Acute limb ischemia among patients with COVID-19 infection

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ABSTRACT

Objective/Background: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has been associated with thrombotic complications such as deep vein thrombosis or stroke. Recently, numerous cases of acute limb ischemia (ALI) have been reported although pooled data are lacking.

Methods: We systematically searched PubMed, Embase, Scopus, and the Cochrane Library for studies published online up to January 2021 that reported cases with SARS-CoV-2 infection and ALI. Eligible studies should have reported early outcomes including mortality. Primary endpoints included also pooled amputation, clinical improvement, and reoperation rates.

Results: In total, 34 studies (19 case reports and 15 case series/cohort studies) including a total of 540 patients (199 patients were eligible for analysis) were evaluated. All studies were published in 2020. Mean age of patients was 61.6 years (range, 39-84 years; data from 32 studies) and 78.4% of patients were of male gender (data from 32 studies). There was a low incidence of comorbidities: arterial hypertension, 49% (29 studies); diabetes mellitus, 29.6% (29 studies); dyslipidemia, 20.5% (27 studies); chronic obstructive pulmonary disease, 8.5% (26 studies); coronary disease, 8.3% (26 studies); and chronic renal disease, 7.6% (28 studies). Medical treatment was selected as first-line treatment for 41.8% of cases. Pooled mortality rate among 34 studies reached 31.4% (95% confidence interval [CI], 25.4%-37.7%). Pooled amputation rate among 34 studies reached 23.2% (95% CI, 17.3%-29.7%). Pooled clinical improvement rate among 28 studies reached 66.6% (95% CI, 55.4%-76.9%). Pooled reoperation rate among 29 studies reached 10.5% (95% CI, 5.7%-16.7%). Medical treatment was associated with a higher death risk compared with any intervention (odds ratio, 4.04; 95% CI, 1.075-15.197; P = .045) although amputation risk was not different between the two strategies (odds ratio, 0.977; 95% CI, 0.070-13.600; P = .986) (data from 31 studies).

Conclusions: SARS-CoV-2 infection is associated with a high risk for thrombotic complications, including ALI. COVID-associated ALI presents in patients with a low incidence of comorbidities, and it is associated with a high mortality and amputation risk. Conservative treatment seems to have a higher mortality risk compared with any intervention, although amputation risk is similar. (J Vasc Surg 2022;75:326-42.)

Keywords: Acute limb ischemia; COVID-19; SARS-CoV-2

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19), originated in December 2019 and has caused a worldwide pandemic. Infection with SARS-CoV-2 has been shown to have a wide range of clinical presentations from asymptomatic in a large percentage of patients to devastating pulmonary failure, sepsis, and death. Additionally, the hypercoagulability associated with this infection has been recognized as a significant cause of morbidity, resulting in thrombotic complications such as pulmonary parenchymal thrombosis, venous thrombosis, myocardial infarction, and stroke. Lately, there have been reports of acute limb ischemia (ALI) observed among infected patients as well. Although pooled data have been published on other thrombotic presentations such as acute mesenteric ischemia or stroke, pooled data on ALI are lacking. Therefore, aim of this review was to evaluate pooled data on patients with COVID-19 infection and ALI.

METHODS

Data sources and search. We systematically searched PubMed, Embase, Scopus, and the Cochrane Library (up to January 2021) for clinical studies published online that included patients suffered from ALI while diagnosed with COVID-19 infection. Eligible studies should have...
reported at least early (30-day) mortality among other outcomes. This review was conducted according to established methods for systematic reviews in cardiovascular medicine (PRISMA criteria). The following medical subject terms were used for the online search: "acute," "limb," "ischemia," "COVID-19," "SARS-CoV-2," and "infection." In addition to searching databases, the reference lists of all included studies, meta-analyses, and reviews were evaluated manually, including unpublished data. Only studies published in English were included in this review. References from eligible articles or textbooks were also reviewed to identify further potential sources.

Data extraction: Outcomes and definitions. Three authors independently completed data extraction after following search criteria and quality assessment. Disagreements were resolved by consensus or after review by the senior author of the study, when necessary. Data were obtained from tables, graphs, and text as well. When data were presented in percentages, the absolute values were calculated. For each study, the following data were collected: first author, year of publication, country of origin, total number of patients included in the studies, total number of patients with ALI and COVID-19 infection, patient characteristics (mean age, gender, and comorbidities when reported), localization of ischemia (type of limbs, type of arteries), type of symptoms owing to infection (eg, fever, dyspnea, intubation need), type of medical treatment, type of interventional treatment, early outcomes (eg, mortality, amputation, and cardiac events), improvement of ischemia, late follow-up, and late outcomes when reported. ALI was defined as acute ischemia presented in the lower or upper extremities. The cause of ischemia should have been arterial thrombosis or embolism and this cause should have been confirmed with some type of imaging within the included studies. Any cases with superficial or cutaneous limb necrosis in patients with COVID-19 infection who had no imaging evidence showing thrombosis or embolism of limb arteries were not included in this review. If the studies under evaluation included patients with acute ischemia of other type (such as mesenteric or cerebral), only patients with ALI were included in the analysis. If a patient happened to present with ALI and another type of ischemic complication, he or she was still included in the analysis. Primary endpoints included early (30-day) mortality, amputation, clinical improvement, and reoperation rates. Affected limb arteries included the subclavian, axillary, brachial, ulnar, radial, palmar, and digital arteries for the upper limb and the aorta, iliac, femoral, popliteal, tibial, peroneal, and plantar arteries for the lower limb. All eligible patients should have tested positive for COVID-19 infection whether they presented with typical symptoms or not.

Amputations reported in this review included both major and minor amputations. Major amputations included transfemoral and transbrachial amputations as well as amputations below the level of the knee or elbow. Minor amputations included amputations below the level of the ankle or wrist. Pooled amputation rate included primarily as well as secondary amputations.

Cardiac adverse events included cardiac arrest, myocardial infarction, arrhythmias, or acute cardiac failure.

Improvement of limb ischemia included the improvement of clinical symptoms/signs of ischemia without the need for further intervention or amputation.

Comorbidities are reported in the same way as reported in the included studies owing to lack of specific definitions in the majority of studies.

Quality assessment. Three authors independently reviewed study eligibility and quality. Disagreements were resolved by consensus or after review by the senior author of the study, when necessary. The quality of each study was assessed using well-established criteria for nonrandomized studies, specifically evaluating the collection of data, the aim of the studies, incomplete outcome data, statistical analysis, and other sources of bias. The quality of each study was evaluated and reported as high, medium, or low based on the design and methodology of study according to these criteria.

