Statistical Analysis Plan

Acute Kidney Injury in COVID-19: secondary analysis of prospective data from the EthICAL study

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Introduction

Our understanding of COVID-19, a disease caused by the novel coronavirus, SARS-CoV-2 has been evolving rapidly since its outbreak in December 2019.[1] Initially understood primarily as a respiratory disease, evidence suggests that the virus has an impact on other organs, including the kidney.[2]

Pathogenesis of renal dysfunction in COVID-19 is likely multifactorial. ACE-2 receptors, the target for viral binding, are richly expressed in the renal tubular epithelium and podocytes.[3] Post-mortem examinations demonstrated that viral particles enter renal cells directly, leading to acute tubular necrosis and lymphocyte infiltration.[4,5,6] In some cases, the virus triggers an overwhelming inflammatory response and cause a cytokine storm, which can cause renal tissue destruction.[7] Additionally, the infection induces a hypercoagulable state,[8] which can lead to small vessel thrombosis within the kidney.[9] Besides the kidney-specific effects, systemic insults: dehydration, cardiac insufficiency, nephrotoxic medication and secondary sepsis all lead to renal underfilling and damage, further compounding the risk of acute kidney injury (AKI).[3]

The exact incidence of AKI in COVID-19 patients is unclear due to extreme heterogeneity of reports. An early Wuhan study found no cases of AKI amongst over a hundred patients in the COVID-19 cohort, even when minimum pre-admission creatinine value was used as baseline.[10] A large meta-analysis of nearly fifteen thousand patients from Europe, Asia and North America found that amongst 20 studies, rates of AKI ranged from 0.5% to 80.3%, with an average of 17%. Two other meta-analyses have recently reported incidence of 10%[11] and 8.4%,[12] respectively.

It remains unknown whether risk of AKI in COVID-19 is elevated compared to the general population of hospital inpatients, estimated at about 20%. [13,14] The first study to make a direct comparison found that among patients hospitalised during the pandemic, those positive for SARS-Cov-2 had a greater risk of AKI (56.9%) than those with a negative result (37.2%); although baseline characteristics varied significantly between groups.[15] Risk factors for AKI in COVID-19 patients seem to mirror those in the general population and include male sex, age, and presence of multiple comorbidities, including chronic kidney disease (CKD). [15–17]

AKI is a major cause of morbidity amongst COVID-19 patients. Although the majority of cases reported are classified as mild,[17] a proportion of patients develop severe renal failure,

with an estimated 5% requiring renal replacement therapy (RRT).[17,18] Amongst survivors, as many as 65.2% never recover their baseline renal function after the episode.[19,20]

AKI is also an independent predictor of mortality, even when adjusting for age, sex, disease severity and comorbidity burden.[21] A meta-analysis estimated mortality rate of up to 52%; individual studies have cited rates between 7% and 100%.[18] Prior to COVID-19, it was demonstrated that amongst hospitalised patients, development of AKI is associated with four-fold increase in risk of death.[13] AKI has been recognised as one of the major sources of preventable harm amongst inpatients, and has been a central focus of the national quality improvement framework in the last decade.[22,23]

In one of the largest and most detailed UK studies on AKI in COVID-19, we will investigate a cohort of nearly two thousand patients with confirmed SARS-Cov-2 infection admitted to five acute hospitals in East London. A previous study on this cohort investigated the association between ethnicity and outcomes.[24] This secondary analysis will focus on the incidence, risk factors and outcomes associated with AKI within this population. We will also examine follow-up data to investigate what proportion of COVID-19 patients who developed an AKI never recovered their renal function and progressed to chronic kidney disease (CKD).

Hypotheses

In line with other research, we expect that the rates of AKI amongst COVID-19 population will be high, and that the occurrence of AKI will be associated with poorer outcomes, including death, risk of ICU admission, and prolonged length of stay.

Study objectives and outcomes

Primary objective

To quantify the incidence of AKI in COVID-19 patients defined and determine risk factors for the development of AKI.

Secondary objective

To determine whether development of AKI in COVID-19 patients is associated with greater disease severity and worse outcomes. The primary outcome measure will be survival to 30-days, secondary outcome measures are listed below.

Outcome measures

Mortality:

- 30-day (**primary**)
- 90-day

Length of stay:

- Duration in hospital
- Duration on ICU

Disease severity:

- Admission to ITU
- Need for organ support
    - Mechanical ventilation

    - Renal replacement therapy (RRT)

Delayed recovery:

- Discharge destination other than usual place of residence
- Subsequent CKD diagnosis

Composite outcome at day 90 (MAKE90)

- Death within 90 days
- Worsened renal function defined as eGFR <70% of baseline in survivors

Methods

Study cohort

This secondary analysis will be carried out using the dataset of all patients included in the EthICAL study on ethnic disparities in COVID-19 outcomes.[24] Details of data collection, data management and permissions are detailed in the EthICAL study documents. This cohort will include patients with a diagnosis of SARS-Cov-2 confirmed on PCR having an inpatient admission to any hospital within Barts Health Trust between 1st March and 13th May 2020. Follow-up data were available up to 1st December 2020. For this analysis, we will exclude only patients with available urea and creatinine data.

Data analysis

Definition of key variables

Acute Kidney Injury

Acute Kidney Injury (AKI) is defined according to KDIGO criteria.[25] The median creatinine value in the 7-365 days prior to admission will be used as baseline value. If no prior results are available, value will be imputed based on eGFR of 75ml/min/1.72m^2 or the admission value, whichever is lower.

