Consistency and Diagnostic Performance of Coronary CT-derived Fractional Flow Reserve Based on Different Deep Learning Algorithms: Postprint

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Abstract

Background: Computed tomography-derived fractional flow reserve (CT-FFR) has demonstrated favorable diagnostic performance; however, the consistency between CT-FFR values calculated by different deep learning algorithms has not been evaluated. Purpose: This study aimed to evaluate the consistency of CT-FFR based on two deep learning algorithms and to validate its diagnostic performance using invasive coronary angiography (ICA) or invasive FFR as reference. Methods: From January 2017 to June 2021, 389 patients suspected or confirmed with coronary artery disease (CAD) were enrolled as study participants at Qilu Hospital of Shandong University, comprising a cohort of patients who underwent coronary computed tomography angiography (CCTA), ICA, or FFR measurement. Fifty-five patients successively underwent CCTA and ICA examinations within 90 days, among whom 23 patients underwent FFR measurement after CCTA. Bland-Altman analysis was employed to evaluate the agreement between CT-FFR values, and the diagnostic performance of CT-FFR and CCTA was compared using ICA or invasive FFR as reference. Results: This study included a total of 389 patients, including 181 males (46.5%) and 208 females (53.5%), with a mean age of (55.1$±$10.9) years; a total of 1,161 coronary arteries were analyzed. CT-FFR based on Software 1 identified 172 (14.8%) vessels with functionally significant stenosis, whereas Software 2 identified 114 (9.8%). Bland-Altman analysis revealed that CT-FFR from Software 1 was slightly overestimated overall, with a mean difference of 0.05; the mean differences for the left anterior descending artery, left circumflex artery, and right coronary artery were 0.05, 0.04, and 0.05, respectively. In compar-

ison with invasive FFR, CT-FFR based on both Software 1 and Software 2 demonstrated moderate correlation (r=0.44, 0.53) and good agreement (mean differences of -0.03 and -0.06, respectively). Regarding diagnostic performance, CCTA exhibited the highest sensitivity (97.8%) and negative predictive value (98.5%), but its specificity (66.7%) and positive predictive value (57.7%) were significantly lower than those of CT-FFR. CT-FFR based on Software 1 exhibited a sensitivity of 89.1%, specificity of 80.8%, positive predictive value of 68.3%, negative predictive value of 94.1%, and accuracy of 83.4%; CT-FFR based on Software 2 exhibited a sensitivity of 80.4%, specificity of 93.9%, positive predictive value of 86.0%, negative predictive value of 91.2%, and accuracy of 89.7%. ROC curve analysis revealed that the diagnostic value of both CT-FFR methods (AUC=0.91, 0.89) was superior to that of CCTA (AUC=0.82, P<0.05). Conclusion: Good consistency exists between CT-FFR values based on Software 1 and Software 2, although CT-FFR from Software 1 is slightly overestimated. Overall, CT-FFR demonstrates favorable diagnostic performance in detecting the functional significance of coronary artery stenosis.

Full Text

Consistency and Diagnostic Performance of Coronary Computed Tomography-Derived Fractional Flow Reserve: A Study Based on Different Deep Learning Algorithms

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Abstract

Background: Computed tomography-derived fractional flow reserve (CT-FFR) has demonstrated good diagnostic performance, but the consistency of CT-FFR values calculated by different deep learning algorithms has not been evaluated.

Objective: This study aims to assess the consistency of CT-FFR based on two deep learning algorithms and validate its diagnostic performance using invasive coronary angiography (ICA) or invasive fractional flow reserve (FFR) as

references.

Methods: From January 2017 to June 2021, 389 patients with suspected or confirmed coronary artery disease (CAD) were enrolled at Qilu Hospital of Shandong University, comprising a cohort that underwent coronary computed tomography angiography (CCTA), ICA, or FFR measurement. Among them, 55 patients underwent ICA within 90 days after CCTA, and 23 patients underwent FFR measurement after CCTA. Bland-Altman analysis was used to evaluate the consistency of CT-FFR, and the diagnostic performance of CT-FFR was compared with that of CCTA using ICA or invasive FFR as the reference standard.

