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Incidence and Risk Factors of Limb Ischaemia in Adult Patients Receiving Veno-Arterial Extracorporeal Membrane Oxygenation: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Limb ischaemia is a serious and potentially limb-threatening vascular complication associated with veno-arterial extracorporeal membrane oxygenation (V-A ECMO). However, substantial heterogeneity has been observed in the reported incidence rates and identified risk factors among published studies.

Aim: To systematically evaluate the incidence and risk factors of limb ischaemia among patients receiving V-A ECMO.

Study Design: PubMed, Web of Science, Embase, Cochrane Library and Scopus were systematically searched from inception to 21 June 2025. Data regarding the incidence of limb ischaemia and associated risk factors among V-A ECMO patients were extracted. The meta-analysis was conducted using Stata software.

Results: Seventeen studies involving 2812 participants were included. The pooled incidence of limb ischaemia among V-A ECMO patients was 16.9% (95% confidence interval [CI]: 12.6%–21.3%; $p_{effect} < 0.001$; $I^2 = 91.3\%$). Significant risk factors included peripheral arterial disease (PAD) (odds ratio [OR] = 6.12; 95% CI: 1.22–30.71; $p_{effect} = 0.028$; $I^2 = 70.1\%$) and unsuccessful percutaneous cannulation (OR = 3.72; 95% CI: 1.90–7.28; $p_{effect} < 0.001$; $I^2 = 0.0\%$). Additionally, shorter patient height was associated with a higher risk of limb ischaemia (weighted mean difference [WMD] = −2.42 cm; 95% CI: −4.05 to −0.80; $p_{effect} = 0.004$; $I^2 = 13.4\%$).

Conclusions: This systematic review and meta-analysis determined a pooled incidence of limb ischaemia of 16.9% among V-A ECMO patients and identified two clinically significant risk factors: PAD and unsuccessful percutaneous cannulation. Moreover, an inverse association was observed between patient height and the risk of limb ischaemia. These findings provide robust evidence to support early detection, prevention and optimised management of limb ischaemia in this population.

Relevance to Clinical Practice: These findings can help clinicians identify high-risk subgroups, implement targeted monitoring and apply preventive strategies to reduce the incidence of limb ischaemia in patients undergoing V-A ECMO.

Trial Registration: PROSPERO number: CRD420250654349

1 | Introduction

Veno-arterial extracorporeal membrane oxygenation (V-A ECMO) is an effective mechanical circulatory support technique that consists of three essential components: a centrifugal pump, a membrane oxygenator and dual cannulas for venous drainage and arterial reinfusion [1]. The centrifugal pump generates negative pressure to withdraw deoxygenated blood from the venous system

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Impact Statements

- What is known about the topic
  - Veno-arterial extracorporeal membrane oxygenation (V-A ECMO) represents an established modality for mechanical circulatory support. However, this technique is associated with specific vascular complications and risks.
  - Limb ischaemia represents a serious vascular complication of V-A ECMO. Severe limb ischaemia can significantly increase morbidity and mortality rates among V-A ECMO patients while adversely affecting long-term quality of life in survivors.
  - A comprehensive understanding of the incidence and risk factors associated with limb ischaemia is crucial for improving clinical outcomes and enhancing quality of life. However, considerable heterogeneity exists in reported incidence rates and identified risk factors across published studies.
- What this paper adds
  - This systematic review and meta-analysis provides a comprehensive assessment of limb ischaemia incidence in patients undergoing V-A ECMO, revealing a pooled incidence rate of 16.9%.
  - This study identifies specific risk factors for limb ischaemia, including peripheral arterial disease and unsuccessful percutaneous cannulation. Additionally, an inverse association was observed between patient height and risk of limb ischaemia.
  - This review highlights the impact of study heterogeneity, warranting cautious interpretation of pooled results. Future large-scale, high-quality prospective studies are needed to validate these findings. Furthermore, variations in limb ischaemia definitions across studies may have affected comparability, underscoring the importance of standardised diagnostic criteria.

through a drainage cannula, propels it through the membrane oxygenator for gas exchange and then returns oxygenated blood under positive pressure to the arterial circulation via a reinfusion cannula [2, 3]. With ongoing technological advances, the indications for V-A ECMO have progressively expanded, and its clinical application has become increasingly widespread, particularly among critically ill patients with refractory cardiac or cardiopulmonary failure [4, 5]. Despite these advancements, V-A ECMO remains associated with substantial risks and complications, which may stem either from the treatment itself or from the underlying severity of illness. Common complications include bleeding, limb ischaemia, acute kidney injury and infections [6, 7].

Limb ischaemia, typically defined as reduced distal perfusion presenting with diminished or absent pulses, pallor, coolness, motor or sensory deficits or compartment syndrome [3], is one of the most serious complications related to peripheral V-A ECMO cannulation. If ischaemia persists for more than 6 h, irreversible tissue injury may occur, severely compromising prognosis and survival [8]. Acute lower-limb ischaemia (ALI) may progress to acute compartment syndrome (ACS), requiring emergent fasciotomy or, in severe cases, limb amputation [9]. These outcomes markedly increase morbidity and mortality [10, 11] and adversely affect long-term quality of life among survivors [12, 13]. Therefore, early identification of risk factors and timely implementation of preventive strategies are essential to reducing the risk and severity of limb ischaemia.

2 | Background

The reported incidence of limb ischaemia in patients receiving V-A ECMO varies substantially across studies, ranging from 7.8% to 50% [14, 15], indicating considerable heterogeneity in patient characteristics, diagnostic criteria and assessment methodologies. Multiple potential risk factors have been identified, including age, sex, duration of ECMO support, diabetes mellitus (DM), absence of a distal perfusion cannula (DPC) and arterial cannula size [16–21]. However, these findings remain inconsistent, primarily due to variations in study designs, sample sizes and analytical approaches. Consequently, a precise estimation of the incidence of this complication and definitive identification of its key risk factors through systematic review are essential for improving patient outcomes and establishing a robust evidence base for targeted preventive strategies in this high-risk population.

Although previous reviews have addressed vascular complications in V-A ECMO-supported patients, most have provided limited insight into the specific burden and determinants of limb ischaemia. For example, Jia et al. [7] conducted a comprehensive meta-analysis of overall vascular complications; however, limb-specific data were not analysed in detail. Marbach et al. [22] investigated perfusion-protection strategies and demonstrated that prophylactic DPC insertion and smaller arterial cannulas significantly reduced ischaemic events; however, patient-level risk factors and pooled incidence estimates were not evaluated.

3 | Aim

To comprehensively evaluate the incidence and identify the risk factors of limb ischaemia in adult patients receiving V-A ECMO, it seeks to provide clinically relevant evidence to guide preventive measures, facilitate early recognition and optimise management strategies.

4 | Design and Methods

This systematic review and meta-analysis was conducted in accordance with the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [23]. The study protocol was prospectively registered in the PROSPERO database (CRD420250654349).

