DOI: 10.62838/jccm-2026-0061

Acute kidney injury in critically ill COVID-19 patients admitted to a regional tertiary icu in south-west romania: prevalence, clinical phenotypes, and outcomes during a high-burden pandemic period

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Abstract

Introduction: Acute kidney injury (AKI) is a frequent and severe complication of critical COVID-19, yet evidence from Eastern European ICUs during peak pandemic surges is scarce and the clinical heterogeneity of AKI in this setting remains poorly understood.

Materials and methods: Retrospective cohort study of 389 adults consecutively admitted to a tertiary regional ICU in south-west Romania between March 2020 and April 2021, spanning the first three pandemic waves. AKI was staged by the 2012 KDIGO criteria over the first seven ICU days, using measured baseline creatinine (n = 292) or MDRD back-estimated values (n = 97); a parallel classification anchored at ICU admission was also derived. In AKI cases, k-means clustering was applied to twelve variables reflecting the first 24 hours of ICU care. ICU mortality was the primary outcome; proportions carry Wilson 95% confidence intervals.

Results: AKI occurred in 251 of 389 patients (cumulative incidence 64.5%, 95% CI 59.6–69.1), of whom 90.0% already met criteria at admission; 11.1% required renal replacement therapy. Mortality rose with maximum KDIGO stage (no AKI 26.8% [20.1–34.8]; stage 1 57.8% [45.6–69.1]; stage 2 92.8% [84.1–96.9]; stage 3 100.0% [96.8–100.0]; $p < 0.001$), with an adjusted Cox hazard ratio of 1.25 per stage (1.08–1.43) and 1.24 (1.10–1.40) under the admission-anchored classification. Four internally stable phenotypes emerged (bootstrap Jaccard 0.81; internal resampling only, not externally validated): P1 hyperinflammatory shock (16%, 100% mortality), P2 inflammatory-respiratory (39%, 100%), P3 cardiorenal/AKI-on-CKD (19%, 94%, 39% RRT), P4 mild/recoverable (25%, 55%). Pre-existing CKD was present in 91.8% of P3, a 3.8-fold enrichment over the cohort baseline of 23.9%. AKI-on-CKD and de novo AKI showed similar mortality (88% vs 87%) but distinct clinical signatures.

Conclusions: AKI affected approximately two thirds of admissions during this surge and stratified mortality steeply by KDIGO stage, with data-driven phenotypes offering pathophysiological insight beyond conventional scores.

Keywords: acute kidney injury; KDIGO; COVID-19; intensive care unit; clinical phenotype; cluster analysis; AKI-on-CKD

Received: 5 june 2026 / Accepted: 9 october 2026

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Introduction

Acute kidney injury (AKI) is one of the most frequent organ failures in intensive care, affecting up to 60% of critically ill patients and conferring stage-dependent excess mortality that extends beyond hospital discharge (1-3). During the COVID-19 pandemic, AKI emerged as a particularly common and prognostically ominous complication, with ICU prevalence ranging from roughly 30% to over 60% depending on case mix, ascertainment, and pandemic phase (4-7). The proposed mechanisms are multifactorial, including direct viral injury to tubular epithelium and podocytes,

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microvascular thrombosis, complement activation, haemodynamic instability from acute respiratory distress, and nephrotoxic exposures over prolonged ICU stays (6, 8-10).

The KDIGO 2012 criteria (11) offer a reproducible severity gradient but treat AKI as a single entity. Growing evidence from ARDS, sepsis, and AKI cohorts shows that data-driven phenotyping of routine admission variables can reveal subgroups with distinct biology and divergent outcomes (12-15). Bhatraju and colleagues described two reproducible AKI subphenotypes, hyperinflammatory and hypoinflammatory, by latent class analysis and demonstrated that the inflammatory subphenotype carries higher mortality and may respond differently to vasopressin therapy (13). Later work has refined this taxonomy in septic and COVID-enriched cohorts (13, 14, 16). Whether comparable phenotypes are recoverable in regional Eastern European ICUs during peak pandemic strain, and how patients with pre-existing chronic kidney disease (CKD) fit within such a taxonomy, remain open questions, particularly given the scarcity of regional data from this part of Europe.

We therefore aimed, in a tertiary ICU cohort from south-west Romania, to: (i) describe the prevalence and KDIGO-stratified outcomes of AKI in critically ill COVID-19 patients admitted during a high-burden phase; (ii) determine whether clinically meaningful AKI phenotypes are identifiable within the first 24 hours of ICU care from routine laboratory and physiological data; and (iii) assess whether AKI on pre-existing CKD versus de novo AKI carries independent prognostic or pathophysiological value beyond KDIGO staging.

Materials and methods

Study design and setting

This was a retrospective, single-centre cohort study conducted at the County Emergency Clinical Hospital of Craiova (Spitalul Clinic Județean de Urgență Craiova, SCJUC), a 1,300-bed tertiary teaching hospital serving as the principal referral centre for the Oltenia region of south-west Romania, with a catchment population of approximately two million, with limited intermediate-level ICU capacity elsewhere in the region during the study period. Patients were consecutively admitted between March 2020 and April 2021. This window spans the first three pandemic waves in Romania, from the ancestral SARS-CoV-2 lineages circulating in spring and autumn 2020 through the Alpha dominated third wave of early 2021; the Delta wave, which affected Romania from autumn 2021, falls entirely outside the study period. The unit was designated as a dedicated COVID-19 ICU and operated under sustained surge conditions throughout. Although the national vaccination campaign began on 27 December 2020, coverage in the regional catchment remained low during the enrolment period and no patient in the analytic cohort had documented complete vaccination at the time of ICU admission.

The study was approved by the institutional ethics committees of the University of Medicine and Pharmacy of Craiova and of SCJUC (approval number 251/6 November 2023) and conducted in accordance with the principles of the Declaration of Helsinki. Because the analysis relied exclusively on de-identified, routinely collected clinical data, the requirement for individual informed consent was waived by the ethics committee.

Patients

We screened all consecutive adults (≥18 years) admitted to the medical-surgical ICU between March 2020 and April 2021. Eligible patients had laboratory-confirmed SARS-CoV-2 infection by reverse transcription polymerase chain reaction and complete admission renal data available for KDIGO classification. Patients receiving chronic dialysis for end-stage renal disease prior to admission, those with an ICU stay shorter than 12 hours, and those transferred to another facility for continued care were excluded. The final analytic cohort comprised 389 patients.

Data sources and variables

Clinical, demographic, and laboratory data were retrieved from the institutional ICU electronic medical record and the hospital biochemistry laboratory information system, and cross-checked against paper observation charts for vital signs and ventilator parameters. The dataset comprised: age, sex, residence (urban/rural), body mass index, and ten pre-specified comorbidities (hypertension, diabetes mellitus, pre-existing CKD, chronic heart failure, atrial fibrillation, chronic obstructive pulmonary disease, ischaemic heart disease, obesity, active malignancy, prior stroke); the Charlson comorbidity index (17); admission Acute Physiology and Chronic Health Evaluation (APACHE) II score (18); admission and day-3 Sequential Organ

Failure Assessment (SOFA) scores (19) with their six individual components; Glasgow Coma Scale; baseline, admission, and peak serum creatinine; 24-hour urine output at admission; admission arterial lactate, arterial pH, and PaO_2/FiO_2 ratio; total leucocyte count, platelet count, C-reactive protein, procalcitonin, total bilirubin, serum albumin, and D-dimer; vasopressor use and peak noradrenaline rate; invasive and non-invasive mechanical ventilation; renal replacement therapy; corticosteroid and antibiotic exposure; ICU length of stay; and ICU outcome (alive discharge or death). Baseline creatinine was defined as the most recent stable outpatient value documented within the three months preceding admission, where available.

