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Research Article

Can we predict lung sequelae in post-COVID-19 patients?

COVID-19 sonrası hastalarda akciğer sekelini baştan tahmin edebilir miyiz?

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Abstract

Aim: Patients hospitalized with COVID-19 pneumonia can progress to lung fibrosis after the infection even though given the standard treatment or the anti-inflammatory regimen for the long term. It is hard to predict which group of patients is going to have a progressive lung disease thus this study aims to define possible biomarkers at the acute onset of infections that might predict lung fibrosis afterwards.

Material and Methods: Patients hospitalized between January - December 2020 with pneumonia and a positive PCR for COVID-19 infection were included in the study. They were followed up for 12 months for post-COVID-19 symptoms and lung sequelae formation.

Results: A total of 64 patients were included with a median age of 62 (R: 17-93) and 42.2% were women (n=27). 35 patients (54.7%) had post-COVID symptoms, 8 (12.5%) of them died and 22 (34.4%) were re-hospitalized. 76.6% had a good clinical course but 54.7% of the patients developed sequelae after infection. The pneumonia score, blood oxygen saturation level, CRP, and troponin levels at admission were significantly related to sequelae development ($p<0.05$). Male gender, elderly age, hospitalization period duration, bad clinical prognosis, and intensive care unit admission together with the presence of Hypertension and post-COVID symptoms were correlated with sequelae formation ($p<0.05$). Age above 63.5, CRP higher than 24.1 and pneumonia score greater than 0.15 were significant cut-off values for lung sequelae prediction.

Conclusion: This study shows that lung sequelae after COVID-19 infection can be predicted from the start of infection and measures might be taken afterwards.

Keywords: Biomarkers, COVID-19, lung sequelae, monitoring

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Öz

Amaç: COVID-19 pnömonisi ile hastaneye yatırılan hastalar, uzun süreli standart tedavi veya antienflamatuar rejim uygulansa bile enfeksiyon sonrası akciğer fibrozisine ilerleyebilir. Hangi hasta grubunun ilerleyici akciğer hastalığına sahip olacağını tahmin etmek zordur. Bu çalışma enfeksiyonun başlangıcından itibaren daha sonra akciğer fibrozisini öngörebilecek olası biyobelirteçleri tanımlamayı amaçlamaktadır.

Gereç ve Yöntemler: Ocak-Aralık 2020 tarihleri arasında COVID-19 pnömonisi nedeniyle yatan ve PCR pozitif olan hastalar çalışmaya alındı. COVID-19 sonrası semptomlar ve akciğer sekel oluşumu açısından hastalar 12 ay boyunca takip edildi.

Bulgular: Çalışmaya ortanca yaşı 62 (R: 17-93) olan toplam 64 hasta dahil edildi ve %42.2 kadındı (n=27). 35 hastada (%54.7) COVID sonrası semptomlar mevcuttu, 8 hasta (%12.5) kaybedildi ve 22'si (%34.4) yeniden hastaneye yatırıldı. Hastaların %76.6'sının klinik seyri iyiydi ancak hastaların %54.7'sinde enfeksiyon sonrası sekel gelişti. Pnömoni skoru, kan oksijen satürasyon düzeyi, CRP ve başvuru sırasındaki troponin düzeyleri sekel gelişimi ile anlamlı olarak ilişkiliydi ($p<0.05$). Erkek cinsiyet, ileri yaş, hastanede yatış süresi, kötü klinik prognoz ve yoğun bakım ünitesine yatış ile birlikte hipertansiyon varlığı ve post-COVID semptomları sekel oluşumu ile korelasyon gösterdi ($p<0.05$). Yaş 63.5'in üzerinde, CRP'nin 24.1'den yüksek olması ve pnömoni skorunun 0.15'in üzerinde olması akciğer sekel tahmini için anlamlı bulundu.

Sonuç: Bu çalışma, COVID-19 enfeksiyonu sonrası akciğer sekellerinin enfeksiyonun başlangıcından itibaren tahmin edilebileceğini ve sonrasında önlem alınabileceğini göstermektedir.