4.1 | Search Strategy

A comprehensive search of five electronic databases—PubMed, Web of Science, Embase, Cochrane Library and Scopus—was conducted from database inception to 21 June 2025. Search strategies were developed using Medical Subject Headings (MeSH) and relevant keywords, including 'Extracorporeal Membrane Oxygenation', 'Venoarterial Extracorporeal Membrane Oxygenation', 'Extracorporeal Life Support', 'Membrane Oxygenation, Extracorporeal', 'ECMO Treatment', 'Oxygenation, Extracorporeal Membrane' and 'Limb Ischemia'. Detailed search strategies for each database are presented in Table S1.

4.2 | Eligibility Criteria

According to the PECOs principle, the inclusion criteria for the literature were established as follows: (1) Population: adult patients (≥ 18 years) receiving V-A ECMO; (2) Exposures: for incidence analyses, exposure was V-A ECMO; for risk factor analyses, candidate exposures included patient- or procedure-related variables (e.g., age, sex, height, detection method and cannula size); (3) Outcomes: incidence of limb ischaemia and associated risk factors; (4) Study type: published case–control or cohort study. Exclusion criteria were as follows: (1) studies rated as low quality (Newcastle–Ottawa Scale [NOS] score < 5); (2) unpublished studies or non-peer-reviewed data; (3) literature with incomplete data; (4) studies published in non-English languages. Inclusion criteria for risk factors required: (1) consistent definition and format across studies, (2) reported in at least two studies and (3) quantitative data suitable for meta-analysis.

Limb ischaemia was defined according to criteria reported in the original studies, including: (1) clinical signs of ischaemia, including the 'six P's' (pain, pallor, pulselessness, paresthesia, paralysis and poikilothermia) [24]; (2) loss of arterial Doppler signal or (3) a decrease in somatic oximetry of > 25% compared to the contralateral leg, absolute near-infrared spectroscopy (NIRS) values below 40% [25]. Given the variability in diagnostic criteria among studies, all definitions were accepted, and the resulting heterogeneity was acknowledged when interpreting pooled results.

4.3 | Data Extraction

After removing duplicate records, the remaining titles and abstracts were screened for relevance. Full-text articles that met the eligibility criteria were subsequently retrieved for detailed evaluation. Data extraction was independently performed by two investigators using a standardised Microsoft Excel form. Discrepancies between the two reviewers were resolved by consensus or, when necessary, through consultation with a third investigator. The following variables were systematically extracted from each study: (A) first author's name, (B) publication year, (C) study period, (D) geographic location, (E) study design, (F) total sample size, (G) mean age, (H) incidence rate of limb ischaemia, (I) identified risk factors, (J) V-A ECMO indication, (K) detection method for limb ischaemia, (L) cannulation approach, (M) arterial cannulation site, (N) DPC strategy and (O) cannulation strategy. The duration of ECMO support was recorded in its originally reported units (hours or days). When data in the primary studies were reported as medians with interquartile ranges (IQRs), they were converted to means ± SDs using established transformation methods [26–28]. To ensure unit consistency, measurements reported in days were converted to hours by multiplying by 24. Both original and converted values were retained to facilitate sensitivity analyses and to evaluate potential conversion effects on the aggregated results.

4.4 | Quality Assessment

The methodological quality of the included studies was independently assessed by two reviewers using the NOS [29]. The NOS evaluates three domains across eight items, with total scores of 7–9 indicating high quality, 5–6 indicating moderate quality and 0–4 indicating low quality. Any disagreements were resolved by a third reviewer.

4.5 | Statistical Analysis

To estimate pooled incidence rates, total sample sizes and event counts of limb ischaemia were extracted from each study. Results are reported as pooled estimates along with τ^2 and I^2 statistics to quantify between-study heterogeneity. For risk factor analyses, only variables evaluated in at least two studies were considered eligible. Effect measures were expressed as odds ratios (ORs) with 95% confidence intervals (CIs) for categorical variables, and as weighted mean differences (WMDs) for continuous variables [30, 31]. Adjusted estimates were prioritised, and adjusted and unadjusted ORs were analysed separately. For stratified analyses, the covariates included in each contributing study were explicitly documented.

Statistical heterogeneity across studies was assessed using the I^2 statistic and τ^2 estimates. A random effects model was applied when I^2 exceeded 50%; otherwise, a fixed effect model was used. Subgroup analyses were performed according to DPC strategy, cannulation approach, detection method, arterial cannula size, geographical region and publication year. Leave-one-out sensitivity analyses were performed when at least three studies were available to evaluate the robustness of pooled estimates. Publication bias was evaluated using funnel plots and Egger's regression test for outcomes including 10 or more studies [32]. When significant asymmetry was detected, the trim-and-fill method was employed to impute potentially missing studies and to calculate adjusted pooled estimates [33]. All statistical analyses were performed using Stata software. A two-sided p value of < 0.05 was considered statistically significant. The p value for the pooled effect estimate is denoted as p_{effect}, and the p value for heterogeneity is denoted as p_{het}.

5 | Results

5.1 | Search Outcome

Figure 1 presents the PRISMA flow diagram outlining the process of study selection for this meta-analysis. A comprehensive search retrieved 2384 records from five electronic databases, including PubMed ($n = 212$), Web of Science ($n = 503$), Cochrane Library ($n = 26$), Embase ($n = 1014$) and Scopus ($n = 629$). After removing

