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CLINICAL RESEARCH

Association of Country Income Level With the Characteristics and Outcomes of Critically Ill Patients Hospitalized With Acute Kidney Injury and COVID-19

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Introduction: Acute kidney injury (AKI) has been identified as one of the most common and significant problems in hospitalized patients with COVID-19. However, studies examining the relationship between COVID-19 and AKI in low- and low-middle income countries (LLMIC) are lacking. Given that AKI is known to carry a higher mortality rate in these countries, it is important to understand differences in this population.

Methods: This prospective, observational study examines the AKI incidence and characteristics of 32,210 patients with COVID-19 from 49 countries across all income levels who were admitted to an intensive care unit during their hospital stay.

Results: Among patients with COVID-19 admitted to the intensive care unit, AKI incidence was highest in patients in LLMIC, followed by patients in upper-middle income countries (UMIC) and high-income countries (HIC) (53%, 38%, and 30%, respectively), whereas dialysis rates were lowest among patients with AKI from LLMIC and highest among those from HIC (27% vs. 45%). Patients with AKI in LLMIC had the largest proportion of community-acquired AKI (CA-AKI) and highest rate of in-hospital death (79% vs. 54% in HIC and 66% in UMIC). The association between AKI, being from LLMIC and in-hospital death persisted even after adjusting for disease severity.

Conclusions: AKI is a particularly devastating complication of COVID-19 among patients from poorer nations where the gaps in accessibility and quality of healthcare delivery have a major impact on patient outcomes.

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KEYWORDS: acute kidney injury; community-acquired AKI; country income; COVID-19; dialysis; in-hospital death
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Since its beginnings in December of 2019, SARS-CoV-2 has infected >680 million people and claimed the lives of 6.8 million more.[1] It has done so indiscriminately of geography, age, race, or socioeconomic status, positioning itself as one of the most consequential and tragic health crisis of this century. Beyond the idiosyncratic and situational factors that have allowed this virus to spread unhindered across entire continents, much of the observed morbidity and mortality has resulted from its capacity for multi-organ involvement followed by rapid deterioration. In this context, AKI has been identified as one of the most common and significant problems in hospitalized patients with COVID-19.[2–4] Whether through direct viral invasion, hemodynamic shifts, or local inflammatory and thrombotic changes,[5] AKI has been shown to be a catalyst for longer admission times, increased need for ICU level care and in-hospital death.[2,6,7] Thus far, most of what we know about AKI in COVID-19 comes from observational studies of patients from HIC. Although largely unaccounted for in the scientific literature, COVID-19 has had a decimating effect on countries and regions with fragmented healthcare systems and large portions of their population living in poverty.[8]

We know from the ISN 0by25 Global Snapshot of AKI study that, in patients from LLMIC, AKI is predominantly community-acquired and is associated with a higher rate of mortality.[9,10] The Global Kidney Health Atlas has shown that access to kidney replacement therapies is critically conditioned by socioeconomic factors and not just clinical indication in resource-limited areas.[11] In patients with COVID-19, the few studies from low and middle income countries have supported these general observations.[12,13] However, their small sample sizes and restricted geographic representation limit the generalizability and robustness of their conclusions.

To further examine this relationship, we undertook the first multinational study comparing the characteristics and outcomes of AKI in patients hospitalized with COVID-19 stratified by country income level. We hypothesized that a larger proportion of CA-AKI and higher AKI-associated mortality would be observed among patients from LLMIC compared with those from higher income countries. Given the resource limitations experienced by lower income countries, we also hypothesized that acute dialysis would be less prevalent among patients with AKI from LLMIC.

METHODS

Study Design

The International Severe Acute Respiratory and Emerging Infection Consortium - World Health Organization Clinical Characterization Protocol for Severe Emerging Infections provided a framework for prospective, observational data collection on hospitalized patients affected by pathogens of public health interest.[14] The protocol, case report forms (CRFs) and study information are available online (https://isaric.org/research/covid-19-clinical-research-resources), of which only the core CRF was used in this study.[15] These CRFs were developed to standardize clinical data collection on patients admitted with suspected or confirmed COVID-19 and have been widely used since the start of the pandemic.[2,16] Collection of serum creatinine measurements across all sites was not time-standardized and the frequency of collection was left to the discretion of each site.

This observational study required no change to clinical management and encouraged patient enrolment in other research projects. Protocol and consent forms are available at https://isaric.net/ccp/. Whereas written consent was obtained in most cases, for some sites the local regulators and ethics committees approved oral consent, or waiver of consent, in the context of the pandemic.

The Clinical Characterization Protocol was approved by the World Health Organization Ethics Review Committee (RPC571 and RPC572, 25 April 2013). Ethical approval was obtained for each participating country and site according to local requirements (Supplementary Statement S1). We reported the study in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guideline (Supplementary Table S1).[17]

Study Population

Inclusion and Exclusion Criteria

All individuals in the International Severe Acute Respiratory and Emerging Infection Consortium - World Health Organization Clinical Characterization Protocol database with clinically diagnosed or laboratory-confirmed SARS-CoV-2 infection and available hospital laboratory data admitted to hospital from January 30, 2020, to September 1, 2022 (criteria for clinical diagnosis in Supplementary Table S2) were included in this analysis. Data were collected and analyzed for the duration of a patient's admission.

Patients younger than 18 years of age and those on maintenance kidney replacement therapies (dialysis or kidney transplantation) were excluded first followed by patients who had not been admitted to the ICU at any point during their hospital stay. Given that a significant proportion of patient data was recruited through the Critical Care Asia-consortium, >98% of the LLMIC participants experienced an ICU admission during their stay. The exclusion was made to reduce this known bias. Patients with fewer than 2 serum

creatinine (sCr) measurements and those with incomplete or unreliable demographic or laboratory data were excluded next. Finally, patients without an admission outcome which included death, discharge, or transfer, either because one was not reported in the CRF or the patient was lost to follow-up, were labeled as "lost to follow-up" and excluded from the analysis.

