

Modality-Specific Cutoffs for ^{18}F -Florbetaben Amyloid PET/CT and PET/MR: A Derivation and External Validation Study

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Abstract

Background

Anti-amyloid monoclonal antibody therapy has increased the need for accurate amyloid- β positron emission tomography ($A\beta$ -PET) assessment, yet decision thresholds vary across imaging workflows. Considering that ^{18}F -florbetaben (FBB) is applied broadly and maintains robustness for quantitative analyses, we aimed to derive and externally validate modality-specific cutoffs for FBB PET/CT and PET/MR, and provide insight of the relationship between visual-intermediate reads and quantitative gray zones.

Methods

The retrospective study derived cutoffs from 689 participants (254 with PET/CT, 439 with PET/MR) at Huashan Hospital for cutoff derivation, with external validation in 88 additional participants (38 PET/CT from PLA General Hospital, 50 with PET/MR from Xuanwu Hospital). All FBB scans were acquired on the same scanners and centrally processed using the same MRI-guided pipeline before adjudicated three-level visual assessment. Single cutoffs maximized the Youden index, while double cutoffs required both $> 90\%$ sensitivity and $> 90\%$ specificity with $\leq 20\%$ gray-zone coverage. Visual-intermediate scans were excluded from derivation and binary performance analyses. Thresholds were applied externally without refitting. PET/MR Centiloid (CL) values were equation-derived estimates without independent calibration of this implementation.

Results

The study identified FBB single cutoffs of 15.1 CL for PET/CT and 43.4 CL for PET/MR, with corresponding double-cutoff intervals of 11.4–26.3 CL and 31.1–50.9 CL, respectively. External single-cutoff AUCs were 1.000 for PET/CT and 0.998 for PET/MR. The double cutoffs assigned 5.9% and 10.9% of PET/CT and PET/MR external participants to the respective gray zones, and yielded 100% sensitivity and specificity among definitively classified cases. Visual and quantitative uncertainty overlapped only partly: 5/18 (27.8%) visual-intermediate PET/CT scans and 11/29 (37.9%) visual-intermediate PET/MR scans fell within the corresponding quantitative gray zones.

Conclusions

FBB cutoffs retained high visual–quantitative agreement within the evaluated workflow. Double-cutoffs preserved quantitative uncertainty, while visual intermediate reads and quantitative gray-zone remained related but non-equivalent categories. Broader clinical application requires further validation.

Introduction

The advent of anti-amyloid monoclonal antibody therapies has elevated amyloid positron emission tomography ($A\beta$ -PET) from a diagnostic biomarker into a clinical decision-support tool that is now integral to biological diagnosis, treatment eligibility, and therapeutic monitoring in Alzheimer's disease (AD) [1, 2]. In the 2024 revised diagnostic criteria, an abnormal result for $A\beta$ -PET serves as a Core 1 reference to establish a biological diagnosis of AD [1]. Meanwhile, accurate assessment of cerebral $A\beta$ pathology is required before initiating approved anti-amyloid therapies [2–4], while serial amyloid PET can quantify consequent plaque removal and, in selected therapeutic pathways, may inform pharmacodynamic assessment or treatment-discontinuation decisions [2, 4, 5]. These applications underscore the need for consistent interpretation of amyloid PET findings.

Among available amyloid PET tracers, ^{18}F -florbetaben (FBB) has shown robust quantitative performance across analytic methods and presented high agreement with visual reads [6]. In mainland China, FBB was the first amyloid- β PET tracer approved by the National Medical Products Administration (NMPA) and the only one available through routine commercial supply during the study period, making locally validated interpretation timely needed [8]. Its clinical availability worldwide [7] provides additional motivation to establish FBB-specific quantitative references for the imaging workflows used in practice.

Clinical interpretation of amyloid PET primarily relies on visual assessment by trained readers, whereas quantification provides a continuous estimate of amyloid burden that can complement visual reads and increase confidence in challenging or borderline cases [9, 10]. The Centiloid (CL) scale was developed to map tracer- and method-specific amyloid PET onto a common quantitative scale [10–13]. An individual participant data meta-analysis by Blazhenets et al., including 49,227 participants across 53 studies, provided general benchmarks of 18 CL using data-driven modeling, 27 CL against visual reads, and an 11.4–26.3 CL intermediate range [10]. These estimates provide a valuable reference for quantitative interpretation. The substantial between-study heterogeneity (I^2 , 80%–97%) also highlights the importance of evaluating their applicability within defined tracer, acquisition, and processing workflow.

Modality-specific quantitative reference thresholds are of great importance because both PET/CT and PET/MR are applied in clinical practice but are not quantitatively interchangeable. A previous head-to-head study reported systematic differences in uncalibrated quantification between PET/CT and PET/MR, due to differences in attenuation correction, detector technology, and reconstruction [14]. Moreover, the published FBB SUVR-to-CL transformation was derived without PET/MR acquisitions [14–17]. We therefore analyzed cutoffs for PET/CT and PET/MR separately and retained native SUVR for PET/MR alongside CL-referenced estimates, without assuming cross-platform equivalence.

Interpretation of images near the decision boundary raised another challenge. While single cutoffs produce binary classifications, double cutoffs preserve an intermediate zone (also referred to as *grey zone* [18] or *gray zone* [19] in previous studies) between high-confidence negative and positive ranges, thereby accommodating uncertainty in borderline cases [10, 20, 21]. Examining the correspondence between these categories can therefore clarify how visual assessment and quantification contribute to the interpretation of borderline findings.

Against this background, we conducted a three-center derivation and validation study using FBB PET acquired on both PET/CT and PET/MR systems, with centralized quantification and adjudicated three-level visual assessment. Our objectives were to (1) derive FBB-specific single and double cutoffs separately for both modalities; (2) assess cutoff robustness and validate the derived thresholds in independent, modality-matched external cohorts without refitting; (3) characterize the correspondence between visual-intermediate reads and quantitative gray zones.

Methods

Study Design and Participants

The primary derivation and validation cohorts in this retrospective study were assembled from three centers. Visual-read–anchored single and double cutoffs were derived separately for FBB PET/CT and PET/MR and subsequently applied without refitting to the corresponding modality-matched external cohorts. Across centers, images were centrally processed using the same MRI-guided pipeline and evaluated using an adjudicated three-category visual assessment. Demographic and imaging variables, including age, sex, radiotracer, and PET acquisition platform, were collected.

The derivation cohort comprised 254 PET/CT and 439 PET/MR examinations acquired at Huashan Hospital, Fudan University, Shanghai, between August 2022 and February 2026. External validation was conducted at two independent centers. For PET/CT cutoff validation, 38 individuals were included from a single-center, open-label FBB bridging trial conducted in the Chinese PLA General Hospital between January 2021 and September 2022. The PET/MR validation cohort comprised 50 FBB examinations from the memory clinic at Xuanwu Hospital, Capital Medical University. A separate PET/MR dataset acquired on a GE Healthcare system from Xuanwu Hospital was included in an exploratory scanner comparison (**Table S2**).

The study protocols were approved by the Institutional Review Board of Huashan Hospital, Fudan University (KY2022-1062); the Medical Research Ethics Committee of Xuanwu Hospital, Capital Medical University ([2023]044); and the Ethics Committee of the Chinese PLA General Hospital. The FBB bridging trial was registered at ClinicalTrials.gov (NCT05527288), and all trial participants provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki [22].

