REVIEW

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Navigating treatment choices in acute limb ischemia case: a systematic review

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ABSTRACT

Background: Acute limb ischemia (ALI) is a critical vascular emergency characterized by the sudden reduction of blood flow to a limb, posing a significant risk of tissue loss or death. The primary etiologies are embolism and thrombosis, commonly associated with atrial fibrillation or atherosclerosis. Treatment strategies—including open surgery (OS), endovascular treatment (ET), and hybrid treatment (HT)—are designed to prevent limb amputation after initial intervention, as reinterventions can increase the risk of complications and mortality. This study aims to evaluate and compare the efficacy and safety of OS, ET, and HT in the management of ALI, as well as to identify predictors of clinical outcomes.

Methods: A systematic review was conducted in accordance with PRISMA guidelines, searching PubMed, ScienceDirect, Scopus, and Web of Science for studies comparing OS, ET, and HT in ALI management. Outcomes assessed included amputation-free survival (AFS) at 12 months, 30-day reintervention, and 30-day mortality.

Results: Six studies comprising 2,511 patients were included. The ET group demonstrated significantly higher AFS rates at 12 months compared to OS and HT. There were no statistically significant differences in 30-day reintervention rates among the three modalities. However, 30-day postoperative mortality was significantly higher in patients undergoing OS and HT than in those treated with ET. Advanced age and comorbidities were associated with poorer outcomes across all interventions.

Conclusion: This review highlights the importance of individualized treatment selection in ALI management, as each modality offers distinct advantages and limitations. ET appears favorable for high-risk patients due to its minimally invasive nature and lower short-term mortality, while HT may be particularly beneficial in anatomically complex cases. Further research is needed to optimize long-term outcomes and refine patient-specific treatment strategies.

Keywords: Acute Limb Ischemia, Amputation-Free Survival, Endovascular Treatment, Open Surgery.
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INTRODUCTION

Acute limb ischemia (ALI) is a severe vascular emergency characterized by sudden limb hypoperfusion, often resulting in tissue ischemia and may lead to limb loss or death.[1-3] In clinical settings, the presentation is classified as acute when it manifests within two weeks of symptom onset. Physical examination typically reveals key signs such as absent pulses beyond the occlusion, cool, pale or mottled skin, along with reduced sensation and muscle strength.[4-6] These hallmark features are often summarized by the mnemonic "6Ps": paresthesia, pain, pallor, pulselessness, poikilothermia and paralysis.[7]

The incidence of ALI is reported to be 1–1.5 individuals per 10,000 individuals per year. Excluding trauma-related cases, the primary causes of ALI are generally classified into embolism and thrombosis. Generally, ALI incidence rates are estimated at 9–16 cases per 100,000 person-years for the lower extremities and approximately 1–3 cases per 100,000 person-years for the upper extremities.[8] Thrombosis in vessels affected by underlying atherosclerosis or peripheral artery disease (PAD) has surpassed embolism as the primary cause of ALI in around 53% of cases. Traditionally, most arterial emboli (44% of cases) were linked with rheumatic or congenital heart disease; however, atrial fibrillation (AF) has now emerged as the primary cardiac source, responsible for up to 80% of ALI cases with an embolic origin.[9] The Rutherford classification aids clinicians in decision-making to assist in determining the severity of ischemia and the appropriate management approach. Patients can be classified into four categories: I, "viable"; IIA, "marginally threatened"; IIB, "immediately threatened"; and III, "irreversible".[10]

Treatment options for ALI include revascularization techniques such as open surgery (OS), endovascular treatment (ET), or hybrid treatment (HT: combination of open and endovascular), and also conservative management with anticoagulation therapy, amputation, or palliative care.[11] The choice of revascularization strategy for ALI whether OS, ET, HT is guided by multi- factors such as the underlying causes, anatomical considerations, thrombus burden, comorbidities, and other risks associated

with each therapy. Additionally, the availability of revascularization devices, including mechanical thrombectomy tools varies across countries. The primary objective of treatment for ALI is to achieve amputation-free survival (AFS) as the outcome significantly enhances the long-term quality of life for patients, as well as to reduce reintervention and mortality rate.[3] The current study aimed to demonstrate the efficacy and safety of OS, ET, and HT in treating ALI, as well as to show the predictors of outcomes.

