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Applications of Receiver Operating Characteristic (ROC) Analysis in Nuclear Cardiology and Neurology: A Narrative Review

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Abstract:

- ***Background:***

Receiver operating characteristic (ROC) analysis and the area under the curve (AUC) are the principal quantitative tools used to establish diagnostic thresholds in nuclear cardiology and neuroimaging, allowing comparison of imaging modalities and biomarkers independent of an arbitrarily chosen cut-point.

- ***Objective:***

To synthesise the methodological basis of ROC/AUC analysis and to review its principal clinical applications in nuclear cardiology (myocardial perfusion imaging, absolute myocardial blood flow, and myocardial flow reserve) and nuclear neurology (amyloid and tau positron emission tomography [PET] and amino-acid PET in neuro-oncology).

- ***Methods:***

A narrative review was conducted of the peer-reviewed literature indexed in PubMed/MEDLINE, Embase and Scopus supplemented by hand-searching of reference lists, covering methodological ROC literature and diagnostic-accuracy studies in nuclear cardiology and nuclear neurology.

- ***Results:***

In nuclear cardiology, positron emission tomography perfusion imaging (82Rb, 13N-ammonia) consistently outperforms single-photon emission computed tomography (SPECT) for detecting obstructive coronary artery disease (pooled AUC approximately 0.88-0.93 versus 0.78-0.84) with cadmium-zinc-telluride detectors and attenuation correction narrowing this gap. Absolute quantification of stress myocardial blood flow and myocardial flow reserve provides incremental discrimination for multivessel and microvascular disease, with ROC-derived cut-offs of approximately 1.8-2.0 mL/min/g and less than 1.5-2.0, respectively. In nuclear neurology, amyloid PET standardised uptake value ratio thresholds (approximately 1.10-1.40) achieve high accuracy against neuropathological reference standards (AUC greater than 0.90), tau PET differentiates Alzheimer's disease from non-Alzheimer's tauopathies with AUC greater than 0.92 and 18F-fluoroethyl-L-tyrosine PET distinguishes tumour recurrence from radiation necrosis with AUC of 0.88-0.92.

- ***Conclusion:***

ROC/AUC methodology underpins threshold-setting and modality comparison across nuclear cardiology and neurology. Verification bias, imperfect reference standards and overfitting in radiomics-based models remain the principal methodological threats to validity, and should be explicitly addressed as artificial-intelligence-based diagnostic models are incorporated into clinical workflows.

Keywords: *ROC Curve; Area Under the Curve; Diagnostic Accuracy; Nuclear Cardiology; Myocardial Perfusion Imaging; Nuclear Neurology; Positron Emission Tomography; Amyloid; Tau; Neuro-Oncology.*

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I. INTRODUCTION

Nuclear medicine depends on continuous or ordinal quantitative outputs — radiotracer uptake ratios, absolute perfusion values expressed in mL/min/g and regional volumetric or kinetic parameters-that must ultimately be converted into binary or multi-class clinical decisions: presence or absence of flow-limiting ischaemia, amyloid-positive or amyloid-negative status, tumour recurrence versus radiation necrosis. This conversion requires a rigorous, reproducible method of threshold selection and receiver operating characteristic (ROC) analysis has become the accepted framework for that purpose [1-4].

ROC analysis plots sensitivity (the true-positive rate) against 1 - specificity (the false-positive rate) across the full range of possible decision thresholds [5,6]. The area under the resulting curve (AUC) summarises diagnostic performance in a single value that is, in principle, independent of disease prevalence and of the threshold eventually chosen for clinical use [7,8].

Within nuclear cardiology and nuclear neurology, ROC methodology performs two distinct functions. First, it enables comparison between imaging systems or radiopharmaceuticals - for example, whether a cadmium-zinc-telluride (CZT) SPECT detector or a novel PET tracer produces a statistically significant improvement in diagnostic accuracy (AUC) over an existing standard [9-12]. Second, it is used to identify optimal operating thresholds for clinical decision-making, typically via the Youden index or the closest to (0,1) criterion [13-15]. This review summarises the statistical foundations of ROC/AUC analysis and synthesises its principal applications across myocardial perfusion imaging, absolute myocardial blood flow quantification, amyloid and tau PET and amino-acid PET in neuro-oncology, before discussing the methodological pitfalls that most commonly threaten the validity of reported AUC estimates in this literature.

II. METHODS

This is a narrative review rather than a systematic review or meta-analysis and no formal protocol was registered. The literature search was conducted in PubMed/MEDLINE, Embase and Scopus for articles published in English, combining the terms receiver operating characteristic OR ROC OR area under the curve OR AUC with domain-specific terms including myocardial perfusion imaging, SPECT, PET, myocardial blood flow, myocardial flow reserve, amyloid PET, tau PET, 18F-FET and neuro-oncology.

