47 patients diagnosed with PNX and/or PNM secondary to COVID-19 pneumonia, detected in the intensive care unit for the COVID-19, emergency services, and COVID-19 clinics in different centers in our province and followed up and treated by our clinic in March–December 2020, were retrospectively analyzed. Tube thoracostomy and closed underwater drainage procedures were applied in patients with PNX. No valve system was used in closed drainage systems. A massive air leak was seen in 19 patients (40%), and an additional closed underwater drainage system was added depending on the first closed underwater drainage system. The patients with PNM in the intensive care unit were followed on MVs, the follow-ups were performed with the lowest possible PEEP and with bedside X-ray measurement, which we call the conservative method, taken every 8 h or immediately in case of respiratory deterioration. Although PNX was not detected in 36% (n=4) of 11 patients diagnosed with PNM, subcutaneous fascia opening and draining of subcutaneous emphysema with a thick granule were performed. PNX developed in 64% (n=7) of patients during follow-up, and tube thoracostomy was performed. As most of the patients were not suitable for thorax CT, the patients were followed up with portable chest X-rays, and thorax CT could be performed for suitable patients. Demographic data, physical examination, laboratory and radiological findings, comorbidities, treatment and follow-up methods, tube thoracostomy times, and COVID-19 combined nasal and pharyngeal swab samples of the patients were analyzed. Moreover, MV mode, positive end-expiratory pressure (PEEP) values, and fraction of inspired oxygen (FiO_2) percentage of patients who developed PNX and/or PNM when under follow-up with a MV in the intensive care unit for the COVID-19 were analyzed. Additionally, the factors affecting mortality in the first 48 h, between 48 h and 7 days, and after 7 days in these patients were also assayed.

Statistical analysis

Frequency distributions of the data are presented as numbers and percentages for categorical variables and as mean±standard deviation for continuous variables. The Chi-squared test and Fisher's exact test were used to evaluate the relationship between categorical variables. The distribution characteristics of continuous variables were evaluated using the Kolmogorov–Smirnov test, and as they did not show normal distribution, the Mann–Whitney U test was used to evaluate the relationship between categorical variables. For all analyses, $p<0.05$ was considered statistically significant, and all statistical analyses were performed using SPSS 18.0 software.

RESULTS

Of the 47 patients included in the present study, 8 were female (17%) and 39 were male (83%). Of these patients, only 2 patients (4%) were between the ages of 20 and 40 years and all of the other patients were over the age of 40 years (96%), and the result was statistically significant ($p<0.03$). Bilateral PNX was seen in 5 patients (11%). There were 29 active smokers (62%) and 7 patients (15%) had chronic obstructive pulmonary disease (COPD) and bullous emphysematous. In addition, it was found that 45% of the patients (n=21) had hypertension (Ht), 25% (n=12) had diabetes mellitus (DM), and 6.4% (n=3) had vitamin D (Vit-D) deficiency. Combined COVID-19 nasal and pharyngeal swab samples studied using the PCR method were found positive (81%) in 38 patients. Forty percent of the patients had a ground-glass appearance in the thorax CT (Table 1), 17% (n=8) of the COVID-19 patients diagnosed with PNX presented to the emergency service with the clinical presentation of PNX, while PNX was seen in 72% of the patients (n=34) who were followed in the intensive care unit. Isolated PNX was seen in 23 patients (49%), isolated PNM was seen in 11 patients (23%) with COVID-19 pneumonia, and no other radiological finding was ob-

Table 1. Demographic and clinical data of patients with COVID-19 and pneumothorax

	n=47 (100%)
Age	
20–40	2 (4)
40–60	12 (26)
60–70	12 (26)
>70	21 (44)
Sex	
Male	39 (83)
Female	8 (17)
Side	
Left	15 (32)
Right	32 (68)
Bilateral	5 (11)
Smoking	
No	18 (38)
Yes	29 (62)
Respiratory comorbidities	
COPD and bullous lung	7 (15)
Comorbidities	
Hypertension	21 (45)
Diabetes mellitus	12 (26)
Vitamin D deficiency	3 (6)

COPD: Chronic obstructive pulmonary disease.