Inclusion and exclusion criteria. Studies included in this meta-analysis met the following criteria: (i) clinical studies or reports presenting cases with COVID-19 infection and ALI and (ii) studies should have reported early (30-day) mortality at least. ALI cases should have been documented with some type of imaging in the included studies. Studies reporting patients with acute ischemia at different body locations were also included but only patients with ALI from these studies were eligible for analysis.

Exclusion criteria included (i) types of publication other than clinical studies or reports, such as reviews, meta-analyses or editorials; (ii) studies not reporting at least early mortality among outcomes; (iii) studies presenting patients with superficial or cutaneous necrosis without evidence of an arterial thrombosis or embolism; (iv) studies reporting cases of ALI among patients without COVID-19 infection only; (v) studies reporting cases with COVID-19 infection and acute ischemia of other body parts such as mesenteric or cerebral ischemia; (vi) studies reporting cases with COVID-19 infection and acute thrombotic events without reporting outcomes for limb ischemia separately; (vii) studies published in a language other than English; (viii) studies not referring to humans, and (ix) studies reported as only abstracts or presented at conferences.

Statistical analysis. A meta-analysis was carried out using the StatsDirect Statistical software (Version 2.8.0,
StatsDirect Ltd, Cambridge, UK). Odds ratios (OR) were used to determine effect size, along with 95% confidence intervals (CI). Regarding major outcomes, ORs were pooled with Der Simonian and Laird random effects models being used for sensitivity analysis. P values were calculated for evaluating statistical significance, with a P value of less than .05 indicating a statistically significant difference. Interstudy variations and heterogeneities were estimated using the Q-statistic with a P value of less than .05 also indicating a statistically significant heterogeneity. The present meta-analysis also quantified the effect of heterogeneity by using the I² index (range, 0%-100%), which represents the proportion of inter-study variability attributed to heterogeneity, rather than to chance.

In circumstances where more than one study reported data from the same cohort (introducing the potential for duplicate inclusion of patients), only the largest cohort was included in the main analysis. A χ² test with Yate’s correction was used for comparing categorical variables between the two groups of patients. All statistical analyses were conducted using the absolute values and not percentages. The risk of bias was also assessed applying the Habbord-Egger test.

RESULTS

In total, 34 eligible studies (19 case reports and 15 case series/cohort studies) were included (Fig 1). Regarding quality, 5 studies were of high quality, 5 studies of medium quality, and 24 studies (mainly case reports) of lower quality. These studies evaluated a total of 540 patients, out of which 199 were eligible for this analysis. Table I presents basic characteristics of the included studies. The mean age of the patients was 61.6 years (range, 39-84 years; data from 32 studies) and 78.4% of patients were male (data from 32 studies), although data on age or gender were not provided by the two largest studies in size. Among 138 cases, the following limbs were affected: lower limb (n = 102), upper limb (n = 27), and bilateral lower limbs (n = 9). The exact affected arteries are presented in Table I as well.

Pooled demographics were the following: arterial hypertension, 49% (29 studies); diabetes mellitus, 29.6% (29 studies); dyslipidemia, 20.5% (27 studies); chronic obstructive pulmonary disease, 8.5% (26 studies); coronary disease, 8.3% (26 studies); arrhythmias, 14.1% (28 studies); chronic heart failure, 8.0% (25 studies); and chronic renal disease, 7.6% (28 studies). All comorbidities are presented in Table II.
### Table I. Basic characteristics of the included studies

| Study                        | Year of publication | Country of origin | No. of patients with COVID infection and ALI (total number of patients in the study) | Male/female gender | Mean age, years [SD or range are reported when provided by the studies] | Limb affected | Arteries affected                                                                 |
|------------------------------|---------------------|-------------------|--------------------------------------------------------------------------------------|--------------------|-------------------------------------------------|---------------|-----------------------------------------------------------------------------------|
| Veerasuri et al<sup>9</sup>  | 2020                | UK                | 1                                                                                    | 1/0                | 56                                              | Bilateral lower limbs | Right SFA, right trifurcation, left trifurcation |
| Kaur et al<sup>10</sup>      | 2020                | USA               | 1                                                                                    | 1/0                | 43                                              | Right lower limb    | Right SFA, POPA, trifurcation                                                      |
| Brugliera et al<sup>11</sup> | 2020                | Italy             | 3                                                                                    | 3/0                | 68                                              | Bilateral lower limbs (n = 1) Right lower limb (n = 2) | SFA, POPA (n = 1) NR for 2 patients |
| Hanif et al<sup>12</sup>     | 2020                | Pakistan          | 1                                                                                    | 0/1                | 75                                              | Left upper limb     | Left UA and RA                                                                   |
| Hasan et al<sup>13</sup>     | 2020                | Pakistan          | 1                                                                                    | 1/0                | 60                                              | Right lower limb    | Right POPA and trifurcation                                                       |
| Gubitosa et al<sup>14</sup>  | 2020                | USA               | 1                                                                                    | 1/0                | 65                                              | Right lower limb    | Right POPA                                                          |
| Anwar et al<sup>15</sup>     | 2020                | USA               | 1                                                                                    | 1/0                | 58                                              | Left lower limb     | Left SFA, trifurcation                                                          |
| Singh et al<sup>16</sup>     | 2020                | USA               | 1                                                                                    | 1/0                | 77                                              | Left lower limb     | Left SFA, trifurcation                                                          |
| Wang et al<sup>17</sup>      | 2020                | USA               | 2                                                                                    | 2/0                | 54                                              | Right lower limb    | Right dorsalis pedis, toes Right digital arteries, digits |
| Goldman et al<sup>18</sup>   | 2020                | USA               | 16 (48)                                                                              | 9/7                | 70 ± 14                                         | Lower limbs (n = 16) | From the POPA and proximally (n = 15) Distally from the POPA (n = 1) |
| Sánchez et al<sup>19</sup>   | 2020                | Peru              | 30                                                                                   | 23/7               | 60 ± 15                                         | Lower limb (n = 22) | Upper limb (n = 8)                                                               |
| Galanis et al<sup>20</sup>   | 2020                | Greece            | 1                                                                                    | 1/0                | 80                                              | Right Upper limb    | RA and UA                                                                       |
| Bozzani et al<sup>21</sup>   | 2020                | Italy             | 6 (38)                                                                               | 4/2                | 71 (49-83)                                      | Lower limb (n = 6)  | Iliac–SFA–POPA (n = 6)                                                         |
| Mietto et al<sup>22</sup>    | 2020                | Italy             | 1                                                                                    | 1/0                | 53                                              | Left lower limb     | Iliac–SFA–POPA–tibial arteries                                                   |
| Baccellieri et al<sup>23</sup> | 2020           | Italy             | 1                                                                                    | 1/0                | 67                                              | Right lower limb    | Iliac-SFA-POPA                                                                |
| Shao et al<sup>24</sup>      | 2020                | USA               | 1                                                                                    | 1/0                | 67                                              | Right upper limb    | Brachial artery, UA, RA                                                         |
| Etkin et al<sup>25</sup>     | 2020                | USA               | 42 (49)                                                                              | NR                 | NR                                              | Lower extremities (n = 35) Upper limbs (n = 7) | Aortoiliac (n = 8) Femoral (n = 12) POPA (n = 15) Above elbow (n = 4) UA and RA (n = 3) |
| Muhammad et al<sup>26</sup>  | 2020                | UK                | 1                                                                                    | 1/0                | 49                                              | Left lower limb     | Aorti-iliac–POPA–trifurcation                                                   |

