Intravascular ultrasound-based analysis of factors affecting minimum lumen area in coronary artery intermediate lesions

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Abstract

Objective To identify clinical characteristics associated with the minimum lumen area (MLA) of proximal or middle intermediate lesions in the left anterior descending (LAD) artery, and to develop a model to predict MLA. Methods We retrospectively analyzed demographic data, medical history, and intravascular ultrasound findings for 90 patients with intermediate lesions in the LAD artery. Linear regression was used to identify factors affecting MLA, and multiple regression was used to develop a model for predicting MLA. Results Age, number of lesions, and diabetes mellitus correlated significantly with MLA of proximal or middle intermediate lesions. A regression model for predicting MLA (mm²) was derived from the data: 7.00 – 0.05 × (age) – 0.50 × (number of lesions). A cut-off value of 3.1 mm² was proposed for deciding when to perform percutaneous coronary intervention. Conclusion This model for predicting MLA of proximal or middle intermediate lesions in the LAD artery showed high accuracy, sensitivity, and specificity, indicating good diagnostic potential.

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Keywords: Intermediate lesions; Intravascular ultrasound; Predictive model; Risk factors

1 Introduction

Intermediate coronary lesions, which involve stenosis of 40%–70% of vessel diameter, are often detected during coronary angiography. Deciding whether such lesions require invasive percutaneous coronary intervention (PCI) is a challenge, since nearly 90% of lesions show < 60% stenosis, yet 6% of intermediate coronary lesions may develop into acute coronary events. If physicians could gain detailed information about the severity of the intermediate lesion, mainly in terms of the minimum lumen area (MLA), they may be able to make a more informed decision about whether PCIs are appropriate.

Intravascular ultrasound is a novel technique that can provide quantitative data about individual blood vessels and lumen area. Using this technique, researchers have identified MLAs < 3.0 or < 2.4 mm² as associated with increased risk of myocardial ischemia. However, the technique is expensive and difficult to perform correctly, and it can cause complications. We wanted to examine the possibility of developing a model to predict MLA that might work well enough to substitute for direct measurement using intravascular ultrasound. Therefore, we aimed to identify clinical characteristics of patients that may influence MLA and build a model to predict MLA. We examined patient characteristics, endovascular imaging data and vessel and plaque measurements.

2 Methods

2.1 Study population

This study included a consecutive sample of 90 coronary artery disease patients with proximal or middle intermediate lesions in the left anterior descending (LAD) artery (RVD ≥ 2.5 mm; diameter stenosis: 40%–70%) who underwent coronary angiography and intravascular ultrasound at our hospital between November 2008 and April 2014. The population comprised 58 men and 32 women, with ages ranging from 41 to 77 years. Among the included patients, 58 were males and 32 were females, with ages ranging from 41 to 77 years. Exclusion criteria were the presence of left main, bifurcation, small vessel, thrombus, and severe calcified lesions, as well as stent restenosis.

2.2 Coronary angiography

Coronary angiography was performed via the radial or
femoral artery using the standard Judkins technique and a Philips Allura Xper FD10 machine (Philips Healthcare, Best, the Netherlands). After catheter positioning, patients were given 200 µg of nitroglycerin intravenously. Typically, six images of the left coronary artery were captured for each patient, and the image showing the most severe stenosis was used in the analysis. The degree of stenosis was estimated independently by two experienced cardiologists.

2.3 Intravascular ultrasound

Patients were given 200 µg of nitroglycerin through the catheter, and intravascular ultrasound data were collected using a 40-MHz catheter (Atlantis SR Pro, Boston Scientific, Natick, MA). The catheter was positioned beyond the target lesion, and images were acquired using automatic pullback at 0.5 mm/s. Ultrasound data were stored on a hard disk and analyzed off-line.

Lesions were analyzed quantitatively using Qlvus (iMap Basic Viewer 2.1.32.0, Medis Medical Imaging Systems, Leiden, the Netherlands). The external elastic membrane (EEM) and lumen cross-sectional area (CSA) were measured using iMap software. Plaque CSA was calculated as the difference between EEM and lumen CSAs, while plaque burden was calculated by combining plaque area and media area, then dividing by the CSA of EEM. The MLA was defined as the minimum obtained after testing various sites. The terms “proximal” and “distal” were defined to refer, respectively, to the normal lumen sites that were within 10 mm of the MLA and that were in front of any large side branches.

