Review

Sarcopenia is an independent unfavorable prognostic factor of non-small cell lung cancer after surgical resection: A comprehensive systematic review and meta-analysis

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ABSTRACT

Background: Whether sarcopenia has any impact on long-term survival of patients with surgically treated non-small cell lung cancer (NSCLC) remains unclear. We conducted a meta-analysis focusing on current topic comprehensively for the first time.
Methods: We systematically searched relevant studies in PubMed, Embase, and Cochrane Library up to July 3, 2018. Data of 5-year overall survival (OS) and disease-free survival (DFS) rates as well as hazard ratio (HR) of OS were collected for analysis by using the STATA 12.0 package.
Results: A total of 6 cohort studies consisting of 1213 patients (422 patients with sarcopenia and 791 patients without) were included for analysis. Meta-analysis showed that patients with sarcopenia had a significantly lower 5-year OS rate (risk ratio (RR) = 1.63; 95% confidence interval (CI) = [1.13, 2.33]; P = 0.008) than those without, which was more prominent in patients with early-stage NSCLC. Sarcopenia was found to be an independent predictor of poor OS in patients with surgically treated NSCLC (HR = 2.85; 95%CI = [1.67, 4.86]; P < 0.001). With a limited sample size, there was no sufficient evidence of significantly different 5-year DFS rate between the two groups (RR = 1.14; 95%CI = [0.59, 2.17]; P = 0.70). However, in the subgroup of patients with early-stage NSCLC, sarcopenia was associated with a significantly lower 5-year DFS rate (RR = 1.59; 95%CI = [1.01, 2.52]; P = 0.046).
Conclusion: Patients with sarcopenia had a significantly worse prognosis than those without after surgical resection of NSCLC especially in those at early stage. Sarcopenia is an independent unfavorable prognostic factor for patients with surgically treated NSCLC. (246 words).

1. Introduction

Lung cancer remains to be the leading cause of cancer-related death worldwide with an estimated incidence rate of 1.8 million cases per year [1] and non-small cell lung cancer is reported to account for nearly 80% of all lung cancers [2]. Surgical resection still remains to be the preferred therapeutic option for patients with resectable NSCLC. Despite the advances of surgery in managing NSCLC, the 5-year survival rate of patients with surgically treated NSCLC ranges from about 25% to 73% according to pathological stage [3]. Therefore, it seems important to investigate the prognostic factors for those NSCLC patients after surgical resection since these factors could help direct the follow-up decision and selection of adjuvant therapy for each individual case.

Sarcopenia, also defined as skeletal muscle depletion, is one of the component of cancer cachexia syndrome, which was reported to be closely correlated to mobility disorder, disability, loss of independence and even increased risk of death [4]. The prevalence of sarcopenia increases with aging reaching to 11%–50% in people of

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more than 80 years old [4]. However, in patients with NSCLC, the rate of sarcopenia was reported to be as high as 46.8% [5]. Sarcopenia has been reported to significantly correlate with the prognosis of patients with advanced lung cancer [6]. However, in patients with surgically treated NSCLC, the prognostic value of sarcopenia remains controversial due to the fact that only several studies investigated its role in predicting the prognosis of NSCLC patients after surgical resection. Some studies found that patients with sarcopenia had a significant worse survival than those without after surgical resection of NSCLC [7,8]; while others found that sacopenia had no impact on survival of those patients [9]. Therefore, in order to draw an objective conclusion about the prognostic value of sarcopenia, we conducted this systematic review and meta-analysis to investigate the actual impact of sarcopenia on survival of patients with surgically treated NSCLC by pooling all those available evidence together. To our knowledge, this is the first meta-analysis focusing on current topic.

2. Methods and materials

2.1. Search strategies

We systematically searched the following databases for retrieving relevant studies up to July 3, 2018: PuMed, Embase, and Cochrane Library. Our searching strategies included the following terms: (((((sarcopenia) OR skeletal muscle index) OR skeletal muscle depletion) OR muscle mass)) AND (((non-small cell lung cancer) OR nonsmall cell lung cancer) OR NSCLC). We also scanned the reference lists from the studies selected by searching to further identify relevant studies.