Table 2. Clinics and treatment methods of patients with COVID-19 and pneumothorax

	n (%)
Clinics	
Emergency service	8 (17)
COVID-19 service	5 (11)
COVID-19 intensive care unit	34 (72)
Radiological finding	
Isolated pneumothorax	23 (49)
Pneumomediastinum	11 (23)
Diffuse subcutaneous emphysema	22 (47)
Treatment	
Tube thoracostomy	40 (85)
Conservative	7 (15)

Table 3. Comorbidity of patients who developed pneumothorax and pneumomediastinum in the COVID-19 intensive care unit

Comorbidities	n=34 (100%)
Heart failure	1 (3)
Cor pulmonale	1 (3)
Atrial fibrillation	2 (6)
Coronary artery disease	3 (9)
Malignancy	1 (3)
Vitamin D deficiency	2 (6)

served. Diffuse subcutaneous emphysema was detected in 22 patients (47%) (Table 2).

Tube thoracostomy was performed in 40 (85%) COVID-19 patients who were followed up depending on PNX and PNM, while the other 7 patients were followed up conservatively. Isolated PNM was detected as a single finding in 11 patients (31%) followed up due to PNX in the COVID-19 intensive care unit. The PNM patients, 6 had Ht (55%), 3 had DM (27%), 1 had COPD (9%), and 6 had smoking (55%), and Vit-D deficiency was observed in 6% (Table 3). All of these patients were under follow-up with a MV, and no patient underwent extracorporeal membrane oxygenation. Additionally, PCR positivity was observed in 9 patients (82%), radiological ground glass appearance was determined in 4 patients (36%), and ARDS was found in 3 patients. All of them had diffuse subcutaneous emphysema, the mean age was 62 years, the mean MV PEEP value was 11 cmH_2O, and the mean FiO_2 was calculated to be 84%. Accordingly, mean age, PEEP, and FiO_2 values are shown in Table 4. Tube thoracostomy was performed in 7 patients (64%) due to the development of PNX during their follow-up, while 4 patients (36%) were followed conservatively by changing ventilator PEEP and tidal volume settings.

When the mortality rates for first 48 h and 7 days were compared, it was shown that no statistically significant differences were observed. However, a significant difference was found in the mortality after 7 days ($p<0.05$). The univariate analyses showed no significant change in the ground glass appearance, HT, DM, COPD, smoking, PNM, follow-up with a MV, and treatment approach (as a conservative approach and tube thoracostomy). On the other hand, PCR positivity was found to be significant in the first 7 days of mortality ($p<0.05$). Vit-D deficiency was detected in the patients with mortality after 7 days ($p=0.05$).

Table 4. Clinical features of COVID-19 patients with pneumomediastinum

Comorbidities	n=11 (100%)
Age	
20–40	0
40–60	3 (27)
60–70	3 (27)
>70	5 (45)
Sex	
Female	2 (18)
Breathing mode	
Spontaneous	0
NIMV	0
Intubated	11 (100)
Pneumothorax	
Yes	7 (64)
No	4 (36)
Tube thoracostomy	7 (64)
Ground-glass opacity	4 (36)
ARDS	3 (27)
PEEP (mean) (cmH_2O)	11 (5–16)
FiO_2 (mean)	84% (40–100)
Mortality	9 (82)

NIMV: Noninvasive mechanical ventilation; ARDS: Acute respiratory distress syndrome; PEEP: Positive end-expiratory pressure.

When patients with PNX in the intensive care unit for the COVID-19 and COVID-19 services were compared, there was no significant difference in mortality in the first 48 h and the first 7 days. However, mortality after 7 days was found to be statistically significant ($p<0.05$). In addition, diffuse subcutaneous emphysema was also statistically significant in mortality after 7 days ($p<0.05$) (Table 5).

Mortality was observed in 82% of the COVID-19 patients who developed PNM (n=9), and all of these patients were under follow-up with a MV. Their mean MV PEEP value was 11±3.4 cmH_2O, the mean value for FiO_2 of these patients was calculated as 84%±23.5%. The mortality in the first 48 h was 9.1%, while 8% in the patients without PNM, and it was not statistically significant ($p=0.937$). While the first 7-day mortality rate was 27.3%, the mortality after the 7th day was 54.5%, and this difference was not found to be statistically significant ($p>0.05$). When the mean MV PEEP and FiO_2 values of patients with and without PNM were compared, no statistically significant difference was found ($p=0.478$).

