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The dynamics and outcomes of AKI progression during the COVID-19 pandemic

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Abstract

Purpose: Acute kidney injury (AKI) associated with COVID-19 is associated with poor prognosis. This study assessed the hitherto uninvestigated impact of COVID-19 on the progression and clinical outcomes of patients with AKI.

Methods: Data from 576 patients with AKI admitted between 13/3/20 and 13/5/20 were studied. Increasingly complex analyses, from logistic regressions to competing-risk and multi-state models, have revealed insights into AKI progression dynamics associated with PCR-confirmed COVID-19 acquisition and death. Meta-analyses of case fatality ratios among patients with AKI were also conducted.

Results: The overall case-fatality ratio was 0.33 [95% CI (0.20–0.36)]; higher in COVID-19 positive (COVID+) patients 0.52 [95% CI (0.46–0.58)] than in their negative (COVID-) counterparts 0.16 [95% CI (0.12–0.20)]. In AKI Stage-3 patients, that was 0.71 [95% CI (0.64–0.79)] among COVID+ patients with 45% dead within 14 days and 0.35 [95% CI (0.25–0.44)] in the COVID- group and 28% died within 14 days. Among patients diagnosed with AKI Stage-1 within 24 h, the probability of progression to AKI Stage-3 on day 7 post admission was 0.22 [95% CI (0.17–0.27)] among COVID+ patients, and 0.06 [95% CI (0.03, 0.09)] among those who tested negative. The probability of discharge by day 7 was 0.71 [95% CI (0.66, 0.75)] in COVID- patients, and 0.27 [95% CI (0.21, 0.32)] in COVID+ patients. By day 14, in AKI Stage-3 COVID+ patients, that was 0.35 [95% CI (0.25, 0.44)] with little change by day 10, that is, 0.38 [95% CI (0.29, 0.47)].

Conclusion: These results are consistent with either a rapid progression in severity, prolonged hospital care, or high case fatality ratio among AKI Stage-3 patients, significantly exacerbated by COVID-19 infection.

Debasish Banerjee and Irina Chis Ster are joint last authors.

KEYWORDS
acute kidney injury dynamics, competing risks and multi-state models, COVID-19, death, meta-analyses

Summary at a glance

Data from patients with AKI were compared based on COVID status. Patients with COVID demonstrated a higher case fatality ratio in AKI Stage-3 patients. COVID positive patients also demonstrated more rapid progression of AKI and prolonged hospital stays compared with COVID negative patients.

1 | INTRODUCTION

Acute kidney injury (AKI) is a syndrome characterized by an abrupt decline in kidney function, encompassing structural damage to nephrons and loss of renal function.[1] The consequences of AKI can be severe, with its presence portending poor outcomes, including morbidity and mortality. It is multifactorial, with sepsis, ischemia, and nephrotoxicity often being confounding risk factors. The diagnostic approach to AKI is based on an acute decrease in the glomerular filtration rate (GFR), as reflected by an acute rise in the surrogate marker, serum creatinine (sCr) levels, and/or a decline in urine output (UO) over a given time interval, as defined by the Kidney Disease Improving Global Outcomes (KDIGO) guidelines. Severe acute respiratory syndrome coronavirus-2 (SARS-COV-2) is responsible for Coronavirus 2019 disease (COVID-19), which is associated with multiorgan failure, including AKI, despite early data suggesting otherwise.[2]

A subsequent systematic review and meta-analysis, including data from 13 137 patients from 20 studies, demonstrated a prevalence of AKI stages 1–3 among COVID-19 positive (COVID+) patients of 17% (range 0.5%–80.3%).[3] Approximately 5% of all patients required kidney replacement therapy (KRT) (range 0.8%–14.7%). The overall mortality rate among COVID+ patients with AKI was 52%, with a reported range of 7%–100%. These results show a great variability in the incidence of AKI within the context of COVID-19.

One source of such considerable variability in these results can be attributed to the wide spectrum of tubular and glomerular pathologies certified by kidney biopsies of patients with COVID-19 and AKI, and it is likely that a diverse range of processes contribute to this heterogeneous patient group.[4–7]

Potential risk factors responsible for AKI evolution include demographics (age, sex, ethnicity, and body mass index) and associated comorbidities (diabetes mellitus, hypertension, pre-existing cardiovascular disease, and underlying kidney disease). Hospital outcomes are also influenced by disease management and control, such as admission to intensive care unit (ICU), ventilation strategies, nephrotoxic drug administration, and disease severity. COVID-19 acquisition during the pandemic added a layer of complexity in planning, particularly during the first wave in early 2020, in no small part due to a lack of vaccines and consensus guidelines.

A number of unanswered questions have been highlighted regarding AKI in COVID+ patients; these have been broken down into epidemiological, pathophysiological, and treatment questions. Areas of interest for research include the role of biomarkers, identification of risk factors for non-recovery, the relative contribution of each of the myriad of associated pathophysiological mechanisms (e.g., haemodynamic factors, direct viral infection, microthrombi, etc.), and whether any disease-specific treatments materially affect renal outcomes.[8]

The current literature does not explore disease dynamics with reference to AKI and COVID-19, with a particular paucity of data on the progression of AKI associated with COVID-19. The COVID-19 pandemic has presented one of the greatest challenges to health-care systems worldwide owing to its rapid development. Disease progression and patient recovery from disease processes routinely exert a considerable influence on the availability of health-care resources. This was particularly magnified during the pandemic, with the additional burden of increased staff sickness due to COVID-19, leading to a significant detrimental impact on stretched workforces.[9] ICU beds are at a premium for cost, staffing, training, consumables (personal protective equipment), and other logistical and technical reasons. The scarcity of resources is likely to have had some impact on clinicians' decision-making regarding the focus of care, including opting for resuscitation or palliation.[10]

Uncomfortable ethical questions have been raised regarding how best to assign resources in extreme circumstances, including whom and how to prioritise care.[11] Novel approaches to AKI have been used with some success under testing conditions, such as acute peritoneal dialysis.[12] Although such approaches are resourceful and commendable, the ideal approach would be to offer uncompromised optimal tailored care to all patients.

The speed and probability of progression between AKI stages, as well as the time to recovery from illness, are critically relevant to inform planning, at least from the most common scenarios during in-hospital stay.

This study investigated the epidemiology of COVID-19 in patients with AKI associated with progression dynamics and death in a cohort of patients admitted to a large teaching hospital during the first wave of the COVID-19 pandemic. These data allowed increasingly complex analyses conducted on hospital outcomes, enabling

insights into the dynamics of AKI progression and hospital outcome (death or discharge), stratified by patients' COVID-19 status.

A prognostic model for hospital outcomes was constructed in response to the main criticisms of previous models; in >80% of papers, patients in the COVID-19 control group were unconfirmed or even untested. Given the high prevalence of asymptomatic disease in many populations, including hospital inpatients, they cannot act as true negative control.[13] All patients in this cohort were investigated using polymerase chain reaction (PCR) testing for COVID-19, the gold standard test for detecting active infection.

Additionally, a systematic review and meta-analyses of publication data collected during the same period are presented, aimed at deriving pooled estimates for the prevalence of AKI and case-fatality ratios among COVID+ patients, and to understand potential sources of heterogeneity. The latter was based on further information derived from these papers, including the geographical origin of the studies, age, gender distribution, ethnicity, and the length of the data collection period for each study.