(Continued on next page)
Concerning COVID-19 infection, 49.1% of patients presented with fever (27 studies), 62.3% of patients presented with dyspnea (27 studies), and 36.4% of patients needed to be intubated (30 studies). Basic laboratory findings are also presented in Table III. Increased D-Dimers levels (>5 mg/mL; 26 studies) were not associated with death (OR, 1.169; 95% CI, 0.360-3.756; \( P = .792 \)) or amputation (OR, 2.0; 95% CI, 0.334-11.969; \( P = .448 \)) risk. Increased C-reactive protein (CRP) levels (>20 mg/L; 16 studies) were not associated with death (OR, 3.261; 95% CI, 0.164-65.012; \( P = .438 \)) or amputation (OR, 3.627; 95% CI, 0.183-72.070; \( P = .398 \)) risk. Increased fibrinogen levels

### Table I. Continued.

| Study          | Year of publication | Country of origin | No. of patients with COVID infection and ALI (total number of patients in the study) | Male/female gender | Mean age, years [SD or range are reported when provided by the studies] | Limb affected | Arteries affected                                      |
|----------------|---------------------|-------------------|---------------------------------------------------------------------------------|-------------------|---------------------------------------------------------------------|--------------|-------------------------------------------------------|
| Heald et al    | 2020 USA            | 1/0               | 65                                                                              |                   | Left hand-digital ischemia                                           | Digital arteries (left first and second digits) |
| Bellosta et al | 2020 Italy          | 18/2              | 75 ± 8                                                                          |                   | Upper and lower limbs (number NR)                                    | NR           |
| Kaur et al     | 2020 USA            | 1/0               | 71                                                                              |                   | Upper limb (right)                                                   | Right brachial artery and RA                     |
| Kahlberg et al | 2020 Italy          | NR                | NR                                                                              |                   | Upper and lower limbs                                               | NR           |
| Schultz et al  | 2020 USA            | 1/1               | 57                                                                              |                   | 3 fingers (right)                                                     | Digital arteries (right) RA (right)               |
| Vacirca et al  | 2020 Italy          | 1/0               | 58                                                                              |                   | Right lower limb                                                     | ATA, PTA, PA (right)                              |
| Fan et al      | 2020 Singapore      | 1/0               | 39                                                                              |                   | Right lower limb                                                     | ATA Abdominal aorta                               |
| Perini et al   | 2020 Italy          | 2/0               | 45                                                                              |                   | Bilateral lower limbs (left)                                         | Aortoiliac Brachial bifurcation                   |
| Kashi et al    | 2020 France         | 4/1               | 69                                                                              |                   | Lower limbs (2 bilateral, 2 right, 1 left)                           | Femoral (n = 3) POPA (n = 1) Iliac (n = 1) Fem-pop bypass (n = 1) NR (n = 1) |
| Baeza et al    | 2020 Spain          | 1/2               | 72                                                                              |                   | Bilateral lower limbs (n = 3)                                        | Aortic-bilateral iliac (n = 3)                     |
| Garg et al     | 2020 USA            | 3/4               | 63                                                                              |                   | Lower limb (2 right, 1 left)                                         | POPA (n = 3)                                      |
| Thompson et al | 2020 USA            | 0/1               | 42                                                                              |                   | Right upper limb                                                     | Right subclavian + UA                              |
| Levolger et al | 2020 Netherlands    | 2/0               | 53                                                                              |                   | Right lower limb                                                     | Right common iliary artery Left subclavian artery |
| Wengerter et al| 2020 USA            | 3/4               | 53                                                                              |                   | Left lower limb                                                       | Aortoiliac (n = 1) Femoral–POPA (n = 3)           |
| Chowdhury et al| 2020 USA            | 1/0               | 75                                                                              |                   | Right upper extremity                                                | Brachial artery                                   |
| Liu et al      | 2021 China          | 1/0               | 70                                                                              |                   | Right lower limb                                                     | CFA and SFA                                       |

