Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Meta-analysis

Coronavirus disease 2019 (Covid-19) outcomes in patients with sarcopenia: A meta-analysis and meta-regression

Yusak Mangara Tua Siahaan [a], Vinson Hartoyo [a], Timotius Ivan Hariyanto [b], Andree Kurniawan [c, *]

[a] Department of Neurology, Faculty of Medicine, Pelita Harapan University, Karawaci, Tangerang, 15811, Indonesia
[b] Faculty of Medicine, Pelita Harapan University, Karawaci, Tangerang, 15811, Indonesia
[c] Department of Internal Medicine, Faculty of Medicine, Pelita Harapan University, Karawaci, Tangerang, 15811, Indonesia

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SUMMARY

Background: Sarcopenia has been associated with patients' poor quality of life, disability, and hospitalization. As of today, evidence that highlights the association between sarcopenia and Covid-19 outcomes remains unclear. This study sought to analyze whether patients with sarcopenia are at higher risk for developing poor Covid-19 outcomes.

Methods: Using specific keywords, we comprehensively go through the potential articles on medRxiv, Europe PMC, and PubMed sources until July 31st, 2021. All published studies on sarcopenia and coronavirus disease 2019 were collected. We were using Review Manager 5.4 and Comprehensive Meta-Analysis 3 software to conduct statistical analysis.

Results: There were 9 studies with 492,245 Covid-19 patients included in the analysis. Evaluation of the data gathered yielded an association between sarcopenia and increased severity of Covid-19 (OR 1.99; 95%CI: 1.37–2.90, $p = 0.0003$, $I^2 = 79\%$, random-effect modelling); and mortality from Covid-19 (OR 1.96; 95%CI: 1.11–3.46, $p = 0.020$, $I^2 = 49\%$, random-effect modelling). The increased risk of developing severe Covid-19 in a sarcopenic patient is also further influenced by cancer.

Conclusions: This study proposes that patients with sarcopenia are at risk of developing poor Covid-19 outcomes. Patients with sarcopenia need special attention and should be prioritized to receive the SARS-CoV-2 vaccine.

Registration details: PROSPERO (CRD42021270725).

1. Introduction

More than one and a half years after December 2019, the pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is still not showing the sign that it will end soon. This coronavirus disease 2019 (Covid-19) pandemic has put together over 193 million confirmed cases, with more than 4 million demises as of July 27th, 2021 [1]. While some SARS-CoV-2 patients may develop mild non-debilitating self-limiting upper-respiratory symptoms, a significant percentage of patients may also develop destructive and progressive symptoms which require hospitalizations and intensive care treatment due to the threat of symptoms progression into acute respiratory distress syndrome (ARDS) and eventually may turn into multi-organ failure (MOF) [2,3].

In light of recent studies, several comorbidities that can increase the probability of developing severe SARS-CoV-2 infections have been well identified such as chronic respiratory disease, diabetes, cardiovascular disease, obesity, and other immunocompromising conditions [4–10]. Identification of these factors would help give a better risk stratification and reallocation of hospital resources. Sarcopenia is a disorder affecting the muscle characterized by reduced muscle mass and reduced muscle strength [11]. Aging, illness, physical inactivity, and malnutrition has been closely related to the development of this disorder [11]. Sarcopenia may cause several adverse health-related effects which include

* Corresponding author. Department of Internal Medicine, Faculty of Medicine, Pelita Harapan University, Boulevard Jendral Sudirman street, Karawaci, Tangerang 15811, Indonesia.
E-mail address: andree.kurniawan@uph.edu (A. Kurniawan).

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poor life quality, disability, higher risk of falls, fractures, and hospitalization [12]. In terms of infection, sarcopenia is associated with a higher incidence of nosocomial infection in elderly patients [13]. It also has been demonstrated as a predictor for postoperative infections and delayed recovery in cancer patients [14,15]. In terms of Covid-19, sarcopenia may be the actual cause of differing Covid-19 courses between patients, but it might also be a mere symptom of other diseases which lead into different Covid-19 courses. All of these associations between sarcopenia and Covid-19 outcomes have not been established yet. The purpose of this systematic review and meta-analysis is to come up with evidence of whether patients with sarcopenia are at risk of developing poor outcomes of Covid-19.

2. Materials and methods

2.1. Eligibility criteria

We conducted a systematic review and meta-analysis study from observational studies. We registered this study protocol in PROSPERO (CRD42021270725). Append research in this systematic review and meta-analysis were chosen as most likely attaining the coming criteria: follow the PICOS framework (P: Populations – Covid-19 patients; I: Interventions – patients with sarcopenia as their comorbidities; C: Comparator/Control - a group of patients without sarcopenia; O: Outcomes – severe Covid-19 and mortality; S: Study Design - cross-sectional, case–control, cohort, and case-series researches). All studies besides original articles (correspondence or review articles), randomized or non-randomized clinical trials, case report studies, studies reported other than in English language, research focusing on the pregnant women and populations of age below 18 years old were excluded.

