The incidence, Risk factors and Prognosis of Acute Kidney Injury in Severe and Critically ill Patients With COVID-19 in ICU of Eka Kotebe Hospital, Addis Ababa Ethiopia.

A Retrospective chart reviews.

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Abbreviations

aHR: -Adjusted hazard ratio

AKI: - Acute kidney injury

CCI: - Charlson Comorbidity Index

CI: - Confidence interval

CKD: - Chronic kidney disease

COVID-19: - Coronavirus disease-19

HR: - Hazard ratio

ICU: - Intensive care unit

IHD: - Intermittent hemodialysis

IQR: - Interquartile range

KDIGO: - Kidney Diseases: Improving Global Outcomes

RRT: - Renal replacement therapy

MDRD: - Modification of Diet in Renal Disease

REC: - Research Ethics Committee

RT-PCR: - Reverse transcriptase-polymerase chain reaction

SCr: - Serum creatinine

SD: - Standard deviation

Abstract

Background-The incidence, clinical characteristics and outcomes of acute kidney injury (AKI) in patients with COVID-19 admitted to intensive care unit and its association with mortality and disease severity.

Objective-To determine the incidence, risk factors, clinical characteristics and outcomes of AKI in a cohort of patients with COVID-19 admitted to Eka Kotebe Intensive Care Unit (ICU), and its association with in-hospital mortality(survival), dialysis requirement, increased need of mechanical ventilation, disease severity and renal status at discharge.

Methods- It's a single centered cohort study from a registry of patients with COVID-19. A total of 174 patients were admitted to medical ICU with confirmed COVID-19 between from 1st October 2020 to 31 may 2021. We classified AKI by comparing highest to lowest recorded serum creatinine in hospital and staged AKI based on the Kidney Disease: Improving Global Outcomes (KDIGO) system. We calculated the unadjusted and adjusted odds ratio for the stage of AKI and the need for mechanical ventilation, and in-hospital mortality.

Measurements-Stage of AKI, LOS, mechanical ventilation, discharge, and in-hospital mortality.

Results-Of the total 174 patients registered to the log book during the study time, and only 156 patients were found to be eligible for study and from this 95(60.9%) developed AKI, 36 (37.9%) presented with AKI, and 59 (62.1%) developed AKI in-hospital. High charlson comorbidity index, low lymphocyte count, low serum albumin level, higher white blood cell counts and Serum alkaline phosphatase measurement, vasopressor need for life support, and mechanical ventilation were found to be associated significantly with increased risk for AKI.

Limitations-a cohort study with small sample size limits precision of estimates. Lack of non-hospitalized and stable admitted patients with confirmed COVID-19 as controls limits causal inferences.

Conclusions-Acute kidney injury, whether it occurs prior to or after hospitalization, is associated with a high risk of poor outcomes in patients with COVID-19. Routine assessment of kidney function in patients with COVID-19 may improve risk.

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1. Introduction

1.1 Background

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection (COVID-19) was originally thought to be a primarily respiratory illness; however, as the pandemic has evolved, its multisystem effects have been increasingly recognized. Acute kidney injury (AKI) is prevalent in coronavirus disease-19 (COVID-19) patients [1]. A binding site for SARS-CoV-2, the angiotensin-converting enzyme 2 (ACE2) receptor, is expressed in abundance in the kidneys and may allow for direct kidney damage [2]. The pathogenesis is multifactorial including possible viral invasion, hypovolemia, systemic inflammation, nephrotoxin exposure, endothelial dysfunction, coagulopathy, and organ crosstalk [*3*, 4].

The reported incidence of AKIs in individuals with COVID-19 varies widely from 2.9% to 46% in various studies, with similar degrees of heterogeneity in mortality rates [5,6,7]. The incidence of AKI varies among geographical regions and clinical settings, ranging from 7 to 57% in hospitalized patients [*5*,*6*,*7*] and 19–80% in patients in the intensive care unit (ICU) [*8*,*9*,*10*,*11*,*12*]. Kidney replacement therapy (RRT) is utilized in 20–60% [*6*, *13*]. Both AKI and RRT are associated with adverse hospital outcomes and increased mortality [*14*]. There is a dearth of studies investigating the association between AKIs in COVID-19 outcomes regarding severity of COVID-19, pre-existing comorbidities, length of admission, admission to intensive care unit (ICU), and mortality. There are still fewer studies investigating outcome measures that stratify individuals based on the severity of their AKI and AKI acquired in the community [15,16]. While AKI is associated with poor outcomes in individuals with COVID-19, there are uncertainties and gaps in our knowledge.

Risk factors for AKI development include increased age, comorbidities, and racial background [*17*]. However, only few studies have examined the impact of COVID related therapies on risk of AKI progression [*18*] or long-term renal outcomes beyond hospital discharge in critically ill patients with COVID-19. Understanding the burden of short- and longer-term complications is critical for prognostication, clinical management, and future resource planning. The objective of this study is to determine whether AKI conferred an increased odd of death for patients admitted to covid-19 medical ICU, as well as disease severity, length of hospital stay and increased need for mechanical ventilation.

1.2 Statement of the problem

Acute kidney injury (AKI) is defined as an abrupt decrease in kidney function occurring over 7 days or less. The management of patients with AKI is supportive, with RRT, indicated in patients with severe kidney injury. Most patients with ARF do not require RRT. The decision to start RRT is made on an individual basis when a number of physiological parameters are considered in association with each other, and therefore is instituted at differing levels of glomerular filtration rate, uremia and urine output. AKI increases the risk for the development or worsening of chronic kidney disease. Patients who survive and recover from an episode of severe AKI requiring dialysis are at increased risk for the later development of dialysis-requiring end-stage kidney disease.

Preliminary reports indicate that AKI and kidney abnormalities seem to be associated with COVID-19 severity and outcomes. A recently published study that utilized autopsy specimens from 26 patients who died of COVID-19 in China demonstrated that there is evidence of the invasion of SARS-CoV-2 into kidney tissue, along with significant acute tubular injury and endothelial damage. As with AKI from other causes, COVID-19-associated AKI (COVID-19 AKI) increase adverse outcomes, including the development or worsening of comorbid disease, greater use of health-care resources and as well as high mortality and serves as an independent risk factor for all-cause in-hospital death in patients with COVID-19.

Similar to the association of AKI with other forms of community-acquired pneumonia, AKI is now recognized as a common complication of COVID-19. However, despite considerable advances in our understanding and management of other forms of AKI, relatively little is known about the pathogenesis or optimal management of COVID-19 AKI. The relationship between respiratory failure and development of AKI was substantial. Among patients who required mechanical ventilation, 1068 of 1190 (89.7%) developed AKI compared with 925 of 4259 (21.7%) in non-ventilated patients. The majority of severe (stage 3) AKI (518 of 619 [83.6%]) and most patients requiring dialysis support (276 of 285 [96.8%]) occurred in patients on mechanical ventilation. RRT was required in 9 of 4259 non-ventilated patients (0.2%) compared with 276 of 1190 patients on ventilators (23.2%). There was a substantial clustering of AKI events at the time of intubation and initiation of mechanical ventilation. Of patients who required ventilation and developed AKI, 52.2% had the onset of AKI within 24 hours of intubation.

