The Role of Intravascular Ultrasound (IVUS) in Predicting the Functional Significance of the Intermediate Coronary Lesions in Correlation with Fractional Flow Reserve (FFR)

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Abstract

Background: It is necessary and of great benefit for the patients to improve diagnostic tools along with the technical development, and as Fraction Flow Reserve (FFR) is considered the gold standard for assessing intermediate coronary lesions. This study aimed to further investigate the correlation between Fractional Flow Reserve (FFR) and Intravascular Ultrasound (IVUS) metrics including Minimal Lumen Area (MLA). Which remains a debatable issue in the assessment of intermediate coronary artery stenosis.

Methods: Thirty patients with thirty eight intermediate stenotic lesions located in the main coronary vessles, were assessed by FFR, IVUS and quantitative angiography. Receiver –Operating Characteristic (ROC) curve analyses were used to identify MLA best cut-off values predictive of FFR value less than 0.80.

Results: The best cut-off value for MLA which is concordant with ischemic FFR values is $<3mm^2$ with a sensitivity and specificity 76.92% and 50% respectively, and a predictive values PPV=45% and NPV=80%.

Conclusion: MLA of intermediate coronary lesions obtained by IVUS showed a good correlation with FFR measurements [IVUS-MLA $\leq 3.0mm^2$ was the best cut off value for identifying FFR <0.8 in coronary vessels With a good negative predictive value of 80%].

Key Words: *Fractional flow reserve – Intravascular ultrasonography – Intermediate lesions – Quantitative coronary angiography.*

Introduction

ANGIOGRAPHY is inaccurate in assessing the functional significance of a coronary stenosis when compared with fractional flow reserve FFR, not only among intermediate lesions (40% to 70%) but also in the angiographically significant stenoses 70-90% [1].

Fractional Flow Reserve (FFR) is an invasive physiologic assessment of significant ischemia and is an important tool to determine whether to proceed with Percutaneous Coronary Intervention (PCI) of intermediate coronary stenosis [2].

The benefits of Percutaneous Coronary Intervention (PCI) for stable coronary artery disease are debated and questioned, especially without the demonstration of significant reversible ischemia. FFR has already been validated in the physiological assessment of coronary artery stenoses, with an FFR value of <0.80 currently proposed as the cut-off to indicate functional significance [3]. Moreover, PCI of coronary stenosis with FFR is greater than either 0.75 or 0.80 without intervention has been safe and cost-effective [4].

On the other hand, Intravascular Ultrasound (IVUS) has been widely used to assess coronary stenosis, either quantitatively or qualitatively. IVUS has been reported to improve clinical outcomes compared to PCI guided by angiography alone [5].

Reported IVUS-derived minimal lumen area cutoff threshold ranges from 2.0 to $4.0mm^2$ and the use of IVUS to guide PCI, has resulted in unnecessary stenting approximately half of the time because of a relatively low positive predictive value [6].

Although the correlation between these complementary tools is still debated, various cutoff points for Minimum Lumen Area (MLA) as assessed by IVUS have been proposed for positive FFR [7].

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Aim of the work:

The purpose of this study is to assess the intermediate coronary lesions detected by visual estimation in coronary angiography by using two invasive modalities fractional flow reserve (FFR) and Intravascular Ultrasound (IVUS).

Patients and Methods

Between May 2015 and October 2017, the severity of 38 intermediate stenoses (40-70% on visual estimation) in 30 patients was assessed using FFR, IVUS and quantative coronary angiography at National Heart Institute, Imbaba and other private centers.

Exclusion criteria:

Patients with chronic total occlusion, left main coronary lesion, previous CABG and patients with contraindication to adenosine administration.

All patients will be subjected to:

- *Full history taking:* Complete and detailed medical history including risk factors of coronary artery disease (diabetes mellitus, hypertension, smoking and dyslipidemia).

- *Laboratory investigations:* Serum urea and creatinine.

- Resting standard 12-leads electrocardiogram.

- *Resting Trans-Thoracic Echocardiography (TTE) was routinely done:* With special stress on Left Ventricular Ejection Fraction (LVEF) measured using modified Simpson's rule, Schiller NB, et al., and resting segmental wall motion abnormalities if present.

- *Coronary angiography:* It was performed according to the standard technique and the goal is to achieve complete anatomic and accurate visualization of coronary arteries.

