Diffusion Weighted Imaging of Different Breast Cancer Molecular Subtypes. A Systematic Review and Meta Analysis.

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Research article

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Abstract

Background: Magnetic resonance imaging can be used to diagnose breast cancer (BC)s. Diffusion weighted imaging and the apparent diffusion coefficient (ADC) can be used to reflect tumor microstructure. The present analysis sought to compare ADC values between molecular subtypes of BC based upon a large patient sample.

Methods: MEDLINE library and SCOPUS databases were screened for the associations between ADC and molecular suptype of BC to April 2020. Primary endpoint of the systematic review was the ADC value in different BC. Overall, 28 studies were suitable for the analysis and included into the present study.

Results: The included studies comprised a total of 2990 tumors. Luminal A type was diagnosed in 865 cases (28.9%), Luminal B in 899 cases (30.1%), Her-2 enriched in 597 cases (20.0%) and triple negative in 629 cases (21.0%). The mean ADC value of the Luminal A type was 0.99×10^{-3} mm^2/s [95% CI 0.94-1.04], of the Luminal B type was 0.99×10^{-3} mm^2/s [95% CI 0.89-1.05], of Her 2-enriched type was 1.02×10^{-3} mm^2/s [95% CI 0.95-1.08] and of the triple negative type was 0.99×10^{-3} mm^2/s [95% CI 0.91-1.07].

Conclusions: ADC values cannot be used to discriminate between molecular subtypes of BC.

Introduction

Magnetic resonance imaging (MRI) has become a cornerstone for the diagnosis of breast cancer (BC) [1-4]. It has the highest sensitivity of all imaging modalities but is confronted with lacks in specificity [5]. To overcome this shortcoming, Diffusion-weighted imaging (DWI) was additionally introduced into the MRI protocol, which is a functional imaging modality based upon Brownian water movement in tissues [6, 7]. This sequence is directly correlated with cell density of tumors, which was utilized in several tumor entities with very promising results around oncology [7].

So, it was identified that benign breast tumors have significant higher apparent diffusion coefficients (ADC) than malignant tumors with a proposed threshold of 1.0 $x10^{-3}$ mm^2/s in a recent meta analysis [8]. Yet, diagnostic shortcomings were reported for discrimination of breast cancer subtypes with no clear significant differences of ADC values [9]. These results were predominantly reported by single center studies with different scanner technology and partial inconclusive results.

However, it would be crucial to discriminate different BC subtypes based upon the receptor status, as prognosis and treatment options differ substantially between types [10, 11]. So, Her2-enriched BC has a worse prognosis compared to hormone receptor positive types (Luminal A and B) but can be treated by Her2-targeted antibody therapy [12]. In clinically routine, the receptor status is defined by immunohistochemical stainings on bioptic specimen [11]. Yet, there might be possible clinical benefit by imaging defined BC receptor status as multifocal lesions or metastasized lesions can differ in receptor status [13]. This would result in different clinical decision making based upon functional imaging.

Therefore, the purpose of the present analysis was to systematically review the published literature regarding ADC values of BC in accordance to molecular subtype and perform a meta analysis to establish, whether ADC values can discriminate BC subtypes or not.

Methods

Search strategy and selection criteria

MEDLINE library and SCOPUS databases were screened for the associations between ADC values and BC up to April 2020.

The following search words were used: “DWI or diffusion weighted imaging or diffusion-weighted imaging or ADC or apparent diffusion coefficient AND breast cancer OR breast carcinoma”. Secondary references were also manually checked and recruited.

The primary endpoint of the systematic review was association between molecular subtype of BC and ADC values.

Studies (or subsets of studies) were included, if they satisfied all the following criteria: (1) patients with BC confirmed by histopathology, (2) pretreatment MRI with DWI and (3) reported mean and standard deviation of the ADC values.

Exclusion criteria were (1) reviews, (2) case reports, (3) studies without data of pretreatment DCE MRI, (4) studies with histopathology performed after treatment, (5) non-English language, and (6) experimental (xenograft or animals model) studies.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was used for the analysis [14]. The paper acquisition is summarized in figure 1.

In total, 28 studies were suitable for the analysis and included into the present study [15-42].

Quality-Assessment

The methodological quality of the acquired studies was independently evaluated by two readers (A.S. and H.J.M.) using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) instrument [43]. Results of QUADAS-2 assessments are shown in figure 2.

