ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΕΣΣΑΛΙΑΣ
ΤΜΗΜΑ ΙΑΤΡΙΚΗΣ
ΠΜΣ «Μεθοδολογία Βιοϊατρικής Έρευνας, Βιοστατιστική και Κλινική Βιοπληροφορική»

ΜΕΤΑΠΤΥΧΙΑΚΗ ΔΙΠΛΩΜΑΤΙΚΗ ΕΡΓΑΣΙΑ

«Η Ταξινόμηση GLASS στην χρόνια απειλητική για το σκέλος ισχαιμία»

«GLASS classification in Chronic limb threatening ischemia»

Τριμελής Συμβουλευτική Επιτροπή:

Μπατσίδης Απόστολος : *Επίκ. Καθηγητής Τμήματος Μαθηματικών, Πανεπιστήμιο Ιωαννίνων.*

Στεφανίδης Ιωάννης: *Καθηγητής Παθολογίας-Νεφρολογίας*

Τμήμα Ιατρικής, Πανεπιστήμιο Θεσσαλίας.

Δοξάνη Χρυσούλα: *Ακαδημαϊκός Υπότροφος στην Ιατρική Βιομετρία, Πανεπιστήμιο Θεσσαλίας.*

Φοιτητής: ΜΠΟΝΤΙΝΗΣ ΒΑΓΓΕΛΗΣ

ΛΑΡΙΣΑ 2021

"Αφιερώνω αυτήν την εργασία στην αγαπημένη μου σύντροφο Χριστίνα.

Χωρίς την στήριξή σου, τίποτα δεν θα ήταν εφικτό.

Σε ευχαριστώ."

Table of Contents

Περίληψη

Εισαγωγή: Η περιφερική αρτηριακή νόσος (ΠΑΝ) αποτελεί κύρια αιτία θνησιμότητας και νοσηρότητας παγκοσμίως. Το τελευταίο στάδιο της (ΠΑΝ) είναι η χρόνια απειλητική για το σκέλος ισχαιμία (ΧΑΣΙ). Το 2019, η Global Vascular Guidelines Committee εισήγαγε ένα νέο σύστημα ταξινόμησης για την ΧΑΣΙ, σε μια προσπάθεια να βοηθήσει την καθημερινή κλινική πρακτική. Το Global Anatomic Staging System (GLASS) είναι ένα σύστημα ανατομικής σταδιοποίησης της νόσου, βασισμένο σε αγγειογραφικά στοιχεία.

Στόχοι: Αξιολόγηση της εφαρμογής και της προγνωστικής αξίας του Global Anatomic Staging System (GLASS) για ασθενείς με ΧΑΣΙ.

Μέθοδοι: Πραγματοποιήσαμε μια συστηματική ανασκόπηση για άρθρα που δημοσιεύτηκαν από τον Ιούνιο του 2019 έως τον Σεπτέμβριο του 2021 σχετικά με μελέτες που ως αντικείμενο είχαν την αξιολόγηση της ταξινόμησης GLASS σε σχέση με μετεγχειρητικά κλινικά αποτελέσματα. Μελέτες που δεν ανέφεραν κλινικά αποτελέσματα με βάση την ταξινόμηση GLASS αποκλείστηκαν. Τα κύρια καταληκτικά σημεία περιελάμβαναν την άμεση τεχνική αποτυχία (ITF) και βατότητα του άκρου ένα έτος μετά την επέμβαση (LBP). Τα δεδομένα συγκεντρώθηκαν και μετα-αναλύθηκαν με την χρήση του προγράμματος R

Αποτελέσματα: Το ITF για τα στάδια GLASS I είναι 5% (95% CI: 3-10), GLASS II 7% (95% CI: 4-12) και GLASS III 27% (95% CI: 15-43). Ο λόγος πιθανοτήτων (OR) και ο σχετικός κίνδυνος (RR) για την ITF στην σύγκριση του GLASS I έναντι του GLASS II δεν είναι στατιστικά σημαντικά (OR, 0.79; 95% CI: 0.43-1.46), (RR, 0.81; 95% CI: 0.46-1.42) Τα OR και RR στην σύγκριση του GLASS II και το GLASS III είναι και τα δύο στατιστικά σημαντικά (OR, 0.26; 95% CI: 0.11-0.59), (RR, 0.26; 95% CI: 0.11-0.59).

Όσον αφορά το στάδιο GLASS III, το συγκεντρωτικό LBP είναι 37% (95% CI: 12-71).Τα OR και RR για τα στάδια GLASS I και GLASS II έναντι του σταδίου GLASS III δεν είναι στατιστικά σημαντικά, (OR, 0.56; 95% CI: 0.18 -1.73) (I2 = 82%, ρ <0.01) (RR, 0.81; 95%CI: 0.56-1.19) (I2 = 67%, ρ = 0.05).

