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Research article

Gender differences in the diagnostic performance of machine learning coronary CT angiography-derived fractional flow reserve -results from the MACHINE registry

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ABSTRACT

Purpose: This study investigated the impact of gender differences on the diagnostic performance of machine-learning based coronary CT angiography (cCTA)-derived fractional flow reserve (CT-FFR_{ML}) for the detection of lesion-specific ischemia.

Method: Five centers enrolled 351 patients (73.5% male) with 525 vessels in the MACHINE (Machine leArning Based CT angiograpHy derIved FFR: a Multi-ceNtEr) registry. CT-FFR_{ML} and invasive FFR ≤ 0.80 were considered hemodynamically significant, whereas cCTA luminal stenosis ≥50% was considered obstructive. The diagnostic performance to assess lesion-specific ischemia in both men and women was assessed on a per-vessel basis.

Results: In total, 398 vessels in men and 127 vessels in women were included. Compared to invasive FFR, CT-FFR_{ML} reached a sensitivity, specificity, positive predictive value, and negative predictive value of 78% (95%CI 72–84), 79% (95%CI 73–84), 75% (95%CI 69–79), and 82% (95%CI: 76–86) in men vs. 75% (95%CI 58–88), 81 (95%CI 72–89), 61% (95%CI 50–72) and 89% (95%CI 82–94) in women, respectively. CT-FFR_{ML} showed no statistically significant difference in the area under the receiver-operating characteristic curve (AUC) in men vs. women (AUC: 0.83 [95%CI 0.79–0.87] vs. 0.83 [95%CI 0.75–0.89], $p = 0.89$). CT-FFR_{ML} was not superior to cCTA alone [AUC: 0.83 (95%CI: 0.75–0.89) vs. 0.74 (95%CI: 0.65–0.81), $p = 0.12$] in women, but showed a statistically significant improvement in men [0.83 (95%CI: 0.79–0.87) vs. 0.76 (95%CI: 0.71–0.80), $p = 0.007$].

Conclusions: Machine-learning based CT-FFR performs equally in men and women with superior diagnostic performance over cCTA alone for the detection of lesion-specific ischemia.

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1. Introduction

Coronary computed tomography angiography (cCTA) is an established non-invasive method to exclude obstructive coronary artery disease (CAD) in patients with low to intermediate pre-test probability [1,2]. However, cCTA tends to overestimate coronary lesion severity when compared with invasive coronary angiography (ICA) and is limited in discriminating between flow-limiting and non-obstructive stenoses, often prompting further functional testing [3]. Invasive fractional flow reserve (FFR) performed during cardiac catheterization is the established reference standard to evaluate the functional significance of indeterminate coronary stenoses and provides guidance for lesion-specific revascularization therapy [4]. Compared to cCTA alone, CT-derived FFR (CT-FFR) offers improved diagnostic accuracy in detecting hemodynamically relevant lesions. This modality has been developed using both offsite computer processing and workstation-based analysis with reduced order computational fluid dynamics [5–8]. The introduction of an artificial intelligence deep machine-learning based CT-FFR (CT-FFR_{ML}) derivation method will allow faster estimation of vessel or lesion specific CT-FFR, a key requirement to increase the clinical usefulness and implementation of this analysis [9].

As the clinical presentation of CAD and associated baseline characteristics differ between genders, a sex-specific approach for the evaluation of CAD seems warranted [10,11]. Furthermore, more prognostic information can be derived from cCTA than from stress tests in women; however, such differences between imaging studies were not observed in men [12]. Women are likely to have coronary artery and myocardium characteristics that could affect both CTA and CT-FFR calculations. In particular, women tend to have smaller coronary arteries, less calcium, lower left ventricular (LV) mass, and more microvascular disease [13,14]. Currently, no data exists regarding the influence of patient gender on the accuracy of CT-FFR_{ML}.

Thus, we sought to investigate the gender-specific diagnostic performance of CT-FFR_{ML} to detect lesion-specific ischemia in both men and women.

2. Material and methods

2.1. Study population

The rationale, design, and overall results of the multicenter MACHINE registry have been reported previously [15] (NCT02805621). Briefly, the MACHINE consortium consists of five institutions from five countries (Netherlands, South Korea, Poland, United States, and Sweden). All included patients had known or suspected CAD and underwent cCTA and ICA with FFR measurement. Patients were excluded for history of intervention in the vessel territories interrogated with invasive FFR measurement, suspected acute coronary syndrome, cardiac event between coronary CT angiography and the invasive FFR procedure, as well as non-diagnostic cCTA image quality. The respective study protocol was approved by the institutional review board at each site and was conducted in compliance with the principles of the Declaration of Helsinki.