Anahtar kelimeler: Biyobelirteçler, COVID-19, akciğer sekelleri, monitorizasyon

Introduction

COVID-19 (Coronavirus disease 19) which is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a pandemic with approximately 692 million people infected and around 6.9 million deaths worldwide (1). The widespread of infection and the variety of clinical presentation and outcomes made it difficult to manage patients and raised a need for continuous development of strategies regarding the diagnosis, treatment and follow-up of these patients. COVID-19 disease is also challenging regarding its multisystem involvement and can lead to multi organ failure (2). Lung is the main organ affected and patients usually present with respiratory related symptoms like cough and dyspnea. Even though the majority of patients presented with mild or even asymptomatic disease a significant number with moderate or severe disease had a need for hospitalization and intensive care unit admission and this group of patients was especially at risk for development of post-COVID symptoms and complications (3,4).

One of the most important issues that pulmonologists are dealing with is the lung sequelae and fibrosis which has caused an impairment of functional status of lung and presence of symptoms that remain even after the virus has been cleared and is not detected by PCR. Many studies have analyzed clinical, radiological and laboratory parameters that can be related with the COVID-19 disease outcome and prognosis, but the data regarding parameters to foresee the lung sequelae are scarce (5-7). One study developed a risk assessment score to predict the pulmonary sequelae, which included many parameters like age, BMI, comorbidities, patient performance and dyspnea perception according to the thorax computed tomography of patients at four months after infection taking in consideration a lung involvement higher than 10 % (8).

The aim of this study was to determine clinical and laboratory parameters that might be used to predict the group of patients that are at risk for lung sequelae development from the diagnosis of disease. The usage of CT for the one-year follow-up of post-COVID-19 patients was used for possible correlations of these parameters and the cut-offs were investigated for practical usage in clinical management of these patients.

Material and Methods

Statement of Ethics

This study was performed in accordance with the Declaration of Helsinki. This human study was approved by the institutional review board of Baskent University Hospital – KA22/92. Adult participant consent was not required because of retrospective study design.

Study population

A total of 64 patients with a positive reverse-transcriptase-

polymerase-chain-reaction (RT-PCR) result for COVID-19 and presence of pneumonia in the thorax computed tomography (CT) who were admitted to the isolated ward of our hospital were included in the study. The patients were recruited by retrospective data collection for patients that were hospitalized from 01/01/2020 to 30/12/2020. 158 patients' data was collected first and only 64 of them were included for analysis. The reason for this was absence of CT or lack of follow up of the patients that were excluded. All the included ones had at least one CT at diagnosis and one CT at the follow-up starting from the first month until 12 months after COVID infection.

Study protocol

Demographic data, past history, clinical symptoms and laboratory parameters at admission together with the CT findings were analyzed. The pneumonia score was calculated by an automated system (Siemens Healthineers, Forchheim, Germany) which provided the lung involvement as a percentage value thus it was expressed as values from a range 0-1 which stands for 0 -100%.

The hospitalization duration, clinical course, together with the development of lung sequelae in the first year after infection were analyzed and their correlations were investigated. The conformity of numerical variables to normal distribution was examined with the Shapiro-Wilk and Kolmogorov-Smirnov normality tests. Numerical variables were presented as mean ± standard deviation and median values (with minimum-maximum), and categorical variables as the number and percentage. Since the variables were not normally distributed, the Mann-Whitney U test was used to compare the differences between groups. Categorical variables were compared using Pearson Chi-square and Fisher Exact test. Receiver Operating characteristic (ROC) curve analysis were performed to determine the cut-off values for the significant variables. Analyzes were performed using SPSS version 25.0 software for Windows. Hypothesis was tested at a= 0.05 significance level.

Results

Baseline characteristics

A total of 64 patients were included in the study with a median age of 62 (R: 17-93). 42.2% (n=27) were women, 57.8% (n=37) were men. The most common comorbidities were: hypertension (60.9%), diabetes mellitus (31%), cancer (20.3%), cardiac disease (25%), solid organ transplant (14%). The most common symptoms at admission were fever, cough and fatigue. The baseline characteristics and laboratory parameters at admission (day 0) are summarized at table 1.

