

COVID-19 infection in adult patients with hematological malignancies: a European Hematology Association Survey (EPICOVIDEHA)

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SARS-CoV-2 infection increases risk of acute kidney injury in a bimodal age distribution

Erica C. Bjornstad^{1*}, Gary Cutter², Pramod Guru³, Shina Menon⁴, Isabella Aldana¹, Scott House¹, Nancy M. Tofil⁵, Catherine A. St. Hill⁶, Yasir Tarabichi⁷, Valerie M. Banner-Goodspeed⁸, Amy B. Christie⁹, Surapaneni Krishna Mohan¹⁰, Devang Sanghavi³, Jarrod M. Mosier¹¹, Girish Vadgaonkar¹², Allan J. Walkey¹³, Rahul Kashyap¹⁴, Vishakha K. Kumar¹⁵, Vikas Bansal¹⁴, Karen Boman¹⁵, Mayank Sharma¹⁴, Marija Bogojevic¹⁴, Neha Deo¹⁴, Lynn Retford¹⁵, Ognjen Gajic¹⁴, Katja M. Gist¹⁶ and SCCM Discovery VIRUS Investigators Group

Abstract

Background: Hospitalized patients with SARS-CoV2 develop acute kidney injury (AKI) frequently, yet gaps remain in understanding why adults seem to have higher rates compared to children. Our objectives were to evaluate the epidemiology of SARS-CoV2-related AKI across the age spectrum and determine if known risk factors such as illness severity contribute to its pattern.

Methods: Secondary analysis of ongoing prospective international cohort registry. AKI was defined by KDIGO-creatinine only criteria. Log-linear, logistic and generalized estimating equations assessed odds ratios (OR), risk differences (RD), and 95% confidence intervals (CIs) for AKI and mortality adjusting for sex, pre-existing comorbidities, race/ethnicity, illness severity, and clustering within centers. Sensitivity analyses assessed different baseline creatinine estimators.

Results: Overall, among 6874 hospitalized patients, 39.6% ($n = 2719$) developed AKI. There was a bimodal distribution of AKI by age with peaks in older age (≥ 60 years) and middle childhood (5–15 years), which persisted despite controlling for illness severity, pre-existing comorbidities, or different baseline creatinine estimators. For example, the adjusted OR of developing AKI among hospitalized patients with SARS-CoV2 was 2.74 (95% CI 1.66–4.56) for 10–15-year-olds compared to 30–35-year-olds and similarly was 2.31 (95% CI 1.71–3.12) for 70–75-year-olds, while adjusted OR dropped to 1.39 (95% CI 0.97–2.00) for 40–45-year-olds compared to 30–35-year-olds.

Conclusions: SARS-CoV2-related AKI is common with a bimodal age distribution that is not fully explained by known risk factors or confounders. As the pandemic turns to disproportionately impacting younger individuals, this deserves further investigation as the presence of AKI and SARS-CoV2 infection increases hospital mortality risk.

Keywords: COVID-19, AKI, Age-spectrum, Hospitalization

Background

The SARS-CoV2 pandemic has killed more than 2.7 million people as of March 2021 [1]. Infection leads to a wide clinical spectrum from asymptomatic to severe multi-organ failure and death. Kidney involvement is increasingly recognized as an important complication of SARS-CoV2 infection, resulting in proteinuria, hematuria, and acute kidney injury (AKI) [2–5]. Kidney

*Correspondence: ebjornstad@uabmc.edu

¹ Department of Pediatrics, Division of Nephrology, University of Alabama at Birmingham, 1600 7th Avenue South, Lowder Suite 516, Birmingham, AL 35233, USA

Full list of author information is available at the end of the article



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involvement is theorized to parallel severity of disease and associated common risk factors of hypoperfusion, ischemia and nephrotoxins. However, another hypothesis for kidney sequelae is related to the virus' affinity for the ACE2 receptor with high density in the kidney [2, 6].

SARS-CoV2-related AKI has been reported in 25–60% of those critically ill, including up to 37% of critically ill children [7–10]. AKI has been associated with worse outcomes in those with Coronavirus Disease 2019 (COVID-19), the disease caused by SARS-CoV2. Initially, adult hospitals saw a rapid rise in the need for acute dialysis during COVID-19 waves [11, 12], yet this was not seen in pediatric hospitals. Overall, children seem less susceptible to infection and severe disease, so one hypothesis proposes lower rates of AKI/dialysis needs in children is a function of disease severity. Assessment of SARS-CoV2-related AKI across the age spectrum has not previously been reported.

The purpose of this study was to evaluate the incidence and epidemiology of SARS-CoV2-related AKI across the age spectrum and determine if age is an independent risk factor for AKI development in patients hospitalized with SARS-CoV2.

Methods

Study Design & Setting

This is a secondary analysis of the observational, international, prospective Viral Infection and Respiratory Illness Universal Study (VIRUS), initiated by Society of Critical Care Medicine (SCCM) in January 2020. VIRUS seeks to ascertain a wide range of clinical and outcome characteristics of patients hospitalized with SARS-CoV2 infection. The unique aspect of this registry is it captures both critically and non-critically ill hospitalized children and adults in the same cohort facilitating comparative evaluations.

Patients included in this analysis were admitted between January 2020 and March 2021; exact admission dates are confidential and not provided to investigators. Detailed methodologies have previously been described [13]. As this was deployed as a rapid registry early in the pandemic, detailed hospital-level characteristics are not available to investigators. Briefly, 298 centers from 26 countries contribute comprehensive pediatric and adult data from hospitalized patients encompassing intensive care units (ICUs) and non-ICUs. Ethical oversight was obtained at each local center and de-identified data stored in REDCap [14].

Patient population

We evaluated all participants in the registry if they had PCR- or antibody-confirmed presence of SARS-CoV2 infection, complete age and 28-day hospital

outcome data, and at least one serum creatinine value. We excluded patients with clinical suspicion but no laboratory confirmation of SARS-CoV2, current pregnancy, chronic dialysis, or chronic kidney disease (CKD) stage 5.

Potential Bias

As this is an ongoing cohort registry, rapidly deployed during an evolving global pandemic, analyses were conducted by complete case analysis methods which could introduce some biases towards the more severe cases or because of imminent deaths. Nevertheless, the major exclusions were those without creatinine values or missing 28-day hospital outcomes as we assumed these patients to have the least complete data entry and highest risk for potential data entry errors.

Outcomes

The primary outcome of interest was AKI development as defined by Kidney Disease Improving Global Outcomes (KDIGO) serum creatinine-only criteria within the first 7 days of hospitalization [15]. AKI is defined as a rise in serum creatinine ≥ 0.3 mg/dL or $> 50\%$ from baseline. Urine output is considered part of the KDIGO AKI definition, but the registry data was determined to be insufficient as $> 60\%$ of our cohort was missing urine output values. We also further stratified AKI into stages and receipt of dialysis. Additional outcomes of interest included hospital mortality, hospital and ICU length of stay (LOS), and hospital-related complications.

The registry did not capture baseline creatinine (Cr_b) values (prior to hospitalization). It is therefore standard practice to estimate Cr_b [15–17]. However, the estimation of Cr_b is not standardized across the age spectrum. Using KDIGO guidelines for adults (≥ 18 years), we estimated a Cr_b by assuming an eGFR of 75 ml/min/1.73m² and back calculating a creatinine with the modification of diet in renal disease (MDRD) equation [15]. No standard international guideline for estimating a Cr_b in children exists. We used the validated method of assuming eGFR of 120 ml/min/1.73m² for children 2–17 years and median normative-based eGFR-for-age in children < 2 years and back calculating creatinine with the height-independent equation [18–20]. For patients with CKD, we used the minimum serum creatinine within the first 7 days of hospitalization as Cr_b estimation.

Though these are standard assumptions in AKI research in their respective fields of adult and pediatric nephrology [15–17], there is no standard acceptance of estimating Cr_b in the transition period from adolescents to adulthood. Therefore, given the lack of standardization for estimating Cr_b across the age spectrum, we conducted two sensitivity analyses: [1] using the full age spectrum (FAS) equation for both adults and children that does not

assume a fixed eGFR by age but instead changes across the age spectrum to overcome this limitation [21] and [2] using the minimum serum creatinine as an assumed Cr_b for all patients. The FAS equation is limited as it has only been validated in Caucasian populations. The assumption of minimum creatinine as a baseline is limited as it assumes all patients return to their baseline within 7 days of hospitalization. In addition, we conducted a sensitivity analysis where race was removed from the MDRD calculation for adults [22].

Exposure

Primary exposure of interest was age; it was entered as years and months (children < 5 years), years (participants 5–90 years), and limited to '>90' for those > 90 years of age for privacy. For analysis, those > 90 were classified as 95 years. Age was evaluated as a continuous variable by years and categorical variable by 5-year and 20-year age increments to explore potential non-linear associations.

Additional variables

As this was an exploratory analysis, we included a variety of additional demographic, pre-hospital, and hospital-related variables from the registry. Sex and race/ethnicity were categorical. The registry de-identified center location except whether the center was in the United States or elsewhere. CDC classifications were used for weight categorization (underweight, normal weight, overweight, obese, severely obese) using BMI data for adults ≥ 18 years, BMI percentiles for children 2–17 years, and weight-for-height percentiles for children < 2 years [23]. CDC does not provide pediatric classification for severely obese, so those are grouped with obese for those < 18 years. SARS-CoV2 testing was determined by local centers. Other clinical data captured included comorbidities and recent pre-hospital medications as well as inpatient medications within the first 7 days. Comorbidities, including CKD, were determined by medical chart review by local investigators.

Illness severity was categorized by variables that span the age spectrum. Severe illness was defined as a composite of received invasive mechanical ventilation, vasopressor(s) and/or inotrope(s), and/or extracorporeal membrane oxygenation (ECMO). Moderate illness was defined by ICU admission without any organ support therapies listed above. Mild illness was defined as hospitalization but without an ICU admission nor organ support therapies as listed above. As some of these therapies may be clustered within centers, we accounted for this potential in our analyses described below. More traditional markers of illness severity were captured but do not translate across pediatric and adult patients so are not the primary marker assessed in this analysis (e.g.,

sequential organ failure assessment (SOFA) scores for adults and pediatric risk of mortality (PRISM) scores for children).

Statistical analyses

Descriptive statistics compared demographic, pre-hospital and inpatient clinical characteristics within the first 7 days of hospitalization among those with and without AKI. Wilcoxon rank sum tests and chi-square tests were used for continuous and categorical variables, respectively. Given the large sample size which leads to highly significant p -values, Cohen's effect size estimates were calculated for continuous variables to better express the magnitude of differences (small effect 0.1–0.3, medium effect 0.3–0.6, large effect > 0.6). Univariate risk differences (RD), odds ratios (OR), and 95% confidence intervals (CIs) were calculated for hospital mortality by AKI stage. To account for common clinical practices, clustering within centers was used via generalized estimating equations (GEE) with logistic regression models to determine if age is an independent risk factor for the development of AKI in SARS-CoV2-related hospitalizations, with adjustments for the potential confounding of sex, hypertension, diabetes mellitus, cancer, CKD, race/ethnicity, and severity of illness as defined above. Determination for potential confounders to include in models were determined by a priori clinical knowledge and directed acyclic graphs. Significance was set at an alpha-level of 0.05. Sensitivity analyses were conducted using different equations for estimating a Cr_b and stratifications by comorbidities and whether center was U.S.-based. All analyses were conducted in SAS, version 9.4 (SAS Institute, Inc., Cary, North Carolina).

