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Audra A. Duncan, MD, SECTION EDITOR

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.[1] 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.[2,3] 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.[4] 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,[5,6] 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

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Author conflict of interest: none.

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The editors and reviewers of this article have no relevant financial relationships to disclose per the JVS policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.

0741-5214

https://doi.org/10.1016/j.jvs.2021.07.222

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).[7] 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 primary 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.[8] 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,

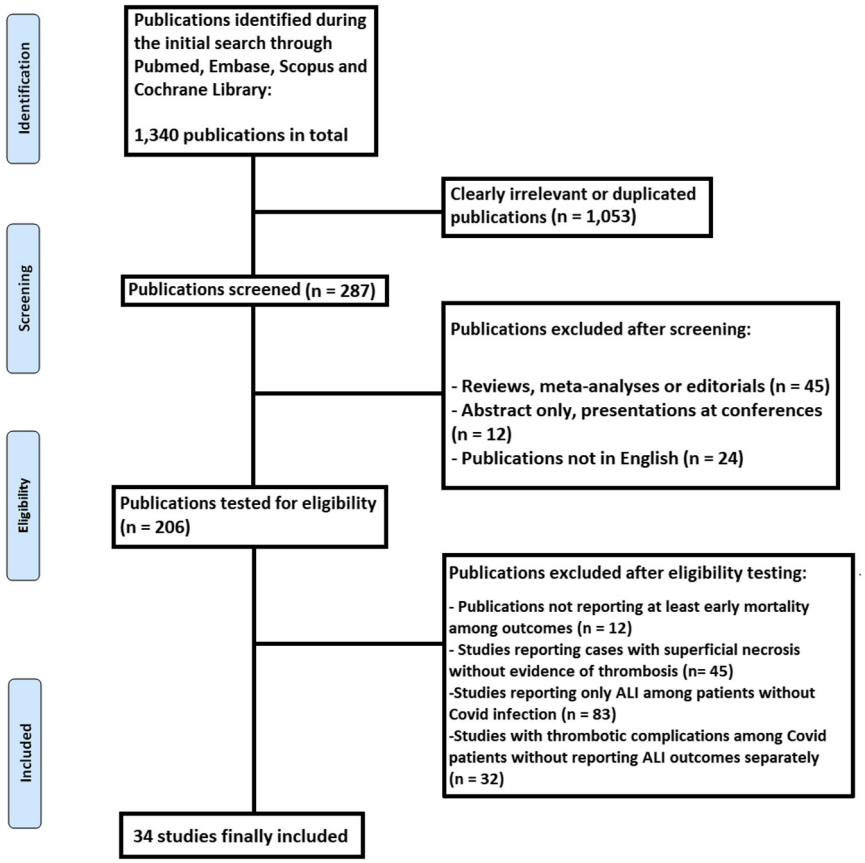

Fig 1. PRISMA flowchart of this review. *ALI,* Acute limb ischemia.

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 I^2 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 χ^2 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[9-42] (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[9]	2020	UK	1	1/0	56	Bilateral lower limbs	Right SFA, right trifurcation, left trifurcation
Kaur et al[10]	2020	USA	1	1/0	43	Right lower limb	Right SFA, POPA, trifurcation
Brugliera et al[11]	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[12]	2020	Pakistan	1	0/1	75	Left upper limb	Left UA and RA
Hasan et al[13]	2020	Pakistan	1	1/0	60	Right lower limb	Right POPA and trifurcation
Gubitosa et al[14]	2020	USA	1	1/0	65	Right lower limb	Right POPA
Anwar et al[15]	2020	USA	1	1/0	58	Left lower limb	Left SFA, trifurcation
Singh et al[16]	2020	USA	1	1/0	77	Left lower limb	Left SFA, trifurcation
Wang et al[17]	2020	USA	2	2/0	54	Right lower limb Right upper limb	Right dorsalis pedis, toes Right digital arteries, digits
Goldman et al[18]	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[19]	2020	Peru	30	23/7	60 ± 15	Lower limb (n = 22) Upper limb (n = 8)	NR
Galanis et al[20]	2020	Greece	1	1/0	80	Right Upper limb	RA and UA
Bozzani et al[21]	2020	Italy	6 (38)	4/2	71 (49-83)	Lower limb (n = 6)	Iliac–SFA–POPA (n = 6)
Mietto et al[22]	2020	Italy	1	1/0	53	Left lower limb	Iliac–SFA–POPA –tibial arteries
Baccellieri et al[23]	2020	Italy	1	1/0	67	Right lower limb	Iliac-SFA-POPA
Shao et al[24]	2020	USA	1	1/0	67	Right upper limb	Brachial artery, UA, RA
Etkin et al[25]	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[26]	2020	UK	1	1/0	49	Left lower limb	Aorti-iliac–POPA –trifurcation

