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REVIEW

COVID-19 in patients with and without acute kidney injury

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ABSTRACT

BACKGROUND AND OBJECTIVE: SARS-CoV-2 as the newest member of Beta-Coronaviruses can cause a complicated disease called COVID-19. This virus is able to penetrate a broad range of human cells, such as liver, heart, and kidney cells via ACE2-associated endocytosis. Heart involvement can result in kidney injuries; it is now testified that kidney congestion occurs following the cardio-renal syndrome. Acute Kidney Injury is one of the most critical damages to the kidney in a wide range of COVID-19-caused kidney injuries (which includes proteinuria, hematuria, etc.). Examination of AKI risk factors in COVID-19 patients can assist physicians to prevent its incidence. The final aim of this systematic review was to collate the condition and risk factors of AKI and non-AKI COVID-19 patients and to investigate AKI incidence in high-risk patients.

METHOD: A complete and comprehensive survey was performed by reviewing original articles and case reports indexed in various databases such as PubMed/Medline, Embase, and WoS to find appropriate articles. The eligible articles then were selected by two authors and entered into the evaluation process. This systematic review conforms PRISMA statement.

RESULTS: After searching for potentially relevant articles, 14 out of the initial 463 articles from 6 countries were selected and evaluated. All of eligible articles have investigated the rate of AKI incidence and its physio-pathological consequences in COVID-19 patients in all conditions (not only patients in critical condition). First, the initial differences between AKI and non-AKI patients were compared. As an instance, our study revealed that mean of White Blood cells (WBC) was much higher in AKI patients which can be responsible for the severe conditions. Then, other variations like differences in laboratory and imaging findings were compared between these two groups. Our outcomes demonstrated that the presence of diabetes mellitus (DM), hypertension (HTN), and male sex can be three significant risk factors in AKI incidence in COVID-19 patients. Fatality rate and treatment methods were also compared among these two groups.

CONCLUSION: As one of kidney damages, AKI can worsen COVID-19 patients' status by causing conditions such as acidosis. Our study shows the common symptoms in AKI COVID-19 patients were fever, cough, and malaise. The results of our study can help physicians to arrange COVID-19 with AKI patients' treatment strategy precisely *(Tab. 8, Fig. 1, Ref. 48)*. Text in PDF *www.elis.sk*

KEY WORDS: COVID-19, SARS-CoV-2, acute kidney injury, cardio-renal syndrome, kidney involvement.

Abbreviations: ACEI/ARB – Angiotensin-converting inhibitor/angiotensin receptor blocker, AKI – Acute kidney injury, ALT – Alanine aminotransferase, ARDS – Acute respiratory distress syndrome, ASA – Aspirin, AST – Aspartate aminotransferase, BUN – Blood urea nitrogen, CHF – Congestive heart failure, CKD – Chronic kidney disease, COPD – Chronic obstructive pulmonary disease, CRP – C-reactive protein, CRRT – Continuous Renal Replacement Therapy, CVD – Cardiovascular disease, DM – Diabetes mellitus, ECMO – Extracorporeal membrane oxygenation, HTN – Hypertension, IVIG – Intravenous immune globulin, LDH – Lactate dehydrogenase, NIPPV – Nasal intermittent positive pressure ventilation, RRT – Renal replacement therapy, SO_2 – Saturation oxygen, WBC – White blood cell

Introduction

Novel corona virus 2019 (2019-nCoV), mostly known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is the newest member of the coronavirus family and the causative agent of COVID-19. SARS-CoV-2 as an RNA virus and a member of the beta-coronaviruses was first identified in December 2019 in Wuhan City, China. Since then, the virus has spread rapidly, forcing the World Health Organization (WHO) to announce a global

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Tab. 1. Characteristics of the included studies.

First author	Country	Time published	Type of study	No. of non-AKI patients with COVID-19	Mean age	Male/Female	No. of AKI patients with COVID-19	Mean age	Male/Female
Bowe B (34)	USA	2021	Retrospective Observational Cohort	3561	69	3300/261	1655	72	1608/47
Chan L (37)	USA	2021	Retrospective Observational Cohort	2158	63	1188/970	1835	71	1101/734
Cheng Y (38)	China	2020	retrospective cohort	1293	63	644/649	99	66	67/32
Fisher M (39)	USA	220	retrospective observational cohort	1442	60	685/757	1903	67	1091/812
Fominskiy EV (40)	Italy	2020	Retrospective Observational Cohort	24	54.5	21/3	72	63	59/13
Naar L (41)	USA	2020	Retrospective Observational Cohort	62	55	31/24	144	61	103/48
Gameiro J (42)	Portugal	2020	Retrospective cohort	85	67	41/44	106	75	59/47
Hamilton P (43)	UK	2020	Retrospective cohort	822	71	438/384	210	71.5	131/79
Hansrivijit P (44)	USA	2021	Retrospective Observational Cohort	`168	60.8	86/82	115	68.8	73/42
Hirsch JS (22)	USA	2020	Retrospective Observational Cohort	3456	61	2047/1409	1993	69	1270/723
Kolhe NV (45)	UK	2020	retrospective cohort	857	71.1	478/379	304	74.9	179/125
Li Q (46)	China	2020	retrospective cohort	59	68	37/22	48	73	32/16
Lim JH (47)	Korea	2020	Retrospective Observational Cohort	130	67	66/64	30	75	20/10
Paek JH (48)	Korea	2020	retrospective cohort	676	57	194/482	28	74.3	16/12

