Journal of Clinical and Translational Research
Peer review process file 06.202001.004

Platelet/ lymphocyte ratio for prediction of no reflow phenomenon in ST elevation myocardial infarction managed with primary percutanous coronary intervention

Hala Mahfouz Badran, Ahmed abdel fatah, Ghada Soltan

Corresponding author:
Hala Mahfouz Badran
Cardiology Department Menoufia University, 55-ElGish street, Tanta, Egypt, P.O box 34

Handeling editor:
Michal Heger
Department of Pharmaceutics, Utrecht University, the Netherlands
Department of Pharmaceutics, Jiaxing University Medical College, Zhejiang, China

Review timeline:

Received: 7 April, 2020
Editorial decision: 18 May, 2020
Revision received: 4 June, 2020
Editorial decision: 11 June, 2020
Revision received: 13 June, 2020
Editorial decision: 15 June, 2020
Revision received: 16 June, 2020
Editorial decision: 18 June, 2020
Published online: 8 July, 2020

1st editorial decision
18-May-2020

Ref.: Ms. No. JCTRes-D-20-00028
Platelet:lymphocyte ratio for prediction of no reflow phenomenon in ST elevation myocardial infarction managed with primary percutanous coronary intervention
Journal of Clinical and Translational Research

Dear Professor Badran,

Reviewers have now commented on your paper. You will see that they are advising that you revise your manuscript. If you are prepared to undertake the work required, I would be pleased to reconsider my decision.

For your guidance, reviewers' comments are appended below.

If you decide to revise the work, please submit a list of changes or a rebuttal against each point which is being raised when you submit the revised manuscript.Also, please ensure that the track changes function is switched on when implementing the revisions. This enables the reviewers to rapidly verify all changes made.
Please pay particular attention to the use of English language and methodological detail.

Your revision is due by Jun 17, 2020.

To submit a revision, go to https://www.editorialmanager.com/jctres/ and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Reviewers' comments:

Reviewer #1: This manuscript reports a study of 200 patients with ST elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PPCI). The authors' primary hypothesis was that the platelet/lymphocyte ratio (PLR) would be correlated with coronary flow after PPCI. 29% of patients had impaired flow after PPCI and PLR was significantly higher in these patients.

The authors propose an interesting hypothesis but it is confusing because of the terminology. No-reflow is generally defined as an acute reduction in coronary flow during PPCI (e.g. a patient has TIMI 3 flow after balloon angioplasty but then flow deteriorates to TIMI 0 - 2 after stent placement). The authors analysis is based on final flow in the coronary artery rather than abrupt changes. It would help if this was clearly stated and the use of different terminology would be helpful.

Specific comments:
* The grammar and spelling could be improved which would enhance the message of the paper
* It would be helpful to have more details about the Methods. Were consecutive patients enrolled and if not, how was selection for the study determined? Were platelet and lymphocyte counts determined on blood samples obtained before PPCI in all patients? How were platelet counts and lymphocyte counts determined?
* For the exclusion criteria, how were 'previous proven systemic inflammatory disease,' 'renal disease' and 'liver disease' defined?
* The text describes the demographics of the patients enrolled in the study and then these data are repeated in table 1. Providing the information in the table is sufficient. Also, table 1 should present the data for the group with TIMI 3 flow versus the group with impaired coronary flow.
* Are troponin values available for these patients? As the authors know, troponin has largely replaced CK-MB as a marker of myocardial injury.
* The authors should discuss why rates of TIMI 3 flow after PPCI were lower in this study than in most reported studies. For example, in the TOTAL study (Jolly, Sanjit S., et al. "Randomized trial of primary PCI with or without routine manual thrombectomy." New England Journal of Medicine 372.15 (2015): 1389-1398) in which patients with STEMI were randomized to thrombus aspiration, the rates of TIMI 3 flow after PCI were 93.1% in both groups. By contrast, the current study reports TIMI 3 flow in only 71% of patients.

Author’s rebuttal

Answers of reviewers' and editors' comments

Ref.: Ms. No. JCTRes-D-20-00028

Platelet: lymphocyte ratio for prediction of no reflow phenomenon in ST elevation myocardial infarction managed with primary percutanous coronary intervention Journal of Clinical and Translational Research

Thank you for your effort and time. We are pleased and appreciated to receive your final adjustments It is excellent addition to the quality of our manuscript. We have done all the changes recommended by the Editor. Below, we are attaching all changes and our point-by-point response to Reviewer's comments.

