Long-term kidney function recovery and mortality after COVID-19-associated acute kidney injury: an international multi-centre observational cohort study

Byorn W. L. Tan,[a,aa] Bryce W. Q. Tan,[a,aa] Amelia L. M. Tan,[b] Emily R. Schriver,[c] Alba Gutiérrez-Sacristán,[b] Priyam Das,[b] William Yuan,[b] Meghan R. Hutch,[d] Noelia García Barrio,[e] Miguel Pedrera Jimenez,[e] Noor Abu-el-rub,[f] Michele Morris,[g] Bertrand Moal,[h] Guillaume Verdy,[h] Kelly Cho,[i] Yuk-Lam Ho,[i] Lav P. Patel,[f] Arianna Dagliati,[j] Antoine Neuraz,[k] Jeffrey G. Klann,[l] Andrew M. South,[m] Shyam Visweswaran,[g] David A. Hanauer,[n] Sarah E. Maidlow,[o] Mei Liu,[f] Danielle L. Mowery,[p] Ashley Batugo,[q] Adeline Makoudjou,[r] Patric Tippmann,[r] Daniela Zöller,[r] Gabriel A. Brat,[b] Yuan Luo,[d] Paul Avillach,[b] Riccardo Bellazzi,[j] Luca Chiovato,[s] Alberto Malovini,[t] Valentina Tibollo,[t] Malarkodi Jebathilagam Samayamuthu,[g] Pablo Serrano Balazote,[e] Zongqi Xia,[u] Ne Hooi Will Loh,[v] Lorenzo Chiudinelli,[w] Clara-Lea Bonzel,[b] Chuan Hong,[x,b] Harrison G. Zhang,[b] Griffin M. Weber,[b] Isaac S. Kohane,[b] Tianxi Cai,[b] Gilbert S. Omenn,[y] John H. Holmes,[p,q] and Kee Yuan Ngiam,[z,*] The Consortium for Clinical Characterization of COVID-19 by EHR (4CE)[b]

[a]Department of Medicine, National University Hospital, 1E Kent Ridge Road, NUHS Tower Block Level 10, Singapore 119228
[b]Department of Biomedical Informatics, Harvard Medical School, 10 Shattuck Street, Boston, MA 02115, USA
[c]Data Analytics Center, University of Pennsylvania Health System, 3600 Civic Center Boulevard, Philadelphia, PA 19104, USA
[d]Department of Preventive Medicine, Northwestern University, 750 North Lake Shore Drive, Chicago, IL 60611, USA
[e]Department of Health Informatics, Hospital Universitario 12 de Octubre, Av. de Córdoba, s/n 28041 Madrid, Spain
[f]Department of Internal Medicine, Division of Medical Informatics, University of Kansas Medical Center, 3901 Rainbow Blvd, Kansas City, KS 66160, USA
[g]Department of Biomedical Informatics, University of Pittsburgh, 5607 Baum Blvd, Pittsburgh, PA 15206, USA
[h]IAM Unit, Bordeaux University Hospital, Place Amélie Rabat Léon, 33076 Bordeaux, France
[i]Massachusetts Veterans Epidemiology Research and Information Center, VA Boston Healthcare System, 2 Avenue De Lafayette, Boston, MA 02130, USA
[j]Department of Electrical, Computer and Biomedical Engineering, University of Pavia, Italy, Via Ferrata 5, 27100 Pavia, Italy
[k]Department of Biomedical Informatics, Hôpital Necker-Enfants Malade, Assistance Publique Hôpitaux de Paris, University of Paris, 149 Rue de Sèvres, 75015 Paris, France
[l]Department of Medicine, Massachusetts General Hospital, 55 Fruit Street, Boston, MA 02114, USA
[m]Department of Pediatrics-Section of Nephrology, Brenner Children's Hospital, Wake Forest School of Medicine, Medical Center Boulevard, Winston Salem, NC 27157, USA
[n]Department of Learning Health Sciences, University of Michigan Medical School, Ann Arbor, Michigan, USA, 100-107 NCRC, 2800 Plymouth Road, Ann Arbor, MI 48109, USA
[o]Michigan Institute for Clinical and Health Research (MICHR) Informatics, University of Michigan, NCRC Bldg 400, 2800 Plymouth Road, Ann Arbor, MI, United States
[p]Department of Biostatistics, Epidemiology, and Informatics, University of Pennsylvania Perelman School of Medicine, 3700 Hamilton Walk, Richards Hall, A202, Philadelphia, PA 19104, USA
[q]Institute for Biomedical Informatics, University of Pennsylvania Perelman School of Medicine, 401 Blockley Hall 423 Guardian Drive Philadelphia, PA 19104, USA
[r]Institute of Medical Biometry and Statistics, Faculty of Medicine and Medical Center, University of Freiburg, Zinkmattenstraße 6a, DE79108 Freiburg, Germany
[s]Unit of Internal Medicine and Endocrinology, Istituti Clinici Scientifici Maugeri SpA SB IRCCS, Via Maugeri 4, 27100 Pavia, Italy
[t]Laboratory of Informatics and Systems Engineering for Clinical Research, Istituti Clinici Scientifici Maugeri SpA SB IRCCS, Pavia, Italy., Via Maugeri 4, 27100 Pavia, Italy
[u]Department of Neurology, University of Pittsburgh, 3501 5th Avenue, BST-3 Suite 7014, Pittsburgh, PA 15260, USA
[v]Department of Anaesthesia, National University Health System, 5 Lower Kent Ridge Road, Singapore 119074
[w]UOC Ricerca, Innovazione e Brand reputation, ASST Papa Giovanni XXIII, Bergamo, P.zza OMS 1 - 24127 Bergamo, Italy
[x]Department of Biostatistics and Bioinformatics, Duke University, 2424 Erwin Road, Durham, NC, United States
[y]Department of Computational Medicine & Bioinformatics, University of Michigan, 2017B Palmer Commons, 100 Washtenaw, Ann Arbor, MI 48109-2218

*Corresponding author. Department of Biomedical Informatics, WiSDM, National University Health Systems Singapore, 1E Kent Ridge Road, NUHS Tower Block Level 8, Singapore 119228.
E-mail address: kee_yuan_ngiam@nuhs.edu.sg (K.Y. Ngiam).
[aa]Equal contributions

[z]Department of Biomedical Informatics, WiSDM, National University Health Systems Singapore, 1E Kent Ridge Road, NUHS Tower Block Level 8, Singapore 119228

eClinicalMedicine
2023;55: 101724
Published Online 7 November 2022
https://doi.org/10.1016/j.eclinm.2022.101724

Summary

Background While acute kidney injury (AKI) is a common complication in COVID-19, data on post-AKI kidney function recovery and the clinical factors associated with poor kidney function recovery is lacking.

Methods A retrospective multi-centre observational cohort study comprising 12,891 hospitalized patients aged 18 years or older with a diagnosis of SARS-CoV-2 infection confirmed by polymerase chain reaction from 1 January 2020 to 10 September 2020, and with at least one serum creatinine value 1–365 days prior to admission. Mortality and serum creatinine values were obtained up to 10 September 2021.

Findings Advanced age (HR 2.77, 95%CI 2.53–3.04, p < 0.0001), severe COVID-19 (HR 2.91, 95%CI 2.03–4.17, p < 0.0001), severe AKI (KDIGO stage 3: HR 4.22, 95%CI 3.55–5.00, p < 0.0001), and ischemic heart disease (HR 1.26, 95%CI 1.14–1.39, p < 0.0001) were associated with worse mortality outcomes. AKI severity (KDIGO stage 3: HR 0.41, 95%CI 0.37–0.46, p < 0.0001) was associated with worse kidney function recovery, whereas remdesivir use (HR 1.34, 95%CI 1.17–1.54, p < 0.0001) was associated with better kidney function recovery. In a subset of patients without chronic kidney disease, advanced age (HR 1.38, 95%CI 1.20–1.58, p < 0.0001), male sex (HR 1.67, 95%CI 1.45–1.93, p < 0.0001), severe AKI (KDIGO stage 3: HR 11.68, 95%CI 9.80–13.91, p < 0.0001), and hypertension (HR 1.22, 95%CI 1.10–1.36, p = 0.0002) were associated with post-AKI kidney function impairment. Furthermore, patients with COVID-19-associated AKI had significant and persistent elevations of baseline serum creatinine 125% or more at 180 days (RR 1.49, 95%CI 1.32–1.67) and 365 days (RR 1.54, 95%CI 1.21–1.96) compared to COVID-19 patients with no AKI.

Interpretation COVID-19-associated AKI was associated with higher mortality, and severe COVID-19-associated AKI was associated with worse long-term post-AKI kidney function recovery.

Funding Authors are supported by various funders, with full details stated in the acknowledgement section.

Keywords: COVID-19; Acute kidney injury; SARS-CoV-2; Chronic kidney disease; Electronic health records

Introduction

While the clinical syndromes of SARS-CoV-2 infection and COVID-19 have wide inter-patient variation ranging from mid-upper respiratory tract infection to critical illness with multiorgan failure, acute kidney injury (AKI) is a common COVID-19 complication in up to 46% of patients.[1,2] AKI is associated with higher mortality in patients with COVID-19,[3] but data on kidney function post-discharge in a large cohort was lacking, with a small study observing decreased kidney function in 182 COVID-19 patients with AKI.[4] As AKI is a clinically significant risk factor for chronic kidney disease (CKD), long-term post-acute sequelae of COVID-19-associated AKI warrants further investigation. However, to date, there have been several key limitations in studies on kidney function recovery outcomes in COVID-19-associated AKI. First, studies on kidney function recovery lacked adequate pre-admission serum creatinine levels to quantitatively measure kidney function decline post-AKI,[5,6] and may underestimate pre-existing undiagnosed CKD prior to admission for COVID-19. Second, kidney function outcomes of COVID-19-associated AKI have been defined either by: a) post-discharge kidney function estimates including estimated glomerular filtration rate (eGFR) which grossly underestimated the baseline serum creatinine levels,[4] or b) clinical measures of major adverse kidney events including kidney replacement therapy (KRT) that underestimated the onset of CKD after the inciting AKI episode.[7] Lastly, the observational periods of these cohort studies ranged from 3 to 10 months, and do not reflect long-term kidney function impairment more than 1-year post-AKI.[4–8]

As early prediction of kidney function trajectory in patients with COVID-19-associated AKI is crucial to mitigating morbidity and mortality, we aimed to characterize temporal trajectories of kidney function preceding and following COVID-19-associated AKI. We also sought to identify clinical factors associated with mortality and impaired long-term kidney function recovery.

