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Reviewer A

Alian et al. studied 121 patients with intermediate coronary disease that underwent intravascular optical coherence tomography. They also examined leukocyte telomere length (LTL) and found that it was independently associated with the possibility of receiving PCI in intermediate coronary lesion patients. LTL is also significantly related to plaque instability features that are evaluated by optical coherence tomography.
This manuscript is generally well-written, and the authors present an interesting study. Nonetheless, there are several issues that need to be addressed by the authors.

Comment 1: How did the author determine the indication for treatment of moderate coronary artery lesions? Usually, treatment for moderate stenosis requires measurement of coronary blood flow reserve ratio with pressure wire and proof of myocardial ischemia with myocardial scintigraphy.

Reply 1: Thanks for your comments. In this retrospective study, PCI was performed when at least one of the following criteria is met: 1) area stenosis (AS) between 50% and 70% and minimal luminal area (MLA) <2.5 mm^2; 2) AS between 50% and 70% and plaque rupture. We have modified our methods section, discussion section, and updated our references in response to this comment.

We agree that major international clinical guidelines on myocardial revascularization support the use of physiological assessment, such fractional flow reserve (FFR), to guide revascularization. Other non-invasive diagnostic tools, such as myocardial scintigraphy or myocardial contrast echocardiography, single-photon emission CT (SPECT) can also be used to assessment of myocardial ischemia. In contrast, optical coherence tomography (OCT), has clearly demonstrated a favorable impact on PCI optimization and a comparison between FFR and OCT shows that OCT guidance is associated with lower occurrence of the composite of major adverse cardiac events or significant angina and FFR guidance is associated with a higher rate of medical management after a follow up of 13 months. However, these tests are often cost-prohibitive for our patients and large-scale prospective studies are warranted if one wishes to include FFR or SPECT. Large-scale prospective study will need in future and we will consider to add FFR or SPECT to provide proof of myocardial ischemia in study design.

Changes in the text: We added data in following sections.
Methods Section (Page 9, lines 165-168): In this retrospective study, PCI was performed when at least one of the following criteria is met: 1) area stenosis (AS)

between 50% and 70% and minimal luminal area (MLA) <2.5 mm^2; 2) AS between 50% and 70% and plaque rupture (15).

Discussion section (Page 14, lines 278-291): Major international clinical guidelines on myocardial revascularization support the use of physiological assessment, such as fractional flow reserve (FFR), to assess the hemodynamic relevance of intermediate-grade stenosis. Other non-invasive diagnostic tools, such as myocardial scintigraphy, myocardial contrast echocardiography, or single-photon emission CT (SPECT) can also be used to assessment of myocardial ischemia (18.19). However, these tests are often cost-prohibitive for patients and large-scale prospective studies are warranted. In contrast, optical coherence tomography (OCT), has clearly demonstrated a favorable impact on PCI optimization (20) and a comparison between FFR and OCT shows that OCT guidance is associated with lower occurrence of the composite of major adverse cardiac events or significant angina and FFR guidance is associated with a higher rate of medical management after a follow up of 13 months (21). It provided support proof that OCT may be as an assessment tool for decision of intermediate coronary lesions. In this retrospective study, we used OCT guidance for PCI treatment.

Reference section (Page 22, lines 426-429,435-445): [15] Burzotta F, Leone AM, De Maria GL, et al. Fractional flow reserve or optical coherence tomography guidance to revascularize intermediate coronary stenosis using angioplasty (FORZA) trial: study protocol for a randomized controlled trial. Trials. 2014 Apr 23; 15:140.
[18] Neumann F-J, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. Eur Heart J 2019; 40:87–165.
[19] Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention. Circulation 2011;124: e574–651.
[20] Jones DA, Rathod KS, Koganti S, et al. Angiography Alone Versus Angiography Plus Optical Coherence Tomography to Guide Percutaneous Coronary Intervention: Outcomes from the Pan-London PCI Cohort. JACC Cardiovasc Interv 2018;11(14):1313-1321.
[21] Burzotta F, Leone AM, Aurigemma C, et al. Fractional Flow Reserve or Optical Coherence Tomography to Guide Management of Angiographically Intermediate Coronary Stenosis: A Single-Center Trial. JACC Cardiovasc Interv 2020;13(1):49-58.

Comment 2: What are the types and frequency of oral medications in each patient group? In particular, what is the frequency of statin and PCSK-9 use? Both drugs are effective in stabilizing and regressing plaques.

