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## Meta-analysis

# The devastating trio of sarcopenia, frailty, and COVID-19 - A systematic review and meta-analysis



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## ARTICLE INFO

### Article history:

Received 22 July 2022

Accepted 29 July 2022

### Keywords:

Sarcopenia  
Nutrition  
Frailty  
Physical activity  
Systematic review

## SUMMARY

**Background & aims:** Sarcopenia, frailty, and COVID-19 appear to be intertwined. Preventive and intervention measures are required to break this link and mitigate the consequences of rising morbidity and mortality among older adults. This study aimed to identify and synthesize important factors related to the interaction of the devastating trio and their impact on the health and mortality of older adults.

**Methods:** Data were gathered via searches of PubMed, Cochrane Library, Google Scholar, and Elsevier Mendeley Website. Study selection and data extraction were conducted by the two authors independently. The primary outcome was mortality, secondary outcomes included hospitalization and risk of development of severe disease among older Covid-19 patients. The study results are presented as adjusted odds and hazard ratios with 95% CI.

**Results:** A total of 1725 studies were identified through our electronic databases searches. After screening and assessing for eligibility, 39 studies were included in this review, a total of 51,796 patients were included in the systematic review. Our results indicated that frail patients recorded a higher mean age compared to non-frail patients ( $p < 0.00001$ ), and COVID-19 frail patients had significantly increased mortality rate compared to non-frail patients, the log adjusted OR was 2.10 (1.63, 2.71);  $I^2 = 78\%$ ;  $p < 0.00001$ .

**Conclusion:** Age and frailty are important risk factors for mortality among older adults COVID-19 patients. COVID-19 patients with sarcopenia had a higher risk of developing severe conditions, including hospitalization and ICU admission. Findings that support the use of frailty and sarcopenia indicators to help in the decision-making process for medical care in older adults COVID-19 patients.

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## 1. Introduction

Worldwide, people are living longer, the percentage of people  $\geq 60$  is growing faster than any other age group [1]. Older age is associated with multifaceted health conditions called geriatric syndromes, these conditions are often the consequence of multiple underlying factors including sarcopenia, frailty, falls and others [1,2].

With advanced age, older adults encounter major challenges in staying healthy and active; one of these major challenges is related to decrease lean body mass due to age-related changes. This condition is known as sarcopenia. Sarcopenia is defined as an age-

related progressive loss of skeletal muscle mass and strength [3,4]. Evidence suggests that this decline in muscle mass may begin in the 3rd or 4th decades of life, it increases with growing older, and it becomes more prominent after the age of 60 years [5–7]. Sarcopenia has been associated with several chronic diseases [8], and it is a significant predictor of hospitalization among older adults [9]. Besides, sarcopenia may lead to overwhelming personal, social, and economic burdens influencing individuals, communities, and health care systems [4,7]. Globally, The prevalence of sarcopenia is rising due to the increased numbers of older adults [10], and it is accompanied by adverse health consequences including falls, functional decline, frailty, and mortality [3,4].

Sarcopenia and physical frailty are linked and often overlapped [11], these are two geriatric syndromes where sarcopenia usually precedes frailty, the devastating curve in this line starts with sarcopenia to frailty and consequently leads to disability and mortality [12,13]. Frailty was defined as a clinical syndrome that includes

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weight loss, exhaustion, weakness, and slowness [14]. A recent systematic review included studies from 62 countries [15], indicating that the estimated prevalence of frailty among older adults was 12%, and for pre-frailty was 46%, the prevalence was higher among females 15% compared to 11% in males. Older adults with frailty have a higher risk of physical and mental health decline, and they are encountering more challenges in terms of incidence of diseases and vulnerability to infection [16]. Frail older adults are more vulnerable to infectious diseases due to the increased inflammatory condition and physiological capacity decline which lead to increased susceptibility to stressors [17,18].

Recently, with the outbreak of the COVID-19 pandemic, compared to other age groups, older people are facing the most serious threats and challenges due to age-related physiological changes and prevailing health conditions that make them at a higher risk for contracting the COVID-19 virus and developing severe illness [19]. COVID-19 pandemic has been remarkably associated with sarcopenia [20], and muscle loss was found as a predictor of ICU hospitalization in COVID-19 patients [21]. Furthermore, frailty contributes independently to adverse outcomes in COVID-19 patients, as well as care needs were increased in survivors of COVID-19 with frailty or older age [22]. On the other hand, evidence suggests that the implications of COVID-19 including prolonged bed rest with hospitalization, quarantine, inadequate nutrient intake and physical inactivity would enhance the acute sarcopenia process due to the increased muscle wasting [23–25] which may lead to frailty if untreated.

