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COVID-19 and kidney diseases: A meta-analysis of clinical outcomes

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Abstract. Novel coronavirus 2019 (COVID-19) is a highly infectious disease that causes multiorgan failure and a high mortality rate. The present study aimed to investigate the association between COVID-19 infection and kidney dysfunction.

Methods. In this meta-analysis study, 68 patients with kidney dysfunction and COVID-19 infection were analysed. Clinical features, laboratory data at initial presentation, management and, outcomes were collected. Risk of acute kidney injury (AKI), acute kidney disease (AKD) and chronic kidney disease (CKD) progression to kidney replacement therapy and graft loss were primary outcomes in this study.

Results. The average age of patients at the time of diagnosis in COVID-19 nephropathy was 52.04 ± 14.42 years. There were ICU admission in 10/68 (14.7%) patients with COVID-19 nephropathy. There were a need for mechanical ventilation in 13/68 (19.1%) patients; 15/68 (22%) patients died during hospital course or post-discharge. There were AKI in 4/68 (5.8%) patients with COVID-19 nephropathy and AKD found in 14/68 (20.5%) patients with COVID-19 nephropathy during the follow-up. The median and interquartile range of SCr during the follow-up period was assessed at 1.74 mg/dl and 1.18 (Q3-Q1=2.73-1.55), respectively. The effect size of COVID-19 on AKI and AKD was assessed 0 and 0.003 using Cohen's-d test. Eventually, 10 of 68 (14.7%) patients with COVID-19 nephropathy stayed on hemodialysis during the follow-up period and one of them remained on RRT but its type was not characterized. There were a total of 36/68 (52.9%) kidney transplant recipients and 10/36 (27.7%) of them developed AKI due to acute rejection. The effect size of elevated IL-6 on decreased estimated glomerular filtration rate (eGFR) in COVID-19 nephropathy was assessed 0.656 (medium effect size).

Conclusion. The COVID-19 had a trivial (small) effect on eGFR declining. Future clinical research is required for investigating novel unknown findings in COVID-19 nephropathy.

Keywords: COVID-19 nephropathy, acute kidney injury, acute kidney disease, chronic kidney disease.

Conflict of interest statement. The author declares no competing interests.

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COVID-19 та хвороби нирок: Мета-аналіз клінічних результатів

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Резюме. Метою дослідження було дослідити взаємозв'язок між інфікуванням коронавірусною хворобою COVID-19 та дисфункцією нирок.

Методи. У цьому мета-аналізі було проаналізовано 68 пацієнтів з гострою та хронічною хворобою нирок, інфікованих COVID-19. Були зібрані клінічні ознаки, лабораторні дані та результати лікування. Ризик прогресування гострого пошкодження нирок (ГПН), гострої хвороби нирок (ГХН) та хронічної хвороби нирок (ХХН) до необхідності ниркової замісної терапії або втрати трансплантата були кінцевими точками дослідження.

Результати. Середній вік пацієнтів на момент встановлення діагнозу COVID-19 з ураженням нирок становив $52,04 \pm 14,42$ років. У відділення інтенсивної терапії госпіталізовано 10/68 (14,7%) пацієнтів, у 13/68 (19,1%) пацієнтів виникла потреба у ШВЛ; 15/68 (22%) пацієнтів померли під час госпітального курсу або після виписки. У 4/68 (5,8%) пацієнтів з COVID-19 було діагностовано ГПН, а у 14/68 (20,5%) хворих з COVID-19 ГПН було діагностовано під час спостереження. Середній діапазон креатиніну сироватки протягом періоду спостереження становив $1,74$ мг/дл ($Q3-Q1 = 2,73-1,55$). Розмір впливу COVID-19 на ГПН та ГХН, оцінений за допомогою тесту Кохена складав від 0 до 0,003. Зрештою, 10 з 68 (14,7%) пацієнтів з нефропатією COVID-19 перебували на гемодіалізі протягом періоду спостереження. Усього було 36/68 (52,9%) реципієнтів з трансплантацією нирки і у 10/36 (27,7%) з них розвинулось ГПН через гостре відторгнення трансплантату. Розмір впливу підвищеного IL-6 на швидкість клубочкової фільтрації у пацієнтів з нефропатією COVID-19 склав 0,656 (середній розмір ефекту).

Висновок. Майбутні клінічні дослідження необхідні для визначення впливу COVID-19 на клінічні результати хворих з хворобами нирок.

Ключові слова: COVID-19, гостре пошкодження нирок, гостра хвороба нирок, хронічна хвороба нирок.

Introduction. Viral pneumonia by novel coronavirus-19 [severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2)] emerged in December 2019 in Wuhan, Hubei province, China for the first time [1]. This new disease has been named novel coronavirus disease-2019 (COVID-19) by the World Health Organization (WHO). Coronavirus belongs to the coronaviridae family, Nidovirales order, and reveals with crown-like projections on its surface. In the late 1960s, it has been isolated from patients with the common cold and identified this virus as B814 by electron microscopy. The virus comprises alpha (α), beta (β), gamma (γ), and delta (δ) subgroups. The main reservoirs of the virus include bats, palm civets, and livestock and animals. These viruses were assumed to transmit among animals till the outbreak of SARS in the 2002 year in Guangdong, China. Thereafter, an outbreak of Middle East respiratory syndrome coronavirus (MERS) emerged in Middle Eastern countries. In the recent outbreak in China, it was thought to have originated from the Hunan seafood market at Wuhan in China. Some have a belief that this virus has evolved from an unknown species of bat

at a Wuhan wet animal market in southern China. The patients were diagnosed with pneumonia of unknown etiology and were related to the seafood market. Gradually, the disease was increased in that region and it was detected in those who had not gone on a journey to the seafood market and at that time purposed possible of person-to-person transmission. Coronavirus is a single-stranded (positive sense) ribonucleic acid (RNA) Beta-coronavirus, enveloped (E-protein) with club-shaped/pear-shaped/petal-shaped glycoprotein projections (S-protein) [1].

This virus is spherical or pleomorphic in shape with 80-120 nanometer (nm) size and includes spikes that are made hemagglutinin esterase. The S-protein mediates the viral attachment and entry to the endoplasmic reticulum. SARS-CoV-2 maintains the classic coronavirus structure like the presence of spike protein and expression of other nucleoproteins, polypeptides, and membrane proteins such as RNA polymerase, 3-chymotrypsin-like protease, papain-like protease, helicase, glycoprotein, and accessory proteins. The pandemic flu phase includes phases 1-3 that predominantly are animal infections and few human infections. Phase 4 comprises sustained human-to-human transmission and phase 3-6/pandemic with widespread human infection. In post-peak, there is the possibility of recurrent events and in post-pandemic, there is disease activity at seasonal levels [2].

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Objectives.