METHODS

Search Strategy and Information Sources

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria. We performed systematic searches in PubMed, Scopus, Web of Science, and ScienceDirect up to October 2024. The search technique utilized terminology to locate pertinent papers concerning acute limb ischemia and surgery techniques: ((Acute Limb Ischemia) OR (ALI)) AND ((hybrid revascularization) OR (hybrid treatment)) AND ((endovascular treatment) OR (open surgery) OR (bypass surgery)). Moreover, we discovered references by examining the reference lists of the included research and pertinent reviews. Our inquiry was confined to reports disseminated in English. Narrative reviews, editorials, letters, opinions, and studies with non-human subjects are excluded.

Selection criteria

The articles that fulfilled the inclusion criteria were downloaded in full text and reviewed. The primary outcome was amputation-free survival (AFS) rates. Secondary outcomes encompass reintervention and mortality. This review will include observational studies (including retrospective cohort studies) and randomized control trials that evaluate the effectiveness of each approach (open surgery, endovascular treatment, hybrid treatment) for acute limb extremities cases. Patients with other limb ischemic (e.g. Chronic Limb-Threatening Ischemia and Peripheral Artery Disease) are excluded.

Data Extraction and Quality Assessment

Following the articles were finalized, two authors (RDPW, NTA) independently extracted the data utilizing a standardized form. Disagreements were resolved through consensus or by consulting a third author (PO). The collected data included overall study information and specific patient details, such as age, sex, and race. Supplementary materials were reviewed as needed. The trial registration records were also reviewed to evaluate incomplete reported outcomes.

The National Institute of Health (NIH) quality assessment tool for observational cohort study to evaluate quality of study and assess risk of bias, categorizing into "good", "fair", or "poor" (Fig S1, supplementary). Randomized control trials were evaluated using the Cochrane Risk of Bias Tool version 2 (RoB 2) for assessing bias risk in randomized trials. The risk of bias was categorized as "low risk", "some concern", or "high risk" (Fig S2, supplementary). Two authors (RDPW, JJ) independently evaluated each domain for bias, resolving any discrepancies with the involvement of a third author (PO).

Statistical Analysis

Due to significant differences in the studies and their outcome measures, we were unable to conduct meta-analyses of the included studies; therefore, we synthesized the evidence narratively.

RESULTS

Study Election

The initial database search identified 310 articles with 129 duplicate articles detected. Following a screening of titles