Statistical analysis

The meta analysis was performed using RevMan 5.3 (2014; Cochrane Collaboration, Copenhagen, Denmark). Heterogeneity was calculated by means of the inconsistency index I^2 [44, 45]. Finally, DerSimonian and Laird [46] random-effect models with inverse-variance weights were performed without any further correction.

Results

Risk of bias

Patient selection was generally well defined within the respective methodology; however, several studies did not report the inclusion criteria clearly which can account for potential bias.

All studies clearly reported methodology of the index test and were accordingly not considered a significant source of potential bias. All studies had as reference test the histopathology with immunohistochemical staining.

The acquired 28 studies comprised a total of 2990 BC. Of the included studies, 6 (21.4%) were of prospective and 22 (78.6%) of retrospective design. Different 1.5T scanners were used in 6 (21.4%) studies and 3T scanners in 20 (71.5%) studies and in 2 studies 1.5 and 3 T scanners were utilized (7.1%). Regarding b-values, most studies (n=19, 67.9%) used b-values 0 and 800 s/mm² or higher. In 3 studies (10.7%) b values 0 and 750 s/mm² and in 2 studies (7.1%) b values 0 and 600 s/mm² were used.

Luminal A type was diagnosed in 865 cases (28.9%), Luminal B in 899 cases (30.1%), Her-2 enriched in 597 cases (20.0%) and triple negative in 629 cases (21.0%).

The mean ADC value of the Luminal A type was 0.99×10^{-3} mm^2/s [95% CI 0.94-1.04, Tau²=0.01, Chi²=310.71, df=14, I²= 95%], of the Luminal B type was 0.99×10^{-3} mm^2/s [95% CI 0.89-1.05, Tau²=0.02, Chi²=715.49, df=12, I²= 98%], of Her 2-enriched type was 1.02×10^{-3} mm^2/s [95% CI 0.95-1.08, Tau²=0.02, Chi²=641.08, df=22, I²= 97%] and of the triple negative type was 0.99×10^{-3} mm^2/s [95% CI 0.91-1.07, Tau²=0.03, Chi²=962.41, df=20, I²= 98%] (figure 3). Figure 4 displays these results as a box plot graph. The ADC values of the BC groups overlapped significantly with no clear proposed threshold to distinguish between types.

Discussion

According to the present analysis, there were no differences of ADC values between the investigated BC types. Therefore, ADC cannot predict hormone receptor status of BC. This finding is very important.

The clinical importance of different BC molecular subtypes is without any questioning [10]. There are distinctive differences in prognosis and therapy in accordance to BC immunohistochemical subtype [10]. So, the BC type with expression of estrogen and progesterone receptors and low expression of proliferation marker Ki 67, namely Luminal A type, has the best prognosis with a 5-years overall survival rate of 95.1% to 78.5% of triple negative type [10, 47]. This is also caused by the possibility of endocrine hormone therapy as a treatment option. Luminal B type is defined by the presence of estrogen and progesterone receptors with additionally a high proliferation rate compared to Luminal A. Her2-enriched type is defined by the expression of the oncogene human epidermal growth factor receptor, which stimulates proliferation and inhibits apoptosis [48]. Importantly, it can be targeted by an antibody

treatment, namely trastuzumab, which shows the utter importance of this receptor [48]. Lastly, the triple negative type is defined by the absence of any of these receptors, resulting in the worst prognosis and limited treatment options [10].

Previously, it was shown that ADC values are associated with cellularity and tumor microstructure [6]. Beyond sole cellularity, ADC values are associated with important histopathology parameters, reflecting proliferation potential (Ki 67) and tumor suppressor genes p53 [49, 50]. However, some immunohistochemical features of angiogenesis were not associated with ADC values [51]. In short, there is ongoing debate which features of tumors can be predicted by imaging.

There are inflicting published results regarding, whether ADC values can also reflect immunohistochemical features in BC. So, in some single center studies, there were reports that Her2-positive tumors have slightly higher ADC values compared to negative tumors [52]. However, Choi et al. could not identify an influence of the Her 2 status on the ADC values [53]. In another study by Montemezzi et al., Luminal A type showed the highest ADC values compared to all other subtypes (0.924 × 10−3± 0.033 mm2/s) [34]. According to other authors, triple negative type showed the highest ADC values [25, 38]. In a first multi center study comprising 661 patients, no significant differences were reported between BC subtypes corroborated by the present results [9].

