Review Paper

COVID-19 Patients With Peripheral Artery Diseases and Comorbidities: Systematic Review and Meta-analysis

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ABSTRACT

Background and Purpose: COVID-19 is a significant cause of hypercoagulability, which is crucial in causing peripheral artery disease (PAD) or exacerbating pre-existing PAD. When comorbidities are present, patients are prone to poor prognosis. Hence, we seek to evaluate the clinical outcomes in COVID-19 patients with PAD and find associated comorbidities.

Materials and Methods: A systematic search was performed through PubMed, Cochrane, ProQuest, Scopus, Wiley, and EMBASE using keywords that matched the MeSH browser, such as PAD, COVID-19, and comorbidities, without any date range limitation. Additionally, we utilized Google Scholar to point out additional articles that could be found in the several databases included but were not found due to the keywords. We looked for observational studies of PAD patients with or without comorbidities until July 22, 2023.

Results: Twenty-one studies were included in this systematic review and meta-analysis. COVID-19 patients with PAD were associated with significantly higher re-thrombolysis (OR=3.09; 95% CI, 1.31%, 7.28%; P=0.01) and mortality rate (OR=3.82; 95% CI, 1.10%, 13.22%; P=0.03). However, a higher amputation rate than non-COVID-19 patients showed lower significance (OR=2.99; 95% CI, 0.90%, 9.89%; P=0.07), and no significant difference in limb salvage rate was observed (OR=0.58; 95% CI, 0.06%, 5.60%; P=0.64). Comorbidities that show significant associations with COVID-19 patients with PAD were hypertension (67.0%; 95% CI, 0.54%, 0.80%), diabetes mellitus (DM) (50.0%; 95% CI, 0.37%, 0.62%), hyperlipidemia (47.0%; 95% CI, 0.30%, 0.64%), heart diseases (28.0%; 95% CI, 0.14%, 0.41%), and atrial fibrillation (16.0%; 95% CI, 0.06%, 0.25%).

Conclusion: This meta-analysis demonstrates a higher re-thrombosis and mortality rate in PAD patients with COVID-19 infection compared to patients without COVID-19. These events are shown to be higher in diabetes, hypertension, and dyslipidemia individuals. Therefore, further treatments are needed for COVID-19 patients with PAD and cardiovascular comorbidities to prevent worse outcomes and to anticipate the possibilities of new COVID-19 variants as well as long COVID-19 syndrome.

Keywords: COVID-19, Peripheral artery diseases (PAD), Re-thrombosis, Mortality, Hypertension, Diabetes mellitus (DM)

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Introduction

The world has been fighting the COVID-19 pandemic for the past few years. Like other viruses, the SARS-CoV-2 virus underwent mutations, leading to new variants. Despite the availability of a vaccine, in January 2022, the COVID-19 virus managed to resurge, with global reports indicating 23.5 million cases per week. Subsequently, in December 2022 and January 2023, the prevalence of COVID-19 surged once more, peaking at 44.2 million cases per week globally. This condition emphasizes the need to continuously expand our understanding of the disease's pathogenesis to ensure effective case management [1, 2].

One significant aspect of this virus's pathogenesis is strongly associated with the overproduction of pro-inflammatory cytokines. COVID-19 patients exhibit markedly increased levels of inflammatory cytokines (interleukin [IL]-6 and tumor necrosis factor [TNF]-α), fibrinogen, D-dimer, factor VIII, and von Willebrand factor (vWF), along with decreased antithrombin levels, leading to a prothrombotic milieu. It is proposed that this phenomenon occurs due to the entry of SARS-CoV-2 into pneumocytes, where it binds to the angiotensin-converting enzyme (ACE-2), resulting in the depletion of available ACE-2. This enzyme acts on degrading angiotensin-II (Ang-II); hence, its depletion leads to an excess of Ang-II. Excess Ang-II then binds to angiotensin receptor-1, exacerbating the hypercoagulable state by increasing cytokine levels and inducing the expression of plasminogen activator inhibitor 1 (PAI-1) on endothelial cells. This state of hypercoagulability plays a key role in the induction or exacerbation of peripheral artery disease (PAD) [1-4].

PAD is a circulatory problem resulting from stenosis and occlusion of medium- to large-sized arteries outside the heart and brain, accounting for coronary artery disease and cerebrovascular disease, respectively. PAD most commonly affects the lower extremities, manifesting as thigh or calf pain during walking or exertion (intermittent claudication) [5, 6]. Statistics corroborate the relevance of COVID-19 and PAD by demonstrating an increase in PAD cases in tandem with the progression of the COVID-19 pandemic [4]. Regarding the outcomes, comorbidities that induce a hypercoagulable state, such as hypertension and diabetes, are believed to worsen the prognosis. Individuals with these conditions often exhibit reduced ACE-2 expression, further contributing to elevated Ang-II levels [3, 7].

Despite the pandemic having subsided, comprehending this aspect remains crucial for enhancing the management of COVID-19 patients with PAD, particularly in light of the potential emergence of new COVID-19 variants and coagulation problems in patients with long COVID-19 syndrome [8]. Furthermore, while COVID-19's association with hypercoagulable conditions is well-established, the interconnections of COVID-19, PAD clinical outcomes, and associated comorbidities have not been clearly explained. Most available studies have relied solely on case reports and case series, with several yielding inconsistent results. Hence, we intend to assess clinical outcomes in COVID-19 patients with PAD and identify significantly associated comorbidities.

Materials and Methods

We conducted our systematic review following the guidelines outlined in the Cochrane handbook for systematic reviews of interventions version 6.2 and adhered to the reporting standards of the PRISMA (preferred reporting items for systematic review and meta-analysis) [9]. Additionally, we have registered this study with an ID of CRD42023405758 in the international prospective register of systematic reviews (PROSPERO) in compliance with international research ethics regulations.

Search strategy

Four independent reviewers conducted an extensive literature search across multiple electronic databases, including PubMed, Scopus, Cochrane, Embase, Wiley, and ProQuest, up to July 22, 2023. Keywords that matched the MeSH browser, such as PAD, acute limb ischemia, critical limb ischemia, intermittent claudication, COVID-19, diabetes mellitus, hypertension, and comorbidities, were employed in the search. Additionally, we utilized Google Scholar as a search engine to point out additional articles that could be found in the several databases included but are being overlooked due to the keywords. Advanced search techniques were employed as applicable and available to refine the search results according to the extra category available in each database.

Study eligibility criteria

Studies were screened based on inclusion and exclusion criteria. The inclusion criteria were observational studies such as cohort prospective and retrospective, PAD patients with COVID-19 with or without comorbidities (with PAD as all arterial diseases outside coronary

