

# A Retrospective Analysis of the Investigative Practices of Acute Limb Ischaemia Presenting with an Unknown Etiology

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## Introduction

Acute limb ischaemia (ALI) is a critical limb and life-threatening condition that requires urgent diagnosis and therapeutic intervention, including either open surgical or endovascular revascularization and is typically managed by the vascular surgeon. It is defined as a sudden decrease in limb perfusion secondary to arterial occlusion that compromises limb viability with clinical presentation occurring within 2 weeks of symptom. Most patients with ALI have a known precipitant at the time of clinical presentation, which includes those with progression of their peripheral arterial disease (PAD) and presumed cardiac embolism due to a known history of atrial fibrillation (AF). However, there are a minority of cases in which a precipitant is not clearly identifiable at time of initial presentation ('unexplained ALI'), and further evaluation to elucidate an underlying cause is warranted to guide treatment and prevent recurrence. If no precipitant is established despite thorough investigation, a diagnosis of cryptogenic ALI is made.

## Research objectives

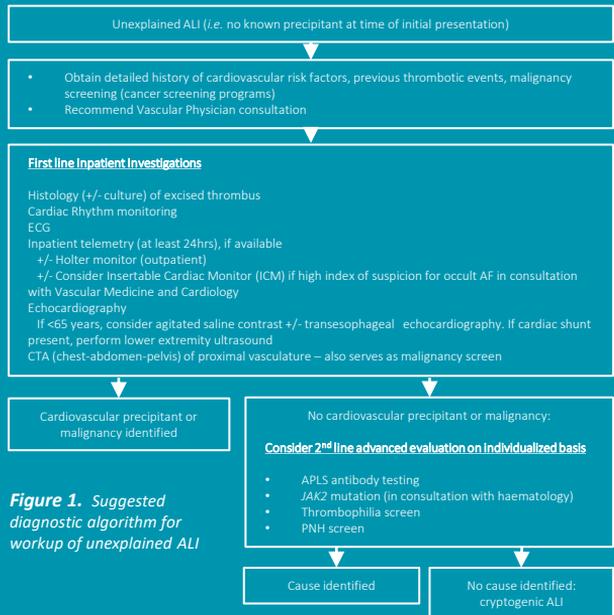
Presently, there are no consensus recommendations to guide clinicians in a systematic manner to investigate for the underlying aetiology of unexplained ALI. Given this ambiguity, we sought to retrospectively describe the current investigative practices at our centre and proceeded to develop a systematic diagnostic algorithm for the workup of 'unexplained ALI'.

## Methods

ALI cases presenting to a tertiary referral centre over a 3-year period were reviewed, and known aetiologies, and investigations undertaken to determine the underlying aetiology of unexplained ALI were obtained.

## Results

In total, 222 patients with confirmed ALI were included in the analysis, with a mean age of 66 years and of whom 69% were male. A total of 27 patients with unexplained ALI (12%) were identified, 21 of whom were found to have an underlying precipitant for ALI after further investigation, whilst 6 cases were cryptogenic. Individuals with unexplained ALI were significantly



**Figure 1.** Suggested diagnostic algorithm for workup of unexplained ALI

younger than those with a known precipitant (mean 59 vs. 68 years,  $P=0.002$ ) and with a higher representation of females (51% vs. 28%,  $P<0.001$ ). Most patients with unexplained ALI had a cardioembolic source identified as the underlying cause (62%), and this included atrial fibrillation, infective endocarditis, cardiac myxoma and intra-cardiac thrombus. Other causes of unexplained ALI were detected by computed tomography (CT) imaging and included newly diagnosed significant atherosclerotic disease (19%), embolism from isolated proximal large vessel thrombus (10%) and metastatic malignancy (10%). There were no cases attributed to thrombophilias, myeloproliferative neoplasms or anti-phospholipid syndrome.

## Discussion

This study evaluated the investigations performed to identify an underlying precipitant in those with unexplained ALI.

We demonstrate that the proportion of cryptogenic ALI is significant in those with unexplained ALI (22%) despite extensive investigations. Secondly, the most common precipitants of unexplained ALI were of cardiac origin (62%) including AF-related thromboembolism, vegetation, cardiac myxoma and thrombus secondary to RWMA, highlighting the importance of comprehensive cardiac evaluation. We suggest consideration of an integrative diagnostic algorithm for the investigation of unexplained ALI (Figure 1).

## Conclusion

Among patients with unexplained ALI, the majority had a cardioembolic source highlighting the importance of comprehensive cardiac investigations. A subset of patients had alternative causes identified on CT imaging. These data support the use of a collaborative and integrative diagnostic algorithm in the evaluation of unexplained ALI.