2.2. cCTA image acquisition and analysis

The participating centers used either a first and/or a second generation dual-source CT scanner (SOMATOM® Definition or SOMATOM® Definition Flash; Siemens Healthineers, Forchheim, Germany). Pharmacological heart rate controlling agents and nitroglycerine were administered at the discretion of the attending physician. All CT scans were reconstructed using a medium-smooth kernel and a section thickness ≤0.75 mm in increments of 0.4 mm. The exact cCTA protocol was left to the discretion of the respective center, but adhered to the guidelines of the Society of Cardiovascular Computed Tomography (SCCT) for the performance of cCTA [16]. All cCTA datasets were evaluated locally by observers with extensive previous experience (at least 5 years) in cardiovascular imaging. All stenoses were classified and graded according to the SCCT guidelines. Hemodynamically relevant coronary stenosis was defined as ≥50% luminal narrowing by visual estimation.

Table 1
Patient and vessel baseline characteristics. Data from 351 patients with 525 vessels.

	Female	Male	*p*-value
Number of patients	93 (26.5%)	258 (73.5%)	
Age, years	64.1 (57.5–70.9)	61.6 (55.6–68.5)	0.036
BMI, kg/m²	28.0 (25.3–30.0)	27.0 (24.3–29.1)	0.034
Obesity, BMI ≥ 30 kg/m²	24 (25.8%)	52 (20.2%)	0.26
Cardiovascular risk factors			
Hypertension	68 (73.1%)	164 (63.6%)	0.098
Hyperlipidemia	63 (67.7%)	147 (57.0%)	0.072
Family history of coronary artery disease	37 (39.8%)	82 (31.7%)	0.16
Current smoker	23 (24.7%)	97 (37.6%)	0.025
Diabetes mellitus	20 (21.5%)	55 (21.3%)	0.97
Previous myocardial infarction	9 (11.1%)	13 (5.0%)	0.066
Previous percutaneous coronary intervention[a]	16 (17.2%)	36 (14.0%)	0.50
Pre-test probability[b],[c], **%**	58 (37.0–58.0)	77 (69.0–84.0)	< 0.0001
Invasive Coronary Angiography (ICA)			
Left anterior descending	65 (51.2%)	216 (54.3%)	0.54
Left circumflex	22 (17.3%)	93 (23.4%)	0.15
Right coronary artery	40 (31.5%)	89 (22.4%)	0.038
ICA stenosis ≥50%[d]	46 (63.5%)	95 (42.6%)	0.0021
Invasive FFR	0.86 (0.79–0.94)	0.80 (0.73–0.91)	< 0.0001
Invasive FFR ≤ 0.80	36 (28.3%)	176 (44.2%)	0.078
Coronary Computed Tomography Angiography (cCTA)			
Image quality, 1-4[e]	3.4 (3.0–4.0)	3.3 (3.0-4.0)	0.099
Agatston-Score[f]	387.6 (28.1–548.3)	523.3 (43.9–731.2)	0.078
Agatston-Score = 0	7 (7.5%)	9 (3.5%)	0.11
Agatston-Score > 400	26 (28.0%)	102 (39.5%)	0.049
cCTA stenosis ≥50%[g]	109 (85.2%)	349 (87.7%)	0.4648
CT-FFR_{ML}	0.84 (0.78–0.93)	0.76 (0.68–0.89)	< 0.0001
CT-FFR_{ML} ≤0.80	35 (27.5%)	195 (49.0%)	< 0.0001

Data are numbers or median of patients, with percentages or interquartile ranges in parentheses.

[a] Not in the vessel territories interrogated with invasive FFR measurement (available in 298 patients).

[b] Available in 238 patients.

[c] According to Genders et al. Eur Heart J 2011.

[d] Available in 295 vessels.

[e] 1, poor; 2, satisfactory; 3; good; 4, excellent.

[f] Available in 314 patients.

[g] Quantitative stenosis grading defined as SCCT-grade. cCTA, coronary computed tomographic angiography; FFR, fractional flow reserve; ICA, invasive coronary angiography; CT-FFR_{ML}, machine-learning based fractional flow reserve from coronary computed tomography angiography.