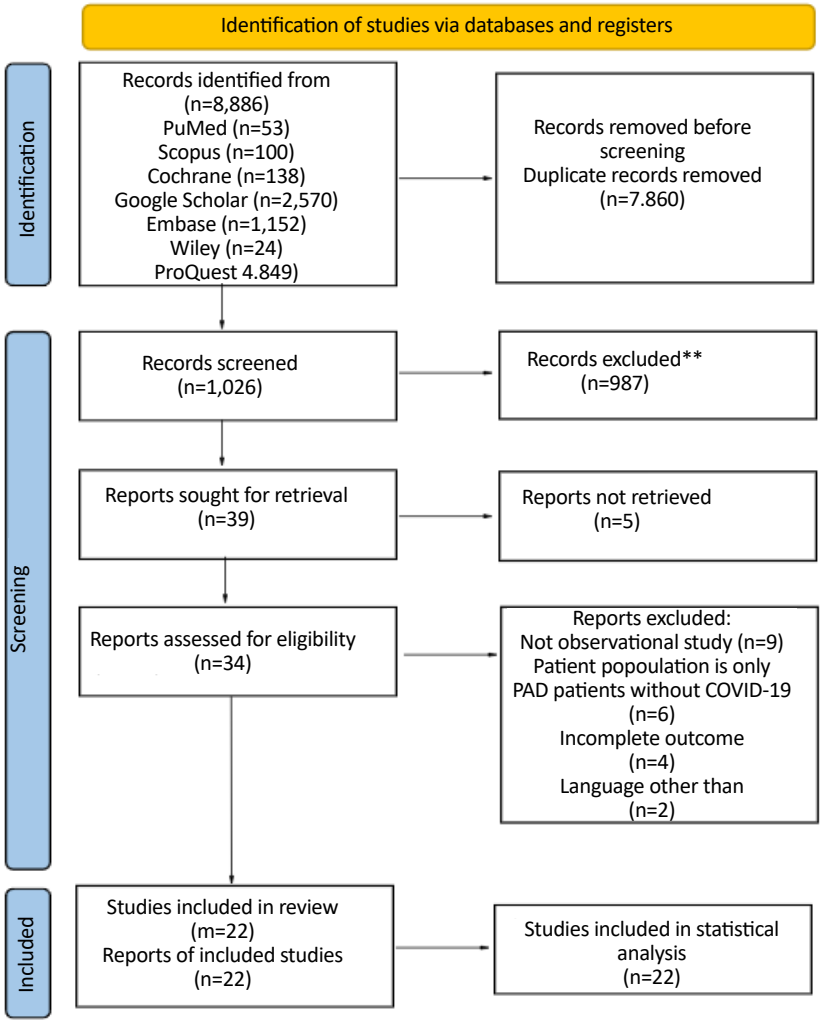


Figure 1. PRISMA diagram

and brain vascular) defined, and qualitative and quantitative outcomes. The exclusion criteria were PAD patients without COVID-19, uncompleted studies, studies in a language other than English, and irretrievable full-text. The planned procedure is shown in Figure 1.

Data extraction

We predetermined the outcome sheet in tabular form (MS Excel® for Mac; Microsoft Corporation, Redmond, WA, 2018) to include the following extracted data: author and year of publication; study characteristics, including the design, location, and length of study; study population, including sample size, subject types, range or mean age, gender, BMI, and comorbidities; and study outcomes. Our study outcomes are re-thrombosis, amputation, limb salvage, and mortality rate. In this data extraction, all authors extracted both qualitative and quantitative characteristics. In addition, all authors rechecked the accuracy of the extracted data while performing statistical analysis. All the disagreements between authors were resolved by the majority of opinions.

Risk of bias in assessment

Critical appraisal was performed following the Newcastle-Ottawa quality assessment scale for cohort studies to assess the bias of the included studies qualitatively [10]. The score is converted to Agency for Healthcare Research and Quality (AHRQ) standards, divided into >6: Good; 4-6: Fair; and 4: Poor. Four reviewers did the quality assessment blind to each other's scores, then discussed until a consensus was reached [11].

Statistical analysis

We conducted the statistical analysis using Review Manager version 5.4 from The Nordic Cochrane Center, the Cochrane Collaboration in Copenhagen. We

extracted the studies' odds ratios and prevalence percentages and interpreted the combined effects. To account for potential heterogeneity among the studies, we applied the DerSimonian-Laird random-effects model as sug- gested by Riley et al. We assessed heterogeneity using the estimated effect (I^2) statistics, following Cochrane thresholds, where values of 0%, 25%, 50%, and 75% in- dicate insignificant, low, moderate, and high heteroge- neity, respectively [12].

Results

Study selection and characteristics

A total of 8886 studies were identified through seven databases, with details listed in Appendix 1. After re- moving 7860 duplicates, 987 were removed based on their relevant "titles" and "abstracts." Also, 5 full texts were not retrieved, and 14 full texts were excluded based on the exclusion criteria. Finally, 21 studies were included for qualitative and quantitative analysis (Figure 1). The characteristics of the included studies are listed in Appendix 2.

Quality assessment

Each study was assessed for its selection, comparability, and outcomes using the Newcastle Ottawa scale (NOS) for cohort studies (Appendices 3 and 4) [13-33]. Overall, the studies were rated as high quality with a low risk of bias. According to the AHRQ, only five studies were deemed "poor quality."

Clinical outcomes

The clinical outcomes of PAD were compared between the control and COVID-19 groups (Figure 2). COVID-19 patients were associated with significantly worse outcomes compared to control, evidenced by a higher mortality rate (OR: 3.82 [95% CI, 1.10%, 13.22%]; P=0.03; I^2=30%) and higher re-thrombolysis rate (OR: 3.09 [95% CI, 1.31%, 7.28%]; P=0.1; I^2=10%), with insignificant to low heterogeneity. However, there is no significant difference between the two groups in amputation rate (OR: 2.99 [95% CI, 0.9%, 9.89%]; P=0.07; I^2=27%) and limb salvage rate (OR: 0.58 [95% CI, 0.06%, 5.60%]; P=0.64; I^2=82%). Low to high heterogeneity was found in these insignificant results.

The associated comorbidities rate in COVID-19 patients is shown in Figure 3. Hypertension was the most common comorbidity (67.0%; 95% CI, 0.54%, 0.80%), followed by diabetes mellitus (DM) (50.0%; 95% CI, 0.37%, 0.62%), hyperlipidemia (47.0%; 95% CI, 0.30%, 0.64%), heart diseases (28.0%; 95% CI, 0.14%, 0.41%), and atrial fibrillation (16.0%; 95% CI, 0.06%, 0.25%) in COVID-19 patients with PAD. However, all these results were correlated with high heterogeneity.

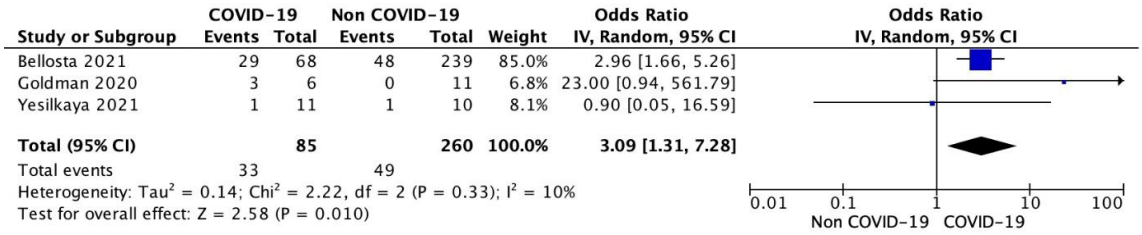
Discussion

In COVID-19 patients, a prothrombotic state and various thrombotic events are prevalent. Compared to other respiratory illnesses like acute influenza or other viral infections, SARS-CoV-2 infection significantly increases the incidence of thrombotic events. These events often manifest with severe clinical symptoms attributed to hypercoagulability induced by cytokine production. While the exact cause of this hypercoagulable state in COVID-19 has remained uncertain, several theories have been proposed, including endothelial dysfunction, coagulation abnormalities, hypoxia-induced endothelial changes, and conventional risk factors. These factors collectively heighten susceptibility to PAD in COVID-19 patients [34].