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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[27]	2020	USA	1	1/0	65	Left hand-digital ischemia	Digital arteries (left first and second digits)
Bellosta et al[28]	2020	Italy	20	18/2	75 ± 8	Upper and lower limbs (number NR)	NR
Kaur et al[29]	2020	USA	1	1/0	71	Upper limb (right)	Right brachial artery and RA
Kahlberg et al[30]	2020	Italy	41 (305)	NR	NR	Upper and lower limbs	NR
Schultz et al[31]	2020	USA	2	1/1	57	3 fingers (right) 2 fingers (right)	Digital arteries (right) RA (right)
Vacirca et al[32]	2020	Italy	1	1/0	58	Right lower limb	ATA, PTA, PA (right)
Fan et al[33]	2020	Singapore	1	1/0	39	Right lower limb	ATA Abdominal aorta
Perini et al[34]	2020	Italy	2	2/0	45	Bilateral lower limbs Upper limb (left)	Aortoiliac Brachial bifurcation
Kashi et al[35]	2020	France	5 (7)	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[36]	2020	Spain	3	1/2	72	Bilateral lower limbs (n = 3)	Aortic-bilateral iliac (n = 3)
Garg et al[37]	2020	USA	3 (4)	2/1	63	Lower limb (2 right, 1 left)	POPA (n = 3)
Thompson et al[38]	2020	USA	1	0/1	42	Right upper limb	Right subclavian + UA
Levolger et al[39]	2020	Netherlands	2 (4)	2/0	53	Right lower limb Left upper limb	Right common iliac artery Left subclavian artery
Wengerter et al[40]	2020	USA	3 (4)	3/0	53	Left lower limb (n = 2) Bilateral lower limbs (n = 1)	Aortoiliac (n = 1) Femoral–POPA (n = 3)
Chowdhury et al[41]	2020	USA	1	1/0	75	Right upper extremity	Brachial artery
Liu et al[42]	2021	China	1	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.

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 μg/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 II. Demographics of the included patients

Study	Arterial hypertension	Diabetes mellitus	Dyslipidemia	COPD	CAD	Arrhythmia	CHF	Renal Disease	Other comorbidities
Veerasuri et al[9]	0	0	0	0	0	0	0	0	None
Kaur et al[10]	1/1	1/1	0	0	0	0	0	0	None
Brugliera et al[11]	3/3	2/3	1/3	1/3	0	0	0	1/3	Hypothyroidism (n = 1)
Hanif et al[12]	0	0	0	0	0	0	0	0	None
Hasan et al[13]	1/1	0	0	0	0	0	0	0	None
Gubitosa et al[14]	1/1	1/1	1/1	0	0	0	0	1/1	Smoking history
Anwar et al[15]	0	0	0	0	0	0	0	0	None
Singh et al[16]	0	0	0	0	0	0	0	0	None
Wang et al[17]	0	0	0	0	0	0	0	0	None
Goldman et al[18]	13/16	8/16	8/16	NR	NR	NR	4/16	0/16	Smoking history (n = 8) PAD (n = 8)
Sánchez et al[19]	10/30	8/30	1/30	NR	4/30	3/30	NR	1/30	Smoking history (n = 3) PAD (n = 4)
Galanis et al[20]	1/1	1/1	0	0	0	0	0	0	Dementia
Bozzani et al[21]	NR	NR	NR	NR	NR	NR	NR	NR	NR
Mietto et al[22]	1/1	0	0	0	0	0	0	0	Obesity
Baccellieri et al[23]	0	0	0	0	0	0	0	0	Obesity
Shao et al[24]	0	0	0	0	0	0	0	0	Lupus anticoagulant positive
Etkin et al[25]	NR	NR	NR	NR	NR	NR	NR	NR	NR
Muhammad et al[26]	NR	NR	NR	NR	NR	NR	NR	NR	NR
Heald et al[27]	1/1	0	0	0	0	0	0	0	History of smoking
Bellosta et al[28]	11/20	3/20	NR	2/20	2/20	5/20	NR	4/20	Previous VS (n = 4) Obesity (n = 4)
Kaur et al[29]	0	1/1	0	0	0	0	0	0	None
Kahlberg et al[30]	NR	NR	NR	NR	NR	NR	NR	NR	NR
Schultz et al[31]	1/2	0	1/2	0	0	0	0	0	Obesity (n = 1)
Vacirca et al[32]	NR	NR	NR	NR	NR	NR	NR	NR	NR
Fan et al[33]	0	0	0	0	0	0	0	0	None
Perini et al[34]	0	0	0	0	0	0	0	0	None
Kashi et al[35]	4/5	1/5	NR	1/5	NR	2/5	NR	1/5	Smoking (n = 2) PAD (n = 2)
Baeza et al[36]	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[37]	1/3	1/3	1/3	NR	NR	1/3	NR	NR	NR
Thompson et al[38]	0	1/1	0	0	0	0	0	0	Rheumatoid arthritis
Levolger et al[39]	0	1/2	0	0	0	0	0	0	-
Wengerter et al[40]	1/3	2/3	1/3	0	0	0	0	0	Smoking (n = 1)
Chowdhury et al[41]	1/1	0	1/1	0	1/1	0	0	0	Dementia
Liu et al[42]	0	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.