2.3. ICA with FFR measurement

ICA with FFR measurement was performed according to the standard clinical protocol of each center, but all were in accordance with societal guidelines [17]. Hyperemia was induced by intravenous or intracoronary administration of adenosine at a rate of 140 μg/kg per minute. The position of the pressure wire during FFR measurement was recorded and used to ensure that CT-FFR calculations were applied to the same position.

2.4. CT-FFR_{ML} analysis

The machine-learning CT-FFR algorithm (cFFR version 2.1, Siemens Healthineers; currently not commercially available) uses mathematical formulas to simulate fluid motion. A three-dimensional blood flow and

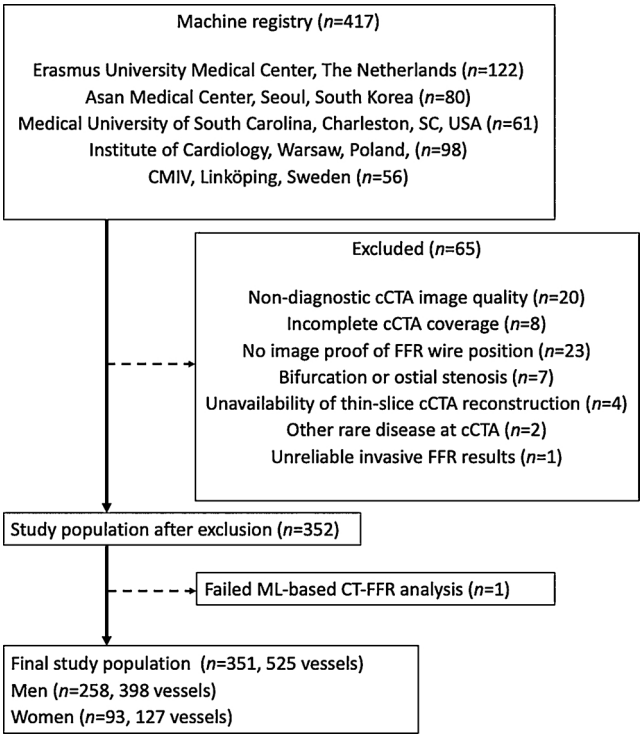

Fig. 1. Flow chart of the study.

pressure simulation of the coronary artery tree is produced using a reduced-order model. Coronary blood flow simulations account for conditions of adenosine-induced hyperemia by virtual reduction of the micro-vascular resistance. The application is based on recognition and previous experience with a framework of inputs to predict outcomes for new cases. Patient and lesion-specific parameters were included in a neural network to simulate the interaction of these features. The deep-learning-based approach of this study used a large data pool of synthetic coronary trees to train the algorithm via a supervised learning technique. Each center used this novel software designed for workstation-based, approximate real-time computation of FFR according to anatomical models extracted from standard cCTA [9]. CT-FFR_{ML} calculations were performed locally by an independent, experienced CT-FFR user who already performed all CT-FFR_{ML} calculations for each previous single-center study. CT-FFR_{ML} was calculated at the same location as invasive FFR measurements, with values ≤0.80 considered to be indicative of lesion specific ischemia.

2.5. Statistical analysis

Continuous variables are presented as means ± standard deviation (SD), interquartile ranges (IQR), or 95% confidence intervals (CI). Absolute variables are reported as frequencies and percentages. Normal distribution was assessed using Kolmogorov-Smirnov testing. Pearson´s correlation coefficients were applied to analyze correlation between CT-FFR_{ML} and invasive FFR values. Bland-Altman statistics were used to plot the difference between CT-FFR_{ML} and invasive FFR against the average of CT-FFR_{ML} and invasive FFR. Performance characteristics (sensitivity, specificity, positive and negative predictive value) of CT-FFR_{ML} to detect functionally significant CAD in men and women were assessed on a per-vessel basis using invasive FFR as the reference standard. Regression analysis was performed with invasive FFR ≤ 0.80 as a dichotomous outcome, with univariate data ($p < 0.05$) to identify possible confounders/independent predictors, and to correct for baseline characteristics. Pre-test likelihood of obstructive CAD was identified as an independent predictor and was incorporated into an adjusted Receiver-operating characteristics (ROC) curve analysis to measure the discriminatory power of cCTA and CT-FFR_{ML} in men and women on a per-vessel basis for the detection of hemodynamically significant stenosis. Comparison of ROC curves was performed according to the method of DeLong [18]. Two-tailed p-values ≤0.05 were considered statistically significant. All statistical calculations were performed using IBM SPSS statistics software version 22.0 (IBM, SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Patient characteristics