COVID-19 directed therapy during the study period

Pharmacological management followed the Romanian national treatment protocol for SARS-CoV-2 infection (Order of the Minister of Health no. 487/2020 and its successive revisions), applied at the discretion of the attending intensivist. The protocol was amended five times within the enrolment window, so the therapeutic context was not uniform across the cohort: systemic corticosteroids became standard of care for patients requiring supplemental oxygen from mid-2020 onward, whereas admissions in spring 2020 predated this recommendation. Systemic corticosteroids were administered to 352 patients (90.5%) and systemic antibiotic therapy to 363 (93.3%). Organ support comprised invasive mechanical ventilation in 154 patients (39.6%), vasopressor support in 147 (37.8%), and renal replacement therapy in 43 (11.1%). Antiviral and immunomodulatory agents, including remdesivir, tocilizumab, and convalescent plasma, were prescribed selectively according to the protocol version in force and to institutional availability; these were not captured as discrete fields in the ICU database and could not be quantified retrospectively.

Definition and staging of AKI

AKI was diagnosed and staged according to the 2012 KDIGO criteria, applying the serum creatinine and renal replacement therapy components (11). Two classifications were derived and are distinguished throughout. The admission classification compares the creatinine value recorded at ICU admission with the patient's baseline and constitutes a genuine time-zero exposure. The peak classification uses the highest creatinine value recorded during the first seven ICU days, together with any initiation of renal replacement therapy, and represents the maximum severity of renal injury sustained; because attaining a higher stage under this definition requires survival long enough for creatinine to rise, it is not a baseline characteristic. Ascertainment was therefore bounded at seven days rather than extending across the whole ICU stay.

The reference creatinine was the measured pre-admission value when available (n = 292; 75.1%); for the remaining patients (n = 97; 24.9%), it was back-estimated using the abbreviated Modification of Diet in Renal Disease (MDRD) equation under the KDIGO-recommended assumption of an estimated glomerular filtration rate of 75 mL/min/1.73 m^2 (11, 20). Stage 1 was assigned for peak creatinine 1.5–1.9 × baseline or an absolute rise ≥0.3 mg/dL; stage 2 for peak 2.0–2.9 × baseline; and stage 3 for peak ≥3.0 × baseline, peak ≥4.0 mg/dL, or initiation of renal replacement therapy. As patient weight was not consistently recorded, the urine output criterion was not used for primary classification; oliguria (24-hour output below 500 mL) is therefore reported descriptively only and did not contribute to staging. One additional sensitivity definition was pre-specified, namely restriction to patients with a measured baseline creatinine (Section 3.7); the admission classification defined above is reported as a parallel principal analysis rather than as a sensitivity analysis (Section 3.6).

Phenotype identification

Phenotype discovery was carried out within the AKI subset (KDIGO 1–3) using k-means clustering on twelve variables reflecting the first 24 hours of ICU care chosen to span complementary pathophysiological axes while avoiding composite scores: age and pre-existing CKD (host); arterial lactate and peak noradrenaline rate (perfusion and vasopressor demand); PaO_2/FiO_2 (oxygenation); C-reactive protein, D-dimer, and leucocyte count (inflammation and coagulopathy); arterial pH and serum albumin (acid–base balance and capillary leak); and admission creatinine and 24-hour urine output (renal injury). Ten of these variables were recorded at ICU admission. Two, peak noradrenaline infusion rate and urine output, are defined over the first 24 hours of ICU care rather than at a single time point and cannot be obtained at the moment of arrival. We therefore describe the feature set as characterising early ICU physiology, and note that phenotype assignment becomes available at the close of the first ICU day.

Missing values in clustering features were imputed

using the median of the AKI cohort, computed before clustering and independently of any cluster assignment, and all variables were standardised to zero mean and unit variance before clustering. The optimal cluster number was selected by jointly evaluating the within-cluster sum of squares, the silhouette coefficient, the Calinski–Harabasz and Davies–Bouldin indices, the gap statistic with twenty Monte Carlo reference samples, and bootstrap stability quantified by the mean Jaccard coefficient over 200 resamples (21). Ward hierarchical clustering on the same standardised matrix served as a sensitivity check. Final k-means solutions used 100 random initialisations with a fixed seed for reproducibility. Three further admission variables, procalcitonin, platelet count, and total bilirubin, were deliberately excluded from the clustering feature set to limit collinearity with C-reactive protein and D-dimer, and were instead reserved as post hoc descriptors used to characterise the resulting clusters. Because they did not contribute to cluster formation, differences between phenotypes in these variables provide a degree of internal corroboration rather than a restatement of the structure imposed on the inputs. Post hoc comparisons across phenotypes used the Kruskal–Wallis test and are exploratory, without adjustment for multiplicity.

Statistical analysis

Continuous variables are summarised as median (interquartile range) and compared between two groups by the Mann–Whitney U test and across more than two groups by the Kruskal–Wallis test; categorical variables are reported as n (%) and compared by the chi-squared or Fisher's exact test, as appropriate. The primary outcome was ICU mortality. Secondary outcomes included ICU length of stay, initiation of renal replacement therapy, invasive mechanical ventilation, vasopressor support, peak serum creatinine, and change in SOFA score from admission to day 3 (ΔSOFA, restricted to patients alive at day 3 with both measurements available). Time-to-event analyses used ICU length of stay as the time scale and in-ICU death as the event, with discharge alive treated as right-censoring; Kaplan–Meier curves were compared by the log-rank test, and adjusted hazard ratios were obtained by Cox proportional hazards regression incorporating a small ridge penalty (0.01) to stabilise estimates given the complete separation observed at higher KDIGO stages. Two multivariable logistic regression models for ICU mortality were fitted, modelling KDIGO stage first as ordinal (test for trend) and then as categorical (each stage referenced to no AKI). Because all stage 3 patients died, the categorical model is reported with the explicit caveat that the stage 3 coefficient is uninformative owing to complete separation. All analyses were performed in Python 3.11 using pandas, scikit-learn, statsmodels, and lifelines. Proportions are reported with 95% confidence intervals calculated by the Wilson score method, which was preferred over the normal approximation because several strata exhibited proportions at or adjacent to the boundary, for which the Wald interval is degenerate. Two-sided $p < 0.05$ was deemed statistically significant.

Results

Cohort characteristics and AKI cumulative incidence

Baseline characteristics, admission severity, and outcomes stratified by AKI status are presented in Table 1. The final analytical cohort comprised 389 critically ill adults (median age 68 years, IQR 59–77; 58.6% male; 30.6% rural residence) admitted to the ICU during the high-burden study period. Overall ICU mortality was 65.8% (256/389; 95% CI 61.0–70.3), median ICU length of stay was 8 days (IQR 4–15), and 39.6% of patients required invasive mechanical ventilation. The most prevalent comorbidities were arterial hypertension (65.6%), diabetes mellitus (30.6%), and obesity (22.6%); pre-existing CKD was documented in 17.0% of patients. The median Charlson comorbidity index was 3 (IQR 1–4) and the median admission APACHE II and SOFA scores were 23 (IQR 15–29) and 6 (IQR 2–10), respectively.