How does this study might work? SARS-CoV-2 (COVID-19) in persons with chronic comorbidities can lead to critical illness easily or cause death. Patients with underlying diseases e.g. cardiac, lung, liver, and kidney damage are at higher risk of COVID-19 infection rather than healthy patients. End-stage kidney disease patients are not exceptional in this rule due to immune system suppression and poor outcomes from this viral infection. Hence, close identification of the association between this viral infection and kidney dysfunction leads to new mechanisms in pathogenesis and novel therapeutic agents. This work aimed to find associations between COVID-19 and impaired kidney function, eventually to create less spread and limitation of viral infection.

Why does this research need? SARS-CoV-2 has been spread out in Dec 2019. It has been isolated in saliva, nasopharynx and lower respiratory tract samples. Viral RNA has been found in the plasma of 15% of the most severely affected patients and viral detection in stool raises the possibility of fecal transmission. Because of the rapid spread, asymptomatic nature and high mortality of the COVID-19 viral infection, this research has been motivated us to obtain explore specific and more knowledgeable scientific pathways to prevent this viral infection.

Materials and Methods. The present systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.

Eligibility criteria. Type of studies. The search identified 1391 full-text articles via electronic search in google scholar and PubMed central databases. Therefore total records of 1391 full-text articles were screened and seven articles were deduplicated (1384). Then 202 full-text articles were eligible and 1182 articles were excluded due to not being related subjects. Therefore, 68 records in 43 published articles were included, and 159 articles were discarded due to non-case reports. These 43 articles included 68 case reports that were examined 68 patients with kidney disease with COVID-19 infection. These participants were enrolled for systematic review and meta-analysis synthesis.

Type of participants. Patients with kidney dysfunction including acute kidney injury (AKI), acute kidney disease (AKD), chronic kidney disease (CKD), and kidney replacement therapy (KRT) that were infected with SARS-CoV-2 were enrolled in this research. Patients were excluded from the study if they had no kidney involvement at an initial time or during the follow-up period.

Primary outcomes. Risk of AKI, AKD, CKD, kidney failure (KF) progression to kidney replacement therapy and graft loss, intensive care unit (ICU) admission, mechanical ventilation, and death were primary outcomes in this study.

Secondary outcomes. Urinary tract infection (UTI), decreased an estimated glomerular filtration

rate (eGFR), and elevated urinary albumin to creatinine ratio (UACR) for detecting proteinuria were secondary outcomes in this study.

Information sources. The paper has been written based on advanced searching via PubMed Central (PMC) and Google Scholar databases to identify articles published from inception to May 2020. The mentioned search was performed with search terms of kidney and COVID-19 and COVID-19 nephropathy. The author reviewed references of all included articles and performed hand-searching of related journals to identify the additional relevant studies.

Study selection. The search strategy was used to obtain titles and abstracts of studies that might be relevant to this review. The 401 plus 990 titles and abstracts were screened via electronic search in PMC and Google Scholar by author, respectively. Total records of 1391 case-reports articles were screened and after deduplication 1384 articles were identified. Among them, 1182 articles were excluded due to non-related subjects, review articles, others and 202 full-text articles were considered for eligibility. However, studies and reviews that might include relevant data or information on studies were retained initially. The 159 articles were excluded and then 43 published articles that were examined 68 patients with COVID-19 infection and renal dysfunction were included for qualitative and quantitative synthesis.

Data collection and analysis. Data extraction was carried out by the author and studies reported in journals as non-English language were translated before assessment. Where more than one publication of a study existed, reports were grouped and the publication with the most complete data was included.

All patients with clinical, laboratory and radiologic presentations of COVID-19 infection and decreased eGFR with or without a positive test for COVID-19 in sputum, stool, urine, peritoneal dialysis fluid, and tissue biopsy-proven specimens were considered in this research. Demographic and clinical features such as age, sex, different symptoms and physical signs were extracted from this study. Furthermore, biochemical variables of serum creatinine (SCr), eGFR, urine protein, nucleic acid testing as quantitative real-time reverse transcriptase-polymerase chain reaction (qRT-PCR) at initial presentation and following days, imaging, management, and outcomes were collected.

Definition of kidney dysfunction. AKI, AKD and CKD can form a continuum whereby initial kidney injury can lead to persistent injury eventually leading to CKD. AKI was defined as an abrupt decrease in kidney function occurring over 7 days or less whereas CKD is defined by the persistence of kidney disease for a period of > 90 days. AKD is defined as acute or subacute damage and/or loss of kidney function for a duration of between seven and 90 days after exposure to an AKI initiating event. Recovery from AKI within 48 h of the initiating event typically heralds rapid reversal of AKI (16th ADQI consensus report of 2017). CKD is classi-

fied zero to five stages (stages of 1, 2, 3a, 3b, 4 and 5) according to eGFR and kidney damage such as proteinuria (>200 mg/day or protein to creatinine ratio >200 mg/g creatinine) or albuminuria (urinary albumin excretion ≥ 30 mg/day or albumin to creatinine ratio ≥ 30 mg/g creatinine).

eGFR was measured according to creatinine clearance (CrCl), Cockcroft-Gault equation, modification of diet in renal disease (MDRD) and chronic kidney disease-epidemiology collaboration (CKD-EPI). CrCl in 24-hr urine collection is expressed using urine creatinine (mg per deciliter or micromole per liter) multiplication by urine volume (milliliter or liter) divided on plasma creatinine (milligram per deciliter or micromole per liter) multiplied in 1440 and its unit is expressed with milliliter per minutes (ml/min).

Definition of infection transmission to others.

Person-to-person spread is thought to occur mainly via respiratory droplets. COVID-19 virus RNA has been detected in blood and stool specimens. Through respiratory droplets generated by sneezing and coughing by the infected person, generally when present nearby. By manual touching of infected surface (having the SARS-CoV-2 virus from the symptomatic or asymptomatic person) and then hand touching the mouth, nose or eyes. Transmission does not occur through simple air (viruses remain contained in sneezing droplets). No vertical mother-to-child transfer in the case of pregnant women was seen [3].

Definition of hyperpyrexia. A morning reading $> 37.2^{\circ}\text{C}$ (98.9°F) or an afternoon temperature of $> 37.7^{\circ}\text{C}$ (99.9°C) was considered a fever. Rectal temperatures are generally 0.6°C (1°F) higher than oral readings. Oral readings are lower probably because of mouth breathing, which is particularly important in patients with respiratory infections and rapid breathing. Tympanic membrane temperature readings are close to core temperature. The normal early morning to late afternoon daily increase is typically 0.5°C (0.9°C). However, in some individuals recovering from a febrile illness, this daily variation can be as high as 1.0°C . During a febrile illness, the daily low early morning and the high evening temperature difference is maintained but shifted upwards to higher levels. In menstruating women, the morning temperature is generally lower during the two weeks before ovulation, rising by about 0.6°C (1.0°F) with ovulation and remaining at that level until menses occur. Seasonal variation in body temperature has been described, but this may reflect a metabolic change and is not a common observation. Elevation in body temperature occurs during the postprandial state, but this is not fever. Pregnancy and endocrinologic dysfunction also affect body temperature. The daily temperature variation appears to be fixed in early childhood. On the other hand, it is well established that the ability to develop a fever in older adults is impaired and that baseline temperature in older adults is lower than in younger adults. Thus, older adult patients with severe infections may only display a modest fever [4].