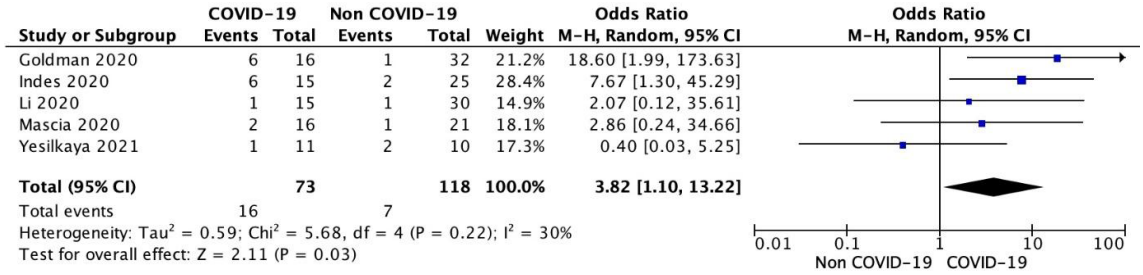
Our systematic review and meta-analysis consistently revealed that COVID-19 patients with PAD are associated with higher rates of re-thrombosis (OR=3.09; 95% CI, 1.31%, 7.28%; P=0.01), mortality (OR=3.82; 95% CI, 1.10%, 13.22%; P=0.03), amputations (OR=2.99; 95% CI, 0.90%, 9.89%; P=0.07), and limb salvage (OR=0.58; 95% CI, 0.06%, 5.60%; P=0.64). Despite the relatively lower statistical significance in the amputation and limb salvage groups, they are included in our analysis due to their substantial relevance to overall prognosis and complications in COVID-19 patients [4]. Our findings related to the mortality rate were in line with systematic review and meta-analysis by Zuin et al. (2022) which found that COVID-19 patients with PAD correlated significantly with higher mortality risk compared to control (OR 2.78 [95% CI, 2.37%, 3.27%]) [35]. Besides, another study by Ren et al. (2023) also supported these results with a pooled OR of 1.29 (95% CI, 1.1%, 1.5%) [36]. The need for amputations was significantly increased in the COVID-19 period, related to patients with PAD up to three times, as reported from a review by Pride et al. (2023) [37]. These findings may also be explained by the indirect impact of COVID-19, which affected healthcare delivery, especially for vulnerable populations.

In accordance with the results of our research, Goldman et al. underscored the impact of COVID-19-induced prothrombotic states on thrombus prevalence in large and medium arteries [17]. This condition contributes to worse outcomes, including amputation

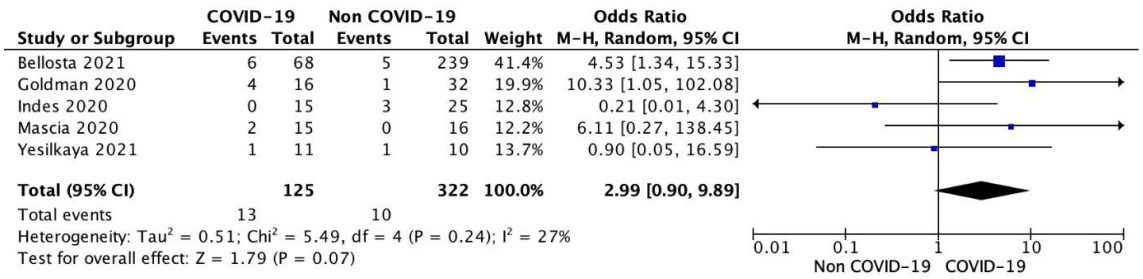
A. Re-thrombolysis rate



B. Mortality rate



C. Amputation rate



D. Limb salvage rate

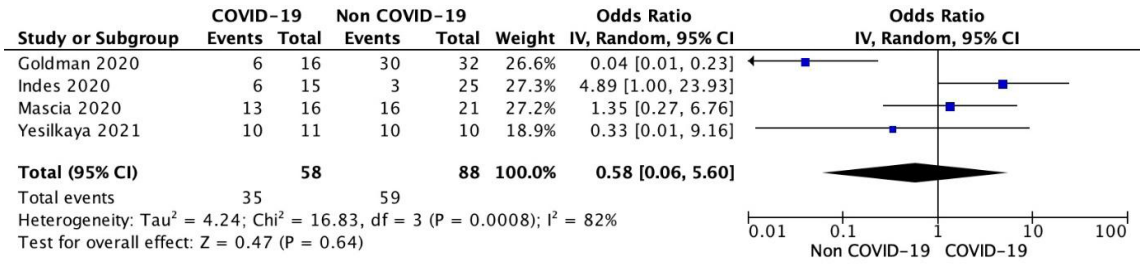


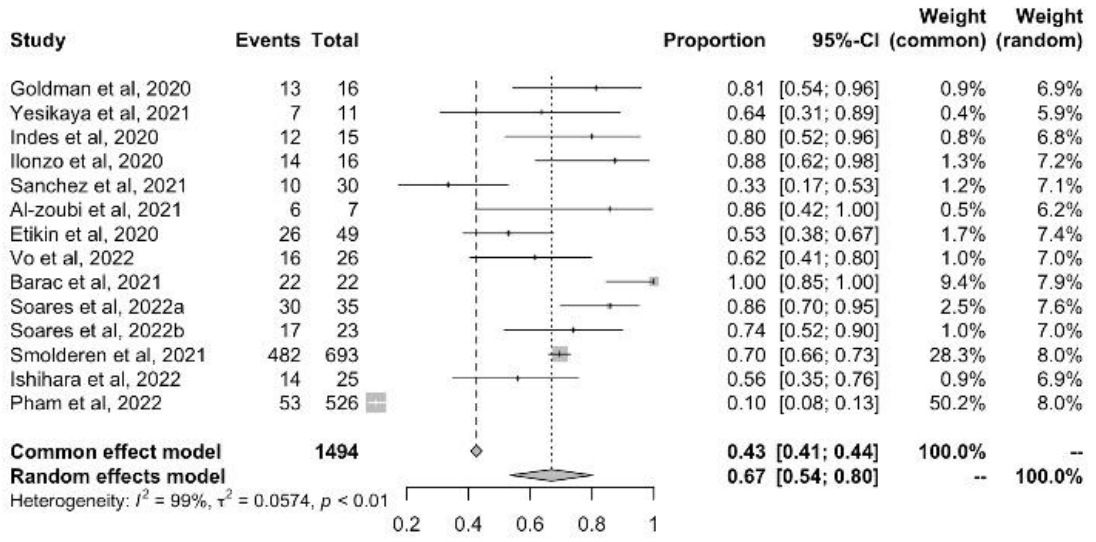
Figure 2. Clinical outcomes of PAD with COVID-19 patients

A) Forest plot for re-thrombolysis rate demonstrating low heterogeneity, B) Forest plot for mortality rate demonstrating moderate heterogeneity, C) Forest plot for amputation rate demonstrating moderate heterogeneity, D) Forest plot for limb salvage rate demonstrating high heterogeneity

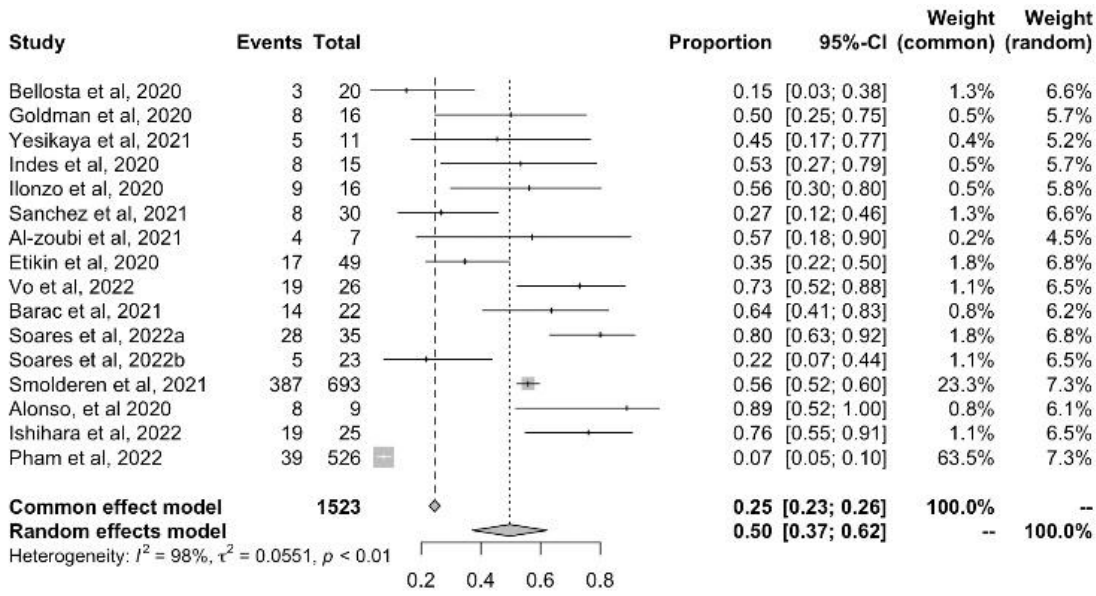
and mortality in COVID-19 patients with PAD. Bellosta et al.'s cohort study further substantiates this, revealing a significant mortality rate (40%) in patients with COVID-19 pneumonia presenting acute lower-extremity ischemia symptoms [16].

