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Erratum: Limitations of Quantitative Blush Evaluator (QuBE) as myocardial perfusion assessment method on digital coronary angiograms

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1st Editorial response

Date: 30-Apr-2018

Ref.: Ms. No. JCTRes-D-18-00011
Limitations of Quantitative Blush Evaluator (QuBE) as myocardial perfusion assessment method on digital coronary angiograms
Journal of Clinical and Translational Research

Dear authors,

Reviewers have now commented on your paper. One reviewer recommended minor revisions, cautioning you regarding the drawn conclusions if you did not write the software. The other reviewer recommended a reject, mainly on the basis that it is very difficult to perform QuBE quantitatively. However, since QuBE is being used in practice and you found that it is not reproducible as reported in previous publications, we would like to give you a chance to defend your position. The paper is well-suited for the special issue on negative results, especially in light of the practical applications of QuBE. However, we do urge you to take the reviewers' comments seriously and address each comment in a point-by-point fashion. Please note that the discussion with the reviewers will appear online as metadata if your manuscript is accepted, which at this point is not guaranteed. Also, please ensure that your paper is checked for spelling and grammar errors before resubmitting a revision. If you are prepared to undertake the work required, I would be pleased to reconsider my decision.

Moreover, please provide the contact details of the software's manufacturer to the editorial board. If your article is accepted, we will invite the manufacturer to write a comment on your paper for full transparency and coverage of the issue.

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 resubmit your work.

Your revision is due by May 30, 2018.

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

Yours sincerely,

Rowan van Golen
Associate Editor
Journal of Clinical and Translational Research

Reviewers' comments:

Reviewer #1: I have read the manuscript with interest, but would like to make the following comments:
1. Quantification of the blush grade is extremely difficult for the following reasons: Very poor signal to noise ratio's of the blush signal; motion artefacts; superimposition of other structures, etc, etc, as indicated also by the authors;
2. It is not clear who delivers the software that was tested. Is it by a company, by another academic institution, by ????; that is not mentioned.
3. Have the authors also contacted the develoeprs of the software? Have they discussed their problems? I would think that is the first thing that one would do if a particular solution does not work or does not seem to work. May be the authors have not read the user manual properly, as an example. It is interesting to also read that the software has been used in other larger studies where acceptable results were obtained; how come?
4. They have compared with the MBG; how reliable is that in their hands? I have not seen any inter-and intra-observer variabilities.
5. I think that this manuscript is an example how a particular software solution should not be tested.

Reviewer #2: From my viewpoint, authors here present negative findings of available QuBE solution.
They conducted an independent study and provide their findings that do not agree with results previously published, in relevant peer review journals.
Authors clearly present objectives and remarks, they support their work with mid-results and objectively discuss the obtained results - which i appreciate (commonly have to read tons of work to understand how end-results are obtained).

Since the point of this work is negation of previous findings, i would like to suggest them to be careful (if they are not authors of QuBE as well), and to use the revision time to even better clarify and support their approach versus these used in literature.

Authors' rebuttal

Review JCTRes-D-18-00011
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Reviewer's Comments
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Reviewer #1: I have read the manuscript with interest, but would like to make the following comments:

1.1 Quantification of the blush grade is extremely difficult for the following reasons: Very poor signal to noise ratio's of the blush signal; motion artefacts; superimposition of other structures, etc, etc, as indicated also by the authors;

We agree with the reviewer and have indicated our awareness of these difficulties in the manuscript.
One of the main motivations of this study was to evaluate whether such difficulties could be overcome.
In the revised manuscript we emphasized more on these points:

Page 2, introduction section, added new lines to the third paragraph:

"In general, angiographic quantification of myocardial blush poses some difficulties including cumbersome assessment because of poor blush signal to noise ratio and superimposition of irrelevant structures. Recognizing and solving these issues are important in developing a blush quantification method such as QuBE."

We modified the last sentence of this paragraph from:

"In this study, we evaluate the accuracy of QuBE in a clinical trial data and analyze whether potential limitations can be resolved with enhanced image analysis methods."

to:

"In this study, we evaluate the accuracy of QuBE in a clinical trial data and analyze whether general difficulties of blush quantification and inherent limitations of QuBE can be resolved with enhanced image analysis methods."

1.2. It is not clear who delivers the software that was tested. Is it by a company, by another academic institution, by ????; that is not mentioned.

We thank the reviewer for this question. QuBE is open source software developed by Vogelzang et al. (Dept. of Cardiology UMCG, the Netherlands). Because the origins of the software was not clear in the initial manuscript, we have improved the manuscript as follow:

Page 2, introduction section, added new lines to the third paragraph:

"QuBE is an open-source computer program, which has been developed by the University Medical
Center Groningen, the Netherlands [1]."

