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ORIGINAL ARTICLE

Status of Kidney Function in Hospitalised COVID-19 Patients in the Southern Gyeonggi Province, South Korea

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경기 남부 일개 병원에 입원한 코로나 19 환자들의 신기능 현황

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ABSTRACT

Coronavirus disease 2019 (COVID-19) is a contagious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This study aimed to investigate the status of renal function in patients with COVID-19. The study surveyed a total of 649 patients hospitalized with COVID-19 at a hospital located in southern Gyeonggi Province, South Korea over a one month period in January 2021. The parameters analyzed were blood urea nitrogen (BUN), creatinine, sodium, potassium, chloride, and estimated glomerular filtration rate (eGFR). The BUN and creatinine of the COVID-19 patients were found to be higher than the normal reference range, specially in males, and in the elderly (60s and 80s or older). The serum electrolyte levels of the patients were observed to be within the reference intervals. Of the subjects, males over 80 years of age had a Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) of 60 mL/min/1.73 m^2 or less. Recent research suggests that some severe cases of COVID-19 are showing signs of kidney damage, even in those with no prior underlying kidney disease. Thus, assessment of kidney function using multiple indicators could help diagnose abnormal renal function in patients with COVID-19.

INTRODUCTION

COVID-19 (coronavirus disease 2019) is the named for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and belongs to the *Coronaviridae* family, Betacoronavirus genus Sarbecovirus subgenus [1, 2]. COVID-19 patient is a person who has been confirmed to be infected with COVID-19 according to the test standards for diagnosis regardless of clinical appearance, then respiratory samples collected from the respiratory tract are diagnosed through genome analysis by RT-qPCR with high sensitivity and accuracy [3, 4]. According to previous studies, clinical symptoms of COVID-19 vary from asymptomatic, mild, moderate, and severe, and the main symptoms are fever (above 37.5°C), cough, dyspnea, chills, muscle pain, headache, sore throat, loss of smell and taste. In addition, fatigue, loss of appetite, phlegm, digestive symptoms (nausea, vomiting, diarrhea, etc.), confusion, dizziness, runny nose or stuffy nose, hemoptysis, chest pain, conjunc-

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tivitis, and skin symptoms appear variously [5-7].

On admission patients with COVID-19 had proteinuria and after that elevated serum creatinine (Scr) [8]. Recent research suggests that not only these symptoms, but also kidney disease. Some severe cases of COVID-19 are showing signs of kidney damage, even those who had no underlying kidney problems before they were infected with the coronavirus. Relevant autopsy data from COVID-19 patients found coronavirus particles with spikes present in renal tubular epithelial cells [9], suggesting that SARS-CoV-2 invade cells via angiotensin-converting enzyme [10, 11], the kidney may be the target of SARS-COV-2.

Based on this background, in the present study, we aimed to be intended to confirm the clinical chemical renal function for patients with COVID-19.

MATERIALS AND METHODS

This study utilized the laboratory information system data (medical records were reviewed, data were collected) of patients hospitalized for COVID-19 at a hospital located in southern Gyeonggi province for one month in January 2021. This study has been conducted according to the principles expressed in the Declaration of Helsinki approved and exemption by Institutional Review Board as an anonymous retrospective study (No. DKU, 2020-12-010 by Dankook University).

1. Subjects

A total of 649 patients hospitalized with confirmed COVID-19 from 1 hospital was included in this study. All patients were confirmed as used a real-time reverse transcription polymerase chain reaction (RT-PCR) assay of nasal and oropharyngeal swabs. RT-PCR were used a gene amplification device, CFX96TM Dx system (Bio-Rad Laboratories Inc, CA, USA) and Real-Q 2019-nCoV detection kit (BioSeum Inc, Seoul, Korea) reagent. We used laboratory information system records from each individual to obtain laboratory parameters, including demographic characteristics, and kidney function serum chemistry test results, and blood electrolyte test results. The clinical laboratory characteristics as well as outcome data of 649 COVID-19 patients were analyzed to the blood urea nitrogen (BUN), Scr, sodium (Na), potassium (K), chloride (Cl) on admission and reviewed. Among these serum chemistry tests, kidney function tests were performed by biochemical tests and electrolyte test equipment TBA-2000FR (Canon Medical systems corporation, Otawara, Japan), and reagents as dry chemistry were used for kidney function tests (FUJIFILM Wako pure chemical corporation, Japan) and electrolyte tests (Toshiba medical, Otawara, Japan).