2.2. Study selections

After retrieving all those relevant studies, we used the following criteria for study inclusion: 1) randomized controlled trials (RCT) or observational studies focusing on patients with surgically treated NSCLC; 2) studies comparing the survival of patients with sarcopenia and those without; 3) studies providing sufficient data of overall survival (OS) and disease-free survival (DFS); 4) if studies were conducted on the same patients, the most recent or completed one was chosen. The exclusion criteria were as follow: 1) patients with small cell lung cancer or with not surgically treated NSCLC; 2) no sufficient data for analysis; 3) studies not published in English; 4) case reports, conference abstracts, reviews, experiments.

2.3. Data extraction and quality assessment

Two authors independently collected the data for analysis by using a standardized data collection form which consisted of first author, year and countries of publication, disease stage, age, sample size, follow-up time, and study design. The outcomes included 5-year OS and DFS rates as well as hazard ratio (HR) of OS. These two authors compared the data independently and if there was a discrepancy, another third author would resolve it. We used the Jadad scale [10] to assess the quality of RCTs and the Newcastle-Ottawa Scale (NOS) as we previously described [11], which consists of three factors: patient selection, comparability of the study groups, and assessment of outcome, to assess the quality and risk-of-bias analysis of observational studies. We assigned a score of 0–9 (allocated as stars) to each observational study and here we defined the high-quality study as a study with quality scores ≥7. We used the name of the first author and year of publication of the study for identification.

2.4. Statistical analysis

We used the STATA 12.0 package (StataCorp, College Station, TX, USA) for all those analyses in accordance to the PRISMA guidelines [12]. For comparing 5-year OS and DFS rates, risk ratio (RR) with 95% confidence interval (CI) was applied, and those data were extracted directly from the text or from the Kaplan–Meier curves from each study. HR with 95% CI was also used to compare OS between patients with sarcopenia and those without. The between-study heterogeneity was assessed by using $\chi 2$-based Q statistics and I^2 test. If high heterogeneity between studies ($P < 0.1$ or $I^2 > 50\%$) was observed, random effects models were applied. Otherwise, fixed effects models were used. Moreover, we conducted the sensitivity analysis by sequentially removing each study. Subgroup analysis based on tumor stage was also conducted. We used a funnel plot to assess publication bias and tested its asymmetry by applying Begg's test and Egger's test [13]. A two-sided P value of less than 0.05 was defined as statistical significance.

3. Results

3.1. Description of studies

A flow chart of our meta-analysis for study assessment was shown in Fig. 1. A total of 315 papers were found after initial search. After initial evaluation, we found 24 papers for detailed evaluation. However, some of those papers were further excluded for including patients with small cell lung cancer or patients without surgical resection or not focusing on survival analysis. One study was also excluded for no relevant data for analysis [14]. Finally, lacking of RCTs, only a total of 6 cohort studies consisting of 1213 patients (422 patients with sarcopenia and 791 patients without) were included for current meta-analysis [7–9,15–17]. The main characteristics extracted from these included studies were shown in Table 1. Nearly all those patients had a localized resectable disease and the majority of those patients had pathologic stage I disease. All those studies except one [9] had a relatively long follow-up time. Nearly all those studies defined sarcopenia by measuring skeletal muscle or total psoas cross sectional area at the level of the third lumbar vertebra using computed tomography images normalized for height. Data analyzed in these included studies consisted of 5-year OS and DFS rates as well as HRs of OS (Table 2). Five-year OS rate could be obtained from all those studies while 5-year DFS rate could be retrieved from only 3 studies. The HR of OS was reported in 5 studies.

3.2. Quality assessment and risk of bias

With only cohort studies included, we assessed the quality assessment and risk-of-bias analysis by using the NOS. Quality assessment of all those studies was listed in Table 1. Four studies were evaluated as high quality while other two studies were evaluated as low quality, suggesting a potential risk of bias.