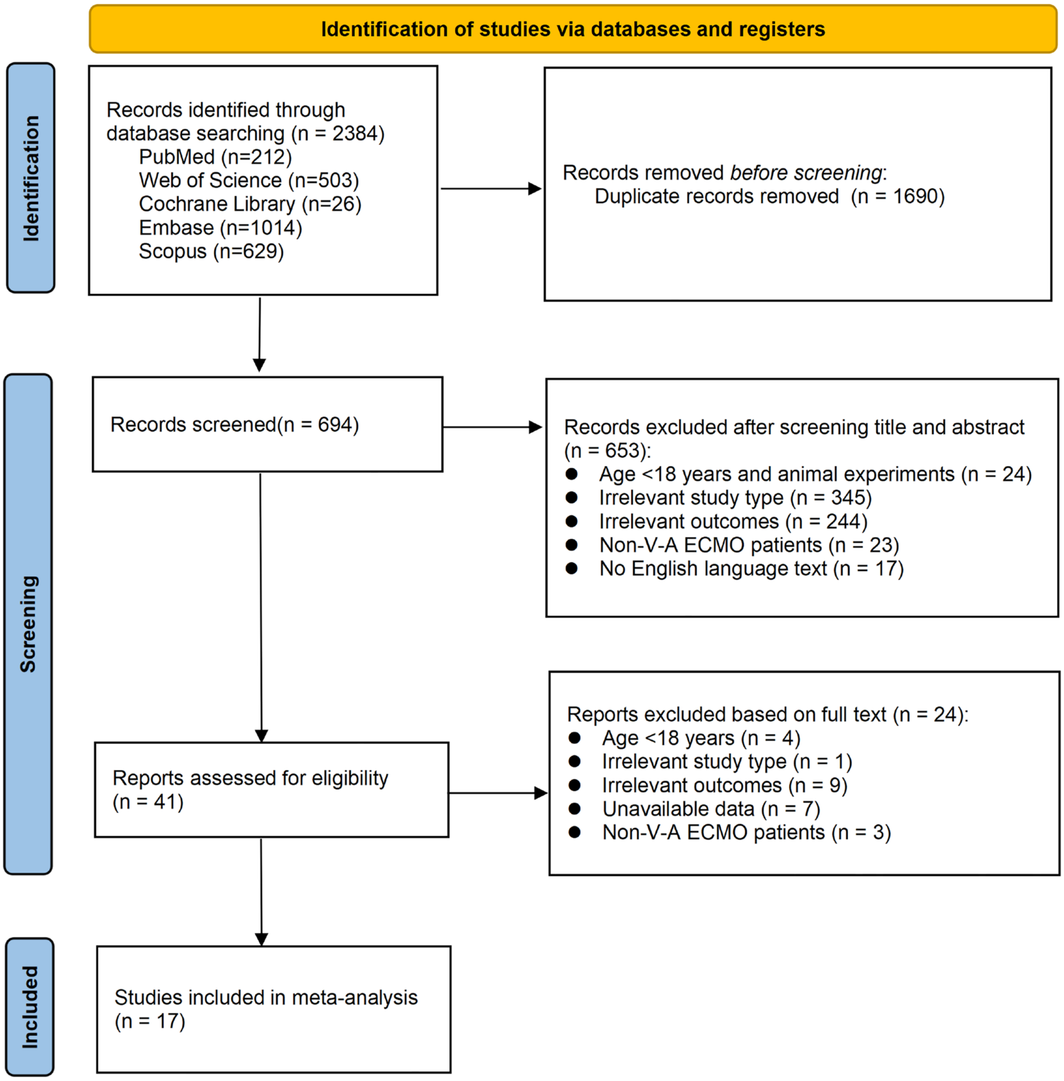

FIGURE 1 | Flow chart of the literature selection process for the present research. V-A ECMO = veno-arterial extracorporeal membrane oxygenation.

1690 duplicate records, 694 unique studies remained for title and abstract screening, of which 653 were excluded. A full-text review of the remaining 41 articles resulted in 17 studies being included in the final systematic review and meta-analysis. Detailed reasons for exclusion at the full-text screening stage are provided in Table S2.

5.2 | Study Characteristics

The 17 included studies were published between 2017 and 2025, encompassing a total of 2812 patients. The mean patient age across studies ranged from 35.3 to 59.0 years. All 17 studies involved adult patients receiving V-A ECMO and reported the incidence of limb ischaemia, while 11 additionally investigated risk factors for this complication [34–44]. Regarding cannulation strategy, 15 studies (88.2%) used peripherally cannulated V-A ECMO, and 2 (11.8%) used mixed cannulation. Geographically, the studies were conducted in North America ($n = 5$), Europe ($n = 3$), Asia ($n = 8$) and the Middle East ($n = 1$). Most studies employed a cohort design ($n = 16$, 94.1%), whereas one was a case–control study ($n = 1$, 5.9%). Detailed study characteristics are summarised in Table 1.

5.3 | Quality Assessment of Included Studies

NOS was applied to assess the methodological quality of 17 included studies (Tables S3 and S4). Overall NOS scores ranged from 6 to 9. Of these, 15 studies were classified as high quality and two as moderate quality.

5.4 | Pooled Incidence of Limb Ischaemia

Across the 17 studies included in the meta-analysis, the reported incidence of limb ischaemia ranged from 5.7% to 33.1%. The pooled incidence, estimated using a random effects model, was 16.9% (95% CI: 12.6%–21.3%) (Figure 2). Substantial heterogeneity was observed among the included studies ($I^2 = 91.3\%$, $\tau^2 = 0.0073$, $p_{het} < 0.001$).

TABLE 1 | Basic characteristics of included literature and evaluation of literature quality ($N=17$).

Authors (year)	Country	Sample size	Limb ischaemia, *n* (%)	Mean age	V-A ECMO indication	Detection method	Cannulation approach	Cannulation strategy	Arterial cannulation site	DPC strategy	Risk factors	NOS score
Lamb et al. (2017) [19]	USA	91	12 (13.2%)	NR	Severe cardiovascular or pulmonary compromise (cardiogenic shock, acute respiratory failure ± ARDS, pulmonary embolism, LVAD failure)	Clinical assessment, Doppler ultrasound, NIRS	Percutaneous	Peripheral	Femoral	Mixed (prophylactic, therapeutic)	NA	8
Jang et al. (2018) [34]	Korea	230	13 (5.7%)	NR	Ischemic/non-ischemic cardiomyopathy, septic shock, refractory arrhythmia, etc.	NR	Percutaneous or surgical cut-down	Peripheral	Femoral	Mixed (prophylactic, therapeutic)	12, 17	9
Yen et al. (2018) [35]	Taiwan	139	46 (33.1%)	NR	NR	Doppler ultrasound	Percutaneous	Peripheral	Femoral	Prophylactic (8%)	1, 2, 3, 5, 6, 7, 13	8
Park et al. (2018) [36]	Korea	255	24 (9.4%)	58.3	Cardiac and/or respiratory failure	Clinical assessment, Doppler ultrasound	Percutaneous	Peripheral	Femoral	Mixed (prophylactic, therapeutic)	1, 2, 3, 4, 5, 6, 9, 14	9
Liao et al. (2020) [37]	China	179	36 (20.1%)	NR	Low cardiac output, acute pulmonary embolism, AMI, FM, cardiomyopathy	Clinical assessment, Doppler ultrasound	Surgical cut-down	Peripheral	Femoral	Prophylactic (100%)	1, 9, 11, 13	8
Laimoud et al. (2021) [38]	Saudi Arabia	65	21 (32.3%)	37.9	Refractory cardiogenic shock	Clinical assessment, Doppler ultrasound, NIRS	Percutaneous or surgical cut-down	Peripheral	Femoral	Prophylactic (80%)	1, 2, 3, 4, 5, 6, 8, 13, 19	7
Son et al. (2021) [39]	USA	105	21 (20.0%)	54.9	Progressive cardiogenic shock or ECPR	NR	Percutaneous or surgical cut-down	Peripheral	Femoral or axillary	Selective Prophylactic (44%)	1, 6, 9, 13, 14, 16, 18	8

(Continues)

TABLE 1 | (Continued)