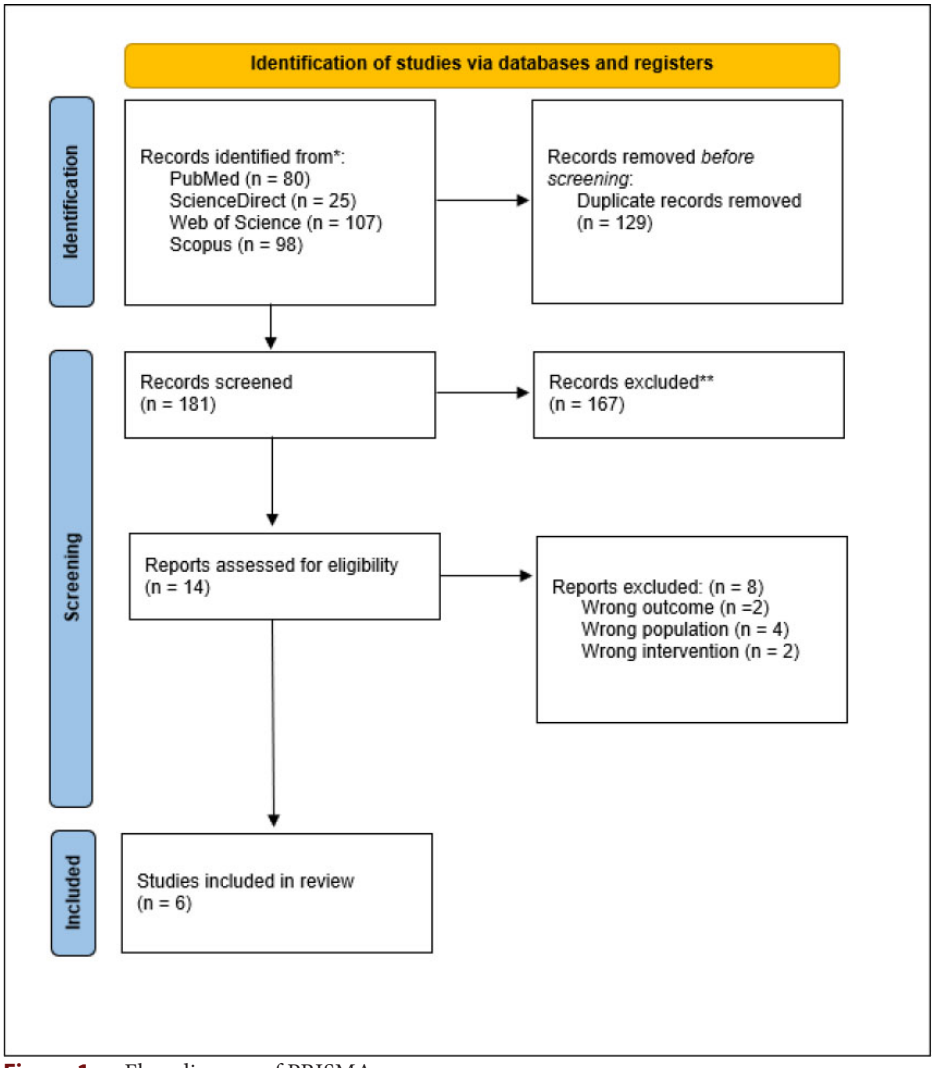

Figure 1. Flow diagram of PRISMA.

and abstracts, 181 articles were deemed potentially eligible for further evaluation. After a full-text screening, six studies met the inclusion criteria and were incorporated into the systematic review. The selection process is detailed in the PRISMA flow diagram provided. This systematic review followed the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines and is registered in the PROSPERO database (CRD42024625662) (Figure 1).

Quality of Assessment

One observational study and four retrospective studies were evaluated with the National Institute of Health (NIH) assessment and showed good quality for each study.[1-4,6] One randomized controlled trial (RCT) had a low risk of bias according to the Cochrane Risk-of-Bias (RoB 2) assessment.[5] A summary of the quality assessment can be found in Supplementary Materials (Tables S2, S3).

Patient Characteristics

Most participants across all studies were male (n=1416, 56.3%). Out of the seven studies, six reported the average age of adult patients undergoing HT, OS, or ET procedures as 71.97±13.65 years, respectively. Only one study[2] reported an average age of over 75 years. Three studies had classified the severity of ALI into Rutherford I-III.[1,3,4] Rutherford I as a viable (non-severe ALI), IIa as a marginally threatened (non-severe ALI), IIb as an immediately threatened (severe ALI), III as an irreversible ischemia (severe ALI). While other studies had no Rutherford classification.[2,5,6]

Study Characteristics

A total of 2,511 patients were included from seven studies that were conducted in Europe, Germany, the USA, and Japan. This review had primary and secondary outcomes that were concluded by data extraction from Microsoft Excel. The primary outcome was AFS, while the second outcomes were reintervention and mortality. Amputation Free Survival (AFS) rate is defined as the duration of time, in this case 12 months of follow-up intervals, during which a patient remains free from limb amputation following a specific intervention, particularly for this context, as in ALI cases. Reintervention was referred to as additional procedures (e.g., surgical bypass, stenting/angioplasty, or combination) following an initial treatment aimed at restoring blood flow to the affected limb and described as durability of initial treatment in this case 30-day follow-up interval. Mortality indicated the average death rate among patients who were diagnosed with a specific period, typically measured within a designated follow-up timeframe (e.g., 30-day follow-up), also associated with rapid progression of the condition and potential complications.