Patients in the final analysis cohort were then divided according to country income level based on the World Bank classification (https://data.worldbank.org/country): LLMIC, UMIC, and HIC. Patients from LLMIC were placed in a single category because of the small patient numbers in low-income countries.

AKI Incidence and Time to Peak AKI

AKI was identified biochemically using the sCr criteria of the Kidney Disease Improving Global Outcomes definition of AKI, which requires a patient to have an increase in sCr by $\geq$ 26.5 μmol/l within 48 hours or an increase to >1.5 times the baseline sCr within 7 days.[18] Urine volume criteria were not used because urine volume was not routinely collected in the CRF. Time to peak AKI from hospital admission and the respective counts for each day were compared by visual inspection of histograms using the first day that a peak stage was reached. The first occurrence of AKI was classified as CA-AKI if it was detected within the first 48 hours of admission and hospital-acquired AKI if it developed thereafter.

From the prespecified data collected in the CRF, information was obtained on patients' comorbidities and preadmission medications as well as signs, symptoms, observations, and laboratory results on admission to hospital. Information collected during the admission included acute treatments, complications, and outcomes. Outcomes included discharge, transfer to another hospital or in-hospital death. Definitions of all collected variables are provided in Supplementary Table S3. Only those variables with <20% missingness, in any income country group, were analyzed.

Statistical Analysis

For continuous variables, characteristics were reported as medians and interquartile ranges (IQR). For categorical variables, counts and percentages were reported. All statistical tests were carried out as pairwise independent samples comparisons. Because of the number of statistical tests conducted, a conservative Bonferroni adjusted significance level of α_b 5 $\times$ 10^{-5} was used to limit the study wide probability of a type I error.[19] For continuous variables, the Mann-Whitney *U* test was used. For categorical variables, Pearson's chi-squared test was performed. Standardized mean differences (SMDs) are presented to describe the differences between cohorts with and without AKI.[20]

A logistic regression model was fitted to assess the relationship between AKI, country income level and in-hospital death. All variables known to indicate disease severity and increased susceptibility to AKI from Table 1 were initially selected. However, many of them were excluded because their sample size was too small, likely from under-reporting, leading to significant class imbalance.

The final list of variables included age, sex and socioeconomic status, mechanical ventilation, and clinical observations on admission. Information pertaining to sex represents "sex at birth". Continuous variables were binned into clinically meaningful categories to help account for nonlinear relationships with mortality. Several categories with few observations were subsequently removed. The reported model was fit to data from the entire inclusion cohort but held HIC as the reference group to specifically evaluate the association between being from a LLMIC with in-hospital death. Multiple imputation by chained equations was used to address variable missingness.

The relationship between AKI, no AKI and in-hospital death and discharge was described for each country income group with a survival curve approximated using a Kaplan–Meier estimator.[21] The follow-up period, measured in days, began on the day of hospital admission and ended on the day of either discharge or death. Hospital discharge and transfer were considered absorbing states, exclusive with hospital morbidity.

All statistical analyses were performed using the R statistical programming language, version 4.1.2.[22,23]

RESULTS

Data were collected for 439,818 individuals from 721 sites and 64 countries. Of these, 32,120 were used as the analysis cohort (Figure 1). A breakdown of the 2 main groups of excluded patients (ICU admission and <2 sCr) by country income level and individual country can be seen in Supplementary Figure S1. There were 5238 patients from 8 LLMICs, 1833 patients from 11 UMICs and 25,049 patients from 30 HICs (Figure 2). The LLMIC group was mainly constituted by patients from various regions in Asia, whereas the UMIC group had a predominance of patients from Latin America, and the HIC group from North America and Western Europe. Admissions peaked in the first half of 2020 for HIC patients and then increased again at the end of that year and in early 2021. Patients from LLMIC were mainly admitted through the first 8 months of 2020 whereas UMIC were more evenly admitted from late 2020 to the second half of 2021 (Figure 3).

The median length of stay was 7 days (IQR 4–11) for LMIC patients, 14 days (IQR 8–24) for UMIC patients,

Table 1. Characteristics of patients with AKI and no AKI grouped by country income level