1.3 Significance of the study/Rationale

The aim of this study is to describe incidence of different stages of AKI, clinical characteristics, risk factors, explore mortality and renal specific outcomes of patients admitted to eka kotebe covid-19 MICU. In the previous SARS pandemic, the reported incidence of AKI was 6.7% with a high mortality of over 90%. Careful monitoring of kidney disease and renal replacement therapy (RRT) is extremely important to manage resources which may become scarce during this pandemic.

2. *Objectives*

2.1 General objectives

- ✓ To determine the incidence and outcomes of AKI among patients with covid-19 requiring ICU admission.

2.2 Specific objectives

- ✓ Describe the demographic and clinical characteristics of covid-19 patients admitted to covid-19 ICU.
- ✓ Determine the incidence of AKI
- ✓ Determine the proportion of patients who require dialysis,
- ✓ Identify factors associated with the development AKI,
- ✓ Determine the overall and renal outcomes during the index hospitalization,
- ✓ Determine mortality and length of stay in hospital.

3. Methods

3.1 Study setting

- ✓ This is a single centered retrospective cohort study of patients with confirmed severe and critical COVID-19 admitted to medical ICU of Eka kotebe hospital, Addis Ababa, Ethiopia with bed capacity of 16.

3.2 Study design

- ✓ This is a retrospective study based on the medical records of patients hospitalized with severe and critical COVID-19. Medical records of patients hospitalized in the study site during the specified periods were reviewed and patients who qualify with a diagnosis of AKI as described in the operational definition were further reviewed.

3.3 Study period

- ✓ From 1st October 2020 to 31 December 2020.

3.4 Source population

- ✓ The source population included all confirmed covid-19 patients admitted to the ICU.

3.5 Study population

- ✓ All confirmed severe and critical Covid-19 patients admitted to ICU.

3.6 Sample size

- ✓ All of patients who were hospitalized between October 1, 2020 and December 31, 2020 were included in the study. As all eligible medical records i.e. all the study population, included, calculation for sample size determination was not needed.

3.7 Eligibility criteria

❖ 3.7.1 Inclusion criteria

- ✓ Age: > or = 18
- ✓ Presence of at least 2 serum creatinine determinations at any point in time.

❖ 3.7.2 Exclusion criteria

- ✓ Age <18 years old
- ✓ ESRD on maintenance dialysis
- ✓ Unavailable or missing data
- ✓ Patients whose hospital outcome was not known

3.8 Sampling technique

- ✓ All medical records of patients who fulfill the inclusion criteria were included; hence, no particular sampling technique was utilized.

3.9 Data collection procedures

3.9.1 Retrieving medical records

- ✓ Medical record number of patients who were hospitalized during the specified period were identified from the admission log books.
- ✓ The records of were requested from the archives of each hospital for the study purpose; they were reviewed within the hospital premises and returned back to the archives within 72 hours.
- ✓ In order to ensure completion of data entry within 72 hours, limited number of medical records were requested at one point in time. For this effect, medical records of admissions which occurred over two weeks period were retrieved for one round of data collection.

3.9.2 Selecting eligible patients' medical records

1. **First round screening**

- ✓ All medical records of patients hospitalized during the study period were checked for the age of the patient and the presence of two serum creatinine determination at any point in time during the index hospitalization.
- ✓ Medical records of patients with age $\geq$ 18 year and with evidence of two documented serum creatinine determinations were forwarded for the second-round screening. The remaining were excluded.

2. **Second round screening**

- ✓ The second-round screening aims at identifying medical records of patients who fulfill the inclusion criteria i.e. the diagnosis of AKI, see **figure 1** for more detail.
- ✓ Check if the time difference between any two serum creatinine determinations are less than or equal to seven days.
- ✓ Evaluate if there is a documented diagnosis of acute kidney injury.

- ✓ Determine if there is at least 50% (1.5) fold increment in serum creatinine in between any two determinations with a time difference of ≤ 7 days. This applies for those with or without a documented physician diagnosis of acute kidney injury.
- ✓ Those which have documented evidence of a 50% or above rise in serum creatinine in ≤ 7 days were included in the study.

2.9.3 Data collection procedures

- ✓ A structured data abstraction form was used to collect the data.
- ✓ Data on demographic parameters, clinical and laboratory characteristics related to COVID-19, severity of COVID-19, treatment provided, comorbidities, severity (stage) of acute kidney injury, clinical and laboratory parameters related to the acute kidney injury, dialysis requirement, and renal as well as overall patient outcome was collected
- ✓ The data collections were done by physicians (General practitioner and internal medicine resident).

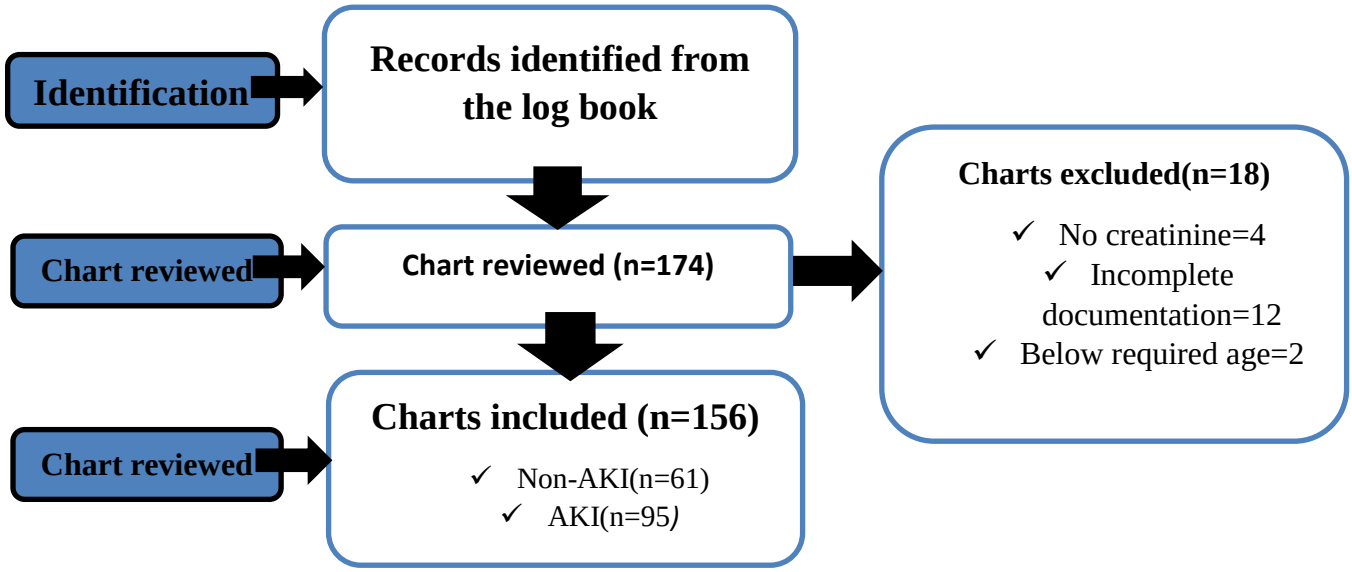


FIGURE 1. FLOW DIAGRAM OF INCLUSION PROCESS OF STUDIES. NOTE. AKI = ACUTE KIDNEY INJURY.