Definition of tachycardia and tachypnea. An equal or elevated heart rate of 100 beats per minute is defined as tachycardia and increased respiratory rate >20 breaths per minute is defined as tachypnea.

Definition of Hypertension. Based on the most recent American Heart Association/American College of Cardiology (AHA/ACC) guidelines, an office blood pressure (BP) of less than 120/80 is considered as normal and office BPs in the range of 120 to $<130/80$ mmHg are considered to be elevated. An office BP of 140/90 mmHg is thought to correlate with an ambulatory blood pressure monitoring (ABPM) in 24-hr with an average BP of 130/80 mmHg (135/85 mmHg daytime and 120/70 mmHg nighttime mean BPs) and home BP of 135/85 mmHg. Hypertension is defined as SBP ≥ 130 and/or DBP ≥ 85 mmHg or under medical treatment for hypertension.

Clinical suspicion or criteria for COVID-19 diagnosis. Up to now, the possibility of COVID-19 infection should be considered primarily in patients with fever and/or lower respiratory tract symptoms who reside in or have recently (within the prior 14 days) traveled to areas where community transmission has been reported (e.g. China, South Korea, Italy, Iran, Japan) or have had recent (within the prior 14 days) close contact with a confirmed or suspected cases of COVID-19. The possibility of COVID-19 should also be considered in patients with severe lower respiratory tract illness when an alternative etiology cannot be identified or exists no clear been no clear contact or exposure with the infected patient [4].

Definition of cell lineages in peripheral blood. Leukocytosis was defined as a total white blood cell (WBC) more than two standard deviations above the mean, or a value greater than 11000 cells/microliter in adults. Leukopenia was defined as a total WBC less than 4400/microliter in peripheral blood. Neutrophilic leukocytosis is defined as a total WBC above 11000 cells/microliter along with an absolute neutrophil count (ANC) more than two standard deviations above the mean (greater than 7700 cells/microliter in adults), moderate between 500 and 1000 cells/microliter and severe with less than 500/microliter. Lymphocytosis is defined as an ALC >4000 cells/microliter (also expressed as more than 4.00 multiplied in $10^3/\text{mm}^3$ or $>4.0 \times 10^9/\text{L}$). Lymphocytopenia has been variously defined in older children and adults as an ALC <1000 or <1500 cells/microliter. Alanine aminotransferase (ALT) >29 to 33 IU/L in males and >19 to 25 IU/L in females) were defined as abnormal serum aminotransferase levels. An aspartate aminotransferase (AST) cut-off of 10 to 40 IU/L in men and 9 to 32 IU/L in women was considered an abnormal value. The normal range of lactate dehydrogenase (LDH) is between 140 to 280 U/l. Normal serum albumin is defined as 3.5-5.5 g/dl.

Procalcitonin (PCT) is a biological marker that is used for distinguishing between bacterial and non-bacterial causes of pneumonia. The normal value for procalcitonin in males is ≤ 19 pg/mL or ≤ 19 ng/L [in-

ternational system of units (SI units)] and < 0.5 ng/ml. Amounts of less than 0.1 micrograms per liter (mcg/l) levels indicate nonantibiotic need and plasma levels above 0.25 mcg/l need antibiotic therapy. The reference range for C-reactive protein (CRP) is < 0.3 mg/dl or < 3 mg/l and for high-sensitivity CRP (hs-CRP) is < 3 mg/l. Normal value for cytokine interleukin-2 receptor antagonist (IL-2R α) level [cluster of differentiation (CD-25)] is 175.3 – 858.2 pg/mL and for IL-1 β is 0.16–10 pg/ml. Cytokine IL-10 level in ages of 1 to 6 years is assessed 11.4 (9.5–12.8), age groups of 7 to 17 years are assessed 11.3 (8.9–13.7) and age groups of ≥ 18 years is assessed 12.6 (8.5–16.7) pg/ml. IL-8 level in ages of 1 to 6 years is assessed 30.9 (23.7–32), age groups of 7–17 years is assessed 32.6 (28.2–39) and age groups of ≥ 18 years is assessed 29.3 (24.4–35.9) pg/ml. Normal value for tumor necrosis factor-alpha (TNF- α) is 23–1500 pg/ml. The reference range of cytokine of IL-6 for a healthy population is less than 17.4 pg/ml (0–5.9). Normal value for d-dimer is < 500 ng/ml or mcg/l (μ g/l), ≤ 0.49 mg/l in healthy persons. The normal value for fibrinogen level in adults is 200–400 mg/dL or 2–4 g/L (SI units). Normal serum creatine phosphokinase (CPK) is defined in amounts of 55–177 units/l. In other references normal CPK is considered 21–232 IU/l in male adults and in female adults this amount is 21–215 IU/l. Normal erythrocyte sedimentation rate (ESR) in males and females was defined based on the following formula: age/2 in males and age +10/2 in females. Elevated ESR was seen in eight of sixty-eight patients (8/68, 11.7%) with a mean average of in COVID-19 nephropathy. The normal ferritin concentration ranges from 40 to 200 ng/ml (mcg/l). Normal serum sodium is 135–145 mEq/l. Resting arterial oxygen saturation (SaO $_2$) ≤ 95 percent or exercise desaturation $\geq$ of 5 percent is considered abnormal.

Definition of the positive test for COVID-19 infection. Patients who meet the clinical criteria undergo testing for SARS-CoV-2 infection. Specimens can be collected from the upper respiratory tract (nasopharyngeal and oropharyngeal swab) and the lower respiratory tract (sputum, tracheal aspirate, or bronchoalveolar lavage) if possible. Induction of sputum is not indicated. Additional specimens (e.g. stool, urine) can be collected. SARS-CoV-2 is detected by polymerase chain reaction (PCR). A positive test for SARS-CoV-2 confirms the diagnosis of COVID-19. If initial testing is negative but the suspicion for COVID-19 infection remains, WHO recommends resampling and testing from multiple respiratory tract sites. Negative RT-PCR tests on oropharyngeal swabs despite computed tomography (CT) findings of viral pneumonia have been reported in some patients who ultimately tested positive for SARS-CoV-2. One important point that should be considered herein is the continuation of the shaded infected virus after improvement as such positive RT-PCR tests for SARS-CoV-2 were reported in four laboratory-confirmed COVID-19 patients after they had clinically improved and had the negative test on two consecutive

tests. Serum immunoglobulin G (IgG) and immunoglobulin M (IgM) antibodies against SARS-CoV-2 are detected by colloidal gold immunochromatography assay (CGIC). This assay is against nucleocapsid (N) protein and with some reactivity to the spike (S) protein. The sensitivity and specificity of this assay were 87.3 and 100%, respectively. Serology may have an important role in diagnosing acute and past SARS infections [5].

Assessment of risk of bias and quality in included articles. Case reports were analyzed using criteria developed by the Joanna Briggs Institute Critical Appraisal tool for case reports that have different assessment tools for each study design in question. The evaluation tool has 8 items for case reports.