2 | MATERIALS AND METHODS

Data were collected for all patients aged over 18 years admitted to St. George's Hospital, London, UK, between 13/03/20 and 13/05/20, where an AKI alert in serum creatinine was detected by the computer database system, on admission, and during their hospital stay. All patients with AKI stages 1–3 were identified by degree of change in serum creatinine levels compared with baseline creatinine values, defined by KDIGO AKI guidelines[1] and tested for COVID-19 using PCR. Patients' baseline serum creatinine levels were approximated from the historical creatinine results pre-dated for at least 12 months.

Survival-type statistical methodologies were employed to learn about the dynamics of disease progression and hospital outcomes in these patients, that is, death or discharge. A competing risk model was employed for hospital outcomes, an extension of the survival analysis paradigm, intrinsically accounting for the length of time to hospital discharge or death. Associations between death and available variables were evaluated using sub-hazard ratios (SHR). A SHR greater/smaller than 1 indicated a harmful/protective association, and *p*-values less than .05 indicated a significant association. The uncertainty of the estimates is expressed as 95% confidence intervals (CIs).

The final multi-state modelling approach used the peak AKI stage as an intermediate state between AKI at admission and the hospital outcome (death or discharge) and allowed quantification of AKI progression dynamics and the associated impact of COVID-19.

A prognostic model was constructed for the hospital outcomes using competing risk models, and time-varying measures of discrimination between death and discharge were evaluated through Receiving Operator Curve analyses and the associated area under the curve statistic (AUC, which is a probability). The closer this probability is to 1, the better the model discriminates between patients who will have poorer or better hospital outcomes. The AUC was evaluated at a series of time points representing important percentiles of the distribution of the length of hospital stay.

A systematic review and a series of meta-analyses were performed to derive a potential pooled estimate for the risk of COVID-19 in patients with AKI, while meta-regression techniques aimed to understand the sources of discrepancies between studies. The literature has been used to investigate a series of outcomes relevant to this research: the risk of AKI in COVID+ patients, the case fatality ratio in COVID+ patients with AKI, the relative risk of death for AKI versus non-AKI in COVID+ patients, and the relative risk of death for COVID+ versus COVID- patients when available. The studies were grouped based on population demographics, including geography/ethnicity (as in China, USA, Europe), predominant gender and age, and, in the absence of clear guidelines for disease management at the time, grouping by length of study and disease severity (requirement for intensive care) were considered. Further details on the data collection, statistical methods, and analytical strategies are outlined in the Supporting Information.

3 | RESULTS

3.1 | Summary statistics

Of the 953 cases of AKI Stage 1–3 identified, 576 satisfied the inclusion criteria (Figure S1). The summary statistics of all variables used in the analyses are presented in Table 1.

Upon admission, 421 patients (73.1%) had AKI Stage-1, 94 (16.3%) AKI Stage-2 and 55 (9.6%) patients AKI Stage-3; 257 (43.6%) patients had COVID-19 diagnosed during their inpatient stay, including those hospitalized for illness related to COVID-19, and those with incidental finding of COVID-19 who were hospitalized for other clinical reasons. A total of 166 (28.8%) patients reached AKI Stage-3, of whom 108 (42%) were COVID+ and 58 (18.2%) were COVID-. Approximately a quarter of the cohort [171 (26.7%)] were admitted to the ICU, of whom 130 (76%) tested COVID+ and 68 (40%) required KRT.

The mean age was 67.3 years; 335 (58.2%) were men, 232 (40.3%) were Caucasian, 191 (33.2%) had diabetes mellitus, 326 (56.6%) had hypertension, 149 (25.9%) had cardiac disease, including ischemic heart disease, and 43 (7.5%) had chronic lung disease. Full medication history was recorded for 574/576 (99.7%) patients; the median (Q1–Q3) number of medications prior to admission was 6.0 (2–9). Approximately one-third (182/576) of the patients were taking an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) on admission. The median (Q1–Q3) baseline serum creatinine level prior to admission was 80 (60–100) μmoles/L, and 92 (16%) patients had pre-existing chronic kidney disease (CKD Stages 3–5). The presence of CKD was defined upon review of the medical records, diagnostic codes, and historical biochemistry results.

Data regarding AKI progression during admission are presented in Table S1 and Figure S2. Overall, 16.8% of patients with AKI Stage-1

TABLE 1 The effect of the available variables on the sub-hazard ratios death versus hospital discharge – adjusted for both COVID status and acute kidney injury (AKI) peak stage. The effect of age on death decreases across peak AKI stage as indicated by the interaction between age and AKI peak stage.

		All	COVID+			COVID-			Death vs. discharge adjusted for COVID and AKI stage		No obs
Variable	Summary/ category	576	All 257	Died 134 (52.1%)	Survived 123 (47.9%)	All 319	Died 52 (16.3%)	Survived 267 (83.7%)	*p*-Value	Sub-hazard ratio 95% CI	
COVID alone	No	319 (55.4%)								1	
	Yes	257 (44.6%)							**<0.001**	3.88 (2.80, 5.37)	576
COVID and	No									1	
AKI peak stage	Yes								**<0.001**	3.07 (2.18, 4.32)	576
AKI peak stage	1	301 (52.3%)	107 (41.6%)	37 (27.6%)	70 (56.9%)	194 (60.8%)	17 (32.7%)	177 (66.3%)		1	
	2	109 (18.9%)	42 (16.3%)	20 (14.9%)	22 (17.9%)	67 (21.0%)	15 (28.9%)	52 (19.5%)	**0.002**	1.97 (1.28, 3.04)	
	3	166 (28.8%)	108 (42.0%)	77 (57.5%)	31 (25.2%)	58 (18.2%)	20 (38.5%)	38 (14.2%)	**<0.001**	3.12 (2.22, 4.38)	
AKI stage	0–1	421 (73.09%)	188 (73.15%)	98 (79.67%)	90 (67.16%)	233 (73.04%)	206 (77.15%)	27 (51.92%)			576
within 24 h	2	94 (16.32%)	44 (17.12%)	14 (11.38%)	30 (22.39%)	50 (15.67%)	36 (13.48%)	14 (26.92%)	**<0.001**	**1.97 (1.41, 2.76)**	
Since admission	3	55 (9.55%)	25 (9.73%)	11 (8.94%)	14 (10.45%)	30 (9.40%)	21 (7.87%)	9 (17.31%)	**0.017**	**1.79 (1.11, 2.88)**	
	Missing	6 (1.04%)	0 (0%)	0 (0%)	0 (0%)	6 (1.88%)	4 (1.50%)	2 (3.85%)			
LOS	Mean/SD	14/16	17/17	11.3/7.3	23.4/22.2	10.7/14	9.1/9.1	11/14.7			576
Original scale	Median (Q1-Q3)	9 (4–17)	14 (7–20)	10 (5–16)	17 (10–32)	7 (3–13)	6 (2–12.5)	7 (3–13)			
	Range	1–169	1–169	1–39	1–169	0–118	1–43	1–118			
LOS	Mean/SD	2.12/1.03	2.47/0.91	2.17/0.81	2.81/0.91	1.84/1.04	1.73/1.04	1.86/1.04	-	-	576
Log scale	Median (Q1-Q3)	2.2 (1.4–2.8)	2.6 (1.9–3.0)	2.3 (1.6–2.8)	2.8 (2.3–3.5)	1.94 (1.10–2.56)	1.79 (0.69–2.52)	1.95 (1.10–2.56)			
	Range	0–5.1	0–5.1	0–3.7	0–5.1	0–4.8	0–3.8	0–4.8			
Age	Mean/SD	67.3/17.7	67.5/15.7	68.6/15	66/16	67.1/19	75.9/16.2	65.4/19.2	**<0.001**	1.24 (1.11, 1.38)	576
5 years effect	Median (Q1–Q3)	70 (56–81)	68 (57–80)	69.9 (59–80)	66 (54–81)	71 (54–82)	80 (68–87)	69 (53–81)	**0.043**	1.14 (1.004, 1.29)	
	Range	18.8–104	21–95	21–93	29–95	18–104	20–104	18–100	0.269	1.04 (0.97, 1.12)	
Gender	Male	335 (58.2%)	177 (68.9%)	94 (70.1%)	83 (67.5%)	158 (49.5%)	30 (57.7%)	128 (47.9%)		1	576
	Female	241 (41.8%)	80 (31.1%)	40 (29.9%)	40 (32.5%)	161 (50.5%)	22 (42.3%)	139 (52.1%)	0.447	0.89 (0.66, 1.20)	
Ethnicity	White	232 (40.3%)	81 (31.5%)	39 (29.1%)	42 (34.2%)	151 (47.3%)	25 (48.1%)	126 (47.2%)		1	
	Others	264 (45.8%)	139 (50.1%)	75 (56.0%)	64 (52.0%)	125 (39.2%)	18 (34.6%)	107 (40.1%)	0.778	0.96 (0.70, 1.31)	496
	Missing	80 (13.9%)	37 (14.4%)	20 (14.9%)	17 (13.8%)	43 (13.5%)	9 (17.3%)	34 (12.7%)			

