

COVID-19

Acute Arterial Occlusions in COVID-19 Times: A Comparison Study Among Patients with Acute Limb Ischemia With or Without COVID-19 Infection

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Background: To determine the impact of coronavirus (COVID-19) infection in patients with acute limb ischemia (ALI), mainly the limb salvage estimates the rate and the overall survival rate.

Methods: This was a prospective, consecutive cohort study of ALI patients with or without COVID-19 infection. Two groups of patients were identified: patients with ALI and COVID-19 infection and patients with ALI and without COVID-19 infection. The comparisons among the 2 groups were performed with proper statistical analysis methods.

Results: Two groups of patients were identified: ALI and COVID-19 infection with 23 patients and ALI without COVID-19 infection with 49 patients. The overall mortality rate (OMR) was 20.8% (15 patients) in total cohort within the first 30 days. COVID-19 group had a higher OMR than non-COVID-19 group (30.4% vs. 16.7%, $P = 0.04$). The limb salvage rate at 30 days was 79.1% in total cohort; however, non-COVID-19 infection group had higher limb salvage rates than COVID-19 infection group (89.7% vs. 60.8%, $P = 0.01$). A univariate and multivariate logistic regression was performed to test the factors related to a major amputation rate. Among the factors evaluated, the following were related to limb loss: D-dimer $> 1,000$ mg/mL (hazards ratio [HR] = 3.76, $P = 0.027$, CI = 1.85–5.89) and COVID-19 infection (HR = 1.38, $P = 0.035$, CI = 1.03–4.75). Moreover, a univariate and multivariate logistic regression analysis was performed to analyze the factors related to overall mortality. Among the factors evaluated, the following were related to OMR: D-dimer $> 1,000$ mg/dL (HR = 2.28, $P = 0.038$, CI: 1.94–6.52), COVID-19 infection (HR = 1.8, $P = 0.018$, CI = 1.01–4.01), and pharmacomechanical thrombectomy > 150 cycles (HR = 2.01, $P = 0.002$, CI = 1.005–6.781).

Conclusions: COVID-19 has a worse prognosis among patients with ALI, with higher rates of limb loss and overall mortality relative to non-COVID patients. The main factors related to overall mortality were D-dimer $> 1,000$ mg/dL, COVID-19 infection, and pharmacomechanical thrombectomy > 150 cycles. The factors related to limb loss were D-dimer $> 1,000$ mg/mL and COVID-19 infection.

Conflicts of Interest: There are no conflicts of interest in this present study.

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INTRODUCTION

Acute limb ischemia (ALI) continues to be a threatening and challenging emergency in vascular surgery, despite the advances in technology and material, and may lead to major amputations and death, if not treated properly.¹ Furthermore, ALI represents one of the most common and dreadful emergencies in vascular surgery, with an incidence ranging from 10 to 22 per 100,000 patients per year.²

The novel coronavirus pneumonia (COVID-19) pandemic has afflicted the worldwide globe and increased coagulopathy disorders; therefore, the presence of a coexisting hypercoagulable state in patients with COVID-19 might be associated with higher mortality and arterial acute ischemia events.^{3,4} Patients infected with COVID-19 suffer a hypercoagulable state that increases the incidence and extension of native arterial occlusion, causing a thrombosis burden. A sudden and significant increase of COVID-19–infected patients who were presenting with ALI has been noted at vascular departments all over the world. The incidence of ALI associated with patients with COVID-19 who require hospitalization ranged from 3% to 15%, compromising 21 per 100,000 hospitalized patients with COVID-19.⁵ In comparison, the rate of ALI in the general population is approximately 10–15 per 100,000 per year including embolic, thrombotic, and traumatic etiologies. In patients with COVID-19, ALI is predominantly due to a large or medium artery thrombosis and embolism, although other etiologies can also occur. As with ALI in the general population, the lower extremity is affected more commonly than the upper extremity.⁶ Therefore, the main objective of this present article was to evaluate the impact of COVID-19 infection on patients with ALI, mainly the limb salvage estimates rate and the overall survival rate, performing a comparison with patients with ALI and without COVID-19 infection.