Statistical analysis. Categorical variables are recorded as frequency (N) and percentage (%). The continuous variables were determined as to whether they were normally distributed using the Kolmogorov-Smirnov or Shapiro-Wilk test. Continuous variables with normal distribution were reported as mean $\pm$ standard deviation (SD). Nonparametric variables were expressed as the median and interquartile range (Q1, Q3 and IQR). Comparisons between continuous variables with normal distribution was done using the two-tailed t-test analysis. Relative risk (RR) and Odds (Ods) ratio were used for assessing effect measures of the risk factor on outcomes of disease. Furthermore, the chi-square test for association between risk factors of COVID-19 and outcomes was used. The effect size of intervention was assessed using Cohens' d test. Correlation between two variables was assessed using Pearson's and Spearman's tests. Significance was assessed with a p-value < 0.05 .

Results. Study description. After searching electronic databases the author identified 1391 records. After duplicated articles were removed (N=7) and 1384 titles and abstracts screened, the author discarded 1182 full-text articles due to non-related subjects. Then 202 articles were eligible and 159 articles were discarded due to not case reports. Of these, 43 published articles (68 case reports) were included and enrolled to participate in the present study.

Risk of bias and quality in the included studies. Assessment of risk of bias and quality of included articles performed using Joanna Briggs Institute critical appraisal tools for case reports (Supplementary Table 1). Based on these criteria, 16/68 (23.5%) case reports obtained 8 scores, 31/68 (45.5%) had 7 scores and 21/68 (30.8%) case reports achieved 6 scores.

Patients Characteristics. Among screened 1391 full-text articles obtained in this research paper, 1182 articles were excluded due to unrelated subjects, review articles and other studies. Then 202 full-text articles were eligible and 159 articles were excluded due to not case report (n=159). Eventually, 43 published articles were included in this study [6–48]. These 43 articles included 68 case reports that were examined 68 patients with clinical, laboratory and radiologic presentations of COVID-19

infection and decreased eGFR with or without a positive test for COVID-19 in sputum, stool, urine, peritoneal dialysis fluid and tissue biopsy-proven specimens who had renal dysfunction were considered for qualitative and quantitative synthesis in this research (Fig. 1).

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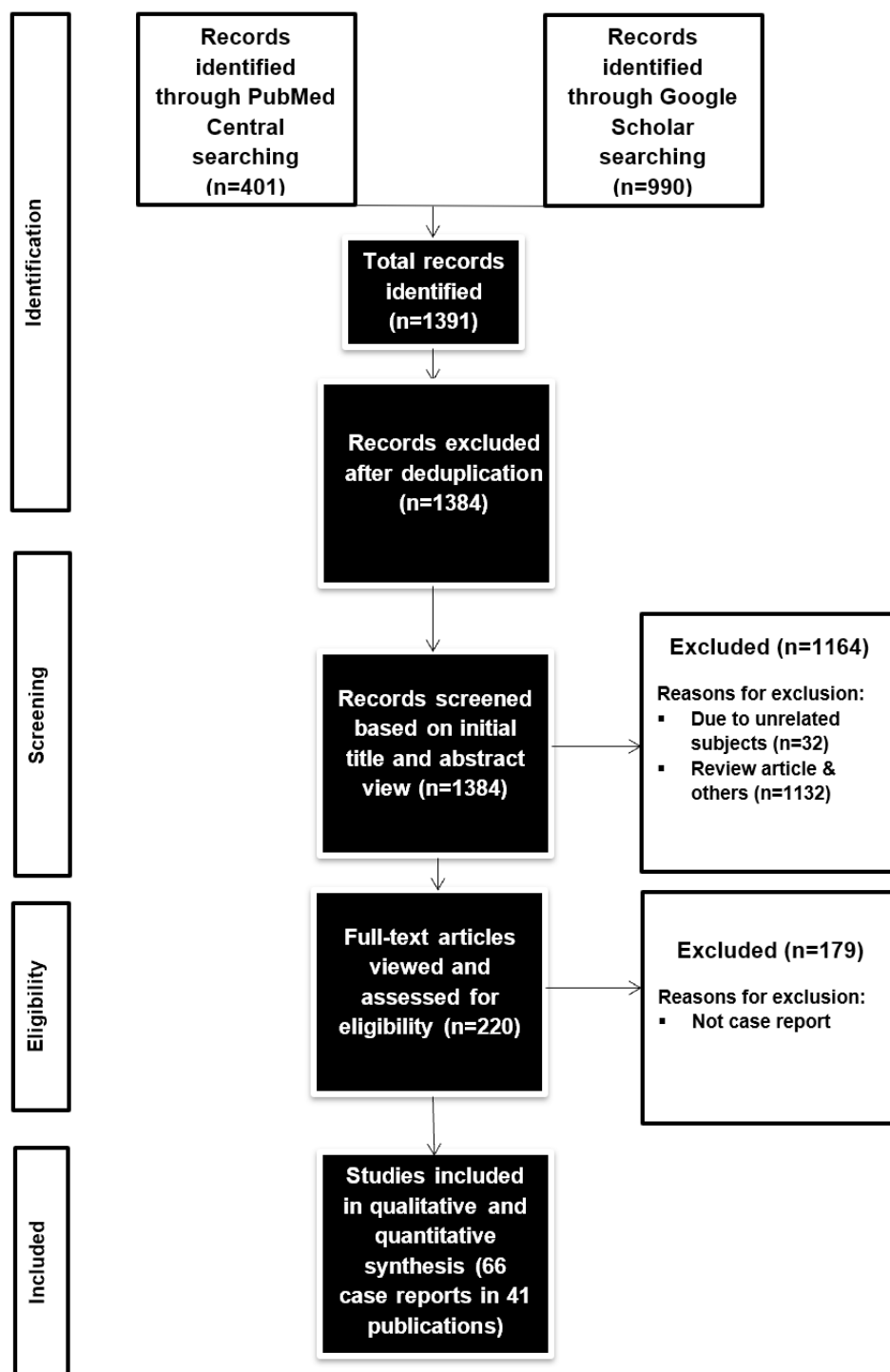


Fig.1. The workflow of included studies.

Fifty of sixty-eight patients were male (50/68, 73.5%) and 18 female (18/68, 26.4%) sex. Twenty-three of sixty-eight patients (23/68, 33.8%) were from Wuhan province of China country, seven of sixty-eight patients from London of UK (7/68, 10.2%), five of

sixty-eight patients (5/68, 7.3%) from USA and Italy, three of sixty-eight patients from Iran, African American, South Korea and France (3/68, 4.4%), two of sixty-eight patients from Turkey and Netherland (2/68, 2.9%), one of sixty-eight patients from Zhengzhou province of China, Spain, Switzerland, America from Hendourasian ethnicity, Switzerland from African an-

cestry, Australia, West Africa, Brazil, Germany, Denmark, Sweden country and Shenzhen of China (1/68, 1.4%). The causes of COVID-19 nephropathy in this research were different that has been described in Supplementary Table 2. The Mean average age of patients at the time of diagnosis in COVID-19 nephropathy was 52.04 ± 14.42 years (ranging from 24 years to 88 years). Of these, fifty patients (50/68, 73.5%) were male and eighteen patients (18/68, 26.4%) were female. Mean $\pm$ SD age of patients in male and female levels at the time of diagnosis in COVID-19 nephropathy were 53.06 ± 14.2 old years (ranging from 24 to 88 years old) and 49.2 ± 15 (ranging from 27 years to 69 years), respectively. There was no statistical significance for age between two sex levels in COVID-19 nephropathy (p-value: 0.36) (Supplementary Table 3).

