OBSERVATIONAL STUDY

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Multistate Modeling of Clinical Trajectories and Outcomes in the ICU: A Proof-of-Concept Evaluation of Acute Kidney Injury Among Critically Ill Patients With COVID-19

Patrick G. Lyons, MD, MSc[1,2]
Aaloke Mody, MD, MPH[1]
Alice F. Bewley, MS[1]
Morgan Schoer, MD[1]
Bharat Neelam Raju, MD[1]
Elvin Geng, MD, MPH[1,3]
Philip R. O. Payne, PhD[1,4]
Pratik Sinha, MBBS, PhD[5]
Anitha Vijayan, MD[1]

IMPORTANCE: Multistate models yield high-fidelity analyses of the dynamic state transition and temporal dimensions of a clinical condition's natural history, offering superiority over aggregate modeling techniques for addressing these types of problems.

OBJECTIVES: To demonstrate the utility of these models in critical care, we examined acute kidney injury (AKI) development, progression, and outcomes in COVID-19 critical illness through multistate analyses.

DESIGN, SETTING, AND PARTICIPANTS: Retrospective cohort study at an urban tertiary-care academic hospital in the United States. All patients greater than or equal to 18 years in an ICU with COVID-19 in 2020, excluding patients with preexisting end-stage renal disease.

MAIN OUTCOMES AND MEASURES: Using electronic health record data, we determined AKI presence/stage in discrete 12-hour time windows and fit multistate models to determine longitudinal transitions and outcomes.

RESULTS: Of 367 encounters, 241 (66%) experienced AKI (maximal stages: 88 stage-1, 49 stage-2, 104 stage-3 AKI [51 received renal replacement therapy (RRT), 53 did not]). Patients receiving RRT overwhelmingly received invasive mechanical ventilation (IMV) ($n = 60$, 95%) compared with the AKI-without-RRT ($n = 98$, 53%) and no-AKI groups ($n = 39$, 32%; $p < 0.001$), with similar mortality patterns (RRT: $n = 36$, 57%; AKI: $n = 74$, 40%; non-AKI: $n = 23$, 19%; $p < 0.001$). After 24 hours in the ICU, almost half the cohort had AKI (44.9%; 95% CI, 41.6–48.2%). At 7 days after stage-1 AKI, 74.0% (63.6–84.4) were AKI-free or discharged. By contrast, fewer patients experiencing stage-3 AKI were recovered (30.0% [24.1–35.8%]) or discharged (7.9% [5.2–10.7%]) after 7 days. Early AKI occurred with similar frequency in patients receiving and not receiving IMV: after 24 hours in the ICU, 20.9% of patients (18.3–23.6%) had AKI and IMV, while 23.4% (20.6–26.2%) had AKI without IMV.

CONCLUSIONS AND RELEVANCE: In a multistate analysis of critically ill patients with COVID-19, AKI occurred early and heterogeneously in the course of critical illness. Multistate methods are useful and underused in ICU care delivery science as tools for understanding trajectories, prognoses, and resource needs.

KEY WORDS: acute kidney injury; COVID-19; critical illness; hospital outcomes; statistical modeling

Analyzing the natural history, response to treatment, and outcomes of critical illness syndromes is made difficult by these syndromes' heterogeneity in terms of organ involvement, severity, clinical interventions, and time (1). For such entities—which are both dynamic and longitudinal—commonly used approaches frequently fall short. For example, cross-sectional

DOI: 10.1097/CCE.0000000000000784

KEY POINTS

- **Question:** What are the trajectories and outcomes of acute kidney injury (AKI) among critically ill adult patients with COVID-19?
- **Findings:** As proof-of-concept, we fit multistate models on electronic health record data from a single hospital to describe longitudinal AKI trajectories, transitions through worsening and recovery, and outcomes of critically ill patients with COVID-19. Of 367 encounters, 241 (66%) experienced AKI (maximal stages: 88 stage-1, 49 stage-2, 104 stage-3 AKI [51 received renal replacement therapy, 53 did not]). At 7 days after stage-1 AKI, 74.0% (63.6–84.4%) were AKI-free or discharged; by contrast, fewer patients experiencing stage-3 AKI were recovered (30.0% [24.1–35.8%]) or discharged (7.9% [5.2–10.7%]) after 7 days.
- **Meaning:** Multistate models can evaluate dynamic longitudinal data and outcomes effectively, making them ideal methodologic approaches for evaluating many critical illness syndromes over time.

evaluations may be at risk for bias due to unequal observation time (2), whereas traditional time-to-event models lack intrinsic handling of competing risks and informative censoring (3, 4) and themselves may be at risk for time-dependent bias (5).