2. Glomerular filtration rate

The eGFR (estimated glomerular filtration rate, mL/min/1.73 m^2) was calculated using the MDRD (Modification of Diet in Renal Disease) equation [12, 13] and CKD-EPI (chronic kidney disease epidemiology collaboration) equation [14].

1) MDRD equation $=175\times(\text{Scr})^{-1.154}\times(\text{age})^{-0.203}\times 0.742$ (if a female) $\times 1.210$ (if black).

2) CKD-EPI calculated by gender and stratified by equation

(1) Female

① Scr ≤0.7 mg/dL

$\text{eGFR}=144\times(\text{Scr}/0.7)^{-0.329}\times(0.993)^{\text{age}}\times 1.159$ (if black).

② Scr >0.7 mg/dL

$\text{eGFR}=144\times(\text{Scr}/0.7)^{-1.209}\times(0.993)^{\text{age}}\times 1.159$ (if black).

(2) Male

① Scr ≤0.9 mg/dL

$\text{eGFR}=141\times(\text{Scr}/0.9)^{-0.411}\times(0.993)^{\text{age}}\times 1.159$ (if black).

② Scr >0.9 mg/dL

$\text{eGFR}=141\times(\text{Scr}/0.9)^{-1.209}\times(0.993)^{\text{age}}\times 1.159$ (if black).

The CKD-EPI equation, expressed as a single equation, is $\text{GFR}=141\times\min(\text{Scr}/\kappa, 1)^{\alpha}\times\max(\text{Scr}/\kappa, 1)^{-1.209}\times 0.993^{\text{Age}}\times 1.018$ [if female] $\times 1.159$ [if black], where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1. In this table, the multiplication factors for race and sex are incorporated into the intercept, which results in different intercepts for age and sex combinations [14].

3. Reference interval of clinical parameters

The reference interval of clinical variables in the study hospital is BUN 7~22 mg/dL, Scr 0.7~1.4 mg/dL, Na 135~145 mEq/L, K 3.5~5.3 mEq/L, Cl 98~110 mEq/L. As the RT-PCR diagnostic criteria for COVID-19, negative was set to a Ct (cycle threshold) value>38, and positive to a Ct value<38.

4. Statistical analysis

All statistical analyses were conducted using SPSS (SPSS version 21.0, SPSS Inc., Chicago, IL, USA) program for windows. Quantitative variables were expressed as mean (M) and standard deviation (SD). Continuous variables used the Kolmogorov-Smirnov test to confirm normal distribution. Continuous variables used the Kolmogorov-Smirnov test to confirm normal distribution. Nonparametric data were analyzed for differences using the Kruskal-Wallis and Mann-Whitney U methods. For each variable, Spearman's correlation analysis was performed. All statistical significance level was presented as proportions and mean with 95% confidence intervals and a *P*-value<0.05 was considered to be statistically significant.

RESULTS

1. Baseline characteristics

A total of 649 patients with COVID-19 were enrolled in January 2021 (Table 1). Their mean age was 71.28±15.69 years, 75.13±15.00 years (306 people, 50.3%) were females and 67.84±15.52 years (343 people, 49.7%) were males. The mean age were statistically significant difference between males and females (*P*<0.01). The age-specific data of this study subject showed a non-normal distribution. As shown in Table 1, the differences according to the average of the age groups were statistically different.

2. Age distribution status by kidney function tests in serum

The mean BUN of the patients hospitalized with COVID-19 during the study period was 20.52±20.11 mg/dL, and the mean of creatinine was 0.98±0.77 mg/dL. There was a statistically significant difference in BUN between men and women and between age groups, respectively (*P*<0.01). There was a statistical difference in creatinine between men and women (*P*< 0.01), but the difference between the ages group were not statistically significant (Table 2, Figure 1).

