Peripheral Artery Disease Diagnostics: Systematic Review with ☸SAIMSARA.

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Abstract: This paper aims to systematically review and synthesize the diverse diagnostic methodologies for peripheral artery disease, as presented in recent academic literature, to identify current trends, highlight promising innovations, and delineate critical gaps for future research. The review utilises 173 studies with 546493 total participants (naïve ΣN). For peripheral artery disease diagnosis, the ankle-brachial index (ABI) demonstrated a median sensitivity of 76.5% (range: 56.5%–95.2%) and a median specificity of 84.3% (range: 68.8%–100%) across various studies. While ABI remains a cornerstone, its generalizability is impacted by the heterogeneity of study populations and comparators. The significant variability in study designs and patient cohorts across the literature most affects certainty. Clinicians should consider combining ABI with other diagnostic modalities or novel biomarkers, especially in high-risk groups or when ABI results are inconclusive, to improve diagnostic accuracy.

Keywords: json; [; Peripheral Artery Disease; Biomarkers; Ankle-Brachial

Review Stats

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- Source: Semantic Scholar
- Scope: All fields
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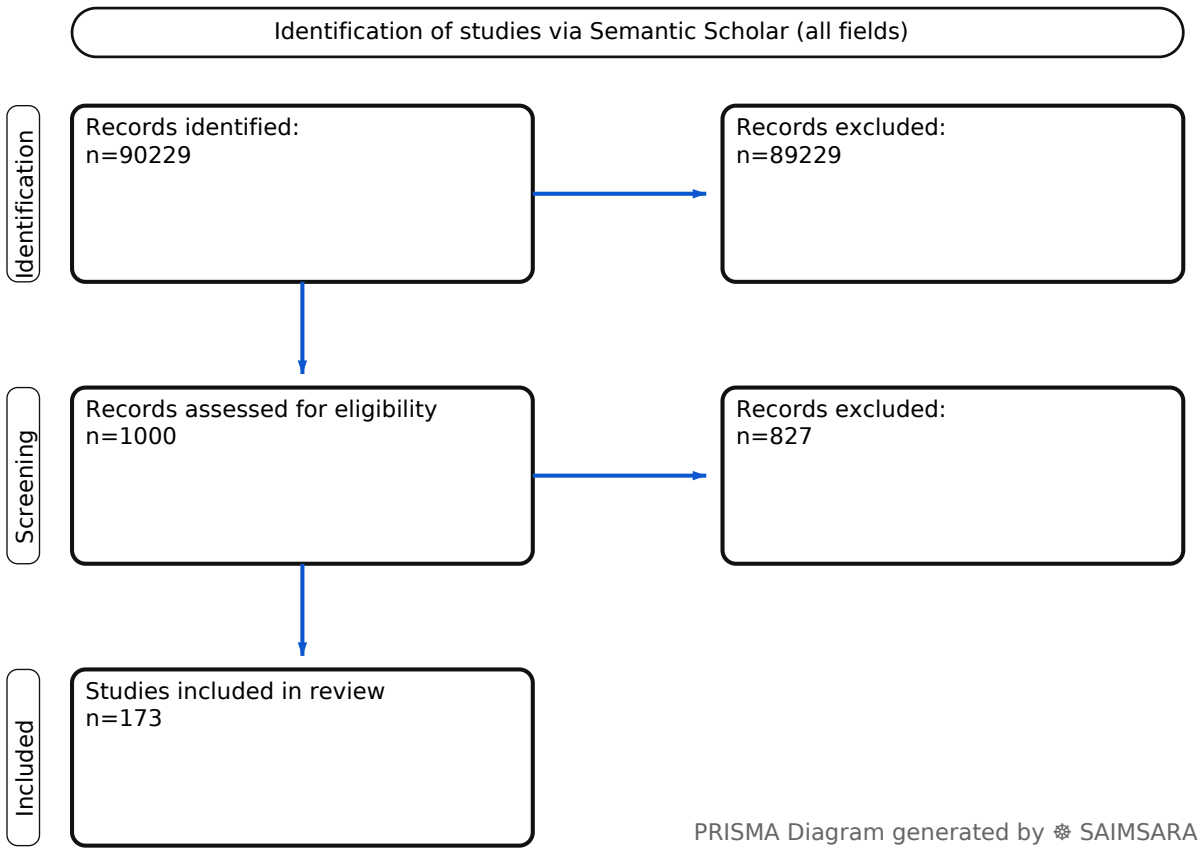
- Included original Abstracts/Papers: 173
- Total study participants (naïve ΣN): 546493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Records excluded:
n=89229
Screening
Records assessed for eligibility
n=1000
Records excluded:
n=827
Included
Studies included in review
n=173
PRISMA Diagram generated by ☸ SAIMSARA