Patients Complaints. The symptoms in this study were different and fifty-five patients (55/68, 80.8%) presented with a history of fever. Thirty-four patients (34/68, 50%) presented with cough, twenty-one of sixty-eight patients with shortness of breath and fatigue (21/68, 30.8%), fifteen of sixty-eight patients with diarrhea (15/68, 22.05%), fourteen of sixty-eight patients with dyspnea (14/68, 20.5%), thirteen of sixty-eight patients with dry cough (13/68, 19.1%), nine of sixty-

eight patients with vomiting (9/68, 13.2%), seven of sixty-eight patients with abdominal pain and runny nose (7/68, 10.2%), five of sixty-eight patients with anorexia (5/68, 7.3%), four of sixty-eight patients with malaise and productive cough (4/68, 5.8%). There was a history of hypertension in twenty-five of sixty-eight patients (25/68, 36.7%) with COVID-19 nephropathy (Supplementary Table 4).

The main clinical sign was fever in 47/68 (69.1%) patients. In 11/68 (16.1%) patients high blood pressure and tachycardia were observed. Tachypnea was present in 12/68 (17.6%) of patients with COVID-19 nephropathy. There were pulmonary edema, dehydration, abdominal tenderness and respiratory distress in 2/68 (2.9%) of the patients; abnormal lung sounds were detected in six 6/68 (8.8%) of them. In signs of COVID-19 nephropathy, there including ground glass opacities in the left lower lobe, mildly increased work of breathing and diffuse rhonchi, crackles in the right lower lung, a small infiltrate in the right upper lobe, mild crackles in both lung fields and small pleural effusion and finally fine bilateral crackles. Elevated body mass index (BMI) was seen in 3.68 (4.4%) patients with COVID-19 nephropathy (Supplementary Table 5).

Laboratory data. Laboratory findings of the enrolled patients are presented in Table 1.

Table 1

Laboratory findings and statistical analysis of acute-phase reactants and cytokines in patients with COVID-19 nephropathy

APRs/ Cytokines	Positive APRs (Hp, SA, fibrinogen, Cp, AAT, AGP, CRP, Lf, C2, C3, C4, C5, C9, Factor B, C1 inhibitor, C4 binding protein), ESR, ferritin	Negative APRs (Albumin, transferrin, transthyretin)	Positive or Negative Growth factor cytokines (IL-2, IL-3, IL-4, IL-7, IL-10, IL-11, IL-12, GM-CSF)	Proinflammatory cytokines (TNF- α / β , IL-1 α / β , IL-6, IFN- α / γ , IL-8, MIP-1)	Anti- inflammatory (IL-1RA, sIL-1Rs, IL1- BP, TNF- α BP) cytokines
Status					
Normal (Percent)	NI CRP: 2/68 (2.9%)	NI Albumin: 5/68 (7.3%)	NI IL-10: 2/ 68 (2.9%)	NI IL-1 β : 2/ 68 (2.9%)	NI TNF- α : 1/68 (1.4%)
	NI C3: 2/68 (2.9%)				
	NI hs-CRP: 1/68 (1.4%)			NI IL-8: 1/ 68 (1.4%)	
	NI C4: 3/68 (4.4%)				
Elevated (Percent)	↑CRP: 42/68 (61.7%)	Hypoalbumi- nemia: 6/68 (8.8%)	↑IL-2R: 2/ 68 (2.9%)	↑IL-6: 14/ 68 (20.5%)	
	hs-CRP: 4/68 (5.88%)				
	↑Fibrinogen: 8/68 (11.7%)				
	↑ferritin: 13/68 (19.11%)				
	↑ESR: 6/68 (8.8%)				
	↑C3: 1/68 (1.4%)				

Abbreviation: APRs, acute phase reactants; AAT, α 1-antitrypsin; AGP, α 1-acid glycoprotein; Cp, ceruloplasmin; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GM-CSF, granulocyte-macrophage colony stimulating factor; Hp, haptoglobin; hs-CRP, high sensitive C-reactive protein; Lf, lactoferrin; IL-1RAs, interleukin-1 receptor antagonists; IL-1 BP, interleukin-1 binding protein; IL-1Rs, interleukin-1 receptors; IL-1BP, interleukin-1 binding protein; IL-2Rs, interleukin-2 receptors; IFN- α , interferon-alpha; MIF-1, macrophage inflammatory protein-1; NI, normal; SA, serum amyloid A; TNF- α , tumor necrosis factor- α ; TNF- α BP, tumor necrosis

factor- α binding factor.

D-dimer was measured in 17/68 (25%) with COVID-19 nephropathy and it was elevated in 13/68 (20.5%) patients with an average mean of 5357.3 ± 7563.3 ng/ml. Serum creatinine was measured in 51/68 (75%) patients with COVID-19 nephropathy. The elevated SCr in these patients was assessed 2.44 ± 1.28 mg/dl. eGFR was measured in 27/68 (39.7%) patients, 2 of them had anuria; the average eGFR level was 45.97 ± 15.12 ml/min/1.73m². Proteinuria (2.34 ± 2.92 gr/24 hr) was found in 4/68 (5.8%) patients, urinary protein to creatinine ratio consisted of 4.89 ± 3.87 g/g. Anemia was observed in 10/68 (14.7%) patients with an average mean of 9.48 ± 1.8 g/dl; thrombocytopenia ($102400 \pm 40636.2/\mu\text{l}$) and elevated fibrinogen (682.3 ± 168 mg/dl) were diagnosed in 7/68 (10.2%) patients with COVID-19 nephropathy. Hyponatremia was found in the only patient, hypocalcemia was revealed in 3/68 (4.4%) patients with an average mean of 6.76 ± 1.69 mg/dl. Prolonged prothrombin time (PT) and partial thromboplastin time (PTT) were seen in 2/68 (2.9%) patients. Hypoxemia was presented in 20/68 (29.41%) patients but its quantitative amount ($88.56 \pm 12.56\%$) was mentioned in 14/68 (20.6%) patients with COVID-19 nephropathy. There was no statistically significant correlation between lymphocytopenia and SCr ($R^2=0.063$; $p=0.33$) (Fig. 2).

The effect size of standardized mean difference of elevated IL-6 on the standardized mean difference of decreased eGFR in COVID-19 nephropathy was assessed 0.656 (medium effect size).

Viral testing in this research.