Amputation Free Survival (AFS)

The systematic review highlighted significant findings related to AFS in patients undergoing various interventions especially OS), ET, HT for ALI revascularization. Three studies evaluated AFS as a percentage of patients remaining free from limb amputation over a follow-up period of 12 months. Argyriou et al., reported that the AFS was no significant difference between patients treated with ET compared with HT.[1] Nevertheless, when compared ET vs OS (91% vs 75%; HR 2.50, 95% CI 1.19 to 5.53, p=0.003); ET vs HT (91% vs 74%; HR 3.10, 95% CI 1.45 to 6.65, p<0.001), ET was associated with significantly reduced overall survival rates than OS and HT. In line with these findings, Konstantinou et al., demonstrated that ET was significantly higher AFS rates during 12 months follow-up compared to OS (75.5% ET vs 60.7% OS; HR: 1.89, 95% CI 1.2–2.9, p<0.001) and HT (61.2% HT vs 75.5% ET; HR: 1.73, 95% CI 1.1–3.1, p<0.001).[4] Lurie et al., revealed AFS involving 60 patients, 33 patients, 28 patients (95% OS vs 100% ET vs 100% HT).[5]

Patients aged 65-75 years were associated with a significantly lower AFS rate compared to those under 65 years (65–75 vs <65 years, HR=2.36, 95% CI=1.4–4, p<0.001). Those aged above 75 years compared to younger age were significantly associated with lower AFS rate as well (>75 vs <65 years, HR=3.63, 95% CI=2.2–5.9, p<0.001).[4]

Reintervention

The reintervention rates across OS, ET, and HT were evaluated at 30 days post-treatment. Out of the seven studies included in this systematic review, four studies specifically reported on 30-day reintervention outcomes that indicated no statistically significant differences between the three treatment modalities (ET vs OS, p=0.79; ET vs HT, p=0.19; OS vs H, p=0.18). However, trends within the data indicate a tendency for higher reintervention following ET, with HT showing intermediate rates and OS the lowest rates. This aligns with findings by Argyriou et al., who reported that ET, though beneficial for minimizing initial surgical risk, was associated with more frequent re-interventions compared to OS, primarily due to the need for repeat procedures to maintain patency in complex or multilevel occlusions.[1]

The intermediate reintervention rates observed in HT likely result from the combined risks of surgical and catheter-related complications, as HT involves both open and endovascular elements. Open surgical interventions, such as embolectomy or bypass, demonstrated the lowest 30-day reintervention rates, suggesting greater initial durability. However, the invasiveness of OS may limit its use in high-risk patients with significant comorbidities.[1,12] Long-term outcomes indicate that ET is generally associated with higher reintervention rates due to restenosis, thrombosis, or reocclusion. However, these differences were not evident within the initial 30-day period analyzed in the included studies, suggesting that all three modalities—ET, OS, and HT—offer comparable short-term efficacy in restoring limb perfusion.[4] The need for additional interventions may become more apparent beyond the first 30 days, particularly in ET.[9,12]

Mortality

The mortality outcomes across OS, ET, and HT were assessed based on 30-day and in-hospital mortality data from the included studies. Three studies reported no significant difference in 30-day mortality among the three treatment modalities, indicating that all approaches, whether OS, ET, or HT, offer comparable

Table 1. Characteristics of included studies

References	Study design	Country	Interventions			Age, years Mean ± SD			Rutherford Classification	Comorbidities	Outcomes		
			OS	ET	HT	OS	ET	HT			AFS in 12 months (%)	Re-interventi on in 30 days (n)	Mortality in 30 days (n)
Argyriou et. al., 2021[1]	R	Europe	70	41	28	70.7±13.1	75.7±11.7	71.2±11.0	Non severe ALI: Rutherford I OS = 10 (14%) HT = NA ET = 35 (86%) Rutherford IIa OS = 32 (46%) HT = 8 (27%) ET = 11 (27%) Severe ALI: Rutherford IIb OS = 45 (65%) HT = 4 (15%) ET = 8 (20%) Rutherford III OS = 50 (72%) HT = 4 (14%) ET = 6(14%)	Smoking status OS = NR HT = NR ET = NR AF OS = 15 HT = 6 ET = 14 CKD OS = 15 HT = 8 ET = 7 CVD OS = NR HT = NR ET = NR	ET = 84% OS = 67% HT = 72%	ET = 8 OS = 8 HT = 4	ET = 3 OS = 7 HT = 1
Davis et al., 2018[2]	O	USA	195	818	467	NA	NA	NA	NA	Smoking status OS = 82 HT = 205 ET = 318 OS = NR HT = NR ET = NR CKD OS = 5 HT = 24 ET = 65 CVD OS = 47 HT = 122 ET = 241	NR AF	ET = 19 OS = 5 HT = 6	ET = 58 OS = 7 HT = 48