Results

Demographics

6874 patients from 142 centers met inclusion criteria (Fig. 1). 28% of participants were from non-U.S. centers (Table 1). A total of 39.6% ($n=2719$) developed AKI within the first 7 days of hospitalization; this was significantly higher among patients in ICUs (1926/4075, 47.3%) compared to non-ICUs (793/2799, 28.3%), p -value < 0.0001. Almost 60% of the cohort were admitted to the ICU ($n=4075$). The median age was 60 years (range 0–95 years) and 9.0% ($n=621$) were < 20 years (Table 1). Those with AKI were more likely to be older (median age 65 years) than those without AKI (median age 55 years), p -value < 0.0001 and effect size 0.45, and more likely to have comorbidities (median 3 versus 1 in those without AKI), p -value < 0.0001 and effect size 0.37. Among those < 20 years, 28% (171/621) developed AKI. Differences in AKI risk based on race/ethnicity

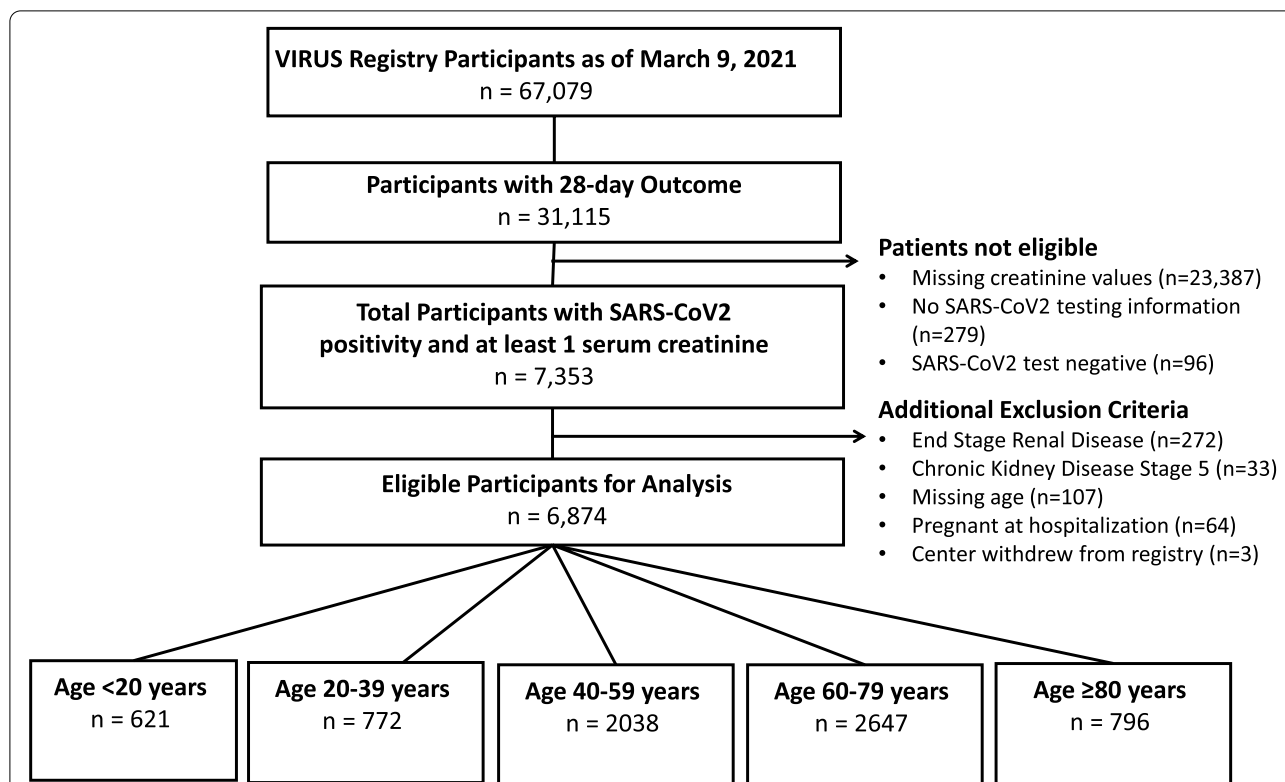


Fig. 1 Participant Inclusion Flow Diagram by STROBE Reporting Guidelines

(p -value<0.0001) were noted. Supplementary Table 1 includes hospital-related associations with AKI.

Comparing patients excluded to those included revealed no significant difference by age, sex, or location of center (i.e., U.S.-based). However, those excluded were more likely to have no comorbidities (26%) compared to those included (20%), and only 31% of the excluded group were admitted to the ICU (compared to 59% in this analysis). As expected, those missing creatinine values were often missing other key variables; BMI data missing for 50% of excluded patients compared to 24% of patients in this analysis.

Hospital complications

Among participants with AKI ($n=2719$), 64% had Stage 1, 14% Stage 2, 19% Stage 3 without dialysis, and 4% Stage 3 with dialysis (Table 2). Of the patients requiring dialysis, the median duration was 5 days (IQR 2.4–12.4) ranging from 0.2–31.8 days (duration missing for 25/104 patients). Only 7% ($n=7$) of those who received dialysis in the first week were from non-U.S. centers. Across AKI stages, there was a significant increase in hospital and ICU LOS (effect sizes 0.48 and 0.38, respectively), with the greatest increase being among those receiving dialysis; hospital LOS median 31 days (IQR 22–48)

for those on dialysis compared to median 6 days (IQR 4–11) for those with no AKI (p -values all <0.0001). Significant differences across AKI stages were also seen for intubation, new home oxygen requirement on discharge, vasopressor(s)/inotrope(s) use, development of thromboses, and inpatient mortality. The absolute risk of hospital mortality increased significantly (p -values<0.0001) for each AKI stage compared to no AKI. Overall, the OR of hospital mortality in those with AKI compared to those without AKI was 4.0 (95% CI 3.5–4.5). These associations did not change significantly when alternative Cr_b estimators were used.

Association of age with AKI risk

Figure 2 depicts a bimodal distribution of AKI risk by age with those of young adolescence (10–15 years) having a higher risk than both very young children (<5 years) and older adolescents/young adults (15–35 years), while those over age 65 years also have a high risk of AKI. Even after adjusting for potential confounders (sex, pre-existing hypertension, diabetes mellitus, cancer, CKD, race/ethnicity, and severity of illness) there remains increased risk of AKI in a bimodal distribution (odds ratio inset in Fig. 2). This pattern of AKI distribution did not change when using alternative Cr_b estimators (Supplementary

Table 1 Demographics of Participants in VIRUS Registry by AKI status

	Total 6874	No AKI 4155 (60.5)	AKI 2719 (39.6)
Age, years, median (IQR)	60 (44–71)	55 (39–68)	65 (53–75)
Age Categories			
< 20 years	621 (9)	450 (11)	171 (6)
20 to < 40 years	772 (11)	615 (15)	157 (6)
40 to < 60 years	2038 (30)	1359 (33)	679 (25)
60 to < 80 years	2647 (39)	1375 (33)	1272 (47)
≥ 80 years	796 (12)	356 (9)	440 (16)
BMI category ^a			
Underweight	137 (2)	78 (2)	59 (2)
Normal	1270 (19)	832 (20)	438 (16)
Overweight	1620 (24)	965 (23)	655 (24)
Obesity	1666 (24)	921 (22)	745 (27)
Severe Obesity	552 (8)	302 (7)	250 (9)
Unknown	1629 (24)	1057 (25)	572 (21)
Sex (male) ^b	3998 (58)	2327 (56)	1671 (62)
Race/Ethnicity ^b			
White, non-Hispanic	2189 (32)	1273 (31)	916 (34)
White, Hispanic	523 (8)	335 (8)	188 (7)
Black, non-Hispanic	1353 (20)	700 (17)	653 (24)
Black, Hispanic	50 (0.7)	37 (0.9)	13 (0.5)
Asian American	95 (1)	53 (1)	42 (2)
South Asian	1027 (15)	842 (20)	185 (7)
East Asian	36 (0.5)	20 (0.5)	16 (0.6)
West Asian	106 (2)	61 (2)	45 (2)
Other/mixed	845 (12)	511 (12)	334 (12)
White, ethnicity not specified	402 (6)	184 (4)	218 (8)
Black, ethnicity not specified	76 (1)	36 (0.9)	40 (2)
Location of Center			
United States	4984 (73)	2872 (69)	2112 (78)
Non-United States	1890 (28)	1283 (31)	607 (22)
Number of Comorbidities, median (IQR)	2 (1, 4)	2 (1, 4)	3 (1, 5)
Healthy (no comorbidities)	1356 (20)	1020 (25)	336 (12)
Comorbidities ^c			
Hypertension	3404 (50)	1722 (41)	1682 (62)
Diabetes	2279 (33)	1169 (28)	1110 (41)
Heart Disease	1577 (23)	732 (18)	845 (31)
Chronic Kidney Disease	754 (11)	339 (8)	415 (15)
Asthma	757 (11)	478 (12)	279 (10)
Chronic lung disease, not asthma	1395 (20)	770 (19)	625 (23)
Stroke/ Neurological disorder	818 (12)	447 (11)	371 (14)
Cancer	904 (13)	497 (12)	407 (15)
Pre-Hospital Medications			
ACE-I/ARBs	1497 (22)	756 (18)	741 (27)
Diuretics	179 (3)	77 (2)	102 (4)
NSAIDs	610 (9)	377 (9)	233 (9)
Aspirin	1127 (16)	554 (13)	573 (21)
Severity of Disease ^d			
Mild disease	2710 (39)	1950 (47)	760 (28)

Table 1 (continued)

	Total 6874	No AKI 4155 (60.5)	AKI 2719 (39.6)
Moderate disease	2064 (30)	1389 (33)	675 (25)
Severe disease	2100 (31)	816 (20)	1284 (47)
Ever admitted to ICU (yes)	4075 (59)	2149 (52)	1926 (71)
SARS-CoV2 Testing			
PCR+	6409 (93)	3858 (93)	2551 (94)
Antibody+	98 (1)	45 (1)	53 (2)
PCR and antibody+	367 (5)	252 (6)	115 (4)

Data presented as number (column percentile), except where specified. ACE-I = angiotensin-converting enzyme-inhibitors; AKI Acute kidney injury, ARB Angiotensin receptor blockers, BMI Body mass index, ECMO Extracorporeal membrane oxygenation, ICU Intensive care unit, IQR Interquartile range, NSAID Non-steroidal anti-inflammatory drugs, PCR Polymerase chain reaction, VIRUS Viral Infection and Respiratory Illness Universal Study

