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Prevalence of pre-existing peripheral artery disease in COVID-19 patients and relative mortality risk: Systematic review and meta-analysis

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Abstract

Introduction: This study aims to assess prevalence and prognostic implications of pre-existing peripheral artery disease (PAD) in patients infected by the SARS-CoV-2 by means of a systematic review and meta-analysis.
Material and methods: We searched MEDLINE and Scopus to locate all the articles published up to 10 December 2021, reporting data on pre-existing PAD among COVID-19 survivors (S) and non survivors (NS). The pooled prevalence of pre-existing PAD in COVID-19 patients was calculated using a random effects model and presenting the related 95% confidence interval (CI), while the mortality risk was estimated using the Mantel–Haenszel random effects models with odds ratio (OR) and related 95% CI. Statistical heterogeneity was measured using the Higgins I^2 statistic.
Results: Eight investigations, enrolling 13,776 COVID-19 patients (mean age: 67.1 years, 3.863 males), met the inclusion criteria and were included in the final analysis. The pooled prevalence of pre-existing PAD was 5.7% of cases (95% CI: 3.8–8.4%, $p < 0.0001$), with high heterogeneity ($I^2 = 84.5\%$), which was directly correlated with age ($p < 0.0001$), previous hypertension ($p = 0.003$), and dyslipidaemia ($p = 0.02$) as demonstrated by the meta-regression. Moreover, pre-existing PAD was significantly associated with higher risk of short-term death in patients with SARS-CoV-2 infection (OR: 2.78, 95% CI: 2.37–3.27, $p < 0.0001$ $I^2 = 0\%$); the sensitivity analysis confirmed yielded results.
Conclusions: Pre-existing PAD represents a comorbidity in about 1 out of 6 COVID-19 patients, but it is associated with a twofold higher risk of short-term mortality.

Keywords

Peripheral artery disease, COVID-19, prevalence, mortality

Introduction

Several investigations have demonstrated a high prevalence of cardiovascular comorbidities in COVID-19 patients, influencing both disease severity and short-term prognosis.[1–4] From an epidemiological perspective, both the prevalence and incidence of peripheral artery disease (PAD) appear to be sharply age-related, rising more than 10% among patients in their 60s and 70s.[5] Moreover, it has been demonstrated that these subjects have a higher risk of cardiovascular events and are six times more likely to die from cardiovascular causes than those without the disease.[6] As is well known, PAD is very frequently associated with other comorbidities, such as arterial hypertension (HT), diabetes mellitus (DM), dyslipidaemia, and coronary artery disease (CAD)[7] which are highly prevalent among COVID-19 patients and associated with poorer outcomes.[8–11] The previous literature has mainly focused

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its attention to the relationship between COVID-19 pandemic and the management of PAD patients, evidencing the lower number of novel PAD diagnosis or the reduction of revascularization procedures performed during this period, while a comprehensive assessment of data regarding the epidemiological and related prognostic role of PAD in SARS-CoV-2–infected individuals has not yet been performed. The aim of the present study is to estimate the pooled prevalence and the influence of PAD on short-term mortality in COVID-19 patients by a systematic review and meta-analysis of the available data.

Methods

Data sources and searches

The study was performed in accordance with the Preferred Report Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Supplementary Material 1).[12] PubMed and Scopus databases were systematically searched for articles published in English language, from inception through 10 December 2021 with the following Medical Subject Heading (MESH) terms: COVID-19 OR SARS-CoV-2 [Title/Abstract] AND "Survivors" OR "Peripheral Artery Disease". In addition, references from the included studies were screened to potentially identify other investigations meeting the inclusion criteria.

Outcomes

The prevalence of PAD in COVID-19 patients was chosen as the primary outcome, while its associated mortality risk was selected as the secondary outcome.

Study selection

Specifically, inclusion criteria were (1) studies enrolling subjects with a confirmed diagnosis of COVID-19 and (2) providing data on the prevalence of PAD and stratifying the population among survivors (S) and non survivors (NS). Conversely, case reports, review articles, abstracts, editorials/letters, and case series with less than 10 participants were excluded. Each included article was independently evaluated by two reviewers (MZ and LR); in case of discrepancies, a third author was involved (CB), and final consensus was achieved through discussion.