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 (μg/mL)	PCT (ng/mL)
Veerasuri et al[9]	1/1	1/1	0	0.8	NR	NR	NR	23.138	NR
Kaur et al[10]	1/1	1/1	1/1	16	484	853	289.7	20	67
Brugliera et al[11]	1/3	3/3	1/3	NR	Normal for all	466.3	NR	20, NR, 5.04	NR
Hanif et al[12]	1/1	0	0	5.9	733	NR	NR	0.867	NR
Hasan et al[13]	1/1	1/1	0	13.9	95	NR	82.5	1.96	0.3
Gubitosa et al[14]	1/1	1/1	1/1	Lymphopenia	82	247	NR	7.955	NR
Anwar et al[15]	1/1	1/1	0	NR	NR	312	25.23	15.653	25.23
Singh et al[16]	0	1/1	0	41	534	NR	301	2.77	0.6
Wang et al[17]	2/2	2/2	2/2	NR	NR	NR	NR	8.25	NR
Goldman et al[18]	3/16	8/16	4/16	13.5 ± 4	NR	NR	NR	NR	NR
Sánchez et al[19]	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[20]	1/1	1/1	1/1	5.6	174	360	166	13.6	0.1
Bozzani et al[21]	NR	NR	2/6	NR	NR	NR	78.17 [3-240]	NR	NR
Mietto et al[22]	0	0	0	NR	NR	NR	NR	NR	NR
Baccellieri et al[23]	1/1	1/1	0	NR	NR	711	114.1	20	NR
Shao et al[24]	0	1/1	1/1	Increased	NR	NR	NR	>5	NR
Etkin et al[25]	NR	NR	NR	NR	NR	NR	NR	NR	NR
Muhammad et al[26]	1/1	1/1	0	11.8	520	NR	12	NR	NR
Heald et al[27]	0	1/1	1/1	NR	NR	NR	NR	0.79	NR
Bellosta et al[28]	NR	NR	NR	14 ± 2	239 ± 82	NR	NR	2.2	NR
Kaur et al[29]	1/1	1/1		8.6	331	-	111.9	1.85	-
Kahlberg et al[30]	NR	NR	NR	NR	NR	NR	NR	NR	NR
Schultz et al[31]	1/2	2/2	2/2	NR	NR	486, NR	25, NR	7.56	NR
Vacirca et al[32]	0	1/1	1/1	6.07	322	524	NR	1.19	0.1
Fan et al[33]	1/1	1/1		NR	NR	770	136.2	2.55	NR
Perini et al[34]	NR	NR	1/2	NR	NR	NR	NR	9.0	NR
Kashi et al[35]	NR	NR	3/5	NR	160	NR (n = 2) 547	NR	NR (n = 3) 20	NR
Baeza et al[36]	3/3	0/3	0/3	18.2	193.7	766.3	4.1	5.07	NR
Garg et al[37]	1/3	2/3	1/3	NR	NR	NR	NR	3.3	NR
Thompson et al[38]	0	0	0	NR	NR	NR	NR	NR	NR
Levolger et al[39]	2/2	1/2	0/2	10.6	360	NR	167	NR	NR
Wengerter et al[40]	1/3	0	1/3	NR	NR	NR	144.3	15.6	NR
Chowdhury et al[41]	1/1	1/1	1/1	8.6	172	NR	20	1.2	NR
Liu et al[42]	0	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.