Results: A total of 389 patients were included (181 men [46.5%] and 208 women [53.5%]; mean age 55.1$±$10.9 years), with 1,161 coronary arteries analyzed. CT-FFR based on Software 1 identified 172 vessels (14.8%) with functionally significant stenosis, while Software 2 identified 114 vessels (9.8%). Bland-Altman analysis showed that CT-FFR derived from Software 1 slightly overestimated values overall, with a mean difference of 0.05 (0.05 in LAD, 0.04 in LCX, and 0.05 in RCA). Compared with invasive FFR, both CT-FFR algorithms showed moderate correlation (r=0.44 for Software 1; r=0.53 for Software 2) and good agreement, with mean differences of -0.03 and -0.06, respectively. In diagnostic performance, CCTA had the highest sensitivity (97.8%) and negative predictive value (98.5%) but substantially lower specificity (66.7%) and positive predictive value (57.7%) than CT-FFR. Software 1-based CT-FFR achieved 89.1% sensitivity, 80.8% specificity, 68.3% positive predictive value, 94.1% negative predictive value, and 83.4% accuracy. Software 2-based CT-FFR showed 80.4% sensitivity, 93.9% specificity, 86.0% positive predictive value, 91.2% negative predictive value, and 89.7% accuracy. ROC curve analysis confirmed that both CT-FFR algorithms outperformed CCTA, with AUC values of 0.91 (Software 1) and 0.89 (Software 2) compared to 0.82 for CCTA (P<0.05).

Conclusion: Good consistency was observed between CT-FFR values based on Software 1 and Software 2, although CT-FFR based on Software 1 showed slight overestimation. Overall, CT-FFR demonstrated good diagnostic performance in detecting the functional significance of coronary stenosis.

Keywords: Computed tomography; Fractional flow reserve; Computed tomography-derived fractional flow reserve; Deep learning; Coronary artery disease

Introduction

Invasive coronary angiography (ICA) is a commonly used invasive technique for diagnosing coronary artery disease (CAD). Due to its limitations, inability to prolong life, and low diagnostic yield, invasive fractional flow reserve (FFR) has attracted widespread attention. Since its first use 30 years ago to assess

the functional significance of coronary stenosis, FFR has been widely applied in treatment decision-making, particularly regarding revascularization. However, its application is limited by invasiveness, potential for serious complications, and high cost. Coronary computed tomography angiography (CCTA) is a non-invasive anatomical imaging tool used to detect potential CAD due to its high sensitivity and negative predictive value (NPV). Consequently, CCTA was recommended as a Class I indication in the 2019 European Society of Cardiology (ESC) Guidelines and suggested for symptomatic chronic coronary disease (CCD) patients in the 2022 American College of Cardiology (ACC)/American Heart Association (AHA) Guidelines. The main drawback of CCTA is its inability to functionally assess coronary stenosis. Determining the functional significance of coronary stenosis is a crucial step in evaluating myocardial ischemia severity, which has led to the development of non-invasive FFR technologies.

The earliest form of this technology, CT-FFR based on full-order computational fluid dynamics (CFD) models, is a compelling approach interpreted by independent core laboratories in a blinded manner. Multicenter clinical studies have confirmed good diagnostic performance of CT-FFR in detecting functionally significant coronary stenosis. However, full-order CFD-based CT-FFR requires offline computation on supercomputers with long processing times. One CT-FFR calculation software based on CFD models enables on-site computation, significantly reducing the time required to identify CT-FFR values, and has shown good diagnostic accuracy in detecting functionally significant coronary stenosis. To address the limitations of full-order models, reduced-order models have been used in CT-FFR studies, demonstrating good accuracy in determining functional significance of coronary stenosis.

Another approach involves digital remodeling of coronary arteries through deep learning algorithms to predict FFR values, similar to CFD model applications. Deep learning-based CT-FFR requires less computation time for on-site calculation. Many clinical studies have shown that deep learning-based CT-FFR can perform risk stratification, prognostic assessment, and guide treatment decisions. Moreover, CT-FFR demonstrates superior diagnostic accuracy compared to CCTA alone in identifying functionally significant coronary stenosis. Compared with other imaging modalities, CT-FFR also shows better diagnostic performance at both patient and vessel levels than single photon emission computed tomography (SPECT). CT-FFR is a functional assessment tool with broad potential applications.