In contrast, modern longitudinal analytic approaches such as multistate models can assess measures that change over time and in response to interventions, offering superiority over aggregate modeling techniques for addressing this type of clinical problem. The multistate model conceptualizes a stochastic process (e.g., a patient's clinical ICU course) in terms of a set of comprehensive, mutually exclusive states and the transitions among them, accounting for competing events at each transition (6, 7). By evaluating patient transitions in and out of these states over time, multistate models explicate longitudinal cohort-level outcomes with high granularity (e.g., some patients with respiratory failure require mechanical ventilation immediately in their critical illness, while others deteriorate slowly and still others have an abrupt late respiratory collapse).

As an example of how such models might inform clinical and administrative decision-making in the ICU, we performed multistate analyses examining the clinical courses and outcomes of critically ill COVID-19 patients at risk for acute kidney injury (AKI) at an academic hospital in 2020. AKI is a well-described complication of COVID-19 critical illness, including high rates of renal replacement therapy (RRT) and (especially during the initial surge) lower-than-expected rates of renal recovery (8–13). Given the frequency of resource constraints—and risks of rationed care—in earlier pandemic waves, a detailed understanding of critically ill patients at risk for AKI and RRT might have informed planning and allocation of finite resources such as RRT devices and supplies, appropriately trained staff, and electrolyte replacement fluids (14–17), which necessitated alterations in dialysis dosing, schedule, modality, and staffing in prior waves (18, 19). In this applied example, we provide insight into the practicalities and pitfalls of using multistate modeling in critical care outcomes research.

MATERIALS AND METHODS

Study Population and Setting

At Barnes-Jewish Hospital, a 1,300-bed urban quaternary care center in St. Louis, MO, we performed a retrospective cohort study of all adults (≥ 18) admitted to an ICU with COVID-19 between March 16, 2020, and December 31, 2020. We included all hospitalizations with a positive polymerase chain reaction test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) within 14 days prior to admission or the first 7 days of hospitalization. We restricted the cohort to index hospitalizations and excluded patients who were receiving RRT prior to hospital admission (i.e., those with end-stage renal disease [ESRD]). All procedures were followed in accordance with the Helsinki Declaration of 1975 and the ethical standards of the Washington University Institutional Review Board, which reviewed this project (No. 202008041, "Clinical Phenotyping of COVID-19 and Other Viral Pneumonias using Unsupervised Machine Learning," August 17, 2021) and waived the need for approval, with a waiver of informed consent.

Data and Measurements

We extracted electronic health record (EHR; Epic, Verona, WI) data from Washington University's institutional research data warehouse (6, 20). These data included admission, discharge, and room change dates and times, sociodemographic information, laboratory results, diagnosis codes, level of care (i.e., inpatient floor, ICU), intubation and mechanical ventilation procedures, and outcomes (i.e., death, discharge) for all patients as charted throughout hospitalization. Via chart review, we confirmed the presence and modality of RRT for each patient's first 14 days of critical care because these data were insufficiently available in the research data warehouse's flowsheets.

We determined the presence and stage of AKI using the Kidney Disease: Improving Global Outcomes system's creatinine-based criteria (21). Due to insufficiently charted data, we did not include urine output within AKI determinations. For each patient, we estimated baseline creatinine values in a two-tiered process. First, we used the mean prehospital serum creatinine from all values recorded between 1 year and 7 days prior to hospitalization (22). If no prehospital data were available, we imputed values according to a gender-fixed equation (23). We chose this equation over race-based alternatives given emerging evidence that such models inflate estimated glomerular filtration rate for Black patients (24), which would inappropriately underclassify their AKI in some instances.

Analyses

We fit two distinct multistate models on the data. Multistate models for continuous-time stochastic processes allow subjects to move—"transition"—among a finite number of states over time (25, 26). State transition models, in their most simple construction, involve one or more initial states, one or more transient states, and one or more absorptive states (**Fig. 1**). Initial states represent patient entry into the model; no transitions into initial states are possible. Absorptive states are those from which patients cannot transition subsequently (e.g., an end state such as death). Between initial states and absorptive states are transient states (e.g., stage I AKI, which can worsen or resolve). These intermediate states occur (or do not) after an initial state but before an end state and change the risk of the subsequent end state if encountered. Transient states can be entered and exited once, more than once, or not at all. Importantly, if an individual enters a transient state, they must also depart said state at some time point. The state structure is then specified by a statistical model of the hazard function for each possible transition.