The three sides of the devastating trio (sarcopenia, frailty, and COVID-19) seem to be convoluted and intertwined. Preventive and intervention measures are necessary to disrupt this connection and minimize the consequences in terms of the rising morbidity, disability, and mortality among older adults. Therefore, this study aimed to review all available studies to get a better insight into the association of the devastating trio of sarcopenia, frailty, and COVID-19.

## 2. Methods & materials

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) updated guidelines [26]. The study protocol was registered at PROSPERO- International prospective register of systematic reviews (registration number is: CRD42022300812).

### 2.1. Eligibility criteria

The inclusion criteria were cohort studies, participants were women and men  $\geq 50$  years old, diagnosis of COVID-19, sarcopenia and/or frailty, and published full text studies in the English language. Exclusion criteria were other types of study design such as review and cross-sectional studies and preprints.

### 2.2. Information sources

Data were gathered via searches of PubMed, Cochrane, Google Scholars, and Elsevier Mendeley Library. The search targeted cohort studies addressing the association of COVID-19, sarcopenia and/or frailty. The date of publication was not limited.

### 2.3. Search strategy

The searching process was proceeded until the 9th of January 2022 by using the following portals' databases, full article accessed 1. PubMed ((sarcopenia [Title/Abstract]) OR (Frailty [Title/Abstract])) AND (Covid-19 [Title/Abstract]) 2. Google Scholar (all

entitled: sarcopenia OR frailty "Covid – 19") 3. Elsevier Mendeley website (frailty + covid-19) or (sarcopenia + covid-19) 4. Cochrane Library website using advanced search box using Keywords: Sarcopenia, Covid-19, Frailty.

### 2.4. Study selection

After excluding duplicates, the retrieved studies were reviewed by the two authors independently, titles and abstracts were evaluated at the initial screening stage, then selected the studies that met the inclusion criteria. In the second stage, full texts were extracted for all potentially eligible studies in this review.

### 2.5. Data extraction

Data were extracted from the studies included authors, journal name, year of publication, country, study tools and outcomes, socio-demographic and clinical characteristics of the participants (e.g., sample size, sex ratio, and mean age). All data were cross-checked by the two authors, any dissimilarities were discussed until consensus was reached.

### 2.6. Assessment of risk bias

Assessment of risk of bias was performed according to the Newcastle Ottawa Scale (NOS) [27] which evaluates the quality of cohort studies based on three categories: selection, comparability, and outcomes. The score ranges from 0 to 9, a higher score indicates better quality.

### 2.7. Statistical analysis

At the initial stage, a narrative synthesis was carried out, descriptive findings related to the participants' demographic clinical characteristics and outcomes were included. Consequently, all included studies in the systematic review were screened for data eligible for meta-analysis such as frailty status based on clinical frailty scale and age data according to frailty status. The quantitative synthesis was carried out for outcomes reported by more than four studies with the same outcome measure. The study's findings were presented as odds ratios (OR) and hazard ratios (HR) with a 95% confidence interval (CI). For odds ratios and mean ages with frailty status meta-analysis, all appropriate data were collected and entered into IBM SPSS Statistics v28. The extracted values of odds ratios with their 95% confidence interval were converted to log odds ratios with Standard Error for processing in different meta-analysis programs [28].

We used Cohen's *d* statistics to determine the effect size of the included studies [29]. Subgroup analyses were performed, patients were classified according to their (Clinical frailty scale) CFS score [30], where patients with a score of six and above were considered frail, a score of 4 and 5 (pre-frail), and scores 1–3 (non-frail). Heterogeneity was assessed using the I-squared test. Publication bias was assessed using Egger's test and presented by the funnel plots. All forest and funnel plots were designed using Cochrane review manager, version 5.4.1.

## 3. Results

A total of 1725 studies were identified through our electronic databases searches. After removing not relevant titles and duplicates, a total of 143 articles were screened for the title and abstract. Accordingly, a total of 98 articles were excluded because they were not cohort studies (e.g., cross-sectional study, review articles), or included different age groups. Of the remaining 45 cohort studies

which were assessed for eligibility, we have included 39 articles [31–69]. The remaining six articles were excluded because, in four of them, participants were not clinically confirmed positive COVID-19 [70–73], and two articles included participants mainly with multi-morbidity conditions such as cancer and renal diseases [74,75] which were not within the scope of this study. Figure 1 illustrates the flow diagram of the literature search and selection process.

