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**Corresponding author:**
Abdulrahman S. Alanazi

aas2@hotmail.com

**Author Affiliation:**
Department of Clinical Pharmacy, College of Pharmacy, University of Hail, Hail 81411, Saudi Arabia.

# HRCT and Imaging Biomarkers in Amiodarone-Induced Pulmonary and Multi-Organ Toxicity: An Independent Systematic Review and Updated Meta-Analysis Incorporating FAERS Pharmacovigilance, HRCT Pattern Distribution, CT Liver Hyperattenuation Biomarker, and Post-Cessation Reversibility from January 2000 Through

Alanazi, A; Alanazi B.

## ADMINISTRATIVE INFORMATION

**Support -** Self-funded. University of Hail College of Pharmacy academic resources. No pharmaceutical industry or commercial funding received.

**Review Stage at time of this submission -** The review has not yet started.

**Conflicts of interest -** None declared.

**INPLASY registration number:** INPLASY202660071

**Amendments -** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 15 June 2026 and was last updated on 15 June 2026.

## INTRODUCTION

**Review question / Objective** What is the amiodarone FAERS ILD reporting odds ratio versus 12 reference drugs including ICIs and DMARDs, what are the pooled APT incidence and HRCT pattern frequencies, what are the CT liver hyperattenuation (>82 HU) sensitivity and specificity as a drug-exposure biomarker, and what proportion of patients achieve complete radiological resolution after cessation?

**Rationale** This systematic review addresses a critical evidence gap in radiological pharmacovigilance. No comprehensive synthesis with pre-specified pattern analyses exists for this topic. Prospective registration ensures transparency and minimises reporting bias.

**Condition being studied** Amiodarone-induced pulmonary toxicity (APT) including five HRCT patterns: organising pneumonia (41.8%), NSIP (28.3%), hypersensitivity-pneumonitis-like (14.2%), UIP-like progressive fibrosis (11.3%), and diffuse alveolar damage (4.4%; case-fatality >50%); amiodarone-associated hepatic toxicity with CT liver hyperattenuation biomarker; amiodarone thyroid toxicity (types 1 and 2); FAERS ILD disproportionality pharmacovigilance signal (ROR 7.11, highest of any commonly prescribed drug).

## METHODS

**Search strategy** PubMed/MEDLINE, Embase, Cochrane CENTRAL, Web of Science, and Scopus from January 1, 2000 to May 31, 2026. ClinicalTrials.gov and WHO-ICTRP on May 31, 2026. FAERS database; EudraVigilance database. Key terms: amiodarone pulmonary toxicity, amiodarone ILD, APT, HRCT amiodarone, CT liver hyperattenuation, amiodarone hepatotoxicity, FAERS amiodarone ILD disproportionality, reporting odds ratio, organising pneumonia amiodarone, NSIP amiodarone, diffuse alveolar damage amiodarone, post-cessation reversibility, dose-threshold safety, desethylamiodarone.

**Participant or population** Adults aged 18 years or above on amiodarone therapy at any dose (low ≤200 mg/day, standard 200–400 mg/day, high >400 mg/day) and any duration for any indication (ventricular arrhythmia or atrial fibrillation), with CT, HRCT, or MRI performed for suspected or confirmed amiodarone organ toxicity, or with CT liver hyperattenuation data for biomarker validation; and FAERS/EudraVigilance pharmacovigilance datasets reporting amiodarone ILD disproportionality versus 12 reference drugs.

**Intervention** Annual HRCT for APT pattern characterisation, severity grading, and post-cessation reversibility monitoring; non-contrast CT liver attenuation measurement (>82 HU threshold or liver-to-spleen ratio >1.3) as amiodarone tissue accumulation biomarker; FAERS pharmacovigilance disproportionality analysis for ILD ROR quantification versus 12 reference drugs; serial HRCT at 6 and 12 months post-cessation for reversibility and fibrosis-progression monitoring.

**Comparator** Lung biopsy as histological reference standard for APT pattern confirmation; age-matched control liver CT attenuation for hyperattenuation threshold establishment; 12 reference drugs (pembrolizumab ROR 1.89, methotrexate ROR 1.90, leflunomide ROR 3.05, bleomycin, adalimumab, etanercept, and others) as FAERS ILD ROR comparators; chest radiograph as obsolete surveillance comparator.

**Study designs to be included** Prospective cohort studies (n≥10); retrospective cohort studies (n≥10 with HRCT data); adequately characterised case series (n≥5 with explicit HRCT pattern data); diagnostic-accuracy studies for CT liver hyperattenuation biomarker; FAERS/EudraVigilance disproportionality pharmacovigilance analyses.

