The relationship between lung fibrosis, EGFR and disease outcomes in Covid-19 pneumonia: A postmortem evaluation

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Abstract

Purpose: The aim of this study is to examine the relationship between the severity of fibrosis in the lung tissue and EGFR positivity in patients who died due to Covid-19 pneumonia, demographic characteristics, comorbidities, biochemistry values, and treatments they receive.

Methods: Fifty patients who died with Covid 19 pneumonia were included in the study. Demographic data of the patients, laboratory tests, thorax CT 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 analyzed statistically.

Results: EGFR involvement were negative in 11 (22%), mild in 20 (40%), moderate in 13 (26%), severe in 6 (12%) patients. The mean C-reactive protein (CRP), d.dimer and mean length of stay in the ICU were found to be statistically different between the groups (respectively p=0.024; p= 0.003; p=0.016). Methylprednisolone usage dose and presence of comorbidity did not differ significantly in EGFR involvement (respectively, p=0.79; p=0.98). CRP cutoff value for EGFR was 161 mg/L (p=0.02, sensitivity 0.667, specificity 0.659), d.dimer cutoff value was 9.75 (p=0.032, sensitivity 0.667, specificity 0.705).

Conclusion: CRP and d.dimer values can be a guide for the severity of pulmonary fibrosis that may develop in severe Covid-19 pneumonia patients . The dose of methylprednisolone used does not make a significant difference in the severity of fibrosis

Introduction

The Covid 19 pandemic due to the Sars-CoV-2 virus continues to increase worldwide. Coronaviruses are enveloped, positive single-stranded RNA viruses [1]. About one-fifth of patients infected with Covid-19 develop severe symptoms with lower respiratory tract involvement and acute respiratory distress syndrome (ARDS). With the entry of the virus into the cells, many different cytokines and inflammatory markers are secreted from the alveolar cells. This causes a cytokine storm. The goal is to fight the virus. However, diffuse alveolar damage (DAH) occurs with the inflammation they create while doing this [2, 3]. DAH is a histopathologically nonspecific process. It has 2 phases: acute alveolar damage (ALI), characterized by hyaline membranes and pulmonary edema as a result of damage to the alveolar epithelium and endothelium; the organized phase, in which interstitial fibroblastic proliferation is predominant, which may result in pneumocyte hyperplasia and fibrosis [3–5]. Inflammation and lung damage continues to spread. It is type 1 and type 2 cause loss of pneumocytes, extensive alveolar damage, and eventually ARDS [2]. However, profibrotic pathways and mediators involved in fibrosis and the severity of fibrosis may differ individually [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 epidermal growth factor receptor (EGFR). It has a stimulating effect on the growth and proliferation of fibroblasts,

keratinocytes, vascular endothelial cells. Interestingly, for many viruses, including SARS-CoV-2, EGFRs play a role in virus entry and replication. It affects the host's immune response. In addition, excessive activation of EGFRs plays a role in developing 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 in order to examine risk factors and prognostic markers [6]. The relationship between the severity of fibrosis and EGFR positivity in the tissues of deceased covid pneumonia patients, their demographic data, comorbidities, and the treatment they receive may guide treatment approaches.

This study aims to examine the relationship between the severity of fibrosis and EGFR involvement in the lung tissue of patients who died due to covid-19 pneumonia with the demographic characteristics, comorbidities, biochemistry values of the patients, and the treatments they received.

Materials Methods

The study was carried out according to the Declaration of Helsinki recommendations and was approved by the Bursa Yüksek İhtisas Training and Research Hospital Ethics Committee (2011-KAEK-25 2021/08–10). Clinical Trials.gov identifier number: NCT05290441

Patients

Between 01 September and 01 December 2021, 201 patients diagnosed with Covid 19 pneumonia were hospitalized in the Intensive Care Unit (ICU) of our hospital for 3 months. One hundred seventeen of our patients died. Among the patients with exitus, consent for participation in the study was requested from the families of 82 Polymerase Chain Reaction test (PCR) positive patients. Biopsy was performed by including 58 of them in the study, whose families consented. Eight biopsy materials were excluded because they did not contain enough lung tissue. The study was continued with 50 patients. Demographic data of the patients, laboratory tests, thorax computerized tomography (CT) findings, comorbidities, length of stay in the ICU, intubation times, and treatments were noted.

Thorax CT

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

Biopsy

Postmortem tru-cut lung biopsy was performed with the transthoracic approach. Biopsy was performed from the dorsolateral region of the 5–6 intercostal space from the hemithorax, where the involvement was more intense, and the material was sent to the pathology laboratory in 10% formol.

EGFR Test

Using the Ventana BenchMark Ultra model device, immunohistochemical staining was performed with ultra view DAB detection kit working solutions and lot number H04603 Anti-Epidermal Growth Factor Receptor Primary Antibody (Fig. 1). According to the established immunohistochemical staining scoring standard, immunostaining grades were evaluated as 0 (negative), 1 (mild), 2 (moderate), and 3 (severe) staining under a 100x microscope [10].