METHODS

Study Design

The study was approved by the ethical committee for research. All patients treated in our institution consented to the use of anonymized and aggregate data linked to the data basis for the purposes of research. No further patient contact was required. This was a prospective, consecutive cohort study of ALI patients subdivided into 2 groups: with COVID-19 infection and without COVID-19 infection admitted at the Vascular and Endovascular Surgery Service of the Hospital do Servidor Público Estadual de São Paulo, between January 2020 and October 2021.

Patient data were obtained from the service database using the Redcap software. The patients' medical records were also consulted as necessary. Information regarding the surgical procedures was obtained from the service database and the patients' medical records.

Patients

Patients with a diagnosis of ALI between January 2020 and October 2021 regardless of symptomatology severity were included in an analysis.

The patients were submitted either to revascularization (endovascular or open surgery) or to clinical treatment, depending on the clinical condition of the patient. Initial technical success of angioplasty was defined as no residual stenosis >30% or dissection at the end of the procedure, together with the prompt restoration of the circulation in the previously stenotic or occluded artery. In the endovascular procedures performed with pharmacomechanical thrombectomy (PMT), the AngioJet Solent Omni Thrombectomy Catheter (Boston Scientific Corporation Marlborough, MA, United States) was the device of choice; it was used to execute mechanical thrombectomy and remove a large amount of thrombus in the operating room. Procedures such as debridement and minor amputations were performed, as necessary, during hospitalization. The COVID-19 infection was treated and controlled both by the vascular surgeon team and by the infectious disease team, and, if necessary, by the intensivist. All patients admitted at the hospital were submitted to reverse transcription polymerase chain reaction test for severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2). If necessary, serologic tests were performed for SARS-Cov-2. Patients with positive diagnostic tests for COVID-19 were systematically submitted to chest–computed tomography (CT), to stratify the pulmonary infection in less or more than 50% of the lungs, or normal. Therapeutic anticoagulation was administered to all patients admitted with ALI. Moreover, all patients submitted to endovascular therapy with stenting implantation received clopidogrel with a loading dose of 300 mg, immediately after the procedure and a maintenance dose of 75 mg/day for 6 months. Furthermore, we performed a subanalysis of patients submitted to PMT with more than 150 cycles, regarding mortality rate and complications.

The major amputations were performed when the attempts to revascularize the limbs were exhausted or if the clinical condition of the patient was extremely deteriorated.

Outcomes

The primary outcome variable was the limb salvage rate and overall mortality. The secondary outcome variables were the factors related to overall mortality, prognosis of the COVID-19 infection and ALI, and the factors related to limb loss.

Statistics

Statistical analyses were performed using SPSS 22.0 for MacApple (SPSS Inc., Chicago, IL, USA). The frequencies of patients and descriptive statistics were calculated. The χ^2 test or Student's *t*-test were used for univariate analyses. Analyses of the factors related to overall mortality rate (OMR) and limb loss were made by a univariate and multivariable analysis using logistic regression. Statistical significance was defined as a *P* value of < 0.05.

RESULTS

All patients were evaluated during hospitalization until discharge or death. Overall, 72 patients with ALI were evaluated. Two groups of patients were identified: ALI and COVID-19 infection in 23 patients and ALI without COVID-19 infection in 49 patients. The mean age of the patients was 69.17 years in the total cohort and most of them were female (51.4%). Regarding the comorbidities, arterial hypertension was the most prevalent (76.4%), followed by diabetes mellitus (34.7%), chronic kidney disease (13.8%), and ischemia heart disease (19.4%). Both groups were similar regarding comorbidities, except for a higher prevalence of arrhythmias on group ALI and non-COVID-19 infection (18.4% vs. 8.7%, *P* = 0.03). Furthermore, the COVID-19 group had higher D-dimer and creatinophosphokinase rates than non-COVID-19 group (1,520 mg/dL vs. 689 mg/dL, *P* = 0.04 and 1,239 mg/dL vs. 580 mg/dL, *P* = 0.03, respectively). These data are summarized in [Table I](#).

