Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

The Journal of Emergency Medicine, Vol. 62, No. 2, pp. 145–153, 2022

0736-4679/$ - see front matter

https://doi.org/10.1016/j.jemermed.2021.10.026

Original Contributions

Fluid Resuscitation and Progression to Renal Replacement Therapy in Patients With COVID-19

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□ **Abstract—Background: Coronavirus disease 2019 (COVID-19) is associated with respiratory symptoms and renal effects. Data regarding fluid resuscitation and kidney injury in COVID-19 are lacking, and understanding this relationship is critical. Objectives: To determine if there is an association between fluid volume administered in 24 h and development of renal failure in COVID-19 patients. Methods: Retrospective chart review; 14 hospitals in Indiana. Included patients were adults admitted between March 11, 2020 and April 13, 2020 with a positive test for severe acute respiratory syndrome coronavirus 2 within 3 days of admission. Patients requiring renal replacement therapy prior to admission were excluded. Volumes and types of resuscitative intravenous fluids in the first 24 h were obtained with demographics, medical history, and other objective data. The primary outcome was initiation of renal replacement therapy. Logistic regression modeling was utilized in creating multivariate models for determining factors associated with the primary outcome. Results: The fluid volume received in the first 24 h after hospital admission was associated with initiation of renal replacement therapy in two different multivariate logistic regression models. An odds ratio of 1.42 (95% confidence interval 1.01–1.99) was observed when adjusting for age, heart failure, obesity, creatinine, bicarbonate, and total fluid volume. An odds ratio of 1.45 (95% confidence interval 1.02–2.05) was observed when variables significant in univariate analysis were adjusted for. Conclusions: Each liter of intravenous fluid administered to patients with COVID-19 in the first 24 h of presentation was independently associated with an increased risk for initiation of renal replacement therapy, supporting judicious fluid administration in patients with this disease.**

□ **Keywords—acute kidney injury; coronavirus; COVID-19; hemodialysis; renal replacement therapy; resuscitation**

Introduction

With hundreds of millions of infected individuals and millions of deaths, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), coronavirus disease 2019 (COVID-19) pandemic continues to profoundly impact the global community (1). Despite its prevalence, given the novel nature of this virus, guidelines for the evaluation and management of individuals infected with COVID-19 are limited. Many treatment recommendations are extrapolated from patients with other disease processes (2).

COVID-19, especially in more severe cases, is most commonly associated with pulmonic symptoms, with > 50% of symptomatic patients experiencing cough and > 30% dyspnea (3). The frequent need for respiratory support in hospitalized patients has led to much research regarding respiratory evaluation and management.

Additionally, SARS-CoV-2 can result in significant damage to the kidneys. Prevalence estimates for acute kidney injury (AKI) in the setting of COVID-19 vary widely from 1–46%, with 1.5–9.0% of these patients requiring

RECEIVED: 6 July 2021; FINAL SUBMISSION RECEIVED: 3 October 2021;
ACCEPTED: 12 October 2021

renal replacement therapy (RRT) in severe disease (4,5). The etiology for renal dysfunction is likely multifactorial, and a variety of mechanisms have been proposed, including, but not limited to, thromboses, inflammation, direct viral effects, and hypovolemia (6). Unsurprisingly, AKI is associated with higher mortality rates in patients with COVID-19 (7).

Although the Surviving Sepsis Campaign (SSC) has issued statements regarding COVID-19 management, covering a breadth of topics including infection control, hemodynamics, ventilation, and various therapies, there is a paucity of direct evidence regarding the prevention and optimal treatment of COVID-19-induced AKI (8). However, the SSC guidelines recommend a conservative fluid strategy based on previous studies comparing conservative and liberal fluid administration among patients with acute respiratory distress syndrome, for which patients with COVID-19 are at risk. These studies have shown increased numbers of ventilator-free days and decreased length of stay, and no difference in progression to renal failure with conservative fluid resuscitation (9,10).