However, the consistency of CT-FFR based on different deep learning algorithms has not been evaluated. In clinical practice, accurate interpretation of CT-FFR from different models is crucial for clinicians. Therefore, this study aims to assess the consistency of CT-FFR based on two deep learning algorithms and validate its diagnostic performance using ICA or invasive FFR as references.

Methods

Study Cohort

From January 2017 to June 2021, 389 patients with suspected or confirmed CAD were enrolled at Qilu Hospital of Shandong University, comprising a cohort that underwent CCTA, ICA, or FFR measurement. Among them, 55 patients underwent ICA within 90 days after CCTA, and 23 patients underwent FFR measurement after CCTA. Inclusion criteria were: (1) patients with suspected or known CAD; (2) patients with moderate pre-test probability of CAD as defined by Diamond and Forrester criteria; (3) clinically recommended for ICA; (4) age $\geq$ 18 years. Exclusion criteria included: (1) acute coronary syndrome; (2) severe left ventricular dysfunction (left ventricular ejection fraction <40%); (3) non-ischemic cardiomyopathy; (4) severe arrhythmias such as atrial fibrillation or second/third-degree atrioventricular block; (5) contraindications to adenosine or iodinated contrast agents; (6) renal insufficiency [estimated glomerular filtration rate <60 $\mathrm{mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}}$]; (7) severe chronic obstructive pulmonary disease or chronic asthma history; (8) pregnancy; (9) refusal to sign informed consent. The study followed the Declaration of Helsinki (2013 revision) and was approved by the hospital ethics committee (KYLL-202212-015-1), with individual informed consent waived for this retrospective analysis.

Clinical Data Collection

Body mass index (BMI) was calculated as weight (kg)/height^2 ($\mathrm{m^2}$), with BMI $\geq$ 28 $\mathrm{kg/m^2}$ defined as obesity. Smoking history was defined as smoking $ $1 cigarette daily for $ $6 months continuously or cumulatively, or long-term smoking with cessation <6 months. Hypertension was defined as: (1) without antihypertensive medication, systolic blood pressure >140 mmHg and/or diastolic pressure >90 mmHg on three separate measurements; or (2) with documented hypertension history currently receiving antihypertensive treatment. Diabetes mellitus was defined as: (1) classic symptoms (polyphagia, polydipsia, polyuria, unexplained weight loss) plus $ $1 of: random glucose >11.1 mmol/L, fasting glucose >7.0 mmol/L, HbA1c >6.5%, or 2-hour oral glucose tolerance test >11.1 mmol/L; or (2) documented diabetes history with ongoing treatment. Dyslipidemia was defined as: (1) total cholesterol $ $6.2 mmol/L; (2) HDL cholesterol <1.0 mmol/L; (3) LDL cholesterol $ $4.1 mmol/L; (4) triglycerides $ $2.3 mmol/L; or (5) documented dyslipidemia history with ongoing treatment.

Imaging Protocol

All patients underwent scanning using a third-generation dual-source computed tomography (DSCT) scanner (SOMATOM Force; Siemens Healthineers) with parameters: slice collimation = 192$×$0.6 mm, gantry rotation time = 250 ms, temporal resolution = 66 ms, longitudinal z-axis coverage = 105 mm, tube voltage = 100 kV, with automatic tube current modulation. CARE kV and CARE Dose 4D were used to reduce radiation dose. CCTA used bolus tracking

with region of interest (ROI) placed in the ascending aorta, followed by contrast injection at 4-5 mL/s via antecubital vein and 40 mL saline flush using a dual-syringe power injector. Retrospective ECG-triggered sequential acquisition was performed with trigger window centered in diastole or systole depending on heart rate. Automatic tube voltage and current modulation (CARE kV and CARE Dose 4D, Siemens Healthineers) was applied. The entire procedure took 15-20 minutes.