Presumably, the reported differences in previous investigations were caused by different scanner technology, measurement, and patient samples. For example, it is a known fact that mucinous carcinoma alone has distinctive higher ADC values due to the histopathology which seems to be more important than the immunohistochemical subtype [54].

So, the present analysis can harmonize these reported differences that no significant differences of ADC values between molecular subtypes of BC can be assumed.

ADC values are reflective of tumor microstructure with a moderate inverse correlation of the cellularity of tumors [6-9]. Presumably, the histopathologic differences of the molecular subtypes are not strong enough that they can be reliably predicted by DWI.

There are other reports highlighting the importance of necrosis on ADC values which was the only independent influencing factor of the ADC values [27]. These relationships resulted in the highest ADC values of the triple negative type because of the high rate of necrosis.

Our results are also in accordance with a recently published meta analysis suggesting that ADC cannot predict outcome to neoadjuvant radiochemotherapy of BC [55].

Yet, there is clear evidence that ADC values can aid in the discrimination between benign and malignant tumors which was shown in a recent meta analysis [56]. So, ADC values can nevertheless aid in important clinical decision making despite the present negative results.

There are some inherent limitations of the present study to address. Firstly, the meta- analysis is based upon published results in the literature. There might be a certain publication bias because there is a trend to report positive or significant results; whereas studies with insignificant or negative results are often rejected or are not submitted. Secondly, there is the restriction to published papers in English language. Thirdly, the study investigated the widely used DWI technique using 2 b-values. However, more advanced MRI sequences, such as intravoxel incoherent motion and diffusion kurtosis imaging might show a better accuracy in discriminating BC phenotypes [57, 58]. Yet, there are few studies using these sequences and thus no comprehensive analysis can be made.

Conclusions

The present systematic review and meta analysis identified that ADC values cannot discriminate immunohistochemical molecular subtypes of BC. Therefore, ADC values cannot provide histopathological information in this regard.

Declarations

- **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

- **Competing interests**

The authors declare that they have no competing interests

- **Funding**

none

- **Authors' contributions**
- **AS, HJM, AW** made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data;

- **AS, AW** were been involved in drafting the manuscript or revising it critically for important intellectual content;
- **AS, 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.