pandemic in March 2020 (1). This virus can cause infection with widespread symptoms such as fever, chest pain, shortness of breath, cough, and lethargy (2). Generally, about five percent of COVID-19 patients develop an acute and critical condition. The acute state of these patients causes various injuries such as internal organs failure (heart, kidneys, and liver) along with Acute Respiratory Distress Syndrome (ARDS) (3). However, kidney involvement may be observed in other patients, even in mild conditions. COVID-19 can trigger a broad range of non-acute injuries such as proteinuria. It may also cause serious injuries such as Acute Kidney Injury (AKI). For instance, the consequences of one study demonstrated that more than 40% of people with COVID-19 admitted to the hospital exhibited some degree of kidney damages, such as proteinuria (4). Besides, in Europe and the USA, 20 to 40 percent of patients in severe conditions admitted to the ICU had experienced AKI (3, 5). The primary cause for hospitalization of COVID-19 patients in the intensive care unit (ICU) is hypoxia (which required mechanical ventilation) or dangerous hypotension (demanding vasopressor support) (3); both of these factors can cause kidney damage or failure.

SARS-CoV-2 generally penetrates its host cells utilizing the angiotensin converting enzyme-2 (ACE2) receptor on their membrane surface. Therefore, ACE2 can be found on the cytoplasmic membrane of many cells and tissues, like lungs, heart, kidneys, and testes (6). Otherwise, renal involvement appears to be a multifactorial injury caused by cardiovascular disorders and other factors such as sepsis and nephrotoxicity (7), but it should be noted that SARS-CoV-2 is able to invade kidney tissue after entering the bloodstream and cause kidney involvement. In general, cardiorenal syndrome, precisely right ventricular dysfunction, can cause kidney congestion and AKI in patients (3). Damages to endothelial cells induced by SARS-CoV-2 infection are also probably the most crucial reason for proteinuria. However, other factors, such as the over-activated immune system and the occurrence of cytokine storms, can also result in extensive harm to kidneys. In addition, micro-emboli, micro-thrombi, and macrophage activation syndrome may also cause AKI in COVID-19 patients (3, 8-10).

AKI is a significant injury because it can make the patient's condition worse and is associated with elevated fatality of SARS-CoV-2 infection. Various factors such as age, ethnicity, and underlying diseases can influence the advancement of AKI in COVID-19 patients (11). Therefore, it is hypothesized that AKI can be used as a predictor of fatality (12). Evaluation of the condition of COVID-19 patients with and without AKI and comparison of the results can help physicians identify the causes of kidney damages or failure in patients with SARS-CoV-2 and thus can be effective in providing appropriate management and strategies for patients' treatment. In the following, this systematic review evaluates the symptoms, injuries, and prognosis of SARS-CoV-2 infected people with and without AKI due to the importance of this issue.

Survey method

This recent study conforms to the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) statement (13).

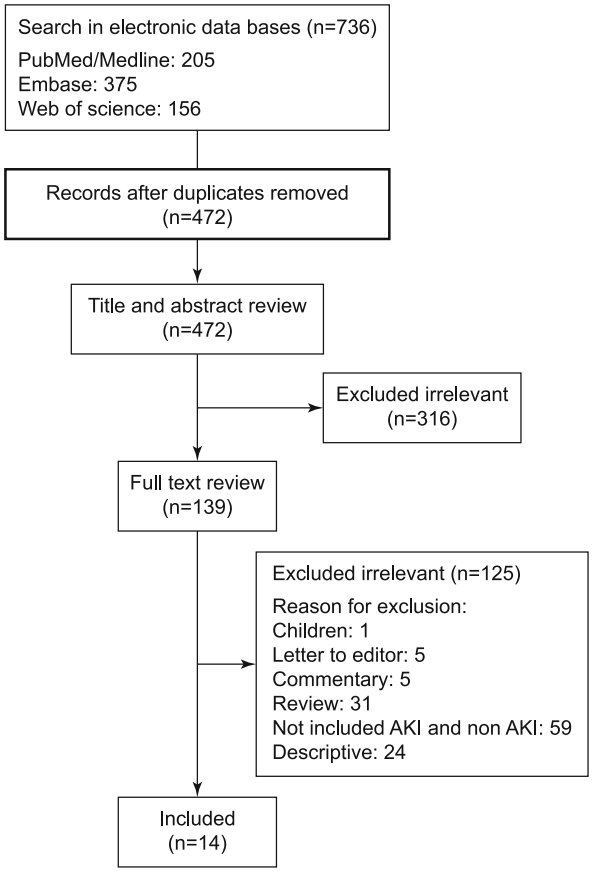

Fig. 1. Flow chart of study selection for inclusion in the systematic review.