- *Intravascular coronary ultrasound (IVUS) examination and measurement:* By using planimetry the Reference Lumen Area (RLA) at the site of intermediate lesion (40% to 70%) can be planimetered and calculated then the Minimal Lumen Area (MLA) was measured.

- *Measurement of coronary Fractional Flow Reserve (FFR):*

  • Hyperemia was induced by the intravenous continuous infusion of adenosine (140micg/kg/min).

  • Lesions with FFR <0.80 were considered functionally significant.

Statistical analysis:

Values are presented as mean ± standard deviation or median (Interquartile Range [IQR]) for continuous variables or as counts and percentages for categorical variables. Clinical, echocardiographic, angiographic or procedure-related characteristics of patients were compared using Student- *t* test, the relationship and variability between FFR and IVUS or QCA parameters were analyzed by Pearson correlation analysis to define correlation coefficients between FFR and IVUS or QCA of lesion severity. Receiver-Operating Characteristic (ROC) curve analyses were performed to establish the cut-off values of MLA, most predictive of FFR value less 0.80.

Table (1): Personal characteristics of the study group.

	No.=30
Age:	
Mean ± SD	59.40±9.45
Range	34-76
Sex:	
Female	9 (30.0%)
Male	21 (70.0%)

Results

The age of the patients ranged from 34 to76 years with mean standard deviation (mean ± SD= 59.40±9.45 years) and as regarding sex category, 21 cases representing (70.0%) of the population were males on the other hand 9 cases only representing (30.0%) of the population were females. There was statistically no difference among populations included in this study as regarding age and sex of the study group.

Also there was statistically no significant difference among the studied group as regard hypertension, dyslipideamia and smoking as shown in (Table 2).

Angiographic data:

By assessment of the data obtained from the coronary angiography performed to our thirty patients there were thirty eight different lesion as six of them showed more than one lesion in the coronary vasculature (four patients showed two diseased vessels and two of our patients showed lesions in three different vessels), and according to the anatomical site of these lesions, 19 of them were found to be in the left anterior descending artery and 7 lesions in the left circumflex artery and the remaining 7 lesions were located in the right coronary.

Visual degree of stenosis, IVUS and FFR data:

The different measurements collected from study group as FFR value, Minimal Luminal Areas (MLA) obtained by IVUS and the percentage of stenosis are tabulated in the following table demonstrating that the minimum and maximum FFR value were 0.7 and 0.1 respectively with mean ± SD of 0.83±0.07, also as regarding to minimal luminal area obtained by IVUS, the minimal and maximal luminal areas were 2.0 and 6.0mm$_2$ respectively with mean standard deviation 3.31 ±0.80.

Table (5) shows the sensitivity, specificity and predictive value of multiple cutoff values for Minimal Luminal Area (MLA) obtained by IVUS in relation to FFR values.

It is clear that the best cut-off value for MLA which is concordant with ischemic FFR values is <3mm^2 with a sensitivity and specificity 76.92% & 50% respectively and a predictive values PPV= 45% and NPV=80%.

Further evaluation of the coronary artery lesion according to the site of the lesions in the main epicardial vessels and and the relation between the MLA collected by IVUS and the FFR values for these lesion in an attempt to come out with the best cut off value for each vessel alone the following measurement were detected:

1- For LAD vessel lesions best cut off MLA was 3.0mm^2, sensitivity and specificity 87.50% and 40% respectively and a predictive values PPV= 53.8% and NPV=80%.

2- For LCX was 2.75mm$_2$ with sensitivity and specificity 33.33% and 100% respectively and a predictive values PPV=100.0% and NPV= 66.7%.

3- For RCA it was 2.8mm$_2$ with sensitivity and specificity 50.0% and 100% respectively and a predictive values PPV=100.0% and NPV= 85.7%.
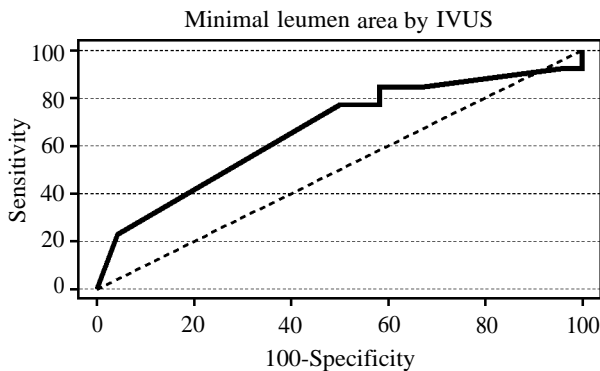

Fig. (1): ROC Curve for detection of the best cut-off value of MLA (3mm^2) in relation to FFR value.

