Pretreatment apparent diffusion coefficient does not predict therapy response to neoadjuvant chemotherapy in breast cancer

Alexey Surov [a, *, 1], Andreas Wienke [b, 1], Hans Jonas Meyer [c, 1]

[a] Department of Radiology and Nuclear Medicine, Otto-von-Guericke University of Magdeburg, Germany
[b] Department of Diagnostic and Interventional Radiology, University of Leipzig, Germany
[c] Institute of Medical Epidemiology, Biostatistics, and Informatics, Martin-Luther-University Halle-Wittenberg, Germany

A B S T R A C T

Background: Some reports indicated that apparent diffusion coefficient can predict pathologic response to treatment in breast cancer (BC). The purpose of the present meta-analysis was to provide evident data regarding use of ADC values for prediction of treatment response in BC.
Methods: MEDLINE library, EMBASE and SCOPUS databases were screened for associations between ADC and treatment response for neoadjuvant chemotherapy in breast cancer (BC) up to March 2020. Overall, 22 studies met the inclusion criteria. For the present analysis, the following data were extracted from the collected studies: authors, year of publication, study design, number of patients/lesions, mean and standard deviation of the pretreatment ADC values. The methodological quality of the included studies was checked according to the QUADAS-2 instrument. The meta-analysis was undertaken by using Rev-Man 5.3 software. DerSimonian and Laird random-effects models with inverse-variance weights were used without any further correction to account for the heterogeneity between the studies. Mean ADC values including 95% confidence intervals were calculated separately for responders and non responders.
Results: The acquired 22 studies comprised 1827 patients with different BC. Of the 1827 patients, 650 (35.6%) were reported as responders and 1177 (64.4%) as non-responders to the neoadjuvant chemotherapy. The pooled calculated pretreatment mean ADC value of BC in responders was 0.98 (95% CI = [0.94; 1.03]). In non-responders, it was 1.05 (95% CI = [1.00; 1.10]). The ADC values of the groups overlapped significantly.
Conclusion: Pretreatment ADC alone cannot predict response to neoadjuvant chemotherapy in BC.

1. Introduction

Magnetic resonance imaging (MRI) a wide used imaging modality for diagnosing, staging, and treatment monitoring of breast cancer (BC) [1–3]. Diffusion-weighted imaging (DWI) is an important complement technique of breast MRI [4]. DWI is based on measure of the free water diffusion in tissues, which can be quantified by the apparent diffusion coefficient (ADC) [5,6]. This water movement is restricted in tissues, mainly caused by cell membranes and cell nuclei. Consequently, the ADC value of tumors is associated with several microstructure features [7]. So, it was reported that the ADC is correlated inversely ($\rho = -0.48$) with tumor cell count, as well as with the proliferation potential in BC [7,8].

ADC can also aid in distinguishing between benign and malignant tumors [4]. Typically, malignant tumors have lower ADC values in comparison to benign lesions [4]. For example, a recent meta-analysis showed that breast cancers had predominantly ADC values below 1.00×10^{-3} mm^2/s and several benign breast lesions had ADC values over this proposed threshold [9]. Notably, this result was independent on technical details like Tesla strength or choice of b values, and measure methods [9].

Some reports indicated that DWI/ADC can also predict pathologic response to treatment in BC [10,11]. However, these reports are associated with important concerns. Firstly, the reported studies regarding ADC as response predictor analyzed small patient samples. Therefore, the results cannot apply as evident. Secondly, the studies proposed different ADC threshold values to discriminate responder and non-responder. Also other statistical data like

* Corresponding author. Leipziger Str. 44, 39112, Magdeburg, Germany.
E-mail addresses: Alexey.Surov@med.ovgu.de (A. Surov), andreas.wienke@uk-halle.de (A. Wienke), Hans-Jonas.Meyer@medizin.uni-leipzig.de (H.J. Meyer).
[1] All authors contributed equally for this work.

specificity, sensitivity, and accuracy values ranged significantly. Therefore, a reliable discrimination of responders and non-responders based on ADC is questionable in clinical practice.

The purpose of the present meta-analysis was to provide evident data regarding use of DWI/ADC for prediction of treatment response in BC based on a large sample.

2. Materials and methods

2.1. Data acquisition and proving

For the present meta-analysis, MEDLINE library, EMBASE and SCOPUS databases were screened for associations between ADC and treatment response for neoadjuvant chemotherapy in breast cancer (BC) up to March 2020. Fig. 1 shows the strategy of data acquisition. The following search terms/combinations were as follows:

"DWI or diffusion weighted imaging or diffusion-weighted imaging or ADC or apparent diffusion coefficient AND breast cancer OR breast carcinoma OR mammary cancer OR breast neoplasm OR breast tumor AND treatment response OR treatment OR response". Secondary references were also manually checked and recruited. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA) was used for the research [12].

