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The value of dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) in the prediction of neoadjuvant chemotherapy response in breast cancer: A Meta-Analysis

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► ***Review article***

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ABSTRACT

Background: The Breast dynamic Contrast-Enhanced Magnetic Resonance Imaging (DCE-MRI) is utilized for screening breast cancer (BC) in women with a total lifetime BC risk of greater than 20-25%. This study aimed to assess the DCE-MRI value in predicting response to neoadjuvant chemotherapy (NAC) in BC patients. ***Materials and Methods:*** International databases, including Medline, PubMed, Embase, and Science Direct, were searched with appropriate keywords. Using the binomial distribution formula, the variance of each study was calculated, and the data were analyzed using Stata 14. Finally, the results of the studies were inputted into the random-effect meta-analysis. ***Results:*** Sixteen studies, with no recognized publication bias by Begg's test, comprising 1868 patients were involved in this study. The sensitivity of DCE-MRI was 0.693, whereas its specificity was 0.754, with 95% confidence intervals (CI) of 0.560-0.826 and 0.605-0.903, respectively. Based on the random-effect model, the results revealed a pooled positive and negative predictive value of 0.458 and 0.901, with 95% CI of 0.339-0.577 and 0.829-0.972, respectively. The pooled DCE-MRI accuracy in predicting pathologic complete response to NAC was 0.768 (95% CI: 0.720-0.817). Finally, a meta-analysis of 10 reports, revealed a pooled AUC 0.779 (95% CI: 0.702-0.856). ***Conclusion:*** Overall, the findings of our study revealed that the DCE-MRI is a sensitive and specific method with an acceptable NPV for predicting response to NAC in BC cases.

INTRODUCTION

Breast cancer (BC), a prevalent cancer type among women, is currently the main reason for mortality from cancer among women and is thought to account for 15% of cancer fatalities [1-3]. It was reported that the healing ratio of breast lesions detected at an early stage is dramatically higher than other breast lesions [4]. BC which is progressed locally is now commonly treated with neoadjuvant chemotherapy (NAC). NAC is a systemic, cytotoxic medication treatment for patients with advanced BC that can minimize the tumor size before performing surgery. This can lead to an increased probability of conserving the breast [5]. The effectiveness of NACT is reliant on the specific treatment plans employed. The most effective chemotherapy regimens for breast cancer patients are anthracyclines and taxanes [6]. Anthracyclines consist of doxorubicin and epirubicin, while taxanes include docetaxel or paclitaxel. Furthermore, these medications are typically administered in conjunction with other drugs such as fluorouracil and cyclophosphamide [6].

In BC patients, molecular markers can predict the response to the NAC. For example, human epidermal growth factor receptor 2 (HER2), and proliferation index (Ki-67) are considered prognostic factors of response to NAC [7, 8]. Early examination of NAC therapy for BC can result in clinical counseling for treatment choice adjustments, suitable timing for surgery, and a reduction in unnecessary overtreatment [9-11]. The strongest indicator of a good long-term result is achieving a minimal residual tumor. The reliable assessment of the treatment

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response to NAC is essential for surgical planning, decision-making, and the prediction of ultimate results [12].

High clinical response rates (70-98 %) after NAC can lead to a pathologically complete response in a small subset of patients [13,14]. Previous studies have shown that people receiving NAC had an equal chance of surviving as individuals receiving adjuvant chemotherapy, while they had a decreased probability of needing a mastectomy, meaning that they are more likely to be eligible for breast conservation therapy [15-17].

Dynamic Contrast-Enhanced Magnetic Resonance Imaging (DCE-MRI) of the breast is employed to screen BC in women with a total lifetime BC risk of greater than 20-25%. principle of the DCE-MRI approach is the fast diffusion of a contrast agent with low molecular mass via the fenestration found in these aberrant microcapillaries. Studies have revealed that the vascular density of the lesion is related to changes in signal intensity. These studies also demonstrated that vascular fenestrations and functional permeability, as well as the interstitial environment that affects the diffusibility determine enhancement rate [18,19]. Parameters linking to the permeability of microvascular vessel wall, and tissue perfusion from the analysis of the signal intensity-time curves can help characterize the underlying pathology [20-22]. Although the uncertainty of the pathophysiological mechanism gives rise to alterations in DCE-MRI parameters, these changes can be utilized to indicate treatment response, although it appears to be correlated to changes in the density of microvessels and the anti-angiogenic impacts of chemotherapy [20]. MRI images before and after chemotherapy in BC patients show in figure 1.