Non-COVID-19 infection group had a higher preoperative ankle-brachial index (0.35 vs. 0.05; *P* = 0.03), whereas COVID-19 group had a higher prevalence of Rutherford IIb classification (73.9% vs. 26.5% *P* = 0.01). As per [Table II](#), when patients with critical ischemia were evaluated, an almost null value of the ankle-brachial index (0.035 on average) was found in those exposed to the virus. When comparing hemodynamic findings between COVID-19 and non-COVID-19 ALI patients, those with COVID-19 had significantly more advanced ischemia with a mean ABI of 0.05 vs. 0.35 for non-COVID-19 patients. The femoropopliteal segment was the most affected by acute arterial occlusion (68.05%), without differences among both groups. The main cause of ALI was arterial thrombosis (58.3%), without differences between groups. There were 2 cases of acute stent occlusion, both in the non-COVID-19 group. The OMR was 20.8% (15 patients) in the total cohort within the first 30 days. The COVID-19 group had a higher OMR

than the non-COVID-19 group (30.4% vs. 16.7%, *P* = 0.04). All cases of mortality in the COVID-19 group were due to COVID-19 pneumonia and complications. The causes of death in non-COVID-19 group were myocardial infarction (3 cases), pneumonia (2 cases), and acute renal failure (3 cases). All these data are summarized in [Table II](#).

Regarding the COVID-19 infection, 11 patients (47.8%) had reverse transcription polymerase chain reaction test for SARS-Cov-2 positive. Fifteen patients (65.2%) had a serology Immunoglobulin M (IgM) positive and 11 patients (47.8%) had a serology Immunoglobulin G (IgG) positive. Four patients (17.4%) had respiratory symptoms and one patient (4.3%) had a chest-CT showing pulmonary infection compromising >50% of the lungs. Three patients (13%) presented acute kidney failure, needing hemodialysis. All patients received any therapeutic anticoagulation drug, most of them enoxaparin (65.2%). Moreover, 6 patients (26.1%) received endovenous dexamethasone. D-dimer was higher than 1,000 mg/dL in 11 patients (47.8%), with mean 1.520 mg/dL. These data are summarized in [Table III](#).

The limb salvage rate at 30 days was 79.1% in the total cohort; however, the non-COVID-19 infection group had higher limb salvage rates than COVID-19 infection group (89.7% vs. 60.8%, *P* = 0.01). Regarding the major amputations, there were 9 transfemoral amputations in COVID-19 group and 5 amputations in non-COVID-19 infection group (4 transfemoral amputations and 1 transtibial). Regarding the type of procedures for limb salvage, in COVID-19 infection group there were 13 (56.5%) endovascular procedures with PMT, 4 bypass surgeries (17.4%), and 6 thromboembolectomy procedures (26.1%). Among the non-COVID-19 group, all patients were submitted to endovascular procedures with PMT. There were 6 patients submitted to a fasciotomy procedure in the total cohort, with no statistical significance among the groups. These data are summarized in [Table IV](#).

A univariate and multivariate logistic regression was performed to test the factors related to a major amputation rate. Among the factors evaluated, the following were related to limb loss: D-dimer > 1,000 mg/mL (hazards ratio [HR] = 3.76, *P* = 0.027, CI = 1.85–5.89) and COVID-19 infection (HR = 1.38, *P* = 0.035, CI = 1.03–4.75). These data are described in [Table V](#).

Moreover, a univariate and multivariate logistic regression analysis was performed to analyze the factors related to overall mortality. Among the factors evaluated, the following were related to OMR: D-dimer > 1,000 mg/dL (HR = 2.28, *P* = 0.038, CI: 1.94–6.52), COVID-19 infection

Table I. Patient characteristics

Variable	Total (<i>n</i> = 72)	Group non-COVID-19 infection (<i>n</i> = 49, 68%)	Group COVID-19 infection (<i>n</i> = 23, 32%)	<i>P</i> value
Age, years	69.17 ± 11.96	69.85 ± 8.3	70.48 ± 7.2	0.73
Females	37 (51.4%)	25 (51%)	12 (52.2%)	0.45
Hypertension	55 (76.4%)	38 (77.6%)	17 (73.9%)	0.57
Diabetes	25 (34.7%)	20 (40.8%)	5 (21.7%)	0.08
Ischemic Heart disease	14 (19.4%)	11 (22.4%)	3 (13%)	0.54
Chronic renal failure	10 (13.8%)	7 (14.6%)	3 (13.04%)	0.58
Arrhythmias	11 (15.2%)	9 (18.4%)	2 (8.7%)	0.03
Tobacco use	26 (36.1%)	17 (34.7%)	9 (39.1%)	0.72
D-Dimer	1,156	689	1,520	0.04
CPK	980	580	1,239	0.03

CPK, creatinophosphokinase.