Given the morbidity and mortality associated with kidney injury, understanding the impact of resuscitation and fluid management on progression to renal failure in patients with COVID-19 is critical. The primary objective of this study was to determine if there is an association between the volume of resuscitative fluid in the first 24 h from presentation and development of renal failure in patients admitted with COVID-19.

Materials and Methods

This is a retrospective chart review deemed by the local institutional review board to be exempt research.

Patients and Settings

The study examined data from a large integrated health system encompassing 14 hospitals across the state of Indiana. (11,12) The combined annual volume of patients seen across the system is in excess of 400,000, with individual facility ranges from 6000 to 90,000.

To be eligible for inclusion, patients had to be adults ($\geq$ 18 years of age) admitted to the hospital directly from the emergency department (ED) between March 11, 2020 and April 13, 2020, and have a positive polymerase chain reaction (PCR) test for SARS-CoV-2 within 3 days of admission. Patients with a PCR test obtained $>$ 3 days after hospital admission were excluded, as they may have been infected in the hospital after being admitted. Patients requiring RRT prior to admission were also excluded.

Data Collection

A list of eligible patients admitted during the study period was queried from the electronic medical record, Cerner (Cerner Corporation, North Kansas City, MO). Then trained data abstractors reviewed the records of each patient and entered the required data into a standard form in REDCap, our secure data collection instrument (13). Extracted data included days from symptom onset to ED presentation, age, gender, comorbidities, ED vital signs, laboratory values (culture and chest imaging results), and level of care at the time of admission. Chest imaging results were based on final radiologist interpretation, and were labeled as "clear," "single lobe infiltrates," "multi-lobar infiltrates," or "clear x-ray with involvement on CT [computed tomography] only." Vital signs included initial and final ED blood pressure, heart rate, oxygen saturation, temperature, and respiratory rate. If an ambulatory oxygen saturation was documented in the electronic medical record (EMR), it was extracted and recorded separately. Comorbidities were based on chart review of the ED note, admission note, and any clinic or primary care notes available in the EMR. The following comorbidities were recorded for each patient: smoking, obesity, hypertension, diabetes, hyperlipidemia, heart failure, previous ischemic heart disease, active cancer, dialysis-dependent renal disease, chronic obstructive pulmonary disease, asthma, active cancer, current chemotherapy, human immunodeficiency virus, history of organ transplantation, and current use of oral immunosuppressants.

Outcomes

The primary outcome was initiation of RRT during hospitalization. We assessed the relationship between the total volume of intravenous (i.v.) fluids received during the first 24 h and initiation of RRT while hospitalized. Patients with newly required RRT during hospitalization were identified via chart review. Reviewers determined volumes via chart review using standardized data extraction forms. The first 24 h was defined as starting at the time of presentation to the ED. Medication (non-crystalloid or non-colloid) drips and blood products were excluded from the calculation of total volume. In addition to total volume of i.v. fluid, abstractors separately calculated the amount of normal saline, lactated Ringer solution, plasmalyte, and albumin that was administered to each patient. Any other type of crystalloid or colloid fluid that was administered in the first 24 h was included in the calculation for total volume, but not recorded separately.

Table 1. Characteristics and Comorbidities of Patients by Outcome.

	Patients Not Started on RRT While Hospitalized (n = 502)	Patients Started on RRT During Hospitalization (n = 23)	*p* Value
Characteristics			
Median age* (IQR)	63 (13)	62 (12)	0.31
Female – n (%)	257 (51)	7 (30)	0.057
Male – n (%)	245 (50)	16 (70)	
Tobacco use – n (%)	42 (8)	1 (4)	0.71
Past medical history† – n (%)			
Obesity	196 (39)	13 (57)	0.13
Diabetes	196 (39)	11 (48)	0.39
Hyperlipidemia	255 (51)	14 (61)	0.40
Hypertension	336 (83)	19 (67)	0.17
Heart failure	65 (13)	4 (17)	0.53
Coronary artery disease	62 (12)	6 (26)	0.10
Cancer	12 (2)	1 (4)	0.44
COPD	64 (13)	2 (9)	0.76
Asthma	52 (10)	3 (13)	0.72
Organ transplant	5 (4)	5 (1)	0.24
Taking immunosuppressants	26 (5)	4 (17)	0.040