Data extraction and quality assessment

Data were independently extracted by two reviewers (MZ and GR) using a standardized protocol. Disagreements were resolved consulting a third author (CB). For this meta-analysis, the following data elements were extracted: type of the study; sample size; mean age; gender; and major cardiovascular comorbidities such as HT, DM, cerebrovascular disease, dyslipidaemia, chronic kidney disease (CKD), and CAD, stratified according to the outcome status (S and NS). The quality of included studies was graded using the Newcastle–Ottawa quality assessment scale (NOS).[13]

Data synthesis and analysis

Continuous variables were expressed as mean ± standard deviation (SD) or as median with corresponding interquartile range (IQR), while categorical variables were expressed as counts and percentages. The cumulative prevalence of PAD (n/N), defined as the ratio between patients with pre-existing PAD (n) and the number of patients enrolled in each study (N), was pooled using a random effects model and presented with the corresponding 95% confidence interval (CI). Mortality risk data were pooled using the Mantel–Haenszel random effects models with odds ratio (OR) as the effect measure with 95% CI. Moreover, a predefined sensitivity analysis (leave-one-out analysis) was performed, removing one study at a time, to evaluate the stability of our results regarding the mortality risk. Statistical heterogeneity between groups was measured using the Higgins I^2 statistic. Specifically, $I^2 = 0$ indicated no heterogeneity while we considered low, moderate, and high degrees of heterogeneity based on the values of I^2 as <25%, 25–75%, and above 75%, respectively. The presence of potential publication bias was verified by visual inspection of the funnel plot. Due to the low number of the included studies (<10), small-study bias was not examined as our analysis was underpowered to detect such bias. To further appraise the impact of potential baseline confounders, a meta-regression analysis using age, gender, prevalence of HT, DM, cerebrovascular disease, CKD, and CAD as moderator variables was performed. All meta-analyses were conducted using Comprehensive Meta-Analysis software, version 3 (Biostat, USA).

Results

Search results

A total of 4,658 articles were obtained by our search strategy. After the preliminary screening excluding duplicates, 1,443 full-text articles were assessed for eligibility. Among them, 1,435 studies were excluded for not meeting the inclusion criteria, leaving 8 investigations fulfilling the inclusion criteria[14–21] (Figure 1).

Study characteristics

Overall, 13,776 COVID-19 hospitalized patients (mean age: 67.1 years, 3.863 males) were included in the analysis. The

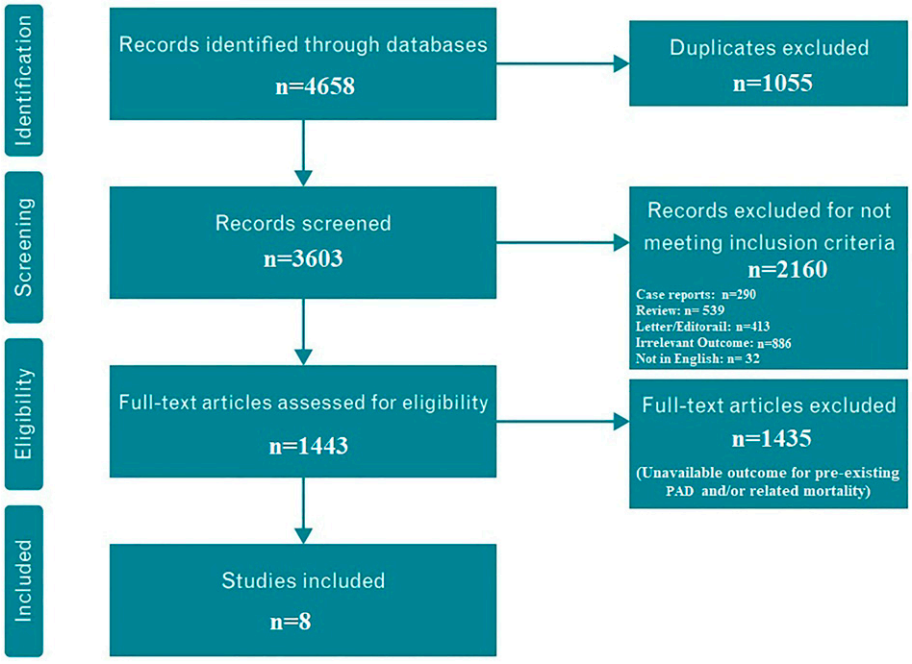

Figure 1. PRISMA flow diagram.

general characteristics of the studies included are shown in Table 1. To this regard, S were significantly younger when compared to NS ($p < 0.001$), while the most prevalent comorbidities were HT followed by DM and dyslipidaemia. The quality assessment of the studies reviewed revealed that all investigations were of high-moderate quality according to the NOS scale (Table 2).

Pooled prevalence of dyslipidemia

The prevalence of dyslipidemia among COVID-19 patients ranged between 2.6 and 14.3%. A random effect model revealed a pooled prevalence of PAD in 5.7% of cases (95% CI: 3.8–8.4%, $p < 0.0001$). However, a high heterogeneity was observed in the analysis ($I^2 = 84.5\%$) (Figure 2, panel a). The relative funnel plot, presented in Supplementary Material 2, disclosed potential publication bias.

