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Impact of CRRT on The Outcome of Critically ill Covid-19 Infected Patients with Acute Kidney Injury. A Retrospective Observational Cross-Sectional Study

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Abstract

Background: Numerous studies have concluded that Acute kidney injury in COVID-19 patients is significantly associated with an increased mortality [1, 2]. Continuous renal replacement therapy (CRRT) is the preferred modality of dialytic therapy in hemodynamically unstable COVID-19 patients who develop an acute renal failure. It should be noted that the number or percentage of patients who recovered renal function after dialysis is variable [3]. Notably, the decision to initiate CRRT in patients with COVID-19 acute kidney injury (AKI) should be individualized and should consider the clinical context. Some earlier studies have reported that CRRT was associated with improved outcomes, including reduced intensive care unit (ICU) and hospital mortality, shorter duration of mechanical ventilation, and shorter ICU stays [8]. On the other hand, others have claimed that CRRT improves renal function, but does not have impact on overall mortality [4].

Objectives: Our aim was to study the association between the development of an AKI in COVID-19 patients and ICU stay as a primary endpoint and to study the influence of CRRT on the recovery of the renal function as secondary endpoints.

Study Population: Our study population had included all adult patients who were above 18 years old and were admitted to our ICU on the background of a laboratory confirmed COVID-19 infection who had developed an AKI during the ICU course according to AKIN criteria. Our included population should have had no previous history of chronic kidney disease or renal replacement therapy.

Methods: Our study is a retrospective cross-sectional study, that was conducted during the period from June 2021 till the end of June 2022.

Statistical analysis: All data have been collected and analyzed by the investigators using Microsoft Excel and Statistical Package for the Social Sciences (SPSS) software version 22.

Results: A total of 108 COVID-19 patients with AKI were admitted to our ICU during the study period. We have identified a significantly increased ICU stay in CRRT group (Median 16 days) as compared to non-CRRT group (Median 4.4 days), P value was 0.00.

Discussion: We have identified a significantly increased ICU stay in CRRT group (Median 16 days) if compared to non-CRRT group (Median 4.4 days), P value 0.00.

Conclusion: We've concluded that the CRRT in Covid-19 patients with AKI is associated with increased ICU stay, even if the kidney function is improved.

Background

The consensus definition for AKI, traditionally defined using only serum creatinine and urine output, was needed to standardize the description for epidemiology and to harmonize eligibility for clinical trials. However, AKI is not a simple disease, but rather a complex and multi-factorial syndrome characterized by a wide spectrum of pathobiology. AKI is now recognized to be comprised of numerous sub-phenotypes that can be discriminated against through shared features such as etiology, prognosis, or common pathobiological mechanisms of injury and damage. The characterization of sub-phenotypes can serve to enable prognostic enrichment (i.e., identify subsets of patients more likely to share an outcome of interest) and predictive enrichment (identify subsets of patients more likely to respond favorably to a given therapy) specially in critically ill patients [5].

The SARS-COVID Infectious Disease 2019 (COVID-19) was first recognized in December 2019 [1]. It is caused by a novel coronavirus structurally related to the virus that causes severe acute respiratory syndrome (SARS) [6].

The COVID-19 pandemic has brought about significant challenges in the management of critically ill patients. COVID-19 is primarily transmitted through respiratory droplets and direct contact [1, 7].

Most patients with COVID-19 have dyspnea as the main clinical manifestation, and some cases may be complicated by heart, kidney, circulatory, liver, nerve and other multisystem injuries [2, 4, 8, 9, 10].

These patients may eventually die of diffuse alveolar injury and progressive respiratory failure. The cytokine storm syndrome involved in the pathogenesis of acute respiratory distress syndrome and organ failure during COVID-19 infection seems to be related to a massive inflammatory reaction.

Viral replication in targeted organs, including the kidneys, induces systemic viral sepsis and systemic inflammatory responses, as well as subsequent cell damage in multiple organs. In addition, renal failure in patients with COVID-19 may occur due to rhabdomyolysis, hypoxemia, dehydration, presence of underlying diseases and improper administration of nonsteroidal anti-inflammatory drugs [3, 4].

Early reports of disease related to the novel COVID-19 from China described a relatively low incidence of acute kidney injury (AKI): 0.5% in all cases and 2.9% in severe cases [6].

However, subsequent reports from the United States have suggested higher incidence of AKI in hospitalized patients of 28-37% [1, 7]. Among patients with COVID-19 and AKI, a significant proportion required acute dialysis, ranging from 20 to over 50% [1, 8, 9].