Positive COVID-19 testing of nasal, oropharyngeal, sputum, bronchoalveolar lavage fluid (BALF), blood, dialysate, peritoneal fluid and tissue samples of patients infected with SARS-CoV-2 in baseline time include 33/68 (48.5%) samples. The exact distribution of the tested sites is presented in Fig. 3.

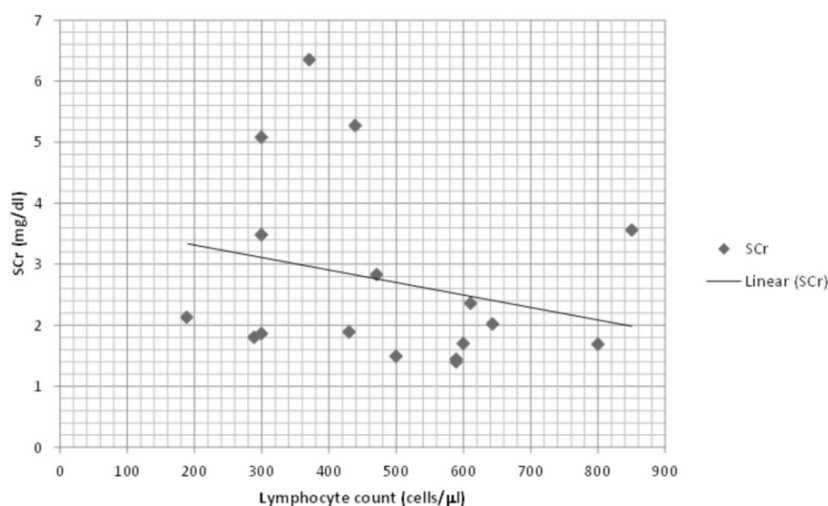


Fig. 2. Distributional diagram of the correlation between lymphocytopenia and serum creatinine in patients with COVID-19 nephropathy. Abbreviation: SCr, serum creatinine.

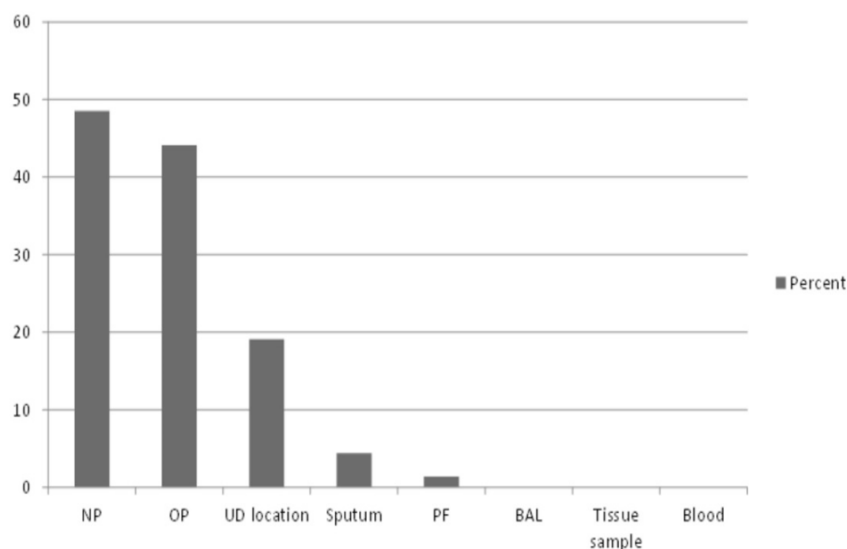


Fig. 3. Distributional diagram of patients with positive COVID-19 tests from different sites. Abbreviation: NP, nasopharyngeal swab, OP, oropharyngeal swab, PF, peritoneal fluid, UD location, undetermined location.

Pathology. A kidney biopsy with characteristics in favor of collapsing glomerulopathy was performed in 3/68 (4.4%) patients with COVID-19 nephropathy. Apolipoprotein L1 (APOL1) genotyping on the biopsy material in one patient was found to be homozygous for the G1 risk allele. Other patients had APOL1 G0G2 in histologic kidney specimens (Supplementary Table 6).

Imaging. There were an abnormal chest x-ray (CXR) in 28/68 (41.1%) patients with COVID-19 nephropathy. Bilateral lung infiltration was seen in 19/68 (27.9%) patients and the only patients had unilateral lung infiltration. Unilateral pleural effusion was observed in 3/68 (4.4%) patients and bilateral pleural effusion in 2/68 (2.9%) patients. Chest CT scan was performed in 19/68 (27.9%) cases. These lesions in the lung include multiple or patchy opacities. Bilateral lung opacities, ground-glass opacities, air bronchogram, nodular opacities as focal, diffuse or multiple were seen in the chest CT scan. Abnormal transthoracic echocardiography (TTE) was seen in 4/68 (5.8%) patients with COVID-19 nephropathy. Renal ultrasound was performed in 2/68 (2.9%) patients (Supplementary Table 7).

Treatment. Therapeutic options included ACE inhibitors, replication inhibitors (Remdesivir), protease inhibitors (lopinavir/ritonavir), heterocyclic antivirals

(chloroquine), nanodelivery drug systems, biological therapeutics and herbal medications (Fig. 4).

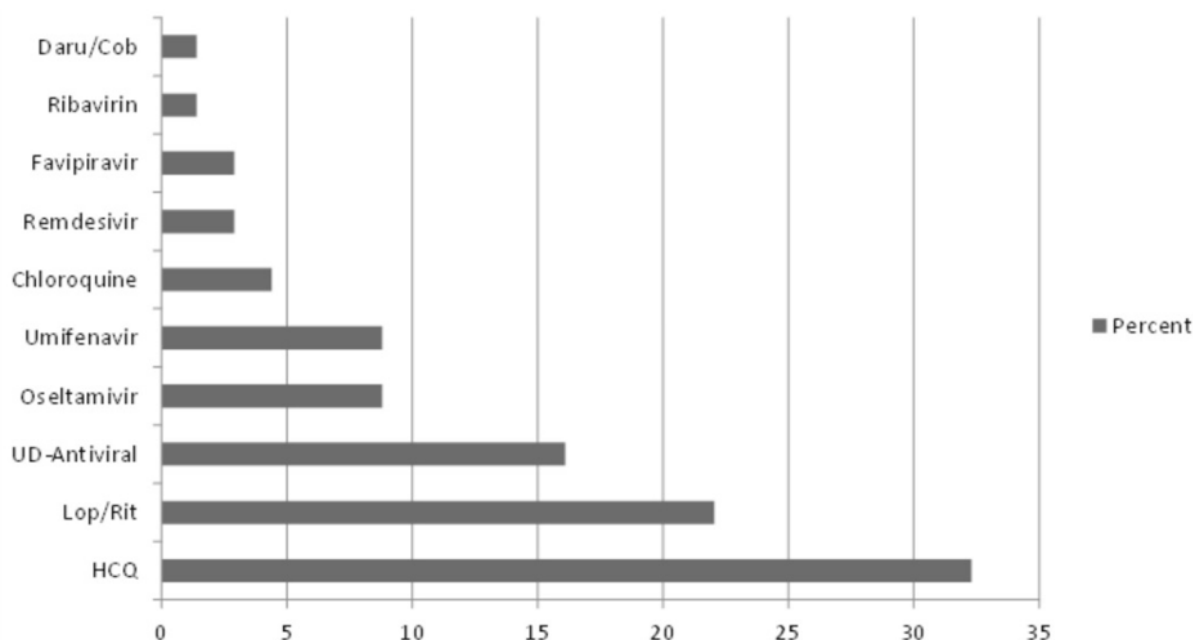


Fig. 4. Diagrammal distribution of different antiviral therapy in patients of COVID-19 nephropathy. Abbreviations: Daru/Cob, darunavir-cobicistat; HCQ, hydroxychloroquine; Lob/Rit, lopinavir/ritonavir; UD, undetermined.