Tab. 2. Summary of the included studies' data.

Variables		Number of studies	n/N*	%
AKI in admission		6	1749/2534	69
AKI after admission		7	1223/4369	27.9
BMI < 30	AKI	5	1938/3775	51.3
	Non-AKI	5	2747/5325	51.5
BMI > =30	AKI	5	1925/5738	33.5
	Non-AKI	5	3108/8651	35.9
BMI>35	AKI	2	518/3896	13.3
	Non-AKI	2	564/4898	11.5
DM	AKI	14	3441/8542	40.2
	Non-AKI	14	4324/14625	29.5
HTN	AKI	10	3127/4290	72.8
	Non-AKI	11	6088/11672	52.1
CVD	AKI	9	1009/4533	22.2
	Non-AKI	9	1548/9162	16.9
Arrhythmia	AKI	3	185/2022	91.6
	Non-AKI	1	19/168	11.3
CHF	AKI	7	438/4699	9.3
	Non-AKI	7	694/9033	7.7
History of hyperlipidemia	AKI	1	56/115	48.7
	Non-AKI	1	65/168	38.7
COPD/Asthma	AKI	10	813/4728	17.2
	Non-AKI	10	1589/9265	17.1
Asthma	AKI	3	227/3900	5.8
	Non-AKI	2	318/3480	9.1
History of CKD	AKI	7	215/888	24.2
	Non-AKI	6	507/4623	11.0
Tumor history	AKI	8	494/4469	11.1
	Non-AKI	7	955/10204	9.4
Smoking	AKI	4	839/1941	43.2
	Non-AKI	4	1679/3799	44.2

n – number of patients with any variables; N – the total number of studied patients

Literature search

Between 2019 and 2020, we performed a systematic search in three main electronic databases (PubMed/Medline, Embase, and Web of Science (WoS)) using specific keywords. The keywords included COVID-19, severe acute respiratory syndrome coronavirus 2, novel coronavirus, SARS-CoV-2, nCoV disease, SARS-2, COVID-19, 2019-nCoV, coronavirus disease-19, coronavirus disease 2019, and 2019 novel coronavirus in combination with acute kidney injury or AKI. Furthermore, we searched the bibliographies of related literature to find suitable studies.

Study selection and data extraction

All prospective or retrospective descriptive studies performed in confirmed patients with COVID-19 who were evaluated for AKI were involved in this study. In addition, information of patients with AKI and non-AKI has been extracted from studies and compared. Abstract, guidelines, commentary, and studies and reports that did not go through a "peer-review" phase were excluded.

The theoretically related articles were reviewed for eligibility in two phases. In the first stage, two authors separately assessed the titles and abstracts of relevant papers. The full text of those abstracts that meet the inclusion criteria was collected and independently evaluated by the same experts in the second level of evaluation. Reviewer authors resolved any disagreements and methodological uncertainties by discussion. Next, two authors collected data from all included studies separately and generated a data extraction form on an Excel sheet. The extracted data included the country where the study was conducted, the number of patients with confirmed COVID-19, the number of patients with and without AKI, clinical signs, laboratory findings, diagnostic tests, outcomes, and treatment. Finally, all steps of data extraction were reviewed and checked by one of the authors.

Quality assessment

The Joanna Briggs Institute (JBI) checklist was exploited to conduct the quality evaluation, and only high-quality studies were evaluated in the final review in this study.

Results

Figure 1 illustrates the process of the search strategy and the selection of the articles. After removing duplicates, an initial number of 463 potentially relevant publications were chosen, and then based on title and abstract examination, 449 of them were elimi-

Tab. 3. Stage of AKI in patients with COVID-19 base on the definition.

	Stages	Number of studies	n/N*	%
Stage of AKI base on the definition	S1	13	3695/8398	43.9
	S2	13	1457/8398	17.3
	S3	14	2355/8542	27.5

n – number of patients with any variables; N – the total number of studied patients

Tab. 4. Sign and Symptoms reported from the included studies .

