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Original article

Comparison of Instantaneous Free Wave Ratio Measurements and Quantitative Coronary Angiography in Patients with Borderline Coronary Lesions

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Abstract:

Background: Quantitative coronary angiography (QCA) can predict late clinical restenosis in patients undergoing drug-eluting and bare metal stent placement by measuring percent diameter stenosis and late lumen loss on follow-up angiography. Our study objective was 2D-QCA stenosis area percentage in predicting the functional significance of intermediate stenosis considering IFR as the gold standard for accurate decision maker regarding revascularization. **Methods:** This study was carried out on 155 patients diagnosed as symptomatic IHD referring for doing ICA and found to have intermediate coronary lesions. All patients underwent both (QCA) and Instantaneous Free Wave Ratio (IFR) for evaluation of each intermediate lesion. Each intermediate lesion was then allocated to one of 3 groups based on the affected vessel LAD group, LCX group and RCA group then dividing borderline lesion stenosis based on QCA AS 50-60 % and 61-70 % comparing with IFR in three vessels. **Results:** There was statistically significant positive correlation between QCA area stenosis 50 to 60 %, 61-70 % in mid LAD lesions (P value= 0.0001, P value= 0.0001) while there was statistically significant negative correlation between QCA area stenosis 50 to 60 % in mid and proximal RCA lesions (P value= 0.0002, P value= 0.0001). **Conclusion:** LCX lesions were the ones where sensitivity and specificity showed the highest in prediction of IFR outcome in area stenosis 50-60 %. While in area stenosis 61-70 % LAD lesions have the highest prediction of IFR outcome.

Keywords: Coronary Angiography; Quantitative Coronary Angiography Area Stenosis; Instantaneous Free Wave Ratio.

Introduction

Invasive coronary angiogram is pivotal in the diagnosis of coronary artery disease (CAD). However, as ischemia is the most important factor related to outcome for patients with CAD, additional functional assessment of coronary artery stenosis is important to evaluate the physiological significance of a coronary stenosis and to guide treatment and management [1, 2].

Quantitative coronary angiography (QCA) can predict late clinical restenosis by the quantitative measurement of percent diameter stenosis and late lumen loss on follow-up angiography in patients undergoing drug-eluting and bare metal stent placement, although controversy remains relating to their use as surrogate markers for clinical outcomes when assessing new generations of coronary stents. Nevertheless, quantitative angiographic methods remain extremely important for the assessment of outcome after new device and drug therapy in patients undergoing intervention for ischemic heart disease [3-5].

In our study assessment of 2D-QCA results in predicting the functional significance of intermediate stenosis considering IFR as the gold standard for accurate decision maker regarding revascularization. Also, our study assessed the accuracy using the 2 diagnostic modalities at the segment level also we considered multiple lesion assessments in the same vessel (not tandem lesions). Also, we considered another factor in classification analysis which was stenosis area as it may affect decision making in routine daily clinical work.

Patients and Methods

This prospective cohort, analytical study was conducted at cardiology departments of National Heart Institute under supervision of professors in faculty of medicine Benha University and National Heart Institute during the period between December 2019 and March 2022, with a follow up period of 6 months for MACE after performing coronary angiography (whether PCI was done or not).

Patients were assessed for border line coronary artery lesions by IFR and QCA and the decision based on IFR was compared by the decisions based on QCA either similar decision with agreement or disagreement to progress to Intervention or medical treatment.

This study was done after approval by the institutional ethical committees and patients were informed about the study & informed consents were also obtained {M.S. 13.11.2019}.

Patients underwent Invasive Coronary Angiography (ICA) then we did IFR and QCA to assess the accuracy of 2D-QCA in prediction of IFR outcome in intermediate lesions depending on 2 classifications; the 1st one was according to “stenosis area” while the 2nd classification was according to the segment of the coronary artery containing the lesion “per-segment assessment”.

Inclusion Criteria were those who were referred for coronary angiography and found to have intermediate coronary lesions based on visual assessment (defined typically as 50-70% stenosis of the vessel diameter) and did both Quantitative coronary angiography (QCA) and Instantaneous Free wave Ratio (IFR) for evaluation of each intermediate lesion also all patients with stable CAD patients who had undergone previous PCI were included.