Research in context

Evidence before this study

While acute kidney injury (AKI) is prevalent in COVID-19 patients, the long-term kidney function recovery outcomes of COVID-19-associated AKI remained poorly understood. Current studies are limited by the lack of appropriate definition of baseline pre-admission serum creatinine, quantitative estimates of long-term kidney function decline, and a large, multi-centre cohort to generalize their findings. Moreover, short follow-up time in current studies precludes accurate estimates of long-term kidney function recovery outcomes.

Added value of this study

COVID-19-associated AKI was prevalent in 49.5% of 12,891 COVID-19 patients in 15 tertiary healthcare centres across five countries. Moreover, COVID-19-associated AKI was associated with worse long-term kidney function recovery, and higher long-term all-cause mortality even in survivors 30 days after the initial AKI event. Advanced age, severe COVID-19, severe AKI, and ischemic heart disease were significantly associated with greater mortality. Severe AKI was significantly associated with worse long-term kidney function recovery, whereas remdesivir use was associated with better kidney function recovery in a subset of patients. In patients with no chronic kidney disease at baseline, advanced age, male sex, severe AKI and hypertension were associated with kidney function impairment, whereas prior exposure to ACE-inhibitors or angiotensin-II receptor blockers, nor redemsivir conferred any reno-protective effects.

Implications of all the available evidence

COVID-19-associated AKI is associated with poor long-term kidney function recovery, and further studies are warranted to identify therapeutic strategies to delay the onset and/or progression into chronic kidney disease after an inciting AKI event.

Methods

Cohort identification

The cohort of patients in this analysis was derived from 15 institutions in 11 healthcare systems participating in the 4CE Consortium (Table S1, appendix pp3),[9] and included all hospitalized patients aged 18 years or older with a diagnosis of SARS-CoV-2 infection confirmed by polymerase chain reaction test from 1 January 2020 to 10 September 2020, and with at least one serum creatinine value 1–365 days prior to admission. Laboratory results, diagnostic and procedure codes obtained between 365 days prior to day of admission and at least 365 days since the first admission up to 10 September 2021 were included in the analyses, except for Northwestern University, which was up to 10 August 2021. To conform to consortium and institutional requirements for patient-level data, patient ages were obfuscated and binned into age groups prior to analysis.

Definitions

Severe COVID-19 was defined as the presence of any of the following in each patient's electronic health record (EHR) exclusively in the first admission for SARS-CoV-2 infection: (i) arterial blood gas results, (ii) medication orders for sedatives, anaesthetics, or vasopressors, (iii) diagnostic codes for acute respiratory distress syndrome and ventilator-associated pneumonia, and (iv) procedure codes for endotracheal tube insertion or invasive mechanical ventilation during the hospitalization (Table S2, appendix pp4). This severity definition was validated against COVID-19 patients across 12 institutions examining the pooled outcome of intensive care unit admission and/or death.[10]

Baseline serum creatinine (bCr) was defined as the lowest creatinine value for a given patient within 365 days prior to AKI onset or 365 days post-AKI. As the initiation of RRT during hospitalization and advanced CKD may severely confound the interpretation of temporal serum creatinine changes, patients with advanced stages of CKD as defined by a bCr of ≥2.25 mg/dL, kidney failure, or the presence of RRT procedure codes either during their index SARS-CoV-2 admission or pre-admission (Table S2, appendix pp4) were excluded from the analyses. The 2.25 mg/dL cutoff was chosen as it corresponds to an eGFR of 30 mL/mL/min/1.73m^2 for a 60-year-old non-Black male using the 2009 CKD-EPI eGFR estimating equation. As there may be imperfect recording of RRT procedure codes across all healthcare systems, we reasoned that a large and rapid decrease of serum creatinine over a short period of time in patients with severe AKI would be likely due to RRT initiation rather than from physiological processes. Thus, we additionally excluded patients who had a 25% decrease in serum creatinine from a value ≥3 mg/dL within 24 h.

AKI was defined by Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for serum creatinine only.[11] The severity of the index AKI episode of the index admission for COVID-19 was graded using the KDIGO definition: stage 1 AKI was defined as a peak serum creatinine:baseline creatinine (pCr/bCr) ratio of 1.5 to <2.0 or a rise in serum creatinine of ≥0.3 mg/dL; stage 2 AKI was defined as a pCr/bCr ratio of 2.0 to <3.0, and stage 3 AKI was defined as a pCr/bCr ratio of ≥3.0. For patients with AKI, time to kidney function recovery was defined as the earliest point in time after pCr in which serum creatinine decreased to ≤125% of bCr.[2]

Medical comorbidities were defined using International Classification of Diseases and Related Health Problems 9th revision (ICD-9) or 10th revision (ICD-10) diagnosis codes (Table S2, appendix pp4). A complete list of antiviral, antiplatelet and anticoagulant medications are defined in Table S3 (appendix pp5).

Patient data collection & federated analysis

The protocol for data collection and aggregation at each institution was described previously.[9] Patient-level data was kept at each institution, and R packages implementing the statistical analysis and quality control required for the study were run locally at each institution (appendix pp3–5). Processed data produced by the R package contains aggregate serum creatinine:baseline creatinine (sCr/bCr) values, hazard ratios (HR) from Cox proportional hazard modelling, and life tables from survival analysis. Only means, standard errors, and total number of patients at each time point were transmitted. Files containing aggregate values were shared from each institution and consolidated for meta-analysis.

Outcomes

The primary outcome was mortality from time of pCr. In patients with AKI, this was defined as time of pCr in the first AKI episode in the index admission. For patients without AKI, this was defined as the time of the highest sCr value in the index admission. Secondary outcomes were (i) time for kidney function recovery to ≤125% of baseline serum creatinine, and, for the subgroup of patients without CKD, (ii) time to chronic kidney function impairment, defined as the time of sustained rise in sCr ≥1.29 mg/dL for at least two consecutive sCr values spaced ≥24 h apart with no further decreases to <1.29 mg/dL. Examples of serum creatinine trends are illustrated in Figure S1 (appendix pp12–13) to demonstrate the times of kidney function recovery and kidney function impairment in the subgroup of patients without CKD.

Figure S1 Case (a) denotes the scenario where a patient with a baseline serum creatinine (sCr) lower than 1.29 mg/dL recovers to a level below 1.25-fold baseline sCr which is also 1.29 mg/dL (time A). Thus, time A corresponds to the time of kidney function recovery. The transient rise above 1.29 mg/dL at time B before decreasing below 1.29 mg/dL does not yet constitute a sustained sCr rise, but the subsequent sustained rise to ≥1.29 mg/dL at time C corresponds to kidney function impairment.

Similarly, for Figure S1 Case (b) where the patient has not recovered to a level below 1.25-fold baseline sCr, this patient is considered to not have achieved kidney function recovery and is considered to only have kidney function impairment from time E onwards. The transient rise ≥1.29 mg/dL between times D and E is not counted as a sustained sCr rise.

Cases where the threshold for kidney function recovery may be above ≥1.29 mg/dL are illustrated in Figure S1 examples (c) and (d). In Figure S1 Case (c) where the patient recovers to a level lower than both ≥1.29 mg/dL and the kidney function recovery threshold, the corresponding time of kidney function recovery is time F, and is considered to only have kidney function impairment from time H onwards. Similarly, the transient rise ≥1.29 mg/dL between times G and H is not counted as a sustained sCr rise.

Figure S1 Case (d) illustrates a patient who recovers to a level lower than 1.25-fold baseline sCr, but never achieves a sCr value lower than 1.29 mg/dL subsequently. Such cases are encountered for patients who may be admitted at a time closest to the peak sCr of the COVID-19-associated AKI. In this case, the time of kidney function impairment is taken to be time I, while the corresponding time of kidney function recovery is time J.

Local data collection, quality control and data analysis standardization

The methods for data extraction at each institution have been previously described.[1] Briefly, each institution executed Structured Query Language (SQL) queries on local clinical databases, using Informatics for Integrating Biology and the Bedside (i2b2) platform, Observational Medical Outcomes Partnership (OMOP) Common Data Model, Epic Clarity, or other clinical database infrastructures, to extract patient-level data. Data fields extracted included demographics characteristics, clinical course, medication classes, International Statistical Classification of Diseases and Related Health Problems, 9th or 10th Edition (ICD-9 or ICD-10) diagnoses codes, and laboratory values identified by logical identifier names and codes (LOINC) at an individual patient level in a format standardized across the 4CE Consortium. Patient level data were strictly kept to each institution for executing analytical code locally, and no patient-level data were transmitted between sites.

To ensure consistency and quality control across all participating institutions, a R package was run at each institution to verify file and column names, data types, code values and ranges, and presence of duplicate values.[9] The functions for quality check from the R package were also implemented in our analytical R package to ensure adequate data quality prior to data analyses. The R package used for quality check can be accessed at https://github.com/covidclinical/Phase2.1DataRPackage.

