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META-ANALYSIS

Prognostic value of computed tomography derived skeletal muscle mass index in lung cancer: A meta-analysis

Xue-Lin Pan, Hong-Jun Li, Zhen Li, Zhen-Lin Li

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Abstract

BACKGROUND

The prognostic role of the skeletal muscle mass index (SMI) derived from computed tomography (CT) imaging been well verified in several types of cancers. However, whether the SMI could serve as a reliable and valuable predictor of long-term survival in lung cancer patients remains unclear.

AIM

To identify the prognostic value of the CT-derived SMI in lung cancer patients.

METHODS

The PubMed, Web of Science, and Embase electronic databases were searched up to November 5, 2021 for relevant studies. The Reference Citation Analysis databases were used during the literature searching and selection. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated to assess the association of the SMI with the overall survival (OS) of lung cancer patients. All statistical analyses were performed with STATA 12.0 software.

RESULTS

A total of 12 studies involving 3002 patients were included. The pooled results demonstrated that a lower SMI was significantly related to poorer OS (HR = 1.23, 95%CI: 1.11-1.37, $P < 0.001$). In addition, the subgroup analyses stratified by treatment (nonsurgery *vs* surgery), tumor stage (advanced stage *vs* early stage), and tumor type (non-small cell lung cancer *vs* lung cancer) showed similar results.

CONCLUSION

The CT-derived SMI is a novel and valuable prognostic indicator in lung cancer and might contribute to the clinical management and treatment of lung cancer patients.

Key Words: Skeletal muscle mass index; Computed tomography; Lung cancer; Prognosis; Meta-analysis

Core Tip: We searched the PubMed, Web of Science, and Embase electronic databases up to November 5, 2021, and a total of 12 studies involving 3002 patients were included. The pooled results demonstrated that a lower skeletal muscle mass index (SMI) was significantly related to poorer overall survival ($P < 0.001$). In addition, the subgroup analyses stratified by treatment (nonsurgery *vs* surgery), tumor stage (advanced stage *vs* early stage), and tumor type (non-small cell lung cancer *vs* lung cancer) showed similar results. The computed tomography-derived SMI is a novel and valuable prognostic indicator in lung cancer and might contribute to the clinical management and treatment of lung cancer patients.

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INTRODUCTION

Lung cancer is the leading cause of tumor-related deaths worldwide and can be categorized into non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC)[1,2]. Despite considerable advances in the clinical diagnosis, treatment, and management of lung cancer, the overall prognosis of lung cancer patients remains poor[3,4]. The tumor-node-metastasis (TNM) staging system is still the most authoritative tool to assess the disease severity and prognosis of lung cancer patients. However, in addition to disease stage, the prognosis of lung cancer patients can be affected or predicted by many factors.

In recent years, an increasing number of common clinical indicators have been identified to play a role in the evaluation of long-term survival in lung cancer, such as the D-dimer level, albumin-to-globulin ratio (AGR), lymphocyte-to-monocyte ratio, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio[5-8]. However, these blood indicators are unstable and may be changed by a number of factors or diseases. There are also some other stable prognostic indicators, such as ctDNA and circulating tumor cells[9-11], but they are relatively expensive and cannot be widely applied in clinics.

The skeletal muscle mass index (SMI) is calculated according to computed tomography (CT) images and can reflect the nutritional status of the body to a large extent. In addition, the two indicators, the area of skeletal muscle and height, involved in the calculation of SMI are both stable and reliable. The prognostic value of SMI in several cancers has been identified, such as gastric cancer, colorectal cancer, pancreatic adenocarcinoma, and renal cell carcinoma[12-16]. However, whether SMI could serve as a reliable and valuable prognostic index in lung cancer remains unclear.

Thus, the aim of this meta-analysis was to assess the prognostic role of CT-derived SMI in lung cancer, which might contribute to the evaluation of long-term survival and the formulation of therapy strategies for lung cancer patients.

MATERIALS AND METHODS

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA 2020) checklist and has been registered in PROSPERO.

Literature retrieval

The PubMed, Web of Science, and Embase electronic databases were searched from inception to November 5, 2021. The search strategy consisted of Medical Subject Heading terms and free-text terms with logical operators. The following terms were used during the literature search: Skeletal muscle mass index, SMI, lung, pulmonary, tumor, cancer, carcinoma, neoplasm, prognostic, survival, and prognosis. In detail, the specific search strategy was as follows: (Skeletal muscle mass index OR SMI) AND (lung OR pulmonary) AND (tumor OR cancer OR carcinoma OR neoplasm) AND (prognostic OR survival OR prognosis). In addition, the reference lists of the included studies were searched to identify additional eligible studies.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) Patients were pathologically diagnosed with lung cancer; (2) The SMI was calculated through CT images before antitumor treatment; and (3) The association between the SMI and overall survival (OS) was explored and assessed by hazard ratios (HRs) with 95% confidence intervals (CIs).