Variables		Number of studies	n/N*	%
Chest pain	AKI	3	32/307	10.4
	Non-AKI	3	43/289	14.9
Dyspenea	AKI	4	227/337	67.4
	Non-AKI	4	280/419	66.8
Sore throat	AKI	1	20/144	13.9
	Non-AKI	1	11/62	17.7
Cough	AKI	4	225/337	66.8
	Non-AKI	4	263/471	55.8
Fever	AKI	4	232/337	68.8
	Non-AKI	4	295/419	70.4
Malaise	AKI	1	30/48	62.5
	Non-AKI	1	38/59	64.4
Fatigue	AKI	3	101/222	45.5
	Non-AKI	3	123/251	49.0
Myalgia	AKI	2	69/174	39.7
	Non-AKI	2	61/192	31.8
Shivering	AKI	2	21/78	26.9
	Non-AKI	2	71/189	37.6
Nausea and vomiting	AKI	3	62/289	21.5
	Non-AKI	3	75/360	20.8
Diarrhea	AKI	3	46/222	20.7
	Non-AKI	3	37/251	14.7
Headache	AKI	3	26/307	8.5
	Non-AKI	3	34/289	11.8
Loss of taste/smell	AKI	1	11/144	7.6
	Non-AKI	1	8/62	12.9
SO2 >93	AKI	1	38/115	33.0
	Non-AKI	1	67/168	39.9
SO2 <93	AKI	1	77/115	67.0
	Non-AKI	1	101/168	60.1
Pulmonary rales	AKI	1	25/115	21.7
	Non-AKI	1	32/168	19.0

n – number of patients with any variables; N – the total number of studied patients

Tab. 5. Laboratory findings in the included studies.

Variables		Number of studies	n/N*	%
Leukopenia	AKI	1	19/115	16.5
	Non-AKI	1	37/168	22.0
Leukocytosis	AKI	1	54/115	47.0
	Non-AKI	1	26/168	15.5
Lymphopenia	AKI	2	107/214	50.0
	Non-AKI	2	722/1461	49.4
Thrombocytosis	AKI	1	55/115	47.8
	Non-AKI	1	54/168	32.1
Anemia	AKI	2	90/205	43.9
	Non-AKI	2	585/1378	42.5
High BUN	AKI	3	139/3634	3.8
	Non-AKI	2	29/5719	0.5
High Troponin	AKI	1	60/115	52.2
	Non-AKI	1	31/168	18.5
High AST	AKI	1	48/1835	2.6
	Non-AKI	1	39/2158	1.8
High ALT	AKI	1	24/115	20.9
	Non-AKI	1	9/168	5.4
High CRP	AKI	2	160/214	74.8
	Non-AKI	2	979/1461	67.0
High Lactate	AKI	1	58/115	50.4
	Non-AKI	1	50/168	29.8
High Procalcitonin	AKI	1	48/115	41.7
	Non-AKI	2	112/253	44.3
D-dimer<1000	AKI	1	71/115	61.7
	Non-AKI	1	64/168	38.1
D-dimer>5000	AKI	1	90/99	90.9
	Non-AKI	1	849/1293	65.7
High LDH	AKI	2	143/214	66.8
	Non-AKI	2	896/1461	61.3
High Ferritin	AKI	1	62/115	53.9
	Non-AKI	1	47/168	28.0
Hyponatremia	AKI	2	277/1863	14.9
	Non-AKI	2	278/2834	9.8
Proteinuria	AKI	5	1679/4000	42.0
	Non-AKI	4	1282/4952	25.9
Hematuria	AKI	3	428/2049	20.9
	Non-AKI	3	474/3510	13.5
Leukocyturia	AKI	2	289/1950	14.8
	Non-AKI	2	134/2217	6.0
Acidosis	AKI	2	71/221	32.1
	Non-AKI	2	25/253	9.9
Acidosis	AKI	2	139/250	55.6
	Non-AKI	1	17/85	20.0

n – number of patients with any variables; N – the total number of studied patients

nated. Ultimately, 14 articles reported from 6 countries with a total number of 23167 patients (15065 males and 8270 females) with confirmed COVID-19 were selected for evaluation. There were 14625 non-AKI patients (9256 men and 5530 women), with an average age of 63.4 years and 8542 AKI patients (5809 males, 2740 females) with mean lifespan of 70.1 years. The KDIGO clinical practice guideline was utilized in all chosen articles to define AKI in all COVID-19 patients. It is worth to note that all COVID-19 patients (not only COVID-19 patients in critical condition) were investigated in this systematic review. Table 1 presents the features of the studies that were included.

Primary differences of AKI and non-AKI COVID-19 patients

AKI in admission was reported in 1749 out of 2534 studied patients (69 %), while 1223 out of 4369 patients (27.9) exhibited AKI after admission. The average length of hospitalization was 18 days for AKI patients and 13 days for non-AKI ones. The mean WBC count was 8025/μL in the AKI patients and 6550/μL in the non-AKI patients. At the time of admission, the mean creatinine level was 1.98 mg/dL and 1.01 mg/dL in patients with and without AKI, respectively. The albumin level in both groups was approximately the same and equal to 3.23 g/dL and 3.52 g/dL, respectively. The mean platelet count in the AKI group was 191333/μL and in the non-AKI group 217000/μL.