^a BMI Category defined by CDC. Weight-for-height percentiles used for those < 2 years of age, BMI percentiles used for those 2–17 years of age and categorized as underweight for < 5%, normal for 5–85%, overweight for 85–95%, obesity for > 95%. BMI categories for those ≥ 18 years of age defined as underweight < BMI 18.5, normal BMI 18.5–< 25, overweight BMI 25–< 30, obesity BMI 30–< 40, and severe obesity BMI ≥ 40

^b Missing data: Sex missing for 1 participant. Race/ethnicity data missing for 172 participants

^c Multiple comorbidities allowed. Most common ones presented. Heart disease defined as heart failure, coronary artery disease, arrhythmias, valvular disease

^d Severity of disease is defined as: severe disease is a composite of the use of invasive organ support therapy (ventilation, use of vasopressor(s) and/or inotrope(s), and/or use of ECMO); moderate disease is defined as patient admitted to an ICU but did not have any of the invasive organ support therapies as defined for severe disease; and mild disease is defined as neither an ICU admission nor invasive organ support therapies for severe disease

Table 2 Hospital Complications by AKI Stages for Patients Admitted with SARS-CoV2 Infection

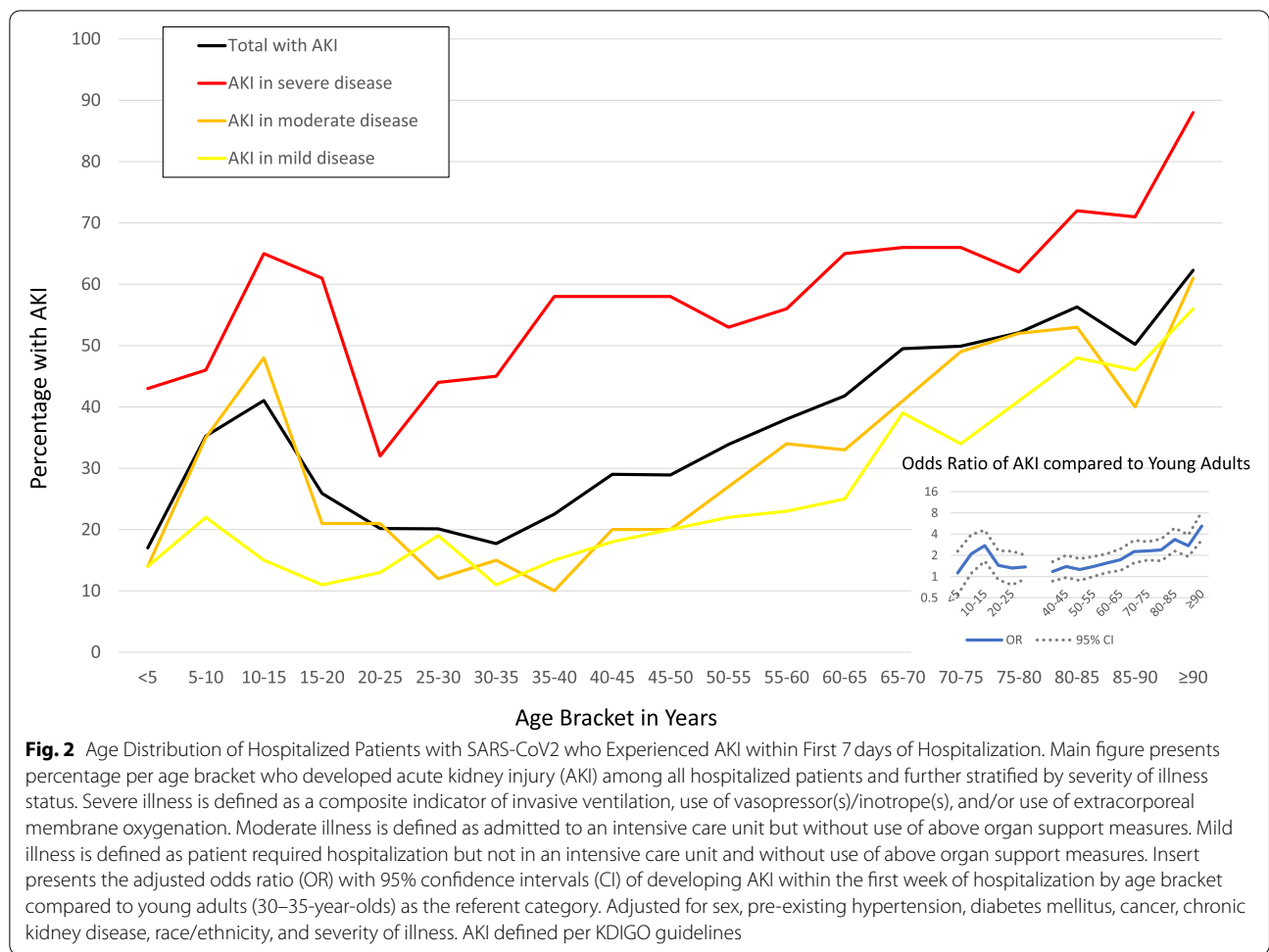
	Total 6874	No AKI 4138 (60.2)	AKI-1 1733 (25.2)	AKI-2 382 (5.6)	AKI-3 (no RRT) 517 (7.5)	AKI-RRT 104 (1.5)
Age Categories						
< 20 years	621 (9)	450 (11)	103 (6)	23 (6)	44 (9)	1 (1)
20 to < 40 years	772 (11)	614 (15)	116 (7)	10 (3)	25 (5)	7 (7)
40 to < 60 years	2038 (30)	1351 (33)	467 (27)	73 (19)	110 (21)	37 (36)
60 to < 80 years	2647 (39)	1369 (33)	773 (45)	191 (50)	259 (50)	55 (53)
≥ 80 years	796 (12)	354 (9)	274 (16)	85 (22)	79 (15)	4 (4)
Admitted to ICU						
Yes	4075 (59)	2136 (52)	1116 (64)	282 (74)	437 (85)	104 (100)
No ^a	2799 (41)	2002 (48)	617 (36)	100 (26)	80 (16)	0 (0)
Hospitalization length of stay (days), median (IQR) ^b	7 (4, 13)	6 (4, 11)	9 (5, 17)	11 (6, 22)	13 (7, 23)	31 (22, 48)
ICU length of stay (days), median (IQR) ^b	5 (2, 11)	4 (2, 9)	6 (2, 13)	8 (2, 18)	6.5 (2.5, 16)	22 (11, 38)
Intubation	1899 (28)	720 (17.4)	596 (34)	185 (48)	298 (58)	100 (96)
Discharged on Oxygen	594 (9)	334 (8)	186 (11)	28 (7)	35 (7)	10 (10)
Vasopressors/ Inotropes	1203 (18)	380 (9)	374 (22)	134 (35)	222 (43)	93 (89)
ECMO	78 (1)	24 (0.6)	32 (2)	10 (3)	10 (2)	2 (2)
Thromboses ^c	337 (5)	140 (3)	112 (7)	22 (6)	40 (8)	23 (22)
Mortality	1314 (19.1)	434 (10.5)	399 (23.0)	157 (41.1)	255 (49.3)	69 (66.4)
RD of Mortality (95% CI)		Reference	12.5% (10.3–14.7)	30.6% (25.6–35.6)	38.8% (34.4–43.2)	55.9% (46.7–65.0)
OR of Mortality (95% CI)		Reference	2.6 (2.2–3.0)	6.0 (4.7–7.5)	8.3 (6.8–10.1)	16.8 (11.1–25.6)

Data presented as number (percentiles), except where specified. AKI Acute kidney injury, AKI-1 AKI stage 1, AKI-2 AKI stage 2, AKI-3 AKI stage 3, CI Confidence intervals, ECMO Extracorporeal membrane oxygenation, ICU Intensive care unit, OR Odds ratio, RRT Renal replacement therapy

^a Of those never admitted to the ICU, $n = 139$ died (5.0%) and $n = 30$ (1.1%) discharged to hospice care

^b Length of stay only among survivors ($n = 5560$). Hospital length of stay missing for 91 patients. Intensive care unit length of stay among only those who were ever admitted to ICU and survived ($n = 2900$). ICU length of stay missing for 81 patients

^c Defined by pre-selected categories of stroke, cerebrovascular accident, deep vein thromboses, and free text entry of the same plus thrombosis, clot, and pulmonary embolism



Figs. 1, 2, 3 and 4), including the full-age spectrum equation. The pattern of AKI distribution held when evaluating those with no comorbidities versus those with comorbidities (Fig. 3) and again when we evaluated only those in the United States (Supplementary Fig. 5). Table 3 depicts a snapshot of representative age ranges and their adjusted OR of developing AKI in these different scenarios, i.e., by different Cr_b estimators and in a population with no pre-existing comorbidities. The data consistently shows an almost 2.5-fold increased odds of developing SARS-CoV2-related AKI for 10–15-year-olds and for 70–75-year-olds when compared to young adults (30–35 years old).

Discussion

In a large and diverse cohort evaluating AKI in COVID-19, we found a high incidence of AKI (39.6%) and that it varies across the age spectrum with a bimodal distribution. Given our cohort’s wide age span, we demonstrate a more nuanced view of SARS-CoV2-related AKI than previous evaluations. In every context of our evaluations,

there was consistently a bimodal age distribution of AKI risk with the older population and early adolescent (10–15years) population at higher risk compared to the young adult populations. This is an interesting phenomenon as to date there are only descriptions of a linear relationship between age and COVID-19 severity and its complications [24, 25]. Other known risk factors for AKI were seen in this cohort, such as sex, pre-existing comorbidities (i.e., hypertension, diabetes mellitus, cancer), and race/ethnicity. However, even after controlling for these potential confounders, there remained an association producing a bimodal age distribution in AKI risk; a 10–15-year-old had a similar odds of AKI as a 70–75-year-old (compared to 30–35-year-olds). The bimodal distribution also persisted after controlling for severity of illness and within-center correlations, which suggests something additional is contributing to the AKI risk. This contradicts an early study on SARS-CoV2-related AKI that found illness severity to be the key risk factor for SARS-CoV2-related AKI, but it was a small study (n=223) with results from the early waves

