Kidney and Blood Pressure Research

Research Article

Kidney Blood Press Res 2024;49:27–37
DOI: 10.1159/000535035

Received: April 26, 2023
Accepted: October 30, 2023
Published online: November 28, 2023

Endothelial Biomarkers in Critically Ill COVID-19 Patients: Potential Predictors of the Need for Dialysis

Marza de Sousa Zaranza[a, b] Gdayllon Cavalcante Meneses[c]
Reinaldo Barreto Oriá[a] Alice Maria Costa Martins[c]
Natalia Linhares Ponte Aragão[b] Nilcyeli Linhares Aragão[a, b]
Saskya Roberta Rodrigues de Andrade[a] Nicole Coelho Lopes[c]
Letícia Machado de Araújo[c] Ranieri Sales de Souza Santos[c]
Álvaro Rolim Guimarães[d] Ana Paula Pires Lázaro[e, f] Andrea Mazza Beliero[b]
Márcia Maria Pinheiro Dantas[a, b] Sandra Mara Brasileiro Mota[a, b]
Geraldo Bezerra da Silva Júnior[e, f]
Polianna Lemos Moura Moreira Albuquerque[b, f] Elizabeth De Francesco Daher[a]

[a]Medical Sciences Postgraduate Program, Department of Internal Medicine, School of Medicine, Universidade Federal do Ceará, Fortaleza, Brazil; [b]Instituto José Frota (IJF) Hospital, Fortaleza, Brazil; [c]Clinical and Toxicological Analysis Department, School of Pharmacy, Federal University of Ceará, Fortaleza, Brazil; [d]School of Medicine, Universidade Federal do Ceará, Fortaleza, Brazil; [e]Public Health Postgraduate Program, School of Medicine, Health Sciences Center, Universidade de Fortaleza, Fortaleza, Brazil; [f]School of Medicine, Health Sciences Center, Universidade de Fortaleza, Fortaleza, Brazil

Keywords
COVID-19 · Dialysis · Endothelium · Biomarkers · ICU · Prognosis

Abstract
Introduction: The aim of this was to evaluate the function of vascular biomarkers to predict the need for hemodialysis in critically ill patients with COVID-19. ***Methods:*** This is a prospective study with 58 critically ill patients due to COVID-19 infection. Laboratory tests in general and vascular biomarkers, such as VCAM-1, syndecan-1, angiopoietin-1, and angiopoietin-2, were quantified on intensive care unit (ICU) admission. ***Results:*** There was a 40% death rate. VCAM and Ang-2/Ang-1 ratio on ICU admission were associated with the need for hemodialysis. Vascular biomarkers (VCAM-1, syndecan-1, angiopoietin-2/angiopoietin-1 ratio) were predictors of death and their cutoff values were useful to stratify patients with a worse prognosis. In the multivariate cox regression analysis with adjusted models, VCAM-1 (OR 1.13 [CI 95%: 1.01–1.27]; $p = 0.034$) and Ang-2/Ang-1 ratio (OR 4.87 [CI 95%: 1.732–13.719]; $p = 0.003$) were associated with the need for dialysis. ***Conclusion:*** Vascular biomarkers,

karger@karger.com
www.karger.com/kbr

Correspondence to:
Gdayllon Cavalcante Meneses, gdayllon@yahoo.com.br

mostly VCAM-1 and Ang-2/Ang-1 ratio, showed better efficiency to predict the need for hemodialysis in critically ill COVID-19 patients.

Plain Language Summary

This study reports the use of endothelial biomarkers as useful tools to predict the first dialysis requirement during the ICU stay in patients with severe COVID-19. Endothelial dysfunction is an important mechanism to explain the pathophysiology of acute kidney injury caused by severe acute respiratory syndrome coronavirus 2 infection.

Introduction

The infection caused by the novel severe acute respiratory syndrome coronavirus 2, named COVID-19, has shown a broad clinical spectrum. The most complicated cases have been characterized by the development of severe acute respiratory syndrome, as well as other organ dysfunctions [1, 2]. Even with the advent of vaccines, there is concern about the emergence of new virus variants, an increase in the number of cases, and the collapse of the health system. In this context, acute kidney injury (AKI) has also gained notoriety, generating great worldwide concern due to the high demand for high-cost therapies, such as hemodialysis [3, 4].

The severe acute respiratory syndrome coronavirus 2 can induce immune dysregulation and the consequent inflammatory hyperactivity result in systemic endothelial dysfunction and a hypercoagulable state. These mechanisms can result in AKI due to intravascular volume depletion, hypotension, and consequent renal hypoperfusion, leading to prerenal AKI or even acute tubular necrosis. The "cytokine storm" may be closely related to alveolar and tubular damage in severe acute respiratory syndrome patients, characterizing a lung-kidney crosstalk [5, 6].

AKI in COVID-19 patients is multifactorial and includes worsening of previous risk factors, acute inflammatory response, cardiorenal syndrome, hemodynamic instability, and hypovolemia. The incidence is similar to that reported in other pandemics, notably in the H1N1 flu, suggesting the systemic inflammatory response may be the major contributor to severe AKI in the setting of virus-related critical diseases [7]. There are yet no effective therapies or strategies to reduce the incidence of AKI in this patient population [8, 9], and hemodialysis remains the main supportive therapy in patients who develop severe kidney injury, showing a strong association with high mortality rates [4].

Endothelial dysfunction and coagulopathy have been reported as the bases of severe AKI associated with COVID-19. The endothelial biomarkers can detect early kidney injury and allow the adoption of efficient measures to prevent disease progression and its complications. This finding could facilitate the monitoring of patients at higher risk [10].

Accordingly, this study aimed to analyze the prediction performance of biomarkers of endothelial damage in relation to the need of hemodialysis in severe COVID-19 patients. These insights can provide early diagnosis strategies, rational use of resources, and encourage the development of new studies about better therapeutic approaches.

Methods

Study Design and Selected COVID-19 Patients

This is a prospective, cross-sectional study, conducted with 58 critically ill patients admitted in the intensive care unit (ICU) due to COVID-19 at Instituto Doutor José Frota Hospital (IJF), a large tertiary hospital in the city of Fortaleza, state of Ceará, Northeastern Brazil, during the period between June 2020 and April 2021. The study included patients of both genders, aged 18 years and older, who had a confirmed diagnosis of COVID-19 by RT-PCR, and who agreed to participate in the research and signed the free and informed consent form. Patients from medical wards and those who were admitted in the ICU after the wards were excluded. Moreover, patients with a previous kidney disease registered in medical records and hospitalized for other causes than COVID-19 or who acquired COVID-19 during hospital stay were excluded. Also, patients who died during the first hours of ICU stay and patients without information on the precise time dialysis was initiated were also excluded.