4. Study variables

4.1 Independent variables

- ✓ Demographic variables: age and sex
- ✓ Comorbidities: Individual comorbidities, Charlson comorbidity index.
- ✓ Severity of COVID-19: severity classification, requirement of oxygen therapy, vasopressor need, and requirement for mechanical ventilatory support.

4.2 Dependent variables

- ✓ Stage of acute kidney injury
- ✓ Complications of acute kidney injury
- ✓ Dialysis requirement
- ✓ Renal outcome
- ✓ Overall patient outcome

5. Statistical analysis

- ✓ Data was entered in to SPSS version 26 for windows.
- ✓ Frequencies, proportions (percentages), measures of central tendency and dispersion (mean with standard division for continuous variables with normal distribution, median with interquartile ranges for discrete variables and skewed continuous variables), appropriate graphs and charts was used for description.
- ✓ To assess the association between independent and dependent variables, independent variables fit into binary logistic regression model. Variables which are found to be significant at a p- value of 0.05 was fitted in to multivariate logistic regression model.
- ✓ P value < 0.05 and 95% confidence interval were used to evaluate statistical significance and precision of associations respectively.

6. Outcome analysis

- ✓ Univariate analysis was performed to ascertain any significant association of baseline variables with mortality in patients with COVID-19 disease. Any variables with significant association in univariate analysis was entered in multivariable logistic regression analysis to ascertain the effects of age, gender, comorbidities, medications, and acute kidney injury on the likelihood of in-hospital death.

7. Data quality management

- ✓ Questionnaire was prepared in English version adopted and modified from different literatures, used to collect data from patient charts. Patient medical record number will be taken from HMIS books and will be given to chart room staffs to get patient charts. The data will be collected by GP medical residents. Information on variables such as demographic characteristics, clinical profile, laboratory values and dialysis and hospital outcome will be collected. Questionnaire will be pre-tested on a 5% of samples. The collected data will be checked for completeness before execution of any data entry process.

8. Data Protection and Patient Confidentiality

The investigator ensured that participant's anonymity is maintained throughout the study and following completion of the study. All documents were stored securely with access restricted to study staff and authorized personnel.

9. Ethical consideration

In accordance of the regulations of the College of Health Sciences, Addis Ababa University the study was submitted to the department of Internal Medicine research ethics review committee and Eka Kotebe REC.

10. Operational definitions

Acute kidney injury (AKI) definition and staging: we will use the KDIGO criteria for the defining and staging. Due to expected inconsistencies in urine output recording the serum creatinine will be used for both defining and staging AKI.

TABLE 1 DEFINITION OF AKI, MODIFIED FROM THE KDIGO CRITERIA.

AKI is defined as any of the following (modified KIDGO definition)

I. **Increase in serum creatinine (SCr) by > or = 0.3 mg/dl within 48 hours**
II. **Increase in SCr to > or = 1.5 times from baseline, which is known or presumed to have occurred within the prior 7 days.**

Adapted from: KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney International Supplements (2012) 2, 2; doi:10.1038/kisup.2012.2

Table 2. Staging of AKI, the KDIGO severity staging

Stage of AKI	Serum creatinine criteria
Stage 1	1.5–1.9 times increase form baseline OR > or = 0.3 mg/dl absolute increase
Stage 2	2.0–2.9 times increase from baseline
Stage 3	3.0 times increase from baseline OR Increase to > or = 4.0 mg/dl OR Initiation of renal replacement therapy(dialysis)

Adapted from: KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney International Supplements (2012) 2, 2; doi:10.1038/kisup.2012.2

Aetiology of AKI-the cause of AKI documented in the medical record of a patient as decided by the managing team based on clinical, laboratory and imaging evidence.

Baseline SCr-was determined from outpatient SCr values between 7 and 365 days before ICU admission. If a historical SCr result was not available, the first SCr on hospital admission [11] was used or SCr was determined by back-calculation using the Modification of Diet in Renal

Disease (MDRD) formula and an assumed estimated glomerular filtration rate (eGFR) of 75 mL/min/1.73 m2.

Recovery from AKI- was defined as the absence of any stage AKI in the last recorded creatinine during discharge (i.e. serum creatinine < 1.5 times the baseline creatinine), in the absence of RRT.

AKI at ICU admission-was defined as any stage AKI present within 48 h of ICU admission [21].

Severe Covid-19- met any of the following criteria

- ✓ Respiratory distress, defined as the respiratory rate ≥ 30 times/min, with cyanosis,
- ✓ Arterial digital oxygen saturation ≤ 93% (at room air),
- ✓ The ratio of partial pressure of oxygen to the fraction of inspired oxygen (PaO2/FiO2) ≤300 mmHg (1 mmHg = 0.133 kPa).

Critical Covid-19- met any of the following criteria

- ✓ Respiratory failure requires mechanical ventilation,
- ✓ Shock,
- ✓ Multiple organ failure requires ICU life support
- ✓ The diagnosis of shock was made if patients represented with at least two of the following conditions,
- ✓ The systolic blood pressure being 13.3 kPa (100 mmHg); or lower; (2) The pulse pressure being 4.0 kPa (30 mmHg); or lower; (3) Symptoms consistent with the presentation of shock (i.e. poor peripheral circulation and tachycardia*).*

11. Outcomes

11.1 Primary outcome- development of the incidence of AKI and the need for RRT.

11.2 Secondary outcomes- assess the risk factors for AKI, the outcomes of renal diseases, and the impact of AKI on the clinical outcomes of Covid-19.

12. Statistical Methods

We described patient characteristics using mean, median, standard deviation and frequency (percentage) as appropriate for the distribution of data. We reported the incidence of AKI by stages in the study population and the crude outcome rates by stage of AKI. We then assessed the associations of interest using unadjusted and adjusted binary logistic regressions, between stage of AKI and in-hospital mortality, length of stay, and mechanical ventilation. We decided on covariates for our regression models based on previously described associations with AKI in both the COVID-19 and general medical literature. These included ages, chronic kidney disease

(CKD) defined as the presence of kidney damage or decreased function for 3 or more months, diabetes mellitus defined by clinician report, and hypertension, defined as persistently elevated blood pressure above 140 systolic or 90 diastolic [19-25]. We reported odds ratios (ORs) with 95% confidence intervals.

13. Results

13.1 Baseline Characteristics

Between 1st November and 31st December 2020, 174 sever to critically ill COVID-19 positive patients were admitted to medical ICU and among them 18 patients were excluded (12 patients' charts were poorly documented and having incomplete data, 4 had only one measurement of creatinine, and the rest of them were below the required age). Finally, we included 156 patients with complete data with required age for inclusion. Of whom two third, 66% (n=103) were males, and over all mean age of admitted patients were, 58.53 yrs. ± SD of 16.052, **see figure 2**. The vast majority of the patient were from Addis Ababa, 85.9% (n=134), 13.5% (n=21) from Oromia and SNNPR contribute to the remaining percent, 0.6% (n=1).