	Low and lower-middle income country patients				Upper-middle income country patients				High income country patients			
Variables	**All**	**AKI**	**No AKI**	**SMD**	**All**	**AKI**	**No AKI**	**SMD**	**All**	**AKI**	**No AKI**	**SMD**
Total count	5238	2789	2449	—	1833	704	1129	—	25,049	7645	17,404	—
Demographics												
Age, y, median (IQR)	60 (50–70)	62 (52–71)	60 (49–70)	−0.13	58.1 (47–69)	63 (52–71)	55.1 (43.1–68)	−0.35	61 (51–70)	63 (54–70)	60 (50–69)	−0.19
Female (%)	1816 (35)	933 (33)	883 (36)	0.06	650 (35)	252 (36)	398 (35)	0.01	8172 (33)	2131 (28)	6041 (35)	0.15
AKI grades and KRT, n (%)												
AKI grade 1	916 (17)	916 (33)	0 (0)	—	145 (8)	145 (21)	0 (0)	—	1973 (8)	1973 (26)	0 (0)	—
AKI grade 2	463 (9)	463 (17)	0 (0)	—	73 (4)	73 (10)	0 (0)	—	841 (3)	841 (11)	0 (0)	—
AKI grade 3 with RRT	1410 (27)	1410 (51)[a]	0 (0)	—	486 (27)	486 (69)[a]	0 (0)	—	4831 (19)	4831 (63)[a]	0 (0)	—
AKI grade 3 w/o RRT		658 (24)[a]				169 (24)[a]				1414 (18)a[a]		
KRT	752 (14)	752 (27)[a]	0 (0)	—	317 (17)	317 (45)[a]	0 (0)	—	3417 (14)	3417 (45)[a]	0 (0)	—
KRT/all grade 3		53%				65%				71%		
		Calculated as a proportion of total AKI[a]				Calculated as a proportion of total AKI[a]				Calculated as a proportion of total AKI[a]		
Comorbidities[b], n (%)												
Chronic kidney disease	138 (3)	100 (4)	38 (2)	0.13	139 (8)	105 (15)	34 (3)	0.45	2047 (8)	1112 (15)	935 (5)	0.31
Chronic cardiac disease	523 (10)	291 (10)	232 (9)	0.03	255 (14)	133 (19)	122 (11)	0.24	3873 (15)	1410 (18)	2463 (14)	0.11
Chronic pulmonary disease	168 (3)	87 (3)	81 (3)	0.01	102 (6)	51 (7)	51 (5)	0.13	2463 (10)	756 (10)	1707 (10)	0.00
Hypertension	2451 (47)	1360 (49)	1091 (45)	0.08	950 (52)	435 (62)	515 (46)	0.36	9681 (39)	3115 (41)	6566 (38)	0.19
Dementia	20 (0)	9 (0)	11 (0)	0.02	23 (1)	6 (1)	17 (2)	0.06	249 (1)	80 (1)	169 (1)	0.01
Liver disease	34 (1)	21 (1)	13 (1)	0.03	26 (1)	17 (2)	9 (1)	0.14	801 (3)	286 (4)	515 (3)	0.04
Malnutrition	16 (0)	5 (0)	11 (0)	0.05	26 (1)	14 (2)	12 (1)	0.08	238 (1)	89 (1)	149 (1)	0.03
Obesity	113 (2)	57 (2)	56 (2)	0.02	517 (28)	216 (31)	301 (27)	0.14	6131 (24)	1923 (25)	4208 (24)	0.03
Signs and symptoms on admission, n (%)												
Altered consciousness/ confusion	137 (3)	85 (3)	52 (2)	0.06	115 (6)	49 (7)	66 (6)	0.12	2563 (10)	894 (12)	1669 (10)	0.10
Diarrhea	185 (4)	99 (4)	86 (4)	0.00	256 (14)	95 (13)	161 (14)	0.03	4981 (20)	1424 (19)	3557 (20)	0.01
Fever	3756 (72)	1994 (71)	1762 (72)	0.02	1135 (62)	396 (56)	739 (65)	0.01	17,996 (72)	5393 (71)	12,603 (72)	0.03
Vomiting/nausea	268 (5)	139 (5)	129 (5)	0.01	160 (9)	47 (7)	113 (10)	0.09	4045 (16)	1137 (15)	2908 (17)	0.02
Muscle aches/joint pain	386 (7)	189 (7)	197 (8)	0.05	476 (26)	145 (21)	331 (29)	0.14	5880 (23)	1617 (21)	4263 (24)	0.04
Headache	184 (4)	96 (3)	88 (4)	0.01	279 (15)	69 (10)	210 (19)	0.22	3116 (12)	810 (11)	2306 (13)	0.06
Cough	1686 (32)	859 (31)	827 (34)	0.07	1009 (55)	356 (51)	653 (58)	0.00	16,925 (68)	4956 (65)	11,969 (69)	0.02
Shortness of breath	3904 (75)	2155 (77)	1749 (71)	0.12	1,144 (62)	442 (63)	702 (62)	0.18	19,462 (78)	5773 (76)	13,689 (79)	0.01
Observations on admission, median (IQR)												
Temperature, C	36.7 (36.7–37)	36.7 (36.7–37)	36.7 (36.7–37.1)	0.10	36.8 (36.2–37.7)	37 (36.3–37.7)	36.8 (36.2–37.6)	−0.08	37.5 (36.8–38.3)	37.5 (36.8–38.4)	37.5 (36.8–38.3)	−0.04
Systolic BP, mmHg	130 (117–143)	130 (117–145)	130 (118–141)	−0.03	130 (116–144)	129 (111–145)	130 (119–143)	0.08	127 (112–142)	127 (110–144)	127 (112–142)	−0.01
Diastolic BP, mmHg	75 (68–83)	75 (66–84)	75 (69–82)	−0.02	76 (66–85)	74 (63–85)	77 (68–85)	0.18	73 (63–82)	71 (60–81)	73 (64–82)	0.14
Heart rate, BPM	91 (82–103)	94 (82.5–107)	90 (81–100)	−0.18	91 (80–106)	94 (80–108)	90 (79–104)	−0.21	94 (82–108)	95 (82–109)	94 (82–108)	−0.05
Respiratory rate, per min	24 (20–29)	24 (21–30)	23 (20–28)	−0.23	22 (18–28)	24 (20–30)	21 (18–26)	−0.38	24 (20–30)	24 (20–31)	24 (20–30)	−0.02
Oxygen saturation, %	93 (90–96)	92.4 (89–96)	94 (90–96)	0.15	94 (90–96)	92 (88–96)	94 (91–97)	0.32	93.3 (89–96)	93 (88–96)	94 (89.8–96)	0.14

(Continued on following page)

Table 1. (Continued) Characteristics of patients with AKI and no AKI grouped by country income level