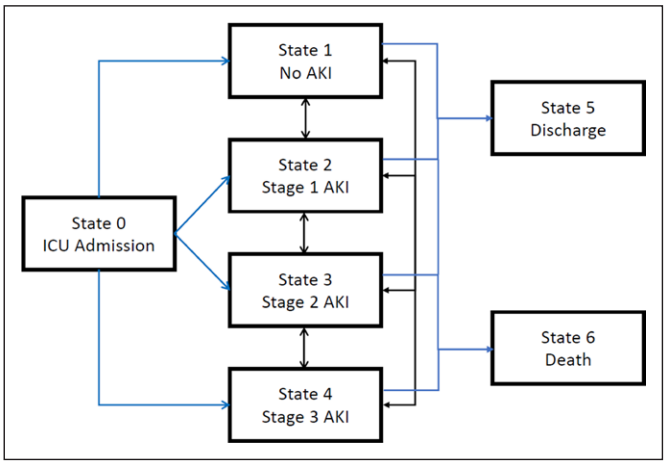

Figure 1. Frameworks for multistate analysis of transitions between acute kidney injury (AKI) stages and related clinical states. *Blue connectors* indicate single-direction transitions, while *black connectors* indicate bidirectional transition possibilities. States are: 1) no AKI, 2) stage 1 AKI, 3) stage 2 AKI, 4) stage 3 AKI, 5) discharge, 6) death. ICU admission is depicted to demonstrate that patients could enter one of several states immediately.

Multistate transition intensities provide individual hazards for movement from one state to another, allowing determination of mean times within a particular state as well as the number of subjects in each state at a certain moment. Thus, for each model, we estimated the longitudinal probability of a patient developing each clinical status after entering one of several specific stages. Each of our models was based in mutually exclusive and exhaustive clinical states involving the patient's worst clinical state within consecutive 12-hour discrete time windows beginning at ICU admission. In the first approach, we categorized patients into one of six clinical states consisting of their current stage of AKI or the competing risks of discharge or death. In the second approach, we condensed the AKI stages into permutations with and without invasive mechanical ventilation (IMV), yielding six total states. These dual approaches allowed us to triangulate the longitudinal dynamics of AKI stages and the relative timing of AKI and IMV. We used Aalen-Johansen nonparametric analyses to evaluate clinical state switching for

individual patients, accounting for unequal observation times among patients (**Supplementary Appendix 1**, http://links.lww.com/CCX/B78) (6, 25, 26). We also used alluvial plots to depict clinical state trajectories over time; alluvial plots demonstrate flow of either individual data points or groups of observations through different categorical states over time (27).

We also estimated instantaneous hazard rates for specific outcomes from prespecified states, regardless of intermediate states (analogous to its role in other time-to-event analyses, the hazard function models the instantaneous risk of transitioning from a particular state to another one, conditional on not having previously made said transition). In the first model, we estimated the instantaneous hazard rates for any AKI, stage 3 AKI, discharge, and death from ICU admission. We also estimated the instantaneous hazard rates for AKI resolution, stage 3 AKI, discharge, and death from the onset of stage 1 AKI, and the instantaneous hazard rates for AKI resolution, discharge, and death from the onset of stage 3 AKI. In the second model, we estimated the instantaneous hazard rate for AKI from the onset of IMV, and the instantaneous hazard rate for IMV from the onset of AKI.

For each analysis, "time zero" was the entry into that particular state. Censoring occurred at discharge, death, or the end of ICU day 14.

Sensitivity Analyses

To demonstrate the robustness of our findings, we conducted two prespecified sensitivity analyses. In the first, we reestimated baseline creatinine using the Modification of Diet in Renal Disease (MDRD) equation instead of gender-fixed imputation (28). In the second, we reestimated baseline creatinine using the first-available creatinine from hospitalization when a known baseline was unavailable (23, 28). We refit all models within each sensitivity analysis.

Analysis Considerations

We summarized data using frequencies with proportions or medians with interquartile ranges and compared data using Kruskal-Wallis and chi-square tests. We considered p values of less than or equal to 0.05 significant. We performed all analyses using R 4.1 (R Foundation for Statistical Computing, Vienna, Austria) and the *tidyverse*, *mstate*, *survival*, and *tableone* packages (29–32).

RESULTS

Of 386 ICU admissions, 19 were excluded for preexisting ESRD. The final cohort contained 367 hospitalizations in the ICU. Overall, 116 patients (32%) had prehospitalization serum creatinine measurements, leaving 251 patients to be imputed according to the gender-fixed formula. Serum creatinine values and results from imputation can be found in **Supplemental Table 1** (http://links.lww.com/CCX/B78) and **Supplemental Figure 1** (http://links.lww.com/CCX/B78).

Of these 367 patients, 241 (66%) experienced AKI of any degree. Specifically, 51 patients (13%) received RRT while in the ICU, and a further 53 (14%) patients experienced stage 3 AKI without receiving RRT. Of the remaining patients experiencing AKI, 49 (13%) sustained stage 2 AKI while in the ICU, and 88 (24%) did not progress beyond stage 1 AKI. Patient characteristics differed among the groups of patients receiving RRT, experiencing AKI but not receiving RRT, and not experiencing AKI (**Table 1**). There were no statistical differences between the initial peak (March–July) and the second peak (August–December) in terms of AKI rates (n = 115 [69%] vs n = 200 [63%]; p = 0.2), but RRT use was significantly lower (n = 31 [19%] vs n = 20 [10%]; p = 0.018; **Supplemental Fig. 2**, http://links.lww.com/CCX/B78) during the second peak.