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none

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Figures

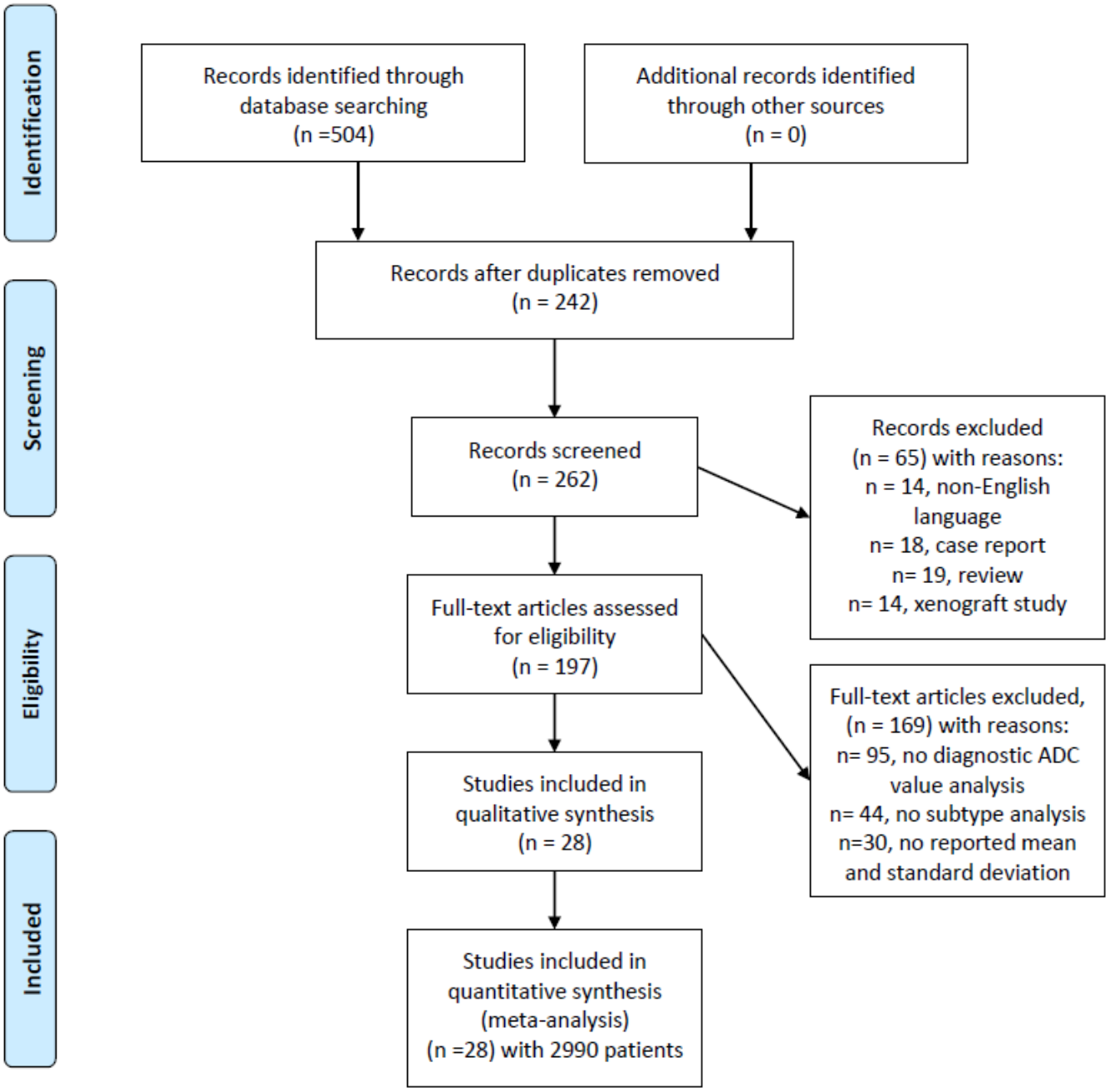

Figure 1

PRISMA flow chart. An overview of the paper acquisition. Overall, 28 studies with 2990 patients were suitable for the analysis.

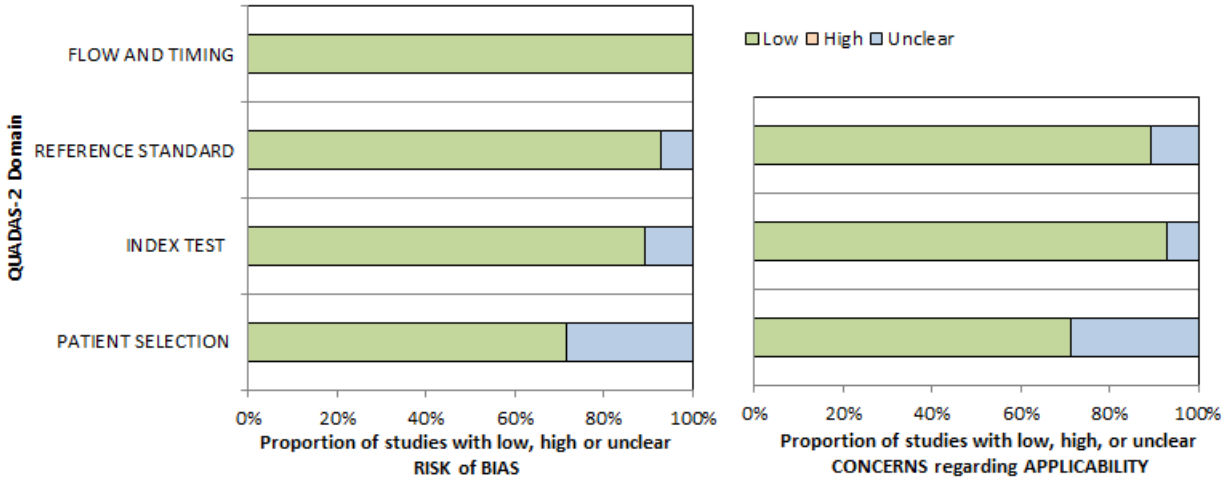

Figure 2

QUADAS-2 quality assessment of the included studies. Most studies showed a low risk of bias.