Συμπέρασμα: Όσον αφορά το ITF, η ταξινόμηση GLASS προέβλεψε σωστά τα αποτελέσματα της τεχνικής επιτυχίας/αποτυχίας. Σχετικά με LBP στο ένα έτος μετά την παρέμβαση, η ταξινόμηση GLASS προέβλεψε σωστά τα αποτελέσματα του σταδίου GLASS III, ενώ απέτυχε να παράγει στατιστικά σημαντικά αποτελέσματα σχετικά με συγκρίσεις μεταξύ σταδίων.

Λέξεις κλειδιά: Παγκόσμιες κατευθυντήριες οδηγίες για τις αγγειακές παθήσεις, Περιφερική αρτηριακή νόσος, Χρόνια απειλητική για το σκέλος ισχαιμία

Abstract

Introduction: Peripheral arterial disease is a leading cause of mortality and morbidity worldwide. The end-stage of PAD is chronic limb-threatening ischemia (CLTI). In 2019, the Global Vascular Guidelines committee introduced a new classification system for CLTI to aid everyday clinical practice. The Global Anatomic Staging System (GLASS) is an anatomic staging system based on angiographic evidence.

Objectives: To assess the applicability and prognostic value of the global anatomical staging system (GLASS) for patients with critical limb threatening ischemia (CLI)

Methods: We conducted systematic review for articles published from June 2019 up to September 2021 regarding studies, assessing association of GLASS classification and clinical outcomes. Studies that did not report on clinical outcomes based on GLASS classification were excluded. Effect estimates, Odds ratios (OR) and Relative Risks (RR) were pooled for individual studies and were consequently meta-analyzed. Primary endpoints included immediate technical failure (ITF) and limb-based patency (LBP).

Results: Pooled ITF rate for GLASS I stage is 5% (95% CI: 3-10), GLASS II 7% (95% CI: 4-12) and GLASS III 27% (95% CI: 15-43). The OR and RR for ITF comparing GLASS I versus GLASS II are non-significant (OR, 0.79; 95% CI: 0.43-1.46), (RR, 0.81; 95% CI: 0.46-1.42) The OR and RR for ITF comparing GLASS II and GLASS III are both statistically significant (OR, 0.26; 95% CI: 0.11-0.59), (RR, 0.26; 95% CI: 0.11-0.59).

Regarding GLASS III stage, the pooled LBP is 37% (95% CI: 12-71) The OR and RR for LBP GLASS I plus GLASS II stages versus GLASS III stage are non significant, (OR, 0.56; 95% CI: 0.18-1.73) (I^2=82%, $p<0.01$) (RR, 0.81; 95% CI: 0.56-1.19) (I^2=67%, $p=0.05$).

Conclusion: Regarding immediate technical failure, GLASS classification correctly predicted technical success/failure outcomes. Regarding limb-based patency one-year post-intervention, GLASS classification correctly predicted GLASS III stage outcomes, while it failed to produce statistically significant outcomes regarding inter-stage comparisons.

Keywords: Global Vascular Guidelines, Peripheral arterial disease, Chronic limb-threatening ischemia

Introduction

Peripheral arterial disease is a leading cause of mortality and morbidity worldwide[1]. Despite its high prevalence, a large proportion of patients remain asymptomatic or present with an atypical set of symptoms and subsequently remain undiagnosed and untreated.

The end-stage of PAD is chronic limb-threatening ischemia (CLTI). Approximately 50% of patients presenting with CLTI are newly diagnosed. The clinical presentation of CLTI includes a variety of acute symptoms, such as rest pain and tissue loss. Prognosis for patients presenting at such a late stage of the disease is rather poor. Mortality rates one year after the initial diagnosis are about 25% with amputation rates being similarly high while survival rates for the amputees are as low as 55% [2, 3].

Options regarding CLTI include endovascular surgery, bypass surgery, nonintervention treatment, such as medical therapy or primary amputation. The decision about the management is multifactorial, including factors such as the patient's status, the severity and stage of the disease.

In 2019 the Global Vascular Guidelines committee proposed a three-stage approach in order to aid to the appropriate and effective revascularization strategy for patients with CLTI. The approach abbreviated as (PAN), which has as a main goal to simplify and elucidate every-day clinical practice includes patient risk estimation, limb staging and anatomic pattern of disease.

Anatomic classification of CLTI is a rather challenging task because of the diffuse nature of the disease. Previously described, anatomic scoring systems are confined to portraying the location and severity of the disease while they fail to incorporate the multilevel characteristics of the lesions [4, 5].

