INPLASY

Clinical Significance of Extracellular Volume of Myocardium (ECV) Assessed by Computed Tomography: A Systematic Review and Meta-Analysis

INPLASY202520109
doi: 10.37766/inplasy2025.2.0109
Received: 25 February 2025
Published: 25 February 2025

Corresponding author:
Adrian Martuszewski

adrian.martuszewski@student.umw.edu.pl

Author Affiliation:
Department of Environmental Health, Occupational Medicine and Epidemiology, Wroclaw Medical University.

Martuszewski, A; Paluszkiewicz, P; Poręba, R; Gać, P.

ADMINISTRATIVE INFORMATION

Support - This research received no external funding. The APC was funded by Wroclaw Medical University (SUBZ.E280.25.064).

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202520109

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 25 February 2025 and was last updated on 25 February 2025.

INTRODUCTION

Review question / Objective This systematic review and meta-analysis included patients (P): amyloidosis, aortic stenosis (AS), heart failure with preserved ejection fraction (HFpEF), dilated cardiomyopathy (DCM), myocarditis, and those undergoing atrial fibrillation ablation or cardiotoxic treatments. Studies were eligible if they reported quantitative ECV measurements obtained via CT. Extracted data included sample sizes (n), mean ECV values, standard deviations (SD), and the CT technique used.
The intervention (I): ECV assessment using standard CTA and advanced imaging techniques, such as dual-energy CT (DECT) and late iodine enhancement DECT (LIE-DECT). Comparisons (C): between study groups (group 1 vs. group 2) and across imaging modalities (CTA vs. DECT/LIE-DECT).
The outcome (O): SMD in ECV values between groups, reported with 95%CI, SE, and precision (1/SE).

Rationale Cardiovascular diseases are the leading cause of mortality worldwide, with myocardial fibrosis playing a crucial role in disease progression and adverse outcomes. Extracellular volume (ECV) quantification has emerged as an important imaging biomarker for assessing myocardial fibrosis, traditionally measured using cardiac magnetic resonance imaging (MRI). However, MRI is not always feasible due to contraindications such as implanted devices, claustrophobia, or limited availability.
Computed tomography (CT) has been increasingly explored as an alternative imaging modality for ECV assessment, offering advantages such as wider accessibility, faster scan times, and improved patient tolerance. Advances in CT technology, including dual-energy CT (DECT) and late iodine enhancement (LIE-DECT), have enhanced its ability to quantify ECV with high accuracy.
Despite these developments, no comprehensive systematic review and meta-analysis have evaluated the diagnostic and prognostic value of CT-derived ECV across different cardiac

conditions. This study aims to fill this gap by systematically synthesizing the available evidence, comparing CT-derived ECV measurements across patient populations, and assessing its clinical utility relative to established imaging modalities.

Condition being studied Myocardial fibrosis is a pathological process characterized by excessive deposition of extracellular matrix components, primarily collagen, within the myocardial tissue. It is a key contributor to the progression of various cardiovascular diseases, including heart failure, cardiomyopathies, ischemic heart disease, and infiltrative disorders such as amyloidosis. Fibrosis leads to myocardial stiffness, impaired cardiac function, and an increased risk of arrhythmias, heart failure, and sudden cardiac death.
Extracellular volume (ECV) fraction is a non-invasive imaging biomarker used to quantify myocardial fibrosis by assessing the expansion of the interstitial space. Traditionally, cardiac magnetic resonance imaging (MRI) with T1 mapping has been the gold standard for ECV measurement. However, computed tomography (CT)-derived ECV has emerged as a viable alternative, particularly for patients with contraindications to MRI. Advances in CT technology, including dual-energy CT (DECT) and late iodine enhancement (LIE-DECT), have improved the accuracy of ECV quantification, allowing for better assessment of diffuse myocardial fibrosis and its impact on cardiac function.

METHODS

Search strategy PubMed, ClinicalTrials.gov, WebOfScience. PubMed was searched (January 7, 2023) with the syntax '((“heart”) OR (“cardiac”) OR (myocard*)) AND (("extracellular volume") OR ("extracellular matrix") OR ("ECV")) AND ((CT) OR ("computed tomography") OR (CCTA) OR (coroCT))'. ClinicalTrials.gov was searched (June 10, 2024) using the terms: ((“heart”) OR (“cardiac”) OR (myocard)) AND (("extracellular volume") OR ("extracellular matrix") OR ("ECV"))* under "Other Terms" and ((CT) OR ("computed tomography") OR (CCTA) OR (coroCT)) under "Intervention/ Treatment.".

Participant or population This systematic review and meta-analysis included patients (P): amyloidosis, aortic stenosis (AS), heart failure with preserved ejection fraction (HFpEF), dilated cardiomyopathy (DCM), myocarditis, and those undergoing atrial fibrillation ablation or cardiotoxic treatments. Studies were eligible if they reported quantitative ECV measurements obtained via CT.

Intervention The intervention (I): ECV assessment using standard CTA and advanced imaging techniques, such as dual-energy CT (DECT) and late iodine enhancement DECT (LIE-DECT).

Comparator Comparisons (C): between study groups (group 1 vs. group 2) and across imaging modalities (CTA vs. DECT/LIE-DECT).