Meta-regression for the pooled prevalence

A meta-regression analysis, carried out to explore the potential causes of such high heterogeneity, showed a significant direct relationship between pre-existing PAD and its prevalence in COVID-19 patients using age ($p < 0.0001$), prevalence of HT ($p = 0.03$), and dyslipidaemia ($p = 0.02$) as moderators (Table 3).

PAD and mortality risk

On pooled analysis, pre-existing PAD resulted in significant association with a higher risk of short-term mortality (OR: 2.78, 95% CI: 2.37–3.27, $p < 0.0001$, $I^2 = 0\%$) (Figure 2, Panel b). Visual inspection of the relative funnel plot (Supplementary Material 2, Panel B) did not reveal publication bias. To evaluate the robustness of the association results, we performed a leave-one-out sensitivity analysis by iteratively removing one study at a time and recalculating the summary OR. The summary ORs remained stable (ranging between OR: 2.77, 95% CI: 2.35–3.25, $p < 0.0001$ and OR: 2.79, 95% CI: 2.37–3.29, $p < 0.0001$), indicating that our results were not driven by any single study.

Discussion

The results of the present meta-analysis, based on more than 13,000 COVID-19 patients, evidenced that pre-existing PAD is present in about 5% of infected patients and associated with a twofold risk of short-term mortality compared to those without. The high heterogeneity observed during the analysis of the pooled prevalence resulted partially explained by aging as well as the prevalence of HT and dyslipidaemia, which are, per se, well-known risk factors and comorbidities of PAD.[5,6] Doubtless, also the observational and retrospective nature of the studies reviewed,

Table 1. General characteristics of the studies revised.

Author	Type of study	No of patients Mean age	Age (years) S	Age (years) NS	PAD Prevalence (%)	Males N, (%) S	Males N, (%) NS	Arterial hypertension N, (%) S	Arterial hypertension N, (%) NS	Diabetes N, (%) S	Diabetes N, (%) NS	Cerebrovascular disease N, (%) S	Cerebrovascular disease N, (%) NS	Dyslipidaemia N, (%) S	Dyslipidaemia N, (%) NS	CKD N, (%) S	CKD N, (%) NS	CAD N, (%) S	CAD N, (%) NS
Zwaenepoel et al.[34]	Prospective Monocentric	100 63.5 [57–71]	61	69	6.0	48 (60.8)	18 (85.7)*	33 (41.8)	9 (42.9)	22 (27.8)	6 (28.6)	NR	NR	27 (34.2)	13 (61.9)	12 (15.1)**	8 (38.0) >	5 (23.8)	12 (15.1)
Katkat et al.[35]	Retrospective Monocentric	508 58 ± 15.5	56.4	68.7	2.6	225 (51.1)	45 (66.2)	188 (42.7)	46 (67.6)	139 (31.6)	26 (38.2)	11 (2.5)	4 (5.1)	78 (17.7)	18 (26.5)	NR	NR	17 (25.0)	57 (12.9)*
de Terwangne et al	Retrospective Monocentric	49 71 [61.5–77]	66.5	73*	14.3	15 (68.1)	19 (70.3)	13 (59.0)	19 (70.0)	10 (45)	10 (37.0)	NR	NR	12 (55.0)	13 (48.0)	NR	NR	2 (9.0)	5 (19.0)
De Negri et al.[43]	Retrospective Monocentric	201 68.5±14.7	65.6	79.7**	8.5	86 (65.4)	25 (59.5)	27 (54.4)	87 (64.3)	26 (16.5)	11 (26.2)	NR	NR	30 (18.4)	7 (16.7)	14 (7.0)	15 (35.7)	14 (33.3)	21 (13.2)*
Mendes et al.[48]	Retrospective Monocentric	235 83.6 ± 6.5	86.0	86.9	11.5	54 (33.9)	48 (63.1)*	112 (70.4)	56 (73.7)	13 (8.2)	10 (13.2)	NR	NR	56 (35.2)	28 (36.8)	41 (25.8)	21 (28.0)	15 (19.7)	19 (11.9)
Knights et al.[19]	Retrospective Cohort study	108 68.7±1.5	63.8	78.9**	1.9	38 (55)	20 (59)	28 (41)	18 (53)	10 (14)	14 (41)*	5 (7)	11 (32)**	NR	NR	2 (3.0)	4 (12.0)	6 (9.0)	9 (26.0)*
Quisi et al.[27]	Retrospective Multicenter	349 56 [20–80]	55.0	69.0**	3.2	139 (44.7)	14 (36.8)	101 (32.5)	20 (52.6)*	93 (29.9)	13 (34.2)	5 (1.6)	2 (5.3)	NR	NR	NR	NR	29 (9.3)	14 (36.8)**
Rodilla et al.[29]	Retrospective Multicenter	12226 67.5 ± 16.1	64.1	79.6**	4.7	539 (56.2)	2530 (61.9)**	432 (45)	1856 (70.6)**	1592 (16.6)	741 (28.2)**	575 (6.0)	373 (14.2)**	NR	NR	413 (4.3)	330 (12.5)	605 (6.3)	372 (14.1)**