Amyloid PET Acquisition and Quantification

Image Acquisition

Primary derivation and validation analyses were restricted to scans acquired on systems from one manufacturer, United Imaging Healthcare (UIH). The derivation PET/CT and PET/MR examinations were acquired on uMI 780 and uPMR 790 systems, respectively. External PET/CT examinations were acquired on a uMI 510 system, and external PET/MR examinations on a uPMR 790 system. All PET examinations were acquired following intravenous administration of FBB using site- and scanner-specific protocols.

A subject-specific T1-weighted MRI was available for every PET/CT scan. Thus, the PET/CT and PET/MR designations refer exclusively to the PET acquisition platform. Data from both modalities subsequently underwent the same subject-specific MRI-guided registration, spatial normalization, and region-of-interest quantification procedures. Images with visible truncation artifacts or marked head motion were excluded [23].

Image Preprocessing

Source imaging data were available in Digital Imaging and Communications in Medicine (DICOM) or Neuroimaging Informatics Technology Initiative (NIfTI) format. DICOM series were converted to NIfTI format using dcm2niix (Chris Rorden's dcm2niix version v1.0.20250505) [24]. All input images were visually inspected to verify spatial orientation, complete brain coverage, and file integrity.

Images from all derivation and external cohorts were then centrally reprocessed using a common MRI-guided quantitative pipeline. Quantitative outputs generated by the source studies were not used. Processing was performed in MATLAB R2022b (MathWorks, Natick, MA, USA) with Statistical Parametric Mapping version 25 (SPM25; version v25.01.02; Wellcome Centre for Human Neuroimaging, London, UK) [25, 26].

For both PET/CT and PET/MR examinations, the image origins of the reconstructed PET image and the corresponding subject-specific T1-weighted MRI were reset to their respective image centers. The PET image was rigidly coregistered and resliced to the T1-weighted image using mutual information as the objective function and fourth-degree B-spline interpolation. The T1-weighted image was segmented using the SPM unified segmentation framework, spatially normalized to Montreal Neurological Institute (MNI) space, and the resulting deformation field was applied to the coregistered PET image. Normalized PET images were written at 2-mm isotropic resolution. Coregistration and spatial normalization were visually reviewed before quantitative extraction.

SUVR and Centiloid Quantification

Before volume-of-interest (VOI) extraction, the normalized PET image was resliced to the normalized T1-weighted image grid using trilinear interpolation. Global cortical FBB uptake was quantified in MNI-152 standard space using the standard 2-mm CL cortical composite target VOI (voi_ctx_2mm.nii) and whole-cerebellum reference VOI (voi_WhlCbl_2mm.nii) obtained from the Global Alzheimer's Association Interactive Network (GAAIN) [15]. Mean tracer activity was extracted from each VOI, and the whole-cerebellum–referenced standardized uptake value ratio (SUVR) was calculated as follows:

$$\text{SUVR} = \text{mean uptake in the cortical composite VOI} / \text{mean uptake in the whole-cerebellum reference VOI}$$

Whole-cerebellum-referenced FBB SUVR was converted to the CL scale using the published equation [15]:

$$\text{CL} = 153.4 \times \text{SUVR}_{\text{FBB}} - 154.9$$

The published conversion equation was derived without PET/MR acquisitions and has not been independently validated for the present PET/MR implementation. PET/MR CL values were therefore interpreted as equation-derived estimates and reported alongside native SUVRs. Accordingly, thresholds were derived and externally evaluated separately for PET/CT and PET/MR, and no threshold was transferred across modalities.

Visual Assessment

All PET images went through interpretations of two experienced neuroradiologists (HZ, > 10 years' experience; JW, > 5 years' experience) independently without access to clinical information. Discrepant interpretations were adjudicated by a third senior specialist (CZ, > 20 years' experience), who was also blinded to the quantitative results.

Images were visually categorized into three groups in this study. Following standard FBB visual interpretation criteria, scans were classified as negative when cortical gray–white matter contrast was preserved without evidence of cortical tracer retention in the predefined regions, and as positive when unequivocal cortical retention or loss of gray–white matter contrast was present in at least 1 predefined cortical region [27]. The intermediate category was assigned when a scan could not be classified confidently as either negative or positive after complete regional review.

In order to fit a threshold with better discrimination performance, only participants with adjudicated visual-negative and visual-positive classifications were included for primary ROC analyses and quantitative cutoff derivation. Visual-intermediate participants were excluded as they did not provide an unequivocal binary reference classification, yet these scans were retained for the prespecified secondary analysis of their correspondence with the quantitatively defined gray zone.

Statistical Analysis

PET/CT and PET/MR data were analyzed separately to derive and evaluate modality-specific quantitative thresholds. All performance metrics were calculated against the adjudicated visual-read reference.

Single-cutoff derivation

Within each derivation dataset, receiver operating characteristic (ROC) analyses were performed using visual-negative and visual-positive scans as the binary reference classification; visual-intermediate scans were excluded. The single cutoff was selected by maximizing the Youden index, with values at or above the cutoff classified as quantitatively positive. Discrimination and agreement were summarized using the area under the receiver operating characteristic curve (AUC), sensitivity, specificity, accuracy, positive predictive values (PPV), and negative predictive values (NPV). Cutoffs were reported in CL units alongside their corresponding SUVR values. 95% confidence intervals (CIs) for cutoffs and diagnostic performance metrics were estimated using non-parametric bootstrapping with 5,000 resamples.

Double-cutoff derivation

Double-cutoff analyses were performed using a previously described constrained-search approach [28, 29]. Candidate lower–upper cutoff pairs were systematically evaluated within each derivation dataset using the visual-negative and visual-positive scans. Eligible pairs were required to achieve greater than 90% in both sensitivity and specificity while assigning no more than 20% of individual cases to the quantitative intermediate zone; the pair with the highest Youden index was selected [28]. By implementing double cutoffs, amyloid loads were classified as quantitatively negative, intermediate, and positive. After threshold selection, visual-intermediate individuals were reintroduced to evaluate their distribution across the 3 quantitative categories. Correspondence between the visual intermediate group and the quantitative gray zone was summarized using category-specific agreement proportions.

External validation

The derived single and double cutoffs were applied without re-estimation or recalibration to the corresponding external PET/CT and PET/MR validation datasets. External performance of the derived cutoff was assessed using the same discrimination and classification approach. Sensitivity, specificity, accuracy, PPV, and NPV among the high-confidence group were calculated after excluding quantitatively intermediate results.

All tests were two-sided, with an adjusted $P < .05$ considered statistically significant. Analyses were performed using R, version 4.6.0 (R Foundation for Statistical Computing).

Results

Cohort Characteristics

The derivation cohort included 689 unique participants, including 439 in the PET/MR dataset and 254 in the PET/CT dataset, with 4 participants represented in both modality-specific datasets (Table 1). The mean (SD) age was 66.9 (9.0) years, and 387 participants (56.2%) were female. Modality-specific demographic characteristics and visual-read distributions are summarized in Table 1. After excluding visually intermediate participants, the derivation ROC analyses included 410 PET/MR and 236 PET/CT participants.

Table 1
Characteristics of the Derivation Cohort by PET Acquisition Modality

Characteristic	Overall	PET/MR	PET/CT
Participants, n	689	439	254
Age, years, mean $\pm$ SD	66.9 $\pm$ 9.0	67.4 $\pm$ 8.9	66.1 $\pm$ 9.0
Female, n (%)	387 (56.2)	245 (55.8)	146 (57.5)
PET scanner			
UIH uMI 780, n (%)	254 (36.7)	0 (0.0)	254 (100.0)
UIH uPMR 790, n (%)	439 (63.3)	439 (100.0)	0 (0.0)
Visual read			
Negative, n (%)	292 (42.1)	208 (47.4)	84 (33.1)
Intermediate, n (%)	47 (6.8)	29 (6.6)	18 (7.1)
Positive, n (%)	354 (51.1)	202 (46.0)	152 (59.8)
Data are presented as mean $\pm$ SD or n (%). Overall age and sex summarize 689 unique participants. Modality-specific scanner and visual-read summaries use 693 participant-modality records because 4 participants contributed one retained record to each modality. Percentages use the corresponding denominator. Abbreviations: PET/CT, positron emission tomography/computed tomography; PET/MR, positron emission tomography/magnetic resonance; SD, standard deviation; UIH, United Imaging Healthcare.			