Table 1. Baseline characteristics of patients at hospital admission

Number of patients (n)	64
Sex	
Male (n, %)	37 (57.8%)
Female (n, %)	27 (42.2%)
Age in years	62.0±16.25 (17-93)
Comorbidity	
Hypertension	39 (60.9%)
Diabetes mellitus	20 (31.3%)
Cancer	16 (25.0%)
Cardiac disease	16 (25.0%)
Solid organ transplant	9 (14.1%)
Chronic respiratory disease	7 (10.9%)
Chronic kidney disease	6 (9.4%)
Chronic liver disease	4 (6.3%)
Hyperthyroidism	4 (6.3%)
Hypothyroidism	2 (3.1%)
Symptoms at admission	
Fever	30 (46.9%)
Cough	29 (45.3%)
Fatigue	28 (43.7%)
Dyspnea	14 (21.9%)
Diarrhea	8 (12.5%)
Sore throat	6 (9.4 %)
Chest pain	2 (3.1%)
Loss of smell or taste	2 (3.1%)
Laboratory results	
CRP (mg/dL)	33.6 (2-285.5)
D-dimer (mg/dL)	0.97 (0.19-35)
Leucocyte count (x1000)	6.67 (1.67-19.09)
Lymphocyte count (x1000)	1.4 (0.07-10.71)
Neutrophil/lymphocyte	3.49 (0.63-88.28)
Ferritin (µg/L)	417 (2-3659)
CK (U/L)	63 (7-507)
Procalcitonin (µ g/L)	0.18 (0.02-100)
Troponin (ng/L)	6 (1-747)
Pneumonia score	0.2 (0-0.08)
SpO2	95 % (38-100)

(CRP: C-reactive protein, CK: creatine kinase, SpO2: oxygen saturation as measured by pulse oximetry)

CT findings and lung sequelae

The CT findings regarding the lung sequelae were analyzed at intervals: 1st, 3rd, 6th, 9th and 12th months. 22 patients had a sequelae detected from the first month, 5 patients at 3rd month, 5 patients at 6th month, 1 patient at 9th month and 2 of them at 12th months. Once the sequelae findings were detected, they were also present at the other CTs afterwards, but for 2 patients the lung findings regressed at 3rd and 6th month at control CTs. The most common CT findings were: atelectasis and sub pleural bands (n=30, 46.8%), mediastinal lymphadenopathy

(n=22,34.4%), fibrosis (n=19,29.7%), ground glass opacity (GGO) (n=19,29.7%), bronchiectasis (n=10,15.6%), consolidation and nodules (n=10,15.6%), honeycombing (n=5,7.8%) and cavitary lesions (n=2,3.1%).

Analysis of routine tests regarding the sequelae formation prediction

At the end of the study 35 patients (54.7%) had post-COVID-19 symptoms. Only 8 patients (12.5%) died whereas 22 patients (34.4%) were re-hospitalized within one year period of follow up. Lung sequelae was present at 35 patients as detected by changes in thorax CT within one year period after COVID-19 infection. Lung sequelae was significantly related to gender and was more common in males (p=0.015) when compared to females. HT was the only comorbidity to be related to lung sequelae (p=0.016). A bad clinical prognosis which was defined mainly as need for intensive care unit admission (p=0.004) together with presence of post-COVID symptoms (p=0.015) were also in correlation with sequelae formation. The lung sequelae could be detected as early as the 1st month post-COVID infection (p=0.013). The changes were usually permanent but 2 patients showed resolution at the end of 3rd and 6th month. Regarding the laboratory, radiological score and clinical parameters age, pneumonia score, blood oxygen saturation level, C-reactive protein (CRP) and troponin levels at admission and the hospitalization duration were significantly related to sequelae development (p<0.05) and are shown in details in table 2.

Table 2. Comparison of clinical, radiological and laboratory parameters of both lung sequelae + and – patients.

Variables	Lung sequelae + (n=35)	Lung sequelae – (n=29)	p value
Age (years)	69 (17-93)	53 (17-73)	0.001*
Pneumonia score (0-1)	0.3 (0.0- 0.8)	0.1 (0.0-0.6)	0.001*
Leucocyte count /μL	6.7 (1.6-19.1)	5.7 (2.9-12.2)	0.735
Lymphocyte count/μL	1.32 (0.07-4.39)	1.41 (0.13-10.7)	0.595
NLR	3.44 (1-88.28)	3.49 (0.63-21.31)	0.720
D-dimer (mg/L)	1 (0.23-35)	0.89 (0.19-9.39)	0.572
CRP (mg/L)	62.2 (3.5-285.5)	14.6 (2-364.9)	0.004*
Ferritin (μg/L)	574.5 (13.8-3659)	212 (2-1676)	0.106
Procalcitonin (μg/L)	0.2 (0.12-100)	0.12(0.02-6.9)	0.268
CK (U/L)	58 (7-331)	64 (19-507)	0.761
Troponin (ng/L)	8.5 (2-747)	3 (1-360)	0.036*
SpO2 (%)	94 (38-100)	95 (89-100)	0.028*
Duration of hospitalization (days)	11 (0-52)	4 (0-30)	0.039*