Patient outcomes were worse in the RRT and non-RRT AKI groups than in the no-AKI group (Table 1). Trends in IMV and RRT use were similar over time (Supplemental Fig. 2, http://links.lww.com/CCX/B78). The presence of AKI and RRT were associated with stepwise increases in the composite of hospital mortality and hospice discharge (AKI: n = 74, 40%; RRT: n = 36, 57%) compared with non-AKI patients (n = 23, 19%; $p < 0.001$). Among patients receiving RRT in the ICU, 10 (16%) were discharged with a persistent RRT requirement.

After 24 hours in the ICU, almost half the cohort was experiencing AKI (44.9%; 95% CI, 41.6–48.2%; **Fig. 2**; **Table 2**), with advanced stages also occurring early in the course of critical illness. At this point, 22.1% of the cohort (17.4–26.7%) had stage 2 or stage 3 AKI. By ICU day 7, these rates were 29.4% with any AKI (20.8–38.0%) and 18.7% (13.3–24.3%) with stage 2 or stage 3 AKI; the competing risks of death or hospice discharge comprised another 11.8% (8.6–15.1%) at this point.

TABLE 1.
Patient Characteristics and Outcomes Stratified by Presence of Acute Kidney Injury and Receipt of Renal Replacement Therapy

Patient Characteristics and Outcomes	No AKI, *n* = 126	AKI Without RRT, *n* = 190	RRT, *n* = 51	*p*
Patient characteristics				
Age, median (IQR)	60.0 (42.0–69.0)	68.0 (60.0–76.0)	65.0 (55.0–70.0)	< 0.001
Female, *n* (%)	55 (44)	65 (34)	16 (31)	0.246
Race, *n* (%)				0.014
Other	12 (9.5)	10 (5.3)	1 (2.0)	
Asian	4 (3.2)	1 (0.5)	1 (2.0)	
Black	58 (46)	107 (56)	37 (73)	
White	52 (41)	72 (38)	12 (24)	
Body mass index, median (IQR)	28.73 (23.41–36.51)	29.29 (25.21–35.42)	31.48 (26.64–37.85)	0.364
Baseline creatinine without imputation, median (IQR)	1.00 (0.91–1.21)	1.26 (0.93–1.63)	2.94 (2.31–4.38)	< 0.001
Chronic kidney disease, *n* (%)	4 (3.2)	61 (32)	15 (29)	< 0.001
Liver disease, *n* (%)	2 (1.6)	3 (1.6)	4 (7.8)	0.061
HIV, *n* (%)	0 (0.0)	2 (1.1)	0 (0.0)	0.619
Cancer, *n* (%)	8 (6.3)	11 (5.8)	2 (3.9)	0.820
Solid tumor, *n* (%)	2 (1.6)	7 (3.7)	3 (5.9)	0.235
Bone marrow transplant, *n* (%)	1 (0.8)	0 (0)	0 (0.0)	0.606
Immunodeficiency, *n* (%)	4 (3.2)	7 (3.7)	2 (3.9)	0.960
Congestive heart failure, *n* (%)	27 (21)	57 (30)	8 (16)	0.057
Hypertension, *n* (%)	76 (60)	148 (78)	39 (76)	0.002
Diabetes, *n* (%)	52 (41)	94 (49)	32 (63)	0.033
Patient outcomes				
Hospital death, *n* (%)	16 (13)	77 (41)	27 (53)	< 0.001
Hospice discharge, *n* (%)	3 (2.4)	9 (4.7)	1 (2.0)	0.435
Hospital LOS, d, median (IQR)	12.1 (5.7–19.7)	14.5 (8.8–24.9)	25.3 (15.0–32.8)	< 0.001
ICU LOS, d, median (IQR)	5.3 (1.9–11.1)	8.0 (3.4–15.2)	18.3 (9.0–25.5)	< 0.001
Invasive mechanical ventilation, *n* (%)	44 (34.9)	104 (54.7)	48 (94.1)	< 0.001
Ventilator-free days at day 28, median (IQR)	28.0 (20.0–28.0)	8.0 (0.0–28.0)	0.0 (0.0–10.0)	< 0.001

AKI = acute kidney injury, IQR = interquartile range, LOS = length of stay, RRT = renal replacement therapy.