AKI occurred in 251 of 389 patients, a cumulative incidence of 64.5% (95% CI 59.6–69.1) over the first seven ICU days. The large majority was present on arrival: 226 of these 251 patients (90.0%) already met KDIGO criteria at ICU admission, while 25 (10.0%) developed AKI subsequently. Median ICU length of stay was comparable across stages (9, 8, 10, and 8 days for stages 0 to 3), indicating no material difference in duration of observation between strata.

KDIGO stages 1, 2 and 3 represented 16.5%, 17.7%, and 30.3% of the cohort, respectively (Figure 1A). Renal replacement therapy was initiated in 43 patients (11.1% of the cohort, 95% CI 8.3–14.6, and 36.4% of those with stage 3 AKI, 28.3–45.4). A measured baseline creatinine was available for 75.1% of the cohort and MDRD back-estimation was applied to the remaining 24.9% (median estimated baseline 1.0 mg/dL, IQR 0.8–1.0). Patients with AKI were significantly older, more likely

Table 1. Baseline characteristics, admission severity, and outcomes of the study cohort, stratified by acute kidney injury status. (new table added in revision)

Characteristic	Total (n = 389)	AKI (n = 251)	No AKI (n = 138)	p
Demographics				
Age, years	68 (59–77)	72 (63–80)	63 (53–70)	<0.001
Male sex	228 (58.6)	156 (62.2)	72 (52.2)	0.071
Urban residence	270 (69.4)	188 (74.9)	82 (59.4)	0.002
Body mass index, kg/m²	26.8 (23.9–30.6)	27.2 (24.4–31.0)	26.0 (23.1–29.6)	0.016
Comorbidities				
Charlson comorbidity index	3 (1–4)	3 (2–4)	2 (1–3)	<0.001
Arterial hypertension	255 (65.6)	163 (64.9)	92 (66.7)	0.817
Diabetes mellitus	119 (30.6)	89 (35.5)	30 (21.7)	0.007
Chronic kidney disease	66 (17.0)	60 (23.9)	6 (4.3)	<0.001
Chronic heart failure	79 (20.3)	62 (24.7)	17 (12.3)	0.006
Atrial fibrillation	75 (19.3)	63 (25.1)	12 (8.7)	<0.001
COPD	31 (8.0)	17 (6.8)	14 (10.1)	0.327
Ischaemic heart disease	46 (11.8)	31 (12.4)	15 (10.9)	0.788
Obesity	88 (22.6)	64 (25.5)	24 (17.4)	0.089
Active malignancy	29 (7.5)	21 (8.4)	8 (5.8)	0.471
Previous stroke	39 (10.0)	32 (12.7)	7 (5.1)	0.025
Severity at ICU admission				
APACHE II score	23 (15–29)	27 (22–33)	14 (10–18)	<0.001
SOFA total score	6 (2–10)	8 (5–12)	2 (1–4)	<0.001
Glasgow Coma Scale	14 (12–15)	13 (11–14)	15 (15–15)	<0.001
Renal parameters				
Baseline creatinine, mg/dL	0.9 (0.8–1.1)	0.9 (0.8–1.2)	0.9 (0.8–1.0)	0.143
Admission creatinine, mg/dL	1.5 (0.9–2.3)	2.1 (1.5–2.7)	0.8 (0.7–0.9)	<0.001
Peak creatinine, mg/dL	1.8 (1.0–2.9)	2.6 (1.9–3.5)	0.9 (0.7–1.0)	<0.001
Urine output, mL/24 h	1066 (693–1498)	870 (561–1181)	1456 (1157–1883)	<0.001
Laboratory and physiological variables at admission				
Lactate, mmol/L	2.7 (2.0–3.7)	3.0 (2.5–5.2)	2.0 (1.5–2.6)	<0.001
Arterial pH	7.38 (7.34–7.41)	7.37 (7.29–7.40)	7.39 (7.37–7.42)	<0.001
PaO_2/FiO_2 ratio, mmHg	225 (144–310)	191 (128–287)	302 (180–343)	<0.001
White cell count, $\times 10^3/\mu L$	11.1 (8.2–15.0)	12.7 (9.7–16.7)	9.3 (6.7–11.9)	<0.001
Platelet count, $\times 10^3/\mu L$	188 (150–214)	173 (122–197)	212 (190–234)	<0.001
C-reactive protein, mg/L	109 (59–175)	148 (96–194)	54 (30–77)	<0.001
Procalcitonin, ng/mL	0.7 (0.4–2.7)	1.4 (0.5–3.8)	0.5 (0.3–0.7)	<0.001
Total bilirubin, mg/dL	0.9 (0.6–1.1)	1.0 (0.7–1.3)	0.7 (0.5–1.0)	<0.001
Albumin, g/dL	3.3 (2.9–3.6)	3.1 (2.8–3.4)	3.6 (3.5–3.8)	<0.001
D-dimer, ng/mL FEU	2000 (1060–3493)	2680 (1700–3936)	1093 (699–1406)	<0.001
Organ support and therapy				
Invasive mechanical ventilation	154 (39.6)	141 (56.2)	13 (9.4)	<0.001
Non-invasive ventilation or CPAP	201 (51.7)	103 (41.0)	98 (71.0)	<0.001
Vasopressor support	147 (37.8)	121 (48.2)	26 (18.8)	<0.001
Renal replacement therapy	43 (11.1; 8.3–14.6)	43 (17.1; 13.0–22.3)	0 (0.0; 0.0–2.7)	<0.001
Systemic corticosteroids	352 (90.5)	231 (92.0)	121 (87.7)	0.223
Systemic antibiotics	363 (93.3)	237 (94.4)	126 (91.3)	0.334
Peak noradrenaline, µg/kg/min	0.00 (0.00–0.28)	0.00 (0.00–0.39)	0.00 (0.00–0.00)	<0.001
Outcomes				
ICU length of stay, days	8 (4–15)	8 (4–14)	9 (4–16)	0.098
ICU mortality	256 (65.8; 61.0–70.3)	219 (87.3; 82.6–90.8)	37 (26.8; 20.1–34.8)	<0.001

Continuous variables are presented as median (interquartile range) and compared using the Mann–Whitney U test; categorical variables are presented as n (%) and compared using the chi-squared test. AKI was defined by KDIGO 2012 criteria applied to the highest creatinine value recorded within the first seven ICU days, together with any initiation of renal replacement therapy. Baseline creatinine was back-estimated by the MDRD equation assuming an eGFR of 75 mL/min/1.73 m² where unavailable. Missing values: body mass index 46 (11.8%), baseline creatinine 97 (24.9%), procalcitonin 77 (19.8%), D-dimer 70 (18.0%), albumin 38 (9.8%), urine output 31 (8.0%); missing-data percentages are calculated on the full cohort of 389, and all other percentages on non-missing observations. For ICU mortality and renal replacement therapy, values are n (% ; Wilson 95% confidence interval). APACHE II, Acute Physiology and Chronic Health Evaluation II; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; SOFA, Sequential Organ Failure Assessment.

to have pre-existing CKD, chronic heart failure, and atrial fibrillation, had higher severity scores at admission, lower oxygenation indices, higher inflammatory and coagulation markers, and lower serum albumin compared to those without AKI (all $p < 0.001$).