Table 1 (Supplementary) shows the characteristics of the 39 included cohort studies [31–69] in our systematic review. The majority of the studies were conducted in Europe (n = 31, 79%) [31–36,39–45,48–53,55–60,63–68], while 3 were performed in Asia [46,47,69], 2 studies in South America [61,62] and 3 were conducted in USA [37,38,54]. Four of the included studies were multicenter international [36,43,45,64] which included 11,055 patients from 266 hospitals and intensive care units in Europe (included countries ranging from 11 to 28 countries), and four studies were a national multicenter cohort in the Netherlands [32], England [57], Denmark [65], and Ireland [34].

All of the articles included subjects who were clinically confirmed positive COVID-19. A total of 51,796 patients were included in the systematic review ranged from 30 participants in a

study conducted in France [44] to 27,961 participants in a study conducted in USA [54]. The median age of the participants ranged from 50 to 89 years. All studies had both sexes with the percentage of women varying between 19.2% [44] and 65.7% [37].

The outcomes of the studies included mortality which was recorded in 32 studies [31–37,39–43,45,47–49,51–62,64–67] and frailty status was recorded in 35 studies [31–43,45,47–49,51–62,64–69]. However, Sarcopenia was recorded in 5 studies [44,46,50,63,68].

### 3.1. Sarcopenia and frailty measurements

Sarcopenia was measured in 3 studies [44,46,50] using strength, assistance with walking, rising from a chair, climbing stairs, and falls (SARC-F) questionnaire. In 2 studies [63,68], sarcopenia was measured via muscle strength with a hand-held handgrip dynamometer and body composition. The percentage of older adults with sarcopenia ranged from 33% [46] to 75% [44].

For frailty measurement, the majority of the studies (28/35, 77%) used the clinical frailty scale (CFS) [31–36,39,41–43,45,48,49,51–53,55–62,64,66,67,69], frailty index was used in 4 studies [37,38,54,69], the Frail Nondisabled