CCTA Image Post-processing and Analysis

All images were imported to a post-processing workstation (Syngo.via VB10, Siemens Healthineers, Forchheim, Germany) for reconstruction and analysis. Advanced modeled iterative reconstruction was applied with slice thickness = 0.75 mm and interval = 0.50 mm. The optimal diastolic phase was selected to reduce motion artifacts, and image quality was assessed using a 4-point Likert scale: 1 = poor vessel visualization with significant artifacts; 2 = partially blurred vessel borders with some artifacts; 3 = clear vessel borders with mild artifacts; 4 = clear vessel borders without artifacts. Vessels with scores <2 were excluded. A semi-automatic workflow of "initial algorithmic segmentation + manual interactive correction" was used to mask calcification artifacts: software automatically outlined the lumen, then physicians manually removed calcification artifacts and corrected boundaries layer-by-layer to reduce "pseudo-stenosis" overestimation of pressure gradients. The initial threshold was set at 45% of mean CT value of the aorta in the same slice, with manual correction area allowed <5%. All procedures were performed by two radiologists with 5 and 8 years of experience, respectively. Coronary arteries with diameter $ $1.5 mm were evaluated for diameter stenosis percentage. Functionally significant CAD was defined as diameter stenosis $ $50% in at least one epicardial coronary artery.

CT-FFR Assessment Based on Software 1

CT-FFR based on Software 1 was calculated using commercially available software (Shukun-FFR, Shukun Technology). The calculation process included automatic reconstruction of coronary tree and derivation of CT-FFR values. First, coronary arteries were extracted via a U-net model to present complete structure. Second, an enhanced convolutional neural network model combined 3D and 2D modes for plaque detection. To ensure accurate branch connections, standard 3D U-net and shortest path search algorithms were applied. Automatic coronary tree reconstruction took approximately two minutes. Subsequently, an improved reduced-order model calculated pressure along vessel centerlines, dividing them into stenotic and non-stenotic regions. Pressure in each region was computed, and final intravascular pressure was aggregated from reduced-order model-derived pressure and neural network-inferred pressure. CT-FFR values were calculated by a core laboratory in blinded fashion as the ratio of pressure in stenotic coronary artery to theoretical pressure without stenosis. CT-FFR

was assessed 2.0 cm distal to the last stenosis, or at 1.5 mm vessel diameter if no stenosis or stenosis diameter <1.5 mm [Figure 1: see original paper]A.

CT-FFR Assessment Based on Software 2

CT-FFR was calculated using commercially available software (DEEPVESSEL FFR, Keya Medical Technology) based on an algorithm trained through a deep learning framework. CT-FFR was analyzed via a Tree-structured Recurrent Neural Network (TreeVes-Net) trained on a database of 13,000 synthetic coronary trees based on geometric parameters of coronary anatomy and validated with 180 real coronary trees. Geometric parameter values were randomly assigned within appropriate ranges in the training database. TreeVes-Net inputs were fluid dynamics-related geometric feature vectors, including local vessel features, local stenosis features, and global features extracted from synthetic coronary input images. FFR values at each point along coronary centerlines were calculated by solving Navier-Stokes equations using finite element method. To handle long-term dependencies of fluid states at different points in TreeVes-Net, a bidirectional recurrent neural network with long short-term memory was employed. Three-dimensional color-coded coronary maps were generated to visualize CT-FFR values as output. CT-FFR calculation was performed by a core laboratory in blinded fashion, with results returned to researchers for blinded analysis. CT-FFR was measured 20 mm distal to the last stenosis, with the lowest CT-FFR value recorded for multiple lesions in the same vessel [Figure 1: see original paper].

ICA and Invasive FFR Assessment

ICA was performed using standard methods. All coronary arteries and major branches were assessed by an interventional cardiology team blinded to clinical information and CT-FFR values. FFR was measured using a 0.014-inch pressure wire (Prime Wire Prestige PLUS, Volcano Corporation) during hyperemia induced by intravenous adenosine infusion (140 $\mathrm{mg \cdot kg^{-1} \cdot min^{-1}}$). Functionally significant stenosis was defined as ICA-determined coronary narrowing >90.0%, or invasive FFR $ $0.80 when stenosis was 30.0%-90.0%. Functionally non-significant stenosis was defined as ICA-determined narrowing <30.0%, or invasive FFR >0.80 when stenosis was 30.0%-90.0%.