Laboratory and Clinical Parameters of COVID-19 Patients

The patients were followed throughout the ICU stay. Medical records were assessed for patient characteristics, such as sociodemographic parameters, symptoms and comorbidities, length of ICU stay, time from ICU admission until the first dialysis, number of dialysis sessions, time between symptom onset and ICU admission, supportive care (vasopressor use, need for mechanical ventilation, and dialysis), and survival. The severity of the patients admitted to the ICU was estimated using the Simplified Acute Physiology Score 3 (SAPS 3). This is an international tool that uses data from patient admission to the ICU to assess the likelihood of death in the hospital outcome [11]. SAPS 3, oxygenation index (calculated using the ratio of

arterial oxygen partial pressure (PaO_2 in mm Hg) to fractional-inspired oxygen, mortality, ICU length of stay, and all the ICU data were calculated from a cloud database program (EpimedTM System®). https://www.epimedsolutions.com/sistema-epimed-monitor-uti/.

All recruited patients had blood samples collected on hospital admission. These samples were centrifuged, aliquoted, and frozen at −80°C until the biomarkers were analyzed. To verify whether the patients had AKI or not, the Kidney Disease: Improving Global Outcome criteria was used [12]. Briefly, AKI stage 1 was considered for patients who had serum creatinine (sCr) increases ≥0.3 mg/dL and up to 2-fold above the basal sCr. Increases within the range of 2 up to 3-fold greater than the basal sCr level were classified as AKI stage 2 and increases in the sCr level more than 3-fold of the basal level, as well as SCr values ≥4 mg/dL were considered as AKI stage 3.

Endothelial Biomarker Measurements

Endothelial biomarkers were quantified by ELISA assays, using isolated serum samples of the enrolled patients. Specific kits were acquired from R&D Systems® for angiopoietin-1 (cat# DY623) and angiopoietin-2 (cat# DY623). In the case of VCAM-1 and syndecan-1, the kits from Abcam® (ab47355 and ab47352) were used, respectively. The procedures were followed according to the manufacturer's recommendations.

Statistical Analysis

Categorical data were expressed as absolute counts and percentages. The χ^2 test or Fisher's exact test was used to evaluate the association between categorical data and dialysis requirement during the ICU stay. The quantitative data were explored, and normality was determined using the Kolmogorov-Smirnov test. Normal data were expressed as the mean ± standard deviation and non-normal data as the median and interquartile range. The quantitative data were compared according to dialysis requirement during ICU stay using Student's *t* test or Mann-Whitney test, according to data normality.

To evaluate the predictive performance of endothelial biomarkers for dialysis requirement during ICU stay, ROC curves were constructed, and the area under the ROC curve (AUC-ROC) together with 95% confidence intervals were estimated. The better cutoff for each biomarker was determined using the highest Youden index (Youden index = sensitivity + specificity – 1). Moreover, the patients were stratified according to selected cutoffs (lower vs. higher than cutoff), aiming to assess the prognostic value during the first 30 days of ICU stay through the Kaplan-Meier analysis using the "first dialysis" as the dependent event. The log-rank test was used to evaluate the statistical difference between the two groups based on the cutoff groups. Moreover, unadjusted and adjusted Cox proportional hazards regression analyses were performed using quantitative levels of endothelial biomarkers and previously associated parameters with dialysis requirement (using as condition $p < 0.05$). Platelet levels, age, gender, and the collinearity of variables were assessed. For the multivariate model, the backward elimination test with the likelihood ratio was used as a stepwise method, with the final models including all variables. The platelet levels were manually removed from specific models aiming to investigate the explanatory models for dialysis requirement without platelet influence. The data were analyzed using SPSS software for Macintosh, version 23 (IBM Corp. Armonk, NY, USA). A value of $p < 0.05$ was considered statistically significant for all analytical tests.

Results

Characteristics of COVID-19 Patients Admitted to ICU and Dialysis Requirement

A total of 368 patients were admitted to the ICU during the period between June 2020 and April 2021, and blood samples were collected for biomarker analysis from 116 patients. Twenty-three patients had a negative RT-PCR result for COVID-19 and 15 patients had another main diagnosis rather than COVID-19 upon ICU admission and were excluded; thus, 78 patients remained in the sample. Moreover, 4 patients with previous CKD and 16 patients who died during the first 24 h were also excluded. Hence, a total of 58 patients with ICU admission due to COVID-19 infection as the leading cause of hospitalization were assessed (Fig. 1, flowchart of the included critically ill COVID-19 patients).

The patients who required dialysis were older (62.4 ± 12.5 vs. 53.5 ± 16.5 years, $p = 0.037$) and had a higher prevalence of AKI (95% vs. 39%, $p < 0.001$). Moreover, the dialysis group required more vasopressor use (70% vs. 26%, $p = 0.001$) and mechanical ventilation (95% vs. 69%, $p = 0.022$) on ICU admission and had a higher mortality rate in comparison with the group that did not require dialysis during the ICU stay. There was no difference regarding the frequencies of comorbidities, including diabetes, hypertension, obesity, and evaluated symptoms, such as dyspnea, hypoxemia, and fever on admission between the groups (Table 1, characteristics, SAPS 3, and laboratory parameters on admission of ICU according to the need for dialysis during ICU stay of the critically ill COVID-19 patients).

Regarding laboratory parameters evaluated on ICU admission, COVID-19 patients who needed dialysis during the ICU stay had decreased platelets and increased lactate dehydrogenase (LDH), urea, and creatinine levels. No statistical significance was observed for D-dimer and C-reactive protein levels, as well as for hemoglobin, any leucogram parameters, and for any liver markers (bilirubin, aspartate transaminase, alanine transaminase). The SAPS 3 on ICU admission was markedly higher in COVID-19 patients who required dialysis during the ICU stay (63 ± 13.8 vs. 49.5 ± 14.2, $p < 0.001$) (Table 1 characteristics, SAPS 3, and laboratory parameters on admission of ICU according to the need for dialysis during ICU stay of the critically ill COVID-19 patients).