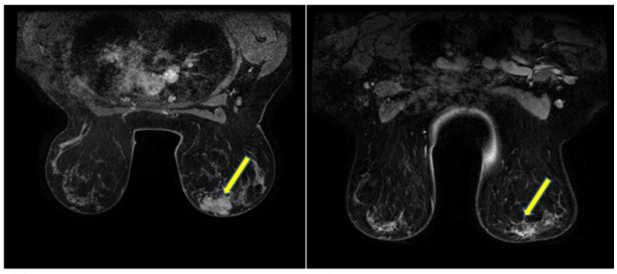

Figure 1. A patient with a moderately differentiated IDC has partial imaging and a pathologic response. A heterogeneous irregular tumour with enhancement in the center of the left breast is visible in (A) axial contrast-enhanced T1-weighted MRI taken prior to therapy (arrow). After therapy, axial contrast-enhanced T1-weighted MRI results show residual non-mass enhancement that is smaller and less intense (arrow), which is consistent with a partial response.

Some studies have already evaluated the performance of DCE-MRI in predicting the response to NAC among BC patients [15,23,24]. However, high-quality studies, are either insufficient, and there are controversies in their findings. Moreover, as mentioned above, the prediction of the response to NAC is of great importance for treatment-related choices. Also, there is not a systematic review and meta-analysis which comprehensively pooled the results of each studies in this topic. Thus, this study aimed to evaluate the DCE-MRI value in predicting response to NAC in BC patients.

MATERIALS AND METHODS

Publication search strategy

Herein, a literature search was accomplished in July 2022 to identify studies providing data on the value of DCE-MRI, for the prediction of the response to NAC among BC cases. One author searched WoS, Medline, Embase, and Google Scholar databases using the following keywords as well as their synonyms, abbreviations, Mesh terms, and all the possible combinations: “Dynamic Contrast-Enhanced Magnetic Resonance Imaging”, “Breast neoplasm” and “Neoadjuvant chemotherapy”.

Study selection

The following criteria were considered to include studies in our review: 1) original articles written in english, 2) studies that compared the results of DCE-MRI with a reference standard, and 3) the results of the histopathological analysis were considered the reference standard. Also, our exclusion criteria were as follows: 1) review articles, editorial articles, book chapters, and case reports, 2) articles that used imaging modalities other than DCE-MRI and 3) studies that evaluated response in BC patients, after receiving NAC.

Screening and data extraction

Two authors independently assessed the identified articles considering inclusion and exclusion criteria. Initially, titles and abstracts were screened. Then, the same two authors evaluated the full text of the selected articles. The articles that were selected by both authors were included in the study, while the ones selected by only one author were evaluated further by a third reviewer. Finally, out of all included studies, the required data were extracted by two authors, independently. The extracted data entailed the first author, his/her country of affiliation, study design, year of publication, gender and age of the patient(s), sample size, complete pathological response, regimen of neoadjuvant chemotherapy, specificity, sensitivity, accuracy, positive and negative predictive value (PPV and NPV, respectively), and area under the curve (AUC). Likewise, when there was a disagreement between the extracted data, all discrepant items were assessed by a third author.

Risk of bias in included studies (Quality assessment)

Using QUADAS criteria, one author assessed the

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quality of selected studies. QUADAS is a quality assessment tool evaluate the risk of bias, and the applicability of primary diagnostic accuracy studies. The quality evaluation of the included studies was carried out in the following domains: patient selection, index test(s), reference standard, and flow and timing.

Risk of bias across studies

To estimate publication bias, we applied the Begg's and Egger tests.