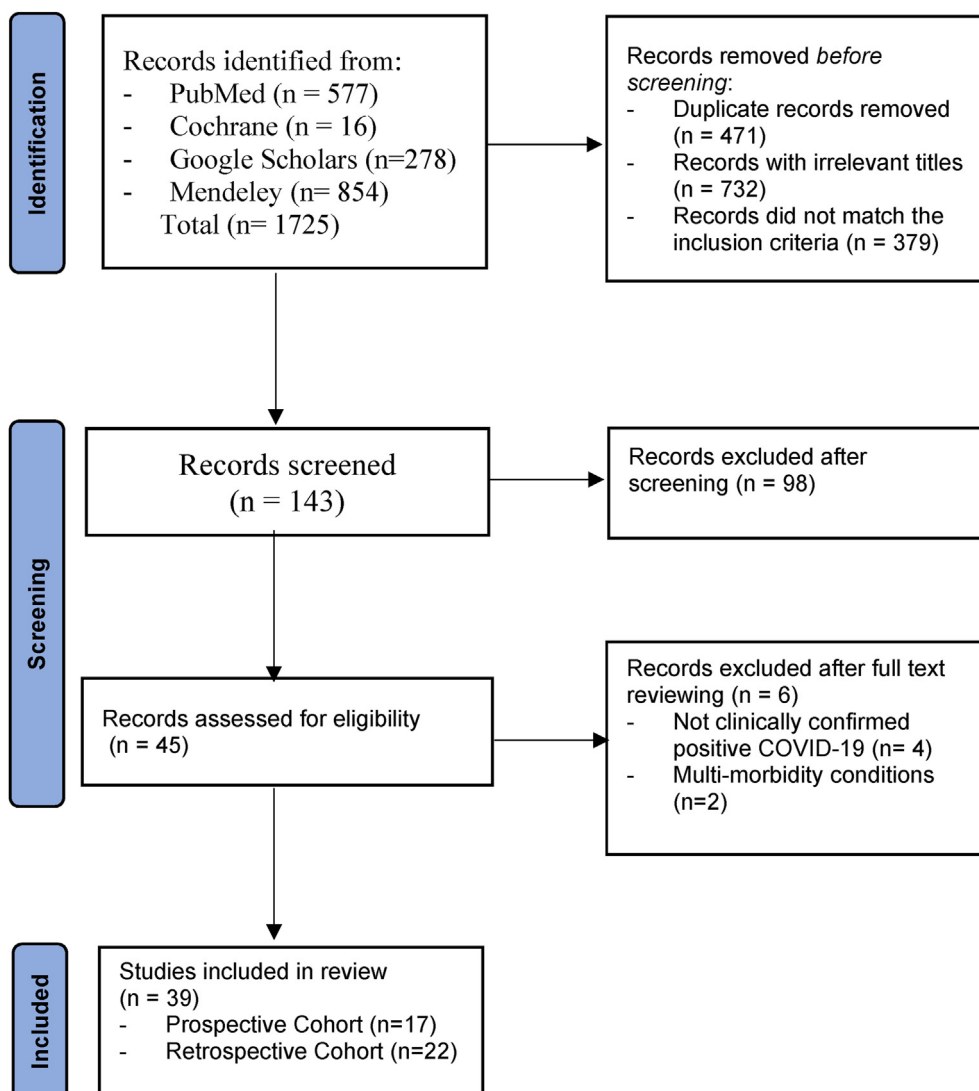


Fig. 1. PRISMA flow chart of the search strategy.

Survey (n = 1) [40], Fried's frailty phenotype (n = 1) [68], Geriatric Frailty symptoms including confusion, difficulty walking and falls (n = 1) [65], and Frail scale (n = 1) [47].

The percentage of older adults with frailty ranged from 21% [64] to 76.6% [33] of the total participants in each study.

### 3.2. Risk of development of severe disease among older Covid-19 patients

The majority of the studies included hospitalized COVID-19 patients (n = 33/39, 82%) [31–34,36,39–53,55–57,59–67,69], community dwelling elderly (n = 2) [38,68], USA Medicare fee-for service–enrolled beneficiaries (n = 1) [54], and long stay and care home residents (n = 3) [35,37,58].

Older age and frailty were described in all studies that addressed mortality and frailty as foremost risk factors associated with mortality in COVID-19 patients. Two studies indicated that the increased age is an independent risk factor for the development of critical illness and increased mortality among COVID-19 patients [33,43]. However, other studies (n = 7) [39,45,53,55,60,67,69] stated that COVID-19 disease outcomes in terms of the development of severe conditions, critical illness, and mortality were better predicted by frailty than either age or comorbidity.

### 3.3. Mortality and frailty

A higher mortality rate has been recorded amongst Covid-19 frail patients. The majority of the conducted studies in Europe 27/31 addressed the association between frailty and mortality rate among Covid-19 patients, where 25 studies [31–36,39,41–43,45,48,51–53,55–60,64–67] indicated that there was an association between frailty and mortality, and (n = 2) [40,49] indicated that the frailty was not correlated with mortality. Two of three studies conducted in the USA indicated that among Covid-19 patients, the mortality increased with frailty [37,54] with a significant difference according to the level of frailty (16.7% in pre-frail, 22.2% in moderately frail, and 50.0% in frail;  $P < 0.001$ ) [37]. One study in Asia (China) [47] indicated that frailty would increase the risk of development of severe disease among older Covid-19 patients as well as increasing mortality rate. In addition, one study in Brazil [62] stated that frailty measures have provided valuable prognostic values among COVID-19 patients.

### 3.4. Mortality and sarcopenia

From the five studies that recorded sarcopenia [44,46,50,63,68], one study has reported a mortality rate among COVID-19 patients with sarcopenia [68], and the same study has recorded frailty as well, results indicated that frailty but not sarcopenia increases the risk of developing COVID-19 in older community-dwelling adults. In four studies, results stated that a high percentage of hospital-admitted COVID-19 patients had a high risk of sarcopenia ranging from 33% [46] to 75% [44] of the participants in each study.

### 3.5. Meta-analysis results

Of the 28 studies that used the clinical frailty scale (CFS), a total of 20 studies [31,32,36,39,41–43,45,48,49,52,53,55,56,58–60,62,64,67] were included in the meta-analysis based on the odds ratio and/or hazard ratio related to mortality according to the frailty status. In 8 of the 28 studies, mortality and/or frailty were not documented in CFS increments or crude patient numbers were unavailable, therefore they were excluded from the meta-analysis. Our results indicated that COVID-19 frail patients had a significantly increased mortality rate compared to non-frail patients, the log

adjusted OR was 2.10 (1.63, 2.71);  $I^2 = 78\%$ ;  $p < 0.00001$  (Fig. 2A). Egger's test indicated publication bias for adjusted OR among the included studies ( $P = 0.0073$ ), as illustrated in the funnel plot (Fig. 2 B).