Reply 2: Thank you for the above valuable suggestions. Oral medication(s) and frequency information have been added. None of the patients analyzed were prescribed with PCSK-9 inhibitor because it was not yet available in China during January 1, 2016 to December 31, 2017. We found no significant difference in anti-platelet, statin, β-blocker, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, calcium channel blocker and insulin use between the two groups.

Changes in the text: We added data as following.

Result section (Page 11, line 226): There were no significant differences in age, hypertension, hyperlipidemia, cerebral infarction kidney dysfunction and use of drugs before admitted or at discharge between the PCI and the non-PCI group.

Table 1 (Pages 25-26, lines 495-500):

Table 1. Baseline clinical characteristics findings.

	Non-PCI (50)	PCI (71)	t/U/χ2 Value	p Value
Age, years	66.14±10.54	64.69±10.38	-0.752	0.454
Men, n (%)	28 (56.0%)	52 (73.2%)	3.892	**0.049**
Hypertension, n (%)	34 (68.0%)	40 (56.3%)	1.68	0.195
DM, n (%)	11 (22.0%)	28 (39.4%)	4.084	**0.043**
Smoker, n (%)	22 (44.0%)	41 (57.7%)	2.221	0.136
Hyperlipidemia, n (%)	20 (40.0%)	35 (49.3%)	1.352	0.245
Family history, n (%)	20 (40.0%)	43 (60.6%)	4.971	**0.026**
Cerebral infarction, n (%)	8 (16.0%)	14 (19.7%)	0.273	0.602
Kidney dysfunction, n (%)	7 (14.0%)	3 (4.2%)	3.697	0.054
TC, mmol/L	4.12±1.17	4.08±1.15	-0.177	0.86
HDL, mmol/L	1.28±0.82	1.03±0.33	-2.062	**0.044**
LDL, mmol/L	2.52±0.98	2.93±1.08	2.143	**0.034**
TG, mmol/L	1.84±1.40	1.42±0.74	-1.938	0.057
Glucose, mmol/L	6.35±2.72	6.03±2.09	-0.714	0.477
WBC, (10^9/L)	6.30±2.03	6.86±2.54	-1.619	0.108
CRP, mg/dl	3.61±2.42	5.77±11.39	1.323	0.188
Cr, umol/L	88.70±33.69	96.51±107.82	0.495	0.622
Treatment before admitted				
Anti-platelet	25(50%)	39(54.9%)	0.286	0.593
Statins	18(36.0%)	26(36.6%)	0.005	0.944
β-blocker	11(22%)	17(23.9%)	0.062	0.803
ACEI/ARB	20(40.0%)	30(42.3)	0.061	0.804
CCB	19(38%)	25(35.2%)	0.099	0.754
Insulin	4(8.0%)	11(15.5)	1.517	0.218
Treatment at discharge				
Anti-platelet	48(96.0%)	71(100%)	2.888	0.089
Statins	47(94.0%)	70(98.6%)	1.935	0.164
β-blocker	15(30.0%)	20(28.2)	0.048	0.827
ACEI/ARB	21(42.0%)	30(42.3%)	0.001	0.978

CCB	17(34.0%)	21(29.6%)	0.266	0.606
Insulin	5(10.0%)	12(16.9%)	1.157	0.282
LTL, kb	15.32±3.72	12.54±2.70	-4.521	**<0.001**

Values were represented by mean ± SD, or n (%); DM: diabetes mellitus. TC: total cholesterol. HDL-C: high density lipoprotein cholesterol. LDL-C: low density lipoproteins cholesterol. TG: triglyceride. WBC: white blood cell. CRP: C-reactive protein. Cr: creatinine. LTL: leukocyte telomere length. ACEI: angiotensin-converting enzyme inhibitors. ARB: angiotensin receptor blockers. CCB: calcium channel block

Comment 3: Was there a difference in the long-term prognosis of MACE between the group that underwent PCI and the group that did not undergo PCI?
Was it helpful to identify the potential presence of plaque instability by measuring LTL and intervene with PCI? Or does it suggest the need for more rigorous lipid management? Please discuss ways to apply this information to clinical practice.