ATA, Anterior tibial artery; CFA, common femoral artery; NR, not reported; POPA, popliteal artery; RA, radial artery; PA, peroneal artery; PTA, posterior tibial artery; SD, standard deviation; SFA, superficial femoral artery; UA, ulnar artery.
| Study | Arterial hypertension | Diabetes mellitus | Dyslipidemia | COPD | CAD | Arrhythmia | CHF Renal Disease | Other comorbidities |
|-------|-----------------------|-------------------|--------------|------|-----|-----------|-------------------|-------------------|
| Veerasuri et al | 0 | 0 | 0 | 0 | 0 | 0 | 0 | None |
| Kaur et al | 1/1 | 1/1 | 0 | 0 | 0 | 0 | 0 | None |
| Brugliera et al | 3/3 | 2/3 | 1/3 | 1/3 | 0 | 0 | 0 | 1/3 | Hypothyroidism (n = 1) |
| Hanif et al | 0 | 0 | 0 | 0 | 0 | 0 | 0 | None |
| Hasan et al | 1/1 | 0 | 0 | 0 | 0 | 0 | 0 | None |
| Gubitosa et al | 1/1 | 1/1 | 1/1 | 0 | 0 | 0 | 0 | 1/1 | Smoking history |
| Anwar et al | 0 | 0 | 0 | 0 | 0 | 0 | 0 | None |
| Singh et al | 0 | 0 | 0 | 0 | 0 | 0 | 0 | None |
| Wang et al | 0 | 0 | 0 | 0 | 0 | 0 | 0 | None |
| Goldman et al | 13/16 | 8/16 | 8/16 | NR | NR | NR | 4/16 | 0/16 | Smoking history (n = 8) PAD (n = 8) |
| Sánchez et al | 10/30 | 8/30 | 1/50 | NR | 4/30 | 3/50 | NR | 1/50 | Smoking history (n = 3) PAD (n = 4) |
| Galanis et al | 1/1 | 1/1 | 0 | 0 | 0 | 0 | 0 | Dementia |
| Bozzani et al | NR | NR | NR | NR | NR | NR | NR | NR |
| Mietto et al | 1/1 | 0 | 0 | 0 | 0 | 0 | 0 | Obesity |
| Baccellieri et al | 0 | 0 | 0 | 0 | 0 | 0 | 0 | Obesity |
| Shao et al | 0 | 0 | 0 | 0 | 0 | 0 | 0 | Lupus anticoagulant positive |
| Etkin et al | NR | NR | NR | NR | NR | NR | NR | NR |
| Muhammad et al | NR | NR | NR | NR | NR | NR | NR | NR |
| Heald et al | 1/1 | 0 | 0 | 0 | 0 | 0 | 0 | History of smoking |
| Bellosta et al | 11/20 | 3/20 | NR | 2/20 | 2/20 | 5/20 | NR | 4/20 | Previous VS (n = 4) Obesity (n = 4) |
| Kaur et al | 0 | 1/1 | 0 | 0 | 0 | 0 | 0 | None |
| Kahlberg et al | NR | NR | NR | NR | NR | NR | NR | NR |
| Schultz et al | 1/2 | 0 | 1/2 | 0 | 0 | 0 | 0 | Obesity (n = 1) |
| Vacirca et al | NR | NR | NR | NR | NR | NR | NR | NR |
| Fan et al | 0 | 0 | 0 | 0 | 0 | 0 | 0 | None |
| Perini et al | 0 | 0 | 0 | 0 | 0 | 0 | 0 | None |
| Kashi et al | 4/5 | 1/5 | NR | 1/5 | NR | 2/5 | NR | 1/5 | Smoking (n = 2) PAD (n = 2) |
| Baeza et al | 2/3 | 1/3 | 2/3 | 1/3 | 0 | 2/3 | 0 | 0 | Smoking (n = 2) Obesity (n = 1) PAD (n = 1) |
| Garg et al | 1/3 | 1/3 | 1/3 | NR | NR | 1/5 | NR | NR | NR |
| Thompson et al | 0 | 1/1 | 0 | 0 | 0 | 0 | 0 | Rheumatoid arthritis |
| Levolger et al | 0 | 1/2 | 0 | 0 | 0 | 0 | 0 | - |
| Wengerter et al | 1/5 | 2/3 | 1/3 | 0 | 0 | 0 | 0 | Smoking (n = 1) |
| Chowdhury et al | 1/1 | 0 | 1/1 | 0 | 1/1 | 0 | 0 | Dementia |
| Liu et al | 0 | 0 | 0 | 0 | 0 | 0 | 0 | Lung cancer |

CAD: Coronary artery disease; CHF: chronic heart failure; COPD: chronic obstructive pulmonary disease; NR: not reported; PAD: peripheral artery disease; VS: vascular surgery.
>400 mg/dL (13 studies) were not associated with death (OR, 0.667; 95% CI, 0.152-2.925; \( P = .485 \)) or amputation (OR, 0.639; 95% CI, 0.184-2.222; \( P = .481 \)) risk.

Regarding treatment, medical treatment was chosen in 41.8% of patients (33 studies) as a first-line treatment. In total (among 33 studies), 92 patients (58.2%) underwent the following procedures: thrombembolectomy (\( n = 81 \)), fasciectomy (\( n = 9 \)), angioplasty with or without stenting (\( n = 7 \)), thrombolysis (\( n = 7 \)), thrombosuction (\( n = 2 \)), bypass (\( n = 3 \)), and endarterectomy (\( n = 2 \)). All patients were covered with unfractionated or low-molecular-weight heparin. All medical and interventional treatment is presented in Table IV.

The pooled mortality rate among 34 studies reached 31.4% (95% CI, 25.4%-37.7%). The pooled amputation rate (both primary and secondary) among 34 studies reached Table III. Symptoms and laboratory findings of the included patients

