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Mini Review

Acute Limb Ischemia in SARS-CoV-2: An Underappreciated Thrombotic Complication

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ABSTRACT

The high degree of variability in clinical severity and presentation among patients infected with SARS-CoV-2 continues to be an ongoing challenge for physicians managing the disease. In addition to acute respiratory distress syndrome, multi-organ dysfunction and shock state, there are now well recognized pro-inflammatory, hypercoagulable and pro-thrombotic complications associated with this infection. Acute Limb Ischemia (ALI) in particular has been documented with increasing frequency during the course of the pandemic with variable management strategies and outcomes. Herein we review the current state of the literature as it pertains to the epidemiology, diagnosis and management of ALI in the context of SARS-CoV-2 infection.

Keywords: ALI; SARS-CoV-2; COVID; Limb ischemia

INTRODUCTION

The emergence of SARS-CoV-2 has proved to be an unprecedented and persistent global health crisis with far reaching implications. Across the broad clinical manifestations of the disease, there is emerging evidence of associated hypercoagulability, endotheliitis and thrombotic angiopathy with potentially severe vascular complications including large vessel thrombosis, ALI and consequent limb loss.

EPIDEMIOLOGY AND CLINICAL PRESENTATION

The relative incidence of ALI in this population has yet to be fully elucidated. Reported incidence among hospitalized SARS-CoV-2 patients range from 0.21%-0.54% whereas contemporary estimates for the general population have ranged from 0.015%-0.026% [1-5]. Some single centers have reported as high as a threefold increase in thrombotic events since the onset of the pandemic [6]. Incidence among critically ill patients appears to be higher although this is not a consistently reproduced finding, with some retrospective cohorts reporting discrepancy between respiratory illness severity and likelihood of developing a major thrombotic event [6,7].

Patients with concomitant ALI and SARS-CoV-2 are more likely to be male, elderly and have multiple cardiovascular comorbidities. A review of case reports reveals typical risk factors for ALI including hypertension, diabetes, hyperlipidemia, atrial fibrillation, peripheral artery disease and tobacco use, although select cases of young patients with minimal predisposing cardiovascular risk factors have also been documented [4,8,9].

Cross sectional studies and case reports suggest most thrombotic events are preceded by prolonged hospitalization although in some pooled analyses, ALI is part of initial clinical presentation in up to 20%-27% of cases [10-12]. In recent case series and observational cohort studies, the mean time to arterial thrombotic event from disease onset has ranged from 5.0-14.7 days [13,14]. Similar patterns were observed by Topcu, with a median duration of 13 days between diagnosed infection and ALI (IQR 11.3-14) [15]. Patients who develop arterial complications commonly have concomitant respiratory symptoms although cases of ALI have occurred in the absence of respiratory pathology or radiographic evidence of SARS-CoV-2 pneumonia [10,16,17].

The anatomic distribution of thrombosis in this population is heterogeneous with limb arteries representing the most common vascular territory affected (39%) followed by cerebral vasculature (24%) and thromboses to the great vessels (19%) [18].

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Comparable patterns were seen in the largest case series to date, wherein 71% of ischemic events occurred in lower extremities, 14% in upper extremities and 10% in cerebral vascular distribution [5]. Distribution in the lower extremity vasculature is also variable with a trend toward more frequent involvement of the femoro-popliteal region relative to aorto-iliac areas [5,6,12].

SARS-CoV-2 patients appear to have radiographically greater thrombotic burden relative to uninfected ALI patients and 12%-18% will have either multiple limb involvement or have co-occurring thromboembolic complications in other major vascular territories/beds [12,19,20].

Diagnosis

As per the 2016 AHA/ACC guidelines on management of peripheral artery disease, clinical judgement, focused history taking and bedside examination, including continuous-wave Doppler ultrasound studies remain the mainstays of dictating whether emergent surgical/endovascular intervention is warranted [21]. When factoring in these critical variables, most patient with infection and ALI have been classified as Rutherford category IIA or IIB at initial presentation highlighting the relevance of prompt evaluation by a provider with expertise in revascularization [22,23].

