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Analysis of the factors that affect survival among patients who developed subcutaneous emphysema monitored on COVID-19 diagnosis: single-centred research

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ABSTRACT

Aim: The COVID-19 patients with pulmonary involvement frequently develop pneumothorax, pneumomediastinum and subcutaneous emphysema due to barotrauma. Reviewing the literature, pneumothorax, pneumomediastinum and subcutaneous emphysema it can be observed among ICU patients due to the pulmonary involvement of the COVID-19 disease, and therefore, can cause mortality and morbidity. This study aims to analyse the factors that affect mortality in COVID-19 patients in ICUs who develop subcutaneous emphysema.

Material and Method: A total of 854 COVID-19 patients who were consulted from all branches in the Chest Surgery Clinic of Ankara City Hospital between September 1, 2020 - March 1, 2021 were retrospectively analyzed. Demographic characteristics, comorbid diseases and COVID-related tests (LDH, D-dimer, procalcitonin, ferritin, CRP, IL-6, lymphocyte percentage and neutrophil and lymphocyte ratio) imaging results and survival of 66 patients with subcutaneous emphysema were analyzed.

Results: Of the patients, 41 (62%) were male and 25 (38%) were female. The mean age was 63 years. 55 (83%) of these patients were followed up with invasive ventilation support due to general health impairment, increased oxygen demand and heart problems. Age, intubation and NLR were found to be statistically significant in terms of survival and death, on survival. It was discovered that age and intubation variables could be risk factors. The mortality rates were 1.01 times higher for the elderly compared to the younger patients and 13.8 times higher for the intubated compared to the non-intubated patients.

Conclusion: Age of patient and intubation can be regarded as risk factors for mortality in COVID-19 patients with subcutaneous emphysema, monitored in ICUs. Furthermore, comorbid diseases increase mortality rates.

Keywords: COVID-19, mortality, subcutaneous emphysema

INTRODUCTION

COVID-19, a viral disease, first appeared in Wuhan, China in December 2019. The disease spread rapidly and caused serious health expenses around the world (1,2). The World Health Organization declared a viral pandemic in March 2020, which is also the date the first case was announced by the Ministry of Health of Turkey (3-5). Thorax CT is crucial for the early diagnosis for COVID-19 (6). The most common CT findings include ground-glass appearance with consolidations (6,7). According to the published data, around 20% of the patients were monitored in intensive care units (ICUs) and they showed vascular and pulmonary complications due to COVID-19 (1-4).

The COVID-19 patients with pulmonary involvement frequently develop pneumothorax, pneumomediastinum and subcutaneous emphysema (8). The severe COVID-19 patients monitorized by invasive and non-invasive mechanical ventilation and positive pressure devices (9). Especially in patients with parenchymal involvement, there may appear life-threatening complications such as barotrauma-related pneumothorax, haemothorax, pneumomediastinum and subcutaneous emphysema (8-10). Subcutaneous emphysema is defined as abnormal level of air and gas in subcutaneous tissues. It may develop due to high pressure ventilation (barotrauma) in case of obstructive pulmonary disease, interstitial pulmonary disease and infective diseases with pulmonary parenchymal involvement (11,12).

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This study aimed to analyze the factors affecting mortality in COVID-19 patients who developed subcutaneous emphysema in intensive care units.

MATERIAL AND METHOD

After obtaining the ethics committee approval (E-21-2021), 6187 patients were consulted to the Ankara City Hospital Thoracic Surgery Clinic from the clinics and polyclinics of our hospital between September 1, 2020 - March 1, 2021; 854 patients diagnosed with COVID-19 were retrospectively reviewed. Consultations that unrelated with COVID-19 excluded. Also those who were COVID-19 negative and developed subcutaneous emphysema for any reason were not included in the study. It was found that 66 patient developed subcutaneous emphysema. The demographic characteristics, comorbid diseases and laboratory analysis (LDH, D-dimer, procalcitonin, ferritin, CRP, IL-6, lymphocyte percentage, and neutrophil and lymphocyte ratio (NLR)) and imaging results were analysed. All computer tomography (CT) images of the thorax of the that admitted to the ICU service and included in this study showed widespread pulmonary parenchymal involvement on the day of their admission. Since the additional disease status of four of the patients was unknown, they were excluded from the survival comparison. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki

Statistical Analysis

The data were analysed using IBM SPSS 25.0 (IBM Corp, Armonk, NY) and MedCalc 15.8 statistics software. Definitive statistical methods (frequency, percentage, average, standard deviation, median, min-max) were employed in the assessment of the research data as well as Chi-Square ($\chi 2$) test in the comparison of qualitative data. The eligibility of the data to normal distribution was evaluated with Kulmogorov-Smirnow test, skewness-kurtosis and graphical methods (histogram, Q-Q Plot, Stem and Leaf, Boxplot). On the other hand, the research applied Independent Samples t test for the intergroup comparisons of the qualitative data that showed normal distribution. Similarly, Mann-Whitney U test was used for the intergroup comparisons of the data that did not show normal distribution. The Kaplan-Meier method was used for the evaluation of the survival of the patients. A logistic regression analysis was performed to identify the effects of the variables (age, intubation and NLR) on survival. Statistical significance level was accepted as $p< 0.05$.

RESULTS

Of 66 patients who developed subcutaneous emphysema the number of male and female patients were 41 (62%) and 25 (38%), respectively. Their ages varied between 20 and 92 while the average was 63. Of these patients, 55 (83%) were intubated due to general impairment of health, increased oxygen need and cardiac issues while the remaining 11 (16.6%) were provided with non-invasive ventilation support (**Table 1**).

Table 1. Characteristics of the patients that developed subcutaneous emphysema during COVID-19

		n=66 Mean.±SD	% Median (Min-Max)
Intubation [a]	Yes	55	83.3
Survival [a]	Dead/Alive	56/10	84.8/15.2
Pneumothorax [a]	Yes/No	28/38	42.5/57.5
Side [a]	Left/Right	16/12	57.1/42.9
Tube Thoracostomy [a]	Yes/No	19/47	28.8/71.2
Lab data			
Ldh (U/L) [b]		600.3±250.1	543.0 (201.0-1253.0)
D-Dimer (mg/L) [b]		6.7±7.6	3.7 (0.2-35.2)
Procalcitonin (µg/L) [b]		1.7±6.0	0.2 (0.0-46.8)
Ferritin (µg/L) [b]		1344.7±2343.5	802.5 (39.0-17641.0)
Lymphocyte % [b]		5.5±4.2	4.5 (0.8-18.0)
Neutrophil/ Lymphocyte Ratio [b]		28.3±21.8	20.4 (4.1-116.5)
Crp (mg/L) [b]		101.9±93.0	71.0 (0.9-427.0)
Il-6 (mg/mL) [b]		458.7±1572.1	50.6 (2.0-10488.0)

[a]: n/%, [b]: Average±SD/Median (Min-Max),

56 patients (84.8%) died during monitoring. There were pneumothorax in 28 (42.5%) patients. The comparison between the patients who died (n=56) and the patients who survived (n=10) concluded that there was a statistically significant difference in terms of age, intubation, lymphocyte and neutrophil/lymphocyte ratio values (**Table 2**). The additional disease of 4 of the 56 patients who died could not be reached. The patients who died were elderly and had higher intubation rates, lower lymphocyte values and higher neutrophil/lymphocyte ratio ($p<0.001$, $p=0.001$, $p=0.046$, $p=0.045$, respectively) (**Table 2**). The effect of additional diseases on survival was not statistically significant ($p=0.478$) (**Table 3**).

Table 2. The effect of variables on survival

		Dead (n=56)	Alive (n=10)	P
Sex	Female/ Male	23/33 (41.1%/58.9%)	2/8 (20%/80%)	0.297 [a]
Age (Month)		798.3±168.6	529.7±206.3	0.000 [b]
Intubation	Yes	51 (91.1%)	4 (40%)	0.001 [a]
Pneumothorax	Yes/No	25/31 (44.6%/55.4%)	3/7 (30%/70%)	0.498 [a]
Side	Left/ Right	15/10 (26.8%/17.9%)	1/2 (10%/20%)	0.560 [a]
Tube Thoracostomy	Yes/No	16/40 (28.6%/71.4%)	3/7 (30%/70%)	1.000 [a]
Lymphocyte %		3.7 (2.2-7.2)	7.8 (4.1-9.5)	0.046 [c]
Neutrophil/Lymphocyte Ratio		25.3 (12.2-42.6)	11.1 (8.5-22.3)	0.045 [c]

[a]: Chi-Square Test (n/%), [b]: Independent Samples t Test (Mean±SD), [c]: Mann-Whitney U Test (Median /IQR))

Table 3. Survival comparison of 62 patients with additional disease information available

Additional Disease	Survival		P*
	Dead (n=52)	Alive (n=10)	
No	18 (34.6%)	5 (50.0%)	0.478
Yes	34 (65.4%)	5 (50.0%)	
HT, DM	8 (23.5%)	--	
HT	4 (11.8%)	1 (20.0%)	
HT, CVD, DM	3 (8.8%)	1 (20.0%)	
HT, DM, Asthma	2 (5.9%)	--	
HT, CeVD	2 (5.9%)	--	
Alzheimer , Parkinson	1 (2.9%)	--	
DM	1 (2.9%)	--	
HT, Asthma	1 (2.9%)	--	
HT, DM, AF, Hypothyroidism	1 (2.9%)	--	
HT, DM, CRF	1 (2.9%)	--	
HT, DM, Multiple myelom	1 (2.9%)	--	
HT, CVD, DM, COPD	1 (2.9%)	--	
HT, CVD, CRF	1 (2.9%)	--	
HT, COPD	1 (2.9%)	--	
CVD	1 (2.9%)	--	
CRF	1 (2.9%)	--	
Multiple myeloma	1 (2.9%)	--	
Rheumatoid arthritis	1 (2.9%)	--	
Cerebral palsy	1 (2.9%)	--	
CVD	1 (2.9%)	--	
HT, Epilepsy	--	1 (20.0%)	
HT, CVD	--	1 (20.0%)	
Wegener disease	--	1 (20.0%)	

*: Chi-Square Test (n/%)
HT hypertension, DM Diabetes mellitus, CVD Coronary vascular disease, AF Atrial fibrilation, CeVD cerebrovascular disease, CRF Chronic renal failure

A logistic regression analysis was performed to identify the effects of the variables (age, intubation and NLR), which were found to be statistically significant in terms of survival and death, on survival. It was discovered that age and intubation variables could be risk factors. It was also found out that the mortality rates were 1.01 times higher for the elderly compared to the younger patients and 13.8 times higher for the intubated compared to the non-intubated patients. No significant difference was found for neutrophil/lymphocyte ratio (**Table 2** and **Table 4**).

Table 4. Possible risk factors for survival

Risk Factor	OR (95% CI)	P*
Age (Month)	1.01 (1.00 - 1.01)	0.008
Intubation	13.78 (1.92 - 99.05)	0.009
N/L Ratio	1.05 (0.98 - 1.13)	0.156

* Binary Logistic Regression
Nagelkerke R^2=0.521, Hosmer and Lemeshow Test=0.530

In this study, an analysis of the time was also conducted from the development of subcutaneous emphysema until the death of patients who died. When divided into two groups as the intubated and non-intubated patients, the patients who died did not show a statistically significant difference in terms of the time between the development of subcutaneous emphysema and death ($p<0.01$). In other words, intubation has no effect on the time from the development of subcutaneous emphysema to death in the patients who died.

DISCUSSION

Declared to be a viral pandemic around the world in March 2020, the COVID-19 disease takes a mortal course in patients who are elderly or has weaker immune system, comorbid diseases and/or pulmonary diseases (1-3).

Pulmonary parenchymal damage among COVID-19 patients brings about complications related to barotrauma (9-11). In a study carried out by Jones et al. (13), barotrauma was found to be a frequent complication in severe COVID-19 patients, and it was predicated that ventilation support to these patients should be adjusted in optimal level. It can be claimed that the patients included in the present study developed pneumothorax, pneumomediastinum and subcutaneous emphysema secondary to barotrauma (9,11).

In the intubated COVID-19 patients with pulmonary parenchymal involvement, there is decreased ventilation and an increased need for oxygen due to the fibrosis effect of parenchymal involvement. Therefore, increased volume and pressure of mechanical ventilation lead to barotrauma effect which, in turn, causes pneumothorax, pneumomediastinum and subcutaneous emphysema. Similarly, non-invasive pressure ventilation (CPAP, hi-flow oxygen support) creates barotrauma effect and brings about complications in patients who are monitored without intubation (12). This study revealed that pneumothorax emerged in the mechanically-ventilated patients during ventilation due to increased pressure and volume. It was also established that 3 (27%) patients in non-invasive mechanical ventilation received oxygen

support only with a nasal oxygen cannula and, therefore, the subcutaneous emphysema developed by the patients was not due to barotrauma but arose spontaneously, and that all of these patients survived.

A study performed by Lemmers et al. (14) indicates that patients with pulmonary parenchymal involvement become dependent on mechanical ventilation within a short period of time, while subcutaneous emphysema develops 7 times more compared to other patients due to parenchymal tissue damage and the barotrauma effect of mechanical ventilation. In this study, the average of the ICU admission and intubation periods of the intubated patients was 3.7 days (1 to 8 days). The intubated patients showed 4.1 times more subcutaneous emphysema which was lower compared to Lemmers et al. This is because the hospital in which this study was held had a considerable experience after accommodating the highest number of COVID-19 patients in Ankara, Turkey and the international monitoring and treatment algorithms for ICU patients took shape as the time progressed.

However, subcutaneous emphysema does not develop only due to barotrauma. The study by Mana et al. (15) identified subcutaneous emphysema and spontaneous pneumomediastinum in 11 non-intubated patients. However, this requires further and wider research as it is believed to be secondary to parenchymal damage. It can be stated that the non-intubated patients in this study developed subcutaneous emphysema as a result of barotrauma which, in turn, came into question due to CPAP applied in order to get over with the respiratory distress of parenchymal damage.

Cut et al. (16) revealed that the male patients who develop subcutaneous emphysema due to COVID-19 experience more severe prognosis compared to female patients. In the present study, compared to the female patients, the mortality rates were found to be higher for the male patients who developed subcutaneous emphysema but the difference was not statistically significant. More reliable results may be obtained as regards to the relation between sex and mortality rates with further studies and meta-analyses to be performed on a wider patient population.

There are also studies which show that the emergence of subcutaneous emphysema adversely affect the prognosis of patients. In this regard, Al-Azzawi et al. (17) published a paper on 3 cases and expressed that subcutaneous emphysema is limited in patients who are not infected with COVID-19 but lead to rather complicated and mortal consequences in COVID-19 patients. The research by Ozsoy et al. (18) divided patients into two groups as patients with and without spontaneous pneumomediastinum and concluded that the need for tube thoracostomy and mechanical ventilation was higher, while there was increased hospital stay and mortality rates in the former group. The meta-analysis by Nasa et al. (19) suggested that COVID-19 patients may develop subcutaneous emphysema, pneumothorax or pneumomediastinum spontaneously without positive pressure ventilation, and that mortality rates were higher for the patients with complications (barotrauma) which develop due to positive pressure ventilation. As specified above, the research by Ozsoy et al. (18) grouped COVID-19 patients as the patients with and without spontaneous pneumomediastinum and concluded that prognosis was poorer in the patients with pneumomediastinum compared to the other group. The present study identified that intubation was particularly risky for mortality in patients with subcutaneous emphysema; however, no significant difference was found in terms of mortality rates for the non-intubated patients although the prognosis was poor (extended hospital stay and additional pathologies). The evaluation between the development of emphysema and the period to death inferred that the period to death was shorter in the intubated patients compared to the non-intubated but the differences was not statistically significant.

We found out that subcutaneous emphysema developed to be more lethal with poorer prognosis in both the intubated and non-intubated patients with chronic diseases, while on the other hand, no statistically significant difference was obtained in terms of survival for the patients without comorbid diseases. It can be indicated that this is because already existing and severe pulmonary parenchymal damage progresses together with cytokine storm and hyperinflammation, and therefore, the condition of patients worsens due to pulmonary fibrosis and shortness of breath which are difficult to reverse. In consequence, patients pass away independent of their chronic diseases.

A retrospective observational study that included 119 COVID-19 patients emphasized that higher NLR is a poor prognostic factor and a reliable parameter that can be easily measurable . Similarly, in the present study we found that higher NLR values were associated with worse outcomes (20).

The limitations of the study include the lack of clear numerical values relating to the mechanical ventilation pressure applied to the patients, failure to include the intubation tube diameters in the study, the exclusion of the data whether non-invasive pressure ventilation support had been given before mechanically-ventilating the intubated patients, failure to identify subcutaneous emphysema in the examination of the patients who developed minimal pneumomediastinum and subcutaneous emphysema, and the limited number of research population.