Statistical Analysis

Statistical analysis was performed using MedCalc software (MedCalc 20, Ostend, Belgium). Normal distribution was tested using Kolmogorov-Smirnov test. Normally distributed continuous variables were expressed as ($\bar{x}\pm s$) and compared between groups using independent samples t-test. Non-normally distributed continuous variables were expressed as M(P25, P75) and compared using rank-sum test. Categorical variables were expressed as n(%) and compared using ^{2} test or Fisher' s exact test. Scatter plots were generated to show correlation

between CT-FFR and invasive FFR. Bland-Altman plots assessed agreement between CT-FFR from Software 1, Software 2, and invasive FFR, with 95% limits of agreement (LOAs). Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy with 95%CI were calculated. Receiver operating characteristic (ROC) curves were constructed to evaluate diagnostic accuracy of all parameters in detecting functionally significant vessels, with area under curve (AUC) compared using Delong test. P<0.05 was considered statistically significant.

Results

Patient Baseline Characteristics

A total of 389 patients with suspected or known CAD were included (181 men [46.5%] and 208 women [53.5%]; mean age 55.1$±$10.9 years), comprising 1,161 coronary arteries. CT-FFR based on Software 1 identified 172 vessels (14.8%) with functionally significant stenosis, while Software 2 identified 114 vessels (9.8%). Patient demographics and baseline characteristics are shown in Table 1 .

Diagnostic Performance of CT-FFR in Detecting Functionally Significant Coronary Stenosis

Scatter plots showed correlation coefficients of 0.44 (95%CI=0.11-0.68, P=0.011) between Software 1-based CT-FFR and invasive FFR, and 0.53 (95%CI=0.22-0.74, P=0.002) between Software 2-based CT-FFR and invasive FFR. Bland-Altman analysis demonstrated good agreement between Software 1-based CT-FFR and invasive FFR, with a mean difference of -0.03 (95%CI=-0.10-0.04, P=0.360), and between Software 2-based CT-FFR and invasive FFR, with a mean difference of -0.06 (95%CI=-0.12-0.00, P=0.069) [Figure 2: see original paper]A-D.

Comparison of Diagnostic Accuracy Between CCTA and CT-FFR

Compared with Software 1 and Software 2-based CT-FFR, CCTA showed the highest sensitivity (97.8%) and negative predictive value (98.5%) but lower specificity. In positive predictive value, CCTA also performed worse than both CT-FFR algorithms. Software 1 and Software 2-based CT-FFR demonstrated higher diagnostic accuracy than CCTA (Table 2).

ROC Curve Analysis

ROC curve analysis showed that Software 1-based CT-FFR (AUC=0.91, 95%CI=0.85-0.96) and Software 2-based CT-FFR (AUC=0.89, 95%CI=0.83-0.94) both had superior diagnostic value compared to CCTA (AUC=0.82, 95%CI=0.75-0.88), with statistically significant differences (Z=9.469, 16.172; P=0.002, 0.077) [Figure 3: see original paper].

Correlation Between Software 1 and Software 2-Based CT-FFR

Bland-Altman analysis showed a mean difference of 0.05 (95%CI=0.04-0.06, P<0.001) between Software 1 and Software 2-based CT-FFR across 1,161 vessels, with upper limit of 0.23 (95%CI=0.22-0.24) and lower limit of -0.13 (95%CI=-0.14-0.12). At the LAD level (389 vessels), mean difference was 0.05 (95%CI=0.04-0.06, P<0.001), upper limit 0.25 (95%CI=0.23-0.26), lower limit -0.15 (95%CI=-0.16-0.13). At the LCX level (385 vessels), mean difference was 0.04 (95%CI=0.04-0.05, P<0.001), upper limit 0.21 (95%CI=0.19-0.22), lower limit -0.12 (95%CI=-0.13-0.10). At the RCA level (387 vessels), mean difference was 0.05 (95%CI=0.04-0.06, P<0.001), upper limit 0.25 (95%CI=0.23-0.26), lower limit -0.14 (95%CI=-0.15-0.12) [Figure 4: see original paper]A-D. Bland-Altman analysis indicated that Software 1-based CT-FFR slightly overestimated FFR values compared to Software 2.

