



The relationship between lung fibrosis, the epidermal growth factor receptor, and disease outcomes in COVID-19 pneumonia: a postmortem evaluation

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Abstract

The aim of this study was to examine the relationship between the severity of fibrosis in lung tissue and epidermal growth factor receptor (EGFR) positivity in patients who died due to COVID-19 pneumonia, demographic characteristics, comorbidities, biochemical values, and treatments received. Fifty patients who died from COVID-19 pneumonia were included in the study. Demographic data for the patients, laboratory tests, thorax computerized tomography findings, comorbidities, length of stay in the intensive care unit (ICU), intubation times, and treatments given were noted. Postmortem Tru-cut lung biopsy was performed. EGFR positivity was examined and grouped as negative, mild, moderate, and severe. Data were analyzed statistically. EGFR involvement was negative in 11 (22%), mild in 20 (40%), moderate in 13 (26%), and severe in 6 (12%) patients. The mean C-reactive protein (CRP) values, D-dimer values, and mean length of stay in the ICU were found to be significantly different between the groups ($p = 0.024$; $p = 0.003$; $p = 0.016$, respectively). Methylprednisolone dose and the presence of comorbidity did not differ significantly in EGFR involvement ($p = 0.79$; $p = 0.98$, respectively). CRP and D-dimer values can be used as a guide to assess the severity of pulmonary fibrosis that develops in severe COVID-19 pneumonia patients. The dose of methylprednisolone used does not make a significant difference in the severity of fibrosis. *Trail registration*: Clinical Trials.gov identifier date and number 01/13/2022 NCT05290441.

Keywords Epidermal growth factor receptor · A typical pneumonias · Pulmonary fibrosis · Postmortem diagnoses · Biopsy

Introduction

The 2019 coronavirus disease (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus continues worldwide. Coronaviruses

are enveloped, positive, and single-stranded RNA viruses [1]. Approximately one-fifth of people infected with COVID-19 develop severe symptoms with lower respiratory tract involvement and acute respiratory distress syndrome (ARDS). Following the entry of the virus into cells, many different cytokines and inflammatory markers are secreted from alveolar cells. This causes a cytokine storm aimed at fighting the virus. During the cytokine storm, however, diffuse alveolar damage (DAH) occurs because of the inflammation caused by the virus [2, 3]. DAH is a histopathologically nonspecific process. It has two phases: the acute alveolar damage (ALI) phase, characterized by hyaline membranes and pulmonary edema as a result of damage to the alveolar epithelium and endothelium, and the organized phase, in which interstitial fibroblastic proliferation is predominant, which may result in pneumocyte hyperplasia and fibrosis [3–5]. In the interim, inflammation and lung damage continue to spread. This causes loss of type 1 and type 2 pneumocytes, extensive alveolar damage, and eventually ARDS [2]. However, the profibrotic pathways and mediators

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involved in fibrosis and the severity of fibrosis may differ from person to person [6].

Epidermal growth factor (EGF) is a protein-structured growth factor that stimulates cell division, differentiation, survival, proliferation, growth, and cell migration. It acts through the EGF receptor (EGFR). It has a stimulating effect on the growth and proliferation of fibroblasts, keratinocytes, and vascular endothelial cells. Interestingly, for many viruses, including SARS-CoV-2, EGFRs play a role in virus entry and replication. They affect the host's immune response. In addition, excessive activation of EGFRs plays a role in the development of pulmonary fibrosis. EGFR is also a tyrosine kinase receptor [3, 7–9].

Considering the course of the pandemic, it is inevitable that we will soon encounter a large number of patients who have had COVID-19 pneumonia and developed pulmonary sequelae. COVID-19 now needs to be included in the current differential diagnosis of pulmonary fibrosis. Therefore, studies involving patients who develop pulmonary fibrosis due to COVID-19 have become essential to examine risk factors and prognostic markers [6]. The relationship between

the severity of fibrosis and EGFR positivity in the tissue of deceased COVID-19 pneumonia patients, their demographic data and comorbidities, and the treatment they receive may guide treatment approaches.