Statistical analysis

The effect size and the 95% confidence intervals (CI) were calculated by Stata 14. The heterogeneity of each group was also measured using the inconsistency index (I^2). An I^2 greater than 50% or a p -value smaller than 0.05 was recognized as significant heterogeneity. In case of high heterogeneity, we used a random-effect model for calculating the pooling effect and the 95% CI. Otherwise, the fixed-effect model was applied. The DCE-MRI value in predicting the NAC pathological response among BC cases was also determined by calculating pooled specificity, sensitivity, PPV, NPV, accuracy, and AUC with 95% CI.

RESULTS

Study selection

At the end of a comprehensive search, 1529 studies were identified. Then, 522 duplicate articles and 896 other articles were excluded by assessing their titles and abstracts. In the next step, 111 remaining articles were fully screened, upon which 99 articles were excluded and 12 articles remained. Noteworthy, the reference lists of eligible articles were also cross-checked, and four articles were included among them. In the end, we selected 16 articles for our investigation (figure 2).

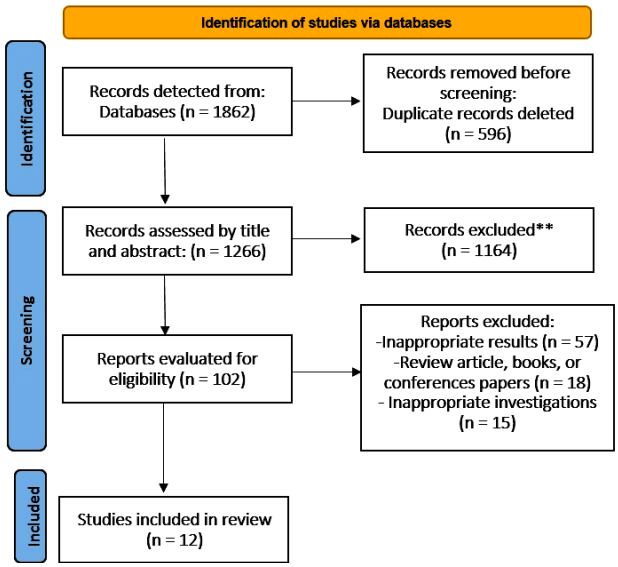

Figure 2. A flow chart of studies selection in this study.

Characteristics of included studies

Characteristics of all selected studies, including 1868 patients, are provided in table 1. In 12 studies, BC cases were enrolled retrospectively, and in the remaining four, patients were enrolled prospectively.

Quality assessment of studies

Using the quality assessment tool, QUADAS-2, we assessed the quality of included studies in four main domains (figure 3). The unclear risk of bias, both in the reference standard and index text domains, emerged from the ambiguity in the manuscript around the reference standard or index test or whether the investigators were blinded to the study or not. Additionally, in two studies, the selection process of patients was unclear and at risk of bias, and in one other study, the bias risk was unclear in the "flow and timing" domain.

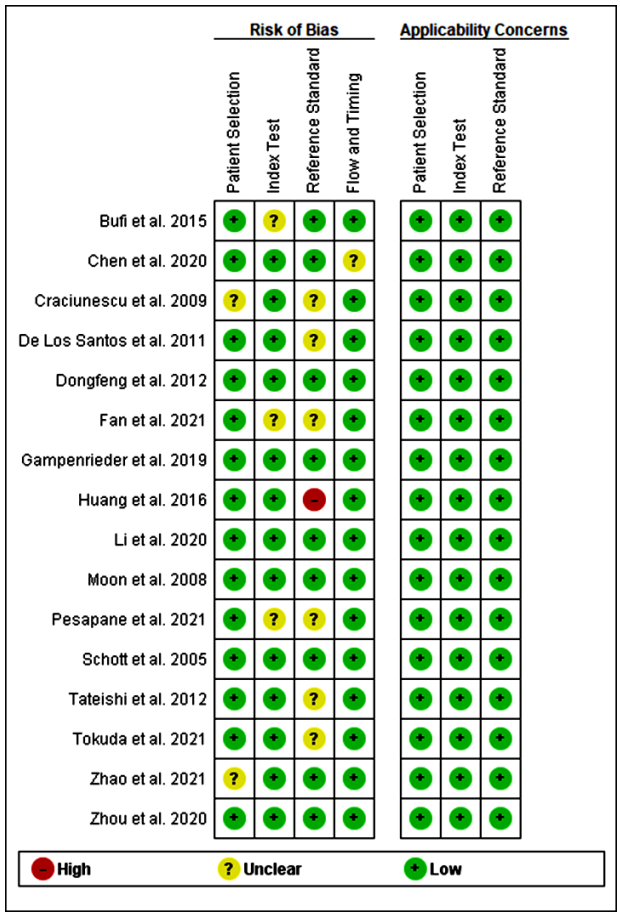

Figure 3. Studies Quality assessment using QUADAS-2.