3.3. Meta-analysis of the impact of sarcopenia on the survival of patients with surgically treated NSCLC

All those studies reported impact of sarcopenia on 5-year OS rate of patients with surgically treated NSCLC with a total of 1213 patients. Patients with sarcopena yielded a significantly lower 5-year OS rate than those without after surgical resection of NSCLC (61.1% VS 74.2%; random effects: RR = 1.63; 95%CI = [1.13, 2.33]; P = 0.008; $I^2 = 73.1\%$) (Fig. 2A). Only three studies reported the impact of sarcopenia on 5-year DFS rate of patients with surgically treated NSCLC with a total of 557 patients. As a result, there was no
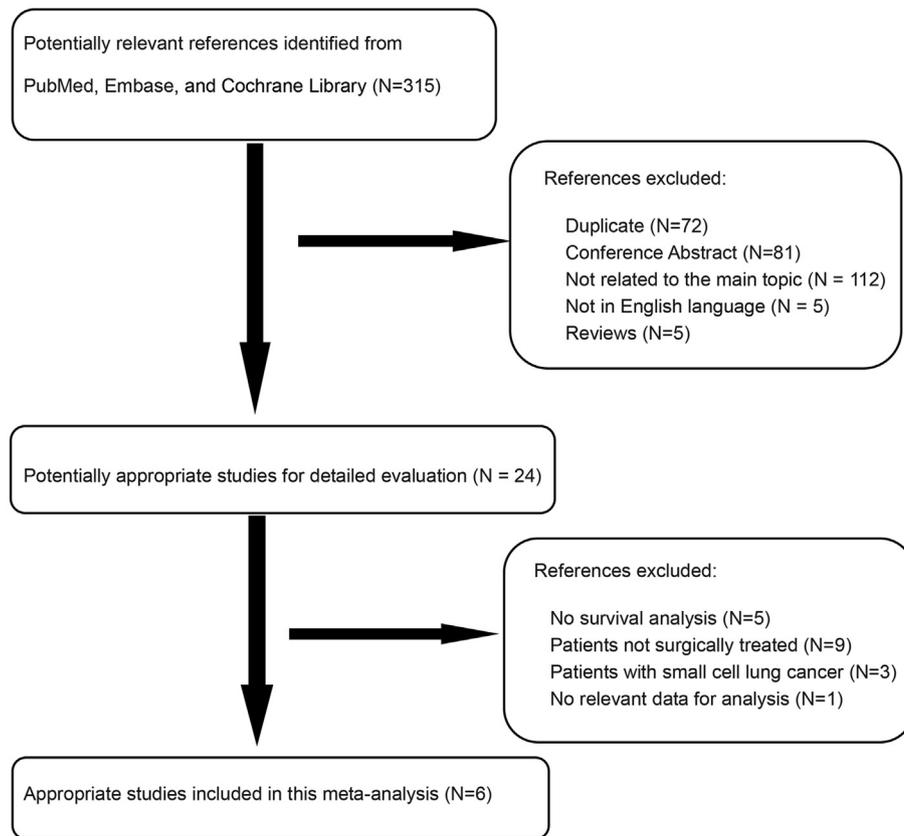
Fig. 1. A flow diagram of the progress of study assessment through the meta-analysis.

significant difference of 5-year DFS rates between patients with sarcopenia and those without (72.1% VS 70.3%; random effects: RR = 1.14; 95%CI = [0.59, 2.17]; P = 0.70; I^2 = 72.1%) (Fig. 2B). Sarcopenia was found to be an independent unfavorable predictor of poor OS in NSCLC patients after surgical resection (random effects: HR = 2.85; 95%CI = [1.67, 4.86]; P < 0.001; I^2 = 64.5%) (Fig. 3). However, it should be noted that potential heterogeneities were observed during analysis.

3.4. Subgroup analysis based on tumor stage

Due to obvious heterogeneities among those included studies, we conducted a subgroup analysis based on tumor stage of those patients to explore possible heterogeneities. Three studies only focused on stage I NSCLC patients with a total of 452 patients [7,8,16], while other three studies included patients at all stages with a total of 761 patients [9,15,17]. In patients with stage I NSCLC, patients with sarcopenia yielded significantly lower 5-year OS (RR = 2.09; 95%CI = [1.51, 2.88]; P < 0.001) (Fig. 2A) and DFS rates (RR = 1.59; 95%CI = [1.01, 2.52]; P = 0.046) (Fig. 2B) than those without; while in patients with all stages of NSCLC, there was no significant difference of 5-year OS (RR = 1.37; 95%CI = [0.78, 2.42]; P = 0.277) (Fig. 2A) and DFS rates (RR = 0.67; 95%CI = [0.42 1.05]; P = 0.080) (Fig. 2B) between patients with sarcopenia and those without. However, sarcopenia was still found to be a significant predictor of poor OS in both patients with stage I NSCLC (HR = 4.68; 95%CI = [2.76, 7.94]; P < 0.001) and those with all stages of NSCLC (HR = 1.71; 95%CI = [1.21, 2.41]; P = 0.003) (Fig. 3).