Jongkind and colleagues recently updated contemporary guidelines for the European Society for Vascular Surgery (ESVS) regarding management of ALI while considering the impact of SARS-CoV-2 (20). In addition to bedside examination, Computed Tomography Angiography (CTA) remains an integral part of their diagnostic approach. The potential benefit of extended CTA imaging, from aortic arch to distal limbs is highlighted given the predilection for multi vessel involvement in this highly prothrombotic cohort.

In cases where SARS-CoV-2 status is unknown, providers should have a low threshold for screening patients emergently. Some studies have suggested that ALI can occur in absence of prototypical respiratory complaints or other signs of systemic infection in up to 23% of patients [10, 22]. Additionally, ALI may be the herald sign of SARS-CoV-2 infection in anywhere from 20%-45% of patients presenting with vascular complications [5,11]. As such, a low threshold for testing and consistent safeguarding of staff via personal protective equipment should remain an essential part of providing care for these patients.

Initial management

To date there is insufficient outcomes data to form an optimal treatment approach to ALI in patients with SARS-CoV-2. A survey of the contemporary literature reveals heterogeneity across centers with therapeutic Anticoagulation (AC), revascularization with catheter directed thrombolysis, percutaneous mechanical thromboembolectomy or open surgery utilized to varying degrees [20].

Several systematic reviews have highlighted a perceived skew toward medical management without surgical intervention, with 36% to 57% of patients receiving therapeutic anticoagulation only [5,12,20,24,25]. Such a trend may be in part dictated by the relative severity and clinical instability of these patients which would make them poor candidates for more aggressive revascularization procedures. There may also be a perception of futility on the part of some providers as an arterial thrombotic event has been shown to raise the risk of in-hospital mortality 3-fold for SARS-CoV-2 patients (16). The perception of futility and apprehension toward pursuing more aggressive treatment modalities may be called into question when considering select reports that do not show correlation between infection severity and likelihood of developing ALI [6].

Anticoagulation and secondary prevention

Therapeutic anticoagulation with heparin products remains a cornerstone of ALI management in this cohort, irrespective of whether interventional or surgical revascularization is pursued. Given the recency of the pandemic, optimal duration of anticoagulation in this population can only be extrapolated based on guidelines and longitudinal studies on prior uninfected cohorts. Generally, full dose anticoagulation is continued after revascularization with treatment duration guided by underlying comorbidities. Long term AC is indicated for native artery thrombosis with associated thrombophilia or patients with associated cardiogenic embolism and atrial fibrillation [26]. If there is evidence of underlying atherosclerotic plaques in the affected vessels, long term antiplatelet therapy may also be indicated [1]. Extrapolation of these recommendations is limited by the lack of data on the proportion of thrombosis *vs* embolus in the SARS-CoV-2 patients with ALI [20]. Whether antiplatelet agents and DOACs reduce recurrence of ALI and improve limb viability remains under active investigation [26].

It remains to be seen whether addition of DOACs or antiplatelet agents to the regimen of already therapeutically anticoagulated SARS-CoV-2 patients is of any added benefit. Some observational data has suggested aspirin use to be associated with improved outcomes in illness severity among hospitalized patients without specifically querying ALI [27]. Rivaroxaban is similarly under current investigation as a means of reducing major venous and arterial thrombotic events including limb ischemia in SARS-CoV-2 patients (PREVENT-HD) [28].

Monitoring coagulopathy

D-dimer, fibrinogen and prothrombin time are frequently monitored in infected patients as a means of determining disease severity and increased risk of thromboembolism. Whether such a practice is universally favorable and applicable to patients with ALI remains unclear.