Although advanced stages of AKI occurred early within ICU stays, patient trajectories from stage 1 AKI most frequently involved rapid resolution (**Fig. 3**, ***A*** and ***B***). Approximately nine in 10 patients experiencing stage 1 AKI had resolved after 24 hours (92.1% [88.5–95.7%]). At 7 days after stage 1 AKI, 74.0% (63.6–84.4%) of patients had either been discharged or were AKI-free. By contrast, fewer patients experiencing stage 3 AKI had recovered (30.0% [24.1–35.8%]) or been discharged (7.9% [5.2–10.7%]) after 7 days. Instantaneous hazard estimations (**Fig. 3*C***) confirmed these findings.

The second multistate model demonstrated that early AKI occurred with similar frequency in patients receiving and not receiving IMV: after 24 hours in the ICU, 20.9% of patients (18.3–23.6%) had AKI and were intubated, while 23.4% of patients (20.6–26.2) were experiencing AKI but were not mechanically ventilated

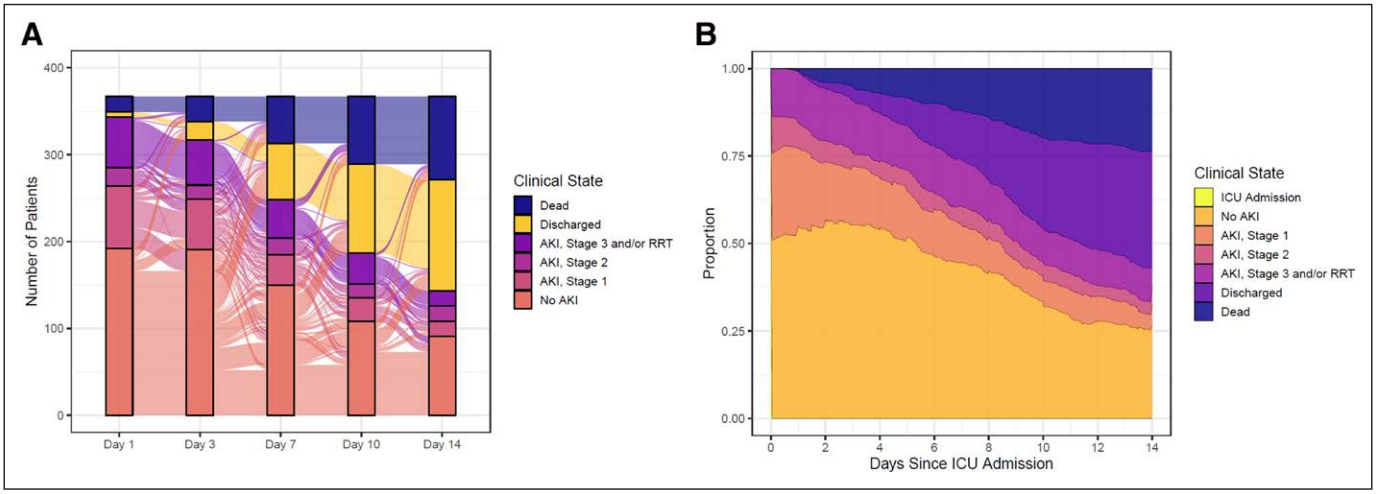

Figure 2. Clinical acute kidney injury (AKI) trajectories and longitudinal outcomes among critically ill patients with COVID-19 in 2020 (*n* = 367). **A**, The *x*-axis of the alluvial plot represents specific days in the ICU, while the *y*-axis indicates the number of patients in the cohort. Each day contains strata (*colored rectangles*) representing the number of patients in a state on that day. Multiple alluvia (*curves color-coded* by current state) demonstrate the number of patients transitioning between states on the days shown. **B**, The proportion of patients estimated to be in each AKI stage at any given time point after ICU admission, accounting for the transitions patients have made over time. All patients had 14 d of observation time after ICU admission. RRT = renal replacement therapy.

TABLE 2.

Multistate-Based Estimated Proportions of Patients in Each Acute Kidney Injury Stage Over Time (*n* = 367)