Concerning comorbidities, worse prognoses in COVID-19 patients are often observed when comorbidities are present. Our study aims to identify the most common comorbidities in COVID-19 patients with PAD, with hypertension (67%), DM (50%), hyperlipidemia (47%),

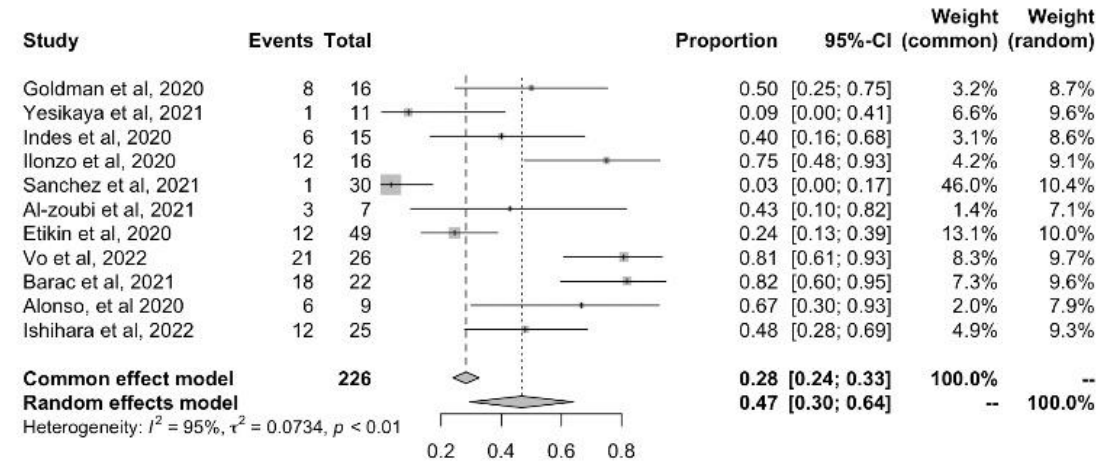
A. Hypertension



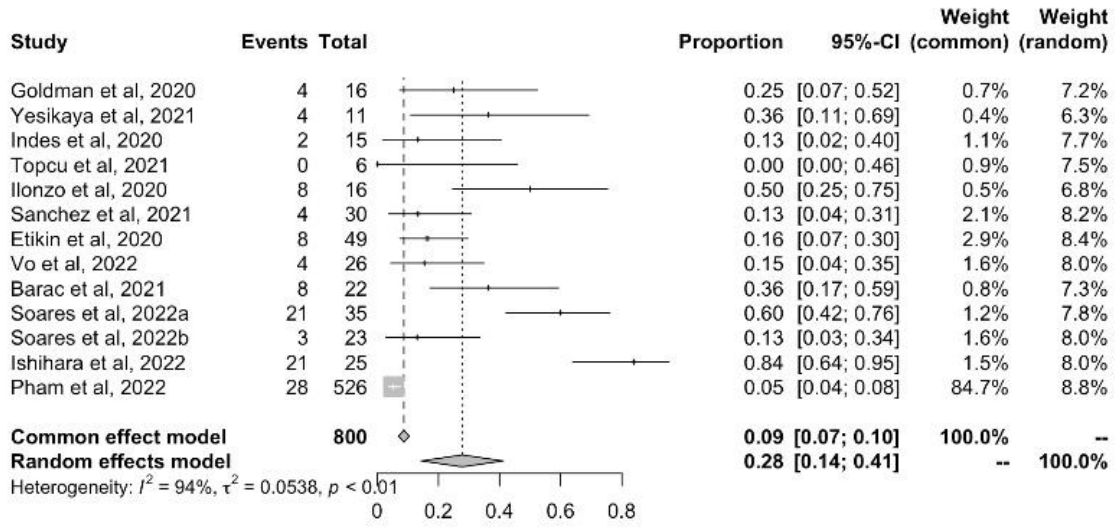
B. Diabetes mellitus



C. Hyperlipidemia



D. Heart disease



E. Atrial fibrillation

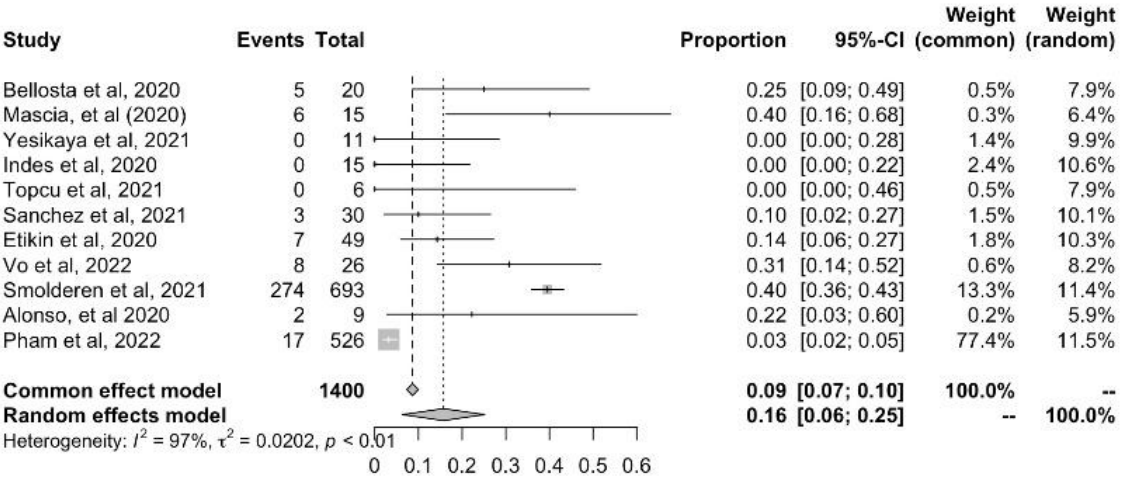


Figure 3. Associated comorbidities of PAD with COVID-19 patients

A) Hypertension, B) DM, C) Hyperlipidemia, D) Heart disease, E) Atrial fibrillation

heart disease (28%), and atrial fibrillation (16%) emerging as the most prevalent. These findings were similar to other systematic reviews by Rostagi et al. (2021), which found that hypertension, diabetes, and hypercholesterolemia were the most frequent comorbidities in order of occurrences in COVID-19 patients with PAD [3]. Hypertension, in particular, stands out due to its association with an activated innate immune response and chronic inflammation, which weaken initial immunity against SARS-CoV-2 infection. Hypertensive and diabetic patients also exhibit pre-existing endothelial dysfunction, increasing their susceptibility to PAD [38]. Rastogi et al. (2021) also revealed that COVID-19 patients with comorbidities of diabetes or hypertension presented with a higher risk of lower limb complications and, therefore, might require anti-coagulation [3]. These findings underscore the importance of evaluating comorbidities in COVID-19 patients with PAD to guide treatment decisions and improve prognosis.