To minimize variations in analytical techniques arising from package version differences in R, most institutions used a standardised Docker image containing Microsoft R Open (R version 4.0.2) and pre-installed

R packages. For institutions which were unable to implement Docker containers locally, the minimum R version (R 4.0.2) and R package versions were met. The R package used for analysis in this study also enforced strict version requirements before analyses could be run. The files necessary to build the Docker image are available at https://github.com/covidclinical/Phase2.1DockerAnalysis.

Statistical analysis

Baseline patient characteristics were summarised as counts and percentages. Fisher's exact test was used to compare categorical variables between groups.

For computation of aggregate sCr/bCr across healthcare systems, means and standard errors for daily sCr/bCr values were weighted with the number of patients with sCr values on that day across each healthcare system. For time-to-event mortality analyses, Kaplan–Meier curves with 95% confidence interval (CI) were plotted from life tables aggregated across all institutions and compared with log-rank test. Patients were censored at the last available electronic record. Incidence rate ratios (IRRs) were calculated for 30-day survivors for computation of all-cause mortality risk. IRR CIs and p-values were computed using exact Poisson confidence limits and mid-P methods respectively. Time-to-event analyses were taken with respect to the first AKI episode in the first admission for SARS-CoV-2 infection.

To explore associations of clinical factors with mortality, kidney function recovery, and kidney function impairment, multivariable Cox proportional hazard models were generated at each healthcare system. Multivariable analyses included age ≥70 years, male sex, COVID-19 severity, AKI KDIGO stage, CKD, hypertension, cirrhosis, ischemic heart disease, chronic obstructive pulmonary disease (COPD), previous venous thromboembolism (VTE), COVID-19-targeting antivirals, antiplatelet and anticoagulant medications. Subgroup analyses on mortality in patients with AKI were performed. Baseline sCr, stratified using cut-off values of 0.92 mg/dL and 1.29 mg/dL (corresponding respectively to eGFRs of 90 mL/min/1.73 m^2 and 60 mL/min/1.73 m^2 in a 60-year-old non-Black male by the 2009 CKD-EPI eGFR equation), and the timing of baseline sCr measurement, were also included in supplemental models. Estimated coefficients for covariates with low event incidences (<5 events) would not be computed at the institution level, and the number of institutions and sample sizes contributing to each estimated coefficient are reported. Data from National University Hospital Singapore was excluded from mortality analysis as no mortality events occurred.

For kidney function recovery and kidney function impairment, competing risk analyses was performed with death as the competing event and censoring at the last available electronic record. Cumulative incidence curves with 95% CI for secondary outcomes were plotted from aggregated life tables and compared with Gray's test. Cause-specific Cox models were constructed for each secondary outcome with the same covariates for mortality analysis as outlined above. Cause-specific Cox regression was chosen as the study was focused on investigating long-term secondary outcomes in the group of patients surviving their initial COVID-19 admission.

To account for differences in inter-institution demographic and comorbidity distribution, a random-effects meta-analysis with the DerSimonian-Laird method was performed to pool estimates for each covariate.

Statistical analysis was done in R version 4.0.2 (R Project for Statistical Computing). Analytical source code is available on GitHub (https://github.com/covidclinical/Phase2.1AKIRPackage). A two-sided p-value of <0.05 was considered statistically significant. To adjust for multiple comparisons in multivariable models for mortality and kidney function recovery, Bonferroni correction was applied with a p-value of <0.0029 (0.05/17 covariates) considered to be statistically significant.

Ethics

This study was determined to be exempt as secondary research by institutional review boards at Bordeaux University Hospital, Istituti Clinici Scientifici Maugeri (Pavia, Lumezzane/Brescia & Milano Hospitals), University of Kansas Medical Center, National University Hospital Singapore, Northwestern University, University of Freiburg Medical Center, University of Michigan, University of Pennsylvania, University of Pittsburgh, Harvard Medical School (VA Boston Healthcare System) and Wake Forest University School of Medicine.

Data access

All aggregate data in a de-identified fashion can be found and downloaded at www.covidclinical.net.

Role of funders

The funders have no role in data collection, analysis, interpretation, writing of the manuscript and the decision to submit the manuscript.

Results

Table 1 presents baseline patient characteristics of the cohort comprising 12,891 patients, with a median follow-up time of 430 days (interquartile range 382–502 days). Fig. 1 presents the flow diagram of patients included in this analysis. Among this cohort, 50.5% of patients had at least one episode of AKI. Patients with AKI were more likely to be male sex (77.8% vs. 71.2%), older (≥70 years old: 55.0% vs. 35.9%), and have severe

		Total	Non-AKI	AKI	P-value
N (%)		12,891 (100.0)	6386 (49.5)	6505 (50.5)	–
Sex (n, %)	Female	3280 (25.4)	1839 (28.8)	1441 (22.2)	<0.0001
	Male	9611 (74.6)	4547 (71.2)	5064 (77.8)	
Deceased (n, %)		2783 (21.6)	667 (10.4)	2116 (32.5)	<0.0001
Age, years (n,%)	18–25	138 (1.1)	91 (1.4)	47 (0.7)	<0.0001
	26–49	1967 (15.3)	1374 (21.5)	593 (9.1)	
	50–69	4913 (38.1)	2625 (41.1)	2288 (35.2)	
	70–79	3435 (26.6)	1371 (21.5)	2064 (31.7)	
	≥80	2432 (18.9)	919 (14.4)	1513 (23.3)	
	Obfuscated	6 (0.0)	6 (0.1)	0 (0.0)	
Ethnicity (n, %)	American Indian	36 (0.3)	21 (0.3)	15 (0.2)	<0.0001
	Asian	235 (1.8)	139 (2.2)	96 (1.5)	
	Black	4393 (34.1)	1949 (30.5)	2444 (37.6)	
	Hawaiian Pacific Islander	34 (0.3)	29 (0.5)	5 (0.1)	
	Hispanic Latino	166 (1.3)	119 (1.9)	47 (0.7)	
	White	6215 (48.2)	3078 (48.2)	3137 (48.2)	
	Others	1682 (13)	993 (15.5)	689 (10.6)	
	Obfuscated	141 (1.1)	58 (0.9)	83 (1.3)	
Severe COVID-19 (n, %)		5589 (43.4)	1778 (27.8)	3811 (58.6)	<0.0001
AKI KDIGO Stage (n,%)	No AKI	6386 (49.5)	6386 (100.0)	–	–
	Stage 1	4480 (34.8)	–	4480 (68.9)	
	Stage 2	1102 (8.5)	–	1102 (16.9)	
	Stage 3	923 (7.2)	–	923 (14.2)	
Time to Kidney Function Recovery (n, %)	≤7 days	2031 (31.2)	–	2031 (31.2)	–
	8–30 days	1398 (21.5)	–	1398 (21.5)	
	31–60 days	367 (5.6)	–	367 (5.6)	
	61–90 days	161 (2.5)	–	161 (2.5)	
	>90 days, or no recovery at end of follow-up	2548 (39.2)	–	2548 (39.2)	
Comorbidities (n, %)	Chronic kidney disease	4938 (38.3)	1829 (28.6)	3109 (47.8)	<0.0001
	Liver cirrhosis	365 (2.8)	155 (2.4)	210 (3.2)	<0.0001
	Hypertension	6601 (51.2)	2710 (42.4)	3891 (59.8)	<0.0001
	Ischaemic heart disease	2260 (17.5)	804 (12.6)	1456 (22.4)	<0.0001
	Chronic obstructive pulmonary disease	1572 (12.2)	610 (9.6)	962 (14.8)	<0.0001
	Rheumatological conditions	453 (3.5)	202 (3.2)	251 (3.9)	<0.0001
	Prior venous thromboembolism	2178 (16.9)	856 (13.4)	1322 (20.3)	<0.0001
Medications (n, %)	Antiplatelet use	1176 (9.1)	456 (7.1)	720 (11.1)	<0.0001
	Anticoagulation use	12,010 (93.2)	5830 (91.3)	6180 (95.0)	<0.0001
COVID-19 Antiviral Therapy (n, %)	All	856 (6.6)	327 (5.1)	529 (8.1)	<0.0001
	Remdesivir	699 (5.4)	252 (3.9)	447 (6.9)	<0.0001
	Other direct-acting antivirals	158 (1.2)	75 (1.2)	83 (1.3)	<0.0001
Prior ACE-i/ARB Use (n, %)		3893 (30.2)	1571 (24.6)	2322 (35.7)	<0.0001
Follow-up time, days (median, IQR)		430 (382–502)	427 (379–500)	432 (385–506)	–
Time from baseline sCr to admission, days (n, %)	0–90	11,391 (88.4)	5922 (92.7)	5469 (84.1)	<0.0001
	91–180	509 (3.9)	175 (2.7)	334 (5.1)	
	181–365	991 (7.7)	289 (4.5)	702 (10.8)	
Baseline sCr, mg/dL (n, %)	<0.92	9048 (70.2)	4996 (78.2)	4052 (62.3)	<0.0001
	0.92–1.29	2593 (20.1)	1143 (17.9)	1450 (22.3)	
	>1.29	1250 (9.7)	247 (3.9)	1003 (15.4)	

Abbreviations: ACE-i: angiontensin-converting enzyme inhibitor; AKI: acute kidney injury; ARB: angiotensin-II receptor blocker; KDIGO: Kidney Disease: Improving Global Outcomes; N: sample size.