Evaluation of DCE-MRI diagnostic performance

The DCE-MRI value in predicting response to NAC was assessed in selected articles. To this end, the data around specificity, sensitivity, accuracy, AUC, NPV, and PPV were pooled using meta-analysis. The pooled data of 14 out of 16 articles on DCE-MRI sensitivity and specificity were 0.693 and 0.754, with 95% CI of 0.560-0.826 and 0.605-0.903, respectively (figures 4 and 5). The meta-analysis of the data from six articles showed a pooled PPV of 0.458 and a

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pooled NPV of 0.90, with 95% CI of 0.339-0.577 and 0.829-0.972, respectively. The pooled DCE-MRI accuracy of six articles to predict pathologic complete response (pCR) to NAC was 0.768 (95% CI 0.720-0.817). Finally, our meta-analysis of 10 surveys that reported AUC, revealed a pooled AUC of 0.779 (95% CI: 0.702-0.856) (figure 6).

Publication bias

After the evaluation, according to Begg's test, there was no publication bias. The results of Begg's test and Begg's funnel plot are presented in figure 7.

Table 1. Characteristics of studies included in the present survey.

Study	Year	No. of patients	Age (year), mean	Study design	MRI	Preoperative therapy (drugs used in regimens)	Receptor status
Bufi *et al.* [7]	2015	225	47	Retrospective	1.5 T	doxorubicin, taxane, cyclophosphamide	143 Luminal, 37 Triple negative, 17 HER2+, 28 Hybrid
Li *et al.* [42]	2020	384	49	Retrospective	-	paclitaxel, anthracycline, cyclophosphamide, trastuzumab	162 HR+/HER2−, 60 HR+/HER2+, 30 HR−/HER2+, 132 HR−/HER2− (triple negative)
Zhou *et al.* [43]	2020	55	50.4	Retrospective	3.0 T	taxol, 5-fluorouracil, epirubicin, cyclophosphamide, doxorubicin	22 Luminal A, 9 Luminal B, 13 HER2+, 11 Triple negative
Gampenrieder *et al.* [44]	2019	246	50	Retrospective	3.0 T	anthracycline, taxane, trastuzumab, pertuzumab	57 Luminal A, 29 Luminal B, 33 HER2+/HR-, 37 HER2+/HR+, 90 Triple negative
Pesapane *et al.* [45]	2021	83	47.26	Retrospective	1.5 T	Chemotherapy, hormone therapy	44 ER+, 41 PR+, 31 HER2+
Chen *et al.* [46]	2020	28	48.48	Retrospective	3.0 T	doxorubicin, cyclophosphamide, docetaxel, trastuzumab	19 ER+, 11 PR+, 15 HER2+
Dongfeng *et al.* [47]	2012	60	55.4	Retrospective	3.0 T	paclitaxel, pirarubicin	31 ER+
Fan *et al.* [48]	2021	114	48	Retrospective	3.0 T	N/A	12 Luminal A, 58 Luminal B, 20 Basal-like, 24 HER2+
Huang *et al.* [36]	2016	59	-	Retrospective	-	N/A	N/A
Zhao *et al.* [49]	2021	87	-	Retrospective	3.0 T	taxane, anthracyclines, cyclophosphamide, carboplatin, trastuzumab	37 HR+/HER2-, 36 HER2+, 14 Triple Negative
Tateishi *et al.* [50]	2012	142	57	Prospective	3.0 T	5-fluorouracil, epirubicin, cyclophosphamide, doxorubicin, paclitaxel, herceptin, docetaxel	100 ER+, 82 PR+, 111 HER2+
Tokuda *et al.* [40]	2021	29	55	Prospective	3.0 T	paclitaxel, trastuzumab, 5-fluorouracil, epirubicin, cyclophosphamide	7 Luminal A, 13 Luminal B, 3 HER2+, 6 Triple Negative
De Los Santos *et al.* [51]	2011	81	50	Retrospective	1.5 T	doxorubicin, paclitaxel, cyclophosphamide	45 HR+, 23 HER2+
Moon *et al.* [41]	2008	212	45.5	Prospective	1.5 T	taxane, anthracyclines, trastuzumab	101 ER+, 68 PR+, 63 HER2+
Craciunescu *et al.* [37]	2009	20	46.5	Retrospective	1.5 T	paclitaxel, liposomal doxorubicin, hormone therapy	N/A
Schott *et al.* [52]	2005	43	48	Prospective	1.5 T	doxorubicin, docetaxel	25 ER+