The Global Anatomic Staging System (GLASS) introduced by the GSV is an anatomic staging system based on angiographic evidence. It incorporates the novel concepts of Target Artery Path (TAP), Limb Based Patency (LPB) and Immediate Technical Failure (ITF).

The strategy behind the application of GLASS involves initially the identification of a TAP (usually the least diseased crural arterial path). Separate grading of the suprapopopliteal (SP) infrapopliteal (IP) and inframalleolar (IM) disease using a grading system from zero to four (0 – 4) for the two and P0 to P2 for the latter follows. Finally, combination of SP, IP and IM grades while simultaneously taking into account the vascular calcification burden produces the overall GLASS stages ranging from one to three (I -III).

Besides, everyday clinical practice, GLASS classification reflects the likelihood of ITF and LBP at 1 year after endovascular intervention. Stage I disease is expected to have ITF < 10% and LBP > 70%. Stage II, ITF < 20% and LBP 50% to 70% and stage III, ITF > 20% or 1-year LBP < 50%[6].

The aim of this study is to evaluate the applicability and prognostic value of GLASS classification system in CLTI.

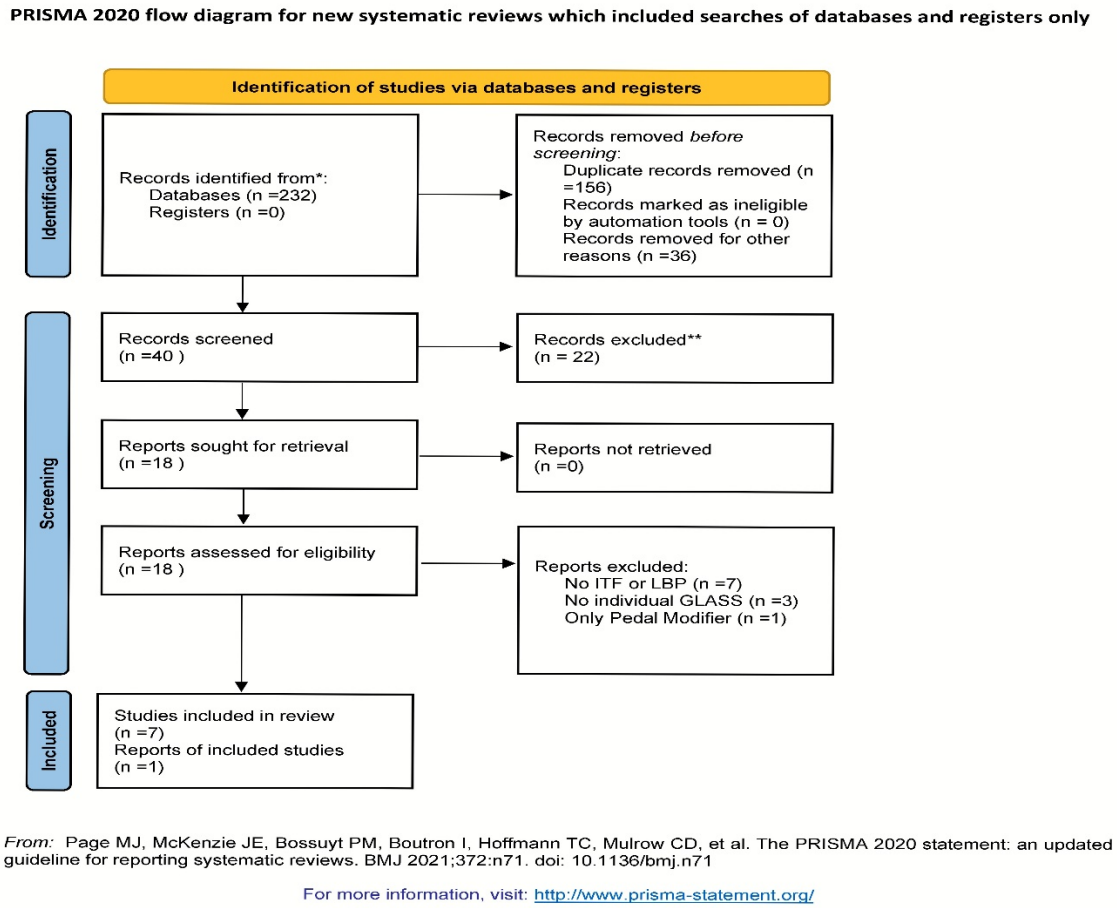
Methods

Information sources and search strategy

We conducted a systematic review according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (**Figure 1)** [7]. Two independent researchers V.B and A.B conducted a systematic electronic search on Medline, Scopus, EMBASE, and Cochrane Library for articles published from June 2019 up to September 2021. Controlled vocabulary supplemented with keywords was employed. The terms and term

combinations for conducting this research included: “GLASS”, Global Limb Anatomic Staging System”, “CLTI” and “Chronic limb-threatening ischemia”. There were no language limitations.