This systematic review and meta-analysis had several limitations. The clinical outcomes of PAD in COVID-19 patients were presented with a small number of studies and subjects included in the analysis. Due to the small number of studies and subjects, we could not perform adequate subgroup analysis. High heteroge-

neity results were found, especially in COVID-19-associated comorbidities, using proportional meta-analysis. Besides, according to the NOS scale, some included studies were of poor quality.

Our study provides valuable insights for future research, potentially informing approaches to reduce mortality risk and enhance patient prognosis in patients with PAD. Furthermore, gaining a deeper understanding of PAD enables us to better inform vulnerable individuals about the importance of disease screening, progression, and prevention more effectively, especially in other comorbidities that may worsen the prognosis. It is important to emphasize that despite the pandemic having subsided, these findings retain their significance and may be helpful in patients with similar conditions. Besides, the COVID-19 pandemic has shown us both direct (such as hypercoagulability) and indirect effects (such as impacts on healthcare delivery). Therefore, better disease-related strategies must be prepared for the future.

Ethical Considerations

Compliance with ethical guidelines

This article is a meta-analysis with no human or animal sample.

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Authors contributions

Conceptualization, methodology, and investigation: Theresia Feline Husen; Data curation: Theresia Feline Husen, and Kelvin Kohar; Software and formal analysis: Kelvin Kohar; Validation and supervision: Nathanael Nathanael; Resources: Theresia Feline Husen, Ilona Nathania, and Kelvin Kohar; Visualization, and the original draft preparation: Theresia Feline Husen, Ilona Nathania, Kelvin Kohar, and Ruth Angelica; Review, and editing: Theresia Feline Husen, Ilona Nathania, and Kelvin Kohar; Final approval: All authors.

Conflict of interest

The authors declared no conflict of interest.

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Appendix 1. Results of databases search

Database	Keyword(s)	Hits
Pubmed	((Peripheral artery disease) OR (peripheral arterial disease) OR (acute limb ischemia) OR (critical limb ischemia) OR (intermittent claudication)) AND((COVID-19) OR (diabetes) OR (diabetes mellitus)OR (hypertension) OR (high blood pressure) OR(comorbidities))	53
Google Scholar	((Peripheral artery disease) OR (peripheral arterial disease) OR (acute limb ischemia) OR (critical limb ischemia) OR (intermittent claudication)) AND((COVID-19) OR (diabetes) OR (diabetes mellitus)OR (hypertension) OR (high blood pressure) OR(comorbidities))	2,570
Cochrane	((Peripheral artery disease) OR (peripheral arterial disease) OR (acute limb ischemia) OR (critical limb ischemia) OR (intermittent claudication)) AND((COVID-19) OR (diabetes) OR (diabetes mellitus)OR (hypertension) OR (high blood pressure) OR(comorbidities))	138
Scopus	((Peripheral artery disease) OR (peripheral arterial disease) OR (acute limb ischemia) OR (critical limb ischemia) OR (intermittent claudication)) AND((COVID-19) OR (diabetes) OR (diabetes mellitus)OR (hypertension) OR (high blood pressure) OR(comorbidities))	100
Wiley	((Peripheral artery disease) anywhere OR (limb ischemia) anywhere OR (intermittent claudication) anywhere AND (COVID-19) anywhere OR (diabetes) anywhere OR (hypertension) anywhere OR (comorbidities) anywhere	24
Embase	('Peripheral artery disease'/exp OR 'peripheral arterydisease' OR (peripheral AND ('artery'/exp OR artery)AND ('disease'/exp OR disease)) OR 'acute limb ischemia':ti,ab,kw OR 'critical limb ischemia':ti,ab,kw)AND 'covid 19':ti,ab,kw	1,152
Proquest	Peripheral artery disease OR acute limb ischemia ORcritical limb ischemia AND COVID 19 OR diabetesOR hypertension → tpi klo kek gni dptnya 300,659 Kalo cuma Peripheral artery disease AND COVID 19 → 4720	4,849
Total		6,573
Full paper screened		342
Included		22

Appendix 2. Characteristics of the included studies

No.	Author, Year	Study Design	Location	Length of Study	Sample Size	Types of Subjects
1	Bozzani et al. 2020 [13]	Retrospective cohort	Italy	March 1-April 30, 2020	6	COVID-19 (+)
2	Bellosta et al. 2020 [14]	Prospective cohort	Italy	January-March, 2020	20	COVID-19 (+)
3a	Mascia et al. 2020 [15]	Prospective cohort	Italy	March-April, 2019 & 2020	16	COVID-19 (+)
3b					21	COVID-19 (-)
4a	Bellosta et al. 2021 [16]	Multicentric, retrospective, observational cohort study	Italy	March 8-May 3 2020	68	COVID-19 (+)
4b					239	COVID-19 (-)
5a	Goldman et al. 2020 [17]	Retrospective cohort	United States	January-April, 2020	16	COVID-19 (+)
5b				January-April 2018 & 2019	32	COVID-19 (-)
6a	Yesilkaya et al. 2021 [18]	Retrospective cohort	Turkey	March 12-December 31, 2020	11	COVID-19 (+)
6b					10	COVID-19 (-)
7a	Goldman et al. 2020 [17]	Retrospective cohort	United States	March 1-April 20, 2020	15	COVID-19 (+)
7b					25	COVID-19 (-)
8	Topcu et al. 2021 [20]	Retrospective cohort	Turkey	September 1- December 31, 2020	6	COVID-19 (+)
9	Ilonzo et al. 2020 [21]	Retrospective cohort	United States	March 1- April 15, 2020	16	COVID-19 (+)
10	Sanchez et al. 2021 [22]	Retrospective cohort (multicentric)	Brazil	March-July, 2020	30	COVID-19 (+)
11	Al-zoubi et al. 2021 [23]	Retrospective cohort	Jordan	November 1-December 31, 2020	7	COVID-19 (+)
12	Etkin et al. 2020 [24]	Retrospective cohort	United States	March 1-May 15, 2020	49	COVID-19 (+)
13a	Li et al. 2020 [25]	Cohort	China	January 24-March 31, 2020	15	COVID-19 (+)
13b				2019	50	COVID-19 (-)
14	Vo et al. 2022 [26]	Cohort Retrospective	United States	March 2020-March 2021	26	COVID-19 (+)
15	Barac et al. 2021 [27]	Retrospective cohort	Timișoara	1 month	22	COVID-19 (+)
16	de Athayde Soares et al. 2022 [28]	Cohort Retrospective	Sao Paolo	March 2020-March 2021	35	COVID-19 (+)
17	de Athayde Soares et al. 2022 [29]	Cohort prospective	Sao Paolo	January 2020-October 2021	23	COVID-19 (+)
18	Smolderen et al. 2021 [30]	Observational study	Connecticut	March 2020-November 2020.	693	COVID-19 (+)
19	Alonso et al. 2020 [31]	Cohort prospective	Carabanchel	March 2020-May 2020	24	COVID-19 (+)
20	Ishihara et al. 2022 [32]	Retrospective cohort	Japan	January 2022	25	COVID-19 (+)
21	Pham et al. 2021 [33]	Retrospective cohort	United States	January 20, 2020-May 20, 2021	526	COVID-19 (+)

No.	Author, Year	Age (Median (IQR)/Mean±SD (y))	Gender (M/F)	BMI	Hypertension	Diabetes Mellitus	Atrial fibrillation	Hyperlipidemia	Heart diseases (CAD/CHF)
1	Bozzani et al. 2020 [13]	71 (IQR 49-83)	4/2	N/A	N/A	N/A	N/A	N/A	N/A
2	Bellosta et al. 2020 [14]	75±9	18/2	N/A	N/A	3 (15.0)	5 (25.0)	N/A	N/A