The primary search identified 499 records. After removing of duplicate articles (n = 383) there were 114 items. On the next step, abstracts of the 114 articles were checked. Articles in non-English language, experimental animals and in vitro studies, reviews, meta-analyses, and case report publications were excluded. There were 41 articles, which were included into the further analysis. Full texts of the 41 identified items were collected and checked. Inclusion criteria for this analysis were:
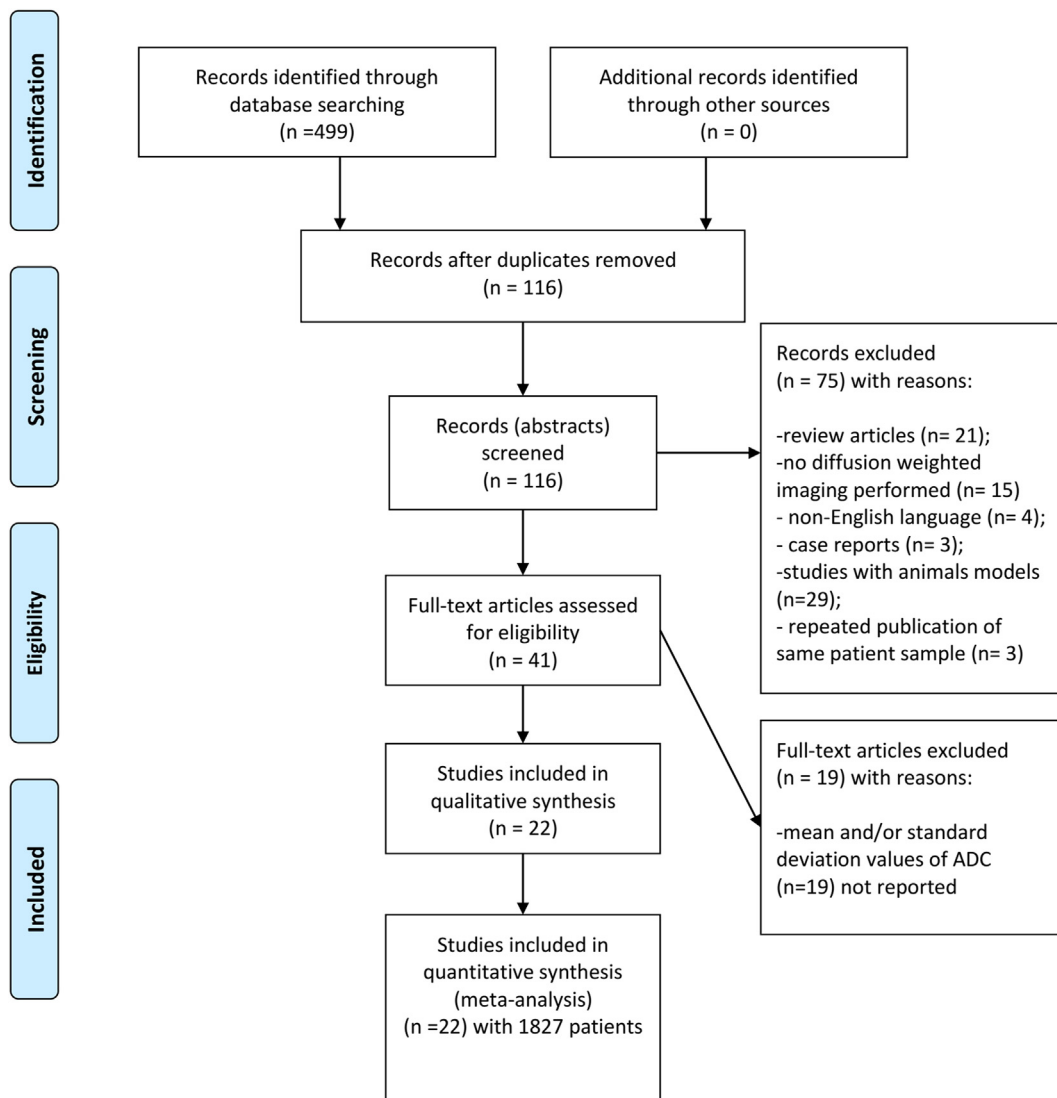

Fig. 1. PRISMA flow chart of the data acquisition.

- Original studies;
- Studies investigated humans;
- Available pretreatment mean and standard deviation ADC values of BC;
- Available data regarding treatment response of BC;
- English language.

After checking of full texts, 19 articles with incomplete data regarding ADC values were excluded. Overall, 22 studies met the inclusion criteria [13–34] (Fig. 1). For the present analysis, the following data were extracted from the collected studies: authors, year of publication, study design, number of patients/lesions, mean and standard deviation of the pretreatment ADC values.

2.2. Meta-analysis

Of the included 22 studies, 11 (50%) were retrospective and 11 (50%) prospective. The methodological quality of the acquired studies was checked according to the Quality Assessment of Diagnostic Studies (QUADAS 2) instrument [35] independently by two observers (A.S. and H.J.M.). The results of QUADAS-2 proving are shown in Fig. 2.

Next, the reported ADC values (mean and standard deviation) of responders and non-responders in every study were acquired.

Furthermore, the meta-analysis was undertaken by using RevMan 5.3 [RevMan 2014. The Cochrane Collaboration Review Manager Version 5.3.]. Heterogeneity was calculated by means of the inconsistency index I^2 [36,37]. In a subgroup analysis, studies were stratified by tumor type. In addition, DerSimonian and Laird random-effects models with inverse-variance weights were used without any further correction [38] to account for the heterogeneity between the studies. Mean ADC values including 95% confidence intervals were calculated separately for benign and malign lesions.

3. Results

The acquired 22 studies comprised 1827 patients with different BC. Of the 1827 patients, 650 (35.6%) were reported as responders and 1177 (64.4%) as non-responders to the neoadjuvant chemotherapy. The pooled calculated pretreatment mean ADC value of BC in responders was 0.98 (95% CI = [0.94; 1.03]) (Fig. 3). In non-responders, it was 1.05 (95% CI = [1.00; 1.10]) (Fig. 4). Fig. 5 shows the graphical distribution of ADC values in responders and non-responders. The ADC values of the groups overlapped significantly.

On the next step, cumulative mean ADC values were calculated in dependence on choice of upper b values. There were two subgroups: a subgroup with b values ≤ 800 (n = 1402 patients), and a subgroup with the upper b value of 1000 (n = 363 patients). In one study the b values were not reported and in another study, the upper b value was 900. Therefore, these 2 reports were excluded from the subanalysis.

In the subgroup with b values ≤ 800, the pooled calculated pretreatment mean ADC value of BC in responders (n = 526) was 0.99 (95% CI = [0.93; 1.04]) (Fig. 6). In non-responders (n = 876), it was 1.04 (95% CI = [0.97; 1.10]) (Fig. 7).