Authors (year)	Country	Sample size	Limb ischaemia, *n* (%)	Mean age	V-A ECMO indication	Detection method	Cannulation approach	Cannulation strategy	Arterial cannulation site	DPC strategy	Risk factors	NOS score
Hanley et al. (2021) [45]	USA	101	18 (17.8%)	55	Cardiogenic, respiratory or ECPR	Clinical assessment	Percutaneous	Peripheral	Femoral	Mixed (prophylactic in 49%, delayed in 11%, none in 40%)	NR	8
Vakil et al. (2021) [46]	USA	90	13 (14.4%)	58.8	Refractory cardiogenic shock or cardiac arrest	NR	Percutaneous (for peripheral)	Mixed (peripheral or central)	Femoral (for peripheral)	Prophylactic (100% for peripheral, $n=77$)	NR	8
Fisser et al. (2022) [40]	Germany	427	108 (25.3%)	NR	Cardiogenic shock and eCPR	Clinical assessment, Doppler ultrasound, NIRS	Percutaneous or surgical cut-down	Peripheral	Femoral	Mixed (prophylactic, therapeutic)	1, 4, 17, 19	9
Hu et al. (2022) [41]	China	179	19 (10.6%)	59	Cardiogenic shock, HR-PCI, ECPR	Clinical assessment, NIRS	Percutaneous	Peripheral	Femoral	Therapeutic	1, 7, 9, 12, 13, 14, 15, 20	9
Saiydoun et al. (2022) [47]	France	120	7 (5.8%)	56.65	Refractory cardiogenic shock or cardiac arrest	NR	Percutaneous or surgical cut-down	Peripheral	Femoral	Prophylactic (97%)	NR	9
Dragulescu et al. (2023) [42]	France	188	12 (6.4%)	52	Refractory cardiogenic shock and cardiac arrest	Clinical assessment, Doppler ultrasound	Surgical cut-down	Peripheral	Femoral	Prophylactic	1, 4, 8, 9, 10, 11, 13, 18, 20	9
Wang et al. (2024) [48]	China	16	2 (12.5%)	35.3	FM with cardiogenic shock, malignant arrhythmia, or cardiac arrest	NR	NR	Mixed (central or peripheral)	NR	Prophylactic (100%)	NR	6
Li et al. (2025) [49]	China	133	26 (19.5%)	57	Refractory cardiogenic shock	Clinical assessment	Semi-open or percutaneous	Peripheral	Femoral	Selective Prophylactic	NR	9
Nejim et al. (2025) [43]	USA	377	107 (28.4%)	53	Cardiac arrest, respiratory failure, heart failure, etc.	Clinical assessment, Doppler ultrasound	NR	Peripheral	Femoral	Prophylactic (53.2%)	1, 10, 11, 12, 13, 14, 15, 16, 17	9

(Continues)

TABLE 1 | (Continued)

Authors (year)	Country	Sample size	Limb ischaemia, *n* (%)	Mean age	V-A ECMO indication	Detection method	Cannulation approach	Cannulation strategy	Arterial cannulation site	DPC strategy	Risk factors	NOS score
Liu et al. (2025) [44]	China	117	22 (18.80%)	NR	Heart and/or lung failure refractory (septic cardiomyopathy, explosive myocarditis, acute myocardial infarction, etc.)	NR	Percutaneous or surgical cut-down	Peripheral	Femoral	78.00%	1, 13, 18	6

Note: (1) Age (years), (2) Height (cm), (3) Weight (kg), (4) BMI (kg/m^2), (5) Body surface area (m^2), (6) Arterial cannula size (Fr), (7) Vasoactive-inotropic score, (8) Platelet count (10^9/L), (9) ECMO duration time (h), (10) Female, (11) Peripheral arterial disease, (12) Diabetes mellitus, (13) Hypertension, (14) Coronary artery disease, (15) Intra-aortic balloon pump, (16) White, (17) DPC placement, (18) Smoking, (19) Unsuccessful percutaneous cannulation, (20) Mechanical ventilation.

Abbreviations: AMI, acute myocardial infarction; ARDS, acute respiratory distress syndrome; DPC, distal perfusion cannula; ECPR, extracorporeal cardiopulmonary resuscitation; FM, fulminant myocarditis; HR-PCI, high-risk percutaneous coronary interventions; LVAD, left ventricular assist device; NA, not applicable; NIRS, near-infrared spectroscopy; NR, not reported; V-A ECMO, veno-arterial extracorporeal membrane oxygenation.

5.5 | Subgroup Meta-Analysis of Incidence

To explore potential sources of the high heterogeneity observed in the primary analysis, we conducted subgroup analyses based on key clinical and study characteristics (Table 2). The analysis of DPC strategies revealed that routine prophylactic (≥ 80%): 16.6% (95% CI: 7.7%–25.5%), selective prophylactic (10%–79%): 22.2% (95% CI: 16.9%–27.5%), no/minimal prophylactic (< 10%): 21.6% (95% CI: −0.4% to 43.6%). Regarding cannulation technique, the percutaneous approach was associated with a higher incidence (15.9%, 95% CI: 9.9%–22.0%) compared to the surgical approach (13.0%, 95% CI: −0.4% to 26.5%), though the latter's estimate had a wide confidence interval and was not statistically significant ($p = 0.057$).

Geographically, studies from the Middle East reported the highest incidence (32.3%, 95% CI: 20.9%–43.7%), again based on a single study. Conversely, studies from Europe showed a significantly lower incidence (12.5%, 95% CI: 0.3%–24.7%). Analyses based on detection method, arterial cannula size and publication year did not reveal statistically significant differences in the incidence of limb ischaemia between subgroups. It is important to note that significant within-subgroup heterogeneity remained high across most analyses, indicating that these factors only partially explain the overall variability.

5.6 | Meta-Analysis of Risk Factors

A meta-analysis was conducted to evaluate the associations between various patient and procedural characteristics and the risk of limb ischaemia (Tables 3 and 4). Pre-existing peripheral arterial disease (PAD) emerged as a significant risk factor (OR = 6.12; 95% CI: 1.22–30.71), despite substantial heterogeneity among studies ($I^2 = 70.1\%$, $p_{het} = 0.035$). Similarly, unsuccessful percutaneous cannulation was a significant predictor of limb ischaemia (OR = 3.72; 95% CI: 1.90–7.28; $I^2 = 0\%$, $p_{het} = 0.910$). Analysis of continuous variables revealed that a lower patient height was significantly associated with limb ischaemia (WMD = −2.42 cm; 95% CI: −4.05 to −0.80; $I^2 = 13.4\%$, $p_{het} = 0.315$). Other investigated factors showed no statistically significant association with the risk of limb ischaemia.

5.7 | Sensitivity Analysis

To assess the robustness of our pooled estimates, we performed leave-one-out sensitivity analyses for each outcome. The pooled incidence of limb ischaemia remained stable, as the estimated effect showed minimal variation when each study was sequentially omitted (Figure 3). In contrast, the stability of risk factor estimates varied across analyses. Given the limited number of studies addressing specific risk factors, the results of these sensitivity analyses should be interpreted with caution.