(>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), fasciotomy (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 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[9]	1/0	NR	NR	NR	1/1	Rivaroxaban	0	None	0
Kaur et al[10]	1/0	1/1	1/1	NR	1/1	NR	0	None	0
Brugliera et al[11]	2/1	3/3	2/3	1/3	3/3	Iloprost (n = 1) ASA (n = 2)	1	None	0
Hanif et al[12]	0/1	0	1/1	0	1/1	NR	1	None	0
Hasan et al[13]	1/0	0	1/1	0	1/1	Rivaroxaban post discharge	0	None	0
Gubitosa et al[14]	0/1	0	0	0	1/1	FDPX	1	Fasciotomy	0
Anwar et al[15]	0/1	1/1	1/1	0	1/1	CTDS, ASA	0	Angioplasty	0
Singh et al[16]	0/1	1/1	1/1	0	1/1	NR	1	None	0
Wang et al[17]	2/0	NR	NR	NR	1/1	Argatroban	0	None	0
Goldman et al[18]	9/7	NR	NR	NR	NR	NR	6	None	0
Sánchez et al[19]	2/28	NR	NR	NR	NR	NR	23	Fasciotomy (n = 6)	2
Galanis et al[20]	1/0	1/1	1/1	0	1/1	FDPX	1	None	0
Bozzani et al[21]	0/6	NR	NR	NR	6/6	ASA (3/6) ASA + clopidogrel (3/6)	6	PTA (n = 2) PTA + stenting (n = 1)	1
Mietto et al[22]	0/1	NR	NR	NR	1/1	Prostacyclin	1	Thrombolysis, fasciotomy	1
Baccellieri et al[23]	0/1	1/1	1/1	NR	1/1	NR	1	Thrombectomy at right upper limb	0
Shao et al[24]	0/1	NR	NR	NR	1/1	NR	1	Thrombolysis, fasciotomy	0
Etkin et al[25]	31/11	NR	NR	NR	NR	NR	9	Endovascular thrombosuction (n = 2)	NR
Muhammad et al[26]	0/1	NR	NR	NR	1/1	ASA 75 mg Dabigatran 150 mg bid	0	Thrombolysis	0
Heald et al[27]	1/0	NR	NR	NR	1/1	NR	0	None	0
Bellosta et al[28]	3/17	NR	NR	NR	20/20	NR	15	Below the knee fempop bypass (n = 2) Additional thrombolysis (n = 2) Kissing stents (n = 2) Femoral endarterectomy (n = 1) Below the knee angioplasty (n = 1)	2
Kaur et al[29]	0/1	1/1	1/1	NR	1/1	NR	1	Endarterectomy of the right arm	0
Kahlberg et al[30]	NR	NR	NR	NR	NR	NR	NR	NR	NR
Schultz et al[31]	2/0	2/2	2/2	2/2	2/2	Nitroglycerin (n = 2) Apixaban (n = 1)	0	None	0
Vacirca et al[32]	0/1	NR	NR	NR	1/1	NR	1	Thrombolysis	0
Fan et al[33]	0/1	NR	NR	1/1	1/1	ASA	1	Aortic stent graft placement	0
Perini et al[34]	1/1	NR	NR	NR	1/1	NR	1	None	1
Kashi et al[35]	4/1	NR	NR	NR	2/5	Apixaban (n = 1) ASA (n = 2)	1	None	NR
Baeza et al[36]	0/3	3/3	3/3	2/3	3/3	Acenocoumarol (n = 1)	2	Aortobifemoral bypass (n = 1)	0
Garg et al[37]	2/1	1/3	1/3	1/3	3/3	–	1	NR	NR
Thompson et al[38]	0/1	0	0	0	1/1	–	1	None	0
Levolger et al[39]	2/0	1/2	0	0	2/2	Rivaroxaban (n = 1) Apixaban (n = 1)	1	Thrombolysis	0
Wengerter et al[40]	0/3	NR	NR	NR	3/3	NR	3	None	NR

(Continued on next page)

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 al[41]	0/1	1/1	1/1	0	1/1	Prednisolone	1	None	0
Liu et al[42]	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 = 3) Dabigatran (n = 1) Argatroban (n = 1) Rivaroxaban (n = 3) CTDS (n = 2) FDPX (n = 1) Acenocoumarol (n = 1) Prostaglandins (n = 2) Nitroglycerine (n = 2) (15 studies NR)	N = 81 (1 study NR)	Thrombolysis (n = 7) PTA/stenting (n = 5) Endarterectomy (n = 2) Fasciotomy (n = 9) Bypass (n = 3) Thrombectomy at other site (n = 1) Thrombosuction Stent graft placement (n = 1)	n = 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, 17.3%-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 (I^2 = 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, .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] 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.[51] 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,[52] 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.[53] COVID-19 causes elevated cytokine levels, including but not limited to tumor necrosis factor-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

