ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

The Effect of Glomerular Filtration Rate and Troponin on the Prognosis of Patients with COVID-19

COVID-19 Hastalarında Glomerüler Filtrasyon Hızı ve Troponinin Prognoza Etkisi

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ABSTRACT

Aim: *During the pandemic, clinicians have generally focused on treating respiratory tract infections. It determined that all organs are affected over time, especially the heart and kidneys, and the clinic deteriorates rapidly. We aimed to determine whether serial glomerular filtration rate and troponin tests would predict prognosis in patients with COVID-19.*

Material and Method: *One hundred seven patients diagnosed with COVID-19 were included in this study. We evaluated in-hospital mortality based on the presence and absence of troponin elevation and renal dysfunction at patients' first and last examinations. We also investigated the correlation of both troponin elevation and renal dysfunction with age, pneumonia severity, and each other.*

Results: *Most surviving patients were female, and the average age was younger than the other group. The most common comorbidity was hypertension. It was observed that the patients with a high last glomerular filtration rate, low last troponin test, and low pneumonia severity survived. The most important factors affecting the prognosis were the severity of pneumonia and the last glomerular filtration rate.*

Conclusion: *Based on the conclusion from this study, the prognosis of patients with rapidly worsening cardiac and renal function can deteriorate. Those tests require close monitoring.*

Key words: *COVID-19; glomerular filtration rate; troponin; pneumonia severity; prognosis*

ÖZET

Amaç: *Pandemi sürecinde klinisyenler genel olarak solunum yolu enfeksiyonlarının tedavisine odaklanmışlardır. Başta kalp ve böbrekler olmak üzere tüm organların zamanla etkilendiği ve kliniğin hızla bozulduğu belirlendi. Glomerüler filtrasyon hızı ve troponin testlerinin takibinin, COVID-19 hastalarında prognozu tahmin edip edemeyeceğini belirlemeyi amaçladık.*

Materyal ve Metot: *Bu çalışmaya COVID-19 tanısı alan 107 hasta dâhil edildi. Hastane içi mortaliteyi, hastaların ilk ve son muayenelerinde troponin yüksekliği ve böbrek fonksiyon bozukluğu olup olmamasına göre değerlendirdik. Ayrıca hem troponin yüksekliği hem de böbrek fonksiyon bozukluğunun yaş, pnömoni şiddeti ve birbiriyle ilişkisini araştırdık.*

Bulgular: *Hayatta kalan hastaların çoğu kadındı ve yaş ortalaması diğer gruptan daha gençti. En sık eşlik eden hastalık hipertansiyondu. Son glomerüler filtrasyon hızı yüksek, son troponin testi düşük ve pnömoni şiddeti düşük olan hastaların hayatta kaldığı görüldü. Prognozu etkileyen en önemli faktörler pnömoninin şiddeti ve son glomerüler filtrasyon hızıydı.*

Sonuç: *Bu çalışmadan elde edilen sonuca göre, kalp ve böbrek fonksiyonları hızla kötüleşen hastaların prognozu kötüleşebilir. Bu testler yakın takip gerektirir.*

Anahtar kelimeler: *COVID-19; glomerüler filtrasyon hızı; troponin; pnömoni şiddeti; prognoz*

Introduction

Since the COVID-19 (Coronavirus Disease) pandemic, caused by SARS-CoV-2 (Severe Acute Respiratory Syndrome-Coronavirus 2), affected the whole world since 2019, it has been thought to cause more respiratory tract infections. It has been determined that over time, trauma develops mainly in the veins, and therefore all organs may be affected. The primary reason for this is hypoxia. The damage is exacerbated by cellular lesions and cytokine storms, which develop after hypercoagulation[1]. In COVID-19 disease, the most feared ischemic findings. The organs most affected by this condition are the heart and kidneys. In the dysfunction of these organs, the risk of developing multiorgan failure increases, and the prognosis worsens rapidly[2,3].