1.3. Have the authors also contacted the develoeprs of the software? Have they discussed their problems? I would think that is the first thing that one would do if a particular solution does not work or does not seem to work. May be the authors have not read the user manual properly, as an example. It is interesting to also read that the software has been used in other larger studies where acceptable results were obtained; how come?

We appreciate concerns of the reviewer. However, the reviewer does not provide any detail on what in his vision we could have done wrong, and we therefore cannot respond to this in a specific way. In general, we should like to point out that that the head of the cardiology research group that developed QuBE, Pim van der Harst, is co-author. Furthermore, the source code and instructions for use for the QuBE software can be found online (https://github.com/mathijs81/qube) and are well documented and fully transparent. With all respect, we do believe we have a substantial track record in the field of clinical image analysis and associated software development. We therefore are confident that our methods are adequate.

In the revised manuscript, we have added the following lines to the third paragraph of the discussion (Page 8):

"Because QuBE is open source, it allowed for detailed inspection of the algorithms that are employed in the software. "

Regarding the studies where QuBE was indeed associated with positive outcomes, we do not have access to the raw data of those studies. Therefore the analysis cannot be made. We clarified this point in discussion section.

Page 10, discussion section:

"Additionally, the trial data used by previous studies that showed positive findings with QuBE were not available, thus, a comparison study could not be performed. However, aside from the particular limitation of the local algorithm, this discrepancy of QuBE performance may also have been caused by a number of other factors. For instance, type and volume of contrast agent, speed of injection, and the configuration of acquisition machine have not been yet standardized. Besides, the infarct location and body mass index has been known to confound QuBE value [2]."

1.4. They have compared with the MBG; how reliable is that in their hands? I have not seen any inter-and intra-observer variabilities.

We thank the reviewer for this question. In our study, we compared the QuBE score with MBG because MBG is generally accepted as the gold-standard in assessing the quality of perfusion [3]. There have been multiple studies showing that MBG has moderate to good inter- and intra-observer agreement [3]–[5]. We added this information in the revised manuscript.

Page 4, materials and methods section, QuBE evaluations and myocardial blush grade subsection, added a few lines to the third paragraph:

"The comparison was made because MBG is the most commonly used angiographic measure to assess myocardial perfusion and has moderate to good inter- and intra-observer agreement [3]–[5]."

1.5. I think that this manuscript is an example how a particular software solution should not be tested.

We do not understand the concerns of the reviewer. This is a very general remark that lacks any detail on what it is then that we should have done differently. Again, we can only respond in general terms: We have performed similar software evaluation studies previously, which have been published in peerreviewed high-impact journals. Our methods have been evaluated by statisticians and are sound in our opinion [6]–[8].

Reviewer #2: From my viewpoint, authors here present negative findings of available QuBE solution.

They conducted an independent study and provide their findings that do not agree with results previously published, in relevant peer review journals.

Authors clearly present objectives and remarks, they support their work with mid-results and objectively discuss the obtained results - which i appreciate (commonly have to read tons of work to understand how end-results are obtained).

Since the point of this work is negation of previous findings, i would like to suggest them to be careful (if they are not authors of QuBE as well), and to use the revision time to even better clarify and support their approach versus these used in literature.

We thank the reviewer for the suggestions. To clarify that the different finding was not a result of improper use of QuBE, we have indicated in the revised manuscript that we used the guidelines provided by the developer in selecting angiogram, delineating ROI, and using the QuBE program.

Page 3, materials and methods section, patients subsection, we edited the last sentence of the paragraph:

"The inclusion criteria for accepted angiogram adhered to the guideline provided in the initial study of QuBE [1]. We included complete blush sequence and no major overlapping of other non-infarct related area in myocardial region of interest."

Some conjectures about what may cause the inconsistency between our finding and previous QuBE studies are added to the revised manuscript (see our response to 1.3, page 10, discussion section).

We also clarified that previous studies only showed the end result of QuBE (i.e., QuBE value) whereas our study also showed mid-results. This clearly allowed for better problem identification and careful analysis of QuBE value calculation.

Page 9, discussion section, we modified the first sentence of the fifth paragraph:

"Describing and visualizing intermediate results in QuBE calculations set this study apart from previous
QuBE studies. This allowed for careful analysis of the limitations of the specific algorithms in QuBE."

[1] M. Vogelzang, P. J. Vlaar, T. Svilaas, D. Amo, M. W. N. Nijsten, and F. Zijlstra, "Computer-assisted myocardial blush quantification after percutaneous coronary angioplasty for acute myocardial infarction: A substudy from the TAPAS trial," *Eur. Heart J.*, vol. 30, no. 5, pp. 594–599, 2009.