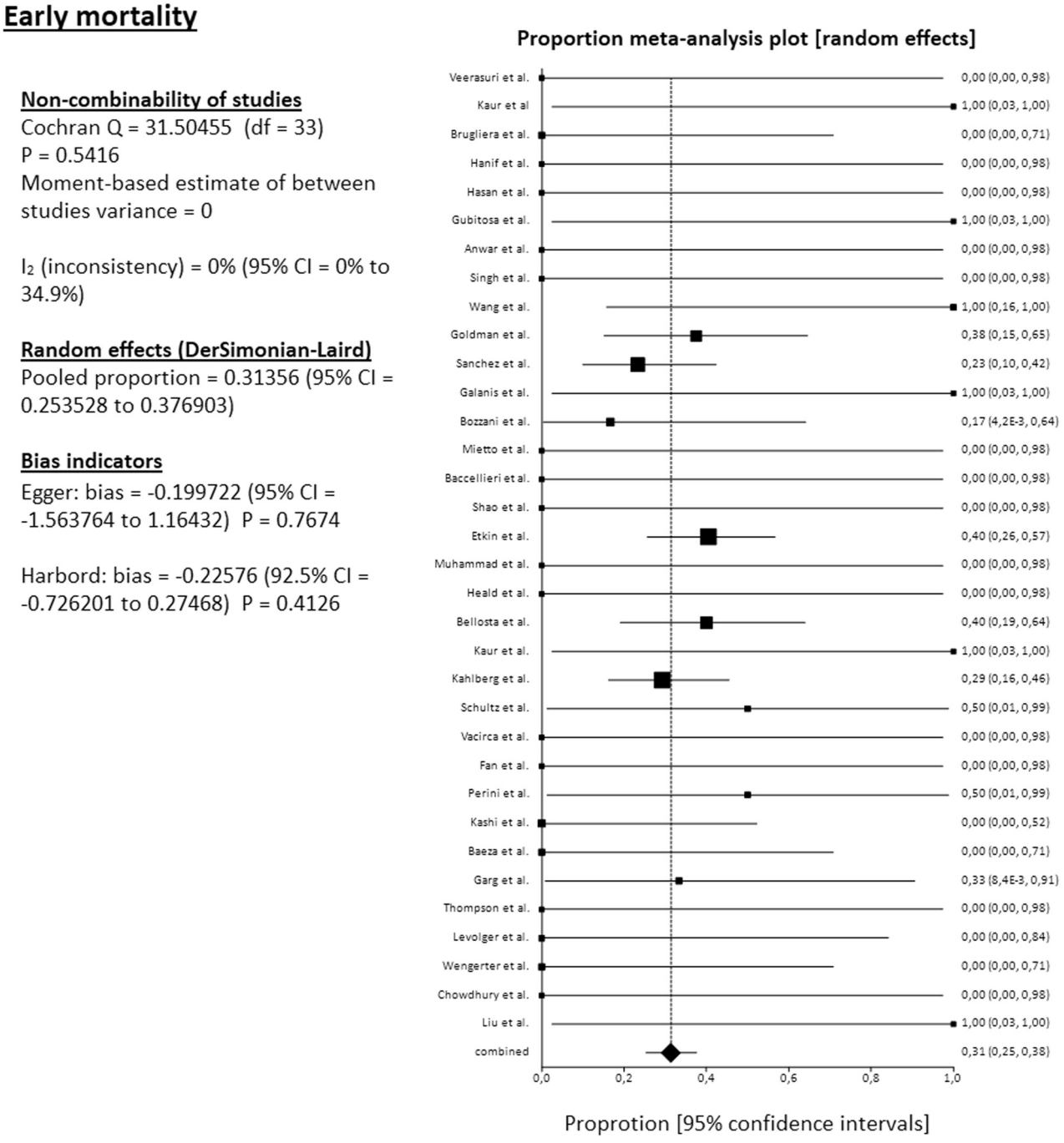

Fig 2. Forest plot on pooled early mortality. *CI,* Confidence interval; *df,* degrees of freedom.

those with severe symptoms had higher CRP levels and a higher thrombotic risk.[58] 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.[59]

There is growing evidence that this virus promotes a procoagulant state producing both microthrombi and macrothrombi.[60] Cutaneous ischemic lesions are frequent in such patients, even in absence of major vessel thrombosis.[61] In particular, severe endothelial injury, widespread thrombosis with microangiopathy, alveolar-capillary microthrombi and new vessel growth have been detected in infected cases.[62] Vascular pathological changes in such patients include partial vascular endothelial shedding, vascular intimal