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Myocardial injury, manifested by elevations in cardiac troponin, is common in patients with COVID-19, and has also been suggested as a prognostic factor[4,5]. The pathogenesis of myocardial damage in COVID-19 has not been established. Still, it is likely multifactorial, including the patient (sex, age, race, and chronic diseases) and disease (SARS-CoV-2 infection induced cardiomyocyte injury and necrosis, inflammation, endothelial damage and hypoxia) specific factors[6]. Therefore, there are important knowledge gaps in understanding the epidemiology and clinical implications of myocardial injury, and markers of myocardial injury should be investigated in COVID-19 by independent prognostic comparative studies. The GFR (Glomerular filtration rate) is used as a measure of kidney function that worsens concomitantly with COVID-19 infection[7]. Some of the mechanisms of kidney injury have been described, including endothelial and tubular damage due to direct infection of SARS-CoV-2 in the kidneys, as well as secondary mechanisms (severe inflammation, hemodynamic factors, microvascular thrombosis, hypoxia) associated with the COVID-19[8]. Although low GFR levels have been described in patients with COVID-19, limited studies describe the relationship between GFR levels and mortality[9].

This study was conducted to predict prognosis in examinations taken at the time of admission and during the follow-up of the patients, with the GFR and cardiac markers.

Material and Method

Study Design

This study was designed to be a single center, retrospective, and observational cohort. Between March and December 2020, patients diagnosed with COVID-19 and receiving outpatient or inpatient treatment were tried to be examined. The data was obtained from the hospital archive, computer records and health system records of the patients. The local Ethics Committee (P202200021-03) has approved this study.

Patient Selection and Clinical Outcomes

This study randomly selected 107 patients over 18 years of age, who were diagnosed with COVID-19 (viral pneumonia detected by PCR [polymerase chain reaction] + or thorax tomography), and who applied to the Emergency Service during the pandemic period. The examinations of the patients at the first application, last if they received inpatient treatment, or tests on the last date of application to the COVID outpatient clinic if they were discharged were examined. Glomerular filtration rate (GFR) and troponin values and pneumonia severity were recorded in these tests. The pneumonia severity score was visually (semiquantitatively) evaluated in chest CT images of each patient. The pneumonia severity score was assessed by a simple CT scoring method described by Chen et al.[10]. The pneumonia severity score was categorized as follows: mild (peripheral and subpleural ground glass attenuation)=1 point, moderate (the high-density shadow of plaques involving multiple lung lobes (≥3), ground glass, cloud flocculent or paving stone like changes, at least two lung lobes show pulmonary consolidation, local pulmonary fibrosis, and air bronchograms sign)=2 points, and severe (diffuse consolidation [minimum of 80% of pulmonary or involving of 4 lobes] or cord like changes, and fibrosis)=3 points according to radiological results for each patient. Glomerular filtration rate value was calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) estimating equations using the serum creatinine value[11]. Patients who received dialysis treatment and a diagnosis of myocardial infarction were excluded from this study. The effects of GFR, troponin, pneumonia severity at admission, and other diseases' presence on the prognosis were investigated.

Statistical Analysis

The data were analyzed using Statistical Package for Social Sciences (SPSS) program version 20.0 (SPSS Inc., Chicago, USA). Differences between demographic and laboratory data (GFR and troponin I) of the COVID-19 patients are analyzed using Student's T-test and Chi-square test. Pearson's correlation coefficient was used to analyze the relationship between clinical parameters. The point biserial correlation coefficient analyses the relationship between clinical parameters and mortality rate. A p value is less than 0.05 are considered statistically significant.

Results

Fifty-one patients included in the study were female (46.7%), and 56 were male (53.3%). The gender difference did not affect prognosis ($p>0.05$). The persons who died were older (mean age 71±10.36) (Table 1). All patients had signs of pneumonia of varying severity, and it was observed that they received

antiviral, symptomatic and anticoagulant treatment. Twenty-two patients (20.5%) died. Last GFR (L-GFR) (p=0.000007) and Pneumonia severity score (p=0.001) were the parameters with the greatest difference between the group of patients who died compared to subjects who survived. Interestingly, no statistically significant difference was observed between the mean values of the first GFR (F-GFR), first troponin (F-Troponin), and last troponin (L-Troponin) when patients who died were compared with subjects who survived (p>0.05) (Table 2). Some patients had more than one comorbidity, and the percentage of patients receiving hypertension treatment was high. Chronic obstructive pulmonary disease, diabetes mellitus, hypertension, chronic renal failure, and hyperlipidemia comorbidities did not affect mortality rates (p>0.05) (Table 3).

