

## Research Article

# Standardized Uptake Values Derived from $^{18}\text{F}$ -FDG PET May Predict Lung Cancer Microvessel Density and Expression of KI 67, VEGF, and HIF-1 $\alpha$ but Not Expression of Cyclin D1, PCNA, EGFR, PD L1, and p53

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**Background.** Our purpose was to provide data regarding relationships between  $^{18}\text{F}$ -FDG PET and histopathological parameters in lung cancer. **Methods.** MEDLINE library was screened for associations between PET parameters and histopathological features in lung cancer up to December 2017. Only papers containing correlation coefficients between PET parameters and histopathological findings were acquired for the analysis. Overall, 40 publications were identified. **Results.** Associations between SUV and KI 67 were reported in 23 studies (1362 patients). The pooled correlation coefficient was 0.44. In 2 studies (180 patients), relationships between SUV and expression of cyclin D1 were analyzed (pooled correlation coefficient = 0.05). Correlation between SUV and HIF-1 $\alpha$  was investigated in 3 studies (288 patients), and the pooled correlation coefficient was 0.42. In 5 studies (310 patients), associations between SUV and MVD were investigated (pooled correlation coefficient = 0.54). In 6 studies (305 patients), relationships between SUV and p53 were analyzed (pooled correlation coefficient = 0.30). In 6 studies (415 patients), associations between SUV and VEGF expression were investigated (pooled correlation coefficient = 0.44). In 5 studies (202 patients), associations between SUV and PCNA were investigated (pooled correlation coefficient = 0.32). In 3 studies (718 patients), associations between SUV and expression of PD L1 were analyzed (pooled correlation coefficient = 0.36). Finally, in 5 studies (409 patients), associations between SUV and EGFR were investigated (pooled correlation coefficient = 0.38). **Conclusion.** SUV may predict microvessel density and expression of VEGF, KI 67, and HIF-1 $\alpha$  in lung cancer.

## 1. Introduction

Lung cancer is one of the most frequent malignancies in humans [1]. It is the largest cause of cancer deaths in the United States [1].

Multiple histopathological factors influence tumor biology in lung cancer. According to the literature, different molecular markers play a key role here [2]. Previous reports investigated numerous biomarkers and suggested that some histopathological parameters can predict tumor behavior in lung cancer [2–5]. It has been shown that they provide information about tumor proliferation, aggressiveness, prognosis, and therapy response [2–5]. According to the literature,

following biomarkers are relevant in lung cancer: proliferation index KI 67, hypoxia-inducible factor- (HIF-) 1 $\alpha$ , tumor suppressor protein p53, vascular endothelial growth factor (VEGF), epidermal growth factor receptor (EGFR), proliferating cell nuclear antigen (PCNA), PD L1, and several cyclins [2–10]. For instance, it has been shown that tumors with high expression of KI 67 and/or VEGF were associated with a worse prognosis [3, 4]. Similar results were also reported for expression of HIF-1 $\alpha$  and p53 [5–7].

Furthermore, some reports analyzed associations between imaging parameters and histopathological features in lung cancer [11–14]. Especially parameters of positron emission tomography (PET) like standardized uptake values

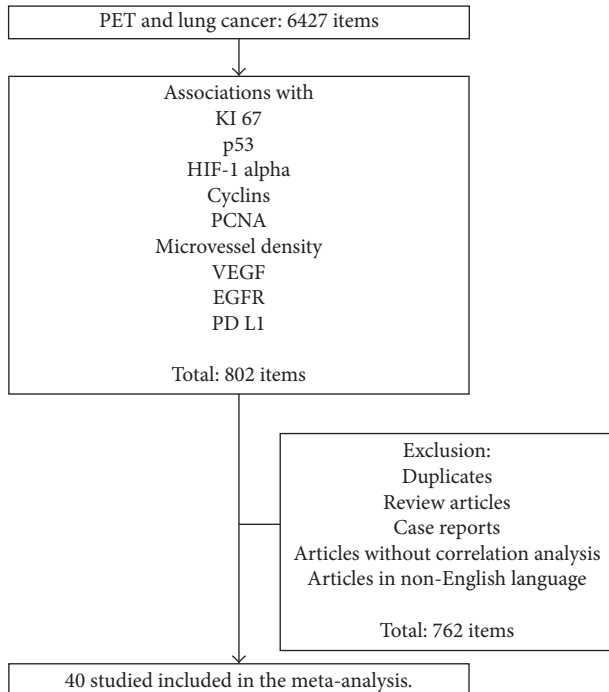


FIGURE 1: Flowchart of the data acquisition.

(SUV) were in focus of the studies. However, the reported data were inconsistent. While some authors found such significant relationships, others did not. Therefore, it is unclear whether SUV can be used as a surrogate parameter reflecting histopathological features in lung cancer or not.