The external validation cohorts included 88 participants, comprising 50 PET/MR and 38 PET/CT participants, each contributing one scan (**Table S1 in Additional file 1**). Four participants in each modality were visually intermediate, leaving 46 PET/MR and 34 PET/CT participants for external ROC evaluation. Visual assessments and quantitative measurements were complete for all included participants.

Single Cutoffs for FBB PET/CT and PET/MR

Derivation of Single Cutoffs

ROC analysis of 236 derivation PET/CT scans with binary visual reads identified 15.1 CL (SUVR, 1.108) as the maximum-Youden cutoff. All 152 visual-positive and all 84 visual-negative participants were classified correctly (AUC, 1.000; 95% CI, 1.000–1.000; sensitivity and specificity, 100%) (Fig. 1).

Among 410 derivation PET/MR participants with binary visual reads, the derived cutoff was 43.4 CL (SUVR, 1.292), with an AUC of 0.999 (95% CI, 0.999–1.000). At this cutoff, 198 of 202 visually positive scans and all 208 visually negative scans received concordant quantitative classifications, yielding 98.0% sensitivity and 100% specificity. The four discordant scans were visually positive but quantitatively negative. The 95% bootstrap CIs for the derived cutoffs were 14.4–21.9 CL for PET/CT and 31.1–46.7 CL for PET/MR (**Figure S1 in Additional file 1**).

External Validation of the Derived Single Cutoffs

The derived cutoffs were then applied without refitting to the corresponding external validation cohorts (Table 2). In the PET/CT external set (n = 34 with binary visual reads), discrimination remained complete (AUC, 1.000; 95% CI, 1.000–1.000). The cutoff correctly classified all 21 visually positive participants and 12 of 13 visually negative participants, yielding 100% sensitivity and 92.3% specificity, while the only discordance was a false-positive quantitative classification.

Table 2
Performance of the Modality-Specific FBB Single Cutoffs in the Derivation and External Validation Cohorts

Modality	Cohort	N	Single cutoff, CL (SUVR)	AUC (95% CI)	Accuracy, % (95% CI)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	Cohen κ
PET/CT	Derivation	236	15.1 (1.108)	1.000 (1.000, 1.000)	100.0 (98.4, 100.0)	100.0 (97.6, 100.0)	100.0 (95.7, 100.0)	100.0 (97.6, 100.0)	100.0 (95.7, 100.0)	1.000
PET/CT	External validation	34	15.1 (1.108)	1.000 (1.000, 1.000)	97.1 (84.7, 99.9)	100.0 (83.9, 100.0)	92.3 (64.0, 99.8)	95.5 (77.2, 99.9)	100.0 (73.5, 100.0)	0.937
PET/MR	Derivation	410	43.4 (1.292)	0.999 (0.999, 1.000)	99.0 (97.5, 99.7)	98.0 (95.0, 99.5)	100.0 (98.2, 100.0)	100.0 (98.2, 100.0)	98.1 (95.2, 99.5)	0.980
PET/MR	External validation	46	43.4 (1.292)	0.998 (0.993, 1.000)	97.8 (88.5, 99.9)	95.8 (78.9, 99.9)	100.0 (84.6, 100.0)	100.0 (85.2, 100.0)	95.7 (78.1, 99.9)	0.957
Cutoffs derived in the derivation cohorts were applied unchanged to the corresponding external cohorts. Visual-intermediate participants were excluded from binary analyses. AUCs were calculated from continuous measures; other performance metrics used fixed modality-specific cutoffs. PET/CT and PET/MR cutoffs were evaluated separately and should not be directly compared. Abbreviations: AUC, area under the receiver operating characteristic curve; CL, Centiloid; NPV, negative predictive value; PET/CT, positron emission tomography/computed tomography; PET/MR, positron emission tomography/magnetic resonance; PPV, positive predictive value; SUVR, standardized uptake value ratio.										

Among 46 external PET/MR participants, the AUC was 0.998 (95% CI, 0.993–1.000). The cutoff correctly classified 23 of 24 visually positive participants and all 22 visually negative participants, yielding 95.8% sensitivity and 100% specificity. The only discordant participant was visually positive but quantitatively negative. Thus, both modality-specific cutoffs retained high visual–quantitative agreement in external validation without recalibration

Double Cutoffs for FBB PET/CT and PET/MR

Derivation of Double Cutoffs

CL distributions exhibited a bimodal pattern with a low-density transition region between negative and positive clusters (Fig. 2). Rank-ordered CL values further illustrated the positions of the lower and upper boundaries relative to individual scans and their visual-read categories in both derivation cohorts (Fig. 3A and B). Across candidate cutoff pairs, widening the quantitative gray zone reduced errors among definitively classified scans at the cost of lower definitive coverage. The prespecified selection procedure identified double cutoffs of 11.4–26.3 CL for PET/CT and 31.1–50.9 CL for PET/MR. These thresholds established modality-specific quantitative gray zones while preserving high rates of definitive classification.

Among 236 PET/CT participants with binary visual reads, 5 (2.1%) were assigned to the gray zone, leaving 231 (97.9%) definitively classified (Table 3). In PET/MR, 16 of 410 participants (3.9%) were assigned to the gray zone, leaving 394 (96.1%) definitively classified. All definitively classified participants in both modalities were fully concordant with the binary visual reads (sensitivity and specificity, 100%; Cohen κ , 1.000), and no case was assigned to the opposite definitive category.

Table 3
Performance of the Modality-Specific FBB Double Cutoffs in the Derivation and External Validation Cohorts

Modality	Cohort	Binary visual-reference, No.	Quantitative gray-zone scans, n (%)	Definitively classified, n (%)	Double cutoff, CL	Accuracy, % (95% CI)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	Cohen κ
PET/CT	Derivation	236	5 (2.1)	231 (97.9)	11.4–26.3	100.0 (98.4, 100.0)	100.0 (97.6, 100.0)	100.0 (95.5, 100.0)	100.0 (97.6, 100.0)	100.0 (95.5, 100.0)	1.000
PET/CT	External validation	34	2 (5.9)	32 (94.1)	11.4–26.3	100.0 (89.1, 100.0)	100.0 (83.9, 100.0)	100.0 (71.5, 100.0)	100.0 (83.9, 100.0)	100.0 (71.5, 100.0)	1.000
PET/MR	Derivation	410	16 (3.9)	394 (96.1)	31.1–50.9	100.0 (99.1, 100.0)	100.0 (98.1, 100.0)	100.0 (98.2, 100.0)	100.0 (98.1, 100.0)	100.0 (98.2, 100.0)	1.000
PET/MR	External validation	46	5 (10.9)	41 (89.1)	31.1–50.9	100.0 (91.4, 100.0)	100.0 (84.6, 100.0)	100.0 (82.4, 100.0)	100.0 (84.6, 100.0)	100.0 (82.4, 100.0)	1.000

Double cutoffs were derived internally and applied externally without recalibration. Binary performance excludes visual-intermediate participants and participants in the quantitative gray zone; reported metrics describe definitively classified participants. Cutoffs are modality-specific. Abbreviations: CI, confidence interval; CL, Centiloid; NPV, negative predictive value; PET/CT, positron emission tomography/computed tomography; PET/MR, positron emission tomography/magnetic resonance; PPV, positive predictive value.