2.2. Search strategy and study selection

Database searching was done systemically towards studies with English-language restriction which were sourced from three databases (medRxiv, Europe PMC, and PubMed). Keywords such as “sarcopenia” OR “sarcopenic” AND “SARS-CoV-2” OR “coronavirus disease 2019″ OR “Covid-19″ were used to filter the intended studies from the period of 2019 until July 31st, 2021. The searching strategies used in this study are listed in Supplementary Table 1. The initial step was the identification of eligible articles through screening of titles and abstracts. Additional evaluation of references from found eligible studies were also conducted to search for more potential articles. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram shows the strategy we employed during our study.

2.3. Data extraction and quality assessment

Two authors conducted the data extraction. Extraction form was developed to list information about the study such as its population characteristic, cancer, chronic obstructive pulmonary disease (COPD), body mass index (BMI), sarcopenia assessment tools, sarcopenia parameters, sarcopenia cut-off values, number of patients with sarcopenia, the control group in included studies, as well as the outcome of Covid-19 patients.

We focused the outcomes of our study on severe Covid-19 and mortality. Severe Covid-19 outcome is defined according to the Guidelines for the Diagnosis and Treatment of New Coronavirus Pneumonia (fifth edition) [16], which includes any of the following features at the time of, or after, admission: (1) respiratory distress (defined as respiratory rates of $\geq$30 breaths per min); (2) resting oxygen saturation of $\leq$93%; (3) ratio of the partial pressure of arterial oxygen (PaO2) to a fractional concentration of oxygen inspired air (fiO2) $\leq$300 mmHg; or (4) critical complication (respiratory failure, septic shock, and or multiple organ dysfunction/failure) or admission into intensive care unit (ICU). Mortality outcome is described by the number of death cases during the follow-up period with a history of positive SARS-CoV-2 infection.

Two authors assessed the quality of each study involved in this review independently. Newcastle–Ottawa Scale (NOS) was used to evaluate the quality of case–control and cohort studies. The assessment process included reviewing the comparability, selection, and outcome of each study, then each research was assigned a total score beginning with zero until nine. Research is graded good if it scores $\geq$7 [17]. Meanwhile, the quality of the included cross-sectional studies was assessed by using the Joanna Briggs Institute (JBI) Critical Appraisal Tools for Cross-Sectional Studies [18].

2.4. Statistical analysis

Meta-analysis was done using Review Manager 5.4 (Cochrane Collaboration) and Comprehensive Meta-Analysis version 3 software. Application of Generic Inverse-Variance formula with random-effect models, regardless of heterogeneity was employed to calculate odds ratio (OR) and its 95% confidence interval (95% CI) for the severe Covid-19 and mortality outcome. In this meta-analysis, heterogeneity between studies was assessed by the Cochrane Q test, tau-squared (τ^2), and I-squared (I^2; Inconsistency). The I^2 statistic with a value of <25% considered as a low degree of heterogeneity, 26–50% moderate degree of heterogeneity, and >50% considered high degree of heterogeneity. I^2 of at least 50% is considered substantial heterogeneity; it means that at least half of the total variability among effect sizes is due to true heterogeneity between studies. The tau-squared (τ^2) statistic is a function of I^2, while p values for the I^2 statistic were derived from the chi-square distribution of the Cochran Q test. Meta-regression with a random-effects model was performed using a restricted-maximum likelihood for pre-specified variables including age, gender, cancer, COPD, and BMI to see the interaction effect between sarcopenia and these variables in influencing the Covid-19 outcomes. Funnel plot analysis was utilized to assess the qualitative risk of publication bias, while Begg and Mazumdar's rank correlation method was used to assess the quantitative risk of publication bias [19].

3. Results

3.1. Study selection and characteristics

Initial database search found 799 studies, from which 692 studies were registered after duplicates removal. We removed 672 records after screening the titles and abstracts as well as matching the inclusion and exclusion criteria. A total of 20 studies with full-text articles were included from which their eligibility was assessed. Five articles did not have enough information about sarcopenia, three articles had no control group, two articles did not provide the outcome of interest, one article was not in English thus resulting in the final number of 9 studies [20–28] which included a total of 492,245 Covid-19 patients for the analysis (Fig. 1). Out of 9 studies, seven were retrospective cohort, one was the prospective cohort, and the remaining one article was cross-sectional studies. Table 1 gives out the details of each included research. The details regarding the assessment tools, parameters, and cut-off values used for sarcopenia diagnosis in each of the included studies are summarized in Table 2. Most of the included studies use skeletal muscle index (SMI) measured through CT-scan at the level of thoracal vertebrae 12 (T12) as diagnostic criteria for sarcopenia.