The purpose of this meta-analysis was to provide evident data about associations between SUV and histopathological parameters in lung cancer.

## 2. Materials and Methods

**2.1. Data Acquisition.** The strategy of data acquisition is shown in Figure 1. MEDLINE library was screened for associations between PET parameters and histopathological findings in lung cancer up to December 2017.

For associations between PET and different biomarkers, the following search words were used:

- (i) *PET and KI 67*: “lung cancer AND PET OR positron emission tomography AND KI 67 OR KI67 OR ki67 OR ki-67 OR mitotic index OR proliferation index OR MIB 1 OR MIB-1 OR mitosis index” (192 items)
- (ii) *PET and expression of p53*: “lung cancer AND PET or positron emission tomography AND p53 OR tumor suppressor protein” (51 items)
- (iii) *PET and expression of VEGF*: “lung cancer AND PET or positron emission tomography AND VEGF OR vascular endothelial growth factor” (82 items)
- (iv) *PET and expression of EGFR*: “lung cancer AND PET or positron emission tomography AND EGFR OR epidermal growth factor receptor” (345 items)

TABLE 1: Methodological quality of the involved 40 studies according to the QUADAS criteria.

QUADAS criteria	Yes (%)	No (%)	Unclear (%)
Patient spectrum	38 (95.0)	—	2 (5.0)
Selection criteria	28 (70.0)	1 (2.50)	11 (27.5)
Reference standard	40 (100)	—	—
Disease progression bias	40 (100)	—	—
Partial verification bias	40 (100)	—	—
Differential verification bias	40 (100)	—	—
Incorporation bias	40 (100)	—	—
Text details	40 (100)	—	—
Reference standard details	40 (100)	—	—
Text review details	16 (40.0)	4 (10.0)	20 (50.0)
Diagnostic review bias	17 (42.5)	4 (10.0)	19 (47.5)
Clinical review bias	39 (97.5)	—	1 (2.5)
Uninterpretable results	39 (97.5)	—	1 (2.5)
Withdrawal explained	38 (95.0)	1 (2.5)	1 (2.5)

- (v) *PET and expression of HIF-1 $\alpha$* : “lung cancer AND PET or positron emission tomography AND HIF-1 $\alpha$  OR HIF1 $\alpha$  OR HIF-1 alpha OR HIF1 alpha OR hypoxia-inducible factor” (38 items)
- (vi) *PET and expression of PCNA*: “lung cancer AND PET or positron emission tomography AND PCNA OR proliferating cell nuclear antigen” (23 items)
- (vii) *PET and expression of cyclins*: “lung cancer AND PET or positron emission tomography AND cyclin” (22 items)
- (viii) *PET and microvessel density*: “lung cancer AND PET or positron emission tomography AND microvessel density OR MVD” (34 items)
- (ix) *PET and expression of PD L1*: “lung cancer AND PET or positron emission tomography AND programmed cell death-ligand 1 OR PD L1” (15 items).

Secondary references were also recruited. Overall, 802 records were identified. After exclusion of doublets, review articles, case reports, non-English publications, and articles, which not contain correlation coefficients between PET and histopathological parameters, there were 40 articles [11–50].

The following data were extracted from the literature: authors, year of publication, number of patients, histopathological parameters, and correlation coefficients, according to our previous descriptions [51–53].

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA) was used for the research [54].

**2.2. Meta-Analysis.** The methodological quality of the acquired 40 studies was independently checked by two observers (Alexey Surov and Hans Jonas Meyer) using the Quality Assessment of Diagnostic Studies (QUADAS) instrument according to previous descriptions [55]. Table 1 shows the results of QUADAS proving.