Table (2): Risk factors for coronary artery disease for the patients included in this study.

	No.=30
HTN:	
No	16 (53.3%)
Yes	14 (46.7%)
D.M:	
No	7 (23.3%)
Yes	23 (76.7%)
Smoking:	
No	14 (46.7%)
Yes	16 (53.3%)
Dyslipidemia (total cholesterol≥200mg/dl);	
No	9 (3 0.0%)
Yes	21 (70.0%)
Creatinine (mg/dl):	
Mean ± SD	0.96±0.23
Range	0.6-1.5

Table (3): Site of coronary artery stenosis in the studied population.

	No.	%
LAD:		
No	11	36.7
Yes	19	63.3
LCX:		
No	23	76.7
Yes	7	23.3
RCA:		
No	23	76.7
Yes	7	23.3

Table (4): Mean and standard deviation of degree of stenosis, FFR value, IVUS measurements for the study group and either an ad-hoc PCI was done or not.

	No.=3 0
Visual degree of stenosis:	
Mean ± SD	58.86±7.58
Range	50-70
FFR measurement:	
Mean ± SD	0.83±0.07
Range	0.7-1
Minimal leumen area by IVUS:	
Mean ± SD	3.31±0.80
Range	2-6

Table (5): Sensitivity, specificity and predictive value of FFR values.

Cut off points	Sensitivity	Specificity	+PV	–PV
≤2mm^2	23.08	95.83	75.0	69.7
≤2.5mm^2	23.1	95.80	75.0	69.7
≤3*mm^2	76.92	50.00	45.5	80.0
≤3.2mm^2	76.92	41.67	41.7	76.9
≤3.4mm^2	84.62	41.67	44.0	83.3
≤3.9mm^2	84.62	33.33	40.7	80.0
≤4mm^2	92.31	4.17	34.3	50.0
≤5mm^2	92.31	0.00	33.3	0.0

Table (6): Sensitivity, specificity and predictive value of multiple cutoff values for Minimal Luminal Area (MLA) obtained by IVUS in relation to FFR in LAD.

MLA cut off point for LAD	Sensitivity	Specificity	+PV	–PV
$\leq 2mm^2$	25.00	90.00	66.7	60.0
$\leq 3mm^2$ *	87.50	40.00	53.8	80.0
$\leq 5mm^2$	87.50	0.00	41.2	0.0

Table (7): Sensitivity, specificity and predictive value of multiple cutoff values for Minimal Luminal Area (MLA) obtained by IVUS in relation to FFR in LCX.

MLA cut off point for LCX	Sensitivity	Specificity	+PV	–PV
$<2.5mm^2$	33.33	100.00	100.0	66.7
$<2.75mm^2$ *	33.33	100.00	100.0	66.7
$\leq 3mm^2$	66.67	50.00	50.0	66.7

Table (8): Sensitivity, specificity and predictive value of multiple cutoff values for Minimal Luminal Area (MLA) obtained by IVUS in relation to FFR in RCA.

MLA cut off point for RCA	Sensitivity	Specificity	+PV	–PV
$<2.8mm^2$	0.00	100.00		75.0
$\leq 2.8mm^2$ *	50.00	100.00	100.0	85.7
$\leq 3mm^2$	100.00	33.33	33.3	100.0

Discussion

The potential of angiography to evaluate the haemodynamic severity of an Intermediate lesion is limited. Moreover, angiographic assessment is often the only decision-making modality for performing coronary angioplasty, especially in the absence of any sort of functional evaluation [8].

Owing to the increased sensitivity of IVUS in identifying disease and its close correlation with pathology, IVUS has become more accurate standard for defining the anatomy of atherosclerosis in vivo. Intravascular ultrasound is a catheter-based technique that provides tomographic images perpendicular to the length of the coronary arteries. High-resolution cross-sectional images of the coronary lumen and the coronary arterial wall can be visualized in real time, and computer-generated reconstruction allows for longitudinal and 3-dimension visualization of the coronary artery [9].