△OSMA Triangle
Effect-of Predictor → Outcome
peripheral artery disease diagnostics → Outcome
0
Harmful for patients ΣN=341604 (63%)
Beneficial for patients ΣN=14839 (3%)
Neutral ΣN=190050 (35%)
△OSMA Triangle generated by ☸SAIMSARA

Outcome-Sentiment Meta-Analysis (OSMA): *(LLM-only)*
Frame: Effect-of Predictor → Outcome • *Source*: Semantic Scholar
Outcome: Outcome Typical timepoints: 2-y, 30-day. Reported metrics: %, CI, p.
Common endpoints: Common endpoints: complications, mortality, functional.
Predictor: peripheral artery disease diagnostics — exposure/predictor. Doses/units seen: 0.675 mg, 1.2 mg. Typical comparator: the reference group, pad-only, using either test alone, angiography for diagnosing pad….

- **1) Beneficial for patients** — Outcome with peripheral artery disease diagnostics — [1], [2], [4], [5], [6], [7], [8], [9], [11], [18], [19], [20], [24], [25], [64], [89], [117], [118], [120], [122], [125] — ΣN=14839
- **2) Harmful for patients** — Outcome with peripheral artery disease diagnostics — [15], [16], [17], [33], [54], [57], [59], [61], [67], [82], [93], [95], [108], [109], [115], [121], [127], [132], [142], [157], [160], [163], [165], [170], [173] — ΣN=341604
- **3) No clear effect** — Outcome with peripheral artery disease diagnostics — [3], [10], [12], [13], [14], [21], [22], [23], [26], [27], [28], [29], [30], [31], [32], [34], [35], [36], [37], [38], [39], [40], [41], [42], [43], [44], [45], [46], [47], [48], [49], [50], [51], [52], [53], [55], [56], [58], [60], [62], [63], [65], [66], [68], [69], [70], [71], [72], [73], [74], [75], [76], [77], [78], [79], [80], [81], [83], [84], [85], [86], [87], [88], [90], [91], [92], [94], [96], [97], [98], [99], [100], [101], [102], [103], [104], [105], [106], [107], [110], [111], [112], [113], [114], [116], [119], [123], [124], [126], [128], [129], [130], [131], [133], [134], [135], [136], [137], [138], [139], [140], [141], [143], [144], [145], [146], [147], [148], [149], [150], [151], [152], [153], [154], [155], [156], [158], [159], [161], [162], [164], [166], [167], [168], [169], [171], [172] — ΣN=190050

1) Introduction

Peripheral artery disease (PAD) represents a significant global health burden, characterized by atherosclerotic stenosis or occlusion in arteries supplying the limbs, most commonly the lower extremities. Accurate and timely diagnosis of PAD is crucial for effective management, prevention of limb loss, and reduction of cardiovascular morbidity and mortality. Traditional diagnostic methods, such as the ankle-brachial index (ABI), face limitations in certain patient populations, particularly those with incompressible arteries due to medial arterial calcification. This necessitates the continuous exploration and validation of novel diagnostic approaches, ranging from advanced imaging techniques and innovative physiological measurements to sophisticated biomarker panels and artificial intelligence (AI)-driven models.

2) Aim

This paper aims to systematically review and synthesize the diverse diagnostic methodologies for peripheral artery disease, as presented in recent academic literature, to identify current trends, highlight promising innovations, and delineate critical gaps for future research.

3) Methods

Systematic review with multilayer AI research agent: keyword normalization, retrieval & structuring, and paper synthesis (see SAIMSARA About section for details).

- **Bias:** Qualitatively inferred from study design fields. Many studies were cohort or mixed designs, with a notable number of cross-sectional and retrospective analyses, which inherently carry risks of selection bias and confounding. Randomized controlled trials (RCTs) were less frequent, limiting the ability to establish causal relationships or robust comparative effectiveness. Sample sizes varied widely, with some studies having very small cohorts (e.g., N=2 [21], N=4 [125], N=5 [30]), impacting statistical power and generalizability. Lack of specified directionality in many studies further complicates bias assessment.

