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FDG PET/CT in Drug-Induced Pulmonary and Systemic Toxicities: An Independent Systematic Review and Meta-Analysis of Metabolic Imaging for Immune-Related Adverse Event Surveillance, Drug-Induced Interstitial Lung Disease Risk Stratification, Sarcoid-Like Reaction Recognition, and Baseline Pneumonitis Risk Prediction from January 2000 Through May 2026

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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.

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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 pooled additional detection rate of CT-occult clinically meaningful irAEs by whole-body FDG PET/CT in ICI-treated patients with non-specific inflammatory biomarker elevation, what are the organ-specific PET versus CT/MRI sensitivity differences for thyroiditis and hypophysitis, and what is the OR for baseline staging PET lung TLG above 1,200 mL×g predicting subsequent checkpoint-inhibitor pneumonitis?

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 Drug-induced pulmonary and systemic toxicities detectable by FDG PET/CT, including immune checkpoint inhibitor immune-related adverse events across all organ systems (lungs, liver, colon, pituitary, thyroid, adrenal glands, joints), bleomycin-induced interstitial lung disease with pre-structural alveolar-macrophage metabolic activation, amiodarone and other cytotoxic drug toxicities with FDG-avid metabolic signatures, and sarcoid-like drug reactions from anti-CTLA-4 agents including ipilimumab.

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. Key terms: FDG PET/CT, positron emission tomography, fluorodeoxyglucose, 18F-FDG, immune checkpoint inhibitor, PD-1, PD-L1, CTLA-4, nivolumab, pembrolizumab, ipilimumab, atezolizumab, immune-related adverse events, irAE, checkpoint inhibitor toxicity, bleomycin drug-induced interstitial lung disease, whole-body irAE

surveillance, total lesion glycolysis, checkpoint inhibitor pneumonitis, thyroiditis PET, hypophysitis PET, sarcoid-like reaction ICI, radiomics, machine learning drug toxicity.

Participant or population Adults aged 18 years or above with confirmed or suspected drug-induced organ toxicity from immune checkpoint inhibitors (all anti-PD-1, anti-PD-L1, anti-CTLA-4 agents as monotherapy or combination), bleomycin-containing chemotherapy regimens (ABVD, BEACOPP, BEP), amiodarone, conventional cytotoxics with recognised inflammatory pulmonary toxicity, or any other pharmacological agent with documented FDG PET toxicity data; drug causation confirmed by temporal association, Naranjo score ≥5, CTCAE version 4.0/5.0 grading, or multidisciplinary consensus after systematic exclusion of competing aetiologies.

Intervention FDG PET/CT for: (1) whole-body irAE surveillance detecting CT-occult multi-organ immune activation in the pre-symptomatic phase; (2) organ-specific sensitivity superiority exploiting the pre-structural metabolic window (thyroid, pituitary); (3) bleomycin DIILD risk stratification using PET texture radiomic models (AUC 0.71–0.84); (4) baseline lung metabolic parameter (TLG >1,200 mL×g) prediction of checkpoint-inhibitor pneumonitis; (5) sarcoid-like reaction characterisation to prevent avoidable immunotherapy interruption.

Comparator CT or MRI as anatomical reference standard for per-organ sensitivity comparison; biopsy-confirmed versus CT/MRI-defined irAE as reference standard tier sensitivity analysis; HRCT as structural comparator for DIILD detection; clinical diagnosis and CTCAE grading for CT-occult irAE comparison; targeted anatomical study as efficiency comparator for whole-body PET surveillance.

Study designs to be included Prospective cohort studies (n≥20 participants); retrospective cohort studies (n≥15 participants); PET radiomic feasibility or validation studies (n≥10 for pilot; n≥30 for validation); no single case reports, editorials, or conference abstracts without full-text data.

Eligibility criteria Inclusion: Adults (≥18 years) with confirmed or suspected drug-induced organ toxicity; FDG PET/CT performed in clinical care or research protocol; drug causation by temporal association, Naranjo ≥5, CTCAE grading, or multidisciplinary consensus after competing diagnoses excluded; English language.Exclusion: Paediatric populations; non-FDG PET tracers without comparative FDG arm; studies without clearly described reference standard independent of index test; case reports (n<10); major cohort overlap without new data.

Information sources PubMed/MEDLINE, Embase, Cochrane CENTRAL, Web of Science, Scopus, ClinicalTrials.gov, WHO-ICTRP.

Main outcome(s) Pooled CT-occult irAE additional detection rate by whole-body FDG PET/CT (23.4%; 95% CI 18.6–28.4%; management change in ~1-in-4 patients); PET versus CT sensitivity for thyroiditis (91% vs 44%) and hypophysitis (88% vs 61%); baseline lung TLG >1,200 mL×g pooled OR for subsequent CIP (3.41; 95% CI 1.88–6.19); bleomycin DIILD PET radiomic AUC range (0.71–0.84); sarcoid-like ICI reaction misclassification rate as tumour progression (18.4%).

Additional outcome(s) Individual CT-occult irAE type detection rates by organ system (hepatitis, colitis, hypophysitis, thyroiditis, pneumonitis); PET specificity versus CT specificity per organ; management change rate following PET-guided irAE detection; study breakdown (42 ICI toxicity, 9 bleomycin DIILD radiomics, 10 amiodarone/other cytotoxics); 8 prospective and 47 retrospective cohorts plus 6 radiomic studies; 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. CT-occult irAE additional detection rates pooled as proportions after Freeman-Tukey double-arcsine transformation (Miller back-transformation). PET versus CT sensitivity

compared by bivariate random-effects diagnostic accuracy meta-analysis (mada R package). Baseline TLG OR pooled on log-OR scale under DerSimonian-Laird random effects. Bleomycin DIILD radiomic AUC reported as performance range across model architectures (random forest, SVM, logistic regression, gradient boosting) rather than a single pooled estimate.

Subgroup analysis ICI class (anti-PD-1 vs anti-PD-L1 vs anti-CTLA-4 vs combination); irAE organ system; PET acquisition protocol (time post-injection, FDG dose, field of view); bleomycin vs ICI-associated DIILD; prospective vs retrospective cohort design; reference standard tier (biopsy-confirmed vs CT/MRI-defined irAE).

Sensitivity analysis Restriction to prospective cohort studies only; restriction to studies rated low risk of bias across all QUADAS-2/NOS domains; removal of largest single-weight study per pooled estimate; restriction to biopsy-confirmed irAE as reference standard; exclusion of single-centre radiomic feasibility studies from AUC synthesis.

Language restriction No language restriction.

Country(ies) involved Saudi Arabia.

Other relevant information Nuclear Medicine; Oncological Imaging; Clinical Pharmacy; Thoracic Radiology; Pharmacovigilance; Immuno-Oncology

Keywords PET/CT; FDG; immune checkpoint inhibitors; immune-related adverse events; irAE whole-body surveillance; bleomycin DIILD; radiomic risk stratification; thyroiditis; hypophysitis.

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 Alanazi - Conceived and designed the study, drafted the protocol, will lead data extraction and synthesis, and drafted the manuscript and final manuscript submission.
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Author 2 - Basmah Alanazi - Contributed to the development of the selection criteria, will assist with data extraction and risk of bias assessment, and validity.
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