

Peer review file

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Reviewer A

Comment 1: Figure 1 of the manuscript extraction flowchart is cited in the paragraph "Sarcopenia Predicts Poor Prognosis After Surgery in Patients with NSCLC" in Results. I don't think this is necessary.

Reply 1: Thank you for pointing out our mistake. We have deleted "Figure 1" in the paragraph, "Sarcopenia Predicts Poor Prognosis After Surgery in Patients with NSCLC" in the Results. Furthermore, we have added a sentence to the study limitations

1. Figure reference has been changed From "Figure 1-3" to "Figure 2-3" (see Page 9, line 141).

2. "Our extracted papers are biased toward the Asian countries (Japan: 8, Korea: 1, and France: 1)" (see Page 19, line 322-323).

Reviewer B

Comment 1: Some analysis or comment on the role of smoking in sarcopenia is needed. There are numerous indications of a link between these factors.

Reply 1: Thank you for your especially important suggestion. We agree with your comment; therefore, we made the following revisions to the Results and Discussion:

1. A paragraph has been added to the results

"The association between sarcopenia and smoking history

Of the ten studies, five reported the smoking history of patients (Table 4). Three studies demonstrated that sarcopenia was significantly associated with smoking history, which included an ever smoker and a current smoker. (see Page 12, line 193-196)

2. A section in the Discussion has been revised.

"Several studies have indicated that smoking may contribute to the development of sarcopenia (41). In our study, three studies showed that the number of patients with a smoking history were larger in sarcopenia than non-sarcopenia. So, quitting smoking may

become one of the therapies for sarcopenia.” (see Page 18, line 305 to 308)

3. Table 4 has been included.

Comment 2: The current Discussion needs focusing. There is too much of a recapitulation of the data already presented in the Results, and little analysis. A major rewrite of the Discussion, with a more concise examination of the factors associated with or arising from sarcopenia that alter outcomes in NSCLC is needed.

Reply 2: We apologize for the several recapitulations and redundant descriptions in the Discussion. We have deleted the recapitulations and focused on the analysis between our results and other literatures. In addition, we clarified our suggestion to alter the outcomes in NSCLC patients with sarcopenia. Finally, the number of characters in the Discussion has decreased from 1669 to 1339.

We modified our text as follows.

1. We have moved the text on page 11, line 172-177 (original manuscript) in the Discussion to page 5, line 79-Page 6, line 86 (revised manuscript) in the Introduction and modified it as follows:

“Recently, reports focusing on patients with early-stage lung cancers are increasing, and they have analyzed the effect of sarcopenia on postoperative short- and long-term outcomes (7, 8, 10-17). Several of these studies indicate that sarcopenia may be a useful risk assessment tool for postoperative complications as well as a prognostic biomarker. However, reports on several factors such as the pathological stage, surgical procedure, diagnostic tool for sarcopenia, and the cut-off value vary. Here, we reviewed these various factors and investigated the ability of sarcopenia to predict postoperative prognosis and complications in lung cancer patients.”

2. We have deleted recapitulation data already presented in the Results (original manuscript; page 11-12, line 179-184).

“In our review of ten studies, nine revealed that patients with sarcopenia had a significantly lower OS rate than those without sarcopenia (Table 1). Although heterogeneities were observed in these studies, the negative impact of sarcopenia on prognosis was also found in the group with the same stage of NSCLC (10-13), or who underwent the same surgical procedure (12, 15). For DFS, of the six studies that were reviewed, three revealed that patients with sarcopenia had a significantly lower DFS rate

than those without sarcopenia (7, 12, 16).”

3. We have modified the following text (original manuscript, page 12, line 192-196)

“sarcopenia may reflect the potential aggressiveness of the cancer. Tsukioka et al. showed that despite having the same stage of cancer, relapse-free survival was worse in patients with sarcopenia (12). Nakamura et al. also showed that pre-operative carcinoembryonic antigen was significantly higher in patients with sarcopenia (8). These two studies imply the potential aggressiveness of cancer which causes inflammation, leading to sarcopenia when patients receive surgery.”

to

“a tumor occurring in sarcopenia patients has a more malignant potential than that occurring in patients without sarcopenia. As a result, even if the pathological stages were the same in both sarcopenia and non-sarcopenia patients, the tumor recurrence will be frequently observed in sarcopenia patients (12)”