Abbreviations: AUC, area under the receiver operating characteristic curve; CL, Centiloid; PET/CT, positron emission tomography/computed tomography; PET/MR, positron emission tomography/magnetic resonance.

External Validation of the derived Double Cutoffs

The derived modality-specific double cutoffs were subsequently applied without recalibration to the corresponding external validation cohorts (Table 3). In the external PET/CT cohort, 2 of 34 binary-reference participants (5.9%) fell within the quantitative gray zone, leaving 32 participants (94.1%) definitively classified. In the external PET/MR cohort, 5 of 46 binary-reference participants (10.9%) fell within the quantitative gray zone, leaving 41 participants (89.1%) definitively classified.

Definitively classified participants in both PET/CT and PET/MR cohorts were all concordant with the visual-read reference, yielding 100% in sensitivity, specificity, and accuracy, and a Cohen κ of 1.000.

Correspondence Between Visual-Intermediate Reads and the Quantitative Gray Zone

Visual and quantitative classifications were highly concordant at the negative and positive extremes (Fig. 4). In PET/CT, 81 of 84 visually negative participants (96.4%) and 150 of 152 visually positive participants (98.7%) received the corresponding definitive quantitative classification. The remaining 5 participants fell within the quantitative gray zone, and none were assigned to the opposite definitive category. The corresponding proportions in PET/MR were 199 of 208 (95.7%) and 195 of 202 (96.5%), respectively, while the remaining 16 participants were within the gray zone, again with no opposite definitive classifications.

Visual-intermediate participants, who did not contribute to cutoff derivation, were distributed across all three quantitative zones. In PET/CT, 6 of 18 (33.3%) were quantitatively negative, 5 (27.8%) were within the gray zone, and 7 (38.9%) were quantitatively positive. The corresponding distribution in PET/MR was 6 of 29 (20.7%), 11 (37.9%), and 12 (41.4%), respectively. Continuous quantitative distributions likewise showed overlap of visual-intermediate participants with both visual extremes (Fig. 5). Conversely, visual-intermediate reads accounted for 5 of 10 (50.0%) PET/CT and 11 of 27 (40.7%) PET/MR gray-zone participants. Thus, visual intermediacy and the quantitative gray zone were partially overlapping but non-equivalent categories of classification uncertainty.

Discussion

In this multicenter study, visual-read–anchored FBB quantification yielded modality-specific single and double cutoffs. The single cutoffs were 15.1 CL (SUVR, 1.108) for PET/CT and 43.4 CL (SUVR, 1.292) for PET/MR, with corresponding double-cutoff intervals of 11.4–26.3 CL and 31.1–50.9 CL. The derived thresholds maintained high agreement with the adjudicated visual classifications when applied to the external cohorts without recalibration. The double-cutoff approach assigned definitive quantitative classifications to most visually negative or positive scans, whereas visual-intermediate reads overlapped only partly with the quantitative gray zones.

The individual participant data meta-analysis provided broad CL benchmarks across tracers and imaging workflows [30]. Our study extends this work by evaluating FBB thresholds separately for PET/CT and PET/MR, with centralized MRI-guided processing of derivation data from one center and validation data from two external centers. Apply the derived thresholds without refitting assessed their performance in modality-matched external cohorts under a consistent processing workflow. Retaining visual-intermediate reads as a separate category also allowed the relationship between visual uncertainty and quantitative gray-zone assignment to be examined. Together, these features extend general CL benchmarks toward an FBB-specific, modality-specific, treatment-era framework for clinical implementation. We further proposed an interpretation pathway using quantitative categories to support

expert visual assessment (Fig. 6). Cases within the quantitative gray zone were highly recommended for reassessment of image and processing quality, expert rereading, and, when appropriate, corroboration with complementary biomarkers and clinical information.

The PET/CT estimates can be interpreted in comparison with established Centiloid benchmarks. Our single cutoff of 15.1 CL (95%CI: 14.4–21.9 CL) (**Figure S1 in Additional file 1**) was lower than the pooled visual-read-based cutoff of 27 CL and numerically closer to the data-driven estimate of 18 CL [10]. FBB thresholds derived from young healthy controls have ranged from 13.5 CL using a standard SPM-based pipeline to 18 CL using the ADNI native-space FreeSurfer pipeline [13, 21]. Differences in reference standards, cohort composition, and processing methods limit direct comparison between these estimates [10, 31, 32]. In particular, numerical similarity to thresholds for early amyloid accumulation does not establish equivalent biological meaning. Our cutoff was optimized against adjudicated visual classifications and should therefore be interpreted as a quantitative reference for agreement with visual reads within the evaluated workflow. The PET/CT double-cutoff interval of 11.4–26.3 CL matched the interval reported in the meta-analysis [10]. Earlier Amyloid Imaging to Prevent Alzheimer's Disease (AMYPAD) recommendations similarly identified values below approximately 10 CL and above approximately 30 CL as high-confidence negative and positive ranges, respectively [12]. This convergence supports the clinical plausibility of retaining an intermediate range, although the exact boundaries remain context-dependent. The potential value of this approach lies in explicitly retaining borderline measurements as indeterminate while maintaining high agreement among definitively classified scans.

PET/CT and PET/MR differ in attenuation correction, detector and reconstruction characteristics, and acquisition protocols; thus, quantitative values and decision thresholds should not be transferred directly between modalities without cross-calibration or modality-specific validation [14, 33–35]. PET/MR values in this study were reported on an equation-derived CL-referenced scale that has not been independently calibrated for this implementation. Comparisons with published PET/MR thresholds therefore provide methodological context rather than evidence of measurement equivalence. Xue et al., reported a single cutoff of 32.0 CL and double cutoffs of 18.7–44.2 CL using florbetapir and PiB on UIH and GE HealthCare PET/MR systems [28]. The corresponding estimates in the present study were higher, at 43.4 CL and 31.1–50.9 CL, although the gray-zone intervals overlapped. Differences in tracer composition, reconstruction, and processing may contribute to this variation, but their individual contributions cannot be determined from comparisons between studies. In the cross-platform sensitivity analysis, quantitative differences between the two scanners ranged from 9.6 to 22.2 CL across the visual categories, with significant differences observed in the visually negative and positive groups (**Table S2 and Figure S2 in Additional file 1**). Because these were unpaired acquisitions, the observed differences may reflect both technical factors and differences in the participants studied. Previous head-to-head studies nevertheless support the possibility of platform-related shifts in amyloid quantification [16, 36, 37]. These observations reinforce the need for local verification of thresholds when tracer, scanner platform, acquisition and reconstruction, or processing method differ from those evaluated here [16, 36, 38].

Visual-intermediate reads corresponded only partly with the quantitative gray zones. Among visually intermediate participants, 27.8% in PET/CT and 37.9% in PET/MR fell within the respective gray zones; conversely, visually intermediate reads accounted for 50.0% and 40.7% of gray-zone participants, respectively (Fig. 4). As visually intermediate cases were excluded from cutoff derivation, this comparison was descriptive and was not intended to validate or challenge visual interpretation. The partial overlap likely reflects differences in what the 2 approaches measure: visual assessment integrates regional tracer distribution and gray–white matter contrast, whereas CL quantification summarizes uptake across a global cortical composite. Focal or asymmetric retention, atrophy, image quality, and processing variation may therefore affect the classifications differently [6, 9, 39]. Previous studies likewise found more visual–quantitative discordance or lower reader confidence at intermediate CL levels [40, 41]. A visual-intermediate scan outside the quantitative gray-zone may therefore remain unresolved; its biological classification cannot be established from the quantitative category alone.