Most (71.8%, n=112) of patients have at least one comorbidity. The three common identified comorbid condition were type 2 diabetes mellitus, HTN, and chronic kidney diseases, 45.5%(n=71), 36.6% (n=57), and 14.1% (n=22), in their respective order of frequency.

Forty two percent (n=66) patients were categorized as having severe disease and the remaining, 57.7%(n=90) patients as having critical disease in their hospital stay. Nearly a half, (51.9%, n=81) patients required invasive mechanical ventilation, 21.8%(n=34) required dialysis for life support, and 48.1%(n=81) patients received vasopressor support.

The patient characteristics was stratified by the presence or absence of AKI. Patients who developed AKI were clinically more likely to have high comorbidity index particularly higher percentage of diabetes, hypertension, and CKD. Patients who developed AKI had also higher baseline white blood cell, increased serum liver enzyme, low serum albumin, low lymphocyte count, and higher covid-19 stage on admission. See **Table 4** for more detail.

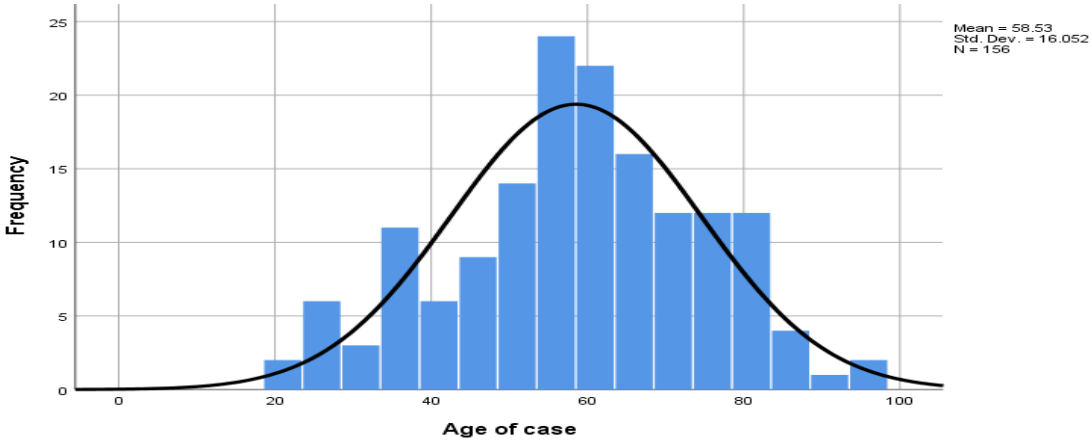


FIGURE 2. AGE DISTRIBUTION OF PARTICIPANT.

Characteristics	***Total***	***AKI***	***Non-AKI***	***P value***
Mean of age in yrs.	***58.5 yrs. ± 16.052***	***63.4 yrs. ± 18.7***	***53.9 yrs. ± 12.8***	
Age category	-	-	-	***P=0.007***
<50 yrs.	*40(25.6%)*	*15(9.6%)*	*25(16%)*	
50-59 yrs.	*35(22.4%)*	*22(14.1%)*	*13(8.3%)*	
60-69 yrs.	*39(25%)*	*25(16%)*	*14(9%)*	
70-79	*24(15.4%)*	*18(11.5%)*	*6(3.8%)*	
>79	*18(11.6%)*	*15(9.6%)*	*3(1.9%)*	
Sex	-	-	-	
Female	*53(34%)*	*26(16.7%)*	*27(17.3%)*	
Male	***103(66%)***	***69(44.2%)***	***34(21.8%)***	***P =0.031***
Region	-	-	-	*P=0.940*
Addis Ababa	*134(85.9%)*	*82(52.6%)*	*52(33.3%)*	
Oromia	*21(13.5%)*	*12(7.7%)*	*9(5.8%)*	
SNNPR	*1(0.6%)*	*1(0.6%)*	-	
AKI stages	***95(60.9%)***	-	-	
Stage I	*25(16%)*	*25(26.3%)*	-	
Stage II	*19(12.2%)*	*19(20%)*	-	
Stage III	*51(32.7%)*	*51(53.7%)*	-	
Severity of covid-19	-	-	-	
Severe	*66(42.3%)*	*19(12.2%)*	*47(30.1%)*	
Critical	***90(57.7%)***	***76(48.7%)***	***14(9%)***	***P=0.000***

Table 3. Baseline characteristics of patients admitted to ICU stratified with respect to the presence or absence of AKI.

Characteristics	*Total*	*AKI*	*Non-AKI*	*P value*
Comorbidity				*P=0.001*
No	*28.2% (44)*	*7.7% (12)*	*20.5% (32)*	
One	*25.5% (40)*	*15.4% (24)*	*10.3% (16)*	*P=0.244*
Two	*29.0% (45)*	*22.4% (35)*	*6.4% (10)*	*P=0=016*
Three or more	*17.3% (27)*	*15.4% (24)*	*1.9% (3)*	*P=0.000*
T2DM	***45.5% (71)***	***34.6% (54)***	***10.9% (17)***	***P =0.002***
HTN	***36.6% (57)***	***28.9% (45)***	***7.7% (12)***	***P =0.001***
CKD	***14.1% (22)***	***14.1% (22)***	***0% (0)***	***P=0.098***
CVS	*18(11.5%)*	*13(8.3)*	*5(3.2)*	*P=0.300*
Cerebrovascular diseases	*13(8.3%)*	*11(7.1%)*	*2(1.3%)*	*P=0.860*
HIV	*7(4.5%)*	*6(3.85%)*	*1(0.6%)*	*P=0.201*
Malignancy	*3(1.9%)*	*2(1.3%)*	*1(0.6)*	*P=0.180*
COPD	*6(3.85%)*	*2(1.3%)*	*4(2.6)*	*P=0.180*

Table 4. Co-morbidity of patients at admission stratified with respect to the presence or absence of AKI.