Table 1. Characteristics of the 649 patients with COVID-19

Age	Male	Female	Total	†Z, ††x^2, †††U
	M±SD (N, %)			
<50 years[a]	38.51±13.19 (43, 3.6)	37.00±13.08 (20, 1.6)	38.03±13.07 (63, 9.7)	†2.86**
50's[b]	55.31±2.53 (48, 5.7)	54.22±3.23 (18, 2.1)	55.02±2.75 (66, 10.2)	††599.69**/ (a<b<c<d<e)**
60's[c]	64.76±1.92 (63, 8.8)	65.27±2.43 (49, 6.9)	64.98±2.16 (112, 17.3)	
70's[d]	73.67±2.38 (97, 15.4)	74.41±2.43 (69, 11.1)	73.98±2.42 (166, 25.6)	
>80 years[e]	84.05±3.98 (92, 16.7)	86.28±5.30 (150, 28.0)	85.43±4.95 (212, 37.3)	
Total	67.84±15.52 (343, 50.3)	75.13±15.00 (306, 49.7)	71.28±15.69 (649, 100)	†††36217.00**

***P*<0.01.
†*P*-values were calculated by Kolmogorov-Smirnov.
††*P*-values were calculated by Kruskal-Wallis.
†††*P*-values were calculated by Mann-Whitney U.

Table 2. Status in serum kidney function tests of the patients with COVID-19

Kidney function tests in serum	Age group	Male	Female	Total	†Z, †† x^2, †††U
		M±SD			
BUN (mg/dL)	<50 years[a]	12.84±3.29	10.30±2.74	12.03±3.32	†0.25**
	50's[b]	13.56±7.17	12.67±4.63	13.32±6.55	
	60's[c]	29.14±25.98	11.41±5.54	21.38±21.64	††60.22** (a<b<d<c<e)**
	70's[d]	24.82±22.93	14.71±10.88	20.62±19.49	
	>80 years[e]	36.84±32.89	16.47±8.45	24.21±23.46	
	Total	25.76±25.36	14.63±8.52	20.52±20.11	†††35822.00**
Creatinine (mg/dL)	<50 years[a]	0.83±2.74	0.65±0.09	0.77±0.22	†0.29**
	50's[b]	0.84±4.63	0.72±0.19	0.81±0.22	
	60's[c]	1.48±5.54	0.71±0.34	1.14±0.93	††3.14 (a<b<d<e<c)**
	70's[d]	0.98±10.89	0.70±0.42	0.87±0.45	
	>80 years[e]	1.65±8.45	0.72±0.29	0.98±0.98	
	Total	1.21±0.95	0.71±0.32	0.98±0.77	†††22085.00**

Abbreviations: BUN, blood urea nitrogen. ***P*<0.01.
†*P*-values were calculated by Kolmogorov-Smirnov.
††*P*-values were calculated by Kruskal-Wallis.
†††*P*-values were calculated by Mann-Whitney U.

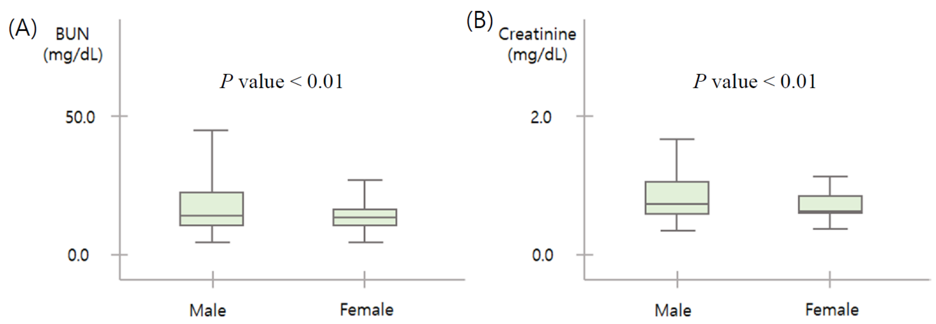

Figure 1. Status in serum kidney function of the patients with COVID-19. (A) Gender differences in serum BUN results, (B) gender differences in serum Creatinine results. Box and plot using the Mann-Whitney U.

