Digestive Diseases

Small and Large Bowel: Systematic Review and Meta-Analysis

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Pretreatment Apparent Diffusion Coefficient Cannot Predict Histopathological Features and Response to Neoadjuvant Radiochemotherapy in Rectal Cancer: A Meta-Analysis

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Keywords
Rectal cancer · Diffusion-weighted imaging · Aapparent diffusion coefficient · Magnetic resonance imaging

Abstract
Aim: Our purpose was to perform a systemic literature review and meta-analysis regarding use of apparent diffusion coefficient (ADC) for prediction of histopathological features in rectal cancer (RC) and to prove if ADC can predict treatment response to neoadjuvant radiochemotherapy (NARC) in RC. ***Methods:*** MEDLINE library, EMBASE, Cochrane, and SCOPUS database were screened for associations between ADC and histopathology and/or treatment response in RC up to June 2020. Authors, year of publication, study design, number of patients, mean value, and standard deviation of ADC were acquired. The methodological quality of the collected studies was checked according to the Quality Assessment of Diagnostic Studies instrument. The meta-analysis was undertaken by using the RevMan 5.3 software. DerSimonian and Laird random-effects models with inverse-variance weights were used to account the heterogeneity between the studies. Mean ADC values including 95% confidence intervals were calculated. ***Results:*** Overall, 37 items (2,015 patients) were included. ADC values of tumors with different T and N stages and grades overlapped strongly. ADC cannot distinguish RC with a high- and low-carcinoembryonic antigen level. Regarding KRAS status, ADC cannot discriminate mutated and wild-type RC. ADC did not correlate significantly with expression of vascular endothelial growth factor and hypoxia-inducible factor 1a. ADC correlates with Ki 67, with the calculated correlation coefficient: –0.52. The ADC values in responders and nonresponders overlapped significantly. ***Conclusion:*** ADC correlates moderately with expression of Ki 67 in RC. ADC cannot discriminate tumor stages, grades, and KRAS status in RC. ADC cannot predict therapy response to NARC in RC.

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Introduction

Rectal cancer (RC) is one of the most frequent cancers worldwide and the second leading cause of oncologic-related mortality around the globe [1]. Magnetic resonance imaging (MRI) plays an important role in staging of RC [2, 3]. For instance, Faletti et al. [4] showed that MRI has a high accuracy for tumoral (T) staging in RC [3].

Furthermore, MRI can not only detect RC but also characterize tumors. Diffusion-weighted imaging (DWI) is a MRI technique based on measure of water diffusion in tissues, and water diffusion is quantified by apparent diffusion coefficient (ADC) [4]. ADC has been shown to inversely correlate with cell count and proliferation activity in benign and malignant lesions [5–7]. Typically, malignant tumors present a higher cell density than benign lesions. Therefore, malignant tumors have lower ADC values in comparison to benign lesions. In fact, ADC can discriminate benign and malignant colorectal lesions [8].

Some authors also indicated that ADC can provide information about immunohistochemical profiling of tumors. So far, ADC has been shown to correlate with expression of hypoxia-inducible factor (HIF)-1α and vascular endothelial growth factor (VEGF) in head and neck cancer [9]. In uterine cervical cancer, ADC predicts expression of epidermal growth factor receptor and histone 3 [10]. In RC, it has been published that ADC correlated with expression of Ki 67 [7]. Furthermore, ADC is also associated with expression of epidermal growth factor receptor [11].

Presumably, ADC can also predict treatment outcome in RC. However, the reported data are based on small number of tumors and, therefore, cannot be applied as evident.

The purpose of the present meta-analysis was to analyze associations between ADC and relevant histopathological features like tumor stage, grade, KRAS status, expression of Ki 67, VEGF, and HIF 1a in RC and to question if baseline tumoral ADC can predict response to neoadjuvant radiochemotherapy (NARC) in RC.

Methods

Data Acquisition

MEDLINE library, Cochrane, EMBASE, and SCOPUS databases were screened for associations between ADC parameters and histopathological features (tumor stage, grade, KRAS status, expression of Ki 67, level of carcinoembryonic antigen (CEA), vascular endothelial factor, and HIF 1a) in patients with RC up to June 2020 (Fig. 1). Furthermore, also articles regarding relationships between pretreatment ADC and response to NARC in RC were screened. The following search terms/combinations were used as follows:

"DWI or diffusion weighted imaging or diffusion-weighted imaging or ADC or apparent diffusion coefficient AND rectal cancer OR rectal carcinoma OR rectum cancer OR rectum carcinoma." In addition, secondary references were manually checked. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement was used for the research [12].

The primary search identified 2,218 records in PubMed (1,016 records), Cochrane database (n = 8), Scopus database (n = 1,194), and EMBASE database (n = 865). After exclusion of duplicate articles, the abstracts of the remaining 217 items were analyzed according to the following inclusion criteria:

- Data derived from DWI;
- Available mean and standard deviation values of ADC;
- Original studies investigated humans;
- English language.

The following articles were excluded from the analysis:

- Studies unrelated to the research subjects;
- Studies with incomplete data;
- Non-English language;
- Experimental animals and in vitro studies;
- Review, meta-analysis, and case report articles.

Overall, 180 articles were excluded from the analysis, and 37 items meet the inclusion criteria [13–49]. The following data were extracted from the literature: authors, year of publication, study design, number of patients, mean value, and standard deviation of ADC. For analysis of correlation between ADC and histopathological features, a pooled Spearman's correlation coefficient was calculated. The reported Pearson correlation coefficients in some studies were converted into Spearman correlation coefficients according to the previous description [50].

Meta-Analysis

On the first step, the methodological quality of the included 38 studies was checked according to the Quality Assessment of Diagnostic Studies instrument [51] by one observer (A.S.) (Fig. 2). On the second step, the reported DWI values (mean and standard deviation) were acquired. On the third step, 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 [52, 53]. 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 [54] to account for the heterogeneity between the studies. Mean ADC values including 95% confidence intervals were calculated separately for different tumor subgroups.

Results

Studies and Patients

Of the included 37 studies, 20 were retrospective and 17, prospective. In most studies (n = 26, 70%), different 3 T scanners were used. In the remaining 11 studies (30%), MRI was performed on several 1.5 scanners.