5.8 | Publication Bias

A funnel plot for incidence reported in 17 studies exhibited asymmetry, prompting adjustment via the trim-and-fill method. The procedure imputed eight hypothetical studies, resulting in a

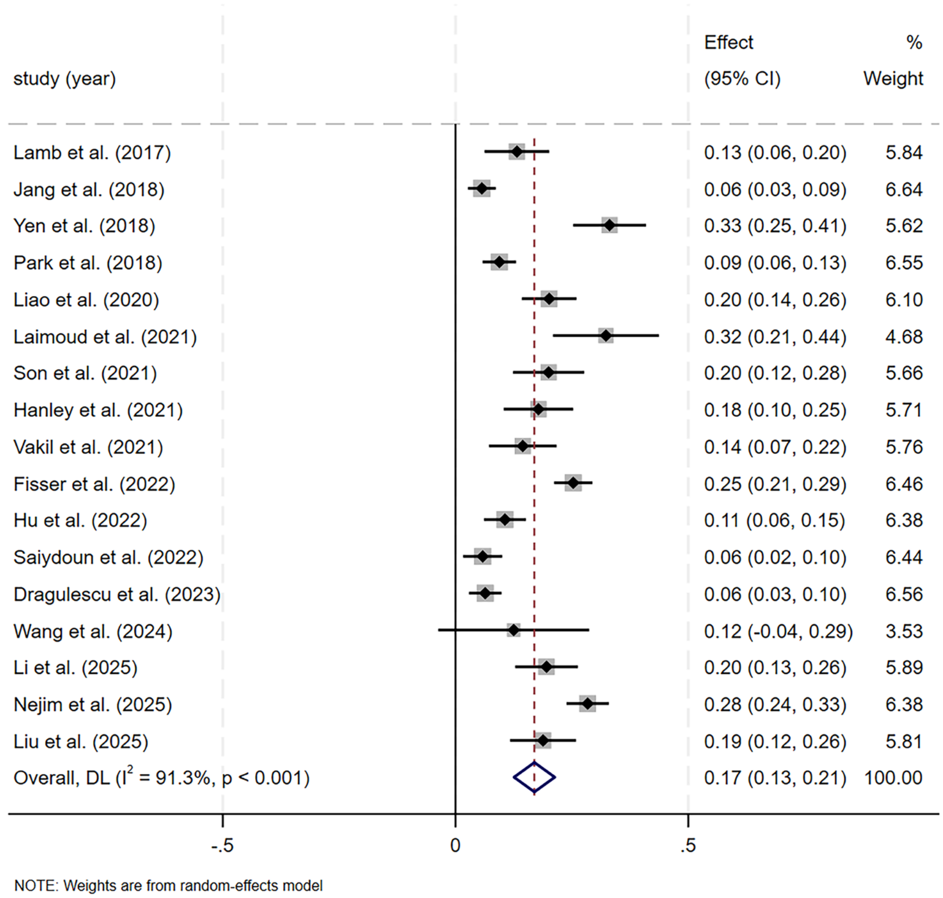

FIGURE 2 | Pooled incidence of limb ischaemia in patients receiving V-A ECMO. V-A ECMO = veno-arterial extracorporeal membrane oxygenation.

symmetrical funnel plot and an adjusted pooled incidence. The adjusted estimate in the random-effects model was 9.5% (95% CI: 4.2%–15.1%) (Figure 4). Publication bias analysis was not conducted for individual risk factors due to the limited number of studies ($n < 10$).

6 | Discussion

This systematic review and meta-analysis identified a pooled incidence of limb ischaemia of 16.9% (95% CI: 12.6%–21.3%, $I^2 = 91.3\%$) in adults receiving peripheral V-A ECMO. Furthermore, our analysis identified several risk factors: While PAD emerged as a powerful but statistically fragile predictor, unsuccessful percutaneous cannulation and shorter patient height were identified as more consistent and reliable predictors. Collectively, these findings provide a critical evidence base for refining clinical risk stratification and informing targeted preventive strategies in this high-risk population.

Our subgroup analysis demonstrated that the substantial heterogeneity observed across subgroups underscores the complex interaction among multiple procedural and patient-related variables, indicating that no single factor, such as DPC strategy, cannulation approach, detection method or arterial cannula size, operates in isolation. The primary clinical implication of this meta-analysis lies not in supporting any single intervention but in recognising the necessity of implementing an integrated, multi-component care bundle. Such a comprehensive bundle should include individualised risk stratification, meticulous procedural techniques, continuous monitoring regardless of modality and, most importantly, a rapid, protocol-driven response to early signs of ischaemia.

Early identification and prevention of risk factors for limb ischaemia are critical. This meta-analysis indicated that PAD was a significant risk factor for limb ischaemia in patients undergoing V-A ECMO (OR = 6.12; 95% CI: 1.22–30.71), consistent with previous studies [37, 50]. Mechanistically, patients with PAD typically exhibit atherosclerotic, stenotic and non-compliant femoral arteries, resulting in reduced vascular reserve. Insertion of a large-bore arterial cannula into such a compromised vessel creates a double-hit scenario that markedly impedes antegrade blood flow and further compromises the already limited collateral circulation [13, 51]. Furthermore, cannulation may dislodge atherosclerotic plaque, resulting in distal arterial embolism [50] (Figure 5). The key clinical implication of this finding is the need to shift from reactive management towards proactive prevention. Given that PAD is a readily identifiable comorbidity, these findings support the adoption of a structured, multi-step preventive strategy for this high-risk population, including systematic pre-procedural risk stratification based on clinical history and vascular imaging, prophylactic measures such as selecting the smallest effective arterial cannula and considering

TABLE 2 | Subgroup analysis of the incidence of limb ischaemia.

Subgroups	No. of studies	Heterogeneity test		Limb ischaemia	
		I^2 (%)	*p*	Incidence, % (95% CI)	*p*
DPC strategy					
Routine prophylactic DPC (≥ 80%)	5	85.7	< 0.001	16.6 (7.7, 25.5)	< 0.001
Selective prophylactic DPC (10% ≤ DPC < 80%)	4	63.6	0.041	22.2 (16.9, 27.5)	< 0.001
No/minimal prophylactic DPC (< 10%)	2	95.8	< 0.001	21.6 (−0.4, 43.6)	0.054
Cannulation approach					
Percutaneous	6	84.4	< 0.001	15.9 (9.9, 22.0)	< 0.001
Surgical	2	93.6	< 0.001	13.0 (−0.4, 26.5)	0.057
Mixed	7	93.3	< 0.001	17.6 (10.0, 25.3)	< 0.001
Detection method					
Clinical/Doppler	7	93.4	< 0.001	19.0 (11.5, 26.5)	< 0.001
With NIRS monitoring	4	90.0	< 0.001	19.7 (10.3, 29.1)	< 0.001
Arterial cannula size (Fr)					
Smaller cannula (mean/median ≤ 17 Fr)	2	96.6	< 0.001	21.0 (−2.2, 44.2)	0.076
Larger cannula (mean/median > 17 Fr)	3	56.0	0.103	22.3 (14.8, 29.8)	< 0.001
Geographical location					
East Asia	8	88.9	< 0.001	15.9 (10.2, 21.7)	< 0.001
Middle East	1	NR	NR	32.3 (20.9, 43.7)	< 0.001
Europe	3	96.6	< 0.001	12.5 (0.3, 24.7)	0.045
North America	5	78.8	0.001	19.1 (12.6, 25.5)	< 0.001
Publication year					
Early period (2017–2020)	5	92.5	< 0.001	15.8 (7.9, 23.6)	< 0.001
Recent period (2021–2025)	12	90.5	< 0.001	17.5 (12.1, 22.9)	< 0.001

Abbreviations: DPC, distal perfusion cannula; NIRS, near-infrared spectroscopy; V-A ECMO, veno-arterial extracorporeal membrane oxygenation.