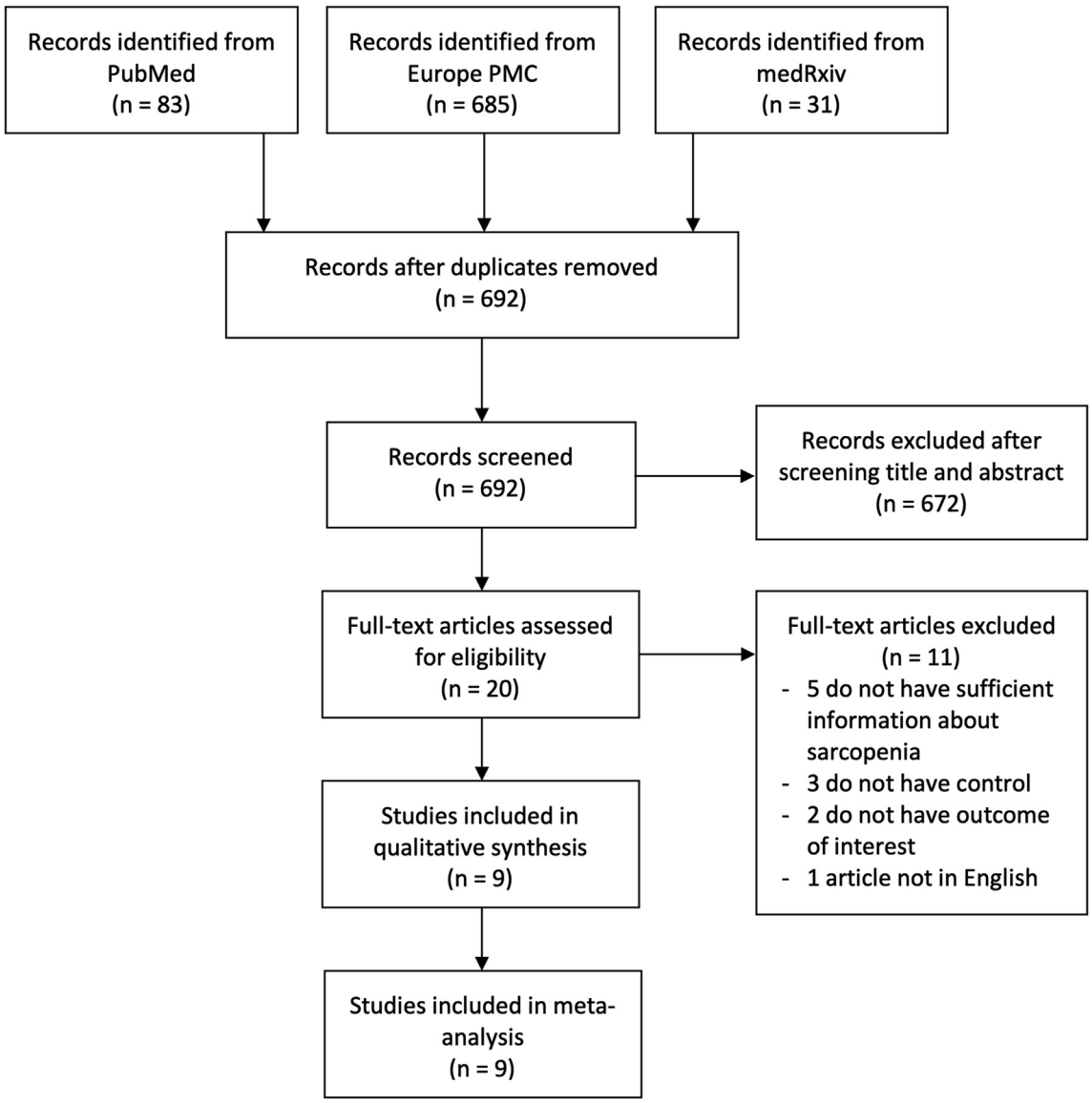

Fig. 1. PRISMA diagram of the detailed process of selection of studies for inclusion in the systematic review and meta-analysis.

Table 1
Characteristics of included studies.

Study	Sample size	Design	Outcome	Age (years)	Male (%)	Cancer (%)	COPD (%)	BMI Mean ± SD (kg/m^2)	Sarcopenia (%)
Giraudo C et al. [20] 2021	150	Retrospective cohort	Severity[a] Mortality	61.3 ± 15	69.3%	N/A	N/A	N/A	28.7%
Kara O et al. [21] 2021	312	Cross-sectional	Severity[b]	46.1 ± 14.8	55.1%	N/A	2.8%	29.3 ± 5.4	12.8%
Kim JW et al. [22] 2021	121	Retrospective cohort	Severity[a] Mortality	62 ± 19.2	36.4%	N/A	17.4%	N/A	23.9%
Ma Y et al. [23] 2021	114	Prospective cohort	Severity[b]	69.5 ± 7.2	50%	7.8%	12.2%	23.4 ± 3.1	33.3%
McGovern J et al. [24] 2021	63	Retrospective cohort	Severity[a] Mortality	72.4 ± 8.5	47.6%	17.5%	22.2%	26.5 ± 4.3	61.9%
Moctezuma-Velazquez P et al. [25] 2021	519	Retrospective cohort	Severity[a] Mortality	51.3 ± 14	63.9%	N/A	N/A	29.9 ± 4.9	22.1%
Schiaffino S et al. [26] 2021	552	Retrospective cohort	Severity[a] Mortality	64.6 ± 15.5	66%	9%	8%	26.6 ± 4.4	N/A
Wilkinson TJ et al. [27] 2021	490,301	Retrospective cohort	Severity[b]	70 ± 13	46%	8%	N/A	N/A	2%
Yi X et al. [28] 2021	234	Retrospective cohort	Severity[b]	44.5 ± 20.7	56.8%	1.7%	3%	N/A	33.3%

[a] Admission into intensive care unit (ICU).
[b] Any of the followings: (1) respiratory distress (≥30 breaths per min); (2) oxygen saturation at rest ≤93%; (3) ratio of the partial pressure of arterial oxygen (PaO2) to a fractional concentration of oxygen inspired air (fiO2) ≤300 mmHg; (4) critical complications.