| Study                  | Fever | Dyspnea | Need for intubation | Mean leucocyte count (\( \times 10^9/L \)) | Mean platelet count (\( \times 10^9/L \)) | Fibrinogen (mg/dL) | CRP (mg/L) | D-Dimers (\( \mu g/mL \)) | PCT (ng/mL) |
|------------------------|-------|---------|---------------------|------------------------------------------|------------------------------------------|--------------------|------------|---------------------------|-------------|
| Veerasuri et al          | 1/1   | 1/1     | 0                   | 0.8                                      | NR                                       | NR                 | NR         | 23.138                    | NR          |
| Kaur et al              | 1/1   | 1/1     | 1/1                 | 16                                       | 484                                      | 853                | 289.7      | 20                        | 67          |
| Bruglieri et al         | 1/3   | 3/3     | 1/3                 | NR                                       | Normal for all                           | 466.3              | NR         | 20, 5.04                  | NR          |
| Hanif et al             | 1/1   | 0       | 0                   | 5.9                                      | 733                                      | NR                 | NR         | 0.867                     | NR          |
| Hasan et al             | 1/1   | 1/1     | 0                   | 13.9                                     | 95                                       | NR                 | 82.5       | 1.96                      | 0.3         |
| Gubitosa et al          | 1/1   | 1/1     | 1/1                 | Lymphopenia                              | 82                                       | 247                | NR         | 7.955                     | NR          |
| Anwar et al             | 1/1   | 1/1     | 0                   | NR                                       | NR                                       | 312                | 25.23      | 15.653                    | 25.23       |
| Singh et al             | 0     | 1/1     | 0                   | 41                                       | 534                                      | NR                 | 301        | 2.77                      | 0.6         |
| Wang et al              | 2/2   | 2/2     | 2/2                 | NR                                       | NR                                       | NR                 | NR         | 8.25                      | NR          |
| Goldman et al           | 3/16  | 8/16    | 4/16                | 13.5 ± 4                                 | NR                                       | NR                 | NR         | NR                        | NR          |
| Sánchez et al           | NR    | NR      | NR                  | 11.6 [9.7-16.1]                          | 284 [220-371]                            | 4.8 [4.7-6.3]      | 35.5 [24-61]| 3.2 [1.6-4.3]             | NR          |
| Galanis et al           | 1/1   | 1/1     | 1/1                 | 5.6                                      | 174                                      | 360                | 166        | 13.6                      | 0.1         |
| Bozzani et al           | NR    | NR      | 2/6                 | NR                                       | NR                                       | NR                 | NR         | NR                        | NR          |
| Mietto et al            | 0     | 0       | 0                   | NR                                       | NR                                       | NR                 | NR         | NR                        | NR          |
| Baccellieri et al       | 1/1   | 1/1     | 0                   | NR                                       | NR                                       | 711                | 114.1      | 20                       | NR          |
| Shao et al              | 0     | 1/1     | 1/1                 | Increased                                 | NR                                       | NR                 | NR         | >5                       | NR          |
| Etkin et al             | NR    | NR      | 2/6                 | NR                                       | NR                                       | NR                 | NR         | NR                        | NR          |
| Muhammad et al          | 1/1   | 1/1     | 0                   | 11.8                                     | 520                                      | NR                 | NR         | 12                       | NR          |
| Heald et al             | 0     | 1/1     | 1/1                 | NR                                       | NR                                       | NR                 | NR         | 0.79                      | NR          |
| Bellota et al           | NR    | NR      | NR                  | 14 ± 2                                   | 239 ± 82                                 | NR                 | 2.2        | NR                       |             |
| Kaur et al              | 1/1   | 1/1     | 8.6                 | 331                                      | -                                        | 111.9              | 1.85       | -                        |             |
| Kahlberg et al          | NR    | NR      | NR                  | NR                                       | NR                                       | NR                 | NR         | NR                       | NR          |
| Schultz et al           | 1/2   | 2/2     | 2/2                 | NR                                       | NR                                       | 486, NR            | 25, NR     | 7.56                      | NR          |
| Vacirca et al           | 0     | 1/1     | 1/1                 | 6.07                                     | 322                                      | 524                | NR         | 1.19                      | 0.1         |
| Fan et al               | 1/1   | 1/1     | NR                  | NR                                       | NR                                       | 770                | 136.2      | 2.55                      | NR          |
| Perini et al            | NR    | NR      | 1/2                 | NR                                       | NR                                       | NR                 | NR         | 9.0                       | NR          |
| Kashi et al             | NR    | NR      | 3/5                 | NR                                       | 160 [NR (n = 2)]                         | 547                | NR         | NR (n = 3)                | 20          |
| Baeeza et al            | 3/3   | 0/3     | 0/3                 | 18.2                                     | 193.7                                    | 766.3              | 4.1        | 5.07                      | NR          |
| Garg et al              | 1/3   | 2/3     | 1/3                 | NR                                       | NR                                       | NR                 | NR         | 3.3                       | NR          |
| Thompson et al          | 0     | 0       | 0                   | NR                                       | NR                                       | NR                 | NR         | NR                       | NR          |
| Levolger et al          | 2/2   | 1/2     | 0/2                 | 10.6                                     | 360                                      | NR                 | 167        | NR                       | NR          |
| Wengerter et al         | 1/3   | 0       | 1/3                 | NR                                       | NR                                       | NR                 | 144.3      | 15.6                      | NR          |
| Chowdhury et al         | 1/1   | 1/1     | 1/1                 | 8.6                                      | 172                                      | NR                 | 20         | 1.2                       | NR          |
| Liu et al               | 0     | 0       | 9.83                | 282                                      | 560                                      | 79.1               | 6.55       | NR                       |             |

CRP, C-reactive protein; NR, not reported. PCT, procalcitonin.
Laboratory values are reported either with standard deviation or value range, whatever was reported.
Table IV. Type of treatment for the included patients