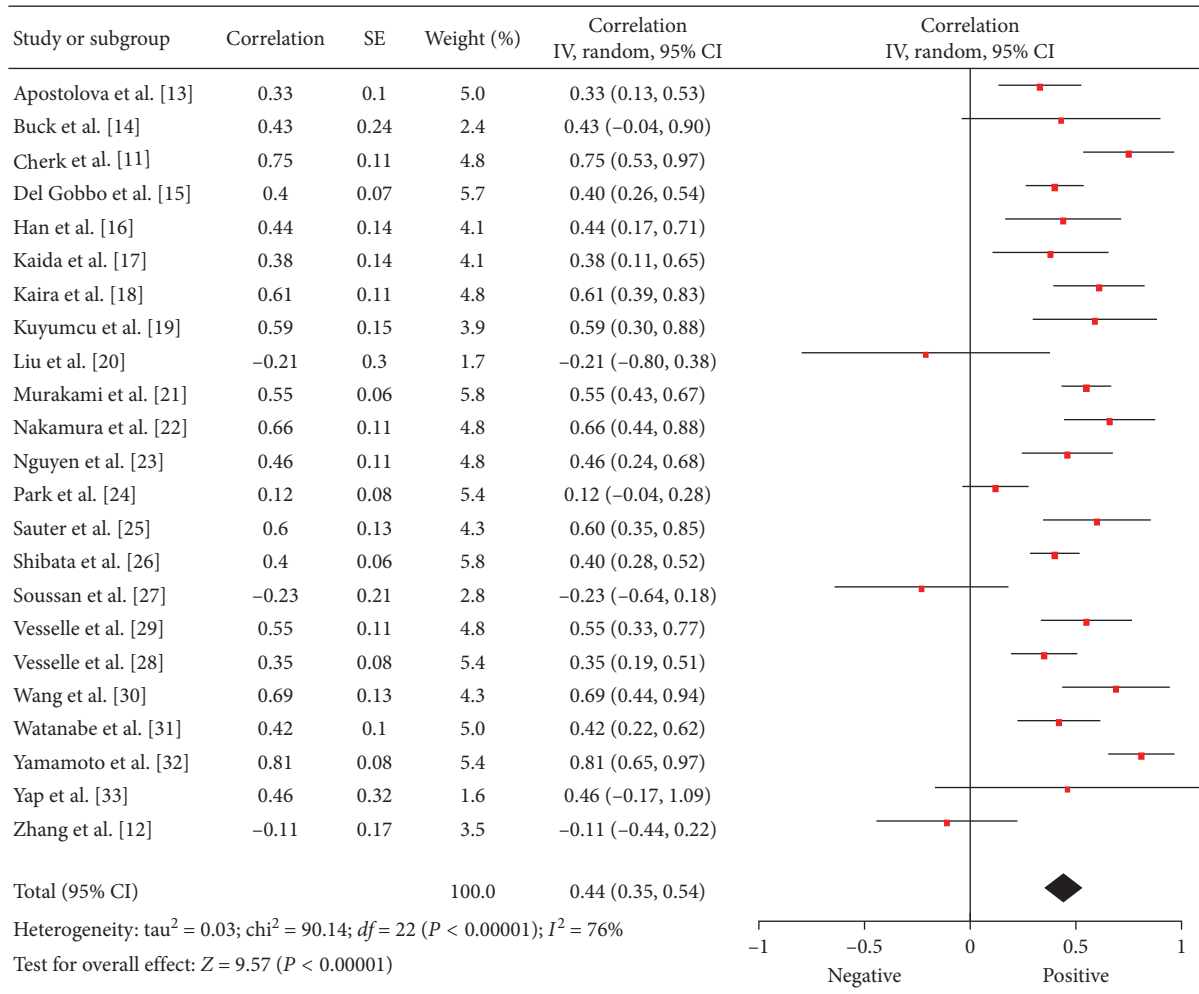


FIGURE 2: Forest plots of correlation coefficients between  $SUV_{max}$  and KI 67 in patients with lung cancer.

Associations between PET and histopathological findings were analyzed by Spearman’s correlation coefficient. The reported Pearson’s correlation coefficients in some studies were converted into Spearman’s correlation coefficients according to the previous description [56].

Furthermore, the meta-analysis was undertaken by using RevMan 5.3 (Computer Program, version 5.3, The Cochrane Collaboration, 2014, The Nordic Cochrane Centre, Copenhagen). Heterogeneity was calculated by means of the inconsistency index  $I^2$  [57, 58]. Additionally, DerSimonian and Laird random-effects models with inverse-variance weights were used without any further correction [59].

### 3. Results

**3.1. KI 67.** Associations between  $^{18}F$ -FDG PET and KI 67 were reported in 23 studies (1362 patients) [11–33]. The calculated correlation coefficients between  $SUV_{max}$  and KI 67 ranged from -0.23 to 0.81 (Figure 2). The pooled correlation coefficient was 0.44 (95% CI = (0.35; 0.54)).

**3.2. Cyclin D1.** In 2 studies (180 patients), relationships between  $^{18}F$ -FDG PET and expression of cyclin D1 were

analyzed [34, 35]. The pooled correlation coefficient between these parameters was 0.05 (95% CI = (-0.36; 0.46)) (Figure 3).

**3.3. HIF-1 $\alpha$ .** Associations between  $^{18}F$ -FDG PET and HIF-1 $\alpha$  were investigated in 3 studies (288 patients) [36–38]. The reported correlation coefficients ranged from -0.19 to 0.99 (Figure 4). The pooled correlation coefficient was 0.42 (95% CI = (0.06; 0.78)).

**3.4. Microvessel Density (MVD).** Associations between  $^{18}F$ -FDG PET and MVD were investigated in 5 studies (310 patients) [25,37–40]. The reported correlation coefficients ranged from -0.23 to 0.91 (Figure 5). The pooled correlation coefficient was 0.54 (95% CI = (0.29; 0.80)).