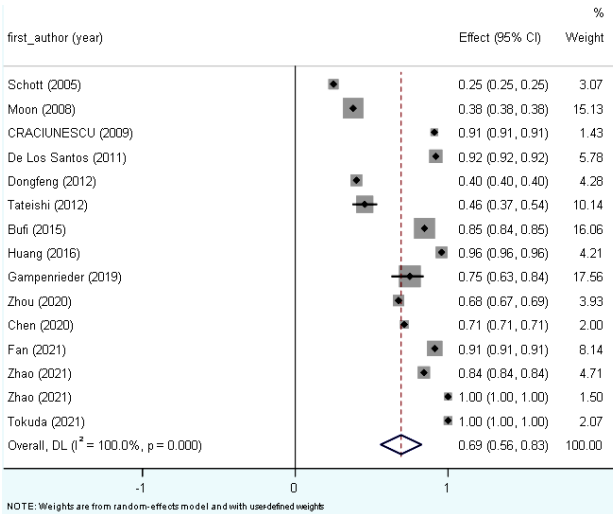

Figure 4. Forest plot of the DCE-MRI sensitivity for the prediction of response to NAC among BC patients.

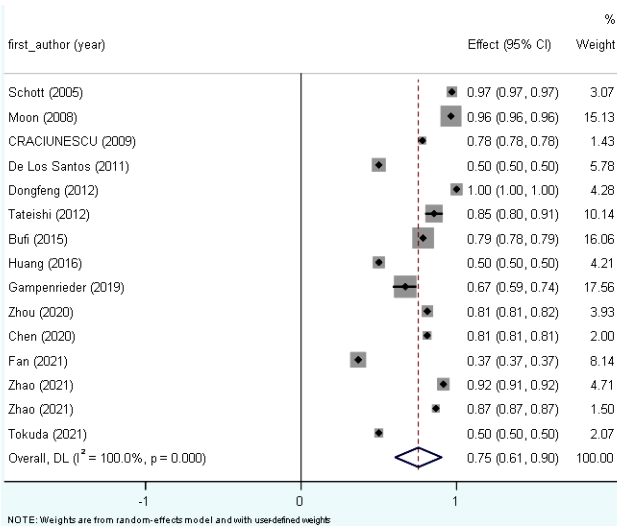

Figure 5. Forest plot of the DCE-MRI specificity for the prediction of response to NAC among BC patients.

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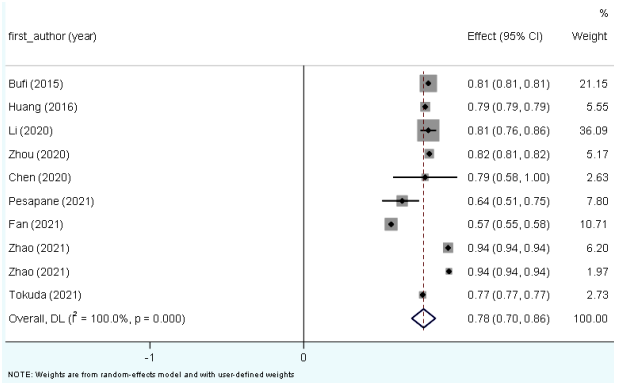

Figure 6. Forest plot of the diagnostic AUC of DCE-MRI for the prediction of response to NAC among BC patients.