TABLE 3 | Meta-analysis of adjusted risk factors for limb ischaemia.

Risk factors	No. of studies	Statistical method	Heterogeneity test		Pooled effect size	
			I^2 (%)	*p*	OR (95% CI)	*p*
Peripheral arterial disease	3	Random	70.10	0.035	6.12 (1.22, 30.71)	0.028
DPC placement	3	Random	85.60	0.001	0.95 (0.19, 4.89)	0.955
Diabetes mellitus	3	Random	54.40	0.112	1.43 (0.59, 3.48)	0.433
Female	2	Random	62.10	0.104	2.11 (0.70, 6.40)	0.188
Intra-aortic balloon pump	2	Fixed	0.00	0.486	0.93 (0.52, 1.67)	0.802

Abbreviation: DPC, distal perfusion cannula.

DPC placement, and intensified post-procedural monitoring with Doppler ultrasound or NIRS to facilitate early ischaemia detection.

Although our meta-analysis initially suggested that PAD is a significant risk factor for limb ischaemia, this finding was not robust in sensitivity analyses, as it was largely driven by a single influential study. This instability likely stems from both the limited number of studies investigating each risk factor and the considerable clinical and methodological heterogeneity among them. Key sources of this heterogeneity included varying definitions of limb ischaemia, divergent cannulation strategies,

TABLE 4 | Meta-analysis of unadjusted risk factors for limb ischaemia.

Risk factors	No. of studies	Statistical method	Heterogeneity test		Pooled effect size	
			I^2 (%)	p	OR/WMD (95% CI)	p
Age (years)	10	Random	65.60	0.002	−0.74 (−3.60, 2.12)	0.614
Height (cm)	3	Fixed	13.40	0.315	−2.42 (−4.05, −0.80)	0.004
Weight (kg)	3	Fixed	43.60	0.170	2.16 (−0.44, 4.75)	0.103
BMI (kg/m^2)	4	Fixed	0.00	0.674	−0.09 (−0.94, 0.76)	0.838
Body surface area (m^2)	3	Fixed	32.80	0.226	0.02 (−0.01, 0.04)	0.180
Arterial cannula size (Fr)	4	Fixed	0.00	0.792	0.07 (−0.16, 0.31)	0.539
Vasoactive-inotropic score	2	Random	98.20	< 0.001	−11.06 (−40.32, 18.20)	0.459
Platelets count (10^9/L)	2	Fixed	0.00	0.505	5.80 (−42.37, 53.97)	0.813
ECMO duration time (h)	5	Fixed	20.60	0.283	3.11 (−11.11, 17.33)	0.668
Hypertension	8	Fixed	0.00	0.708	1.05 (0.80, 1.39)	0.729
Coronary artery disease	4	Fixed	0.00	0.618	0.80 (0.55, 1.16)	0.244
White	2	Fixed	0.00	0.333	0.90 (0.52, 1.58)	0.722
Smoking	3	Fixed	0.00	0.766	1.32 (0.71, 2.45)	0.382
Unsuccessful percutaneous cannulation	2	Fixed	0.00	0.910	3.72 (1.90, 7.28)	< 0.001
Mechanical ventilation	2	Fixed	0.00	0.999	2.04 (0.90, 4.64)	0.089

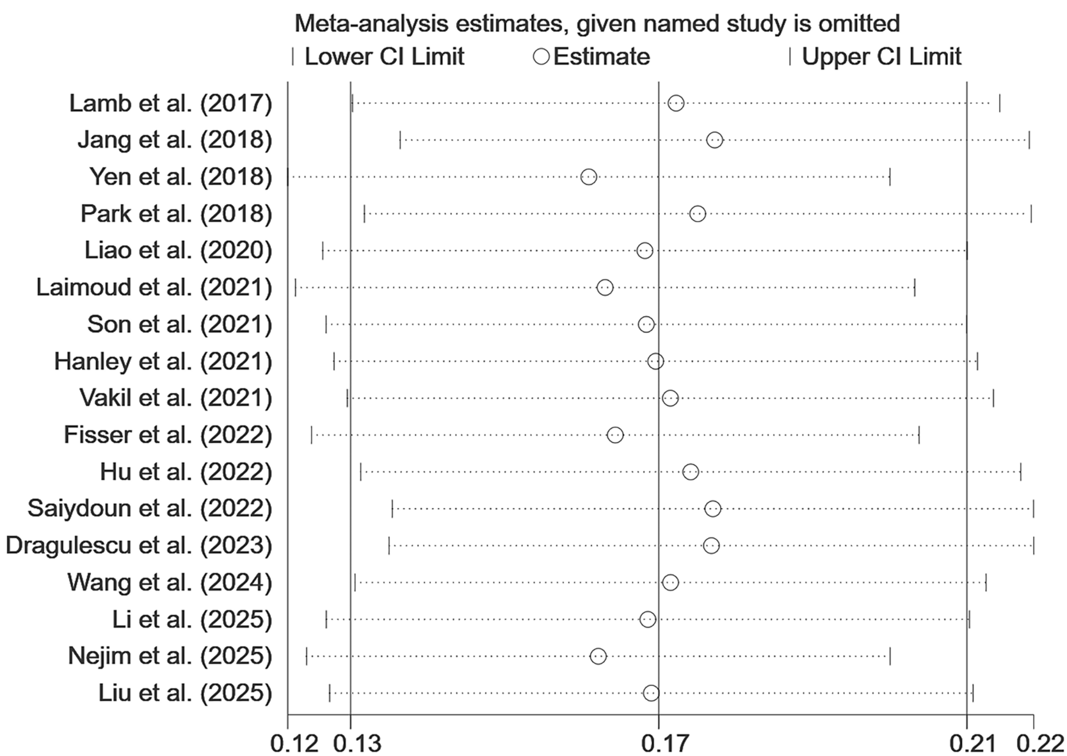

FIGURE 3 | Leave-one-out sensitivity analysis for the pooled incidence of limb ischaemia.

heterogeneous patient populations and inconsistent statistical adjustment for confounding variables. These limitations underscore the urgent need for large-scale, prospective, multicentre studies that adhere to standardised protocols.