Patient Characteristics and Outcomes	No AKI, % (95% CI)	AKI Stage 1, % (95% CI)	AKI Stage 2 (95% CI)	AKI Stage 3 and/or RRT, % (95% CI)	Discharged, % (95% CI)	Dead/Hospice, % (95% CI)
Days since ICU admission						
1	55.1 (51.8–58.4)	22.3 (18.6–26.1)	7.2 (4.8–9.5)	14.9 (12.6–17.2)	0 (0–0)	0.6 (0–1.3)
3	55.4 (51–59.7)	16.8 (12.9–20.7)	3.9 (1.9–5.8)	15.2 (12.2–18.1)	3.9 (1.9–5.8)	5 (2.8–7.1)
7	44.6 (39.7–49.5)	10.7 (7.5–14)	5.5 (3.2–7.8)	13.2 (10.1–16.4)	14 (10.5–17.6)	11.8 (8.6–15.1)
14	26.4 (22.1–30.8)	6.1 (3.7–8.4)	5.2 (3.2–7.3)	5.2 (3.2–7.2)	33.3 (28.6–38.1)	23.7 (19.4–28)
Days since AKI stage 1						
1	92.1 (88.5–95.7)	5.6 (2.6–8.5)	0.6 (0–1.6)	1.2 (0–2.6)	0 (0–0)	0.6 (0–1.5)
3	79 (73.9–84)	8.8 (5.6–12.1)	1.2 (0.2–2.3)	2.4 (0.8–4.1)	6 (3–9)	2.5 (0.7–4.4)
7	55.5 (49.8–61.3)	10.1 (6.8–13.4)	3.5 (1.8–5.2)	4.2 (2.2–6.1)	18.6 (13.8–23.1)	8.2 (5.2–11.3)
Days since AKI stage 2						
1	30.6 (23.2–38.1)	59.3 (51.1–67.5)	4.1 (1.3–6.9)	5 (2–8.2)	0 (0–0)	0.9 (0–2.5)
3	48.9 (42.1–55.8)	29.8 (23.2–36.4)	4.6 (2.1–7.1)	9 (5.4–12.5)	2.8 (1.3–4.3)	5 (2.1–7.9)
7	45.5 (39.9–51.1)	13.1 (9.2–17.1)	6.4 (3.7–9.1)	9.5 (6.2–12.8)	13.1 (9.6–16.6)	12.4 (8.4–16.3)
Days since AKI stage 3 and/or RRT						
1	4.7 (0.6–8.8)	35.7 (25.2–46.2)	44.8 (32.6–57)	14.5 (7.2–21.7)	0 (0–0)	0.3 (0–0.9)
3	21.1 (14.4–27.9)	30.6 (23.2–37.9)	11.6 (6–17.2)	25.3 (17.7–33)	0.8 (0.3–1.4)	10.6 (4.3–16.8)
7	30 (24.1–35.8)	12.7 (8.7–16.8)	9 (5.2–12.8)	21.2 (14.9–27.5)	7.9 (5.2–10.7)	19.1 (12.5–25.7)

AKI = acute kidney injury, RRT = renal replacement therapy.