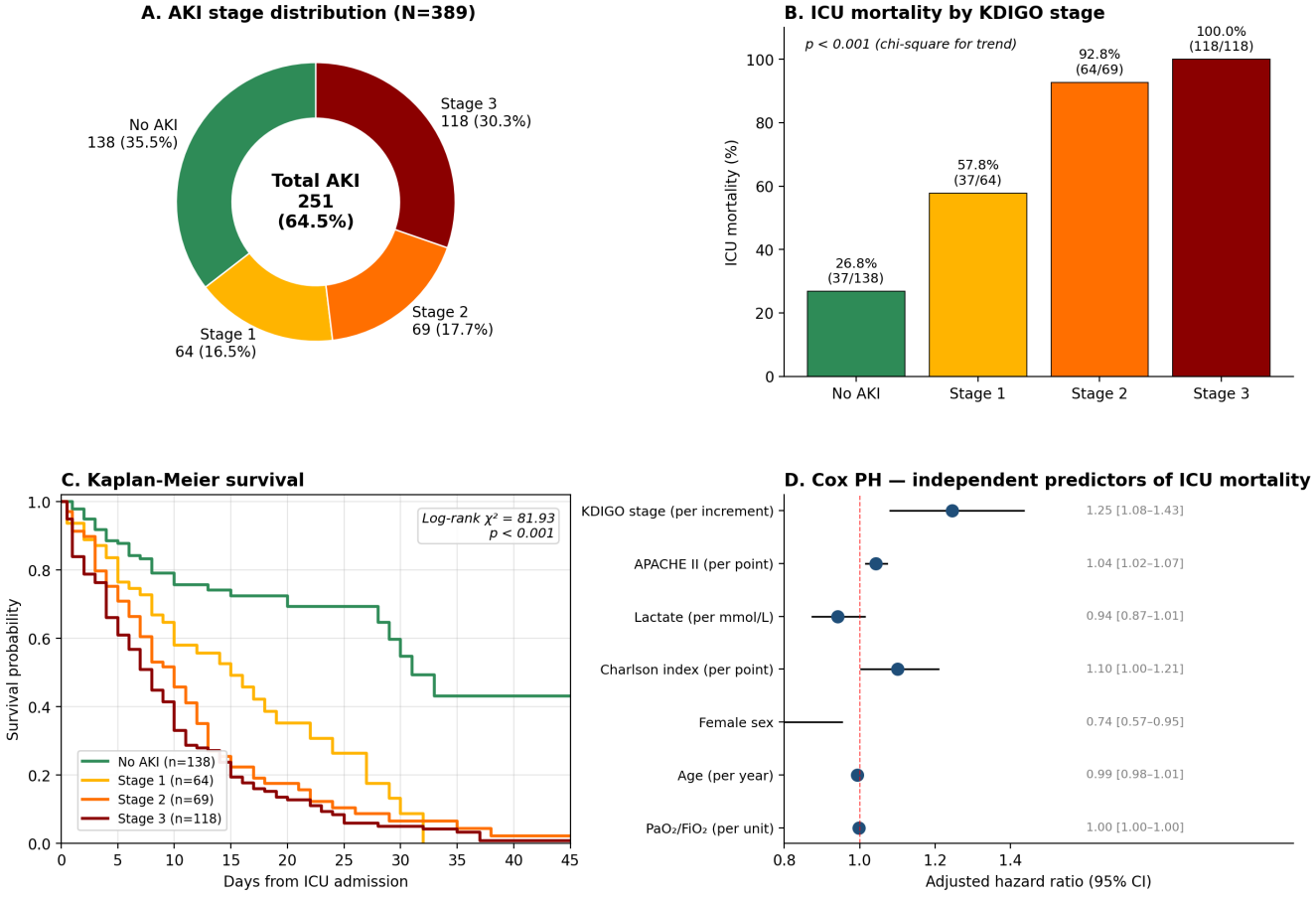


Figure 1. AKI cumulative incidence and outcomes by KDIGO stage in a high-burden ICU cohort (N = 389). (A) Distribution of patients across KDIGO stages, with total AKI cumulative incidence (64.5%) shown centrally. (B) ICU mortality by KDIGO stage; bars show percentage with absolute frequencies in parentheses; chi-squared test for trend $p < 0.001$. (C) Kaplan–Meier survival curves by KDIGO stage; censoring at ICU discharge; log-rank $\chi^2 = 81.93$, $p < 0.001$. (D) Forest plot of adjusted hazard ratios from a multivariable Cox proportional hazards model with KDIGO stage entered as an ordinal trend; covariates as listed.

KDIGO stage and clinical outcomes

ICU mortality rose steeply and monotonically with maximum KDIGO stage: 26.8% (37/138; 95% CI 20.1–34.8) in patients without AKI, 57.8% (37/64; 45.6–69.1) at stage 1, 92.8% (64/69; 84.1–96.9) at stage 2, and 100.0% (118/118; 96.8–100.0) at stage 3 (Figure 1B; chi-squared test for trend $p < 0.001$). The need for vasopressor support, invasive mechanical ventilation, and renal replacement therapy increased in parallel. Kaplan–Meier survival curves separated clearly between stages, with the steepest early drop observed in stage 3 and the most gradual decline in stage 1 (Figure 1C; log-rank $\chi^2 = 81.93$, $p < 0.001$). Median ICU length of stay did not differ markedly across AKI strata (8–10 days), consistent with the rapid attrition observed at higher stages rather than prolonged hospitalisation.

After multivariable adjustment for age, sex, Charlson index, admission APACHE II, lactate, and PaO_2/FiO_2, maximum KDIGO stage remained independently associated with ICU mortality in both regression frameworks. Because this classification is defined over the first seven ICU days, the estimates below describe the maximum renal injury sustained rather than a baseline predictor evaluated at time zero; the admission-anchored counterpart is reported in Section 3.6. In the ordinal-trend logistic model, each one-stage increment

in KDIGO category was associated with an adjusted odds ratio for ICU death of 1.81 (95% CI 1.05–3.12; p = 0.033). In the Cox proportional hazards model with the same covariates, the adjusted hazard ratio per KDIGO stage was 1.25 (95% CI 1.08–1.43; p = 0.002); APACHE II (HR 1.04 per point, p = 0.002) and Charlson index (HR 1.10 per point, p = 0.042) were also independently associated with mortality, while female sex was associated with a lower hazard (HR 0.74, 95% CI 0.57–0.95, p = 0.020) (Figure 1D). In the categorical logistic model the adjusted odds ratios for stages 1 and 2 versus no AKI were 1.32 and 1.87, while the stage 3 coefficient is uninformative because all patients in that stratum died; the model is unstable under this separation, and the ordinal specification is therefore retained as the principal effect estimate.