Figure 1 Prisma Flow Chart



Selection process and Data collection process

The method behind of data collection involved two independent researchers reviewing the titles and abstracts of the retrieved literature. Publications in which their titles and abstracts met the inclusion criteria were collected in full, analyzed, and processed using the same terms by both researchers, while the rest of the publication were excluded from the analysis. When disagreement emerged, a consensus was achieved through consultation with a third researcher.

Eligibility criteria

Inclusion criteria

1. Studies that reported on the evaluation of GLASS classification system on either LBP or ITF were included.

Exclusion criteria

1. Studies that reported on LBP and/or ITF without specifying the results distinctively for different GLASS stages were excluded.
2. Studies that did not provide neither raw data nor Kaplan Meier curves with designated patients at risk information for a given time interval on LBP and ITF were also excluded.

Data items

Primary end-points include LBP and ITF. LBP is defined as the preservation of a patent TAP all along the arterial axis. ITF is defined as the inability to cross the targeted lesion or provide in-line flow to the TAP.

Effect measures and synthesis methods

Where raw data were not provided, individual patient data (IPD) were obtained using the technique previously described by Guyot et al.[8]. We calculated the pooled effect estimates as the back transformation of the weighted mean of the transformed proportions, using the logit transformation and the DerSimonian-Laird weights of random effects model (REM) by employing the “metaprop” function. Log odds ratios (OR) and Log relative risks (RR) were generated using the inverse

variance method and the default continuity correction of 0.5 in studies where zero frequencies appeared. For this purpose, the "metabin" function was employed. A formal statistical test for heterogeneity using the I^2 test was performed. Publication bias was not assessed due to the small number of the included studies. For the statistical analysis, we used RStudio (R Foundation for Statistical Computing, Vienna, Austria, v 4.1.0).

Results

Baseline study characteristics

Seven studies with 1447 patients (approximately 850 male patients) were included in the metanalysis[9-15]. All studies included were retrospective cohort studies.

Five out of the seven studies, including 1268 patients, reported on ITF data[9, 11-14]. Three out of seven studies, including 287 patients, reported on LBP at one year data[10, 11, 15].

Meta-analysis of eligible studies

Immediate technical failure

Immediate technical failure was reported by five out of seven studies. The pooled ITF rates for GLASS I stage is 5% (95% CI: 3-10) (I^2=52%, p=0.08) (**Figure 2),** GLASS II 7% (95% CI: 4-12) (I^2=48%, p=0.10) (**Figure 3),** and GLASS III 27% (95% CI: 15-43) (I^2=91%, p<0.01) (**Figure 4)**.

The OR and RR for ITF comparing GLASS I versus GLASS II was non significant (OR, 0.79; 95% CI: 0.43-1.46) (I^2=0%, p=0.91) (**Figure 5)**, (RR, 0.81; 95% CI: 0.46-1.42) (I^2=0%, p=0.91) (**Figure 6)**. The OR and RR for ITF comparing GLASS II versus GLASS III were both statistically

significant (OR, 0.26; 95% CI: 0.11-0.59) (**Figure 7)** (I^2=74%, p<0.01), (RR, 0.26; 95% CI: 0.11-0.59) (I^2=66%, p=0.02) (**Figure 8)**.