Several limitations should be considered. First, the cutoffs were derived against adjudicated visual reads rather than an independent biological or neuropathological standard. The performance estimates therefore reflect visual–quantitative agreement and should not be interpreted as direct measures of accuracy for underlying A β neuropathology. Second, as the unified standardized design was restricted to FBB on the same scanner systems to improve methodological consistency, the derived cutoffs should be referred to with caution when applying to other tracers, reconstruction methods, or processing pipelines [16, 31, 36, 38, 42]. Third, the absence of longitudinal imaging and clinical follow-up precluded evaluation of subsequent category transitions and the long-term prognostic value. Finally, the proposed interpretation pathway was not independently evaluated, and the study did not assess whether these cutoffs improve treatment selection or patient outcomes. Their potential clinical utility therefore warrants prospective evaluation.

Conclusions

This multicenter study identified modality-specific FBB single cutoffs of 15.1 CL for PET/CT and 43.4 CL for PET/MR, with corresponding double-cutoff intervals of 11.4–26.3 CL and 31.1–50.9 CL recommended for clinical practice. Together, these findings provide a practical framework for integrating FBB quantification with expert visual interpretation, supporting more consistent assessment of amyloid status and management for borderline scans in diagnostic and anti-amyloid treatment pathways.

Abbreviations

A β
Amyloid- β
AD
Alzheimer's disease

AUC
Area under the receiver operating characteristic curve
CI
Confidence interval
CL
Centiloid
DICOM
Digital Imaging and Communications in Medicine
FBB
18F-florbetaben
GAAIN
Global Alzheimer's Association Interactive Network
MNI
Montreal Neurological Institute
MRI
Magnetic resonance imaging
NIfTI
Neuroimaging Informatics Technology Initiative
NMPA
National Medical Products Administration
NPV
Negative predictive value
PET
Positron emission tomography
PET/CT
Positron emission tomography/computed tomography
PET/MR
Positron emission tomography/magnetic resonance
PPV
Positive predictive value
ROC
Receiver operating characteristic
SD
Standard deviation
SPM25
Statistical Parametric Mapping version 25
SUVR
Standardized uptake value ratio
UIH
United Imaging Healthcare
VOI
Volume of interest

Declarations

Ethics approval and consent to participate

The derivation study was approved by the Ethics Committee of Huashan Hospital, Fudan University (KY2022-1062). The external PET/MR study was approved by the Medical Research Ethics Committee of Xuanwu Hospital, Capital Medical University ([2023]044). The external PET/CT cohort was derived from a study approved by the Ethics Committee of the Chinese PLA General Hospital (ClinicalTrials.gov identifier NCT05527288). Written informed consent was obtained from all participants. All procedures were conducted in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable. No identifiable individual participant information is presented in this article.

Availability of data and materials

The imaging data supporting the findings of this study are not publicly available because of participant privacy and institutional data-governance restrictions.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

The study was conceived by CTZ and designed by SMY and JW. SMY contributed to image data collection and organization in the derivation cohort. SSY coordinated participant recruitment and data acquisition in external cohorts. HHZ and JW performed the visual assessments and CTZ contributed to adjudication of visual interpretation. JW and LL confirmed the image-processing pipeline and SMY performed the statistical analyses. SMY drafted the manuscript. CTZ and QHZ supervised the study. All authors critically revised the manuscript, read and approved the final version, and agreed to be accountable for the work.

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Figures

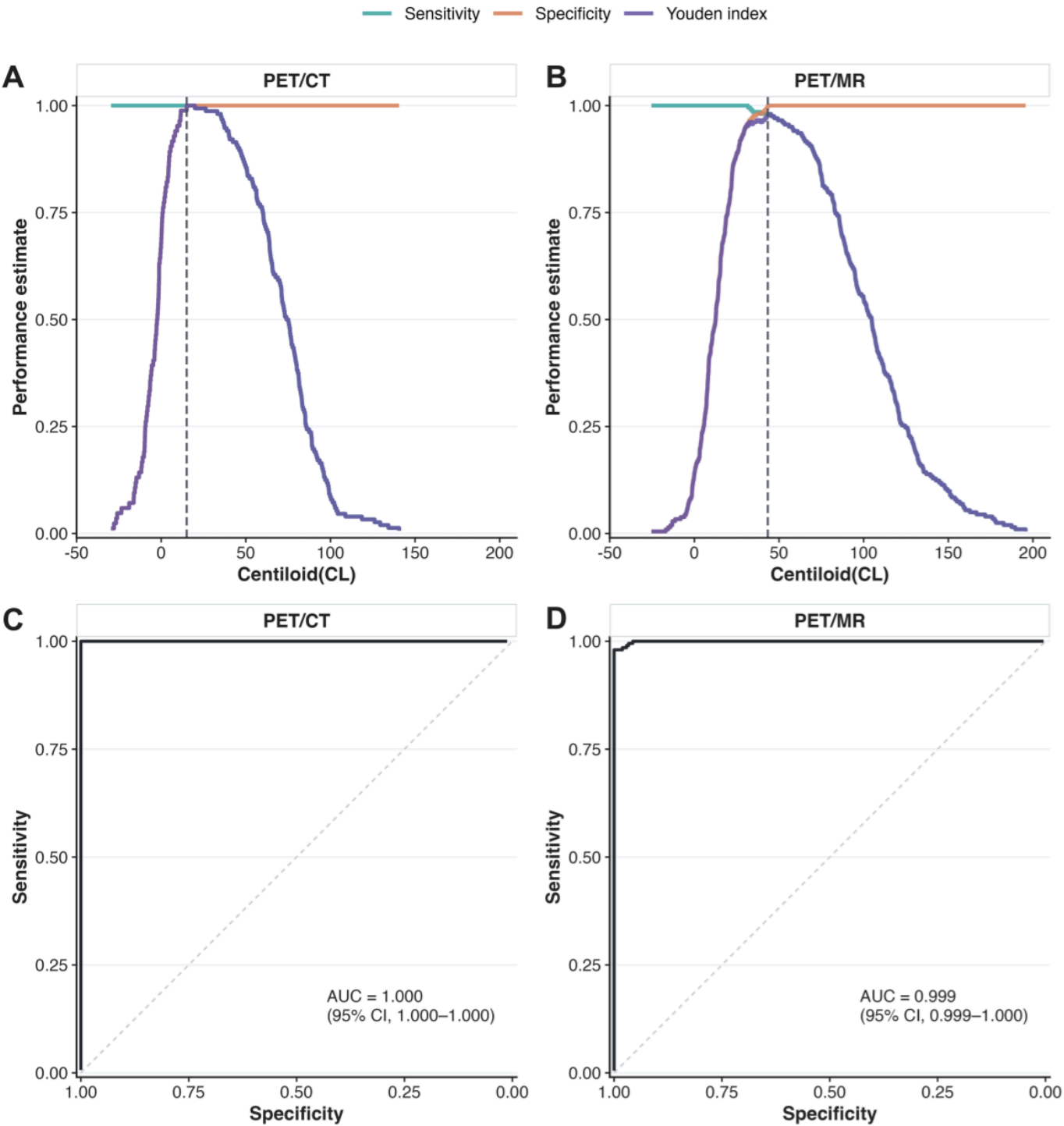


Figure 1

Derivation of Single Cutoffs for FBB PET/CT and PET/MR

A and B, Sensitivity, specificity, and Youden index across candidate CL thresholds for PET/CT and PET/MR, respectively. Dashed lines indicate the selected cutoffs of 15.065 CL for PET/CT and 43.357 CL for PET/MR. **C and D**, Receiver operating characteristic curves for discriminating visual-positive from visual-negative scans using continuous CL values. AUCs were 1.000 (95% CI, 1.000–1.000) and 0.999 (95% CI, 0.999–1.000), respectively; diagonal lines indicate chance discrimination.