Identification and characterisation of AKI clinical phenotypes

Cluster validity indices supported either a two-cluster or a four-cluster solution; the two-cluster solution captured a global severity dichotomy with limited clinical resolution, while the four-cluster solution showed acceptable internal stability under bootstrap resampling of the same cohort (mean Jaccard coefficient 0.81 over 200 resamples) and clinically interpretable phenotype signatures. The Jaccard coefficient measures the robustness of the partition to sampling variation within this dataset and not its reproducibility in an independent population. The four-cluster k-means partition was therefore retained as the primary phenotype solution; Ward hierarchical clustering produced overlapping groups with concordant standardised feature profiles.

Four AKI phenotypes were identified (Figure 2A). The first (P1, n = 40, 15.9% of the AKI cohort) was characterised by extreme tissue hypoperfusion (median lactate 8.5 mmol/L), severe acidaemia (median pH 7.21), universal vasopressor dependence with high peak noradrenaline rates (median 0.9 μg/kg/min), profound systemic inflammation (median CRP 236 mg/L), and, among variables not used to define the clusters, markedly elevated procalcitonin (median 23.7 ng/mL, IQR 16.1 to 34.1) and severe thrombocytopenia (median platelet count 76 $\times 10^3$/μL, IQR 15 to 104), and frequent oliguria (median 24-hour urine output 412 mL; 55% below 500 mL); we label this phenotype hyperinflammatory shock. The second (P2, n = 98, 39.0%) showed predominantly inflammatory–respiratory derangement with moderately elevated CRP and D-dimer, marked oxygenation impairment, and high rates of invasive mechanical ventilation (65.3%) but, notably, only a small fraction of patients with pre-existing CKD (1.0%); we label this phenotype inflammatory-respiratory. The third (P3, n = 49, 19.5%) was dominated by structural renal injury: pre-existing CKD was present in 91.8% of patients within this phenotype, a 3.8-fold enrichment over the AKI cohort baseline of 23.9% (60/251 patients with AKI had pre-existing CKD), capturing 75% of all AKI-on-CKD patients in a single cluster, with the highest baseline (median 1.5 mg/dL) and peak (3.8 mg/dL) creatinine values observed, and renal replacement therapy initiated in 38.8%; despite this severe renal profile, inflammatory and haemodynamic markers were lower than in P1 or P2, accordingly we label this phenotype cardiorenal/AKI-on-CKD. The fourth (P4, n = 64, 25.5%) was characterised by the mildest derangement across every axis examined, with best preserved oxygenation (median PaO_2/FiO_2 290), normal pH, conserved urine output, low inflammation, and predominance of KDIGO stage 1, and is referred to as the mild/recoverable phenotype.

The four phenotypes captured information not redundant with KDIGO staging. Phenotype P3 was predominantly composed of stage 3 AKI patients (81.6%), whereas P4 was predominantly stage 1 (65.6%); P1 and P2 spread across stages 2 and 3 with similar mortality but divergent pathophysiological profiles (Figure 2C). This pattern indicates that the phenotypes orthogonalise the staging axis rather than merely recapitulating it.

Both post hoc descriptors separated the phenotypes sharply despite not having contributed to cluster formation. Median procalcitonin was 23.7 ng/mL in P1, against 1.7, 0.8, and 0.5 ng/mL in P2, P3, and P4 (Kruskal–Wallis $p < 0.001$), and median platelet count was 76 $\times 10^3$/μL in P1, against 171, 179, and 198 $\times 10^3$/μL ($p < 0.001$), with 95.0% of P1 patients thrombocytopenic (<150 $\times 10^3$/μL) against 30.6%, 26.5%, and 4.7% respectively. Total bilirubin followed the same pattern (median 2.3 mg/dL in P1 against 0.9, 0.9, and 0.8 mg/dL; $p < 0.001$). The gradient in these independently measured variables corroborates the septic-like character of P1 and supports the internal coherence of the partition.

To assess whether the phenotype structure depends on the two features not available at arrival, we repeated the clustering using only the ten variables recorded at ICU admission, applying the same standardisation, initialisation, and model selection procedure. The four-