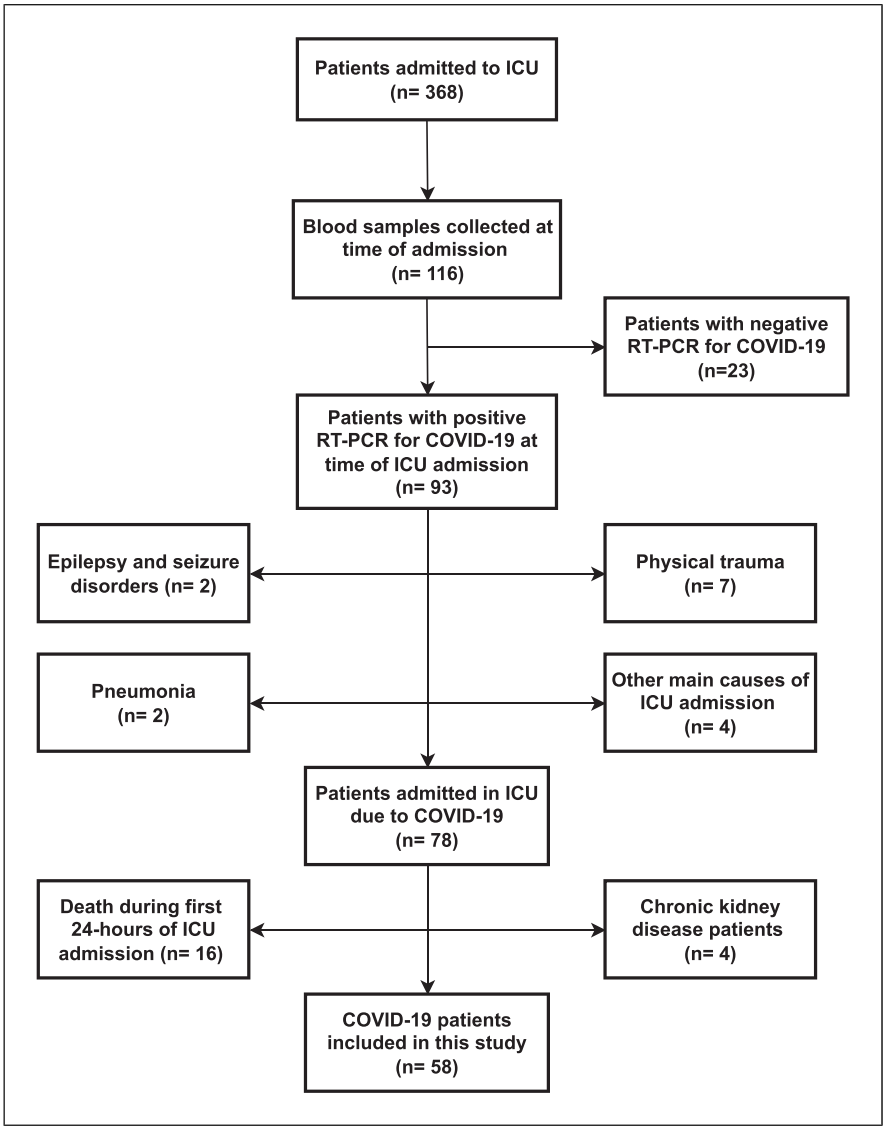

Fig. 1. Flowchart of the included critically ill COVID-19 patients.

Early Endothelial Biomarker Levels and Dialysis Requirement in Critically Ill COVID-19 Patients

The levels of the endothelial biomarkers on admission were compared between the groups according to the need for dialysis in the ICU. VCAM-1 and Ang-2/Ang-1 ratio were increased in the dialysis group. Syndecan-1 showed a tendency toward significance (p = 0.065) and its level was higher in the dialysis group (Fig. 2, levels of systemic endothelial biomarkers of critically ill COVID-19 patients according to the need for dialysis).

All endothelial biomarkers were evaluated using the ROC curve analysis to predict dialysis requirement during the ICU stay. The Ang-2/Ang-1 ratio had a better AUC-ROC (0.684, 95% CI: 0.536–0.833; p = 0.022), followed by VCAM-1 (0.673, 95% CI: 0.521–0.826; p = 0.031). In a combined approach using VCAM-1 and syndecan-1 levels and Ang-2/Ang-1 ratio, the AUC-ROC improved to 0.713, 95% CI: 0.568–0.858; p = 0.008. The better cutoff value for VCAM-1, Ang-2/Ang-1 ratio, syndecan-1, and combined approach was 1,329, 0.245, 300, and 5,490 ng/mL, respectively (Table 2, prediction performance of endothelial biomarkers to the need for dialysis in severe COVID-19 patients).

The Kaplan-Meier analysis with the previously determined cutoffs of endothelial biomarkers showed that COVID-19 patients admitted to the ICU with levels above the cutoff levels of syndecan-1, VCAM-1, and Ang-2/Ang-1 ratio needed dialysis sooner, with statistical significance using the log-rank test (Fig. 3, survival curves for the first dialysis during ICU stay of critically ill COVID-19 patients stratified according to the better cutoff of endothelial

Table 1. Characteristics, SAPS 3, and laboratory parameters on admission in ICU according to the need for dialysis during ICU stay of the critically ill COVID-19 patients