Exclusion criteria were who had angiographically significant left main coronary artery disease or coronary total occlusions, CABG or extremely tortuous or calcified coronary arteries. Culprit vessels in STEMI or ACS patients and acute heart failure, Cardiogenic shock, hemodynamic instability (heart rate < 50 beats per minute, systolic blood pressure < 90mmHg) or patients on IABP at the time of intervention also Significant hepatic or lung disease and Pregnant females were excluded.

All patients were subjected to: Full history taking (Full analysis of the chest pain, and full analysis of dyspnea and its grade according to New York Heart Association (NYHA) grading from I to IV, Past history with Coronary artery disease (CAD) risk factors including: DM, hypertension (HTN), dyslipidemia, and Family history of CAD and/or its risk factors and medication history, Thorough physical examination and risk assessment including: Pulse and blood pressure, oedema of lower limbs, abdominal and chest examination., cardiac examination, the patients who had developed heart failure (HF), Resting 12-lead standard surface electrocardiogram (ECG): Diagnosis of IHD ischemic changes in form ST segment depression, T wave inversion, poor R wave progression in pericardial leads and pathological Q wave and Blood samples for (Cardiac enzymes (cTNI), Renal function tests, and Complete blood count).

Transthoracic echocardiography (ECHO): Comprehensive M-mode, 2-Dimentional, and Doppler ECHO assessment were performed. Examination was done with the patient in the left semi-lateral position, utilizing left parasternal long axis, short axis, apical 4 (A4C), apical 5, and apical 2-chamber (A2C) views according to the recommendations of the American society of echocardiography.

Systolic function parameters: Cardiac dimensions and functions including left ventricular end diastolic dimension (LVEDD), left ventricular end diastolic dimension (LVESD), Ejection fraction (EF) using M-mode.

Diastolic function parameters: Mitral flow E wave velocity, A velocity, E/A ratio and E-wave deceleration time

Invasive Coronary Angiography (ICA): Conventional ICA was performed by 2 experienced operators (each with >10 years of experience in coronary intervention). Angiographic cine images were acquired at 15 frames per second. After angiography, the images were reviewed, Syntax I score were calculated and the operators were asked to prospectively document their plans for angioplasty regarding any moderate lesion (50-70%) (Whether or not angioplasty will be done) based on their visual assessment. Quantitative assessment of angiographic data (QCA) was routinely done before any physiological measurements with Instantaneous Free Wave Ratio (IFR) and the following criteria were also recorded and correlated if they had any role in accuracy of QCA prediction for IFR value. Diseased coronary artery (LAD-LCX-RCA). Site of lesion (proximal-mid-distal). 3) Lesions in a native coronary artery or inside a stent.

Instantaneous Free wave ration (IFR): Using Volcano software, IFR settings were fully automated, as performed by the console. Each patient had the ECG attached to the console. Measurement of IFR was done according to institutional protocols which approved with published scientific techniques.

Quantitative Coronary Angiography (QCA): Two-dimensional quantitative coronary angiography was performed offline using standard commercial software (Paxera-View PRO workstation). Automated distance calibration was used to determine pixel size. All analyses were performed during the end-diastolic frame. Angiographic views with the least foreshortening and yielding the best depiction of the stenosis were used.

The percentage area stenosis, minimum luminal diameter (MLD), and lesion length were measured using 2D-QCA. All measurements were performed twice and averaged by a single experienced cardiologist blinded to the IFR results. Inter-observer error was determined by a second cardiologist. To compare correlation between IFR and QCA in eccentric vessels and non-eccentric vessels. We classified the lesions in each vessel into 2 groups according to lesion