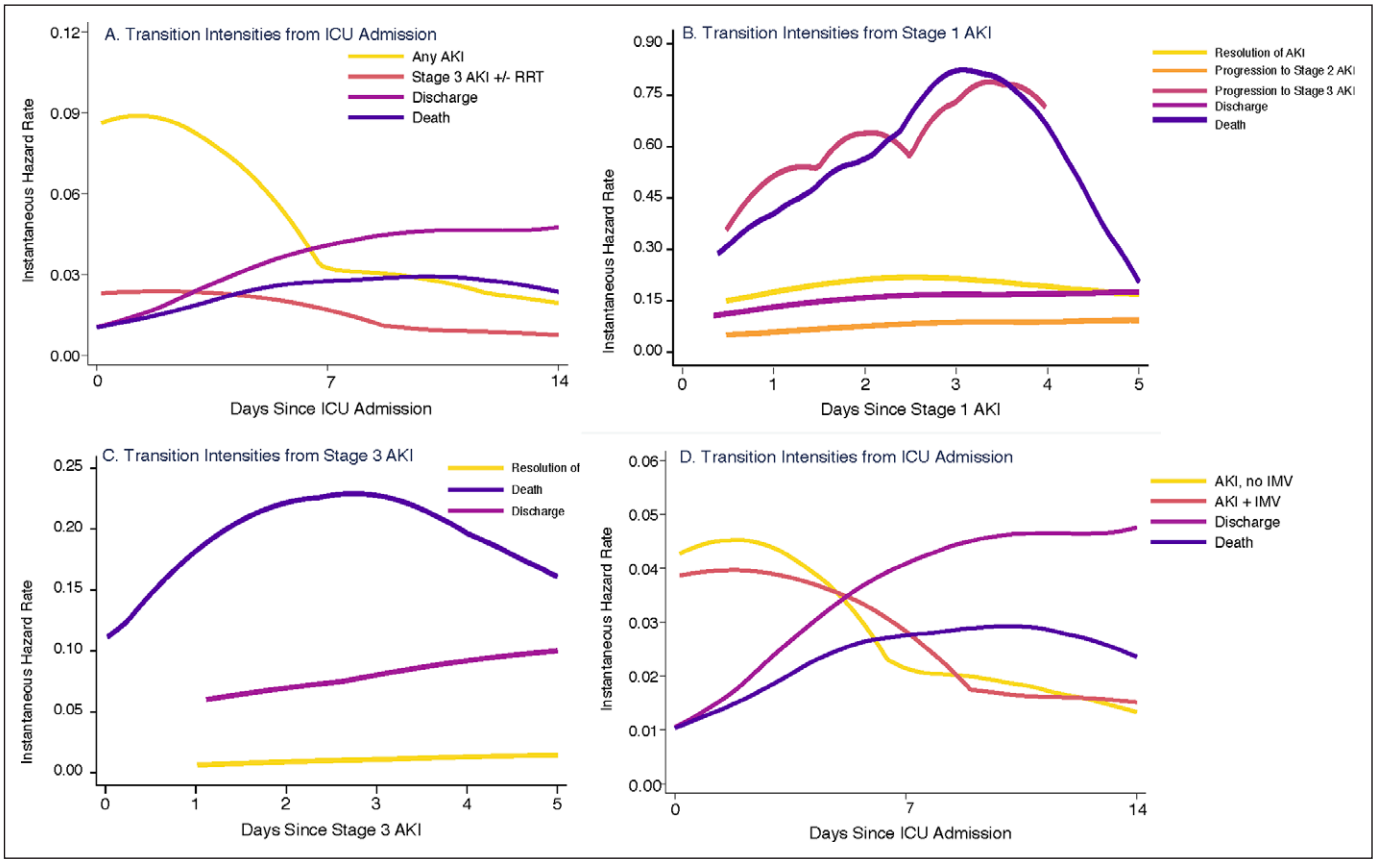

Figure 3. Instantaneous hazards of outcomes from prespecified acute kidney injury (AKI)-related states in the ICU based on multistate models. **A**, Hazards for any AKI, stage 3 AKI, hospital discharge, and the composite of death or hospice from ICU admission. **B**, Hazards from stage 1 AKI for AKI progression, resolution, hospital discharge, and death. **C**, Hazards from stage 3 AKI for resolution, discharge, and death. **D**, Hazards for AKI without invasive mechanical ventilation (IMV), AKI with IMV, hospital discharge, and the composite of death or hospice from ICU admission.

(**Fig. 4**; **Supplemental Table 2**, http://links.lww.com/CCX/B78). Among patients who were intubated and had not yet experienced AKI, 29.1% (20.2–38.0%) had AKI on day 7, with an additional 10.3% (5.0–15.6%) having died at this point. Conditional on being intubated with AKI, however, almost two-thirds of patients had died or were still experiencing AKI 7 days later (62.6% [44.8–80.3%]). Of these patients, exceedingly few were discharged (3.2% [1.5–4.8%]) or free of both IMV and AKI (7.4% [4.4–10.4%]) at 7 days. The hazard of death rose more quickly than those of recovery or discharge (Fig. 3*D*) at all time points.

Prespecified sensitivity analyses showed similar findings to those of the primary analysis, with the expected finding of slightly lower AKI prevalence at all time points. Multistate models fit after missing data were imputed with either the MDRD-based equation (**Supplemental Tables 3** and **4**, http://links.lww.com/CCX/B78) or with the first-recorded serum creatinine on hospitalization **Supplemental Tables 5** and **6** http://links.lww.com/CCX/B78) redemonstrated the early resolution of many stage 1 AKI instances as well as similar time point prevalences of AKI between mechanically ventilated and nonventilated patients.

DISCUSSION

Multistate modeling is a powerful and potentially valuable methodological approach to evaluating longitudinal and dynamic clinical courses and outcomes, with particular strengths including accounting for competing risks and conditional probabilities. In this applied example, we demonstrate these strengths by highlighting the granular and longitudinal nature of these models' results, including the specific measurement of individual transition hazards and the visualizations, which can be generated from the overall model. For instance, differentiating the anticipated

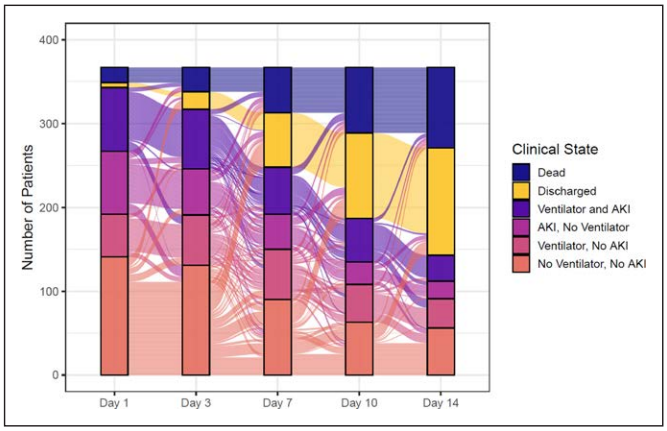

Figure 4. Clinical acute kidney injury (AKI) and invasive mechanical ventilation (IMV) trajectories and longitudinal outcomes among critically ill patients with COVID-19 in 2020 ($n = 367$). The *x*-axis of the alluvial plot represents specific days in the ICU, while the *y*-axis indicates the number of patients in the cohort. Each day contains strata (*colored rectangles*) representing the number of patients in a state on that day. Multiple alluvia (*curves color-coded by current state*) demonstrate the number of patients transitioning between states on the days shown. The proportion of patients estimated to be in each AKI- and IMV-related state at any given time point after ICU admission, accounting for the transitions patients have made over time. All patients had 14 d of observation time after ICU admission.

short- and intermediate-term courses of stage 1 AKI instances from those of more advanced AKI could inform both clinical management strategies and ICU administrative decisions such as RRT device allocation.

