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Risk Factors for Acute Kidney Injury and Death in Patients Infected With the Yellow Fever Virus During the 2018 Outbreak in São Paulo, Brazil

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Introduction: There have been few studies investigating acute kidney injury (AKI) in patients with yellow fever (YF). The objective of this study was to identify the risk factors for AKI and death in such patients.

Methods: We evaluated 95 consecutive critically ill adult patients with the sylvatic form of YF, as confirmed by reverse-transcriptase polymerase chain reaction, in Brazil. The outcome measures were AKI (as defined by Kidney Disease: Improving Global Outcomes [KDIGO] criteria) and in-hospital death.

Results: Of the 95 patients, 73 (76.8%) had AKI and 59 (62.1%) died from it. A total of 70 patients (73.7%) required dialysis because of AKI. After adjusting for age, sex, and the Simplified Acute Physiology Score 3 (SAPS 3), we found that elevated fractional excretion of sodium and requiring dialysis were independent risk factors for in-hospital mortality and that proteinuria correlated with AKI-associated mortality.

Conclusion: Our findings indicate that, in patients with sylvatic YF, AKI is common and is associated with significant mortality. The data presented here could prove useful for improving understanding of the pathogenesis of AKI in YF and informing decisions regarding the care of the affected patients.

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YF is an epidemic-prone mosquito-borne disease that typically manifests as influenza-like illness, being self-limited in most cases. Up to 25% of individuals infected with the YF virus (YFV) develop severe or fulminant multisystem YF owing to an imbalance between the immune and inflammatory responses, the reported lethality of that form of the disease being 60%.[1,2] AKI has been identified as a major risk factor for YF-related mortality.[3] Nevertheless, there have been few studies evaluating the frequency of, risk factors for, and clinical course of YF-associated AKI.[4] Most of the existing information on YF-associated AKI is from case reports, small case series, or small experimental studies.[5,6]

A number of risk factors have been implicated in the development of AKI in critically ill patients with YF, such factors including hemodynamic instability/shock, glomerular/vascular deposition of fibrin, an unbalanced inflammatory response, direct effects of YF viruses on the kidney tissue, and bilirubin-induced tubular toxicity.[7] Histologic studies of patients with YF have revealed that the disease results in mild proliferation of mesangial cells, swelling of the endothelial cells, fibrinogen deposition in the glomerular capillary loops, interstitial/tubular cell edema, bile staining, and granular/hyaline casts in the distal tubules.[8,9] In patients who died from YF, the YFV-specific antigen has been detected by immunohistochemistry in the kidneys, which is suggestive of direct viral injury.[3] Acute tubular necrosis, interstitial nephritis, and glomerular injury, including viral mRNA in the kidney tissue,

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have also been observed in necropsy studies of YFV-infected monkeys.[10,11]

Here, we present the clinical and biochemical characteristics of AKI in critically ill patients infected with YFV during the 2018 outbreak in the city of São Paulo, Brazil. We also address aspects of the dialysis therapy and outcomes among those patients.

METHODS

In São Paulo, Brazil, the largest city in Latin America, there was an outbreak of sylvatic YF from December 2017 to May 2018. During that period, a referral system was established, in which critically ill patients with suspected or confirmed YF were admitted to the Hospital das Clínicas of the University of São Paulo School of Medicine. To be transferred to one of the intensive care units (ICUs) of the hospital, patients needed to be ≥18 years of age and to have developed sudden-onset high fever accompanied by jaundice or bleeding, with at least one of the following features: serum aspartate aminotransferase or alanine aminotransferase level >3000 U/l; prothrombin international normalized ratio >1.5; platelet count <90,000/mm^3; AKI; encephalopathy; or hemodynamic instability.

After admission, YFV infection was confirmed by reverse-transcriptase polymerase chain reaction, serology, or both, in blood samples. The diagnosis of AKI, as defined in the KDIGO clinical practice guideline, was based solely on an increase in serum creatinine (SCreat) level from baseline to 72 hours after ICU admission. Urine output was measured on the first day of dialysis.

To reduce delays in management and improve treatment efficacy, renal replacement therapy was used if the SCreat level was ≥2.0 mg/dl or urine volume was <0.5 ml/kg per hour in an 8-hour period, in the presence of at least one of the following: vasoactive drug use; mechanical ventilation; noninvasive ventilation with a fraction of inspired oxygen > 40%; pulmonary congestion; bleeding; positive fluid balance; encephalopathy; ammonia level ≥100 μmol/l; and bicarbonate level ≤15 mEq/l. This protocol was created by our AKI group.

The choice between sustained low-efficiency dialysis and continuous venovenous hemodialysis (CVVHD) as the initial renal replacement therapy modality was based on the clinical profile of the patient, with special attention being paid to the hemodynamic status, presence of encephalopathy, and correction of acidosis. Complete recovery of renal function was defined as a postdischarge SCreat level ≤10% higher than baseline. If there was no reliable baseline SCreat level on record, we used the lowest SCreat level obtained during hospitalization or we estimated the baseline SCreat level using the Modification of Diet in Renal Disease formula with an assumed glomerular filtration rate of 75 ml/min per 1.73 m^2 for all patients. The SCreat level was used to diagnose and stage AKI on the basis of the KDIGO criteria. We also evaluated SCreat level at 3, 6, 9, and 12 months after hospital discharge. All dialysis sessions were analyzed in terms of the renal replacement therapy method (CVVHD or sustained low-efficiency dialysis), catheter insertion site, duration, electrolyte concentration, and volume removed. We also calculated the SAPS 3, as a predictor of in-hospital mortality, including the Sequential Organ Failure Assessment score, the Model for End-Stage Liver Disease score, and the Acute Physiology and Chronic Health Evaluation II score.