	Low and lower-middle income country patients				Upper-middle income country patients				High income country patients			
Variables	**All**	**AKI**	**No AKI**	**SMD**	**All**	**AKI**	**No AKI**	**SMD**	**All**	**AKI**	**No AKI**	**SMD**
Laboratory results on admission, median (IQR)												
Potassium (mmol/l)	4.2 (3.7–4.6)	4.2 (3.7–4.6)	4.1 (3.7–4.5)	−0.14	4.1 (3.7–4.5)	4.2 (3.8–4.6)	4.1 (3.7–4.5)	−0.24	4.1 (3.7–4.4)	4.2 (3.8–4.6)	4 (3.7–4.4)	−0.24
sCr (μmol/l)	88.4 (70.7–132.6)	97.2 (70.7–177.5)	84 (68.1–106.1)	−0.48	87.8 (67.4–117.6)	100.8 (71.5–150.5)	83.1 (66.1–102.6)	−0.48	84.9 (67.2–111)	98 (74.3–153)	80.4 (65–101)	−0.50
eGFR (ml/min per 1.73 m^2)	73 (44.2–96.5)	64 (30.9–93.9)	80.4 (57.2–98.7)	0.45	78 (52.2–99.5)	61.6 (37–93.1)	84.3 (63.4–102.4)	0.58	80.7 (55.9–98)	66.3 (36.8–90.6)	85.3 (63.9–100.4)	0.59
Hemoglobin (g/l)	128 (111–141)	126 (109–140)	129 (115–142)	0.17	135 (123–148)	130 (116.2–145)	138 (126–150)	0.38	135 (120–147)	131 (114–145)	136 (122–148)	0.26
Sodium (mmol/l)	137 (134–141)	138 (134–142)	137 (133.8–141)	−0.10	137 (134.3–140)	137 (134–140)	137 (135–140)	0.01	136 (133–139)	136 (133–139)	136 (133–139)	0.01
Admission Treatment, n (%)												
Antiviral and COVID-19 targeting agents	2633 (50)	1464 (52)	1169 (48)	0.09	256 (14)	108 (15)	148 (13)	0.16	11,066 (44)	2663 (35)	8403 (48)	0.27
Antibiotic agents	4733 (90)	2640 (95)	2093 (85)	0.30	1399 (76)	506 (72)	893 (79)	0.34	22,631 (90)	7145 (93)	15,486 (89)	0.19
Antifungal agents	133 (3)	86 (3)	47 (2)	0.07	205 (11)	127 (18)	78 (7)	0.41	4119 (16)	1865 (24)	2254 (13)	0.34
Corticosteroids	3699 (71)	2183 (78)	1516 (62)	0.36	1180 (64)	455 (65)	725 (64)	0.19	12,018 (48)	3907 (51)	8111 (47)	0.10
Invasive mechanical ventilation	4851 (93)	2668 (96)	2183 (89)	0.25	1060 (58)	557 (79)	503 (45)	1.12	16,769 (67)	6582 (86)	10,187 (59)	0.65
Complications[b], n (%)												
Bacterial pneumonia	192 (4)	120 (4)	72 (3)	−0.05	478 (26)	266 (38)	212 (19)	0.60	5582 (22)	2044 (27)	3538 (20)	0.19
Cardiac arrest	570 (11)	386 (14)	184 (8)	−0.15	192 (10)	140 (20)	52 (5)	0.61	1725 (7)	1048 (14)	677 (4)	0.37
Coagulation disorder	167 (3)	93 (3)	74 (3)	−0.01	79 (4)	68 (10)	11 (1)	0.49	2180 (9)	937 (12)	1243 (7)	0.21
Rhabdomyolysis	1 (0)	1 (0)	0 (0)	−0.02	16 (1)	12 (2)	4 (0)	0.17	429 (2)	224 (3)	205 (1)	0.14
Outcomes, n (%)												
Transferred	244 (5)	89 (3)	155 (6)	0.15	72 (4)	31 (4)	41 (4)	0.04	2542 (10)	925 (12)	1617 (9)	0.09
Discharged	1801 (34)	494 (18)	1307 (53)	0.80	1113 (61)	208 (30)	905 (80)	1.18	14,402 (57)	2591 (34)	11,811 (68)	0.72
Death	3193 (61)	2206 (79)	987 (40)	0.86	648 (35)	465 (66)	183 (16)	1.17	8105 (32)	4129 (54)	3976 (23)	0.68
Length of stay (median, IQR)	7 (4–11)	8 (5–13)	6 (4–9)	−0.36	14 (8–24)	18.5 (11–30)	12 (7–20)	−0.48	17 (10–28)	20 (11–33)	16 (10–25)	−0.26

AKI, acute kidney injury; BP, blood pressure; BPM, beats per minute; eGFR, estimated glomerular filtration rate (estimated using the CKD-EPI equation); IQR, interquartile range; RRT, renal replacement therapy; RRT, renal replacement therapy; sCr, serum creatinine; SMD, standardized mean difference.

[a]Calculated as a proportion of total AKI.

[b]Definitions of comorbidities, complications and outcomes from the CRFs are presented in Supplementary Table S2.

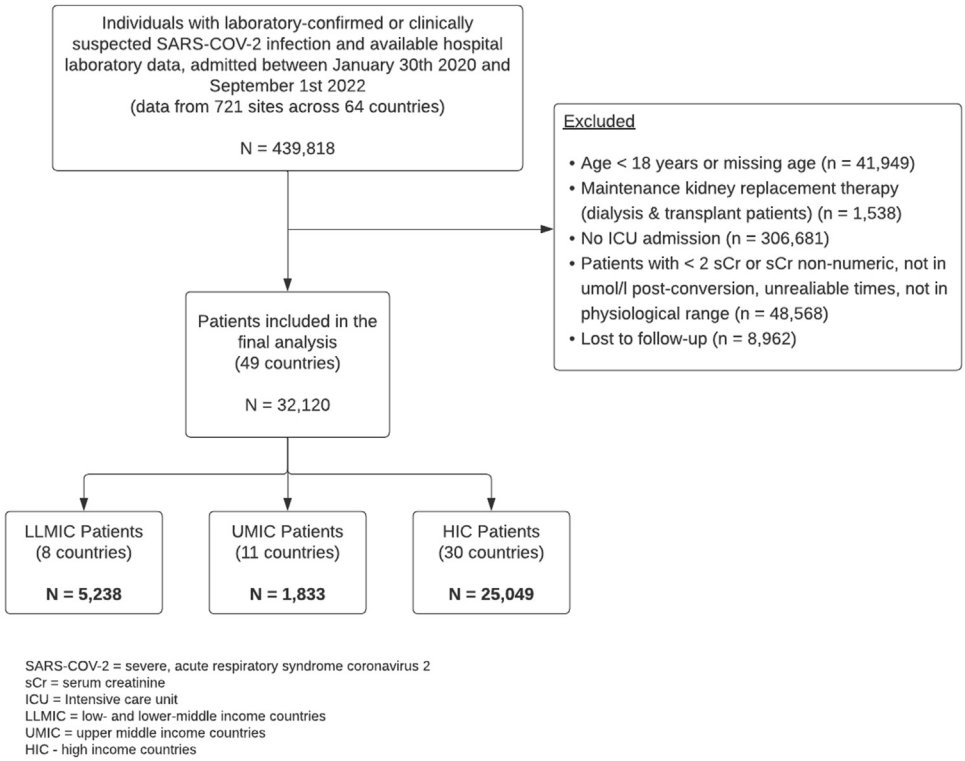

Figure 1. Flowchart of the study.

and 17 days (IQR 10–28) for HIC patients (Table 1). Missing data were highly variable between country income groups (Supplementary Table S4).