No.	Author, Year	Age (Median (IQR)/Mean±SD (y))	Gender (M/F)	BMI	Hyper-tension	Diabetes Mel-litus	Atrial fibrila-tion	Hyper-lipid-emia	Heart diseases (CAD/CHF)
3a	Mascia et al. 2020 [15]	N/A	N/A	N/A	N/A	N/A	6	N/A	N/A
3b		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
4a	Bellosta et al. 2021 [16]	73±12	N/A	N/A	N/A	N/A	N/A	N/A	N/A
4b		75±12	N/A	N/A	N/A	N/A	N/A	N/A	N/A
5a	Goldman et al. 2020 [17]	70±14	9/7	28.0±5.6	13 (81.0)	8 (50.0)	N/A	8 (50.0)	4 (25.0)
5b		71±15	16/16	28.2± 5.9	26 (81.0)	16 (50.0)	N/A	16 (50.0)	7 (22.0)
6a	Yesilkaya et al. 2021 [18]	71.2±13.9	5/6	26.54±3.83	7 (63.6)	5 (45.5)	0 (0.0)	1 (9.1)	4 (36.4)
6b		61.8±15.5	6/4	24.9±4.86	6 (60.0)	2 (20.0)	2 (20.0)	2 (20.0)	6 (60.0)
7a	Goldman et al. 2020 [17]	64.0 (54.5-65.5)	10/15	32.6 (28.0-32.8)	12 (80.0)	8 (53.3)	0 (0.0)	6 (40.0)	2 (13.3)
7b		70.0 (61.0-80.0)	10/25	25.5 (22.7-30.0)	23 (92.0)	14 (56.0)	1 (4.0)	12 (48.0)	9 (36.0)
8	Topcu et al. 2021 [20]	62 (59-64.3)	5/1	N/A	N/A	N/A	0 (0.0)	N/A	0 (0.0)
9	Ilonzo et al. 2020 [21]	63.3	8/8	33.6	14 (87.5)	9 (56.3)	N/A	12 (75.0)	8 (50.0)
10	Sanchez et al. 2021 [22]	60±15	23/7	N/A	10 (33.3)	8 (26.7)	3 (10.0)	1 (3.3)	4 (13.3)
11	Al-zoubi et al. 2021 [23]	65.56±1.13	5/2	N/A	6 (85.7)	4 (57.1)	N/A	3 (42.9)	N/A
12	Etkin et al. 2020 [24]	67(58–75)	37/12	28(25-32)	26 (53.0)	17 (35.0)	7 (14.0)	12 (24.0)	8 (16.0)
13a	Li et al. 2020 [25]	70.93±10.18	12/3	N/A	N/A	N/A	N/A	N/A	N/A
13b		69.22±9.67	38/12	N/A	N/A	N/A	N/A	N/A	N/A
14	Vo et al. 2022 [26]	61.7 (33–82)	N/A	N/A	16 (61.5)	19 (73.1)	8 (30.8)	21 (80.8)	4 (15.4)
15	Barac et al. 2021 [27]	64.91±9.57	15/7	31.63±6.47	22 (100)	14 (63.64)	N/A	18 (85.71)	Cardiac ins-suficiency 8 36.36)
16	de Athayde Soares et al. 2022 [28]	72.51	21/14	N/A	30 (85.7)	28 (80)	N/A	N/A	21 (60)
17	de Athayde Soares et al. 2022 [29]	70.48±7.2	11/12	N/A	17 (73.9)	5 (21.7)	N/A	N/A	3 (13)
18	Smolderen et al. 2021 [30]	72.5±13.6	349/344	N/A	482 (69.6)	387 (55.8)	274 (39.5)	N/A	N/A
19	Alonso et al. 2020 [31]	70±10	7/2	N/A	N/A	8 (88.89)	2 (22)	6 (67.0)	N/A
20	Ishihara et al. 2022 [32]	73.8±4.8	16/9	21.4±4.4	14 (56)	19 (76)	N/A	12 (48.0)	21 (84.0)
21	Pham et al. 2021 [33]	65.2±14.7	64/462	N/A	53 (10.1)	Type 1=5 (0.95) Type 2=34 (6.5) Both=39 (7.4)	17 (3.2)	N/A	28 (5.3)

No.	Author, Year	Laboratorium Parameters							
		Previous Vascular Diseases/Surgery	Smoking History	Obesity BMI >30 kg/m²	History of using Antiaggregant	History of Using Anticoagulant	Dimer (Media)n (IQR)) (ng/mL)	Platelets (Mean±SD/Mean/ Median (IQR) (thousands/µL))	International Normalized Ratio (Mean±SD/Mean/ Median (IQR))
1	Bozzani et al. 2020 [13]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
2	Bellosta et al. 2020 [14]	4 (20.0)	N/A	4 (20.0)	N/A	5 (25.0)	2200 (158-301)	239±82	N/A
3a	Mascia et al. 2020 [15]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
3b		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
4a	Bellosta et al. 2021 [16]	N/A	N/A	N/A	186 (60.6)	82 (26.7)	N/A	N/A	N/A
4b		N/A	N/A	N/A			N/A	N/A	N/A
5a	Goldman et al. 2020 [17]	8 (50.0)	8	N/A	N/A	N/A	N/A	264±91	1.41±0.82
5b		19 (59.0)	20	N/A	N/A	N/A	N/A	264±94	1.14±0.22
6a	Yesilkaya et al. 2021 [18]	3 (27.3)	2 (18.2)	N/A	4 (36.4)	3 (27.3)	N/A	N/A	N/A
6b		5 (50.0)	7 (70.0)	N/A	7 (70.0)	4 (40.0)	N/A	N/A	N/A
7a	Goldman et al. 2020 [17]	2 (13.3)	6 (42.9)	N/A	N/A	N/A	8.5 (3.5-17.1)	295.5 (170.5-318.0)	N/A
7b		13	17 (68.0)	N/A	N/A	N/A	2.0 (1.5-2.7)	261.0 (192.0-331.0)	N/A
8	Topcu et al. 2021 [20]	1 (16.7)	N/A	N/A	N/A	N/A	7.085 (1712.5-13942.5)	N/A	N/A
9	Ilonzo et al. 2020 [21]	6 (37.5)	8 (50.0)	N/A	5 (31.3)	3 (18.8)	654.3	367	1.25
10	Sanchez et al. 2021 [22]	4 (13.3)	3 (10.0)	10 (33.3)	N/A	7 (23.3)	3.2 (1.6-4.3)	284 (220-371)	1.06 (0.92-1.26)
11	Al-zoubi et al. 2021 [23]	N/A	6 (85.7)	4 (57.1)	N/A	5 (71.4)	N/A	N/A	N/A
12	Etkin et al. 2020 [24]	2 (4.0)	9 (18.0)	N/A	14 (29.0)	7 (14.0)	2,673 (723–7139)	N/A	N/A
13a	Li et al. 2020 [25]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
13b		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
14	Vo et al. 2022 [26]	4 (15.4)	10 (38.4)	10 (38.4)	N/A	5 (19.2)	N/A	N/A	N/A
15	Barac et al. 2021 [27]	N/A	10 (45.45)	16 (72.72)	19 (86.36)	N/A	957±518.6	275545±82299	N/A
16	de Athayde Soares et al. 2022 [28]	N/A	N/A	N/A	N/A	33 (94.3)	18 (51.4)	N/A	N/A
17	de Athayde Soares et al. 2022 [29]	N/A	9 (39.1)	N/A	N/A	N/A	N/A	N/A	N/A
18	Smolderen et al. 2021 [30]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
19	Alonso et al. 2020 [31]	5 (55)	4 (44)	7 (78)	5 (55)	1 (11)	N/A	N/A	N/A
20	Ishihara et al. 2022 [32]	Stroke - 7 (28)	4 (16) > current smoking	N/A	N/A	N/A	1.6 (0.7-3.0)	159.9±65.0	N/A
21	Pham et al. 2021 [33]	N/A	N/A	Obes +over-weight 19 (3.6)	Aspirin 35 (6.7)	56 (10.6)	N/A	N/A	N/A