In total, the registry included 351 patients (73.5% male) who underwent cCTA followed by ICA with invasive FFR. Average patient age was 64.1 ± 9.5 years in women vs. 61.6 ± 9.2 years in men, $p = 0.036$ (Table 1). Women had a significantly higher mean BMI compared to men (28.0 ± 4.6 vs. 27.0 ± 3.6 kg/m^2, $p = 0.034$); however, the rate of obesity (BMI > 30kg/m^2) was similar between cohorts (25.8% vs. 20.2%, $p = 0.26$). The prevalence of cardiovascular risk factors was comparable in both genders; however, more men had a history of smoking than women (37.6% vs. 24.7%, $p = 0.025$). The majority of included patients had an intermediate or high pre-test

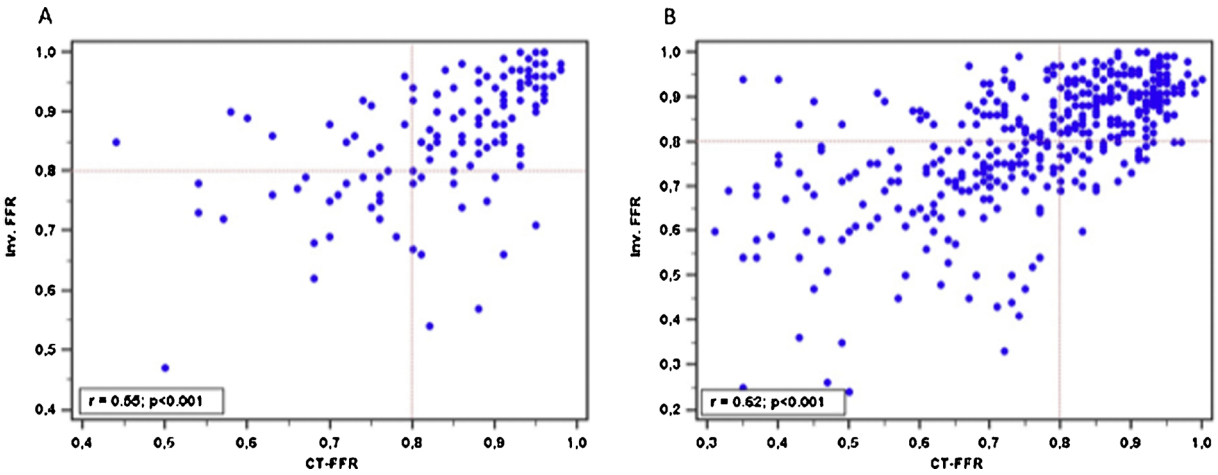

Fig. 2. Scatter plots for the association of machine-learning based CT-FFR (CT-FFR_{ML}) and invasive FFR.
Pearson´s correlation coefficients demonstrated moderate to good correlation between CT-FFR_{ML} and invasive FFR. Correlation coefficient was (A) $r = 0.55$ in women and (B) $r = 0.62$ in men.