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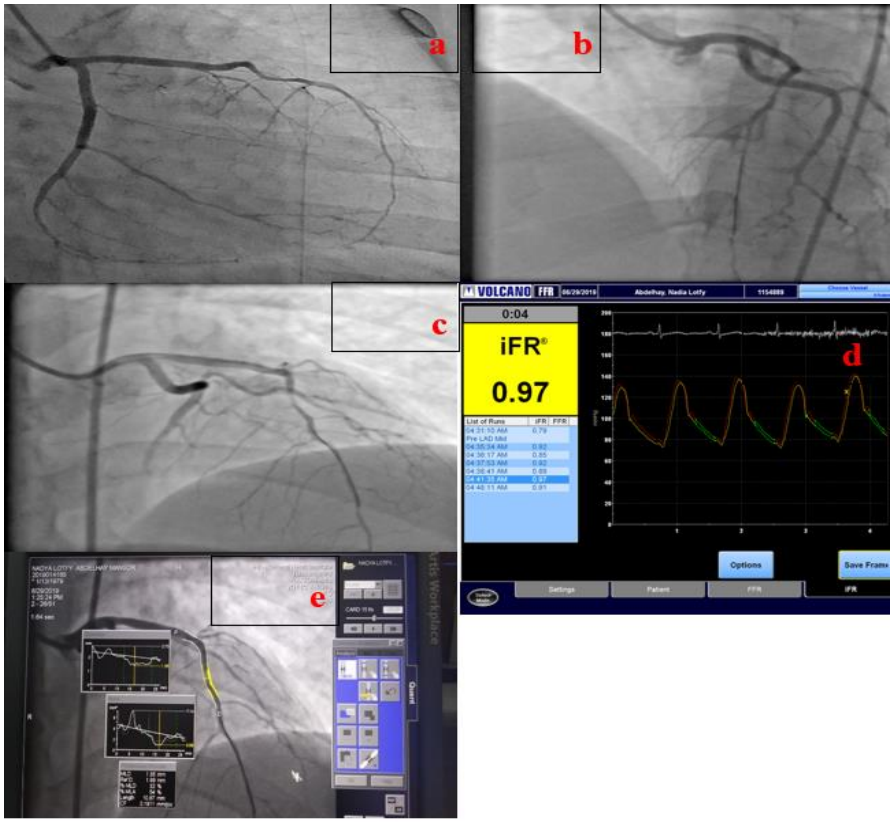
severity (percentage of stenosis area). 1st group 50-60%, 2nd group 61-70%.

Cases:

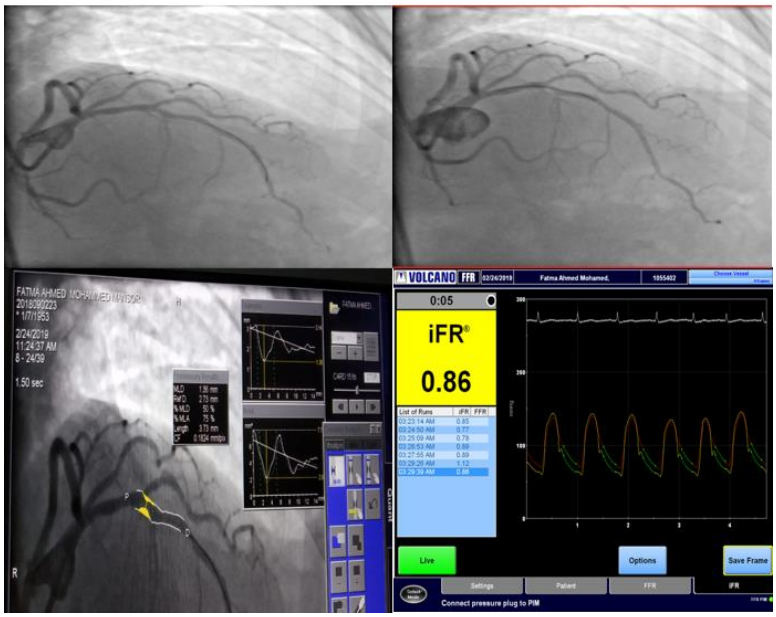
Case from LAD group 50-60 % QCA area stenosis a female patient, 44 years old, DM, HTN, Dyslipidemia, non-smoker, no family history of coronary artery disease and no past history of ischemic heart disease before. She complained of chest pain increasing with moderate exercise, relieved by rest and radiating to back, her chest pain increased and associated with sweating and nausea. On examination she was pale, distressed, with limiting chest pain, normal neck veins and no lower limb edema, her SBP was 140/90, HR 90 bpm, Temp 37.5 c, RR 25/min. ECG Normal sinus rhythm, ST segment depression 1 mm in leads I, aVL, T wave inversion in leads II, III & aVF, no pathological Q waves and normal R wave progression in chest leads. Blood test HB: 12.1 (gm/dl), WBC: 10.3 (x10^3/U), Platelet: 347 (x10^3/UL), INR: 1.09, Serum creatinine: 1.1 (mg/dl), Serum potassium: 4 mmol/L, Serum sodium: 137 mmol/L, Cardiac Troponin: negative. Echo findings EF: 60 %, LV diastolic dysfunction grade I and segmental wall motion abnormalities in form hypokinesia basal & mid lateral wall. ICA showed LAD artery showing atherosclerotic vessel with mid segment border line lesion IFR for LAD lesion was 0.97 and QCA area stenosis for same lesion was 54 %. (Figure 1).