Incidence, Staging, and Timing of Peak AKI

Among patients with COVID-19 admitted to the ICU, AKI incidence was highest in LLMIC, followed by UMIC and HIC patients (53%, 38% and 30%, respectively) (Figure 4 and Supplementary Figure S2 for individual country breakdown). Among all patients with AKI, those from UMIC had the highest proportion of stage 3 AKI (69%), followed by HIC (63%) and LLMIC (51%) (Figure 4). Patients from HIC with AKI had the highest rate of acute dialysis treatment overall (45%) and as a proportion of all patients with stage 3 AKI (71%) (Table 1). The lowest rate of dialysis overall and as a proportion of stage 3 AKI was seen in LLMIC patients (27% and 53%, respectively) with UMIC

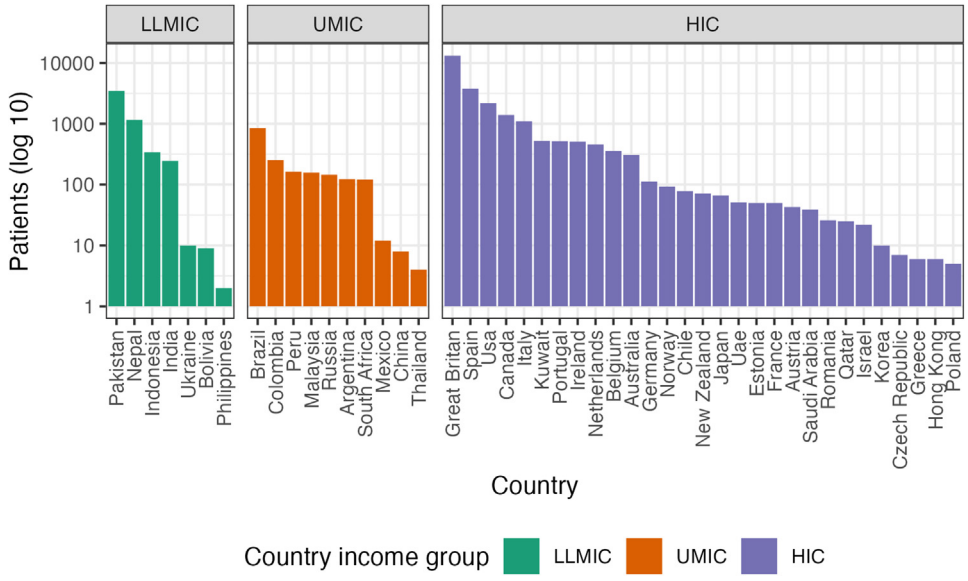

Figure 2. Analysis cohort contributing countries. HIC, high income country; LLMIC, low- and low-middle income country; UMIC, upper-middle income country.
* Countries that contributed only 1 patient are not presented in this figure.

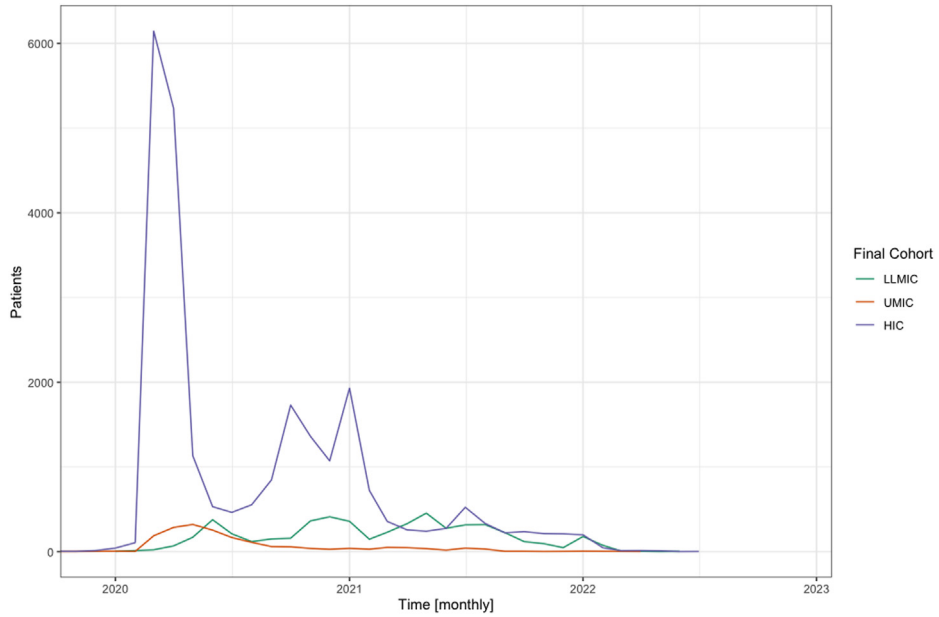

Figure 3. Temporal distribution of admissions by country income group. HIC, high income country; LLMIC, low- and low-middle income country; UMIC, upper-middle income country.

falling in the middle. The rates of AKI stage 3 without dialysis were similar between the 3 groups, with the highest observed in LLMIC and UMIC (24%) and lowest in HIC (18%). Peak sCr occurred more frequently on days 1 to 3 of admission in LLMIC patients and decreased sequentially thereafter, whereas for UMIC and HIC, peak AKI was spread variably across admission days (Supplementary Figure S3). Whereas hospital-acquired AKI was the predominant type of AKI, LLMIC patients had the largest proportion of CA-AKI (34% vs. 17% in HIC and UMIC) (Figure 5 and Supplementary Figure S4 for individual country breakdown)