Statistics

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

Statistical Package for Social Sciences (SPSS) (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) program was used. Numeric values are mean and standard deviation for normal distribution; For non-normal distributions, median (med) and minimum-maximum (min-max) are given. Distributions were analyzed with the Kolmogorov-Smirnov test. Categorical values were presented as percentages. Mann Whitney-U One-way Anova test or Kruskal Wallis Test to compare averages; Fisher test was used to compare rates. Spearmen correlation test was used to examine the correlations. Cut-off point were calculated with the Roc analysis test. $P < 0.05$ values were considered as a statistically significant difference.

Results

Demographic data of 50 patients included in our study are given in Table 1. Radiographically, Covid-19 pneumonia involvement was detected in less than 25% in 15 (30%) patients; ≥25%-<50% in 13 (26%) patients; 22 (44%) patients between ≥ 50-<75% in Thorax Ct. EGFR involvement was absent in 11 (22%) patients. Mild in 20 (40%) patients, moderate in 13 (26%) patients, severe involvement was detected in 6 (12%) patients. Table 2 shows the statistical evaluations of the data among the groups separated according to the severity of EGFR involvement. C-reactive protein (CRP), d.dimer and mean length of stay in ICU were statistically different between the groups. EGFR groups for CRP, d.dimer, and ICU length of stay were compared in pairs (Table 3). Severity of EGFR and extent of radiological involvement, mean of CRP and d.dimer were correlated ($p = 0.03$, $r = 0.307$; $p = 0.006$, $r = 0.382$; $p < 0.001$, $r = 0.532$, respectively). CRP cut off point was 161 mg/L ($p = 0.02$, sensitivity 0.667, specificity 0.659), d.dimer cut-off point was 9.75 ($p = 0.032$, sensitivity 0.667, specificity 0.705).

Table 1

Demographic data of the patients. [1] mean ± standard deviation, [2]n(%), [3] median (minimum-maximum).WBC: White blood cell, CRP: C-reactive protein, LDH: Lactate dehydrogenase, AST: Acetyl transferase ALT: Alanin Transferaz, ICU: Intensive Care Unit

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]			14.73 (0.92–41.4)

Age[1]	**64 ± 16.5**
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 (240-30470)
Ferritin[3]	2000 (174–4000)
AST[3]	98 (5-16290)
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 ICU (days) [3]	9 (1–31)
intubation time (days) [3]	6,5 (1–27)

Table 2

Statistical comparison of EGFR test and fibrosis severity groups.[1]Mean±standard deviation, [2]n(%), 3Median (minimum-maximum), [a]One way Anova test, [b]Fisher test, [c]Kruskal Wallis test, *p < 0.05. WBC: White blood cell, CRP: C-reactive protein, LDH: Lactate dehydrogenase, AST: Acetyl transferase ALT: Alanin Transferaz, ICU: Intensive Care Unit

EGFR		Negative n = 11	Mild n = 20	Moderate n = 13	Severe n = 6	p
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]
SpO2 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)	
None	yok	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]

EGFR		Negative n = 11	Mild n = 20	Moderate n = 13	Severe n = 6	p
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 (406-30470)	845 (240–4500)	759 (443–3324)	3141 (457-13500)	0.765[c]
Ferritin[3]		2000 (502–2000)	1705 (174–2000)	2000 (298–2000)	2000 (77.6–4734)	0.449[c]
AST[3]		101 (5-16290)	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 [2]	0 mg/g	1 (9.1)	1 (5)	2 (15.4)	0 (0)	0.793[b]
	80 mg/g	3 (27.3)	6 (30)	2 (15.4)	1 (16.7)	

EGFR	Negative n = 11	Mild n = 20	Moderate n = 13	Severe n = 6	p
250mg/g	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 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]

Table 3
Pairwise comparison of the averages of CRP, D.dimer and Length of stay in ICU days in EGFR groups. *p < 0.05.CRP: C-reactive protein, ICU: Intensive Care Unit

EGFR groups p value (Mann Whitney U test)		Negative	Mild	Moderate	Severe
Negative	CRP	-	0.836	0.119	0.027*
	D.dimer	-	0.201	0.004*	0.007*
	Length of stay in 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 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 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 ICU (days)	0.019*	0.38	0.022*	-

Discussion

The most important findings of our study are that EGFR involvement and severity of pulmonary fibrosis are associated with CRP, d.dimer, and length of stay in the intensive care unit. 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 alveolo-capillary membrane increases. Barrier function is essential for rapid and

efficient restoration of the alveolar epithelium, and the barrier function is activated by the Human Epidermal Growth Factor Receptor (HER) family [11, 12]. Initial epithelial repair events in ALI include proliferation, proliferation, and migration of ATII cells. Then differentiation into ATI cells develops.