4) Results

4.1 Study characteristics

The reviewed studies predominantly employed cohort, cross-sectional, or mixed designs, with some prospective and retrospective analyses. Populations varied, including general PAD patients, those with diabetes mellitus (T2DM), critical limb ischemia (CLI), and specific conditions like abdominal aortic aneurysm (AAA) or chronic kidney disease (CKD). Follow-up periods, when specified, ranged from short-term assessments (e.g., 1 hour post-intervention [33]) to several years (e.g., 4.3 years [31], 25 years [171]).

4.2 Main numerical result aligned to the query

For peripheral artery disease diagnosis, the ankle-brachial index (ABI) demonstrated a median sensitivity of 76.5% (range: 56.5% [36]–95.2% [24]) and a median specificity of 84.3% (range: 68.8% [98]–100% [135]). These values reflect variability across studies, which utilized different comparators and patient populations, including asymptomatic individuals and those with suspected claudication.

4.3 Topic synthesis

- **Biomarker Panels and Individual Markers:** A 3-biomarker panel (CINC-1, CD95, fractalkine) achieved an AUROC of 0.85 [2] for PAD diagnosis. Neopterin was significantly higher in PAD patients [3] and, combined with fibrinogen and cystatin C, showed high

accuracy [5]. Other promising markers include urinary Cystatin C (uCystatinC) [15], urinary Fatty Acid Binding Protein 3 (uFABP3) [17, 54], remnant cholesterol (RC) (AUC 0.727) [12], asprosin [13], galectin-3 [34], VCAM-1 (AUC 0.76) [37], D-dimer (AUC 0.7034 for AAA in PAD) [16], miR-124-3p [57], plasma NAP2 (AUC 0.743) [51], and a clinical/proteomic panel (HART PAD) (AUC 0.85) [31]. Serum IL-6, IL-8, ICAM, and VCAM were also elevated in T2DM patients with PAD [45].

- **Physiological and Functional Assessments:** The foot-toe glucose index (FTGI) showed higher sensitivity than cuff/ultrasound Doppler methods [1]. Doppler ultrasonography (DUS) derived maximal systolic acceleration (ACCmax) correlated highly with stenosis ($r = -0.884$) [9]. Pulse Wave Handheld Doppler (PWHD) achieved 100% sensitivity and specificity compared to angiography [24]. Multi-site photoplethysmography (MPPG) had comparable sensitivity (79.8%) to ABPI (80.2%) [18]. Combining post-exercise ABI with exercise-transcutaneous oxygen pressure (exercise-TcPO2) improved sensitivity to 81% [20]. Gait variability parameters identified PAD with >70% accuracy [26]. Toe-brachial index (TBI) and maximal acceleration time (ATmax) of pedal arteries showed utility for lower limb perfusion and critical limb ischemia detection [48, 49].
- **Advanced Imaging Modalities:** Dual-energy computed tomography angiography (DE-CTA) with automatic plaque removal (DE-APR) combined with standard reconstruction (DE-SR) achieved 95.20% diagnostic accuracy for significant stenosis [19]. Duplex ultrasound (DUS) showed good concordance with digital subtraction angiography (DSA) and higher accuracy than CT angiography (CTA) in the infra-geniculate area [25]. Magnetic resonance angiography (MRA) is a well-established diagnostic modality [131], with non-contrast MRA being an alternative for impaired renal function [114], and 3 T FSD-MRA providing good quality images without contrast [44]. Digital Variance Angiography (DVA) allowed ~70% radiation reduction with superior image quality in the crural region [117, 125]. Multispectral optoacoustic tomography (MSOT) demonstrated impaired oxygenation in PAD patients [55]. Infrared thermography (IRT) distinguished temperature differences between feet in PAD patients [27].
- **Artificial Intelligence and Machine Learning:** A deep learning model achieved 83.4% Dice accuracy for artery segmentation and vascular calcification measurement [8]. An Artificial Intelligence PAD score (AI-PAD) differentiated stable from unstable PAD patients [7]. A body acceleration-based model achieved 92% accuracy in distinguishing PAD patients from controls using reflective marker data [6]. Machine learning also contributed to a cardiovascular disease (CVD) risk prediction model for CKD patients (AUC 0.89) [69].
- **Diabetes-Specific Diagnostics:** The atherogenic index of plasma (AIP) had good diagnostic value (AUC 0.914) for predicting diabetic foot osteomyelitis (DFO) in PAD patients [11]. Remnant cholesterol (RC) levels were independently associated with PAD severity in type 2 diabetic patients [12]. Circulating asprosin levels were higher in T2DM patients with