Table 5. Multivariate analysis of mortality in the COVID-19 patients who developed pneumothorax and/or pneumomediastinum(significance values were bold)

	Mortality in the first 48 h (n=4)			Mortality in the first 7 days (n=13)			Mortality after 7 days (n=18)		
	Yes, n (%)	No, n	p	Yes, n (%)	No, n	p	Yes, n (%)	No, n	p
COVID-19 intensive care unit (34–77%)	4 (100)	30	0.56	12 (92)	22	0.14	17 (94)	17	**0.03**
COVID-19 Service (13–23%)	0	13	0.56	1 (7.7)	12	0.14	1 (5.6)	12	**0.03**
Groundglass appearance (18–38%)	0	18	0.28	4 (31)	14	0.73	7 (39)	11	0.94
PCRpositivity (38–81%)	4 (100)	34	0.57	13 (100)	25	0.04	15 (83)	23	1.00
Hypertension (21–45%)	3 (75)	18	0.31	6 (46)	15	0.90	9 (50)	12	0.56
Diabetes mellitus (12–26%)	2 (50)	10	0.26	5 (39)	7	0.26	3 (17)	9	0.32
COPD (7–15%)	1 (25)	6	0.48	1 (8)	6	0.65	4 (22)	3	0.40
Vitamin D deficiency (3–6%)	0	3	1.00	0	3	0.55	3 (17)	0	**0.05**
Smoking (29–62%)	1 (25)	28	0.15	7 (54)	22	0.52	12 (67)	17	0.58
Diffuse subcutaneous emphysema (24–51%)	2 (50)	22	1.0	7 (54)	17	0.81	13 (72)	11	**0.02**
Isolated pneumomediastinum (11–23%)	1 (25)	10	1.0	3 (23)	8	1.0	6 (33)	5	0.29
ECMO (3–6%)	0	3	1.0	0	3	0.55	3 (17)	0	**0.05**
Mechanical ventilation (30–64%)	4 (100)	26	0.28	10 (77)	20	0.32	14 (78)	16	0.11
Conservative treatment (7–15%)	1 (25)	6	0.48	3 (23)	4	0.37	1 (6)	6	0.22
Tube thoracostomy (41–87%)	3 (75)	38	0.43	10 (77)	31	0.32	17 (94)	24	0.38
Pneumothorax as first finding (12–26%)	0	12	0.55	2 (15)	10	0.46	2 (11)	10	0.09

COPD: Chronic obstructive pulmonary disease; ECMO: Extracorporeal membrane oxygenation.

DISCUSSION

In the literature, it is stated that PNX is a common complication of COVID-19 pneumonia and is seen in 5.9% of patients connected to positive-pressure ventilation.[2] Sihoe et al.[3] reported that the incidence of PNX was 1.7% in patients with severe acute respiratory syndrome (SARS), and PNX was seen as a late complication in these patients. Martinelli et al.[6] showed that PNX was also seen in nonintubated patients with COVID-19, and it may be associated with COVID-19.

In the literature, lung parenchymal cyst formation, which is seen radiologically as a result of ARDS due to SARS, is shown to be the result of ischemic lung parenchymal damage and inflammation.[7] Bellini et al.[8] had previously shown that microvessel inflammation and capillary wall thickening have an important role in the pathogenesis of the disease in patients with COVID-19 virus infection. Aiolfi et al.[9] also observed edema, protein-rich exudate, vascular congestion, and inflammatory changes in the pathology of the disease in case of lung involvement from COVID-19. Therefore, overinflation of the lungs induced by MV and high PEEP in COVID-19 pneumonia may lead to alveolar and/or bleb rupture in fibrotic and hypoplastic lungs and may complicate the treatment of PNX.