Table 2
Sarcopenia diagnosis in each of the included studies.

Study	Sarcopenia assessment tool	Sarcopenia parameters	Cut-off used
Giraudo C et al. [20] 2021	Chest CT-scan at T12 level	Skeletal muscle density measured in Hounsfield unit (Hu)	Hounsfield unit (Hu) values < 30
Kara O et al. [21] 2021	Electronic Smedley hand dynamometer	Handgrip strength (in kg)	Two standard deviations below the gender-specific peak mean value of the healthy young adults (i.e. <32 kg in males and <19 kg in females).
Kim JW et al. [22] 2021	Chest CT-scan at T12 level	Skeletal muscle index (SMI)	- Men: ≤24 cm^2/m^2 - Women: ≤20 cm^2/m^2
Ma Y et al. [23] 2021	SARC-F scale by experienced geriatricians within 24 h of admission	SARC-F scale which consist of five component: strength; assistance walking; rise from a chair; climb stairs; and falls (score 0–10)	Total score ≥4
McGovern J et al. [24] 2021	Abdominal CT-scan at L3 level	Body mass index (BMI) and Skeletal muscle index (SMI)	- Men: BMI <25 kg/m^2 and SMI <43 cm^2/m^2, or BMI ≥25 and SMI <53 cm^2/m^2 - Women: BMI <25 and SMI <41 cm^2/m^2, or BMI ≥25 and SMI <41 cm^2/m^2
Moctezuma-Velazquez P et al. [25] 2021	Chest CT-scan at T12 level	Skeletal muscle index (SMI)	- Men: <42.6 cm^2/m^2 - Women: <30.6 cm^2/m^2
Schiaffino S et al. [26] 2021	Chest CT-scan at T12 level	Skeletal muscle area (SMA)	SMA_{T12} <3100 mm^2
Wilkinson TJ et al. [27] 2021	Bioelectrial impedance analysis (BIA)	Appendicular lean mass (ALM)/$height^2$ index or ALM/body mass index (BMI)	- ALM index (ALM/$height^2$) <7.26 kg/m^2 for men and <5.45 kg/m^2 for women as per EWGSOP2 criteria; or - ALM/body mass index (BMI) < 0.789 in men and <0.512 in women as per Foundation for the National Institutes of Health Sarcopenia Project criteria
Yi X et al. [28] 2021	Chest CT-scan at T12 level	Skeletal muscle index (SMI)	ALM index (ALM/$height^2$) <7.26 kg/m^2 for men and <5.45 kg/m^2 for women as per EWGSOP2 criteria

3.2. Quality of study assessment

NOS scale was used to evaluate the quality assessment of cohort and case–control studies, which indicated all included studies had good quality (Table 3). Meanwhile, we used Joanna Briggs Institute Critical Appraisal checklist for evaluation of cross-sectional studies and found that all included studies were deemed fit to be included in the meta-analysis [21] (see Table 4).

3.3. Sarcopenia and Severe Covid-19

Nine studies (n = 492,245) reported severe Covid-19 as the outcome of patients with sarcopenia and Covid-19. Our pooled analysis revealed that sarcopenia as a comorbidity was correlated with an enhanced risk of severe Covid-19 (OR 1.99; 95%CI: 1.37–2.90, $p = 0.0003$, random-effect modeling) (Fig. 2A). Heterogeneity was statistically significant with $I^2 = 79\%$, $\tau^2 = 0.18$, $p < 0.00001$.

3.4. Sarcopenia and mortality of Covid-19 patients

The mortality outcome was revealed in five studies (n = 1405). The pooled estimate indicated that sarcopenia was associated with higher mortality from Covid-19 (OR 1.96; 95%CI: 1.11–3.46, $p = 0.020$, random-effect modeling) (Fig. 2B). Heterogeneity was not statistically significant with $I^2 = 49\%$, $\tau 2 = 0.18$, $p = 0.10$.

3.5. Meta-regression

Our meta-regression suggested the only statistically significant variables which influence the association between sarcopenia as comorbidity and severe Covid-19 outcome was cancer ($p = 0.009$) (Fig. 3A), where the increase in cancer prevalence tend to worsen the Covid-19 severity in sarcopenic patients. Our meta-regression also revealed that the Covid-19 severity in sarcopenic patients was also increase by age ($p = 0.412$) (Fig. 3B), decrease by male gender prevalence ($p = 0.710$) (Fig. 3C), increase by COPD prevalence ($p = 0.831$) (Fig. 3D), and decrease by BMI ($p = 0.396$)

Table 3
Newcastle–Ottawa quality assessment of observational studies.