2.4 Statistical analysis

Demographic data, medical history, and ultrasound data were analyzed using SAS 9.1 (SAS, Cary, USA) and SPSS 13.0 (IBM, Chicago, USA); two-sided \( P < 0.05 \) was defined as the threshold of significance, unless otherwise noted. The entire dataset was randomly divided into a training set (80%), which was used to identify factors associated with MLA and to build a predictive model; and a validation set (20%), which was used to test the model. To identify factors associated with MLA, the training dataset was analyzed by linear regression in which MLA was the dependent variable and the other variables were independent variables. Factors potentially associated with MLA were then analyzed by multiple linear regression that combined global optimization and stepwise regression (inclusion level = 0.05, exclusion level = 0.10) in order to generate the final model. The regression equation predicted a positive value for MLAs < 3.0 mm² or a negative value otherwise.

The predictive power of the model was evaluated using a receiver operating characteristic (ROC) curve. Predictive power was considered significant if the area under the curve (AUC) was > 0.5; this cut-off value was based on the Youden index (sensitivity + specificity − 1).

3 Results

3.1 Patient characteristics and intravascular ultrasound results

Clinico-demographic data, medical history, and intravascular ultrasound findings for the patients in the study are shown in Tables 1–2.

3.2 Univariate analysis of factors affecting MLA

Linear regression in which numerous clinico-demographic variables were tested individually for their association with MLA identified the following covariates with \( P < 0.15 \): age, weight, sex, number of affected vessels, diabetes mellitus, highly sensitive C-reactive protein (hs-CRP), triglycerides (TG), and hematocrit (HCT) (Table 3).

3.3 Multivariate analysis of factors associated with MLA

Factors associated with \( P < 0.15 \) in the univariate analysis were considered in a multiple linear regression model, which was built using 80% of the total dataset (Table 4). The resulting model performed well against the data \( (P = 0.0019) \); the model took the form MLA (mm²) = 7.07685 − 0.04216 × (age) − 0.46879 × (number of affected vessels). This model shows a decline in MLA of 0.04216 units with each 1-year increase in age, and a decline in MLA of 0.46879 units with each additional affected vessel.

ROC curve analysis showed an AUC of 0.780 (95% CI: 0.661–0.899) (Figure 1A), suggesting high accuracy and good diagnostic performance. To facilitate clinical application, we simplified the model to MLA (mm²) = 7.00 − 0.05 × (age) − 0.5 × (number of affected vessels). This simplified form shows an AUC of 0.777 (95% CI: 0.658–0.896) under the ROC curve \( (P = 0.001) \) (Figure 1B). This model indicates an optimal MLA cut-off of 3.10 mm² based on the Youden index (sensitivity + specificity − 1).

The ability of the simplified model to predict MLA below 3.1 mm², which emerged here as the cut-off value for deciding whether to perform PCI, was assessed against the training dataset (80% of the total data; Table 5), as well as against the validation dataset (the remaining 20% of the total data; Table 6).
Table 1. Demographic and clinical data for 90 patients with proximal or middle intermediate lesions in the left anterior descending artery.

| Metric | Mean ± SD | Minimum | Maximum | Median | 95% CI (25%, 75%) |
|--------|-----------|---------|---------|--------|------------------|
| Age, yrs | 59.52 ± 9.70 | 41.00 | 77.00 | 57.00 | (51.00, 69.00) |
| Weight, kg | 72.18 ± 10.95 | 47.00 | 105.00 | 72.00 | (65.00, 79.00) |
| Affected vessels, n | 1.61 ± 0.77 | 1.00 | 3.00 | 1.00 | (1.00, 2.00) |
| WBC, × 10^9/L | 6.38 ± 1.62 | 3.06 | 11.19 | 6.32 | (5.35, 7.43) |
| PLT, × 10^9/L | 200.05 ± 56.21 | 53.60 | 351.00 | 193.00 | (158.00, 238.00) |
| HGB, g/L | 137.72 ± 16.79 | 92.60 | 225.00 | 136.00 | (127.00, 148.00) |
| hs-CRP, mg/L | 2.84 ± 3.96 | 0.08 | 19.93 | 1.40 | (0.50, 2.78) |
| TG, mmol/L | 1.69 ± 1.36 | 0.54 | 9.81 | 1.34 | (0.93, 1.85) |
| CHO, mmol/L | 4.47 ± 2.29 | 1.28 | 14.10 | 3.95 | (3.28, 4.85) |
| LDL-C, mmol/L | 2.29 ± 0.75 | 0.87 | 3.92 | 2.16 | (1.69, 2.91) |
| HDL-C, mmol/L | 1.03 ± 0.32 | 0.59 | 3.07 | 0.98 | (0.85, 1.15) |
| GLU, mmol/L | 5.31 ± 1.18 | 2.71 | 10.70 | 5.09 | (4.59, 5.69) |
| CRE, μmol/L | 70.86 ± 17.83 | 38.00 | 140.00 | 68.00 | (59.00, 78.00) |
| cGFR, mL/min per 1.73 m² | 96.75 ± 23.75 | 40.00 | 169.00 | 96.00 | (83.00, 109.00) |
| HCT, % | 39.82 ± 4.15 | 26.33 | 49.48 | 39.66 | (36.63, 42.31) |
| FIB, mg/L | 304.75 ± 58.08 | 204.00 | 458.00 | 265.00 | (265.00, 339.00) |
| MLA, mm² | 3.82 ± 1.38 | 1.60 | 9.08 | 2.98 | (2.98, 4.36) |
| EEM, mm² | 11.56 ± 4.05 | 4.36 | 24.10 | 8.43 | (8.43, 14.77) |
| Plaque burden, % | 64.69 ± 11.38 | 34.00 | 92.00 | 57.00 | (57.00, 73.00) |