Table 1: **Demographics and baseline patient characteristics across all institutions.**

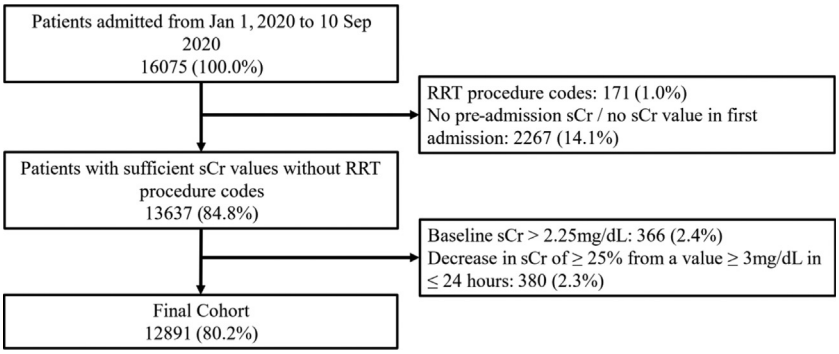


***Fig. 1:* Flow diagram of study construct**. Abbreviations: mg/dL: milligram per decilitre; RRT: renal replacement therapy; sCr: serum creatinine.

COVID-19 (58.6% vs. 27.8%). Patients with COVID-19-associated AKI were more likely to have CKD (47.8% vs. 28.6%), cirrhosis (3.2% vs. 2.4%), hypertension (59.8% vs. 42.4%), ischemic heart disease (22.4% vs. 12.6%), COPD (14.8% vs. 9.6%), and prior VTE (20.3% vs. 13.4%). Patients with AKI were also more likely to be on anticoagulants (95.0% vs. 91.3%), antiplatelets (11.1% vs. 7.1%) and antiviral medications (8.1% vs. 5.1%). Compared to patients without AKI, patients with AKI had higher mortality (32.5% vs. 10.4%), and 39.2% of patients with AKI did not achieve kidney function recovery within 90 days or by the end of the follow-up period. The temporal sCr/bCr trends of patients with or without COVID-19-associated AKI are shown in Figure S2 (appendix pp14).

AKI and higher mortality

Fig. 2a presents the survival curves of COVID-19 patients with or without AKI. Fig. 2b presents the survival curves of COVID-19 patients stratified by the severity of AKI. Significantly, we observed that the mortality incidence in patients with KDIGO stage 2 (75th percentile, 74 days, 95%CI 42–149 days) or stage 3 AKIs (75th percentile, 13 days, 95%CI 11–16 days) were higher than patients with KDIGO stage 1 AKI (75th percentile, 289 days, 95%CI 212–362 days) or no AKI (75th percentile not reached) (Fig. 2b). Fig. 2c represents IRRs of all-cause mortality in patients who survived 30 days from the peak serum creatinine. Compared to patients with no AKI, patients with KDIGO stage 1 AKI (IRR 2.59, 95%CI 2.25–2.98, $p < 0.0001$), stage 2 AKI (IRR 3.50, 95%CI 2.88–4.23, $p < 0.0001$), and stage 3 AKI (IRR 4.90, 95%CI 4.01–5.96, $p < 0.0001$) had higher incidences of all-cause mortality between 30 days and 365 days post-AKI. Table S4 (appendix pp6) presents the pooled number of deaths, time in person-years and IRRs of Fig. 2c mortality data.

Table 2 presents the associations of clinical and sociodemographic factors associated with mortality. Advanced age (HR 2.77, 95%CI 2.53–3.04, $p < 0.0001$), severe COVID-19 (HR 2.91, 95%CI 2.03–4.17, $p < 0.0001$), severe AKI (KDIGO stage 3: HR 4.22, 95% CI 3.55–5.00, $p < 0.0001$), and ischaemic heart disease (HR 1.26, 95%CI 1.14–1.39, $p < 0.0001$) were associated with increased mortality in both the overall cohort and subgroup analyses of patients with AKI (Tables S5–S7, appendix pp7–9). With respect to medications, no significant association was observed between remdesivir (HR 0.83, 95%CI 0.53–1.30, $p = 0.42$), antiplatelet use (HR 0.96, 95%CI 0.77–1.19, $p = 0.70$), or ACE-i/ARB use (HR 0.93, 95%CI 0.85–1.01, $p = 0.089$) and mortality. Although COPD (HR 1.19, 95%CI 1.07–1.32, $p = 0.0008$) and anticoagulation use (HR 0.53, 95%CI 0.37–0.77, $p = 0.0008$) were significantly associated with mortality outcomes (Table 2), these associations were not significant in the subgroup analyses of patients with AKI (Table S5, appendix pp7). Tables S6 and S7 (appendix pp8 and 9) present analyses of all patients, and of patients with AKI respectively, adjusted for baseline sCr, and the timing of baseline sCr measurement. The effect estimates of individual institution used in the meta-analyses in Table 2 and Tables S5–S7 (appendix pp7–9) are presented in Figures S3 and S4 (appendix pp15–26).

COVID-19-associated AKI and CKD progression

Fig. 3a presents cumulative incidence curves of kidney function recovery defined by ≤125% of baseline serum creatinine, and death as competing events in patients with AKI stratified by KDIGO stage. Recovery times were longest in patients with KDIGO stage 3 AKI (median not reached) compared to KDIGO stage 2 AKI (median 34 days, 95%CI 27–41 days) and KDIGO stage 1 AKI (median 13 days, 95%CI 12–14 days). Figure S5 (appendix pp27) presents the cumulative incidence curves for kidney function recovery in our cohort. Table 3 presents the associations of clinical and sociodemographic factors with kidney function recovery with COVID-19-associated AKI. While severe AKI (KDIGO stage 3 AKI: HR 0.41, 95%CI 0.37–0.46, $p < 0.0001$) was significantly associated with poorer kidney function recovery, we observed an unexpected significant

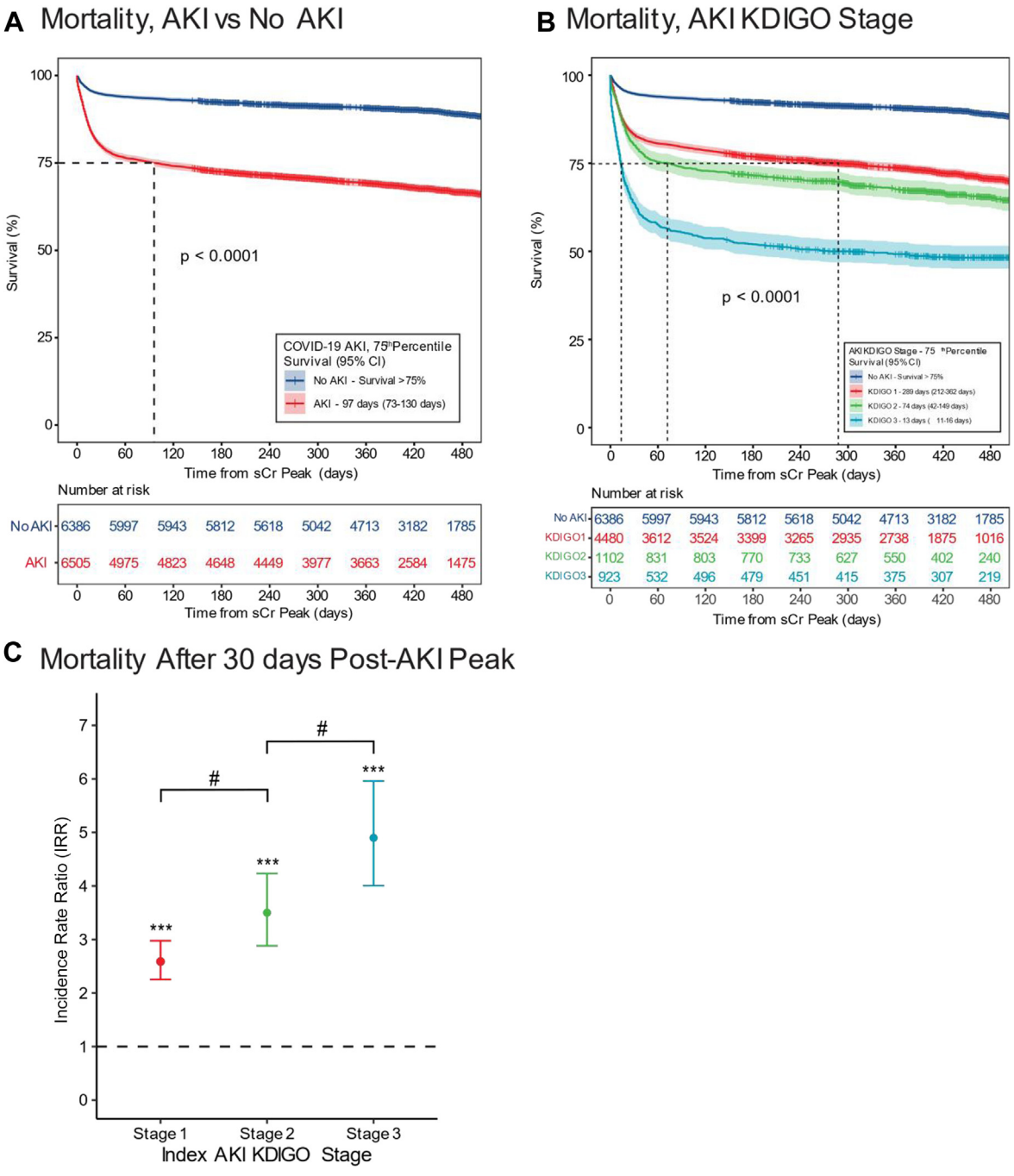


***Fig. 2:* Mortality outcomes of COVID-19 patients with or without AKI**. (a) Kaplan–Meier survival curves of COVID-19 patients, stratified by COVID-19-associated AKI occurrence. The p-value was computed from a log-rank test comparing the survival curves. (b) Kaplan–Meier survival curves of COVID-19 patients, stratified by COVID-19-associated AKI KDIGO stage. Dashed lines indicate 75th percentile survival times. The p-value was computed from a log-rank test comparing the survival curves. (c) Corresponding incidence rate ratios (IRRs) for mortality 30-days post-peak serum creatinine, compared to patients with no COVID-19-associated AKI. The dashed horizontal line represents the reference value of 1. Shaded areas and error bars represent the 95% confidence interval. ***p < 0.0001 compared to reference range of 1 (no AKI). #p < 0.0001 compared between AKI KDIGO stages. A p-value of <0.05 was considered statistically significant.