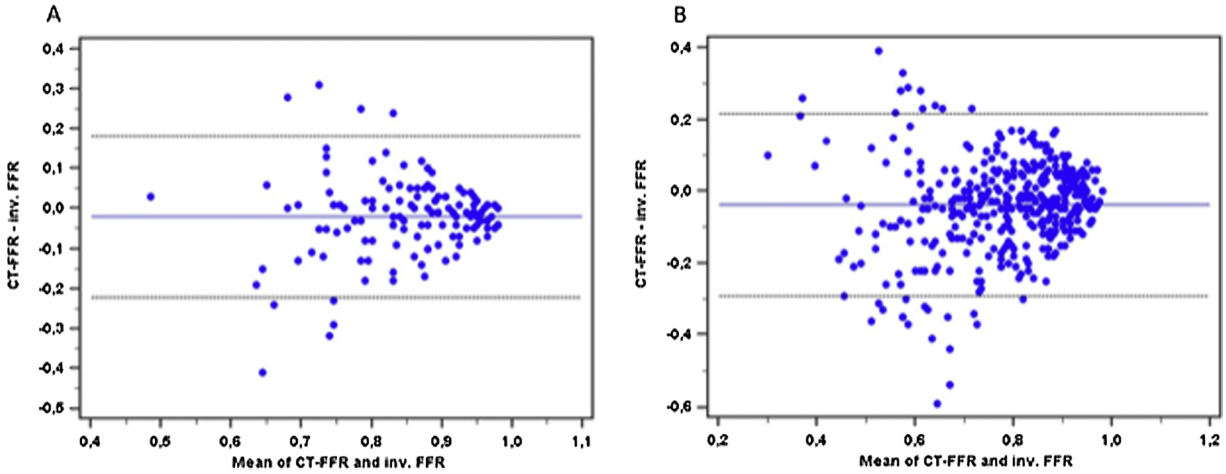

Fig. 3. Bland-Altman analysis plot comparing machine-learning based CT-FFR (CT-FFR$_{ML}$) and invasive FFR.
Bland-Altman analysis showed no systematic bias in **(A)** women (mean difference -0.02, limits of agreement: −0.22 to 0.18) and **(B)** men (mean difference -0.04, limits of agreement: −0.29 to 0.22).

Table 2
Diagnostic performance of cCTA and machine-learning based CT-FFR (CT-FFR$_{ML}$) for the detection of lesion-specific ischemia on a per-vessel level.

Parameter	Women (n = 127)		Men (n = 398)	
	cCTA ≥50% stenosis [95%CI]	CT-FFR$_{ML}$ ≤0.80 [95%CI]	cCTA ≥50% stenosis [95%CI]	CT-FFR$_{ML}$ ≤0.80 [95%CI]
Sensitivity (%)	83% [67–94%]	75% [58–88%]	89% [84–93%]	78% [72–84%]
Specificity (%)	64% [53–74%]	81% [72–89%]	62% [55–68%]	78% [72–84%]
PPV (%)	48% [40–55%]	61% [50–72%]	65 [61–69%]	75% [69–79%]
NPV (%)	91% [82–95%]	89% [82–94%]	88% [82–92%]	82% [76–86%]

cCTA, coronary computed tomographic angiography; FFR, fractional flow reserve; CT-FFR, machine-learning based fractional flow reserve from coronary computed tomography angiography; NPV, negative predictive value; PPV, positive predictive value.

likelihood of obstructive CAD, while female gender was associated with a significantly lower pre-test likelihood of obstructive CAD (58% vs. 77%, $p < 0.0001$).

Of the 525 vessels (75.8% in the male population) studied, 36 (28.3%) in women and 176 (44.2%) in men were considered ischemic with invasive FFR ≤ 0.80. The lesion of interest was most often located in the left anterior descending artery (53.5%), followed by the right coronary artery (24.6%) and left circumflex (21.9%). The mean Agatston score did not differ between genders (523.3 ± 673.7 vs. 387.6 ± 514.3, $p = 0.078$). Further clinical baseline characteristics of the study cohorts and vessel characteristics of ICA, cCTA, and CT-FFR$_{ML}$ are provided in Table 1. A flow chart of the study is illustrated in Fig. 1.

3.2. Correlation of CT-FFR$_{ML}$ with FFR

Pearson´s correlation coefficient was moderate to good between CT-FFR$_{ML}$ and invasive FFR values in both women ($r = 0.55$, $p < 0.0001$) (Fig. 2A) and men ($r = 0.62$, $p < 0.0001$) with no statistical difference in comparison of correlation coefficients ($p = 0.43$) (Fig. 2B). The Bland-Altman plot indicates a slight underestimation of CT-FFR$_{ML}$ compared with invasive FFR in both women (mean difference: −0.02 [limits of agreement: −0.22 to 0.18], Fig. 3A) and men (mean difference: −0.04 [limits of agreement: −0.29 to 0.22], Fig. 3B).

3.3. Diagnostic performance of CT-FFR$_{ML}$ and cCTA for detecting lesion-specific ischemia

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of CT-FFR$_{ML}$ and cCTA to detect lesion-specific ischemia on a per-vessel basis is presented in Table 2. Receiver-operating characteristics (ROC) curve analysis revealed an overall area under the curve (AUC) of CT-FFR$_{ML}$ of 0.83 [95%CI 0.80–0.87], with an AUC of 0.83 [95%CI 0.75–0.89] in women vs. 0.83 [95%CI 0.79–0.87] in men with no statistically significant difference between genders ($p = 0.89$).