First author, year	Study design	Selection[a]	Comparability[b]	Outcome[c]	Total score	Result
Giraudo C et al. [20] 2021	Cohort	***	**	**	7	Good
Kim JW et al. [22] 2021	Cohort	***	**	***	8	Good
Ma Y et al. [23] 2021	Cohort	***	**	**	7	Good
McGovern J et al. [24] 2021	Cohort	***	**	***	8	Good
Moctezuma-Velazquez P et al. [25] 2021	Cohort	***	**	***	8	Good
Schiaffino S et al. [26] 2021	Cohort	***	**	***	8	Good
Wilkinson TJ et al. [27] 2021	Cohort	***	**	***	8	Good
Yi X et al. [28] 2021	Cohort	***	**	***	8	Good

[a] (1) representativeness of the exposed cohort; (2) selection of the non-exposed cohort; (3) ascertainment of exposure; (4) demonstration that outcome of interest was not present at start of study.
[b] (1) comparability of cohorts on the basis of design or analysis, (maximum two stars).
[c] (1) assessment of outcome; (2) was follow-up long enough for outcomes to occur; (3) adequacy of follow up of cohorts.

Table 4
Joanna Briggs Institute Critical Appraisal tool for cross-sectional study.

	Kara O et al. [21] 2021
1. Were the criteria for inclusion in the sample clearly defined?	Yes
2. Were the study subjects and the setting described in detail?	Yes
3. Was the exposure measured in a valid and reliable way?	Yes
4. Were objective, standard criteria used for measurement of the condition?	Yes
5. Were confounding factors identified?	Yes
6. Were strategies to deal with confounding factors stated?	No
7. Were the outcomes measured in a valid and reliable way?	Yes
8. Was appropriate statistical analysis used?	Yes
Quality	Include study

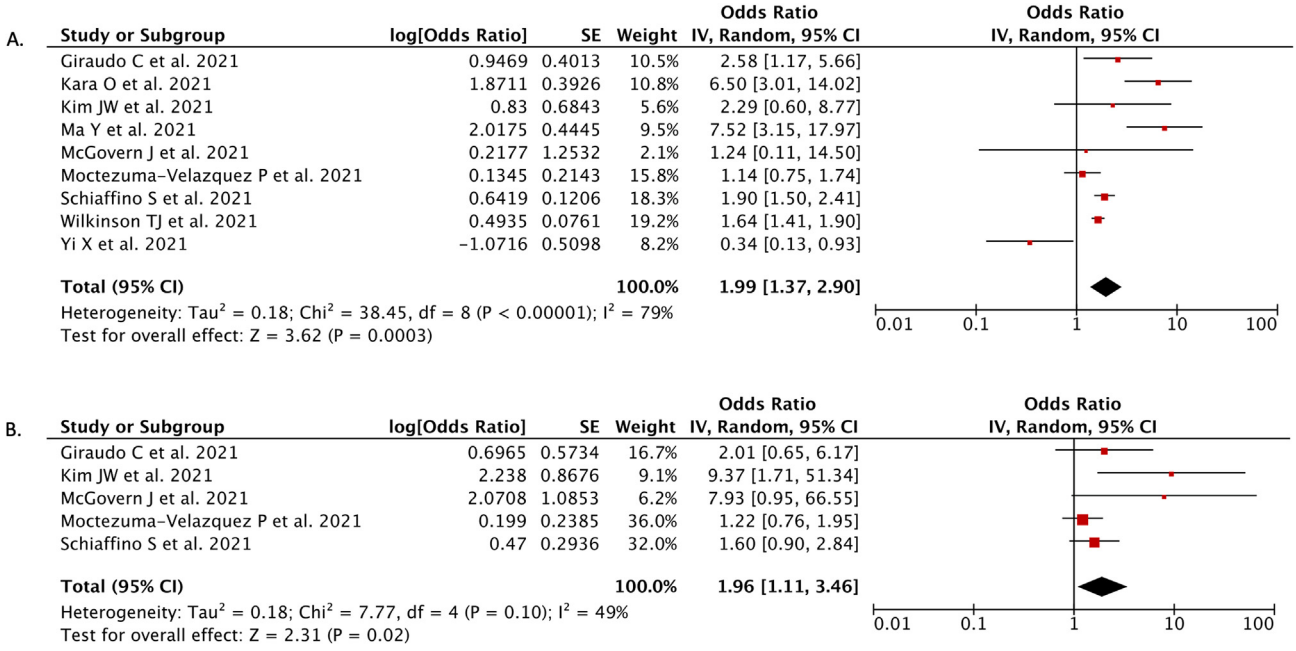

Fig. 2. Forest plot that demonstrates the association of sarcopenia with severe Covid-19 (A) and mortality outcomes (B).

(Fig. 3E), however all these associations are not statistically significant.

Our meta-regression also found that the association between sarcopenia as comorbidity and mortality from Covid-19 was affected by gender, where the decrease in male gender prevalence tend to worsen the Covid-19 mortality rate, and this association was statistically significant ($p = 0.026$) (Fig. 4A). However, the role of increasing age in worsening the Covid-19 mortality rate in sarcopenic patients was not statistically significant ($p = 0.206$) (Fig. 4B). Meanwhile, the meta-regression analysis for other variables, such as cancer, COPD, and BMI cannot be done because of not enough information about these variables and mortality outcomes from the included studies.