3.5. Sensitivity analysis and publication bias

We conducted a sensitivity analysis by sequential removal of

each study to evaluate the stability of our results based on 5-year OS rate and OS, and we found that sequentially removing each study did not change outcomes of primary analysis (Fig. 4). Publication bias was tested by a funnel plot for the analysis of 5-year OS rate and the plot had a symmetrical appearance (Begg's test: P = 0.85; Egger's test: P = 0.48) (Fig. 5), which indicated no publication bias.

4. Discussion

The prognostic value of sarcopenia in patients with surgically treated NSCLC remains undetermined and it is reasonable that previous studies have drawn controversial conclusions since only several studies have been carried out with a limited sample size [7—9,15—17]. Hence, we conducted this meta-analysis for the first time to figure out the actual impact of sarcopenia on survival of NSCLC patients after surgical resection by pooling all those available evidence together. In our meta-analysis, we included 6 cohort studies with a total of 1213 patients with surgically treated NSCLC (422 patients with sarcopenia and 791 patients without). We found that patients with sarcopenia had a significantly lower 5-year OS rate than those without (P = 0.008) while there was no sufficient evidence of significantly different 5-year DFS rate between the two groups (P = 0.701). Moreover, sarcopenia was found to be an independent predictor of poor OS in patients with surgically treated NSCLC (HR = 2.85; 95%CI = [1.67, 4.86]; P < 0.001). However, when subgrouped by tumor stage, sarcopenia was found to have a significant negative impact on both 5-yeasr OS and DFS rates of patients with stage I NSCLC, while it was not significantly correlated to that of patients with NSCLC of all stages after surgical resection. Therefore, our meta-analysis added to the evidence that sarcopenia had a significant unfavorable impact on prognosis of NSCLC

Table 1
Characteristics of the included studies in this meta-analysis.

Author	country	Patients	Age (years)	Follow-up	Sample size (N)	Sarcopenia definition	Sarcopenia (N)	Non-sarcopenia (N)	Study design	Quality assessment
Suzuki 2016	Japan	patients with stage I NSCLC undergoing wedge resection, segmentectomy, or lobectomy	Mean: 68.7 ± 8.7	NA	90	SMCA at the level of the third lumbar vertebra using CT images normalized for height (m^2) $\leq$41.10 cm^2/m^2 for women and $\leq$43.75 cm^2/m^2 for men.	32	58	Cohort study	NOS: 7 stars
Hervochon 2017	France	Patients with pathologic stage I-IV treated with pneumonectomy	Mean: 62.6 ± 10.3	NA	161	The cross-sectional total psoas area at the third lumbar vertebra level using CT images $\leq$1601 mm^2 for men and $\leq$999 mm^2 for women	53	108	Cohort study	NOS: 6 stars
Tsukioka 2017	Japan	male patients with pathological stage I NSCLC undergoing segmentectomy or lobectomy	Median: 68 (46−93)	Median: 61 months	215	SMCA at the level of the third lumbar vertebra using CT images normalized for height (m^2) $\leq$49 cm^2/m^2.	30	185	Cohort study	NOS: 8 stars
Shoji 2017	Japan	patients with pathological stage I NSCLC undergoing wedge resection, segmentectomy, or lobectomy	Median: 68 (42−86)	Median: 59 months (range: 0−94 months)	147	SMCA at the level of the third lumbar vertebra using CT images normalized for height (m^2) $\leq$41.10 cm^2/m^2 for women and $\leq$43.75 cm^2/m^2 for men.	57	90	Cohort study	NOS: 8 stars
Kim 2017	Korea	Patients with pathologic stage I-IV treated with segmentectomy, lobectomy, bilobectomy, or pneumonectomy	Mean: 62.9 ± 9.6	Median: 26.3 months	272	SMCA at the level of the third lumbar vertebra using CT images normalized for height (m^2) $\leq$39 cm^2/m^2 for women and $\leq$55 cm^2/m^2 for men.	61	211	Cohort study	NOS: 6 stars
Nakamura 2018	Japan	patients with pathological stage 0-III NSCLC undergoing sublobar resection, lobectomy, or more	Median: 71 (38−87)	Median: 35.5 months (range: 1−145 months)	328	The cross-sectional total psoas area at the third lumbar vertebra using CT images normalized for height (m^2) $\leq$3.92 cm^2/m^2 for women and $\leq$6.36 cm^2/m^2 for men.	183	145	Cohort study	NOS: 7 stars

Note: NSCLC = non-small cell lung cancer; NA = not available; SMCA = skeletal muscle cross sectional area; CT = computed tomography; NOS=Newcastle-Ottawa Scale.