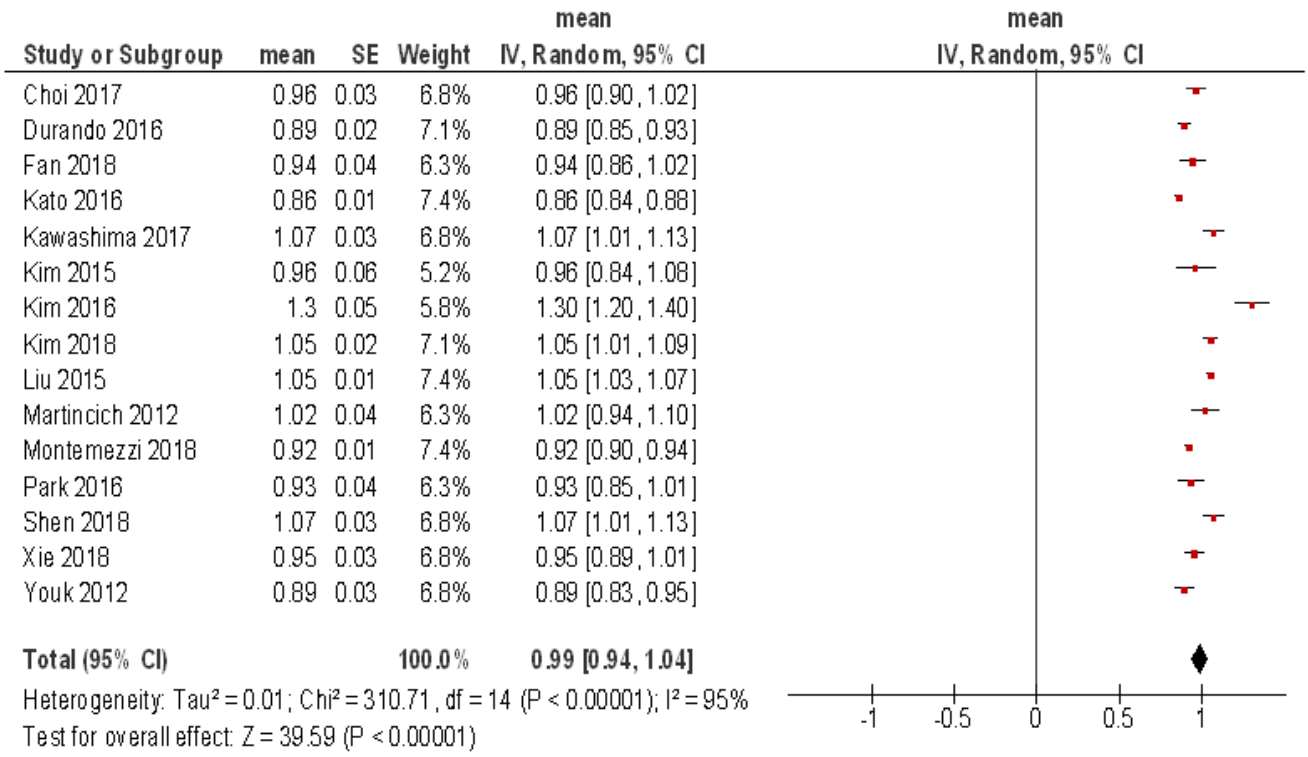

Figure 3

Forrest plots of the mean ADC values of the Luminal A type. The pooled mean ADC value was 0.99 × 10−3 mm2/s [95% CI 0.94-1.04, Tau²=0.01, Chi²=310.71, df=14, I²= 95%].