Table II. Patient's treatment data

Variable	Total (<i>n</i> = 72)	Group non-COVID-19 infection (<i>n</i> = 49, 68%)	Group COVID-19 infection (<i>n</i> = 23, 32%)	<i>P</i> value
ABI pre	0.25	0.35	0.05	0.03
ABI post	0.8	0.9	0.87	0.14
Rutherford class				
I	22 (30.5%)	19 (38.8%)	3 (13%)	0.02
IIa	20 (27.7%)	17 (34.7%)	3 (13%)	0.03
IIb	30 (41.6%)	13 (26.5%)	17 (73.9%)	0.01
Segment occluded				
Aortoiliac	16 (22.2%)	13 (27.1%)	3 (13%)	0.08
Femoropopliteal	49 (68.05%)	29 (60.4%)	20 (87%)	0.36
Infrapopliteal	14 (19.4%)	7 (14.2%)	7 (30.4%)	0.07
Causes of ALI				
Thromboembolism	28 (38.8%)	16 (33.3%)	12 (52.2%)	0.38
Cardiac origin	20 (27.7%)	13 (26.5%)	7 (30.4%)	0.38
Aorta thrombi	8 (11.1%)	3 (6.1%)	5 (21.7%)	0.04
Arterial thrombosis	42 (58.3%)	31 (63%)	11 (47.8%)	0.78
Angioplasty occlusion	2 (2.77%)	2 (3.7%)	0	0.04
Overall Mortality	15 (20.8%)	8 (16.7%)	7 (30.4%)	0.04

ABI, ankle brachial index.

(HR = 1.8, *P* = 0.018, CI = 1.01–4.01), and PMT >150 cycles (HR = 2.01, *P* = 0.002, CI = 1.005–6.781) (Table VI).

DISCUSSION

Acute thrombotic complications burden associated with SARS-CoV-2 infection present in a variety of ways and symptoms. One of the most severe conditions, ALL, the sudden decrease in perfusion to an extremity, is a dramatic clinical event more typically reported in association with severe infection; however, it has been reported in patients with few or none of the respiratory symptoms associated with COVID-19, even sometimes being the first initial manifestation of COVID-19 infection.^{7,8}

Meanwhile, the precise physiopathology of thromboembolic events in patients with COVID-19 remains unclear and challenging; the occurrence of such complication is associated with ALL, resulting in a high limb loss and mortality. Etkin et al.⁸ have reported a rate of limb loss of 18% among patients with COVID-19 and concomitant ALI and an OMR of 46%. Furthermore, Inessa et al.⁹ published an article comparing 16 SARS-CoV-2 positive patients who underwent lower extremity CT angiogram (CTA) of the lower extremities and 32 SARS-CoV-2 negative patients observed from January to April in 2018–2020. All COVID-19 patients (100%, 95% confidence interval [CI]: 79–100%) had at least one thrombus in the arterial system, whereas only 69% (95% CI: 50–84%) of controls had any kind of thrombi (*P* = 0.02). COVID-19 patients presenting

Table III. Patient's COVID-19 infection data

Variable	Total = 23 patients
RT-PCR test positive	11 (47.8%)
IgM positive serology	15 (65.2%)
IgG positive serology	11 (47.8%)
Respiratory symptoms	4 (17.4%)
Chest-CT pulmonary	
Normal	8 (34.8%)
Less than 50%	14 (60.9%)
More than 50%	1 (4.3%)
Acute kidney failure	3 (13%)
Anticoagulation usage	23 (100%)
Type of anticoagulation	
Enoxaparin	15 (65.3%)
Unfractionated heparin	7 (30.4%)
Rivaroxaban	1 (4.3%)
Dexamethasone usage	6 (26.1%)
D-dimer > 1000 mg/dL	11 (47.8%)