Analyses included 236 PET/CT and 410 PET/MR participants with binary visual classifications; visual-intermediate participants were excluded. The Youden index was calculated as sensitivity + specificity – 1. AUCs reflect continuous discrimination rather than fixed-cutoff performance. PET/MR values are presented on the equation-derived CL-referenced scale.

Abbreviations: AUC, area under the receiver operating characteristic curve; CL, Centiloid; PET/CT, positron emission tomography/computed tomography; PET/MR, positron emission tomography/magnetic resonance.

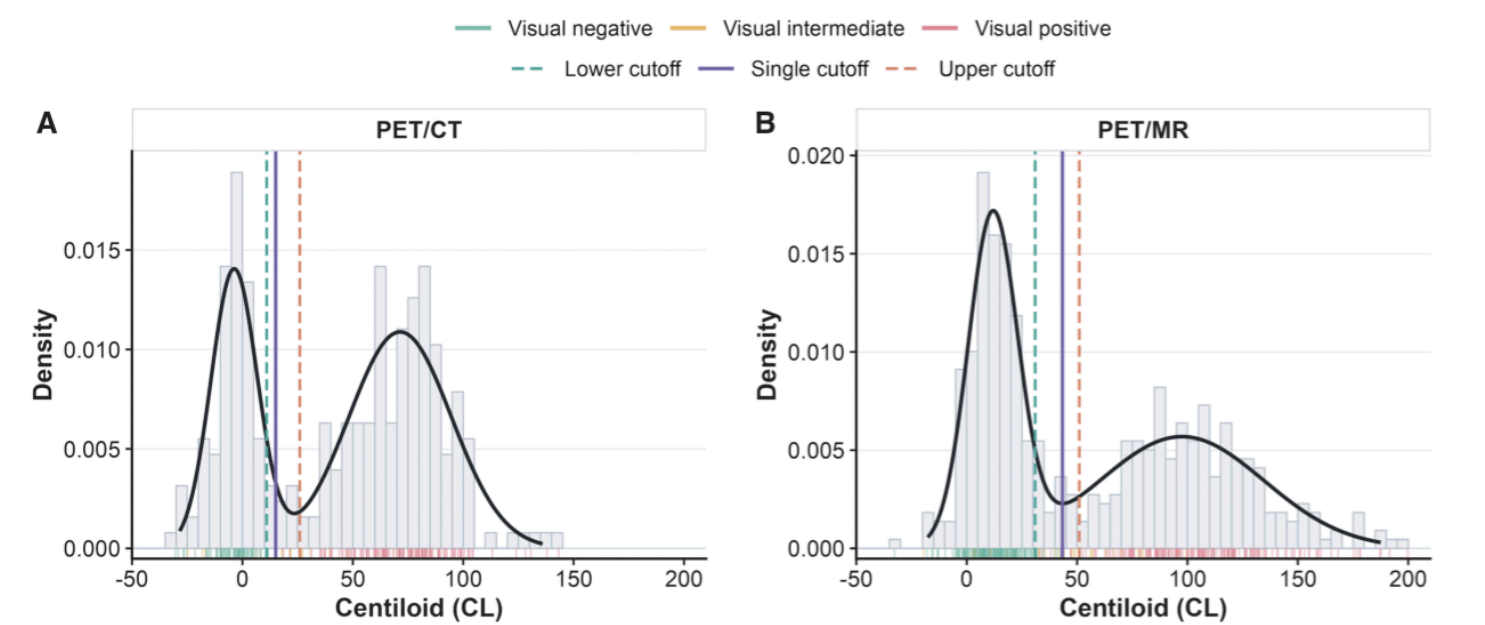


Figure 2

Centiloid Distribution and Single and Double Cutoffs in the Derivation Cohorts

Histograms and kernel density curves show CL distributions in the derivation PET/CT (A; n = 254) and PET/MR (B; n = 439) cohorts. Rug marks represent individual participants and are colored by 3-level visual classification. Vertical lines indicate the lower, single, and upper cutoffs: 11.4, 15.1, and 26.3 CL for PET/CT and 31.1, 43.4, and 50.9 CL for PET/MR, respectively.

Single cutoffs were derived by maximizing the Youden index after excluding visual-intermediate participants, who remain displayed. Under the two-cutoff rule, values equal to or below the lower cutoff were classified as negative, values above the lower cutoff and equal to or below the upper cutoff constituted the gray zone, and values above the upper cutoff were classified as positive. Abbreviations: CL, Centiloid; PET/CT, positron emission tomography/computed tomography; PET/MR, positron emission tomography/magnetic resonance.