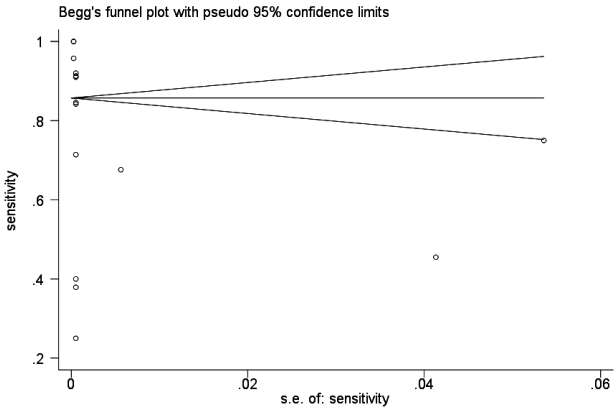

Figure 7. Publication bias test using Begg's funnel plot test.

DISCUSSION

NAC has been standardized to decrease the size of breast tumors or downstaging the BC, which can decline the progression of cancer, enhance the survival of BC cases, and improve their life quality [25, 26]. Previous studies showed that the clinicopathological findings and improvements upon NAC were various in different types of invasive BCs [27]. Therefore, we evaluated the DCE-MRI value in predicting the NAC response in BC patients. Our findings showed that the pooled specificity of DCE-MRI to predict the reaction to NAC in BC patients was 75%, while the DCE-MRI sensitivity was 69%. Furthermore, we observed that the pooled NPV of DCE-MRI was 90%.

Multiple studies have already evaluated the DCE-MRI performance in assessing the pathological response to NAC in BC cases [5,28-30]. According to a meta-analysis by Jun *et al.* [5], DCE-MRI is capable of monitoring NAC for BC with high sensitivity and specificity despite a high degree of heterogeneity in published studies. In another meta-analysis, Cheng *et al.* [31] pooled the surveys assessing the value of DCE-MRI in the evaluation of the response to NAC in patients with BC. However, in the current study, we pooled the data reporting the predictive DCE-MRI value in BC cases receiving NAC. However, Prevos *et al.* [32] showed that the value of MRI in this regard is still unclear. In the study of Li *et al.* [33], the signal enhancement ratio washout volume, as well as k_{ep} of DCE-MRI, successfully predicted the response of BC after one cycle of NAC. Also, Atuegwu *et al.* [34] reported that the radiomics features of DCE-MRI and Diffusion-Weighted Imaging (DWI-MRI) could be utilized for the prediction of the treatment response in BC cases at the end of chemotherapy. Finally, a study by Marinovich *et al.* [35] determined that the heterogeneity of the study method precluded definitive conclusions. Notably, many differences were observed between mentioned studies in their clinicopathological details such as tumor type, NAC regimen, pathological reaction ,imaging like time point testing, and analysis methods, including pharmacokinetic models.

Our study, like other investigations, suffers from some limitations. First, in the studies reviewed in our study, the data was not reported based on the pathological types of BC, and since NAC treatment may produce different responses relative to the pathological type of BC, it may cause heterogeneity in the results. Second, the stage of BC was not reported in some studies [36,37], and those revealed did not clearly report their data based on the stage of BC. Third, various NAC regimens were applied in different studies. Fourth, some studies [14,38,39] reported the predictive value of some radiomics features of DCE-MRI, which cannot be presented in our study. Finally, some studies [40,41] reported the predictive value of DCE-MRI using different indices. Therefore, further studies need to be performed to overcome these limitations.

CONCLUSION

To sum up, the findings of our study revealed that the DCE-MRI is not only a sensitive but also a specific method with an acceptable NPV for predicting the response to NAC in BC cases. Thus, a clinician can make a decision on a treatment regimen before NAC and treat some patients who do not benefit from NAC with another appropriate regimen.

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Availability of data and materials: All data generated or analyzed during this study are included in this published article.

Authors' contributions: H.D, A.A, and N.A contributed to the study concept and design; H.D, R.A, M.A, and M.S collected the data; A.A and N.A carried out analysis and interpretation of data; H.D performed drafting of the manuscript; H.D, R.A, and M.S performed critical revision of the manuscript for

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important intellectual content. All authors read and approved the final manuscript.

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Competing interests: The authors declare that they have no competing interests.

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