Laboratory findings	*Total*	*AKI*	*Non-AKI*	*P value*
Wbcs.				
> 11,000	***98(62.8%)***	***70(44.9%)***	***28(17.9%)***	***P=0.002***
4,000-11,000	*54(34.6%)*	*24(15.4%)*	*30(19.2%)*	
<4,000	*4(2.6%0*	*1(0.6%)*	*3(1.9%)*	
Lymphocyte count				
>1.500	*27(17.3%)*	*8(5.1%)*	*19(12.2%)*	
1,000-1,500	*26(16.7%)*	*6(3.8%(*	*20(12.8%)*	
500-1,000	*39(25%)*	*24(15.4%)*	*15(9.6%)*	
<500	***64(41%)***	***57(36.5%)***	***7(4.5%)***	***P=0.000***
Hemoglobin				
>12 mg/dl	*121(77.5%)*	*64(41%)*	*57(36.5%)*	
<12 mg/dl	***35(22.4%)***	***31(19.9%)***	***4(2.6%)***	***P=0.007***
Platelet				***P=0.236***
>150,000k	*133(85.2%)*	*75(48%)*	*53(34%)*	
100,000-150,000	*12(7.7%)*	*10(6.4%)*	*2(1.3%)*	
50,000-100,000	*6(3.8%)*	*5(3.2%)*	*1(0.6%)*	
<50,000	*5(3.2%)*	*5(3.2%)*	*0(0%)*	
Serum albumin level				
>3.5 gm//dl	*63(40.4%)*	*10(6.4%)*	*53(34%)*	
<3.5 gm/dl	***93(59.6%)***	***85(54.5%)***	***5.1% (8)***	***P=0.000***
ALP				

Normal	*84(53.8%)*	*27(17.3%)*	*57(36.5%)*	
Increased	***46.2% (72)***	***43.6% (68)***	***4(2.6%)***	***P=0.000***
AST	-	-	-	
<2x	*79(50.6%)*	*24(15.4%)*	*35.3% (55)*	
>2x	***49.4% (77)***	***71(45.5%)***	***6(3.8%)***	***P=0.000***
ALT	-	-	-	
<2x	*83(53.2%)*	*18.6% (29)*	*34.6% (54)*	
>2x	***73(46.8%)***	***66(42.3%)***	***7(4.5%)***	***P=0.000***

TABLE 5. BASELINE INVESTIGATION OF PATIENTS WITH RESPECT TO THE PRESENCE AND ABSENCE OF AKI.

Treatment	***Total***	***AKI***	***Non-AKI***	***P value***
Aspirin	*5(3.2%)*	*3(1.92%)*	*2(1.3%)*	
ACEI or ARBS	*10(6.4%)*	*7(4.5%)*	*3(1.92%)*	
Atorvastatin	*25(16%)*	*18(11.5%)*	*7(4.5%)*	
HAART	*7(4.9%)*	*6(3.85%)*	*1(0.6%)*	
Metformin	*9(5.8%)*	*4(2.6%)*	*5(3.2%)*	
Mechanical ventilation	***81(51.9%)***	***43.6% (68)***	***8.3% (13)***	***P =0.000***
Vasopressor	***75(48.1%)***	***44.2% (69)***	***3.8% (6)***	***P =0.000***

Table 6. Baseline treatment of patients at admission stratified with respect to the presence or absence of AKI.

13.2 Risk factors associated with AKI

Patients with AKI were significantly more likely to be critical, (48.7% vs. 9% (n=14), P = 0.000) and **Odds ratio 13.43 within 95% CI**, of have T2DM (34.6% vs. 10.9%, P = 0.002), and hypertension (28.9% vs. 7.7%, p =0.001), higher elevated white blood cell count (44.9% vs. 17.9%, P = 0.002), higher serum alkaline phosphatase level (43.6% vs. 2.6%, P =0.000). Patients with AKI more frequently received MV (43.6% vs. 8.3%, P =0.000) and vasopressor treatment (44.2% vs. 3.8%, P=0.000). Males were likely to have AKI compared to females, (44.2% vs. 16.7%, P=0.031). Furthermore, patients with AKI had markedly lower level of serum albumin below normal range and low lymphocyte count. In the multivariate regression model patients with very low level of serum albumin, higher serum ALP, need for vasopressor treatment, and mechanical ventilation were highly associated with an increased risk for AKI in hospital. See **Table 7**. For more detail.

Variables	*AKI*	*No-AKI*	*P value*	*Cru. OR*	*CI*	*P value*	*Adj. OR*	*CI*
Age category (>60 yrs.)	*37.2%*	*14.7%*	*=0.007*	*1.039*	*[1.106-1.062]*	*=0.010*	*1.038*	*[1.015-1.061]*
Presence of HTN	*28.8%*	*7.8%*	*=0.001*	*3.675*	*[1.738-7.771]*	*=0.004*	*1.984*	*[0.870-1.509]*
Presence of T2DM	*34.6%*	*10.9%*	*=0.002*	*2.846*	*[1.648-4.916]*	*=0.018*	*1.450*	*[1.021-3.067]*
Mean LOS prior to death or discharge	*11.23*	*6.45*	*=0.002*	*1.572*	*[1.288-1.919]*	*=0.040*	*1.151*	*[0.805-1.645]*
Increased serum ALP	***43.6%***	***2.6%***	***=0.000***	***3.033***	***[1.616-5.690]***	***=0.000***	***2.952***	***[1.337-3.750]***
Lymphocyte count <500	*36.5%*	*4.5%*	*=0.000*	*3.010*	*[2.085-4.345]*	*=0.012*	*2.821*	*[0.570-1.902]*
Wbcs > 11,000	*44.9%*	*17.9%*	*<0.002*	*3.033*	*[1.616-5.690]*	*=0.002*	*1.591*	*[0.942-2.056]*
Serum albumin < 2 gm/dl	***29.5%***	***2.6%***	***=0.000***	***13.15***	***[6.225-27.77]***	***=0.000***	***2.156***	***[0.980-1.084]***
Need for Vasopressor	***44.0%***	***3.8%***	***=0.000***	***24.34***	***[9.354-63.27]***	***=0.000***	***2.937***	***[0.190-0.195]***
MV requirement	*43.6%*	*8.3%*	*<0.000*	*9.299*	*[4.358-1981]*	*<0.001*	*6.810*	*[1.452-2.736]*
Presence of Critical covid-19	*48.7%*	*8.9%*	*<0.000*	*2.074*	*[2.340-1.562]*	*<0.03*	*1.450*	*[0.268-0.691]*

TABLE 7. RISK FACTORS ASSOCIATED WITH AKI IN THE MULTIVARIATE REGRESSION ANALYSIS AMONG PATIENTS WITH COVID-19.

13.3 AKI Incidence

AKI was found in 60.9%(n=95), patients admitted to medical ICU with COVID-19. Of whom 26.3%(n=25) had AKI stage I, 20%(n=19) stage II, and 53.7%(n=51) stage III, 29.5%(n=28). AKI was there at presentation in, 29.5% (n=28) and 70.5% (n=67) developed AKI after admission to hospital. See **table 3** for more detail.

13.4 Presumed Causes of AKI

Sepsis related AKI was the most common one accounting 38.4%(n=61), followed by pre-renal and covid-19 related AKI, 32.1% (n=51), 27% (n=43) respectively. Only one patient had interstitial nephritis, 0.6%. See **figure 4** below.