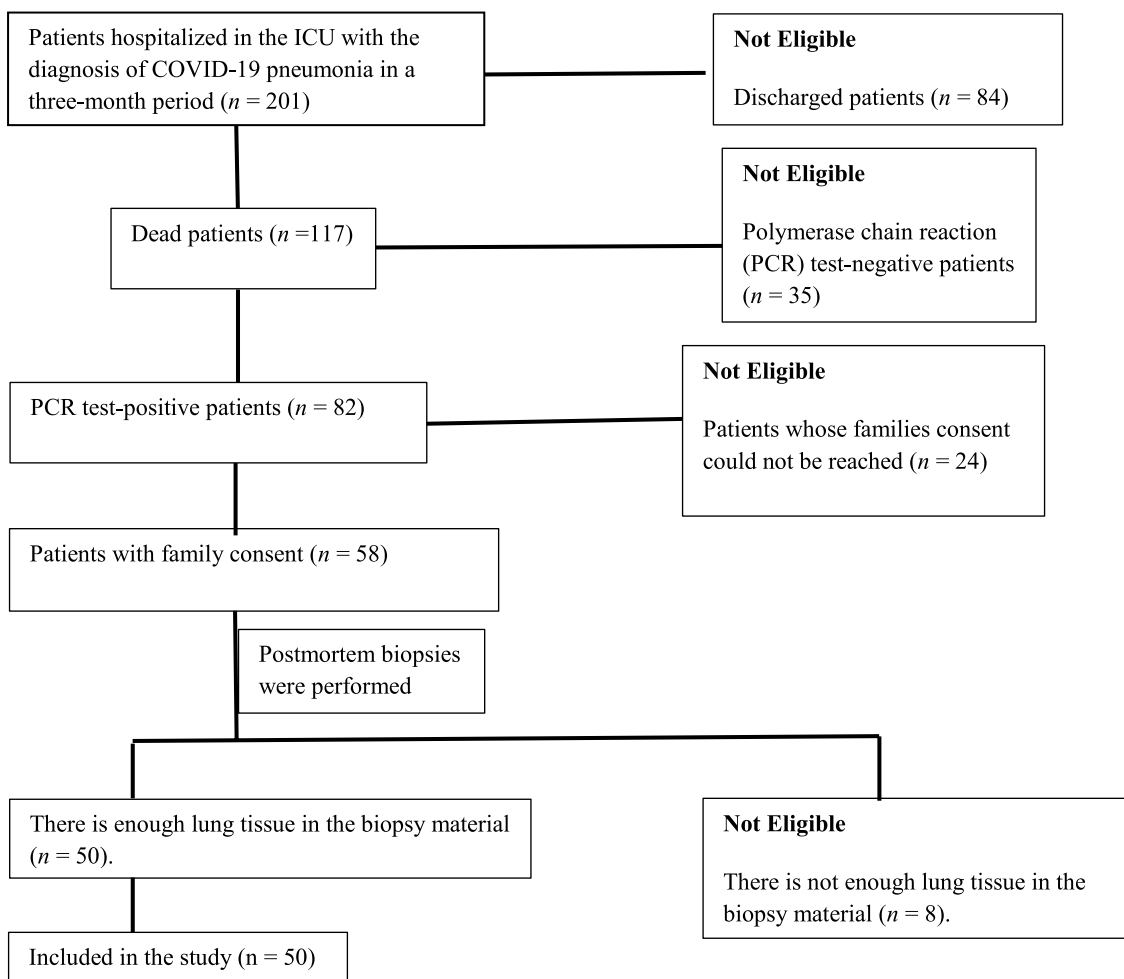
This study examines the relationship between the severity of fibrosis and EGFR involvement in the lung tissue of people who died due to COVID-19 pneumonia and their demographic characteristics, comorbidities, and biochemical values, as well as the treatments they received.

Materials and methods

Patients

Between September 1 and December 1, 2021 50 patients were included in this study. The inclusion–exclusion process is shown in Table 1. The patients' demographic data, laboratory tests, thorax computerized tomography (CT) findings, comorbidities, length of stay in the intensive care unit (ICU), intubation times, and treatments were noted.