References	Study design	Country	Interventions			Age, years Mean ± SD			Rutherford Classification	Comorbidities	Outcomes		
			OS	ET	HT	OS	ET	HT			AFS in 12 months (%)	Re-interventi on in 30 days (n)	Mortality in 30 days (n)
Tan et al., 2024[3]	R	Japan	79	66	40	73±16	79±11	75±14	Non severe ALI: Rutherford I OS = 39 (49%) HT = 20 (50%) ET = 8 (12%) Rutherford IIa OS = 24 (30%) HT = 13 (33%) ET = 32 (48%) Severe ALI: Rutherford IIb OS = 15 (19%) HT = 6 (15%) ET = 22 (33%) Rutherford III OS = 1 (1%) HT = 1 (3%) ET = 4 (6%)	Smoking status OS = 42 HT = 16 ET = 30 AF OS = 24 HT = 15 ET = 30 CKD OS = 29 HT = 11 ET = 24 CVD OS = 4 HT = 5 ET = 5	NR	NR	NR
Konstantinou et al., 2023[4]	R	Germany	150	147	98	73±14.8	69±12.5	71.3±12.8	Non severe ALI: Rutherford I OS = 1 (1%) HT = 2 (2%) ET = 21 (14%) Rutherford IIa OS = 26 (17%) HT = 24 (24%) ET = 74 (50%) Severe ALI: Rutherford IIb OS = 81 (54%) HT = 47 (48%) ET = 47 (32%) Rutherford III OS = 42 (28%) HT = 25 (25%) ET = 5 (3%)	Smoking status OS = 54 HT = 41 ET = 54 AF OS = 59 HT = 37 ET = 31 CKD OS = NR HT = NR ET = NR CVD OS = 71 HT =47 ET = 68	ET = 81% OS = 41% HT = 40%	ET = 36 OS = 41 HT = 26	ET = 5 OS = 25 HT = 14

References	Study design	Country	Interventions			Age, years Mean ± SD			Rutherford Classification	Comorbidities	Outcomes		
			OS	ET	HT	OS	ET	HT			AFS in 12 months (%)	Re-interventi on in 30 days (n)	Mortality in 30 days (n)
Lurie et al., 2015[5]	RCT	USA	60	33	28	66.71±13.87	69.87±14.85	65.57±12.42	Non severe ALI: Rutherford I OS = 1 (1%) HT = NR ET = NR Rutherford IIa OS = 52 (87%) HT = 24 (86%) ET = 31 (94%) Severe ALI: Rutherford IIb OS = 4 (7%) HT = 2 (7%) ET = 1 (3%) Rutherford III OS = 3 (5%) HT = 2 (7%) ET = 1 (3%)	NR	ET = 100% OS = 95% HT = 100%	ET = 5 OS = 4 HT = 4	ET = NR (CDT 2; CDTA 1) OS = 1 HT = NR
Vaidya et al., 2016[6]	R	USA	60	33	28	66.7±13.9	69.9±14.9	65.6±12.4	NA	Smoking status OS = NR HT = NR ET = NR AF OS = 4 HT = NR ET = 2 CKD OS = NR HT = NR ET = NR CVD OS = 1 HT = NR ET = NR	NR	NR	ET = NR (CDT 2; CDTA 1) OS = 1 HT = NR

short-term survival outcomes.[2,5,6]

Konstantinou et al. reported that 30-day postoperative mortality was significantly higher in patients who underwent OS and HT compared to those treated with ET ($p < 0.001$).[4] Additionally, both OS and HT exhibited higher rates of re-occlusion and access-related complications in the early post-procedural period, further contributing to the complexity of patient management during recovery. In contrast, ET with its minimally invasive nature demonstrated better outcomes in terms of early complications and procedural safety. Argyriou's study further examined both in-hospital and 30-day mortality. The reported in- hospital mortality was 8%, with no significant differences between the three groups. However, the 30-day mortality rate increased to 16%, highlighting the potential risks associated with these interventions. This study also found that ET was associated with lower morbidity and fewer in-hospital complications compared to OS and HT approaches, suggesting a safer profile for patients with significant comorbidities.[1]