Reply 3: Thank you for your rigorous comment. We have gone back and analyzed the long-term prognosis of MACE between the two groups. The total incidence of MACE was 3.3% (4/121), lesser than the multicenter study which reported 6% in intermediate coronary lesions, and we found no significant difference between the two groups (Figure 4, p = 0.84). There was no death and AMI in the both groups. Two patients suffered from target lesion revascularization (TLR) in the Non-PCI group (2/50, 4%) and 2 patients experienced TLR in the PCI group (2/71, 2.8%).

Compared to IVUS and FFR which can be cost-prohibitive, our results support the use of LTL as an alternative readout for plaque instability in patients with intermediate coronary lesions. LTL can be combined with other risk factors to provide superior risk stratification. For high-risk patients, OCT, IVUS, or FFR may be second line options if angiography shows intermediate coronary lesions. Those patients should be followed up more closely and have more rigorous lipid management whether underwent PCI or not. The DNA extraction and PCR reaction procedure is relative standardized and implementation wise we foresee this test can be performed at the time of admission, prior to surgery.

Changes in the text: We add some data as follows.
Methods section (Page 10, lines 191-200; Page 11, lines, 210-211):
5. MACE assessment
Follow-up information was collected from a comprehensive medical record database generated based on clinical visits or phone call interviews. All patients were followed up for at least 24 months. Major adverse clinical events (MACE) were defined as cardiac death, acute myocardial infarction (AMI), and/or target lesion revascularization (TLR). Cardiac deaths were defined as all deaths without clear non-cardiac causes; 2) myocardial infarctions were defined based on the diagnostic criteria of the 4th universal definition of myocardial infarction consensus; 3) target lesion revascularizations (TLR) were defined as PCI or coronary artery bypass grafting on

target lesion.
The incidence of MACE, was studied using the Kaplan-Meier method and compared using the log-rank test.

Results section (Pages 13, lines 264-268): During the 24 months follow-up period, the total incidence of MACE was 3.3% (4/121). There was no death and AMI in both groups. Two patients suffered from TLR in the Non-PCI group (2/50, 4%) and two patients experienced TLR in the PCI group (2/71, 2.8%). There was no significant difference between the two groups (p=0.84) (Figure 4).

Discussion section (Page 14, lines 276-277): There was no significant difference in total incidence of MACE between the two groups during our 24 months follow-up.

Figure 4 (Page 35, line 612)

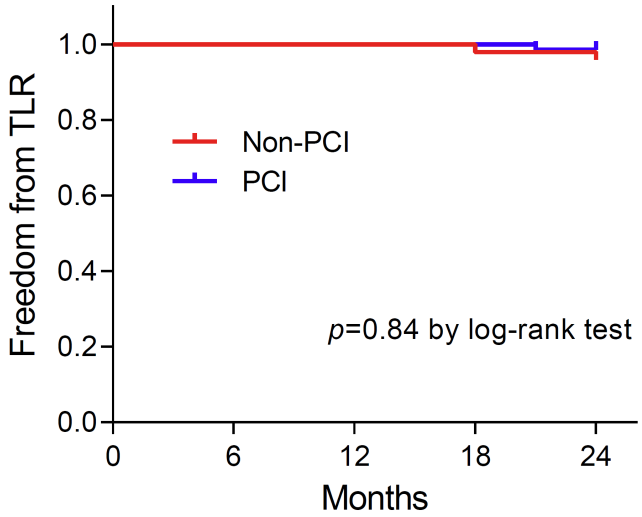

Figure 4. Freedom from target lesion revascularization in PCI and Non-PCI groups. TLR: target lesion revascularization.

Comment 4: Are there any malignant tumors or inflammatory diseases involved in telomere shortening? Also, it may depend on the degree of frailty, but was there any difference between the two groups?

Reply 4: Thank you for pointing out this problem in manuscript. In our study, we did not include any patients with malignant tumor or inflammatory diseases and we have updated our exclusion criteria to reflect this point. A priori frailty assessments were not performed given this is a retrospective study.

Changes in the text:
Methods section (Page 7, line 123): Exclusion criteria include: (1) st-segment elevation myocardial infarction (STEMI) and non-st-segment elevation myocardial infarction (NSTEMI); (2) left main disease, chronic total occlusion, extremely tortuous or heavily calcified vessels; (3) previous PCI or coronary artery bypass graft (CABG) on the target vessel; (4) serious liver and kidney dysfunction; (5) malignant tumors; (6) inflammatory diseases.