The study protocol (reference number 3.401.962) was approved by the local institutional review board. Because of the observational (noninterventional), retrospective nature of the study, with guaranteed confidentiality, the requirement for informed consent was waived. All analyses were based on the laboratory tests performed at admission or within the first 48 hours after admission.

Statistical Analysis

Continuous variables were described as mean and SD if they followed a normal distribution and as median and interquartile range (IQR) if they had an asymmetric distribution. The Shapiro–Wilk test was used to test for normality of the data distribution. Comparisons between groups, namely survivors versus nonsurvivors and AKI versus no AKI, were made with a Student t test or the Mann–Whitney U test for continuous variables and with the χ^2 test or Fisher exact test for categorical variables.

Multivariable logistic regression analyses were performed to evaluate the association of clinical and biochemical variables with the outcome of in-hospital death. Results are displayed as odds ratios (ORs) and 95% CIs. The level of statistical significance was established at $P < 0.05$. We constructed a Kaplan–Meier curve for survival since hospital admission. Statistical analyses were performed with R software (version 3.2.5; R Foundation for Statistical Computing, Vienna, Austria) and the Predictive Analytics Software package, version 18.0 (SPSS Inc., Chicago, IL).

RESULTS

From 2017 to 2018, a total of 1470 suspected cases of YF were reported in the Metropolitan Area of São Paulo. Among those 1470 cases, YFV infection was confirmed in 571 (38.8%). Among the 513 patients (89.8%) who

were residents of the Metropolitan Area of São Paulo, there were 192 deaths, translating to a mortality rate of 37.4%.

Our sample comprised 15 women (2 of whom were pregnant) and 80 men. The median age was 42.0 years (IQR: 31.0–55.0 years). In all the patients, YFV infection was confirmed by reverse-transcriptase polymerase chain reaction, serology, or both, in blood samples. Comorbidities were present in 25 patients: hypertension, in 12; diabetes mellitus, in 3; hypertension plus diabetes mellitus, in 3; immunosuppression, in 2; obesity in 1; and cardiovascular disease, in 4. There were 21 patients who had a history of alcohol use disorders.

The clinical and biochemical characteristics of the patients admitted to the ICU with severe YF are found in Table 1, which also reveals a comparison between the survivors and nonsurvivors. The median time from the onset of symptoms to hospital admission was 5 days (IQR: 4–7 days), and the median time from onset of symptoms to death among the nonsurvivors was 9.0 days (IQR: 7–12 days).

Table 1. Clinical and biochemical characteristics of patients with yellow fever admitted to the intensive care unit: survivors versus nonsurvivors