Variable		HR (95% CI)	p-value	No. of institutions	No. of patients in contributing institutions
Age ≥70 years		**2.77 (2.53–3.04)**	**<0.0001**	**13**	**12,560**
Severe COVID-19		**2.91 (2.03–4.17)**	**<0.0001**	**14**	**12,808**
Male sex		1.23 (1.07–1.43)	0.0051	14	12,808
AKI KDIGO stage	No AKI	Reference			
	KDIGO 1	**1.93 (1.75–2.14)**	**<0.0001**	**14**	**12,808**
	KDIGO 2	**2.32 (2.02–2.67)**	**<0.0001**	**14**	**12,808**
	KDIGO 3	**4.22 (3.55–5.00)**	**<0.0001**	**14**	**12,808**
Comorbidities	Chronic kidney disease	1.06 (0.95–1.17)	0.31	12	12,402
	Cirrhosis	1.49 (1.07–2.08)	0.019	8	10,990
	Hypertension	0.94 (0.84–1.05)	0.28	13	12,650
	Ischaemic heart disease	**1.26 (1.14–1.39)**	**<0.0001**	**11**	**12,044**
	Chronic obstructive pulmonary disease	**1.19 (1.07–1.32)**	**0.0008**	**10**	**11,650**
	Rheumatological conditions	1.07 (0.88–1.30)	0.50	9	11,511
	Prior venous thromboembolism	1.06 (0.96–1.17)	0.22	12	12,402
Medications	Antiplatelet use	0.96 (0.77–1.19)	0.70	10	11,669
	Anticoagulation use	**0.53 (0.37–0.77)**	**0.0008**	**8**	**9275**
	Remdesivir	0.83 (0.53–1.30)	0.42	3	3521
	Other direct acting antivirals	1.52 (0.93–2.48)	0.097	3	1980
	Prior ACE-i/ARB use	0.93 (0.85–1.01)	0.089	13	12,450

The bold values highlight the significant covariates (p < 0.0029). Abbreviations: ACE-i: angiontensin-converting enzyme inhibitor; AKI: acute kidney injury; ARB: angiotensin-II receptor blocker; HR: hazard ratio; KDIGO: Kidney Disease: Improving Global Outcomes; N: sample size; 95%CI: 95% confidence interval.

Table 2: **Clinical and sociodemographic factors associated with mortality in patients with COVID-19.**

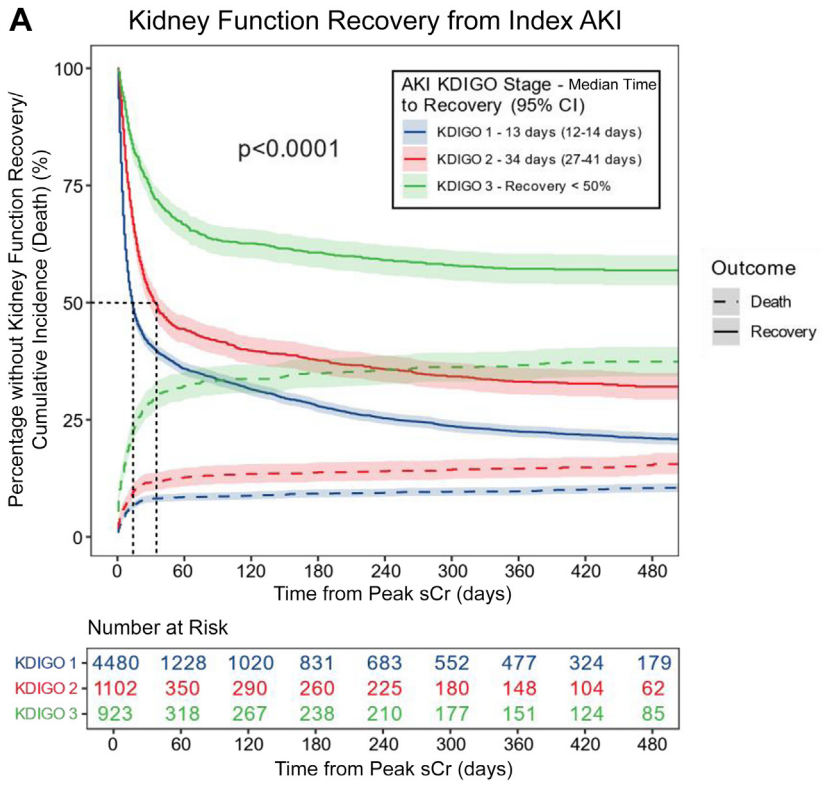
association of severe COVID-19 disease with better kidney function recovery (HR 1.17, 95%CI 1.09–1.24, p < 0.0001). With respect to medications, remdesivir was associated with better kidney function recovery (HR 1.34, 95%CI 1.17–1.54, p < 0.0001), whereas prior ACE-i/ARB use was not significantly associated with kidney function recovery (HR 1.00, 95%CI 0.93–1.08, p = 0.97). Table S8 (appendix pp10) presents the effect estimates of these covariates after adjustment for baseline sCr and timing of baseline sCr.

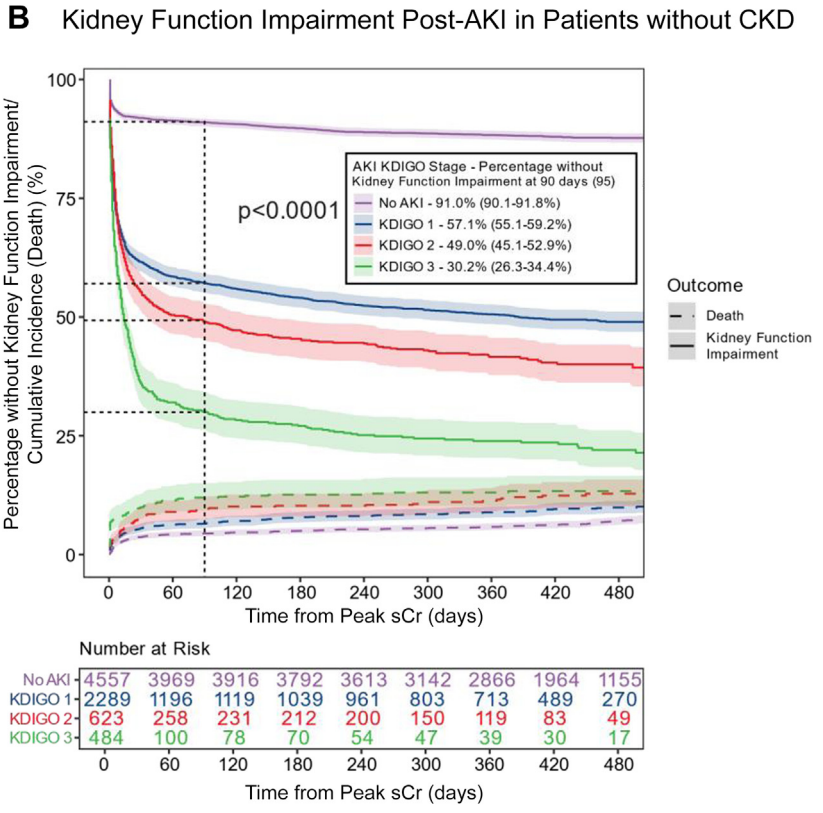
Fig. 3b presents cumulative incidence curves of kidney function impairment, defined by a post-AKI serum creatinine baseline ≥1.29 mg/dL, and death as competing events in patients without CKD stratified by KDIGO stage. In the subgroup of patients without CKD at admission, kidney function impairment at 90 days post-AKI was highest in KDIGO stage 3 AKI patients (69.8%, 95% CI 65.6–73.7%) compared to KDIGO stage 2 AKI (51.0%, 95% CI 47.1–54.9%), KDIGO Stage 1 AKI (42.9%, 95% CI 40.8–44.9%) and non-AKI patients (9.0%, 95% 8.2–9.9%) (Fig. 3b). Figure S6 (appendix pp28) presents the cumulative incidence curves for kidney function impairment. Advanced age (HR 1.38, 95%CI 1.20–1.58, p < 0.0001), male sex (HR 1.67, 95% CI 1.45–1.93, p < 0.0001), severe AKI (KDIGO stage 3: HR 11.68, 95%CI 9.80–13.91, p < 0.0001), and hypertension (HR 1.22, 95%CI 1.10–1.36, p = 0.0002) were associated with onset of kidney function impairment post-AKI (Table 3). With respect to medications, no significant reno-protective effects were observed with remdesivir (HR 0.86, 95%CI 0.54–1.37, p = 0.53) or prior ACE-i/ARB use (HR 1.14, 95%CI 1.01–1.28, p = 0.028). Table S9 (appendix pp11) presents the effect estimates of these covariates after adjustment for baseline sCr and timing of baseline sCr. The effect estimates of individual institution used in the meta-analyses in Table 3 are presented in Figures S7 and S8 (appendix pp29–39).

Finally, we investigated if patients with COVID-19 that did not experience an inpatient AKI event demonstrated a similar long-term relative kidney function decline as that observed in patients with COVID-19-associated AKI. Fig. 4 presents the risk ratios of relative kidney function decline, defined as persistently raised sCr ≥1.25-fold baseline sCr, in patients with AKI compared to patients without AKI. Patients with AKI had significant shifts in bCr of 125% or more at 90 days (RR 1.34, 95%CI 1.19–1.51), 180 days (RR 1.49, 95%CI 1.32–1.67) and 365 days (RR 1.54, 95%CI 1.21–1.96) compared to the control group of COVID-19 patients with no AKI (Fig. 4).