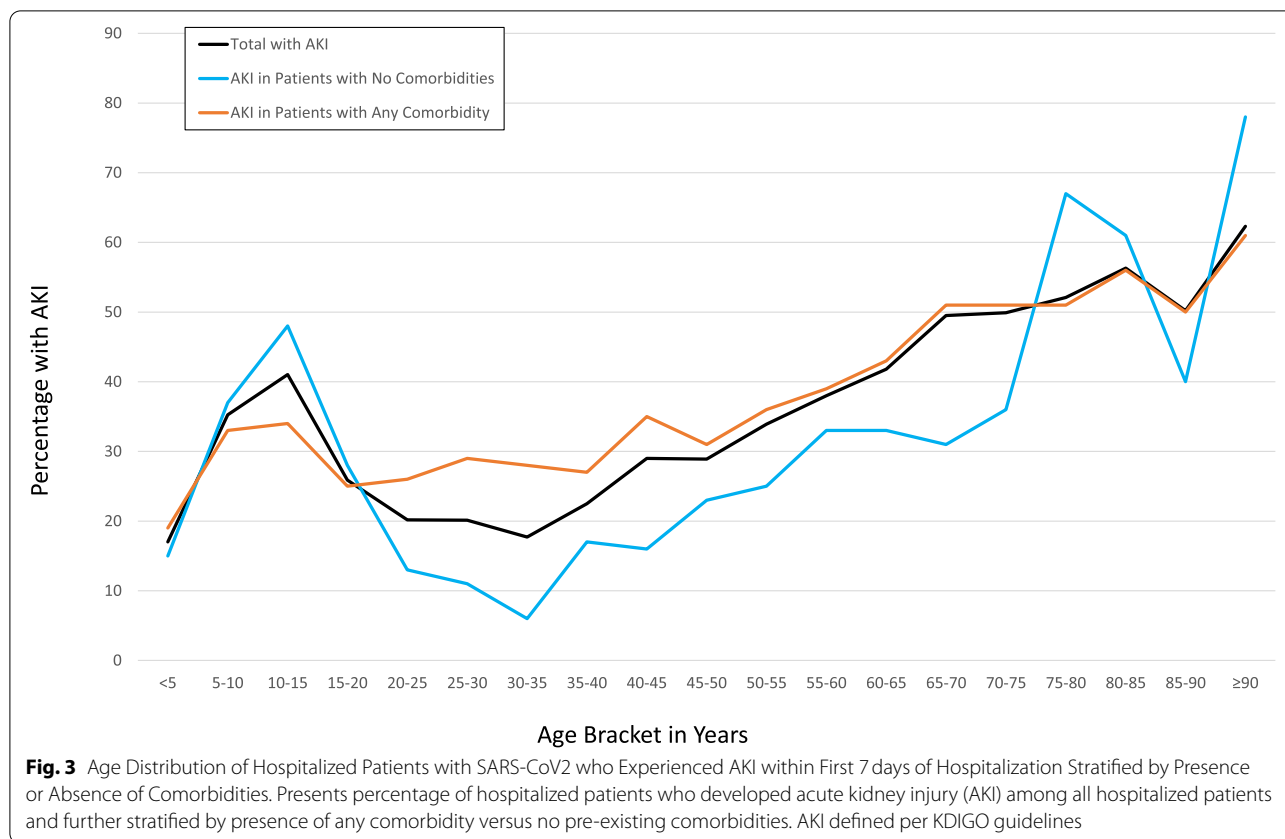


Table 3 Adjusted Odds Ratios of Developing AKI by Different Definitions/Populations

Age Bracket	Original	Full-Age Spectrum	Modified MDRD	No Pre-Existing Comorbidities
10–15-year-olds	2.74 (1.66–4.56)*	2.49 (1.47–4.22)**	2.66 (1.60–4.41)**	5.35 (2.42–11.81)*
40–45-year-olds	1.39 (0.97–2.00)	1.34 (1.00–1.80)***	1.48 (1.03–2.11)***	1.24 (0.65–2.37)
70–75-year-olds	2.31 (1.71–3.12)*	2.79 (2.09–3.94)*	2.48 (1.87–3.29)*	2.34 (1.13–4.84)***

Table presents snapshot of odds ratios (95% confidence intervals) for developing acute kidney injury (AKI) compared to 30–35-year-olds. Odds ratios adjusted for sex, race/ethnicity, hypertension, diabetes mellitus, cancer, chronic kidney disease, and severity of illness. Original column defines AKI per KDIGO guidelines when making assumptions about estimating a baseline creatinine. Full-age spectrum column defines AKI per KDIGO guidelines but assumes a more gradual change in eGFR across the age spectrum and uses the previously validated full age spectrum equation to estimate a baseline creatinine. Modified MDRD column defines AKI per KDIGO guidelines when making assumptions about estimating a baseline creatinine, but for adult patients does not include race as a variable in the MDRD equation. The final column only includes hospitalized patients with no pre-existing comorbidities, as such its adjustment model is limited to sex, race/ethnicity, and severity of illness

* $p < 0.0001$

** $p < 0.001$

*** $p \leq 0.05$

(March–June 2020), and excluded children [26]. Interestingly this bimodal distribution differs from previous non-SARS-CoV2 AKI literature which suggests a U-shaped distribution (peaks in infancy and older adults) [27–29].

The differences in AKI risks across the age spectrum found here were not explained by different Cr_b estimators. KDIGO is a standard guideline for defining AKI, yet it lacks a standard method for estimating a Cr_b in

children when one is not known. We therefore evaluated variety of Cr_b estimators in pediatric and adult populations. Yet, a bimodal distribution of AKI risk by age remained even with several sensitivity analyses, including a Cr_b estimator (FAS) validated across the age spectrum of 2–90 years. The FAS equation assumes a slow transitional change in eGFR from childhood into adulthood [18–20]. In addition, the bimodal age distribution

of SARS-CoV2-related AKI development persisted when evaluating only hospitalized patients with no pre-existing comorbidities or evaluating only U.S.-based centers, suggesting that comorbidity differences nor center or country specifics do not explain the bimodal pattern.

The persistence of the bimodal pattern by age, despite multiple iterative analyses, suggests there may be something unique about SARS-CoV2 and its relationship with AKI. One could hypothesize that the propensity of the SARS-CoV2 virus to attack the endothelium could also contribute to the differences seen in the older population and their risk with AKI beyond illness severity [30], though it does not explain the higher risk in early adolescence. There may be a hormonal influence in early adolescence that makes the endothelium more prone to injury compared to younger adults, but this would not fully explain the higher AKI rates in the elderly. We postulate that the bimodal AKI distribution could perhaps be a combination of SARS-CoV2-related vasculopathy and hormonal influences. There may also be yet unknown biological mechanisms that are contributing to this bimodal pattern. For example, we could not account for the different strains or clinical spectrum of SARS-CoV2 presentations which may be an important driver of the bimodal age pattern. A recent report of 2600 hospitalized adults with SARS-CoV2 infection found similarly that high AKI rates are not fully explained by known risk factors and need further exploration [31]. Fully understanding the bimodal age distribution of SARS-CoV2-related AKI risk is even more important now as countries are seeing a shift in age distribution of SARS-CoV2 infections as children are not yet eligible worldwide for vaccinations and new variants may disproportionately affect younger populations. Further in-depth epidemiological studies and animal models may be needed to understand the biological mechanisms underpinning the age distribution in SARS-CoV2-related AKI.

Similar to other studies [7–9, 32], this cohort demonstrates a high rate of AKI in COVID-19 patients; among ICU patients the AKI rate was 47.3% and in non-critically ill patients was 28.3%. Only a few studies report SARS-CoV2-related AKI rates outside of ICUs [33], and our results suggest a high-percentage of non-critically ill patients are at risk.

Other literature has found that SARS-CoV2-related AKI has an increased risk of mortality [4, 8, 9, 34]. In addition to this, we report a strong relationship with mortality and other hospital complications that is proportional to AKI's severity and seen even in non-critically ill patients and those with mild increases in serum creatinine (≥ 0.3 mg/dL). Very few reports thus far have explored the complications associated with the varying degrees of AKI severity [2, 10]. This is important as

even the slightest degree of AKI may be associated with long-term morbidity and mortality among those hospitalized with SARS-CoV2. Interestingly, though young adolescents had higher risks of AKI compared to middle adulthood, the rates of dialysis were higher in middle adulthood (20–40 years) compared to children (<20 years). These may be related to center practice differences or the overall small sample of dialysis needs in both of these groups in this cohort ($n=7$ for 20–40 year-olds and $n=1$ for <20 year-olds).

Limitations

The VIRUS registry has been a real-time assessment of the COVID-19 pandemic, so we may have introduced bias by excluding participants missing data. However, the large sample size provides real-time insight to ongoing trends and allows comparisons across the ages. Comparing the cohort of those with and without creatinine values, we found that we likely had some selection bias toward sicker patients; however, 40% of our participants were never in the ICU. A limitation of evaluating AKI across the age spectrum is the lack of standard Cr_b estimators, but our results were similar when using multiple estimators, suggesting there is a true phenomenon of bimodal age distribution in SARS-CoV2-related AKI that deserves further exploration. The registry includes multiple centers and as such risks introducing bias through practice pattern differences between pediatric versus adult centers and regional variations, but we controlled for this in our analyses by accounting for clustering within centers. However, evaluating data from across multiple regions and centers allows a broader view of the epidemiology of SARS-CoV2-related AKI, which is needed to plan for more in-depth case-control or randomized clinical trials evaluating different management and treatment strategies for improved outcomes in SARS-CoV2-related AKI.

Conclusions

Patients hospitalized with SARS-CoV2 have a high risk of AKI, irrespective of illness severity. We demonstrate an interesting phenomenon of a bimodal age distribution of SARS-CoV2-related AKI risk – high in the elderly and early adolescence – that deserves more in-depth exploration as it was not explained by pre-existing comorbidities, illness severity, eGFR equations, or clustering within centers. Our study reiterates other findings that SARS-CoV2-related AKI at any stage increases patients' morbidity and mortality. However, as the pandemic lingers, outbreaks will continue, and while younger children remain unvaccinated, it is even more important to understand if there are biological reasons or other unexplored risk factors behind this bimodal age distribution of AKI

risk that may guide clinical care improvements in the management of SARS-CoV2 infections and/or provide insights into the pathophysiology of this unique virus.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12882-022-02681-2>.

Additional file 1: Supplementary Table 1. Initial Hospital-related Associations with SARS-CoV2-related AKI. These therapies or complications occur within the first 7 days of hospitalization when SARS-CoV2-related AKI is defined. Data presented as number (column percentiles), except where specified. ACE-I = angiotensin-converting enzyme-inhibitors; AKI = acute kidney injury; ARB = angiotensin receptor blockers; IVIG = intravenous immunoglobulin; NSAID = non-steroidal anti-inflammatory drugs; PRISM = Pediatric Risk of Mortality Score; SOFA = Sequential Organ Failure Assessment. ¹Initial PRISM score missing for 497 pediatric patients. Baseline SOFA score missing for 2741 adult patients; maximum SOFA score missing for 2016 adult patients.

Additional file 2: Supplementary Fig. 1. Age Distribution of Hospitalized Patients with SARS-CoV2 who Experienced AKI within First 7 days of Hospitalization-different baseline creatinine estimators. Main figure presents percentage per age bracket who developed acute kidney injury (AKI) among all hospitalized patients. The original AKI definition (blue) assumes a baseline creatinine based on KDIGO guidelines for adults (eGFR 75 ml/min/1.73m² and back calculates using MDRD equation) and common pediatric definitions assuming an eGFR of 120 ml/min/1.73m² and back calculating using height-independent equation, except for patients with CKD when minimum serum creatinine during first 7 days of hospitalization is assumed to be their baseline creatinine value. Orange line assumes that the minimum creatinine during the first 7 days of hospitalization is the baseline creatinine for all participants. Gray line uses the KDIGO guidelines but back calculates the baseline creatinine for all participants using the FAS equation. Yellow line uses the original definition but uses the MDRD equation minus the race variable. Abbreviations: AKI = acute kidney injury, CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate, FAS = full age spectrum, KDIGO = Kidney Disease Improving Global Outcomes, MDRD = modification of diet in renal disease.