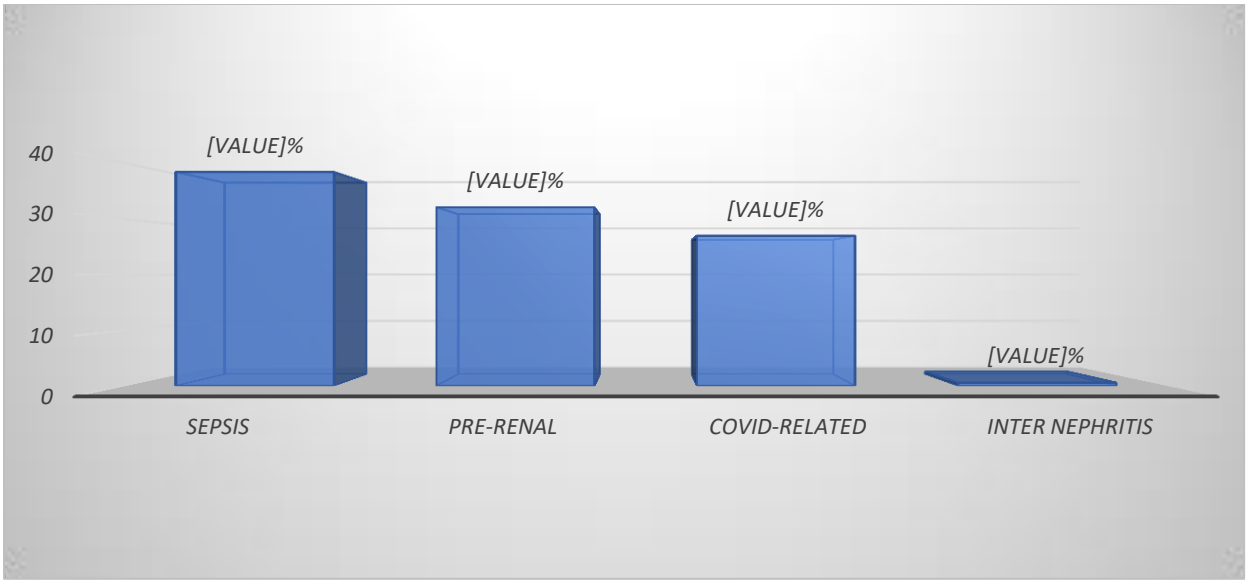


FIGURE 3. PRESUMED CAUSES OF AKI

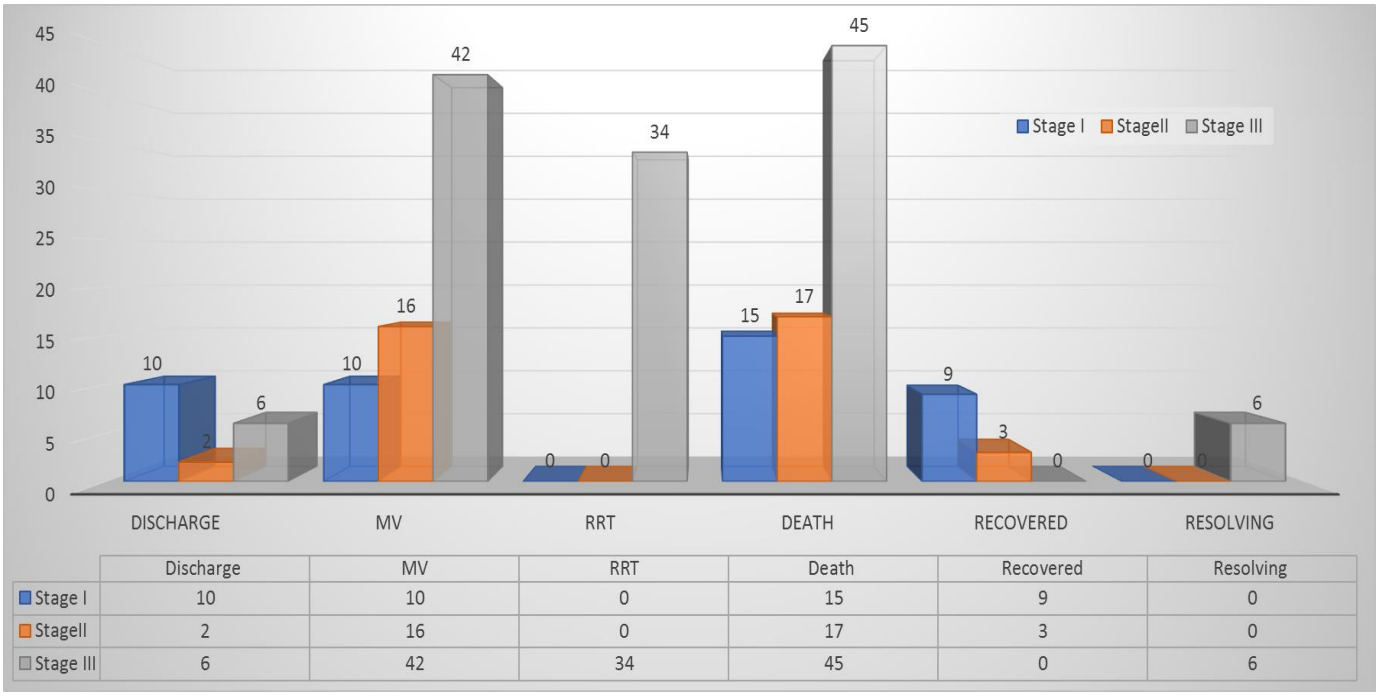
13.5 Outcomes

The overall rate of death was 57.1%(n=89) and the vast majority were from those having AKI, 49.4% (n=77) with **Odds ratio for death of 17.468 within 95% of CI [7.743-39.404]** and only 7.7% (n=12) were in the non-AKI group. 81(51.9%) out of 156 patients were required mechanical ventilation with higher rate of requirement, 43.6% (n=68) in the AKI group, with **Odds ratio of 9.29 with 95% CI [4.35-19.841].** Only 8.3% (n=13) required mechanical from the non-AKI groups. A total of 48.1% (n=75), patients were also required vasopressor for life support and 44.2% (n=69) were from those having AKI with **Odds ratio of 24.37 within 95% CI [9.354-63.267**]. Only 3.8% (n=6) were from the non-AKI patients.

The mean length of stay prior to death or discharge were found to be longer in AKI patients compared to non-AKI ones, with odds ratio for LOS **6.849** within 95% CI. See **table 8** for more detail.

Outcome	***Total***	***AKI***	***Stage I***	***Stage II***	***Stage III***	***Non-AKI***
Mechanical ventilation	*51.9% (81)*	***68(43.6%)***	*10(6.4%)*	*16(10.3%)*	***42(26.9%)***	*13(8.3%)*
Discharged	*67(42.9%)*	***18(11.5%)***	*10(6.4%)*	*2(1.3%)*	***6(3.9%)***	*49(31.4%)*
Death	*89(57.1%)*	***77(49.4%)***	*15(9.6%)*	*17(10.9%)*	***45(28.8%)***	*12(7.7%)*
Renal replacement therapy	*34(21.8%)*	***34(21.8%)***	-	-	***34(21.8%)***	-
Mean LOS prior to death or discharge	***11.3 days***	***13.8 days***	-	-	-	***6.5 days***

TABLE 8. OUTCOMES OF PATIENTS WITH RESPECT TO STAGES OF AKI AND NON-AKI.