**3.5. P53.** In 6 studies (305 patients), relationships between  $^{18}F$ -FDG PET and p53 were analyzed [13,22,34,41–43]. The pooled correlation coefficient between these parameters was 0.30 (95% CI = (0.13; 0.47)) (Figure 6).

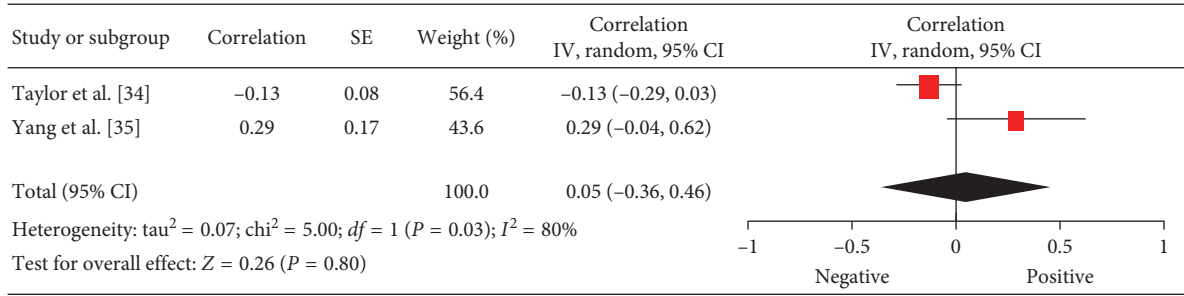


FIGURE 3: Forest plots of correlation coefficients between  $SUV_{max}$  and expression of cyclin D1.

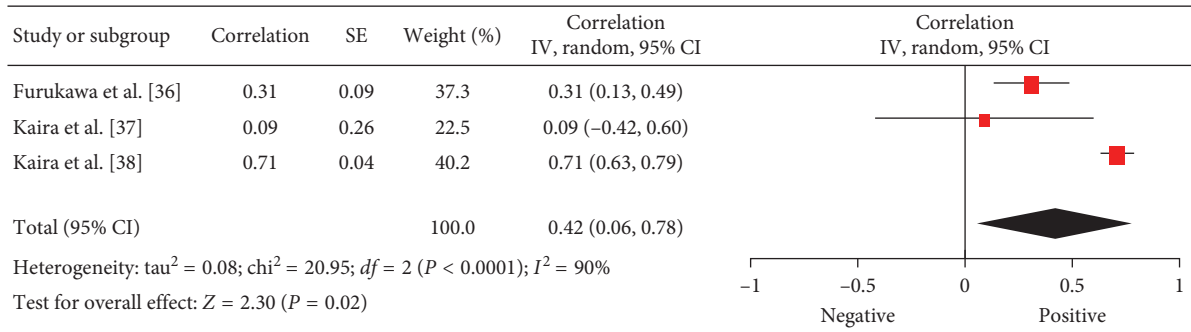


FIGURE 4: Forest plots of correlation coefficients between  $SUV_{max}$  and expression of HIF-1 $\alpha$  in lung cancer.

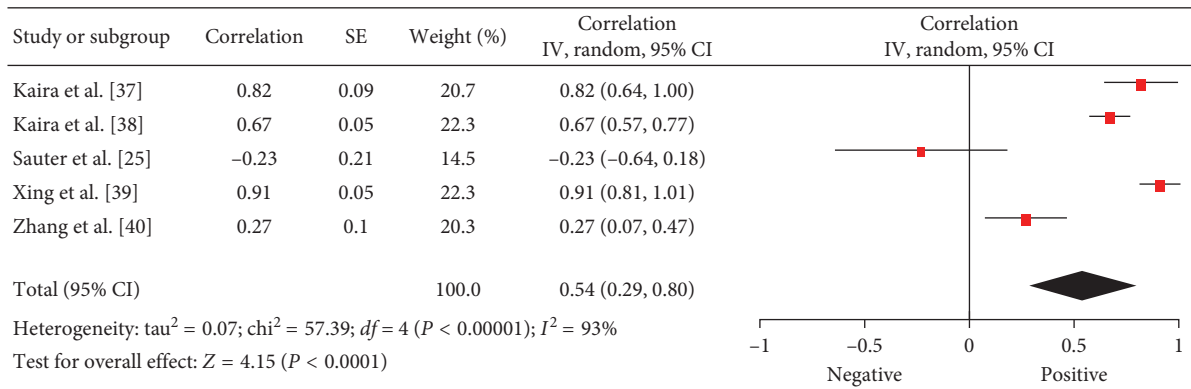


FIGURE 5: Forest plots of correlation coefficients between  $SUV_{max}$  and microvessel density.