S: survivors; NS: non survivors; CKD: chronic kidney disease; CAD: coronary artery disease; PAD: peripheral artery disease; []: interquartile range.
*$p < 0.05$ between survivors and non survivors; **$p < 0.0001$ between survivors and non survivors.

Table 2. Quality of the included studies assessed using the Newcastle–Ottawa quality assessment scale.

	NOS			
Study	Selection	Comparability	Outcome	Total score
Zwaenepoel et al.[14]	★★★	★★	★★	7
Katkat et al.[15]	★★★	★★	★★	**7**
de Terwangne et al.[16]	★★★	★★	★★	6
De Negri et al.[17]	★★★	★★	★★	**7**
Mendes et al.[18]	★★	★★	★★	7
Knights et al.[19]	★★	★★	★	7
Quisi et al.[20]	★★	★★	★★	6
Rodilla et al.[21]	★★★	★★	★★	7

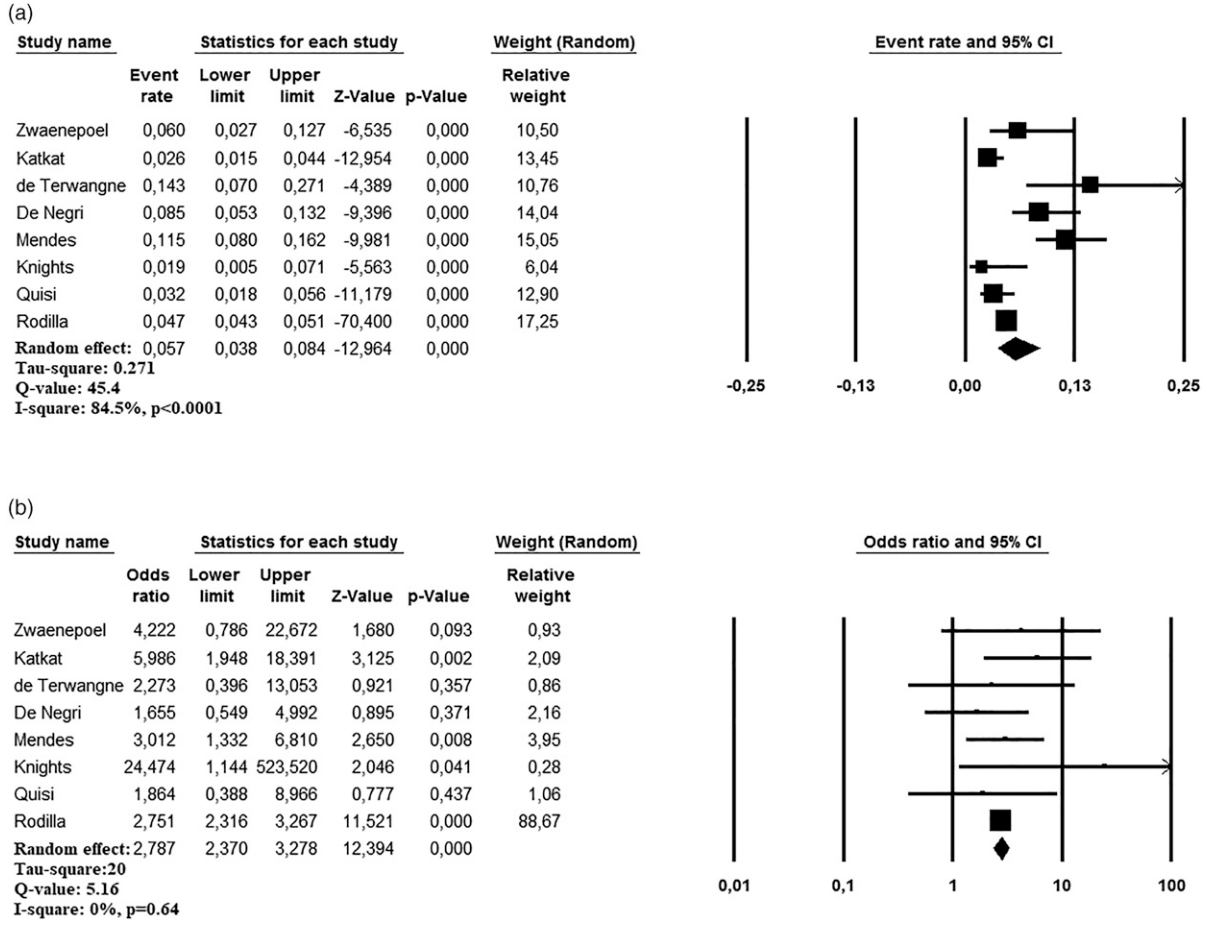

Figure 2. (a) Pooled prevalence of pre-existing peripheral artery disease in COVID-19 patients; (b) Forest plot investigating the mortality risk due pre-existing peripheral artery disease in COVID-19 patients using a random effect model.

with their intrinsic and inherited biases may have contributed to the high heterogeneity observed. Conversely, the absence of heterogeneity in the estimation of short-term mortality risk in COVID-19 patients with PAD as well as the results of the related sensitivity analysis confirmed the robustness of our results regarding the prognostic implications of pre-existing CAD in such patients.

Our findings are also in accordance with those presented by Smolderen et al.[22] which evidenced that PAD patients with SARS-CoV-2 infection have a >40% odds of mortality

Table 3. Meta-regression for the prevalence of pre-existing coronary artery disease in COVID-19 patients.

Moderator	N° of interactions	Coeff	SE	95% CI	p
Age	8	0.057	0.016	0.025–0.089	<0.0001
Gender (male)	8	0.013	0.019	−0.024–0.051	0.475
HT	8	0.025	0.012	0.001–0.050	0.03
DM	8	−0.011	0.021	−0.053–0.031	0.60
Cerebrovascular disease	4	−0.034	0.066	−0.164–0.095	0.60
Dyslipidaemia	5	0.033	0.015	0.004–0.063	0.02
CKD	5	0.064	0.035	−0.005–0.134	0.07
CAD	8	0.110	0.260	−0.398–0.620	0.669

HT: arterial hypertension; DM: diabetes mellitus; CKD: chronic kidney disease; CAD: coronary artery disease; SE: standard error; CI: confidence interval.

and major adverse cardiovascular events (MACE) when compared to those without and independently of concomitant known risk factors. Probably, the higher risk of short-term mortality observed cannot be referred only to complications of pre-existing PAD but more realistically to the occurrence of acute complications of chronic cardiovascular complications, such as cardiovascular injuries, in which atherosclerosis is the common substrate.