Table 1 Flowchart of the inclusion–exclusion of the patients.



Thorax computerized tomography (CT)

COVID-19 pneumonia involvement in the patients' thorax was evaluated by a radiologist through a thorax CT. According to the ratio of the involved segments to the total lung segments, the prevalence was classified as $\leq 25\%$, $> 25\% - \leq 50\%$, $> 50\% - \leq 75\%$, and $> 75\%$.

Biopsy

Postmortem Tru-Cut lung biopsies were performed using the transthoracic approach. The biopsies were taken from the dorsolateral region of the 5–6 intercostal space from the hemithorax, where the involvement was more intense, and the material sent to the pathology laboratory in 10% formalin.

EGFR test

Using the Ventana BenchMark ULTRA model device, immunohistochemical staining was performed with ultraView DAB Detection Kit working solutions and lot number H04603 Anti-Epidermal Growth Factor Receptor primary antibody. According to the established immunohistochemical staining scoring standard, the immunostaining grades were evaluated as 0 (negative), 1 (mild), 2 (moderate), and 3 (severe) staining under a microscope at 100x [10].

Statistics

The severity of fibrosis and the degree of EGFR involvement were analyzed according to the demographic data of the patients, their laboratory test results, the treatments given to them, their length of stay in the ICU, and the duration of their intubation.

The Statistical Package for Social Sciences (SPSS) version 21.0 program (IBM Corp., 2015) was used for analysis. The values for normal distributions are given as the mean and standard deviation, and for nonnormal distributions, the median (med) and the minimum–maximum (min–max). The distributions were analyzed with the Kolmogorov–Smirnov test. The categorical values are presented as percentages. The Mann–Whitney U test, one-way analysis of variance (ANOVA), or Kruskal–Wallis test was used to compare averages, and Fisher's exact test was used to compare rates. The Spearman rank correlation test was used to examine the correlations. The cutoff points were calculated with Roc analysis. A difference of $p < 0.05$ was considered statistically significant.

Results

The demographic data of the 50 patients included in our study are shown in Table 2. Radiographically through thoracic CT, COVID-19 pneumonia involvement was detected in less than 25% of 15 (30%) patients; $\geq 25\% - < 50\%$ of 13 (26%) patients; and between $\geq 50\%$ and $< 75\%$ of 22 (44%) patients.

EGFR involvement was absent in 11 (22%) of the patients, mild in 20 (40%), moderate in 13 (26%), and severe in 6 (12%). Sample views of the severity of EGFR involvement are shown in Fig. 1.

Table 3 shows the data for the groups according to the severity of their EGFR involvement. C-reactive protein (CRP), D-dimer, and mean length of stay in the ICU differed significantly between the groups.

CRP, D-dimer, and ICU length of stay of the EGFR groups were compared in pairs (Table 4). The severity of EGFR and the extent of its radiological involvement, the mean CRP level, and the D-dimer level were correlated ($p = 0.03$, $r = 0.307$; $p = 0.006$, $r = 0.382$; $p < 0.001$, $r = 0.532$, respectively). The CRP cutoff point was 161 mg/L ($p = 0.02$, sensitivity = 0.667, specificity = 0.659), and the D-dimer cutoff point was 9.75 ($p = 0.032$, sensitivity = 0.667, specificity = 0.705).

Discussion

The most important finding of our study is that EGFR involvement and severity of pulmonary fibrosis are associated with CRP levels, D-dimer levels, and length of stay in the ICU. The dose of methylprednisolone used did not make a significant difference in the severity of fibrosis.

The alveolar epithelial surface consists of alveolar type I (ATI) and type II (ATII) cells. Acute alveolar injury (ALI) occurs when SARS-CoV-2 enters these cells [2, 3]. The barrier function of the cells is lost, and the permeability of the alveolar-capillary membrane increases. Barrier function is essential for rapid and efficient restoration of the alveolar epithelium and is activated by the human epidermal growth factor receptor (HER) family [11, 12]. Initial epithelial repair events in ALI include proliferation and migration of ATII cells. Then, differentiation into ATI cells occurs.