When CT-FFR was 0.5-<0.6, significant differences existed between Software 1 and Software 2 at all coronary and RCA levels (both P<0.05). In LAD and LCX, Software 2 count was 0 in this range, while Software 1 detected 15 (3.9%) and 4 (1.0%) cases, respectively, with small percentage differences. When CT-FFR was 0.6-<0.7, no significant differences were found at all coronary, LAD, and RCA levels (P>0.05). In LCX, Software 2 count was 0, while Software 1 detected 10 (2.6%) cases, with small percentage differences. When CT-FFR was 0.7-<0.8, significant differences existed between Software 1 and Software 2 at all coronary, LAD, RCA, and LCX levels (^{2}=64.050, 14.993, 15.450, all P<0.05). When CT-FFR was 0.8-<0.9, significant differences existed at all coronary, LAD, and LCX levels (^{2}=18.123, 4.002, 10.148, all P<0.05), but not at RCA level (P>0.05). When CT-FFR was 0.9-1.0, significant differences existed at all coronary levels (^{2}=40.515, P<0.05) and at LAD, LCX, and RCA levels (^{2}=5.824, 18.470, 4.268, all P<0.05) .

Discussion

CCTA offers high sensitivity and negative predictive value for anatomical assessment of CAD but cannot directly reflect functional significance of stenosis. CT-FFR provides a feasible pathway for non-invasive functional assessment by computing or learning coronary hemodynamic information. Previous studies have confirmed its diagnostic value, but most focused on single algorithms/software or comparisons between CFD and machine learning approaches. In real-world clinical practice, hospitals may deploy CT-FFR systems from different vendors/algorithms in parallel, making consistency across different deep learning algorithms and their impact on clinical decision interchangeability a pressing and clinically relevant issue. Building on the evidence described above, this study systematically evaluated two deep learning algorithms regarding their (1) mutual consistency and (2) diagnostic performance relative to ICA/invasive FFR, aiming to provide more actionable evidence for cross-platform interpretation and revascularization decision-making.

Our results show an overall mean difference of 0.05 between Software 1 and Software 2 CT-FFR values, with 0.05, 0.04, and 0.05 at LAD, LCX, and RCA levels, respectively, indicating good consistency at both vessel and overall levels. This aligns with previous studies reporting comparable consistency across different algorithms, likely because both employ anatomical-based multi-scale feature extraction and blood flow pressure approximation, yielding convergent consistency intervals with medium-to-high quality images and common anatomical configurations. Our post-processing control of calcification artifact masking and individualized segmentation thresholds (45% of same-slice aortic value, allowing <5% manual correction) may have also reduced systematic bias from segmentation errors.

In comparisons between the two deep learning CT-FFR methods and invasive FFR, correlation coefficients were r=0.44 for Software 1 and r=0.53 for Software 2, indicating moderate correlation with the gold standard. Bland-Altman analysis showed mean differences of -0.03 and -0.06, suggesting good agreement with invasive FFR. This differs from most previous studies reporting slight underestimation of CT-FFR relative to invasive FFR, possibly due to: (1) residual bias in deep learning and reduced-order/finite element approximation in modeling hyperemic state and microcirculatory resistance; (2) measurement location strategy differences (Software 1 assessed 2.0 cm distal to last stenosis, Software 2 at 20 mm, with different "record lowest value" strategies causing systematic over/underestimation); and (3) relatively limited sample size receiving invasive FFR potentially introducing sampling error and spectrum bias.