As of February 2021, the National Institute of Health noted insufficient evidence to recommend either for or against routine monitoring of these coagulation markers in hospitalized patients [29]. Interim guidelines by the International Society of Thrombosis and Haemostasis from March 2020 advised monitoring D-Dimer and PT in context of studies showing

correlation with disease severity and mortality [30,31]. The American Society of Hematology notes no consensus on how often D-Dimer should be measured or how results should be acted upon in the hospitalized SARS-CoV-2 patient but does advise monitoring D-Dimer, PT/aPTT and fibrinogen for patients suspected of having COVID-19 associated coagulopathy/DIC as markers of disease severity [32,33].

The utility of continued monitoring of the above markers, is compounded by the generally poor specificity of D-dimer, which in the postoperative setting is often elevated as a result of the activation of the fibrinolytic system. Multiple studies have re-demonstrated that elevated D-dimer in the postoperative setting is a common occurrence and does not correlate well with thrombotic burden [34,35].

DISCUSSION

Mortality

All-cause mortality estimates for patients with ALI have ranged from 20.4% to as high as 50% during hospitalization [5,11,17,22,36]. While the risk of death with any arterial thrombotic events increases mortality risk 3 fold for SARS-CoV-2 patients, deaths are more commonly attributed to ARDS or multi-organ failure than any further thromboembolic complication [22,37].

Revascularization success and amputation

Initial attempts at revascularization have been met with lower success rates relative to that in the general population. Similarly, chronological data shows limb salvage rates in general have decreased from 83.6% to 72.4% since the onset of the pandemic, although the cause of this trend has yet to be fully elucidated [38]. Rates of major amputation are high among SARS-CoV-2 patients, ranging between 7 to 35%. Primary amputation rates for unsalvageable limbs at presentation range from 4% to 10% [5,6,12].

Meta-analysis by Attisani showed a 68% success rate for revascularization with 13% of patient requiring re-intervention for either recurrent or persistent limb ischemia [12]. 31% of patients needing further intervention ultimately required secondary amputation. Pooled clinical improvement was similarly 66.6% in another systematic review with a 10.5% reoperation rate and a pooled amputation rate of 23.2% [25]. Risk of amputation across these studies was comparable for invasive intervention and medical management, although the latter approach appears to be associated with higher mortality overall (OR, 4.04; 95% CI, 1.075-15.197; P=0.045). In a single center study with comparable revascularization rates, a significant association was found between survival and the use of heparin infusion in the post-operative period whereas continuous heparin use was not associated with risk of early re-occlusion or major amputation [17].

In a retrospective study, limb amputation was more common among infected patients relative to propensity score-matched control patients. Of note, patients presenting with ALI symptoms in isolation were less likely to require amputation and had more favorable survival rates than patients with both ALI and respiratory disease [19].

Further variables associated with treatment failure and amputation risk have not been consistently reported and may mirror those of ALI in uninfected patients, including prolonged duration of ischemia or premature failure after initial revascularization. Although delayed presentation during the pandemic has been perceived to contribute to poor outcomes, reports are conflicting on whether patients with ALI or worsening chronic limb ischemia are delaying pursuit of medical care [39,40].

CONCLUSION

SARS-CoV-2 continues to be an ongoing health crisis despite best efforts at public health initiatives and the availability of efficacious vaccines. ALI has emerged as one of the dire consequences of SARS-CoV-2 infection and is associated with worse survival rates and poorer rates of limb salvage. Limb ischemia has been associated with prolonged hospitalization and systemic disease burden but cases of ALI as the herald sign of infection and occurring in relatively mild systemic disease have also been reported. Providers need to remain vigilant of SARS-CoV-2 as a potential etiology of ALI given its associated prothrombotic state. Therapeutic anticoagulation remains the mainstay of management with relatively high rates of deferred intervention likely in part because of clinical instability but also perhaps an erroneous perception of medical futility among these critically ill patients. Further research is needed to elucidate the optimal medical strategies for anticoagulation and interventional/surgical strategies that maximize both successful revascularization and limb salvage.

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