Any rise in creatinine meeting criteria within the first 7 days of admission with be classified as AKI. Patients with AKI will be stratified into three groups based on severity: Stage 1 (peak creatinine 1.5-1.9 times baseline or ≥ 26.5 μmol/L increase in 48h); Stage 2 (peak creatinine 2.0-2.9 times baseline); and Stage 3 (peak creatinine 3 times baseline; ≥ 26μmol/L increase to a value of 353.6 μmol/L or higher; or initiation of RRT).

Stage	Serum creatinine	Urine output
1	1.5–1.9 times baseline or ≥0.3 mg/dl (≥26.5 μmol/l) increase	<0.5 ml/kg/h for 6–12 h
2	2.0–2.9 times baseline	<0.5 ml/kg/h for ≥12 h
3	3 times baseline or ≥4.0 mg/dl (≥353.6 μmol/l) increase or initiation of RRT or in patients <18 years a decrease in eGFR <35 ml/min/1.73 m^2	<0.3 ml/kg/h for ≥24 h or anuria ≥12 h

Table 1: KDIGO criteria for diagnosis of Acute Kidney Injury. [25] In this analysis, only biochemical criteria will be used as there is no data regarding urine outputs is available.

Comorbidity and Hospital Frailty Risk score

ICD-10 codes for all previous hospital encounters up to the current admission will be used to identify significant pre-admission co-morbidities. Cumulative Charlson comorbidity index[26] and Hospital Frailty Risk Score will be calculated using this information.[27]

Body mass index (BMI)

BMI will be calculated using weight and height taken at current or (if unavailable) penultimate admission episode.

Chronic Kidney Disease (CKD)

Cases of moderate-to-severe CKD will be defined as three or more months of eGFR of <60 mL/min/1.73m2, corresponding to moderate-to-severe CKD based on 2005 KDIGO classification. [28]

		Classification by severity		
Stage	Description	GFR mL/min/1.73 m^2	Related terms	Classification by treatment
1	Kidney damage with normal or ↑ GFR	≥90	Albuminuria, proteinuria, hematuria	
2	Kidney damage with mild ↓ GFR	60–89	Albuminuria, proteinuria, hematuria	
3	Moderate ↓ GFR	30–59	Chronic renal insufficiency, early renal insufficiency	T if kidney transplant recipient
4	Severe ↓ GFR	15–29	Chronic renal insufficiency, late renal insufficiency, pre-ESRD	
5	Kidney failure	<15 (or dialysis)	Renal failure, uremia, end-stage renal disease	
				D if dialysis (hemodialysis, peritoneal dialysis)

Abbreviations are: GFR, glomerular filtration rate; ESRD, end-stage renal disease.
Related terms for CKD stages 3 to 5 do not have specific definitions, except ESRD.

Table 2: KDIGO classification of Chronic Kidney Disease.[28]

Mortality

Up to date information regarding death was extracted on 1st December 2020. Death is defined as the presence of date of death or "patient died" as discharge destination in the EMR database (synchronised with NHS Spine to capture out of hospital deaths).

Software

Data will be stored in Microsoft Excel (2019; version 16.34) and analysed using R software (R core team; 2020)

Statistical analysis

Baseline characteristics

Baseline characteristics for patients with and without AKI will be summarised. AKI will be categorised by stage. Numbers (%), means (SD), and medians (IQR) will be provided separately for each group. The study groups will be compared using simple univariate tests. The difference between means of continuous variables will be analysed using ANOVA. For dichotomous data, Pearson Chi-square or Fisher exact test (if expected number <5) will be used.

	no AKI	AKI Stage 1	AKI Stage 2	AKI Stage 3	p value
Age					
Sex					
Smoking					
BMI					
Hospital Frailty Risk Score					
Cumulative Charlson Co-morbidity Index					
MI					
CHF					
PVD					
CVD					
Dementia					
COPD					
Rheum disease					
Peptic ulcer					
Mild liver disease					
cDM					

DM					
Haemiplegia/ paraplegia					
Backg CKD					
ESRD					
Malignancy					
New CKD					
Death					
RRT					
Mechanical ventilation					

Sample Table 1: The assessment of risk factors and outcomes associated with AKI amongst COVID-19 patients

Comparison of clinical outcomes

Survival analyses will be carried out using Cox-proportional hazard models to determine the difference in 30-day mortality between the patients who develop AKI compared to patients who do not. Multivariable models will adjust for baseline risk factors including:

- Age
- Sex
- Smoking status
- Co-morbidities
    - Diabetes
    - HTN
    - CKD

Logistic and linear regression models will be used to assess the between-group differences for additional categorical and continuous secondary outcomes, respectively.

Sensitivity analysis

Secondary analysis of outcomes will be carried out for the following groups:

- **Late AKI** – patients who only developed AKI after day 7 of admission
- **Persistent AKI** – patients whose AKI persisted at day 7, including those who died before day 7 and all RRT patients
- **Recovered AKI** – patients no longer meeting criteria for AKI at day 7 or at any later point during the admission
- **Relapsed AKI** – patients recovered at day 7 who met criteria for AKI again at a later point during the admission

Baseline creatinine values will be the same as in primary analysis.

Survival will also be assessed using 90-day mortality.

Subgroup analysis will be carried out in patients without pre-existing CKD.

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