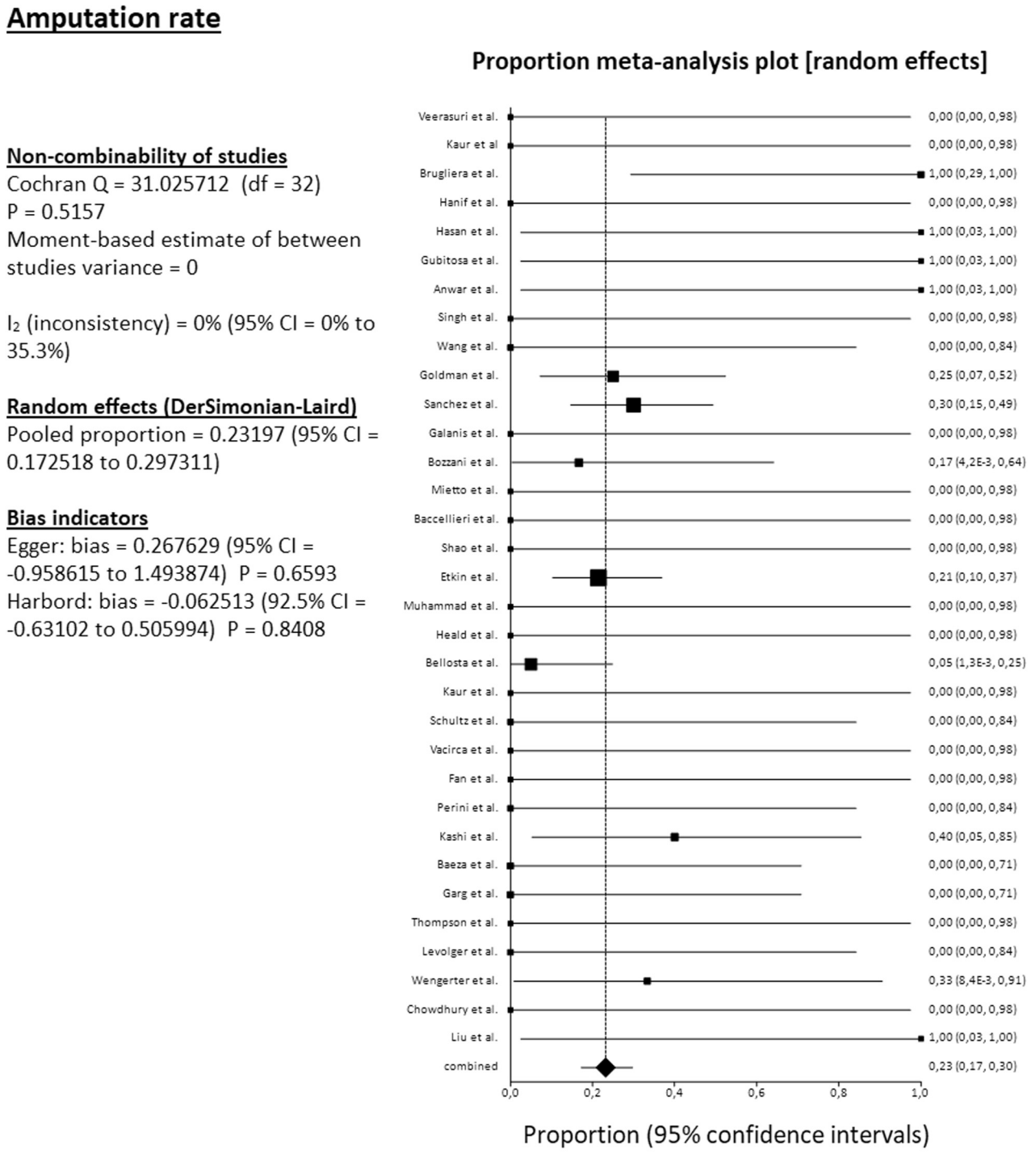

Fig 3. Forest plot on pooled amputation rate. *CI,* Confidence interval; *df,* degrees of freedom.

inflammation, and thrombosis.[63] Varga et al[63] 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.[33] The viral infection itself leads to decreased platelet function secondary to decreased production, platelet consumption, and production of autoantibodies such as antiphospholipid antibodies.[64,65] 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.[66,67]