Figure 2. Forest plot of ITF GLASS I

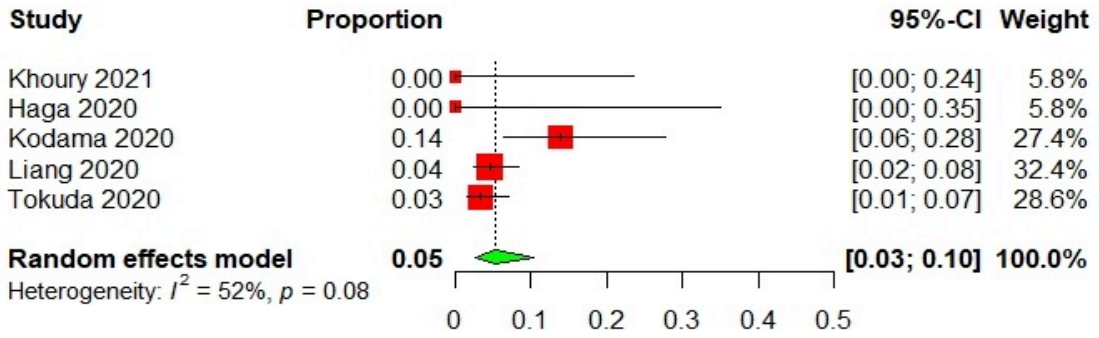


Figure 3. Forest plot of ITF GLASS II

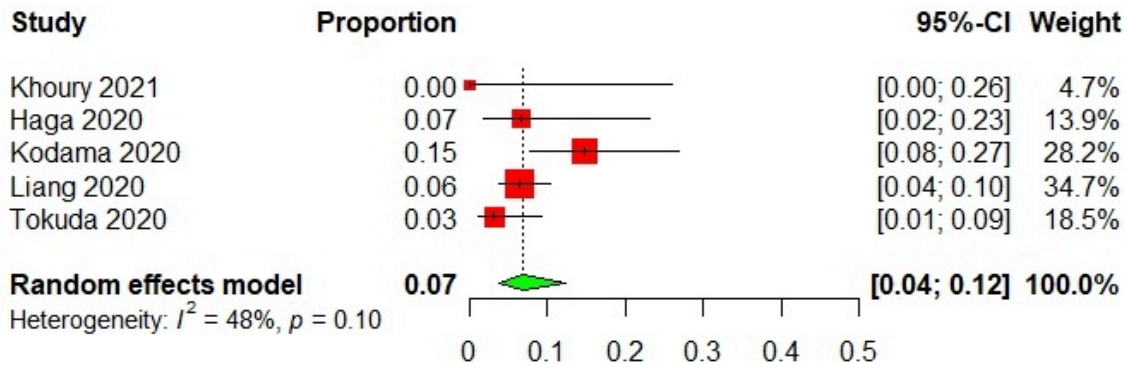


Figure 4. Forest plot of ITF GLASS III

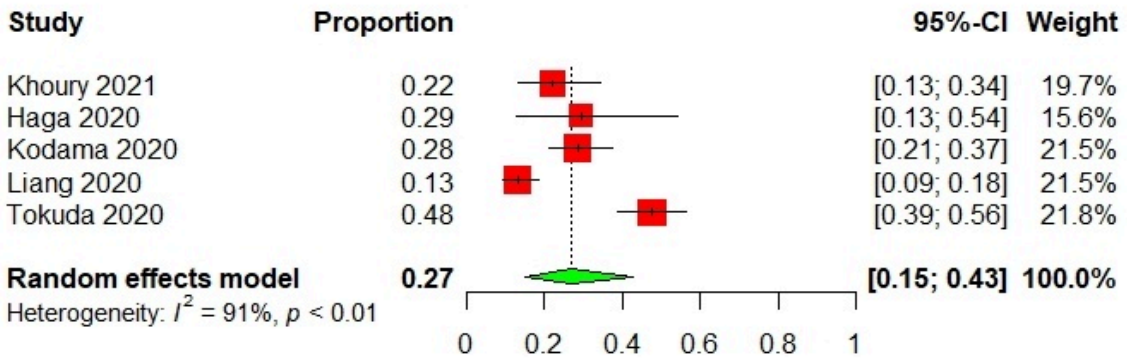


Figure 5. Forest plot of ITF GLASS I vs. GLASS II (OR)

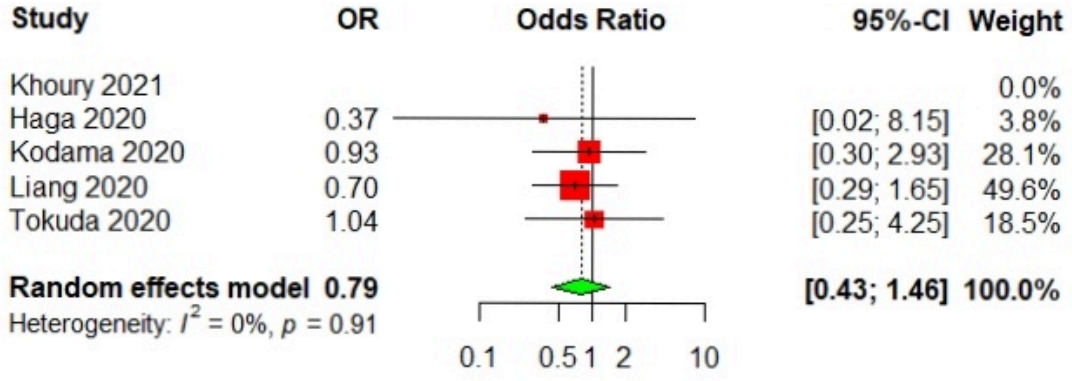


Figure 6. Forest plot of ITF GLASS I vs. GLASS II (RR)