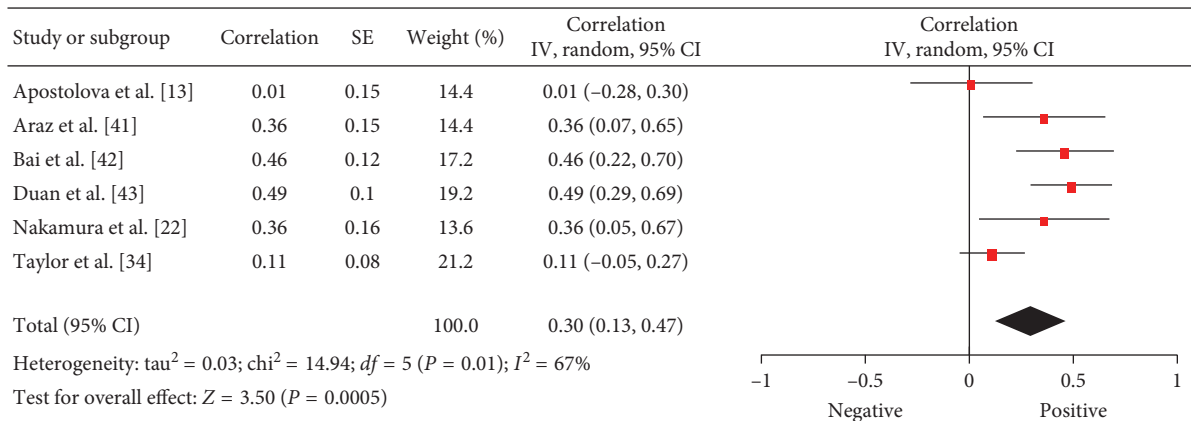


FIGURE 6: Forest plots of correlation coefficients between  $SUV_{max}$  and expression of p53.

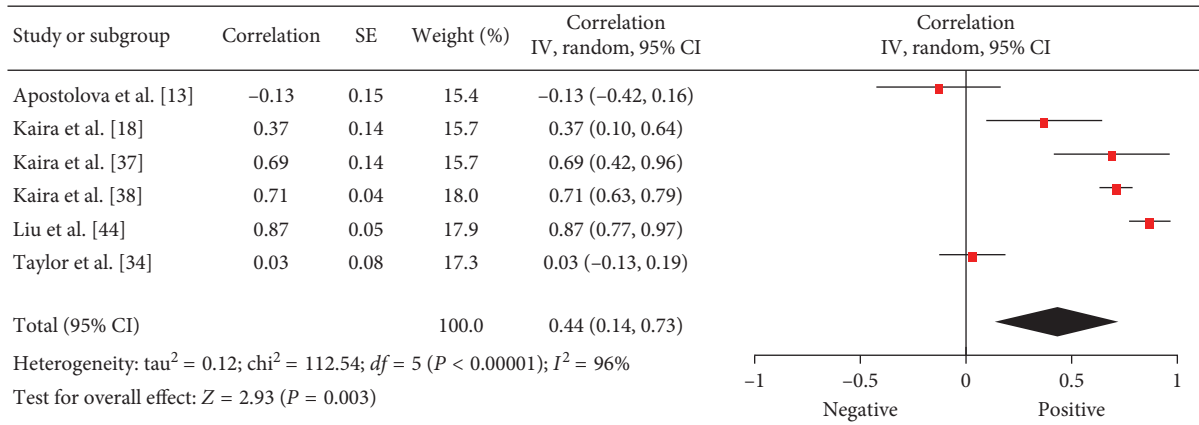


FIGURE 7: Forest plots of correlation coefficients between SUV<sub>max</sub> and VEGF expression.

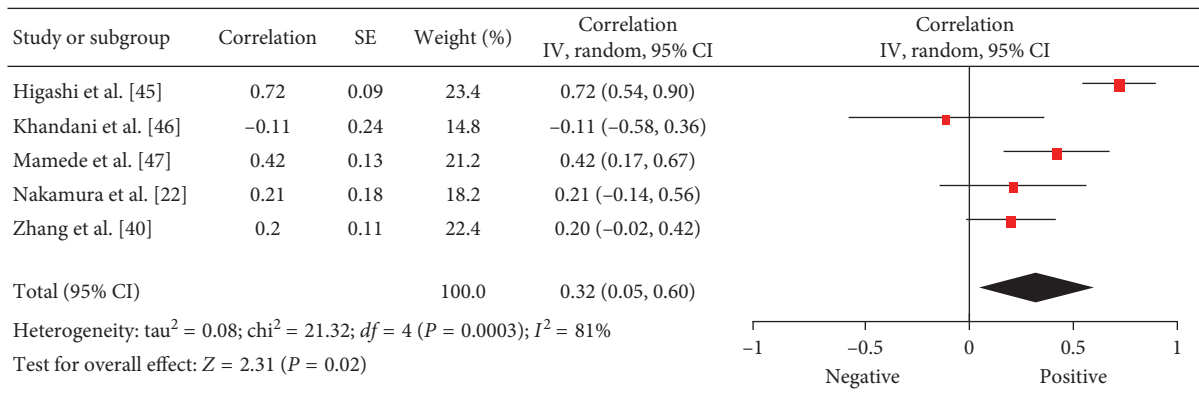


FIGURE 8: Forest plots of correlation coefficients between SUV<sub>max</sub> and PCNA.