CHO: cholesterol; CRE: creatinine; EEM: external elastic membrane; eGFR: estimated glomerular filtration rate; FIB: fibrinogen; GLU: glucose; HCT: hematocrit; HDL-C: high-density lipoprotein-cholesterol; HGB: hemoglobin; hs-CRP: highly sensitive C-reactive protein; LDL-C: low-density lipoprotein-cholesterol; MLA: minimal lumen area; TG: triglycerides; PLT: platelets; WBC: white blood cells.

Table 2. Classification of patients based on coronary and vascular parameters.

| Number of affected vessels | One | Two | Three |
|---------------------------|-----|-----|-------|
|                           | 51(56.67) | 23(25.56) | 16(17.78) |

| Hypertension | Yes | No |
|--------------|-----|----|
|              | 58(64.44) | 32(35.56) |

| Diabetes mellitus | Yes | No |
|-------------------|-----|----|
|                   | 25(27.78) | 65(72.22) |

| Dyslipidemia | Yes | No |
|-------------|-----|----|
|             | 33(36.67) | 57(63.33) |

| Family history of coronary disease | Yes | No |
|-----------------------------------|-----|----|
|                                   | 17(18.89) | 73(81.11) |

| ST-segment depression, mV | 0 | 0.05 | 0.1 |
|---------------------------|---|------|-----|
|                           | 64(71.11) | 22(24.44) | 4(4.44) |

| Minimal lumen area, mm² | ≥ 4.0 | < 4.0 |
|-------------------------|-------|------|
|                         | 32(35.56) | 58(64.44) |

| Minimal lumen area, by category | ≥ 3.0 mm² | < 3.0 mm² |
|---------------------------------|---------|---------|
|                                 | 67(74.44) | 23(25.56) |

4 Discussion

Coronary angiography is widely regarded as the gold standard for diagnosing coronary atherosclerotic heart disease, but physicians typically use it as a qualitative tool when deciding whether to perform invasive PCI. This may not be the best way to triage intermediate lesions, some of which (6%) may develop into acute coronary syndrome and yet most of which (87%) involve < 60% stenosis. Many physicians perform interventional therapy only when intermediate lesions present together with typical angina pectoris or objective evidence of myocardial ischemia. This remains an important treatment dilemma for cardiologists, highlighting the need for a more quantitative imaging-based approach to assessing stenosis severity. 

One such approach is intravascular ultrasound, which combines non-invasive ultrasound and invasive catheter technology to provide accurate measurements of EEM area, MLA, and plaque burden. Several researchers have sought to correlate MLA values measured by ultrasound with flow fractional reserve (FFR). The prognostic importance of FFR was shown when patients in the FAME study were stratified by FFR: 20% of patients with lesion stenosis > 70% of vessel diameter based on coronary angiography nevertheless did not experience myocardial ischemia, while 35% of patients with lesion stenosis of 50%–70% experi-

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Table 3. Simple linear regression to identify factors associated with MLA.