Table 1. *Demographic data of the COVID-19 patients*

Variables	Non-survivors Mean ± SD (n)	(%)	Survivors Mean ± SD (n)	(%)	P
Age (years)	71±10.36	20.5	63±11.79	**79.5**	**0.005**
Sex					
Female	8	7.5	43	**40.2**	0.234
Male	14	13.1	42	39.3	

SD: Standard deviation.

Table 2. *Comparison of patients' test results average*

	Non-survivors	Survivors	p
First GFR (mL/min/1.73 m²)	74.91±27.83	87.72±33.74	0.104
Last GFR (mL/min/1.73 m²)	58.05±48.03	100.98±35.13	**0.000007**
First Troponin I (pg/mL)	26.45±26.18	18.44±23.08	0.161
Last Troponin I (pg/ml)	69.59±112.13	32.31±125.40	0.207
Pneumonia severity score	2.59±0.67	1.98±0.76	**0.001**

GFR: Glomerular filtration rate.

Table 3. *Patients' comorbidities rate*

Comorbidities	Odds ratio (95% CI)	P
COPD	0.627 (0.072–5.497)	0.671
DM	1.636 (0.605–4.426)	0.329
HT	1.959 (0.698–0.500)	0.197
CRF	1.600 (0.289–8.859)	0.587
Hyperlipidemia	1.184 (0.296–4.730)	0.811

COPD: Chronic Obstructive Pulmonary Disease; DM: Diabetes Mellitus; HT: Hypertension; CRF: Chronic Renal Failure; CI: Confidence Interval.

According to statistical analyses in Table 4. There is a strong negative correlation between L-GFR and age (rp=-0.380**, p<0.0001). A strong positive correlation exists between F-Troponin and age (rp=0.394**, p<0.0001).

There is a strong negative correlation between F-GFR and F-Troponin (rp=-0.452**, p<0001), and there is a negative correlation between L-GFR and L-Troponin (rp=-0.251**, p=0.009).

A strong positive correlation exists between pneumonia severity and age (rp=0.323**, p=0.001). A strong negative correlation exists between F-GFR and pneumonia severity (rp=-0.302**, p=0.002). A strong positive correlation exists between F-Troponin and pneumonia (rp=0.253**, p=0.008).

A solid and positive significant relationship exists between age and prognosis (rp=0.271**, p=0.005). A strong negative correlation exists between L-GFR and prognosis (rp=-0.418**, p<0.0001). A strong positive correlation exists between pneumonia severity and prognosis (rp=0.321**, p=0.001). There is no significant relationship between F-GFR, F-Troponin, L-Troponin and prognosis (p>0.05).

Discussion

This study has been trying to determine whether deteriorated GFR and increased troponin values can determine the prognosis during COVID-19 infection.

Table 4. *Percentmap of data results*

	Age	F-GFR	L-GFR	F-Troponin	L-Troponin	Pneumonia	Prognosis
Age	100%	37%	38%	39%	31%	32%	27%
F-GFR	-0.365**	100%	67%	45%	15%	30%	16%
L-GFR	-0.380**	0.674**	100%	40%	25%	36%	42%
F-Troponin	0.394**	-0.452**	-0.397**	100%	67%	25%	14%
L-Troponin	0.307**	-0.146	-0.251**	0.674	100%	2%	12%
Pneumonia	0.323**	-0.302**	-0.360**	0.253**	0.016	100%	32%
Prognosis	0.271**	-0.158	-0.418**	0.137	0.123	0.321**	100%

F-GFR and F-Troponin: First value; L-GFR and L-Troponin: Last value.
Percent map representing the correlation between continuous features included in mortality risk prediction model for COVID-19 using Pearson's correlation and Point biserial coefficient. The percentage in the plot represents the correlation coefficients. The higher the rate stronger the monotonic relationship. The lower, the weaker the monotonic relationship. The rate represents the absolute value of the correlation coefficient. The numbers in the lower triangle represent the value of the correlation coefficient.