	Dialysis in the ICU		
	no (n = 37)	yes (n = 21)	p value*
Age, years	53.5±16.5	62.4±12.5	**0.037**
Gender (male)	22 (59.5)	11 (52.4)	0.601
Time from ICU admission until the first dialysis, days	–	6 (2–7)	–
Number of dialysis sessions	–	5.5 (2–10)	–
Time between onset of symptoms and ICU admission, days	10 (8–15)	10 (6–13)	0.684
Symptoms and comorbidities			
Comorbidities	23 (63.9)	16 (76.2)	0.335
Fever on admission	20 (62.5)	15 (78.9)	0.221
Dyspnea	34 (91.9)	19 (90.5)	1.000
Saturation	23 (63.9)	14 (66.7)	0.832
Heart disease	7 (20)	6 (31.6)	0.506
Liver disease	0 (0)	1 (5.3)	0.358
Asthma	2 (5.9)	1 (5.3)	1.000
Diabetes	9 (24.3)	8 (40)	0.217
Neurological disease	2 (5.9)	1 (5)	1.000
Lung diseases	1 (2.9)	0 (0)	1.000
Obesity	13 (36.1)	6 (31.6)	0.737
Arterial hypertension	14 (37.8)	11 (52.4)	0.282
Acute kidney injury	14 (38.9)	19 (95)	<**0.001**
Vasopressors use	9 (25.7)	14 (70)	**0.001**
Mechanical ventilation use	24 (68.6)	19 (95)	**0.022**
Outcome			<**0.001**
Survivors	37 (100)	5 (23.8)	
Nonsurvivors	0 (0)	16 (76.2)	
Unit length stay, days	12 (6–17)	10,5 (6–19)	0.944
SAPS 3 and laboratory data			
SAPS 3 score	49.5±14.2	63±13.8	<**0.001**
Hemoglobin, g/L	121±21	115±22	0.348
Leukocyte count, × 10^9/L	12±4.5	13.5±4.3	0.226
Lymphocyte count, × 10^9/L	0.8 (0.6–1.2)	0.7 (0.6–1.15)	0.468
Platelet count, × 10^9/L	291±95	193±102	0.001
Urea, mg/dL	39 (28–55)	100 (40–170)	<**0.001**
Creatinine, mg/dL	0.7 (0.6–0.95)	1.6 (1–2.6)	<**0.001**
Potassium, mEq/L	4.26±0.67	4.2±0.77	0.756
AST, U/L	48 (30–63)	55 (32–83)	0.337
ALT, U/L	48 (29–68)	50 (28–71)	0.912
LDH, U/L	707 (556–892)	888 (743.5–1,355)	**0.014**
Total bilirubin, mg/dL	0.52 (0.31–0.76)	0.52 (0.34–0.91)	0.677
CRP, pg/mL	145.5 (36.8–208.3)	161.1 (72.5–210.1)	0.525
D-Dimer, ng/mL	1.81 (0.78–2.46)	2.26 (0.58–6.09)	0.646

Continuous data are expressed as the median and interquartile range between parenthesis for non-normal data, or as mean ± standard deviation for normal data. AST, aspartate transaminase; ALT, alanine transaminase; LDH, lactate dehydrogenase; CRP, C-reactive protein. *The χ^2 or exact Fisher test was used for categorical data. *The Mann-Whitney or Student's t test was applied according to normality of the data.

biomarkers levels). Then, all these selected endothelial biomarkers and all hospital admission clinical and laboratory parameters were investigated using univariate Cox regression (using "first dialysis" as the dependent event) in the univariate and multivariate models.

In the univariate cox regression analysis, older age, vasopressor use, increased SAPS 3 score, LDH, VCAM-1, syndecan-1 levels, Ang-2/Ang-1 ratio, and decreased platelet levels contributed for dialysis requirement (hazard ratio >1.00). In the adjusted models with platelet

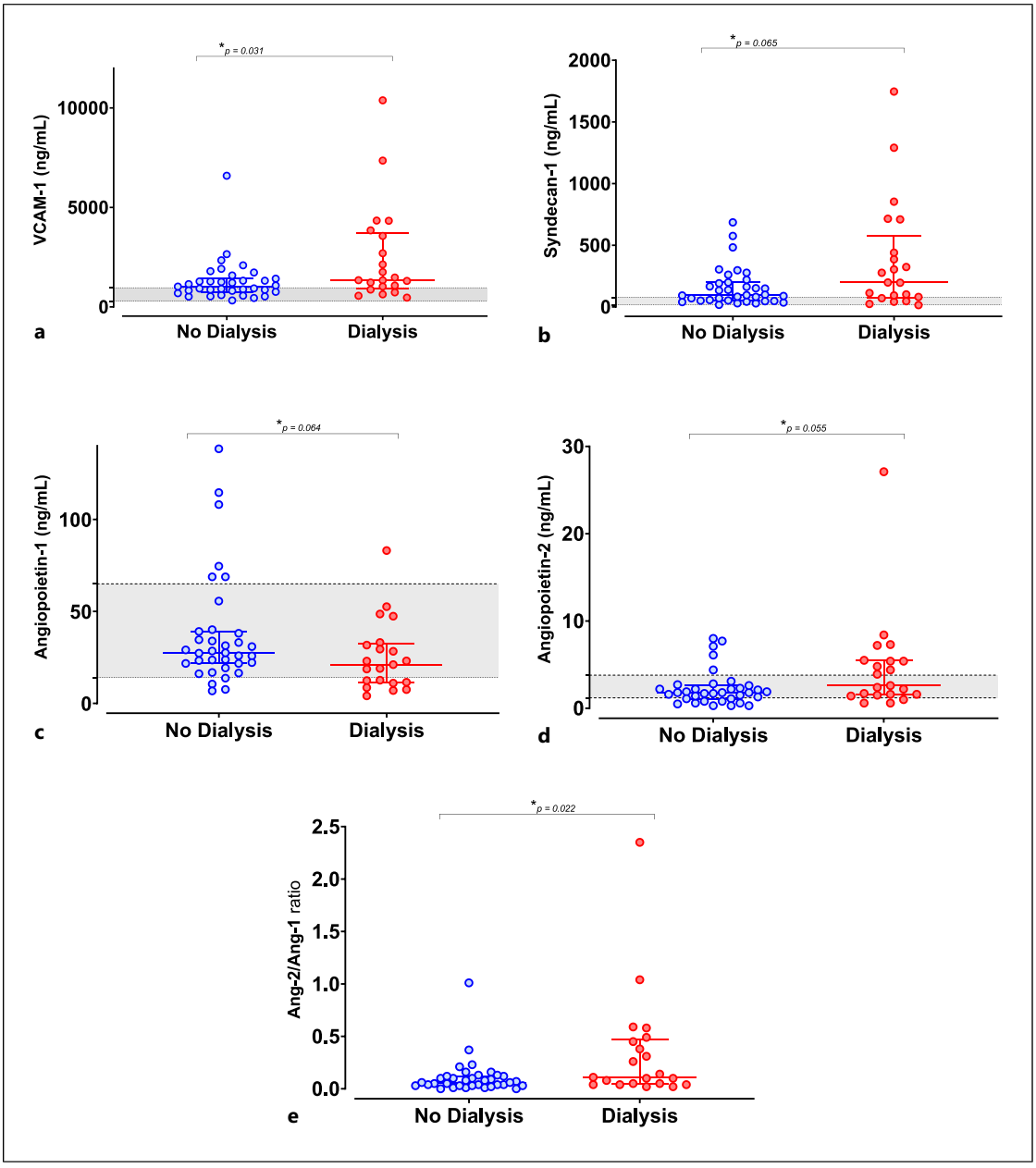

Fig. 2. Levels of systemic endothelial biomarkers of critically ill COVID-19 patients according to the need for dialysis.

inclusion, only age, SAPS 3 score, mechanical ventilation use, platelet, and VCAM-1 levels remained associated with dialysis requirement. In another context without the inclusion of platelets in the multivariate models, the Ang-2/Ang-1 ratio emerged as an explanatory parameter for dialysis requirement, together with SAPS 3 score and VCAM-1 level in the final model (Table 3, cox regression to the need for dialysis with unadjusted values and models according to the presence or absence of platelets).

Discussion

Among the proposed pathways to explain the pathophysiology of COVID-19-associated AKI, evidence points to a complex and multifactorial mechanism, in which the role of endothelial dysfunction and coagulopathy stands out [13]. This study reports the use of endothelial biomarkers as useful tools to predict the first dialysis requirement during the ICU stay in patients with COVID-19 and prognosis.

Table 2. Prediction performance of endothelial biomarkers to the need for dialysis in severe COVID-19 patients

	Cutoff	AUC-ROC (CI 95%)	Sensitivity, %	Specificity, %	*p* value
VCAM-1, ng/mL	1,329	0.673 (0.521–0.826)	57	74	0.031
Syndecan-1, ng/mL	300	0.648 (0.487–0.809)	43	89	0.065
Angiopoietin-1, ng/mL	23	0.649 (0.495–0.803)	62	69	0.064
Angiopoietin-2, ng/mL	3.5	0.654 (0.502–0.807)	48	86	0.055
Ang-2/Ang-1 ratio	0.245	0.684 (0.536–0.833)	43	94	0.022
Combined[a], ng/mL	5,490	0.713 (0.568–0.858)	81	54	0.008

Cutoffs were determined using the Youden index. [a]VCAM-1, syndecan-1, and Ang-2/Ang-1 ratio.

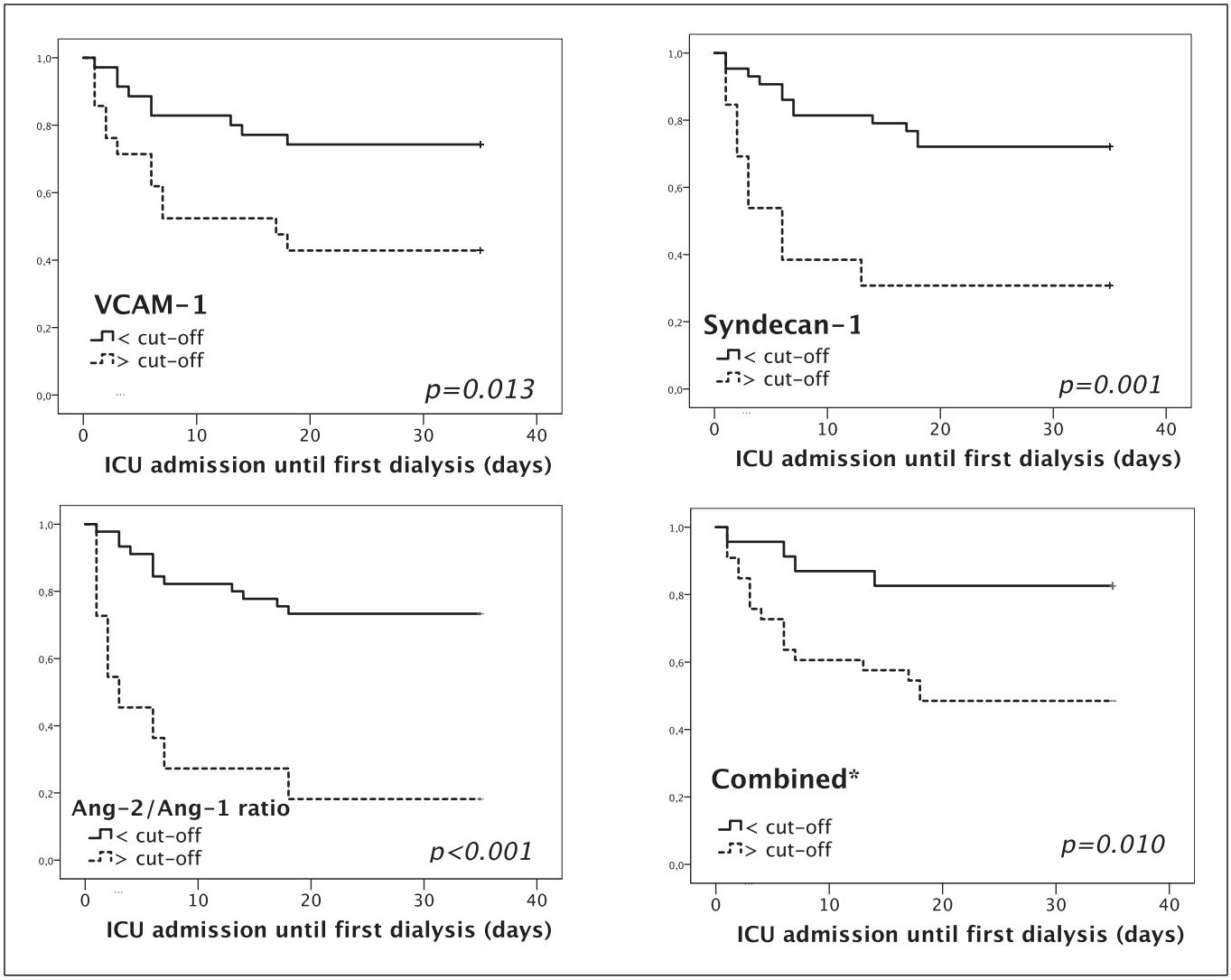

Fig. 3. Survival curves for the first dialysis during ICU stay of critically ill COVID-19 patients stratified according to the better cutoff of endothelial biomarkers levels. Cutoffs were determined using Youden index. *VCAM-1, syndecan-1 and Ang-2/Ang-1 ratio.

Table 3. Cox regression to the need for dialysis with unadjusted values and models according to the presence or absence of platelets

	Unadjusted		Model 1[a]		Model 2[a]	
	HR (CI 95%)	*p* value	HR (CI 95%)	*p* value	HR (CI 95%)	*p* value
Age, years	1.032 (1.001–1.064)	0.042	1.066 (1.015–1.121)	0.011	1.039 (0.993–1.087)	0.095
Gender (female)	1.247 (0.53–2.939)	0.613	–	–	–	–
SAPS 3 (each point)	1.05 (1.018–1.083)	0.002	1.084 (1.029–1.143)	0.003	1.055 (1.009–1.103)	0.018
Vasopressors use	4.4 (1.684–11.49)	0.002	–	–	–	–
Mechanical ventilation use	6.63 (0.887–49.57)	0.065	14.38 (1.39–148.42)	0.025	5.182 (0.64–41.98)	0.123
LDH (for each 500 U/L)	2.325 (1.163–4.646)	0.017	–	–	–	–
Platelets (each 50 (10^3/mm^3) decrement)	1.803 (1.314–2.474)	<0.001	1.685 (1.239–2.292)	0.001	–	–
VCAM-1 (for each 500 ng/mL)	1.112 (1.028–1.203)	0.008	1.134 (1.01–1.274)	0.034	1.141 (1.021–1.275)	0.020
Syndecan-1 (for each 50 ng/mL)	1.102 (1.045–1.163)	<0.001	–	–	–	–
Ang-2/Ang-1 ratio	4.63 (2.001–10.72)	<0.001	–	–	4.874 (1.732–13.719)	0.003

LDH; lactate dehydrogenase. [a]The backward method was applied: Model 1 = platelets were included from the first step; model 2 = platelets were manually removed and did not participate in any step.

In the present study, most of the patients were elderly males. Aging causes a dysfunction in the immune system that generates a decline in immune response [14]. These alterations associate with the failure to control COVID-19 infection and predispose to evolution to severe forms [15]. In addition, senescence exhibits a chronic state of low-grade systemic inflammation, increased incidence of comorbidities, and moderate to severe frailty [16].

Our data revealed that higher SAPS 3, vasopressor use, and mechanical ventilation on ICU admission were associated with the need for dialysis. Some studies support the association between dialysis and elevated mortality [17, 18]. In addition, the correlation between elevated SAPS 3 and pulmonary and renal dysfunction in predicting mortality has been reported [19].

Hospitalized patients often develop secondary infections and have an increased risk of sepsis-associated AKI [20]. Hypovolemia, vasodilation, increased vascular permeability, and restricted volume use are some mechanisms proposed to explain hypotension in critically ill patients, which justifies the greater need for vasoactive drugs in this clinical scenario.

Invasive mechanical ventilation is an essential supportive therapy in the ICU. The use of positive pressure ventilation can activate the sympathetic tone and lead to the activation of the renin-angiotensin-aldosterone system [21]. Modifications in lung compliance usually require a high positive end-expiratory pressure, which leads to increased intrathoracic pressure. This alteration has multiple hemodynamic effects. For example, a decrease in the venous return to the heart, a reduction of the cardiac output, and an increase in the intra-abdominal pressure are potential complications in these patients. This may result in a higher renal venous pressure, then a lower glomerular filtration rate [22]. Other studies have also reported the association between AKI with the need for mechanical ventilation and prolonged hospital stays [23].

Activation of platelets in COVID-19 is a key mechanism in the characteristic inflammatory thrombotic response involved in the pathogenesis of the disease [24, 25]. Microvascular obstruction of renal capillaries by fibrin thrombi relates to ischemia, hypoxemia, and hypercoagulability, which may explain the relationship between thrombocytopenia, AKI, and hemodialysis as demonstrated in the present study [26].

The present findings evidenced the association between elevated LDH enzyme levels in COVID-19 patients and the need for dialysis. LDH is an enzyme found in the cells of almost all organs [27]. Thus, abnormal values result from tissue damage and decreased oxygenation. For instance, severe infections can cause cytokine-mediated tissue damage and LDH release [28]. Moreover, elevated LDH levels have been associated with severe COVID-19 pneumonia and thrombotic microangiopathy, which can lead to renal injury [29]. Other studies have also demonstrated elevated LDH levels in patients with COVID-19 and the need for dialysis [18].

The present study demonstrates the association between admitting serum levels of endothelial biomarkers and the need for dialysis. Under normal conditions, the endothelium regulates blood coagulation, volume, and

electrolyte balance, and then can prevent thrombosis, microangiopathies, and diffuse intravascular coagulation [30]. The results confirm a major role of microcirculatory dysfunction in the pathophysiology of severe COVID-19 infection, which could explain multiple clinical complications of the disease. Patients who presented these biomarker levels above the cutoff established in our analyses progressed more rapidly with severe renal dysfunction and required dialysis earlier.

VCAM-1 is a biomarker detected only after endothelial cell stimulation by cytokines and has been studied as a diagnostic and prognostic agent for various diseases [31]. In this study, higher levels of VCAM-1 were associated with the need for dialysis and rapid progression to severe renal dysfunction.

Ang-1 has vascular protective effects and stimulates vessel remodeling and angiogenesis [32]. In contrast, Ang-2 plays a role in endothelial activation, inflammation, vascular hyperpermeability, and apoptosis [33]. High serum Ang-2 levels have been evidenced in severe COVID-19 patients [34]. Experimental studies with rats and ventilator-induced lung injury have also correlated higher levels of these biomarkers with AKI [35]. The imbalance between Ang-1 and Ang-2 levels with a consequent increase in the Ang-2/Ang-1 ratio and the breakdown of homeostasis due to their antagonistic effects may explain the association of these biomarkers with the need for dialysis and the speed of progression of renal injury in the group of patients studied.