TABLE 1 (Continued)

		All	COVID+			COVID-			Death vs. discharge adjusted for COVID and AKI stage		No obs
Variable	Summary/ category	576	All 257	Died 134 (52.1%)	Survived 123 (47.9%)	All 319	Died 52 (16.3%)	Survived 267 (83.7%)	*p*-Value	Sub-hazard ratio 95% CI	
BMI	Mean/SD	26.2/6.7	26.7/6.7	27.3 /6.6	26.1/6.7	25.9/6.7	26.4/8.3	25.8/6.3	0.758	1.004 (0.98, 1.03)	513
	Median (Q1–Q3)	25.3 (22–29)	25.9 (23–30)	26.3 (22.6–31)	25.3 (22–29)	25.2 (22–29)	25.4 (22–29)	25.1 (21.7–29)			
	Range	13.9–52.3	15.1–65.3	15.2–55.1	15.1–65.3	11.2–54.4	13.7–54.4	11.2–52.3			
	Missing	63 (11%)	36 (14%)	20 (14.9%)	6 (5%)	27 (8.5%)	7 (13.5%)	20 (8.1%)			
ICU	No	405 (70.3%)	127 (49.4%)	50 (37.3%)	77 (62.6%)	278 (87.2%)	36 (69.2%)	242 (90.6%)		1	
	Yes	171 (26.7%)	130 (50.6%)	84 (62.7%)	46 (37.4%)	41 (12.9%)	16 (30.8%)	25 (9.4%)	0.063	1.44 (0.98, 2.12)	576
*ICU – intubated during admission	No	438 (76.0%)	139 (54.1%)	55 (41.0%)	84 (68.3%)	299 (93.7%)	43 (82.7%)	256 (95.9%)		1	
	Yes	138 (23.9%)	118 (45.9%)	79 (59.0%)	39 (31.7%)	20 (6.3%)	9 (17.3%)	11 (4.1%)	0.057	1.45 (0.99, 2.13)	576
*ICU – NIV – during admission	No	550 (95.5%)	250 (97.3%)	130 (97.0%)	120 (97.6%)	315 (98.8%)	50 (96.2%)	265 (99.3%)		1	
	Yes	26 (4.5%)	7 (2.7%)	4 (3.0%)	3 (2.4%)	4 (1.2%)	2 (3.9%)	2 (0.7%)	0.401	0.78 (0.442, 1.39)	576
*ICU	No	474 (82.3%)	176 (68.5%)	65 (48.5%)	111 (90.2%)	298 (93.4%)	40 (76.9%)	258 (96.6%)		1	
Inotropes/vasopressors during admission	Yes	102 (17.7%)	81 (31.5%)	69 (51.5%)	12 (9.8%)	21 (6.6%)	12 (23.1%)	9 (3.4%)	**<0.001**	2.44 (1.76, 1.39)	576
ACR/ARB on	No	392 (68.1%)	182 (70.8%)	91 (67.9%)	91 (74%)	210 (65.8%)	32 (61.5%)	178 (66.7%)			
Admission	Yes	182 (31.6%)	74 (28.8%)	42 (31.3%)	32 (26%)	108 (33.9%)	19 (36.5%)	89 (33.3%)	0.734	1.12 (0.58, 2.15)	574
	Missing	2 (0.4%)	1 (0.4%)	1 (0.8%)	0 (0%)	1 (0.3%)	1 (1.7%)	0 (0%)			
RRT	No	508 (88.2%)	201 (78.2%)	95 (70.9%)	106 (86.2%)	307 (96.2%)	49 (94.2%)	258 (96.6%)		1	
	Yes	68 (11.8%)	56 (21.8%)	39 (29.1%)	17 (13.8%)	12 (3.8%)	3 (5.8%)	9 (3.4%)	**0.021**	0.66 (0.46, 0.94)	576
Lymphocytes	Mean/SD	−0.45/0.66	−0.58/0.60	−0.68/0.64	−0.47/0.54	−0.35/0.69	−0.64/0.74	−0.28	**0.004**	0.666 (0.50, 0.88)	588
Log scale	Median	−.51	−0.51	−0.69	−0.51	−0.36	−0.69	−0.22			
	(Q1–Q3)	(−.92, 0)	(−0.92, −0.22)	(−1.2 to −0.22)	(−0.92, −0.11)	(−0.92–0.10)	(−0.92–0.34)	(−0.69–0.18)			
	Range	−2.3–2.7	−2.3–2.7	−2.3–2.7	−2.3–2.7	−2.3–2.5	−2.3–0.74	−2.3–2.5			
Lymphocytes ($\times 10^9$/L)	Mean/SD	0.82/0.95	0.71/0.99	0.69/1.31	0.72/0.41	0.91/0.91	0.65/0.44	0.96/0.97			
Original scale	Median	0.6	0.6	0.5	0.6	0.7	0.5	0.8			
	(Q1–Q3)	(0.4–1)	(0.4–0.8)	(0.3–0.8)	0.4–0.9	(0.4–1.1)	(0.4–0.9)	(0.5–1.1)			

(Continues)

TABLE 1 (Continued)