3. Status in serum electrolytes of the patients with COVID-19

Electrolyte test results of the subjects, the mean of sodium was 136.50±7.40 mEq/L, the mean of potassium was 4.11±4.17 mEq/L, and the mean of chloride was 101.51±7.16 mEq/L. Sodium, potassium and chloride were statistically significant difference between age groups, respectively (*P*<0.01). In sodium, statistically significant difference was not observed between males and females. A statistically significant difference was observed in that potassium (*P*<0.01) was higher in women and chloride (*P*<0.05) was higher in men (Table 3, Figure 2).

4. Status in serum eGFR of the patients with COVID-19

The differences in eGFR according to the age group for gender are shown in Table 4. The statistical difference status of MDRD eGFR was observed to be higher in female than in male (*P*<0.01). The statistical difference status of CKD-EPI creatinine, no significant trends, according to the gender, were observed. MDRD eGFR and CKD-EPI creatinine status were related to a significantly statistical difference in each age groups (*P*<0.01) (Table 4, Figure 3).

5. Correlation of kidney function, electrolytes and age of the patients with COVID-19

According to the age of the study subjects, BUN was observed with a significant positive correlation (r=0.288,

Table 3. Status in serum electrolytes of the patients with COVID-19

Electrolytes in serum	Age group	Male	Female	Total	†Z, ††χ^2, †††U
		M±SD			
Na (mEq/L)	Under 50 years[a]	138.67±4.08	138.85±2.54	137.37±3.78	†3.56**
	50's[b]	138.29±3.88	138.55±3.10	138.36±3.66	††22.86** (d<e<c<a<b)**
	60's[c]	137.63±3.90	136.51±2.69	137.14±3.45	
	70's[d]	135.07±4.89	135.65±4.99	135.32±4.92	
	Over 80 years[e]	137.47±6.63	135.59±12.60	136.30±3.75	
	Total	138.84±5.16	136.14±9.28	136.50±7.40	†††51683.00
K (mEq/L)	Under 50 years[a]	4.08±0.43	3.91±0.28	4.03±0.40	†9.57**
	50's[b]	3.88±0.39	4.14±0.47	3.95±4.27	††52.60** (d<b<a<e<c)**
	60's[c]	4.41±0.71	4.17±0.48	4.30±0.63	
	70's[d]	3.96±0.54	3.80±0.52	3.90±0.54	
	Over 80 years[e]	4.05±0.85	4.37±8.62	4.24±6.80	
	Total	4.07±0.85	4.16±6.04	4.11±4.17	†††40605.50**
Cl (mEq/L)	Under 50 years[a]	100.12±3.30	103.40±3.36	101.16±3.63	†2.86**
	50's[b]	103.02±4.36	100.39±2.73	102.30±4.13	††26.86** (d<a<c<b<e)**
	60's[c]	103.00±5.39	100.04±3.93	101.71±5.01	
	70's[d]	99.80±5.38	99.59±5.00	99.72±5.21	
	Over 80 years[e]	105.21±7.73	100.89±10.56	102.53±9.79	
	Total	102.33±6.17	101.16±3.63	101.51±7.16	†††47084.50*

*P<0.05, **P<0.01.
†P-values were calculated by Kolmogorov-Smirnov.
††P-values were calculated by Kruskal-Wallis.
†††P-values were calculated by Mann-Whitney U.

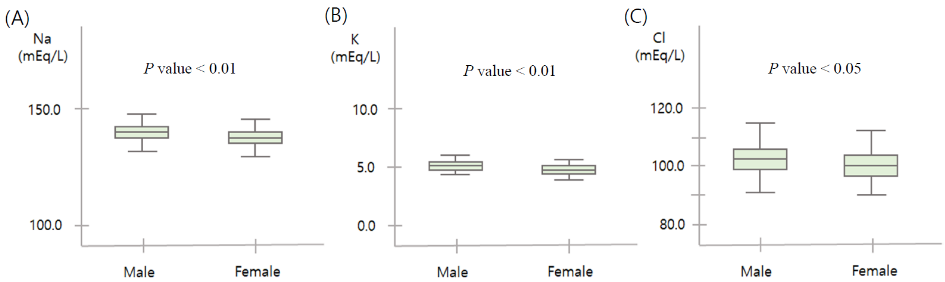

Figure 2. Status in serum electrolyte of the patients with COVID-19. (A) Gender differences in serum sodium results, (B) gender differences in serum potassium results, (C) gender differences in serum chloride results. Box and plot using the Mann-Whitney U.

P<0.01). Potassium (r=−0.288, P<0.01) MDRD (r=−0.292, P<0.01) and CKD-EPI (r=−0.614, P<0.01) according to age were statistically significant with a negative correlation. BUN was observed in a positive relationship with creatinine (r=0.588, P<0.01), potassium (r=0.112, P<0.01) and chloride (r=0.128, P<0.01), and was statistically significant with a negative relationship with MDRD (r=−0.577, P<0.01) and CKD-EPI (r=−0.594, P<0.01). Creatinine was statistically significant with a positive correlation with sodium (r=0.080, P<0.05), potassium (r=0.228, P<0.01) and chloride (r=0.194, P<0.01), and a very strong relationship negative with MDRD (r=−0.887, P<0.01) and CKD-EPI (r=−0.700, P<0.01). Sodium was very strong relationship negatively correlated with potassium (r=−0.079, P<0.05), very strong relationship positively correlated with chloride (r=0.778, P<0.01), and very strong relationship negatively correlated with MDRD (r=−0.085, P<0.05). Potassium was very strong relationship negatively correlated with chloride (r=−0.078, P<0.05) and strong relationship negatively MDRD (r=−0.615, P<0.01). Chloride was statistically significant in a negligible negative relationship with MDRD eGFR (r=−0.192, P<0.01) and CKD-EPI (r=−0.180, P<0.01). MDRD eGFR was statistically significant in a very strong positive relationship with CKD-EPI (r=0.887, P<0.01) (Table 5, Figure 4).

Table 4. Status in eGFR of the patients with COVID-19

eGFR	Age group	Male	Female	Total	†Z, ††x^2, †††U
		M±SD			
MDRD eGFR (mL/min/1.73 m^2)	Under 50 years[a]	122.77±72.81	112.43±42.55	119.48±64.58	†2.73**
	50's[b]	104.72±38.11	89.64±18.32	100.60±34.41	
	60's[c]	75.25±37.16	93.73±28.95	83.34±34.91	††49.47** (e<c<d<b<a)**
	70's[d]	87.73±33.65	94.45±28.06	90.52±31.53	
	Over 80 years[e]	64.16±36.45	90.08±35.41	80.23±37.89	
	Total	85.88±46.28	93.09±32.89	89.28±40.65	†††45242.00**
CKD-EPI creatinine (mL/min/1.73 m^2)	Under 50 years[a]	114.14±26.36	114.16±16.93	114.15±23.63	†3.43**
	50's[b]	99.31±17.96	94.85±17.14	98.09±17.72	
	60's[c]	73.42±34.02	89.00±17.38	80.24±28.94	††229.72** (e<c<d<b<a)**
	70's[d]	80.54±21.55	84.23±17.20	82.07±19.89	
	Over 80 years[e]	58.00±28.41	74.50±17.88	68.23±23.81	
	Total	80.03±31.97	82.80±20.43	81.34±27.16	†††51706.50

Abbreviations: eGFR, estimated glomerular filtration rate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.
**P<0.01.
†P-values were calculated by Kolmogorov-Smirnov.
††P-values were calculated by Kruskal-Wallis.
†††P-values were calculated by Mann-Whitney U.

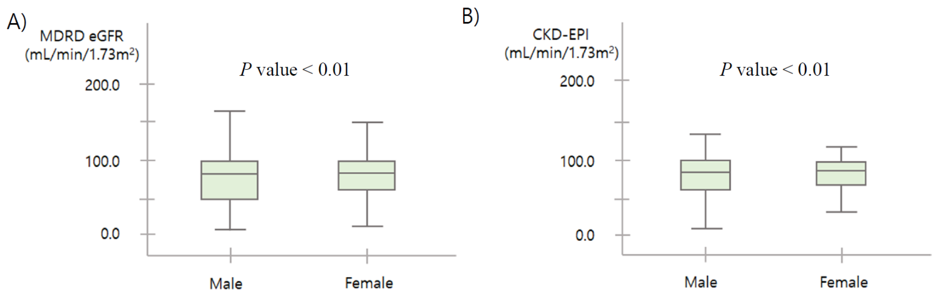

Figure 3. Status in eGFR of the patients with COVID-19. (A) Gender differences in serum MDRD eGFR, (B) gender differences in CKD-EPI. Box and plot using the Mann-Whitney U.