Inflammatory reactions can induce endothelial glycocalyx degradation and the release of its components, such as syndecan-1 [36]. This process allows increased vascular permeability, dysregulated vasodilation, and microvessel thrombosis, which leads to the maintenance of endothelial damage, inflammation, and coagulopathy [37]. Syndecan-1 levels gradually increase while renal dysfunction progresses [38]. Patients with COVID-19 and high syndecan-1 levels develop more exacerbated endothelial damage and inflammatory reactions and have higher mortality [39]. Some studies showed that these biomarkers were independently associated with severe AKI in other settings [40]. The results of the present study revealed that syndecan-1 is a potential marker for the prediction of hemodialysis requirement in patients with COVID-19.

The present study had limitations. The small sample size may compromise the effect for detecting relevance of some variables that could have involvement in kidney dysfunction. Moreover, despite early association between endothelial biomarkers with the need for hemodialysis, even in adjusted multivariate models, the data cannot prove a causality link among them.

In conclusion, early levels of endothelial dysfunction biomarkers on ICU admission in COVID-19 patients were associated with the need for hemodialysis and prognosis since vascular and coagulation disorders seem to be crucial elements in this scenario. Further prospective studies with larger number of patients should evaluate the role of endothelial dysfunction biomarkers for the incidence of kidney diseases in these patients and prognostic value for others sequelae.

Summary Points

- Evidence points to the role of endothelial dysfunction and coagulopathy in the pathophysiology of COVID-19-associated AKI.
- Endothelial biomarkers can predict the first dialysis requirement during the ICU stay in patients with COVID-19 and prognosis.
- Older patients, higher SAPS 3, vasopressor use, and mechanical ventilation on ICU admission were associated with the need for dialysis.
- Microvascular obstruction of renal capillaries may explain the relationship between thrombocytopenia, AKI, and hemodialysis.
- Higher LDH enzyme levels in COVID-19 patients were associated with the need for dialysis.
- Higher levels of VCAM-1 were associated with the need for dialysis and rapid progression to severe renal dysfunction.
- The increase in the Ang-2/Ang-1 ratio may explain the association of these biomarkers with the need for dialysis and the speed of progression of renal injury.
- Syndecan-1 is a potential marker for the prediction of hemodialysis requirement in patients with COVID-19.

Acknowledgments

We are very grateful to the entire team of professionals at Instituto Dr. José Frota Hospital who joined forces to care for the critically ill patients with COVID-19 and contributed to the collection of their samples used in this study.

Statement of Ethics

This study was approved by the National Research Ethics Committee under CAAE number:30579020.4.1001.0008. The patients were informed about the study purpose, and upon

acceptance to participate, they signed the free and informed consent form before the beginning of evaluation. As some admitted patients required immediate ICU care and were unable to sign the term, it was signed by a family member previously authorized by the patient.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

Brazilian Coordination of Postgraduation – Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) supported this study through grants given to the co-authors (PLMMA). Number of the process: 88882.306447/2018-01.

Brazilian Coordination of Postgraduation – Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) supported the materials used. Number of process support 1: 88881.505364/2020-01. Number of process support 2: 88881.507066/2020-01.

Edson Queiroz Foundation/University of Fortaleza for the financial support.

Author Contributions

M.S.Z., P.L.M.M.A., and G.C.M. conceived the study and conducted the selection, interpretation of the data, and project administration. N.L.P.A., N.L.A., A.R.G., A.P.P.L., A.M.B., and M.M.P.D. contributed with the study design and selection of the studies. S.M.B.M., S.R.R.A., N.C.L., L.M.A., and R.S.S.S. contributed with the management and storage of biological samples and ELISA assays for biomarkers measurements. R.B.O., A.M.C.M., G.B.S.J., and E.F.D. revised this manuscript. G.C.M. performed the design and interpretation of the data and formal analysis. E.F.D. and P.L.M.M.A. were responsible for the funding acquisitions. All authors read and approved the final version of the manuscript.

Data Availability Statement

The submitting authors hereby declare that this contribution is original. The work has not been published previously in any language and is not currently under evaluation by another publisher. Each author has made substantial contributions to the conception or design of the work, or to the acquisition, analysis, or interpretation of data for the work. All authors approved the final version to be published. All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

References

1 Wang L, Li X, Chen H, Yan S, Li D, Li Y, et al. Coronavirus disease 19 infection does not result in acute kidney injury: an analysis of 116 hospitalized patients from Wuhan, China. Am J Nephrol. 2020;51(5):343–8.
2 Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382(8):727–33.
3 Cheng Y, Luo R, Wang K, Zhang M, Wang Z, Dong L, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. Kidney Int. 2020;97(5):829–38.
4 Hirsch JS, Ng JH, Ross DW, Sharma P, Shah HH, Barnett RL, et al. Acute kidney injury in patients hospitalized with COVID-19. Kidney Int. 2020;98(1):209–18.
5 Jose RJ, Manuel A. COVID-19 cytokine storm: the interplay between inflammation and coagulation. Lancet Respir Med. 2020;8(6):e46–7.
6 Ye Q, Wang B, Mao J. The pathogenesis and treatment of the `Cytokine Storm' in COVID-19. J Infect. 2020;80(6):607–13.
7 Pettilä V, Webb SA, Bailey M, Howe B, Seppelt IM, Bellomo R. Acute kidney injury in patients with influenza A (H1N1) 2009. Intensive Care Med. 2011;37(5):763–7.
8 Su H, Yang M, Wan C, Yi LX, Tang F, Zhu HY, et al. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. Kidney Int. 2020;98(1):219–27.
9 Ronco C, Reis T, Husain-Syed F. Management of acute kidney injury in patients with COVID-19. Lancet Respir Med. 2020;8(7):738–42.
10 Coca SG, Yalavarthy R, Concato J, Parikh CR. Biomarkers for the diagnosis and risk stratification of acute kidney injury: a systematic review. Kidney Int. 2008;73(9):1008–16.
11 Moreno RP, Metnitz PGH, Almeida E, Jordan B, Bauer P, Campos RA, et al. Saps 3-- from evaluation of the patient to evaluation of the intensive care unit. Part 2: development of a prognostic model for hospital mortality at ICU admission. Intensive Care Med. 2005;31(10):1345–55.
12 Kellum JA, Lameire N; KDIGO AKI Guideline Work Group. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). Crit Care. 2013;17(1):204.
13 Nadim MK, Forni LG, Mehta RL, Connor MJ Jr, Liu KD, Ostermann M, et al. COVID-19-associated acute kidney injury: consensus report of the 25th Acute Disease Quality Initiative (ADQI) Workgroup. Nat Rev Nephrol. 2020;16(12):747–64.
14 Mueller AL, McNamara MS, Sinclair DA. Why does COVID-19 disproportionately affect older people? Aging. 2020;12(10):9959–81.
15 Rydyznski Moderbacher C, Ramirez SI, Dan JM, Grifoni A, Hastie KM, Weiskopf D, et al. Antigen specific adaptive immunity to SARS-CoV-2 in acute COVID-19 and associations with age and disease severity. Cell. 2020;183(4):996–1012.e19.
16 Hewitt J, Carter B, Vilches-Moraga A, Quinn TJ, Braude P, Verduri A, et al. The effect of frailty on survival in patients with COVID-19 (COPE): a multicentre, European, observational cohort study. Lancet Public Health. 2020;5(8):e444–51.
17 Silver SA, Beaubien-Souligny W, Shah PS, Harel S, Blum D, Kishibe T, et al. The prevalence of acute kidney injury in patients hospitalized with COVID-19 infection: a systematic review and meta-analysis. Kidney Med. 2021;3(1):83–98.e1.
18 Kemec Z, Akgul F. Relationship between acute kidney injury requiring renal replacement treatment and mortality in patients with COVID-19. Niger J Clin Pract. 2022;25(8):1348–56.
19 Lázaro APP, Albuquerque PLMM, Meneses GC, Zaranza MS, Batista AB, Aragão NLP, et al. Critically ill COVID-19 patients in northeast Brazil: mortality predictors during the first and second waves including SAPS 3. Trans R Soc Trop Med Hyg. 2022;116(11):1054–62.
20 Cuadrado-Payán E, Montagud-Marrahi E, Torres-Elorza M, Bodro M, Blasco M, Poch E, et al. SARS-CoV-2 and influenza virus co-infection. Lancet. 2020;395(10236):e84.