CT-FFR$_{ML}$ was not significantly superior to cCTA alone for the detection of lesion-specific ischemia in women [AUC: 0.83 (95%CI: 0.75–0.89) vs. 0.74 (95%CI: 0.65–0.81), $p = 0.12$] (Fig. 4A), but showed a significant improvement in men [0.83 (95%CI: 0.79–0.87) vs. 0.76 (95%CI: 0.71–0.80), $p = 0.007$] (Fig. 4B).

4. Discussion

In this retrospective, international multicenter registry of patients with suspected or known CAD undergoing clinically indicated cCTA, we examined the diagnostic accuracy of a machine-learning based CT-FFR algorithm to detect significant ischemia using a gender-specific approach.

CT-FFR$_{ML}$ is a technique for the identification of hemodynamically relevant stenosis that uses standard cCTA datasets without the need for additional scans, adenosine infusion, or other pharmacological stressors. Several multicenter trials demonstrated the incremental value of CT-FFR in terms of specificity and PPV compared to cCTA alone, using invasive FFR as the reference standard [19–21]. Likewise, several single-center studies used a fast and simplified on-site workstation-based approach with promising initial results [5,7,8,22].

Machine-learning computer algorithms have previously been shown to be an accurate and time-effective prediction method for clinical decision making in cardiovascular medicine [23,24]. Computer-based algorithms hold the promise to handle complex datasets and recognize subtle pattern combinations, which can reliably predict outcomes and enable data transformation into readily available results in order to reduce the frequency of unnecessary downstream assessment [25]. Machine-learning methods have been successfully implemented in real-word scenarios and are also able to tackle complex learning tasks. Indeed, the use of machine-learning for the diagnosis of cardiac disease

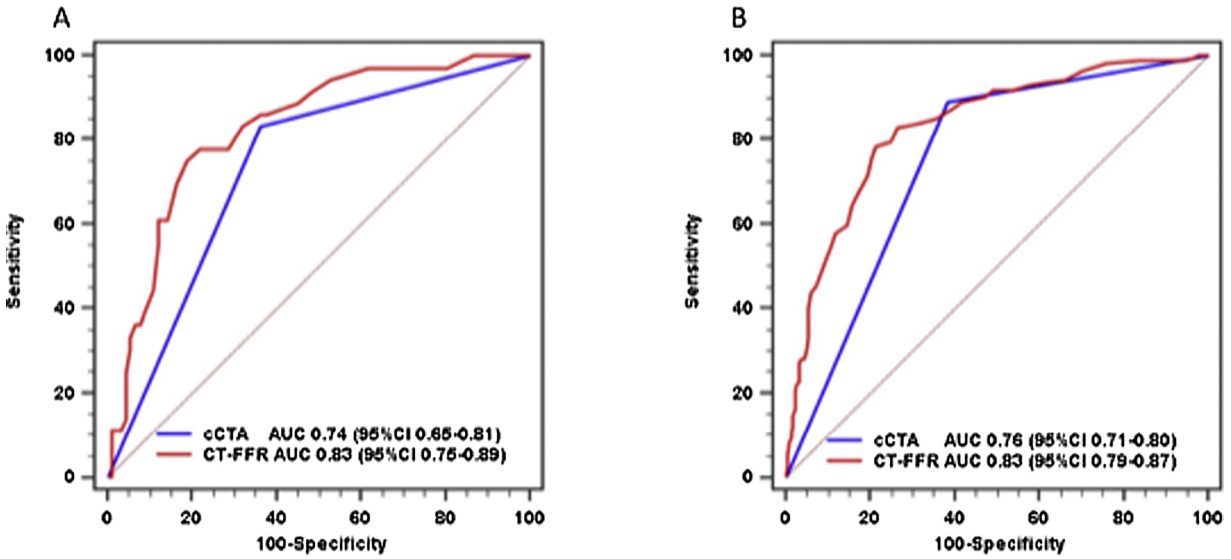

Fig. 4. Comparison of the diagnostic performance of cCTA and machine-learning based CT-FFR (CT-FFR_{ML}) for the detection of lesion-specific ischemia. Receiver-operating characteristic (ROC) curves with the area under the curve (AUC) are illustrated for the detection of ischemia with CT-FFR_{ML} (≤0.80) and cCTA (≥50% stenosis) on a per-vessel level using invasive FFR as the reference standard. Comparison of the AUC curve for CT-FFR_{ML} vs. cCTA showed no significantly higher performance of CT-FFR_{ML} over cCTA in women **(A)** (AUC 0.83 [95%CI 0.75–0.89], red ***line*** vs. AUC 0.74 [95%CI 0.65–0.81], blue ***line***, $p = 0.12$), but improvement of CT-FFR_{ML} over cCTA in men **(B)** (AUC 0.83 [95%CI 0.79–0.87], red ***line*** vs. AUC 0.76 [95%CI 0.71–0.80], blue ***line***, $p = 0.007$) (adjusted ROC curves for pre-test likelihood of obstructive CAD).