Also, the log adjusted hazard ratio (HR) data recorded significant differences related to mortality among the frail and non-frail groups, the total (95% CI) HR was 3.14 (3.32, 4.26);  $I^2 = 87\%$ ;  $p < 0.00001$  (Fig. 3 A). Egger's test indicated no publication bias for adjusted HR among the included studies ( $P = 0.9069$ ) as illustrated in the funnel plot (Fig. 3 B).

In terms of age, frail patients recorded a higher mean age compared to non-frail patients ( $p < 0.00001$ ) as shown in Fig. 4A.

Egger's test indicated no publication bias related to the mean age among the included studies ( $P = 0.6614$ ), as illustrated in the funnel plot Fig. 4. B (Supplementary).

### 3.6. Risk of bias

Results of risk of bias are presented in Table 2 (Supplementary) according to the Newcastle Ottawa Scale (NOS). The results were based on three categories: selection, comparability, and outcomes. 24 studies scored 8–9 indicating good quality with low risk of bias, and 15 studies scored 7 indicating fair quality with moderate risk of bias.

## 4. Discussion

Due to age-related physiological changes and persisting health problems, older persons confront the most acute hazards and challenges compared to other age groups, putting them at a larger risk of contracting the COVID-19 virus and experiencing severe disease [19]. This was consistent with our findings, which revealed that the majority of the studies (82%) comprised hospitalized COVID-19 patients. In which of them were four multicenter international studies [36,43,45,64] that included 11,055 patients from 266 hospitals and intensive care units in Europe. Indicating that the risk of development of severe disease, hospitalization, and ICU admission is prominent among older Covid-19 patients. Globally, the rising number of older adults is accompanied by a multifaceted of health conditions, many of which are the result of various underlying factors such as sarcopenia and frailty [1].

In this systematic review, we found that sarcopenia was recorded in 5 studies [44,46,50,63,68], all studies stated that COVID-19 patients with higher sarcopenia risk were more likely to develop severe conditions. In four studies [44,46,50,63], results stated that a high percentage of hospital-admitted COVID-19 patients had a high risk of sarcopenia ranging from 33% [46] to 75% [44] of the participants in each study. On the other hand, one study stated that COVID-19 infection combined with ICU admission and related complications can lead to acute sarcopenia [63], this opposite direction in the devastating trio might be related to prolonged bed rest, inadequate nutrient intake and physical inactivity throughout the quarantine period as well as during hospitalization [23,76]. Indicating that COVID-19 infection also may exacerbate sarcopenia due to increased muscle wasting caused by systematic inflammation among COVID-19 patients [24].

In terms of mortality, no mortality rate was clearly recorded in the five studies addressing sarcopenia. A finding that was also evident in a study conducted among COVID-19 older community-dwelling adults [68], stated that frailty but not sarcopenia nor malnutrition increases the risk of developing COVID-19. This might be attributed to that sarcopenia is being considered as a less severe condition compared to frailty where sarcopenia usually precedes frailty [11]. The devastating curve in this line starts with sarcopenia to frailty and consequently leads to disability and mortality [12,13].