	Discharge	MV	RRT	Death	Recovered	Resolving
Stage I	10	10	0	15	9	0
StageII	2	16	0	17	3	0
Stage III	6	42	34	45	0	6

FIGURE 4. OUTCOMES OF PATIENT WITH RESPECT TO STAGES OF AKI.

13.6 Renal replacement therapy (RRT)

Of 156 patient who were admitted to ICU, 21.8%(n=34) received RRT during in hospital stay and the modality was intermittent hemodialysis (IHD) in all of them. A sum of 129 session were done with mean requirement of 3.79 session per individual. Patient who required RRT were more prone to at increased risk of mortality and need for MV with **Odds ratio for death of 2.234, and Odds ratio for MV of 4.539, within 95% CI,** respectively**.** Among dialysis requiring patient the vast majority, 85.3%(n=29) were ended up in death and only, 14.7%(n=5), were discharged home. Indications for RRT were metabolic acidosis 23.4%(n=32), anuria 22.6%(n=31), uremic encephalopathy 21.2%(n=29), hyperkaliemia 19% (n = 26), refractory fluid overload 9.5%(n=13), uremic gastropathy 4.4%(n=6), and uremic bleeding in their respective order of frequency. Common identified dialysis related complications include, intradialytic hypo/hypertension (73.9%, n=17), catheter related infection (8.7%, n=2), and catheter related thrombosis, (8.7%, n=2) in respective order of frequency.

13.7 Renal status at discharge

Twelve (66.7%) of survived patients with AKI had complete recovery to their baseline renal function up on discharge and all of them were having AKI stage I and stage II. Patient with recovering kidney function on discharge, 33.3% (n=6) all had stage III AKI.

14. Discussion

In this study, we report that 60.9% (n=95) of COVID-19 patients admitted to intensive care for respiratory support developed an AKI and 21.8% (n=34) of the total ICU cohort required renal replacement therapy and confirms the high prevalence of AKI in critically ill COVID-19 patients. Most patients developed AKI stage III, 32.7%(n=51), and the majority of AKI occurred after 48 hrs., 62.1%(n=51) of ICU admission. Whether AKI occurred prior to or after admission, it was associated with a graded odd of increased mortality, and need for mechanical ventilation, as seen in previous literature [1-2,26,27-39]. Overall hospital mortality for stage III AKI was higher than stage I or Stage II AKI, 28.8%, n=45.

These findings underscore the importance of assessing kidney function in patients with COVID-19. Importantly, these findings suggest that whether you develop AKI in or outside of hospital, your odds of serious outcomes increase significantly. Survived patients with AKI had high rate of complete recovery to their baseline renal function (66.7%). The high incidence of AKI in our study compared with other studies [*40-44*] might have several explanations. First, most patients required multi-organ support, including mechanical ventilation, and vasopressor support. Second patients were referred from other institutions for dialysis treatment (where the only center giving dialysis for confirmed covid-19 patients and might contribute for the higher prevalence of AKI in our study). Finally, there might have been strict admission criteria to ICU, given the pandemic and the relatively low number of ICU beds.

Patients presented with AKI at ICU admission were generally older, had a higher charlson comorbidity index, were more acutely ill as evidenced by higher number of vasopressor requirements, mechanical ventilation, lower serum level of albumin, higher frequency of elevated liver enzyme and white blood cell count, and lower lymphocyte count. As suggested by other studies, this suggests that AKI is a marker of disease severity, and that inflammation might contribute to AKI development [*45-48*]. Of 95 patient who had AKI, 35.8%(n=34) received RRT during in hospital stay. Renal recovery after AKI is important for patients, families, and all stakeholders involved. Our study showed that 66.7%(n=12) had recovered kidney function up on discharge based on SCr results and the rest, 33.3%(n=6) of patients being discharged with recovering kidney function and only one patient was transferred for maintenance dialysis, which is almost similar to many studies. Other studies reported renal recovery rates between 17 and 84% and dialysis dependence rates between 8 and 56.5% [*49*-56]. Our low dialysis dependence rates on discharge perhaps may be due to a relatively low proportion of patients with pre-existing CKD,14.1%(n=22).

AKI is an independent risk factor for increased mortality in all critical illness [57,58]. The reported incidence of AKI among critically ill COVID 19 patients in earlier cohorts from China was approximately 20–30% and it is regarded as a marker of disease severity [47,48]. Although the incidence of AKI in our cohort is higher than these early reports, it is comparable to the other international studies from Brazil [61] and USA [3]. Our renal replacement rate is also

comparable to the reports from larger cohorts with a rate of 20–31% [3,4]. However, in studies of mostly invasively ventilated critically ill COVID 19 patients, the incidence of AKI was reported to be as high as 75% with an RRT rate of 17.7–51% [59,18,19]. In contrast, our cohort was inclusive of patients with noninvasive ventilation, which may account for the difference in AKI prevalence, RRT rate and mortality.

14.1 In Relation to AKI in Other Disease

SARS-CoV-2 is hypothesized to directly injure kidneys and/ or to have a high risk of AKI. The risk of AKI in patients admitted to medical ICU with COVID-19 in our study was just over 60.9%. In cohorts of patients admitted to critical care with pneumonia, the risk of AKI was in between 18.0% to 34%. Similarly, in a cohort of patients admitted to the ICU with influenza in Korea, only 22.6% developed AKI [47]. Lower rates of AKI could simply reflect lesser severity of infection in non-COVID-19 cohorts, which may reflect attitudes toward admissions for patients with COVID-19. Our findings of AKI incidence in patients with COVID-19 are consistent with a systematic review conducted which found around 50-60% frequency of AKI in severe to critical COVID-19 populations, with an incidence of around 15% for AKI in patients with COVID-19 not stratified for severity [48]. It is interesting that AKI was so substantially more common in our cohort, when one considers the biologic rationale for direct kidney injury by the virus, compared to the commonly hypothesized ischemia reperfusion injury.

A recent multicenter cohort study further introduced how occurrence of AKI remained associated with COVID-19 and was not fully explained by adjustment for known renal risk factors such as demographic variables, comorbidities, and laboratory results. Whether the mechanism by which COVID-19 causes AKI is shared with other infections, its association with poor outcomes is very consistent. A meta-analysis of AKI in a mixture of surgical and critical care settings suggests mild, moderate, and severe AKI are associated with risk ratios for death of 1.67, 2.73, and 3.04, respectively [30]. Newly published studies follow the same trend of increasing mortality with increasing AKI severity, indicating little respite despite advances in clinical management [31].

Individual studies vary considerably in the magnitude of the association (e.g., 1.60 to 29.17 for severe to critical AKI) and our estimates are consistent within these ranges. While the relative risks of death associated with AKI are consistent, it is important to note that the relative risk of death in our study is high at almost over 50% for those with AKI, while existing literature notes absolute risk difference for AKI mortality to be 21.5% and relative risk at 3.63 (cumulative incidence of 29.6% in patients with AKI and 8.1% in non-AKI patients). These findings underscore the potential severity of COVID19 infections in patients admitted to hospital. Clinicians and investigators should be aware of these high risks of AKI, poor outcomes, and plan resources accordingly.