No.	Author, Year	Treatment (No. (%))								Primary Outcomes
		Artial thromboplastin time (Mean±SD Mean/Median (IQR) (sec))	Activated partial thromboplastin time (sec)	Length of hospital stay (Mean±SD)	Usage of Anticoagulants with/ without other intervention	Limb salvage	Rethrombolysis	Amputation	Mortality	
1	Bozzani et al. 2020 [13]	N/A	N/A	N/A	N/A	5 (83.3)	2 (33.3)	1 (16.7)	1 (16.7)	Post-operative mortality and amputation rate
2	Bellosta et al. 2020 [14]	N/A	N/A	N/A	With others:20 (100.0)	16 (80.0)	2 (10.0)	1 (5.0)	8 (40.0)	Successful revascularization, early (<30 days) and late survival, and limb salvage
3a	Mascia et al. 2020 [15]	N/A	N/A	N/A	With others: 16 (100.0)	13 (81.3)	2 (13.3)	2 (13.3)	2	Limb salvage
3b		N/A	N/A	N/A	With others: 21 (100.0)	16 (76.2)	N/A	0 (0.0)	1 (6.25)	
4a	Bellosta et al. 2021 [16]	N/A	N/A	N/A	N/A	68 (100.0)	29 (42.6)	6 (8.8)	N/A	Freedom from in-hospital death
4b		N/A	N/A	N/A	N/A	239 (100.0)	48 (20.0)	5 (2.0)	N/A	
5a	Goldman et al. 2020 [17]	38.0±14.3	N/A	N/A	N/A	6 (37.5)	3/11 (27.3)	4 (25.0)	6 (37.5)	Clot burden in patients with COVID-19
5b		33.0±13.2	N/A	N/A	N/A	30 (93.7)	0/11 (0.0)	1 (3.125)	1 (3.125)	
6a	Yesilkaya et al. 2021 [18]	N/A	N/A	12.81±9.29	N/A	10 (90.9)	1 (9.1)	1 (9.1)	1 (9.1)	Clinical characteristics of patients histopathological characteristics of thromboembolic material
6b		N/A	N/A	14.5±9	N/A	10 (100.0)	1 (10)	1 (10)	2 (20.0)	
7a	Goldman et al. 2020 [17]	15.9 (14.7-20.8)	39.1 (32.0-47.4)	5.0 (5.0-7.3)	Without others:4 (26.7)	6 (4.0)	N/A	0 (0.0)	6 (40.0)	Identify potential risk factors for arterial thromboembolic disease
7b		15.2 (14.3-17.1)	33.1 (29.5-45.7)	5.0 (3.0-10.5)	Without others: 5 (20.0)	3 (12.0)	N/A	3 (12.0)	2 (8.0)	
8	Topcu et al. 2021 [20]	N/A	N/A	N/A	Without others: 3 (50.0) With others: 3 (50.0)	Intervention: 1 (16.7) Anticoagulation only:1 (16.7)	N/A	2 (33.3)	Overall: 2 (33.3) Intervention: 1 (16.7) Anti-coagulation only:1 (16.7)	Outcomes of COVID-19 patients with ALI

No.	Author, Year	Treatment (No. (%))								Primary Outcomes
		Artial thromboplastin time (Mean±SD Mean/Median (IQR) (sec))	Activated partial thromboplastin time (sec)	Length of hospital stay (Mean±SD)	Usage of Anticoagulants with/ without other intervention	Limb salvage	Rethrombolysis	Amputation	Mortality	
9	Ilonzo et al. 2020 [21]	36	N/A	N/A	With others: 16 (100.0)	Intervention: 7 (43.8) Anticoagulation only: 2 (12.5)	N/A	0 (0.0)	Overall: 4 (25.0) Intervention: 2 (12.5) Anti-coagulation only:1 (6.3)	Mortality secondary: primary patency and morbidity
10	Sanchez et al. 2021 [22]	N/A	32.5 (28.3-37.8)	N/A	With others: 30 (100.0)	18 (60.0)	N/A	9 (30.0)	7 (23.3)	Clinical and surgical characteristics
11	Al-zoubi et al. 2021 [23]	N/A	N/A	N/A	N/A	1 (14.3)	1 (14.3)	1 (14.3)	5 (71.4)	Demography and outcomes
12	Etkin et al. 2020 [24]	N/A	N/A	N/A	Without others: 28 (57.0) With others: 21 (43.0)	13	N/A	5	21	
13a	Li et al. 2020 [25]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1 (6.7)	Complications and death
13b		N/A	N/A	N/A	N/A	N/A	N/A	N/A	1 (2.0)	
14	Vo et al. 2022 [26]	N/A	N/A	N/A	4 (15.4)	13 (50.0)	N/A	7 (26.9)	8 (30.8)	Outcomes of COVID-19 patients with ALI
15	Barac et al. 2021 [27]	N/A	N/A	N/A	Anti-platelet + anticoagulant preoperative 22 (100.00)	18 (81.8)	Revascularization 4 (18.2)	3 (13.6)	3 (13.6)	
16	de Athayde Soares et al. 2022 [28]	N/A	N/A	N/A	33 (94.3)	92.60%	N/A	8 (23.5)	14 (40)	The limb salvage rate and overall mortality
17	de Athayde Soares et al. 2022 [29]	N/A	N/A	N/A	23 (100)	60.80%	N/A	4 (25)	6 (38)	The limb salvage rate and overall mortality
18	Smolderen et al. 2021 [30]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	16 (24.5)	Mortality

No.	Author, Year	Treatment (No. (%))								Primary Outcomes
		Artial thromboplastin time (Mean±SD Mean/Median (IQR) (sec))	Activated partial thromboplastin time (sec)	Length of hospital stay (Mean±SD)	Usage of Anticoagulants with/ without other intervention	Limb salvage	Rethrombolysis	Amputation	Mortality	
19	Alonso et al. 2020 [31]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Acro-Isch-emia
20	Ishihara et al. 2022 [32]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	5 (20)	30-day mortality
21	Pham et al. 2021 [33]	N/A	N/A	N/A	N/A	N/A	Revascu-larization 89 (16.9)	31 (5.894)	130 (24.715)	Outcomes of ALI COVID-19 180-day mortality, amputation

Appendix 3. Quality assessment of studies based on Newcastle-Ottawa quality assessment scale

		Selection									
	Scale	Bozzani et al. 2020 [13]	Bellosta et al. 2020 [14]	Mascia et al. 2020 [15]	Bellosta et al. 2021 [16]	Goldman et al. 2020 [17]	Yesilkaya et al. 2021 [18]	Indes et al. 2020 [19]	Topcu et al. 2021 [20]	Ilonzo et al. 2020 [21]	Sanchez et al. 2021 [22]
Representativeness of the exposed cohort	Truly representative of the average PAD with COVID-19 patients in the community	√				√					v
	Somewhat representative of PAD with COVID-19 patients in the community		√	√	√						
	Selected group of users (e.g. nurses, volunteers)						v	v	v	v	
	No description of the derivation of the cohort										
Selection of the non-exposed cohort	Drawn from the same community as the exposed cohort	√	√	√	√	√	v	v	v	v	v
	Drawn from a different source										
	No description of the derivation of the non-exposed cohort										

Selection											
Scale		Bozzani et al. 2020 [13]	Bellosta et al. 2020 [14]	Mascia et al. 2020 [15]	Bellosta et al. 2021 [16]	Goldman et al. 2020 [17]	Yesilkaya et al. 2021 [18]	Indes et al. 2020 [19]	Topcu et al. 2021 [20]	Ilonzo et al. 2020 [21]	Sanchez et al. 2021 [22]
Ascertainment of exposure	Secure record (e.g. medical records)	√	√	√	√	√	v	v	v	v	v
	Structured interview										
	Written self-report										
Demonstration that outcome of interest was not present at start of study	Yes	√	√	√	√	√	v	v	v	v	v
	No										