(NLR: neutrophil to lymphocyte ratio, CRP: C-reactive protein, CK: creatine kinase, SpO2: oxygen saturation as measured by pulse oximetry)

3.3 ROC curves for possible biomarkers

The continuous parameters that were found to be significant for the lung sequelae prediction were further analyzed for a cut off value that can be used to follow-up the patients. Regarding the ROC curves CRP with a cut off value of 24.1 mg/L (AUC=0.713), age above 63.5 years (AUC=0.794) and pneumonia score of 0.15 (AUC= 0.732) were significant and could be used as biomarkers to predict the lung sequelae formation from the start of COVID-19 infection (Figure 1).

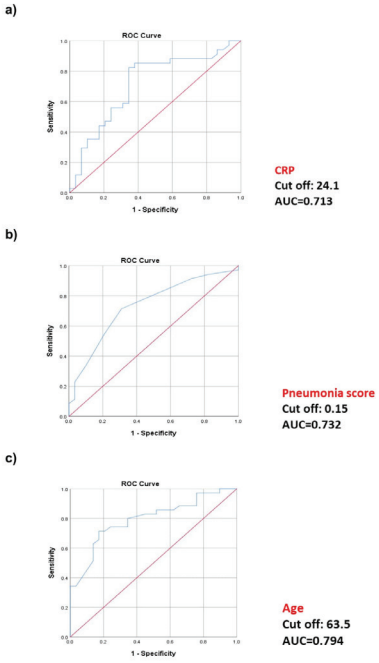

Figure 1. ROC curves for a) CRP, b) Pneumonia score and c) Age

Discussion

This study reports that lung sequelae after COVID-19 infection can be predicted by simple laboratory and radiological techniques that have been routinely used for this group of patients at the admission. A long follow-up period of one year post-COVID has shown that a large group of patients (54.7%) develop changes at lungs after infection and should be closely monitored. CRP, older age and pneumonia score at admission together with male gender predominance, persistence of symptoms even after discharge, length of hospitalization and need for intensive care unit were all significantly correlated with pulmonary sequelae.

Up to date there have been many studies that have reported factors which are related to the COVID-19 disease progression, outcome and severity, but the data regarding the relationship of such risk factors to the lung sequelae formation are scarce (3, 5-9).

Advanced age, severe illness, prolonged ICU stay, smoking, presence of acute respiratory distress syndrome (ARDS) and higher inflammatory markers have all been associated with a worse outcome (3-4,9-10). Biomarkers are helpful as they can provide an objective information about the disease status and can also be evaluated at many different centers as well. Lymphocyte count, neutrophil to lymphocyte ratio (NLR), CRP, erythrocyte sedimentation rate (ESR), procalcitonin , interleukin-6 (IL-6), D-dimer, troponin and creatine kinase (CK) have been found to be related with progression of COVID-19 disease (5). As the development of lung sequelae cannot be predicted from the start we analyzed if such parameters related to disease progression could also be used to predict lung changes afterwards in order to enable earlier intervention to prohibit the permanent changes that might lead to both functional capacity impairment and persistent symptoms in long-term. We could find that similarly to the disease severity and outcome parameters like CRP and troponin could be also used to predict lung sequelae formation as well. Especially for CRP with a cut off 24.1 mg/L and higher had a stronger correlation when compared to troponin levels.

The main tool that was used to detect lung changes both at diagnosis and at the follow-up was the radiological techniques like x-ray, CT, high resolution CT (HRCT) and lung ultrasound (11). A meta-analysis showed that the CT severity score (CTSS) and consolidations were the most common predictors among the studies for the post-COVID-19 sequelae (11). Lung ultrasound score (LUS) could also be used to diagnose and track changes of lungs in patients where CT could not be used (11).

There are different studies that have assessed lung changes at variable times after COVID-19 infection mainly at 3, 4, 6, 7 and 12 months (12-16). Froidure A. et al (12) have reported that up to 35 % of patients still have symptoms after COVID-19 and that 21 % of them developed lung fibrosis. Interestingly the pulmonary function tests and radiological changes were not related to the degree of post-COVID symptoms (12). In our study 29.7 % of patients had fibrosis and there was a relation of post-covid symptoms with lung sequelae formation (p=0.015), but 17 patients that did not have any radiologically detected sequelae still had post covid symptoms. This phenomenon may be explained with the extrapulmonary involvement and multi organ disease which might have an effect to mainly dyspnea and fatigue development afterwards at long term (17).