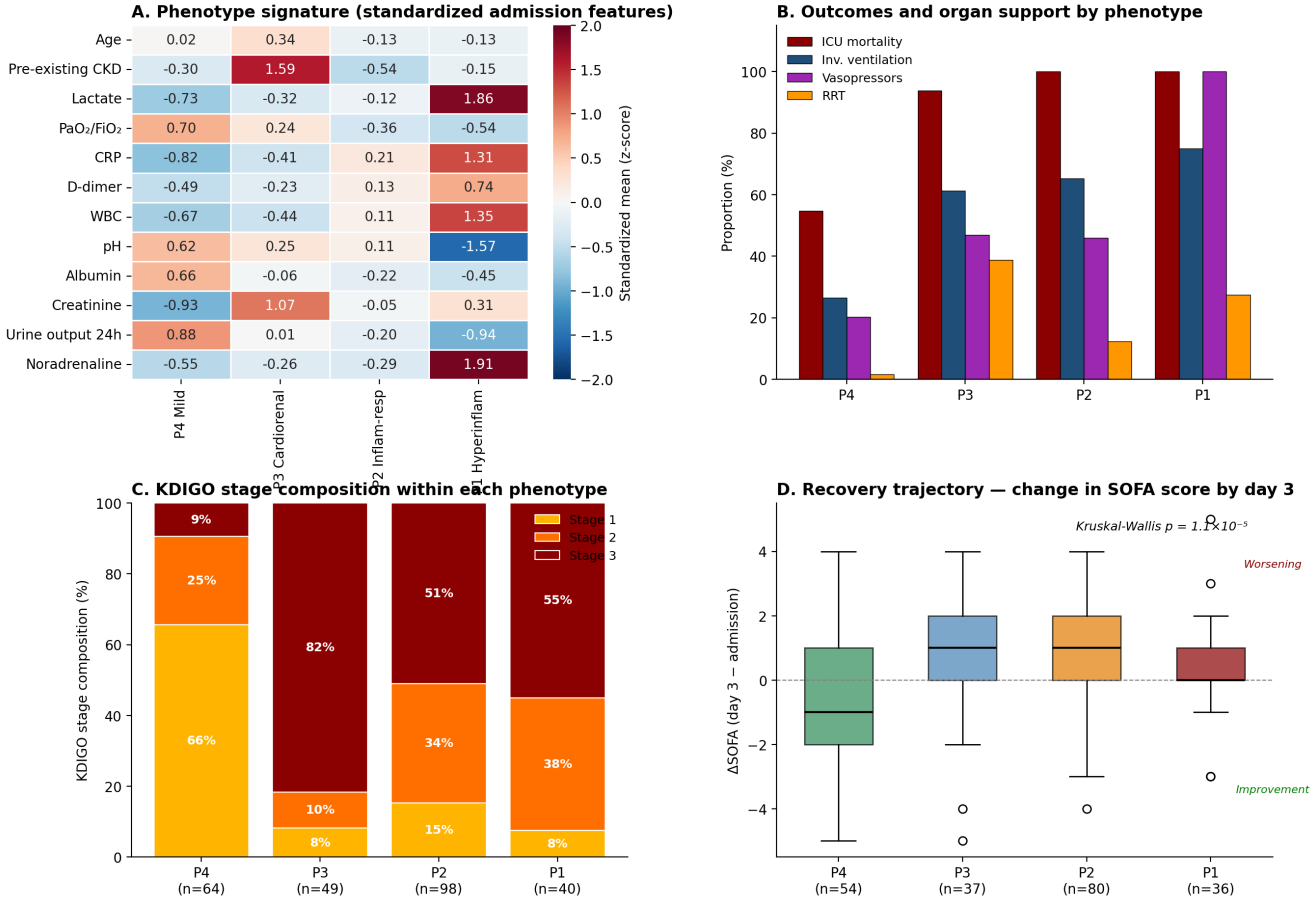


Figure 2. AKI clinical phenotypes, composition, outcomes, and recovery dynamics (n = 251 patients with AKI). (A) Heatmap of standardised early-ICU feature means (z-scores) for the four k-means phenotypes, ordered from least to most severe; values >0 (red) and <0 (blue) indicate above- and below-cohort-mean levels respectively. (B) Frequency of in-ICU mortality, invasive mechanical ventilation, vasopressor support, and renal replacement therapy by phenotype. (C) KDIGO stage composition within each phenotype, illustrating the orthogonalisation between phenotype and conventional staging. (D) Change in total SOFA score from admission to day 3 (ΔSOFA) by phenotype, among patients with both measurements available; values below zero indicate organ-function improvement; Kruskal–Wallis p = 1.1 × 10^{-5}.

cluster architecture was reproduced, comprising 88, 60, 53, and 50 patients. The cardiorenal phenotype was recovered with closely similar composition, containing 50 patients of whom 92.0% had pre-existing CKD, with 90.0% mortality, against 49 patients, 91.8%, and 93.9% in the primary solution. Agreement between the two partitions was moderate to substantial (adjusted Rand index 0.579), indicating that the phenotype architecture is not driven by the two post-admission features, while individual cluster assignment is not fully stable across feature sets.

Phenotype-specific outcomes and recovery dynamics

ICU mortality differed markedly across phenotypes (chi-squared $p < 0.001$): 100.0% in P1 (95% CI 91.2–100.0), 100.0% in P2 (96.2–100.0), 93.9% in P3 (83.5–97.9), and 54.7% in P4 (42.6–66.3) (Figure 2B). Renal replacement therapy was most frequent in P3 (38.8%; 95% CI 26.4–52.8) followed by P1 (27.5%; 16.1–42.8), reflecting the renal- and shock-dominant injury patterns of these two clusters respectively. Invasive mechanical ventilation was required in 75.0% of P1, 65.3% of P2, 61.2% of P3, and only 26.6% of P4 patients. Kaplan–Meier curves separated P4 markedly from the other three phenotypes, while P1, P2, and

P3 followed broadly similar survival trajectories with subtle early-time differences consistent with their distinct profiles. After adjustment for age, sex, Charlson index, APACHE II, PaO_2/FiO_2, and lactate, phenotype remained associated with mortality in the Cox proportional hazards model, although only one contrast reached conventional significance: relative to the mild/recoverable phenotype, P2 (inflammatory-respiratory) carried a hazard ratio of 1.68 (95% CI 1.07–2.65, p = 0.024) and P3 (cardiorenal/AKI-on-CKD) of 1.68 (95% CI 0.99–2.84, p = 0.053), while the small P1 cluster yielded a hazard ratio of 1.59 (95% CI 0.69–3.65, p = 0.274) with wide uncertainty driven by sample size and complete mortality. These estimates are compatible with phenotype assignment carrying information not fully captured by APACHE II, but the width of the intervals and the fact that only the P2 contrast reached significance mean that this should be regarded as suggestive rather than established.

Recovery dynamics, indexed by the change in total SOFA score between admission and day 3 (ΔSOFA), further discriminated phenotypes. Among patients alive at day 3 with both measurements available, the median ΔSOFA was −1 (IQR −2 to +1) in P4, indicating organ function improvement, was 0 (IQR 0 to +1) in P1, and was +1 in each of P2 and P3 (IQR 0 to +2 in both), indicating persistent or worsening organ dysfunction (Kruskal–Wallis p = 1.1×10^{-5}; Figure 2D). Substantial early improvement (ΔSOFA ≤ −2) occurred in 27.8% of P4 patients but in only 5.6%–10.8% of patients across the three severe phenotypes, suggesting that phenotype assignment within the first ICU day identifies not only static severity but also the likelihood of early biological recovery.

AKI-on-CKD versus de novo AKI

Given the prominence of pre-existing CKD in the P3 phenotype, we performed a pre-specified subgroup analysis comparing three clinically defined groups: no AKI (n = 138), de novo AKI (AKI without pre-existing CKD, n = 191), and AKI-on-CKD (n = 60). ICU mortality was nearly identical between de novo AKI (86.9%; 95% CI 81.4–91.0) and AKI-on-CKD (88.3%; 77.8–94.2) and both differed sharply from no AKI (26.8%; log-rank $\chi^2 = 68.95$, p < 0.001; Figure 3A). However, the two AKI groups showed markedly different clinical profiles (Figure 3B). Patients with AKI-on-CKD did not differ significantly in age (median 75 vs 72 years, p = 0.17) but carried a substantially higher comorbidity burden (median Charlson 5 vs 3, p < 0.001), had higher both baseline (1.7 vs 0.8 mg/dL, p < 0.001) and peak (3.6 vs 2.3 mg/dL, p < 0.001) creatinine, and required RRT considerably more often (38.3% [95% CI 27.1–51.0] vs 10.5% [6.9–15.6], p < 0.001). In contrast, admission APACHE II and SOFA were not significantly different, and C-reactive protein was lower in the AKI-on-CKD group (132.5 vs 155.0 mg/L, p = 0.02). Together, these patterns suggest that AKI-on-CKD pa-

