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Acute Limb Ischemia in COVID-19 Patients: A Retrospective Cohort Study

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This study aimed to show the incidence, presentation, management, and outcome of acute limb ischemia (ALI) in patients diagnosed with COVID-19 pneumonia, and prove the association between them. A multi-centre retrospective cohort study in the middle and south of Iraq, comparing 400 patients admitted to the isolation hospitals for COVID-19 pneumonia with a matched control group at period from 1st June 2020 to 1st August 2020. A total of 21/400 cases of ALI in COVID-19 pneumonia and only 4/400 cases in the non-COVID-19 group. Relative Risk (Risk Ratio= 5.25, 95%CI=1.818-15.157, *P* = 0.001). There were 291 (72.7%) males and 109 (27.2%) females. The average time from diagnosis of COVID-19 to the onset of ALI was (9.4±6.4 days). The mean ischemic time was (22.05 ±18.8 hours) in the COVID-19 group, while it was (11.75±8.7 hours) in the non-COVID-19 group. The mean D-dimer level for the patient with COVID-19 pneumonia without ALI is (1705±1256 µg/L), while it is (3730±2373 µg/L) for the patient with COVID-19 pneumonia. The embolectomy done in 14 patients (66.6%) of the COVID-19 pneumonia group, and it was successful in 10 patients (71.4%). In comparison, it was done in 3 patients (75%) of the control group and was successful in 2 (66.6%). Amputation was done in 4 patients (19%) of the COVID-19 pneumonia group, while only one patient (25%) in the control group had amputation. The association between COVID-19 pneumonia and ALI incidence; the D-dimer level is also associated with ALI in COVID-19 pneumonia cases. The anticoagulants, antiplatelet, vasodilators, and embolectomy had a management success rate.

Keywords: acute limb ischemia; COVID-19 pneumonia; D-dimer

I. INTRODUCTION

In the past 20 years, the world had witnessed many epidemics, like severe acute respiratory coronavirus syndrome (SARS-CoV), influenza A subtype H1N1, and Middle East coronavirus respiratory syndrome (MERS-CoV) (Cascella *et al.,* 2020). The COVID-19 is highly contagious and spread very fast across the world, and WHO declared the pandemic on 30th January 2020 (Chen *et al.,* 2020). COVID-19 has a broad spectrum of presentation ranged from asymptomatic to severe respiratory distress, multiple organ dysfunction, and death (Yazan *et al.,* 2020). Data suggest that COVID-19 is associated with a hypercoagulable state and elevated D-dimer level (Yazan *et al.,* 2020). Acute limb ischemia (ALI) can occur due to concomitant cardiovascular or cerebrovascular disease and ischemia-reperfusion injury and may be ended with amputation, unless appropriate treatment is initiated (Norgren *et al.,* 2007). It is associated with a mortality rate of (15–20%) due to concomitant cardiovascular or cerebrovascular disease and ischemia-reperfusion injury (Norgren *et al.,* 2007). The aetiology of ALI classified into embolism (46%) and thrombosis (54%), and atrial fibrillation account for most cases of embolism (Norgren *et al.,* 2007). The femoral artery is the most common site where embolus is lodged (Norgren *et al.,* 2007). The

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thrombosis can occur from plaque breakdown, circulatory failure, or a hypercoagulable state and include thrombotic occlusion of stents and bypass grafts (Howard *et. al.,* 2015; Creager *et al.,* 2012).

D-dimer is the end product of the degradation of fibrin, and it is a marker of the activated hemostatic system (Pagana *et al.,* 2019). The level of D-dimer increase in thrombosis, pregnancy, inflammation, malignancy, trauma, postsurgical treatment, liver disease, and heart disease (Spring *et al.,* 2014). The D-dimer level is elevation is associated with increased mortality in COVID-19 patients (Zhang *et al.,* 2020).

II. MATERIALS AND METHOD

Study design and setting

This is a multi-centre retrospective cohort study done in middle and south of Iraq comparing 400 COVID-19 patients admitted to the infectious isolation hospitals with another 400 non-COVID-19 patients admitted to other infectious isolation hospitals in the same period from 1st June to 1st August 2020.

Diagnosis

The ALI was either diagnosed before or after the admission by clinical assessment and duplex scan. According to WHO, COVID-19 infection was confirmed by positive real-time reverse transcription–PCR (RT–PCR) of nasal and pharyngeal swabs or was determined by typical findings on chest CT scan when laboratory testing was inconclusive.