As a result, COVID-19 related surges in patients with AKI have resulted in potential shortages in renal replacement therapy (RRT) availability [4, 9].

Studies also have shown that patients infected with SARS-CoV-2 had significantly increased serum creatinine (SCr) and hospital mortality after AKI [7, 11, 12].

However, another study showed that COVID-19 did not cause AKI, and did not aggravate kidney damage in patients with complication of chronic kidney disease [13]. To understand the incidence of COVID-19 in conjunction with AKI and its impact on prognosis, we systematically analyzed the relationships between AKI incidence, demographic characteristics, clinical characteristics and prognosis in patients with COVID-19 to provide references for the diagnosis, treatment and prognosis of patients with COVID-19 complicated by AKI in clinical practice.

The need for dialysis usually arises during the second week of infection, with studies reporting up to 25% of patients in ICU required RRT [1, 8, 9].

AKI is more common among patients with severe infection of COVID-19 and is considered a negative prognostic factor with respect to survival. AKI-RRT is associated with a hospital mortality rate of >60%. Among those who survive to discharge, one in three still depends on RRT at discharge, and one in six remains RRT dependent 60 days after ICU admission [1, 2].

Many studies reported that CRRT was associated with improved outcomes, including reduced ICU and hospital mortality, shorter duration of mechanical ventilation, and shorter ICU stays [2, 10].

CRRT has been used in the treatment of COVID-19 patients with multiple organ failure, especially when accompanied by refractory CRS (cytokine release syndrome), and in some critical patients with acute kidney injury (AKI). One case report suggests that CRRT is initially effective in the treatment of patients with COVID-19 [14].

However, as little data on this topic exists, there is no definitive conclusion regarding the effectiveness of CRRT. In this study, we retrospectively collected and analyzed the clinical data of COVID-19 patients with acute kidney injury and needed CRRT versus those who did not need, outcome and intensive care unit (ICU)stay were evaluated.

The effect of CRRT was evaluated against improvement of kidney function, mortality and ICU stay.

Objectives

Objective

To study the relation between acute kidney injury and ICU stay in critically ill COVID-19 patients admitted to ICU.

Methodology

Type of the study

This is a retrospective cross-sectional observational study.

Setting

108 COVID-19 patients admitted to ICU who developed acute kidney injury (AKI) (out of whom, fifty patients were in need for CRRT, and 58 patients were treated conservatively) in Kuwait hospital Dubai EHS, in the period from June 2021 to the end of June 2022.

Study Population

Inclusion criteria

1. Patients above 18 years old.
2. Patients admitted to ICU due to lab confirmed PCR COVID-19 infection.
3. All patients who had developed Acute Kidney Injury (AKI) according to AKIN criteria, including those who required Continuous Renal Replacement Therapy (CRRT).

Exclusion criteria

1. Patients less than 18 years old.
2. History of Chronic kidney disease
3. or regular dialysis therapy.

Study Procedure

Patient informed consent

No informed consent owing to the anonymous retrospective data collective nature of the study.

Intervention

All patients had received standard care based on the clinical data, and no special intervention was offered, all study patient population are going to be subjected to the following data collection:

a) Demographic characteristics including Age, sex, weight, Pre-existing co-morbidities.
b) SOFA scoring in the first 24 hours to adjust for clinical severity.
c) Confirmed AKI according to Acute Kidney Injury Network (AKIN) criteria.
d) Documented need for CRRT.
e) Required modality and duration of CRRT.
f) Primary outcome: ICU stay.
g) Secondary outcomes: Recovery of renal function, Need for continuous regular hemodialysis.

Data was collected from the hospital electronic records and noted on an excel sheet.

Patient withdrawal

Not applicable as it is a retrospective collection of data.

Data Management

Data storage

The excel sheet recording all the data was stored on a computer with access provided only to investigators.

Privacy and confidentiality

All data can only be accessed by the study investigators.

Future of data

The data will be used for publication in peer-reviewed journals.

Adverse Event Reporting

No adverse events were expected as the study does not involve any new intervention.

Statistical Analysis

The data was analyzed by the investigators using Microsoft Excel and Statistical Package for the Social Sciences (SPSS) software version 22.

Quality Assurance, Monitoring and Safety

The principal investigator Had ensured proper data collection, data collection and safe keeping of records.

Finance and Resource Use

No funding available, no conflict of interest.