In terms of BMI, no discernible variation was observed in the patients with and without AKI. Most patients in both groups had a BMI below 30. Evaluation of important comorbidities in both groups was done. The prevalence of diabetes was 40.1 % in the AKI group, and 29.5 % in the non-AKI group. Hypertension was also higher in the AKI group (72.8 %) than in the non-AKI group (52.1 %). Nine studies examined cardiovascular disease rates in these patients, which according to 22.2 % and 16.9 % of patients in AKI and non-AKI groups had it, respectively. According to one study, there was a history of hyperlipidemia in 48.7 % of AKI patients and 38.7 % of non-AKI patients. History of CKD was reported in 24.2 % and 11 % of patients with and without AKI, respectively, which demonstrates CDK is an important risk factor for AKI incidence in COVID-19 patients. Four studies examined patients' smoking status, and based on their results, this rate was approximately the same in both groups and was about 43 %. Table 2 summarizes more comprehensive information about the patients studied in both groups.

Thirteen studies reported the stage of AKI, according to which 43.9 % of patients (3695/8398) had stage I (Tab. 3).

Comparison of symptoms in AKI and non-AKI patients

As it can be observed in Table 4, according to the outcomes of studies evaluating the signs and symptoms in patients, fever, cough, dyspnea, and malaise were among the most prevalent symptoms in both groups of patients. 68.8 % of patients with AKI and 70.4 % of non-AKI patients had a fever. Dyspnea was almost the same in both groups (67.4 % in AKI vs 66.8 % in non-AKI patients). The same trend was observed for malaise (62.5 % in AKI vs 64.4 % in non-AKI patients). Based on the results of 4 studies, the incidence of cough was 66.8 % in patients with AKI and 55.8 % in patients without AKI. Headache was among the most minor reported symptoms in patients with AKI (8.5 %). Similarly, in the non-AKI patients, headache was reported in only 11.8 % of patients. One study evaluated blood oxygen saturation levels (SO_2) based on its results, 33 % (38/115) of patients with AKI showed $SO_2 > 93$, and 67 % (77/115) had $SO_2 < 93$. These values were reported to be 39.9 % and 60.1 % in patients without AKI, respectively.

Tab. 6. Imaging findings in the included studies.

Variables		Number of studies	n/N*	%
Pleural effusion	AKI	1	13/115	11.3
	Non-AKI	1	11/168	6.5
Consolidation	AKI	2	64/78	82.1
	Non-AKI	2	132/189	69.8
Chest infiltration	AKI	1	24/28	85.7
	Non-AKI	1	335/676	49.6
Opacity/Infiltration	AKI	1	87/115	75.7
	Non-AKI	1	122/168	72.6
Ground-glass opacity	AKI	1	87/115	75.7
	Non-AKI	1	122/168	72.6
Pulmonary congestion	AKI	1	15/115	13.0
	Non-AKI	1	15/168	8.9

n –number of patients with any variables; N – the total number of studied patients

Tab. 7. Prognosis and outcome in the included studies.

Variables		Number of studies	n/N*	%
ICU admission	AKI	10	2386/6303	37.9
	Non-AKI	9	1402/11062	12.7
Ventilation	AKI	11	3326/8296	40.1
	Non-AKI	11	760/14577	5.2
Septic shock	AKI	2	43/78	55.1
	Non-AKI	1	9/59	15.3
ARDS	AKI	3	70/184	38.0
	Non-AKI	2	24/144	16.7
Vasopressor use	AKI	6	2107/4196	50.2
	Non-AKI	4	347/3678	9.4
Death	AKI	12	2774/6609	42.0
	Non-AKI	12	1268/13221	9.6
Recovered	AKI	6	3482/5776	60.3
	Non-AKI	6	8205/9452	86.8

n –number of patients with any variables; N – the total number of studied patients

Laboratory findings

Information on laboratory findings in COVID-19 patients with and without AKI extracted from the reviewed studies is presented in Table 5. The D-dimer > 5000 was reported in 90.9 % of AKI patients and 65.7 % of non-AKI ones. The other most common findings in AKI patients were high CRP, high LDH, and elevated ferritin reported from 74.8 % (160/214), 66.8 % (143/214), and 53.9 % (62/115) of these patients, respectively. High CRP and high LDH were also the most reported laboratory findings in non-AKI patients (67 % and 61.3 %, respectively).

Comparison of imaging findings and prognosis in AKI and non-AKI patients

Several studies have reported imaging findings in these patients; based on their results, ground-glass opacity presentation was reported in 75.7 % and 72.6 % of patients with and without AKI, respectively. Chest infiltration (85.7 %) and consolidation (82.1 %) were among the most common imaging findings in the AKI group. These findings were reported in 49.6 % and 69.8 % percent of patients in the non-AKI group, respectively. More information about imaging findings is summarized in Table 6.

In terms of prognosis (Tab. 7), ICU hospitalization and the demand for a ventilator were reported in 37.9 % and 40.1 % of AKI patients, respectively. These values were much lower in non-AKI patients (12.7 % and 5.2 %, respectively).

Vasopressor administration was more common among AKI, which was applied in 50.2 % (2107/4196) of them. Usage of this agent was reported in 9.4 % (347/3678) of non-AKI patients. The incidence of septic shock and ARDS in AKI group was higher than non-AKI ills and was 55.1 % vs 15.3 % and 38 % vs 16 %, respectively.