If damage persists, ATII cell proliferation becomes unregulated and excessive. Fibroblasts and myofibroblasts proliferate. The extracellular matrix, including collagen and fibronectin, is stored excessively and irregularly, replacing the original tissue. With the failure of normal ATII regeneration, pulmonary fibrosis develops. The

Table 2 Patient demographic data

Age ¹			64 ± 16.5
Gender (male) ²			22 (44)
Symptom days ³			6 (0–15)
Positive days at admission ³			0 (0–10)
SpO ₂ in application ³			88 (40–99)
Variant ²	None		20 (40)
	L452R		29 (58)
	VOC2020-12-01		1 (2)
Vaccine ²	None		13 (26)
	Sinovac		22 (44)
	BioNTech		15 (30)
Smoking ²	None		18 (36)
	Current smoker		22 (44)
	Ex-smoker		10 (20)
Comorbidity ²	41 (82)	Diabetes mellitus ²	18 (36)
		Hypertension ²	15 (30)
		Chronic renal failure ²	8 (16)
		Malignancy ²	7 (14)
		Coronary artery disease ²	6 (12)
		Congestive heart failure ²	6 (12)
		Pregnancy ²	2 (4)
		Postpartum ²	2 (4)
		Others	15 (30)
	WBC ³		
Lymphocyte ³			0.57 (0.14–2.63)
Hemoglobin ¹			9.69 ± 5.57
Hematocrit ³			29.77 (14.9–41.2)
Platelet ³			178.5 (25–484)
CRP ³			154.5 (25.8–456)
Fibrinogen ³			470 (92–888)
D-dimer ³			6 (0.77–9.46)
LDH ³			741.5 (240–30,470)
Ferritin ³			2000 (174–4000)
AST ³			98 (5–16,290)
ALT ³			60 (4–6282)
Sodium ³			143 (126–162)
Calcium ³			7.4 (5–11.9)
Potassium ¹			5.57 ± 1.34
Length of stay in the clinic (days) ³			0 (0–16)
Length of stay in the ICU (days) ³			9 (1–31)
Intubation time (days) ³			6.5 (1–27)

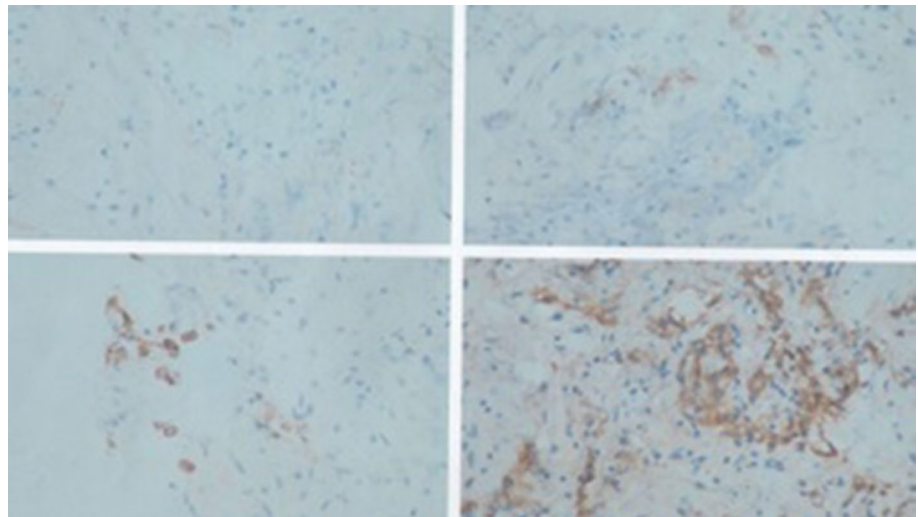
¹Mean ± standard deviation, ²n (%), ³median (minimum–maximum)