Discussion

Among 12,891 hospitalized patients who had SARS-CoV-2 infection in this large, international multicentre study, 50.5% had at least one episode of AKI during their hospitalization. Among patients with AKI,


A
Kidney Function Recovery from Index AKI
Percentage without Kidney Function Recovery/ Cumulative Incidence (Death) (%)
AKI KDIGO Stage - Median Time to Recovery (95% CI)
KDIGO 1 - 13 days (12-14 days)
KDIGO 2 - 34 days (27-41 days)
KDIGO 3 - Recovery < 50%
p<0.0001
Outcome
Death
Recovery
Time from Peak sCr (days)
Number at Risk
KDIGO 1 4480 1228 1020 831 683 552 477 324 179
KDIGO 2 1102 350 290 260 225 180 148 104 62
KDIGO 3 923 318 267 238 210 177 151 124 85
Time from Peak sCr (days)


B
Kidney Function Impairment Post-AKI in Patients without CKD
Percentage without Kidney Function Impairment/ Cumulative Incidence (Death) (%)
AKI KDIGO Stage - Percentage without Kidney Function Impairment at 90 days (95)
No AKI - 91.0% (90.1-91.8%)
KDIGO 1 - 57.1% (55.1-59.2%)
KDIGO 2 - 49.0% (45.1-52.9%)
KDIGO 3 - 30.2% (26.3-34.4%)
p<0.0001
Outcome
Death
Kidney Function Impairment
Time from Peak sCr (days)
Number at Risk
No AKI 4557 3969 3916 3792 3613 3142 2866 1964 1155
KDIGO 1 2289 1196 1119 1039 961 803 713 489 270
KDIGO 2 623 258 231 212 200 150 119 83 49
KDIGO 3 484 100 78 70 54 47 39 30 17
Time from Peak sCr (days)

Variable		Kidney function recovery (AKI patients)				Kidney function impairment (Non-CKD patients)			
		HR (95% CI)	p-value	No. of institutions	No. of patients in contributing institutions	HR (95% CI)	p-value	No. of institutions	No. of patients in contributing institutions
Age ≥70 years		1.10 (1.03–1.17)	0.0032	14	6494	**1.38 (1.20–1.58)**	**<0.0001**	**13**	**7621**
Severe COVID-19		**1.17 (1.09–1.24)**	**<0.0001**	**15**	**6505**	1.05 (0.96–1.16)	0.27	15	7953
Male sex		1.09 (1.00–1.18)	0.060	14	6494	**1.67 (1.45–1.93)**	**<0.0001**	**11**	**5993**
AKI KDIGO stage	No AKI					Reference			
	KDIGO 1	Reference				**5.56 (4.47–6.93)**	**<0.0001**	**15**	**7953**
	KDIGO 2	**0.70 (0.64–0.76)**	**<0.0001**	**15**	**6505**	**7.01 (5.59–8.78)**	**<0.0001**	**15**	**7953**
	KDIGO 3	**0.41 (0.37–0.46)**	**<0.0001**	**15**	**6505**	**11.68 (9.80–13.91)**	**<0.0001**	**15**	**7953**
Comorbidities	Chronic kidney disease	0.95 (0.84–1.08)	0.46	12	6353				
	Cirrhosis	0.89 (0.75–1.06)	0.18	9	5776	1.14 (0.80–1.62)	0.46	6	5143
	Hypertension	0.98 (0.90–1.07)	0.62	12	6353	**1.22 (1.10–1.36)**	**0.0002**	**12**	**7469**
	Ischaemic heart disease	0.92 (0.82–1.03)	0.16	11	6202	1.13 (0.98–1.31)	0.086	11	7135
	Chronic obstructive pulmonary disease	0.94 (0.83–1.06)	0.29	11	6202	0.83 (0.71–0.97)	0.017	8	6354
	Rheumatological conditions	0.90 (0.76–1.05)	0.19	11	6202	1.35 (0.84–2.15)	0.21	6	5160
	Prior venous thromboembolism	0.91 (0.83–0.99)	0.023	11	6202	0.89 (0.78–1.02)	0.087	10	6841
Medications	Antiplatelet use	0.93 (0.84–1.03)	0.17	11	6188	1.08 (0.92–1.26)	0.35	9	6512
	Anticoagulation use	0.84 (0.68–1.05)	0.12	7	4167	0.83 (0.63–1.09)	0.17	7	5539
	Remdesivir	**1.34 (1.17–1.54)**	**<0.0001**	**3**	**1812**	0.86 (0.54–1.37)	0.53	3	2703
	Other direct acting antivirals	0.86 (0.57–1.32)	0.50	3	1068	0.98 (0.63–1.54)	0.94	2	492
	Prior ACE-i/ARB use	1.00 (0.93–1.08)	0.97	11	6202	1.14 (1.01–1.28)	0.028	11	6896

The bold values highlight the significant covariates (p < 0.0029). Abbreviations: ACE-i: angiontensin-converting enzyme inhibitor; AKI: acute kidney injury; ARB: angiotensin-II receptor blocker; HR: hazard ratio; KDIGO: Kidney Disease: Improving Global Outcomes; N: sample size; 95%CI: 95% confidence interval.

Table 3: **Clinical and sociodemographic factors associated with kidney function recovery from AKI and kidney function impairment onset in patients with COVID-19.**

67.5% survived to the end of the study period, and 39.2% did not achieve kidney function recovery at 90 days post-AKI. These findings are consistent with previous studies,[1,2] although the lack of a non-COVID-19 control population precludes any comparison with kidney function recovery or survival in other types of viral community acquired pneumonias. Moreover, we observed that severe AKI was associated with increased all-cause mortality risk in 30-day survivors from the index AKI episode.

We observed that severe AKI, advanced age, severe COVID-19, and ischemic heart disease were significantly associated with higher mortality. With respect to the associations of AKI severity with 1-year all-cause mortality in 30-day survivors, our results are consistent with a previous study which observed that elevated inpatient serum creatinine was associated with higher mortality in survivors of acute myocardial infarction.[12] With respect to medications, we did not observe any mortality benefit of anticoagulant use in COVID-19 patients with AKI, which is in line with randomized controlled trials that did not observe any mortality differences with therapeutic anticoagulant dosing over prophylactic dosing.[13,14] As with other observational studies, it is possible that time-dependent bias may have contributed to these observations.[15]

Fig. 3: **Kidney function recovery and kidney function impairment outcomes of COVID-19 patients**. (a) Cumulative incidence curves of kidney function recovery in the subgroup of COVID-19 patients with AKI, stratified by COVID-19-associated AKI KDIGO stage. Solid lines indicate kidney function recovery, and coloured dashed lines indicate mortality as a competing event. Black dashed lines indicate the median time to kidney function recovery. (b) Cumulative incidence curves of kidney function impairment, defined as a sustained increase in baseline sCr to ≥1.29 mg/dL, in the subgroup of COVID-19 patients without CKD, stratified by COVID-19-associated AKI KDIGO stage. Solid lines indicate kidney function impairment, and coloured dashed lines indicate mortality as a competing event. Black dashed lines indicate the percentage without kidney function impairment at 90 days post-AKI. Shaded areas represent the 95% confidence interval. P-values shown are computed from Gray's test comparing cumulative incidence curves of the event of interest. Abbreviations: KDIGO: Kidney Disease: Improving Global Outcomes; CKD: chronic kidney disease; sCr: serum creatinine; 95%CI: 95% confidence interval.