Table 5. Correlation of kidney function and electrolytes of the patients with COVID-19

Variables	MDRD eGFR (mL/min/1.73 m^2)	CKD-EPI (mL/min/1.73 m^2)
BUN (mg/dL)	−0.577**	−0.594**
Creatinine (mg/dL)	−0.887**	−0.700**
Na (mEq/L)	−0.085*	−0.022
K (mEq/L)	−0.165**	−0.058
Cl (mEq/L)	−0.192**	−0.180**

Abbreviations: Cr, Creatinine; See Table 2, 4.
*P<0.05, **P<0.01 by Spearman's correlation test.

DISCUSSION

We investigated the status of electrolyte and kidney function of patients hospitalized for COVID-19 at a hospital located in southern Gyeonggi Province for one month in January 2021. In this study, we report the renal laboratory and electrolytes findings in 649 COVID-19 patients. Although respiratory symptoms with high fever are the main features of COVID-19, the involvement of other organs also need to be considered. Previous research considers that acute kidney impairment (AKI) is more common in COVID-19 patients than in patients with other coronavirus syndromes, and that kidney impairment associates with mortality [8]. It's possible for COVID-19 to lead to serious kidney issues. Research suggests that people hospitalized with COVID-19 can an acute kidney damage. That's a sudden instance of kidney damage, and in some severe instances, kidney failure, that happens within hours or days. European Renal Association European Dialysis and Transplant Association suggested that Chronic kidney disease patients hold an increased risk for COVID-19

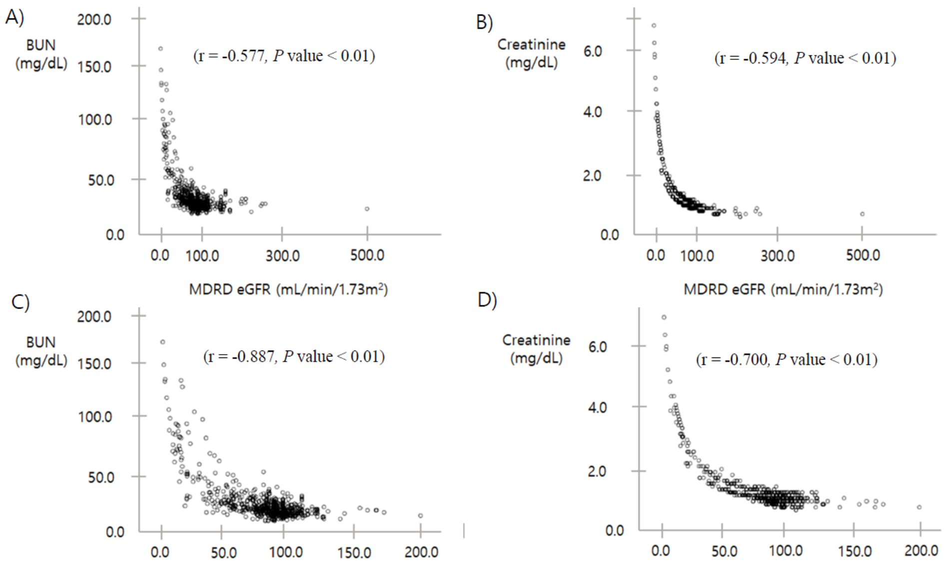

Figure 4. Spearman's correlation of kidney function and eGFR of the patients with COVID-19.

and related mortality [15]. Reports refer that kidney involvement is frequent and ranges from mild proteinuria to an forward AKI that clinical evidence has shown the increase of serum creatinine and blood urea nitrogen in 701 COVID-19 cases in a large prospective study in China [8, 16]. BUN and creatinine of the COVID-19 patients reviewed in this study also showed increased patterns. Among the subjects of this study, men's BUN was higher than the reference interval. It was particularly high in those in their 60s and 80s or older, and creatinine levels were also observed in a similar manner (Table 2). Studies found that hypokalemia has been described in COVID-19 patients in China [17]. Hyponatremia has been reported in COVID-19 patients in a clinical case and in a small study in the United States and hyponatremia and hypokalemia were reported in a series of 12 patients in China [17-20]. In this study, the electrolyte test of the patients was not observed at all outside the normal range (Table 3). According to a recent study eGFR was <60 mL/min/1.73 m^2 in 44.1% (N=207) of the COVID-19 patients. In the same study, patients with an eGFR <60 mL/min/1.73 m^2 at presentation were significantly older, more likely to be males [21].