In our study, PNX and/or PNM was seen in a total of 47 patients with COVID-19, 83% of them were male, 96% of them were over 40 years of age, and it was found to be statistically significant (p<0.05). Of the patients, 72% (n=34) were in the intensive care unit, and clinical presentation was detected as spontaneous PNX in 8 patients (17%). COVID-19 pneumonia, a lung disease that causes secondary PNX, suggests the possibility of being predisposing, the literature supports it in this direction.[10]

Martinelli et al.[6] stated that none of the patients with COVID-19 who developed PNX were operated on due to the high risk of anesthesia and infection. Bellini et al.[8] reported that the first two cases of COVID-19 pneumonia developed spontaneous and recurrent PNX, which they treated surgically. They also stated that the atelectasis areas did not re-expand during pulmonary re-ventilation, and this was due to the loss of parenchymal compliance despite the use of positive pressure air flows.[8] Additionally, they suggested that, although rarely, COVID-19 may present with PNX, and surgical treatment methods can be performed safely and effectively in these patients.[8] In our study, tube thoracostomy was sufficient for 85% of the patients, and the conservative approach was used in 7 patients. No operation was performed on any patient. The reason for this is that these patients did not live long enough to develop prolonged air leak, which is the most common indication for the operation of PNX. Otherwise, we believe that COVID-19 does not pose any risk in terms of operation in PNX patients.

PNM is not very common in viral pneumonias, but it has been reported in the literature that PNM may be associated with ARDS.[11–14] In its pathophysiology, alveolar rupture causes air accumulation in the interstitium, which circulates centripetally from the venous sheaths to the hilum and mediastinum (Macklin effect). The reason for this was the pressure in the mediastinum is lower than that in the lung periphery.[12] The most common predisposing factor is asthma (8%–39%),[12] and thorax CT is the gold standard method for diagnosis.[15] Although it is a benign condition, the underlying lung disease can lead to the development of PNM and complicate the disease, and also the development of PNX and the coexistence of COVID-19 be life-threatening.[10] Mohan and Tauseen had shown that the development of PNM in COVID-19 infection is an indicator of the worsening of the disease.[16] In our study, the number of patients who developed PNM was 11, and all of them were followed with a MV. PNX developed in 64% (n=7) of these patients during their follow-up who underwent tube thoracostomy. Mortality was observed in 82% of COVID-19 patients who developed PNM. As a result of the comparison of the PEEP and FiO_2 values, which are the ventilator parameters of intensive care, no significant change was observed (p=0.478). Accordingly, we foresee that earlier application of neuromuscular blocking agents may be a factor to prevent the development of PNM.

It has been stated in the literature that the development of PNX during coronavirus infection is an important prognostic factor.[10,15] In addition, it has been reported that the incidence of PNX is about 1% and that two-thirds of these patients can survive. Over 70 years of age and the presence of acidosis are poor prognostic factors during COVID-19 infection.[10] The incidence of PNX and PNM was reported to be 15% in patients followed up with a MV in the intensive care units, and it was also stated that the mortality risk was clearly higher.[10] McGuinness et al.[10] revealed that the frequency of PNX and PNM were 9% and 10%, respectively, and showed in multinomial regression analyses that it was closely associated with barotrauma and associated with mortality. In the postmortem evaluation of 10 patients with COVID-19, acute and organized diffuse alveolar damage and resistant virus in the respiratory tract were detected histopathologically and were stated as the cause of death.[13] Factors such as ground-glass appearance, HT, DM, COPD, smoking, PNM occurring, MV, conservative approach, and tube thoracostomy, which are among the parameters that we think may be associated with mortality in our series, were not found to be statistically significant. PCR positivity was found to be significant in the first 7-day mortality (p<0.05). Vit-D deficiency was prominent in mortality after the 7th day (p=0.05). Although this is predicted to be statistically significant, we think that it can be demonstrated by studies with a high population. In mortality analysis, there was no significant difference in mortality rates of patients who developed PNX and/or PNM in the first 48 h and first 7 days, while a statistically significant difference was found in mortality rates after the 7th day and in the diffuse subcutaneous emphysema (p<0.05).