Oxygen therapy was used in 32/68 (47%) patients with COVID-19 nephropathy. Antibacterial therapies included moxifloxacin, amoxiclav, ciprofloxacin, linezolid, ceftaroline, meropenem, ceftriaxone, vancomycin, azithromycin, ceftazidime, cefepime, cefuroxime, amoxicillin, piperacillin-tazobactam, anti-tuberculous agents, antimalarial agents in this research.

Antihypertensive agents included losartan, ramipril, atenolol, nifedipine, olmesartan, hydralazine, clonidine, amlodipine, valsartan, lisinopril. Diuretics included furosemide, amiloride, spironolactone, hydrochlorothiazide and other drugs such as immunosuppressive agents, corticosteroids and antiviral drugs included ribavirin (5/68, 7.3%), favipiravir (2/68, 2.9%), remdesivir (2/68, 2.9%), lopinavir-ritonavir (15/68, 22.05%), darunavir-cobicistat, arbidol or umifenavir (5/68, 7.3%), oseltamivir (8/68, 11.7%). Moreover, statins, anticoagulative agents, intravenous immunoglobulins, interferons (5/68, 7.3%), proton-pump inhibitors hypoglycemic agents, and vasopressors were used. Anti-cytokines included tocilizumab (9/68, 13.2%), alemtuzumab, rituximab, belatacept and eculizumab.

Other therapeutic modalities included plasma exchange, mechanical ventilation, personal protective equipment (PPE) and non-invasive ventilation such as continuous positive airway pressure (CPAP) and positive end-expiratory pressure (PEEP) were also used. The full list of treatment options is presented in (Supplementary Table 8).

Follow-up and outcomes in patients with COVID-19 nephropathy. There were negative COVID-19

testing in 15/68 (22%) patients with COVID-19 nephropathy during the follow-up period. Positive COVID-19 testing was found in 2/68 (2.9%) included patients. Ten of 68 patients with COVID-19 nephropathy stayed on HD during follow up and one of them remained on RRT but its type was not characterized. One of 68 patients stayed on dialysis treatment at the time of writing this report. ECMO continued in 1/68 (2.9%) patients with COVID-19 nephropathy during the follow-up period. There were a total of 36/68 (52.9%) kidney transplant recipients (KTRs) and 10/68 (14.7%) of them developed AKI due to acute rejection. Fourteen patients (20.5%) underwent different modalities of dialysis in-hospital course and stayed on dialysis during the follow-up. One patient underwent one session of HD during the follow-up period (Supplementary Table 9).

Primary end-points. There were ICU admission in 10/68 (14.7%) patients with COVID-19 nephropathy. There were a need for mechanical ventilation in 13/68 (19.1%) patients; 15/68 (22%) patients died during hospital course or post-discharge. There were AKI in 4/68 (5.8%) patients with COVID-19 nephropathy and AKD found in 14/68 (20.5%) patients with COVID-19 nephropathy during the follow-up. The median and interquartile range of SCr during the follow-up period was assessed at 1.74 mg/dl (Q3-Q1=2.73-1.55). The effect size of COVID-19 on AKI and AKD was assessed 0 and 0.003 using Cohen's-d test.

The mean difference of AKI at baseline and follow-up time was assessed -1.34 with a 95% confidence interval (CI) of -6.1089 to 6.108. Comparison of two effect sizes using the mean difference was calculated

0.464 with 95% CI of -5.47 to -0.232. The mean average of SCr in AKD at baseline time was assessed 3.22 ± 3.81 mg/dl with 95% CI of 1.0202-5.4198 and the mean average of SCr in AKD at follow-up was assessed 3.155 ± 3.33 mg/dl with 95% CI of -2.7099; 2.8499.

The mean difference of AKD at baseline and follow-up time was assessed at 1.48 with a 95% CI of -457 to 3.016. Comparison of two effect sizes (mean difference of Scr changes vs. mean difference of time) using the mean difference was calculated at 0.019 with a

95% CI of 1.23 to 5.07. Relative risk and odds ratio of AKD in COVID-19 nephropathy were assessed at 0.57 and 0.4, respectively ($p = 0.422$). Upper and lower CI included 0.04 and 3.9 in this research. By following per under with Cohen's "Rules of Thumb", the effect size of AKD was assessed 0.4 (not effect). Correlation between SCr changes and time of emergent AKI, AKD and CKD was assessed with R^2 of 0.0003 and $p = 0.94$ (Fig. 5).

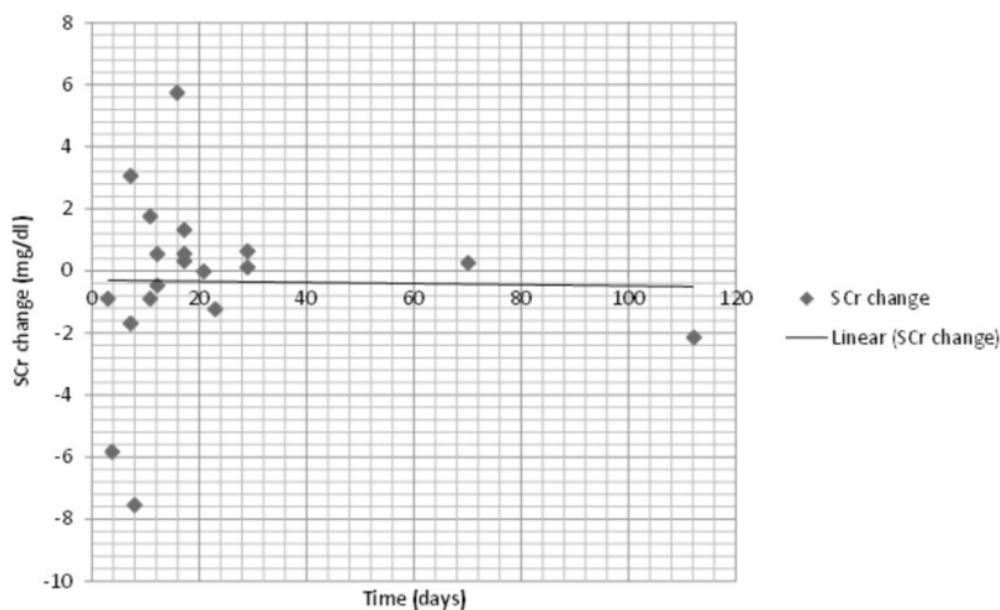


Fig. 5. Correlation between serum creatinine change and time of emergent acute kidney injury, acute kidney disease in COVID-19 nephropathy. Abbreviation: SCr, serum creatinine.