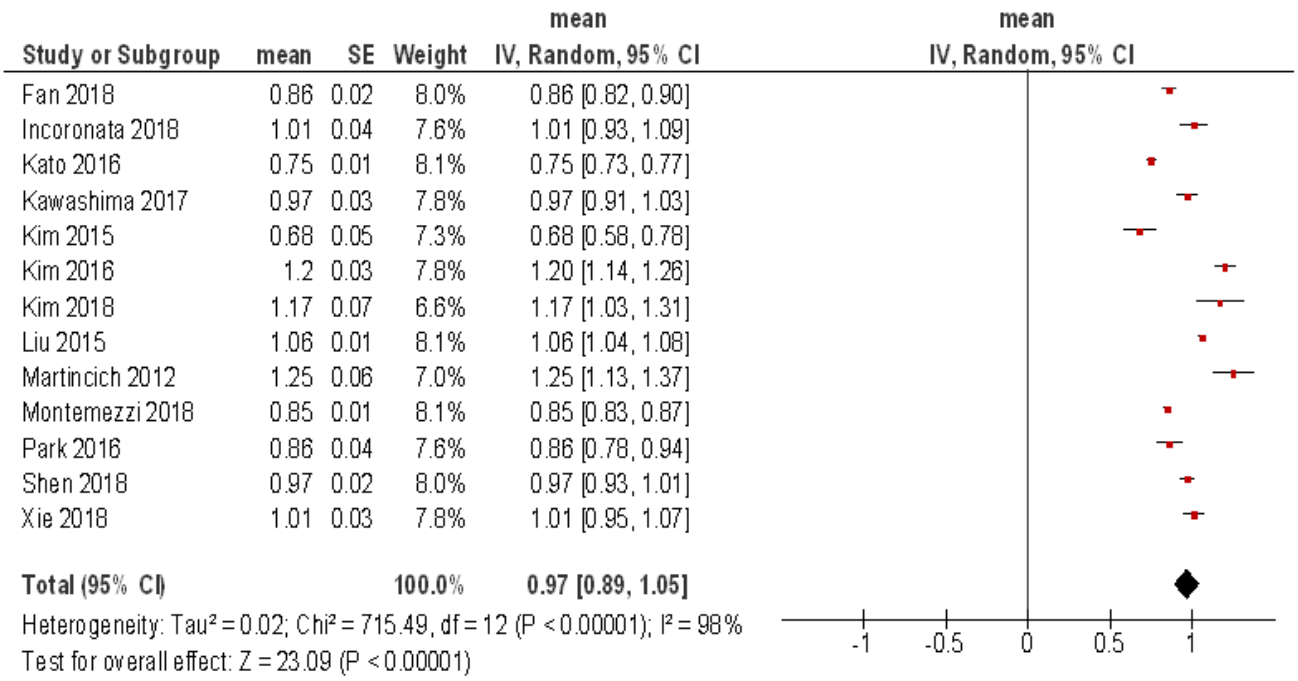

Figure 4

Forrest plots of the mean ADC values of the Luminal B type. The pooled mean ADC value was 0.99 × 10−3 mm2/s [95% CI 0.89-1.05, Tau²=0.02, Chi²=715.49, df=12, I²= 98%].