		All	COVID+			COVID-			Death vs. discharge adjusted for COVID and AKI stage		No obs
Variable	Summary/ category	576	All 257	Died 134 (52.1%)	Survived 123 (47.9%)	All 319	Died 52 (16.3%)	Survived 267 (83.7%)	*p*-Value	Sub-hazard ratio 95% CI	
	Range	0.1–15.1	0.1–15.1	0.1–15.1	0.1–2.4	0.1–12.5	0.1–2.1	0.1–12.5			
Peak CRP*	Mean/SD	4.8/1.28	5.3/0.99	5.7/0.69	4.9/1.11	4.4/1.3	5.1/0.8	4.2/1.4	**<0.001**	1.66 (1.34, 2.07)	568
Log scale	Median (Q1–Q3)	5.1 (4.3–5.8)	5.7 (4.9–5.9)	5.8 (5.5–6.1)	5.2 (4.5–5.9)	4.7 (3.7–5.3)	5.3 (4.6–5.7)	4.6 (3.5–5.2)			
	Range	0–6.6	0.5–6.6	1.5–6.6	0.5–6.5	0–6.5	2.8–6.2	0–6.5			
Peak CRP mg/L*	Mean/SD	203.7/156	276.8/160	340.6/146.7	207.2/144.1	143.3/124	205.2/118.1	130.9/121.4			
Original scale	Median	172	287	340	179	110	198	100			
	(Q1–Q3)	73–324	143–379	247–433	94–327	41–206	99–297	35–186			
	Range	1–700	1.7–700	4.6–700	1.7–672	1–667	17–469	1–667			
	Missing	8 (1.4%)	0 (0%)	0 (0%)	0 (0%)	8 (3.1%)	0 (0%)	8 (2.5%)			
Peak Ferritin	Mean/SD	6.4/1.4	6.9/1.4	7.2/1.1	6.5/1.5	6/1.3	6.7/1.4	5.9/1.3	**0.021**	1.20 (1.03, 1.40)	294
Log scale	Median (Q1-Q3)	6.5 (5.6–7.3)	6.9 (6.2–7.6)	7.2 (6.6–7.8)	6.8 (5.8–7.5	6 (5–6.8)	6.7 (5.6–8.2)	6.0 (4.9–6.7)			
	Range	2.1–10.8	3.1–10.8	3.8–10.8	3.1–9.7	2.1–10.5	4.8–8.9	2.1–10.5			
Peak Ferritin (ug/L)	Mean/SD	1678.6/4230	2203.8/4691	2783.3/6114.2	1631.4/2535	1033.2/2100	1326/1936	1011/3630			
Original scale	Median	687	1056	1352	885	417	682	410			
	(Q1–Q3)	262–1493	473–1985	710–2494	323–1843	148–845	260–845	142–839			
	Range	8–50 960	22–50 960	43–50 960	22–16 155	8–38 092	117–6868	8–38 092			
	Missing	292 (49.3%)	96 (37.4%)	54 (40.3%)	42 (34.1%)	188 (55.8%)	39 (75%)	149 (55.8%)			
Peak D-dimer	Mean/SD	7.4/1.2	7.7/1.1	8/0.97	7.4/1.2	6.9/1.1	7.7/1	6.8/1.1	0.069	1.29 (0.98, 1.69)	**258**
Log scale	Median (Q1–Q3)	7.7 (6.5–8.6)	8.2 (7–8.7)	8.6 (7.8–8.7)	7.7 (6.5–8.3)	6.8 (6–7.9)	8 (6.9–8.3)	6.7 (5.9–7.7)			
	Range	4.2–8.9	4.2–8.9	5.2–8.7	4.2–8.9	4.2–8.8	5.2–8.7	4.2–8.8			
Peak D-dimer (ug/L)	Mean/SD	2758/2250	3485/2267	4114/2180	2633/2113	1699/1756	2566/1831	1543/1706			
Original scale	Median	2269	3480	5481	2279	939	2572	865			
	(Q1-Q3)	639–5467	1086–6000	2446–6000	671–3979	408–2537	945–3463	64–6906			
	Range	64–7449	64–7449	185–6000	64–7449	64–6906	186–6000	64–6906			
	Missing	318 (55.2%)	104 (40.5%)	46 (34.3%)	58 (47.2%)	223 (67.0%)	39 (67.2%)	184 (66.9%)			
Baseline	Mean/SD	4.4/0.45	4.4/0.42	4.4/0.37	4.4/0.47	4.4/0.47	4.5/0.43	4.4/0.48	0.843	1.03 (0.76, 1.39)	571
Creatinine	Median (Q1–Q3)	4.4 (4.1–4.6)	4.4 (4.1–4.6)	4.4 (4.2–4.6)	4.4 (4.1–4.6)	4.4 (4.1–4.6)	4.4 (4.2–4.8)	4.4 (4.1–4.6)			

TABLE 1 (Continued)

		All	COVID+			COVID-			Death vs. discharge adjusted for COVID and AKI stage		No obs
Variable	Summary/ category	576	All 257	Died 134 (52.1%)	Survived 123 (47.9%)	All 319	Died 52 (16.3%)	Survived 267 (83.7%)	*p*-Value	Sub-hazard ratio 95% CI	
Log scale	Range	3.0–6.0	3.2–6.4	3.4–5.6	3.2–6.4	3–6.4	3.6–5.6	3–6.4			
Baseline	Mean/SD	91.9/58.6	92.2/54.7	89.4/35.9	95.3/69.6	91.7/61.6	95.4/45.3	91/64			
Creatinine (μmol/L)	Median	80	85	85	80	80	80	80			
Original scale	(Q1–Q3)	60–100	60–100	70–100	60–100	60–100	70–120	60–100			
	Range	20–600	25–600	30–280	25–600	20–600	38–260	20–600			
	Missing	18 (3%)	10 (3.9%)	6 (4.5%)	4 (3.3%)	8 (2.5%)	5 (9.6%)	2 (0.7%)			
Peak Creatinine	Mean/SD	5.2/0.68	5.4/0.69	5.6/0.65	5.2/0.68	5.1/0.64	5.4/0.6	5.1/0.62			
Log scale	Median (Q1–Q3)	5.2 (4.8–5.6)	5.4 (4.9–6)	5.6 (5.2–6.2)	5.1 (4.6–5.7)	5.0 (4.7–5.4)	5.3 (5–5.9)	4.9 (4.7–5.4)			
	Range	3.5–7.3	3.7–6.9	4.1–6.9	3.7–6.9	3.5–7.3	3.9–6.6	3.5–7.3			
Peak	Mean/SD	242.1/196	285.8/204.7	336/215	231/178.4	206.9/180.8	261.9/166.9	196.1/181.8			
Creatinine (μmol/L)	Median	176	211	264	159	154	200	144			
Original scale	(Q1–Q3)	119–284	133–400	173–471	102–301	110–225	140–329	106–217			
	Range	32–1477	41–1037	61–1037	41–984	32–1477	53–720	32–1477			
Discharge	Mean/SD	4.6/0.5	4.6/0.5		4.6/0.5	4.6/0.5		4.6/0.5			
Creatinine	Median (Q1–Q3)	4.5 (4.2–4.8)	4.5 (4.2–4.8)	NA	4.5 (4.2–4.8)	4.5 (4.2–4.9)	NA	4.5 (4.2–4.9)	NA	NA	392
Log scale	Range	3.5–6.1	3.7–6.3		3.8–5.8	3.5–6.1		3.5–6.1			
Discharge	Mean/SD	115.1/89.2	111.3/77		111.3/77	116.8/94		116.8/94			
Creatinine (μmol/L)	Median (Q1–Q3)	92 (68–127)	89 (68–122)		89 (68–122)	94 (69–132)		94 (69–132)			
Original scale	Range	20–1078	43–554		43–554	20–1078		20–1078			
	Missing	192 (33.3%)	137 (53.3%)		3 (2.4%)	52 (16%)		3 (1%)			
Diabetes	No	385 (66.8%)	160 (62.3%)	82 (61.2%)	78 (63.4%)	225 (70.5%)	37 (71.2%)	188 (70.4%)		1	
	Yes	191 (33.2%)	97 (37.7%)	52 (38.8%)	97 (36.6%)	94 (29.5%)	15 (28.9%)	79 (29.6%)	0.853	0.97 (0.74, 1.29)	576
HTN	No	250 (43.4%)	113 (44%)	55 (41%)	58 (47.2%)	137 (42.9%)	14 (26.9%)	123 (46.1%)		1	
	Yes	326 (56.6%)	144 (56%)	79 (59%)	65 (52.8%)	182 (57.1%)	38 (73.1%)	144 (53.9%)	0.093	1.27 (0.96, 1.67)	576
CARDIAC	No	427 (74.1%)	202 (78.6%)	109 (81.3%)	93 (75.6%)	225 (70.5%)	32 (61.5%)	193 (72.3%)		1	
	Yes	149 (25.9%)	55 (21.4%)	25 (18.7%)	30 (24.4%)	94 (29.5%)	20 (38.5%)	74 (27.7%)	0.232	1.228 (0.87, 1.72)	576
CKD	No	482 (83.7%)	214 (83.3%)	115 (85.8%)	99 (80.5%)	268 (84.0%)	41 (78.9%)	227 (85.1%)		1	