Table 2
Main outcomes extracted from the studies included in our meta-analysis.

Author	Comparisons	5-year OS rate[a]		5-year DFS rate[b]		OS	
		Sarcopenia	Non-sarcopenia	Sarcopenia	Non-sarcopenia	hazard ratio	95% confidence interval
Suzuki 2016	Sarcopenia vs Non-sarcopenia	10/28 (72.8%)	7/45 (85.8%)	9/29 (75.0%)	8/44 (85.0%)	7.09	2.30–23.20
Hervochon 2017	Sarcopenia vs Non-sarcopenia	43/10 (19.6%)	70/38 (34.8%)	NA	NA	1.57	1.01–2.45
Tsukioka 2017	Sarcopenia vs Non-sarcopenia	17/13 (42.5%)	48/137 (73.8%)	11/19 (63.8%)	42/143 (77.5%)	3.30	1.31–7.56
Shoji 2017	Sarcopenia vs Non-sarcopenia	13/44 (77.4%)	11/79 (87.3%)	NA	NA	5.14	2.31–11.68
Kim 2017	Sarcopenia vs Non-sarcopenia	10/51 (83.8%)	45/166 (78.8%)	16/45 (73.8%)	83/128 (60.9%)	NA	NA
Nakamura 2018	Sarcopenia vs Non-sarcopenia	71/112 (61.0%)	23/122 (84.0%)	NA	NA	1.94	1.11–3.39

Note: a: Expressed as no. alive/no. dead and percentage; b: Expressed as no. with other survival status/no. alive without disease and percentage; OS = overall survival; DFS = disease-free survival; NA = not available.
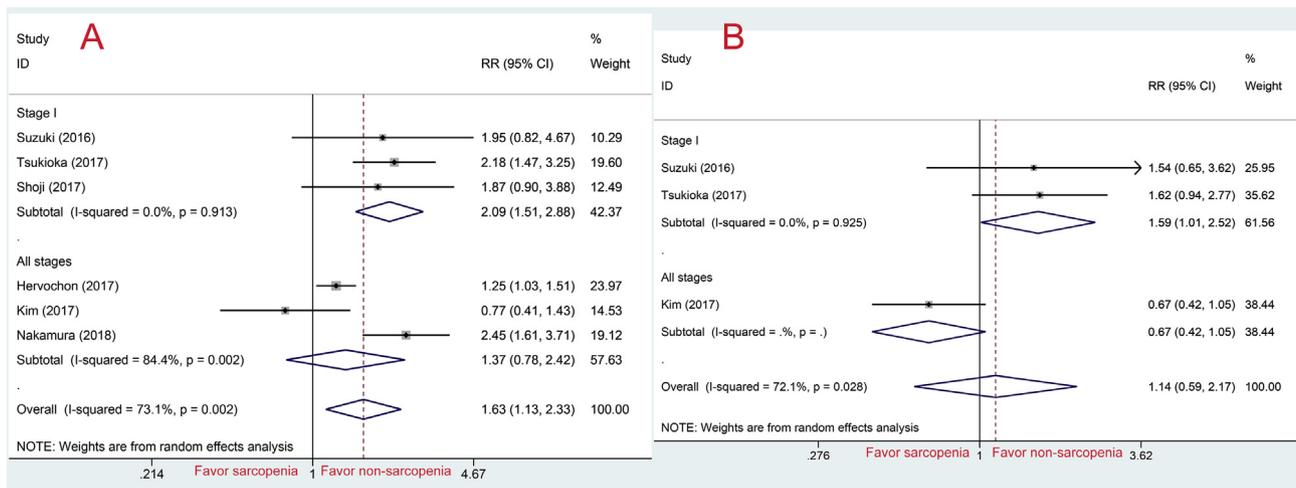