Characteristics	Survivors ($n = 36$)	Nonsurvivors ($n = 59$)	*P*	*N*	All ($N = 95$)
Age (yr), median (IQR)	39.0 (26.8–47.0)	45.0 (33.5–57.5)	0.031	95	42.0 (31.0–55.0)
Male sex, *n* (%)	28 (77.8)	52 (88.1)	0.292	95	80 (84.0)
BMI (kg/m^2), median (IQR)	24.2 (22.8–26.1)	25.7 (22.9–28.7)	0.403	88	24.8 (22.8–27.9)
SOFA score,[a] median (IQR)	7.00 (5.00–12.0)	10.0 (8.00–15.0)	0.02	76	9.50 (7.75–13.0)
SAPS 3,[a] median (IQR)	49.0 (42.0–64.0)	62.0 (54.5–80.5)	<0.001	92	59.5 (48.0–71.5)
APACHE II score,[a] median (IQR)	13.0 (7.50–17.0)	17.0 (13.0–24.0)	0.028	76	16.0 (11.0–21.0)
MELD score,[a] median (IQR)	16.5 (11–29.75)	40.5 (31.75–46.25)	<0.001	71	34.5 (18–43)
Mechanical ventilation, *n* (%)	9 (25.0)	58 (98.3)	<0.001	95	67 (70.5)
Vasopressor use, *n* (%)	7 (19.4)	59 (100)	<0.001	95	66 (69.5)
Blood transfusion, *n* (%)	19 (52.8)	55 (93.2)	<0.001	95	74 (77.9)
Albumin (g/dl),[a] median (IQR)	3.20 (2.75–3.50)	3.10 (2.70–3.50)	0.921	74	3.15 (2.70–3.50)
Amylase (IU/l),[a] median (IQR)	110 (80.2–148)	187 (105–385)	0.004	78	149 (95.5–302)
Lipase (IU/l),[a] median (IQR)	167 (96.0–330)	330 (146–1037)	0.017	77	259 (127–835)
Ammonia (μmol/l),[a] median (IQR)	56.0 (50.2–87.2)	102 (70.0–155)	<0.001	76	96.0 (60.5–141)
Bilirubin (mg/dl),[a] median (IQR)	4.97 (1.92–7.30)	5.88 (4.54–7.84)	0.138	78	5.84 (4.21–7.79)
INR,[a] median (IQR)	1.63 (1.27–1.89)	2.60 (2.07–3.32)	<0.001	77	2.34 (1.69–3.15)
Fibrinogen (mg/dl),[a] median (IQR)	102 (85.0–136)	89.0 (70.5–128)	0.253	74	93.5 (72.2–132)
Factor V activity (%),[a] median (IQR)	63.5 (32.2–85.5)	29.5 (16.8–42.0)	0.001	76	32.5 (19.0–56.0)
D dimer (ng/ml)[a], median (IQR)	8170 (4550–9945)	10,000 (6829–10,000)	0.18	34	9945 (6292–10,000)
GGT (U/l),[a] median (IQR)	317 (190–396)	277 (206–427)	0.572	78	284 (202–422)
AST (U/l),[a] median (IQR)	6712 (4857–7603)	11,009 (6632–15,818)	0.006	71	8546 (6386–14,470)
ALT (U/l),[a] median (IQR)	3633 (2080–4348)	5009 (3204–7119)	0.01	79	4094 (2830–6729)
Lactate (mg/dl),[a] median (IQR)	19.5 (16.0–26.0)	39.0 (26.0–66.0)	<0.001	74	35.0 (20.2–54.0)
LDH (U/l),[a] median (IQR)	3125 (2596–4140)	4350 (3324–5180)	0.013	49	4082 (3125–4873)
CPK (U/l),[a] median (IQR)	524 (213–1288)	748 (422–1772)	0.085	73	653 (307–1405)
Sodium (mEq/l),[a] mean ± SD	137 ± 6.01	137 ± 4.85	0.953	79	137 ± 5.13
Potassium (mEq/l),[a] mean ± SD	4.46 ± 0.50	5.01 ± 0.88	0.001	79	4.87 ± 0.83
Creatinine (mg/dl),[a] median (IQR)	3.91 (2.36–9.29)	5.52 (3.00–8.16)	0.497	71	5.17 (2.73–8.37)
Urea (mg/dl),[a] median (IQR)	89.0 (45.8–124)	113 (64.5–154)	0.146	79	111 (57.5–151)
pH,[a] median (IQR)	7.37 (7.33–7.41)	7.34 (7.24–7.40)	0.161	77	7.34 (7.27–7.40)
Bicarbonate (mEq/l),[a] mean ± SD	19.0 ± 3.86	14.8 ± 5.63	0.001	76	15.8 ± 5.53
Ionized calcium (mg/dl),[a] mean ± SD	4.32 ± 0.36	3.76 ± 0.61	<0.001	78	3.90 ± 0.60
Phosphorus (mg/dl),[a] median (IQR)	4.00 (3.00–4.90)	6.70 (4.00–8.10)	0.002	78	5.50 (3.80–7.80)
Chlorine (mEq/l),[a] mean ± SD	104 ± 6.64	101 ± 9.11	0.139	78	102 ± 8.60
Hemoglobin (g/dl),[a] median (IQR)	14.4 (12.3–14.8)	14.1 (12.7–15.4)	0.281	79	14.2 (12.6–15.3)
Leukocytes (cells/mm^3),[a] median (IQR)	4464 (2930–6008)	4760 (2671–7325)	0.652	79	4480 (2785–7275)
Platelets (×10^3/mm^3),[a] median (IQR)	61.5 (50.8–86.5)	76.0 (52.5–91.5)	0.588	79	74.0 (52.0–91.0)
CRP (mg/dl),[a] median (IQR)	5.85 (3.05–14.1)	8.60 (4.40–13.7)	0.218	77	7.80 (4.10–13.9)
FeNa (%),[a] median (IQR)	0.78 (0.35–3.97)	4.42 (1.96–9.68)	<0.001	71	2.91 (0.65–6.78)
Days from symptom onset to death,[b] median (IQR)	NA	9.0 (7.0–12.0)	NA	58	NA
Length of hospital stay, median (IQR)	10.0 (7.00–27.0)	4.00 (2.00–6.50)	<0.001	94	6.00 (2.25–11.0)
RRT required, *n* (%)	14 (38.9)	56 (94.9)	<0.001	95	70 (73.7)

ALT, alanine aminotransferase; APACHE II, Acute Physiology and Chronic Health Evaluation II; AST, aspartate aminotransferase; BMI, body mass index; CPK, creatine phosphokinase; CRP, C-reactive protein; FeNa, fractional excretion of sodium; GGT, gamma-glutamyltransferase; INR, international normalized ratio; IQR, interquartile range; LDH, lactate dehydrogenase; MELD, Model for End-Stage Liver Disease; RRT, renal replacement therapy; SAPS 3, Simplified Acute Physiology Score 3; SOFA, Sequential Organ Failure Assessment; NA, not applicable.
[a]At intensive care unit admission.

Table 2. Logistic regression analysis of the association between fractional excretion of sodium and in-hospital mortality

	Risk			
	Crude		Adjusted	
Variables	OR (95% CI)	*P*	OR (95% CI)	*P*
FeNa[a]				
Quartile 2 (0.65–2.91)	3.5 (0.86–16.31)	0.09[b]	4.68 (1.01–25.82)	0.058[b]
Quartile 3 (2.91–6.78)	6.42 (1.54–31.77)	0.015[b]	3.54 (0.70–20.02)	0.134[b]
Quartile 4 (6.78–63.8)	17.5 (3.73–110.57)	<0.001[b]	13.50 (2.42–103.75)	0.006[b]
Age			1.03 (0.99–1.08)	0.19
SAPS 3			1.03 (0.99–1.08)	0.17
Sex			4.52 (0.89–27.66)	0.08

FeNa, fractional excretion of sodium; OR, odds ratio; SAPS 3, Simplified Acute Physiology Score 3.
[a]Restricted to the 71 patients in whom FeNa was measured.
[b]Versus quartile 1.