In the subgroup with the upper b value of 1000, responded BC (n = 106) showed the pooled calculated pretreatment mean ADC value of 0.98 (95% CI = [0.85; 1.12]) (Fig. 6). In non-responders (n = 257), it was 1.07 (95% CI = [1.02; 1.13]) (Fig. 7).

4. Discussion

Prediction of response to neoadjuvant chemotherapy with DW MR imaging is an important clinical aspect. It may help to individualize treatments and to avoid ineffective chemotherapy. Pathologic complete response (pCR) is the best outcome for neoadjuvant chemotherapy in BC [39,40]. As reported previously, it is an important prognostic factor for both disease-free survival and overall survival in patients with BC [39,40]. So far, patients with pCR of BC have an improved 5-year disease-free survival rate of 87% and a 5-year overall survival rate of 89% in comparison to patients without pCR [41].

Previously, some investigations analyzed the possibility to predict pCR in BC based on MR images. So far, Li et al. performed a meta-analysis including 13 studies with 575 patients and found that the pooled sensitivity of MRI was 0.88 (95% CI, 0.78; 0.94) and the pooled specificity was 0.69 (95% CI, 0.51; 0.83) in prediction of pCR [42]. The authors acquired studies with "conventional" MRI of the breast including T2 weighted and dynamic contrast enhancing images.

The role of DWI/ADC was also investigated previously. Theoretically, ADC might be able to predict pCR. In fact, as already
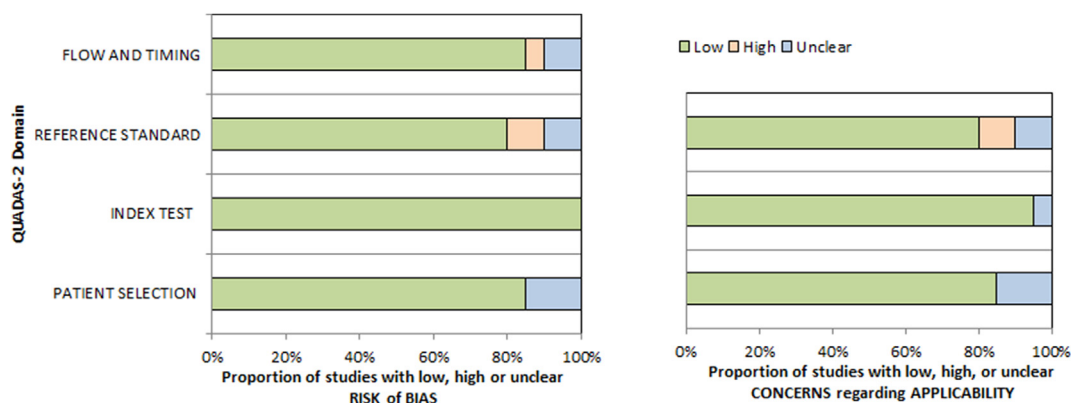

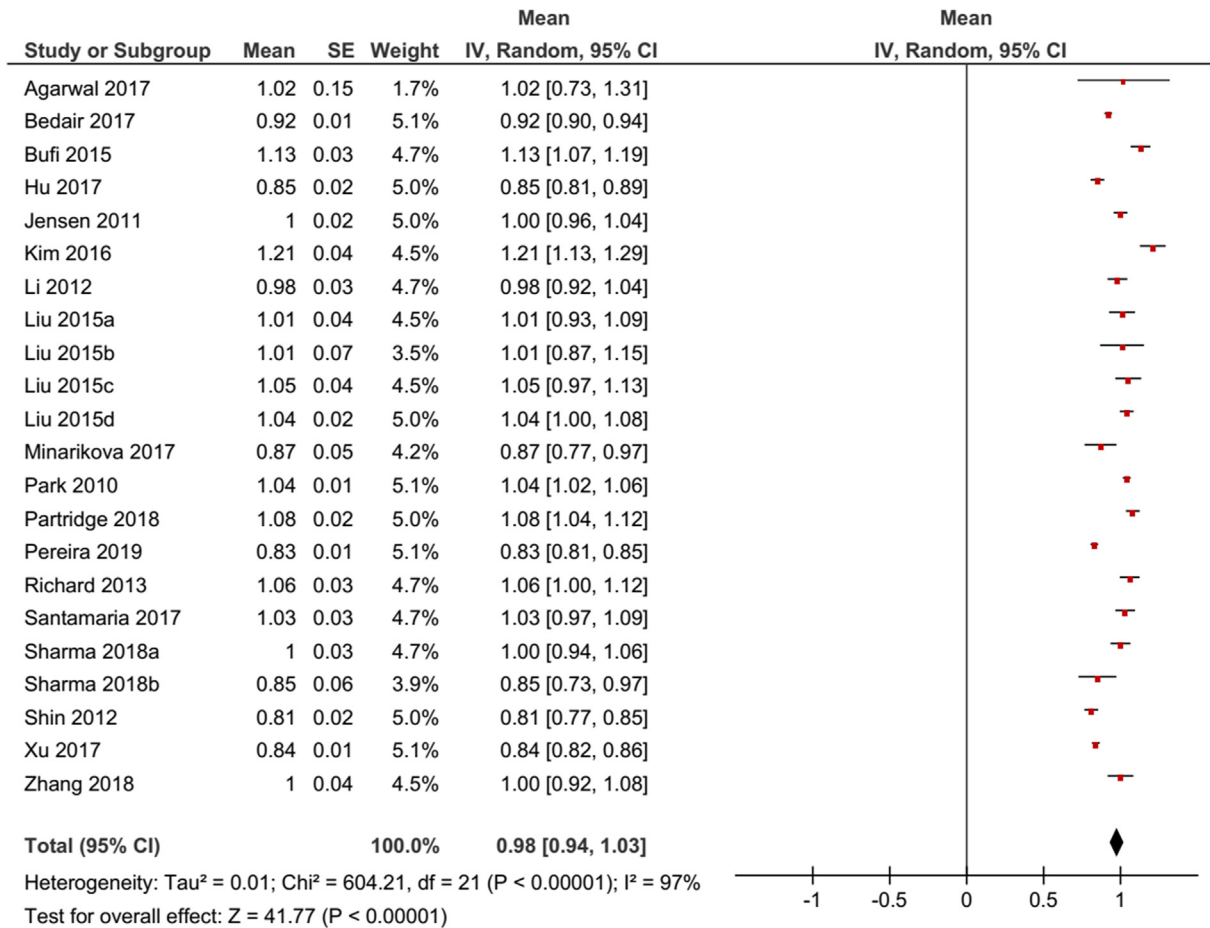Fig. 2. QUADAS-2 quality assessment of the included studies.