CONCLUSION

Although not rare, COVID-19 patients who are monitored in ICUs do not frequently develop subcutaneous emphysema. Advanced age and intubation can be regarded as risk factors for mortality in patients with subcutaneous emphysema. Prognosis takes a very poor course for these patients. Furthermore, comorbid diseases increase mortality rates. However, more comprehensive studies are required in this regard with wider case series.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara City Hospital Noninvasive/ Clinical Researches Ethics Committee (Decision No: E-21-2021)

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. World Health Organization (WHO) Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected: Interim guidance. Available from: https: //www.who.int/emergencies/diseases/novelcorona virus-2019 Accessed date: March 14 2020.
2. Çiftçi B. The effect of coronavirus disease-2019 (COVID-19) according to gender on health-related quality of life. J Health Sci Med 2022; 5: 1030-5.
3. Wu Z, McGoogan JM. characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese center for disease control and prevention. JAMA 2020; 323: 1239-42.
4. Halaclı B, Kaya A, Topeli A. Critically ill COVID-19 patient. Turk J Med Sci 2020; 50: 585-91.
5. Güngörer B. Baseline demographic, clinical and laboratory risk factors for predicting admission to intensive care unit in patients diagnosed with COVID-19 in the emergency department. Anatolian Curr Med J 2021; 3; 279-83.
6. Demirköse M, Ünver Ulusoy T, Solak Grassie S, et al. The role of chest tomography in the diagnosis of COVID-19. J Med Palliat Care 2022; 3: 1-6.
7. Kesmez Can F, Alay H, Yılmaz S, et al. The thorax tomography correlation in COVID-19 RT-PCR positive patients. Anatolian Curr Med J 2021; 3; 145-50.
8. Karaali R, Ersöz H, Akyol PY, Yurtsever G, Topal FE. Comparison of the tube thoracostomy techniques on treatment in COVID-19 patients with pneumothorax. J Health Sci Med 2022; 5: 306-12.
9. Ertürk T, İnangil D, Pakdil EL, et al. Medical device related pressure injuries in COVID-19 patients followed up in an intensive care unit. J Health Sci Med 2022; 5: 227-33.
10. Guven BB, Erturk T, Kompe Ö. Serious complications in COVID-19 ARDS cases: pneumothorax, pneumomediastinum, subcutaneous emphysema and haemothorax. Epidemiol Infect 2021; 149: 137.
11. Koç İ, Dökme A, Bayraktar A, Kaya A. Noninvazif mekanik ventilasyon sonrası gelişen iyatrojenik pnömotoraks olgusu. J Clin Exp Invest 2014; 5.
12. Talan L, Şaşal Solmaz FG, Ercan U. COVID-19 pneumonia and pneumothorax: case series. Tuberk Toraks 2020; 68: 437-43.
13. Jones E, Gould A, Pillay TD. Subcutaneous emphysema, pneumomediastinum, and pneumothorax in critically ill patients with coronavirus disease 2019: a retrospective cohort study. Crit Care Explor 2020; 2: 210
14. Lemmers DHL, Abu Hilal M, Bnà C. Pneumomediastinum and subcutaneous emphysema in COVID-19: barotrauma or lung frailty? ERJ Open Res 2020; 6: 385-2020
15. Manna S, Maron SZ, Cedillo MA. Spontaneous subcutaneous emphysema and pneumomediastinum in non-intubated patients with COVID-19. Clin Imaging 2020; 67: 207-213
16. Cut TG, Tudoran C, Lazureanu VE, Marinescu AR, Dumache R, Tudoran M. Spontaneous pneumomediastinum, pneumothorax, pneumopericardium and subcutaneous emphysema-not so uncommon complications in patients with COVID-19 pulmonary infection-a series of cases. J Clin Med 2021; 10: 1346.
17. Al-Azzawi M, Douedi S, Alshami A. Spontaneous subcutaneous emphysema and pneumomediastinum in COVID-19 patients: an indicator of poor prognosis? Am J Case Rep 2020; 21: 925557
18. IE Ozsoy, MA Tezcan. Is spontaneous pneumomediastinum a poor prognostic factor in COVID-19? J Coll Physicians Surg Pak 2021; 31: 132-7.
19. Nasa P, Juneja D, Jain R. Air leak with COVID-19 - A meta-summary. Asian Cardiovasc Thorac Ann 2022; 30: 237-44.
20. Jimeno S, Ventura PS, Castellano JM, et al. Prognostic implications of neutrophil- lymphocyte ratio in COVID-19. Eur J Clin Invest 2021; 51: 13404.