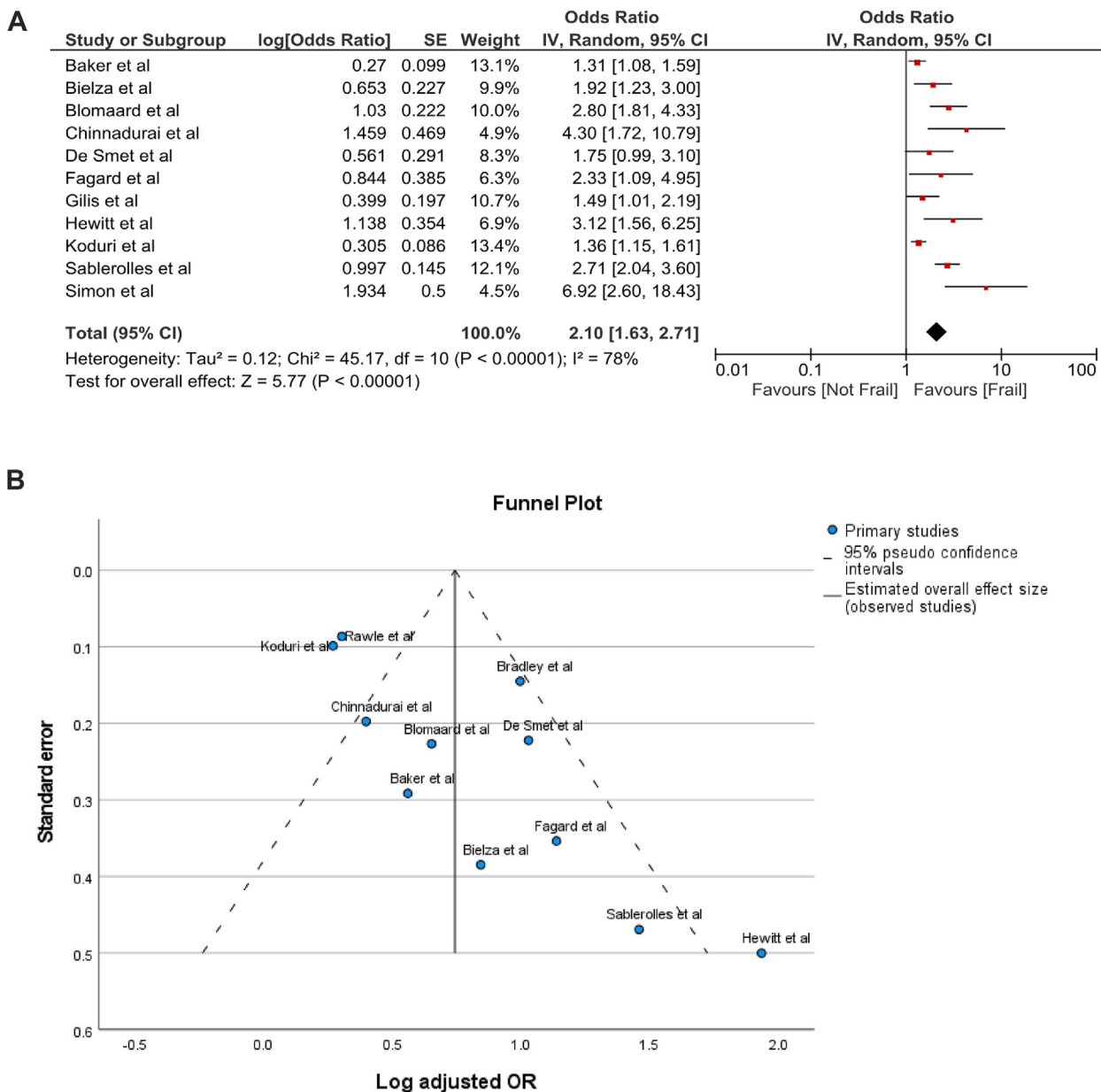


Fig. 2. A. Forest plot of adjusted OR of mortality related to frailty status. B. Funnel plot of adjusted OR of mortality related to frailty status.

All of the included studies in this review that recorded mortality and frailty in COVID-19 patients identified older age and frailty as the leading causes of mortality. Increasing age was found as an independent risk factor for critical illness and higher mortality in COVID-19 patients [33,43]. Our results indicated that a significant difference was recorded ( $p < 0.001$ ) according to age differences between frail and non-frail COVID 19 patients. However, frailty, rather than age or comorbidity, was found to be a stronger predictor of COVID-19 disease outcomes in terms of the development of severe diseases, critical illness, and mortality [39,45,53,55,60,67,69]. Therefore, frailty was described as an important predictor of COVID-19 prognosis and should not be overlooked.

Evidence suggests that frailty contributes independently to adverse outcomes in COVID-19 patients, as well as care needs were increased in survivors of COVID-19 with frailty or older age [22,45]. This might be related to increased inflammatory conditions and

physiological capability decline, frail older persons are more susceptible to infectious diseases, resulting in greater vulnerability to stressors [17,18]. Corresponding with our findings, the majority of the included studies in this systematic review indicated that a higher mortality rate has been recorded amongst Covid-19 frail patients, and the mortality increased with frailty [37,54], with a significant difference according to the level of frailty. Our results indicated that COVID-19 frail patients had a significantly increased mortality rate compared to non-frail patients ( $p < 0.00001$ ). Findings that highlight the importance and support the use of frailty indicators to help in the decision-making process for medical care in older adults COVID-19 patients.