Demographic and Clinical Characteristics

Baseline characteristics at hospital admission, acute interventions, complications, and outcomes for patients with AKI versus no-AKI for each country income group are provided in Table 1. Median age was between 58 and 61 years across the 3 groups and similar proportions, approximately one-third, were female. With the exception of hypertension, the prevalence of all comorbidities among LLMIC patients, particularly with regards to chronic kidney disease, appeared significantly underreported considering known global estimates.[24] Hypertension was highly prevalent in all patient groups, especially among patients with AKI

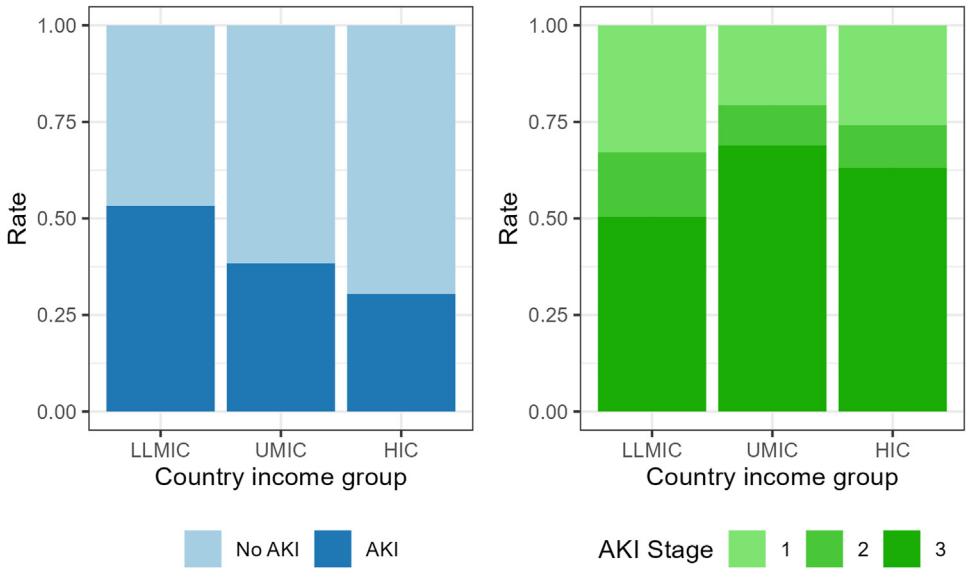

Figure 4. AKI incidence and breakdown by country income group. AKI, acute kidney injury; HIC, high income country; LLMIC, low- and low-middle income country; UMIC, upper-middle income country.

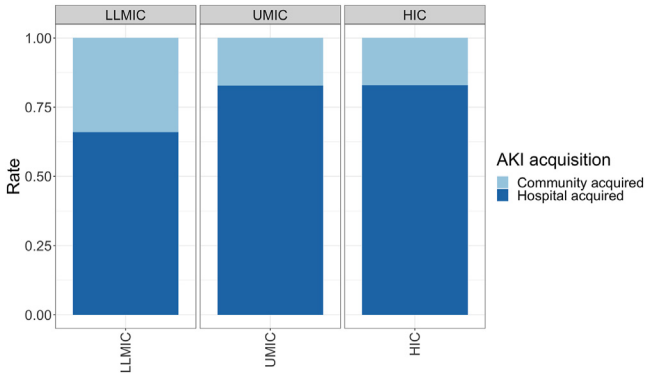

Figure 5. Community-acquired versus hospital-acquired acute kidney injury based on 48 hour cutoff from admission by country income group. AKI, acute kidney injury; HIC, high income country; LLMIC, low- and low-middle income country; UMIC, upper-middle income country.

who are from LLMIC (49%) and UMIC (62%) whereas approximately one-quarter of UMIC and HIC patients (28% and 24%, respectively) were obese. Shortness of breath, cough, and fever were the most common presenting symptoms on admission in all patients.

Kidney function on admission in patients with and without AKI was comparable between country income groups. However, a significant improvement in estimated glomerular filtration rate (estimated with CKD-EPI equation and no "if black" correction), and concurrent drop in sCr, between patients with AKI and those without AKI could be seen in all income groups (median estimated glomerular filtration rates, LLMIC: 64 vs. 80 ml/min per 1.73 m^2, UMIC: 62 vs. 84 ml/min per 1.73 m^2, HIC: 66 vs. 85 ml/min per 1.73 m^2) (SMD 0.45 to 0.59).

Patients with AKI from LLMIC were the most likely to be treated with antivirals and COVID-19 related medications (52%), antibiotics (95%), corticosteroids (78%), and be supported with invasive mechanical ventilation (96%) (Supplementary Figure S5).

Outcomes

In-hospital death was highest among patients from LLMIC (61%) with a significant difference observed between patients who developed AKI (79%) and those who did not (40%) ($P < 0.001$, SMD 0.80). Approximately one-third (32%) of all patients from HIC died, and this proportion increased to 54% among patients with AKI. Interestingly, this difference in mortality based on AKI status was most pronounced in patients from UMIC among whom 66% of those with AKI but only 16% of those without AKI died, making the mortality of patients without AKI from UMIC and HIC comparable (Figure 6).

After adjusting for markers of disease severity and AKI susceptibility, the risk of in-hospital death with AKI persisted and increased with AKI severity (Table 2). Being from LLMIC (vs. HIC) was associated with an increased risk of death; however, this was not the case for patients from UMIC (vs. HIC). Other factors that were associated with a significantly higher risk of death included age over 65 years and treatment with antibiotics.