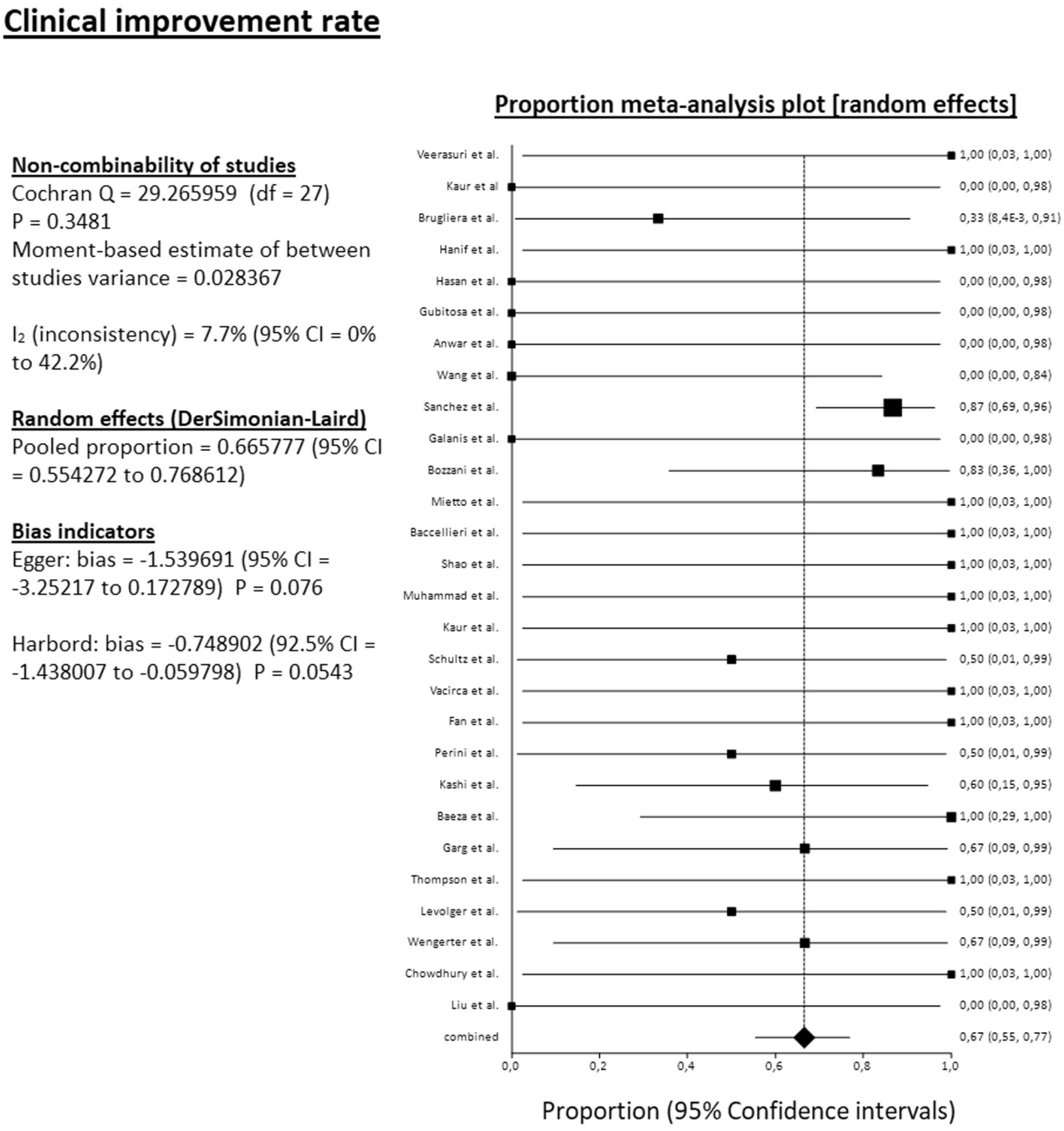

Fig 4. Forest plot on pooled clinical improvement rate. *CI,* Confidence interval; *df,* degrees of freedom.

Regarding thrombotic markers, high D-dimers, fibrinogen degradation products, and a prolonged thromboplastin time have been associated with greater in-hospital mortality, need for mechanical ventilation, and thrombotic complications in infected patients.[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.[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.[71] However, an optimal cut-off level and prognostic value are still not known.[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.[44] However, we could not establish an