WBC: White blood cell, CRP: C-reactive protein, LDH: Lactate dehydrogenase, AST: Acetyl transferase, ALT: Alanine transferase, ICU: Intensive Care Unit

barrier function of epithelial cells is crucial for ATI restoration and inhibition of fibrosis. The HER family that regulates barrier function is activated by tyrosine kinase and comes in four types in humans: HER 1 or EGFR, HER 2, HER 3, and HER 4 [13]. In our study, EGFR involvement was not detected in 11 (22%) patients, whereas it was mild in 20 (40%) patients, moderate in 13 (26%)

patients, and severe in 6 (12%) patients. We could not find any previous study that examined EGFR uptake in pulmonary tissue in COVID-19 pneumonia with a postmortem biopsy. Based on our research, this study is the first to address this. In a study that examined pulmonary fibrosis through Masson's trichrome staining of biopsy material in patients with ARDS, the presence of fibrosis was

Fig. 1 Sample image ($\times 400$) of the staining results with the EGFR kits



associated with the death from the disease [14]. Although not related to COVID-19, it supports our study, as it also examined ARDS that developed in patients with COVID-19 pneumonia.

In a radiologic study, Huang et al. found that more than one-third of patients who recovered from COVID-19 pneumonia developed fibrotic abnormalities upon discharge from the hospital [15]. However, their study included severe COVID-19 pneumonia survivors, and EGFR was not studied. In our research, 78% of the patients were found to have pulmonary fibrosis when examined radiologically and pathologically postmortem. The extent of involvement was considered radiologically and correlated with EGFR involvement.

CRP is a nonspecific acute-phase protein induced by interleukin 6, with a potent proinflammatory effect. It is a sensitive biomarker of inflammation, infection, and tissue damage [16]. In this study, CRP averages significantly differed between groups depending on the severity of EGFR involvement. Our data also support the study of Yu et al. in which 32 patients with confirmed COVID-19 pneumonia had signs of fibrosis on their thorax CT [17]. In the radiological study by Huang et al., CRP was significantly higher in the group with fibrosis than in the group without fibrosis [15]. However, pathological data were not included in these two studies. Although our sample group was small, the cut-off value was 161 mg/L. In Liu et al.'s study of 141 cases of COVID-19 pneumonia, the probability of developing severe disease was higher in patients with a CRP level > 41.8 mg/L [16]. We could not find any previous studies on the risk of death in this case.

Coagulation steps are activated as a result of tissue damage in ALI due to COVID-19. A thrombus develops in small vessels. D-dimer rises as a marker of fibrin disruption and abnormal coagulation [18]. In our study, the severity

of EGFR involvement and the prevalence of radiological involvement were associated with D-dimer elevation. We confirmed the findings of the studies on the relationship between D-dimer and pulmonary fibrosis with thorax CT by performing a pathological examination [15, 19].

ARDS, which can develop in SARS and Middle East respiratory syndrome (MERS) infections, is partially caused by host immune responses. Corticosteroids suppress inflammation in the lung. However, they also inhibit the virus's immune response and clearance [20]. In Wu et al.'s study of 201 patients with COVID-19 pneumonia, it was found that the use of methylprednisolone in patients with ARDS reduced the risk of death [21]. Methylprednisolone was used in the treatment of 92% of our patients, since the World Health Organization also recommends the use of corticosteroids in patients with severe COVID-19 pneumonia [22]. In our study, there was no significant difference in the occurrence of pulmonary fibrosis between patients who did not receive methylprednisolone, those who received 80 mg/day, and those who received 250 mg/day. Chen et al. reported no difference in the in-hospital mortality rates of COVID-19 patients who received low-, medium-, and high-dose methylprednisolone [23]. However, we could not find a study that examined methylprednisolone doses and pulmonary fibrosis rates in patients with COVID-19 pneumonia.

Some studies have found that age, male sex, smoking, comorbidities, leukocytosis, lymphopenia, and high lactate dehydrogenase (LDH) are risk factors for the development of pulmonary fibrosis [15, 17, 24]. These studies used thorax CT findings in patients that survived. In our pathological study, age, sex, smoking, comorbidity, leukocytosis, lymphopenia, and high LDH did not affect the severity of pulmonary fibrosis in severe COVID-19 pneumonia.