If damage persists, there is unregulated and excessive ATII cell proliferation. Fibroblasts and myofibroblasts proliferate. Extracellular matrix, including collagen and fibronectin, is stored excessively and irregularly, eliminating the original tissue. With the failure of normal ATII regeneration, pulmonary fibrosis develops. The 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 is of 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, while there was mild in 20 (40%) patients, moderate in 13 (26%) patients, and severe involvement in 6 (12%) patients. We could not find any previous study examining EGFR uptake in pulmonary tissue in Covid 19 pneumonia with post mortem biopsy. Our study is the first study on this subject as far as we can research. In a study examining pulmonary fibrosis by Masson trichrome staining of biopsy material in patients with ARDS, the presence of fibrosis was associated with the death of the disease [14]. Although not related to Covid-19, it can be considered to support our study as it also examines ARDS that develops in patients with Covid-19 pneumonia.

In the study of Huang et al., it was said that radiologically, more than one-third of patients who recovered from Covid pneumonia developed fibrotic abnormalities upon discharge from the hospital [15]. However, this study included severe covid 19 pneumonia survivors, and the EGFR was not studied. In our research, post-mortem 78% of the patients had pulmonary fibrosis radiologically and pathologically. The extent of involvement considered radiologically, and EGFR involvement was correlated.

CRP is a non-specific acute phase protein induced by Interleukin 6, with a potent proinflammatory effect. A sensitive biomarker indicates inflammation, infection, and tissue damage [16]. In this study, CRP averages were significantly different between groups separated according to the severity of EGFR involvement. Our data also supported the study of Yu et al., with 32 patients with confirmed Covid-19 pneumonia, examining signs of fibrosis on thorax CT [17]. In the study of Huang et al. based on radiological data, CRP was statistically 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 cutoff value was 161 mg/L. In Liu et al.'s study of 141 cases with Covid 19 pneumonia, the probability of developing severe disease was higher in patients with CRP > 41.8 mg/L [16]. We could not find any previous study on the risk of death in this regard.

Coagulation steps are activated as a result of tissue damage in ALI due to Covid-19. Thrombus develops in small vessels. D.dimer rises as a marker of fibrin disruption and abnormal coagulation balance [18]. In our study, the severity of EGFR involvement and the prevalence of radiological involvement were associated with d.dimer elevation. We have confirmed the studies discussing 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 MERS infections, is partially caused by host immune responses. Corticosteroids suppress inflammation in the lung. However, it also inhibits pathogen virus's immune response and clearance [20]. Wu et al., in their study with 201 patients with covid 19 pneumonia, stated 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 recommended 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, who received 80 mg/day, and those who received 250 mg/day. Chen et al. reported no difference in in-hospital mortality rates among covid 19 patients receiving low, medium, and high-dose methylprednisolone [23]. However, we could not find a study examining methylprednisolone doses and pulmonary fibrosis rates in patients with Covid 19 pneumonia.

There are studies indicating that age, male gender, smoking, comorbidities, leukocytosis, lymphopenia, and high lactate dehydrogenase (LDH) are risk factors for the development of pulmonary fibrosis [15, 17, 24]. These studies were evaluated according to thorax CT findings and in surviving patients. In our research, pathologically, age, gender, 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 can be listed as follows; First of all, our case number is relatively small. Studies with a larger sample group and perhaps autopsy material may provide more information. We did not have the authority to treat our patients before death in the ICU. Our colleagues who administered the treatment were blind to our study. We think that studies to be conducted by comparing treatment options, including antifibrotic therapy, will shed light on the treatment of pulmonary fibrosis that may develop after Covid-19.

Interpretation

CRP and d.dimer values can guide the severity of pulmonary fibrosis that may develop in patients followed up in the ICU due to Covid 19 pneumonia. The data of our study is that the dose of methylprednisolone used does not make a significant difference in the severity of fibrosis. This study, in which EGFR uptake is monitored in Covid 19 pneumonia, maybe a preliminary idea for studies that will examine the indications of antifibrotic drugs in pulmonary fibrosis due to Covid 19.

Declarations

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[Erhan Özhan]. The first draft of the manuscript was written by [Seyhan Us Dülger] and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval: This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Bursa Yüksek İhtisas Training and Research Hospital (Date: 11.08.2021. / No: 2011-KAEK-25 2021/08-10).

Consent to participate: Written informed consent was obtained from first-degree relatives of the patients.

Consent to publish: The authors affirm that human research participants provided informed consent for publication of the images in Figure 1.

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Figures

Figure 1

Sample image (x400) of staining results with EGFR Kits. a: Negative, b: Mild involvement, c: Moderate involvement, d: Severe involvement