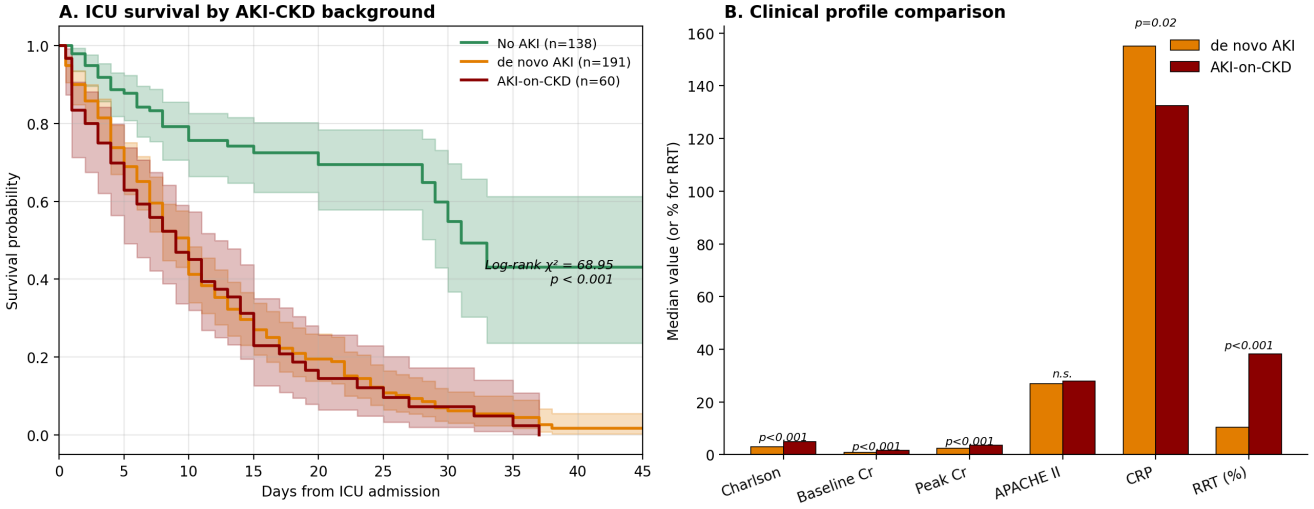


Figure 3. AKI-on-CKD versus de novo AKI, distinct clinical profile despite similar mortality. (A) Kaplan–Meier survival curves by AKI–CKD background; shaded bands show 95% confidence intervals; log-rank $\chi^2 = 68.95$, p < 0.001. (B) Comparison of selected clinical and laboratory variables between de novo AKI (n = 191) and AKI-on-CKD (n = 60) groups; values are medians (or proportion for RRT); p-values from Mann–Whitney U or chi-squared test as appropriate.

tients reach the threshold of severity that drives mortality predominantly through renal structural injury and chronic comorbid burden, while de novo AKI patients reach the same threshold predominantly through acute inflammatory and haemodynamic decompensation.

Survival analysis anchored at ICU admission

Because the peak classification incorporates information accruing after ICU admission, we repeated the survival analysis using the admission classification, which is fixed at time zero. Under this definition, 227 patients (58.4%) met KDIGO criteria at admission, distributed as 92 at stage 1, 81 at stage 2, and 54 at stage 3, with 162 patients at stage 0. Mortality rose monotonically across strata, from 33.3% (95% CI 26.5–40.9) at stage 0 to 76.1% (66.4–83.6), 96.3% (89.7–98.7), and 100.0% (93.4–100.0) at stages 1, 2, and 3 respectively (log-rank $\chi^2 = 77.09$, 3 df, $p < 0.001$). In a ridge-penalised Cox model adjusted for age, Charlson comorbidity index, and APACHE II score, each increment in admission KDIGO stage was associated with a hazard ratio of 1.24 (95% CI 1.10–1.40, $p < 0.001$), closely comparable to the estimate of 1.25 obtained under the peak classification. Charlson index (HR 1.12, 95% CI 1.03 to 1.21) and APACHE II score (HR 1.04, 95% CI 1.02 to 1.05) remained independently associated with mortality, whereas age did not (HR 0.99, 95% CI 0.98 to 1.00). The concordance between the two specifications indicates that the stage-mortality gradient is not an artefact of exposure ascertainment after admission.

Missing data and sensitivity to baseline creatinine estimation

Baseline creatinine was unavailable in 97 patients (24.9%) and was back-estimated by the MDRD equation assuming an eGFR of 75 mL/min/1.73 m^2. Among the clustering features, D-dimer was missing in 70 patients (18.0%), albumin in 38 (9.8%), and urine output in 31 (8.0%); procalcitonin, which was reserved as a post hoc descriptor and did not contribute to cluster formation, was missing in 77 (19.8%). All percentages refer to the full cohort of 389 patients. Restricting the analysis to the 292 patients with a measured baseline creatinine yielded a closely similar picture: AKI incidence was 63.4%, stage distribution was 107, 45, 53, and 87 patients across stages 0 to 3, and stage-specific mortality was 28.0%, 53.3%, 94.3%, and 100%. Under the admission classification in this subgroup, mortality was 33.1%, 76.4%, 98.3%, and 100%. The consistency of these estimates with the full cohort indicates that back-estimation of baseline creatinine did not materially distort the findings.

Discussion

In this regional Romanian tertiary ICU cohort assembled during a high-burden phase of the COVID-19 pandemic, AKI affected approximately two thirds of critically ill patients and stratified ICU mortality with a gradient steeper than most of those reported in the international literature on COVID-19–associated AKI (4-7, 22). Three findings emerge that we believe are of broader clinical and epidemiological relevance. First, the burden of AKI in critically ill Romanian patients during the high-burden phase mirrored, and at the more severe end of the distribution exceeded, the burden reported from larger Western academic centres, despite the considerable structural differences in healthcare provision. Second, four internally stable AKI phenotypes could be identified within the first 24 hours of ICU care using routinely collected laboratory and physiological data; these phenotypes carried information additional to static severity scores, although only one phenotype contrast reached conventional significance in the adjusted Cox model, and they discriminated early biological trajectories indexed by ΔSOFA. Third, a phenotype dominated by pre-existing CKD emerged spontaneously from the data, supporting the conceptualisation of AKI-on-CKD as a distinct clinical entity rather than a simple administrative category.

The prevalence and stage distribution we observed lie at the higher end of published estimates. Population-based and large multicentre analyses of COVID-19–related AKI in critical care typically report cumulative AKI rates of 30–60% and stage 3 rates of 5–25% (4-7). The cohort we describe was assembled during a phase of ICU capacity strain in which only the most severely ill patients reached intensive care, which probably explains both the absolute prevalence figures and the unusually steep mortality gradient. Of note, the mortality observed in stage 3 AKI (100%), while consistent with reports from other surge-phase European cohorts (22-24), represents an outcome that effectively saturates regression models and motivated our use of an ordinal-trend logistic specification and a small ridge penalty in the Cox model. The independent prognostic effect of KDIGO stage after adjustment for APACHE II, lactate, and comorbidity is consistent with previous work demonstrating that AKI carries information be-

yond conventional severity scores in ICU populations (3, 11, 19).

Beyond staging, our analysis identifies four internally stable AKI phenotypes whose early-ICU signatures are clinically interpretable and not redundant with KDIGO. The hyperinflammatory shock phenotype (P1) recapitulates, in the AKI subset, the well-described severe-COVID picture of cytokine-driven multi-organ failure with profound haemodynamic collapse (13, 25). The inflammatory–respiratory phenotype (P2) more closely resembles the predominantly pulmonary ARDS pattern, with moderate inflammation and severe oxygenation impairment; despite a less catastrophic admission profile, the universally fatal outcome of P2 underlines the limited reserve of patients in whom AKI complicates an already advanced respiratory failure. The mild/recoverable phenotype (P4) is the only group with appreciable survival and the only group in which early biological recovery is the median trajectory rather than the exception. The most novel finding, however, is the emergence of the cardiorenal/AKI-on-CKD phenotype (P3), in which patients with pre-existing CKD self-organised into a single cluster (capturing 75% of all AKI-on-CKD patients) characterised by severe structural renal injury, the highest rate of RRT, the oldest age, and the highest comorbidity burden, but with inflammatory markers that were paradoxically lower than in the other severe phenotypes. The phenotype therefore reaches the same outcome ceiling through a mechanistically distinct path.