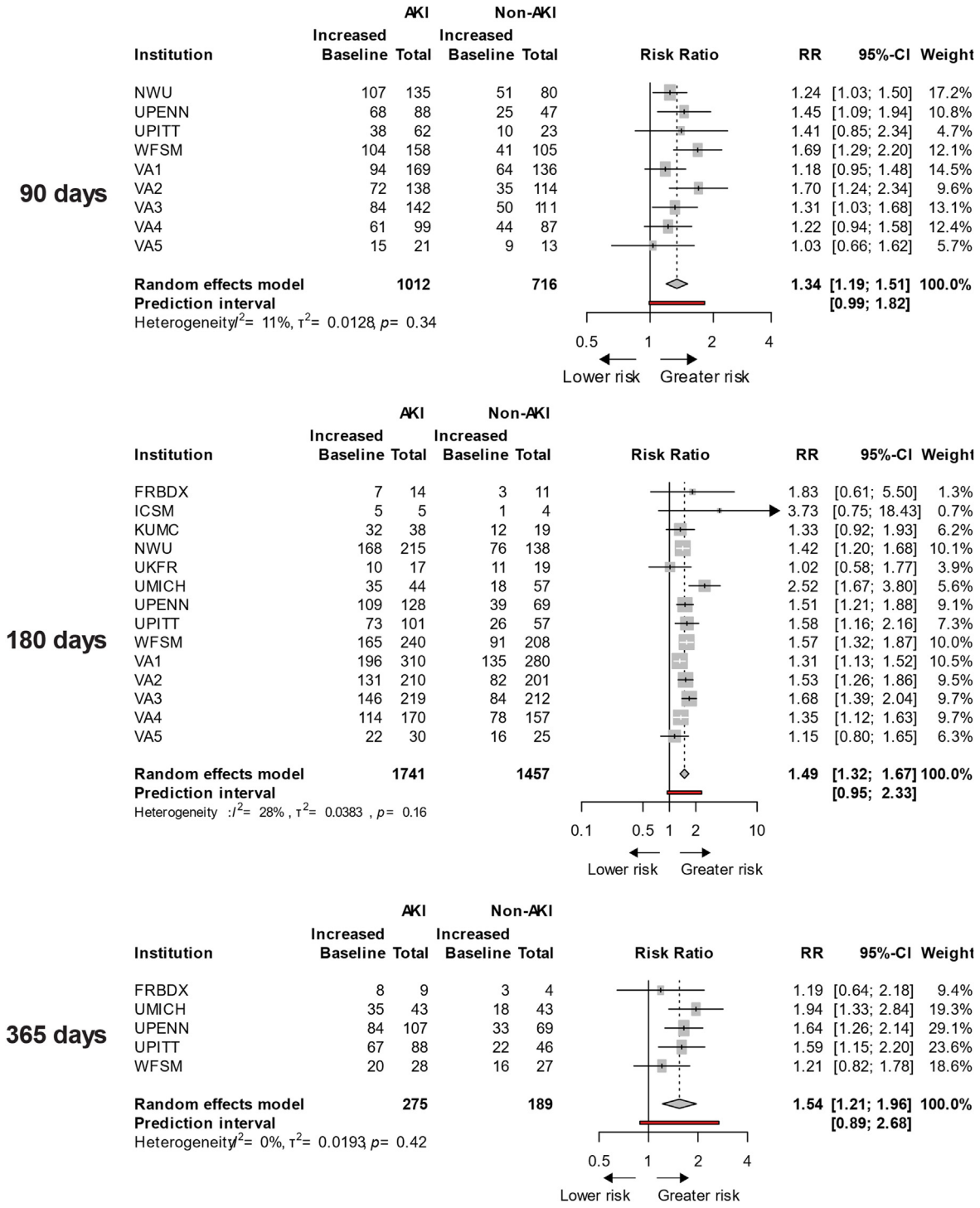


Fig. 4: **Long-term kidney function recovery outcomes of COVID-19-associated AKI**. Forest plots of the risk of COVID-19-associated AKI in long-term kidney function decline, at 90-, 180- and 365-days post-AKI peak (AKI patients) or peak sCr in the first admission (non-AKI patients). Relative kidney function decline at each time point was defined as persistently raised serum creatinine values ≥1.25-fold baseline serum creatinine. Abbreviations: RR: risk ratio; 95%CI: 95% confidence interval.

Our study observed the persistence of worse kidney function recovery in patients with COVID-19-associated AKI compared to patients without AKI using pre-admission serum creatinine to accurately determine baseline kidney function, in keeping with a previous study that observed longitudinal 1-year kidney function decline after COVID-19 infection.[16] Aside from the severity of the inciting AKI event, we unexpectedly observed a significant association of severe COVID-19 disease with better kidney function recovery, but not with kidney function impairment in a subgroup of patients with no CKD. One possibility is the use of cause-specific analyses in our models to account for competing risks of death in patients with severe COVID-19, whereas prior studies did not include critical illness as a covariate,[4] examined binary outcomes of kidney function recovery and did not account for competing risks of death,[17] or involved only 30-day survivors of COVID-19.[18] Moreover, the lack of pre-admission serum creatinine or diagnostic codes to establish if a patient has subclinical CKD in these studies preclude appropriate conclusions drawn about long-term kidney function outcomes in patients with COVID-19-associated AKI.

On the other hand, the lack of significant associations of kidney function recovery with advanced age and CKD is in contrary to prior studies that observed significant associations of advanced age and CKD with poor kidney function recovery post-AKI.[19–21] However, one major limitation of those studies[19–21] is the lack of large, multi-centre observational data for the multifaceted aetiology of the AKI, hence these findings may not be generalized to all COVID-19 patients. Another plausible biological reason for these conflicting results could be differences in AKI pathophysiological mechanisms between younger and older patients.[22] However, it is possible that selection and misclassification biases precluded our ability to observe significant associations with CKD. The inclusion of patients with pre-admission serum creatinine may have pre-selected patients who are more likely to be followed up in the hospital system for other medical conditions. In addition, our study construct could not distinguish between admissions for COVID-19, and admissions with COVID-19.

With respect to the subgroup of patients with no CKD, we observed a significant association of hypertension with increased risk of kidney function impairment, whereas no significant association was observed with ACE-i/ARB. While the pathophysiology of hypertension-induced kidney damage has been well investigated,[23] the link with post-AKI kidney function impairment remain poorly understood. On the other hand, post-AKI hypertension has been previously described,[24] but the role of hypertension in mediating post-AKI kidney function impairment remains unknown. Our findings warrant further studies to understand how hypertension-induced kidney disease may predispose to post-AKI kidney function impairment, and therapeutic strategies to slow down or reverse post-AKI kidney function impairment in this subgroup of patients.

Finally, we observed significant associations of remdesivir with better kidney function recovery in a subset of 1812 patients in three healthcare systems, although no significant association was observed with kidney function impairment in a subgroup of patients with no prior CKD at admission. It was previously proposed that COVID-19-associated AKI may be due to direct viral infection of kidney parenchyma and microvascular thrombosis, a pathogenic process not commonly observed in non-COVID-19 AKI.[25] This may be a plausible mechanism of action by remdesivir in kidney function recovery, although our study suggests that remdesivir may not have sustained reno-protective effects in patients without CKD. Nonetheless, our small sample sizes with available data on remdesivir use warrants further studies to validate our findings.

While kidney function decline after hospital discharge in patients with COVID-19-associated AKI has been reported,[4] inferences on the effects of COVID-19-associated AKI on kidney function recovery were challenging in prior studies due to the lack of pre-admission serum creatinine values. Moreover, the lack of data pertaining to oliguria and proteinuria, two important estimates of acute and chronic kidney function aside from serum creatinine, precludes analyses on CKD aside from using post-AKI serum creatinine baseline estimations as a surrogate marker of kidney function impairment. Furthermore, temporal trends of kidney function recovery can be severely confounded with the initiation of RRT in critically ill patients, or in patients with advanced CKD. To address these sources of bias, our study excluded these subgroups of patients from the analyses, and nonetheless observed consistent and significant inverse associations between AKI severity and kidney function recovery. However, as advanced CKD and RRT initiation are poor prognostic factors of long-term kidney function recovery and mortality,[7,26] our study may have under-estimated the effect of COVID-19-associated AKI on mortality and long-term kidney function recovery. Also, our study has a low proportion of females and may not be powered to examine sex differences in kidney function recovery from COVID-19-associated AKI. Another limitation of our study is the lack of temporal relationship of the cessation and continuation of ACE-i/ARBs in patients who had prior exposure to ACE-i/ARBs, due to the heterogenous nature of healthcare systems across countries. This may underestimate the associations of ACE-i/ARB with kidney function impairment outcomes observed in non-COVID AKI.[27] Lastly, the lack of eGFR data warranted the use of surrogate sCr levels corresponding to 30, 60, or 90 ml/min/1.73m^2 in a 60 year old non-Black male using the CKD-EPI 2009 formulae to define kidney

function outcomes and our exclusion criteria, which may not truly represent the whole population, and may have underestimated kidney function in some age groups if the CKD-EPI 2021 formulae were to be used.

Our cohort comprises of unvaccinated patients infected by wild-type SARS-CoV-2 strain before the emergence of the Alpha variant[28] in December 2020 and before the rollout of mass vaccination campaigns. Additionally, there was no clear standard-of-care treatment in our cohort, which came before the announcement of clinical trials for remdesivir[29] and dexamethasone.[30] While it remains unclear how vaccinations alter long-term kidney function recovery, our cohort represents COVID-19 patients who have the least protection against severe COVID-19. Further studies are warranted to study the long-term kidney function sequelae of COVID-19-associated AKI in patients infected with the Delta and Omicron SARS-CoV-2 variants. Moreover, as the corticosteroid dosing regimen and administration varied widely across sites and clinical practice in the time period of our study, we did not analyse the effect of corticosteroid use in kidney function recovery outcomes.

The strengths of our study include: 1) the large sample size of 12,891 patients across five countries and 15 tertiary care institutions worldwide, conferring statistical power to investigate clinically relevant risk factors of AKI-related kidney function recovery and mortality, 2) the inclusion of patients with available pre-admission serum creatinine to establish baseline and post-AKI serum creatinine changes, 3) long follow-up time (median follow-up time of 430 days) to measure long-term post-AKI kidney function recovery outcomes, and 4) temporal resolution of AKI peak using the sCr/bCr method which allowed us to more precisely characterize kidney function recovery. In addition to previously discussed limitations, the international and federated nature of our analysis precluded manual chart reviews across institutions to determine AKI aetiologies. We intend to explore these areas in future studies of the 4CE.

In conclusion, COVID-19-associated AKI is associated with higher mortality and impaired chronic kidney function recovery in a large, international, electronic health records-based cohort.

Contributors

Concept and design: BWL Tan, BWQ Tan, ALM Tan, Holmes, Loh, Weber, Bonzel, Hong, Kohane, Cai, Omenn and Ngiam.

Acquisition, analysis or interpretation of data: BWL Tan, BWQ Tan, ALM Tan, Schriver, Gutiérrez-Sacristán, Das, Yuan, Hutch, García Barrio, Pedrera Jimenez, Abu-el-rub, Moris, Moal, Verdy, Schubert, Cho, Ho, Patel, Dagliati, Neuraz, Klann, South, Visweswaran, Hanauer, Liu, Mowery, Batugo, Brat, Luo, Avillach, Bellazzi, Chiovato, Malovini, Tibollo, Samayamuthu, Serrano Balazote, Xia, Loh, Chiudinelli, Weber, Hong, Zhang, Bonzel, Kohane, Cai, Omenn, Maidlow, Makoudjou, Tippmann, Zöller and Ngiam.

Drafting of the manuscript: BWL Tan, BWQ Tan, ALM Tan, South, Mowery, Holmes, Loh, Cai, and Ngiam.