Additional file 3: Supplementary Fig. 2. Age Distribution of Hospitalized Patients with SARS-CoV2 who Experienced AKI within First 7 days of Hospitalization-baseline creatinine estimator FAS equation. Main figure presents percentage per age bracket who developed acute kidney injury (AKI) among all hospitalized patients and further stratified by severity of illness status. Severe illness is defined as a composite indicator of invasive ventilation, use of vasopressor(s)/inotrope(s), and/or use of extracorporeal membrane oxygenation. Moderate illness is defined as admitted to an intensive care unit but without use of above organ support measures. Mild illness is defined as patient required hospitalization but not in an intensive care unit and without use of above organ support measures. Insert presents the adjusted odds ratio (OR) with 95% confidence intervals (CI) of developing AKI within the first week by age bracket compared to young adults (30–35-year-olds) as the referent category. Adjusted for sex, race/ethnicity, pre-existing hypertension, diabetes mellitus, cancer, chronic kidney disease, and severity of illness. AKI defined per KDIGO guidelines, but baseline creatinine estimator uses full-age spectrum (FAS) equation for all participants.

Additional file 4: Supplementary Fig. 3. Age Distribution of Hospitalized Patients with SARS-CoV2 who Experienced AKI within First 7 days of Hospitalization-baseline creatinine estimator MDRD equation removing race. Main figure presents percentage per age bracket who developed acute kidney injury (AKI) among all hospitalized patients and further stratified by severity of illness status. Severe illness is defined as a composite indicator of invasive ventilation, use of vasopressor(s)/inotrope(s), and/or use of extracorporeal membrane oxygenation. Moderate illness is defined as admitted to an intensive care unit but without use of above organ support measures. Mild illness is defined as patient required hospitalization

but not in an intensive care unit and without use of above organ support measures. Insert presents the adjusted odds ratio (OR) with 95% confidence intervals (CI) of developing AKI within the first week by age bracket compared to young adults (30–35-year-olds) as the referent category. Adjusted for sex, race/ethnicity, pre-existing hypertension, diabetes mellitus, cancer, chronic kidney disease, and severity of illness. AKI defined per KDIGO guidelines, but baseline creatinine estimator uses modified MDRD equation removing race component for adults (≥ 18 years) and height-independent equation for children (< 18 years).

Additional file 5: Supplementary Fig. 4. Age Distribution of Hospitalized Patients with SARS-CoV2 who Experienced AKI within First 7 days of Hospitalization-baseline creatinine estimator as minimum serum creatinine. Main figure presents percentage per age bracket who developed acute kidney injury (AKI) among all hospitalized patients and further stratified by severity of illness status. Severe illness is defined as a composite indicator of invasive ventilation, use of vasopressor(s)/inotrope(s), and/or use of extracorporeal membrane oxygenation. Moderate illness is defined as admitted to an intensive care unit but without use of above organ support measures. Mild illness is defined as patient required hospitalization but not in an intensive care unit and without use of above organ support measures. Insert presents the adjusted odds ratio (OR) with 95% confidence intervals (CI) of developing AKI within the first week by age bracket compared to young adults (30–35-year-olds) as the referent category. Adjusted for sex, race/ethnicity, pre-existing hypertension, diabetes mellitus, cancer, chronic kidney disease, and severity of illness. AKI defined per KDIGO guidelines, but baseline creatinine estimator uses minimum serum creatinine value within first 7 days of hospitalization for all participants.

Additional file 6: Supplementary Fig. 5. Age Distribution of Hospitalized Patients with SARS-CoV2 who Experienced AKI within First 7 days of Hospitalization Stratified by U.S. versus non-U.S. Hospital. Presents percentage of hospitalized patients who developed acute kidney injury (AKI) among all hospitalized patients and further stratified by hospital center based in the United States versus not in the United States. AKI defined per KDIGO guidelines.

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SCCM Discovery VIRUS Investigators Group.

Jean-Baptiste Mesland¹⁵, Pierre Henin¹⁵, H  l  ne Petre¹⁵, Isabelle Buelens¹⁵, Anne-Catherine Gerard¹⁵, Philippe Clevenbergh¹⁶, Rolando Claire-Del Granado¹⁷, Jose A. Mercado¹⁷, Esdenka Vega-Terrazas¹⁷, Maria F. Iturricha-Caceres¹⁷, Dragana Markotic¹⁸, Ivana Bošnjak¹⁸, Oscar Y Gavidia¹⁹, Felipe Pachon¹⁹, Yeimy A Sanchez¹⁹, Danijel knezovic²⁰, Tanja Kovacevic²¹, Josko Markic²¹, Tatjana Catipovic Ardic²¹, Branka Polic²¹, Ivo Ivi  ²¹, Dominko Carev²¹, Robert Glavinic²¹, Mohamed El Kassas²², Mohamed Badr²², Ahmed Tawheed²², Ahmed Tawheed²², H  nd Yahiya²², Dimitrios Kantas²³, Vasileios Koulouras²³, Sierra-Hoffman²⁴, Fernando Valerio²⁴, Oscar Diaz²⁴, Jose Luis Ramos Coello²⁵, Guillermo Perez²⁵, Ana Karen Vallecillo Lizardo²⁵, Gabina Mar  a Reyes Guillen²⁵, Helin Archaga Soto²⁵, Csaba Kopitko²⁶,   gnes Bencze²⁶, Istv  n M  h  sz²⁶, Zs  fia Gerendai²⁶, Phaneendra Doddaga²⁷, Neethi Chandra²⁷, Girish Vadgaonkar¹⁰, Rekha Ediga¹⁰, Shilpa Basety¹⁰, Shwetha Dammareddy¹⁰, Phani Sreeharsha Kasumalla¹⁰, Umamaheswara Raju²⁸, Janaki Manduva²⁸, Naresh Kolakani²⁸, Shreeja Sripathi²⁸, Sheetal Chaitanya²⁸, Anusha Cherian²⁹, Sreejith Parameswaran²⁹, Magesh Parthiban²⁹, Menu Priya A.²⁹, Chetak Basavaraja³⁰, Madhav Prabhu³¹, Vishal Jakati³¹, Puneet Rijhwani³², Ashish Jain³², Aviral Gupta³², Ram Mohan Jaiswal³², Ambika Tyagi³², Nimish Mathu³², Mradul Kumar Daga³³, Munisha Agarwal³³, Ishan Rohtagi³³, Sridhar Papani³⁴, Mahesh Kamuram³⁴, Kamlesh Kumar Agrawal³⁵, Vijendra Baghel³⁵, Kirti Kumar Patel³⁵, Surapaneni Krishna Mohan⁸, Ekambaram Jyothisree⁸, Mukur Petrolwala³⁶, Bharat Ladva³⁶, Yuki Itagaki³⁷, Akira Kodate³⁷, Reina Suzuki³⁷, Akira Kodate³⁷, Yuki Takahashi³⁷, Koyo Moriki³⁷, Michihito Kyo³⁸, Hidenobu Shigemitsu³⁹, Yuka Mishima³⁹, Nobuyuki Nosaka³⁹, Michio Nagashima³⁹, Abdulrahman Al-Fares⁴⁰, Rene Rodriguez-Gutierrez⁴¹, Jose Gerardo Gonzalez-Gonzalez⁴¹, Alejandro Salcido-Montenegro⁴¹, Adrian Camacho-Ortiz⁴¹, Fatimah Hassan-Hanga⁴², Hadiza Galadanci⁴², Abubakar Shehu Gezawa⁴², Halima M. S. Kabara⁴², Taiwo Gboluwaga Amole⁴², Halima Kabir⁴²,