Reviewer B

In this study, the association between Leukocyte telomere length (LTL) and percutaneous coronary intervention (PCI) was assessed in a sample of 121 hospital patients who undergone intravascular ocular coherence tomography. The authors found that patients with shorter LTL were significantly more likely to receive PCI even after multivariable adjustment. The analysis is justified adequately, the results are presented clearly and the manuscript is written well. I have only a few relatively minor comments:

Comment 1: The title of the article refers to the severity of coronary lesions, however the main comparison in the analysis was between patients who received PCI vs those who did not. Does PCI mean worse (more severe) lesions? Or are there other criteria that needs to be considered when deciding on PCI intervention (as it is described in lines 156-159)? A few notes regarding the relationship between the severity of lesions and PCI intervention should be included in the Background/Methods and potentially also in the Discussion part of the article.

Reply 1: We thank the reviewer for this insightful comment. The decision of whether to provide PCI treatment for patients with intermediate coronary lesions is a daily clinical challenge. This study aimed to investigate if LTL can be an indicator for PCI intervention in patients with intermediate coronary lesions. The goal of this retrospective study was to examine if LTL can be an indicator for PCI intervention in patients with intermediate coronary lesions. Then two groups were divided according to whether receiving PCI or not. It showed that LTL was shorter in PCI group than Non-PCI group. Furthermore, LTL was inversely correlated with lipid length, lipid arc, lipid index, and positive correlation with FCT.

As Reviewer suggested that we added some data about criteria for treatment. In this retrospective study, PCI was performed when at least one of the following criteria is met: 1) area stenosis (AS) between 50% and 70% and minimal luminal area (MLA) <2.5 mm^2; 2) AS between 50% and 70% and plaque rupture. We have modified our methods section (Page 8, lines 166-171), discussion section (Page 13-14, lines 283-301), and updated our references (Page 20, lines 443-453).” In fact, PCI means plaque instability and high risk lesions in our study. Based on this, the title was not rigorous and we changed it to ‘The association of leukocyte telomere length and intermediate coronary lesions - a retrospectively study’.

Changes in the text:

Title (Page 1, lines 1-2): The association of leukocyte telomere length and intermediate coronary lesions - a retrospectively study

Methods Section (Page 9, lines 165-168): In this retrospective study, PCI was performed when at least one of the following criteria is met: 1) area stenosis (AS) between 50% and 70% and minimal luminal area (MLA) <2.5 mm^2; 2) AS between

50% and 70% and plaque rupture.

Discussion section (Page 14, lines 278-291): Major international clinical guidelines on myocardial revascularization support the use of physiological assessment, such as fractional flow reserve (FFR), to assess the hemodynamic relevance of intermediate-grade stenosis. Other non-invasive diagnostic tools, such as myocardial scintigraphy, myocardial contrast echocardiography, or single-photon emission CT (SPECT) can also be used to assessment of myocardial ischemia (17.18). However, these tests are often cost-prohibitive for patients and large-scale prospective studies are warranted. In contrast, optical coherence tomography (OCT), has clearly demonstrated a favorable impact on PCI optimization (19) and a comparison between FFR and OCT shows that OCT guidance is associated with lower occurrence of the composite of major adverse cardiac events or significant angina and FFR guidance is associated with a higher rate of medical management after a follow up of 13 months (20). It provided support proof that OCT may be as an assessment tool for decision of intermediate coronary lesions. In this retrospective study, we used OCT guidance for PCI treatment.

Reference section (Page 22, lines 431-441): [17] Neumann F-J, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. Eur Heart J 2019; 40:87–165.
[18] Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention. Circulation 2011;124: e574–651.
[19] Jones DA, Rathod KS, Koganti S, et al. Angiography Alone Versus Angiography Plus Optical Coherence Tomography to Guide Percutaneous Coronary Intervention: Outcomes from the Pan-London PCI Cohort. JACC Cardiovasc Interv 2018;11(14):1313-1321.
[20] Burzotta F, Leone AM, Aurigemma C, et al. Fractional Flow Reserve or Optical Coherence Tomography to Guide Management of Angiographically Intermediate Coronary Stenosis: A Single-Center Trial. JACC Cardiovasc Interv 2020;13(1):49-58.

Comment 2: In the title please write "retrospective" instead of "retrospectively"

Reply 2: Thank you for your careful check. The title now reads: ‘The association of leukocyte telomere length and intermediate coronary lesions - a retrospective study’.