Fatality rate and treatment methods in AKI and non-AKI patients

Twelve studies evaluated the death rate in these two groups of patients; based on their results, the mortality rate in patients with AKI was 42 %, and patients without AKI was 9.6 %. Six studies

Tab. 8. Treatment strategies used in the included studies.

Variables		Number of studies	n/N*	%
Nasal O_2	AKI	1	86/115	74.8
	Non-AKI	1	121/168	72.0
NIPPV	AKI	2	91/214	42.5
	Non-AKI	2	196/1461	13.4
Intubation	AKI	2	1237/2108	58.5
	Non-AKI	1	11/168	6.5
ECMO	AKI	4	74/2255	3.3
	Non-AKI	3	40/1520	2.6
CRRT	AKI	2	100/967	10.3
	Non-AKI	1	3/59	5.1
HCQ	AKI	3	126/249	50.6
	Non-AKI	3	317/929	34.1
Remdesivir	AKI	2	83/214	38.8
	Non-AKI	2	1174/1461	80.4
Ritonavir	AKI	1	21/28	75.0
	Non-AKI	1	243/676	35.9
Azitromycin	AKI	1	73/115	63.5
	Non-AKI	1	109/168	64.9
Tocilizumab	AKI	1	9/115	7.8
	Non-AKI	1	3/168	1.8
Convalescent plasma	AKI	1	20/115	17.4
	Non-AKI	1	16/168	9.5
IVIG	AKI	1	29/48	60.4
	Non-AKI	1	32/56	57.1
Steroid	AKI	4	157/368	42.7
	Non-AKI	4	658/1605	41.0
RRT	AKI	7	492/2786	17.7
Haemodialysis	AKI	3	13/658	2.0
A.S.A	AKI	2	338/1727	19.6
	Non-AKI	2	590/3585	16.5
ACE/ARB	AKI	6	1482/4367	33.9
	Non-AKI	6	2352/10074	23.3
β-Blocker	AKI	2	603/1727	34.9
	Non-AKI	2	957/3585	26.7
Steroid	AKI	2	98/171	57.3
	Non-AKI	2	949/1317	72.1
Diuretic	AKI	2	762/1754	43.4
	Non-AKI	2	1037/4854	21.4
Statin	AKI	1	14/72	19.4
	Non-AKI	1	1/24	4.2
Oral Diabetes Medications	AKI	1	29/99	29.3
	Non-AKI	1	252/1293	19.5

n – number of patients with any variables; N – the total number of studied patients

also reported the survival rate of these patients, which was 60.3 % and 86.8 % in AKI and non-AKI groups, respectively (Tab. 7).

The medications and treatment strategies administered in these patients are presented in Table 8.

Summarizing the results of studies that reported the treatment strategies used in these patients showed that intubation was performed for 58.5 % of patients with AKI. In comparison, this rate was only 6.5 % for patients without AKI. CRRT in patients with AKI and without AKI was 10.3 % (100/967) and 5.1 % (3/59), respectively. Ritonavir was the most common antiviral drug applied for AKI patients (75 %), while in the non-AKI patients, remdesivir was the most commonly used antiviral agent (80.4 %). The rate of hydroxychloroquine utilization was greater in AKI patients than in non-AKI ones (50.6 % vs 34.1 %). The use of azithromycin was almost the same in both groups of patients (63.5 % and 64.9 %). Information on other treatment strategies and drugs used in both groups of patients is entirely described in Table 8.

Discussion

Main findings

SARS-CoV-2 is commonly known as respiratory disease, but it has now been testified to be able to infect other tissues and organs (14). Currently, various publications have stated that SARS-CoV-2 can directly infect kidney cells due to the presence of ACE2 on the membrane of renal cells (15–18). Kidneys can also be affected indirectly by pathophysiological mechanisms (such as ARDS) caused by COVID-19. Non-acute damages (such as proteinuria or hematuria without renal failure) or acute injuries (such as AKI) are some instances of SARS-CoV-2 infection impacts on kidneys (3, 19). In previous studies, the incidence of AKI in COVID-19 patients was reported from 0.5 % to 80 % (in patients with severe conditions) (20, 21). For example, in one study, the incidence of AKI in 701 SARS-CoV-2 infected patients was only 5.1 % (4). Various factors can play a role in causing these differences, including the presence or absence of underlying diseases in patients. Logically, when the underlying disease rates in the study population enhances, the incidence of AKI also increases (22). In addition, other factors such as age and ethnicity of patients, variety in the definition of critical and severe words in different countries, differences in patient assessment methods, and variation in measuring and interpreting factors indicating kidney function and health status can effectively create these differences (23, 24). Simultaneous evaluation of COVID-19 patients with and without AKI is important because a strong association has been reported between AKI and extensive damage to the respiratory system (potentially leading to respiratory failure). In fact, the occurrence of AKI (before or during SARS-CoV-2 infection) can worsen the patient's condition and requirement of mechanical ventilation (22).