with ALI only were more likely to avoid amputation or death than patients presenting also with pulmonary or systemic symptoms ($P = 0.001$). Among 16 patients with COVID-19 infection, there were 6 deaths (38%) and 4 cases of amputation (25%). Similarly, there are reports in overall literature describing OMR of 25% and limb loss of 25% among patients infected with COVID-19 and ALI.¹⁰ These data are comparable with those found in this present study, whereas the OMR among patients with COVID-19 and ALI was 30.4% and the rate of limb loss was 39.2%, which was higher than the patients with ALI and non-COVID-19 infection. Furthermore, the patients in this present cohort with COVID-19 infection and ALI were most of them classified as Rutherford IIb, denoting higher levels of ischemia when compared to patients with ALI and non-COVID-19 infection. Overall, the mortality rate of COVID-19 for those who require hospitalization is more than 20%.¹¹ In most cases, the cause of death has been attributed to respiratory failure, sepsis, cardiac failure, kidney injury, or the consequences of coagulation abnormalities. Among patients who develop ALI, mortality rates are as high as 50%.⁶ In a review of 571 COVID-19 patients, the risk of death was nearly 3-fold higher in patients who had arterial thrombotic events (HR 2.96, 95% CI 1.4–4.7).^{5,6} This review showed that a concentration of D-dimer more than 1,250 ng/mL increased the risk of arterial thrombotic events in COVID-19+ patients by more than 7 (subdistribution HR, 7.68; 95% CI, 2.9–20.6; $P < 0.001$). Similarly, in this present study, a univariate and multivariate logistic regression analysis showed that D-dimer higher than 1,000 mg/dL was related to overall

mortality (HR = 2.28, $P = 0.038$, CI: 1.94–6.52) and limb loss (HR = 3.76, $P = 0.027$, CI = 1.85–5.89). Furthermore, the COVID-19 group had higher D-dimer and creatinophosphokinase rates than non-COVID-19 group (1,520 mg/dL vs. 689 mg/dL, $P = 0.04$ and 1,239 mg/dL vs. 580 mg/dL, $P = 0.03$, respectively). These data probably should have collaborated to the higher rates of mortality rate and limb loss among patients with COVID-19 infection and ALI.

Recently, an important trial with 1,098 patients showed that in critically ill patients with COVID-19, an initial strategy of therapeutic-dose anticoagulation with heparin did not result in a greater probability of survival to hospital discharge or a greater number of days free of cardiovascular or respiratory organ support than did usual-care pharmacologic thromboprophylaxis.¹² The percentage of patients who survived to hospital discharge was similar in the 2 groups (62.7% and 64.5%, respectively; adjusted odds ratio, 0.84; 95% credible interval, 0.64–1.11). Major bleeding occurred in 3.8% of the patients submitted to therapeutic-dose anticoagulation and in 2.3% of those who received usual-care pharmacologic thromboprophylaxis. Specifically, in this present article all patients were submitted to therapeutic-dose anticoagulation, due to major thrombotic events such as ALI and the necessity of therapeutic anticoagulation. This type of comparison was not performed in this present article; however, it is important to notice that these patients in this present cohort presented with a major complication, such as ALI, which has a considerable morbidity and mortality in patients with and without COVID-19 infection.

Another important data point in this article showed that patients submitted to PMT >150 cycles had a higher risk of death (HR = 2.01, $P = 0.002$, CI = 1.005–6.781) regardless of COVID-19 infection status. This result is comparable with another article in literature that demonstrated a higher rate of complications such as myoglobinuria, hematuria, acute renal failure, and death in the subgroup of patients in whom these were performed more than 150 cycles/sec during the PMT surgery ($P < 0.001$).¹ The risk of acute kidney injury after percutaneous PMT using AngioJet in venous and arterial thrombosis is considerable and well reported in overall literature. Some studies reported that the odds of acute kidney injury were increased only by an AngioJet use (odds ratio [OR]: 8.2, 95% CI: 1.98–34.17, $P = 0.004$). In conclusion, AngioJet use is an independent risk factor for acute kidney injury and may be related to hemolysis from the device, especially with a high PMT (more than 150).^{1,13}

Table IV. Surgical and endovascular procedures for limb salvage

Variable	Total (<i>n</i> = 72)	Group non-COVID-19 infection (<i>n</i> = 49, 68%)	Group COVID-19 infection (<i>n</i> = 23, 32%)	<i>P</i> value
Endovascular procedure	62 (86.1%)	49 (100%)	13 (56.5%)	0.035
Bypass surgery	4 (5.55%)	0	4 (17.3%)	0.035
Femorofemoral	1 (1.38%)	0	1 (4.34%)	0.035
Aortofemoral bypass	3 (4.16%)	0	3 (13.04%)	
Thromboembolectomy	6 (8.3%)	0	6 (26%)	0.035
PMT Cycles >150	17 (23.6%)	11 (22.4%)	6 (26%)	0.84
Fasciotomy	6 (8.3%)	3 (6.1%)	3 (13.04%)	0.10