21 Dudoignon E, Moreno N, Deniau B, Coutrot M, Longer R, Amiot Q, et al. Activation of the renin-angiotensinaldosterone system is associated with acute kidney injury in COVID-19. Anaesth Crit Care Pain Med. 2020;39(4):453–5.
22 Koyner JL, Murray PT. Mechanical ventilation and lung-kidney interactions. Clin J Am Soc Nephrol. 2008;3(2):562–70.
23 Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020;8(5):475–81.
24 Guo L, Rondina MT. The Era of thromboinflammation: platelets are dynamic sensors and effector cells during infectious diseases. Front Immunol. 2019;10:2204.
25 Zhang L, Feng X, Zhang D, Jiang C, Mei H, Wang J, et al. Deep vein thrombosis in hospitalized patients with COVID-19 in wuhan, China: prevalence, risk factors, and outcome. Circulation. 2020;142(2):114–28.
26 Kerlin BA, Waller AP, Sharma R, Chanley MA, Nieman MT, Smoyer WE. Disease severity correlates with thrombotic capacity in experimental nephrotic syndrome. J Am Soc Nephrol. 2015;26(12):3009–19.
27 Hsu PP, Sabatini DM. Cancer cell metabolism: warburg and beyond. Cell. 2008;134(5):703–7.
28 Martinez-Outschoorn UE, Prisco M, Ertel A, Tsirigos A, Lin Z, Pavlides S, et al. Ketones and lactate increase cancer cell "stemness," driving recurrence, metastasis and poor clinical outcome in breast cancer: achieving personalized medicine via metabologenomics. Cell Cycle. 2011;10(8):1271–86.
29 Zhang T, Chen H, Liang S, Chen D, Zheng C, Zeng C, et al. A non-invasive laboratory panel as a diagnostic and prognostic biomarker for thrombotic microangiopathy: development and application in a Chinese cohort study. PLoS One. 2014;9(11):e111992.
30 Rajendran P, Rengarajan T, Thangavel J, Nishigaki Y, Sakthisekaran D, Sethi G, et al. The vascular endothelium and human diseases. Int J Biol Sci. 2013;9(10):1057–69.
31 Page AV, Liles WC. Biomarkers of endothelial activation/dysfunction in infectious diseases. Virulence. 2013;4(6):507–16.
32 Brindle NP, Saharinen P, Alitalo K. Signaling and functions of angiopoietin1 in vascular protection. Circ Res. 2006;98(8):1014–23.
33 Li F, Yin R, Guo Q. Circulating angiopoietin-2 and the risk of mortality in patients with acute respiratory distress syndrome: a systematic review and meta-analysis of 10 prospective cohort studies. Ther Adv Respir Dis. 2020;14:1753466620905274.
34 Smadja DM, Guerin CL, Chocron R, Yatim N, Boussier J, Gendron N, et al. Angiopoietin-2 as a marker of endothelial activation is a good predictor factor for intensive care unit admission of COVID-19 patients. Angiogenesis. 2020;23(4):611–20.
35 Hepokoski M, Englert JA, Baron RM, Crotty-Alexander LE, Fuster MM, Beitler JR, et al. Ventilator-induced lung injury increases expression of endothelial inflammatory mediators in the kidney. Am J Physiol Ren Physiol. 2017;312(4):F654–60.
36 Uchimido R, Schmidt EP, Shapiro NI. The glycocalyx: a novel diagnostic and therapeutic target in sepsis. Crit Care. 2019;23(1):16.
37 Johansson PI, Stensballe J, Rasmussen LS, Ostrowski SR. A high admission syndecan-1 level, a marker of endothelial glycocalyx degradation, is associated with inflammation, protein c depletion, fibrinolysis, and increased mortality in trauma patients. Ann Surg. 2011;254(2):194–200.
38 Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, et al. Dysregulation of immune response in patients with coronavirus 2019 (COVID-19) in wuhan, China. Clin Infect Dis. 2020;71(15):762–8.
39 Zhang D, Li L, Chen Y, Ma J, Yang Y, Aodeng S, et al. Syndecan-1, an indicator of endothelial glycocalyx degradation, predicts outcome of patients admitted to an ICU with COVID-19. Mol Med. 2021;27(1):151.
40 de Melo Bezerra Cavalcante CT, Castelo Branco KM, Pinto Júnior VC, Meneses GC, de Oliveira Neves FM, de Souza NMG, et al. Syndecan-1 improves severe acute kidney injury prediction after pediatric cardiac surgery. J Thorac Cardiovasc Surg. 2016;152(1):178–86.e2.