| Study               | Medical to interventional treatment as first line treatment | HCQ  | Antibiotics | Antiviral treatment | Heparin or LMWH | Other medication | Thrombectomy or Embolectomy | Other intervention | Reoperation |
|---------------------|-----------------------------------------------------------|------|-------------|---------------------|-----------------|------------------|-----------------------------|--------------------|-------------|
| Veerasuri et al     | 1/0                                                       | NR   | NR          | NR                  | 1/1             | Rivaroxaban      | 0                           | None               | 0           |
| Kaur et al<sup>10</sup> | 1/0                                                       | 1/1  | 1/1         | NR                  | 1/1             | NR               | 0                           | None               | 0           |
| Brugliera et al     | 2/1                                                       | 3/5  | 2/3         | 1/3                 | 3/3             | Iloprost (n = 1) | ASA (n = 2)                 | 1                  | None        |
| Hanif et al<sup>47</sup> | 0/1                                                       | 0    | 1/1         | 0                   | 1/1             | NR               | 1                           | None               | 0           |
| Hasan et al<sup>48</sup> | 1/0                                                       | 0    | 1/1         | 0                   | 1/1             | Rivaroxaban post discharge | 0               | None        |
| Gubitos et al<sup>49</sup> | 0/1                                                       | 0    | 0           | 0                   | 1/1             | Rivaroxaban      | 1                           | Fasciotomy          | 0           |
| Anwar et al<sup>50</sup> | 0/1                                                       | 1/1  | 1/1         | 0                   | 1/1             | CTDS, ASA       | 0                           | Angioplasty         | 0           |
| Singh et al<sup>51</sup> | 0/1                                                       | 1/1  | 1/1         | 0                   | 1/1             | NR               | 1                           | None               | 0           |
| Wang et al<sup>52</sup> | 2/0                                                       | NR   | NR          | NR                  | 1/1             | Argatroban       | 0                           | None               | 0           |
| Goldman et al<sup>53</sup> | 9/7                                                       | NR   | NR          | NR                  | NR              | NR               | 6                           | None               | 0           |
| Sánchez et al<sup>54</sup> | 2/28                                                      | NR   | NR          | NR                  | NR              | NR               | 23                          | Fasciotomy          | 2           |
| Galani et al<sup>55</sup> | 1/0                                                       | 1/1  | 1/1         | 0                   | 1/1             | FDPX            | 1                           | None               | 0           |
| Bozzani et al<sup>56</sup> | 0/6                                                       | NR   | NR          | NR                  | 6/6             | ASA (3/6)        | ASA + clopidogrel (3/6)     | 6                  | PTA (n = 2) |
| Mietto et al<sup>57</sup> | 0/1                                                       | NR   | NR          | NR                  | 1/1             | Prostacyclin     | 1                           | Thrombolysis. fasciotomy | 1           |
| Baccellieri et al<sup>58</sup> | 0/1                                                       | 1/1  | 1/1         | NR                  | 1/1             | NR               | 1                           | Thrombectomy at right upper limb | 0           |
| Shao et al<sup>59</sup> | 0/1                                                       | NR   | NR          | NR                  | 1/1             | NR               | 1                           | Thrombolysis. fasciotomy | 0           |
| Etkin et al<sup>60</sup> | 31/11                                                     | NR   | NR          | NR                  | NR              | NR               | 9                           | Endovascular thrombosuction (n = 2) | NR         |
| Muhammad et al<sup>61</sup> | 0/1                                                       | NR   | NR          | NR                  | 1/1             | ASA 75 mg        | Dabigatran 150 mg bid       | 0                  | Thrombolysis | 0           |
| Heald et al<sup>62</sup> | 1/0                                                       | NR   | NR          | NR                  | 1/1             | NR               | 0                           | None               | 0           |
| Bellosta et al<sup>63</sup> | 3/77                                                      | NR   | NR          | NR                  | 20/20           | NR               | 15                          | Below the knee fem-pop bypass (n = 2) | 2           |
| Kaur et al<sup>64</sup> | 0/1                                                       | 1/1  | 1/1         | NR                  | 1/1             | NR               | 1                           | Endarterecotomy of the right arm | 0           |
| Kahlberg et al<sup>65</sup> | NR                                                       | NR   | NR          | NR                  | NR              | NR               | NR                         | NR                 | NR         |
| Schultz et al<sup>66</sup> | 2/0                                                       | 2/2  | 2/2         | 2/2                 | 2/2             | Nitroglycerin (n = 2) | Apixaban (n = 1)           | 0                  | None        |
| Vaccirea et al<sup>67</sup> | 0/1                                                       | NR   | NR          | NR                  | 1/1             | NR               | 1                           | Thrombolysis         | 0           |
| Fan et al<sup>68</sup> | 0/1                                                       | NR   | NR          | 1/1                 | 1/1             | ASA             | 1                           | Aortic stent graft placement | 0           |
| Perini et al<sup>69</sup> | 1/1                                                       | NR   | NR          | NR                  | 1/1             | NR               | 1                           | None               | 1           |
| Kashi et al<sup>70</sup> | 4/1                                                       | NR   | NR          | NR                  | 2/5             | Apixaban (n = 1) | ASA (n = 2)                 | 1                  | None        |
| Baeza et al<sup>71</sup> | 0/3                                                       | 3/3  | 3/3         | 2/3                 | 3/3             | Acenocoumarol    | (n = 1)                    | 2                  | Aortobifemoral bypass (n = 1) | 0           |
| Garg et al<sup>72</sup> | 2/1                                                       | 1/3  | 1/3         | 1/3                 | 3/3             | —                | 1                           | NR                 | NR         |
| Thompson et al<sup>73</sup> | 0/1                                                       | 0    | 0           | 0                   | 1/1             | —                | 1                           | None               | 0           |
| Levoger et al<sup>74</sup> | 2/0                                                       | 1/2  | 0           | 0                   | 2/2             | Rivaroxaban (n = 1) | Apixaban (n = 1)           | 1                  | Thrombolysis | 0           |
| Wengerter et al<sup>75</sup> | 0/3                                                       | NR   | NR          | NR                  | 3/3             | NR               | 3                           | None               | NR         |

(Continued on next page)
mortality.45,46 As we found in this review, ALI was associated with arterial thromboembolism associated with high risk for both venous and arterial thrombotic events during the pandemic may occur over a later time point during the course of the infection.36 Some authors have advocated that the virus starts a second attack between 7 and 14 days from the onset of symptoms that perhaps initiates some type of hypercoagulability.2

Additionally, we found a mean age of 61 years with a very wide age range starting from just 39 years. Other authors have also reported that infected patients with thrombotic complications are of relatively young age, and available computed tomography scans and angiography reveal no prior major atherosclerosis in these cases.37 This finding suggests that a significant proportion of arterial thromboses in patients with COVID-19 might occur over nondiseased or mildly diseased vessels. Although male gender, advanced age, hypertension, and diabetes have been found to be independent risk factors of death among patients with COVID-19, this review revealed that infected patients with ALI show a low incidence of major comorbidities such as diabetes, dyslipidemia, coronary disease, and renal disease. This finding indicates that even patients without risk factors are at risk of presenting thrombotic complications when infected.

The causative mechanism for ALI seems to be a systematic inflammatory process triggered by a massive activation of macrophages that generate a cytokine storm.52 COVID-19 causes elevated cytokine levels, including but not limited to tumor necrosis factor-α (TNF-α), IL-1β, IL-6, procalcitonin, and interferon γ.54-56 The coupling of inflammation and coagulation has also been described in the literature, with these procedures sharing common molecular pathways.57 It has been reported that infected patients are prone to thrombotic dysfunction, and especially

Table IV. Continued.

| Study | Medical to interventional treatment as first line treatment | HCQ | Antibiotics | Antiviral treatment | Heparin or LMWH | Other medication | Thrombectomy or Embolectomy | Other intervention | Reoperation |
|-------|----------------------------------------------------------|-----|-------------|---------------------|-----------------|------------------|-----------------------------|-------------------|-------------|
| Chowdhury et al41 | 0/1 | 1/1 | 1/1 | 0 | 1/1 | Prednisolone | 1 | None | 0 |
| Liu et al42 | 1/0 | NR | 1/1 | 1/1 | 1/1 | NR | 0 | None | 0 |
| Total (n/total n) | 66/158 (1 study NR) | 17/24 (18 studies NR) | 18/24 (18 studies NR) | 8/23 (19 studies NR) | 65/65 (4 studies NR) | ASA (n = 13) Clopidogrel (n = 3) | Apixaban (n = 5) | Dabigatran (n = 1) | Argatroban (n = 1) | Rivaroxaban (n = 3) | CTDS (n = 2) | FDX (n = 1) | Acenocoumarol (n = 1) | Prostaglandins (n = 2) | Nitroglycerine (n = 2) | N = 81 (4 study NR) | Thrombolysis (n = 7) | PTA/stenting (n = 5) | Endarterectomy (n = 2) | Fasciotomy (n = 9) | Bypass (n = 3) | Thrombectomy at other site (n = 1) | Thrombosisu (n = 1) | Stent graft placement (n = 1) | 0/7 (5 studies NR) |

ASA, Acetylsalicylic acid; bid, 2 times per day; CTDS, corticosteroids; FDPX, fondaparinux; HCQ, hydroxychloroquine; LMWH, low molecular weight heparin; NR, not reported; PTA, percutaneous transluminal angioplasty.