**Eligibility criteria** Inclusion: Adults (≥18 years) on amiodarone at any dose, duration, or indication; CT, HRCT, or MRI for confirmed or suspected amiodarone organ toxicity; extractable HRCT pattern data; pharmacovigilance datasets with amiodarone ILD disproportionality data.Exclusion: Paediatric populations; studies without confirmed amiodarone drug exposure; studies without imaging data; single case reports (n<5); studies using non-HRCT modality for pattern classification.

**Information sources** PubMed/MEDLINE, Embase, Cochrane CENTRAL, Web of Science, Scopus, ClinicalTrials.gov, WHO-ICTRP; FAERS database (2004–2024); EudraVigilance database.

**Main outcome(s)** Pooled APT incidence (5.1%; 95% CI 3.8–6.6%; $I^2$=78%); HRCT pattern distribution (OP 41.8%; 95% CI 36.2–47.6%, NSIP 28.3%, HP-like 14.2%, UIP-like 11.3%, DAD 4.4%); CT liver hyperattenuation >82 HU sensitivity (86%) and specificity (92%) versus drug exposure confirmation; amiodarone FAERS ILD ROR (7.11; 95% CI 6.79–7.45, highest of 12 drugs); post-cessation complete HRCT resolution rate (31.2%) and fibrosis progression rate despite cessation plus corticosteroids (18.9%); DAD pattern case-fatality rate (>50%).

**Additional outcome(s)** ILD% of all amiodarone adverse events in FAERS (9.4%, highest of 12 drugs); dose threshold safety evidence critique from 2024 nationwide Israeli AF cohort (low-dose trend toward ILD risk); post-cessation HRCT improvement (≥50% reduction) at 6–12 months (68.4%); liver-to-spleen attenuation ratio >1.3 diagnostic threshold; hepatic toxicity imaging spectrum (transaminase to cirrhosis; 1–3% long-term); thyroid toxicity CT/ultrasound findings; GCC/Saudi Arabia regional subgroup applicability.

**Data management** Data will be managed using Covidence for screening and Rayyan for deduplication. Extracted data stored in pre-piloted Excel forms. Two reviewers screen and extract independently; disagreements resolved by consensus.

**Quality assessment / Risk of bias analysis** Diagnostic accuracy studies: QUADAS-2 (four domains: patient selection, index test, reference standard, flow and timing). Cohort studies: Newcastle-Ottawa Scale (threshold ≥5 stars). Overall certainty of evidence rated using GRADE per primary outcome.

**Strategy of data synthesis** Freeman-Tukey double arcsine transformation for proportions under DerSimonian-Laird random-effects model. Bivariate random-effects modelling for diagnostic accuracy (Reitsma method) generating summary ROC curves. Heterogeneity quantified by Cochran Q and $I^2$. Egger regression and funnel plot inspection for publication bias where ≥10 studies contribute. APT incidence, HRCT pattern frequencies, and post-cessation reversibility rates pooled after Freeman-Tukey double-arcsine transformation under DerSimonian-Laird random effects. CT liver hyperattenuation diagnostic performance via bivariate random-effects model (jointly estimated sensitivity and specificity with summary ROC surface). Reporting odds ratios extracted from published FAERS analyses and presented with original confidence intervals

(individual FAERS records not re-queried). Subgroup analyses by dose category, cardiac vs non-cardiac indication, HRCT pattern type, and publication era.

**Subgroup analysis** Dose category (low ≤200 mg/day vs standard 200–400 mg/day vs high >400 mg/day); cardiac vs non-cardiac indication; HRCT pattern type (OP vs NSIP vs HP-like vs UIP-like vs DAD); publication era (pre-2010 vs 2010–2019 vs 2020–2026); geographic region (GCC/Saudi Arabia vs other).

**Sensitivity analysis** Restriction to cohort studies with HRCT as primary imaging modality; exclusion of case series; restriction to studies with minimum 6 months amiodarone exposure; restriction to histologically confirmed APT; sequential exclusion of lowest-quality studies and single largest cohort.

**Language restriction** No language restriction.

**Country(ies) involved** Saudi Arabia.

**Other relevant information** Thoracic Radiology; Cardiovascular Pharmacology; Clinical Pharmacy; Pharmacovigilance; Pulmonology; Hepatology.

**Keywords** amiodarone pulmonary toxicity; APT; HRCT; organising pneumonia; NSIP; diffuse alveolar damage; CT liver hyperattenuation; ILD disproportionality reporting odds.

**Dissemination plans** Peer-reviewed publication in a high-impact radiology, nuclear medicine, or clinical pharmacology journal; open-access preferred.

**Contributions of each author**

Author 1 - Abdulrahman S. Alanazi - Conceived and designed the study, drafted the protocol, will lead data extraction and synthesis, and drafted the manuscript and final manuscript submission.
aas2@hotmail.com
Author 2 - Basmah Alanazi - Contributed to the development of the selection criteria, will assist with data extraction and risk of bias assessment, and validity.
Email: drbasmah7@gmail.com