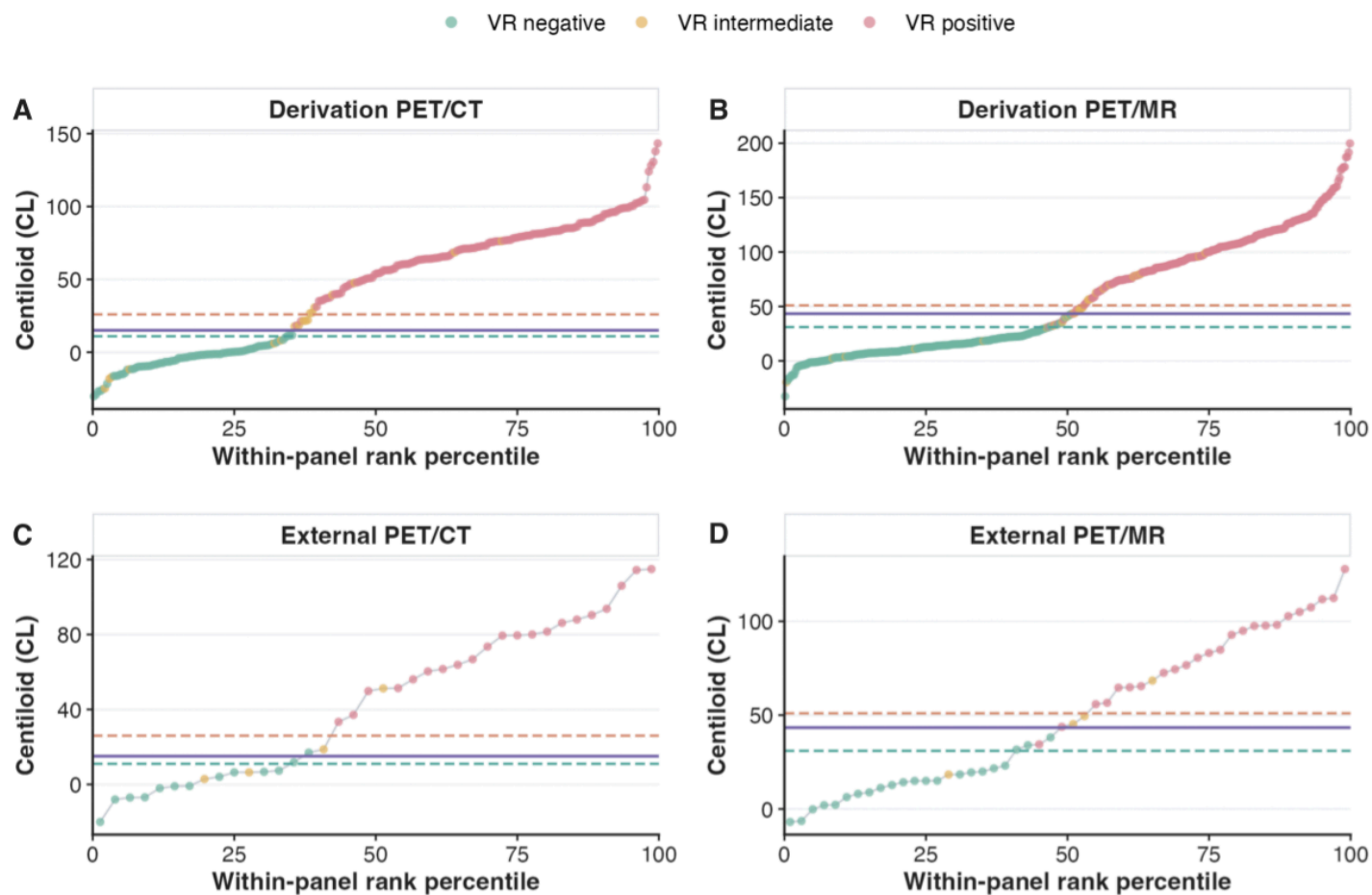


Figure 3

Rank-Ordered Centiloid Values and Cutoffs in the Derivation and External Validation Cohorts

Rank-ordered CL distributions are shown for the derivation PET/CT (A), derivation PET/MR (B), external PET/CT (C), and external PET/MR (D) cohorts. Each point represents one participant, ordered by CL value and colored by visual classification. Dashed lines indicate the lower and upper cutoffs of 11.4 and 26.3 CL for PET/CT and 31.1 and 50.9 CL for PET/MR. The derived cutoffs were applied unchanged to the corresponding external cohorts. Visual-intermediate participants are shown but were excluded from cutoff derivation and binary performance analyses. Rank ordering is for visualization only and does not represent paired or longitudinal data. Abbreviations: CL, Centiloid; PET/CT, positron emission tomography/computed tomography; PET/MR, positron emission tomography/ magnetic resonance.

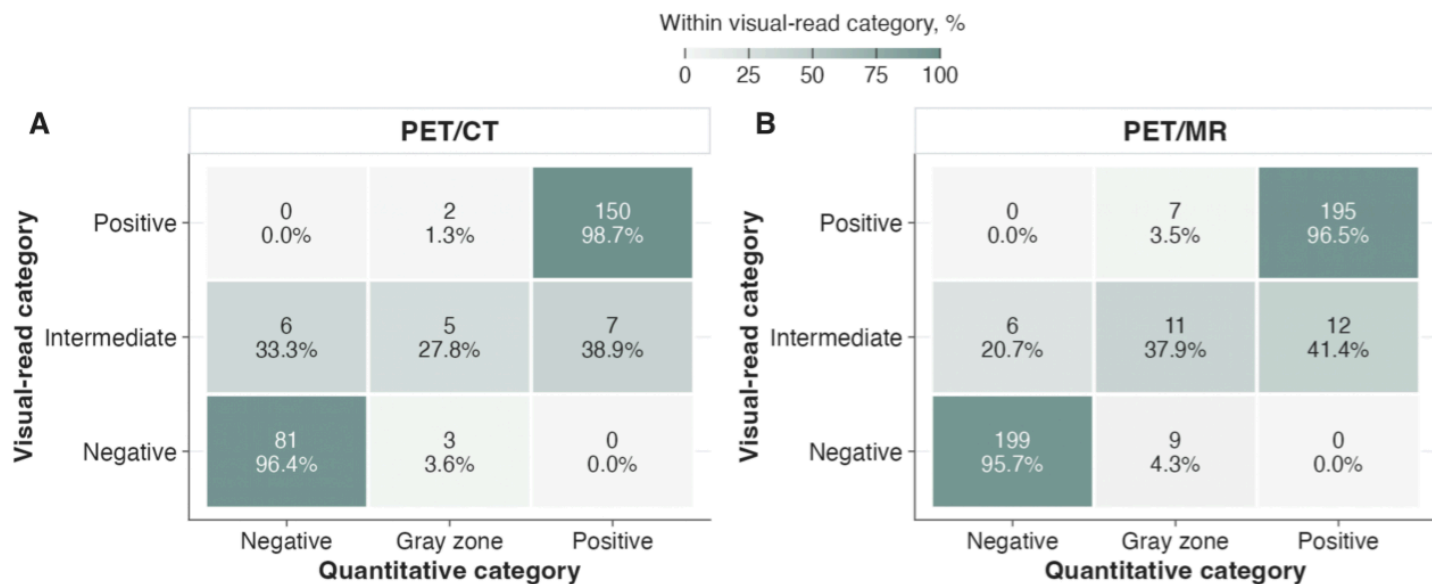


Figure 4

Cross-Classification of Visual-Read and Modality-Specific Quantitative Categories

Cells show the number and row percentage of participants assigned to each quantitative category within each visual-read category in the derivation PET/CT (A; n = 254) and PET/MR (B; n = 439) cohorts. Quantitative negative, gray-zone, and positive categories were defined using the locked double cutoffs of 11.4 to 26.3 CL for PET/CT and 31.1 to 50.9 CL for PET/MR. Darker shading indicates a larger proportion within the corresponding visual-read category. Visual-intermediate participants were excluded from double-cutoff derivation but were included in this cross-classification analysis. Percentages may not total 100 because of rounding. Abbreviations: CL, Centiloid; PET/CT, positron emission tomography/computed tomography; PET/MR, positron emission tomography/magnetic resonance.