In this study, 463 potentially related articles were reviewed, and finally, 14 appropriate studies consisting of 23167 patients from 6 countries were selected for data extraction. The subjects were split into two main groups of COVID-19 patients with and without AKI, and their data were analyzed regardless of gender. Based on the reported articles, the results of this study indicated that the clinical signs, symptoms, laboratory findings, applied medications, and used strategies for treating patients with and without AKI differed significantly in several cases, while some of the factors were the same between the two groups. For instance, white blood cell counts (which may be counted as an indicator for high cytokines synthesis) were remarkably higher in AKI patients than in non-AKI patients (8025/μL in AKI vs 6550/ μL in non-AKI). Although our results demonstrated leukocytosis has occurred in COVID-19 patients with AKI in comparison to non-AKI COVID-19 patients, various articles have reported that complete blood count profile of SARS-CoV-2 individuals has been accom-

panied by leukopenia, lymphopenia in these patients; however they also report the possibility of leukocytosis and thrombocytosis in all COVID-19 patients (14, 25). The rate of high CRP was shown to be more common in AKI patients than in non-AKI patients according to our outcomes. Despite high CRP has been reported to be a surrogate of cytokine storm (26, 27) but it also may be an indicator for cytokine storm occurrence due to an elevation in its synthesis during infections and tissue damages. It has been proven that heart involvement can occur in COVID-19 due to the direct invasion of SARS-CoV-2. As a result, there is a possibility of the cardio-renal syndrome, which in turn can cause damage to the kidney (28, 29) and increases creatinine in the blood. Although no particular data was reported on cardio-renal syndrome or heart failure in AKI and non-AKI COVID-19 patients, but as stated, cardio-renal syndrome has been discussed to be an effective cause of AKI incidence. It should also be noted that the rate of cardiovascular diseases as important underlying diseases and risk factors was 22.2 % and 16.9 % in AKI and non-AKI COVID-19 patients, respectively. It is crucial since it has been proven that underlying diseases can lead to critical condition in COVID-19 patients, which can cause AKI or other harmful damages. As mentioned, the blood creatinine levels of COVID-19 patients with and without AKI were 1.98 mg/dL and 1.01 mg/dL, respectively. In their analysis, Jamie S. Hirsch et al (22) stated the most important risk factors for AKI in COVID-19 patients that can be severe indicators are extensive damage to the respiratory tract (followed by the demand for ventilator support) and the utilization of vasopressor (following high blood pressure). Other significant factors such as vitamin D deficiency, gender, age, BMI, and underlying disease (like diabetes) are reported to play a significant role in the severity of COVID-19 and, in consequence, AKI incidence (28, 30–33). However, the outcomes of our study demonstrated that BMI was not significantly different among COVID-19 patients with and without AKI. A notable point among COVID-19 patients with or without AKI was the gender of patients. Our studies revealed that AKI incidence in men with COVID-19 is significantly higher than in women with COVID-19. For instance, in one study, the number of male COVID-19 patients with AKI was 34 times higher than that of women (1608 vs 47) (34). In other studies, the number of COVID-19 male patients with AKI was always higher than female. Male gender may be a significant risk factor for COVID-19 patients with AKI.

One crucial point about the AKI incidence is the rate of its occurrence before and after admission and hospitalization of patients. The results of our study demonstrated that 69 % of COVID-19 patients had AKI during admission and 27.9 % exhibited AKI after being admitted. This consequence shows that drug administration, while patients were admitted, is not an important factor in AKI incidence. The outcomes of our review also determined that the two underlying diseases DM and HTN, are two major risk factors for AKI occurrence in COVID-19 patients; 40 % of patients in the AKI group and only 29.5 % of patients in the non-AKI group had DM. The HTN rate was 72.8 in AKI patients and 52.1 in non-AKI patients. Although the difference rate of HTN patients in the AKI and non-AKI groups was higher than DM, the results confirm that both HTN and DM factors are very influential in AKI incidence.

Our studies also demonstrated that COVID-19 patients in the AKI group in comparison to non-AKI patients had a higher rate of other underlying diseases such as CVD (22.2 % vs 16.9 %), CHF (9.3 % vs 7.7 %), history of hyperlipidemia (48.7 % vs 38.7 %), history of CKD (24.2 % vs 11.0 %), tumor history (11.1 % vs 9.4 %), respectively. These disorders were much higher in the AKI group. Arrhythmia with a rate of 91.6 % in patients in the AKI group and 11.3 % in non-AKI patients had the highest variance between these groups. However, the smoking rate and COPD/asthma incidence were not significantly different between the two groups, and even the asthma rate was higher in non-AKI patients than in AKI patients. Other variables with their percentage are available in Table 2. In terms of symptoms, our findings explicated that COVID-19 patients in the non-AKI group had a higher incidence rate of Chest pain, Sore throat, Fatigue, although the difference rate of these symptoms among the two groups was not more than 5 %. Shivering as a symptom of the disease in the non-AKI group was far more common than AKI-group individuals (37.9 % vs 26.9 %). We also comprehend that the cough was more common in AKI patients than non-AKI patients with prevalence of 66.8 % vs 55.8 %. However, there was no significant difference between the two groups of AKI and non-AKI patients regarding other symptoms. The incidence rate of other symptoms in the AKI and non-AKI groups can be observed in Table 4.