Dissemination of Results and Publication Policy

All the procedure has gone according to rules and regulations.

Results

Our study was conducted on 108 Covid patients diagnosed with AKI, out of whom fifty patients were treated with CRRT and the remaining 58 patients were treated conservatively, according to the response to diuretics, urine output and absence of electrolyte imbalance.

Upon exploring the demographic characteristics of our studied population, the average age in the group of patients treated with CRRT was significantly higher if compared to non-CRRT group (69.1±14.4 versus 61.4 ±18.6, respectively, P value 0.02).

On the other hand, the gender variance was insignificantly distributed between CRRT and non-CRRT groups (38 of the fifty patients in CRRT group were males, while 44 of the 58 in the non-CRRT group were males, P value 0.99), yet with a clear significant gender variance in COVID-19 patients who developed AKI (82 males versus 26 females, P value 0.00).

Trying to adjust for the severity of critical illness in our studied population, there was no significant difference in median SOFA scores of CRRT group when compared to non-CRRT group {(6 IQR (4-9) versus 5 IQR (4-7.25), respectively, P value 0.6}.

			Group		*Total*
			CRRT	*No CRRT*	
GENDER	Males	Count	38	44	82
		% within Group	76.0%	75.9%	75.9%
	Females	Count	12	14	26
		% within Group	24.0%	24.1%	24.1%
Total		Count	50	58	108
		% within Group	100.0%	100.0%	100.0%

Table 1B: GENDER * Group Crosstabulation.

	Value	*Exact Sig. (2-sided)*
Pearson Chi-Square	.000[a]	
Fisher's Exact Test		1.000
a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 12.04.		

Table 2B: Chi-Square Tests.

	Group	*N*	*Mean*	*Std. Deviation*	*Std. Error Mean*
AGE	CRRT	50	69.1000	14.39990	2.03645
	No CRRT	58	61.4483	18.61444	2.44420
SOFA	CRRT	50	6.4600	3.85031	.54452
	No CRRT	58	6.1379	3.20881	.42134

Table 3B: Group statistics t test values.

	t-test for Equality of Means	
	t	*Sig. (2-tailed)*
AGE	2.360	.020
SOFA	.474	.636

Table 4B: Independent Samples Test.

Variables		*CRRT (n=50)*	*No CRRT (n=58)*	*P-value*
Age		69.1±14.4	61.4 ±18.6	0.020[a]
Gender	Male	38(76.0)	44(75.9)	0.999[b]
	Female	12(24.0)	14(24.1)	
SOFA	Median (IQR)	6.00 (4-9)	5.00(4-7.25)	0.611[c]
ICU stay (days)	Median (IQR)	16.0(11.7-26.0)	4.4 (1.9 - 14.2)	0.001[c]

IQR= *Inter quartile range,* [a] *independent t-test,* [b] *Chi-square test,* [c] *Mann-Whitney test.*

Table 1C: General characteristics of the study groups.

Our results have clearly identified a significantly longer ICU stay in CRRT group if compared to non-CRRT group (Median 16.0 IQR (11.7-26.0), and 4.4 IQR (1.9 - 14.2), respectively, P value 0.001).

	Group	*N*	*Mean*	*Std. Deviation*	*Std. Error Mean*
ICU STAY	CRRT	50	26.2400	35.20584	4.97886
	No CRRT	58	10.2632	14.91879	1.95893

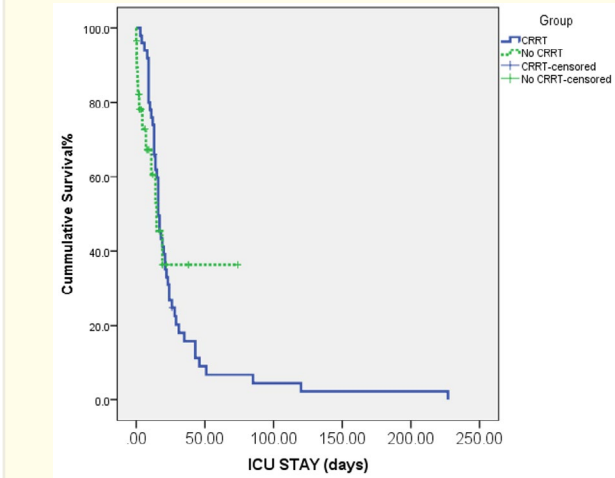
Table 5B: Group Statistics.