| | | | | Mean | Mean |
Study or Subgroup	Mean	SE	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Agarwal 2017	1.02	0.15	1.7%	1.02 [0.73, 1.31]	
Bedair 2017	0.92	0.01	5.1%	0.92 [0.90, 0.94]	
Bufi 2015	1.13	0.03	4.7%	1.13 [1.07, 1.19]	
Hu 2017	0.85	0.02	5.0%	0.85 [0.81, 0.89]	
Jensen 2011	1	0.02	5.0%	1.00 [0.96, 1.04]	
Kim 2016	1.21	0.04	4.5%	1.21 [1.13, 1.29]	
Li 2012	0.98	0.03	4.7%	0.98 [0.92, 1.04]	
Liu 2015a	1.01	0.04	4.5%	1.01 [0.93, 1.09]	
Liu 2015b	1.01	0.07	3.5%	1.01 [0.87, 1.15]	
Liu 2015c	1.05	0.04	4.5%	1.05 [0.97, 1.13]	
Liu 2015d	1.04	0.02	5.0%	1.04 [1.00, 1.08]	
Minarikova 2017	0.87	0.05	4.2%	0.87 [0.77, 0.97]	
Park 2010	1.04	0.01	5.1%	1.04 [1.02, 1.06]	
Partridge 2018	1.08	0.02	5.0%	1.08 [1.04, 1.12]	
Pereira 2019	0.83	0.01	5.1%	0.83 [0.81, 0.85]	
Richard 2013	1.06	0.03	4.7%	1.06 [1.00, 1.12]	
Santamaria 2017	1.03	0.03	4.7%	1.03 [0.97, 1.09]	
Sharma 2018a	1	0.03	4.7%	1.00 [0.94, 1.06]	
Sharma 2018b	0.85	0.06	3.9%	0.85 [0.73, 0.97]	
Shin 2012	0.81	0.02	5.0%	0.81 [0.77, 0.85]	
Xu 2017	0.84	0.01	5.1%	0.84 [0.82, 0.86]	
Zhang 2018	1	0.04	4.5%	1.00 [0.92, 1.08]	
Total (95% CI)			100.0%	0.98 [0.94, 1.03]	

Heterogeneity: Tau² = 0.01; Chi² = 604.21, df = 21 (P < 0.00001); I² = 97%
Test for overall effect: Z = 41.77 (P < 0.00001)

Fig. 3. Forrest plots of ADC values reported for breast cancers responded to neoadjuvant chemotherapy.

mentioned, ADC correlated inversely with cell count. Ideally, neoadjuvant chemotherapy reduces tumor cell count completely. Therefore, ADC values during/after neoadjuvant chemotherapy should increase. Numerous studies confirmed this hypothesis. For example, Belli et al. showed that ADC values of BC increased during the neoadjuvant chemotherapy [43]. Moreover, increase of ADC values during the neoadjuvant chemotherapy was reported as a more sensitive parameter to discriminate responders and non-responders in comparison to tumor size or volume [26].

However, a more important question is a possibility to predict NAC success based on pretreatment values. The reported data about this are contradictory. While some authors found an association between pretreatment ADC and pCR after neoadjuvant chemotherapy in BC, others did not. So far, Bedair et al. reported that responders had lower pretreatment ADC values ($\times 10^{-3}$ mm^2/s) in comparison to non-responders, namely 0.92 ± 0.02 and 1.20 ± 0.02, respectively (p < 0.001) [14]. Similar results were reported by Liu et al. [20]. However, in the study of Bufi et al. there were no significant differences of pretreatment ADC values ($\times 10^{-3}$ mm^2/s) between responders and non-responders: 1.13 ± 0.19 vs 1.09 ± 0.19, respectively [15].

The present analysis based on a large cohort showed that pretreatment DWI cannot predict treatment outcome in BC because baseline ADC values of responders to NAC and non-responders did not differ and overlapped significantly. Furthermore, this result was independent on choice of b values. This finding is very important and suggests that pretreatment ADC cannot be used as a prognostic surrogate marker for pCR in BC. Our finding may also indicate that pretreatment cell density and other histopathological feature, which are reflected by DWI/ADC, do not influence treatment success. This is in agreement with some previous reports. For example, according to a large multicenter investigation, ADC was not associated with tumor grade, stage and morphological histological appearances in BC [44]. More importantly, it has been shown that ADC did not correlate with the hormone receptor status in BC [45].