The limitations of our study are as follows. First, the number of cases is relatively small. Studies with a larger

Table 3 Statistical comparison of the results of the EGFR test of the fibrosis severity groups

EGFR		Negative (<i>n</i> = 11)	Mild (<i>n</i> = 20)	Moderate (<i>n</i> = 13)	Severe (<i>n</i> = 6)	<i>p</i>
Age ¹		67.5 ± 21.8	65 ± 14	64.7 ± 14	52 ± 16.5	0.338 ^a
Gender (male) ²		5 (45)	9 (45)	6 (46.2)	2 (33.3)	0.95 ^b
Symptom days ³		7 (2–15)	5.5 (0–10)	5 (3–15)	7.5 (4–15)	0.159 ^c
Positive days at admission ³		0 (0–4)	3.5 (0–10)	0 (0–10)	4.5 (0–9)	0.177 ^c
SpO ₂ in application ³		85 (70–98)	86 (40–98)	89 (76–99)	91 (72–96)	0.857 ^c
Variant ²	None	5 (45.5)	8 (40)	4 (30.8)	3 (50)	0.394 ^b
	L452R	5 (45.5)	12 (60)	9 (69.2)	3 (50)	
	VOC2020-12-01	1 (9.1)	0 (0)	0 (0)	0 (0)	
Vaccine	None	4 (36.4)	4 (20)	4 (30.8)	1 (16.7)	0.238 ^b
	Sinovac	6 (54.5)	6 (30)	6 (46.2)	4 (66.7)	
	BioNTech	1 (9.1)	19 (50)	3 (23.1)	1 (16.7)	
Smoking ²	None	5 (45.5)	9 (45)	2 (15.4)	2 (33.3)	0.155 ^b
	Current smoker	2 (18.2)	9 (45)	7 (53.8)	4 (66.7)	
	Ex-smoker	4 (36.4)	2 (10)	4 (30.8)	0 (0)	
Comorbidity ²		9 (81.2)	16 (80)	11 (84.6)	5 (83.2)	0.989 ^b
WBC ³		14.99 (0.92–30.4)	14.1 (5.4–41.4)	19 (2.6–32.6)	11.6 (6.94–18.8)	0.667 ^c
Lymphocyte ³		0.43 (0.14–1.2)	0.63 (0.17–2.63)	0.75 (0.23–1.63)	0.65 (0.19–1.5)	0.656 ^c
Hemoglobin ¹		9.15 ± 1.88	10.07 ± 2.3	10.13 ± 1.78	8.46 ± 0.92	1.494 ^a
Hematocrit ¹		28 ± 4.42	31.14 ± 7.18	32.02 ± 5.46	27.8 ± 2.84	1.445 ^a
Platelet ¹		166.9 ± 132.3	174.85 ± 92.3	172.7 ± 106.1	205.83 ± 97.2	0.202 ^a
CRP ³		122 (25.8–281)	115 (49.4–247)	167 (47.9–360)	228.5 (155–456)	0.024 ^{c*}
Fibrinogen ¹		475 ± 195.1	444.5 ± 164	560 ± 172.5	554.6 ± 207.9	0.261 ^a
D-dimer ³		2.46 (1.14–12.8)	5.47 (0.77–80)	12 (12.26–75.5)	11.75 (8.1–25.9)	0.003 ^c
LDH ³		705 (406–30,470)	845 (240–4500)	759 (443–3324)	3141 (457–13,500)	0.765 ^c
Ferritin ³		2000 (502–2000)	1705 (174–2000)	2000 (298–2000)	2000 (77.6–4734)	0.449 ^c
AST ³		101 (5–16,290)	124.5 (19–4000)	58 (5–1049)	3603 (27–9633)	0.190 ^c
ALT ³		111 (4–6282)	67.5 (12–2047)	32 (14–329)	2169 (12–5475)	0.172 ^c
Sodium ³		139 (126–149)	144.5 (131–159)	142 (136–162)	146 (139–154)	0.309 ^c
Calcium ³		7.8 (6.8–11.9)	7.5 (5–10.6)	7.1 (5.8–8.8)	7.2 (5.8–9.3)	0.435 ^c
Potassium ¹		5.12 ± 1.49	5.46 ± 1.52	5.64 ± 1.52	6.35 ± 0.65	1.01 ^a
Radiological Involvement prevalence ²	< 25%	6 (54.5)	5 (25)	3 (23.1)	1 (16.7)	0.426 ^b
	< 50% – ≥ 25%	3 (27.3)	6 (30)	3 (23.1)	1 (16.7)	
	< 75% – ≥ 50%	2 (18.2)	9 (45)	7 (53.8)	4 (66.7)	
	≥ 75%	0 (0)	0 (0)	0 (0)	0 (0)	
Methylprednisolone treatment dose (mg/g) ²	0	1 (9.1)	1 (5)	2 (15.4)	0 (0)	0.793 ^b
	80	3 (27.3)	6 (30)	2 (15.4)	1 (16.7)	
	250	7 (63.6)	13 (65)	9 (69.2)	5 (83.3)	
Length of stay in the clinic (days) ³		0 (0–0)	0 (0–9)	1 (0–16)	0.5 (0–13)	0.233 ^c
Length of stay in the ICU (days) ³		8 (1–24)	9 (3–31)	9 (3–17)	13 (9–28)	0.016 ^{c*}
Intubation time (days) ³		3 (1–10)	7 (2–27)	6 (1–17)	10 (2–19)	0.167 ^c