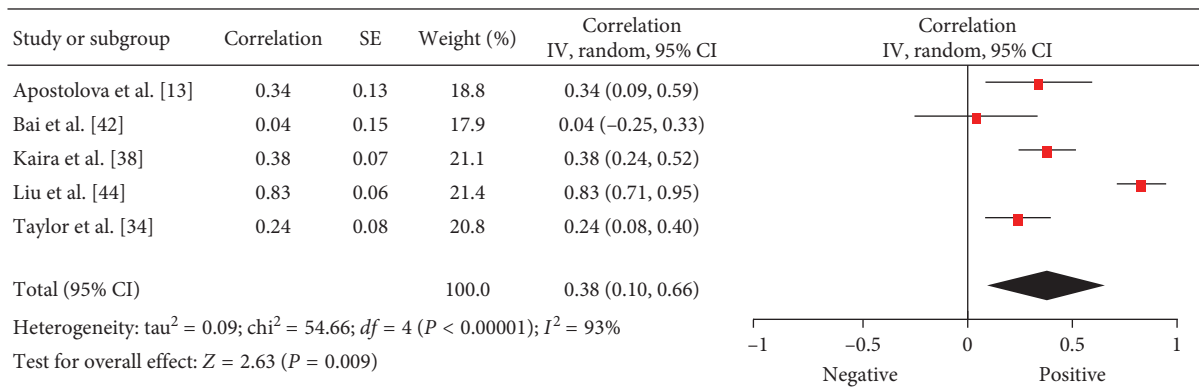


FIGURE 9: Forest plots of correlation coefficients between SUV<sub>max</sub> and EGFR expression.

3.6. *VEGF*. There were 6 studies (415 patients) which investigated associations between SUV and expression of VEGF in lung cancer [13, 18, 34, 37, 38, 44]. The reported correlation coefficients ranged from -0.13 to 0.77 (Figure 7). The pooled correlation coefficient was 0.44 (95% CI = (0.14; 0.73)).

3.7. *PCNA*. There were 5 studies (202 patients) which investigated associations between <sup>18</sup>F-FDG PET and PCNA in lung cancer [22,40,45-47]. The reported correlation

coefficients ranged from 0.04 to 0.83 (Figure 8). The pooled correlation coefficient was 0.32 (95% CI = (0.05; 0.60)).

3.8. *EGFR*. There were 5 studies (409 patients) which investigated associations between <sup>18</sup>F-FDG PET and expression of EGFR in lung cancer [13, 34, 38, 42, 44]. The reported correlation coefficients ranged from 0.04 to 0.83 (Figure 9). The pooled correlation coefficient was 0.38 (95% CI = (0.10; 0.66)).

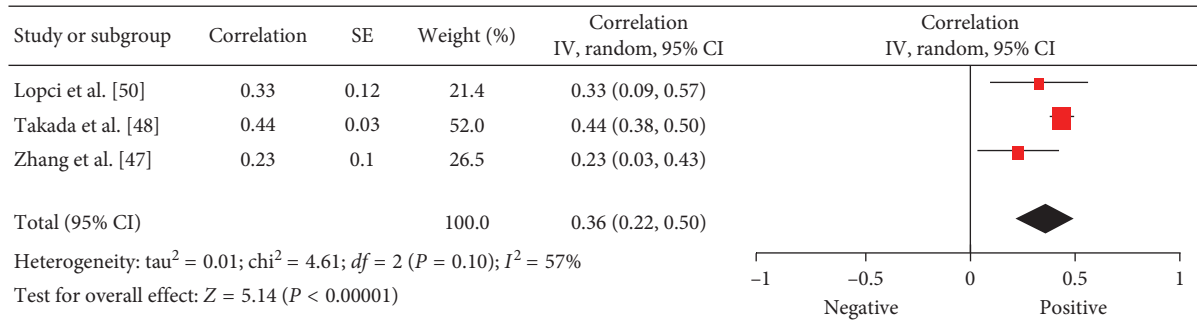


FIGURE 10: Forest plots of correlation coefficients between  $SUV_{max}$  and EGFR expression.