Dalha Gwarzo Haliru⁴², Abdullahi S Ibrahim⁴², Muhammad Sohaib Asghar⁴³, Mashaal Syed⁴³, Syed Anosh Ali Naqvi⁴³, Sidra Ishaque⁴⁴, Ali Faisal Saleem⁴⁴, Naveed Ur Rehman Siddiqui⁴⁴, Salima SherAli⁴⁴, Yasmin Hashwani⁴⁴, Shafia Ishaque⁴⁴, Igor Borisovich Zabolotskikh⁴⁵, Konstantin Dmitrievich Zytin⁴⁵, Sergey Vasilevich Sinkov⁴⁵, Tatiana Sergeevna Musaeva⁴⁵, Marwa Ridha Amer⁴⁶, Mohammed Abdullah Bawazeer⁴⁶, Talal I. Dahhan⁴⁶, Eiad Kseibi⁴⁶, Abid Shahzad Butt⁴⁶, Syed Moazzum Khurshid⁴⁶, Muath Rabee⁴⁶, Mohammed Abujazar⁴⁶, Roazan Alghunaim⁴⁶, Maal Abualkhai⁴⁶, Abeer Turki AlFirm⁴⁶, Eiad Kseibi⁴⁶, Syed Moazzum Khurshid⁴⁶, Muath Rabee⁴⁶, Mohammed Abujazar⁴⁶, Razan Alghunaim⁴⁶, Razan K Alamoudi⁴⁷, Hassan M. AlSharif⁴⁷, Sarah A. Almazwaghi⁴⁷, Mohammed S Elskran⁴⁷, Mohamed A Aid⁴⁷, Mouaz A Darwich⁴⁷, Omnia M Hagag⁴⁷, Salah A Ali⁴⁷, Alona Rocacorba⁴⁷, Kathrine Supeña⁴⁷, Efen Ray Juane⁴⁷, Jenalyn Medina⁴⁷, Jowany Baduria⁴⁷, Mohammed A Almazayad⁴⁸, Mohammed I Alarifi⁴⁸, Jara M Macarambon⁴⁸, Ahmad Abdullah Bukhari⁴⁸, Hussain A. Albahrani⁴⁸, Kazi N Asfina⁴⁸, Kaltham M Aldossary⁴⁸, Ana Andrijevic⁴⁹, Srdjan Gavrilovic⁴⁹, Vladimir Carapic⁴⁹, Pedja Kovacevic⁵⁰, Predrag D Stevanovic⁵¹, Dejan S Stojakov⁵¹, Duska K Ignjatovic⁵¹, Suzana C Bojic⁵¹, Marina M Bobos⁵¹, Irina B Nenadic⁵¹, Milica S Zacic⁵¹, Marko D Djuric⁵¹, Vladimir R Djukic⁵¹, Santiago Y. Teruel⁵², Belen C. Martin⁵², Santiago Y. Teruel⁵², Varsha P Harpune⁵³, Usman Raheemi⁵³, Kenneth W. Dodd⁵⁴, Nicholas Goodman⁵⁴, Kathleen Hesse⁵⁴, Paige Bird⁵⁴, Chauncey Weinert⁵⁴, Nathan Schoenrade⁵⁴, Abdulrahman Altaher⁵⁴, Esmael Maya⁵⁴, Matthew Aronson⁵⁴, Tyler Cooper⁵⁴, Monica Logan⁵⁴, Brianna Miner⁵⁴, Gisele Papo⁵⁴, Suzanne Barry⁵⁵, Christopher Wolf⁵⁵, Gregory Wu⁵⁵, Erin Carrole⁵⁵, Kathryn Burke⁵⁵, Mustafa Mohammed⁵⁵, Catherine A. St. Hill⁴, Roman R. Melamed⁴, David M. Tierney⁴, Love A. Patel⁴, Vito S. Raj⁴, Barite U. Dawud⁴, Narayana Mazumder⁴, Abbey Sidebottom⁴, Alena M. Guenther⁴, Benjamin D. Krehbiel⁴, Nova J. Schmitz⁴, Stacy L. Jensen⁴, Lynn Sipsy⁴, Anna Schulte⁴, Whitney Wunderlich⁴, Cecely Hoyt⁴, Abhijit A Raval⁵⁶, Andrea Franks⁵⁶, Katherine Irby⁵⁷, Ronald C. Sanders Jr.⁵⁷, Glenda Heffley⁵⁷, Jennifer M. Jarvis⁵⁸, Anmol Kharbanda⁵⁹, Sunil Jhahria⁵⁹, Zachary Fyffe⁵⁹, Stephen Capizzi⁶⁰, Bethany Alicia⁶⁰, Martha Green⁶⁰, Lori Crockarell⁶⁰, Amelia Drennan⁶⁰, Kathleen Dubuque⁶⁰, Tonya Fambrough⁶⁰, Nikole Gasaway⁶⁰, Briana Krantz⁶⁰, Peiman Nebi⁶⁰, Jan Orga⁶⁰, Margaret Serfass⁶⁰, Alina Simion⁶⁰, Kimberly Warren⁶⁰, Cassie Wheeler⁶⁰, CJ Woolman⁶⁰, Amy B. Christie⁷, Dennis W. Ashley⁷, Rajani Adiga⁷, Andrew S. Moyer⁶¹, George M. Verghese⁶¹, Andrea Skolka Newsome⁶², Christy C. Forehand⁶², Rebecca Bruning⁶², Timothy W. Jones⁶², Moldovan Sabov⁶³, Fatema Zaid⁶³, Fiona Tissavirasingham⁶³, Dhatri Malipeddi⁶³, Jarrod M Mosier⁹, Karen Lutrick⁹, Beth Salvaggio Campbell⁹, Cathleen Wilson⁹, Patrick Rivers⁹, Jonathan Brinks⁹, Mokenge Ndiva Mongoh⁹, Boris Gilson⁹, Donna Lee Armaignac⁶⁴, Don Parris⁶⁴, Maria Pilar Zuniga⁶⁴, Ilea Vargas⁶⁴, Viviana Boronat⁶⁴, Anneka Hutton⁶⁴, Navneet Kaur⁶⁴, Prashank Neupane⁶⁴, Nohemi Sadule-Rios⁶⁴, Lourdes M. Rojas⁶⁴, Aashish Neupane⁶⁴, Priscilla Rivera⁶⁴, Carlos Valle Carlos⁶⁴, Gregory Vincent⁶⁴, Christopher M Howard⁶⁵, Cameron McBride⁶⁵, Jocelyn Abraham⁶⁵, Orlando Garner⁶⁵, Katherine Richards⁶⁵, Keegan Collins⁶⁵, Preethi Antony⁶⁵, Sindhu Mathew⁶⁵, Valerie C. Danesh⁶⁶, Gueorgui Dubroca⁶⁶, Amber L. Davis⁶⁶, Marissa J Hammers⁶⁶, ill M. McGahey⁶⁶, Amanda C. Farris⁶⁶, Elisa Priest⁶⁶, Robyn Korsmo⁶⁶, Lorie Fares⁶⁶, Kathy Skiles⁶⁶, Susan M. Shor⁶⁶, Kenya Burns⁶⁶, Corrie A Dowell⁶⁶, Gabriela "Hope" Gonzales⁶⁶, Melody Flores⁶⁶, Lindsay Newman⁶⁶, Debora A Wilk⁶⁶, Jason Ettlinger⁶⁶, Jaccallene Bomar⁶⁶, Himani Darji⁶⁶, Alejandro Arroliga⁶⁶, Alejandro C Arroliga⁶⁶, Corrie A. Dowell⁶⁶, Gabriela Hope Conzales⁶⁶, Melody Flores⁶⁶, Lindsay Newman⁶⁶, Debora A. Wilk⁶⁶, Jason Ettlinger⁶⁶, Himani Darji⁶⁶, Jaccallene Bomar⁶⁶, Paras B. Khandhar⁶⁷, Elizabeth Krings⁶⁷, Valerie M. Banner-Goodspeed⁶, Somnath Bose⁶, Lauren E. Kelly⁶, Melisa Joseph⁶, Marie McGourty⁶, Krystal Capers⁶, Benjamin Hoenig⁶, Maria C. Karamourtopoulos⁶, Anica C. Law⁶, Elias N. Baedorf Kassis⁶, Allan J. Walker¹¹, Sushrut S. Waikar¹¹, Michael A. Garcia¹¹, Mia Colona¹¹, Zoe Kibbelaar¹¹, Michael Leong¹¹, Daniel Wallman¹¹, Kanupriya Soni¹¹, Jennifer Maccaroni¹¹, Joshua Gilman¹¹, Ycar Devis¹¹, Joseph Chung¹¹, Munizay Paracha¹¹, David N. Lumelsky¹¹, Madeline DiLorenzo¹¹, Najla Abdurrahman¹¹, Shelsey Johnson¹¹, Maj Andrew M. Hersh⁶⁸, CPT Stephanie L Wachs⁶⁸, Brittany S. Swigger⁶⁸, CPT Stephanie L Wachs⁶⁸, Capt Lauren A. Sattler⁶⁸, Capt Michael N. Moulton⁶⁸, Aaron S. Miller⁶⁹, Edwin L. Anderson⁶⁹, Rosemary Nagy⁶⁹, Ravali R. Inja⁶⁹, Pooja A. Nawathe⁷⁰, Isabel Pedraza⁷⁰, Jennifer Tsing⁷⁰, Karen Carr⁷⁰, Anila Chaudhary⁷⁰, Kathleen Guglielmino⁷⁰, Raghavendra Tirupathi⁷¹, Alymer Tang⁷¹, Arshad Safi⁷¹, Cindy Green⁷¹, Jackie Newell⁷¹, Katja M. Gist¹⁴, Imran A Sayed¹⁴, John Brinton¹⁴, Larisa Strom¹⁴, Kathleen Chiotos⁷², Allison M. Blatz⁷², Giyoung Lee⁷², Ryan H. Burnett⁷², Guy I. Sydney⁷², Danielle M. Traynor⁷², Karissa Nauert⁷³, Annika Gonzalez⁷³, Mariel Bagley⁷³, Anita Santpurkar⁷³, Sreekanth Cheruku⁷⁴, Farzin Ahmed⁷⁴, Christopher Deonarine⁷⁴, Ashley Jones⁷⁴, Mohammad-Ali Shaikh⁷⁴, David Preston⁷⁴, Jeanette Chin⁷⁴, Vidula Vachharajani⁷⁵, Abhijit Duggal⁷⁵, Prabalini Rajendram⁷⁵, Omar Mehkri⁷⁵, Siddharth Dugar⁷⁵, Michelle Biehl⁷⁵, Gretchen Sacha⁷⁵, Stuart Houltham⁷⁵, Alexander King⁷⁵, Kiran Ashok⁷⁵, Bryan Poynter⁷⁵, Mary Beukemann⁷⁵, Richard Rice⁷⁵, Susan Gole⁷⁵, Valerie Shaner⁷⁵, Adarsh Conjeevaram⁷⁵, Michelle Ferrari⁷⁵, Narendrakumar Alappan⁷⁵, Steven Minear⁷⁵, Jaime Hernandez-Montfort⁷⁵, Syed Sohaib Nasim⁷⁵, Ravi Sunderkrishnan⁷⁵, Debasis Sahoo⁷⁵, Steven K. Daugherty⁷⁶, Sam Atkinson⁷⁶, Kelly Shrimpton⁷⁶, Sidney Ontai⁷⁷, Brian Contreras⁷⁷, Uzoma Obinwanko⁷⁷, Nneka Amamasi⁷⁷, Amir Sharafi⁷⁷, Sarah Lee⁷⁸, Zahia Esber⁷⁸, Chetna Jinjvadia⁷⁸, Christine Waller⁷⁹, Kara Kallies⁷⁹, Jonean Thorsen⁷⁹, Alec Fitzsimmons⁷⁹, Haley Olsen⁷⁹, Heda R. Dapul⁸⁰, Sourabh Verma⁸⁰, Alan Salas⁸⁰, Ariel Daube⁸⁰, Michelle Korn⁸⁰, Michelle Ramirez⁸⁰, Logi Rajagopalan⁸⁰, Laura Santos⁸⁰, Héctor Collazo Santiago⁸¹, Ricardo Alan Hernandez⁸¹, Orma Smalls⁸², Atul Malhotra⁸³, Abdurrahman Husain⁸³, Qais Zawaydeh⁸³, J.H. Steuernagle⁸⁴, Steven Q. Davis⁸⁵, Valentina Jovic⁸⁵, Valentina Jovic⁸⁵, Max Masuda⁸⁵, Amanda Hayes⁸⁵, Kristen Lee Gossett⁸⁶, Jennifer Nason⁸⁶, Sarah Morris⁸⁶, Sarah Deans⁸⁶, Stephanie Houston⁸⁶, Michael Smith⁸⁷, William Snow⁸⁷, Riley Liptak⁸⁷, Hannah Durant⁸⁷, Valerie Pendleton⁸⁷, Alay Nanavati⁸⁷, Risa Mrozowski⁸⁷, Namrata Nag⁸⁸, Jeff Brauer⁸⁸, Ashwin Dharmadhikari⁸⁸, Sahib Singh⁸⁸, Franco Laghi⁸⁸, Ghania Naem⁸⁸, Andrew Wang⁸⁸, Kevin Bliden⁸⁸, Amit Routh⁸⁸, Jaime Barnes⁸⁸, Martin Gesheff⁸⁸, Asha Thomas⁸⁸, Melbin Thomas⁸⁸, Alicia R. Liendo⁸⁸, Jovan Milosavljevic⁸⁸, Kenan Abbasi⁸⁸, Nicholas B. Burley⁸⁸, Nicole Rapista⁸⁸, Samuel Amankwah⁸⁸, Sanjay K Poudel⁸⁸, Saroj Tamilsina⁸⁸, Sauradeep Sarkar⁸⁸, Oluwasayo Akinyosoye⁸⁸, Shashi K. Yamanchilli⁸⁸, Sheena Moorthy⁸⁸, Sonia Sugumar⁸⁸, Jonathan Ford⁸⁸, Martin C. Taylor⁸⁸, Charlotte Dunderdale⁸⁸, Alyssa Henshaw⁸⁸, Mary K. Brunk⁸⁸, Jessica Hagy⁸⁸, Shehryar Masood⁸⁸, Sushrutha Sridhar⁸⁸, Manoj K Gupta⁸⁹, Francene E. Oulds⁸⁹, Akshay Nandavar⁸⁹, Yuk Ming Liu⁹⁰, Sarah Zavala⁹⁰, Sarah Zavala⁹⁰, Esther Shim⁹⁰, Andy Y. Wen⁹¹, Allie DaCar⁹¹, Ronald A. Reilkoff⁹², Julia A. Heneghan⁹², Sarah Eichen⁹², Lexie Goertzen⁹², Scott Rajala⁹², Ghislaine Feussom⁹², Ben Tang⁹², Christine C. Junia⁹³, Robert Lichtenberg⁹³, Hasrat Sidhu⁹³, Diana Espinoza⁹³, Sheldon Rodrigues⁹³, Maria Jose Zabala⁹³, Daniela Goyes⁹³, Ammu Susheela⁹³, Buddhi Hatharalyadda⁹³, Naveen Rameshkumar⁹³, Amulya Kasireddy⁹³, Genessis Maldonado⁹³, Lisseth Beltran⁹³, Akshata Chaugule⁹³, Hassan Khan⁹³, Namrata Patil⁹⁴, Ruhi Patil⁹⁴, Rodrigo Cartin-Ceba⁹⁵, Ayana Sen⁹⁵, Amanda Palacios⁹⁵, Giyuth M. Mahdi⁹⁵, Rahul Kashyap¹², Ongjen Gajic¹², Vikas Bansal¹², Aysun Tekin¹², Amos Lal¹², John C. O'Horo¹², Neha N. Deo¹², Mayank Sharma¹², Shahraz Qamar¹², Juan Pablo Domecq¹², Romil Singh¹², Alex Niven¹², Marija Bogojevic¹², Abigail La Nou⁹⁶, Barbara Mullen⁹⁶, Devang Sanghavi², Pablo Moreno Franco², Pramod Guru², Karthik Gnanapandithan², Hollie Saunders², Zachary Fleissner², Juan Garcia², Alejandra Yu Lee Mateus², Siva Naga Yarrarapu², Nirmaljit Kaur², Abhisekh Giri², Syed Anjum Khan⁹⁷, Juan Pablo Domecq⁹⁷, Nitesh Kumar Jain⁹⁷, Thoyaja Koritala⁹⁷, Alexander Bastidas⁹⁸, Gabriela Orellana⁹⁸, Adriana Briceño Bierwirth⁹⁸, Eliana Milazzo⁹⁸, Juan Guillermo Sierra⁹⁸, Thao Dang⁹⁸, Rahul S Nanchal⁹⁹, Paul A Bergi⁹⁹, Jennifer L Peterson⁹⁹, Travis Yamanaka¹⁰⁰, Nicholas A. Barreras¹⁰⁰, Michael Markos¹⁰⁰, Anita Fareeduddin¹⁰⁰, Rohan Mehta¹⁰⁰, Chakradhar Venkata¹⁰¹, Miriam Engemann¹⁰¹, Annamarie Mantese¹⁰¹, Yasir Tarabichi⁵, Adam Perzynski⁵, Christine Wang⁵, Dhatri Kotekal⁵, Adriana C Briceño Bierwirth¹⁰², Gabriela M Orellana¹⁰², Gerardo Catalasan¹⁰², Shohana Ahmed¹⁰², Carlos F Matute¹⁰², Ahmad Hamdan¹⁰², Ivania Salinas¹⁰², Genesis Del Nogal¹⁰², Angel Tejada¹⁰², Anna Eschler¹⁰³, Mary Hejna¹⁰³, Emily Lewandowski¹⁰³, Kristen Kusmierski¹⁰³, Clare Martin¹⁰³, Nasar A Siddiqi¹⁰⁴, Lesly Jurado¹⁰⁴, Lindsey Tincher¹⁰⁴, Carolyn Brown¹⁰⁴, Prithvi Sendi¹⁰⁵, Meghana Nadiger¹⁰⁵, Balagangadhar Totapally¹⁰⁵, Bhagat S. Aulakh¹⁰⁶, Sandeep Tripathi¹⁰⁶, Jennifer A. Bandy¹⁰⁶, Lisa M. Kreps¹⁰⁶, Dawn R. Bollinger¹⁰⁶, Jennifer A. Bandy¹⁰⁶, Roger Scott Stienecker¹⁰⁷, Andre G. Melendez¹⁰⁷, Tressa A. Brunner¹⁰⁷, Sue M Budzon¹⁰⁷, Jessica L. Heffernan¹⁰⁷, Janelle M. Souder¹⁰⁷, Tracy L. Miller¹⁰⁷, Andrea G. Maisonneuve¹⁰⁷, Roberta E. Redfern¹⁰⁸, Jessica Shoemaker¹⁰⁸, Jennifer Micham¹⁰⁸, Lynn Kenney¹⁰⁸, Gabriel Naimy¹⁰⁸, Holly Balcer¹⁰⁹, Sara Utley¹⁰⁹, Dawn Bouknight¹⁰⁹, Radha Patel¹⁰⁹, Lama Alfehaid¹⁰⁹, Majdi Hamarshi¹¹⁰, Jeannette Ploetz¹¹⁰, Nick Bennett¹¹⁰, Kyle Klindworth¹¹⁰, Moustafa Younis¹¹⁰, Adham Mohamed¹¹⁰, Antonia L. Vilella¹¹¹, Sara B. Kutner¹¹¹, Kacie Clark¹¹¹, Danielle Moore¹¹¹, Shina Menon³, John K McGuire³, Deana Rich³, Howard A. Zaren¹¹², Stephanie J. Smith¹¹², Grant C. Lewis¹¹², Lauren Seames¹¹², Cheryl Farlow¹¹², Judy Miller¹¹², Gloria Broadstreet¹¹², Anthony Martinez¹¹³, Micheal Allison¹¹³, Aniket Mittal¹¹³, Rafael Ruiz¹¹³, Aleta Skaanland¹¹³, Robert Ross¹¹³, Umang Patel¹¹⁴, Jordesha Hodge¹¹⁴, Krunal Kumar Patel¹¹⁴, Shivani Dalal¹¹⁴, Himanshu Kavani¹¹⁴, Sam Joseph¹¹⁴, Paul K Mohabir¹¹⁵, Connor G O'Brien¹¹⁵, Komal Dasani¹¹⁵, William Marx¹¹⁶, Ioana Amzuta¹¹⁶, Asad J. Choudhry¹¹⁶, Mohammad T. Azam¹¹⁶, Neha Gupta¹¹⁷, Tracy L Jones¹¹⁷, Shonda C Ayers¹¹⁷, Amy B Harrell¹¹⁷, Brent R