The exclusion criteria were as follows: (1) The HRs with 95%CIs were not directly reported in articles; (2) Reviews, meeting abstracts, letters, editorials, or case reports; and (3) Overlapping or duplicated data.

The Reference Citation Analysis databases were used during the literature searching and selection.

Data extraction

The following information was collected from the included studies: The first author, publication year, country, sample size, treatment (nonsurgery *vs* surgery), TNM stage, cutoff value of the SMI, tumor type, and HR with corresponding 95%CI.

Study quality assessment

The quality of the included studies was evaluated according to the Newcastle Ottawa Scale (NOS), and studies with an NOS score of 6 or higher were defined as high-quality studies[17].

The literature retrieval, selection, data extraction, and quality assessment were all conducted by two investigators independently. Any disagreement was resolved by team discussion.

Statistical analysis

All statistical analyses were conducted with STATA 12.0 software (College Station, TX, United States). The HRs with 95%CIs were calculated to assess the association between the SMI and OS. Heterogeneity was evaluated by Cochran's Q test and Higgins I^2 statistic; $P < 0.10$ and/or $I^2 > 50\%$ were defined as significant heterogeneity among studies, and the random effects model was applied for the pooled effect estimates; otherwise, the fixed effects model was used[18]. Subgroup analyses stratified by the treatment, tumor stage, and tumor type were further conducted. Sensitivity analysis for OS was performed by removing individual studies from the meta-analysis each time. Begg's funnel plot and Egger's test were conducted to evaluate publication bias. Significant publication bias was defined as a *P*-value less than 0.05, and the trim-and-fill method was applied to assess the influence of potentially unpublished papers on the stability of the pooled results[19].

RESULTS

Literature retrieval and selection

The detailed literature retrieval and selection process is presented in Figure 1. Ultimately, a total of 12 relevant retrospective studies were included in this meta-analysis[20-31].

Basic characteristics of the included studies

A total of 3002 lung cancer patients were enrolled among the 12 studies, with sample sizes ranging from 46 to 734. In most included studies, the patients were diagnosed at an advanced stage and received nonsurgical treatment. In addition, most studies only included NSCLC patients, and all studies were of high quality, with an NOS score of 6 or higher (Table 1).

Results of meta-analysis for association between SMI and OS

The pooled results demonstrated that a lower SMI was significantly related to poorer OS in lung cancer patients (HR = 1.23, 95%CI: 1.11-1.37, $P < 0.001$; $I^2 = 84.7\%$, $P < 0.001$) (Figure 2). Then, subgroup analyses based on the treatment [nonsurgery (HR = 1.15, 95%CI: 1.06-1.26, $P = 0.002$) *vs* surgery (HR = 5.71, 95%CI: 2.94-11.10, $P < 0.001$)], tumor stage [advanced stage (HR = 1.34, 95%CI: 1.07-1.68, $P = 0.011$) *vs* early stage (HR = 5.71, 95%CI: 2.94-11.10, $P < 0.001$)], and tumor type [NSCLC (HR = 1.97, 95%CI: 1.33-2.93, $P = 0.001$) *vs* lung cancer (HR = 1.07, 95%CI: 1.03-1.11, $P < 0.001$)] were performed, which showed similar results (Table 2). In addition, according to the subgroup analysis, the treatment strategy and tumor stage might be potential sources of heterogeneity (Table 2).

Sensitivity analysis

The sensitivity analysis indicated that the results of this meta-analysis were stable and that none of the included studies had a significant impact on the overall results (Figure 3).

Publication bias

Begg's funnel plot was asymmetric (Figure 4A), and Egger's test was significant ($P < 0.001$); therefore, significant publication bias was observed. The trim-and-fill method was used to detect potentially