DISCUSSION

In the first and largest study of the association of country income level with the characteristics and outcomes of hospitalized patients with AKI and COVID-19, we observed that ICU patients from lower income countries were more likely to develop AKI, more likely to acquire

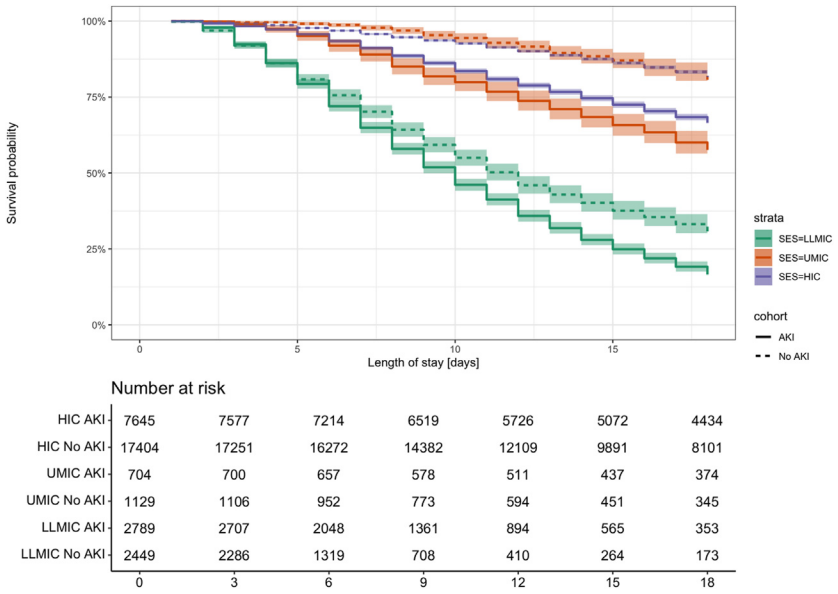

Figure 6. Kaplan–Meier Survival plot stratified across acute kidney injury and country income groups. Confidence bars are used to illustrate a 95% confidence interval. AKI, acute kidney injury; HIC, high income country; LLMIC, low- and low-middle income country; SES, socioeconomic status; UMIC, upper-middle income country.

Table 2. Logistic regression fitted to assess the association between AKI and in-hospital death

Variables	Odds ratio	95% confidence interval		*P*-value
		Lower	Upper	
(intercept)	0.109	0.099	0.120	< 0.001
AKI grade 1	2.026	1.863	2.203	< 0.001
AKI grade 2	4.290	3.796	4.852	< 0.001
AKI grade 3	5.230	4.903	5.579	< 0.001
SES: LLMIC	2.699	2.509	2.902	< 0.001
SES: UMIC	1.066	0.951	1.194	0.271
Age 65+[a]	2.838	2.686	2.998	< 0.001
Female	0.895	0.847	0.945	< 0.001
Hypertension	0.944	0.895	0.996	0.035
Temperature [0, 36]	0.935	0.825	1.059	0.292
Temperature [38+]	0.940	0.885	0.998	0.042
Systolic BP [0, 100]	1.126	1.027	1.233	0.011
Systolic BP [140+]	0.996	0.941	1.055	0.9
Heart rate [0, 60]	0.877	0.743	1.033	0.12
Heart rate [100+]	1.129	1.069	1.193	< 0.001
Respiratory rate [0, 12]	1.237	0.837	1.817	0.281
Respiratory rate [20+]	1.047	0.977	1.122	0.193
Oxygen saturation [0, 90]	1.600	1.499	1.708	< 0.001
Oxygen saturation [90 - 95]	1.088	1.0231	1.156	0.007
Mechanical ventilation	1.690	1.586	1.801	< 0.001

AKI, acute kidney injury; BP, blood pressure; LLMIC, low- and low-middle income country; MiCE imputation used for variable missingness; ref, reference; SES, socioeconomic status; UMIC, upper-middle income country.
[a]Reference for age = 18 - 65 years old.
Multiple imputation by chained equations.

AKI in the community, less likely to receive acute dialysis, and approximately twice as likely to die than patients from wealthier countries, with or without AKI.

The incidence of AKI in COVID-19 cohort studies since 2020 has been enormously variable and subject to differences in the proportions of critically ill patients, the definitions used to diagnose AKI, the levels of resourcing to detect AKI by individual sites, and the predominant COVID variant at the time.[25] Differences in AKI incidence must therefore be examined and interpreted within this context of variability. Our reported incidences of AKI among patients from HIC, UMIC, and LLMIC are consistent with the current limited available literature. The HIC incidence of 30% is similar to a Belgian multicenter study that examined an ICU-only cohort.[26] The UMIC AKI incidence of 38% is comparable to that of 2 separate studies from general hospital patients in Mexico and 1 study from 2 tertiary centers in South Africa (30%–34%).[12,27,28] The LLMIC incidence (53%), has also been reported in small cohorts of both critical and noncritical hospitalized patients from India and Pakistan.[29,30] Higher incidences of AKI (up to 85%) have been reported in HIC ICU patient studies that include the urine output component of the Kidney Disease Improving Global Outcomes definition, suggesting that combining both elements of the definition captures a far broader class of patients than considered here.[26,31]

Whereas patients from LLMIC had a higher proportion of CA-AKI (~30%) using the 48 hour threshold definition, hospital-acquired AKI remained the predominant form of AKI in all groups. A registry wide study of AKI in COVID-19 conducted by the Sociedad Latinoamericana de Nefrologia e Hipertension of 872 patients from 12 countries in the region, similarly found that 64% of patients with AKI had hospital-acquired AKI.[32] The higher proportion of CA-AKI in LLMIC, than in UMIC and HIC, agrees with the global AKI literature and likely reflects limitations in access to health care, particularly in the community, as well as a greater reluctance to seek medical attention leading to delayed presentations.[9,12,33]