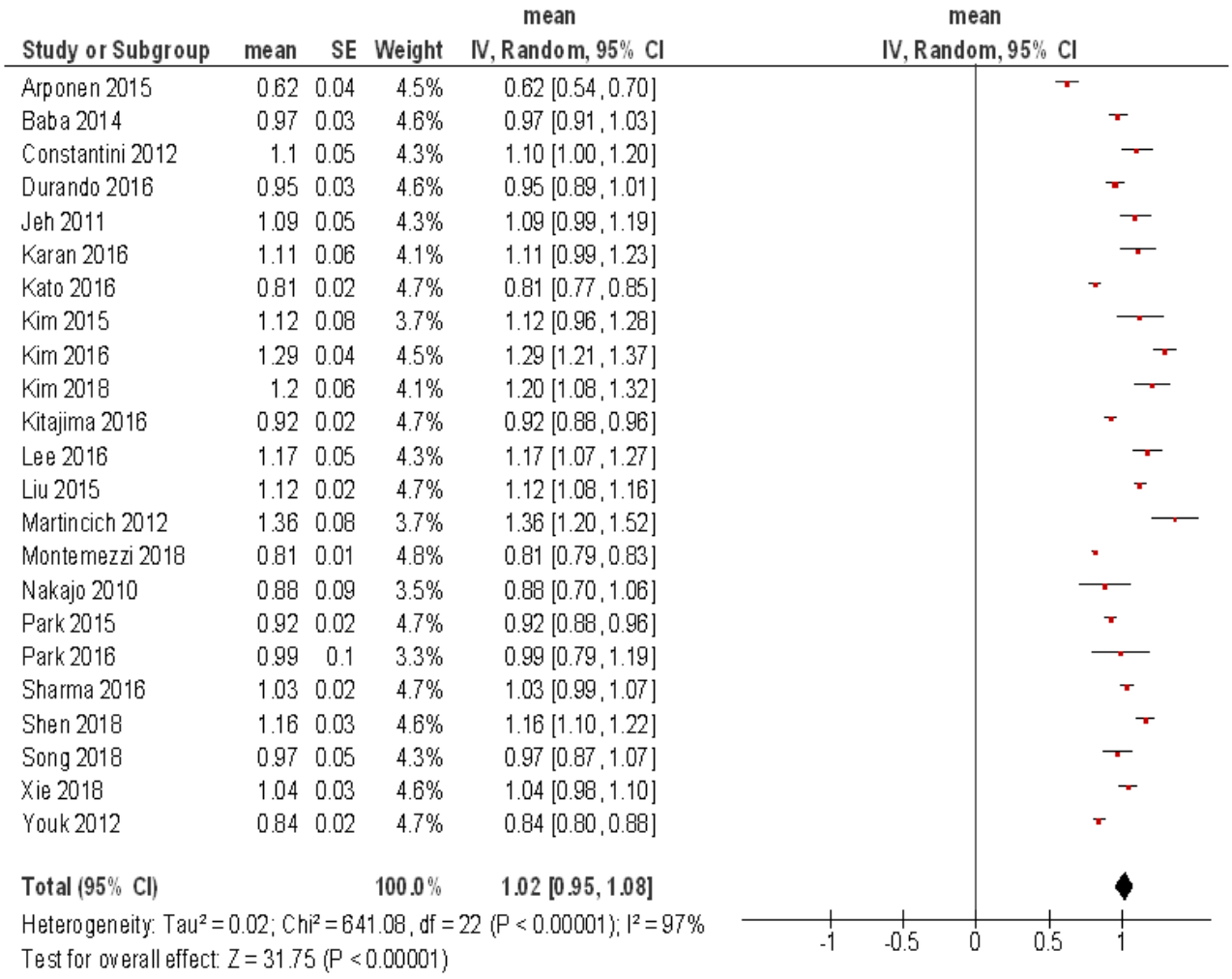

Figure 5

Forrest plots of the mean ADC values of the Her 2-enriched type. The pooled mean ADC value was 1.02 × 10− 3 mm2/s [95% CI 0.95-1.08, Tau²=0.02, Chi²=641.08, df=22, I²= 97%].a