(see Page 13, line 209-213)

4. We have modified the following text (original manuscript: page 13, line 211-217)

“It was thought that sarcopenia in patients with surgically resected cancer was associated with increased postoperative inflammatory response. This response might play a role in the high incidence of postoperative complications along with sarcopenia (27). Exercise might lead to an anti-inflammatory environment, as muscle-derived IL-6 inhibits TNF production and stimulates the production of the anti-inflammatory cytokines IL-1ra and IL-10 (20). Thus, anti-inflammatory cytokines may be insufficient in patients with sarcopenia and inflammation after surgery cannot be adequately controlled, leading to the development of postoperative complications.”

to

“Muscle-derived IL-6 inhibits TNF production and stimulates the production of the anti-inflammatory cytokines IL-1ra and IL-10 (20). Therefore, patients with sarcopenia experience a high inflammatory response after surgery due to low levels of anti-inflammatory cytokines, leading to the development of postoperative complications (27).”

(see Page 14, line 230-234)

5. We have deleted the recapitulation of data already presented in the Results (original manuscript: page 14, line 225-227).

“All diagnostic tools reflect the skeletal muscle mass of the whole body, and they could predict the prognosis of patients after surgery. However, only PMI could be used to

predict postoperative complications (8, 15).”

6. We have deleted some descriptions presented in the Discussion; (original manuscript: page 14-15 line 237-239).

“These proposals suggest to physicians that patients with severe sarcopenia are not good candidates for high morbidity treatments and may need limited resection strategies such as wedge resection or segmentectomy.”

7. We have deleted the recapitulation of data already presented in the Introduction (original manuscript: page 5, line 62-68).

“Significant loss of muscle mass is the most prevalent and serious cancer-related symptom, and it strongly correlates with poor prognoses (29).”

8. We have deleted a citation and its related sentence (original manuscript: page 15, line 250-252).

“Irwin et al., demonstrated that among 933 patients with breast cancer, exercise was associated with a 67% decrease in the risk of death (33).”

9. We have modified a sentence (original manuscript; page 16, line 266-268) in the Discussion from

“Although there are a few reports on nutritional intervention, sarcopenic patients may benefit from exercise and nutritional rehabilitation programs.”

to

“Nutrition is also crucial in the treatment of sarcopenia; however, there are few reports on nutritional interventions.” (revised manuscript page 17, line 278-279)

10. We have modified the following text (original manuscript; page 17, line 275-277) from

“Myostatin inhibits muscle hypertrophy; exercise causes the liver to secrete follistatin, a myostatin inhibitor, which leads to muscle enlargement. Myostatin is a drug target in the treatment of sarcopenia (20)”

to

“Myostatin, which inhibits muscle hypertrophy, may become the target in the treatment of sarcopenia (20).” (revised manuscript page 18, line 300-301)

11. To clarify our proposal on the prevention of postoperative complications, the optimal

diagnostic tool for sarcopenia, and optimal therapeutic approach, we had added new sentences as the last paragraph in some sections of the discussion.

As a prevention of postoperative complications.

“Based on these results, sarcopenia can be used to identify patients at a high risk of postoperative complications, and it requires intensive care after surgery. Furthermore, surgeons can consider a less-invasive treatment such as limited resection or stereotactic irradiation for patients with sarcopenia (27)” (page 14, line 235-238)

As an optimal diagnostic tool for sarcopenia:

“Based on these results, the optimal cut off values of PMI in predicting prognosis are 6.36 cm²/m² in male patients and 3.92 cm²/m² in female patients, and those used in predicting postoperative complications are 3.70 cm²/m² in male patients and 2.50 cm²/m² in female patients (Table 3).” (page 15, line 257-page 16, line 260)

As a prevention using an optimal therapeutic approach:

“we believe that interventions for sarcopenia with a resectable lung cancer also improve their prognosis. Presently, we propose exercise and an improvement of the nutritional status. Muscle mass can improve with exercise and administration of nutrients (42), which can improve their prognosis.” (page 18, line 310- page 19, line 314)

*These revisions led to a major rewrite of the Discussion; if new modifications become necessary, we will be glad if the reviewers provide their valuable suggestions.

Reviewer C

Comment 1: I was undoubtful that the method using Revman was in order with systematic review.