Multistate models do have potential limitations and pitfalls. First, even sophisticated models are vulnerable to poor-quality or unavailable input data. For example, time-based RRT status and urine output were not ascertainable from structured data within our EHR repository. While the first issue was addressable through chart review (which would still preclude full automation of such modeling for near-real-time multistate reports or forecasts), the second was not due to limited charting. These barriers speak to the intrinsic challenges of this type of pragmatic EHR-based research and underscore the need to develop valid heuristics to identify diagnoses, syndromes, and interventions automatically from extant data in the EHR (20, 33). Similarly, the inability to estimate baseline creatinine from many patients' structured EHR data hampers efforts to scale dynamic renal failure models (34, 35); in this example, we intentionally performed relevant sensitivity analyses to check the reliability of our baseline assumptions.

Second, and relatedly, interval censoring of observations affects how precisely time spent within states can be modeled. Because serum creatinine is typically measured daily or bid, we deliberately chose to assess patient status in 12-hour discrete time windows. The availability of, for example, hourly urine output measurements could have permitted assessment of transitions at narrower intervals. The extent to which such granularity matters will likely depend on the clinical question to be answered by modeling.

Third, multistate models have certain intrinsic assumptions, including time homogeneity (i.e., transition probabilities will remain constant over time) (36) and (generally) nonexistence or triviality of time-dependent covariates (37), neither of which may be held in some clinical scenarios. Finally, multistate models "spend" statistical degrees of freedom with each transition rate estimated. The key implication of this fact is that for a desired statistical power, sample sizes must be larger than for less-complex approaches toward answering a given question.

In terms of AKI during COVID-19 critical illness, our findings validate prior descriptions of AKI occurring early and heterogeneously in the course of critical illness. Although the epidemiology of COVID-associated AKI has been described, the critical illness trajectories of this syndrome have been less well defined, particularly in terms of the timing and intensity of AKI burden. We also found that the presence of IMV was not strongly associated with AKI development, as we had hypothesized it would be. However, this finding is limited by the absence of control for potential confounders such as severity of illness, therapeutic interventions (e.g., corticosteroids), supportive care, or temporal trends in other unmeasured factors.

Important limitations of our study include its single-center dataset from the early stages of the COVID-19 pandemic. These data precede the emergence of the delta and omicron variants, as well as the widespread use of SARS-CoV-2 vaccines, monoclonal antibodies, and anti-inflammatory therapy such as tocilizumab and baricitinib. As such, these results are not generalizable to other settings or to the current stage of the pandemic and are instead meant to illustrate a set of methods and processes that are transferrable to myriad analogous clinical syndromes and settings. Finally, because decisions regarding RRT initiation may be

subjective, we created models in including and excluding RRT as a component of state definitions.

CONCLUSIONS

In a multistate analysis of critically ill patients with COVID-19, we demonstrated that AKI occurred early and heterogeneously in the course of critical illness. These underused analytic approaches may ultimately translate into decision-making tools to improve the safety and outcomes of hospitalized patients with AKI and other high-risk syndromes through anticipating resource needs and optimizing responses.

1 *Department of Medicine, Washington University School of Medicine, St. Louis, MO.*

2 *Healthcare Innovation Lab, BJC HealthCare, St. Louis, MO.*

3 *Center for Dissemination and Implementation, Washington University School of Medicine, St. Louis, MO.*

4 *Institute for Informatics, Washington University School of Medicine, St. Louis, MO.*

5 *Department of Anesthesiology, Washington University School of Medicine, St. Louis, MO.*

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccejournal).

Dr. Lyons was supported by National Institutes of Health National Center for Advancing Translational Sciences UL1 TR002345, National Institutes of Health National Center for Advancing Translational Sciences KL2 TR002346, and Doris Duke Charitable Foundation Number 2015215; he is Associate Editor of Critical Care Explorations; and he recuses from review and decisions for this work. Dr. Mody was supported by National Institutes of Health National Center for Advancing Translational Sciences KL2 TR002346. Dr. Geng was supported by K24 AI134413. The remaining authors have disclosed that they do not have any potential conflicts of interest.

For information regarding this article, E-mail: plyons@wustl.edu

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