These findings underscore that while all three treatment modalities can achieve comparable survival in many cases, ET may offer a distinct advantage in reducing early complications and postoperative mortality, particularly for patients at higher surgical risk. However, the choice of treatment must still consider the patient's clinical presentation, anatomical factors, and potential long-term outcomes.

DISCUSSION

The management of ALI is a critical challenge requiring urgent intervention to prevent limb loss and reduce mortality risks. Interventions of ALI have traditionally included OS options like thrombo-embolectomy, thrombo-endarterectomy, and bypass surgery, as well as primary amputation when necessary. However, advancements in ET including thrombolytic therapy with catheter-directed thrombolysis (CDT), percutaneous transluminal angioplasty (PTA) and/or stent, or stent alone, the field has been a shift away from OS towards less invasive methods.[13]

Randomized trials in the 1990s, such as the STILE trial, demonstrated that ET could achieve similar outcomes to OS and often allowed patients to avoid surgical intervention altogether.[14] ET provided benefits, including rapid clot removal, faster blood flow restoration, and reduced bleeding risks. Although a study by Davis et al.m found that both OS and HT showed a significantly greater need for blood transfusions compared to ET.[2] Previous studies have indicated that ET for ALI is associated with higher rates of bleeding and transfusion requirement.[15-17] Age also influenced the decision making of the procedure choices. In the older population, ET avoided due to increased risks associated with thrombolytic therapy. In line with these advancements, HT combining generally OS (e.g. thrombo-embolectomy) with ET (e.g. balloon dilation or stenting) have gained traction, especially when pre-existing vessel lesions complicate treatment and have been shown to improve outcomes in complex cases. Hybrid procedure has been documented since the mid-1990s.[18] Over time, HT has become more popular as vascular surgeons have gained more experience with ET. The hybrid procedure aimed to reduce invasiveness in helping high-risk patients while ensuring adequate revascularization. For multi-level disease, HT helped to prevent complications like vessel dissection, though outcomes remain like OS alone.[1] The European Society for Vascular Surgery (ESVS) 2020 guidelines recommend performing HT in angiographically equipped operating rooms, highlighting the growing importance of these multimodal strategies. Hybrid treatment (HT) has proven especially useful in cases where OS alone is insufficient.[19]

The Thrombolysis or Peripheral Arterial Surgery (TOPAS) trial, which included 544 patients with ALI, showed that no significant differences were found in AFS rates between ET and OS. At 6 months follow-up, the rates were 71.8% for ET vs 74.8% for OS (P=0.43), and at 12 months, the rates were 65.0% vs 69.9% (P=0.23).[16] Other studies also found no significant difference in AFS outcomes over 12 months between ET and those receiving HT.[1,5,9] These showed that both treatment strategies yield comparable outcomes in terms of AFS over the 12 months. However, a study conducted by Ouriel et al. showed a 12-month AFS rate of 75% for the ET group compared to 52% for the OS group, and had a risk of limb loss or death respectively 25% and 48%.[15] Other studies also reported higher AFS rates at one year with ET compared to OS and HT.[4,8,17] Age and smoking status have been consistent predictors of AFS in ALI, with older age >65 years and smoking history associated with poorer outcomes across studies.[17,20,21] Patients with atrial fibrillation (AF) and end-stage kidney disease (ESKD) or those undergoing hemodialysis (HD) also show poorer AFS outcomes.[22-24] However, cerebrovascular disease (CVD) was not significant as a predictor of risk in AFS or any outcomes.[1,2,4]