3.9. *PD L1*. In 3 studies (718 patients), relationships between  $^{18}F$ -FDG PET and expression of PD L1 were analyzed [48–50]. The pooled correlation coefficient between these parameters was 0.36 (95% CI = (0.22; 0.50)) (Figure 10).

#### 4. Discussion

Analysis of interactions between imaging findings, in particular, between PET and histopathology can significantly improve oncologic diagnostics [60]. The possibility to characterize histological tissues by imaging can also personalize anticancer treatment [60]. Although PET is an established investigation of lung cancer in clinical practice, only few reports analyzed the question if there are relationships between PET findings and different histopathological parameters. However, this is a key question. In fact, if PET parameters do correlate with several histopathological findings reflecting proliferation or other features of lung cancer, then PET values can also be used as biomarkers.

Our meta-analysis showed that SUV can reflect different histopathological parameters in lung cancer. As shown, SUV correlated moderately with KI 67. This finding is not surprisingly. KI 67 is a nonhistone, nuclear protein synthesized throughout the whole cell cycle except the G0 phase and has been shown to be responsible for cell proliferation [61]. It is an established biomarker in lung cancer for prediction of tumor behavior. Our data are in agreement with those of previous investigations and also analyzed relationships between expression of KI 67 and SUV in lung cancer [62, 63]. However, we found weak correlations between  $SUV_{max}$  and other proliferation markers, namely, PCNA (0.32). This finding is difficult to explain. Theoretically, SUV reflects metabolic activity and, therefore, might correlate stronger with several proliferation biomarkers. Obviously, metabolic activity and proliferation are not associated directly.

Similarly, our analysis found only slight correlation between  $SUV_{max}$  and expression of EGFR (0.38). EGFR is a cell membrane tyrosine kinase receptor [64, 65]. As reported previously, EGFR signaling is critical in development and cellular homeostasis, proliferation, and growth [64–66]. EGFR is overexpressed in most lung cancers [64–66]. Overexpression of EGFR is associated with a poor prognosis in non-small-cell lung cancer [66]. In addition, EGFR overexpression is also associated with chemoresistance in non-small-cell lung cancer [64, 66]. The present meta-

analysis showed that  $SUV_{max}$  cannot be used as a surrogate marker for EGFR expression in lung cancer.

Furthermore, we analyzed associations between  $SUV_{max}$  and expression of p53. As seen, these parameters correlate weakly (0.30). According to the literature, p53 is a protein encoded by the TP53 gene and plays a key role in tumor suppression and in the cellular response to DNA damage [2, 5]. Some authors indicated that high expression of p53 can be used as a predictor for better overall survival [2]. However, in the study of Tsao et al., p53 protein overexpression was a significant prognostic marker of shortened survival [5]. Relationships between  $SUV_{max}$  and p53 were analyzed in 6 previous studies with divergent results [13,22,34,41–43]. Our data suggest that SUV cannot be used as a surrogate marker for expression of p53.

Programmed cell death-ligand 1 or PD L1 is another very important biomarker in lung cancer [67]. PD L1 is an immune modulator that promotes immunosuppression by binding to PD-1 receptor [68]. PD L1 on the surface of tumor cells inhibits an immune-mediated attack by binding to PD-1 on cytotoxic T-cells [68, 69]. According to the literature, high expression of PD L1 is associated with shorter overall survival in patients with non-small cell lung cancer [70]. Therefore, prediction of PD L1 expression by imaging may be of interest in clinical practice. Our analysis identified only a slightly correlation (0.36) between  $SUV_{max}$  and PD L1 expression in lung cancer; that is,  $SUV_{max}$  cannot be used as a surrogate marker for PD L1 status.

Our analysis also showed that  $SUV_{max}$  cannot predict expression of cyclin D1 in lung cancer. As reported previously, data of the role of this protein are inconsequent. For example, Gautschi et al. found a strong pathological role for cyclin D1 deregulation in bronchial neoplasia [71]. However, Zhang et al. suggested in their meta-analysis that the expression of cyclin D1 is unlikely to be useful as a prognostic marker for NSCLC in clinical practice from current evidence [72].

The present meta-analysis identified a moderate pooled correlation between  $SUV_{max}$  and hypoxia-inducible factor-1 alpha (HIF-1 $\alpha$ ). According to the literature, HIF-1 $\alpha$  characterizes cellular responses to hypoxic stress [6, 7]. It has been reported that patients with lung cancer and positive HIF-1 $\alpha$  expression in tumor tissues had lower overall survival rate than patients with negative HIF-1 $\alpha$  expression [6, 7]. Furthermore, in a recent meta-analysis, it was suggested that HIF-1 $\alpha$  expression may be a prognostic

biomarker for lung cancer [6]. In addition, it is discussed that HIF-1 $\alpha$  might be a target for therapy in lung cancer [7]. Therefore, associations between PET parameters and HIF-1 $\alpha$  may be also of clinical importance.