Secondary end-points. Decreased eGFR was found in 8/68 (11.7%) patients with an average mean of 42.22 ± 17.27 ml/min/1.73m² in COVID-19 nephropathy during follow-up; 37.5% of the patients were in CKD category G3b, 25% in CKD G 2 and G IV, 12.5% in CKD G3a in this research. The effect size of COVID-19 on declined eGFR using Cohen's-d test was assessed 0.157 (trivial) and comparison between decreased eGFR of baseline time and follow-up time using paired t-test was assessed 0.36 (not significant). Proteinuria in different tests was observed in 5/68 (7.35%) patients and only one patient had UTI during follow-up.

Discussion. Coronavirus belongs to a big family of viruses that cause a wide range of diseases mainly related to the respiratory system and infection may vary from the common cold to more severe respiratory diseases. This virus may cause infection in other systems such as the kidney, heart, brain, and even cause multiorgan failure and culminate in death. Several factors can differentiate between viral and bacterial infections. In patients with lower respiratory tract infections, PCT can serve as a helpful adjunct for guiding antibiotic therapy and resolving diagnostic uncertainty [4]. PCT is a marker for bacterial infections induced by bacteriotoxin but suppressed by interferon. In this research, it was measured in 9/68 (13.2%) patients and it was elevated in 7.3% cases.

The pathogenesis of SARS is unknown but some reports believe that cytokine storm syndrome or cytokine release syndrome involves its pathogenesis. These proinflammatory cytokines and chemokines include IL-6, TNF- α , IL-1, IL-12, IL-8, interferon-gamma. In COVID-19 nephropathy, cytokines such as IL-2, IL-7, IL-6, IL-10, interferon-gamma inducible protein 10 (IP10), monocyte chemoattractant protein (MCP1), macrophage inflammatory protein 1A and TNF- α are increased highly in peripheral blood. Some are in the belief that proinflammatory cytokines increase in proportion to disease severity and IL-6 is an important key cytokine in this disease. Acute phase reactants in COVID-19 nephropathy need specific consideration. Classification of acute-phase reactants is dependent on the change in acute phase proteins (APPs) concentration. A 10-100-fold elevation is considered major; a 2-10 fold elevation is considered moderate, and; a less than 2 fold elevation is considered minor. The APPs that elevate in major APRs include CRP and serum amyloid (SA); the APPs that elevate in a moderate APR include α 1 acid glycoprotein (AGP); and the APPs that elevate in a minor APR include fibrinogen, haptoglobin (Hp), and ceruloplasmin (Cp). Eight proteins are overexpressed in APRs denoted as 'positive' APPs, including Hp, SA, fibrinogen, Cp, AGP, α 1 antitrypsin (AAT), lactoferrin (Lf)

and CRP. Similarly, there are several 'negative' APPs the expression levels of which are reduced, including albumin, transferrin and transthyretin. The APP is elicited by cytokines, including those functioning as positive and negative growth factors and cytokines with pro-inflammatory or anti-inflammatory activity. Positive or negative growth factor cytokines involved include Interleukin (IL) 2; IL3; IL4; IL7; IL10; IL11; IL12; and granulocyte-macrophage colony-stimulating factor. Proinflammatory cytokines involved include TNF α / β ; IL1 α / β ; IL6; IFN- α / γ ; IL8; and macrophage inhibitory protein1. Cytokines involved in the anti-inflammatory response include: IL1 receptor antagonists; soluble IL1 receptors; IL1 binding protein; and TNF α binding protein. Moreover, ESR and ferritin increase in these patients. Covid-19 with hyperinflammatory pulmonary symptoms is associated with a cytokine storm involving interleukins and chemokine dysregulation. Of important cytokine is interleukin-6 [49]. One of the achievements of this research is the effect of elevated IL-6 on decreased eGFR and this effect on kidney failure can be substantial. About to with concerning relation to this result, tocilizumab is recommended in severely infected cases with elevated IL-6 in serum. In our research, tocilizumab has been used in 13.2% (9/68) of patients and two of sixty-eight patients (2/68, 2.9%) were expired. As such we know ceruloplasmin is one of the positive APRs, and associated cytokines include TNF- α , IL-1 β and IFN-1. Other points in this research are the usage of interferons that were used in six of sixty-eight patients (6/68, 8.8%) and response to it in 7.3% cases (5/68). Angiotensin-converting enzyme-2 (ACE2) is the acellular receptor for SARS-CoV and SARS-CoV-2. ACE2 shares some homology with ACE but is not inhibited by angiotensin-converting enzyme inhibitors (ACEIs). ACE2 is expressed in the lung, heart, kidney, and intestine as SARS-CoV-1, it may be hypothesized that chloroquine also interferes with ACE2 receptor glycosylation thus preventing SARS-CoV-2 binding to target cells. Different therapeutic modalities have been used in COVID-19 nephropathy so far. A recent case report described the beneficial effect of thalidomide (100 mg daily) plus low-dose glucocorticoids [50]. Previously, Amirshahrokhi in an experimental study in mice demonstrated the effect of thalidomide in ameliorating the histological and biochemical lung alterations induced by paraquat (PQ). Thalidomide decreased the production of inflammatory, and fibrogenic cytokine TNF- α ,

IL-1 β , IL-6, and transforming growth factor-beta1 (TGF- β 1). Moreover, myeloperoxidase (MPO) activity, nitric oxide (NO) and hydroxyproline content in lung tissue was declined [51].

Our study revealed the most common symptoms include the history of fever (80.8%) and cough (50%) and the most common laboratory findings include elevated CRP (50%) and lymphocytopenia (45.5%) that were in agreement with the previously published studies [52, 53]. In our study there was male predominance to female gender (73.5% vs. 26.4%) that is in disagreement with the study by Shang et al with female predominance versus (vs) male group (53% vs. 47%) [5].

Conclusion. In our research, COVID-19 had a trivial (small) effect on eGFR declining. Future studies are needed to evaluate the clinical findings and impact of COVID-19 on kidney outcomes.

Abbreviations. ACR, albumin-to-creatinine ratio; AHA/ACC, American Heart Association/American College of Cardiology; ANC, absolute neutrophil count; BALF, bronchoalveolar lavage fluid; CKD-EPI, chronic kidney disease-epidemiology collaboration; CrCl, creatinine clearance; KRT (kidney replacement therapy); KF (kidney failure); MDRD, modification of diet in renal disease; nCOVID-19 (novel coronavirus disease-2019); RNA (ribonucleic acid); PER, protein excretion rate; qRT-PCR, quantitative real-time reverse transcriptase-polymerase chain reaction; ITU, intensive therapy unit; WHO, World Health Organization.

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