Our analysis has some limitations. Firstly, BC represents a heterogenous tumor groups consisting of carcinomas with various receptor statuses. We were unable to perform subgroup analyses because in the acquired studies ADC data in tumor subgroups were not reported. Secondly, the half of the acquired studies were retrospective with known inherent concerns. Thirdly, some studies had patient selection bias.
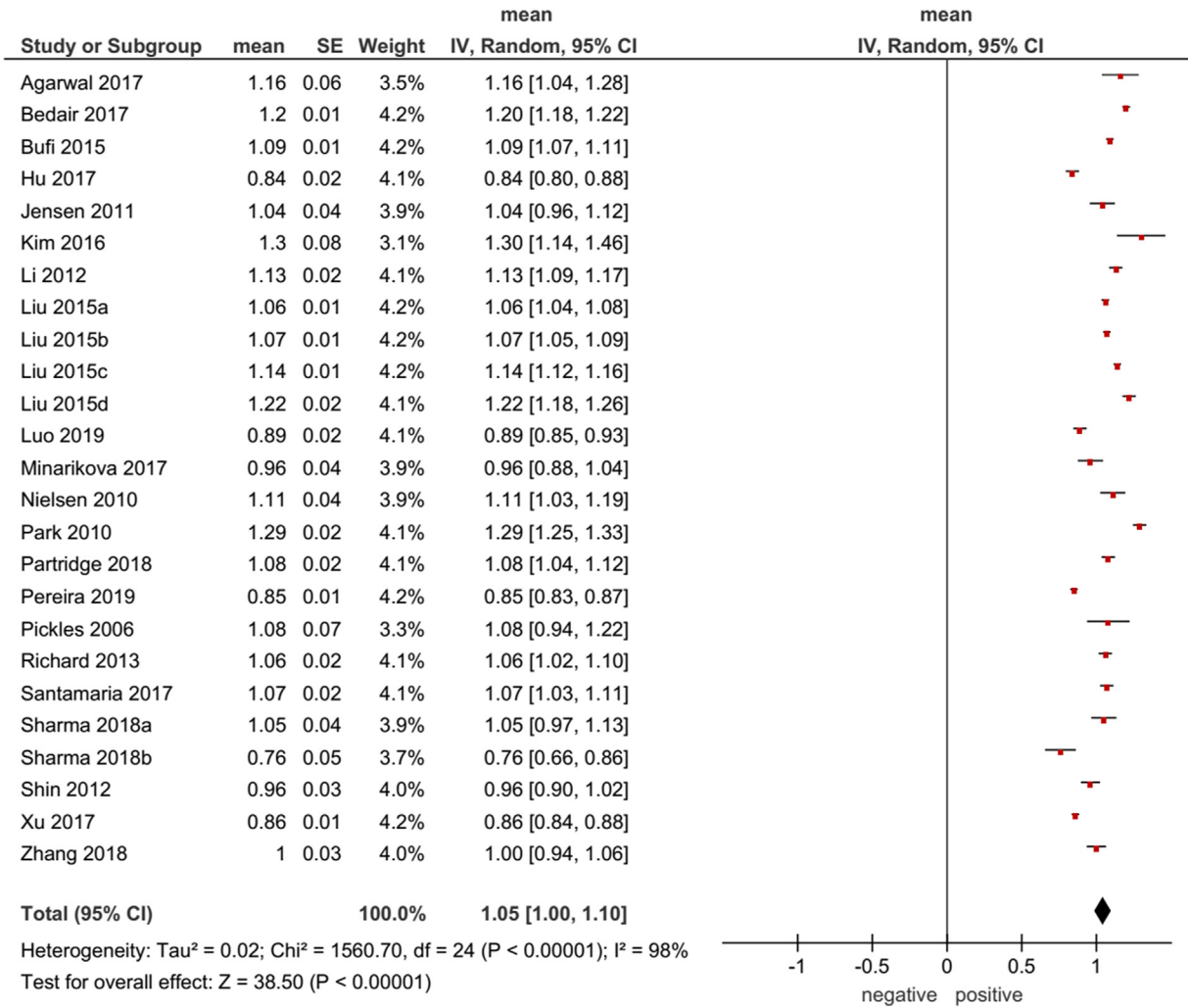
Study or Subgroup	mean	SE	Weight	mean IV, Random, 95% CI	mean IV, Random, 95% CI
Agarwal 2017	1.16	0.06	3.5%	1.16 [1.04, 1.28]	
Bedair 2017	1.2	0.01	4.2%	1.20 [1.18, 1.22]	
Bufi 2015	1.09	0.01	4.2%	1.09 [1.07, 1.11]	
Hu 2017	0.84	0.02	4.1%	0.84 [0.80, 0.88]	
Jensen 2011	1.04	0.04	3.9%	1.04 [0.96, 1.12]	
Kim 2016	1.3	0.08	3.1%	1.30 [1.14, 1.46]	
Li 2012	1.13	0.02	4.1%	1.13 [1.09, 1.17]	
Liu 2015a	1.06	0.01	4.2%	1.06 [1.04, 1.08]	
Liu 2015b	1.07	0.01	4.2%	1.07 [1.05, 1.09]	
Liu 2015c	1.14	0.01	4.2%	1.14 [1.12, 1.16]	
Liu 2015d	1.22	0.02	4.1%	1.22 [1.18, 1.26]	
Luo 2019	0.89	0.02	4.1%	0.89 [0.85, 0.93]	
Minarikova 2017	0.96	0.04	3.9%	0.96 [0.88, 1.04]	
Nielsen 2010	1.11	0.04	3.9%	1.11 [1.03, 1.19]	
Park 2010	1.29	0.02	4.1%	1.29 [1.25, 1.33]	
Partridge 2018	1.08	0.02	4.1%	1.08 [1.04, 1.12]	
Pereira 2019	0.85	0.01	4.2%	0.85 [0.83, 0.87]	
Pickles 2006	1.08	0.07	3.3%	1.08 [0.94, 1.22]	
Richard 2013	1.06	0.02	4.1%	1.06 [1.02, 1.10]	
Santamaria 2017	1.07	0.02	4.1%	1.07 [1.03, 1.11]	
Sharma 2018a	1.05	0.04	3.9%	1.05 [0.97, 1.13]	
Sharma 2018b	0.76	0.05	3.7%	0.76 [0.66, 0.86]	
Shin 2012	0.96	0.03	4.0%	0.96 [0.90, 1.02]	
Xu 2017	0.86	0.01	4.2%	0.86 [0.84, 0.88]	
Zhang 2018	1	0.03	4.0%	1.00 [0.94, 1.06]	
Total (95% CI)			**100.0%**	**1.05 [1.00, 1.10]**	