The treatment of ALI is complex, with reintervention needs and mortality rates varying significantly between different therapeutic options. Reintervention was noted to be most frequent following ET, reflecting the need for repeat procedures such as re-ballooning or additional stenting to maintain vessel patency, especially in patients with complex or multilevel occlusions. This aligns with prior studies suggesting that ET, while minimally invasive, carries a higher risk of restenosis, thrombosis, or reocclusion, especially in cases involving complex anatomy or multilevel disease.[9] In contrast, HT demonstrated intermediate reintervention rates, likely due to the combination of surgical and endovascular approaches, which may introduce both catheter-related and surgical wound complications.[12] Although OS interventions showed the lowest reintervention rates, suggesting greater durability, the invasiveness of these procedures limits their use in patients with significant comorbidities, as previously reported.[1]

Mortality outcomes further highlight the complexity of treatment decisions. Most studies suggest that all approaches offer comparable short-term survival.[2,5,6] However, Konstantinou et al., found that both OS and HT were associated with significantly higher postoperative mortality compared to ET, indicating that ET may offer a safer profile for patients with multiple comorbidities or advanced age.[4] This reflects the advantages of the minimally invasive nature of ET, which

reduces perioperative risks and allows for faster recovery. Conversely, OS and HT are more frequently used for patients with more severe ischemia, such as Rutherford class IIb and III, where the need for immediate revascularization outweighs the higher risks of complications. These findings support the notion that while OS offers durable outcomes, it may not be the optimal choice for high-risk or elderly patients.[3]

The variability in outcomes across treatment strategies is consistent with earlier studies. For example, the STILE and TOPAS trials highlighted that both OS and thrombolysis (as part of ET) can achieve comparable AFS. Still, ET offers a safer profile for patients at higher surgical risk.[14-16] Over the years, advancements in catheter-directed thrombolysis (CDT) and mechanical thrombectomy have further improved the safety and efficacy of ET.[19] However, the increased reintervention rates observed with ET emphasize the need for careful patient selection and closer post-procedural monitoring to detect early signs of restenosis or thrombosis. In addition, HT has become an attractive option for complex cases where angiographic assessment reveals underlying lesions that require both surgical and endovascular intervention. Despite its comprehensive approach, the dual nature of HT also introduces higher risks, which can complicate recovery.[12] The data suggest that HT can be particularly valuable for managing anatomically challenging cases, though it requires standardized protocols to reduce complications. Future advancements in hybrid techniques may further enhance outcomes for these difficult-to-treat patients. This review has several notable limitations that warrant consideration. The primary constraint is the small number of included studies (n=6) and their predominantly retrospective, observational design, which introduces inherent selection biases and limits causal inference. Significant heterogeneity existed across studies in patient populations, ALI severity classification (inconsistent Rutherford grading), and outcome definitions, preventing meta-analysis. Geographic representation was limited to high-income countries (Europe, USA, Japan), reducing generalizability to resource-limited settings. Additionally, long-term outcomes beyond 12 months were inconsistently reported, and detailed comorbidity data (e.g., smoking status, renal function) were often incomplete, potentially confounding outcome comparisons. The absence of standardized protocols for hybrid interventions further complicates direct comparisons of complication rates.

CONCLUSION

Tailored treatment selection is crucial in acute limb ischemia (ALI). Open surgery (OS) should be reserved for cases where less invasive options are unsuitable, given its higher risks in elderly or frail patients. Endovascular treatment (ET) offers a minimally invasive approach with quicker recovery and lower perioperative risk, though it is associated with higher reintervention rates. Hybrid treatment (HT) is valuable for complex cases but requires careful management due to increased complication risks from combining surgical and endovascular techniques. Future prospective studies comparing long-term outcomes of OS, ET, and HT are needed to refine treatment algorithms and improve patient-centered care, especially considering the impact of comorbidities on outcome

ETHICAL APPROVAL

Institutional review board approval was not required for this systematic review.

FUNDING

This study was conducted without any financial help or support from the public, commercial, or non-profit organizations.

CONFLICT OF INTEREST

No potential conflicts of interest relevant to this study were reported

AUTHOR CONTRIBUTIONS

R.D.P.W and J.J. were responsible for the study concept, literature review, and supervision of the manuscript. R.D.P.W and N.T.A. carried out the research. P.O. N.A.H. performed data analysis contributed as the primary manuscript drafter. R.D.P.W and N.T.A. served as guarantors of the study, having full access to all data and assuming responsibility for the integrity and accuracy of the data presented.

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