[2] Y. L. Gu *et al.*, "Computer-assisted quantification of myocardial reperfusion after primary percutaneous coronary intervention predicts functional and contrast-enhanced cardiovascular magnetic resonance outcomes in patients with ST-segment elevation myocardial infarction.," *Catheter. Cardiovasc. Interv.*, vol. 77, no. 2, pp. 174–181, 2011.

[3] a. W. J. van `t Hof, a. Liem, H. Suryapranata, J. C. a. Hoorntje, M.-J. de Boer, and F. Zijlstra,
"Angiographic Assessment of Myocardial Reperfusion in Patients Treated With Primary Angioplasty for Acute Myocardial Infarction : Myocardial Blush Grade," *Circulation*, vol. 97, no. 23, pp. 2302–2306, 1998.

[4] J. P. S. Henriques *et al.*, "Angiographic assessment of reperfusion in acute myocardial infarction by myocardial blush grade," *Circulation*, vol. 107, no. 16, pp. 2115–2119, 2003.

[5] G. Korosoglou *et al.*, "Quantitative evaluation of myocardial blush to assess tissue level reperfusion in patients with acute ST-elevation myocardial infarction. Incremental prognostic value compared with visual assessment," *Am. Heart J.*, vol. 153, no. 4, pp. 612–620, 2007.

[6] H. A. Marquering, P. J. Nederkoorn, L. Smagge, H. A. Gratama Van Andel, R. Van Den Berg, and C. B. Majoie, "Performance of semiautomatic assessment of carotid artery stenosis on CT angiography: Clarification of differences with manual assessment," *Am. J. Neuroradiol.*, vol. 33, no. 4, pp. 747–754, 2012.

[7] J. Borst *et al.*, "Diagnostic accuracy of 4 commercially available semiautomatic packages for carotid artery stenosis measurement on CTA," *Am. J. Neuroradiol.*, vol. 36, no. 10, pp. 1978– 1987, 2015.

[8] J. J. Reimerink *et al.*, "Semiautomatic sizing software in emergency endovascular aneurysm repair for ruptured abdominal aortic aneurysms," *Cardiovasc. Intervent. Radiol.*, vol. 37, no. 3, pp. 623–630, 2014.

2nd Editorial response

Date: 23-Jun-2018

Ref.: Ms. No. JCTRes-D-18-00011R1
Limitations of Quantitative Blush Evaluator (QuBE) as myocardial perfusion assessment method on digital coronary angiograms
Journal of Clinical and Translational Research

Dear authors,

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 resubmit your work.

Your revision is due by Jul 23, 2018.

To submit a revision, go to https://jctres.editorialmanager.com/ and log in as an Author. You will see a menu item called 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 #2: I would like to accomplish clarifications and improvements made during the revision.

Although changes/referees' comments were not major, they added important missing information to this study.

Reviewer #3: The authors present a well-written manuscript on a well-designed study investigating the limitations of a myocardial perfusion assessment method, QuBE, by comparison to Myocardia Blush Grade (MBG) scores. Several image filter settings were tested, and their effect on the relation between QuBE and MBG scores were determined. I have two main comments:

1. In the Results section, data seems to be reported multiple times in Table 1, Figure 3, and Figure 5, yet the values seem to differ sometimes. Please check the Tables and Figures.

2. Although the authors provide some arguments on why the QuBE may not be reliable in their patient population, the authors could focus the discussion more on why the findings in the different studies differ, and how this could be extrapolated to other populations and how this could be used to improve the reliability in these groups.

Authors' rebuttal

Review JCTRes-D-18-00011R1
Limitations of Quantitative Blush Evaluator (QuBE) as myocardial perfusion assessment on digital coronary angiograms
Journal of Clinical and Translational Research
Reviewer's Comments
==========

Reviewer #2: I would like to accomplish clarifications and improvements made during the revision. Although changes/referees' comments were not major, they added important missing information to this study.

Thank you. We indeed believe your comments helped us to strongly improve the manuscript.

Reviewer #3: The authors present a well-written manuscript on a well-designed study investigating the limitations of a myocardial perfusion assessment method, QuBE, by comparison to Myocardia Blush Grade (MBG) scores. Several image filter settings were tested, and their effect on the relation between QuBE and MBG scores were determined. I have two main comments:

2.1. In the Results section, data seems to be reported multiple times in Table 1, Figure 3, and Figure 5, yet the values seem to differ sometimes. Please check the Tables and Figures.