PAD and negatively correlated with ABI [13]. Elevated plasma miRNA-4739 levels were associated with critical limb ischemia (CLI) in T2DM patients (AUC 0.94) [121].

- **Risk Stratification and Prognosis:** Urinary Cystatin C and uFABP3 predicted worsening PAD status and major adverse limb events (MALE) [15, 17]. Serum endothelin-1 (ET-1) showed 85% sensitivity and specificity for predicting post-operative restenosis after endovascular therapy [33]. Low ABI was associated with a higher rate of recurrent vascular events in stroke/TIA patients [127]. Plasma hydrogen sulfide (H2S) levels were reduced in PAD patients, with lower production capacity linked to increased mortality [118].
- **Emerging Technologies and Methodologies:** A robotized ultrasound system showed feasibility for autonomously scanning peripheral arteries in a phantom [86]. Optical coherence tomography (OCT) provided better visualization of vessel and plaque characteristics than intravascular ultrasound (IVUS) [107]. Nanotechnology is explored for theranostics, combining therapeutics with imaging for improved diagnosis and treatment monitoring [146]. Lanthanide-based nanoprobes offered superior vasculature visualization and dynamic blood perfusion assessment in PAD mouse models [119].

5) Discussion

5.1 Principal finding

The ankle-brachial index (ABI), a foundational diagnostic tool for peripheral artery disease, demonstrates a median sensitivity of 76.5% (range: 56.5%–95.2%) and a median specificity of 84.3% (range: 68.8%–100%) across various studies, indicating its continued relevance despite acknowledged limitations in certain contexts [18, 24, 36, 98, 135].

5.2 Clinical implications

- **Enhanced Screening:** Novel biomarkers and advanced physiological measurements offer potential for earlier and more accurate PAD screening, especially in high-risk populations like those with diabetes, where ABI alone may be insufficient [1, 11, 13, 22].
- **Improved Risk Stratification:** Biomarkers like urinary Cystatin C and uFABP3 can predict worsening PAD status and major adverse limb events, aiding in personalized risk stratification and treatment planning [15, 17].
- **Personalized Treatment Monitoring:** Light transmission aggregometry (LTA) can personalize antiplatelet therapy in atherosclerotic patients, including those with PAD, identifying non-responders to current dosages [10].
- **Optimized Imaging Workflows:** Advanced imaging techniques such as DE-CTA with virtual non-contrast (VNC) imaging offer comparable reliability to true non-contrast (TNC) imaging, potentially reducing radiation dose and optimizing workflow [56].

- **Addressing Diagnostic Challenges:** Combining post-exercise ABI with exercise-TcPO2 significantly improves sensitivity for arterial stenoses, particularly in patients with exertional limb pain and normal resting ABI [20].

5.3 Research implications / key gaps

- **Standardized Biomarker Panels:** Further research is needed to validate and standardize multi-biomarker panels for PAD diagnosis and prognosis across diverse populations and clinical settings [2, 5, 31].
- **AI Model Generalizability:** Large-scale, prospective studies are required to validate the generalizability and clinical utility of AI-based diagnostic and prognostic models for PAD beyond specific cohorts or phantom studies [6, 7, 8, 86].
- **Comparative Effectiveness of Imaging:** Head-to-head comparative studies are needed to establish the superior diagnostic accuracy and cost-effectiveness of emerging imaging modalities (e.g., DVA, MSOT, FSD-MRA) against established gold standards like DSA or CTA [25, 44, 55, 117, 125].
- **Longitudinal Prognostic Value:** More long-term follow-up studies are essential to confirm the sustained prognostic value of novel biomarkers and physiological parameters for predicting major adverse cardiovascular and limb events in PAD patients [15, 17, 33, 118].
- **Integration of Multi-modal Data:** Research should explore the optimal integration of diverse diagnostic data (biomarkers, imaging, physiological, AI-derived) to create comprehensive, highly accurate diagnostic and predictive platforms for PAD [29, 36].