Study designs to be included This review includes observational studies (both prospective and retrospective), cohort studies, and diagnostic accuracy studies that assess the use of computed tomography (CT) for extracellular volume (ECV) quantification in various cardiac conditions. Studies must report quantitative ECV measurements obtained through CT imaging, including standard computed tomography angiography (CTA), dual-energy CT (DECT), and late iodine enhancement DECT (LIE-DECT). Systematic reviews and meta-analyses that meet methodological quality criteria were also considered if they provided relevant pooled data on ECV quantification and its diagnostic or prognostic value in cardiac diseases.

Eligibility criteria In addition to the PICOS criteria, this review excluded studies that lacked full-text availability, were not published in peer-reviewed journals, or were written in languages other than English. Studies with incomplete or insufficient data for effect size calculation, as well as those focusing solely on experimental imaging techniques without clinical validation, were also excluded. Furthermore, research involving non-human subjects or pediatric populations was not considered to maintain relevance to adult cardiovascular disease assessment.

Information sources The information sources for this review included **electronic databases** such as **PubMed** and **Web of Science**, which were systematically searched for relevant studies up to January 2023. Additionally, **ClinicalTrials.gov** was reviewed to identify registered trials related to myocardial extracellular volume (ECV) assessment using computed tomography (CT). **Manual searches** of reference lists from retrieved articles and systematic reviews were conducted to identify additional relevant studies.
Unpublished or grey literature, including preprints, conference abstracts, and non-peer-reviewed sources, was excluded to ensure methodological rigor and data reliability. Contact with study authors was not planned as part of the data collection process.

Main outcome(s) The primary outcome of this review was the **quantification of extracellular volume (ECV) using computed tomography (CT) in various cardiac conditions**, including amyloidosis, aortic stenosis, heart failure with preserved ejection fraction (HFpEF), dilated cardiomyopathy (DCM), and myocarditis.
For each included study, the **mean ECV values (%) and standard deviations (SD)** were extracted for both the pathological and control groups. The effect measure used in the synthesis was the **standardized mean difference (SMD)** with **95% confidence intervals (CI)**, calculated according to Cochrane Handbook guidelines.
Additional outcomes included **comparisons across different CT imaging techniques** (standard CTA vs. DECT/LIE-DECT) and **clinical correlations of ECV with disease severity, prognosis, and mortality risk**. Heterogeneity was assessed using the **I^2 statistic**, and sensitivity analyses were conducted by sequential exclusion of studies to evaluate the robustness of the findings.

Quality assessment / Risk of bias analysis The risk of publication bias was assessed using Egger's test and funnel plot analysis. Egger's test was performed to detect potential asymmetry in the funnel plot, which would indicate small-study effects or publication bias. The funnel plot visually represented the distribution of standardized mean differences (SMD) against their standard errors (SE), allowing for an evaluation of study heterogeneity and potential reporting bias.
The quality assessment of primary studies was conducted using multiple validated tools depending on the study design. Diagnostic accuracy studies were evaluated using the QUADAS-2 tool, which assesses four key domains: patient selection, index test, reference standard, and flow and timing. Cohort studies were assessed with the Newcastle-Ottawa Scale (NOS), which evaluates participant selection, comparability of groups, and outcome assessment. For non-randomized interventional studies, the ROBINS-I tool was used to assess the risk of bias across seven domains, including confounding and participant selection. Additionally, systematic reviews included in the analysis were evaluated with the AMSTAR-2 checklist to ensure methodological rigor. The overall risk of bias and study quality were considered when interpreting results, and any discrepancies in assessments were resolved through discussion among the reviewers.

Strategy of data synthesis The data were analyzed using R (version 4.4.2) within RStudio, employing the meta and metafor packages for statistical computations. Standardized mean differences (SMD) with 95% confidence intervals (CI) were calculated to compare extracellular volume (ECV) values between pathological and control groups. Random-effects models were used to account for between-study variability, with heterogeneity assessed using the I^2 statistic, τ^2 variance, and Cochran's Q test.
Subgroup analyses were conducted to compare different imaging techniques (CTA vs. DECT/LIE-DECT) and assess their impact on pooled estimates. Sensitivity analyses were performed using a leave-one-out approach, sequentially removing individual studies to evaluate the robustness of the findings. Publication bias was assessed using Egger's test and funnel plot analysis, ensuring transparency in the synthesis process.

Subgroup analysis Subgroup analyses were performed to compare extracellular volume (ECV) measurements across different computed tomography (CT) imaging techniques, specifically standard CTA versus advanced methods such as DECT and LIE-DECT. The results were stratified to evaluate whether the choice of imaging modality influenced the standardized mean difference (SMD) in ECV values.

Sensitivity analysis Sensitivity analysis was conducted using a leave-one-out approach, where each study was sequentially removed to assess its impact on the overall pooled standardized mean difference (SMD). This method helped evaluate the robustness and stability of the findings by identifying whether any single study disproportionately influenced the results. Additionally, heterogeneity was reassessed after each exclusion to determine the consistency of the effect size across studies. The results of the sensitivity analysis confirmed the reliability of the meta-analysis conclusions.

Country(ies) involved Poland.

Keywords Myocardium; Cardiac fibrosis; Computed tomography; Extracellular volume; Cardiac imaging.

Contributions of each author
Author 1 - Adrian Martuszewski.
Email: adrian.martuszewski@student.umw.edu.pl
Author 2 - Patrycja Paluszkiewicz.
Email: patrycja.paluszkiewicz@op.pl
Author 3 - Rafał Poręba.
Email: rafal.poreba@umw.edu.pl
Author 4 - Paweł Gać.
Email: pawel.gac@umw.edu.pl