Our survey outcomes also exhibited that comparing the two groups of COVD-19 patients with or without AKI is associated with significant results in terms of laboratory findings. As an example, COVID-19 patients in the AKI group had higher rates of leukocytosis (47.0 % vs 15.5 %), high troponin (52.2 % vs 18.5 %), and high ALT (20.9 % vs 5.4 %) rather than the non-AKI group. It is noteworthy that the lymphopenia rate was almost the same in both groups of patients (50.0 % in AKI vs 49.0 % in non-AKI). On the other hand, the consequences of our examination revealed that the D-dimer <1000 and D-dimer >5000 are also higher in patients of the AKI group than the non-AKI group, which may indicate a higher possibility of lung injury in AKI patients. Higher acidemia in the AKI group than in the non-AKI group may be caused by COVID-19-induced renal impairment. Our other laboratory findings can be viewed in Table 5. The imaging findings from various studies pointed out that pleural effusion was higher in patients in the AKI group than in non-AKI patients (11.3 % vs 6.5 %). In terms of treatment methods, the outcomes showed that using ACE / ARB drugs in the AKI group is more common than the non-AKI group, which may confirm the importance of HTN in patients as a risk factor for AKI.

Results and outcomes

As mentioned before, in both groups of COVID-19 patients with and without AKI, symptoms such as fever, dry cough, dyspnea, and malaise were observed. However, what was significant about the results of our studies was the lower rates of symptoms such as fever (68.8 % in AKI vs 64.4 % non-AKI) and malaise

(66.8 % in AKI in contrast to 55.8 % in non-AKI) in patients with AKI. However, dyspnea had the same rate in both groups of patients, and dry cough was more common in patients without AKI than in patients with AKI (62.5 % in AKI vs 64.4 % in non-AKI). However, there does not appear to be a significant association between these symptoms and the risk of developing AKI. In the treatment regimen of COVID-19 patients, ritonavir was the most widely consumed antiviral in AKI patients, while Remdesivir was most commonly used in non-AKI patients. The utilization of angiotensin-renin and aldosterone system blockers in hospitalized patients has also been vastly discussed (35, 36). However, Hirsch et al. stated no significant association between administering these drugs and AKI incidence (22). According to a study by Su et al. in Wuhan, China, in 26 patients, 19 non-AKI patients may also have some degree of non-acute kidney damage, such as tubular injury (16). In our study, mortality was not considered due to limited resources among AKI and non-AKI patients. However, Hirsch et al (22) reported that about 35 % of patients who developed acute kidney injury passed away.

Clinical implications

So far, lots of articles have examined the incidence of AKI in COVID-19 patients and its effect on the severity and prognosis of COVID-19 in patients. Ronco et al (7) conducted one of the first studies to explain the cause and pathophysiology of AKI in COVID-19 patients and how to manage it. Jamie S. Hirsch et al (22) also conducted an extensive study on AKI in COVID-19 patients. However, these studies did not compare the symptoms, laboratory findings, and medications used for COVID-19 patients with and without AKI. Our concentration in this systematic review focused on analyzing and comparing COVID-19 patients with and without AKI. It should be noted that many people with SARS-CoV-2 and AKI may not have been expressed or counted in reference studies.

Limitations

Our study faced various challenges and limitations, including the lack of segregation of outcomes by gender. The eligible articles for this systematic review divided the COVID-19 patients into two groups, AKI, and non-AKI. However, they only mentioned the gender of the number of people in these two groups and did not count the impact of gender on the outcomes. It is crucial because physiological differences in men and women can be effective in the study results. Reviewed articles have stated that all individuals' BMI in both the AKI and non-AKI groups were less than 30 and mentioned no association between the severity of their disease or the occurrence of AKI in them. More detailed studies of patients with different BMIs (above 30) can increase the accuracy of the results and evaluations. Differences in health systems, reporting methods, and applied strategies in various countries and studies can also affect our results. Finally, it should be noted that as SARS-CoV-2 evolves, more studies are required to understand its dimensions, including AKI, better.

Conclusion

As one of the kidney injuries, AKI can occur due to kidney tissue involvement in patients infected by SARS-CoV-2 and can effectively worsen their condition by causing acidosis, etc. The most common symptoms in COVID-19 patients with AKI are dyspnea, fever, and cough. Male gender, diabetes mellitus, and blood hypertension can be effective as three significant risk factors in AKI development in COVID-19 patients. Comparing laboratory data and expressing their differences between AKI and non-AKI groups can help physicians to prepare treatment methods for these patients more precisely. However, to improve the treatment methods, more studies are demanded in AKI patients, and their results should be compared with non-AKI patients.

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