5.4 Limitations

- **Study Heterogeneity** — The included studies exhibited significant variability in design, patient populations, and diagnostic endpoints, limiting direct comparisons and meta-analysis.
- **Sample Size Variability** — Many studies, particularly those on novel biomarkers or imaging techniques, involved small sample sizes, which can affect statistical power and the generalizability of findings.
- **Lack of Gold Standard Comparison** — Some novel diagnostic methods were compared to other non-invasive tests rather than a universally accepted gold standard like angiography, potentially overestimating their accuracy.
- **Focus on Specific Cohorts** — A considerable number of studies focused on specific patient groups (e.g., T2DM, CLI), which may limit the applicability of their findings to the broader

PAD population.

- **Limited Economic Evaluation** — The economic implications and cost-effectiveness of many emerging diagnostic tools were not consistently addressed, hindering their potential clinical implementation.

5.5 Future directions

- **Standardized Diagnostic Protocols** — Develop and validate standardized protocols for novel PAD diagnostic tools across diverse populations.
- **Large-Scale Prospective Trials** — Conduct large-scale prospective trials to confirm the diagnostic and prognostic utility of promising biomarkers and imaging techniques.
- **AI-Powered Integrated Diagnostics** — Explore the development of AI-powered platforms that integrate multi-modal diagnostic data for comprehensive PAD assessment.
- **Cost-Effectiveness Analyses** — Perform rigorous cost-effectiveness analyses for new diagnostic technologies to inform clinical adoption and resource allocation.
- **Point-of-Care Device Development** — Advance the development of user-friendly, accurate point-of-care diagnostic devices for early PAD detection in primary care settings.

6) Conclusion

For peripheral artery disease diagnosis, the ankle-brachial index (ABI) demonstrated a median sensitivity of 76.5% (range: 56.5% [36]–95.2% [24]) and a median specificity of 84.3% (range: 68.8% [98]–100% [135]) across various studies. While ABI remains a cornerstone, its generalizability is impacted by the heterogeneity of study populations and comparators. The significant variability in study designs and patient cohorts across the literature most affects certainty. Clinicians should consider combining ABI with other diagnostic modalities or novel biomarkers, especially in high-risk groups or when ABI results are inconclusive, to improve diagnostic accuracy.

References

SAIMSARA Session Index — session.json

Figure 1. Publication-year distribution of included originals

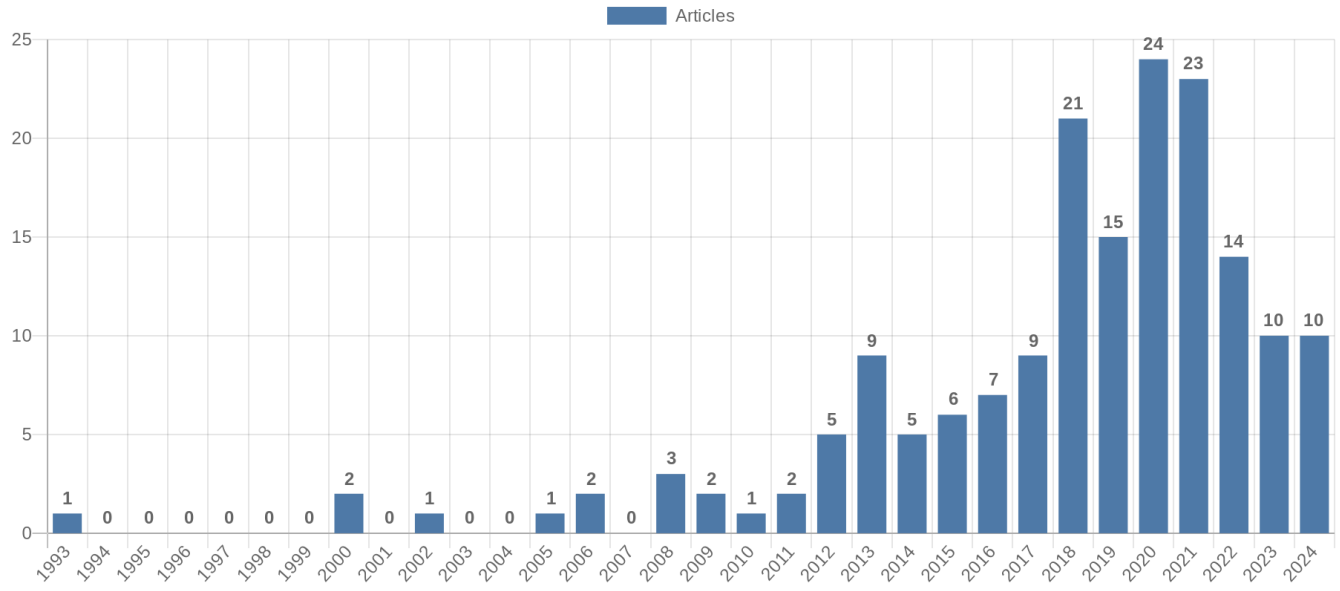

Figure 2. Study-design distribution of included originals

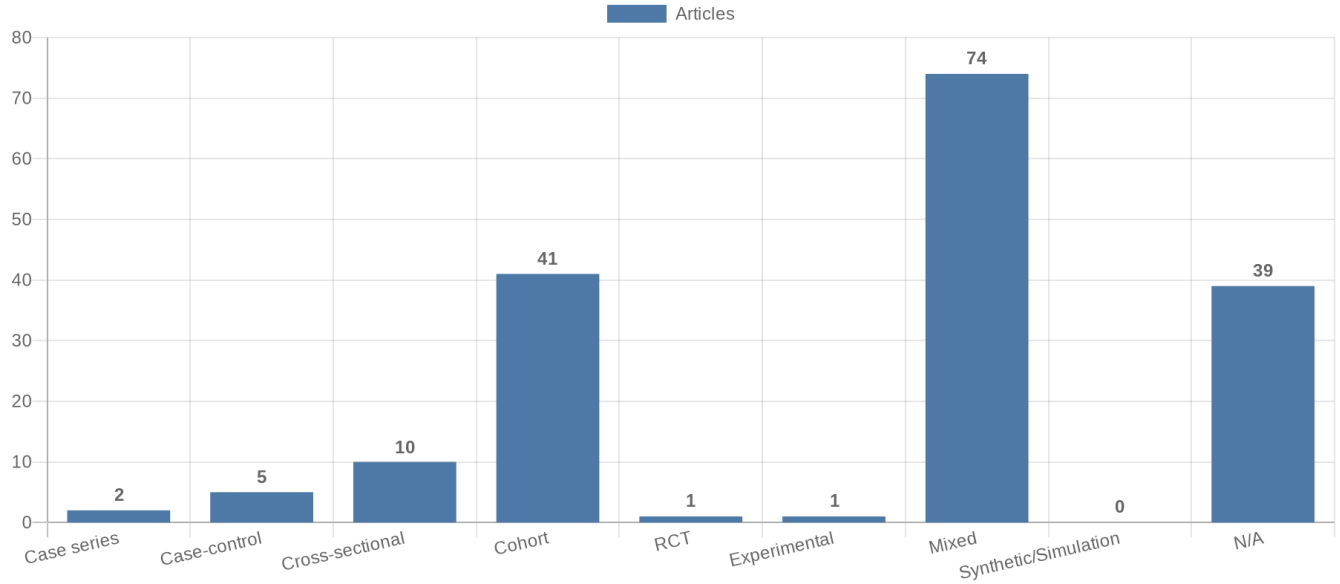