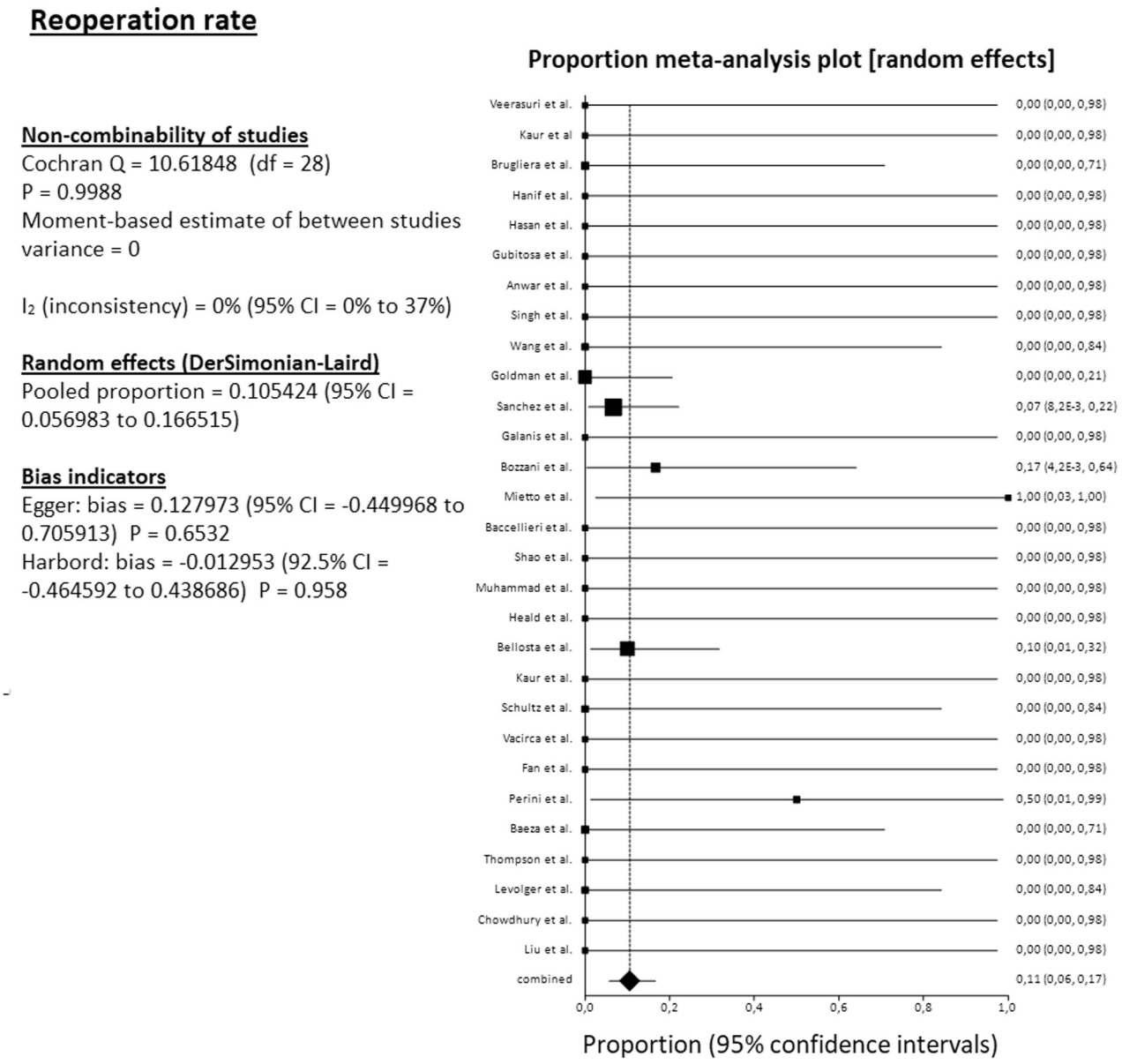

Fig 5. Forest plot on pooled reoperation rate. *CI,* Confidence interval; *df,* degrees of freedom.

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.[73] However, ALI can even occur among patients already receiving thromboprophylaxis,[74] and this outcome has been observed in some cases included in the present review. Despite thromboprophylaxis, the risk of venous thromboembolism remains high in hospitalized patients with COVID-19.[75] One study of 94 patients with confirmed COVID-19 demonstrated a statistically significant relative deficiency of antithrombin III compared with control.[76] This acquired deficiency would promote further coagulation and could decrease the efficacy of anticoagulant treatment in such patients. 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[11]	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
Gubitosa 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	NR	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
Etkin et al[25]	17	9 (NR)	NR	NR	NR	NR	NR
Muhammad et al[26]	0	0	0	NR	1	6 weeks	Full recovery
Heald et al[27]	0	0	0	0	NR	NR	NR
Bellosta et al[28]	8	1 (major)	1	NR	NR	NR	NR
Kaur et al[29]	1	0	1	NR	1	NR	NR
Kahlberg et al[30]	12	NR	NR	NR	NR	NR	NR
Schultz et al[31]	1	0	0	Septic shock, ARDS, AKI (n = 2) DVT (n = 2) Hemorrhagic shock (n = 1)	1	NR	NR
Vacirca et al[32]	0	0	0	0	1	NR	NR
Fan et al[33]	0	0	0	NR	1	NR	NR
Perini et al[34]	1	0	0	0	1	NR	NR
Kashi et al[35]	0	2 (NR)	NR	DVT (n = 1)	3	NR	NR
Baeza et al[36]	0	0	0/3	0	3	NR	NR
Garg et al[37]	1	0	0	DVT (n = 1) Stroke (n = 1)	2	NR	NR
Thompson et al[38]	0	0	0	–	1	Several days	Digit tip gangrene
Levolger et al[39]	0	0	0	Contralateral limb ischemia (n = 1)	1	NR	NR

(Continued on next page)

Table V. Continued.

Study	Death	Amputations	Cardiac	Other complications	Improvement of the ischemia	Mean follow-up	Late outcomes
Wengerter et al[40]	0	1 (BTK)	0	Stroke (n =1)	2	NR	NR
Chowdhury et al[41]	0	0	0	0	1	NR	NR
Liu et al[42]	1	1 (TF)	0	0	0	NR	NR
Total (n)	61	34 (1 study NR)	4 (5 studies NR)	DVT/PE (n = 7) Rethrombosis (n = 2) Stroke (n = 1) AKI/hemodialysis (n = 4) Encephalopathy (n = 1) Shock (n = 2) Other limb ischemia (n = 2) Rhabdomyolysis (n = 1) HIT (n = 1) Other (n = 3) (8 studies NR)	56 (6 studies NR)	0-2 months (28 studies NR)	No new event (n = 2) Digit gangrene (n = 2) Numbness/nerve impairment (n = 2) (28 studies NR)

ARDS, Acute respiratory distress syndrome; *AKI,* acute kidney injury; *BTK,* below the knee; *DVT,* deep vein thrombosis; *GI,* gastrointestinal; *HIT,* heparin-induced thrombopenia; *NR,* not reported; *PE,* pulmonary embolism; *TF,* transfemoral.

thrombosis.[30] 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 al[78] 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 thrombembolectomy, 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

Data collection: GG, MF, KV, DV, CT, VM
Writing the article: GG, AS, MF, KV, DV, CT, VM
Critical revision of the article: GG, FS, KF
Final approval of the article: GG, AS, MF, KV, DV, CT, VM, FS, KF
Statistical analysis: GG
Obtained funding: Not applicable
Overall responsibility: KF

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Submitted Mar 30, 2021; accepted Jul 27, 2021.