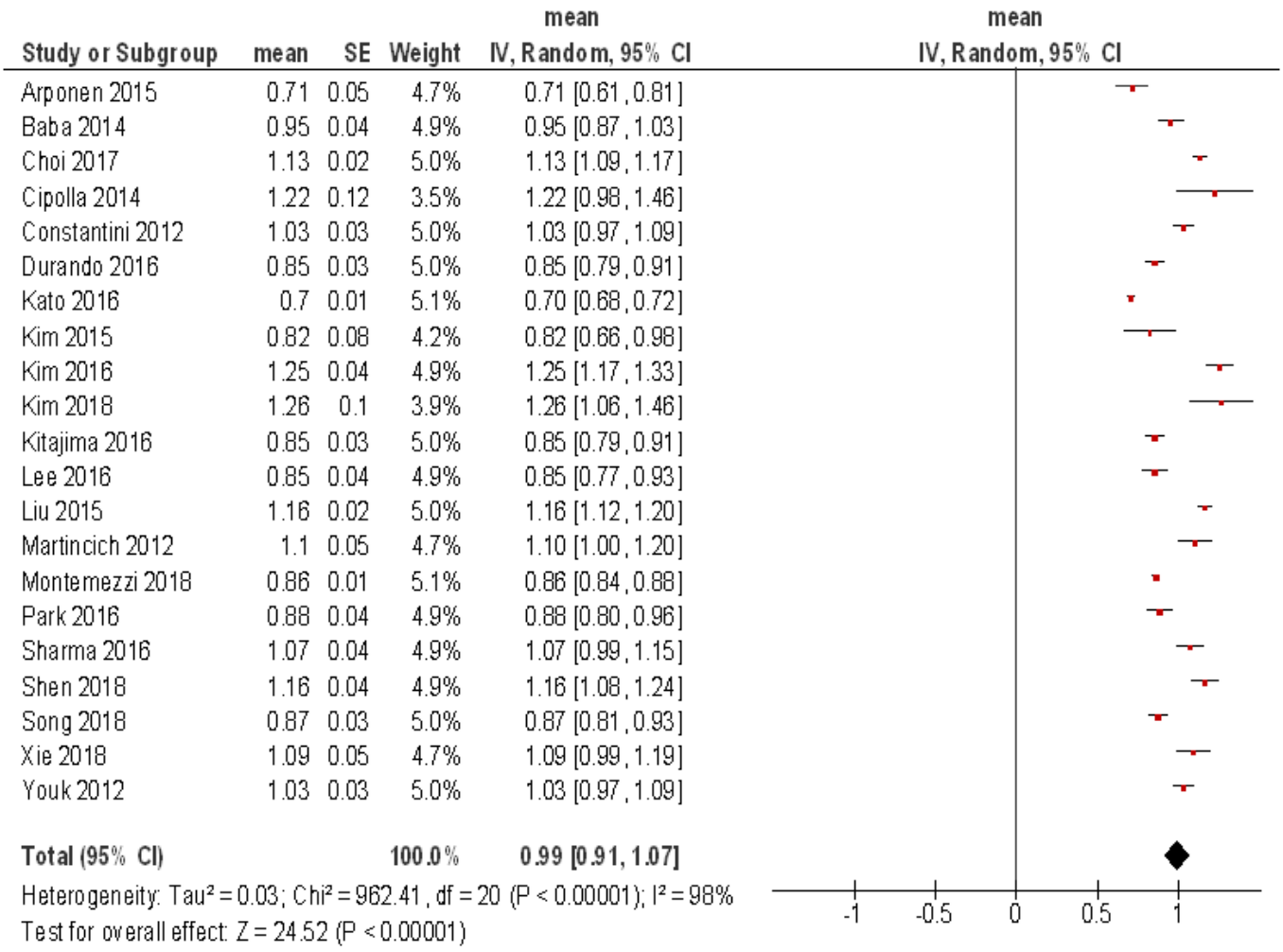

Figure 6

Forrest plots of the mean ADC values of the triple negative type. The pooled mean ADC value was 0.99 × 10− 3 mm2/s [95% CI 0.91-1.07, Tau²=0.03, Chi²=962.41, df=20, I²= 98%].

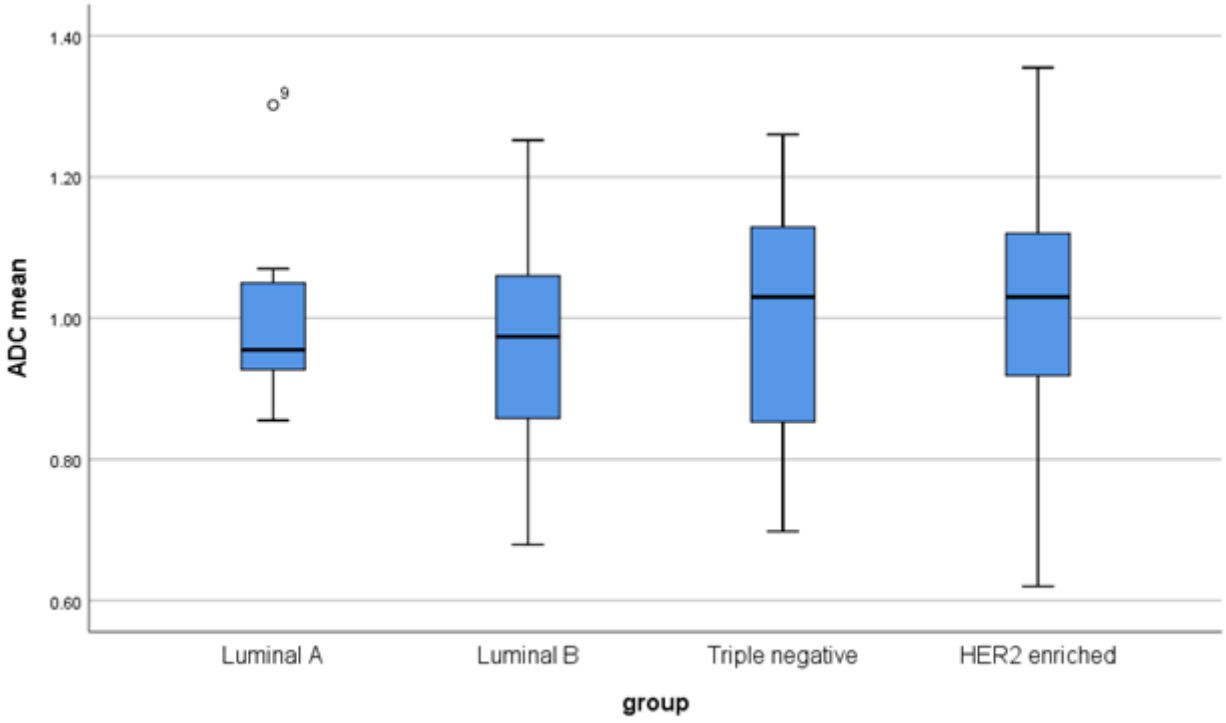

Figure 7

Box plots of the mean ADC values in accordance to the BC molecular subtype. The ADC values of the BC groups overlapped significantly with no clear threshold value to distinguish between subtypes.