The univariate analysis revealed that in-hospital mortality correlated with the following variables ($P < 0.001$ for all): SAPS 3 (OR = 1.01; 95% CI: 1.005–1.019); mechanical ventilation (OR = 6.44; 95% CI: 3.19–13.006); amylase (OR = 1.006; 95% CI: 1.003–1.009); ammonia (OR = 1.014; 95% CI: 1.008–1.020); aspartate aminotransferase (OR = 1; 95% CI: 1.000–1.000); alanine aminotransferase (OR = 1; 95% CI: 1.000–1.000); lactate (OR = 1.038; 95% CI: 1.019–1.057); lactate dehydrogenase (OR = 1; 95% 1.000–1.000); potassium (OR = 1.27; 95% CI: 1.14–1.41); and phosphorus (OR = 1.26; 95% CI: 1.14–1.39).

In the multivariate analysis, requiring dialysis was associated with in-hospital mortality (crude OR = 29.3; 95% CI: 8.69–137.13, $P < 0.001$). After adjusting for the SAPS 3, age, and sex, we found that requiring dialysis was still clearly an independent risk factor for in-hospital mortality (OR = 15.58; 95% CI: 4.23–76.57, $P < 0.001$), as was the fractional excretion of sodium (Table 2).

AKI Characteristics

A nephrology consultation was requested for 73 (76.8%) of the 95 patients evaluated. Of those patients, 70 presented AKI at ICU admission and the 3 remaining patients had developed AKI during the ICU stay.

The median hospital stay was longer for patients with AKI than for those with normal renal function—29 days (IQR: 11–184 days) versus 7 days (IQR: 3–13 days)—and the difference was statistically significant ($P = 0.005$). The clinical and biochemical characteristics of the AKI and non-AKI groups are found in Table 3. Urinalysis was performed in 57 (78.1%) of the 73 patients in the AKI group and in 19 (86%) of the 22 patients in the non-AKI group. Proteinuria level >1 g/g urinary creatinine was more common in the AKI group than in the non-AKI group (85.7% vs. 52.4%; $P = 0.005$). In the AKI group, the mean proteinuria level was 4.7 ± 6.2 g (range: 0–60 g) protein/g urinary creatinine. Of the 57 patients in the AKI group who submitted to urinalysis, 25 (43.8%) presented with nephrotic proteinuria. Granular casts were identified in 47.4% of the patients in the AKI group, compared with only 27.3% of those in the non-AKI group ($P = 0.095$). For all 73 patients followed by the nephrology team, the KDIGO criteria were used at ICU admission, the AKI thus being classified as stage 0 in 8 patients (11.0%), stage 1 in 9 (12.3%), stage 2 in 6 (8.2%), and stage 3 in 50 (68.5%).

There were 7 patients who underwent liver transplantation, and 4 (57.1%) of those patients died in the postoperative period. The molecular adsorbent recirculating system was used, as a bridge to liver transplantation, in 4 patients.

AKI-Associated Mortality

Of the 73 patients with AKI, 58 (79.5%) died. Among those patients, in-hospital mortality was found to be associated with mechanical ventilation, a high Sequential Organ Failure Assessment score, vasopressor use, and a high international normalized ratio, together with low factor V activity, low bicarbonate level, low ionized calcium level, low urine output, and high levels of ammonia, amylase, aspartate aminotransferase, alanine aminotransferase, potassium, phosphorus, lactate, and lactate dehydrogenase (Table 4). We found that proteinuria level >2.6 mg/g creatinine at ICU admission and a KDIGO stage of 2 or 3 were associated with higher mortality.

Dialysis

Of the 95 patients evaluated, 70 (74%) required dialysis, corresponding to 95% of the 73 YFV-infected patients followed by the nephrology team. Furthermore, 1 pregnant woman died from AKI before the nephrology consultation, and another patient died before starting dialysis. Applying the KDIGO criteria on the day of the first dialysis session, we classified the AKI as stage 0 in 3 patients (4.1%), stage 1 in 1 (1.4%),

Table 3. Clinical and biochemical characteristics of patients with yellow fever admitted to the intensive care unit: acute kidney injury versus no acute kidney injury