Intervention

An anticoagulant in the form of enoxaparin 4000 IU once daily was routinely given to all hospitalized patients with COVID-19 pneumonia even if they were not bedridden, whereas it is only given to bedridden in the control group.

Data collection

We recorded demographic data, co-morbidities, laboratory tests, the anatomical location of the occlusion, the ischemic time, the intervention, complications, and the time of onset of limb ischemia from the diagnosis of COVID-19 pneumonia.

Ethical approval and patients consent

Written informed consent was obtained from the patients or the parents/guardians of minors for those below the age of 18 years for participating in this study, and was conducted according to the ethical standards established by the 1964 Declaration of Helsinki. The Medical Ethical Committee of Kufa University and Najaf Cardiac Center approved this study (code:2020NCC172).

Statistical analysis

We use mean and standard deviation to represent the data while describing variables presented using their numbers and parentage. Relative risk ratio used to estimated risk. Two-sided paired t-test for variables was used. SPSS version 22 (Chicago, US) was used for data entry and analysis. P-value was considered significant if <0.05.

III. RESULT AND DISCUSSION

21/400 (5.25%) cases of ALI in COVID-19 pneumonia and only 4/400 (1%) cases in non-COVID-19 patients. Relative Risk (Risk Ratio) of patients with COVID-19 reliable to develop ALI was 5.25 (95%CI=1.818-15.157, *P*=0.001). The mean age of all patients was (51±12.3 years), while the mean age of patients with ALI was (54.1±11.1 years).

The average time from diagnosis of COVID-19 to onset of ALI was (9.4±6.4 days) except for one individual, who had ALI as the presenting complaint.

The mean ischemic time was (22.05±18.8 hours), ranging from 3 to 72 hours in the COVID-19 group, while it was (11.75±8.7 hours) range from 5 to 24 hours in the non-COVID-19 group, (*P*=0.000). Three cases of COVID-19 pneumonia ALI group had associated with deep vein thrombosis (14.2%), whereas this was not found in non-COVID-19 group.

The mean D-dimer level for the patient with COVID-19 pneumonia without ALI is (1705±1256 μg/L), while it was (3730±2373 μg/L) for the patient with COVID-19 pneumonia and ALI (*P*=0.002). The commonest anatomical arterial occlusion location is in the femoral, popliteal, and tibial arteries (as shown in Figure 1). Embolectomy was done in 14 patients (66.6%) of the COVID-19 pneumonia group. It was successful in 10 patients (71.4%). At the same time, it was done in 3 patients (75%) of the non-COVID-19 and was successful in 2 (66.6%), (*P*= 0.36).

Amputation was done in 4 patients (19%) of COVID-19 pneumonia, while it has done in one patient (25%) in the non-COVID-19 group, (*P*=0.4). One patient with posterior tibial artery thrombosis had been treated successfully with catheter-directed thrombolysis (as shown in Figure 2).