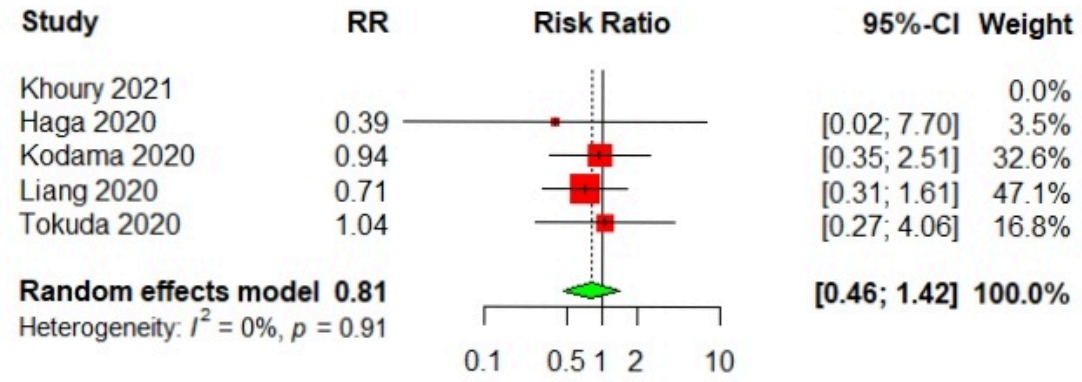


Figure 7. Forest plot of ITF GLASS II vs. GLASS III (OR)

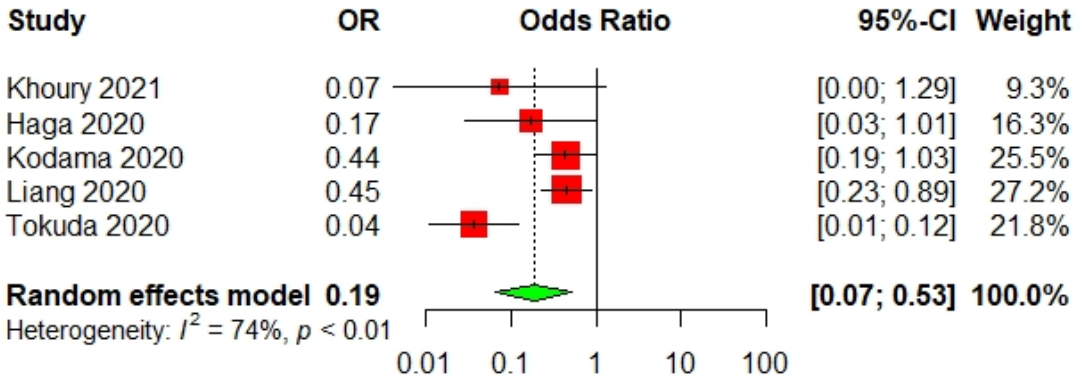
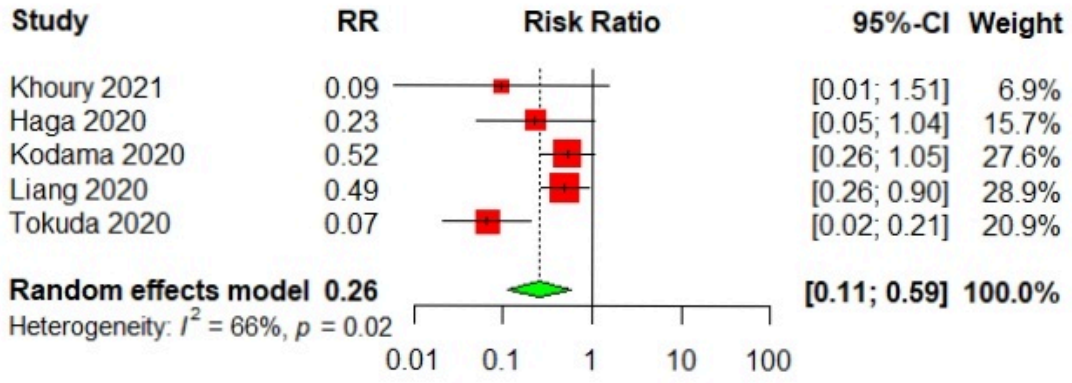


Figure 8. Forest plot of ITF GLASS II vs. GLASS III (RR)



Limb based patency

Limb based patency was reported by three out of the seven included studies. One study reported a composite endpoint (GLASS I plus GLASS II) so we proceeded into pooling the data solely regarding GLASS III stage[11]. The pooled LBP rates at one year post intervention for the composite endpoint of GLASS I plus GLASS II stages is 37% (95% CI: 12-71) (I^2=93%, p<0.01) **(Figure 9)**.