Comparability											
Scale		Bozzani et al. 2020 [13]	Bellosta et al. 2020 [14]	Mascia et al. 2020 [15]	Bellosta et al. 2021 [16]	Goldman et al. 2020 [17]	Yesilkaya et al. 2021 [18]	Indes et al. 2020 [19]	Topcu et al. 2021 [20]	Ilonzo et al. 2020 [21]	Sanchez et al. 2021 [22]
Comparability of cohorts on the basis of the design or analysis	Study controls for PAD without COVID-19	√	√	√	√	√	v	v			
	Study controls for any additional factor (This criteria could be modified to indicate specific control for a 2nd important factor)			√			v	v	v	v	v

Outcome											
Scale		Bozzani et al. 2020 [13]	Bellosta et al. 2020 [14]	Mascia et al. 2020 [15]	Bellosta et al. 2021 [16]	Goldman et al. 2020 [17]	Yesilkaya et al. 2021 [18]	Indes et al. 2020 [19]	Topcu et al. 2021 [20]	Ilonzo et al. 2020 [21]	Sanchez et al. 2021 [22]
Assessment of outcome	Independent blind assessment										
	Record linkage	√	√	√	√	√	v	v	v	v	v
	Self-report										
	No description										

Outcome												
Scale		Bozzani et al. 2020 [13]	Bellosta et al. 2020 [14]	Mascia et al. 2020 [15]	Bellosta et al. 2021 [16]	Goldman et al. 2020 [17]	Yesilkaya et al. 2021 [18]	Indes et al. 2020 [19]	Topcu et al. 2021 [20]	Ilonzo et al. 2020 [21]	Sanchez et al. 2021 [22]
Was follow-up long enough for outcomes to occur	yes (1 month of the follow-up period for the outcome of interest)	√					v	v	v	v	v
	No	√		√	√	√					

Selection												
Scale		Al-zoubi et al. 2021 [23]	Etkin et al. 2020 [24]	Li et al. 2020 [25]	Vo et al. 2022 [26]	Barac et al. 2021 [27]	de Athayde Soares et al. 2022 [28]	de Athayde Soares et al. 2022 [29]	Smolder en et al. 2021 [30]	Alonso et al. 2020 [31]	Ishihara et al. 2022 [32]	Pham et al. 2021 [33]
Representativeness of the exposed cohort	Truly representative of the average PAD with COVID- 19 patients in the community		√				√	√	√	√	√	
	Somewhat representative of PAD with COVID- 19 patients in the community	√										
	Selected group of users (e.g. nurses, voluntees)											
Representativeness of the exposed cohort	No description of the derivation of the cohort											
	Drawn from the same commun ity as the exposed cohort *	√	√	√	√	√					√	
Selection of the non exposed cohort	Drawn from a different source											
	No description of the derivation of the non exposed cohort						√	√	√	√		√

Selection												
Scale		Al-zoubi et al. 2021 [23]	Etkin et al. 2020 [24]	Li et al. 2020 [25]	Vo et al. 2022 [26]	Barac et al. 2021 [27]	de Athayde Soares et al. 2022 [28]	de Athayde Soares et al. 2022 [29]	Smolder en et al. 2021 [30]	Alonso et al. 2020 [31]	Ishihara et al. 2022 [32]	Pham et al. 2021 [33]
	Secure record (e.g. medical records)	√	√		√	√	√	√	√	√	√	√
Ascertainment of exposure	Structure d interview											
	Written self-report			√								
	No description											
Demonstration that outcome of interest was not present At start of study	Yes	√	√	√	√	√	√	√	√	√	√	√
	No											

Comparability												
Scale		Al-zoubi et al. 2021 [23]	Etkin et al. 2020 [24]	Li et al. 2020 [25]	Vo et al. 2022 [26]	Barac et al. 2021 [27]	de Athayde Soares et al. 2022 [28]	de Athayde Soares et al. 2022 [29]	Smolder en et al. 2021 [30]	Alonso et al. 2020 [31]	Ishihara et al. 2022 [32]	Pham et al. 2021 [33]
Comparability of cohorts on the b asis of the design or analysis	Study controls for PAD without COVID- 19			√	√	√	√	√	√	√	√	√
	Study controls for any additional factor. (This criteria could be modified to indicate specific control for a second important factor)				√	√		√	√		√	√

Outcome												
Scale		Al-zoubi et al. 2021 [23]	Etkin et al. 2020 [24]	Li et al. 2020 [25]	Vo et al. 2022 [26]	Barac et al. 2021 [27]	de Athayde Soares et al. 2022 [28]	de Athayde Soares et al. 2022 [29]	Smolder en et al. 2021 [30]	Alonso et al. 2020 [31]	Ishihara et al. 2022 [32]	Pham et al. 2021 [33]
Assessment of outcome	Independent blind assessment											
	Record linkage	√	√	√	√	√	√	√	√	√	√	√

		Outcome										
Scale		Al-zoubi et al. 2021 [23]	Etkin et al. 2020 [24]	Li et al. 2020 [25]	Vo et al. 2022 [26]	Barac et al. 2021 [27]	de Athayde Soares et al. 2022 [28]	de Athayde Soares et al. 2022 [29]	Smolder en et al. 2021 [30]	Alonso et al. 2020 [31]	Ishihara et al. 2022 [32]	Pham et al. 2021 [33]
Assessment of outcome	Self-report											
	No description											
Was follow-u p long enough for outcomes to oc-cur?	Yes (1 month of the follow-u p period for the outcome of interest)		√		√	√	√	√	√	√	√	√
	No		√		√				√	√		
Adequacy of follow up of cohorts Subjects lost to follow up unlikely to introduce bias - small number lost >95 % follow up, or description provided of those lost)	Complete follow up all subjects accounted		√		√	√	√	√	√	√	√	√
	Follow up rate <95% (select an adequate %) and no description of those lost											
	No statement	√		√								
Total stars		5	7	5	9	9	7	8	8	7	9	8

Appendix 4. Studies quality assessment based on Newcastle-Ottawa quality assessment scale-AHRQ standards

No.	Author, Year	Selection	Comparability	Outcome	Quality Assessment based on AHRQ
1	Bozzani et al. 2020 [13]	4	1	1	6 (poor)
2	Bellosta et al. 2020 [14]	4	1	3	8 (good)
3	Mascia et al. 2020 [15]	4	2	1	7 (poor)
4	Bellosta et al. 2021 [16]	4	1	3	8 (good)
5	Goldman et al. 2020 [17]	4	1	3	8 (good)
6	Yesilkaya et al. 2021 [18]	3	2	3	8 (good)
7	Goldman et al. 2020 [17]	3	2	3	8 (good)
8	Topcu et al. 2021 [20]	3	1	3	7 (good)
9	Ilonzo et al. 2020 [21]	3	1	3	7 (good)
10	Sanchez et al. 2021 [22]	4	1	3	8 (good)
11	Al-zoubi et al. 2021 [23]	4	0	1	5 (poor)
12	Etkin et al. 2020 [24]	4	0	3	7 (poor)
13	Li et al. 2020 [25]	3	1	1	5 (poor)
14	Vo et al. 2022 [26]	3	2	3	9 (good)
15	Barac et al. 2021 [27]	4	2	3	9 (good)
16	Soares et al. 2022 [28]	3	1	3	7 (good)
17	Soares et al. 2022 [29]	3	2	3	8 (good)
18	Smolderen et al. 2021 [30]	3	2	3	8 (good)
19	Alonso et al. 2020 [31]	3	1	3	7 (good)
20	Ishihara et al. 2022 [32]	4	2	3	9 (good)
21	Pham et al. 2021 [33]	3	2	3	8 (good)

Notes: There are five studies with poor quality.

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