Several instruments were used to assess frailty among COVID-19 patients, however, the clinical frailty scale (CFS) seems to be the most used instrument in the literature [77], and this finding was prominent in our study, as we found that the majority of the articles addressing frailty 28/36 have used the CSF. This could be related to

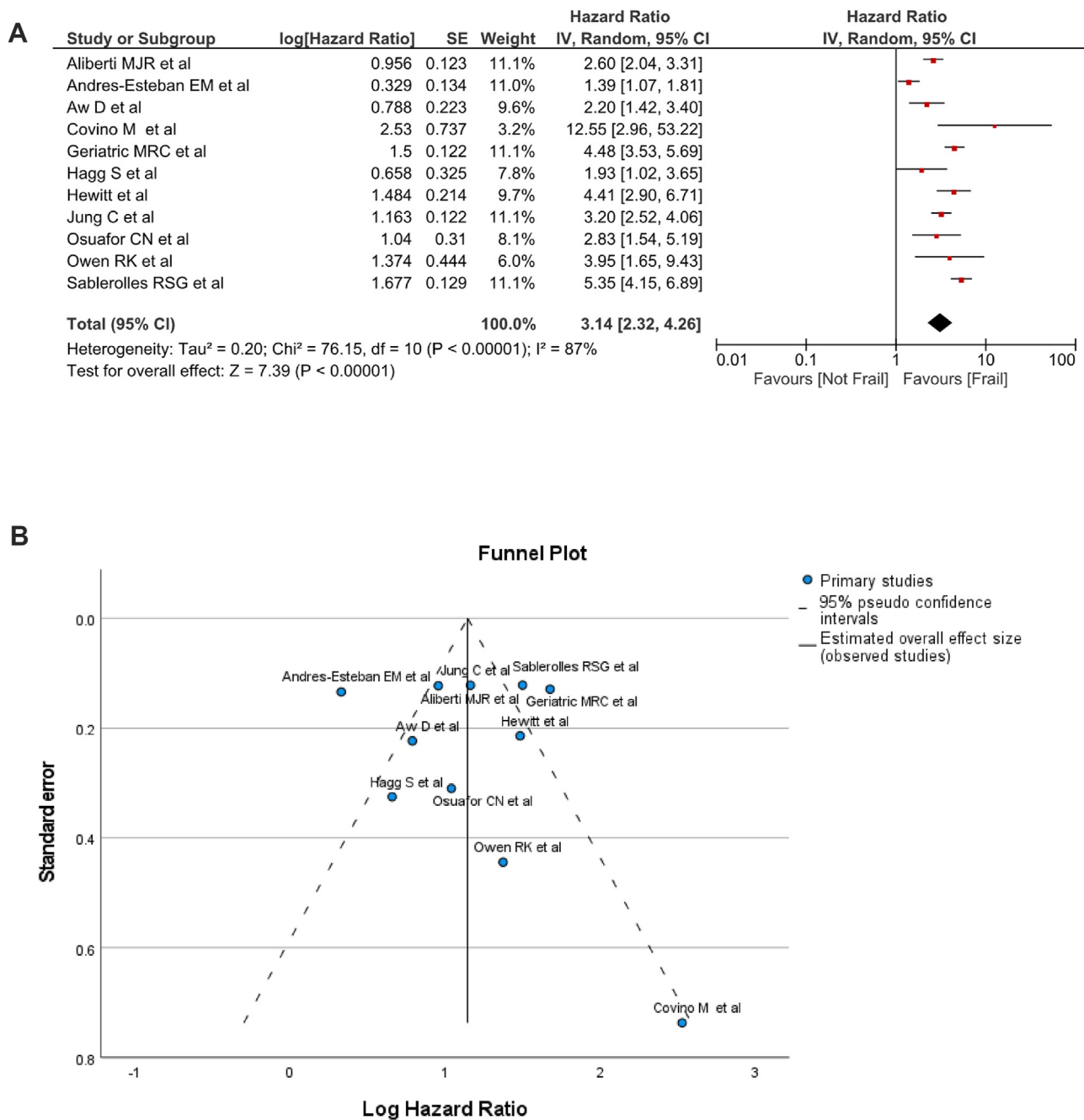


Fig. 3. A. Forest plot of adjusted HR of mortality related to frailty status. B. Funnel plot of adjusted HR of mortality related to frailty status.

the datum that CFS scoring may allow for differential frailty stratification in the context of the COVID-19 pandemic; CFS was identified as a prognostic indicator of mortality in COVID-19 as shown in a recent systematic review [77], with CFS 1–3 patients being considered at low risk, CFS 4–5 at moderate risk, and CFS 6–9 patients being considered at high risk of mortality regardless of age. The differential diagnosis characteristics of the CFS in addition to the abundance of the studies that used CFS as a scale for identifying the level of frailty have contributed to proceeding with the meta-analysis in this study.