and precision in cardiovascular medicine has gained traction over recent years [26]. Therefore, the machine-learning approach for real-time computation of FFR from cCTA used in this investigation represents yet another example of the rapidly expanding role of artificial intelligence in patient care.

The potential risk of CAD in women is often underestimated, especially after the protective influence of estrogen has ceased in the postmenopausal period. This relative underestimation can be observed through the clinical presentation of ischemic heart disease in women compared to men, in which women describe atypical chest pain and concomitant symptoms (e.g. abdominal pain, dyspnea or nausea) more frequently and develop these symptoms later in life [27]. Aside from differences in clinical presentation, important anatomical and physiological variations of the cardiac system exist between the genders, which may contribute to the discrepant results observed in the current study. In terms of anatomical differences, women have significantly smaller hearts and coronary artery diameters. It is plausible that diminution of vessel diameter in women may cause inaccuracies during CT-FFR calculation, either due to poor attenuation in distal segments or a detrimental impact on fluid dynamic simulation. Also, a lower LV mass in comparison to their male counterparts may have implications on the accuracy of functional testing. Interestingly, Lubbers et al. describe in a sub-study of the CRESENT trial that a reduced need for further testing after cCTA compared with functional testing was most evident in women ($p = 0.009$), while the incremental value of CT-FFR_{ML} in our study was only manifested in men ($p = 0.007$) [28].

A similar trend, albeit not statistically significant, was observed among the women in our study ($p = 0.12$) due to the limited statistical power with an under-representation of women (26.5%). In addition, previous studies have highlighted gender differences in coronary stenoses, coronary plaque burden, and plaque composition. For example, women presented with a lower number of coronary segments containing calcified or mixed plaques than men [29]. Thus, when considering the significant differences between the genders, ranging from clinical presentation to anatomical and physiological characteristics, it is apparent that a gender-specific approach during the clinical work-up of CAD is warranted. The paradox that exists in female CAD, characterized by a lower prevalence of obstructive disease but higher prevalence of clinical presentation, ischemia, symptomatic complaints, and mortality compared to men, elucidates the current disparity in sex-specific medical treatment for heart disease. The use of CT-FFR in a gender-specific manner may provide insights into the discrepancies between male and female characteristics of CAD.

Our study has several limitations that should be addressed and considered when interpreting the results. First, almost three-quarters of our population are male. Although this distribution represents a real-world population referred for clinically indicated cCTA, comparisons between the groups may be affected. Second, the registry is limited by potential selection and referral bias, which leads to a relatively high pre-test probability due to the underlying study design. Notably, the pre-test probability for obstructive CAD differs significantly between genders, which was an expected limitation during the study-design phase. However, low risk patient samples might be equally under-represented for both genders in our study. Lastly, information regarding further diagnostic strategies and clinical outcomes of the patients in the study cohort following CT-FFR_{ML} evaluation is not available. Future prospective, randomized multicenter trials may provide clarification regarding the influence of the CT-FFR_{ML} application on downstream patient care and outcomes.

Notwithstanding these limitations, the MACHINE registry represents the largest cohort of patients evaluated by CT-FFR_{ML}, and the current study adds to existing data by establishing the value of CT-FFR_{ML} in a gender-specific context.

Declaration of Competing Interest

Dr. Schoepf receives institutional research support from Astellas, Bayer, GE, Medrad, and Siemens and has received honoraria for consulting and speaking from Bayer, GE, Guerbet, and HeartFlow. Dr. De Cecco is a consultant for Guerbet. Dr. Nieman receives research support from Bayer Healthcare, GE Healthcare, Siemens Medical Solutions, and HeartFlow. Dr. Renker receives consulting fees/honoraria from Symetis. All other authors have no conflicts of interest to disclose. The concepts and information presented are based on research and are not commercially available.

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