[23,24] From a pathophysiological perspective, it is likely that the hypercoagulable state shared by PAD and SARS-CoV-2 infection plays a pivotal role since the viral infection may additionally promote the occurrence of arterial thromboembolic events in infected patients.[25,26] Although these theories need to be confirmed in larger studies, our results may be useful in both clinical practice and prevention strategies. Indeed, hospitalized COVID-19 patients with pre-existing PAD might require a closer monitoring and more aggressive therapeutical strategies since the beginning of the disease to reduce their short-term mortality risk. Moreover, these subjects might benefit from an earlier anti–SARS-CoV-2 immunization, considering their higher risk of poor outcome if infected.

Limitations

Our investigation has several limitations related to the observational nature of the studies reviewed with all inherited biases. Moreover, very few investigations on the COVID-19 infection, stratifying the cohort into S and NS and reporting data on PAD have been published, limiting the number of the studies included in the meta-analysis and the related number of patients. Furthermore, the present analysis is based on a generic definition of PAD, which encompasses distinctive clinical phenotypes with different prognostic significance. To this regard, we were not able to perform adequate sub-analysis regarding the clinical status of the disease (i.e., symptomatic or asymptomatic disease), the anatomical location of arterial obstruction/s, the length of the disease, need for revascularization or amputation, as well as the impact of previous or current revascularization treatments (i.e., during the infection) which may impact the prognosis of analyzed patients; indeed, none of the studies reviewed reported these data.

Conclusions

Pre-existing PAD is present in about 5% of patients with SARS-CoV-2 infection, and is associated with an increased risk of short-term mortality in COVID-19 patients. Our findings reinforce the concept that cardiovascular comorbidities and risk factors play a pivotal role in determining the COVID-19 patient's outcome, and suggest that PAD patients might benefit from an earlier anti–SARS-CoV-2 immunization, considering their higher risk of poor outcome, if infected.

Declaration of Conflicting Interests

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Supplemental material

Supplemental material for this article is available online.

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