(Continues)

TABLE 1 (Continued)

Variable	Summary/category	All 576	COVID+ All 257	COVID+ Died 134 (52.1%)	COVID+ Survived 123 (47.9%)	COVID- All 319	COVID- Died 52 (16.3%)	COVID- Survived 267 (83.7%)	Death vs. discharge adjusted for COVID and AKI stage p-Value	Death vs. discharge adjusted for COVID and AKI stage Sub-hazard ratio 95% CI	No obs
	Yes	92 (16%)	43 (16.7%)	19 (14.2%)	24 (19.5%)	49 (15.4%)	9 (17.3%)	40 (14.9%)	0.497	0.87 (0.59, 1.29)	574
	Missing	2 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.6%)	2 (3.9%)	0 (0%)			
COPD/asthma	No	533 (92.5%)	236 (91.8%)	118 (88.1%)	118 (95.1%)	297 (93.1%)	48 (92.3%)	249 (93.3%)		1	
	Yes	43 (7.5%)	21 (8.2%)	16 (11.8%)	5 (4.1%)	22 (6.9%)	4 (7.7%)	18 (6.7%)	**0.013**	1.543 (1.095, 2.18)	576
Thrombotic events	No	514 (89.2%)	216 (84.1%)	104 (77.6%)	112 (91.1%)	298 (93.4%)	46 (88.5%)	252 (94.6%)		1	
	Yes	62 (10.8%)	41 (15.9%)	30 (22.4%)	11 (8.9%)	21 (6.6%)	6 (11.5%)	15 (5.6%)	**0.039**	1.42 (1.01, 1.99)	576

Note: Bold values indicate statistical significance ($p < 0.05$).

on admission progressed to AKI Stage-3; the percentage was significantly higher among COVID+ patients (31.4%) than among COVID- (5.2%) patients. Among those with AKI Stage-3 on admission, 14/25 (56%) of the COVID+ patients died compared with 9/30 (30%) of the COVID- patients.

3.2 | Case fatality ratio in AKI patients in the context of COVID-19 pandemic

According to the competing risk model, death was almost four times more likely in COVID+ patients [SHR = 3.88 (2.80, 5.37)]. Case fatality ranged from 10% (6.3%–13.1%) among COVID- patients with AKI Stage-1, to 71% (64%–79%) among patients with AKI Stage-3 (Figure 1). Figures 2 and 3 and Table S2 depict the daily dynamics and cumulative incidence of hospital outcomes stratified by COVID-19 status (Figure 2) and AKI peak stage (Figure 3). Among COVID+ patients, those with AKI Stage-3 displayed either the fastest increase in the daily cumulative incidence of death or the longest hospital stay (Figure 3).

The overall estimated case-fatality percentage among patients with AKI was 32.5% (28.8%–36.3%). Stratified by COVID status, this was 16% (12%–20%) in COVID- and 52% (46%–58%) in COVID+ patients. Stratified by peak AKI stage, the figures were: 10% (6.3%–13.1%) in COVID- versus 33% (25%–41%) in COVID+ for patients who did not progress beyond AKI Stage-1, 19% (12%–27%) in COVID- versus 52% (41%–64%) in COVID+ for patients who reached AKI Stage-2 and 35% (25.4%–44.4%) in COVID- versus 71% (64%–79%) in COVID+ in AKI Stage-3.

Blood CRP concentration (log scale) was a strong indicator of death in patients with AKI after adjusting for COVID-19 status and AKI stage ($p < .001$). This is also reflected in the summary of the original values across the groups (Table 1). For example, among surviving COVID+ inpatients, the median [Q1–Q3] values for blood CRP concentration were higher [340 (247–433)] than those in COVID- [100 (35–186)]. Similarly, among COVID+ inpatients, lymphocyte count was lower [0.5 (0.3–0.8) vs. 0.8 (0.5–1.1)], peak ferritin level was higher [1352 (710–2494) vs. 410 (142–839)], and peak D-dimer level was higher [5481 (2446–6000) vs. 845 (388–2154)]. Patients with thrombotic events including deep vein thrombosis and pulmonary emboli were 2.02 times (CI 1.13–3.61) more likely to test COVID+. After controlling for COVID-19 status and peak AKI stage, these patients were 1.42 (1.01–1.99) times more likely to die (Table 1).

3.2.1 | The dynamics of the progression to severe stages of AKI and/or to death or discharge

Table S1 indicates the raw transition probabilities illustrated in Figure S2, which captures all possible forward transitions that indicate evolution towards more severe stages. The corresponding daily predicted probabilities stratified by the COVID-19 status are shown in Figure 4.