Table 1 Basic characteristics of included studies

Ref.	Year	Country	Sample size	Treatment	TNM stage	Threshold of SMI (cm^2/m^2)	Tumor type	NOS
Jafri *et al*[20]	2015	United States	112	Non-surgery	IV	40	NSCLC	7
Suzuki *et al*[22]	2016	Japan	90	Surgery	I	Male: 43.75; female: 41.10	NSCLC	7
Sjøblom *et al*[21]	2016	Norway	734	Non-surgery	III-IV	NR	NSCLC	7
Shoji *et al*[24]	2017	Japan	147	Surgery	I	Male: 43.75; female: 41.10	NSCLC	7
Nattenmüller *et al*[23]	2017	Germany	200	Non-surgery	I-IV	NR	LC	7
Roch *et al*[28]	2020	France	142	Non-surgery	NR	Male: 52.4; female: 38.5	NSCLC	6
Abbass *et al*[25]	2020	United Kingdom	643	Non-surgery	III-IV	Male: 43; female: 41	LC	6
Dolan *et al*[26]	2020	United Kingdom	119	Non-surgery	I-III	Male: 53; female: 41	NSCLC	6
Magri *et al*[27]	2019	Israel	46	Non-surgery	IV	NR	LC	6
Katsui *et al*[29]	2021	Japan	60	Non-surgery	III	Male: 43; female: 24	NSCLC	7
Lee *et al*[30]	2021	Republic of Korea	70	Non-surgery	IIIB-IV	Male: 46; female: 29	SCC	6
Yang *et al*[31]	2021	China	639	Non-surgery	IIIB-IV	Male: 32.48; female: 27.82	NSCLC	7

TNM: Tumor-node-metastasis; SMI: Skeletal muscle mass index; NOS: Newcastle-Ottawa Scale; NR: Not reported; NSCLC: Non-small cell lung cancer; LC: Lung cancer; SCC: Squamous cell cancer.

Table 2 Results of meta-analysis

	No. of studies	HR	95%CI	*P* value	I^2 (%)	*P* value
Overall survival	12	1.23	1.11-1.37	< 0.001	84.7	< 0.001
Treatment						
Non-surgery	10	1.15	1.06-1.26	0.002	80.4	< 0.001
Surgery	2	5.71	2.94-11.10	< 0.001	0.0	0.655
Tumor stage						
Advanced stage	7	1.34	1.07-1.68	0.011	80.8	< 0.001
Early stage	2	5.71	2.94-11.10	< 0.001	0.0	0.655
Tumor type						
Non-small cell lung cancer	9	1.97	1.33-2.93	0.001	87.3	< 0.001
Lung cancer	3	1.07	1.03-1.11	< 0.001	0.0	0.471

HR: Hazard ratios; CI: Confidence interval.

unpublished articles and their impact on the overall results. Six potentially unpublished papers were identified (Figure 4B), and the pooled HR was 1.019 (95%CI: 1.005-1.033, P = 0.006) and 1.063 (95%CI: 0.949-1.192, P = 0.293) after combining these six studies, respectively. Thus, the six potentially unpublished studies might impact the overall results, and more high-quality studies are still needed to verify the above findings.

DISCUSSION

The current meta-analysis demonstrated that a lower pretreatment CT-derived SMI was significantly associated with poorer OS in lung cancer patients and might serve as a reliable and valuable prognostic indicator in lung cancer. The results of subgroup analyses based on the treatment, tumor stage, and tumor type all further verified the above findings.

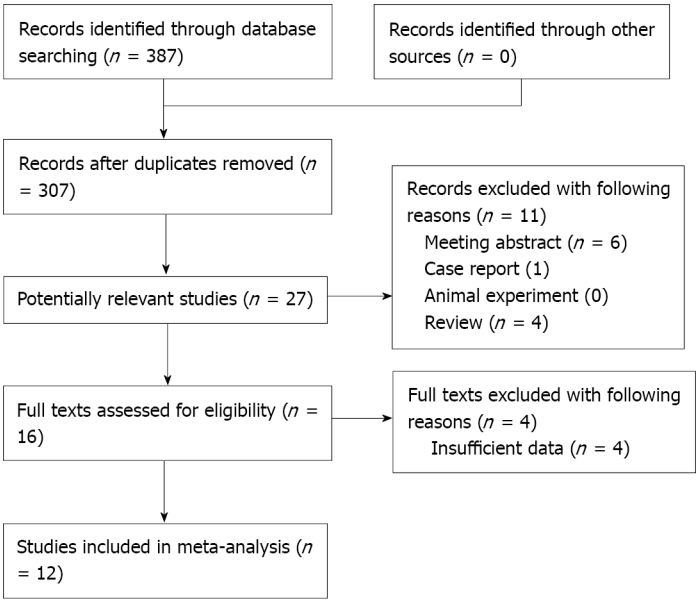

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Figure 1 Flow diagram of the meta-analysis.