Characteristics[a]	AKI ($n = 70$)	No AKI ($n = 25$)	*P*	*N*	All ($N = 95$)
Age (yr)	44.5 (33.75–64.9)	35.0 (21.5–46)	0.011	95	42.0 (31.0–55.0)
Male sex, *n* (%)	59 (84.3)	21 (84.0)	0.973	95	80 (84.2)
BMI (kg/m^2)	24.9 (22.4–28.5)	24.5 (22.8–29.0)	<0.001	88	24.8 (22.8–27.9)
SOFA score[b]	10 (8.0–13.5)	5.5 (3.75–8.0)	<0.001	76	9.50 (7.75–13.0)
SAPS 3[b]	63.5 (52.7–82.2)	47.0 (41.5–55.2)	<0.001	92	59.5 (48.0–71.5)
APACHE II score[b]	17.0 (11.7–21.2)	5.5 (4.0–11.7)	<0.001	76	16.0 (11.0–21.0)
MELD score[b]	39 (31–45.2)	14 (9.0–19.5)	<0.001	71	34.5 (18–43)
Albumin (g/dl)[b]	3.25 (2.7–3.5)	3.3 (2.8–3.6)	0.577	74	3.15 (2.70–3.50)
Amylase (IU/l)[b]	164 (99–332)	83 (64–143)	<0.001	78	149 (95.5–302)
Lipase (IU/l)[b]	271 (131–944)	66 (31–127)	<0.001	77	259 (127–835)
Ammonia (μmol/l)[b]	96 (57.7–147.2)	61 (45–83)	0.001	76	96.0 (60.5–141)
Bilirubin (mg/dl)[b]	5.8 (4.1–7.8)	3.6 (0.9–5.6)	<0.001	78	5.84 (4.21–7.79)
INR[b]	2.3 (1.68–3.15)	1.26 (1.07–1.75)	<0.001	77	2.34 (1.69–3.15)
Fibrinogen (mg/dl)[b]	93 (72.5–134.5)	123 (105–156)	0.013	74	93.5 (72.2–132)
Factor V activity (%)[b]	32 (19–53)	85 (45–123)	<0.001	76	32.5 (19.0–56.0)
D dimer (ng/ml)[b]	10,000 (8778–10,000)	5063 (3647–10,000)	0.002	34	9945 (6292–10,000)
GGT (U/l)[b]	274 (190–420)	265 (162–430)	0.839	78	284 (202–422)
AST (U/l)[b]	7529 (5950–14,376)	2747 (1298–6668)	<0.001	71	8546 (6386–14,470)
ALT (U/l)[b]	4199 (2770–6696)	3203 (1416–3942)	0.007	79	4094 (2830–6729)
Lactate (mg/dl)[b]	35.0 (20.0–56.0)	16.0 (11.0–26.0)	<0.001	74	35.0 (20.2–54.0)
LDH (U/l)[b]	4542 (3178–6000)	1424 (832–4009)	<0.001	49	4082 (3125–4873)
CPK (U/l)[b]	748 (406–1524)	285 (145–1107)	0.007	73	653 (307–1405)
Sodium (mEq/l)[b]	136 (133–140)	135 (132–140)	0.258	79	137 (5.13)
Potassium (mEq/l)[b]	4.8 (4.37–5.42)	4.1 (3.85–4.55)	<0.001	79	4.87 (0.83)
Creatinine (mg/dl)[b]	5.14 (2.75–8.26)	0.96 (0.74–1.17)	<0.001	71	5.17 (2.73–8.37)
Urea (mg/dl)[b]	111 (72–155)	34 (25–45)	<0.001	79	111 (57.5–151)
Serum pH[b]	7.33 (7.26–7.38)	7.43–7.41–7.44)	<0.001	77	7.34 (7.27–7.40)
Bicarbonate (mEq/l)[b]	15.75 (11.27–19.57)	22.0 (20.0–24.0)	<0.001	76	15.8 (5.53)
Ionized calcium (mg/dl)[b]	3.93 (3.40–4.35)	4.45 (4.18–4.65)	<0.001	78	3.90 (0.60)
Phosphorus (mg/dl)[b]	5.5 (3.9–7.9)	2.5 (2.2–2.9)	<0.001	78	5.50 (3.80–7.80)
Chloride (mEq/l)[b]	102 (95.7–108)	105 (101–108)	0.177	78	102 (8.60)
Hemoglobin (g/dl)[b]	14.1 (12.5–15.2)	14.8 (13.6–16.0)	0.062	79	14.2 (12.6–15.3)
Leukocytes (cells/mm^3)[b]	4960 (3170–7410)	2790 (2410–4504)	0.002	79	4480 (2785–7275)
Platelets ($\times 10^3$/mm^3)[b]	75.0 (51.5–91.25)	72 (54.5–96.0)	0.839	79	74.0 (52.0–91.0)
CRP (mg/dl)[b]	8.45 (4.4–14.22)	3.0 (1.0–7.0)	0.001	77	7.80 (4.10–13.9)
FeNa (%)[b]	4.42 (2.01–8.37)	0.39 (0.23–0.71)	<0.001	71	2.91 (0.65–6.78)
FeK (%)[b]	43.11 (28.32–65.80)	6.88 (4.65–12.92)	<0.001	68	33.19 (13.21–57.95)
FeUrea (%)[b]	0.40 (0.25–0.51)	0.43 (0.40–0.50)	0.453	30	0.43 (0.31–0.51)
Urinary pH[b]	5.50 (5.00–6.00)	6.00 (5.00–6.125)	0.626	76	6.00 (5.00–6.00)

AKI, acute kidney injury; ALT, alanine aminotransferase; APACHE II, Acute Physiology and Chronic Health Evaluation II; AST, aspartate aminotransferase; BMI, body mass index; CPK, creatine phosphokinase; CRP, C-reactive protein; FeK, fractional excretion of potassium; FeNa, fractional excretion of sodium; FeUrea, fractional excretion of urea; GGT, gamma-glutamyltransferase; INR, international normalized ratio; LDH, lactate dehydrogenase; MELD, Model for End-Stage Liver Disease; RRT, renal replacement therapy; SAPS 3, Simplified Acute Physiology Score 3; SOFA, Sequential Organ Failure Assessment.
[a]Results expressed as median (interquartile range), except where otherwise indicated.
[b]At intensive care unit admission.

stage 2 in 2 (2.7%), and stage 3 in 64 (87.7%). Dialysis for patients with AKI classified as stage 0 or 1 was due to severe metabolic acidosis and elevated serum ammonia levels.

The initial dialysis method was CVVHD in 47 of the 70 patients (67.2%) dialyzed. Because of the increased risks of blood dyscrasia and liver failure associated with the use of heparin and citrate, dialysis was performed without anticoagulation. Temporary catheters were used in all 70 patients, with the main insertion sites being a femoral vein in 39 (55.7%) and the right jugular vein in 28 (40.0%).

There were 3 patients who had severe acidemia and therefore required dialysis that was started at a higher concentration of bicarbonate—mean of 38 ± 6 mEq/l; median of 35 mEq/l (IQR: 35–50 mEq/l). Because the patients in our sample were in liver failure and some had cerebral edema, sodium concentration in the dialysate was a major concern. Nevertheless, because most had low serum sodium concentrations at admission, the increase in sodium during dialysis was slow and gradual. Therefore, the sodium concentration in the dialysate was typical—mean of 141.0 ± 4.4 mEq/l; median of 139.5 mEq/l (IQR: 131.0–150.0 mEq/l).