* Means for age compared using *t*-test for unequal variances, ratio between the two standard deviations was significantly different from 1 by variance ratio test ($p = 0.045$).
†Comorbidities compared by Fisher's exact test, the comparison of patients on immunosuppressant therapy demonstrated a difference that reached statistical significance.
RRT = renal replacement therapy; IQR = interquartile range; COPD = chronic obstructive pulmonary disease.

Statistical Analysis

In univariate analyses, we compared demographic, laboratory, clinical findings, and total volume of fluid given in the first 24 h between patients who did and did not require RRT. To test the independent association between fluid volume and need for RRT, we performed two different multivariate regression analyses. In the first, we included variables commonly associated with RRT or COVID-19 outcomes (age, heart failure, obesity, creatinine, bicarbonate, lactate, and total fluid volume in the first 24 h) (14,15). In the second model, only variables (among those listed above) that were statistically associated (at a *p* value of 0.05) with the outcome were included. Remdesivir was not available in our system in March and April 2020. No patients in this study received remdesivir, so it was not included in our models.

Comparisons of means were conducted with two-sided *t*-test or analysis of variance if standard deviations or Bartlett's tests were not found to be significantly different. For means with unequal variances, a two-sided *t*-test for unequal variances was conducted. Categorical data were compared based on continuous RRT results with Fisher's exact test. All statistical analyses were performed using Stata/IC 16.1 (StataCorp LLC, College Station, TX).

Results

There were 542 adults with a positive COVID-19 PCR test admitted during the study period. Of these, 17 had documented end-stage renal disease prior to presentation and were excluded. Demographic data for the 525 patients included in the study are provided in Table 1. Twenty-three patients (4.4%) underwent initiation of RRT during hospitalization. Patients started on RRT during hospitalization were of similar age (62.9 vs. 60.3 years; $p = 0.31$) but tended to be more often male (69.6% vs. 49.8%; $p = 0.057$), compared with those who did not undergo RRT. Regarding comorbidities, more patients started on RRT were documented as taking immunosuppressive medications (17.4% vs. 5.2%; $p = 0.040$). No other statistically significant differences in medical

Table 2. Characteristics, Vitals, Radiographic and Laboratory Findings on Initial Presentation.

Initial Presentation	Patients Not Started on RRT While Hospitalized	Patients Started on RRT During Hospitalization	*p* Value
Days since symptom onset, Mean* (SD)	7.2 (5.4)	7.1 (5.4)	0.99
Initial vital signs, Mean† (SD)			
Temperature (Celsius)	37.6 (1.0)	37.9 (1.4)	0.012
Heart rate	98.4 (20.6)	97.2 (22.4)	0.78
Respiratory rate	22.8 (6.7)	23.4 (7.9)	0.66
Systolic blood pressure	134.6 (22.5)	135.2 (25.1)	0.91
Diastolic blood pressure	78.2 (17.1)	75.8 (16.0)	0.52
Pulse oximetry reading	91.8 (7.8)	88.1 (11.4)	0.004
Radiology results, n (%)			
No radiographic findings	57 (12)	2 (9)	0.90
Single lobe involvement	50 (10)	3 (13)	
Multilobe involvement	363 (74)	17 (74)	
Positive CT without positive radiograph	20 (4)	1 (4)	
Laboratory results, Mean‡ (SD)			
Hemoglobin	13.4 (1.9)	12.9 (2.1)	0.23
Sodium	136.0 (4.6)	134.8 (5.2)	0.23
Potassium	3.9 (0.6)	4.2 (0.7)	0.018
Bicarbonate	25.2 (4.2)	23.0 (3.8)	0.015
Creatinine§	1.3 (0.7)	2.5 (1.9)	0.0051
Blood urea nitrogen	23.3 (19.2)	35.9 (24.1)	0.0025
Glomerular filtration rate	64.8 (23.8)	40.9 (23.7)	< 0.000
Lactate dehydrogenase	416.2 (225.4)	563.8 (168.9)	0.026
D-dimer§	764.4 (87.9)	5843.5 (3963.2)	0.22

* Two-sample *t*-test with equal variances for difference between means used for days since symptom onset. Standard deviations and variances were not significantly different.