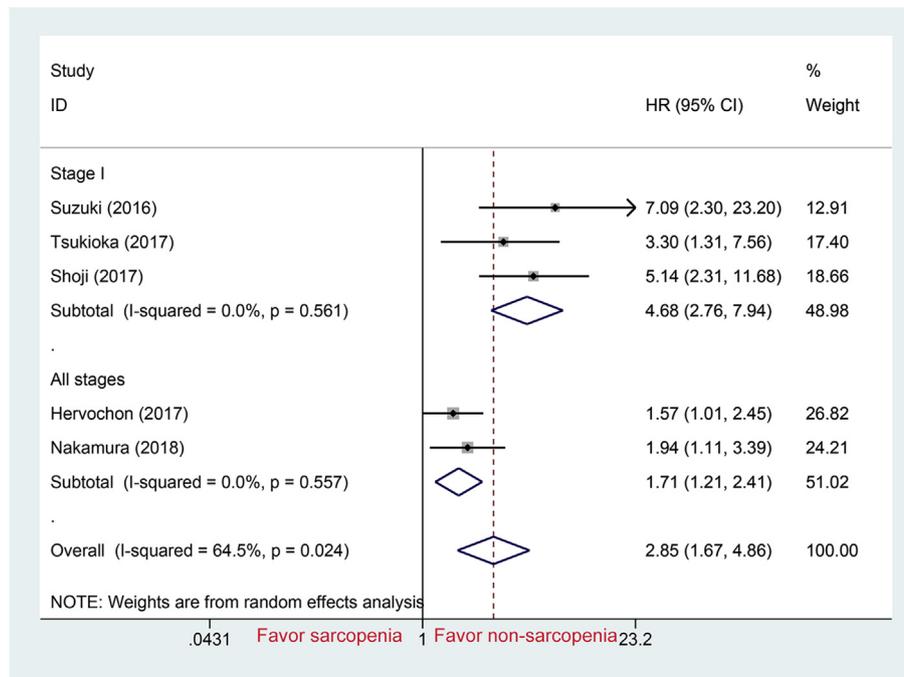**Fig. 2.** Forest plot of (A): 5-year overall survival rate, (B): 5-year disease-free survival rate.

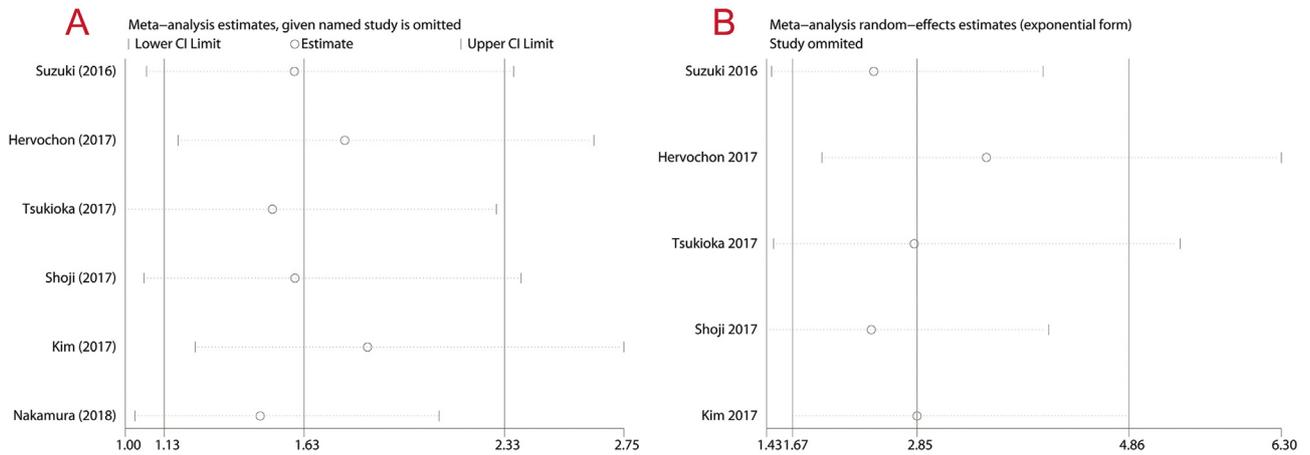

Fig. 3. Forest plot of overall survival.