Table 4. Clinical and biochemical characteristics of patients with yellow fever admitted to the intensive care unit and followed by the nephrology team

Characteristics	Survivors ($n = 15$)	Nonsurvivors ($n = 58$)	*P*	All ($N = 73$)
Age (yr), mean ± SD	42.2 ± 15.6	46.1 ± 14.8	0.392	45.3 ± 14.9
Male sex, *n* (%)	11 (73.3)	52 (89.7)	0.199	63 (86.3)
BMI (kg/m^2), mean ± SD	24.8 ± 3.39	26.1 ± 4.25	0.223	25.8 ± 4.10
SOFA score,[a] median (IQR)	8.00 (5.50–12.0)	10.0 (8.00–15.0)	0.048	10.0 (8.00–13.0)
SAPS 3,[a] median (IQR)	64.0 (52.0–72.0)	62.0 (54.2–79.2)	0.848	62.0 (54.0–77.0)
APACHE II score,[a] median (IQR)	15.0 (11.5–18.5)	17.0 (13.0–24.0)	0.169	17.0 (11.8–21.0)
MELD score,[a] median (IQR)	31.5 (22.0–39.2)	41.0 (31.5–46.5)	0.008	39 (28.7–45.2)
Mechanical ventilation, *n* (%)	8 (53.3)	57 (98.3)	<0.001	65 (89.0)
Vasopressor use, *n* (%)	7 (47.0)	58 (100)	<0.05	65 (89.0)
Blood transfusion, *n* (%)	15 (100)	54 (93.1)	0.575	69 (94.5)
Plasmapheresis, *n* (%)	3 (20.0)	16 (27.6)	0.745	19 (26.0)
Albumin (g/dl),[a] median (IQR)	3.00 (2.65–3.30)	3.20 (2.73–3.50)	0.362	3.10 (2.70–3.50)
Amylase (IU/l),[a] median (IQR)	109 (81.5–166)	187 (105–385)	0.018	160 (97.0–329)
Ammonia (μmol/l),[a] median (IQR)	58.0 (51.2–94.5)	101 (69.0–155)	0.005	97.0 (63.0–146)
Bilirubin (mg/dl),[a] median (IQR)	5.90 (2.66–7.38)	5.89 (4.53–7.85)	0.557	5.90 (4.49–7.82)
INR,[a] median (IQR)	1.76 (1.45–1.96)	2.61 (2.07–3.33)	0.001	2.46 (1.82–3.20)
Fibrinogen (mg/dl),[a] median (IQR)	101 (82.0–135)	89.0 (70.5–128)	0.444	91.0 (71.0–132)
Factor V activity (%),[a] median (IQR)	46.0 (29.0–76.5)	31.0 (17.8–42.2)	0.026	32.0 (19.0–49.0)
D dimer (ng/ml)[a], median (IQR)	7556 (2784–9918)	10,000 (6590–10,000)	0.174	9945 (5913–10,000)
AST (U/l),[a] median (IQR)	6792 (4938–7894)	11,009 (6632–15,818)	0.011	8633 (6437–14,562)
ALT (U/l),[a] median (IQR)	3587 (1970–4286)	5009 (3388–7238)	0.017	4212 (2880–6822)
Lipase (IU/l),[a] median (IQR)	225 (126–385)	272 (145–1038)	0.089	264 (128–858)
Lactate (mg/dl),[a] median (IQR)	19.0 (16.0–27.5)	38.0 (26.0–64.5)	<0.001	35.0 (22.2–54.0)
LDH (U/l),[a] mean ± SD	3151 ± 1110	4229 ± 1268	0.015	3953 ± 1307
CPK (U/l),[a] median (IQR)	524 (213–1288)	748 (422–1772)	0.130	668 (344–1405)
Sodium (mEq/l),[a] mean ± SD	136 (6.38)	136 (4.51)	0.627	136 (4.91)
Potassium (mEq/l),[a] mean ± SD	4.41 ± 0.52	5.03 ± 0.87	0.001	4.90 ± 0.85
Creatinine (mg/dl),[a] median (IQR)	3.91 (2.36–9.29)	5.52 (3.00–8.16)	0.497	5.17 (2.73–8.37)
Urea (mg/dl),[a] median (IQR)	107 (47–144)	116 (72–156)	0.476	112 (64.75–210)
Serum pH,[a] median (IQR)	7.35 (7.30–7.41)	7.34 (7.24–7.39)	0.360	7.34 (7.27–7.40)
Bicarbonate (mEq/l),[a] mean ± SD	18.7 ± 4.03	14.6 ± 5.49	0.003	15.4 ± 5.45
Ionized calcium (mg/dl),[a] mean ± SD	4.24 ± 0.37	3.79 ± 0.60	0.001	3.88 ± 0.59
Phosphorus (mg/dl),[a] median (IQR)	4.40 (3.75–5.30)	6.70 (4.00–8.10)	0.017	5.50 (3.88–7.82)
Chloride (mEq/l),[a] mean ± SD	103 ± 7.69	101 ± 9.17	0.298	101 ± 8.89
Hemoglobin (g/dl),[a] median (IQR)	13.0 (11.7–14.8)	14.2 (12.9–15.5)	0.061	14.1 (12.5–15.3)
Leukocytes (cells/mm^3),[a] median (IQR)	4480 (3275–6806)	4644 (2612–7278)	0.881	4529 (2790–7280)
Platelets (×10^3/mm^3),[a] median (IQR)	61.0 (50.5–83.5)	76.0 (52.2–91.0)	0.457	74.0 (52.0–91.0)
CRP (mg/dl),[a] median (IQR)	6.00 (4.10–14.2)	8.60 (4.30–13.8)	0.510	8.25 (4.25–14.0)
FeNa (%),[a] median (IQR)	4.40 (2.51–6.23)	4.42 (1.96–9.68)	0.687	4.42 (1.96–8.38)
RRT required, n (%)	14 (93.3)	58 (100)	0.205	72 (98.6)