Heterogeneity: Tau² = 0.02; Chi² = 1560.70, df = 24 (P < 0.00001); I² = 98%
Test for overall effect: Z = 38.50 (P < 0.00001)

(axis: -1 -0.5 0 0.5 1 ; negative positive)

Fig. 4. Forrest plots of ADC values reported for non-responded breast cancers in dependency on upper b values.

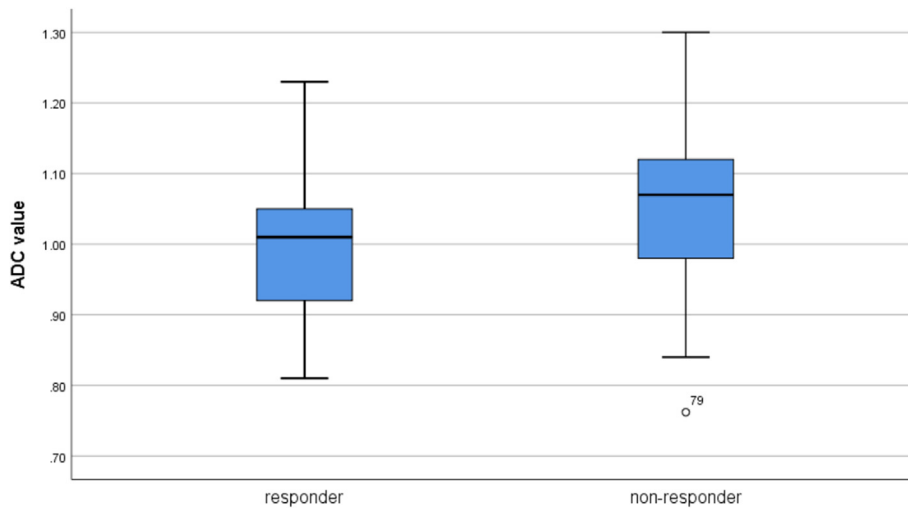**Fig. 5.** Comparison of ADC values between responders and non-responders.
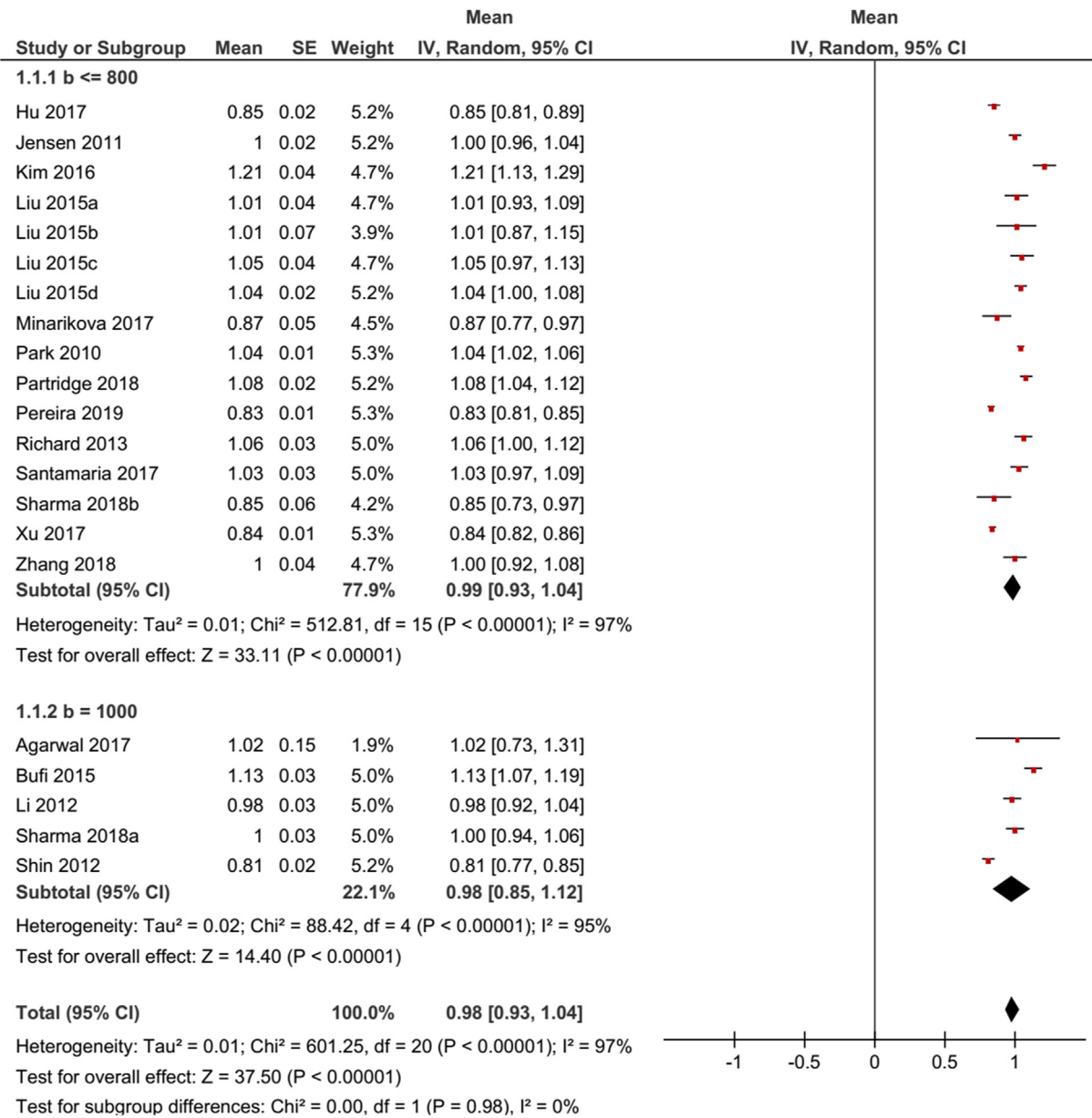
Study or Subgroup	Mean	SE	Weight	Mean IV, Random, 95% CI	Mean IV, Random, 95% CI
1.1.1 b <= 800					
Hu 2017	0.85	0.02	5.2%	0.85 [0.81, 0.89]	
Jensen 2011	1	0.02	5.2%	1.00 [0.96, 1.04]	
Kim 2016	1.21	0.04	4.7%	1.21 [1.13, 1.29]	
Liu 2015a	1.01	0.04	4.7%	1.01 [0.93, 1.09]	
Liu 2015b	1.01	0.07	3.9%	1.01 [0.87, 1.15]	
Liu 2015c	1.05	0.04	4.7%	1.05 [0.97, 1.13]	
Liu 2015d	1.04	0.02	5.2%	1.04 [1.00, 1.08]	
Minarikova 2017	0.87	0.05	4.5%	0.87 [0.77, 0.97]	
Park 2010	1.04	0.01	5.3%	1.04 [1.02, 1.06]	
Partridge 2018	1.08	0.02	5.2%	1.08 [1.04, 1.12]	
Pereira 2019	0.83	0.01	5.3%	0.83 [0.81, 0.85]	
Richard 2013	1.06	0.03	5.0%	1.06 [1.00, 1.12]	
Santamaria 2017	1.03	0.03	5.0%	1.03 [0.97, 1.09]	
Sharma 2018b	0.85	0.06	4.2%	0.85 [0.73, 0.97]	
Xu 2017	0.84	0.01	5.3%	0.84 [0.82, 0.86]	
Zhang 2018	1	0.04	4.7%	1.00 [0.92, 1.08]	
Subtotal (95% CI)			**77.9%**	**0.99 [0.93, 1.04]**	