Fractional Flow Reserve (FFR) has been proposed as the gold standard to assess functional severity of coronary artery stenosis and to stratify which lesions should be subjected to intervention (Percutaneous Coronary Intervention [PCI] or not [10].

So, the aim of this study was to further assess the correlation between Quantitative Coronary Angiography (QCA), FFR, quantitative and qualitative IVUS to elucidate the use of MLA derived from IVUS as an indicator in the diagnosis of functionally significant coronary artery stenosis.

According to an expert consensus statement published by Amir Lotfiet et al., it revealed that FFR was first validated using a cutoff value of 0.75. With further experience with the technique, investigators appreciated that by extending the cutoff value to 0.80, the sensitivity of FFR could be improved without greatly compromising the specificity [11].

For this reason, a cutoff value of <0.80 was used in FAME 1 and FAME 2 studies as well as our study and shown to be clinically valid. It is now the recommended ischemic reference standard for the invasive functional assessment of myocardial ischemia [12].

Our study showed a statistically highly significant relation ($p=0.0001$) between FFR value and PCI, as all cases with FFR value <0.80 (14 cases) already performed PCI and those with a FFR value >0.80 did not. The current study analyzed 38 intermediate non left main coronary lesions located in large coronary vessels with RVD ranged between (3-4mm). Majority of the targeted lesions were located in the proximal and mid coronary segments of the vessels avoiding any leison in the small branches as diagonal and small obtuse marginal branches to prevent affecting the end result regarding the optimal MLA that could predict the functional significance of any intermediate coronary artery lesion affecting the main coronary vessels.

As regard demographic data and coronary risk factors, there was no statistically significant difference among population except for diabetes mellitus as 12 patients out of 12 with FFR value less than 0.8 were diabetic also there was a significant correlation between FFR value and DM reflecting the impact of glycemic state on FFR value and this coincide with a clinical research done by [13], which showed that intermediate lesions from diabetics versus non diabetics differed significantly in both haemodynamic relevance (FFR <0.80, 37.7% versus 24.2% $p=0.018$) and lesion length (10.91±5.79mm vs. 9.23±3.85mm $p=0.005$) [13].

The use of IVUS to determine the functional significance of coronary artery lesions remains a matter for debate. As regard IVUS measurements obtained from this study including minimal luminal area and percent of stenosis. According to our study it is demonstrated that the best cut-off value for MLA which is corresponding to the results FFR values was an MLA $<3mm^2$, with a sensitivity and specificity 76.92% & 50% respectively and a predictive values PPV=45% and NPV=80%.

The major differences between our study and FIRST registry were related to:

First: Number of patients included in both studies being only 30 patients in our study and 350 patients (367 lesions) in FIRST registry.

Second: The majority of targeted lesions in this study located in proximal and mid segments of main coronary vessels not in distal segments or side branches.

The results of the FIRST [7] will certainly reinforce the view that IVUS is not a reliable alternative for FFR in functional assessment of angiographically intermediate stenoses. FFR is superior for physiology and IVUS is superior for anatomy, although a very high negative predictive value for IVUS-MLA >3.07mm may basically rule out functionally significant stenosis. However, the issue of superiority between these 2 modalities might be irrelevant because IVUS and FFR should be complementary techniques to be used in the catheterization laboratory to provide critical anatomic and functional data that permit more accurate decisions [7].

In our study further evaluation of the coronary artery lesion according to the site of the lesions in the main epicardial vessels and and the relation between the MLA collected by IVUS and the FFR values for these lesion in an attempt to come out with the best cut off value for each vessel alone the following measurement were detected for LAD vessel lesions best cut off MLA was $3.0mm^2$, and for LCX was $2.7mm^2$, and for RCA it was $2.8mm^2$, this concept was also evaluated by Bon-Kwon Koo et al., [14] who published a study aimed to determine the optimal MLA obtained by Intravascular Ultrasound (IVUS) and its diagnostic accuracy for defining the functional significance of intermediate coronary stenoses in different locations of the coronary tree among patients with already FFR value less than 0.08. Like our study which evaluated the precise anatomical site of lesion of interest in relation to MLA, Bon-Kwon Koo et al., revealed in their study that the diagnostic accuracy of MLA

was highly variable according to the location of lesions. The best cutoff value of MLA to define the functional significance was 3.0mm for proximal left (LAD) lesions and 2.75mm for mid-LAD lesions located before the second diagonal branch. However, the appropriate MLA to predict the functional significance of lesions could not be found in other segments. So When IVUS parameters are used to determine the functional significance of lesions in patients with intermediate coronary artery stenoses, different criteria should be used according to lesion location. In segments or vessels with anatomic variations, IVUS cannot be used for functional assessment of a stenosis [14].