Reference lists of retrieved articles and relevant reviews were hand-searched to identify additional primary studies and key methodological papers. Priority was given to multicentre or multi-reader multi-case (MRMC) studies, studies validated against an independent reference standard (invasive coronary angiography, fractional flow reserve, neuropathology or long-term clinical follow-up) and widely cited methodological papers underpinning ROC statistical practice. Given the narrative design, this review does not report a PRISMA flow diagram or a formal risk-of-bias assessment; readers requiring a systematic synthesis of a specific clinical question should consult the meta-analyses cited within each section.

III. STATISTICAL FRAMEWORK FOR ROC/AUC ANALYSIS IN MOLECULAR IMAGING

Three methodological considerations recur throughout the nuclear cardiology and nuclear neurology literature and are summarised here before the clinical applications are discussed.

➢ *Global AUC and Partial AUC*

The global AUC integrates diagnostic performance across the entire range of false-positive rates, from 0.0 to 1.0. In practice, however, clinical use often demands high specificity - to avoid unnecessary invasive coronary angiography or unnecessary brain biopsy - so performance in the low-false-positive-rate region is of disproportionate clinical interest [16-18]. Partial AUC (pAUC) restricts the integration to a clinically relevant interval of the false-positive rate, typically below 15-20% and thereby provides a more clinically informative summary than the global AUC in these settings [19,20]. Formally, pAUC over the interval (e1,e2) is the definite integral of the ROC function ROC(f) with respect to the false-positive rate evaluated from e1 to e2.

➢ *Multi Reader Multi Case (MRMC) Paradigms*

Because interpretation of nuclear cardiology and nuclear neurology studies is subject to inter-reader variability, MRMC ROC designs are used to separate true differences in modality performance from variability attributable to individual readers. Analysis of variance and resampling approaches - most notably the Dorfman-Berbaum-Metz and Obuchowski-Rockette methods - are the standard statistical frameworks for this purpose and have been applied extensively to compare conventional SPECT with PET-based perfusion quantification [21-25].

➢ *Optimal Cut-off Criteria*

Selection of an operating threshold from an empirical ROC curve is most commonly performed using one of two criteria [26,27]:

- Youden's index (J): J = sensitivity + specificity − 1, maximised at the threshold that gives equal weight to false positives and false negatives.
- Closest-to-(0,1): the threshold minimising $d^2 = (1 - \text{sensitivity})^2 + (1 - \text{specificity})^2$, i.e., the point on the curve nearest to perfect classification.

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Neither criterion is universally superior; the choice should reflect the relative clinical cost of false-positive and false-negative misclassification in the specific diagnostic context [6].

➢ *ROC Applications in Nuclear Cardiology*

Nuclear cardiology applies ROC methodology to two related but distinct questions: how imaging modalities compare for the qualitative or semi-quantitative detection of perfusion defects and what quantitative thresholds of absolute myocardial blood flow best identify haemodynamically significant or microvascular coronary disease [28-32].

- *Modality Comparison: SPECT Versus PET Perfusion Imaging*

Multi-reader multi-case studies of myocardial perfusion imaging consistently show higher diagnostic accuracy for PET perfusion tracers (82Rb, 13N-ammonia) than for conventional SPECT tracers (99mTc-sestamibi, 99mTc-tetrofosmin) in detecting obstructive coronary artery disease, defined angiographically as ≥50% or ≥70% stenosis [33-38]. Reported AUC ranges by modality are summarised in Table 1.

Table 1 Modality Comparison: SPECT Versus PET Perfusion Imaging

Modality	Typical AUC	Key references
Conventional SPECT (planar or standard reconstruction)	0.78–0.84	[39,40]
CZT-SPECT / attenuation-corrected SPECT	0.84–0.88	[41–43]
PET myocardial perfusion imaging (82Rb, 13N-ammonia)	0.88–0.93	[44–46]

Cadmium-zinc-telluride detector technology and CT-based attenuation correction reduce soft-tissue attenuation artefact and produce a modest but statistically significant improvement in AUC relative to conventional SPECT (AUC approximately +0.05 to +0.08) [47-50], narrowing but not eliminating the gap with PET.

- *Absolute Quantitation: Stress Myocardial Blood Flow and Myocardial Flow Reserve*

Relative perfusion imaging is limited in multivessel or balanced triple-vessel disease, where no territory of preserved perfusion remains available for internal comparison. Absolute PET quantification of stress myocardial blood flow (sMBF) and myocardial flow reserve (MFR, the ratio of stress to rest MBF) addresses this limitation directly [51-54]. ROC analysis across several large prospective cohorts has established the operating thresholds summarised in Table 2 [55-58].

Table 2 Absolute Quantitation: Stress Myocardial Blood Flow and Myocardial Flow Reserve

Parameter	ROC-derived cut-off	Clinical application	Typical AUC
Stress MBF (sMBF)	1.8–2.0 mL/min/g	Detection of haemodynamically significant stenosis (FFR ≤ 0.80)	0.85–0.89 [55,56,59]
Myocardial flow reserve (MFR)	< 1.5–2.0	Multivessel CAD, coronary microvascular dysfunction, MACE risk	0.86–0.92 [57,58,60]

➢ *ROC Applications in Nuclear Neurology*

In neurodegenerative disease and neuro-oncology, molecular imaging targets pathological protein deposition, regional glucose metabolism or amino-acid transporter activity and ROC analysis is used to establish diagnostic and prognostic thresholds for each of these targets [61-65].