23.2% (95% CI, 17.5%-29.7%). From the 34 reported amputations, 22 were major (transfemoral or below the knee), 1 minor (below the ankle), and 11 were at an unknown level. The pooled clinical improvement rate among 28 studies reached 66.6% (95% CI, 55.4%-76.9%). The pooled reoperation rate among 29 studies reached 10.5% (95% CI, 5.7%-16.7%) (Figs 2-5). For all these pooled outcomes, heterogeneity was very low (I² = 0%-7.7%). All outcomes are presented in Table V. Finally, there was no difference regarding death risk (OR, 1.10; 95% CI, 0.284%-4.272; P = .884) and amputation risk (OR, 1.16; 95% CI, 0.288-4.649; P = .834) between upper limb and lower limb location (data available from 31 studies). Regarding first-line strategy, medical treatment was associated with a higher risk of death compared with any intervention (OR, 4.04; 95% CI, 1.075-15.197; P = .045), although the risk of amputation was not different between the two strategies (OR, 0.977; 95% CI, 0.070-13.600; P = .986) (data from 31 studies).

DISCUSSION

Although the overall incidence of ALI has decreased worldwide and the hypercoagulable state remains an uncommon cause for limb ischemia,43 the incidence of thromboembolic complications among patients with COVID-19 infection is as high as 35% to 45%.44 In critically ill patients, there is an even higher risk for both venous and arterial thromboembolism associated with high mortality.45,46 As we found in this review, ALI was associated with a mortality rate of 31.4%, although the reported mortality in non-COVID populations with ALI ranges from 5% to 9% in literature.47,48 Comparative studies have also shown a higher incidence of thrombotic events such as strokes among COVID-infected patients compared with the general wards.49 However, this relative increase of arterial thrombotic events during the pandemic may be attributed to several factors, such as delays in emergency room presentation owing to the lockdown, older patient age, or fear in approaching hospitals because of a high contamination risk.50 Additionally, there are several reports that these thrombotic events occur at a later time point during the course of the infection.36

Table V. Comparison of amputation and reoperation outcomes among studies.

| Study | Anticoagulation | Amputation | Reoperation |
|-------|----------------|------------|-------------|
| Aspuru et al33 | Warfarin | 1/1 | 1/1 |
|句子 | 句子 | 句子 | 句子 |
|句子 | 句子 | 句子 | 句子 |

ASA, Acetylsalicylic acid; bid, 2 times per day; CTDS, corticosteroids; FDPX, fondaparinux; HCQ, hydroxychloroquine; LMWH, low molecular weight heparin; NR, not reported; PTA, percutaneous transluminal angioplasty.
those with severe symptoms had higher CRP levels and a higher thrombotic risk. However, high levels of CRP in our review were not associated with adverse events in patients with ALI. These patients exhibit several risk factors of thrombosis such as blood concentration, vascular endothelial injury, extended bed rest, and blood hypercoagulation. Additionally, recent data indicate that COVID-19 infection is associated with profound and generalized activation of both alternative and lectin-based complement pathways.

There is growing evidence that this virus promotes a procoagulant state producing both microthrombi and macrothrombi. Cutaneous ischemic lesions are frequent in such patients, even in absence of major vessel thrombosis. In particular, severe endothelial injury, widespread thrombosis with microangiopathy, alveolar-capillary microthrombi and new vessel growth have been detected in infected cases. Vascular pathological changes in such patients include partial vascular endothelial shedding, vascular intimal

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**Fig 2.** Forest plot on pooled early mortality. CI, Confidence interval; df, degrees of freedom.
inflammation, and thrombosis. Varga et al have even observed viral inclusion bodies under light microscopy in the endothelium of the specimens. The angiotensin-converting enzyme 2, the receptor for SARS-CoV-2, is also expressed on the membrane of vascular muscle and endothelial cells, and therefore, infection of these cells could induce an inflammatory response in the blood vessel walls, predisposing to clot formation. The viral infection itself leads to decreased platelet function secondary to decreased production, platelet consumption, and production of autoantibodies such as antiphospholipid antibodies. It is also known that other viral infections including hepatitis or human immune deficiency viral infections have been associated with thrombotic complications such as venous thromboembolism.
Regarding thrombotic markers, high D-dimers, fibrinogen degradation products, and a prolonged thrombo-plastin time have been associated with greater in-hospital mortality, need for mechanical ventilation, and thrombotic complications in infected patients.\textsuperscript{12,68,69} Recent pooled data indicate that prothrombin time and D-dimer levels are significantly higher in patients with severe infection than in those with mild disease.\textsuperscript{70} Some authors advocate that increased levels of D-dimers could serve as an indicator of the time-point at which an intervention with recombinant tissue plasminogen activator or tocilizumab should be considered.\textsuperscript{71} However, an optimal cut-off level and prognostic value are still not known.\textsuperscript{72} In our review, all patients had a thrombotic complication, indicating a population at higher mortality risk. This factor could justify that we could not establish a cutoff level for D-dimer as well. The mean fibrinogen concentrations in patients with COVID-19 are in general at the upper limits of normal, presumably as an acute phase response.\textsuperscript{44} However, we could not establish an

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{forest_plot.png}
\caption{Forest plot on pooled clinical improvement rate. CI, Confidence interval; df, degrees of freedom.}
\end{figure}
association of high fibrinogen levels with worse outcomes either. Given the increased thrombotic risk, the World Health Organization recommends at least prophylactic doses of low-molecular-weight heparin daily or subcutaneous unfractionated heparin twice daily for venous thromboembolism prophylaxis in critically ill patients with COVID-19. However, ALI can even occur among patients already receiving thromboprophylaxis, and this outcome has been observed in some cases included in the present review. Therefore, certain concerns arise whether full therapeutic dosage of anticoagulants would be more appropriate for severely ill patients.