¹Mean ± standard deviation, ²*n* (%), ³median (minimum–maximum), ^aone-way ANOVA test, ^bFisher's exact test, ^cKruskal–Wallis test, **p* < .05

WBC: White blood cell, CRP: C-reactive protein, LDH: Lactate dehydrogenase, AST: Acetyl transferase, ALT: Alanine transferase, ICU: Intensive Care Unit

sample size and perhaps autopsy material may provide more information. We did not treat our patients before death in the ICU. Our colleagues who administered the treatment were blinded to our study. We think that studies that compare treatment options, including antifibrotic therapy, will

shed light on the treatment of pulmonary fibrosis that may develop after COVID-19. Unfortunately only the EGFR kit was used. We hope to provide insight into future studies that may be performed with other proinflammatory histopathology markers.

Table 4 Pairwise comparison of the averages of the CRP level, D-dimer level, and length of stay in the ICU in days of the EGFR groups

EGFR Group	<i>p</i> value	Negative	Mild	Moderate	Severe
<i>(Mann–Whitney U test)</i>					
Negative	CRP	–	0.836	0.119	0.027*
	D-dimer	–	0.201	0.004*	0.007*
	Length of stay in the ICU (days)	–	0.047*	0.32	0.019*
Mild	CRP	0.836	–	0.068	0.007*
	D-dimer	0.201	–	0.055	0.006*
	Length of stay in the ICU (days)	0.047*	–	0.038*	0.38
Moderate	CRP	0.119	0.068	–	0.293
	D-dimer	0.004*	0.055	–	0.661
	Length of stay in the ICU (days)	0.32	0.038*	–	0.022*
Severe	CRP	0.027*	0.007*	0.293	–
	D-dimer	0.007*	0.006*	0.661	–
	Length of stay in the ICU (days)	0.019*	0.38	0.022*	–

**p* < .05. CRP: C-reactive protein, ICU: Intensive Care Unit

Conclusion

CRP and D-dimer values can indicate the severity of pulmonary fibrosis that may develop in patients who are in the ICU due to COVID-19 pneumonia. The data in our study showed that the dose of methylprednisolone used does not make a significant difference in the severity of fibrosis. This study, in which EGFR uptake was monitored in COVID-19 pneumonia, may provide a preliminary data for studies that will examine the indication for use of anti-fibrotic drugs in pulmonary fibrosis due to COVID-19.

Author contributions All the authors contributed to the study conception and design. The material preparation and the data collection and analysis were performed by Seyhan Us Dülger, Nazmi Mutlu, İlkyay Ceylan, and Erhan Özhan. The first draft of the manuscript was written by Seyhan Us Dülger, and all the authors commented on previous versions of the manuscript. All the authors read and approved the final manuscript.

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Declarations

Conflict of interests The authors declare that they have no conflicts of interest.

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