We thank the reviewer for pointing out this differences. We indeed found a mistake in figure 3 where we included also the other kernel sizes data instead of only the native QuBE data. We have fixed it and also checked the corresponding statistical analysis (see the revised Table 1 and Figure 3). This correction did not affect the result of the study except for a slight different p-value for Kruskal-Wallis test (from $\boldsymbol{p} = 0.38$ to $\boldsymbol{p} = 0.22$). We also used this opportunity to ensure that other figures, statistical analysis, and numbers in our paper have been double checked and we are ensured that they are correct and appropriate, scrupulously adhering to the practice of rigorous research.

The following changes were made:

Materials and methods section, statistical analysis subsection, page 5:

Table 1 (revised). MBG and QuBE score of 117 patients

		MBG 0	MBG 1	MBG 2	MBG 3
n		70	14	13	20
QuBE score	Kernel Size 20×20	4.2(1.1-24)	4.0(1.4-9.4)	4.7(2.3-8.6)	4.9(2.4-9.0)
	Kernel Size 35×35 (Native)	14(3.3-31)	12(3.0-22)	15(8.5-19)	12(4.1-29)
	Kernel Size 50×50	15(4.0-35)	12(5.0-22)	15(7.9-18)	13(4.7-36)

QuBe scores are presented as median (and interquartile range); MBG, Myocardial Blush Grade; QuBE, Quantitative Blush Evaluator.

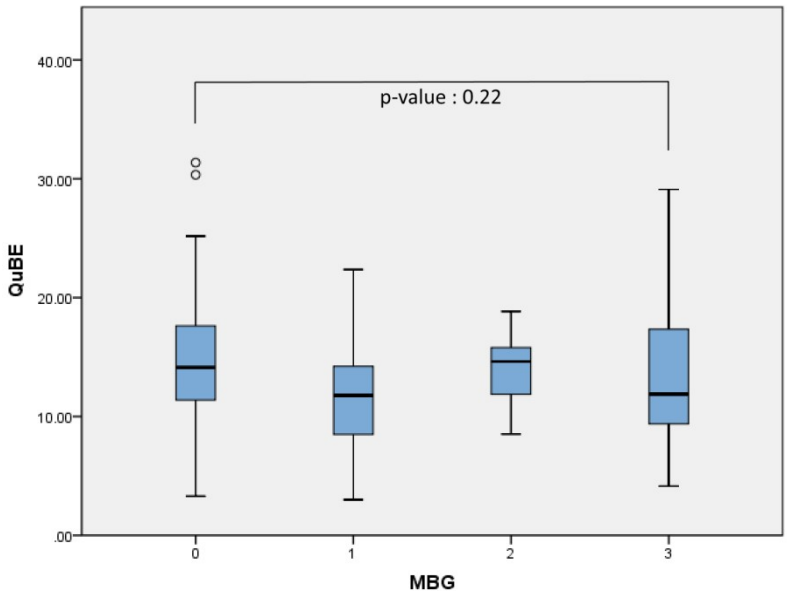

Figure 3 (revised). Association of myocardial blush grade with QuBE. MBG 0: no myocardial blush; MBG 1: minimal myocardial blush; MBG 2: moderate myocardial blush; MBG 3: normal myocardial blush.

Results section, 1st paragraph, page 7:

From:

"The correlation between QuBE score and MBG was not significant (***p***=0.14) and no significant differences were found between the grades (***p***=0.38)."

To:

The correlation between QuBE score and MBG was not significant (***p***=0.14) and no significant differences were found between the grades (***p***=0.22).

2.2. Although the authors provide some arguments on why the QuBE may not be reliable in their patient population, the authors could focus the discussion more on why the findings in the different studies differ, and how this could be extrapolated to other populations and how this could be used to improve the reliability in these groups.

We thank the reviewer for this comment. We have briefly touched on the subject in the 5th paragraph of the discussion where we listed several potential factors that may cause the inconsistency between studies. As suggested by the reviewer we extended the discussion on the differences with previous literature and how to use this information to improve the generalizability and reliability of QuBE.

Discussion section, 4th paragraph, page 10:

"However, aside from the limitation of the filtering algorithm, this discrepancy of QuBE performance may also have been caused by a number of other factors. For instance, type and volume of contrast agent, speed of injection, and the configuration of acquisition machine have not been yet standardized. Besides, the infarct location and body mass index has been known to confound QuBE value.[7] If the image acquisition protocol is standardized and the known confounders are controlled, QuBE may give a more reliable assessment. This information should be incorporated in the guidelines on the use of QuBE to assess myocardial perfusion."

3rd Editorial decision

Date: 2-Jul-2018

Ref.: Ms. No. JCTRes-D-18-00011R2
Limitations of Quantitative Blush Evaluator (QuBE) as myocardial perfusion assessment method on digital coronary angiograms
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.

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: