

INPLASY

Diagnostic accuracy of skin biopsy, imaging, and circulating biomarkers for calciphylaxis: protocol for a systematic review of diagnostic test accuracy

INPLASY2026100010

doi: 10.37766/inplasy2026.10.0010

Received: 2 October 2026

Published: 2 October 2026

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ADMINISTRATIVE INFORMATION**Support** - No support.**Review Stage at time of this submission** - Preliminary searches.**Conflicts of interest** - None declared.**INPLASY registration number:** INPLASY2026100010**Amendments** - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 2 October 2026 and was last updated on 2 October 2026.**INTRODUCTION**

Review question / Objective To determine the diagnostic accuracy and reliability of histopathology (histologic features, calcium stains, biopsy technique, and interpretation), imaging (radiography, mammography, computed tomography, ultrasonography, and bone scintigraphy), and circulating and physiologic biomarkers in adults with suspected or established uremic or nonuremic calciphylaxis. PICOS: Population, adults with suspected or established calciphylaxis (calcific uremic arteriolopathy), and tissue from patients without calciphylaxis for false-positive frequency of histologic features; Index tests, histopathologic, imaging, and biomarker tests; Comparator/reference standard, any reference standard as reported (clinical diagnosis, histology, or composite); Outcomes, sensitivity, specificity, positivity among confirmed cases, discriminative features, area under the receiver operating characteristic curve, interrater reliability, and between-group biomarker differences; Study designs, diagnostic accuracy, case-control, cohort,

cross-sectional, case-only series of 10 or more patients, and interrater reliability studies.

Rationale Calciphylaxis lacks a validated diagnostic test. Skin biopsy, the conventional reference standard, samples a patchy process, must include subcutaneous fat, and may itself provoke ulceration and infection, and expert guidance on its role diverges. Reported prevalence varies widely between settings, which likely reflects case ascertainment as much as biology. Diagnostic performance of histopathology, imaging, and biomarkers has been summarized only narratively, so a systematic assessment of test accuracy, reliability, and certainty of evidence is needed to inform diagnostic algorithms.

Condition being studied Calciphylaxis, or calcific uremic arteriolopathy, is an occlusive vasculopathy of the dermis and subcutaneous fat defined by arteriolar calcification, intimal proliferation, and thrombosis. It presents with painful livedo, indurated plaques, and necrotic ulcers, predominantly in patients receiving dialysis, and

carries high mortality. Nonuremic calciphylaxis also occurs. Diagnosis is frequently delayed.

METHODS

Search strategy MEDLINE (PubMed): ("Calciphylaxis"[Mesh] OR calciphylaxis[tiab] OR "calcific uremic arteriopathy"[tiab] OR "calcific uraemic arteriopathy"[tiab] OR "calcific uremic arteriopathies"[tiab]) AND ("Sensitivity and Specificity"[Mesh] OR "Biopsy"[Mesh] OR "Diagnostic Imaging"[Mesh] OR "Biomarkers"[Mesh] OR "Observer Variation"[Mesh] OR "Reproducibility of Results"[Mesh] OR "Diagnosis, Differential"[Mesh] OR "diagnosis"[sh] OR "diagnostic imaging"[sh] OR "pathology"[sh] OR sensitivit*[tiab] OR specificit*[tiab] OR accurat*[tiab] OR diagnos*[tiab] OR "predictive value"[tiab] OR biops*[tiab] OR histopatholog*[tiab] OR histolog*[tiab] OR "von Kossa"[tiab] OR "alizarin red"[tiab] OR scintigra*[tiab] OR "bone scan"[tiab] OR "bone scans"[tiab] OR radiograph*[tiab] OR mammogra*[tiab] OR ultrason*[tiab] OR ultrasound[tiab] OR "computed tomography"[tiab] OR radiomic*[tiab] OR "magnetic resonance"[tiab] OR "positron emission"[tiab] OR biomarker*[tiab] OR "matrix Gla"[tiab] OR fetuin*[tiab] OR pyrophosphate*[tiab] OR "calcification propensity"[tiab] OR T50[tiab] OR interobserver[tiab] OR interrater[tiab] OR "inter-rater"[tiab] OR "inter-observer"[tiab] OR reliabilit*[tiab] OR kappa[tiab]).

Web of Science Core Collection: TS=(calciphylaxis OR "calcific uremic arteriopathy" OR "calcific uraemic arteriopathy") AND TS=(sensitivit* OR specificit* OR accurat* OR diagnos* OR "predictive value*" OR biops* OR histopatholog* OR histolog* OR "von Kossa" OR "alizarin red" OR scintigra* OR "bone scan*" OR radiograph* OR mammogra* OR ultrason* OR ultrasound OR "computed tomography" OR radiomic* OR "magnetic resonance" OR "positron emission" OR biomarker* OR "matrix Gla" OR fetuin* OR pyrophosphate* OR "calcification propensity" OR T50 OR interobserver OR interrater OR "inter-rater" OR "inter-observer" OR reliabilit* OR kappa).

Cochrane Library (title, abstract, keyword): calciphylaxis OR "calcific uremic arteriopathy" OR "calcific uraemic arteriopathy" OR "calcific uremic arteriopathies".

ClinicalTrials.gov (all fields): calciphylaxis OR "calcific uremic arteriopathy" OR "calcific uraemic arteriopathy".

No date, language, or publication-type limits.

Participant or population Adults with suspected or established uremic or nonuremic calciphylaxis. Studies of tissue from patients without calciphylaxis are eligible when they quantify the false-positive frequency of a histologic feature used for diagnosis.

Intervention Index tests in three domains: (1) histopathology, including histologic features, calcium stains (e.g., von Kossa, alizarin red), biopsy technique, and interpretation; (2) imaging, including plain radiography, mammography, computed tomography (including radiomics), ultrasonography, and bone scintigraphy; (3) circulating and physiologic biomarkers (e.g., pyrophosphate, matrix Gla protein species, fetuin-A, calcification propensity [T50], transcutaneous oxygen tension).

Comparator Reference standard as reported by each study (clinical diagnosis, histopathology, or composite). Comparator groups include patients with suspected but unconfirmed disease, patients with end-stage kidney disease or chronic kidney disease without calciphylaxis, patients with mimicking conditions, and healthy controls.

Study designs to be included Diagnostic accuracy studies, case-control, cohort, and cross-sectional studies, case-only series of 10 or more patients, and interrater reliability studies.

Eligibility criteria Exclusion criteria: case reports; case-only series of fewer than 10 patients; reviews; correspondence without primary data; experimental (animal or in vitro) studies. Conference abstracts are eligible when sufficient data are reported.

Information sources MEDLINE (via PubMed), Web of Science Core Collection (all editions), Cochrane Library (Cochrane Database of Systematic Reviews and CENTRAL), and ClinicalTrials.gov.

Main outcome(s) Diagnostic accuracy of each index test: sensitivity and specificity (or two-by-two data allowing their derivation), with 95% confidence intervals, likelihood ratios, and area under the receiver operating characteristic curve where reported.

Additional outcome(s) Positivity of index tests among confirmed cases; frequency of histologic features in tissue without calciphylaxis; discriminative features against defined comparators; interrater reliability (e.g., kappa,

Krippendorff alpha); between-group differences in biomarker concentrations.

Data management Records are deduplicated sequentially across sources by digital object identifier, PubMed identifier, trial registration number, and normalized title. Screening decisions, reasons for full-text exclusion, and extracted data are recorded in electronic logs. Extracted items comprise setting, design, participants, index test and positivity criteria, reference standard, and results. Two-by-two tables are recorded only when reported or unambiguously reconstructable, and derived cells are flagged.

Quality assessment / Risk of bias analysis Risk of bias is assessed with QUADAS-2, with signalling questions addressing case-control sampling, incorporation of the index test into the reference standard, and partial verification. Certainty of evidence for each index test is rated with the GRADE approach for test accuracy.

Strategy of data synthesis Bivariate random-effects meta-analysis of sensitivity and specificity is planned for any index test evaluated by at least four studies with a common positivity criterion, a comparable reference standard, and complete two-by-two data. Otherwise, results are synthesized narratively by domain (histopathology, imaging, biomarkers). Single proportions reported with numerator and denominator by at least three studies may be pooled on the logit scale with a random-effects model using restricted maximum likelihood and Hartung-Knapp-Sidik-Jonkman confidence intervals; heterogeneity is summarized with I-squared.

Subgroup analysis No subgroup analyses. Results are presented separately by index-test domain (histopathology, imaging, biomarkers).

Sensitivity analysis Where pooled proportions are estimated, sensitivity analyses vary the denominator definitions (e.g., restricting to adequate biopsy specimens) and the unit of analysis (patient-level versus lesion-level data).

Language restriction None.

Country(ies) involved United States.

Other relevant information The review is reported in accordance with PRISMA-DTA.

Keywords Calciphylaxis; Calcific uremic arteriopathy; Diagnostic test accuracy; Skin biopsy; Bone scintigraphy; Pyrophosphate.

Dissemination plans Publication in a peer-reviewed journal.

Contributions of each author

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