Because of the limited number of available data, these meta-regression analyses are only based on few number of studies and the results should be interpreted carefully.

3.6. Publication bias

Because the number of included studies in each outcomes are fewer than 10 studies, the funnel plots and statistical tests for detecting publication bias are not much reliable when compared with whenever there are more than 10 included studies in each outcomes [29,30]. Therefore, the test for publication bias was not performed in this study.

4. Discussion

According to our pooled analysis, it was discovered that sarcopenia as a comorbidity was associated with increased severity and mortality from Covid-19. Further regression analysis showed that increasing in cancer prevalence may increase the Covid-19 severity in sarcopenic patients and this association is statistically significant. Meanwhile, the other factors such as increasing in age, decreasing in male gender, increasing in COPD prevalence, and increasing in BMI may also influence the Covid-19 outcomes by increasing its severity in patients with sarcopenia, but these associations are not statistically significant. The role of cancer in influencing the relationship between sarcopenia and severe Covid-19 is not surprising as cancer itself has been demonstrated by several meta-analysis to be associated with poor Covid-19 outcomes [31,32]. Higher expression of transmembrane protease serine 2 (TMPRSS2) and angiotensin-converting enzyme 2 (ACE2) in cancer patients may facilitates the entry of SARS-CoV-2 into host cells [32]. Immunocompromised state of cancer patients will also make them more vulnerable to severe complications and contribute to the development of severe Covid-19 [32]. Not only that, interleukin-6 (IL-6) as one of the major cytokines in tumor microenvironment has been found to be elevated, deregulated in cancer patients and inhibit the host's immune response to cancer cells [33,34]. On the other side, IL-6 can contribute to the