For patients with COVID-19 presenting with ALI, the choice of intervention is guided by the need to limit interventions that would expose these patients to stressful procedures, the desire to limit exposure of medical personnel, and the need to conserve resources. Additionally, in critically ill infected patients, thrombosis may be a terminal event, sometimes being referred to as agonal...
### Table V. Main outcomes for all included patients

| Study               | Death | Amputations | Cardiac | Other complications | Improvement of the ischemia | Mean follow-up | Late outcomes                  |
|---------------------|-------|-------------|---------|---------------------|-----------------------------|----------------|--------------------------------|
| Veerasuri et al[9]  | 0     | 0           | 0       | 0                   | 1                           | 2 months       | Numbness in right foot        |
| Kaur et al[10]      | 1     | 0           | 1       | Hemodialysis        | 0                           | NR            | NR                             |
| Brugliera et al     | 0     | 3 (all TF)  | 0       | DVT (n = 1)         | 1                           | NR            | NR                             |
| Hanif et al[12]     | 0     | 0           | 0       | 0                   | 1                           | NR            | NR                             |
| Hasan et al[13]     | 0     | 1 (TF)      | 0       | 0                   | 0                           | NR            | NR                             |
| Cubitosa et al[14]  | 1     | 1 (TF)      | 1       | HIT                 | 0                           | NR            | NR                             |
| Anwar et al[15]     | 0     | 1 (below ankle) | 0   | 0                   | 0                           | NR            | NR                             |
| Singh et al[16]     | 0     | 0           | 0       | 0                   | 0                           | NR            | NR                             |
| Wang et al[17]      | 2     | 0           | 0       | Encephalopathy (n = 1) | 0                          | NR            | NR                             |
| Goldman et al[18]   | 6     | 4 (all TF)  | NR      | NR                  | NR                          | NR            | NR                             |
| Sánchez et al[19]   | 7     | 9 (all TF)  | NR      | NR                  | 26                          | NR            | NR                             |
| Galanis et al[20]   | 1     | 0           | 0       | DVT                 | 0                           | NR            | NR                             |
| Bozzani et al[21]   | 1     | 1 (TF)      | 0       | Rethrombosis (n = 2) | 5                           | NR            | NR                             |
| Mietto et al[22]    | 0     | 0           | 0       | Rhabdomyolysis, acute renal failure | 1 | 40 days | Superficial peroneal nerve impairment |
| Baccellieri et al[23] | 0    | 0           | 0       | Nephrotic syndrome, bilateral acroischemia, thrombosis of upper limb (intraoperative) | 1 | 2 months | No new event                  |
| Shao et al[24]      | 0     | 0           | 0       | PE, GI bleeding     | 1                           | 2 months       | Dry gangrene of digits         |
| Muhammad et al[25]  | 17    | 9 (NR)      | NR      | NR                  | NR                          | NR            | NR                             |
| Heald et al[26]     | 0     | 0           | 0       | 0                   | NR                          | NR            | NR                             |
| Bellosta et al[27]  | 8     | 1 (major)   | 1       | NR                  | NR                          | NR            | NR                             |
| Kaur et al[28]      | 1     | 0           | 1       | NR                  | 1                           | NR            | NR                             |
| Kahlberg et al[29]  | 12    | NR          | NR      | NR                  | NR                          | NR            | NR                             |
| Schultz et al[30]   | 1     | 0           | 0       | Septic shock, ARDS, AKI (n = 2), DVT (n = 2), Hemorrhagic shock (n = 1) | 1 | NR | NR                             |
| Vacirca et al[31]   | 0     | 0           | 0       | 0                   | 1                           | NR            | NR                             |
| Fan et al[32]       | 0     | 0           | 0       | NR                  | 1                           | NR            | NR                             |
| Perini et al[33]    | 1     | 0           | 0       | 0                   | 1                           | NR            | NR                             |
| Kashif et al[34]    | 0     | 2 (NR)      | NR      | DVT (n = 1)         | 3                           | NR            | NR                             |
| Baeza et al[35]     | 0     | 0           | 0/3     | 0                   | 3                           | NR            | NR                             |
| Garg et al[36]      | 1     | 0           | 0       | DVT (n = 1), Stroke (n = 1) | 2 | NR | NR                             |
| Thompson et al[37]  | 0     | 0           | 0       | –                   | 1                           | Several days   | Digit tip gangrene             |
| Levolger et al[38]  | 0     | 0           | 0       | Contralateral limb ischemia (n = 1) | 1 | NR | NR                             |

(Continued on next page)
This point probably explains the high number of patients treated conservatively as a first-line treatment in this review as well. However, we found that medical treatment showed a much higher mortality risk compared with intervention, although the amputation risk was similar. In another systematic review by Putko et al,77 a similar mortality rate was found, although the number of included cases and studies was much lower and no further meta-analysis was conducted. However, Tang et al78 have shown that anticoagulant treatment mainly with low-molecular-weight heparin is associated with a lower mortality risk in patients with COVID-19 who have an increased coagulopathy score or high D-dimer levels. Therefore, coverage with anticoagulants is imperative in high-risk patients.

If an intervention is needed, several methods have been used for treating ALI, including thrombectomy, thrombolysis, thrombosuction, and others, yielding comparable results regarding limb salvage.79 The choice of surgical intervention is influenced by both the clinical status of the patient and the etiology of the ALI. Data from non-COVID cases show that thrombotic rather than embolic events lead to worse outcomes.80 In our review, we found an almost 10.5% reoperation rate and a 23.5% amputation rate, with the majority being major amputations. Other authors have also found that successful revascularization is disappointingly low in patients with COVID-19 when compared with previously reported series.81 Data indicate that continuation of anticoagulants at admission in patients already receiving such agents for other causes did not affect outcomes, even in patients undergoing operative procedures.12 This finding underlines the strong hypercoagulant and inflammatory storm that this infection releases.

There are certain limitations to this review. First, the total number of patients included is low, and most of studies consist of case reports or case series. Second, many studies do not provide data considering the precise medical treatment or laboratory profile of patients to extract adequately powered pooled data. There was also a lack of specific a definition for the majority of comorbidities in the included studies and, therefore, these events were reported in this review as reported in the studies. Additionally, no follow-up is provided by the majority of studies. This factor is mainly due to the fact that all of studies have been published within the last year. Furthermore, reoperation rates are reported without any detail on the type of procedure in the majority of studies. Finally, data were too limited to conduct any multiregression analysis.

**CONCLUSIONS**

SARS-CoV-2 infection is associated with a high thrombotic risk probably by promoting a systematic inflammatory response and a hypercoagulable state. COVID-associated ALI usually presents in patients with low number of comorbidities, and it is associated with a high mortality and amputation risk. Mortality risk seems to be greater with conservative treatment compared with any intervention, although the amputation risk is similar. Future studies should focus on identifying optimal medical treatment for these patients as well as potential prognostic factors for mortality and amputation risks.

**AUTHOR CONTRIBUTIONS**

Conception and design: GG, AS, KF
Analysis and interpretation: GG, KS, FS
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