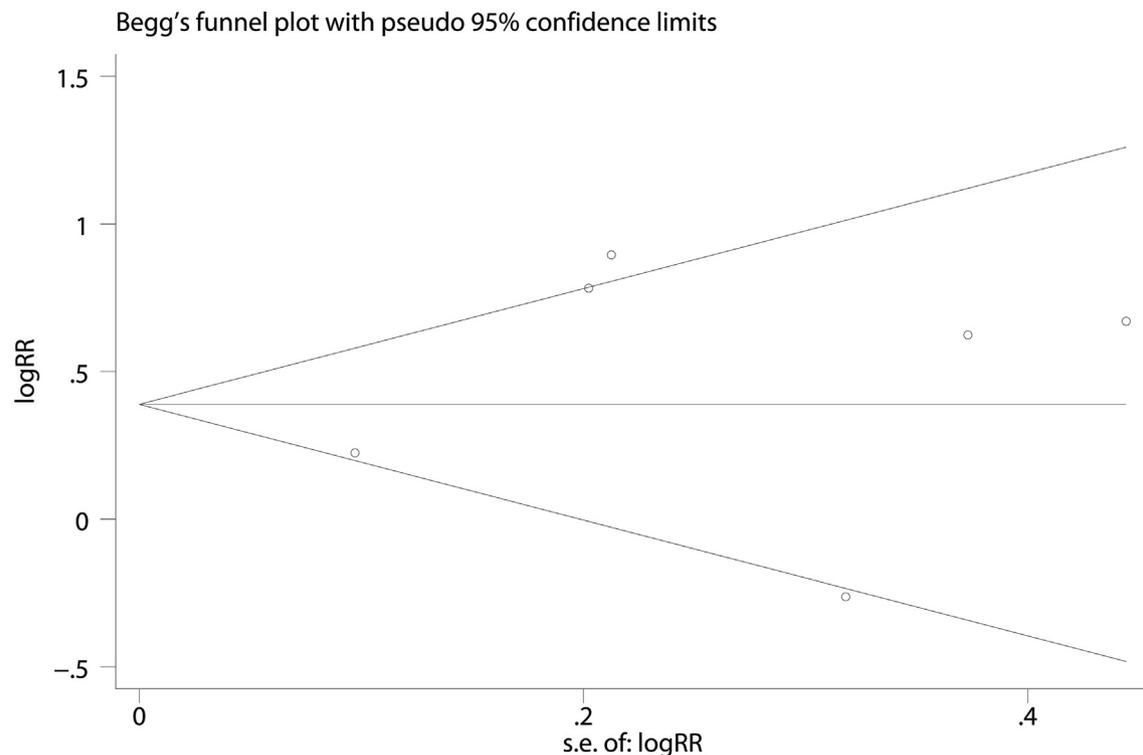**Fig. 4.** Sensitivity analysis for (A): 5-year overall survival rate, (B): overall survival.

Fig. 5. Funnel plot of the included studies for the analysis of 5-year overall survival rate. Begg's test: P = 0.85; Egger's test: P = 0.48.

patients after surgical resection, especially in patients with early-stage NSCLC.

Sarcopenia, defined as age-associated loss of skeletal muscle mass and function, is highly prevalent in cancer patients [18]. Previously, sarcopenia was found to be significantly and independently associated with postoperative complications, chemotherapy-induced toxicity and poor survival in cancer patients [19], such as esophageal cancer [20], gastric cancer [21], pancreatic cancer [22] and colorectal cancer [23]. In patients with advanced NSCLC, sarcopenia was correlated to chemotherapy-induced hematological toxicity [24] and also significantly associated with poor prognosis of patients treated with chemotherapy [25]. However, the impact of sarcopenia on patients with NSCLC undergoing surgical resection remains unclear. For short-term outcomes, some reported that sarcopenia was a risk factor of

developing postoperative major complications [17]; while other found that there was no significant correlation between sarcopenia and risk of postoperative complications [9]. However, as for long-term survival, most of previous studies found that patients with sarcopenia had a significantly worse OS than those without and sarcopenia was an independent predictor of poor OS in NSCLC patients after surgical resection [7,8,15–17]; while only one study reported that sarcopenia seemed to have no significant impact on survival of patients with surgically treated NSCLC [9]. However, this study was biased by the unbalanced baseline characteristics between the two groups and a relatively short follow-up time (median: 26.3 months) [9]. After pooling those evidence together, we found that sarcopenia had a significantly unfavorable impact on long-term OS of patients with NSCLC after surgical resection, especially in patients with early-stage NSCLC. However, similar to