According to the other studies 21 % had fibrosis and 44% of patients had GGO changes at 4th month, whereas another study showed that up to 72 % of patients had fibrosis like changes at the 6th month after infection (13-14). Another study showed that 29 % had fibrosis at 7th month and that elderly patients were the most effected ones (15). Our study also had a similar percentage (29.7%) and the patients included were mainly the elderly ones as the median was 62 years which explains the higher rate of lung sequelae up to 54.7%. At one year after COVID-19 infection fibrotic –like changes could be detected up to 22.7 % of patients and the radiological lung involvement at admission was one risk factor related to these long-term changes (16). In our study the pneumonia score at admission was also significantly related and the cut off 0.15 (15% of lung parenchyma) or higher could predict the lung sequelae with an AUC of 0.732.

There are also studies that have shown that radiological findings can be improved with time (18) and that the risk of fibrosis is not very high thus no hurry for immediate treatment is needed especially for the first 3 months (4,18). On the other hand other studies showed that up to 90% of patients can experience sequelae after COVID-19 and even though the recovery rate is around 50 % at first 3 months it decreases to 35 % between 6 to 9 months and down to 15 % afterwards (19). In our study the majority of patients that developed lung sequelae had radiological findings from the first month and only 2 cases could recover afterwards at 3rd and 6th months respectively, which suggests a low rate of improvement and regression of radiological findings that might have been related to the elderly population included in the study. Regarding the high number of infected people globally it is also hard to detect lung changes if patients are not followed up, thus chest radiography should be recommended within 3 months after discharge and also oxygen saturation measurements should be performed in the primary care so that patients can then be referred to the pulmonologists (20).

Biomarkers which have been related to the oxidative stress like TNF–alpha have been associated with prediction of pulmonary complications and could be used as therapeutic targets as well (21). The usage of such biomarkers might not be practical for routine usage and might not be performed widely in different centers. Thus a need for biomarkers that are often used and sometimes a combination of them to develop risk assessment scores for pulmonary sequelae in COVID-19 have been developed to help physicians in their daily practice (8). Yet further studies and multicenter involvement is needed to draw definite conclusions and implementation of them in patient care.

Early detection of lung sequelae might help to treat patients promptly and slow the progression or functional impairment. Early treatment with corticosteroids have been shown to improve both functional and radiological findings in post-COVID patients (22). It is suggested to think about anti-fibrotic drugs especially after the 3rd month after which the improvement rate falls significantly (3). The pulmonary sequelae of COVID-19 include also the thromboembolic disease and 2 patients in our study also had a pulmonary embolism detected thus appropriate treatment regarding vascular disease should also be given if necessary (17). There is also a need for new therapies for patients that progress and have a decreased functional capacity and also pulmonary rehabilitation should be offered to manage the post-COVID -19 breathlessness (17,19).

Study limitations

This study has some limitations regarding the few numbers of patients as it was mainly performed in one center. Another limitation is the retrospective nature of the study which also reduced the number of patients included, as the data could not be achieved. Finally, because at our center during pandemics we did not utilize the spirometry laboratory we could not make a functional assessment of the lungs at these patients thus we mainly concentrated at clinical, laboratory and radiological results.

Conclusion

Since the burden of COVID-19 infection will continue for a long term regarding the high number of infected patients and the diverse clinical outcome together with development of lung sequelae afterwards, a need for biomarkers is still present nowadays. It is essential to develop easily achievable and widely accessed parameters that might help to define the population at risk for lung sequelae in order to follow and treat these patients properly. This study has shown that laboratory, clinical and radiological measurements that are performed at admission can predict the lung sequelae from the initial stage of the infection.

Ethics permission

This study was performed in accordance with the Declaration of Helsinki. This human study was approved by the institutional review board on 18/02/2022 by No: KA22/92.

Informed consent: Adult participant consent was not required because of retrospective study design.

Peer-reviewed: Externally peer-reviewed.

Authorship Contributions

Concept: D.E, Design: D.E., Data Collection or Processing: all authors, Analysisor

Interpretation: D.E, Literature Search: all authors, Writing: D.E.

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