Conclusion:

Although IVUS has an important role in day-to-day practice in assessing vessel size, plaque morphology, stent expansion and apposition, its role in identifying lesions as functionally significant is limited. However, it can help the operator if a lesion is likely to be insignificant when MLA is large enough, as a modest, yet significant correlation was observed between MLA and FFR. The high negative predictive value of large MLAs (namely $\geq 3mm^2$) may provide some degree of confidence to the interventionalist that the lesion in question is not functionally significant, which could be of particular importance especially in cases where FFR/adenosine are contraindicated or not tolerated.

References

1- TONINO P.A., FEARON W.F., De BRUYNE B., OLD-ROYD K.G., LEESAR M.A., VER LEE P.N., et al.: Angiographic versus functional severityof coronary artery stenoses in the FAME study fractional flow reserve versus angiography in multivessel evaluation. J. Am. Coll. Cardiol., 55: 2816-21, 2010.

2- BECH G.J., De BRUYNE B. and PIJLS N.H.: Fractional flow reserve to determine the appropriateness of angioplasty in moderate coronary stenosis: A randomized trial. Circulation, 103: 2928-34, 2001.

3- PUYMIRAT E.1., PEACE A., MANGIACAPRA F., CONTE M., NTARLADIMAS Y., BARTUNEK J., VANDERHEYDEN M., WIJNS W., De BRUYNE B. and BARBATO E.: Long-term clinical outcome after fractional flow reserve-guided percutaneous coronary revascularization in patients with small-vessel disease. Circ. Cardiovasc. Interv., Feb. 1, 5 (1): 62-8, 2012.

4- FEARON W.F., BORNSCHEIN B., TONINO P.A., et al.: Economic evaluation of fractional flow reserve-guided percutaneous coronary intervention in patients with multivessel disease. Circulation, 122: 2545-50, 2010.

5- JANG J.S., SONG Y.J., KANG W., et al.: Intravascular ultrasound-guided implantation of drug-eluting stents to improve outcome: A metaanalysis. J.A.C.C. Cardiovasc. Interv., 7: 233-43, 2014.

6- KANG S.J., AHN J.M., SONG H., et al.: Comprehensive intravascular ultrasound assessment of stent area and its impact on restenosis and adverse cardiac events in 403 patients with unprotected left main disease. Circ. Cardiovasc. Interv., 4 (6): 562-9, 2011.

7- WAKSMAN R., LEGUTKO J., SINGH J., ORLANDO Q., MARSO S. and SCHLOSS T.: First Fractional flow reserve and intravascular ultrasound relationship study. J. Am. Coll. Cardiol., 61: 917-23, 2013.

8- WIJNS W., De BRUYNE B. and VANHOENACKER P.K.: What does the clinical cardiologist need from non-invasive cardiac imaging: Is it time to adjust practices to meet evolving demands? J. Nucl. Cardiol., 366: 14-70, 2007.

9- JENNIFER A., TREMMEL, TOMOMI KOIZUMI, AIDEN O.D. LOUGHIN and ALAN C.: Intramural hematoma appearing as new lesion after coronary stenting JACC Cardiovascular Interventions, Vol. 4, No. 1, 2011.

10- NASCIMENTO B.R., BELFORT A.F., MACEDO F.A., SANT'ANNA F.M., PEREIRA G.T., COSTA M.A. and RIBEIRO A.L.: Meta-analysis of deferral versus performance of coronary intervention based on coronary pressure-derived fractional flow reserve Am. J. Cardiol., 115 (3): 385-91, 2015.

11- AMIR LOTFI, ALLEN JEREMIAS, WILLIAM F.FEARON, MARC D. FELDMAN, ROXANA MEHRAN, JOHN C. MESSENGER, CINDY L. GRINES, LARRY S. DEAN, MORTON J. KERN and LLOYD W. KLEIN: Catheterization and Cardiovascular Interventions November (2013) angiography with 64-section CT: Effect of average heart rate and heart rate angiography. Am. J. Cardiol., 87: 525-31, 2013.