Heterogeneity: Tau² = 0.01; Chi² = 512.81, df = 15 (P < 0.00001); I² = 97%
Test for overall effect: Z = 33.11 (P < 0.00001)

1.1.2 b = 1000					
Agarwal 2017	1.02	0.15	1.9%	1.02 [0.73, 1.31]	
Bufi 2015	1.13	0.03	5.0%	1.13 [1.07, 1.19]	
Li 2012	0.98	0.03	5.0%	0.98 [0.92, 1.04]	
Sharma 2018a	1	0.03	5.0%	1.00 [0.94, 1.06]	
Shin 2012	0.81	0.02	5.2%	0.81 [0.77, 0.85]	
Subtotal (95% CI)			**22.1%**	**0.98 [0.85, 1.12]**	

Heterogeneity: Tau² = 0.02; Chi² = 88.42, df = 4 (P < 0.00001); I² = 95%
Test for overall effect: Z = 14.40 (P < 0.00001)

Total (95% CI)			**100.0%**	**0.98 [0.93, 1.04]**	

Heterogeneity: Tau² = 0.01; Chi² = 601.25, df = 20 (P < 0.00001); I² = 97%
Test for overall effect: Z = 37.50 (P < 0.00001)
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.98), I² = 0%

Fig. 6. Forrest plots of ADC values reported for breast cancers responded to neoadjuvant chemotherapy in dependency on upper b values.
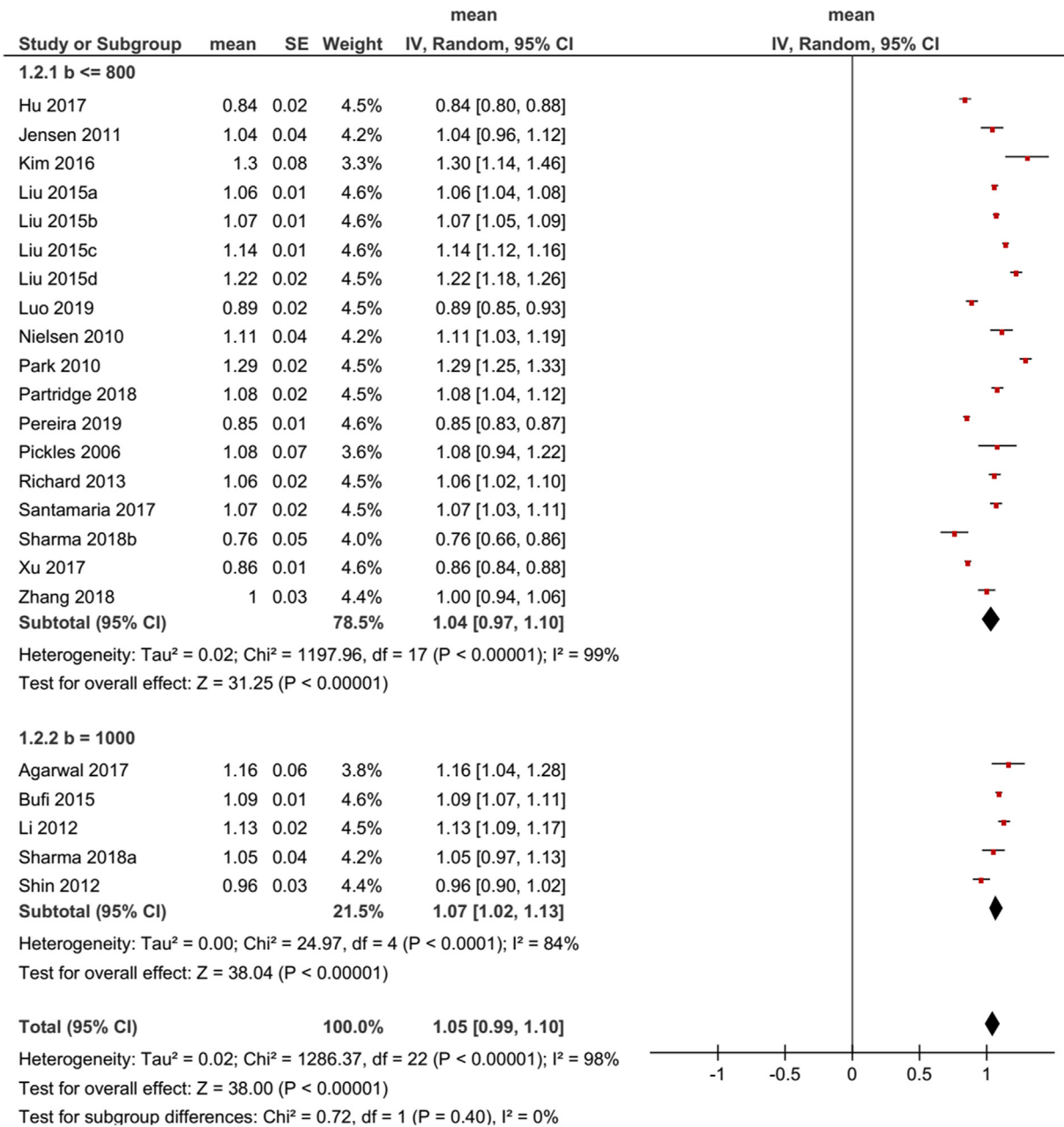
Study or Subgroup	mean	SE	Weight	mean IV, Random, 95% CI
1.2.1 b <= 800				
Hu 2017	0.84	0.02	4.5%	0.84 [0.80, 0.88]
Jensen 2011	1.04	0.04	4.2%	1.04 [0.96, 1.12]
Kim 2016	1.3	0.08	3.3%	1.30 [1.14, 1.46]
Liu 2015a	1.06	0.01	4.6%	1.06 [1.04, 1.08]
Liu 2015b	1.07	0.01	4.6%	1.07 [1.05, 1.09]
Liu 2015c	1.14	0.01	4.6%	1.14 [1.12, 1.16]
Liu 2015d	1.22	0.02	4.5%	1.22 [1.18, 1.26]
Luo 2019	0.89	0.02	4.5%	0.89 [0.85, 0.93]
Nielsen 2010	1.11	0.04	4.2%	1.11 [1.03, 1.19]
Park 2010	1.29	0.02	4.5%	1.29 [1.25, 1.33]
Partridge 2018	1.08	0.02	4.5%	1.08 [1.04, 1.12]
Pereira 2019	0.85	0.01	4.6%	0.85 [0.83, 0.87]
Pickles 2006	1.08	0.07	3.6%	1.08 [0.94, 1.22]
Richard 2013	1.06	0.02	4.5%	1.06 [1.02, 1.10]
Santamaria 2017	1.07	0.02	4.5%	1.07 [1.03, 1.11]
Sharma 2018b	0.76	0.05	4.0%	0.76 [0.66, 0.86]
Xu 2017	0.86	0.01	4.6%	0.86 [0.84, 0.88]
Zhang 2018	1	0.03	4.4%	1.00 [0.94, 1.06]
Subtotal (95% CI)			78.5%	1.04 [0.97, 1.10]
Heterogeneity: Tau² = 0.02; Chi² = 1197.96, df = 17 (P < 0.00001); I² = 99%				