The present study revealed that unsuccessful percutaneous cannulation was significantly associated with limb ischaemia in patients undergoing V-A ECMO (OR = 3.72; 95% CI: 1.90–7.28). However, this finding was derived from only two studies and

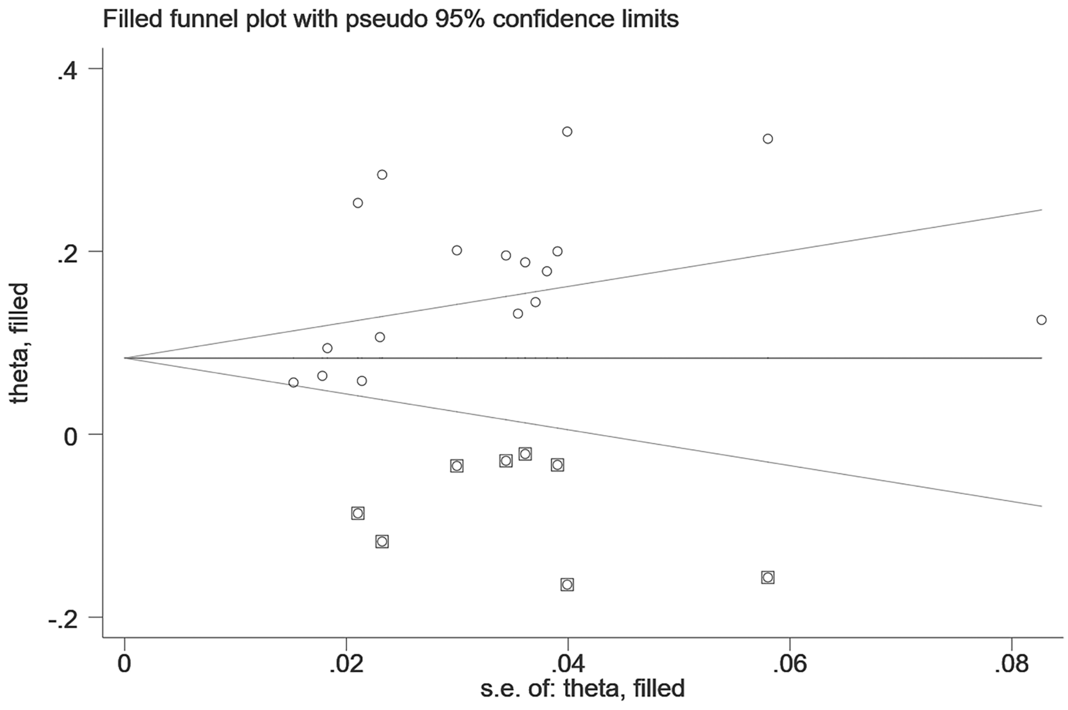

FIGURE 4 | Funnel plot with trim-and-fill analysis (evaluating and adjusting for potential publication bias in the pooled incidence of limb ischaemia).

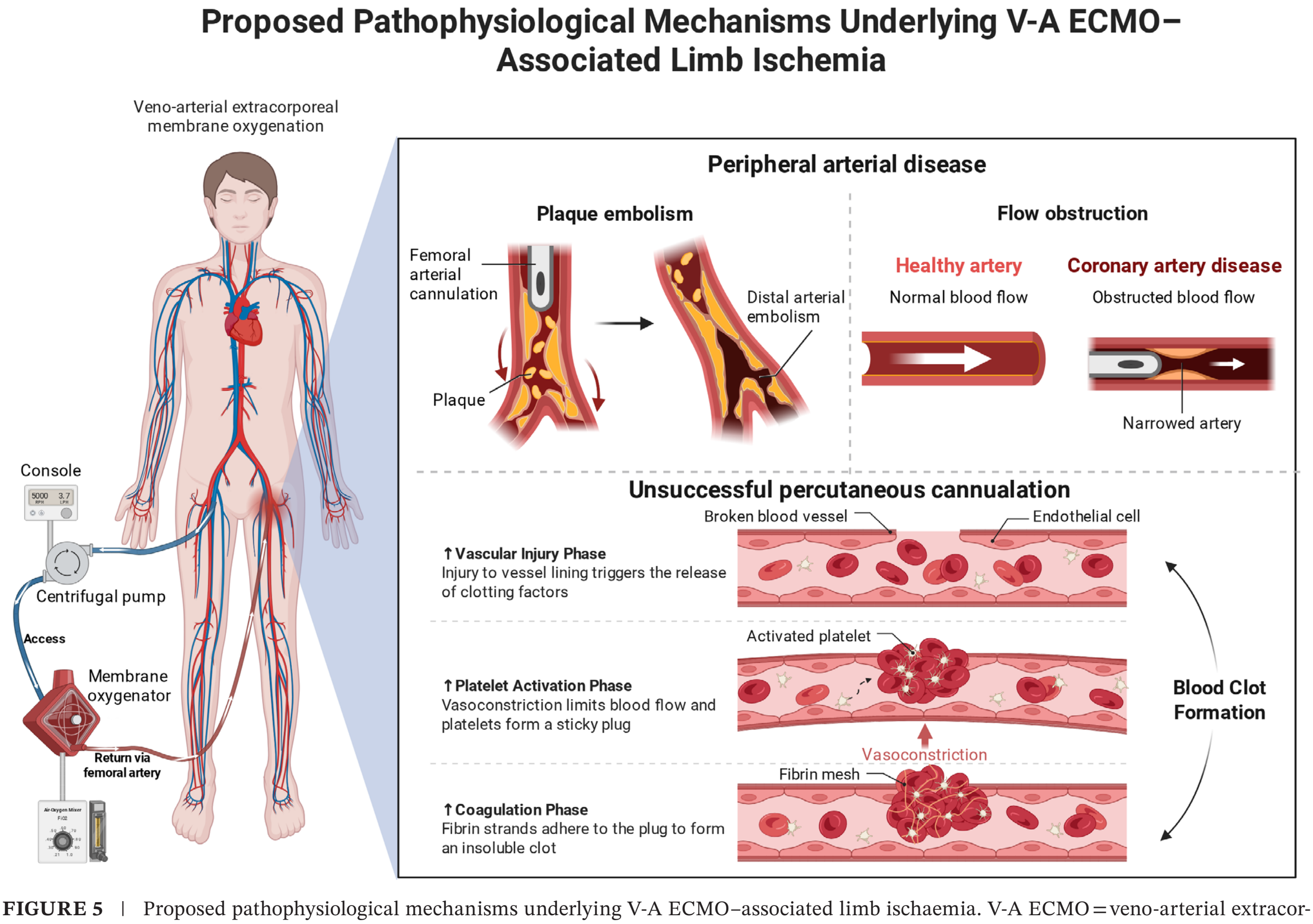

FIGURE 5 | Proposed pathophysiological mechanisms underlying V-A ECMO–associated limb ischaemia. V-A ECMO = veno-arterial extracorporeal membrane oxygenation. This figure is created by BioRender.

should therefore be interpreted with caution. Mechanistically, repeated puncture attempts may cause endothelial injury, arterial spasm or hematoma formation, thereby narrowing the arterial lumen and impairing distal perfusion [52, 53] (Figure 5). Clinically, this factor represents a modifiable, procedure-related risk, emphasising the importance of preventive strategies. In elective or semi-urgent cases, pre-procedural vascular assessment using ultrasonography or computed tomography may help identify anatomical challenges, such as calcified or small-calibre vessels, and guide optimal cannulation strategies. However, in hyper-acute situations such as eCPR, rapid bedside ultrasonography or clinical evaluation is the most practical approach to avoid delays in initiating extracorporeal support. During cannulation, real-time ultrasound guidance facilitates an optimal puncture trajectory and minimises inadvertent vascular injury [54–57]. Furthermore, early recognition of difficult vascular access should prompt timely conversion to surgical cannulation or the placement of a distal perfusion cannula to preserve limb perfusion. Therefore, unsuccessful percutaneous cannulation should be considered not merely a technical complication but as an important clinical indicator emphasising the necessity of proactive preventive measures.