Reply 1: We agree with your comment. Several systematic review articles used Review manager of Cochrane.

Comment 2: The author should consider the bias (or deviations of a number of pts) as for Staging in each publication in the discussion.

Reply 2: We have added the following sentence to the Limitations as one of the important

biases; “In addition, the tumor stage and the number of patients involved in the analysis of the prognosis in each article was varied.” (see Page 19, line 321-323)

Comment 3: in the discussion section, the descriptions were too redundant. Be more concise.

Reply 3: We apologize for the several recapitulations and redundant descriptions in the Discussion. We have deleted the recapitulations and focused on the analysis between our results and other studies. Finally, the number of characters in Discussion decreased from 1669 to 1339. We have modified our text as follows.

1. We have moved the text on page 11, line 172-177 (original manuscript) in the Discussion to page 5, line 78-page 6, line 86 (revised manuscript) in the Introduction and modified it as follows:

“Recently, reports focusing on patients with early-stage lung cancers are increasing, and they have analyzed the effect of sarcopenia on postoperative short- and long-term outcomes (7, 8, 10-17). Several of these studies indicate that sarcopenia may be a useful risk assessment tool for postoperative complications as well as a prognostic biomarker. However, reports on several factors such as pathological stage, surgical procedure, diagnostic tool and the cut-off value vary. Here, we reviewed these various factors and investigated the ability of sarcopenia to predict postoperative prognosis and complications in lung cancer patients.”

2. We have deleted the recapitulation of data already presented in the Results (original manuscript; page 11-12, line 179-184).

“In our review of ten studies, nine revealed that patients with sarcopenia had a significantly lower OS rate than those without sarcopenia (Table 1). Although heterogeneities were observed in these studies, the negative impact of sarcopenia on prognosis was also found in the group with the same stage of NSCLC (10-13), or who underwent the same surgical procedure (12, 15). For DFS, of the six studies that were reviewed, three revealed that patients with sarcopenia had a significantly lower DFS rate than those without sarcopenia (7, 12, 16).”

3. We have modified the following text (original manuscript; page 12, line 192-196)

“sarcopenia may reflect the potential aggressiveness of the cancer. Tsukioka et al. showed that despite having the same stage of cancer, relapse-free survival was worse in patients with sarcopenia (12). Nakamura et al. also showed that pre-operative carcinoembryonic antigen was significantly higher in patients with sarcopenia (8). These two studies imply

the potential aggressiveness of cancer which causes inflammation, leading to sarcopenia when patients receive surgery.”

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“a tumor occurring in sarcopenia patients has a more malignant potential than that occurring in patients without sarcopenia. As a result, even if the pathological stages were the same in both sarcopenia and non-sarcopenia patients, the tumor recurrence will be frequently observed in sarcopenia patients (12)”

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“Muscle-derived IL-6 inhibits TNF production and stimulates the production of the anti-inflammatory cytokines IL-1ra and IL-10 (20). Therefore, patients with sarcopenia experience a high inflammatory response after surgery due to low levels of anti-inflammatory cytokines, leading to the development of postoperative complications (27).”

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“Myostatin, which inhibits muscle hypertrophy, may become the target in the treatment of sarcopenia (20).” (revised manuscript page 18, line 300-301)

*These revisions led to a major rewrite of Discussion; if new modifications become necessary, we will be glad if the reviewers provide their valuable suggestions.

Comment 4: How will the author suggest to improve outcome or reduce postoperative complication from acquired results from the study for the readers? Clarify it in the discussion section.

Reply 4: To clarify our proposal on the prevention of postoperative complications, optimal diagnostic tools for sarcopenia, and an optimal therapeutic approach, we have

added sentences as a last paragraph in some sections of the Discussion.

As a prevention of postoperative complications:

“Based on these results, sarcopenia can be used to identify patients at a high risk of postoperative complications, and it requires intensive care after surgery. Furthermore, surgeons can consider a less-invasive treatment such as limited resection or stereotactic irradiation for patients with sarcopenia (27).” (page 14, line 235-238)

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As a prevention using an optimal therapeutic approach:

“we believe that interventions for sarcopenia with a resectable lung cancer also improve their prognosis. Presently, we propose exercise and an improvement of the nutritional status. Muscle mass can improve with exercise and administration of nutrients (42), which can improve their prognosis.” (page 18, line 310-page 19, line 314)