previous studies which had a limited sample size [7–9], we also found that sarcopenia had no significant impact on DFS of patients with surgically treated NSCLC of all stages but a significant impact of DFS of patients with early-stage NSCLC. Previous studies also found that there was a trend towards worse 5-year DFS in patients with sarcopenia [7,8]. Moreover, there was evidence that sarcopenia remained to be an independent predictor of postoperative early recurrence in patients with pathologic N2-positive NSCLC after surgical resection [14]. Therefore, if given more cases, we believe that the difference of DFS between patients with sarcopenia and those without might be observed. Taken together, our study proved that sarcopenia had a significant negative impact on the prognosis of patients with NSCLC after surgical resection, especially in patients with early-stage NSCLC. Therefore, our study highlighted the awareness of clinical prognostic value of sarcopenia in NSCLC patients especially in those at early stage and that patients with sarcopenia intended for surgery required careful planning. For example, perioperative correction of sarcopenic status, close postoperative follow-up and optimal adjuvant therapy plan might be more emphasized for patients with sarcopenia intended for surgical resection of NSCLC even when they were at early stage.

The detailed interaction between sarcopenia and poor prognosis of patients with surgically treated NSCLC remains to be determined. Previous studies showed that sarcopenia status was significantly correlated to immune-nutritional parameters such as geriatric nutritional risk index and controlling nutritional status, which enables evaluation of nutritional status, protein reserve, calorie depletion, and immune defense [16]. Therefore, sarcopenia status was commonly accompanied with malnutrition and disabled immune function. Moreover, patients with sarcopenia had a higher neutrophil/lymphocyte ratio than those without [14] and the elevated neutrophil/lymphocyte ratio indicated a relative lymphocytopenia, which may exhibit a poor lymphocyte-mediated immune response to cancer [26]. As a result, sarcopenia innately decreased the anticancer ability of cancer patients, thus leading to a poor prognosis of those patients. Moreover, sarcopenia had a significant linear relationship with systemic inflammatory markers such as serum C-reactive protein, which played key roles in carcinogenesis and was shown to be of prognostic significance in lung cancer [27]. Other studies reported that sarcopenia may give rise to chemotherapy toxicities and a poorer response to chemotherapy and thus it seemed possible that patients with sarcopenia were less likely to receive and complete the multidisciplinary team-planned treatment especially in patients with advanced NSCLC [28]. Therefore, further studies are needed to elucidate the actual interaction between sarcopenia and lung cancer.

Several limitations existed in our meta-analysis. First, only several retrospective cohort studies with a limited sample size could be included for analysis, which might reduce the statistical power. Second, potential heterogeneities during analysis and low quality of several studies could also affect the validity of our results. Third, data of 5-DFS rate could be obtained from only 3 studies, and as a result, the impact of sarcopenia on DFS in those patients should be further verified. Moreover, the definition of sarcopenia varied among those studies. For example, some studies measured total skeletal muscle area in the third lumbar vertebra while others only measured total psoas muscle area and they utilized slightly different cut-off points for defining sarcopenia, which could cause significant heterogeneities. Hence, consensus on well-recognized definition of sarcopenia should be made for better investigation on the prognostic value of sarcopenia in patients with surgically treated NSCLC. Therefore, further well-conducted studies are needed to confirm and update our conclusions.

5. Conclusion

We conducted the first meta-analysis to investigate the impact of sarcopenia on long-term survival of patients with surgically treated NSCLC. We found that patients with sarcopenia had a significantly worse prognosis than those without after surgical resection especially in patients with early-stage NSCLC. Therefore, sarcopenia remains to be an independent unfavorable prognostic factor for patients with surgically treated NSCLC. Further studies, however, are needed to confirm and update our conclusions.

Author's contribution

Han-Yu Deng, Liang Hou, and Panpan Zha drafted the manuscript. Kai-Li Huang and Lei Peng collected those medical data. Han-Yu Deng, Liang Hou, and Panpan Zha revised the manuscript. Han-Yu Deng and Liang Hou designed the study.

Conflict of interests

None declared.

Acknowledgement

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