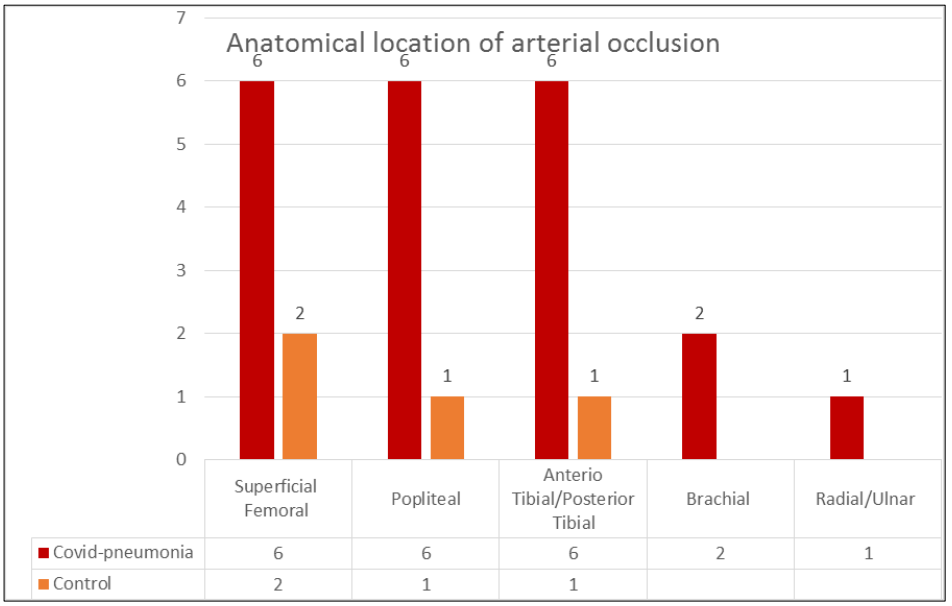

Figure 1. The anatomical location of arterial occlusion

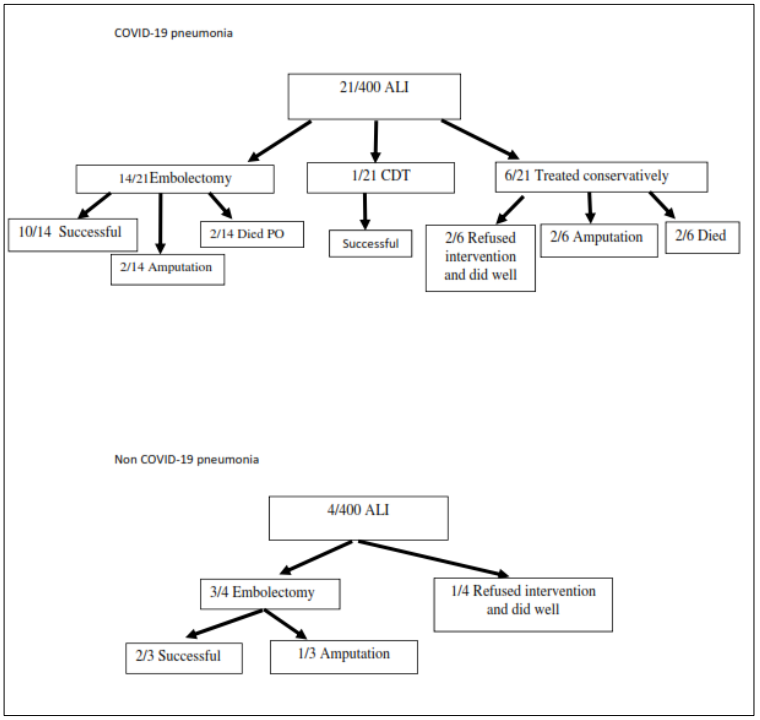

Figure 2. The flow chart of the two arms of the study

Italian team from the Lombardy region reported in April 2020 a significantly increased ALI incidence during the COVID-19 pandemic (Bellosta *et al.,* 2020). They observed a lower success rate of revascularization than expected, which may be due to the hypercoagulable state induced by the virus, and they recommended prolonged systemic heparin use (Bellosta *et al.,* 2020).

In Iraq, ALI's first case report in COVID-19 was published in July 2020 (Fahad *et al.,* 2020). An exponential increase in the number of COVID-19 cases, associated with an increased incidence of ALI cases. The younger patients than what was seen in Italian study due to the demography difference between the two countries as Italy is the sixth country by life expectancy while Iraq is 130th (www.worldometers.info.2020).

The mean ischemic time is that the COVID-19

pneumonia group was significantly higher than the non-COVID-19, which can be explained by the overwhelming of the already collapsed health system. The non-COVID-19 group is still higher than the ischemic time in Italy COVID-19 hospital, where it does not exceed 3 hours (Bellosta *et al.,* 2020).

High D-dimer level is associated with acute thrombotic events (Chiu & Huang, 2009), and D-dimer level is already known to increase in COVID-19 patients and is associated with increased mortality (Zhang *et al.,* 2020). Here, the conclusion is that a higher D-dimer level is significantly associated with ALI in COVID-19 patients. The presence of associated DVT in the COVID-19 pneumonia group also support the hypercoagulable state theory as the cause of limb ischemia.

We did not do embolectomy either because of late presentation with a gangrenous limb or patient refusal. Our intervention rate is lower than seen in other studies due to longer ischemic time in our patients, but the success rate is comparable (Bellosta *et al.,* 2020).

Our study's mortality rate was significantly lower than the Italian series, which we believe due to younger people in our research, and COVID-19 is well-known to kill older people (Zhou *et al.,* 2020).

IV. CONCLUSION

There is an association between COVID-19 pneumonia and the incidence of ALI. D-dimer level is also associated with ALI in COVID-19 pneumonia cases. Anticoagulants, antiplatelet, vasodilators, and embolectomy had a success rate in management.

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