Test for overall effect: Z = 31.25 (P < 0.00001)				
1.2.2 b = 1000				
Agarwal 2017	1.16	0.06	3.8%	1.16 [1.04, 1.28]
Bufi 2015	1.09	0.01	4.6%	1.09 [1.07, 1.11]
Li 2012	1.13	0.02	4.5%	1.13 [1.09, 1.17]
Sharma 2018a	1.05	0.04	4.2%	1.05 [0.97, 1.13]
Shin 2012	0.96	0.03	4.4%	0.96 [0.90, 1.02]
Subtotal (95% CI)			21.5%	1.07 [1.02, 1.13]
Heterogeneity: Tau² = 0.00; Chi² = 24.97, df = 4 (P < 0.0001); I² = 84%				
Test for overall effect: Z = 38.04 (P < 0.00001)				
Total (95% CI)			100.0%	1.05 [0.99, 1.10]
Heterogeneity: Tau² = 0.02; Chi² = 1286.37, df = 22 (P < 0.00001); I² = 98%				
Test for overall effect: Z = 38.00 (P < 0.00001)				
Test for subgroup differences: Chi² = 0.72, df = 1 (P = 0.40), I² = 0%				

Fig. 7. Forrest plots of ADC values reported for non-responded breast cancers

5. Conclusion

Pretreatment ADC alone cannot predict response to neo-adjuvant chemotherapy in BC.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable".

Availability of data and material

The data that support the findings of this study are available from professor Surov but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of professor Surov.

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None.

Authors' contributions

AS made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data;

HJM, AW been involved in drafting the manuscript or revising it critically for important intellectual content;

HJM, AW given final approval of the version to be published. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content; and.

AS, HJM, AW agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of competing interest

The authors declare that they have no competing interests.

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Abbreviations

BC	breast cancer
MRI	magnetic resonance imaging
DWI	diffusion weighted imaging
ADC	apparent diffusion coefficient

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