Reviewer's Comments:

Reviewer 1:

Q1) The authors propose an interesting hypothesis but it is confusing because of the terminology. No-reflow is generally defined as an acute reduction in coronary flow during PPCI (e.g. a patient has TIMI 3 flow after balloon angioplasty but then flow deteriorates to TIMI 0 - 2 after stent placement). The authors' analysis is based on final flow in the coronary artery rather than abrupt changes. It would help if this was clearly stated and the use of different terminology would be helpful.

Answer: **Done. The following paragraph is added: Page 3 methods section paragraph 4:**
Angiographic slow/no reflow during PCI was defined as TIMI flow grade ≤II during the procedure without evidence of dissection, residual stenosis, distal embolism, or vasospasm

The patients were divided into 2 groups based on the post-intervention infarct related artery (IRA) flow; **Normal-reflow** group: included patients with post intervention TIMI grade III flow and **no-reflow** group: consisted of patients with post-intervention TIMI grade 0, I and I1 flow.

Q2) The grammar and spelling could be improved which would enhance the message of the paper

Answer: Done

Q3) It would be helpful to have more details about the Methods. Were consecutive patients enrolled and if not, how was selection for the study determined? Were platelet and lymphocyte counts determined on blood samples obtained before PPCI in all patients? How were platelet counts and lymphocyte counts determined?

Answer: Done

Q3A-Were consecutive patients enrolled and if not, how was selection for the study determined?
This paragraph is added in page 2 paragraph 4
Answer: changed to: We investigated 200 consecutive patients presented in two tertiary referral centers.
Q3B-Were platelet and lymphocyte counts determined on blood samples obtained before PPCI in all patients? ? How were platelet counts and lymphocyte counts determined?

Answer: Yes, the following paragraph is added page 3 paragraph 2:
Blood analysis:

Routine laboratory investigation including platelet, lymphocyte, hemoglobin, serum creatinine and cardiac enzyme (CK-MB) were accomplished. Venous blood samples were drawn from antecubital

veins immediately after patient evaluation and obtaining ECG. Whole blood components count was analyzed by a Sysmex K-1000 and Sysmex XN-10 Automated Hematology Analyzer (Sysmex Corporation, Kobe, Japan) auto-analyzer immediately following blood sampling. Whole blood sample collected in ethylene diamine teteraacetic acid (EDTA) containers.

Q4 For the exclusion criteria, how were 'previous proven systemic inflammatory disease,' 'renal disease' and 'liver disease' defined?
Answer: The following paragrapg is added page 2, last paragraph:
Previous proven systemic inflammatory diseases, renal diseases and liver diseases and known malignancy were excluded from the study. These illnesses were diagnosed from patient prior history, previous laboratory analysis or taking related medications and from patient's records.

Q5 The text describes the demographics of the patients enrolled in the study and then these data are repeated in table 1. Providing the information in the table is sufficient. Also, table 1 should present the data for the group with TIMI 3 flow versus the group with impaired coronary flow.

Answer:
Done: Table 1, is removed and it related text remained. Table presents the data for the group with TIMI 3 flow versus the group with impaired coronary flow is added , Page 4 paragraph 1

Q6 Are troponin values available for these patients? As the authors know, troponin has largely replaced CK-MB as a marker of myocardial injury.
Answer: yes it is added in table 1 and table 2

Q7: The authors should discuss why rates of TIMI 3 flow after PPCI were lower in this study than in most reported studies. For example, in the TOTAL study (Jolly, Sanjit S., et al. "Randomized trial of primary PCI with or without routine manual thrombectomy." New England Journal of Medicine 372.15 (2015): 1389-1398) in which patients with STEMI were randomized to thrombus aspiration, the rates of TIMI 3 flow after PCI were 93.1% in both groups. By contrast, the current study reports TIMI 3 flow in only 71% of patients.

In fact the incidence of no-reflow during PCI ranged widely from 11% to 41% of patients according to numerous studies 1,2,3,4,5

1. Abbo KM, Dooris M, Glazier S, O'Neill WW, Byrd D, Grines CL, Safian RD. Features and outcome of no-reflow after percutaneouscoronary intervention. Am J Cardiol 1995;75:778e782.

2. Morishima I, Sone T, Okumura K, Tsuboi H, Kondo J, Mukawa H,Matsui H, Toki Y, Ito T, Hayakawa T. Angiographic no-reflow phenomenon as a predictor of adverse long-term outcome in patients treated with percutaneous transluminal coronary angioplasty for first acute myocardial infarction. J Am Coll Cardiol 2000;36:1202e1209.