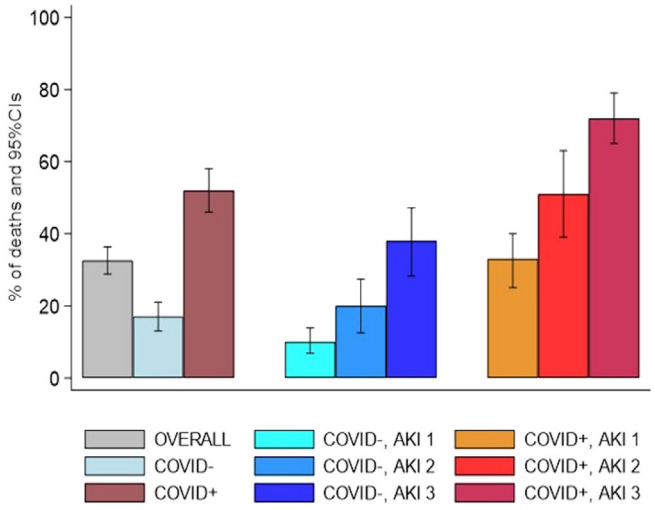

FIGURE 1 The estimated case-fatality percentages and their uncertainty in acute kidney injury (AKI) patients – overall [32.5% (28.8%–36.3%)] and stratified by COVID status [16% (12%–20%] in COVID- versus 52% (46%–58%) in COVID+). Further yields stratified by AKI peak stage: 10% (6.3%–13.1%) in COVID- versus 33% (25%–41%) in COVID+ for patients who did not progress beyond AKI stage 1, 19% (12%–27%) in COVID- versus 52% (41%–64%) in COVID+ for patients who reached AKI stage 2 and 35% (25.4%–44.4%) in COVID- versus 71% (64%–79%) in COVID+ in AKI stage 3.

A series of predictions based on these curves are presented in Table S3. For example, the probability of transition from AKI Stage-1 to Stage-3 on day 7 was 6% (3%, 9%) among COVID- patients. This was more than threefold higher in COVID+ patients [22% (17%, 27%)]. By day 33, there was a 13% (9%, 10%) chance that patients with AKI Stage-1 would die if COVID-, but 50% (44%, 56%) if COVID +. Surviving inpatients who were COVID+ had the longest median [Q1–Q3] length of stay [17 (10–32) days], with only 19% (14%, 24%) discharged by day 14. Within the same time span, 33% (28%, 39%) of the COVID+ patients died, increasing to 45% (36%, 54%) among those who reached AKI Stage-3. The probability of progression from AKI Stage-1 to AKI Stage-3 peaked on day 6 at 7% (4%, 10%) in COVID- patients and on day 8 at 24% (19%, 30%) in COVID+ patients. The probabilities of progression to more severe AKI stages at various time points stratified by COVID-19 status are displayed in Table S3 and Figure 4.

The prognostic model (Table 2) is based on the most parsimonious multivariable competing risk model, with retained age, COVID-19 status, AKI peak stage, and creatinine as the strongest predictors. The model also retained a significant interaction between creatinine and AKI-peak stages, indicating that creatinine levels associate with death differently across AKI-peak stages; the risk of death increases faster with creatinine levels in AKI-1 patients than in AKI-3 patients. The discriminatory power of this model based on time-varying ROC analysis results in AUC = 0.76 (0.71–0.81) on the 29th day and AUC = 0.77 (0.72–0.82) on the 40th day, by which 95% of the patients either died or were discharged from the hospital. The AUC did not change beyond this time point (Table S4).

3.3 | Meta-analyses

A total of 48 articles fulfilled our criteria to be included in Systematic Review and meta-analyses (Figure S3). Studies were classified by geographical location and included papers published from China ($n = 14$), United States of America ($n = 15$), Europe ($n = 5$), Middle East/India ($n = 5$), South America ($n = 3$), South Korea ($n = 3$), and United Kingdom ($n = 3$) (Supporting Information).

Overall risk of AKI in COVID+ patients was estimated at 0.30 (0.24, 0.37), but exhibited values between 0.005 and 0.9 in studies, resulting an I^2 value of 99.65% highlighting significant heterogeneity between studies (supplementary meta-analyses Figure 1). Further analysis suggested differences in geographical regions with highest incidence in American studies and lowest incidence in Chinese studies ($p < .001$), and tendency towards male gender dominance ($p < .001$), however, variability within regions remained high ($I^2 > 90\%$) (supplementary meta-analyses Figures 2 and 4). Case-fatality ratio of COVID + patients ranged from 1% to 52% (supplementary meta-analyses Figure S11) with large heterogeneity within different geographical regions (supplementary meta-analyses Figure S12).

Further comprehensive analysis of meta-analyses is detailed in the Supporting Information.

4 | DISCUSSION

This study investigated a large cohort of patients with AKI using statistical techniques (Supporting Information) and demonstrated consistent information regarding the dynamics of hospital outcomes and AKI progression. The current KDIGO guidelines divide AKI into stages 1, 2, or 3 based on specific urine output and/or increases in the serum creatinine level and/or the requirement for KRT.[14] While it is broadly accepted that each stage represents a stepwise negative prognostic milestone, there is a paucity of data quantifying how patients progress between stages.

In these data analyses, we sought to assess AKI progression in a novel fashion, thus moving away from estimating sample proportions, but also estimating the transition dynamics to more severe stages in patients with AKI. By subdividing this cohort into COVID-19 positive and negative groups, these data further benefited from the possibility of isolating and quantifying the effect of the first wave of the COVID-19 pandemic on AKI progression.

The overall case fatality in COVID- patients was 16% (12%–20%). The UK Renal Registry published a national AKI audit report on the nationwide collection of AKI warning test scores from 2018.[15] From this report, 18% of patients with AKI episode died within 30 days of first alert in 2018; this figure is well consistent with our estimate and its 95% confidence interval of 16% (12%–20%). Furthermore, in the same document, it has been stated that the risk of death within 30 days from hospital admission reported by the UK Renal Registry also increased with peak AKI stage: 13% for AKI-1, 29% for AKI-2 and 33% for AKI-. All these results are consistent with case-fatality within

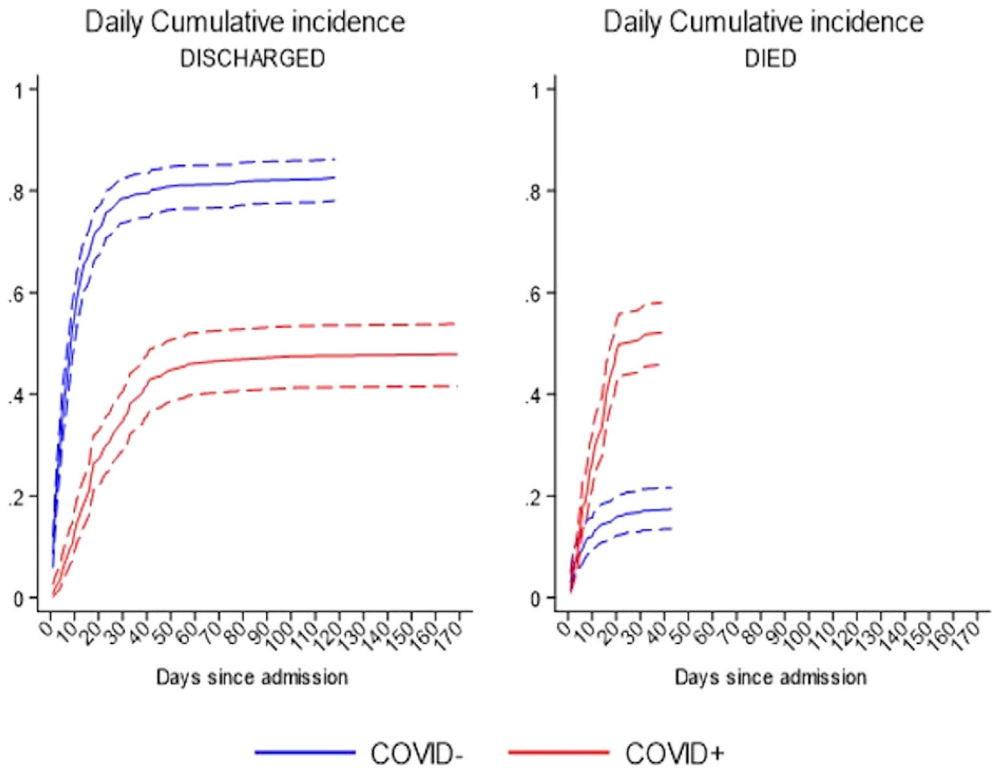

FIGURE 2 Insight into the dynamics of death and discharge in acute kidney injury patients stratified by COVID status. Associated estimates with these figures are given in the first line of Table S2.