15. Conclusion

Acute kidney injury is a common feature in severe and critically ill patients with COVID-19 pneumonia presenting with acute hypoxic respiratory failure. It is more common in patients with immunosuppression, hypertension and diabetes. The development of AKI is associated with increased severity of illness, prolonged duration of hospitalization and increased mortality. Reassuringly, most surviving patients recovered from their acute kidney injury over time prior to their hospital discharge.

16. Limitations

Our study has several limitations. Firstly, this is a small cohort study of patients admitted with COVID-19 characterized by acute hypoxic respiratory failure and needing respiratory support may not be representative of all hospitalized COVID-19 patients. Secondly, due to the retrospective design, some laboratory results were not available for all patients. Third, we did not perform additional renal specific urine biological investigations (urinalysis and urine microscopy) to characterize the AKI, which limits our ability to evaluate the mechanism of renal injury. was not consistently performed in all patients. Fourth, we judged renal recovery based on SCr results at hospital discharge, but acknowledge that this may have over-estimated kidney function. Although this is a common problem in patients with AKI, we acknowledge that muscle wasting has been reported as a particularly common problem in COVID-19 infection. lastly, true baseline SCr results were not available in most of the patients and we used the SCr results on admission to hospital.

17. Strength

Whilst we recognize these limitations, our study has several strengths. It's the first in kind in our country and open a door for researcher who are interested in this area. we were still able to identify the prevalence, risk factors associated with the development of AKI and outcome of AKI recovery. Reassuringly, most patient who recovered from their acute illness have also completely recovered from their acute kidney injury. *Our results, however, are consistent with others globally.* data were collected from all severe and critically ill patients who were admitted consecutively, reducing selection bias.

18. Funding

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19. Recommendation

- ✓ Clinicians should be cognizant of this higher incidence of AKI in severe and critical covid-19 patients
- ✓ Efforts should be made to alleviate the risk including, the employment of good infection prevention practice to avoid hospital acquired infection that could contribute significantly to hospital acquired AKI and poor outcome in covid-19 patients.
- ✓ Given the high incidence of AKI, it's worth monitoring the renal status of patients after hospital discharge to further understand the natural course and help in the individual patient's management.
- ✓ We strongly recommend post discharge follow up of those patients.

20. Affiliations

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21. Ethics declaration

20.1 Ethical approval and consent to participate

- ✓ Ethical approval was obtained from TASH and Eka kotebe hospital REC.

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23. AKI questionnaire

TABLE 2.SOCIO-DEMOGRAPHIC DATA

1. **Age**
2. **Sex**
3. **Clinical setting**
   Medical covid-19 ICU
4. **Region**

TABLE 3.CHARLSON CO-MORBIDITY INDEX

1. Age	**<50 years (0)**		
	50- 59 years (+1)		
	60-69 years) +2)		
	70-79 years (+3)		
	>=80(+4)		
2. Diabetes mellitus	None or diet controlled (0)		
	Uncomplicated (+1)		
	End – organ damage (+2)		
3. Liver disease	None (0)		
	Mild (+1)		
	Moderate to severe (+3)		
4. Malignancy			
Solid tumor	None (0)		
	Localized (+2)		
	Metastatic (+6)		
Leukemia	Yes (+2)	No (0)	
Lymphoma	Yes (+2)	No (0)	
5. AIDS	Yes (+6)	No (0)	
6. Moderate to severe CKD	Yes (+2)	No (0)	
7. CHF	Yes (+1)	No (0)	
8. Myocardial infarction	Yes (+1)	No (0)	
9. COPD	Yes (+1)	No (0)	
10. Peripheral vascular disease	Yes (+1)	No (0)	
11. CVA OR TIA	Yes (+1+	No (0)	
12. Dementia	Yes (+1)	No (0)	
13. Hemiplegia	Yes (+2)	No (0)	
14. Connective tissue disease	Yes (+1)	No (0)	

15. Peptic ulcer disease	Yes (+1)	No (0)

TABLE 4. PATIENT CHARACTERISTICS

1. Hgb.	**>12 gm/dl**
	8-12 gm/dl
	<8 gm/dl
2. WBC	<4000
	4000-11,000
	>11,000
3. Lymphocyte count	>1500
	1000-1500
	500-1000
	<500
4. Platelet count	>150,000
	100,000-150,000
	50,000-100,000
	<50,000
5. Albumin	>3.5
	2-3.5
	<2
6. Proteinuria dip stick	Nill
	+1
	+2
	+3
7. Hematuria	0 Negative or trace
	+1 small
	+2 moderate
	+3 large
8. Sodium	<135
	135-145
	>145
9. Potassium	>6.5
	5.5-6.5
	3.5-5.5
	<3.5
10. Liver enzyme	<2x
AST	2-5x
Upper limit of lab. Normal	5-10x
	>10x
ALT	<2x
Upper limit of lab. Normal	2-5x
	5-10x
	>10x
ALK	Normal
Upper limit of lab. Normal	Increased/Raised

11. Peak AKI (from base line)	Stage I
	Stage II
	Stage III
12. Severity of Covid-19	Asymptomatic
	Mild
	Moderate
	Sever
	Critical
13. Vasopressor Need	Yes
	Yes
14. Mechanical ventilation	Yes
15. Outcome	
LOS (days)	
Mortality	Yes
Discharge	Yes
RRT	Yes
16.Treatment	
ACEI or ARBs	Yes
Metformin	Yes
ASA	Yes
Atorvastatin	Yes
HAART	Yes
16. Renal status at Discharge	Recovered
	Resolving
	Non-resolving
	Undetermined

TABLE 5. PROXIMATE CAUSE

Cause	Yes	No
1. Hypovolemia		
2. Sepsis		
3. Covid-19 related		
4. Obstructive Uropathy		
5. Nephrotoxic drugs		
6. Interstitial nephritis		
7. Undetermined		

Table 6: Indication for dialysis

Indication	Yes	No
1. Refractory fluid overload		
2. Uremic sign or symptoms		
a. Pericarditis		

b. **Encephalopathy**
c. **Uremic bleeding**

3. **Refractory hyperkaliemia**
4. **Anuria**
5. **Metabolic acidosis**

a. **Clinical**
b. **ABG**

TABLE 6.DIALYSIS AND CATHETER RELATED COMPLICATION

Events	Yes	No
1. Intra dialytic death		
2. Catheter related infection		
3. Vascular access thrombosis		
4. Reason for discontinuation		
5. Number of dialysis		

TABLE 7.DIALYSIS OUTCOME

Outcome	Yes	No
1. Resolving or resolved AKI		
2. Non –resolving		
3. Undetermined course		

TABLE 8.IMMEDIATE CAUSE OF DEATH

Cardiogenic shock	
Refractory septic shock	
Respiratory failure	
Sudden cardiac death	
Undetermined	
Others	

TABLE 9.FOR HOSPITAL ACQUIRED AKI

1. **Admission diagnosis**
2. **Cr. at admission**
3. **Cr .at dialysis**
4. **Proximate cause of AKI**
5. **Indication for dialysis**
6. **Outcome**