| Variable                      | Regression coefficient | P     |
|-------------------------------|------------------------|-------|
| Age                           | -0.04476               | 0.0084|
| Weight                        | 0.02578                | 0.1210|
| Sex (male)                    | 0.53232                | 0.1269|
| Affected vessels              | -0.47225               | 0.0183|
| Hypertension (yes)            | -0.02877               | 0.9335|
| Diabetes mellitus (yes)       | -0.83316               | 0.0171|
| Dyslipidemia (yes)            | -0.08385               | 0.8048|
| Family history (yes)          | -0.14774               | 0.7922|
| WBC                           | 0.08124                | 0.4014|
| PLT                           | -0.00080               | 0.7789|
| HGB                           | 0.01064                | 0.2528|
| hs-CRP                        | -0.08336               | 0.0951|
| TG                            | 0.22573                | 0.1152|
| CHO                           | -0.07469               | 0.2599|
| LDL-C                         | -0.07732               | 0.7326|
| HDL-C                         | -0.52058               | 0.4577|
| GLU                           | -0.06956               | 0.6060|
| CRE                           | 0.00056                | 0.9478|
| eGFR                          | 0.00817                | 0.2059|
| HCT                           | 0.06148                | 0.1034|
| FIB                           | -0.00390               | 0.1860|
| ST-segment depression         | -0.31708               | 0.3073|

CHO: cholesterol; CRE: creatinine; EEM: external elastic membrane; eGFR: estimated glomerular filtration rate; FIB: fibrinogen; GLU: glucose; HCT: hematocrit; HDL-C: high-density lipoprotein-cholesterol; HGB: hemoglobin; hs-CRP: highly sensitive C-reactive protein; LDL-C: low-density lipoprotein-cholesterol; MLA: minimal lumen area; TG: triglycerides; PLT: platelets; WBC: white blood cells.

Table 4. Multiple linear regression to identify variables that predict minimal lumen area.

| Variable                      | Estimate | SE    | t      | P      |
|-------------------------------|----------|-------|--------|--------|
| Lumen area                    | 7.07685  | 0.98767| 7.17   | <0.0001|
| Age                           | -0.04216 | 0.01598| -2.64  | 0.0103 |
| Number of affected vessels    | -0.46879 | 0.19241| -2.44  | 0.0175 |

While substantial evidence suggests that intravascular ultrasound can provide a rigorous quantitative basis for deciding whether or not to perform PCIs on patients with intermediate lesions, the technique is not available or even feasible in many medical environments. The apparatus is expensive and requires expert training for proper operation and analysis. The technique can cause complications, which can increase the costs and duration of hospitalization. Therefore, we wanted to know whether we could use intravascular ultrasound to develop a predictive model that clinicians could rely upon in the absence of direct measurements to estimate likely MLA and therefore decide whether PCI is appropriate. Our model focused on the LAD artery since this is a major blood vessel, it is the most important coronary artery branch, and it strongly influences FFR.[17] Based on our data, we derived a simplified model MLA (mm²) = 7.00 – 0.05 × (age) – 0.5 × (number of affected vessels), with a cut-off value of 3.10 mm². The high sensitivity and specificity of the model when applied against both the original training dataset and the validation dataset suggest satisfactory discrimination. Given the high negative
Table 5. Performance of simplified predictive model against the training dataset.

| Prediction MLA ≥ 3.1 mm² (negative) | MLA < 3.1 mm² (positive) | Total |
|------------------------------------|--------------------------|-------|
| MLA ≥ 3.1 mm²                       | 35                       | 3     | 38   |
| MLA < 3.1 mm²                       | 19                       | 14    | 33   |
| Total                               | 54                       | 17    | 71   |

Sensitivity, 82.35%; specificity, 64.81%; positive predictive value, 42.42%; negative predictive value, 92.11%. MLA: minimal lumen area.

Table 6. Performance of simplified predictive model against the validation dataset.

| Prediction MLA ≥ 3.1 mm² (negative) | MLA < 3.1 mm² (positive) | Total |
|------------------------------------|--------------------------|-------|
| MLA ≥ 3.1 mm²                       | 9                        | 1     | 10   |
| MLA < 3.1 mm²                       | 3                        | 5     | 8    |
| Total                               | 12                       | 6     | 18   |

Sensitivity, 83.33%; specificity, 75.00%; positive predictive value, 62.50%; negative predictive value, 90.0%. MLA: minimal lumen area.

prediction rate, we suggest that when MLA ≥ 3.10 mm², not performing PCI on an intermediate lesion is a reasonable treatment choice, and when no further imaging or functional examinations can be performed. We attribute the low positive prediction rate of the model to our small sample size, so larger studies are needed to verify our results. We caution that model-based MLA prediction should be used in conjunction with other diagnostic methods in order to determine the most appropriate therapy.

Our results should be interpreted conservatively since they are based on a small, single-center, retrospective study, raising the risk of several kinds of bias. In addition, since we identified age as a significant contributor to MLA, future studies should recruit large numbers of patients with diverse ages to allow robust subgroup analysis by age.

Despite these limitations, the model presented here may guide future work in defining evidence-based MLA cut-offs for deciding when to perform invasive procedure to treat intermediate lesions.

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