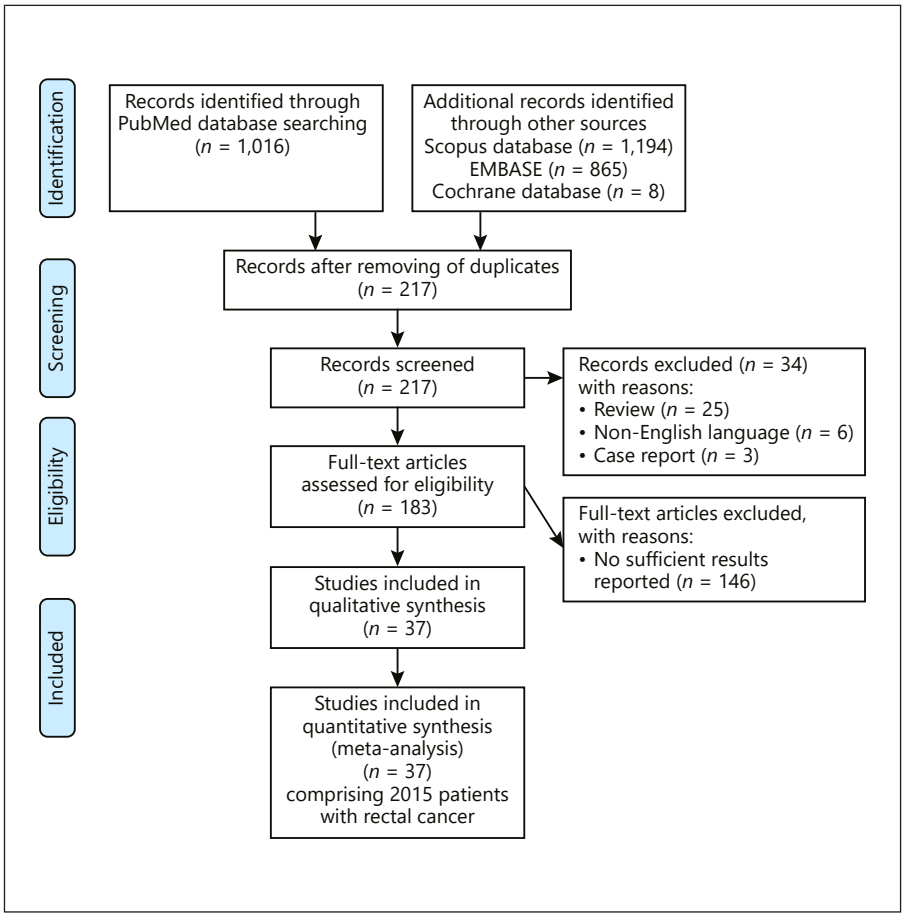


Fig. 1. PRISMA flowchart of the data acquisition.

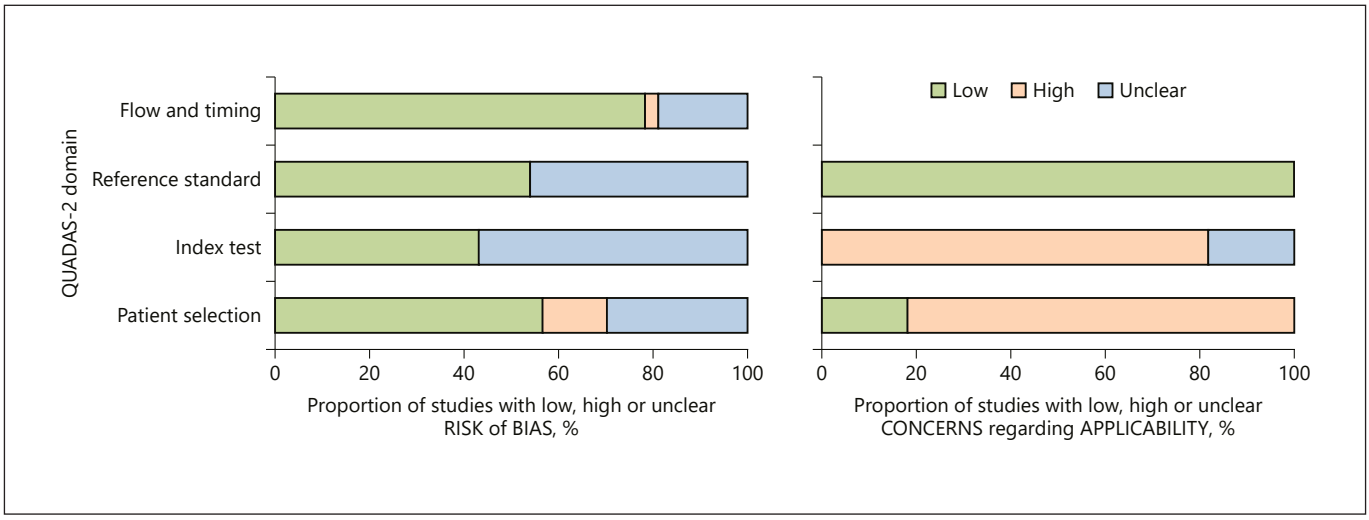
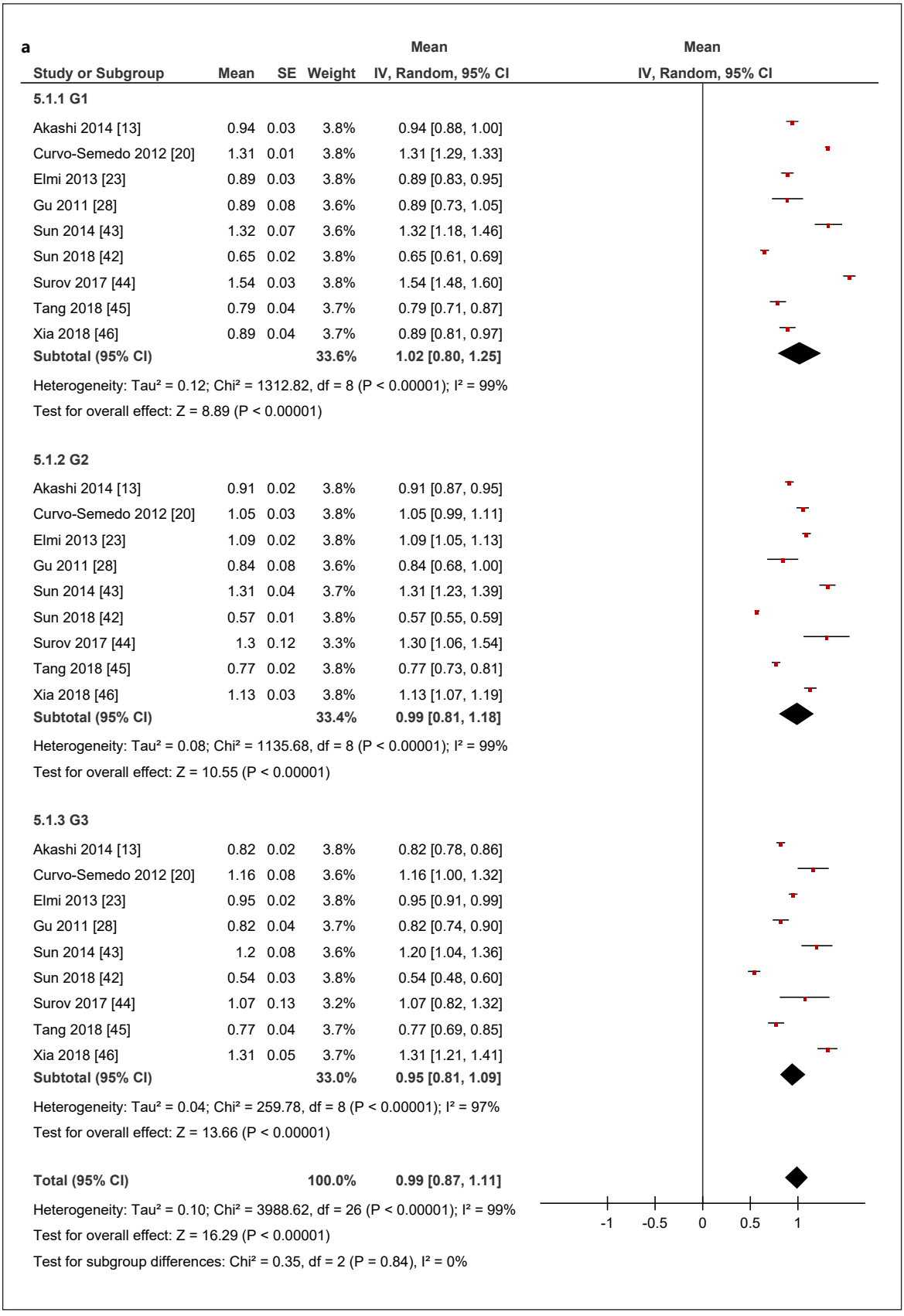


Fig. 2. QUADAS-2 quality assessment of the included studies.



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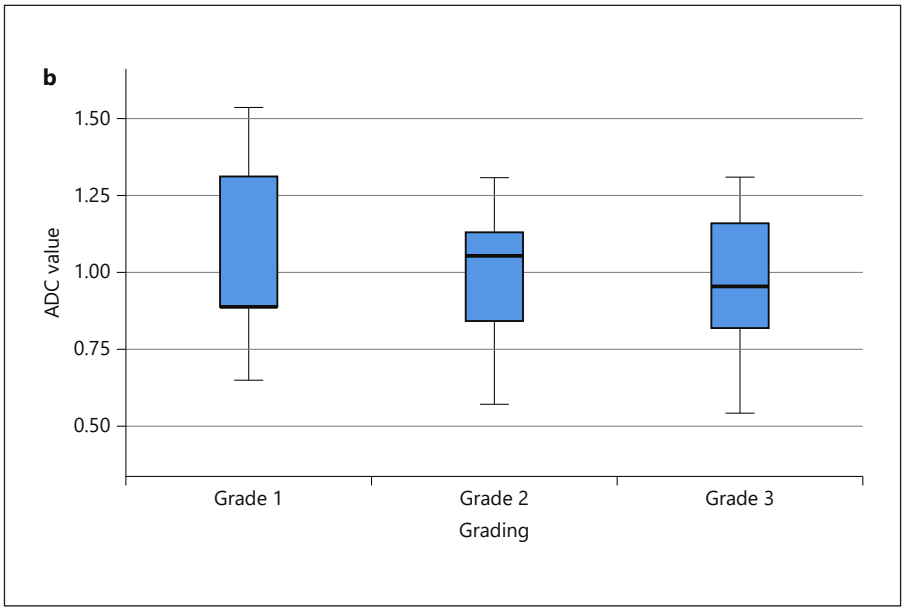


Fig. 3. a Forest plots of ADC values reported for RCs with different tumor grades. **b** Graphical distribution of ADC values of RCs with different tumor grades. ADC, apparent diffusion coefficient; RC, rectal cancer; CI, confidence interval.

For risk of bias, the quality was variable across each domain. In the patient selection domain, 21 were judged to be at low risk, 5 were considered high risk, and 11 were unclear in risk. In the index test domain, 17 studies were considered low risk, and 20 studies were unclear in risk. For the reference standard domain, 21 were considered low risk, and 16 studies were unclear in risk. In the domain flow and timing, 29 studies had low risk, 2 studies had high risk, and 4 studies had unclear risk.

The acquired 37 studies comprised a total of 2,015 patients with RC. There were 1,142 men and 607 women. In 266 patients, the gender was not given. The calculated mean age of the patients was 60.5 years, range, 49.5–72 years.

ADC Values and Tumor Grades

Associations between tumor grade and ADC were reported in 9 studies (477 patients) [13, 20, 23, 28, 42–46]. Grade 1 tumors were identified in 75 cases (15.7%), grade 2 in 321 patients (67.3%), and grade 3 in 81 cases (17%). The calculated mean ADC values ($\times 10^{-3}$ mm^2/s) of RC were 1.02, 95% confidence interval (CI) (0.80, 1.25) for grade 1 lesions, 0.99, 95% CI (0.81, 1.18) for grade 2, and 0.95, 95% CI (0.81, 1.09) for grade 3 carcinomas (Fig. 3a).

The graphical distribution of ADC in different tumor grades is shown in Figure 3b. ADC values of the tumors with diverse differentiating overlapped strongly.

ADC Values and T Stage

Relationships between different tumor stages and ADC values were reported in 6 studies (352 patients) [14, 40, 43–46]. There were 29 patients (8.2%) with T1 stage, 141 patients (40.1%) with T2 stage, 145 patients (41.2%) with T3 stage, and 37 patients (10.5%) with T4 stage.

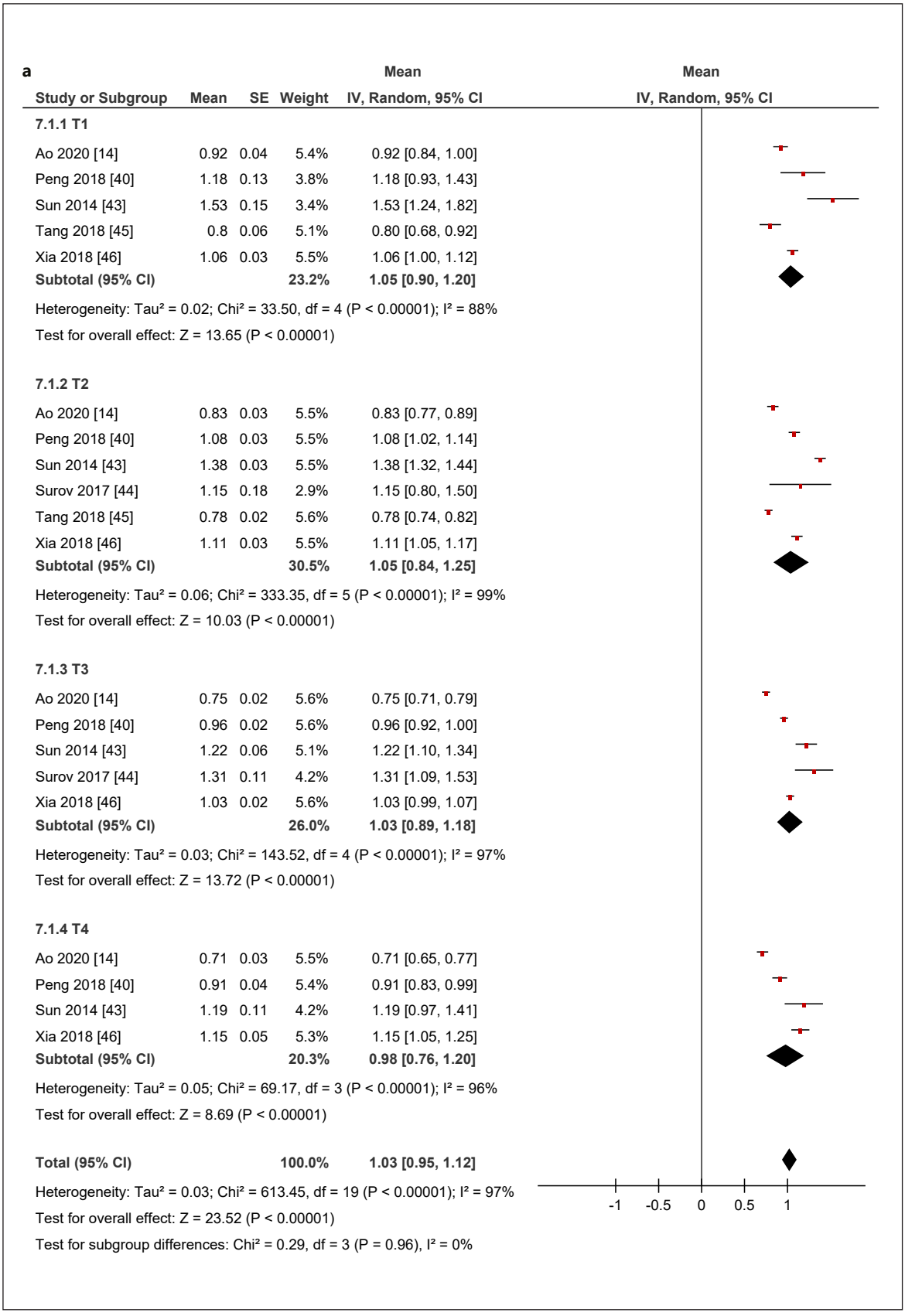
The calculated mean ADC values ($\times 10^{-3}$ mm^2/s) of tumors were as follows: 1.05, 95% CI (0.90, 1.20) in T1 tumors, 1.05, 95% CI (0.84, 1.25) in T2 tumors, 1.03, 95% CI (0.89, 1.18) in T3 tumors, and 0.98, 95% CI (0.76, 1.20) in T4 tumors (Fig. 4a). The graphical distribution of ADC in different tumor grades is shown in Figure 4b.

ADC Values and N Stage

ADC values in RC with different N stages were reported in 8 studies (402 patients) [13, 20, 23, 36, 42–45]. N0 stage was identified in 188 cases (46.8%), and N+ stage was found in 214 patients (53.2%). The calculated mean ADC value ($\times 10^{-3}$ mm^2/s) of RC with N0 stage was 0.98, 95% CI (0.84, 1.11). It was 0.92, 95% CI (0.80, 1.05) for RC with N+ stage (Fig. 5a). Figure 5b shows the graphical distribution of ADC values in N0 and N+ tumors.

ADC Values and CEA Level

Comparison of ADC values between tumors with different levels of pretreatment CEA was performed in



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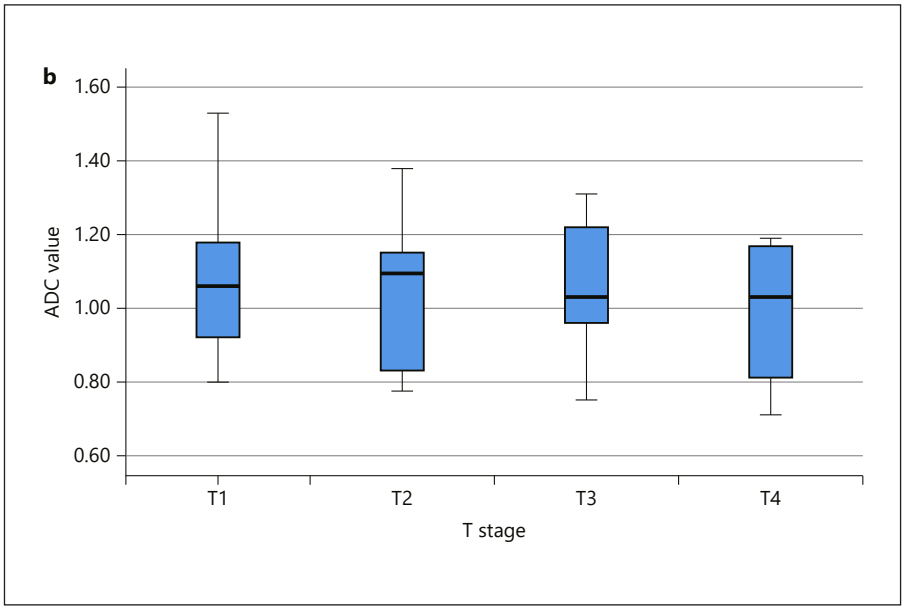


Fig. 4. a Forest plots of ADC values reported for RCs with different tumor stages. **b** Graphical distribution of ADC values of RCs with different tumor stages. ADC, apparent diffusion coefficient; RC, rectal cancer; CI, confidence interval.

6 studies (339 patients) [13, 20, 23, 42, 43, 46]. RC with a CEA level under 5 ng/mL (n = 209, 61.7%) had a calculated mean ADC value ($\times 10^{-3}$ mm^2/s) of 0.97, 95% CI (0.82, 1.13) (Fig. 6a). It was 0.93, 95% CI (0.77, 1.09) in RC with a CEA level >5 ng/mL (n = 130, 38.3%). ADC values of the tumors with different CEA levels overlapped strongly (Fig. 6b).

ADC and Histopathological Markers in RC

Three studies (274 patients) analyzed associations between ADC values and KRAS status in RC [19, 32, 47]. Mutated RC (n = 124, 45.3%) had the calculated mean ADC value ($\times 10^{-3}$ mm^2/s) of 1.12, 95% CI (0.93, 1.30) (Fig. 7a). Wild-type RC (n = 150, 54.7%) had the calculated mean ADC value ($\times 10^{-3}$ mm^2/s) of 1.24, 95% CI (1.03, 1.33).

In 4 studies with 234 patients, associations between ADC and the proliferation marker Ki 67 were analyzed [14, 38, 43, 44]. The calculated pooled correlation coefficient was −0.52, 95% CI (−0.69, −0.35) (Fig. 7b).

Furthermore, in 2 studies (102 patients) correlation between ADC and expression of VEGF was studied [38, 44]. The calculated pooled correlation coefficient was −0.08, 95% CI (−0.60, 0.44) (Fig. 7c).

Finally, in 2 studies (102 patients) correlation between ADC and expression of HIF 1a was analyzed [38, 44]. The calculated pooled correlation coefficient was −0.07, 95% CI (−0.63, 0.50) (Fig. 7d).

ADC Values and Response to NARC

In 21 studies, comprising pretreatment ADC values (mean and standard deviation) were reported in regard to therapy response. Egger's test revealed a significant publication bias (p < 0.001) among these studies (Fig. 8).

The collected 21 articles contained 964 patients. Of the 964 patients, 380 (35.6%) were reported as responders and 584 (64.4%) as nonresponders to the NARC. The pooled calculated pretreatment mean ADC value of RC in responders was 0.96 (95% CI = [0.91; 1.01]) (Fig. 9a). In nonresponders, it was 1.04 (95% CI = [0.95; 1.12]) (Fig. 9a). Figure 8b shows the graphical distribution of ADC values in responders and nonresponders. The ADC values of the groups overlapped strongly.

On the next step, cumulative mean ADC values were calculated in dependence on scanner type (Tesla strength). Overall, 348 patients were investigated on 1.5 T scanners and 578 patients on 3.0 T scanners.

In the subgroup investigated by 1.5 T scanners, 150 patients were reported as responders and 198 patients as nonresponders to the NARC. In the subgroup investigated by 3.0 T scanners, 221 patients were reported as responders and 357 patients as nonresponders. The pooled calculated pretreatment mean ADC values of RC did not differ strongly between the subgroups (Fig. 10a, b).

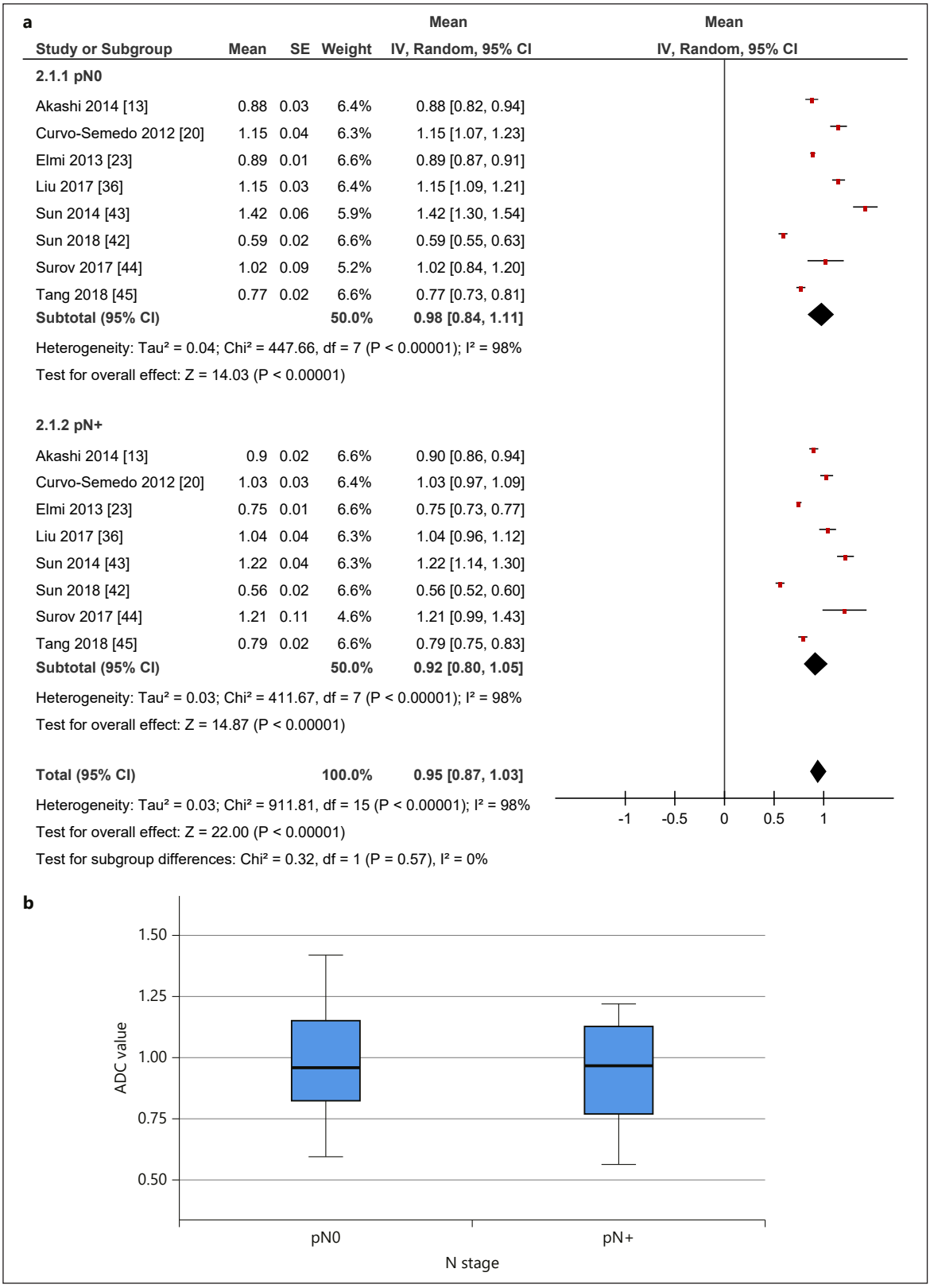


Fig. 5. a Forest plots of ADC values reported for RCs with different nodal stages. **b** Graphical distribution of ADC values of RCs with different nodal stages. ADC, apparent diffusion coefficient; RC, rectal cancer; CI, confidence interval.

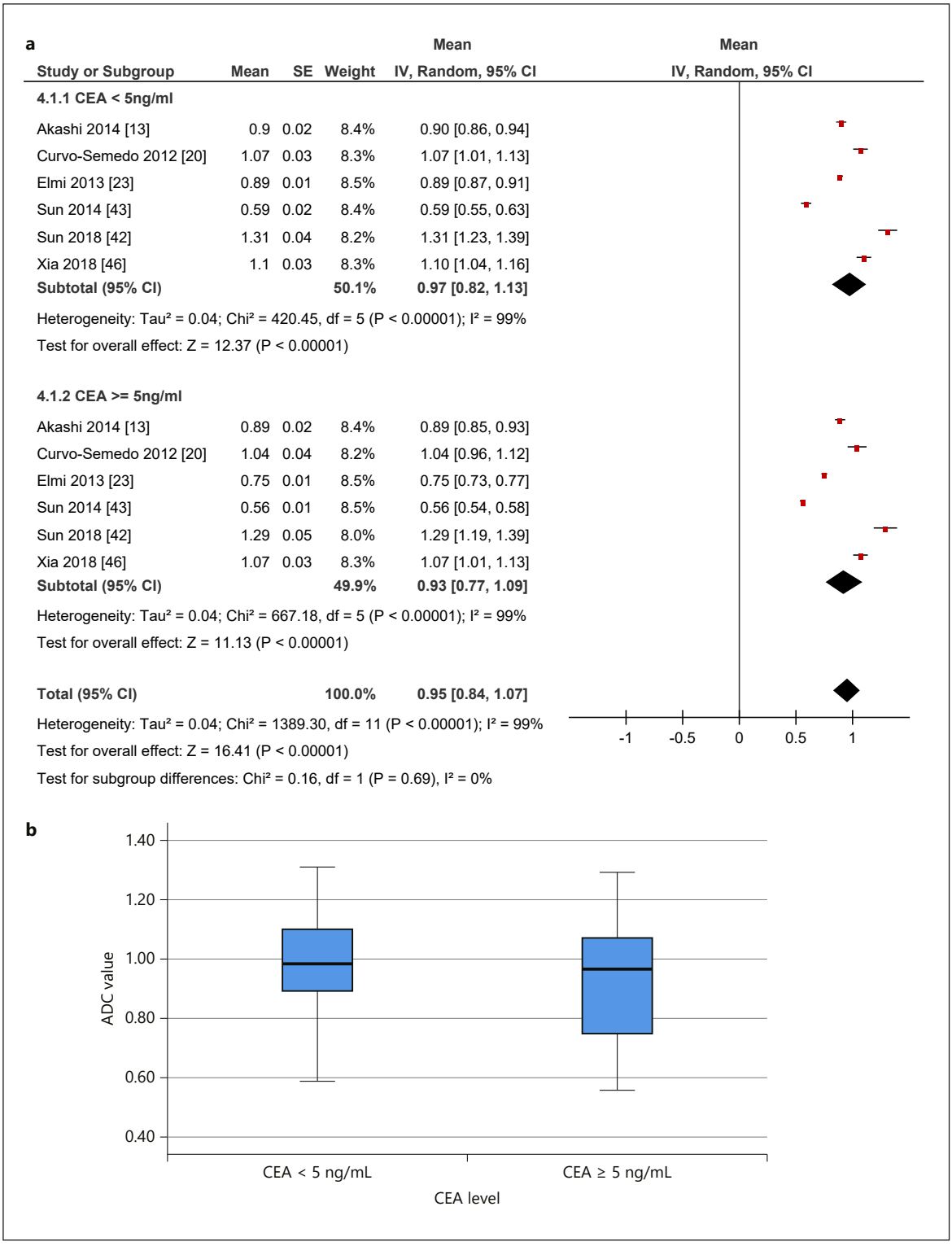
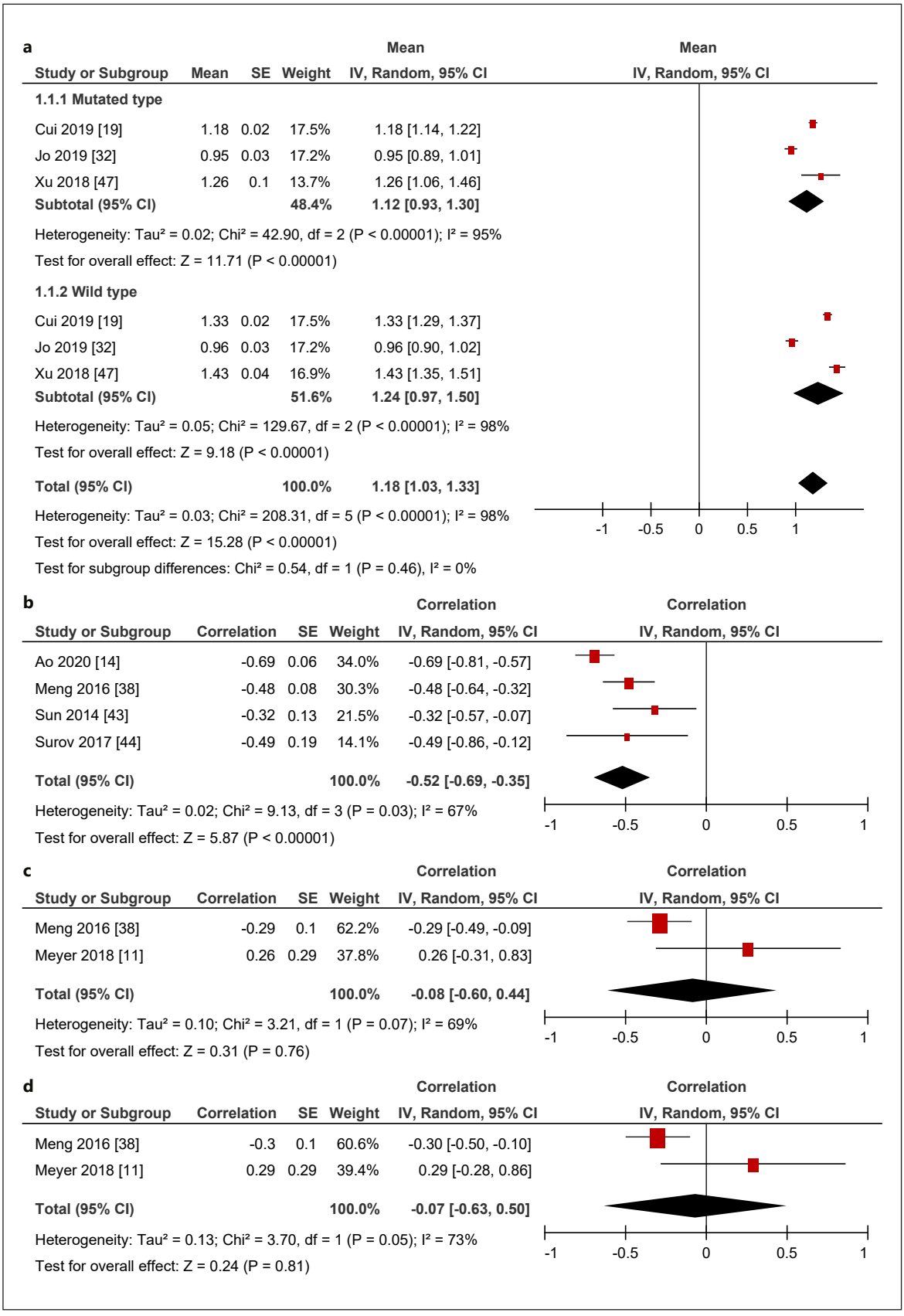


Fig. 6. a Forest plots of ADC values reported for RCs with different CEA levels. **b** Graphical distribution of ADC values of RCs with different CEA levels. ADC, apparent diffusion coefficient; RC, rectal cancer; CEA, carcinoembryonic antigen; CI, confidence interval.



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Discussion

The question of imaging, in particular DWI/ADC, can reflect histopathological features in oncology is very important. In fact, if so, then ADC can be recommended as surrogate markers for tumoral biology.

Previously, some reports suggested that ADC values can reflect tumor grade and stage in several tumors [55–57]. For example, in meningioma, ADC can discriminate benign and high-grade lesions [55]. Similar results were reported also for uterine cervical cancers [56]. In prostatic cancer, ADC correlates with the Gleason score [57]. Furthermore, more interestingly, ADC correlates also with presence/absence of nodal and distant metastases [58, 59]. So far, in breast cancer, some reports indicated that ADC values of nodal metastasized tumors were statistically significant lower in comparison with nonmetastasized tumors [58, 59].

In RC, however, the reported data are controversial. For instance, Akashi et al. [13] showed that mean tumor ADC values were different when comparing groups stratified by histologic differentiation grades (p = 0.0192). There was no significant difference in mean ADCs when stratifying patients according to CEA levels, T stage, N stage, and the presence of lymphangiovascular invasion [13]. Curvo-Semedo et al. [20] also found that mean tumor ADCs differed between the several groups of histological differentiation grades (p = 0.025). However, they mentioned that N0 versus N+ cancers had different ADC values (p = 0.011) [20]. In the study of Sun et al. [43], RC with different tumor differentiation did not show statistically significant differences of ADC values. Furthermore, higher T-stage values correlated with lower ADC values [43].

The present analysis provides evident data regarding relationships between ADC and histopathology in RC based on a large sample. Summarizing the published literature so far, this meta-analysis found no evidence to support that ADC values varied according to T and N stages, tumor grading, as well as KRAS mutation. Furthermore, ADC does not correlate with expression of VEGF and HIF 1a and does not correlate with CEA plasma level. Our findings suggest that ADC cannot predict relevant histopathological features in RC. ADC does correlate with proliferation index of Ki 67 only. Therefore, ADC cannot be used as a surrogate parameter for tumor histopathology in RC.

Independent on associations with histopathology, a key question is, if pretreatment ADC can predict response to NARC in RC or not. The possibility to stratify tumors regarding response to NARC is very important in clinical practice. This stratification may guide individualization of patient treatment in order to maximize therapeutic outcomes and minimize treatment toxicity. NARC often leads to excellent response. In fact, according to the literature, in approximately 24% of patients treated with NARC, no residual tumor tissue is present in the resection specimen (complete tumor response) [60]. Patients with complete response have a better prognostic outcome. Therefore, in these patients, organ-saving treatment may be applied [60–63]. Also, pretreatment selection of nonresponders to NARC is even very important.

The published data about the role of ADC in prediction of response to NARC are contradictory. While some authors found an association between pretreat-

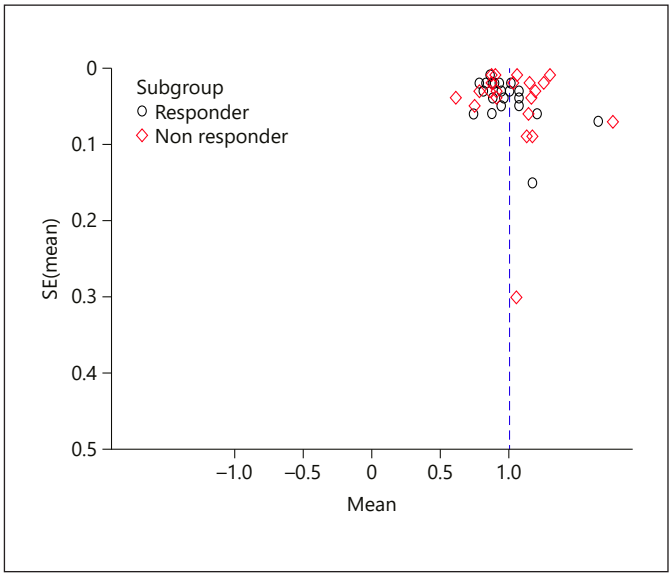
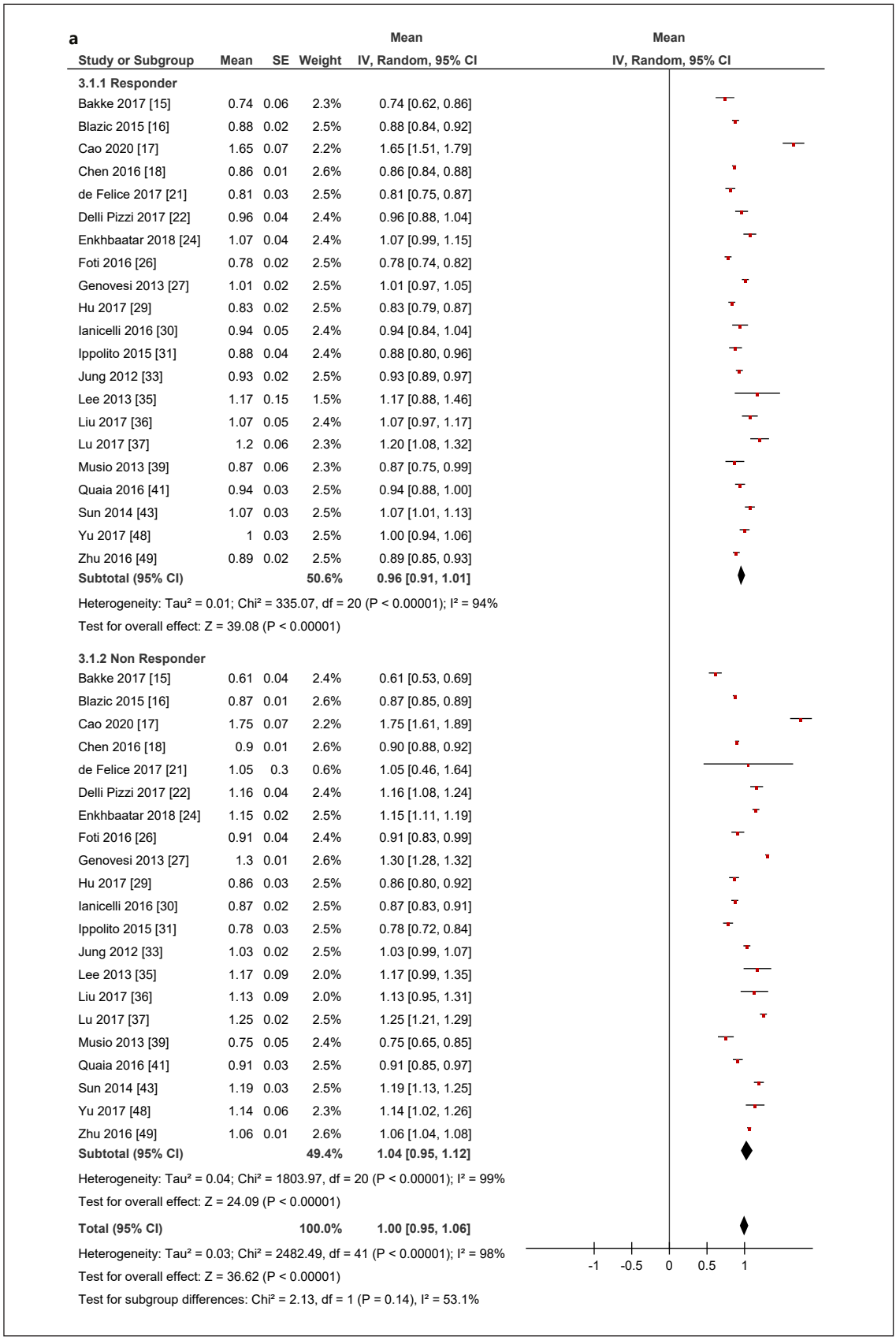


Fig. 8. Funnel plot of the publication bias (articles regarding apparent diffusion coefficient values in responders and nonresponders to neoadjuvant radiochemotherapy). Egger's test revealed a significant publication bias ($p < 0.001$).

Fig. 7. a Forest plots of ADC values reported for RCs with different KRAS status. **b** Forest plots of correlation coefficients between tumoral ADC values and expression of Ki 67. **c** Forest plots of correlation coefficients between tumoral ADC values and expression of VEGF. **d** Forest plots of correlation coefficients between tumoral ADC values and expression of HIF 1a. ADC, apparent diffusion coefficient; VEGF, vascular endothelial growth factor; HIF 1a, hypoxia-inducible factor 1a; CI, confidence interval; RC, rectal cancer.



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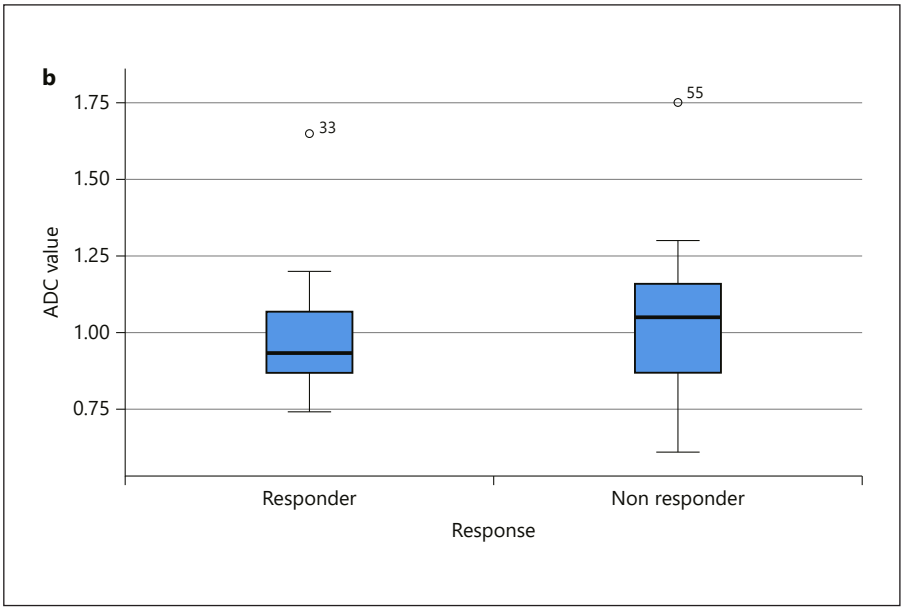

Fig. 9. a Forrest plots of ADC values reported for RCs responded and nonresponded to NARC. **b** Graphical distribution of ADC values of RCs responded and nonresponded to NARC. ADC, apparent diffusion coefficient; RC, rectal cancer; NARC, neoadjuvant radiochemotherapy.

ment ADC and pathologic response scores after NARC in RC, others did not.

The present analysis based on a large cohort shows that pretreatment DWI cannot predict treatment outcome in BC because baseline ADC values of responders to NAC and nonresponders did not differ and overlapped significantly. Furthermore, this result is independent from Tesla strength. Our finding is in agreement with those of Amedo et al. [64], who also showed that pretreatment ADC values did not differ significantly. Therefore, ADC does not play a prognostic role in patients with RC underwent NARC.

The present study has several limitations. It is based on published results in the literature with a known publication bias. Unfortunately, only a small number of studies met the inclusion criteria for this analysis, and several studies were excluded because some data, for example, ADC mean values and/or standard deviation were missing. Furthermore, only publications in English language were included. Therefore, the subgroups with analyses of associations between histopathological features like tumor stage, grade, and expression of relevant biomarkers include a small number of articles and small number of patients/tumors. Furthermore, different study designs, different MR techniques like Tesla strength, DWI sequences, and *b* values, and the use of different reference standards among studies are also limitations of the present analysis. Therefore, a high heterogeneity among the collected studies is shown in some subgroups. Also, some collected studies show high bias and/or are unclear in risk, especially for the domains patient selection and index test. Finally, publication bias is shown among the studies regarding associations between ADC and therapy response.

These facts may relativize our results. However, the identified methodological constellation represents a real clinical situation about data acquisition and technical details. Furthermore, the results of the present meta-analysis are based on a large cohort and provide evident data regarding the current state of ADC in RC.

ADC correlates moderately with expression of Ki 67 in RC. ADC cannot discriminate tumor stages, grades, and KRAS status in RC. ADC cannot predict therapy response to NARC in RC.

Statement of Ethics

All the procedures in the study involving human material and data were performed in accordance with World Medical Association's Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Subject. Patients' informed consent and Ethical Committee approval were not needed.

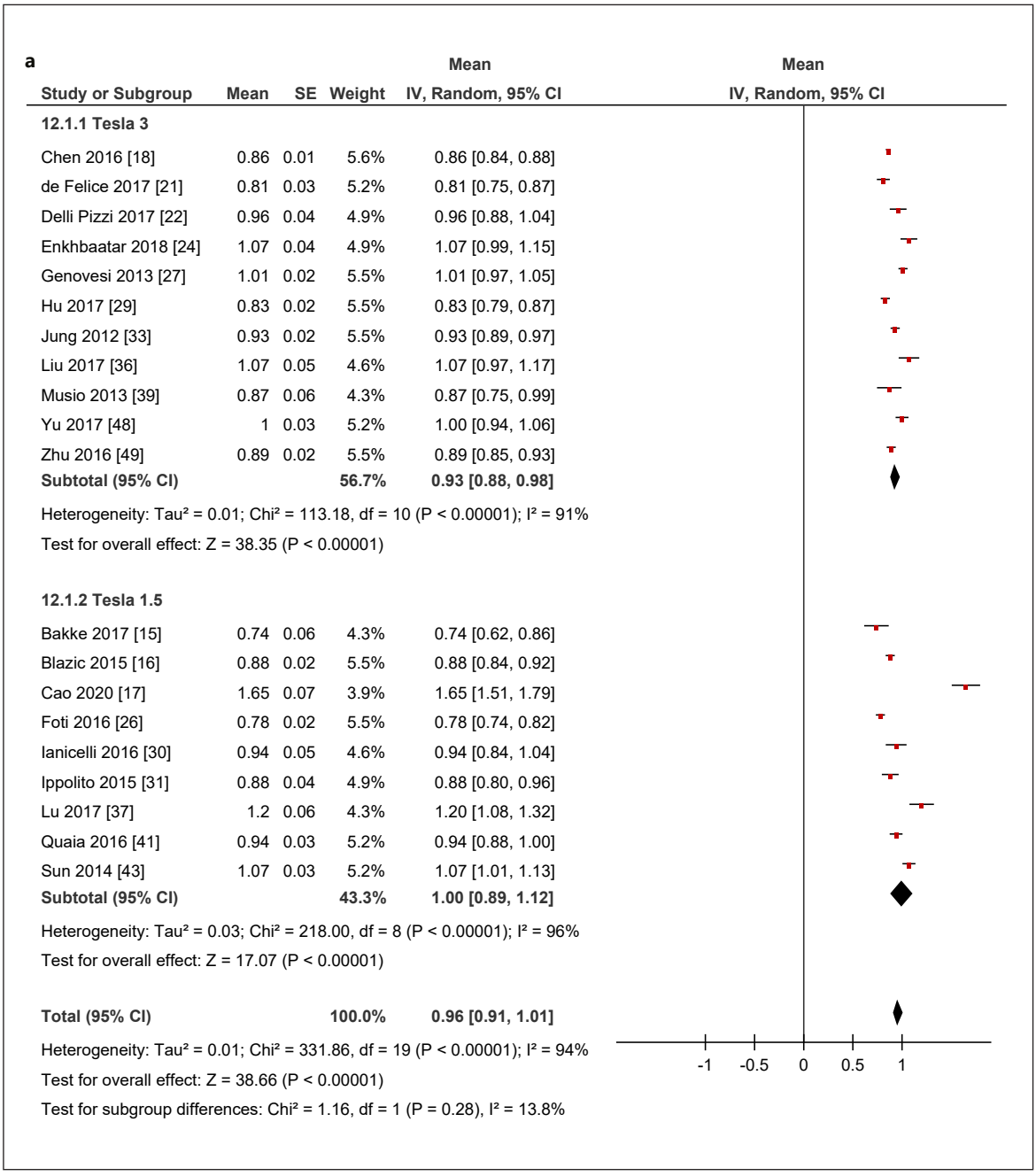

Fig. 10. a Forrest plots of ADC reported for RCs responded to NARC in dependency on Tesla strength. **b** Forrest plots of ADC reported for RCs nonresponded to NARC in dependency on Tesla strength. ADC, apparent diffusion coefficient; RC, rectal cancer; NARC, neoadjuvant radiochemotherapy; CI, confidence interval.

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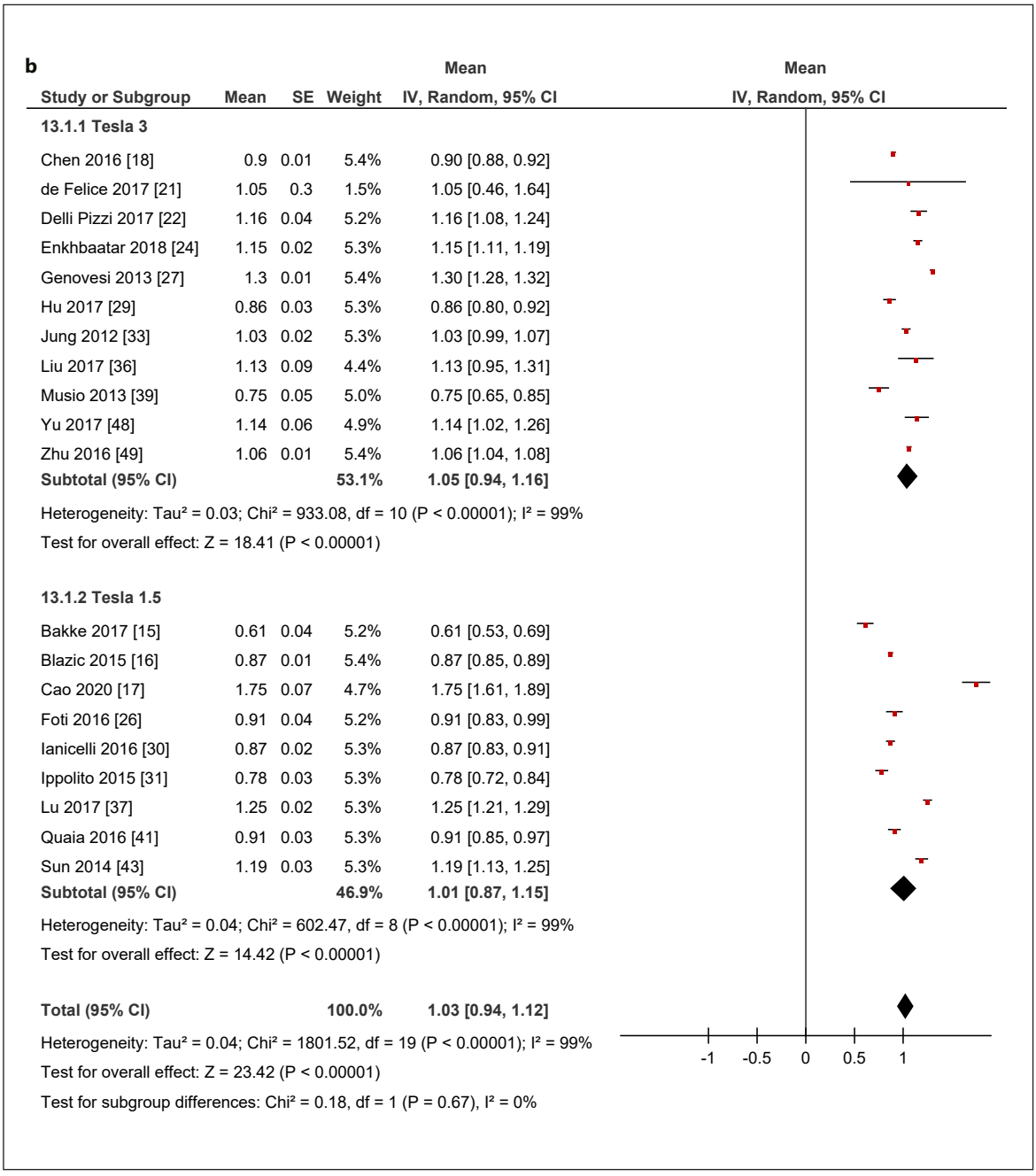

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

A.S. and A.W.: conceived and designed the study; A.S., M.P., M.P., and K.W.: collection and analysis of data; all authors: manuscript writing; and M.P. and A.W.: critical revision of the manuscript. All the authors approved the final manuscript submitted.

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