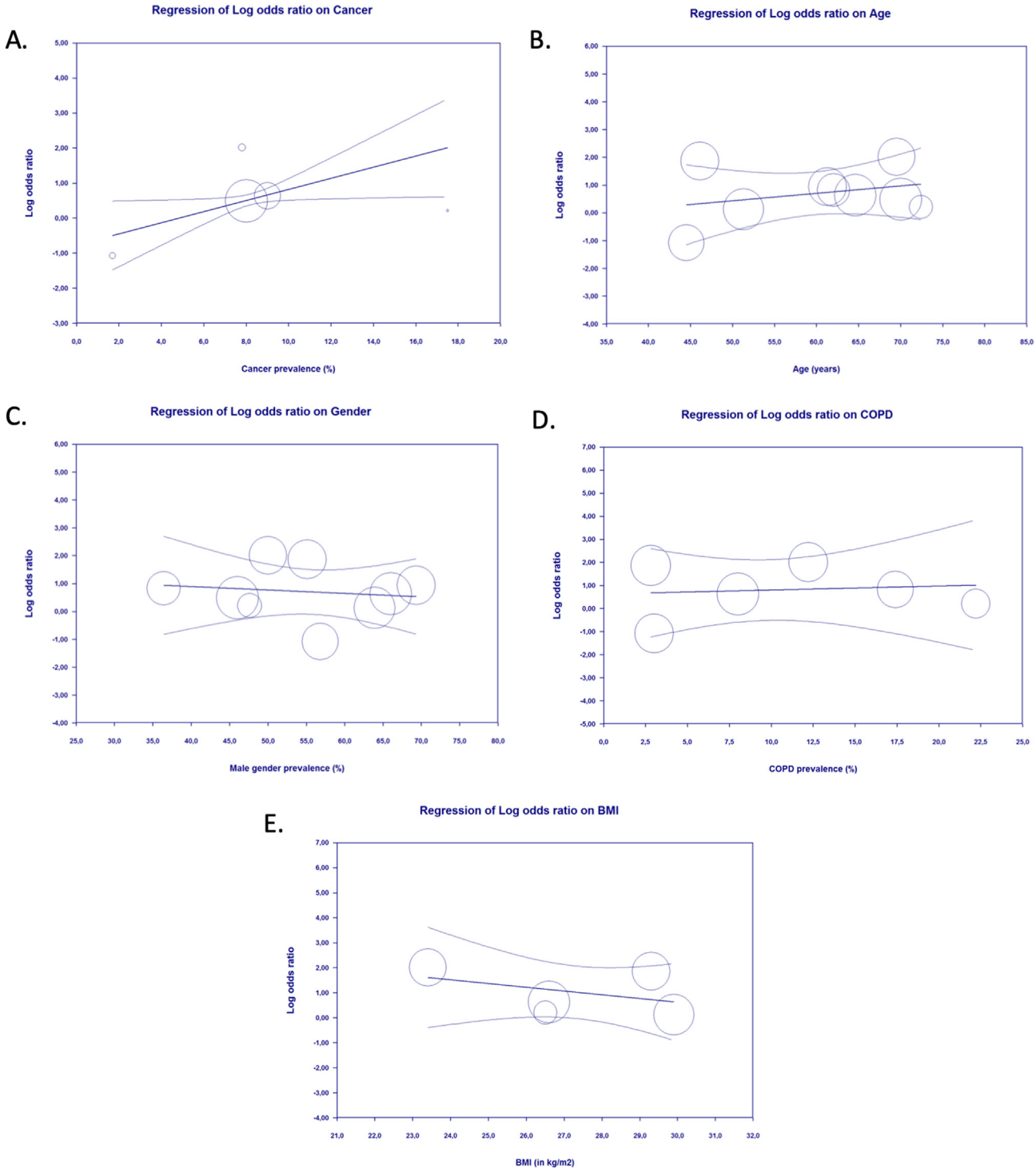

Fig. 3. Bubble-plot for meta-regression. A bubble shows a study and the size of bubble is proportional to the inverse of the variance of the log-odds ratio. Meta-regression analysis showed that the association between sarcopenia and higher severity of Covid-19 was significantly affected by an increase in cancer prevalence (A). The association between sarcopenia and higher severity of Covid-19 were also affected by an increase in age (Fig. 3B), decrease in male gender prevalence (Fig. 3C), increase in COPD prevalence (Fig. 3D), and decrease in BMI (Fig. 3E), however all these associations are not statistically significant.

development of cytokine storm and is a good predictor for poor Covid-19 outcomes [35]. Besides cancer, obesity is also closely related with sarcopenia because there is a condition called sarcopenic obesity where low skeletal muscle mass is coupled with high levels of adiposity [36]. Sarcopenic obesity is commonly seen in older adults [36]. Obesity and BMI itself has been demonstrated to worsen the Covid-19 outcomes [37,38]. It is also reflected in our meta-regression analysis where BMI also affect the relationship between sarcopenia and Covid-19 severity, although this relationship is not statistically significant. Meanwhile, the association