3. Magro M, Nauta ST, Simsek C, Boersma E, van der Heide E, Regar E, van Domburg RT, Zijlstra F, Serruys PW, van Geuns RJ. Usefulness of the SYNTAX score to predict "no reflow" in patients treated with primary percutaneous coronary intervention for ST-segment elevation myocardial infarction. Am J Cardiol 2012;109:601e606.

4. Mehta RH, Harjai KJ, Boura J, Cox D, Stone GW, O'Neill W, Grines CL. Prognostic significance of transient no-reflow during primary percutaneous coronary intervention for ST-elevation acute myocardialinfarction. Am J Cardiol 2003;92:1445e1447.

5.Yip HK, Chen MC, Chang HW, Hang CL, Hsieh YK, Fang CY, Wu CJ. Angiographic morphologic features of infarct-related arteries and timely reperfusion in acute myocardial infarction: predictors of slowflow and no-reflow phenomenon. Chest 2002;122:1322e1332

In addition there are several; studies reported similar no reflow incidence:
-Predictive value of admission red cell distribution width-platelet ratio for no-reflow phenomenon in acute ST segment elevation myocardial infarction undergoing primary percutaneous coronary intervention Cardiology Journal 2016, Vol. 23, No. 1, 84–92 DOI: 10.5603/CJ.a2015.0070: In this study no reflow occurred in 33% of included primary PCI patients

-Relation of Neutrophil/Lymphocyte Ratio to Coronary Flow to In-Hospital Major Adverse Cardiac Events in Patients With ST-Elevated Myocardial Infarction Undergoing Primary
Coronary Intervention Am J Cardiol 2012;110:621– 627 In this study no reflow occurred in 37.8% of included primary PCI patients

---

2nd editorial decision
11-Jun-2020

Ref.: Ms. No. JCTRes-D-20-00028R1
Platelet:lymphocyte ratio for prediction of no reflow phenomenon in ST elevation myocardial infarction managed with primary percutanous coronary intervention
Journal of Clinical and Translational Research

Dear Professor Badran,

Reviewers have now commented on your paper. You will see that they again are advising that you revise your manuscript mainly because you did not properly address their previous instructions and/or did not properly rebut the requested modifications. Also, JCTR takes the linguistic part of writing seriously, upholds the highest scientific standards, and grants little leeway with respect to sloppiness. If you are prepared to undertake the work required, I would be pleased to reconsider my decision. But I kindly ask you to put more effort into the revision.

For your guidance, reviewers' comments are appended below.

If you decide to revise the work, please submit a list of changes or a rebuttal against each point which is being raised when you submit the revised manuscript.Also, please ensure that the track changes function is switched on when implementing the revisions. This enables the reviewers to rapidly verify all changes made.

Your revision is due by Jul 11, 2020.

To submit a revision, go to https://www.editorialmanager.com/jctres/ and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Reviewers' comments:

Reviewer #1: This revised manuscript reports a study of 200 patients with ST elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PPCI). The authors' primary hypothesis was that the platelet/lymphocyte ratio (PLR) would be correlated with coronary flow after PPCI. 29% of patients had impaired flow after PPCI and PLR was significantly higher in these patients.

The manuscript is improved but there are still several issues that need to be addressed.

Specific comments:
* The grammar and spelling are improved but still poor in places
* The enrollment criteria are still not well defined. In the Methods section, there is no mention of prior ACS being an exclusion criteria but this is listed in the Discussion ('In our study we investigated 200 patients presented with STEMI with no previous history of acute coronary syndrome.') The authors really need to define the patient population and recruitment strategy completely.
* The authors did not respond to the prior query about what constitutes 'Previous proven systemic inflammatory diseases', 'renal diseases' and 'liver diseases'. These exclusion criteria need to be better defined. For example, how was 'renal diseases' defined? Was there a GFR cut-off for the study or were only patients on dialysis excluded? What constitutes a 'systemic inflammatory disease' and what diagnoses fall into this category? Did the patients have to be actively treated for the condition?
* The percentages listed in table 1 should be based on the number of patients in the column and not in the row.
* Table 1 should include data on platelet counts and lymphocyte counts
* In the paragraph on Limitations, the authors should discuss the high rate of no-reflow. While there are other studies which also demonstrate high rates, most large, contemporary studies do not and it is not clear if PLR would have the same prognostic information if the no-reflow rate was smaller.
* On page 9, 'Azabet al.' should be 'Azabet et al.'
* On page 10, 'none-reflow group' should be 'no reflow group'