RAO: Right Anterior Oblique LAD: Left Anterior descending artery LCX: Left Circumflex artery, LAO: Left Anterior Oblique IFR: Instantaneous Free wave Ratio QCA: Quantitative Coronary Angiography PA: Posterior-Anterior.

Figure 1: a) Modified RAO caudal view showing proximal & mid LAD & LCX b) LAO cranial view showing IFR wire in LAD c) PA cranial view with right angulation showing IFR wire in LAD d) IFR 0.97 indicates non-significant stenosis at mid LAD e) QCA area stenosis in mid LAD lesion in PA view was 54 %.

Case from LAD group 61-70 % QCA area stenosis a female patient, 66 years old, DM, not HTN, Dyslipidemia, non-smoker, positive family history of coronary artery disease and no past history of ischemic heart disease before. She complained of chest pain increasing with moderate exercise, relived by rest and radiating to back, her chest pain increased and associated with sweating. On examination she was pale, distressed, with limiting chest pain, normal neck veins and no lower limb edema, her SBP was 140/90, HR 90 bpm, Temp 37.5 c, RR 25/min. ECG Normal sinus rhythm, no ST segment deviation, T wave inversion in leads V4, 5, 6, no pathological Q waves and normal R wave progression in chest leads. Blood test HB: 11.1 (gm/dl), WBC: 9.4 (x10^3/U), Platelet: 362 (x10^3/UL), INR: 1.1, Serum creatinine: 1.2 (mg/dl), Serum potassium: 3.9 mmol/L, Serum sodium: 135 mmol/L, Cardiac Troponin: negative. Echo findings EF: 56 %, LV diastolic dysfunction grade I and segmental wall motion abnormalities in form hypokinesia basal & mid anterior wall. ICA showed LAD artery showing atherosclerotic vessel with proximal to mid segment border line lesion IFR for LAD lesion was 0.86 and QCA area stenosis for same lesion was 70 %. (Figure 2).



RAO: Right Anterior Oblique LAD: Left Anterior descending artery, IFR: Instantaneous Free wave Ratio QCA: Quantitative Coronary Angiography.

Figure 2: a) RAO cranial view showing proximal & mid borderline lesion in LAD with IFR wire distal to lesion, b) RAO cranial view showing IFR wire proximal to lesion in LAD, c) QCA area stenosis in LAD lesion in RAO view was 70 %, d) IFR 0.86 indicates significant stenosis at proximal to mid LAD.

Statistical analysis:

Statistical analysis was done by SPSS v22 (IBM Inc., Armonk, NY, USA). Quantitative parametric data were presented as mean and standard deviation (SD) and analysed by Student's t- test or Mann-Whitney test for non-parametric data. Qualitative data were presented as frequency and percentage (%), and chi-square test was used to determine whether there is an association between two categorical variables. Odds Ratio (OR) was used to estimates of risk statistics. P-value <0.05 was considered significant.

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Results

There was statistically significant positive correlation between QCA area stenosis 50 to 60 %, 61-70 % in mid LAD lesions (P value= 0.0001, P value= 0.0001) while there was statistically significant negative correlation between QCA area stenosis 50 to 60 % in mid and proximal RCA lesions (P value= 0.0002, P value= 0.0001) (Table 1,2).

Regarding the specificity in QCA area stenosis 50-60 % LCX had the highest specificity 78.9 % (P=0.001) followed by LAD 73.9 % (P=0.001) and RCA the least 66.7 % (P=0.002), while in QCA area stenosis 61-70 % LAD had the highest specificity 30.2 % (P=0.001) (Table 3).

Table 1: MLD & QCA AS 50-60% with IFR in different lesion sites in LAD, LCX & RCA.

			QCA AS 50-60%				
LAD	Site of lesion		MLD mm	**P value**	QCA AS%	**P value**	IFR
	Mid	Mean ±SD	1.8 ±0.6	0.0009	53.8 ±3.4	0.0001	0.87 ±0.02
	Distal	Mean ±SD	1.2 ±0.14	0.1467	55.5 ±0.7	0.0035	0.83 ±0.06
	Proximal	Mean ±SD	1.91 ±0.39	0.0006	53.47 ±3.09	0.0001	0.899 ±0.001
LCX	Site of lesion		MLD mm	**P value**	QCA AS%	**P value**	IFR
	Mid	Mean ±SD	2 ±0.5	0.0001	51.9 ±2.4	0.0001	0.899 ±0.008
	Distal	Mean ±SD	1.6 ±0.38	0.0003	53.3 ±3.9	0.0001	0.95 ±0.15
	Proximal	Mean ±SD	2.3 ±0.57	0.0001	51 ±1.77	0.0004	0.91 ±0.08
RCA	Site of lesion		MLD mm	**P value**	QCA AS%	**P value**	IFR
	Mid	Mean ±SD	2.06 ±0.58	0.0002	52.8 ±3.6	0.0002	0.899 ±0.008
	Distal	Mean ±SD	1.95 ±0.35	0.0996	50 ±0	0.0013	0.82 ±0.04
	Proximal	Mean ±SD	2 ±0.5	0.0009	53.8 ±3.6	0.0001	0.98 ±0.08

MLD: Minimum Lumen Diameter. **QCA:** Quantitative Coronary Angiography. **AS:** Area Stenosis. **IFR:** Instantaneous Free wave ratio.

Table 2: MLD & QCA AS 61-70% with IFR in different lesion sites in LAD, LCX & RCA

			QCA AS 61-70%				
LAD	Site of lesion		MLD mm	**P value**	QCA AS%	**P value**	IFR
	Mid	Mean ±SD	1.37 ±0.35	0.0003	66.6 ±3.5	0.0001	0.84 ±0.05
	Distal	Mean ±SD	#DIV/0!	NA	#DIV/0!	NA	#DIV/0!
	Proximal	Mean ±SD	1.46 ±0.48	0.0072	65.5 ±3	0.0004	0.75 ±0.2
LCX	Site of lesion		MLD mm	**P value**	QCA AS%	**P value**	IFR
	Mid	Mean ±SD	1.17 ±0.2	0.0041	66.8 ±4.4	0.0004	0.66 ±0.18
	Distal	Mean ±SD	#DIV/0!	NA	#DIV/0!	NA	#DIV/0!
	Proximal	Mean ±SD	1.39 ±0.9	0.3677	67 ±4.2	0.0287	0.78 ±0.12
RCA	Site of lesion		MLD mm	**P value**	QCA AS%	**P value**	IFR
	Mid	Mean ±SD	1.1 ±0.1	0.0004	69.4 ±1.3	0.0003	0.67 ±0.07
	Distal	Mean ±SD	1.46 ±0.22	0.099	69 ±1.4	0.0083	0.84 ±0.05
	Proximal	Mean ±SD	1.38 ±0.25	0.1867	67.5 ±3.5	0.0238	0.78 ±0

MLD: Minimum Lumen Diameter. **QCA:** Quantitative Coronary Angiography **AS:** Area Stenosis. **IFR:** Instantaneous Free wave ratio.

Table 3: Sensitivity and Specificity for QCA AS in different coronary arteries Vs IFR

Coronary artery	Sensitivity				Specificity			
	50-60%	P value	61-70%	P value	50-60%	P value	61-70%	P value
LAD	69.8%	0.001	26.08%	0.001	73.9%	0.001	30.2%	0.001
LCX	92.3%	0.001	21.05%	0.004	78.9%	0.001	7.7%	0.004
RCA	92.3%	0.002	33.3%	0.003	66.7%	0.002	7.7%	0.003

QCA: Quantitative Coronary Angiography **AS:** Area Stenosis. **MID:** Middle.
LAD: Left Anterior Descending artery. **LCX:** Left Circumflex Artery. **RCA:** Right Coronary Artery.