- Brown¹¹⁷, Utpal S. Bhalala¹¹⁸, Joshua Kuehne¹¹⁸, Melinda Garcia¹¹⁸, Morgan Beebe¹¹⁸, Heather Herrera¹¹⁸, Chris Fick¹¹⁹, Stephanie Guo¹¹⁹, May Vawer¹¹⁹, Beth Blackburn¹¹⁹, Katherine A. Belden¹²⁰, Michael Baram¹²⁰, Devin M. Weber¹²⁰, Rosalie DePaola¹²⁰, Yuwei Xia¹²⁰, Hudson Carter¹²⁰, Aaron Tolley¹²⁰, Mary Barletta¹²⁰, Mark Steele¹²¹, Laurie Kemble¹²¹, Joshua L. Denson¹²², A. Scott Gillet¹²², Margo Brown¹²², Rachael Stevens¹²², Andrew Wetherbie¹²², Kevin Tea¹²², Mathew Moore¹²², Benjamin J Sines¹²³, Thomas J Bice¹²³, Rajany V. Dy¹²⁴, Alfredo Iardino¹²⁴, Jill Sharma¹²⁴, Julia Christopher¹²⁴, Marwan Mashina¹²⁴, Kushal Patel¹²⁴, Erica C. Bjornstad¹, Nancy M. Tofil¹, Scott House¹, Isabella Aldana¹, Nikhil K. Meena¹²⁵, Jose D. Caceres¹²⁵, Nikhil K Meena¹²⁵, Sarenthia M. Epps¹²⁵, Harmeen Goraya¹²⁵, Kelsey R. Besett¹²⁵, Ryan James¹²⁵, Lana Y. Abusalem¹²⁵, Akash K. Patel¹²⁵, Lana S Hasan¹²⁵, Casey W Stulce¹²⁶, Grace Chong¹²⁶, Ahmeneh Ghavam¹²⁶, Anoop Mayampurath¹²⁶, Dina Gomaa¹²⁷, Michael Goodman¹²⁷, Devin Wakefield¹²⁷, Anthony Spuzzillo¹²⁷, John O. Shinn II¹²⁷, Patrick W. McGonagill¹²⁸, Colette Galet¹²⁸, Janice Hubbard¹²⁸, David Wang¹²⁸, Lauren Allan¹²⁸, Aditya Badheka¹²⁸, Madhuradhar Chegondi¹²⁸, Usman Nazir¹²⁹, Garrett Rampon¹²⁹, Jake Riggie¹²⁹, Nathan Dismang¹²⁹, Ozan Akca¹³⁰, Rainer Lenhardt¹³⁰, Rodrigo S. Cavallazzi¹³⁰, Ann Jerde¹³⁰, Alexa Black¹³⁰, Allison Polidori¹³⁰, Haily Griffey¹³⁰, Justin Winkler¹³⁰, Thomas Brenzel¹³⁰, Pauline Park¹³¹, Andrew Admon¹³¹, Sinan Hanna¹³¹, Rishi Chanderraj¹³¹, Maria Pliakas¹³¹, Ann Wolski¹³¹, Jennifer Cirino¹³¹, Dima Dandachj¹³², Hariharan Regunath¹³², Maraya N. Camazine¹³², Grant. E. Geiger¹³², Abdoulie O. Njai¹³², Baraa M. Saad¹³², Faraaz Ali Shah¹³³, Byron Chuan¹³³, Sagar L. Rawal¹³³, Rachel Piracha¹³³, Joseph E. Tonna¹³⁴, Nicholas M. Levin¹³⁴, Kayte Suslavich¹³⁴, Manel Tsolinas¹³⁴, Zachary T. Fica¹³⁴, Chloe R. Skidmore¹³⁴, Renee D. Stapleton¹³⁵, Anne E. Dixon¹³⁵, Olivia Johnson¹³⁵, Sara S. Ardren¹³⁵, Stephanie Burns¹³⁵, Anna Raymond¹³⁵, Erika Gonyaw¹³⁵, Kevin Hodgdon¹³⁵, Chloe Housenger¹³⁵, Benjamin Lin¹³⁵, Karen McQuesten¹³⁵, Heidi Pecott-Grimm¹³⁵, Julie Sweet¹³⁵, Sebastian Ventrone¹³⁵, Murtaza Akhter¹³⁶, Rania Abdul Rahman¹³⁶, Mary Mulrow¹³⁶, Erin M. Wilfong¹³⁷, Kelsi Vela¹³⁷, Markos G. Kashiouris¹³⁸, Tamas Gal¹³⁸, Manasi Mahashabde¹³⁸, Alexandra Vagonis¹³⁸, Rebecca Uber¹³⁸, Haseeb Mahmud¹³⁸, Stefan Leightle¹³⁸, Zoe Zhang¹³⁸, Nicole Vissicelli¹³⁸, Oliver Karam¹³⁸, Alia O'Meara¹³⁸, Heloisa De Carvalho¹³⁸, Katie Rocawich¹³⁸, Ashish K. Khanna¹³⁹, Lynne Harris¹³⁹, Bruce Cusson¹³⁹, Jacob Fowler¹³⁹, David Vaneenaenam¹³⁹, Glen McKinney¹³⁹, Imoh Udoh¹³⁹, Kathleen Johnson¹³⁹, Patrick G. Lyons¹⁴⁰, Andrew P. Michelson¹⁴⁰, Sara S. Haluf¹⁴⁰, Lauren M. Lynch¹⁴⁰, Nguyet M. Nguyen¹⁴⁰, Aaron Steinberg¹⁴⁰, Vishwanath Pattan¹⁴¹, Jessica Papke¹⁴¹, Ismail Jimada¹⁴¹, Nida Mhid¹⁴¹, Samuel Chakola¹⁴¹.
- ¹⁵Centre Hospitalier Jolimont, Belgium.
¹⁶The Brugmann University Hospital, Belgium.
¹⁷Clinica Los Olivos, Bolivia.
¹⁸Univresity Clinical Hospital, Mostar, Bosnia and Herzegovina.
¹⁹Clinica Medical SAS, Columbia.
²⁰Clinical Hospital Center Rijeka, Croatia.
²¹University Hospital of Split, Croatia.
²²Helwan University, Egypt.
²³CU University Hospital of Ioannina, Greece.
²⁴CEMESA Hospital, Honduras.
²⁵Honduras Medical Center, Honduras.
²⁶Uzsoki Teaching Hospital, Hungary.
²⁷ACSR Government Medical College and Hospital, India.
²⁸Gandhi Medical College and Hospital, Hyderabad, India.
²⁹Jawaharlal Institute of Postgraduate Medical Education and Research, Pondicherry, India.
³⁰JSS Medical College, India.
³¹KLEs Dr. Prabhakar Kore Hospital, India.
³²Mahatma Gandhi Hospital, Jaipur, India.
³³Maulana Azad Medical College and Lok Nayak Hospital, India.
³⁴Medicover Hospitals, India.
³⁵Om Superspecialty Hospital, Raipur, India.
³⁶Tristar Hospital, India.
³⁷Sapporo City General Hospital, Japan.
³⁸Hiroshima University, Japan.
³⁹Tokyo Medical and Dental University, Japan.
⁴⁰Al-Amiri and Jaber Al-Ahmed Hospitals, Kuwait Extracorporeal Life Support Program, Kuwait.
⁴¹Hospital Universitario, Universidad Autonoma de Nuevo León, Mexico.
⁴²Aminu Kano Teaching Hospital/Bayero University, Kano, Nigeria.
⁴³Dow University Hospital, Pakistan.
⁴⁴The Aga Khan University Hospital, Pakistan.
⁴⁵Kuban State Medical University with affiliation Territorial Hospital #2, Russia.
⁴⁶King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia.
⁴⁷King Fahad Armed Forces Hospital, Saudi Arabia.
⁴⁸King Saud University, Saudi Arabia.
⁴⁹Institute for Pulmonary Diseases of Vojvodina, Sremska Kamenica, Serbia.
⁵⁰University Clinical Centre of the Republic of Srpska, Banja Luke, Bosnia and Herzegovina, Serbia.
⁵¹University Hospital Center 'Dr Dragisa Misovic-Dedinje', Serbia.
⁵²Hospital Universitario La Paz, Spain.
⁵³Advocate Children's Hospital, IL, USA.
⁵⁴Advocate Christ Medical Center, USA.
⁵⁵Albany Medical Center, USA.
⁵⁶AnMed Health, USA.
⁵⁷Arkansas Children's Hospital, USA.
⁵⁸Ascension St. Mary's Hospital, USA.
⁵⁹Ascension St. Vincent Hospital, USA.
⁶⁰Ascension/St. Thomas Research Institute West Campus, USA.
⁶¹Augusta Health, USA.
⁶²Augusta University Medical Center, USA.
⁶³Aultman Hospital, USA.
⁶⁴Baptist Health South Florida, USA.
⁶⁵Baylor College of Medicine, Baylor St. Lukes Medical Center, USA.
⁶⁶Baylor Scott & White Health, USA.
⁶⁷Beaumont Children's Hospital, USA.
⁶⁸Brooke Army Medical Center, USA.
⁶⁹Cardinal Glennon Children's Hospital, USA.
⁷⁰Cedars Sinai Medical Center, USA.
⁷¹Chambersburg Hospital, USA.
⁷²Children's Hospital of Philadelphia, USA.
⁷³CHRISTUS Santa Rosa Health System, USA.
⁷⁴Clements University Hospital at UT Southwestern Medical Center, USA.
⁷⁵Cleveland Clinic (Main Campus, Fairview Hospital, Florida-Weston, Hillcrest Hospital, Marymount Hospital), USA.
⁷⁶Cox Medical Center Springfield, USA.
⁷⁷Detar Family Medicine Residency, USA.
⁷⁸Detroit Medical Centre, USA.
⁷⁹Gundersen Health System La Crosse Wisconsin, USA.
⁸⁰Hassenfeld Children's Hospital at NYU Langone, USA.
⁸¹Hospital Auxilio Mutuo, USA.
⁸²Howard University Hospital, USA.
⁸³Jacobs Medical Center UC San Diego Health – La Jolla, USA.
⁸⁴Johns Hopkins School of Medicine, USA.
⁸⁵JPS Health Network, USA.
⁸⁶KCPCRU at Norton Children's Hospital Louisville, USA.
⁸⁷Lakes Region General Hospital, USA.
⁸⁸LifeBridge Health/Sinai and Northwest Hospitals, USA.
⁸⁹Lincoln Medical Center, USA.
⁹⁰Loyola University Medical Center, USA.
⁹¹Lucile Packard Children's Hospital Stanford, USA.
⁹²M Health-Fairview, University of Minnesota, USA.
⁹³MacNeal Hospital Loyola Medicine, USA.
⁹⁴Mass General Brigham Hospital, USA.
⁹⁵Mayo Clinic Arizona, USA.
⁹⁶Mayo Clinic, Eau Claire, USA.
⁹⁷Mayo Clinic, Mankato, USA.
⁹⁸Medical Center Health System, Odessa, USA.
⁹⁹Medical College of Wisconsin, USA.
¹⁰⁰Mercy Hospital and Medical Center, Chicago, USA.
¹⁰¹Mercy Hospital, Saint Louis, USA.
¹⁰²Midland Memorial Hospital, Texas Tech University Health Sciences Center, USA.
¹⁰³Millard Fillmore Suburban Hospital, USA.
¹⁰⁴New Hanover Regional Medical Center, USA.
¹⁰⁵Nicklaus Children's Hospital, USA.
¹⁰⁶OSF Saint Francis Medical Center, USA.
¹⁰⁷Parkview Health System, Fort Wayne, USA.
¹⁰⁸ProMedica Toledo Hospital, USA.
¹⁰⁹Roper St. Francis Healthcare, USA.
¹¹⁰Saint Luke's Hospital, USA.
¹¹¹Sarasota Memorial Hospital, USA.
¹¹²St. Joseph's Candler Health System, USA.