Critical revision of manuscript for important intellectual content: BWL Tan, BWQ Tan, ALM Tan, Schriver, Gutiérrez-Sacristán, Das, Yuan, Hutch, García Barrio, Pedrera Jimenez, Abu-el-rub, Moris, Moal, Schubert, Cho, Ho, Patel, Dagliati, Neuraz, Klann, South, Visweswaran, Hanauer, Liu, Mowery, Brat, Luo, Avillach, Bellazzi, Chiovato, Malovini, Tibollo, Samayamuthu, Serrano Balazote, Xia, Loh, Chiudinelli, Weber, Hong, Zhang, Bonzel, Kohane, Cai, Omenn, Maidlow, Makoudjou, Tippmann, Zöller and Ngiam.

Ngiam, BWL Tan, and BWQ Tan have accessed and verified the data, and all authors are responsible for the decision to submit the manuscript. All authors have read and approved the final version of the manuscript.

Data sharing statement

The analytic code is made available on GitHub (https://github.com/covidclinical/Phase2.1AKIRPackage).

Declaration of interest

Dr Hanauer reported having developed an electronic resource of clinical synonyms, EMERSE, that is licensed by the University of Michigan and receiving a portion of the licensing fees for this resource outside the submitted work. Dr Omenn reported being an early investor and serving on the board of Angion Biomedica Corporation, New York, which has conducted clinical trials of drug candidates for overcoming acute kidney injury following cardiopulmonary surgery or kidney transplantation. The former was terminated early based on unsatisfactory efficacy/adverse effects assessment; the latter had insufficient benefit to warrant proposing a Phase III trial. The company is moving in other directions, to be determined. No further work on kidney is anticipated. Dr Holmes disclosed participation as an NIH/NIDDK T2 Coach R01DK113189. Dr Malovini disclosed being a shareholder of Biomeris s.r.l. Dr Bellazzi reported receiving honoraria from Pfizer, and disclosed being a shareholder of University of Pavia spin-off Biomeris. Dr Klann reports consulting fees from i2b2 tranSMART foundation, for work to enhance open-source data warehouse platform. He reports no direct relationship to this work, except that the data model for analysis in this manuscript was inspired by this platform.

Acknowledgements

BWQT is supported by the National Medical Research Council Research Training Fellowship (MOH-000195-00). WY is supported by the National Institutes of Health (NIH) (T32HD040128). MH is supported by the NIH National Library of Medicine (NLM) (5T32LM012203-05). NGB is supported by Carlos III Health Institute (PI18/00981). NA is supported by the NIH National Center for Advancing Translational Science (NCATS) (CTSA Award #UL1TR002366). LPP is supported by the NIH NCATS (CTSA Award #UL1TR002366). AMS is supported by the NIH National Heart Lung and Blood Institute (NHLBI) (K23HL148394, L40HL148910) and NCATS (UL1TR001420). SV is supported by the NIH NLM (R01LM012095) and NCATS (UL1TR001857). DAH is supported by NIH NCATS (UL1TR002240). ML is supported by the NIH NCATS (CTSA Award #UL1TR002366) and National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) (R01DK116986). DLM is supported by the NIH NCATS CSTA award (UL1-TR001878). YL is supported by NIH NLM (1R01LM013337). RB is supported by European Union Periscope Project (101016233). ZX is supported by the NIH National Institute of Neurological Disorders and Stroke (NINDS) (R01NS098023). GMW is supported by NIH NCATS (UL1TR002541 and UL1TR000005), NIH NLM (R01LM013345) and NIH NHGRI (3U01HG008685-05S2). GSO is supported by the NIH (P30ES017885, U24CA210967). JHH is supported by NIH/NCATS Institutional Clinical and Translational Science Award (UL1-TR001878).

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2022.101724.

References

1 Hirsch JS, Ng JH, Ross DW, et al. Acute kidney injury in patients hospitalized with COVID-19. *Kidney Int*. 2020;98(1):209–218.
2 Chan L, Chaudhary K, Saha A, et al. AKI in hospitalized patients with COVID-19. *J Am Soc Nephrol*. 2021;32(1):151–160.
3 Gupta S, Hayek SS, Wang W, et al. Factors associated with death in critically ill patients with coronavirus disease 2019 in the US. *JAMA Intern Med*. 2020;180(11):1436–1446.
4 Nugent J, Aklilu A, Yamamoto Y, et al. Assessment of acute kidney injury and longitudinal kidney function after hospital discharge among patients with and without COVID-19. *JAMA Netw Open*. 2021;4(3):e211095.
5 Zhang NH, Cheng YC, Luo R, Zhang CX, Ge SW, Xu G. Recovery of new-onset kidney disease in COVID-19 patients discharged from hospital. *BMC Infect Dis*. 2021;21(1):397.
6 Lumlertgul N, Pirondini L, Cooney E, et al. Acute kidney injury prevalence, progression and long-term outcomes in critically ill patients with COVID-19: a cohort study. *Ann Intensive Care*. 2021;11(1):123.
7 Gupta S, Coca SG, Chan L, et al. AKI treated with renal replacement therapy in critically ill patients with COVID-19. *J Am Soc Nephrol*. 2021;32(1):161–176.
8 Strohbehn IA, Zhao S, Seethapathy H, et al. Acute kidney injury incidence, recovery, and long-term kidney outcomes among hospitalized patients with COVID-19 and influenza. *Kidney Int Rep*. 2021;6(10):2565–2574.
9 Brat GA, Weber GM, Gehlenborg N, et al. International electronic health record-derived COVID-19 clinical course profiles: the 4CE consortium. *NPJ Digit Med*. 2020;3(1):109.
10 Klann JG, Estiri H, Weber GM, et al. Validation of an internationally derived patient severity phenotype to support COVID-19 analytics from electronic health record data. *J Am Med Inf Assoc*. 2021;28(7):1411–1420.
11 Section 2: AKI definition. *Kidney Int Suppl*. 2012;2(1):19–36.
12 Cardarelli F, Bellasi A, Ou FS, et al. Combined impact of age and estimated glomerular filtration rate on in-hospital mortality after percutaneous coronary intervention for acute myocardial infarction (from the American College of Cardiology National Cardiovascular Data Registry). *Am J Cardiol*. 2009;103(6):766–771.
13 Spyropoulos AC, Goldin M, Giannis D, et al. Efficacy and safety of therapeutic-dose heparin vs standard prophylactic or intermediate-dose heparins for thromboprophylaxis in high-risk hospitalized patients with COVID-19: the HEP-COVID randomized clinical trial. *JAMA Intern Med*. 2021;181(12):1612–1620.
14 Lopes RD, de Barros e Silva PGM, Furtado RHM, et al. Therapeutic versus prophylactic anticoagulation for patients admitted to hospital with COVID-19 and elevated D-dimer concentration (ACTION): an open-label, multicentre, randomised, controlled trial. *Lancet*. 2021;397(10291):2253–2263.
15 Cohen JB, D'Agostino McGowan L, Jensen ET, Rigdon J, South AM. Evaluating sources of bias in observational studies of angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker use during COVID-19: beyond confounding. *J Hypertens*. 2021;39(4):795–805.
16 Gu X, Huang L, Cui D, et al. Association of acute kidney injury with 1-year outcome of kidney function in hospital survivors with COVID-19: a cohort study. *EBioMedicine*. 2022;76:103817.
17 Pei G, Zhang Z, Peng J, et al. Renal involvement and early prognosis in patients with COVID-19 pneumonia. *J Am Soc Nephrol*. 2020;31(6):1157–1165.
18 Al-Aly Z, Xie Y, Bowe B. High-dimensional characterization of post-acute sequelae of COVID-19. *Nature*. 2021;594(7862):259–264.
19 Schmitt R, Coca S, Kanbay M, Tinetti ME, Cantley LG, Parikh CR. Recovery of kidney function after acute kidney injury in the elderly: a systematic review and meta-analysis. *Am J Kidney Dis*. 2008;52(2):262–271.
20 Sawhney S, Mitchell M, Marks A, Fluck N, Black C. Long-term prognosis after acute kidney injury (AKI): what is the role of baseline kidney function and recovery? A systematic review. *BMJ Open*. 2015;5(1):e006497.
21 Ponte B, Felipe C, Muriel A, Tenorio MT, Liano F. Long-term functional evolution after an acute kidney injury: a 10-year study. *Nephrol Dial Transplant*. 2008;23(12):3859–3866.
22 Pascual J, Liano F. Causes and prognosis of acute renal failure in the very old. Madrid Acute Renal Failure Study Group. *J Am Geriatr Soc*. 1998;46(6):721–725.
23 Griffin KA. Hypertensive kidney injury and the progression of chronic kidney disease. *Hypertension*. 2017;70(4):687–694.
24 Hsu CY, Hsu RK, Yang J, Ordonez JD, Zheng S, Go AS. Elevated BP after AKI. *J Am Soc Nephrol*. 2016;27(3):914–923.
25 Legrand M, Bell S, Forni L, et al. Pathophysiology of COVID-19-associated acute kidney injury. *Nat Rev Nephrol*. 2021;17(11):751–764.
26 De Corte W, Dhondt A, Vanholder R, et al. Long-term outcome in ICU patients with acute kidney injury treated with renal replacement therapy: a prospective cohort study. *Crit Care*. 2016;20(1):256.
27 Gayat E, Hollinger A, Cariou A, et al. Impact of angiotensin-converting enzyme inhibitors or receptor blockers on post-ICU discharge outcome in patients with acute kidney injury. *Intensive Care Med*. 2018;44(5):598–605.
28 Galloway SE, Paul P, MacCannell DR, et al. Emergence of SARS-CoV-2 B.1.1.7 lineage - United States, December 29, 2020-January 12, 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70(3):95–99.
29 Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19 - final report. *N Engl J Med*. 2020;383(19):1813–1826.
30 Group RC, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med*. 2021;384(8):693–704.