†Analysis of variance was performed for comparison of initial vital signs with variance ratio test and Bartlett's test for equal variances to determine validity.

‡Analysis of variance performed to determine if difference between groups was statistically significant. Bartlett's test for equal variances used to determine if comparison is valid. If comparison was not valid, then *t*-test for unequal variances was implemented. Laboratory values not shown that had unequal variances or no statistically significant difference: white blood cell count, absolute lymphocyte count, chlorine, glucose, troponin, lactate, international normalized ratio, D-dimer, C-reactive protein, procalcitonin.

§Two-sample *t*-test with unequal variances conducted for creatinine and D-dimer.

CT = computed tomography; RRT = renal replacement therapy.

Table 3. Intravenous Fluid Resuscitation by Group

Fluids Administered	Patients Not Started on RRT While Hospitalized Mean (SD)	Patients Started on RRT During Hospitalization	*p* Value*
0.9% Normal saline (mL)	655 (40.0)	859 (271.7)	0.47
Lactated ringers (mL)	352 (30.2)	599 (201.2)	0.24
Plasmalyte (mL)	21 (7.8)	289 (192.0)	0.18
Total i.v. fluids received in first 24 h (mL)	1034 (45.2)	1747 (348.3)	0.054

*Due to unequal variances all comparisons were made using a two-sample *t*-test with unequal variances.
RRT = renal replacement therapy.

Table 4. Outcome by Group

Outcome	Patients Not Started on RRT While Hospitalized n (%)	Patients Started on RRT During Hospitalization	*p* Value†
Intubated within 24 h of admission	82 (16)	10 (44)	0.003
Intubated during hospitalization	137 (27)	22 (96)	< 0.001
Admitted to ICU within first 24 h	42 (10)	4 (29)	0.048
Death during hospitalization*	64 (13)	10 (44)	< 0.001

*No deaths within 24 h of admission in the continuous renal replacement therapy (CRRT) group. Four deaths within 24 h in the no CRRT group.
†Comparisons made with Fisher's exact test.
RRT = renal replacement therapy; ICU = intensive care unit.

comorbidities were identified, although nearly all comorbidities were more frequent in patients requiring RRT.

Vital signs and chest radiographic data were similar between patients started on RRT and those not requiring RRT during hospitalization (Table 2). Select laboratory results, stratified by those patients for which RRT was initiated, are also displayed. Statistically significant differences in presenting potassium (4.2 vs. 3.9), bicarbonate (23.0 vs. 25.2), lactate dehydrogenase (225 vs. 169), creatinine (2.5 vs. 1.3), and blood urea nitrogen (24.1 vs. 19.2) levels, as well as glomerular filtration rate (40.9 vs. 64.8), were identified in patients progressing to RRT compared with those who did not require RRT.

Patients who had RRT initiated during hospital admission tended to receive a larger volume of i.v. fluids during the first 24 h of admission (1747 mL vs. 1034 mL; $p = 0.054$), as shown in Table 3. This was consistent among all types of fluids recorded, with the largest difference in balanced solutions of lactated Ringer solution (599 mL vs. 352 mL; $p = 0.24$) and plasmalyte (289 mL vs. 21 mL; $p = 0.18$).

As shown in Table 4, patients who progressed to RRT during admission were more often intubated (95.7% vs. 27.3%; $p < 0.001$) and were more likely to be intubated within the first 24 h of admission (43.5% vs. 16.3%; $p = 0.0030$). These patients were more frequently admitted to the intensive care unit (28.6% vs. 9.8%; $p = 0.048$) and had a higher rate of death during hospitalization (43.5% vs. 12.8%; $p < 0.001$).

In regression models, we tested for associations between RRT and the following variables: age, heart failure, obesity, creatinine, bicarbonate, lactate, and total fluid volume in the first 24 h. In univariate analysis, only creatinine (odds ratio [OR] 2.1, 95% confidence interval [CI] 1.51–2.92), bicarbonate (OR 0.89, 95% CI 0.81–0.98), and fluid volume (OR 1.64, 95% CI 1.19–2.25 for each additional liter) were statistically associated with receiving RRT. Because lactate values were missing in nearly half of the cohort, and were not associated with RRT, we excluded lactate from the multivariate regression models. In our first regression model, after adjusting for all of the above variables except lactate, only creatinine (OR

Table 5. Logistic Regressions Results for Odds Ratio of Having RRT Started During Hospitalization.

Variable	Units	Odds Ratio	95% Confidence Interval
Univariate			
Age		0.99	0.97–1.02
Heart failure		1.42	0.47–4.29
Obesity		2.03	0.87–4.72
Creatinine		2.1	1.51–2.92
Glomerular filtration rate		0.96	0.94–0.98
Bicarbonate		0.89	0.81–0.98
Lactate		1.24	0.96–1.62
Fluids given in 24 h		1.64	1.19–2.25
Multivariable 1 – all included variables*			
Age	Years	0.98	0.95–1.02
Heart failure		0.83	0.21–3.22
Obesity		2.57	0.98–6.74
Creatinine		2.02	1.40–2.90
Bicarbonate		0.94	0.85–1.05
Fluids given in 24 h	Per L/24 h	1.42	1.01–1.99
Multivariable 2 – univariate significant variables only			
Creatinine		1.89	1.34–2.67
Bicarbonate		0.96	0.87–1.06
Fluids given in 24 h	Per L/24 h	1.45	1.02–2.05

* Lactate removed from multivariable regression due to missing data.RRT = renal replacement therapy.

2.02, 95% CI 1.40–2.90) and fluid volume (OR 1.42, 95% CI 1.01–1.99) were statistically significantly associated with the primary outcome (OR 1.25, 95% CI 0.78–2.03). In our second regression model including those variables that were significant in the univariate analysis, both fluid volume (OR 1.45, 95% CI 1.02–2.05) and creatinine (OR 1.89, 95% CI 1.34–2.67) remained significantly associated with initiation of RRT. Bicarbonate was no longer independently associated with RRT. Results for all three models are displayed in Table 5.

Discussion

In patients admitted with PCR-confirmed COVID-19, each liter of resuscitative crystalloid given during the first 24 h of hospitalization was independently associated with receiving RRT. This correlation was persistent across two different multivariate logistic regression models. Of note, the patients progressing to renal failure in this study received greater amounts of each of the commonly utilized crystalloid resuscitative fluids (normal saline, lactated Ringer, and plasmalyte).

Various mechanisms for COVID-19-induced kidney injury have been proposed, including acute tubular necrosis secondary to shock and poor perfusion (5,7,16). Acute kidney injury and the progression to renal failure is well known as an independent risk factor for in-hospital mortality, including in patients with COVID-19 (5,17). Conservative strategies for fluid resuscitation have been recommended in the treatment of patients with COVID-19, primarily for theoretical lung protection; however, no data exist regarding the ideal fluid resuscitation volume and its effect on renal function in this patient population (8). This lack of evidence can create challenging scenarios for clinicians faced with treating COVID-19 patients. Current guidelines proposed by the SSC call for judicious fluid administration, but clinicians may instinctively reach for crystalloid resuscitation in patients who may present similarly to those with bacterial sepsis (18). Patients with COVID-19 may present hypovolemic or poorly perfused, creating a conundrum whereby the usual method for resuscitation may create harm by worsening respiratory status. This study adds further data to the debate around how to approach these patients, in showing that more aggressive early fluid resuscitation is also associated with

renal failure and being started on RRT during hospitalization.