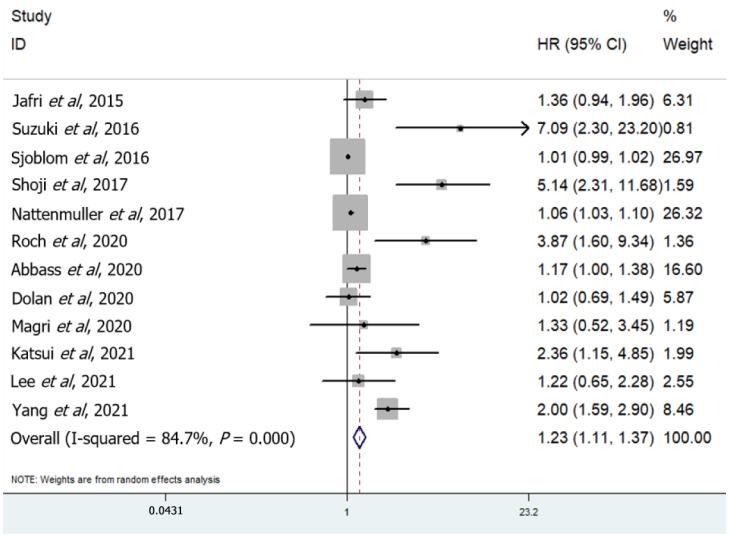

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Figure 2 Forest plot for association between skeletal muscle mass index and overall survival of lung cancer patients.

The SMI is a novel indicator reflecting nutritional status, and it is well known that the nutritional condition of the body is essential for the prognosis of lung cancer patients. The clinical role of a number of nutritional indicators has been widely explored in lung cancer. Li *et al*[6] included eight studies involving 3496 patients and demonstrated that a low pretreatment AGR was a predictor of poor OS (HR = 1.88, 95%CI: 1.49-2.38, $P < 0.001$) and disease-free survival (DFS) (HR = 2.09, 95%CI: 1.56-2.81, $P < 0.001$) in lung cancer[6]. In addition, Li *et al*[32] included ten relevant studies involving 5085 patients and showed that a low prognostic nutritional index calculated based on the peripheral serum albumin level and total lymphocyte count was significantly related to unfavorable OS (HR = 1.72, 95%CI: 1.43-2.06, $P = 0.000$) in lung cancer, especially in NSCLC (HR = 1.93, 95%CI: 1.56-2.37, $P = 0.000$)[32]. Furthermore, a high pretreatment controlling nutritional status score calculated based on the peripheral serum albumin level, total blood cholesterol level, and total lymphocyte count was identified to be positively correlated with poor OS (HR = 1.63, 95%CI: 1.40-1.88, $P < 0.001$), DFS/recurrence-free survival (HR = 1.65, 95%CI: 1.35-2.01, $P < 0.001$), and postoperative complications (odds ratio = 1.58, 95%CI: 1.21-2.06, $P = 0.001$) in NSCLC patients[33]. However, the clinical application of these indices is severely limited because they are unstable and could be affected by many factors.

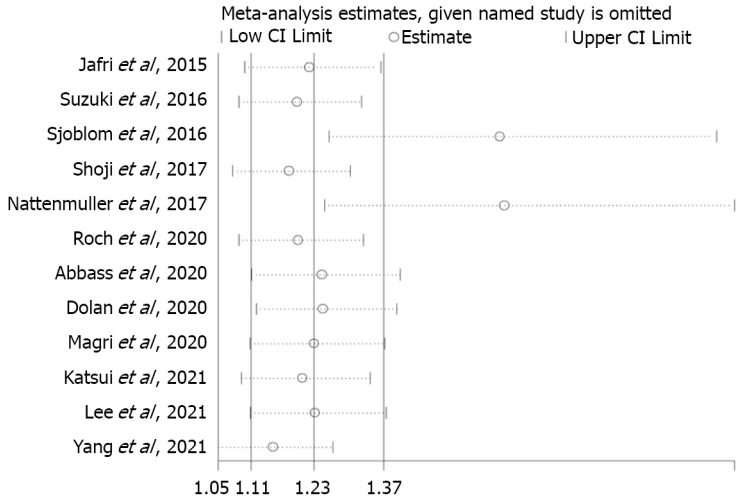

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Figure 3 Sensitivity analysis of association between skeletal muscle mass index and overall survival of lung cancer patients.