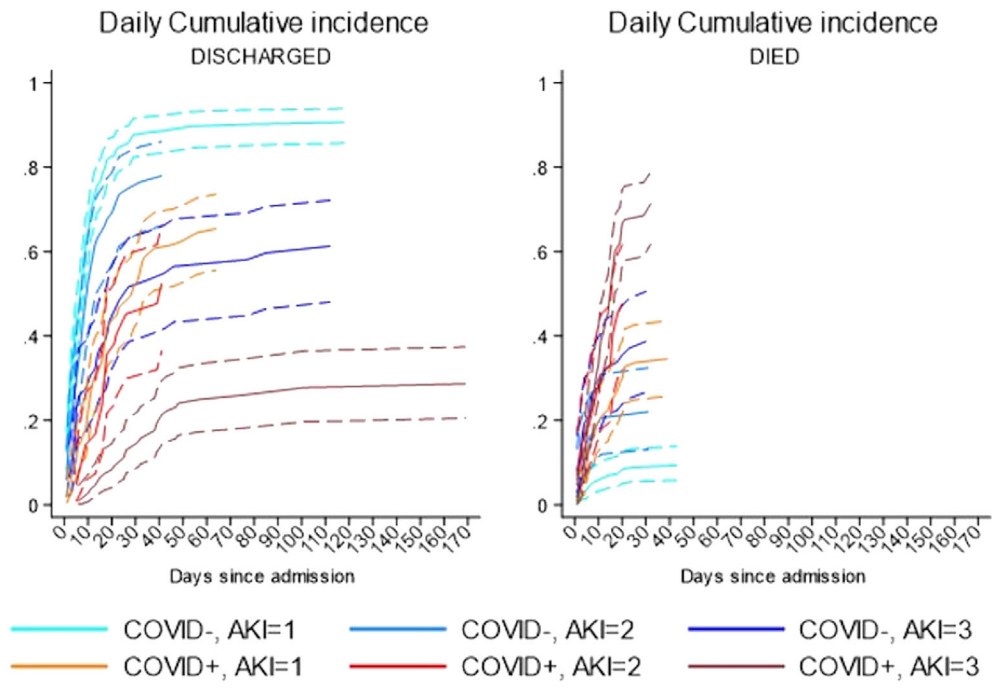

FIGURE 3 Insight into the dynamics of death and discharge in acute kidney injury (AKI) patients further stratified by COVID status and AKI stage. Associated estimates with these figures are given in the last three lines of Table S2.

the COVID- group of our cohort stratified by AKI peak stage, and within or very close range of their 95% confidence intervals.

From a clinician's perspective, these data highlight that progression between AKI stages during the first wave could be exacerbated by COVID-19 infection, with severe or fatal consequences. While clinicians may look at trends in creatinine, we believe that our statistical modelling offers insight into predicting potential deterioration, with greater accuracy, based on evidence informed by the available data. This could represent a paradigm shift from a largely qualitative approach to a more quantitative and thus more scientific methodology.

Our approach demonstrated considerable differences in the severity and progression of AKI (as well as other patient-centred metrics) in those who were COVID+ compared with those who were negative. The devastation from what was initially considered to be a primary respiratory illness has subsequently been shown to have

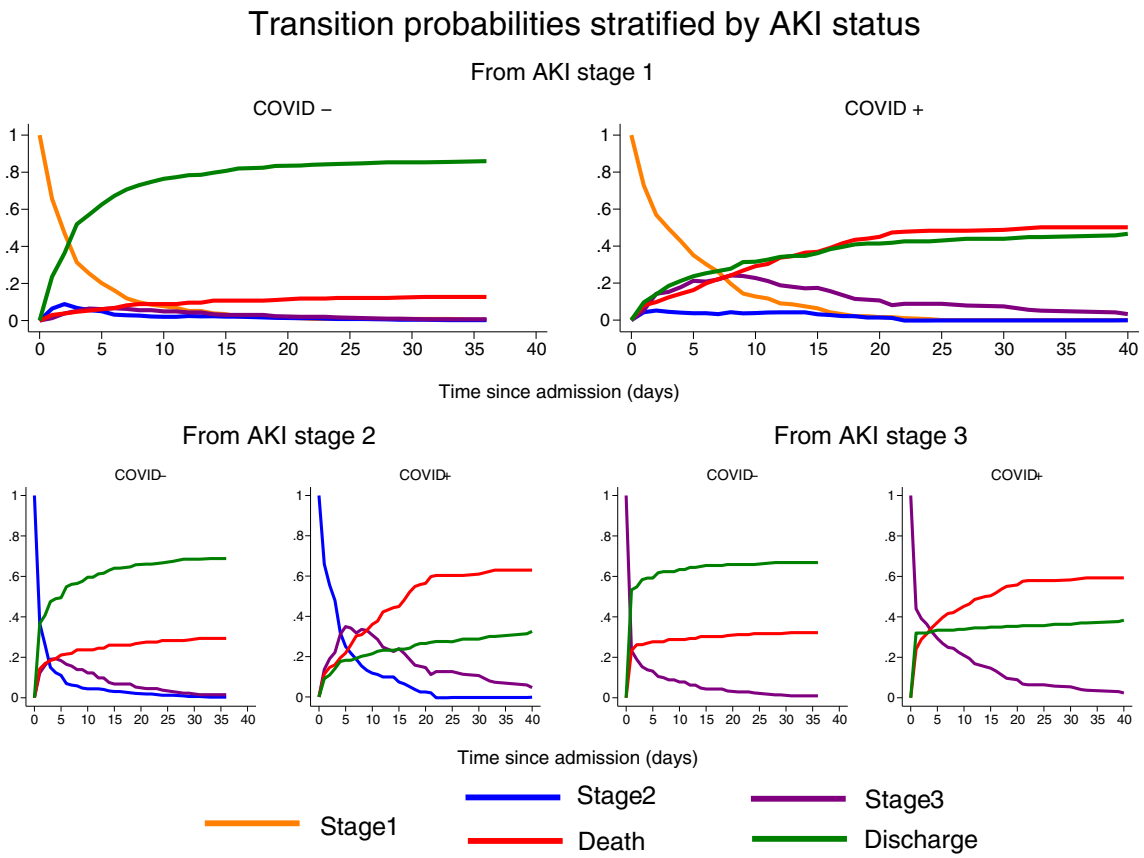

FIGURE 4 The estimated acute kidney injury (AKI) transition probabilities describing the dynamics of AKI evolution during the first 40 hospital days stay from admission stratified by COVID status. Transition probabilities values on day 7, 14 and peak values and the day since admission they have been achieved are given in Table S3.