	ICU STAY
Z	-5.344
. Sig. (2-tailed)	.000
a. Grouping Variable: Group	

Table 6B: Mann-Whitney Test.

Group					
CRRT			*No CRRT*		
Median	Minimum	Maximum	Median	Minimum	Maximum
16.0000	3.00	227.00	4.4334	.03	74.00

Table 7B: ICU STAY.



Discussion

The Corona Virus Infectious Disease 2019 (COVID-19) was first recognized in December 2019. It is caused by a novel coronavirus structurally related to the virus that causes severe acute respiratory syndrome (SARS) [6].

The COVID-19 pandemic has brought about significant challenges in the management of critically ill patients. One such challenge has been the management of patients with acute kidney injury [7].

Acute kidney injury (AKI) affects up to 30% of critically ill patients infected with coronavirus [1, 6-8]. The need for CRRT usually arises during the second week of infection, with studies reporting up to 25% of patients in ICU required RRT. Continuous renal replacement therapy is the preferred modality of dialytic therapy in hemodynamically unstable COVID-19 patients who develop an acute renal failure [1, 5, 9].

AKI is considered a negative prognostic factor with respect to survival. AKI-CRRT is associated with a hospital mortality rate of >60%. Among those who survive to discharge, one in three still depends on RRT (Renal Replacement Therapy) at discharge and one in six remains RRT dependent 60 days after ICU admission [1, 2].

Some studies reported that CRRT was associated with improved outcomes including reduced ICU and hospital mortality, shorter duration of mechanical ventilation, and shorter ICU stays [10].

We had conducted our study on 108 COVID-19 patients admitted to ICU who developed acute kidney injury (AKI) (out of whom, fifty patients were in need for CRRT and 58 patients were treated conservatively) in Al Kuwait hospital Dubai EHS during the period from June 2021 to the end of June 2022.

Our aim was to study the impact of CRRT on the ICU stay of critically ill Covid-19 infected patients with acute kidney injury, in a retrospective observational cross-sectional study.

Upon exploring the demographic characteristics of our studied population, the average age in the group of patients treated with CRRT was significantly higher as compared to non-CRRT group (69.1±14.4 versus 61.4 ±18.6, respectively, P value 0.02). In other studies [15], the mean age was 54.8 years in the CRRT group, which is relatively comparable to ours. In agreement with our study, Ashraf et al. had higher age as a predictor of kidney injury in COVID-19 patients and also patients who experienced CRRT were older than those who did not do [16].

In another study done by Al Abri and colleagues in 2023 [17], it showed that the study population included 68.5% (196/286) males. The median age was 56 years (interquartile range, IQR: 43-66.25). The incidence of AKI was 55.2% (158/286) overall. Univariate analysis for the development of AKI showed the following significant variables: age (p=0.005; odds ratio, OR 1.024; 95% confidence interval, CI 1.007-1.041), and this was going hand in hand with our study. In a study done by Karin and colleagues in 2021 [18], the majority of patients were males, and this was going hand in hand with our study. Samaan and colleagues in 2022 also postulated that AKI was more in men than females and of course the use of CRRT was more in males [19]. Although the Kidney Disease Improving Global Outcomes guideline includes female sex on the list of susceptibilities for AKI [20], a higher prevalence of males with severe forms of AKI has been described for patients with and without COVID-19 [21].

In our study, the gender variance was insignificantly distributed between CRRT and non-CRRT groups (38 of the fifty patients in CRRT group were males, while 44 of the 58 in the non-CRRT group were males, P value 0.99), yet with a clear significant gender variance in Covid-19 patients who developed AKI (82 males versus 26 females, P value 0.00). In a study done by Maria Teresa Ferretti in 2020 and colleagues, they denoted that comorbidities were equally split between men and women in covid-19 infected patients [22].

In the same previous study [22] in Higher Institute of Health, it was found that not only do men constitute almost 60 percent of people with confirmed cases of COVID-19, but also that more than 70 percent of those have died of the infection. In 2021, in a study

published by medical forum it was observed that the findings published on June 21st in the peer-reviewed journal *Current Medical Research and Opinion*, showed that the chance of females developing long-COVID syndrome, where complications persisted more than four weeks after initial infection, was 22% higher in females as compared to males [23].

In conclusion, we observe that most studies agreed that COVID-19 infection was much more prevalent in males than in females, but the long-term consequences are more frequently encountered in females. On the other hand, overall deaths were significantly higher in men. With reference to the interplay between sex, COVID-19 and acute kidney injury, the literature approaching this triple relation is limited. However, most citations were only hitting the relation between sex, COVID-19 and death. For example, in the study done by Melissa, and colleagues in 2022, there was no sex difference in both groups [24, 27].