This meta-analysis identified an inverse association between height and limb ischaemia (WMD = −2.42 cm; 95% CI: −4.05 to −0.80). However, although this finding corroborates a previous study [36], it was derived from only three studies and should therefore be interpreted with caution. Despite this limitation, the association appears mechanistically plausible. Rather than a modest absolute difference with limited clinical applicability, height likely serves as a convenient surrogate for a more fundamental determinant: cannula-to-vessel size mismatch. In patients with smaller femoral arteries, a standardsised arterial cannula occupies a disproportionately large cross-sectional area, which in turn impedes antegrade blood flow and predisposes the distal limb to ischaemia. Consequently, the primary clinical relevance of this finding lies not in defining a specific height cut-off but in promoting greater vigilance for smaller stature patients. These results highlight the importance of adopting a personalised cannulation strategy, which should encompass routine pre-procedural vascular ultrasound to assess vessel diameter and the evidence-based selection of a smaller-calibre arterial cannula or prophylactic DPC placement in this high-risk cohort. Clinicians must carefully balance target flow requirements with patient-specific anatomical factors to minimise ischaemic risk while maintaining adequate ECMO support.

Equally important for a comprehensive understanding are factors that did not show a significant association with limb ischaemia in our pooled analysis, which may indicate methodological limitations rather than a true absence of effect. The relationship between patient age and the risk of limb ischaemia remains inconclusive. In our meta-analysis, age analysed as a continuous variable showed no linear association with limb ischaemia, consistent with previous findings [38]. By contrast, other studies have identified advanced age as a significant risk factor [16], possibly reflecting age-related vascular changes, including atherosclerosis and arterial stiffness. Similarly, some evidence has shown a higher incidence of ischaemia among younger patients [18], possibly related to an immature arterial system, limited collateral development and smaller vessel calibres predisposing to cannulation injury [21, 58]. These contrasting findings suggest that age may exert a non-linear, possibly U-shaped influence on ischaemia risk, driven by different pathophysiological mechanisms at the extremes of age. Such discrepancies are likely amplified by methodological heterogeneity, including differences between continuous-variable analyses and categorical age classifications. To clarify the influence of age, future large-scale studies should adopt standardised age stratification and apply statistical models capable of detecting potential non-linear relationships.

Previous studies have reported that limb ischaemia can occur in elderly or critically ill intensive care unit (ICU) patients even in the absence of ECMO support and is often associated with advanced age, PAD, prolonged immobility, vasopressor use, systemic hypoperfusion and coagulopathy [59–61]. Thus, the observed incidence is likely to reflect a combination of ECMO-specific mechanical factors and the underlying pathophysiology of critical illness. The identification of PAD and unsuccessful cannulation as significant risk factors supports a substantial contribution of ECMO to the development of this complication. Nevertheless, the lack of non-ECMO control groups in the included studies precludes definitive causal inference. Future prospective or registry-based studies that incorporate matched non-ECMO control groups are warranted to clarify the independent impact of ECMO on the risk of limb ischaemia.

7 | Strengths and Limitations

A total of 2812 V-A ECMO patients with 507 limb ischaemia events were included in this study. This meta-analysis was conducted rigorously in accordance with the PRISMA guidelines. A comprehensive literature search was performed across five databases, and study quality was appraised using a validated assessment tool, thereby enhancing the internal validity of the analysis. Nevertheless, several inherent limitations should be acknowledged in this study. First, most of the included studies were observational in design and limited to English-language publications, which may have introduced confounding bias and limited the comprehensiveness of the evidence base. Second, substantial heterogeneity persisted among studies despite subgroup analyses, warranting cautious interpretation of the pooled estimates. Third, the robustness of several estimates was limited by the small number of contributing studies, and insufficient data on specific risk factors precluded further stratified analyses. Fourth, it should be emphasised that the findings primarily represent the limb ischaemia profile associated with peripherally cannulated V-A ECMO, and extrapolation to central or alternative cannulation strategies should be approached with caution. Fifth, variations in the definitions of limb ischaemia among studies may have compromised comparability, underscoring the need for standardised diagnostic criteria. Finally, sensitivity analyses regarding ECMO duration lacked robustness due to inconsistent reporting units, emphasising the importance of adopting standardised metrics (e.g., hours) in future studies. In summary, although this study provides valuable preliminary insights, its findings should be interpreted with caution. Large-scale, prospectively designed studies with standardised reporting are warranted to validate the identified risk factors and produce more definitive estimates.

8 | Implications for Practice and Further Research

Clinically, unsuccessful percutaneous cannulation represents a modifiable procedural risk, emphasising the need for preventive strategies, such as pre-procedural vascular assessment, real-time ultrasound guidance and timely selection of alternative cannulation approaches to reduce the risk of limb ischaemia. Although pre-existing PAD was identified as a significant risk factor, its statistical instability requires cautious interpretation, and clinicians should avoid relying solely on PAD without accounting for the broader clinical context. To address these limitations and strengthen the evidence base, future research should prioritise large-scale, prospective, multicentre studies to validate and refine identified risk factors. Establishing standardised diagnostic criteria for limb ischaemia is essential to ensure methodological consistency and comparability across studies. Future investigations should systematically collect and report key variables identified in this analysis, including patient anthropometrics, vascular imaging findings, and procedural characteristics, to facilitate the development of refined risk stratification models. These measures will enhance the accuracy of risk factor identification and provide a stronger scientific basis for developing effective preventive and management strategies.

9 | Conclusion

In conclusion, this systematic review and meta-analysis provide a comprehensive quantitative synthesis of current evidence, delineating the incidence and principal predictors of limb ischaemia in adult V-A ECMO patients. Pre-existing PAD and unsuccessful percutaneous cannulation emerged as significant risk factors, while lower patient height was associated with an increased risk. These findings have direct implications for clinical practice by facilitating the early identification of high-risk individuals and the implementation of targeted preventive strategies, thereby improving patient outcomes. However, these results should be interpreted with caution due to the aforementioned methodological limitations. Therefore, large-scale, prospective studies are urgently warranted to generate higher-quality evidence and to strengthen the reliability and generalisability of these findings.

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Ethics Statement

The authors have nothing to report.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** nicc70365-sup-0001-supinfo.docx.