Changes in the text:
Title (Page 1, lines 1-2): The association of leukocyte telomere length and intermediate coronary lesions - a retrospective study

Comment 3: In the Methods section of the Abstract, please say which LTL groups were compared to obtain the OR of 0.952 in relation to PCI vs. non-PCI groups. (i.e. is this the OR per 1 unit increase in LTL?)

Reply 3: Thank you for pointing out this problem in manuscript and it is very helpful. We have modified the text: “Logistic regression revealed that LTL was independently

associated with PCI after adjusting for confounding factors (OR 0.952, CI 0.930-0.974, per 1 unit increase, $p<0.001$)".

Changes in the text:
Abstract (Page 3, lines 62-64): Logistic regression revealed that LTL was independently associated with PCI after adjusting for confounding factors (OR 0.952, CI 0.930-0.974, per 1 unit increase, $p<0.001$)

Comment 4: Line 108: It would be better to say "Study sample" rather than "Study cohort". In fact, throughout the text, it would be good to replace the term "cohort" to "sample". The term "cohort" suggests prospective study.

Reply 4: Thank you for your rigorous suggestion. We have modified our text as advised.

Changes in the text:
Methods (Page 6, lines 114-115)
1. Study sample
Study sample were retrospectively selected with patients that exhibited 40-70% diameter stenosis (based on coronary angiography) and whom underwent OCT examinations, from Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine from the period of January 1, 2016 to December 31, 2017.

Figure 1(Page 32, line 569): Figure 1. Flowchart of the study sample

Comment 5: Line 185: Please say that logistic regression models were used.

Reply 5: Thank you for pointing out this problem in manuscript. We have modified our text as advised accordingly.

Changes in the text:
Methods section (Page 10, line 206-207): Logistic regression models were used to explore the influence of independent variables on PCI as the dependent variable.

Comment 6: In my opinion, the first paragraph of the Results would be more suitable to be placed in the "Study cohort" (Or "Study sample") section of the Methods.

Reply 6: Thank you for the above suggestion. We have modified our text as advised. The first paragraph of the Results was placed in the "Study sample" section of the Methods.

Changes in the text:
Methods section (Page 6, line 114-118): From total of 3106 patients that underwent angiogram, 417 patients exhibiting intermediate coronary lesion (40-70% diameter stenosis) underwent OCT. Patients were divided into two groups according to whether they had PCI (PCI group, n = 71) or not (non-PCI group, n = 50).

Comment 7: Line 247, please replace "Table 4" with "Table 5"

Reply 7: Thank you so much for your careful check. We apologize for this error and have modified accordingly (Page 13, line 275).

Changes in the text:
Results section (Page 13, line 261-263): Furthermore, LTL was inversely correlated with lipid length (r=-0.190, p=0.037), lipid arc (r=-0.301, p=0.001), lipid index (r=-0.182, p=0.046), and positive correlation with FCT (r=0.213, p=0.034) (Table 5).

Comment 8: In Table 3, please use the terms "Univariable" and "Multivariable" instead of "Univariate" and "Multivariate". Also in this table, in a footnote, please say that in the multivariable adjusted models, all dependent variables were adjusted for each other. Finally, also in table 3, please indicate which gender is the reference category.

Reply 8: Thank you for pointing out this problem in manuscript and we gratefully appreciate for your valuable suggestion. We have modified accordingly.

Changes in the text:
Table 3 (Page 29, line 540-543):
Table 3. Univariable and Multivariable logistic regression model for prediction of PCI in study population

	Univariable analysis	*p* Value	Multivariable analysis	*p* Value
	OR (95% CI)		OR (95% CI)	
Age	0.987 (0.952-1.022)	0.451	0.972 (0.931-1.016)	0.206
Male	2.15 (0.999-4.629)	0.05	3.029 (1.177-7.790)	**0.022**
Smokers	0.575 (0.277-1.194)	0.137	0.586 (0.210-1.631)	0.306
Diabetes	2.309 (1.016-5.248)	**0.046**	3.798 (1.305-11.055)	**0.014**
Family history	0.434 (0.207-0.909)	**0.027**	0.573 (0.214-1.535)	0.268
LDL-C	1.5 (1.022-2.202)	**0.038**	1.286 (0.796-2.075)	0.304
LTL	0.958 (0.938-0.978)	**<0.001**	0.952 (0.930-0.974)	**<0.001**

In the multivariable adjusted models, all dependent variables were adjusted for each other.

CHD: cardio vascular disease; LTL: leukocyte telomere length; LDL-C: low-density lipoproteins-cholesterol.