12- MELIKIAN N., De BONDT P., TONINO P. , De WINTER O., WYFFELS BARTUNEK J., HEYNDRICKX G.R., FEARON W.F., PIJILS N.H.J., WIJNS W. and De BRUYNE B.: Fractional flow research and myocardial perfusion imaging in patients with angiographic multivessel coronary artery disease. J. Am. Coll. Cardiol. Intv., 3: 307-14, 2010.

13- SEBASTIAN REITH, SIMONE BATTERMANN, MARTIN HELLMICH, NIKOLAUS MARX and MATHIAS BURGMAIER: Cinical Res earch in Cardioloigy March 2014, Volume 103 Issue 3, pp. 191-2014.

14- BON-KWON KOO, HYOUNG-MO YANG, JUN-HYUNG DOH, HYUNMIN CHOE, SUNG-YUN LEE, CHANG-HWAN YOON, YUN-KYEONG CHO, CHANG-WOOK NAM, SEUNG-HO HUR, HONG-SEOK LIM, MYEONG-HO YOON, KYUNG-WOO PARK, SANG-HOON NA, TAE-JIN YOUN, WOO-YOUNG CHUNG, SEUNGHYUN MA, SUE-KYUNG PARK, HYO-SOO KIM and SEUNG-JEATAHK: J. Am. Coll. Cardiol. Intv., 4 (7): 803-11, 2011.

دور الموجات فوق الصوتية داخل الأوعية الدموية
فى التنبؤ بالأهمية الوظيفية لقصور الشرايين التاجية من الدرجة الوسطى وعلاقتها بكسور التدفق الإحتياطى

على الرغم من تقدم وسائل تشخيص آمراض قصور الشرايين التاجية إلا آن تلك الأمراض ما تزال الأكثر آنتشارا، وتتسبب فى عدد كثير من الوفيات سنويا وبما آن تقييم الإصابة متوسطة الضيق فى الشرايين لا يزال يشكل معضلة علاجية لأمراض القلب وحيث آن الأشعة فوق الصوتية داخل الأوعية الدموية: هى تقنية تقدم صور مقطعية عمودية على طول الشرايين التاجية عن طريق القسطرة كما آنها تسمح برؤية واقعية لجدار الشريان كما آن كسور التدفق الإحتياطى للشريان التاجى الطبيعى يساوى ١.٠ والقيمة آقل من ٠.٧٥ تعنى إن الإصابة تسبب قصور للارواء، والقيم بين ٠.٧٥ و٠.٨٠ تعتبر محور إختلاف، وبالتالى كان الهدف من البحث تحديد قيمة الأشعة فوق الصوتية داخل الأوعية الدموية فى تقييم الإصابة المتوسطة للشرايين التاجية ومدى تأثير تلك الإصابة على قصور الارواء مع الأخذ فى الإعتبار معدل التدفق الجزئى لمخزون الدم (كسور التدفق الإحتياطى) لتلك الشرايين المصابة بالضيق. وإشتملت هذه الدراسة على ثلاثون مريض ممن إتضحت إصابتهم بضيق فى الشرايين التاجية وتم إستبعاد المرضى الذين خضعوا لإجراء عملية قلب مفتوح لعمل وصلات على الشرايين التاجية والمرضى المصابين بضيق فى الجذع الرئيسى آو المصابون بالحساسية من عقار الأدينوسين وتم إخضاع جميع النتائج للتحليل الإحصائى المفصل شاملا الوسط والإنحراف المعيارى وقد آفادت هذه الدراسة بأنه عند إجراء موجات فوق صوتية للشرايين التاجية تكون آفضل قيمة معبرة عن آقل مساحة مقطعية للشرايين يمكن آن تؤدى إلى إعاقة مسار الدم داخل الشرايين هى ٣.٠سم٢ حيث آن تلك القيم لديها حساسية وخصوصية تصل إلى ٧٦.٩٢٪ & ٥٠ ٪ على التوالى وكذلك قيمة تنبؤية تصل إلى ٨٠٪ وقيمة تنبؤية سلبية تصل إلى ٤٥٪.