Recent data have intimated the presence of a reciprocal relationship between COVID-19 and kidney function. The pathogenesis of kidney disease in COVID-19 patients is explained to be multifactorial, possibly including direct cytopathic effects on kidney tissue, endothelial damage, deposition of immune complexes, and virus-induced cytokines or mediators and also eGFR as a prognostic marker for mortality [22]. The observed drop in eGFR among patients with COVID-AKI was independent of patient demographics, comorbidities, or the severity of the AKI, suggesting it was the result of the hyperinflammatory state associated with COVID-19 or the residual effects of the virus, researchers said. These patients continued to have faster decline in eGFR after discharge, increasing the likelihood of long-term kidney disease, dialysis, and death [23]. In the subjects of this study, males over 80 years of age had a CKD-EPI of 60 mL/min/1.73 m^2 or less. All other CKD-EPI results were observed to be 60 mL/min/1.73 m^2 or higher (Table 4, Figure 3). The major blood tests for homeostasis and renal function are sodium and potassium are electrolytes. In a clinical study involving 3,603 men and women aged 25 to 75 years who underwent health screening, eGFR decreased with increasing age and serum Na in most parameters, including age and blood pressure. The proposed conclusion was suggested that high serum Na concentrations, even within the normal range, are independently associated with elevated BP and impaired kidney function [24]. Studies conducted GFR declines, usually beginning after 30~40 years of age. The rate of decline may accelerate after age 50~60 years. This decline appears to be a part of the normal physiologic process of cellular and organ senescence and is associated with structural changes in the kidneys [25]. The correlation of the variables in this study also showed the very strong relationship (Table 5, Figure 4). BUN and serum creatinine are commonly used indicators for the detection of renal function. Thus, detection of kidney function tests and electrolytes of multiple indicators assessment could be helpful for discovering abnormal renal function in patients with COVID-19. However, the data of the variables in this study have limitations in that the underlying diseases of the subjects are not reflected. Therefore, this study is expected to contribute to research such as clinical treatment of COVID-19. Moreover, studies, especially large prospective cohort studies, that clinical chemistry research related to COVID-19 should be continuously performed.

요 약

코로나바이러스 감염증 19는 중증급성호흡기증후군 코로나바이러스 2의 명칭에서 명명되었다. 이 연구는 코로나바이러스 감염증 19 환자의 신기능 상태를 조사하는 것을 목적으로 하였다. 본 연구는 경기도 남부 한 병원에서 코로나바이러스 감염증 19로 입원한 649명 환자를 대상으로 하였다. 이번 연구에서 검토한 코로나바이러스 감염증 19 환자의 혈액요소질소와 크레아티닌은 증가된 패턴을 보였다. 본 연구의 대상자 중 남성의 혈액요소질소는 정상 범위보다 높았다. 특히 60대, 80대 이상에서 높게 나타났고, 크레아티닌 수치도 비슷하게 나타났다. 이 연구에서 환자의 전해질 검사는 정상 범위에서 벗어나는 결과는 관찰되지 않았다. 이 연구의 대상에서 80세 이상의 남성은 60 mL/min/1.73 m^2 이하의 만성신장질환 역학협력 사구체여과율을 나타냈다. 최근 연구에 따르면 COVID-19의 일부 심각한 사례는 코로나바이러스에 감염되기 전에 기저 신기능의 문제가 없었던 사람들에게도 콩팥 손상의 징후를 보이고 있다. 따라서 여러 지표 평가의 신기능 검사는 검사결과의 검토는 코로나19 환자의 비정상 신기능 발견에 도움이 될 수 있다.

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