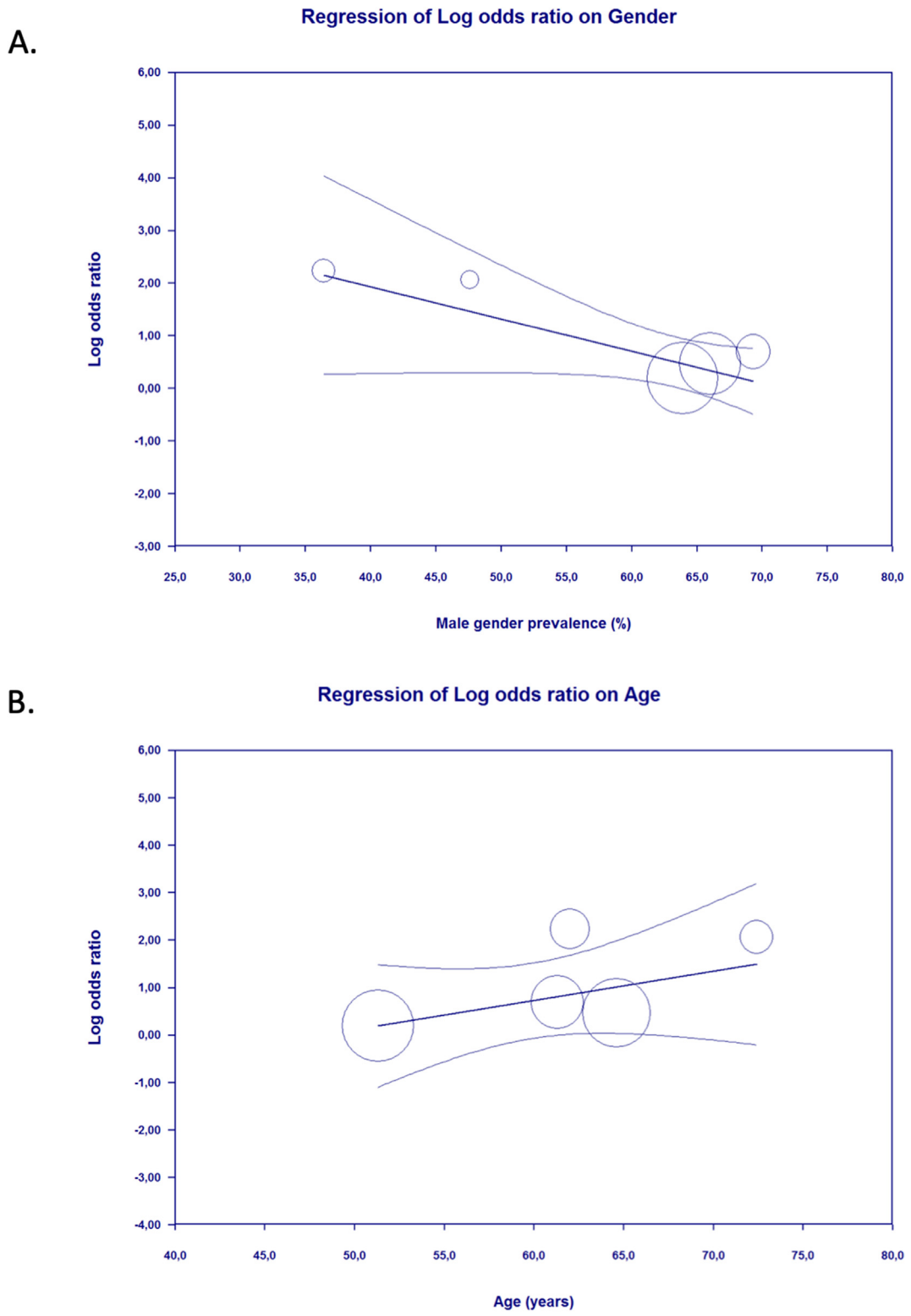

Fig. 4. Bubble-plot for meta-regression. A bubble shows a study and the size of bubble is proportional to the inverse of the variance of the log-odds ratio. Meta-regression analysis showed that the association between sarcopenia and higher mortality from Covid-19 was significantly affected by decrease in male gender prevalence (Fig. 4A). However, the role of increasing age in worsening the Covid-mortality rate in sarcopenic patients was not statistically significant (Fig. 4B).

between sarcopenia and higher mortality from Covid-19 was influenced by increasing age and decreasing in male gender prevalence, but only statistically significant for male gender prevalence.

There are some explanations of how sarcopenia could affect the prognosis of Covid-19 patients. First, as we know, patients with sarcopenia have a reduction in skeletal muscle mass. Recent pieces of literature have shown that skeletal muscle cells may have

immune modulation function by signaling through different soluble factors, cell surface molecules, or cell-to-cell interactions [39,40]. Skeletal muscle can produce several myokines/cytokines which can exert autocrine, paracrine, and endocrine action on numerous tissues. One of the myokines that skeletal muscle produced is interleukin-15 (IL-15) [41]. IL-15 plays an important role in immune functions as it induces the NK-cells' proliferation, activation, and distribution. Not only that, but IL-15 also modulates the CD8 T-cell homeostasis and promotes survival of naïve T-cells [40,42]. Both NK-cells and CD8 T-cells are necessary for the effective clearance of viral pathogens. Therefore, the lack of IL-15 in sarcopenic patients may impair the host's defense system against viral infection, including SARS-CoV-2 infection [43]. Besides IL-15, another cytokine involved in the pathogenesis of sarcopenia is IL-6. IL-6 inhibits muscle anabolism and may directly promote muscle catabolism, facilitating muscle atrophy seen in sarcopenic patients [40,44]. In an experimental study conducted by Tsujinaka et al. [45], a marked loss of muscle mass was seen in transgenic mice which overexpressing IL-6 chronically and treating these mice with IL-6 receptor antibody could mitigate the detrimental effect of IL-6 on muscle. On the other side, IL-6 is among the inflammatory markers associated with higher severity and mortality in Covid-19 patients [46–48]. Finally, the loss of skeletal muscle mass seen in patients with sarcopenia may also affect the respiratory muscles, such as pectoralis and intercostal muscles [49]. Respiratory muscles are important during the generation of cough, together with internal laryngeal muscles. The cough itself is one of the body's defense mechanisms against lung infections [50]. Therefore, respiratory muscle impairment in patients with sarcopenia may disrupt the normal cough reflex and may also cause failure in ventilation which ultimately will lead to a higher risk of developing severe infections, including Covid-19 [51].

This study is not free from limitations. Our analyses were based on relatively small number of studies because of limited number of currently available data. Studies included in our analysis are also dominantly from European and Asian countries. However, we are not limiting our inclusion criteria based on region/country and we strictly follow the protocol of our study to minimize the selection bias. We also have performed rigorous searching on the three databases (PubMed, Europe PMC, medRxiv) to capture all potentially eligible articles (published and unpublished studies), and to minimize the publication bias. Notable heterogeneities were also identified on most of the outcomes of interests included in this study. This might be due to differences in the type of sarcopenia assessment tools, parameters, and cut-off values used in each of the included studies. More studies that focus on the course of Covid-19 in patients with sarcopenia with larger sample sizes are still needed to confirm the results from our study.

5. Conclusion

Our systematic review and meta-analysis indicated that patients with sarcopenia were at higher risk of developing poor outcomes from Covid-19, in terms of severity and mortality rate. This review proposes that patients with sarcopenia should be considered as the population at risk which needs special attention during the Covid-19 pandemic. They should be prioritized to receive SARS-CoV-2 vaccines, along with other comorbidities which were already established as a risk factor for Covid-19. Even so, more studies with larger sample sizes of patients with sarcopenia and Covid-19 are still required to further verify the results from our study.

Ethics approval and consent to participate

Not applicable.

Funding

None.

Authors' contributions

YMTS: conceptualization, methodology, formal analysis, data curation, writing-original draft, visualization, writing-review, and editing. VH: conceptualization, methodology, formal analysis, data curation, writing-original draft, writing-review and editing. TIH: conceptualization, validation, supervision, writing-review and editing. AK: conceptualization, validation, supervision, writing-review and editing. All authors read and approved the final manuscript.

Consent for publication

Not applicable.

Availability of data and materials

Data analyzed in this study were a re-analysis of existing data, which are openly available at locations cited in the reference section.

Declaration of competing interest

The authors declare that they have no competing interests.

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None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2022.01.016.

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