The OR and RR for LBP comparing the composite endpoint of GLASS I plus GLASS II stages versus GLASS III stage were non-significant, (OR, 0.56; 95% CI: 0.18-1.73) (I^2=82%, p<0.01) (**Figure 10)**, (RR, 0.81; 95% CI: 0.56-1.19) (I^2=67%, p=0.05) (**Figure 11)**

Figure 9. Forest plot of LBP GLASS III

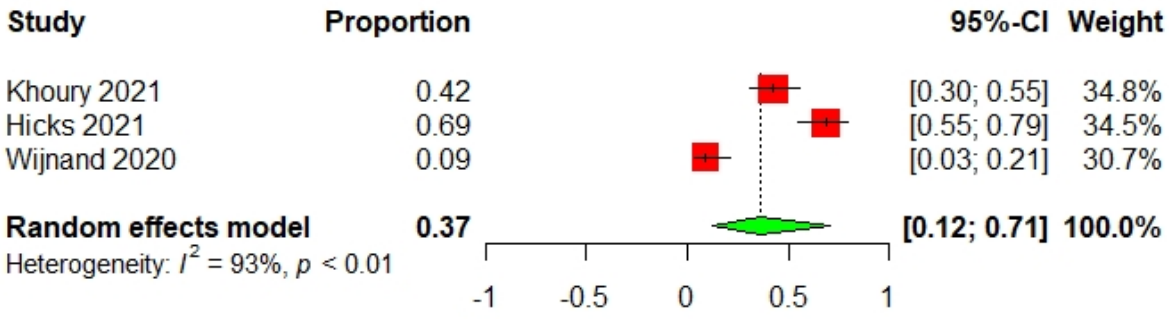


Figure 10 Forest plot of LBP GLASS I, II vs. GLASS III (OR)

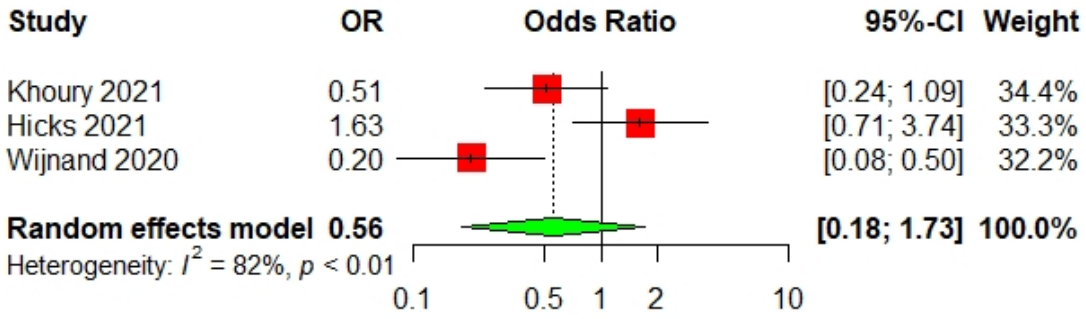
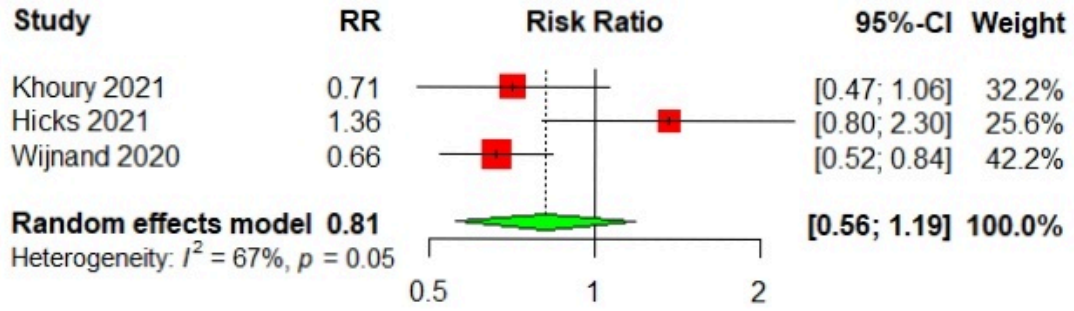


Figure 11 Forest plot of LBP GLASS I, II vs. GLASS III (RR)



Conclusions

Regarding immediate technical failure, GLASS classification correctly predicted technical success outcomes. Even though statistically significant OR and RR rates were produced exclusively when comparing GLASS II versus GLASS III stages, that is expected given the closely related GLASS I and GLASS II categories and the small number of studies included. Regarding limb-based patency one-year post-intervention, GLASS classification correctly predicted GLASS III stage outcomes while it failed to produce statistically significant outcomes regarding inter-stage comparisons.