This study aimed to get a better insight into the association of the devastating trio of sarcopenia, frailty, and COVID-19. To our knowledge, this is the first study that addresses the association of the three components among older adults patients. However,

recent systematic reviews have addressed the association of frailty with adverse outcomes including mortality in patients with COVID-19 [78–80]. There is still a need to address this topic, particularly in older persons, because the COVID-19 adverse outcomes and mortality rate are higher in this age group [19], and more research is needed to identify sarcopenia and frailty markers at the prevention level [81].

We thought that addressing sarcopenia is a vital added value to our study, it's evidenced that sarcopenia is a primary component of physical frailty; where sarcopenia usually precedes frailty [12,13]. Therefore, preventing sarcopenia was considered as a major modifiable cause of frailty in the elderly, where it can be reversed by interventions such as physical activity, exercise [82], and nutrition [50]. Acute sarcopenia, on the other hand, occurs in COVID-19

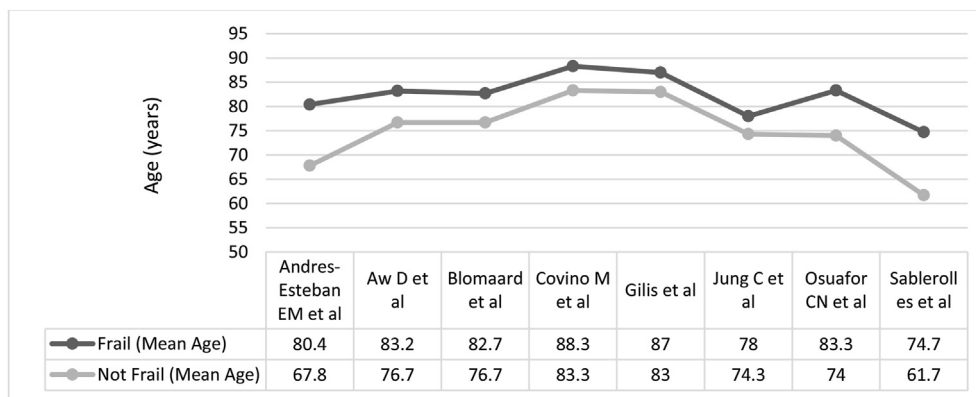


Fig. 4. A. Mean age analysis according to the frailty status.

survivors; and older persons are the most vulnerable group [25]. This line in the devastating trio might be delinked if preventive measures of tailored physical activity and adequate nutrition are taken to prevent muscle wasting in older adults that may occur due to systematic inflammation [23,24,76]. The interventions that target skeletal muscles in terms of physical activity, exercises and protein intake, in particular, are expected to disrupt the cycle in this devastating trio and assist the treatment of both disorders, where sarcopenia can be reversed and the prevention and treatment of COVID-19 can be enhanced [24].

A possible limitation of this study was that several instruments were used to assess frailty or sarcopenia, since the clinical frailty scale (CFS) was the most used instrument, our quantitative analysis was confined to the studies that used it. More review studies are needed to address the association of frailty with adverse outcomes among Covid-19 patients, where frailty is being assessed with different instruments. Also, regarding sarcopenia, still limited evidence is available, further studies are needed for studying the association of sarcopenia and adverse outcomes among older adults Covid-19 patients in the two directions.

## 5. Conclusions and implications

We found that age and frailty are important risk factors for mortality among older adults COVID-19 patients. A significant difference was recorded according to age between frail and non-frail COVID 19 patients. Frail patients had a significantly increased mortality rate compared to non-frail. Also, COVID-19 patients with sarcopenia were more likely to develop severe conditions in terms of hospitalization and ICU admission. Findings that highlight the importance and support the use of frailty and sarcopenia indicators to help in the decision-making process for medical care in older adults COVID-19 patients. Interventions including nutritional therapy in terms of adequate nutrition and protein intake, as well as tailored physical activity are vital to disrupt the cycle in this devastating trio, which can enhance the prevention and treatment of sarcopenia, frailty and COVID-19 in older adults.

## Funding statement

“This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.”

## Declaration of conflicting interests

The authors declare that there is no conflict of interest.

## Author contributions

We acknowledge that all authors (HH and IG) contributed to the study conceptualization and design, data curation, and formal analysis. HH contributed to the writing of the original draft, and HH and IG read and gave final approval for the manuscript.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.clnesp.2022.07.015>.

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