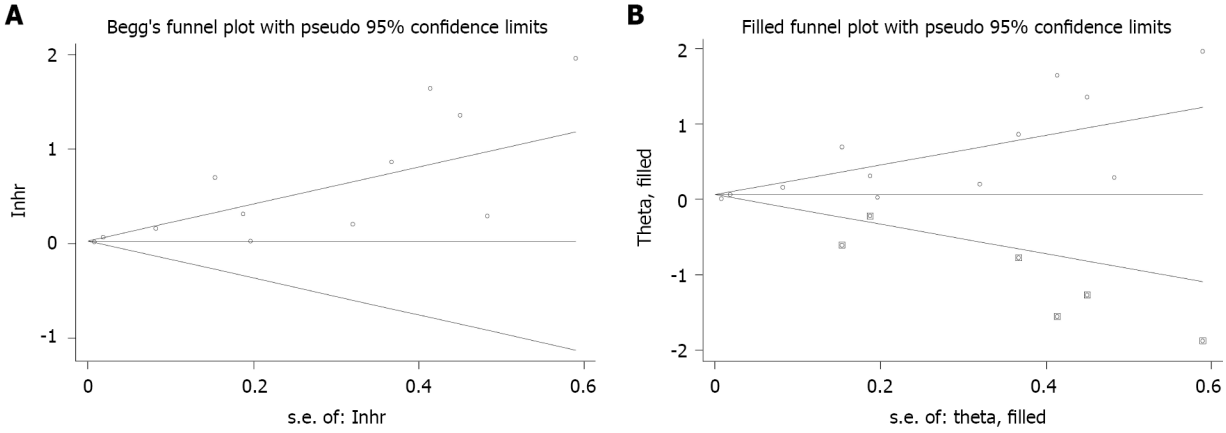

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Figure 4 Association between skeletal muscle mass index and overall survival of lung cancer patients. A: Begg's funnel plot; B: Filled funnel plot.

In most of the included studies, the patients were divided into high or low SMI groups according to the values of SMI. However, the thresholds of SMI in the included studies were different, which means that the optimal cutoff values of SMI in different groups of lung cancer should be inconsistent. Although most relevant studies differentiated cutoff values based on sex, we deem that age should also be considered because age is a very important factor affecting the basic nutritional status. Thus, more rigorously differentiated thresholds should be applied in future relevant studies. In addition, SCLC is a pathological type with a high degree of malignancy and rapid progression, and most SCLC patients are diagnosed at an advanced stage. SCLC patients are prone to recurrence and metastasis, and the application of the current staging system for SCLC is extremely limited clinically. Unfortunately, none of the included studies focused on this type of lung cancer and explored the prognostic value of the SMI in SCLC. However, we believe that the SMI might be a novel and valuable predictor of survival and therapeutic effects in SCLC patients. Thus, we hope that more scholars could pay attention to the clinical role of the SMI in SCLC in the future.

There are several limitations in this meta-analysis. First, all included studies were retrospective, and the sample sizes were relatively small. Second, more specific subgroup analyses could not be conducted due to the lack of detailed data. Third, significant heterogeneity was observed in our meta-analysis, but the sources of heterogeneity were not identified.

CONCLUSION

The CT-derived SMI is a novel and valuable prognostic indicator in lung cancer and might contribute to the clinical management and treatment of lung cancer patients. However, more prospective high-quality studies are still needed to verify the above findings.

ARTICLE HIGHLIGHTS

Research background

The prognostic role of the skeletal muscle mass index (SMI) calculated through computed tomography (CT) images in several types of cancers has been demonstrated.

Research motivation

Whether the SMI could serve as a reliable and valuable predictor for long-term survival in lung cancer remains unclear.

Research objectives

To verify the prognostic value of the CT-derived SMI in lung cancer patients.

Research methods

Several electronic databases were searched up to November 5, 2021 for relevant studies. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated to assess the association of the SMI with the overall survival (OS) of lung cancer patients. All statistical analyses were performed with STATA 12.0 software.

Research results

The pooled results demonstrated that a lower SMI was significantly related to poorer OS (HR = 1.23, 95%CI: 1.11-1.37, $P < 0.001$). In addition, the subgroup analyses stratified by treatment (nonsurgery *vs* surgery), tumor stage (advanced stage *vs* early stage), and tumor type (non-small cell lung cancer *vs* lung cancer) showed similar results.

Research conclusions

The CT-derived SMI is a novel and valuable prognostic indicator in lung cancer.

Research perspectives

The SMI might contribute to the clinical management and treatment of lung cancer patients.

FOOTNOTES

Author contributions: Li ZL made substantial contributions to the conception and design of the work; Pan XL and Li HJ searched and selected the materials and extracted the data; Pan XL wrote the manuscript; Pan XL, Li HJ, Li Z, and Li ZL revised the paper carefully and also contributed to the statistical analysis; all authors have read and approved the final manuscript.

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