- *Amyloid PET (11C-PiB, 18F-Florbetapir, 18F-Florbetaben, 18F-Flutemetamol)*

ROC analysis underlies the derivation of standardised uptake value ratio (SUVr) thresholds - typically referenced to cerebellar grey matter or whole cerebellum - used to classify scans as amyloid-positive or amyloid-negative [66-70]. When validated against post-mortem neuritic plaque burden, SUVr thresholds of approximately 1.10-1.40 achieve AUC values exceeding 0.90-0.95 [71-74]. ROC-optimised baseline composite cortical SUVr thresholds are also used prognostically, to predict conversion from mild cognitive impairment to clinically overt Alzheimer's disease over a 3–5-year horizon [75-77].

- *Tau PET (18F-Flortaucipir/AV-1451, 18F-MK-6240)*

Tau neurofibrillary tangle burden correlates more closely with cognitive decline than amyloid burden, which tends to plateau earlier in the disease course [78-81]. ROC analysis of entorhinal, temporal and neocortical tau SUVr distinguishes Alzheimer's disease from non-Alzheimer's tauopathies-including progressive supranuclear palsy, corticobasal degeneration and frontotemporal dementia - with AUC greater than 0.92 [82-85]. AUC metrics are also used to validate multi-marker models that combine amyloid (A), tau (T) and neurodegeneration (N, typically assessed with 18F-FDG) within the ATN framework for staging neurodegenerative disease [86-88].

- *Amino-Acid PET in Neuro-Oncology (18F-FET)*

18F-FDG PET is limited in neuro-oncology by high physiological glucose uptake in healthy cortex, which obscures tumour-to-background contrast. Amino-acid PET using O-(2-18F-fluoroethyl)- L-tyrosine (18F-FET) which targets the overexpressed LAT1/LAT2 amino-acid transporters, provides substantially better contrast [89-91].

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ROC curves have been used to evaluate both static uptake ratios - tumour-to-background ratio, expressed as TBRmax and TBRmean and dynamic kinetic parameters, with the thresholds summarised in Table 3 [92-95].

Table 3 Amino-Acid PET in Neuro-Oncology (18F-FET)

Clinical indication	Diagnostic parameter	ROC-derived cut-off	AUC benchmark
Recurrence vs radiation necrosis	TBRmax	2.0–2.3	0.88–0.92 [92,93,96]
Pseudo progression differentiation	TBRmean	1.7–1.9	0.85–0.89 [94,97]
Glioma grading (low-grade vs high-grade)	TBRmax + kinetic Tmax	TBRmax > 2.5 / early time-to-peak	0.89–0.94 [95,98–100]

IV. METHODOLOGICAL PITFALLS AND BEST PRACTICES

Three recurring methodological threats should be considered when interpreting AUC estimates reported in the nuclear cardiology and nuclear neurology literature and when designing future diagnostic-accuracy studies in this field.

- Verification bias arises when patients with a positive index test are preferentially referred for the reference-standard procedure (invasive coronary angiography or brain biopsy), which artificially inflates sensitivity and depresses specificity; correction methods such as that of Begg and Greenes should be applied where selective verification is present [18,26].
- Imperfect reference standards are common: histopathological confirmation is rarely available in routine cardiology practice or in living patients with dementia, so long-term clinical follow-up or composite multimodal endpoints are frequently substituted, with corresponding uncertainty in the resulting AUC estimates [61,72].
- Overfitting in radiomics- and AI-based models is a growing concern as high-dimensional PET/SPECT feature sets are evaluated by ROC analysis; strict separation into independent training, validation and multicentre test sets is required for reported AUC values to generalise across scanner platforms and patient populations [48,88].

V. LIMITATIONS OF THIS REVIEW

As a narrative rather than a systematic review, this synthesis is subject to selection bias in the studies cited and no formal quality or risk-of-bias appraisal was performed. Reported AUC ranges are drawn from heterogeneous patient populations, scanner platforms and reference standards, and should be interpreted as indicative rather than as pooled, meta-analytic estimates. Rapidly evolving areas - in particular AI-based and radiomic diagnostic models are likely to be superseded by newer evidence in the near term.

VI. CONCLUSION

ROC and AUC analyses remain the central statistical framework for validating diagnostic and prognostic performance in nuclear cardiology and nuclear neurology. They underpin the optimisation of quantitative perfusion parameters (stress MBF, myocardial flow reserve) the derivation of neurodegenerative protein-burden thresholds (amyloid and tau SUVr) and the discrimination of tumour progression from treatment effect (18F-FET TBR). As artificial intelligence, deep learning and radiomics are increasingly incorporated into molecular imaging workflows, rigorous ROC methodology - with explicit attention to verification bias, reference standard quality and out-of-sample validation - will remain essential to establishing and maintaining clinical trust in these diagnostic tools.

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