The lower incidence of acute dialysis in our LLMIC population (27% vs. 45% in HIC and UMIC) is likely due to multiple factors. A possible explanation is that the limited dialysis capacity in LLMIC sites meant that patients with AKI stage 3 and borderline indications for dialysis were more likely to be treated conservatively, at least initially. The recommendations for dialysis in COVID-19 have been the same as those set forth by general guidelines, with no particular indication toward earlier starts or bypassing of diuretic challenges in fluid overloaded patients.[34] Alternatively, the observed differences in dialysis rates between socioeconomic groups in our study may result squarely from inequities in kidney care capacity and delivery. Resource shortage leading to selective treatment allocation has been a critical challenge during this pandemic, especially among health facilities in low-income and middle-income countries.[35] Acute dialysis, usually in the form of continuous hemodialysis, is not only costly but requires highly trained staff to support it. The ISN dialysis outcomes and practice patterns survey described major supply disruptions in hemodialysis consumables like dialyzers and dialysate solutions as well as disruptions to hemodialysis water processing and more frequent reduction in dialysis session length in LLMIC.[36] In the Sociedad Latinoamericana de Nefrologia e Hipertension study, 43 patients (4.9%) had indications for dialysis but did not receive it, presumably because of supply shortages, and 18% of nephrologists surveyed stated that they were not able to provide dialysis because of limited resource allocation.[32] Although it is not possible to know whether this is what led to the observed differences across income groups, the global inequities in kidney care have been well documented over time and demand greater action from ruling national authorities as well as the nephrology community at large.[37]

Although it is known that AKI is associated with an increased risk of death in COVID-19, our finding that this risk almost doubled when shifting from an HIC to

an LLMIC population is a powerful reminder of the impact of socioeconomic circumstance. Susantitaphong *et al*. clearly illustrate this inverse relationship between AKI-associated mortality and gross national income per capita suggesting there may be significant, but often underreported, differences in health care delivery that account for these findings.[10] At present, of the 12 nations with the highest burden of COVID-19 related deaths, 8 are middle or low-income countries.[38] The infection fatality rate is estimated to be 2.7 times higher in the general population and up to 5.4 times higher among people between the ages of 60 and 80 years in these countries.[8,38] In this context, our finding of income level, particularly LLMIC, being an independent predictor of death is not surprising. Similarly, the ISN dialysis outcomes and practice patterns survey of dialysis units around the world, revealed an excess mortality from COVID-19 in patients from LLMIC on maintenance hemodialysis of over 50%.[36] Although COVID-19 served to expose the fragility in the healthcare infrastructure of these countries, factors such as the ability to isolate within one's own home and to work remotely without facing financial hardship became key drivers of infection in these regions.[39] Furthermore, the rise in vaccine nationalism among wealthy nations meant that those with the highest burden of infection and limited capacity to isolate or access quality healthcare, were the last to be vaccinated and the first to die.[40]

There are some key limitations in our study. The ISARIC data collection was a voluntary assembly of data generated during an evolving pandemic. The representation of individual countries or regions was therefore conditioned by the capacity and resources of healthcare workers and institutions to collect and process data, leading to sampling bias and limiting comparisons to global estimates. Considering that this was an ICU-only study, treatment and outcome differences will inevitably reflect differences in the ICU admission criteria of each country during the pandemic. With limited resources and large case numbers, it is likely that ICUs in LLMICs had to apply a higher threshold for admission, thereby selecting a more critically ill population. This would explain why a greater proportion of these patients were treated with mechanical ventilation, corticosteroids, and antivirals when compared with those in higher income country ICUs. Nevertheless, as the largest and most diverse international data set of hospitalized COVID-19 patients, our study provides invaluable insights into the impact of this outbreak on people from widely variable demographic, cultural, and socioeconomic backgrounds.[41] In our study, the exclusion of patients without an ICU admission or 2 sCr measurements may have introduced a degree of selection bias and the lack of a time-standardized collection of sCr across all sites also represents a limitation of the study. The exclusion of patients lost to follow-up may have also introduced further bias. Finally, the predominant representation of patients from Asian countries in the LLMIC group and the fact that these sites collected data from ICU patients only, means that generalizability to other LLMIC regions and settings is uncertain.

To our knowledge, this is the first study to systematically examine the association of country income level with the characteristics and outcomes of patients with AKI and COVID-19. Our population is, as far as we know, the largest and only multinational cohort of patients with COVID-19 from all country income levels with data extending to the latter part of 2022. Patients from poorer countries had more AKI, received less dialysis, and died at twice the rate of patients from wealthier countries. Experiencing an episode of AKI and being from an LMIC country were independent predictors of mortality, suggesting that AKI is a particularly devastating complication of COVID-19 in patients from poorer nations, especially when admitted to an ICU, where the gaps in accessibility and quality of healthcare delivery have a major impact on patient outcomes.

APPENDIX

Members of the ISARIC Clinical Characterization Group

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DATA AVAILABILITY STATEMENT

The data that underpin this analysis are highly detailed clinical data on individuals hospitalized with COVID-19. Because of the sensitive nature of these data and the associated privacy concerns, they are available via a governed data access mechanism following review of a data access committee. Data can be requested via the IDDO COVID-19 Data Sharing Platform (http://www.iddo.org/covid-19). The Data Access Application, Terms of Access and details of the Data Access Committee are available on the website. Briefly, the requirements for access are a request from a qualified researcher working with a legal entity who have a health and/or research remit; a scientifically valid reason for data access which adheres to appropriate ethical principles. The full terms are at https://www.iddo.org/document/covid-19-data-access-guidelines. A small subset of sites who contributed data to this analysis have not agreed to pooled data sharing as above. In the case of requiring access to these data, please contact the corresponding author in the first instance who will look to facilitate access.

SUPPLEMENTARY MATERIALS

Supplementary File (PDF)

Supplementary Statement S1. Study ethics approval.

Supplementary Table S1. STROBE Statement - checklist of items that should be included in reports of observational studies.

Supplementary Table S2. Definitions used for clinical COVID-19.

Supplementary Table S3. Definition of comorbidities, complications, and outcomes from the ISARIC case report forms (CRF).

Supplementary Table S4. Missingness (%) from variables in Table 1.

Supplementary Figure S1. Breakdown by country income level and individual country of patients excluded on the basis of (A) not having an ICU admission or (B) having less than 2 serum creatinine measurements.

Supplementary Figure S2. Breakdown of patients with AKI by individual country.

Supplementary Figure S3. Day of peak AKI by country income level.

Supplementary Figure S4. Community vs. hospital-acquired AKI based on 48 hour cut-off from admission by individual country.

Supplementary Figure S5. Admission treatments and outcomes stratified by AKI status and country income level.

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