This pattern aligns with (and extends) earlier phenotyping work in critically ill AKI cohorts. Bhatraju et al. demonstrated by latent class analysis that two AKI subphenotypes differing in inflammatory and endothelial markers carry markedly different mortality and may exhibit differential responses to vasopressor therapy (13). Wiersema et al., applying latent class analysis to a sepsis-associated AKI cohort from the FINNAKI study, replicated the two-phenotype structure (an inflammatory–endothelial-injury class and a less inflammatory class) and confirmed their differential association with 90-day mortality and renal recovery (14). Our four-phenotype solution can be read as the conjunction of an inflammatory axis (P1 high, P2 moderate, P3 low, P4 lowest) and a structural-renal axis (P3 dominant), with the mild/recoverable group representing the residual cluster without major derangement on either axis. The clinical utility of such a partitioning would lie in the rapid bedside recognition of the cardiorenal/AKI-on-CKD pattern, in whom early nephrology consultation and RRT planning may be particularly important, and in distinguishing P1 patients, in whom the locus of intervention should be haemodynamic and infection-source control, from P2 patients, in whom respiratory optimisation predominates.

The pre-specified subgroup analysis comparing AKI-on-CKD with de novo AKI demonstrates that, while the two groups share an essentially identical mortality, they reach that outcome through different mechanisms. AKI-on-CKD patients are older, more comorbid, more renally compromised at baseline, and considerably more likely to require RRT, but exhibit less intense inflammatory signalling. This finding is consistent with the conceptual framework articulated by Chawla and colleagues, in which acute and chronic kidney injury are reciprocally interlinked through both shared risk factors and self-perpetuating pathophysiology (26, 27), and supports the inclusion of pre-existing CKD as a stratifier in AKI prognostic models.

Strengths and limitations

The strengths of our analysis include the use of consecutive admissions from a defined geographical catchment area, the application of contemporary KDIGO criteria with both measured and MDRD back-estimated baseline approaches, the use of an externally interpretable feature set for clustering with multiple validity indices and internal bootstrap stability assessment, and pre-specified sensitivity analyses across alternative AKI definitions.

Several limitations should be acknowledged. First, the analysis is retrospective and single-centre, which limits external generalisability and precludes the assignment of causality to phenotype membership. The phenotype solution has not been externally validated; bootstrap resampling establishes only that the partition is stable to sampling variation within this cohort, and whether the same phenotypes recur in an independent population remains untested. The taxonomy should therefore be regarded as hypothesis-generating pending replication. Second, body weight was not consistently recorded, precluding the routine application of the urine output component of the KDIGO criteria; urine output was therefore used descriptively only, and mild or very early AKI may consequently be under-ascertained. Third, the use of MDRD back-estimation under the assumption of normal baseline kidney function is a recognised but imperfect strategy that may overesti-

mate AKI in patients with undiagnosed CKD and underestimate severity in younger or muscular individuals; baseline creatinine was unavailable in 97 patients (24.9%); the sensitivity analysis restricted to the 292 patients with measured baselines, reported in Section 3.7, nonetheless gave near-identical results. Fourth, two features of our exposure definitions are not anchored at ICU admission. The peak KDIGO classification is defined over the first seven ICU days and is therefore not a baseline characteristic, so survival estimates stratified by it are in principle subject to immortal time bias; three considerations bound its likely magnitude here, namely that 90.0% of patients with AKI already met criteria at admission, that median ICU length of stay was comparable across strata, and that the admission-anchored Cox model reported in Section 3.6 returned an almost identical estimate. A time-dependent specification would nonetheless be preferable, but our dataset retains creatinine values without measurement timestamps and does not permit reconstruction of the longitudinal trajectory. Similarly, two of the twelve clustering features, peak noradrenaline rate and urine output, are defined over the first 24 hours rather than at arrival, so phenotype membership is established at the close of day one rather than at the bedside on admission. Fifth, the 100% mortality observed in stage 3 AKI and in the P1 and P2 phenotypes precludes the use of multivariable models in which these strata serve as outcome categories, and motivated our use of ordinal and ridge-penalised approaches. Sixth, the cohort was assembled during a high-burden period and may not represent the typical post-pandemic case mix; we therefore frame our findings as characterising AKI in a high-burden Eastern European ICU rather than as estimates of stable steady-state AKI epidemiology. Finally, follow-up was limited to the ICU stay and we cannot speak to longer-term renal outcomes, including CKD progression and dialysis dependence among survivors, which constitute a priority for future prospective work in this population.

Ascertainment of AKI over the first seven ICU days rather than at a single fixed time point means that detection depends in part on the duration of observation, so patients with very short stays may be under-ascertained. Median ICU length of stay was, however, similar across strata, which limits the scope for differential ascertainment.

A further limitation concerns treatment exposure. The enrolment window spans five successive revisions of the national treatment protocol, and pharmacological therapy was individualised and documented in unstructured form, precluding reliable patient-level quantification of specific COVID-19 directed agents. We were consequently unable to adjust for or stratify by treatment, and the phenotype-outcome associations reported here should be interpreted as reflecting admission physiology within a heterogeneous and evolving therapeutic context.

Conclusion

In a regional Romanian tertiary ICU cohort during a high-burden phase of the COVID-19 pandemic, AKI affected approximately two thirds of critically ill patients and stratified ICU mortality steeply by KDIGO stage. A data-driven, four-phenotype clinical taxonomy, hyperinflammatory shock, inflammatory-respiratory, cardiorenal/AKI-on-CKD, and mild/recoverable, was identifiable from data available within the first 24 hours of ICU care, showed acceptable internal stability, and carried information additional to conventional severity scoring beyond static severity scores, and distinguished early biological recovery trajectories. The emergence of a coherent cardiorenal/AKI-on-CKD phenotype, dominated by pre-existing chronic kidney disease but with less intense systemic inflammation, supports the conceptualisation of AKI-on-CKD as a distinct clinical entity rather than a simple administrative descriptor and identifies a subgroup that may benefit from early nephrology engagement and RRT planning. Whether these phenotypes generalise beyond high-burden COVID-19 cohorts, and whether they predict differential responses to targeted interventions, warrants prospective multicentre confirmation.

Authors' contribution

Conceptualization, M.B.N., R.C.V. and V.C.D.; methodology, R.C.V., A.-D.R.-Z. and L.R.; software, A.-D.R.-Z.; validation, V.C.D., A.-G.S. and L.R.; formal analysis, A.-D.R.-Z. and R.C.V.; investigation, M.B.N., A.-G.S. and R.C.V.; resources, M.B.N. and V.C.D.; data curation, M.B.N. and A.-D.R.-Z.; writing—original draft preparation, A.-D.R.-Z., R.C.V. and M.B.N.; writing—review and editing, V.C.D., A.-G.S., L.R. and M.B.N.; visualization, A.-D.R.-Z.; supervision, V.C.D. and L.R.; project administration, V.C.D. and A.-G.S.; funding acquisition, V.C.D. All authors have read and agreed to the published version of the manuscript. M.B.N. and

R.C.V. contributed equally to this work and share first authorship.

Acknowledgments

The authors thank the ICU nursing and medical staff at the County Emergency Clinical Hospital of Craiova for their dedication during the high-burden period. Generative artificial intelligence tools were used solely for language editing of the manuscript; they were not used to generate, analyse, or interpret data. All AI-assisted text was reviewed and verified by the authors, who take full responsibility for the content, accuracy, and integrity of the work.

Conflict of interest

The authors declare no conflict of interest.

Funding

No external funding was received.

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