- ¹¹³St. Agnes Hospital, USA.
¹¹⁴St. Mary Medical Center, Langhorne, USA.
¹¹⁵Stanford Hospital and Clinics, USA.
¹¹⁶SUNY Upstate Medical University, USA.
¹¹⁷The Children's Hospital at OU Medicine, USA.
¹¹⁸The Children's Hospital of San Antonio, Baylor College of Medicine, USA.
¹¹⁹The Queen's Medical Center, USA.
¹²⁰Thomas Jefferson University Hospital, USA.
¹²¹Truman Medical Centers, USA.
¹²²Tulane University Medical Center and University Medical Center New Orleans, USA.
¹²³UNC Medical Center, USA.
¹²⁴University Medical Center of Southern Nevada Las Vegas, University of Nevada Las Vegas, USA.
¹²⁵University of Arkansas for Medical Sciences, USA.
¹²⁶University of Chicago, USA.
¹²⁷University of Cincinnati, USA.
¹²⁸University of Iowa Carver College of Medicine, USA.
¹²⁹University of Kansas Medical Center, USA.
¹³⁰University of Louisville Hospital, USA.
¹³¹University of Michigan Health System.
¹³²University of Missouri, Columbia, USA.
¹³³University of Pittsburgh, USA.
¹³⁴University of Utah Health, USA.
¹³⁵University of Vermont Larner College of Medicine, USA.
¹³⁶Valleywise Health (formerly Maricopa Medical Center), USA.
¹³⁷Vanderbilt University Medical Center, USA.
¹³⁸Virginia Commonwealth University Medical Center, USA.
¹³⁹Wake Forest University School of Medicine, Wake Forest Baptist Health Network, USA.
¹⁴⁰Washington University School of Medicine and Barnes-Jewish Hospital, USA.
¹⁴¹Wyoming Medical Center, USA.

Authors' contributions

ECB, GC, PG, SM, KMG researched literature and conceived the study and analysis plan. ECB, GC, KMG, AJW, RK, VKK, VB, KB, MS, MB, ND, LR, OG were involved in protocol development. All authors were responsible for gaining local ethical approval and data collection. ECB and GC were responsible for data analysis. ECB and IA wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author/society of critical care medicine on reasonable request.

Declarations

Ethics approval and consent to participate

All research was conducted in accordance with the Declaration of Helsinki, and the University of Alabama at Birmingham declared the study exempt as there was no human-to-human interaction and consent was waived. The ethical approval boards at all individual VIRUS participating sites also declared exempt or approved the study. No participant interaction occurred and consent was waived.

Consent for publication

Not applicable.

Competing interests

The authors declare no financial or competing interests.

Author details

¹Department of Pediatrics, Division of Nephrology, University of Alabama at Birmingham, 1600 7th Avenue South, Lowder Suite 516, Birmingham, AL 35233, USA. ²Department of Biostatistics, University of Alabama

at Birmingham, Birmingham, AL, USA. ³Mayo Clinic, Jacksonville, FL, USA. ⁴Seattle Children's Hospital, Seattle, WA, USA. ⁵Department of Pediatrics, University of Alabama at Birmingham, Birmingham, AL, USA. ⁶Allina Health (Abbott Northwestern Hospital, United Hospital, Mercy Hospital), Minneapolis, MN, USA. ⁷MetroHealth Medical Center, Cleveland, OH, USA. ⁸Beth Israel Deaconess Medical Center, Boston, MA, USA. ⁹Atrium Health Navicent, GA, Macon, USA. ¹⁰Panimalar Medical College Hospital & Research Institute, Chennai, Tamil Nadu, India. ¹¹University of Arizona College of Medicine-Tucson, Tucson, AZ, USA. ¹²BSES MG Hospital, Mumbai, India. ¹³Boston University School of Medicine, Boston, MA, USA. ¹⁴Mayo Clinic, Rochester, MN, USA. ¹⁵Society of Critical Care Medicine, Mount Prospect, IL, USA. ¹⁶University of Colorado Anschutz Medical Campus, Aurora, CO, USA.

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