In this study, the mean age of the discharged patients was observed to be lower than the ex-patients, and the prognosis of the male population was poor. According to this result, it can be said that the young population survived the disease with fewer complications, and the female population was more successful in complying with the hygiene conditions and preventing infection[12]. Research has shown that as age increases, troponin increases and GFR decreases[13]. Therefore, the elderly population can be considered vulnerable to COVID-19 infection.

It has been determined that the SARS-CoV-2 virus enters the cell using ACE-2 (Angiotensin Converting Enzyme-2). Since this enzyme is found in the kidneys, heart, lungs, and intestines, these organs are exposed to toxic effects[14].

An acute or chronic condition in which the functions of two organs are impaired is known as cardiorenal syndrome[15]. As seen in many diseases, this is also the case with COVID-19 infection[16]. The most critical mechanism in acute renal injury is thrombus in COVID-19, which develops with hypoxia after endothelial damage, coagulation, and hormone mechanism disruption. After inflammation, the number of cells in the immune system increases, the release of cytokines and the trauma and formation of thrombus become more severe, and a vicious cycle develops. Furthermore, using antibiotics or anti-virals in treatment also negatively affects this process[17]. A significant problem may occur because of resistant bacteria from the antibiotics used[18]. In a post-mortem study, tubular damage has been demonstrated to develop post-COVID-19 infection[19]. Cardiac damage is thought to be caused by a similar mechanism. Cardiac markers increase with dysfunction that develops with increased adrenergic activity in respiratory problems, increased myocardium workload, vasculitis development, and direct toxic effect of the virus[20,21]. In other studies, the prognosis of patients with high troponin levels was poor[22,23]. Likewise, in this study, the prognosis was poor in the patient group with a decreased GFR, increased troponin, and the continuation of these conditions.

In a different research, pneumonia severity and the incidence of acute renal injury were directly proportional. Especially in patients who developed ARDS (Acute Respiratory Distress Syndrome) and received mechanical ventilator support, this situation was found to be more severe[24]. In this study, the severity of pneumonia was the most significant factor affecting the prognosis. This may have been caused by the ongoing hypoxia-induced coagulation cascade triggering the development of multiorgan dysfunction. The increase in GFR values in surviving patients and the decrease in troponin values support this theory. Therefore, adding an anticoagulant was a good choice in patients with increased troponin levels and decreased GFR. That group is a micro-macro thrombus that was considered[25]. The fact that some patients died despite administering anticoagulants shows that DIC (Disseminated Intravascular Coagulopathy) may have begun.

Organ dysfunction may occur during infection or treatment, but irreversible results are more common in viral infections. This situation includes other diseases, viral load, old age, the type of treatment applied, and the immune system response to them[26,27]. For COVID-19 infection, since the tendency of the virus to form vascular pathology is detected at a higher rate, multi-organ dysfunction is observed more quickly[28].

In this study, the rate of patients receiving hypertension treatment is higher than in the others. As a result, they may be considered the population most affected by COVID-19[29].

Limitations of the Study

This study determined that other diseases did not directly affect the prognosis. This result may have been due to the small study population, but it should be noted that multiple factors determine the prognosis during infection.

Conclusion

It seems that the SARS-CoV-2 virus is a pathogen that destroys the system. Therefore, the clinician should be alert to upper and lower respiratory tract infections and pathology that may develop in all organs. As a result, with COVID-19 disease, impaired renal and cardiac function can predict prognosis. Therefore, supportive treatment, timely consultation, and even classification will be beneficial.

Complying with the rules of protection from the virus and hygiene individually and participating in vaccination programs as a social responsibility should be considered. This vulnerable population with co-morbidities should also have easy and reliable access to health services[30].

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