In conclusion, PNX and/or PNM, which can be seen as a complication of COVID-19 in patients followed up with a MV in the intensive care units, may develop due to high PEEP used during ventilation as well as hypoxia. Drainage and resorption can be achieved with tube thoracostomy and adjustment of PEEP pressures, and standard treatment methods usually can be sufficient. In our study, the development of PNX and/or PNM during the course of COVID-19 infection in mortality especially after the 7th day was statistically significant and compatible with the literature. We have experienced that tube thoracostomy is a highly adequate form of treatment in COVID-19 patients with PNX followed in the service conditions. As the development of PNM is a high risk for PNX in patients on MVs, more sensitive and lung-protective ventilation strategies should be applied to these patients.

Ethics Committee Approval

This study approved by the Recep Tayyip Erdoğan University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (Date: 18.02.2021, Decision No: 2021/37).

Informed Consent

Retrospective study.

Peer-review

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Authorship Contributions

Concept: G.S., K.T., H.T.; Design: G.S., K.T., H.T.; Supervision: G.S., K.T., H.T.; Data: G.S.; Analysis: G.S.; Literature search: G.S., H.T.; Writing: G.S., H.T.; Critical revision: G.S., H.T.

Conflict of Interest

None declared.

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COVID-19 Pnömonisine Bağlı Pnömotoraks ve Pnömomediastinum Gelişen Hastalarda Erken Dönem Sonuçlarımız: Tek Merkez 47 Hasta Klinik Deneyi

Amaç: Pnömotoraks ve/veya pnömomediastinum COVID-19 tanısı ile yoğun bakımda takip edilen ve adult respiratory disease syndrome gelişen mekanik ventilatör desteğindeki hastalarda görülebilen geç bulgular olarak ortaya çıkabilen antitelerdir. Bu çalışmada, COVID-19 enfeksiyonuna ikincil gelişen pnömotoraks (PNX) ve/veya pnömomediastinum (PNM) nedeni ile, yönetimi kliniğimiz tarafından yapılan hastaların geriye dönük analizi ile morbidite ve mortaliteye etki eden faktörlerin incelenmesi amaçlandı.

Gereç ve Yöntem: Mart–Aralık 2020 tarihleri arasında COVID-19 pnömonisi ile ilişkili PNX ve/veya PNM tanısı konan, kliniğimiz tarafından yönetilen toplam 47 hasta geriye dönük olarak incelendi. Hastaların demografik verileri, muayene ve radyolojik bulguları, ko-morbiditeleri, positive end-expiratory pressure (peep) değerleri, fraction of inspired oxygen (FiO_2) yüzdeleri, ile ilk 48 saat, 48 saat ile 7 gün arası ve 7 gün sonrası mortalite analiz edildi.

Bulgular: Toplam 47 hastanın sadece 2'si (%4) 20 ile 40 yaş aralığında olup istatiksel olarak anlamlı ($p<0.03$) olarak bulundu. Bilateral pnömotoraks 5 hastada (%11) görüldü. Hastaların 40'ına (%85) tüp torakostomi uygulandı, 7 hasta ise konservatif yöntemle takip edildi. Hastaların 11' inde (%31) sadece izole PM saptandı, hepsinde yaygın cilt altı amfizemi mevcuttu. Bu hasta grubunda ortalama yaş 62, MV ortalama PEEP değeri 11 cmH_2O ve ortalama FiO_2 değeri ise %84 olarak hesaplandı. İlk 48 saat ve ilk 7 günlük mortaliteleri karşılaştırıldığında istatistiksel olarak anlamlı fark saptanmazken, 7. günden sonra görülen mortalitelerde anlamlı fark bulundu ($p<0.05$). Çoklu değişken analizinde hastalarda yaygın cilt amfizeminin eşlik etmesi 7. gün sonraki mortalitelerde istatistiksel olarak anlamlı bir risk faktörü olarak tespit edildi ($p<0.05$).

Sonuç: Tüp torakostomi COVID-19 hastalarında görülen pnömotoraks tedavisinde oldukça etkili bir yöntemdir. Mekanik ventilatöre bağlı hastalarda pnömomediastinum gelişmesinin pnömotoraks için yüksek risk olması bakımından bu hastalarda daha hassas ve daha erken akciğer koruyucu ventilasyon stratejilerinin uygulanması gerektiğinin önermekteyiz.

Anahtar Sözcükler: COVID-19; pneumomediastinum; pnömotoraks; SARS CoV-2;