Regarding per-vessel Sensitivity and Specificity of 2D-QCA for predicting IFR outcome We found that according to direct comparison between the sensitivity and specificity of three main coronary vessels in QCA area stenosis 50-60 % and 61-70 %, LAD, LCX and RCA had higher sensitivity and specificity in QCA area stenosis 50-60 % group than QCA area stenosis 61-70% group, also LCX and RCA had higher sensitivity 92.3 % for each (P=0.001, P=0.002) respectively than LAD which had sensitivity 69.8 % (P=0.001) in area stenosis 50-60 % while in area stenosis 61-70 % RCA had the highest sensitivity 33.3 % (P=0.003) among the study groups followed by LAD 26.08 % (P=0.001), while the LCX was the least by 21.05 % (P=0.004) (Table 4).

Table 4: Sensitivity and Specificity of 2D-QCA in different studies.

Study (year)		Lesion (n)	QCA AS	Sens.	Specif.	Comparison between
Our results 2023	**LAD**	122	AS →50-60% AS →61-70%	69.80% 26.08%	73.90% 30.20%	2D-QCA Vs IFR **(0.89)**
	LCX	51	AS →50-60% AS →61-70%	92.30% 21.05%	78.00% 7.70%	
	RCA	37	AS →50-60% AS →61-70%	92.30% 33.20%	66.70% 7.70%	
Bartúnek et al., 1995		157	MLD→ <1.5 mm AS →>50%	96% 93%	89% 85%	2D-QCA Vs FFR **(0.72)** (NON-SELECTIVE COHORT)
Saad et al., 2009		41	AS →45-57% AS→ >57%	88.9% 88.9 %	90.6 % 87.5%	3D-QCA Vs FFR **(0.75)**
Young et al., 2011		63	AS→ >60% MLD →1.2MM	80% 75%	79.2% 66.7%	3D&2D QCA Vs FFR **(0.75)** (NON-SELECTIVE COHORT)
Xu et al., 2017		332	AS→ ≥ 50%	49.6%	72.2%	2D-QCA &QFR Vs FFR **(0.8)**
Westra et al., 2018		317	AS→ ≥ 50%	44.2%	76.5%	

MLD: Minimum Lumen Diameter. **QCA:** Quantitative Coronary Angiography **AS:** Area Stenosis.
IFR: Instantaneous Free wave ratio. **FFR:** Fractional Flow Reserve.

Discussion

The specificity for QCA AS 50-60 % reported in this study was nearly similar to the specificity stated in the studies done by [6 ,7] regarding LAD and LCX specificity. However, in this study sensitivity was higher with LAD, LCX and RCA. This may be explained by the fact that these studies depended on FFR cut off value of 0.8 which may have decreased the prediction of 2D-QCA according to the finding of the study done by [8].

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On the other hand, our results showed lower specificity than the results obtained [9, 8] which may be explained by the fact that the previous studies included a non-selective cohort, where some patients had mild lesions with larger MLD, However the sensitivity for QCA AS 50-60 % in LAD, LCX and RCA is nearly the same. This may increase the diagnostic accuracy more than a study devoted to intermediate lesions cohort [7, 10,11] .

Study limitations.

Because of limited randomized data this study included both prospective and retrospective studies. Therefore, more than half the included studies were retrospective analyses, furthermore, lesions of different characteristics were incorporated because limited studies were found comparing angiography-guided and FFR-guided PCI also sample size was limited for better assessment, validation, more comparisons and explanations regarding these results.

Conclusion

Overall, these results indicate that the lesion severity (area stenosis) together with lesion position (affected segment) and affected vessel will affect the overall sensitivity and specificity of 2D-QCA for prediction of IFR outcome and hence the decision whether further intervention (PCI) is needed (sensitivity) or not (specificity).

We conclude that LCX lesions were the ones where sensitivity showed the highest in prediction of IFR outcome. We also found that in stenosis area percent (50-60%) was accompanied by increase in sensitivity and specificity.

Also, 2D-QCA readily available in all work stations in the cath lab and can be done without any additional cost this would reduce the cost and time that may be needed for intervention and reduce the need for functional assessment so that it can be utilized in specific situations only, furthermore, we considered another factor in classification analysis which was stenosis area as it may affect decision making in routine daily clinical work.

Finally, 2-D QCA has the ability to guide the decision for intermediate stenosis in each coronary segment within the three main coronary vessels in comparison with IFR results. We also found that stenosis area percent (50-60%) was accompanied by increase in sensitivity and specificity. However, LCX lesions were the ones where sensitivity showed the highest in prediction of IFR outcome.

Conflict of interest

None of the contributors declared any conflict of interest

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