Similarly, we calculated a moderate pooled correlation between SUV<sub>max</sub> and expression of VEGF. Previous reports indicated that VEGF overexpression is associated with poor prognosis for NSCLC patients [3]. Furthermore, VEGF plays an important role in sustaining the development and progression of lung cancer [73]. Notably, some reports indicated a great potential of anti-VEGF agents in therapy of lung cancer [74]. Therefore, possible relationships between VEGF expression and SUV in lung cancer may play a significant role to plane chemotherapy. In fact, if SUV or other PET parameters may predict VEGF expression and tumors with overexpression, respectively, then PET may also be used for therapy control with anti-VEGF agents.

Finally, the strongest correlation was found between SUV<sub>max</sub> and microvessel density (0.54). This finding seems to be logical. In fact, high metabolic activity may induce a high perfusion, which is associated with more vessels. SUV may identify hypervascularized tumor areas. Therefore, SUV may be used for evaluation of response to therapy with angiogenesis inhibitors.

The present meta-analysis also identified several other problems. Overall, most analyzed biomarkers are associated with SUV. This finding suggests that SUV<sub>max</sub> may reflect different histopathological features in lung cancer. However, as mentioned above, the calculated pooled correlations are slightly-to-moderate. Therefore, our analysis showed that SUV<sub>max</sub> cannot be used as an ultimate one-to-one surrogate marker for different receptor expressions in lung cancer.

Some reports suggested that other PET parameters like metabolic tumor volume or total lesion glycolysis are more sensitive than SUV<sub>max</sub> [75]. In fact, pretreatment SUV is commonly used as a relative measure of <sup>18</sup>F-FDG uptake and is considered a prognostic factor for risk stratification in different malignancies. However, as suggested previously, it does not reflect the heterogeneity of a tumor [76]. Therefore, to overcome this drawback of SUV, other PET parameters, such as metabolic tumor volume and total lesion glycolysis that reflect metabolic volume and activity, have been proposed as quantitative indexes of tumor metabolism [76, 77]. According to the literature, these parameters can be used as prognostic factors for survival in several malignant diseases like non-small lung cancer, pleural mesothelioma, and ovarian cancer [77–79]. Clearly, further researches are needed to investigate possible associations between several PET parameters and histopathology in lung cancer.

Furthermore, lung cancer involves several carcinomas with different histopathological features and behavior. Presumably, different subtypes of lung cancer may have also different associations between PET and histopathology. This question should also be analyzed by further investigations.

There were also other problems. Only 40 reports with small number of patients investigated associations between

PET parameters and histopathological features in lung cancer. Furthermore, most of the acquired studies were retrospective. Finally, according the QUADAS criteria, all involved studies showed partial verification bias, differential verification bias, and incorporation bias. Also, most of the studies had clinical review bias and diagnostic review bias. Clearly, further prospective studies with more patients are needed to investigate associations between PET and histopathology in lung cancer.

Some recent reports indicated that other histopathological markers like tumor-infiltrating CD8-positive T lymphocytes, cyclooxygenase-2, and survivin play also a great role in lung cancer [3, 4]. However, there were either no data or in each case only one report about relationships between PET and these histopathological factors. This should be also the purpose for further investigations.

In conclusion, our meta-analysis showed that SUV<sub>max</sub> may predict microvessel density and expression of VEGF, KI 67, and HIF-1 $\alpha$  in lung cancer. There were no significant associations between SUV<sub>max</sub> and expression of cyclin D1, EGFR, PD L1, PCNA, and p53.

## Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

## Ethical Approval

The study was approved by the institutional review board of the University of Leipzig. All procedures performed in the study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

## Conflicts of Interest

There are no conflicts of interest.

## Authors' Contributions

Alexey Surov conceptualized the data. Alexey Surov, Hans Jonas Meyer, and Andreas Wienke performed data curation. Alexey Surov, Hans Jonas Meyer, and Andreas Wienke did formal analysis. Alexey Surov, Hans Jonas Meyer, and Andreas Wienke investigated the data. Alexey Surov, Hans Jonas Meyer, and Andreas Wienke designed the methodology. Alexey Surov administered the project. Alexey Surov, Hans Jonas Meyer, and Andreas Wienke collected resources. Alexey Surov, Hans Jonas Meyer, and Andreas Wienke designed the software. Alexey Surov helped in supervision. Alexey Surov validated the data. Alexey Surov, Hans Jonas Meyer, and Andreas Wienke visualized the data. Alexey Surov wrote the original draft. Alexey Surov, Hans Jonas Meyer, and Andreas Wienke wrote, reviewed, and edited the data. All authors contributed equally to this work.

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