TABLE 2 Prognostic model presenting adjusted estimates associated with death based on a competing risk regression model. The presence of interaction between acute kidney injury (AKI) stages and log peak creatinine suggests that this variable associate with death differently across AKI stages. For example, the effect of creatinine is more preeminent in AKI Stage-1 compared with AKI Stage-3.

Prognostic model					
Variables	**Category/effect**	**SHR**	***p*-Value**	**95% CI low**	**95% CI high**
Age	5 years effect	1.14	<0.001	1.08	1.21
Covid	Yes vs. no	2.26	<0.001	1.57	3.24
AKI	Stage 2 vs. Stage 1	2.11	0.005	1.26	3.56
	Stage 3 vs. Stage 1	2.82	<0.001	1.65	4.81
Creatinine	Log scale effect – Stage 1	2.72	<0.001	1.74	4.26
AKI × Creat	Log scale effect – Stage 2	1.04	0.877	0.65	1.65
	Log scale effect – Stage 3	1.74	0.003	1.20	2.51

immediate and longer-lasting implications for multiple organ systems in the absence of preventive measures or clear clinical management guidelines. Patient-centred outcomes, such as length of stay and survival, are particularly useful for planning health-care provision and resource allocation. This delineation was admittedly from a pre-vaccination cohort, and although outcomes have greatly improved following widespread vaccination[16] it does not limit the utility of our dataset in highlighting how these metrics can differ from pre-pandemic times. A vast upscaling of health-care resources is required to manage not only the respiratory complications of COVID-19 but also the associated prolonged length of stay and use of KRT resources. These data provide a useful platform for research, which may even be applicable to future waves of COVID-19, generated by new variants or other future infections, including data needed to improve the understanding of the real-time evolution of AKI under duress caused by novel agents.

Three increasingly complex statistical techniques (Supporting Information) investigating COVID-19 infection and hospital outcomes provided consistent results and yet increasingly detailed information regarding the dynamics of hospital outcomes and AKI progression to more severe stages and/or death. We only used AKI upon admission, AKI peak stage, and hospital outcome, but this approach can

accommodate disease regression from AKI stage-3 to AKI stage-2 and back again. Daily longitudinal data collection on AKI stages is imperative in the presence of novel agents so that all possible scenarios can be captured.

There was a disproportionate burden of severe AKI and severe illness exacerbated by COVID-19, as evidenced by high levels of inflammatory markers, ICU admission, and requirement for intubation and KRT. This has been corroborated by other global studies.[17–23]

Adjusted for peak AKI stage, men were twice as likely to be COVID+ as women; non-Caucasian patients were almost twice as likely to be COVID+ as COVID-, which is consistent with published literature.[18,23–26] There was no evidence to suggest an association between patients with hypertension, cardiac comorbidities, and COVID-19, in line with the current research.[19,24,27] Even large multicentre studies failed to show sufficient statistical evidence that hypertension may have an impact on outcomes following COVID-19 infection[28] and meta-analyses have also shown significant heterogeneity with regard to cardiovascular risk factors and complications among COVID+ patients.[29]

These analyses did not benefit from the date of COVID-19 swab or assessment; hence, it is impossible to disentangle which event occurred first, that is, COVID infection or AKI progression. It was also impossible to assess whether the patients attended the hospital with COVID-19 infection or acquired it during their hospital stay. For example, if the date of the PCR results was known, the patients would have been classified as COVID+ (within 48 h after admission) or acquired during hospitalization (COVID+ after 48 h). The dates would have been irrelevant to the onset of infection but would have offered further insights into the intertwined dynamics between AKI and COVID-19.

Of 48 eligible studies worldwide, in a mixture of hospital patients of different degrees of severity, attempts to derive valid pooled estimates for outcomes were hampered by a high degree of heterogeneity between these studies ($I^2 > 95\%$) present in all analyses (Supporting Information).

Three studies[26,30,31] compared the outcomes of patients with AKI in both COVID+ and COVID- patients, allowing more detailed comparisons to be made. All three studies[26,30,31] identified male sex, non-Caucasian ethnicity, admission to the ICU for mechanical ventilation, and/or KRT as common factors among AKI patients who were COVID+ compared with COVID- patients, in agreement with this study. Other risk factors associated with COVID+ status among AKI patients include diabetes mellitus,[26,31] obesity,[26] CKD,[26] and older age.[26] All three studies reported higher case-fatality in patients who were COVID+ compared with COVID-. Kohle et al.[30] found case-fatality of patients with AKI and COVID+ to be 60.5%, comparable to 52% we obtained from our cohort. These are much higher than reported by Fisher et al.[26] (33.7%) and Moledina et al.[31] (29.6%). These differences could be attributed to differences in patient management, as these studies were conducted during a time period prior to vaccination and where there were no standardised guidelines for management of COVID-19. It is also difficult to specifically quantify the exact contribution of AKI stage to death in the presence of many other contributing risk factors such as age and co-morbidities. To our knowledge, no studies specifically analysing the extent to which mortality in this population is attributable to AKI and/or its stages Nevertheless, the evidence strongly supports that presence of AKI in the context of COVID-19 is associated with poorer prognosis.

This study investigated the hospital outcomes and dynamics of AKI during the first wave of the COVID-19 pandemic. These data demonstrated a more rapid progression to severe forms of AKI or death, higher case fatality ratios, and longer lengths of stay among COVID+ patients who suffered AKI compared with COVID- patients. This study highlighted a several-fold increased requirement for dialysis, use of general and high-dependency hospital beds, and enhanced use of specialized staff to manage COVID+ AKI patients. This will be particularly pertinent when considering the potential impact of novel COVID-19 variants, especially among unvaccinated patients with AKI associated with similar infections in the future, and will aid tailored planning for this vulnerable patient group.

AUTHOR CONTRIBUTIONS

Aruni Ratnayake: Study conception and design, data collection, drafting and revision of the article, review of the manuscript prior to submission. **Alexander Sarnowski:** Study conception and design, data collection, drafting and revision of the article, review of manuscript prior to submission. **Fiona Sinclair:** Study conception and design, data collection, and review of manuscript prior to submission. **Nicholas M. P. Annear:** Study conception and design, revision of article, review of manuscript prior to submission. **Debasish Banerjee:** Study conception and design, revision of the article, review of the manuscript prior to submission. **Irina Chis Ster:** Study conception and design, statistical analytical strategy and implementation, drafting and revision of article, review of manuscript prior to submission.

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CONFLICT OF INTEREST STATEMENT

DB has received speaker fees from AstraZeneca, ViforPharma, Grants from AstraZeneca, Kidney Research UK, Honoraria from Bayer; NMPA has previously received grants from the NIHR, the Kathleen Valles Charitable Trust and Novartis, and honoraria from Novartis Vifor Pharma, Aeovian Pharmaceuticals, and Jazz Pharmaceuticals. ICS has previously received grants from AstraZeneca, NIHR, and MRC. The remaining authors have no conflicts of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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