In our study, we've tried to adjust for the severity of critical illness in our study population and there was no significant difference in median SOFA scores of CRRT group when compared to non-CRRT group {(6 IQR (4-9) versus 5 IQR (4-7.25), respectively, P value 0.6}. We've used SOFA score as a surrogate measure for the severity of critical illness, but in other studies [17], APACHE score was preferred. We've failed to detect any significant relation between the use of CRRT and the SOFA score, on the other hand, it was found that the higher the SOFA score, the higher the incidence of AKI and this was expected after the adjustment of severity indices.

In another study done by Joseph et al. in 2020, they've found that a modified SOFA score on admission was independently linked with the development of AKI only in COVID-19 ICU patients, however, such a link couldn't be established with the need for CRRT [25]. We believe that our results are in the same track regarding the use of severity scores, even if the purpose behind the score choice might be different. But in general, we've appreciated the same endpoints that the incidence of AKI is increasing with rising values of the severity scores. Karin and colleagues [18], used SAPSIII SCORE as a severity score and the results were the same like ours concluding that the incidence of AKI in COVID-19 patients goes hand in hand with the severity of critical illness as evidenced by the use of critical illness severity scoring models.

Our results have clearly identified a significantly longer ICU stay in CRRT group as compared to non-CRRT group (Median 16.0 IQR (11.7-26.0), and 4.4 IQR (1.9 - 14.2), respectively, P value 0.001). This agreed with the study done by Karin and colleagues in 2021 [18]. Also, in a study done by Rosa Melero and colleagues in 2021, they have concluded that CRRT patients have longer ICU stay. However, survivor patients who develop AKI requiring CRRT in the ICU do not require long-term dialysis if they have normal baseline renal function 1 year after discharge, no patients have recovered their renal function and have lost half of kidney function after SARS-CoV-2 infection, most of the urinary sediment alterations have disappeared by 1 year and lastly, these results support that these patients require post-discharge nephrologist care [26]. In another study done by Samaan and others in 2022 [19], it was concluded that 22.3% (23/103 patients) of the survivor patients were discharged while dependent on CRRT.

Meanwhile, the whole length of ICU stay was longer for those in need for CRRT, on the other hand, non-survivors exhibited a shorter hospital stay than survivors [19, 28].

In relation to the efficiency of CRRT, the longer ICU stay in the CRRT group might be in part explained by the efficient CRRT therapy they were receiving however, it has exerted no impact on the overall mortality.

To further support our results, Anees A. Sindi in 2023, had reached a conclusion that the use of renal replacement therapy among critically ill COVID-19 patients could potentially predict worse outcomes [29]. Furthermore, Urmila Anandh and colleagues concluded that AKI requiring CRRT in critically ill COVID-19 pneumonia patients had a high mortality which was independently predicted by age, altered sensorium at presentation, need for ventilatory support and CRRT [30].

On the other hand, Jing Qian and colleagues in 2021/2022, claimed that early CRRT can reduce the all-cause in-hospital mortality in patients with severe COVID-19, but not improve multi-organ impairment or increase the risk of AKI. Early initiation of RRT merits an optional strategy in critically ill patients with COVID-19 (ChiCTR2000030773) [31].

In our study we were concentrating on the length of ICU stay which really was longer in these ICU patients even with improving kidney functions as the mortality was mostly adopted to multiorgan failure including AKI as one predictor.

Revisiting Lirong and colleagues' findings in 2020, they've advised that the risk of in-hospital death was significantly increased in patients with COVID-19 complicated by AKI [32].

We can summarize our conclusion that the age is an independent factor for risk of AKI in COVID-19 patients admitted in ICU, it was clear that mortality was higher in CRRT group and also the length of stay as well even with the efficient and early dialysis done which improved the kidney function but there was no impact on improving outcome.

Conclusion

Critically ill covid-19 patients admitted to ICU with multiple organ dysfunction may have AKI as a part of the disease and many need CRRT. Renal replacement therapy can improve the kidney function, but overall results indicated that the length of stay in ICU is increased in these patients.

Recommendations

The era of COVID-19 is ending and we recommend more retrospective studies from other centers about the same subjects for doing a meta-analysis study with unique recommendations for the future.

Conflict of interest

None.

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