References

1. Hirsch, A.T., M.H. Criqui, D. Treat-Jacobson, J.G. Regensteiner, M.A. Creager, J.W. Olin, et al., *Peripheral arterial disease detection, awareness, and treatment in primary care.* Jama, 2001. **286**(11): p. 1317-24.
2. Conte, M.S., A.W. Bradbury, P. Kolh, J.V. White, F. Dick, R. Fitridge, et al., *Global vascular guidelines on the management of chronic limb-threatening ischemia.* J Vasc Surg, 2019. **69**(6s): p. 3S-125S.e40.
3. Abu Dabrh, A.M., M.W. Steffen, C. Undavalli, N. Asi, Z. Wang, M.B. Elamin, et al., *The natural history of untreated severe or critical limb ischemia.* J Vasc Surg, 2015. **62**(6): p. 1642-51.e3.
4. Dormandy, J.A. ,R.B. Rutherford, *Management of peripheral arterial disease (PAD). TASC Working Group. TransAtlantic Inter-Society Consensus (TASC).* J Vasc Surg, 2000. **31**(1 Pt 2): p. S1-s296.
5. Hardman, R.L., O. Jazaeri, J. Yi, M. Smith, R. Gupta, *Overview of classification systems in peripheral artery disease.* Semin Intervent Radiol, 2014. **31**(4): p. 378-88.
6. Patel, M.R., M.S. Conte, D.E. Cutlip, N. Dib, P. Geraghty, W. Gray, et al., *Evaluation and treatment of patients with lower extremity peripheral artery disease: consensus definitions from Peripheral Academic Research Consortium (PARC).* J Am Coll Cardiol, 2015. **65**(9): p. 931-41.
7. Page, M.J., J.E. McKenzie, P.M. Bossuyt, I. Boutron, T.C. Hoffmann, C.D. Mulrow, et al., *The PRISMA 2020 statement: an updated guideline for reporting systematic reviews.* Bmj, 2021. **372**: p. n71.
8. Guyot, P., A.E. Ades, M.J.N.M. Ouwens, N.J. Welton, *Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves.* BMC Medical Research Methodology, 2012. **12**(1): p. 9.
9. Haga, M., S. Shindo, S. Motohashi, A. Nishiyama, M. Kimura, H. Inoue, et al., *Early evaluation of the infrainguinal revascularization strategy selection tool of the Global Vascular Guidelines for chronic limb-threatening ischemia patients.* J Vasc Surg, 2021.
10. Hicks, C.W., G.Q. Zhang, J.K. Canner, M.L. Weaver, Y.W. Lum, J.H. Black, et al., *The Global Anatomic Staging System Does Not Predict Limb Based Patency of Tibial Endovascular Interventions.* Ann Vasc Surg, 2021. **75**: p. 79-85.
11. El Khoury, R., B. Wu, C.T. Edwards, E.M. Lancaster, J.S. Hiramoto, S.M. Vartanian, et al., *The Global Limb Anatomic Staging System is associated with outcomes of infrainguinal revascularization in chronic limb threatening ischemia.* J Vasc Surg, 2021. **73**(6): p. 2009-2020.e4.
12. Kodama, A., L. Meecham, M. Popplewell, G. Bate, M.S. Conte, A.W. Bradbury, *Editor's Choice - Relationship Between Global Limb Anatomic Staging System (GLASS) and Clinical Outcomes Following Revascularisation for Chronic Limb Threatening Ischaemia in the Bypass Versus Angioplasty in Severe Ischaemia of the Leg (BASIL)-1 Trial.* Eur J Vasc Endovasc Surg, 2020. **60**(5): p. 687-695.
13. Liang, P., C.L. Marcaccio, J.D. Darling, D. Kong, V. Rao, E. St John, et al., *Validation of the Global Limb Anatomic Staging System in first-time lower extremity revascularization.* J Vasc Surg, 2021. **73**(5): p. 1683-1691.e1.
14. Tokuda, T., Y. Oba, R. Koshida, Y. Suzuki, A. Murata, T. Ito, *Prediction of the Technical Success of Endovascular Therapy in Patients with Critical Limb Threatening Ischaemia*

Using the Global Limb Anatomical Staging System. Eur J Vasc Endovasc Surg, 2020. **60**(5): p. 696-702.

15. Wijnand, J., D. Zarkowsky, T. Sorrentino, B. Wu, Z. Pallister, J. Chung, et al., *The New Global Limb Anatomic Staging System (GLASS) for CLTI: Assessment of its Utility in Two Limb Preservation Centers.* European Journal of Vascular and Endovascular Surgery, 2019. **58**(6): p. e577.