Figure 3. Study-type (directionality) distribution of included originals

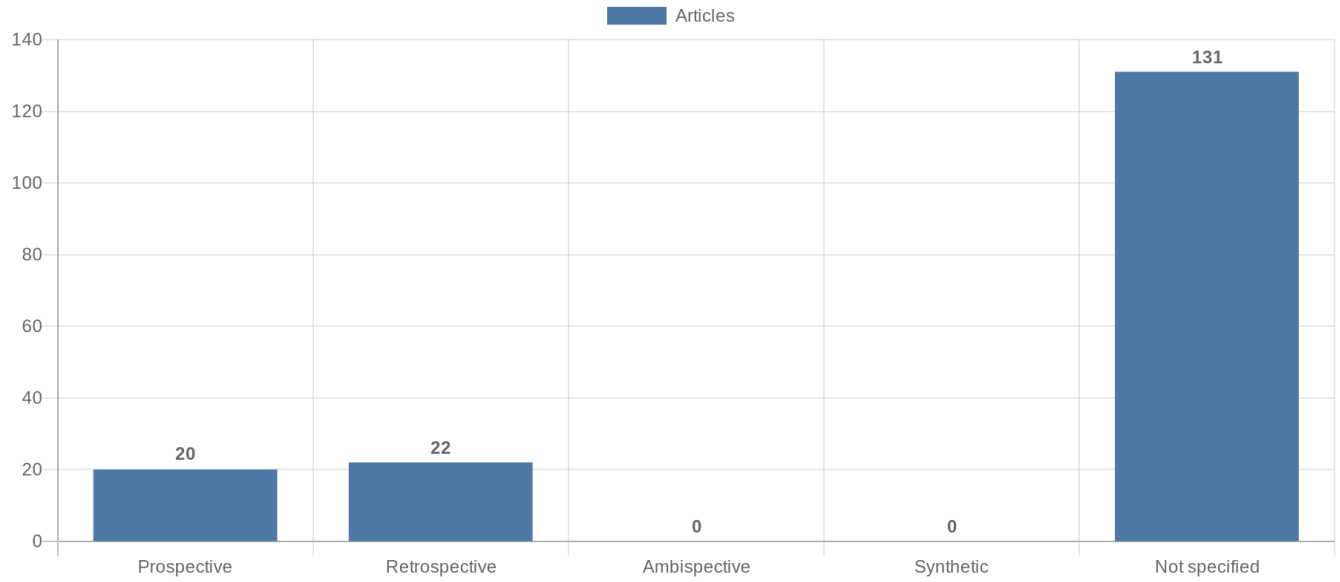

Figure 4. Main extracted research topics

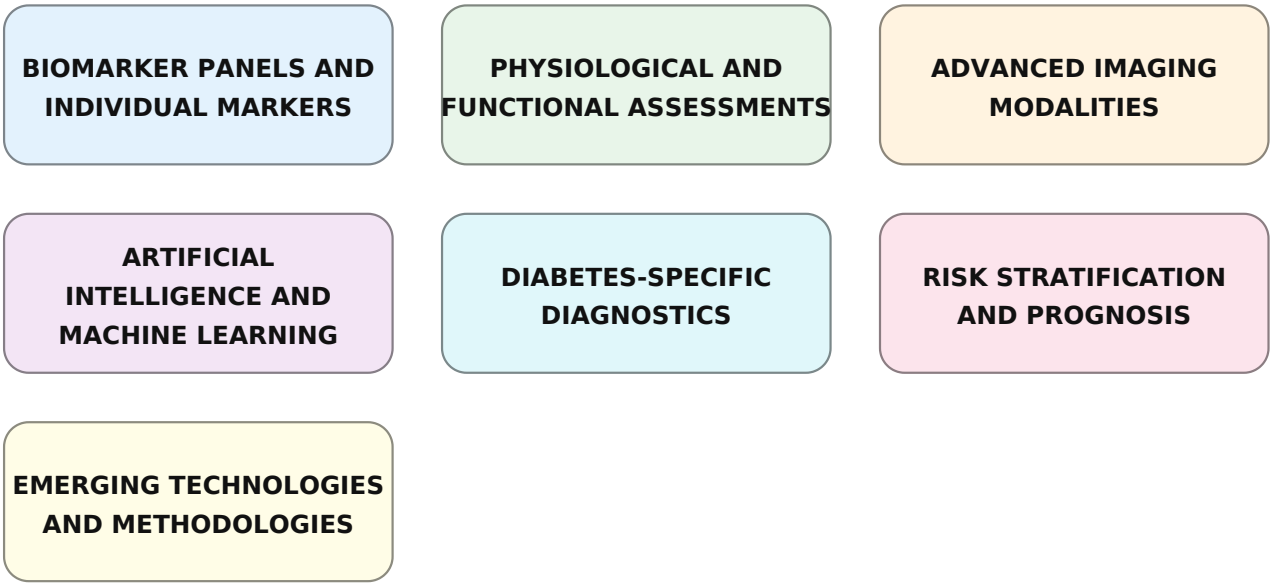

Figure 5. Limitations of current studies (topics)

Figure 6. Future research directions (topics)