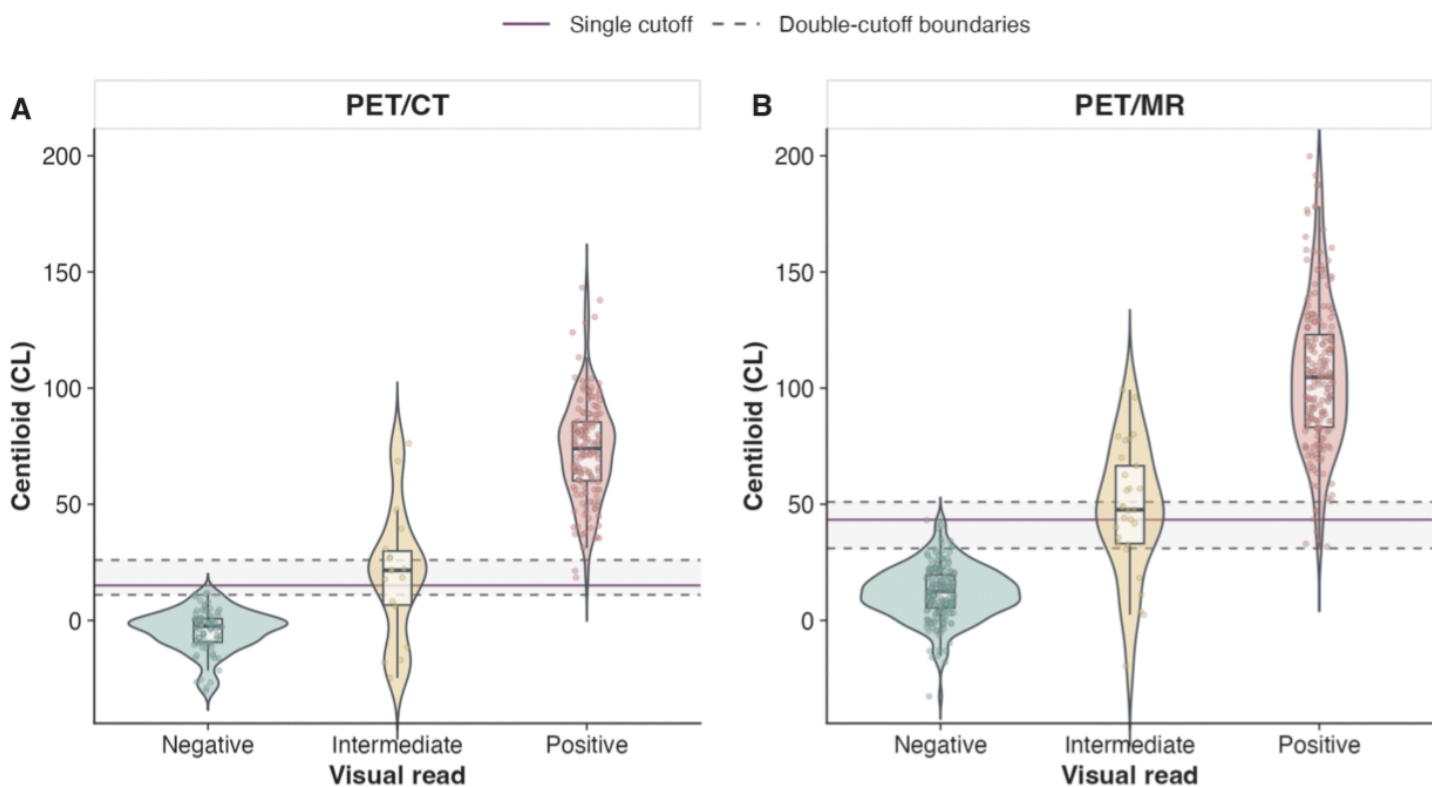


Figure 5

Centiloid Distributions by Visual-Read Categories in the Derivation Cohorts

Violin plots show CL distributions by visual classification in the derivation PET/CT (A; n = 254) and PET/MR (B; n = 439) cohorts. Points represent individual participants; box plots show medians and interquartile ranges. Solid lines indicate the single cutoffs (PET/CT, 15.065 CL; PET/MR, 43.357 CL), and dashed lines indicate the lower and upper cutoffs (PET/CT, 11.4 and 26.3 CL; PET/MR, 31.1 and 50.9 CL). Visual-intermediate participants are shown but were excluded from cutoff derivation. Abbreviations: CL, Centiloid; PET/CT, positron emission tomography/computed tomography; PET/MR, positron emission tomography/magnetic resonance.

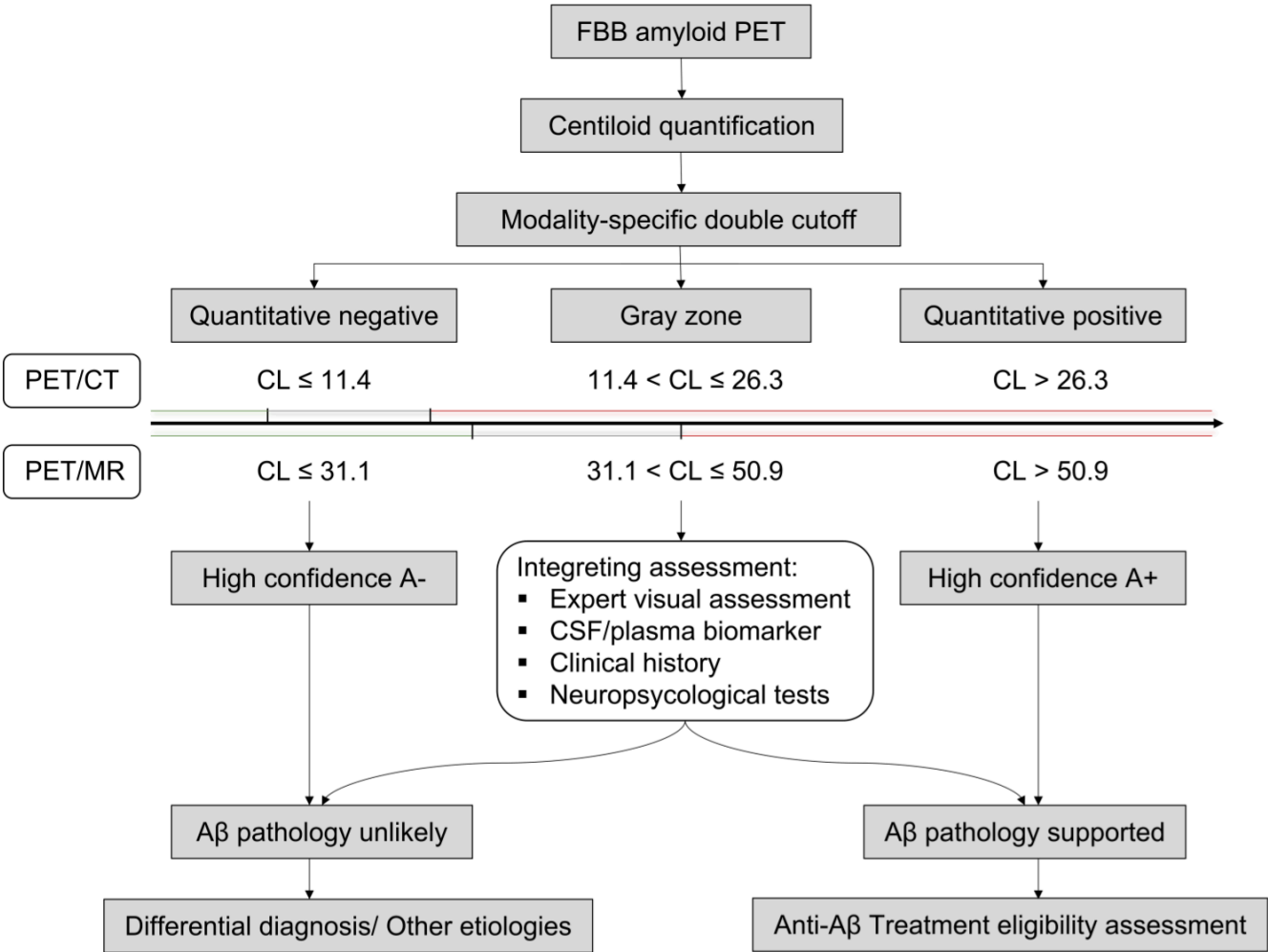


Figure 6

Proposed Interpretation of Modality-Specific ¹⁸F-Florbetaben PET Double Cutoffs

The diagram presents a proposed clinical interpretation pathway based on modality-specific two-cutoff classifications derived against adjudicated visual reads. Quantitatively negative, gray-zone, and positive ranges were 31.1 CL or lower, above 31.1 through 50.9 CL, and above 50.9 CL for PET/MR; and 11.4 CL or lower, above 11.4 through 26.3 CL, and above 26.3 CL for PET/CT. Results outside the gray zone may support concordant visual interpretations, whereas gray-zone or discordant results warrant review of image and processing quality and, when appropriate, corroborating CSF or validated plasma biomarkers. Subsequent evaluation of alternative etiologies or anti-amyloid treatment eligibility requires integrated clinical assessment. This proposed pathway was not independently evaluated. Quantification is intended to complement, not replace, expert visual interpretation and clinical judgment. PET/MR CL values are equation-derived, implementation-specific estimates rather than validated platform-independent measurements. High confidence denotes agreement with visual classification, not neuropathologic certainty. Abbreviations: Aβ, amyloid-β; CL, Centiloid; CSF, cerebrospinal fluid; PET/CT, positron emission tomography/computed tomography; PET/MR, positron emission tomography/magnetic resonance.

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