ALT, alanine aminotransferase; APACHE II, Acute Physiology and Chronic Health Evaluation II; AST, aspartate aminotransferase; BMI, body mass index; CPK, creatine phosphokinase; CRP, C-reactive protein; FeNa, fractional excretion of sodium; INR, international normalized ratio; IQR, interquartile range; LDH, lactate dehydrogenase; MELD, Model for End-Stage Liver Disease; RRT, renal replacement therapy; SAPS 3, Simplified Acute Physiology Score 3; SOFA, Sequential Organ Failure Assessment.
[a]At intensive care unit admission.

Dialysis was initiated within the first 12 hours after hospital admission in 34 (48.6%) of the 70 patients dialyzed, and only 6 (8.6%) underwent dialysis >48 hours after admission. The dialysis method was changed in 30 (42.9%) of the cases, with 19 (63.3%) being switched from sustained low-efficiency dialysis to CVVHD because of rapid clinical worsening.

The median duration of the CVVHD sessions was 42 hours (IQR: 17–127 hours), and the median volume removed was 43 ml/h (IQR: 12–82 ml/h), translating to final hourly ultrafiltration values ranging from 0.00 ml/kg to 1.50 ml/kg of the admission body weight. Table 5 compares the survivors and nonsurvivors among the patients on dialysis. Supplementary Figure S1 reveals the Kaplan–Meier curve for survival since hospital admission, comparing the patients who required dialysis with those who did not.

Renal Function Recovery

Of the 15 patients who survived, 14 required dialysis during hospitalization but not after discharge. There was only one who progressed to end-stage renal disease, and, at this writing, that patient is undergoing dialysis 3 times a week at our dialysis facility. We followed 12 of the 15 patients after hospital discharge. The median time to AKI recovery (time from the first

Table 5. Clinical and biochemical characteristics of patients with yellow fever-induced acute kidney injury undergoing dialysis in the intensive care unit ($n = 70$): survivors versus nonsurvivors

Characteristics	Survivors ($n = 12$)	Nonsurvivors ($n = 58$)
Vasopressor use,[a] *n* (%)	3 (25.0)	24 (41.3)
ALT (U/l),[a] median (IQR)	3587 (2189–4479)	5009 (3204–7119)
AST (U/l),[a] median (IQR)	6631 (4873–7312)	11,008 (6673–15,721)
Bicarbonate (mEq/l),[a] mean ± SD	18.3 ± 4.0	14.6 ± 5.3
Phosphorus (mg/dl),[a] median (IQR)	4 (2.3–5.1)	6.5 (4.0–8.1)
Mechanical ventilation,[a] n (%)	8 (66.6)	53 (91.3)
Ionized calcium (mg/dl),[a] mean ± SD	4.2 ± 0.3	3.78 ± 0.6
Ammonia (μmol/l),[a] median (IQR)	58 (52.0–91.5)	101 (68–168)
Potassium (mEq/dl),[a] mean ± SD	4.4 ± 0.5	5.0 ± 0.9
Amylase,[a] median (IQR)	107 (81–147)	187 (106–382)
LDH (U/l),[a] mean ± SD	3024 ± 1260	4177 ± 1283
INR,[a] median (IQR)	1.7 (1.4–2.0)	2.6 (2.0–3.4)
Factor V activity (%),[a] median (IQR)	51 (30–71)	30 (17–42)
Continuous RRT,[a] n (%)	8 (66.6)	53 (91.3)
Urine output (ml/24 h),[b] median (IQR)	395 (162–835)	140 (0–450)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; IQR, interquartile range; LDH, lactate dehydrogenase; RRT, renal replacement therapy.
[a]$P < 0.05$.
[b]Before the start of dialysis.

dialysis session to discharge from nephrology) was 24 days (IQR: 10–38 days). The mean SCreat level at 30, 60, 90, 180, and 365 days after hospital discharge was 1.05 ± 0.29, 1.14 ± 0.42, 1.09 ± 0.42, 1.08 ± 0.40, and 1.03 ± 0.30 mg/dl, respectively. All but one of the 15 patients had complete recovery of renal function.

DISCUSSION

There is a paucity of data regarding AKI in YFV infection. In patients with YF, early renal changes have been found and AKI is most often observed before death.[3] In one recent study, also conducted in Brazil, an SCreat level ≥1.2 mg/dl was found to be an independent risk factor for mortality among patients with YF.[12]

In cases of YF, renal dysfunction develops between the fifth and seventh days after symptom onset, mainly in severe cases, including those that evolve to azotemia, proteinuria, or anuria.[13] Plasma urea levels >100 mg/dl have been associated with higher mortality in YF.[14] As previously mentioned, the possible pathophysiological mechanisms of YF include hemodynamic instability/shock, glomerular/vascular deposition of fibrin, an unbalanced inflammatory response, the direct effects of YFVs on the kidney tissue, and bilirubin-induced tubular toxicity.[7] An autopsy study, also conducted at our hospital during the 2018 outbreak, revealed that acute tubular necrosis and mesangial proliferative glomerulonephritis were the main kidney alterations responsible for AKI development in YFV-infected patients.[15] Other studies have revealed that YFV can be detected in the semen and urine up to 21 days after the onset of symptoms, which suggests that the genitourinary tract is a persistent reservoir of the virus.[16,17] In an autopsy study, Duarte-Neto et al.[17] analyzed 4 of the fatal cases of YF among the patients treated at our hospital during the 2018 outbreak. Those authors described pathologic findings similar to ours, including YF antigens detectable by immunohistochemistry in the tubular cells. They also reported a novel finding: YF RNA detectable by reverse-transcriptase polymerase chain reaction in human kidney tissue samples.