Author's rebuttal

Answers of reviewers' and editors' comments
Ref.: Ms. No. JCTRes-D-20-00028

Platelet: lymphocyte ratio for prediction of no reflow phenomenon in ST elevation myocardial infarction managed with primary percutanous coronary intervention
Journal of Clinical and Translational Research

Thank you for your effort and time. We are pleased and appreciated to receive your second adjustments. It is important addition to the quality of our manuscript. We have done all the changes recommended by the Editor. Below, we are attaching all changes and our point-by-point response to Reviewer's comments.

Reviewer's Comments:

Reviewer 1:

Reviewer #1:
The manuscript is improved but there are still several issues that need to be addressed.
Specific comments:

Q1 The grammar and spelling are improved but still poor in places
Answer: *Done*

Q2: The enrollment criteria are still not well defined. In the Methods section, there is no mention of prior ACS being an exclusion criteria but this is listed in the Discussion ('In our study we investigated 200 patients presented with STEMI with no previous history of acute coronary syndrome.') The authors really need to define the patient population and recruitment strategy completely.
Answer:
Done : page 2 paragraph 6: Patients with one or more of the following criteria were excluded from the study, patients with prior acute coronary syndrome, patients with non-STMI, unstable angina, STEMI duration more than 12 hours, cardiogenic shock on admission, and treatment with thrombolytic therapy in the previous 24 hours.

Q3The authors did not respond to the prior query about what constitutes 'Previous proven systemic inflammatory diseases', 'renal diseases' and 'liver diseases'. These exclusion criteria need to be better defined. For example, how was 'renal diseases' defined? Was there a GFR cut-off for the study or were only patients on dialysis excluded? What constitutes a 'systemic inflammatory disease' and what diagnoses fall into this category? Did the patients have to be actively treated for the condition?

Answer: *Done, page 6 paragraph 6 : Patients with one or more of the following criteria were excluded from the study: prior acute coronary syndrome, non-STEMI, unstable angina, STEMI duration more than 12 hours, cardiogenic shock, treatment with thrombolytic therapy in the previous 24 hours estimated glomerular filtration rate less than 60 ml/min/1.73 m/ or on renal dialysis, active systemic inflammatory diseases/ or active treatment for the condition e.g allergy, asthma, autoimmune diseases, glomerulonephritis,*
hepatitis, inflammatory bowel disease; and known malignancy.

Q4: The percentages listed in table 1 should be based on the number of patients in the column and not in the row.
Answer: Done

	TIMI 0-II (n=58)	***TIMI III (n=142)***	***P value***
Male (%)	*49(84.5%)*	*111(78.2%)*	*0.2*
Female (%)	*9(15.5%)*	*31 (21.8%)*	
Obese (%)	*9(15.5%)*	*26 (18.3%)*	*0.84*
Diabetic (%)	*26(44.8%)*	*62 (43.7%)*	*0.92*
HTN (%)	*31(53.4%)*	*71(50%)*	*0.87*
Dyslipidemia (%)	*7(12.1%)*	*34 (23.9%)*	*0.23*
Smokers (%)	*37(63.8%)*	*81 (57%)*	*0.22*

+ ve family history (%)		*4(6.8%)*	*24 (16.9%)*	*0.11*
Troponin (ng/ml)		*8.2±3*	*5.1±2.4*	*0.07*
CK-MB (IU/L)		*195±35*	*104±24*	*0.01*
Ejection fraction (%)		*40±6*	*56±4*	*0.03*
Platelet (x10^{3}µl)		*345±114*	*228±84*	*0.0001*
Lymphocyte(x10^{3}µl)		*1.73±0.5*	*2.2±0.9*	*0.02*
Platelet /lymphocyte ratio		*199.4±52*	*102±53*	*0.001*
Infarction site	*Anterior (%)*	*44(35.7%)*	*79 (64.2%)*	*0.07*
	Lateral (%)	*1(50%)*	*1 (50%)*	
	Inferior (%)	*13(17.3%)*	*62 (82.7%)*	
Left anterior descending (%)		*44(35.7%)*	*79 (64.2%)*	*0.4*
Left circumflex (%)		*3(14.3%)*	*18 (85.7%)*	
Obtuse marginal 1 (%)		*1(33.3%)*	*2 (66.7%)*	
Obtuse marginal 3 (%)		*0(0.0%)*	*1 (100%)*	
Right coronary artery (%)		*10(19.2%)*	*42 (80.8%)*	

Q5 Table 1 should include data on platelet counts and lymphocyte counts
Answer: *It is added in table 1*

Q6: In the paragraph on Limitations, the authors should discuss the high rate of no-reflow. While there are other studies which also demonstrate high rates, most large, contemporary studies do not and it is not clear if PLR would have the same prognostic information if the no-reflow rate was smaller.