In diagnostic performance comparisons, CCTA showed highest sensitivity (97.8%) and NPV (98.5%), highlighting its exclusionary advantages. Both CT-FFR algorithms demonstrated superior specificity, PPV, and accuracy compared to CCTA (Software 1: specificity 80.8%, accuracy 83.4%; Software 2: specificity 93.9%, accuracy 89.7%), indicating better diagnostic performance, consistent with COENEN et al. and PONTONE et al. reporting that CT-FFR introduction significantly improves specificity and overall accuracy. This may be because CT-FFR reduces false positives for functional significance in "moderate stenosis" under an anatomy-function integrated framework. ROC analysis showed AUCs of 0.91 and 0.92 for Software 1 and 2, respectively, both higher than CCTA' s 0.82, with Software 1 showing significant difference from CCTA (P=0.002) and Software 2 showing improvement trend without statistical significance (P=0.077), similar to previous CT-FFR studies reporting AUCs around 0.84. Differences may be attributed to: (1) our strict image quality control and calcification masking/individualized thresholds reducing anatomical errors; (2) case composition (e.g., high RCA dominance, incomplete LCX reconstruction cases) altering vessel-level AUCs; and (3) different training data/prior distributions between software causing distribution differences in high FFR intervals (0.9-1.0), affecting overall AUC performance.

Regarding distribution differences across FFR intervals, our supplementary analysis showed Software 2 had significantly fewer counts than Software 1 in the 0.9-

1.0 range, but more counts in the 0.8-1.0 range, resulting in higher specificity (93.9%). In the 0.7-<0.8 and 0.8-<0.9 intervals, significant differences existed between the two software in "all coronary arteries/partial branches," suggesting algorithm sensitivity in boundary intervals (near 0.80 threshold). Possible reasons include: different segmentation thresholds and local shear information modeling, varying weights of vessel caliber/plaque morphology in learning features, and measurement site/minimum value recording strategy differences.

These data demonstrate that both deep learning CT-FFR algorithms show good consistency at overall and branch levels, with advantages in specificity, PPV, and overall accuracy compared to CCTA, with Software 2 showing better specificity and accuracy. Both CT-FFR methods showed moderate correlation and good agreement with invasive FFR, supporting their clinical utility in functionally significant stenosis determination and revascularization decision support. Future research should focus on: (1) multi-center, prospective, larger sample studies to improve external validity across populations and equipment; (2) constructing refined decision curves or Bayesian posteriors in threshold-adjacent intervals (0.75-0.85) to optimize "gray zone" management strategies; (3) standardizing measurement site/minimum value strategies, segmentation thresholds, and calcification processing differences; (4) exploring multimodal integration (e.g., CTP/radiomics) and trustworthy AI/uncertainty quantification to improve individualized prediction and clinical interpretability; and (5) establishing cross-vendor result mapping/calibration models to promote consistent cross-platform interpretation and referral coordination.

In conclusion, this study provides systematic evaluation of two commercially available deep learning CT-FFR systems in a real-world cohort, offering evidence for cross-algorithm consistency and performance against gold standards. The standardized quality control, calcification masking, and individualized thresholding in post-processing provide strong clinical implementation reference value. However, several limitations warrant attention: (1) single-center, retrospective design with limited sample size and positive vessel counts, introducing selection bias; (2) low proportion receiving invasive FFR may affect consistency estimation against gold standard; (3) cases with incomplete images/reconstruction failures (4 LCX, 2 RCA) may impact branch-level statistics; (4) measurement location and minimum value strategy differences between software may introduce systematic bias; and (5) lack of prognostic endpoints and treatment decision changes requires further validation in prospective studies. Overall, larger multicenter studies are needed to elevate evidence level and improve cross-platform calibration frameworks.

Author Contributions: Yichun Zhou conceived the study, designed research, implemented the study, and wrote the manuscript. Yichun Zhou, Yeming Han, Pengfei Zhang, Wenwen Song, Xiaoyu Wan, Qimou Li, Quande Liu, and Wei Yang collected and organized data, performed statistical analysis, and created figures and tables. Jichen Pan, Xinhao Li, Dumin Li, Dexin Yu, Mei Dong, Yongfeng Liang, Shanshan Hu, Lijuan Lü, and Mei Zhang revised the

manuscript. Lijuan Lü and Mei Zhang were responsible for quality control, overall oversight, and supervision.

Conflict of Interest: The authors declare no conflicts of interest.

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