Limitations

There are several important limitations to this study. First, these data are observational, and the results could have been driven by unmeasured confounders. Patients who went on to require RRT had higher baseline creatinine and lower bicarbonate levels, among other markers of baseline illness. As such, providers may have been compelled to try to resuscitate them more aggressively. Although we performed multiple versions of logistic regression to try to account for these baseline imbalances, other unmeasured confounders may have contributed to our finding of an association between fluid volume and need for RRT.

Only patients with PCR-confirmed COVID-19 within 3 days of hospital admission were included. The system at the time of this study was testing nearly all admitted patients for COVID-19, however, this would exclude patients that may have presented with COVID-19-like symptoms but were not tested within the defined period of 3 days. However, we found only three cases of patients admitted with a first positive COVID-19 PCR drawn after 3 days, so it is likely that very few patients were missed for this reason.

Regarding fluids, only i.v. fluids documented in the EMR as having been administered as a bolus or as maintenance fluids were included. Our EMR's data entry system allowed for specification of the amount of normal saline, lactated Ringer, or plasmalyte given, but not other fluid types. However, all other bolus and maintenance fluids were included in total i.v. fluids given and were a small proportion of the total fluids administered. Only 9 patients were found to have received non-blood product i.v. fluids outside of those three formulations, all in small amounts. Given inconsistencies in the entry of urine output in the EMR, we were unable to reliably measure net fluid balance.

We collected fluid totals for the first 24 h of the hospital stay for each individual patient. We are unable to reliably determine whether these fluids represent primarily fluid boluses received in the ED or were given over longer periods of time as maintenance fluids or repeated small boluses. It is possible that there is a difference in the effect of aggressive fluid boluses in the first hours of resuscitation vs. that of spreading out i.v. fluid volume over the initial 24 h.

Laboratory and imaging work-up was provider dependent, leading to instances of data that were not collected. Notably, lactate levels were not obtained in nearly half of the cohort. We had planned to include lactate levels in our initial multivariate logistic regression model, but had to exclude it due to so many missing data points. Among those who did have a lactate level drawn, it was not associated with the primary outcome. Patients without any bolus or maintenance fluids documented in the EMR were presumed to have received 0 intravenous fluids in our data and calculations. However, system policy is such that documentation of fluids given is required, so we expect this to be an accurate assumption.

Lastly, we had a small number of cases (n = 23) requiring RRT among the study population, resulting in relatively wide confidence intervals, which came very close to the line of no effect, weakening confidence that the association between fluid volume and RRT represent any type of cause-and-effect relationship. Additionally, with so few cases, the validity of including six variables in one of our regression models is questionable. However, we felt it important to try to account for those factors, which are strongly associated with outcomes including RRT in COVID-19.

Given that these data were collected from one health care system located in one state, the generalizability of these results may be limited as well.

Conclusions

Among patients with PCR-confirmed COVID-19 infection, each liter of crystalloid received in the first 24 h after presentation was independently associated with an increased risk of renal failure requiring RRT. Although these results support judicious administration of i.v. fluid volumes during the resuscitation of patients with COVID-19, confidence in this association is limited due to small sample size, wide confidence intervals, and the limitations of this observational data set. Further prospective studies, controlling for fluid types, volume of resuscitation, and monitoring of patient fluid balance, are needed.

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ARTICLE SUMMARY

1. Why is this topic important?

Patients with coronavirus disease 2019 (COVID-19) may experience harmful renal effects. The impact of fluid resuscitation on renal function in patients with COVID-19 is not well understood and data are sparse.

2. What does this study attempt to show?

That there is an association between the volume of fluids administered in resuscitating patients with COVID-19 and renal impairment.

3. What are the key findings?

In patients with COVID-19 infection, each liter of crystalloid received in the first 24 h from presentation was independently associated with an increased risk of renal failure requiring renal replacement therapy.

4. How is patient care impacted?

These results support judicious and thoughtful resuscitation with intravenous fluids in patients with COVID-19.