Table V. Logistic regression analysis of factors associated with Limb Loss

Variable	Univariate analysis				Multivariate analysis			
	B	HR	95% CI	<i>P</i>	B	HR	95% CI	<i>P</i>
Rutherford classification	0.988	0.065	0.330–2.760	0.931	0.597	0.065	0.226–10.060	0.880
D-dimer > 1000 mg/dL	1.805	3.76	1.85–5.89	0.038	1.805	3.76	1.85–5.89	0.038
Chronic kidney disease	2.392	3.40	2.45–11.1	0.890	1.532	3.40	1.45–11.1	0.890
Diabetes	0.346	0.56	1.341–1.372	0.349	0.664	1.220	1.311–14.294	0.349
COVID infection	2.147	1.385	1.03–4.75	0.035	2.147	1.385	1.03–4.75	0.035
PMT >150	1.285	0.987	1.87–20.90	0.89	1.897	0.890	1.98–5.69	0.89
Type of surgery	2.256	1.878	1.98–3.45	0.98	2.256	1.878	1.84–3.56	0.98

Table VI. Logistic regression analysis of factors associated with mortality rate

Variable	Univariate analysis				Multivariate analysis			
	B	HR	95% CI	<i>P</i>	B	HR	95% CI	<i>P</i>
Rutherford classification	0.988	0.065	0.330–2.760	0.931	0.597	0.065	0.226–10.060	0.880
D-dimer > 1000 mg/dL	1.805	2.28	1.94–6.52	0.027	1.805	2.28	10.49–26.52	0.027
Chronic kidney disease	1.382	2.30	1.45–9.10	0.790	1.332	2.40	1.35–10.1	0.700
Diabetes	0.445	0.36	1.312–3.372	0.359	0.564	0.36	1.312–4.294	0.359
COVID infection	1.147	1.80	1.03–4.75	0.018	1.147	1.80	1.03–4.75	0.018
PMT >150	1.385	2.01	1.005–6.781	0.002	1.385	2.01	1.005–6.781	0.002
Type of surgery	1.456	4.56	1.980–5.689	0.87	1.789	4.56	1.890–5.895	0.87

Thrombus macerating and removal systems are associated with renal and cardiac impairment due to the massive liberation of proinflammatory cytokines and blood factors, and as more cycles/pulses are used, more toxic substances are released into the blood flow, potentializing the ischemia-reperfusion injury in ALI. Products of hemolysis have also been suggested as a possible cause for arrhythmias. The AngioJet system causes significant hemolysis and is associated with an increase in free plasma hemoglobin levels in various thrombectomy series. Potassium liberated from lysed erythrocytes can be associated with ST-segment elevations, promoting higher mortality in patients submitted to PMT.^{1,14–16} These effects can be specially increased in patients infected with COVID-19, due to the cytokines storm, that leads to extensive activation of cytokine-secreting cells with innate and adaptive immune mechanisms both of which contribute to a poor prognosis.

Finally, among both groups there were differences regarding the type of surgery, with higher open surgery procedures such as thromboembolectomy and bypasses in COVID-19 infection and ALI, whereas all patients in non-COVID-19 infection group were submitted to endovascular surgery. This difference may be explained by the higher degrees of ischemia and thrombosis among COVID-19 group, requiring open surgery to guarantee a successful revascularization. Despite these data, the type of surgery did not influence the limb loss rates and OMR in this present cohort. These data are comparable with the overall literature, with several studies showing similar survival and limb salvage rates among open surgery and endovascular procedures (13% vs. 10.1% and 90.6% vs. 79.2%, respectively).^{17,18}

This study has some limitations, mainly the sample size and lack of randomization. Notably, very few studies have compared patients with and without COVID-19 infection and ALI. Larger and randomized trials should be performed to clarify these data consistently.

CONCLUSION

COVID-19 has a worse prognosis among patients with ALI, with higher rates of limb loss and overall mortality relative to non-COVID-19 patients. The main factors related to overall mortality were D-dimer > 1,000 mg/dL, COVID-19 infection, and PMT >150 cycles. The factors related to limb loss were D-dimer > 1,000 mg/mL and COVID-19 infection.

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