Answer: *The following paragraph is added to limitations section page 10,11*

Third, the incidence of no-reflow during PCI ranged widely from 1 to 41%.[3-8] While there are other studies which also demonstrate high rates, most large, contemporary studies do not. The possible explanation for this difference might lie in the clinical and procedural characteristics, the application of a standardized definition of no-reflow. Although no-reflow is commonly recognized as transient, angiographically visible flow impairment despite epicardial coronary patency, other studies have included more liberal definitions, such as a failure to achieve TIMI III flow at the end of the procedure or decreased myocardial flow after PCI as shown by perfusion imaging. [37, 38] So it is not clear if PLR would have the same prognostic information if the no-reflow rate was smaller

Q6: On page 9, 'Azabet al.' should be 'Azabet et al.'
Answer: *Done : page 9 Prior studies demonstrated the association between PLR and cardiovascular events. Azabet et al.[34] showed*

Q7: On page 10, 'none-reflow group' should be 'no reflow group'
Answer: *Done : (defined as post- intervention TIMI grade 3) and no-reflow group (consist of both patients with angiographic no-reflow*

3rd Editorial decision
15-June-2020

Ref.: Ms. No. JCTRes-D-20-00028R2
Platelet:lymphocyte ratio for prediction of no reflow phenomenon in ST elevation myocardial infarction managed with primary percutanous coronary intervention
Journal of Clinical and Translational Research

Dear author(s),

Reviewers have submitted their critical appraisal of your paper. The reviewers' comments are appended below. Based on their comments and evaluation by the editorial board, your work was FOUND SUITABLE FOR PUBLICATION AFTER MINOR REVISION. However, and in reiteration, the language must be polished before we can proceed with the publication of your manuscript, as is clearly specified in our author guidelines (https://www.jctres.com/en/author-guidelines/). Please follow these to the very detail.

If you decide to revise the work, please itemize the reviewers' comments and provide a point-by-point response to every comment. An exemplary rebuttal letter can be found on at http://www.jctres.com/en/author-guidelines/ under "Manuscript preparation." Also, please use the track changes function in the original document so that the reviewers can easily verify your responses.

Your revision is due by Jul 15, 2020.

To submit a revision, go to https://www.editorialmanager.com/jctres/ and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely,

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Reviewers' comments:

Reviewer #1: The manuscript continues to improve but there are still numerous places where the grammar could be improved.

Author’s rebuttal

Answers of reviewers' and editors' comments
Ref.: Ms. No. JCTRes-D-20-00028

Platelet: lymphocyte ratio for prediction of no reflow phenomenon in ST elevation myocardial infarction managed with primary percutanous coronary intervention
Journal of Clinical and Translational Research

Thank you for your final recommendations. We have done all the changes recommended by the Editor.

Reviewer's Comments:

Reviewer #1: The manuscript continues to improve but there are still numerous places where the grammar could be improved.
Answer:
We have made changes with regard to English languish, grammar and punctuation.

4th editorial decision
18-Jun-2020

Ref.: Ms. No. JCTRes-D-20-00028R3
Platelet/ lymphocyte ratio for prediction of no reflow phenomenon in ST elevation myocardial infarction managed with primary percutanous coronary intervention
Journal of Clinical and Translational Research

Dear authors,

I am pleased to inform you that your manuscript has been accepted for publication in the Journal of Clinical and Translational Research. Congratulations! I have attached the revised manuscript, which needed some more work in terms of language polishing. I understand you submitted the second revision to a paid language editing service (Enago) in accordance with the reviewer's and editor's advice. Please feel free to use my version to make an attempt to get your money back.

You will receive the proofs of your article shortly, which we kindly ask you to thoroughly review for any errors.

Thank you for submitting your work to JCTR.

Kindest regards,

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Comments from the editors and reviewers: