

Correlation between apparent diffusion coefficient (ADC) and cellularity is different in several tumors: a meta-analysis

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ABSTRACT

The purpose of this meta-analysis was to provide clinical evidence regarding relationship between ADC and cellularity in different tumors based on large patient data.

Medline library was screened for associations between ADC and cell count in different tumors up to September 2016. Only publications in English were extracted. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA) was used for the research.

Overall, 39 publications with 1530 patients were included into the analysis. The following data were extracted from the literature: authors, year of publication, number of patients, tumor type, and correlation coefficients.

The pooled correlation coefficient for all studies was $\rho = -0.56$ (95 % CI = [-0.62; -0.50]),. Correlation coefficients ranged from $\rho = -0.25$ (95 % CI = [-0.63; 0.12]) in lymphoma to $\rho = -0.66$ (95 % CI = [-0.85; -0.47]) in glioma. Other coefficients were as follows: ovarian cancer, $\rho = -0.64$ (95% CI = [-0.76; -0.52]); lung cancer, $\rho = -0.63$ (95 % CI = [-0.78; -0.48]); uterine cervical cancer, $\rho = -0.57$ (95 % CI = [-0.80; -0.34]); prostatic cancer, $\rho = -0.56$ (95 % CI = [-0.69; -0.42]); renal cell carcinoma, $\rho = -0.53$ (95 % CI = [-0.93; -0.13]); head and neck squamous cell carcinoma, $\rho = -0.53$ (95 % CI = [-0.74; -0.32]); breast cancer, $\rho = -0.48$ (95 % CI = [-0.74; -0.23]); and meningioma, $\rho = -0.45$ (95 % CI = [-0.73; -0.17]).

INTRODUCTION

Diffusion weighted imaging (DWI) is a magnetic resonance imaging (MRI) technique based on measure of water diffusion in tissues [1]. Beside diagnostic potential, DWI

can distinguish malignant from benign lesions [2, 3]. As reported previously, malignant tumors showed lower apparent diffusion coefficient (ADC) values in comparison to benign lesions [2, 3].

According to the literature, DWI can also provide additional information about tissue microstructure [1, 4–6]. Experimental studies showed a strong association between ADC and cell count *in vitro* [4–6]. It has been

shown that increase of cell density restricted water diffusion and decreased ADC [5, 6]. However, published data of clinical investigations were inconsistent. While some authors identified significant correlations between ADC and cellularity in different tumor, other did not [7–11]. Moreover, there was a wide spectrum of reported correlation coefficients ranging from 0.1 to -0.79 [7–12]. Furthermore, the number of investigated patients/tumors in most studies was up to 50 [7–12]. Only few reports analyzed relative large collectives ranging from 102 to 138 patients [13–16]. Therefore, the reported data cannot be considered as evident. Overall, these facts question the possibility to use ADC as a surrogate biomarker for cellularity in clinical practice.

The purpose of this meta-analysis was to provide clinical evidence regarding relationship between ADC and cellularity in different tumors based on large patient data.

RESULTS

Overall, the pooled correlation coefficient for all studies (Figure 1) was $\rho = -0.56$, (95 % CI = [-0.62; -0.50]), heterogeneity $\tau^2 = 0.02$, ($p < 0.00001$), $I^2 = 67\%$, test for overall effect $Z = 18.01$ ($p < 0.00001$).

On the next step, correlation coefficients for every tumor entities were calculated. For this analysis, only data for primary tumors were acquired (Figure 2). The calculated correlation coefficients ranged from $\rho = -0.25$ (95 % CI = [-0.63; 0.12]) in lymphoma to $\rho = -0.66$ (95 % CI = [-0.85;

-0.47]) in glioma. Other coefficients were as follows: ovarian cancer, $\rho = -0.64$ (95% CI = [-0.76; -0.52]); lung cancer, $\rho = -0.63$ (95 % CI = [-0.78; -0.48]); uterine cervical cancer, $\rho = -0.57$ (95 % CI = [-0.80; -0.34]); prostatic cancer, $\rho = -0.56$ (95 % CI = [-0.69; -0.42]); renal cell carcinoma, $\rho = -0.53$ (95 % CI = [-0.93; -0.13]); head and neck squamous cell carcinoma (HNSCC), $\rho = -0.53$ (95 % CI = [-0.74; -0.32]); breast cancer, $\rho = -0.48$ (95 % CI = [-0.74; -0.23]); meningioma, $\rho = -0.45$ (95 % CI = [-0.73; -0.17]).

DISCUSSION

The present analysis provides evidence regarding correlation between ADC, in particular ADC_{mean}, and cellularity in different tumors based on a large sample.

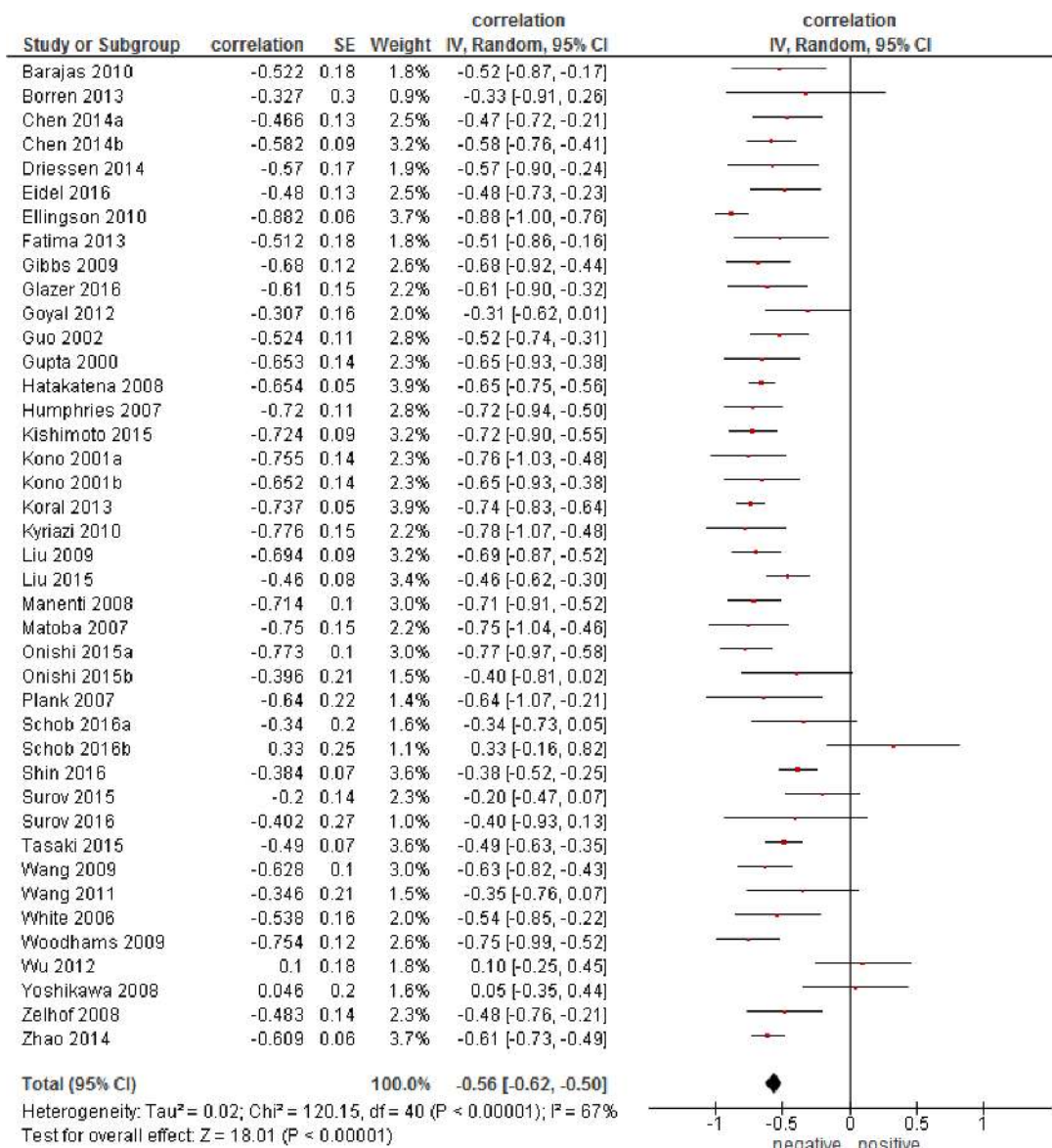
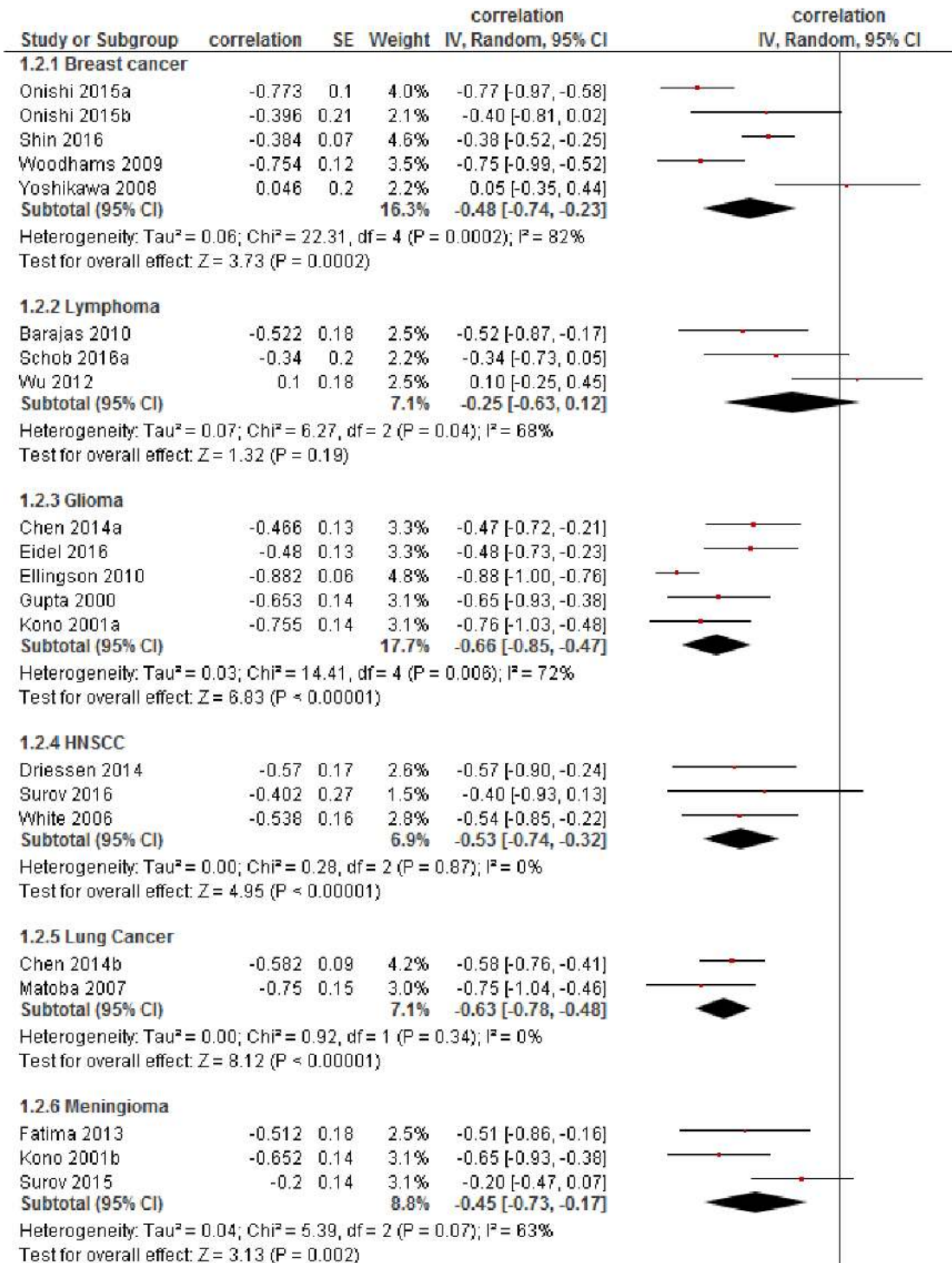


Figure 1: Forest plots of correlation coefficients between ADC_{mean} and cellularity in patients from all involved 39 studies.

Previously, numerous studies investigated associations between ADC and cell density in several tumors [7-46]. Overall, most reports showed significant correlations between these parameters [7, 9, 15, 16, 21, 32, 33, 41, 43]. So, Woodhams et al. found a strong inverse correlation ($\rho = -0.75, p = 0.001$) between ADC and cell count in mucinous breast carcinoma [43]. Based on the reported data, it has been postulated that DWI, namely ADC is an imaging tool to estimate tumor cellularity [43].

However, there were also reports, in which no significant correlations between ADC values and cell count were found [11, 38]. For example, in different lymphomas, the correlation coefficient between cell count and ADC was $\rho = 0.1$ ($p = 0.58$) [10]. Similar negative results were published for head and neck carcinoma ($\rho = -0.418, p = 0.201$) [39], meningioma ($\rho = -0.20, p = 0.164$) [38], and breast cancer ($\rho = 0.048, p = 0.812$) [11]. Some previous reports attempted to explain their negative



1.2.7 Ovarian cancer

Kyriazi 2010	-0.776	0.15	3.0%	-0.78 [-1.07, -0.48]
Zhao 2014	-0.609	0.06	4.8%	-0.61 [-0.73, -0.49]
Subtotal (95% CI)			7.7%	-0.64 [-0.76, -0.52]

Heterogeneity: $\text{Tau}^2 = 0.00$; $\text{Chi}^2 = 1.07$, $\text{df} = 1$ ($P = 0.30$); $I^2 = 6\%$
 Test for overall effect: $Z = 10.36$ ($P < 0.00001$)

1.2.8 Prostatic cancer

Borren 2013	-0.327	0.3	1.3%	-0.33 [-0.91, 0.26]
Gibbs 2009	-0.68	0.12	3.5%	-0.68 [-0.92, -0.44]
Glazer 2016	-0.61	0.15	3.0%	-0.61 [-0.90, -0.32]
Wang 2011	-0.346	0.21	2.1%	-0.35 [-0.76, 0.07]
Zelhof 2008	-0.483	0.14	3.1%	-0.48 [-0.76, -0.21]
Subtotal (95% CI)			13.0%	-0.56 [-0.69, -0.42]

Heterogeneity: $\text{Tau}^2 = 0.00$; $\text{Chi}^2 = 3.05$, $\text{df} = 4$ ($P = 0.55$); $I^2 = 0\%$
 Test for overall effect: $Z = 7.84$ ($P < 0.00001$)

1.2.9 Renal cell carcinoma

Goyal 2012	-0.307	0.16	2.8%	-0.31 [-0.62, 0.01]
Manenti 2008	-0.714	0.1	4.0%	-0.71 [-0.91, -0.52]
Subtotal (95% CI)			6.7%	-0.53 [-0.93, -0.13]

Heterogeneity: $\text{Tau}^2 = 0.07$; $\text{Chi}^2 = 4.65$, $\text{df} = 1$ ($P = 0.03$); $I^2 = 79\%$
 Test for overall effect: $Z = 2.61$ ($P = 0.009$)

1.2.10 Uterine cervical cancer

Liu 2009	-0.694	0.09	4.2%	-0.69 [-0.87, -0.52]
Liu 2015	-0.46	0.08	4.4%	-0.46 [-0.62, -0.30]
Subtotal (95% CI)			8.5%	-0.57 [-0.80, -0.34]

Heterogeneity: $\text{Tau}^2 = 0.02$; $\text{Chi}^2 = 3.78$, $\text{df} = 1$ ($P = 0.05$); $I^2 = 74\%$
 Test for overall effect: $Z = 4.90$ ($P < 0.00001$)

Total (95% CI)			100.0%	-0.55 [-0.62, -0.47]
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Heterogeneity: $\text{Tau}^2 = 0.03$; $\text{Chi}^2 = 91.60$, $\text{df} = 31$ ($P < 0.00001$); $I^2 = 66\%$
 Test for overall effect: $Z = 14.17$ ($P < 0.00001$)

Test for subgroup differences: $\text{Chi}^2 = 6.63$, $\text{df} = 9$ ($P = 0.68$), $I^2 = 0\%$

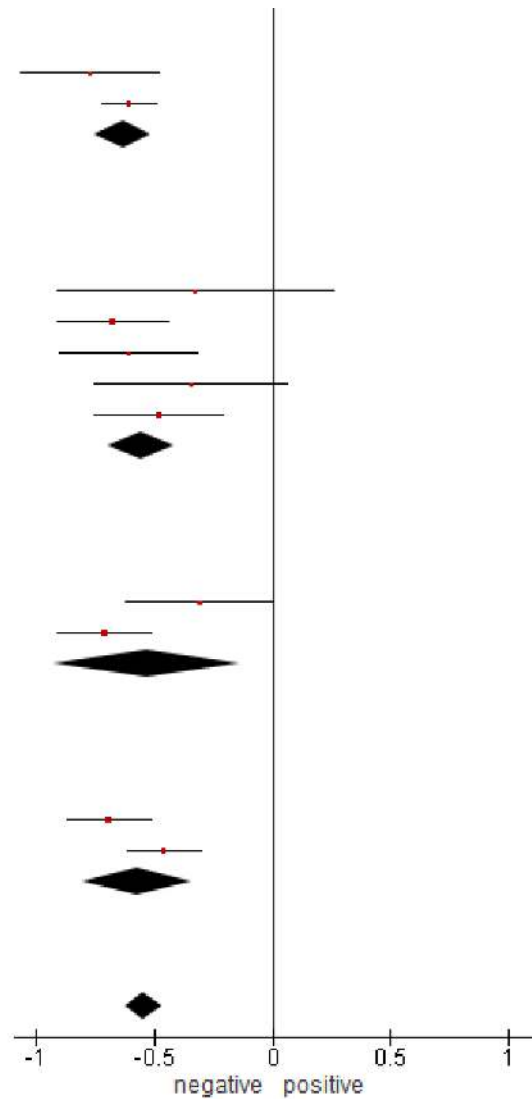


Figure 2: Forest plots of correlation coefficients between ADCmean and cellularity in different primary tumors.

findings by small number of patients [37, 39]. However, another cause of the controversial results in the literature is possible. Presumably, different tumors may have also different associations between ADC and tumor cell count. Our results confirmed this assumption. As seen, ADC showed a moderate inverse correlation with cellularity in the general collective. However, this finding did not apply for each tumor entity, and, therefore, cannot be used in clinical practice. We found that the correlation ADC vs cellularity ranged significantly in different tumors. It was weak in lymphomas, weak-to-moderate in breast cancer and meningiomas, moderate in most investigated epithelial tumors, and strong in gliomas, ovarian cancer, and lung cancer. It is still unclear, why ADC correlates well with cell count in some tumors, whereas in other does not. Presumably, not only cell count, but also other histopathological features, such as extracellular

matrix, nucleic areas, ratio stroma/parenchyma, and /or microvessel density may play a role here. In fact, some studies found statistically significant associations between nucleic size and ADC in several lesions [46, 47]. Overall, our findings suggest that ADC does not reflect cellularity in all tumors.

Our analysis also identified another problem. There are no reports regarding associations between ADC and cellularity in most gastrointestinal tumors: esophageal cancer, gastric cancer, colorectal carcinoma, gastrointestinal stromal tumors, hepatocellular carcinoma, pancreatic carcinomas, and gall bladder cancer. Also in malignancies of cutis, such as malignant melanoma, no reports about ADC/cell count could be identified. Except renal cell carcinoma and prostatic cancer, no data exist for urological malignancies. In addition, several tumors involved into the present meta-analysis, for

Table 1: Patients involved into the study

Diagnosis	<i>n</i>	%
Different breast tumors	402	26.28
Different brain tumors	318	20.78
Uterine muscle sarcoma	134	8.76
Uterine cervical cancer	130	8.50
Prostatic cancer	119	7.78
Ovarian cancer	110	7.19
Lymphoma	71	4.64
Lung cancer	69	4.51
Renal cell carcinoma	59	3.86
HNSCC	48	3.14
Endometrial cancer	30	1.96
Pancreatic neuroendocrine tumor	18	1.18
Thyroid cancer	14	0.92
Spinal epidural tumors	8	0.52
Total	1530	100

HNSCC, head and neck squamous cell carcinoma

example, HNSCC, renal cell carcinoma, lung cancer, and lymphomas contained small number of patients. This relativizes the calculated results. Finally, for some tumors, such as pancreatic neuroendocrine carcinoma [41], soft tissue sarcomas [15], and thyroid cancer [37], only one report was published, respectively. Therefore, no evident data could be estimated for these entities. Clearly, further researches are needed to investigate possible associations between ADC and cellularity in these tumors. Thereafter, a similar meta-analysis is also needed to prove new data.

In conclusion, different inverse correlations were identified between ADC and cell count in the analyzed tumors. ADC correlated strongly with cell count in gliomas, followed by ovarian cancer, and lung cancer. Therefore, in these tumors, ADC can be used as an imaging marker to estimate cellularity. Moderate inverse correlations were identified between ADC and cell count in prostatic cancer, renal cell carcinoma, uterine cervical cancer, and head/neck squamous cell carcinomas.

Furthermore, weak-to-moderate correlations were found in breast cancer and meningioma. This finding relativizes the possibility of ADC use to predict cellularity in these tumors. Finally, weak correlation was identified in lymphomas. Therefore, ADC cannot be used as a cellularity biomarker in this entity.

No evident data can be provided to date for other malignancies.

MATERIALS AND METHODS

Data acquisition and proving

MEDLINE library was screened for associations between ADC and cell count in different tumors up to September 2016. The following search words were used: “DWI or diffusion weighted imaging or diffusion-weighted

imaging or ADC or apparent diffusion coefficient AND cellularity or cell density or cell count or cell number”. Only publications in English were extracted. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA) was used for the research [48].

After exclusion of duplicates, a total of 494 publications was identified. These reports were involved into the further analysis. For this work, only data regarding ADC_{mean} derived from diffusion weighted imaging (DWI) were acquired. Papers which did not contain correlation coefficients between ADC and cell count were excluded. In addition, data retrieved from diffusion tensor imaging and other DWI parameters, such as D, ADC_{max}, and ADC_{min} were also excluded. Finally, we excluded experimental animals and *in vitro* studies. Overall, 455 publications were excluded. Therefore, the present analysis comprises 39 publications with 1530 patients [7-46]. The following data were extracted from the literature: authors, year of publication, number of patients, tumor type, and correlation coefficients. Most frequently, different breast, followed by several brain tumors, uterine sarcomas, uterine cervical cancer, prostatic cancer, and ovarian cancer were reported (Table 1). Other tumors were rarer.

Meta-analysis

The methodological quality of the 39 included studies was independently checked by two observers (A.S. and H.J.M.) using the Quality Assessment of Diagnostic Studies (QUADAS) instrument according to previous descriptions [49, 50]. The results of QUADAS proving are shown in Table 2.

Spearman’s correlation coefficient was used to analyze associations between ADC_{mean} and cell count. The reported Pearson correlation coefficients in some publications were converted into Spearman correlation coefficients as reported previously [51].

Table 2: Methodological quality of the involved 39 studies according to the QUADAS criteria

	Yes (%)	No (%)	Unclear (%)
Patient spectrum	24 (61.54)	8 (20.51)	7 (17.95)
Selection criteria	25 (64.10)	10(25.64)	4(10.26)
Reference standard	39 (100)		
Disease progression bias	39 (100)		
Partial verification bias	39 (100)		
Differential verification bias	39 (100)		
Incorporation bias	39 (100)		
Text details	39 (100)		
Reference standard details	39 (100)		
Text review details	18 (46.15)	8 (20.51)	13 (33.33)
Diagnostic review bias	18 (46.15)	9 (23.08)	12 (30.77)
Clinical review bias	38 (97.44)		1 (2.56)
Uninterpretable results	38 (97.44)		1 (2.56)
Withdrawals explained	38 (97.44)		1 (2.56)

The meta-analysis was undertaken by using RevMan 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. Furthermore, DerSimonian and Laird random-effects models with inverse-variance weights were used without any further correction [54].

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