In the present study, dialysis and mechanical ventilation were found to be risk factors for mortality. Liver failure, as indicated by the Model for End-Stage Liver Disease score, liver enzyme levels, lactate dehydrogenase level, and factor V activity, underscores the importance of hemorrhagic events owing to fulminant liver failure in YF-associated mortality. Lipase level was also found to be an independent risk factor for in-hospital mortality, which indicates that pancreatitis is a relevant event in the outcome of YF. The high prevalence of pancreatitis in our sample was a surprising finding, which has been attributed to worse outcomes in patients with YF.[18,19]

In our study, imbalances in serum electrolyte levels, such as elevated phosphorus, elevated potassium, and low calcium, were also correlated with mortality. That is probably due to severe YF-induced multiorgan cellular injury mainly affecting the liver, striated muscle, and kidneys. We also found that acidosis and elevated lactate levels correlated with disease severity, with some patients presenting very low levels of serum bicarbonate even in the presence of hemodynamic stability.

The predominance of males among our patients who died from YF might be explained by the greater exposure to YF vectors and lower vaccination rate

among men. As expected, age and severity scores (Sequential Organ Failure Assessment, SAPS 3, Acute Physiology and Chronic Health Evaluation II, and Model for End-Stage Liver Disease) were independent variables that had a negative impact on the clinical outcomes. In a recent study involving >200 patients with laboratory-confirmed YF of varying clinical severities,[20] advanced age, male sex, leukocytosis, elevated aspartate aminotransferase/alanine aminotransferase level, elevated total bilirubin level, elevated creatinine level, altered prothrombin time, and increased plasmatic RNA viral load were found to be predictors of mortality, similar to what was found in the present study.

Among the patients followed by our nephrology team (i.e., the patients with AKI), urinalysis revealed leukocyturia, hematuria, cylindruria, and proteinuria. Nephrotic proteinuria, possibly related to glomerular injury, was identified in 44% of the samples. Previous studies have revealed that patients with YF have glomerular injury with basement membrane duplication, together with mesangial proliferative glomerulonephritis, acute tubular necrosis, and interstitial nephritis.[2,15,21]

Despite the renal tubular injury, urine density and urinary pH were normal in our patient sample. These findings should not be underestimated, because glomerular injury (probably caused by the virus) is a major indicator of severity (mortality being 84% in this scenario). Future studies should address the pathophysiological mechanisms of YF-induced glomerular injury and its impact on mortality, which remains unclear.

In our patient sample, the survivors had lower fractional excretions of sodium and potassium, suggestive of renal tubular integrity. In contrast, all the patients who were followed by the nephrology team presented higher fractional excretions of sodium and potassium, which are suggestive of acute tubular injury, and urine output at admission was lower in the nonsurvivors.

We also found that the use of CVVHD was associated with higher in-hospital mortality, which was attributed to the fact that the patients requiring that dialysis modality presented with a worse clinical picture (hemodynamic instability) at ICU admission. Nevertheless, long-term follow-up failed to reveal a difference between CVVHD and sustained low-efficiency dialysis, in terms of the mortality rate. Fewer than half of our patients were submitted to dialysis within the first 12 hours after hospital admission. That could be explained by the fact that the patients would need to receive plasma and platelets before insertion of the dialysis catheter. We hypothesize that the delay in starting dialysis had an impact on survival.

To our knowledge, ours is the first study to report the frequency of, risk factors for, and clinical course of YF-associated AKI and being the first to evaluate postdischarge renal function in YFV-infected patients with AKI. After 3 months from hospital discharge, complete recovery of renal function was achieved in 75% of the AKI survivors, with only one of whom remained dialysis dependent. We found no association between previous renal dysfunction and partial recovery of renal function after YF-associated AKI. Although all of our patients with AKI presented proteinuria at ICU admission, only one still had proteinuria after renal recovery. In that patient, renal biopsy results revealed IgA nephropathy. The remaining 25% of the AKI survivors achieved late partial recovery of renal function, which indicates that there is a need for longer follow-up periods in such patients.

CONCLUSION

In summary, the severe form of YF progresses rapidly and leads to multiple organ failure, with a high mortality rate. In our study, death occurred only in the patients who developed AKI. It is likely that the development of AKI in patients with YF involves multiple mechanisms, including hemodynamic instability, liver failure, and a direct effect of YFV on the kidney. Our findings suggest that certain clinical and biochemical indicators can help clinicians recognize potentially fatal cases of YF. In YFV-infected patients who develop AKI, renal function should be monitored after hospital discharge.

DISCLOSURE

All the authors declared no competing interests.

AUTHOR CONTRIBUTIONS

MFA and LA conceived and designed the study. MFA, CER, BVR, MADS, HYL, LMM, and LA were involved in data collection. VFS and PRGL analyzed the data and prepared the figures and tables. MFA and LA wrote the manuscript, and all coauthors revised and approved it.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. Survival curve of patients with yellow fever-induced acute kidney injury undergoing dialysis in the intensive care unit: survivors versus nonsurvivors.

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