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Frailty and gender on mortality risk in elderly with coronavirus disease-19 (COVID-19): a meta-analysis

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A – Study Design, **B** – Data Collection, **C** – Statistical Analysis, **D** – Data Interpretation, **E** – Manuscript Preparation, **F** – Literature Search, **G** – Funds Collection

Summary **Background.** Frailty was believed to reflect patients' prognosis better than age, but studies regarding the association between these factors are controversial. Moreover, studies highlighting the association of gender to mortality risk in frail patients are limited.

Objectives. We aimed to investigate the association of frailty to mortality risk with the dose-response relationship of CFS and the association of gender to mortality risk in frail elderly with COVID-19.

Material and methods. We performed a comprehensive literature search from several databases, such as EuropePMC, PubMed and DOAJ on 9 July 2021. We searched for studies investigating the association between frailty and mortality in COVID-19 patient.

Results. A total of 16,438 patients from 15 studies were included. Frailty was found in 52.67% of the patients. The lowest mean age was 65.4 ± 15.8 years. Pre-frailty (OR 2.07 [1.53–2.79]; $p < 0.00001$; I^2: 72%), mild frailty (OR 2.24 [1.48–3.38]; $p = 0.00001$; I^2: 80%), moderate frailty (OR 2.55 [1.75–3.71]; $p < 0.00001$; I^2: 79%) and severe frailty (OR 3.57 [2.35–5.43]; $p < 0.00001$; I^2: 83%) increase the mortality risk in elderly with COVID-19. Each 1-point increase in CFS increases the mortality risk by 1.4 [1.3–1.5]; $p = 0.000$; I^2: 98.6%. Men had a lower risk of frailty (OR 0.58 [0.43–0.78]; $p = 0.0004$; I^2=36%) but higher mortality risk.

Conclusions. This meta-analysis showed that pre-frailty and frailty increase the mortality risk in elderly with COVID-19. Each 1-point increase in CFS increased the mortality risk by 1.4. Men had a lower risk of frailty but higher mortality risk.

Key words: frailty, frail elderly, COVID-19, aged, mortality.

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Background

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) was first found at the end of 2019 and has been spreading worldwide causing a pandemic [1]. This can cause non-specific symptoms, such as cough, fever, diarrhoea or arthro-myalgia. The disease might then evolve into pneumonia and progress to acute respiratory distress syndrome (ARDS), multi-organ failure and eventually death [2].

The mortality in patients with Corona Virus Disease-19 (COVID-19) has been shown to rise exponentially with age [1]. Patients older than 65 years had a higher prevalence of comorbidities, more severe symptoms and were more likely to develop multi-organ failure and die [3]. As the pandemic progressed, studies showed that age did not count for the enormous heterogeneity of the older population and was not reliable enough to make medical decisions in managing COVID-19. Therefore, a more comprehensive approach to act as a predictor for mortality is necessary [4].

One of the predictors proposed for predicting mortality in COVID-19 patients was frailty. Frailty is defined as a medical syndrome with multiple causes and contributors characterised by diminished strength and endurance and reduced physiologic function that increases an individual's vulnerability for developing increased dependency and/or death [5]. The elderly are often associated with frailty because of their increased vulnerability to stressors and dysregulated immune function [2]. Frailty is more prevalent in the elderly, but it can also affect the middle-aged population [6]. The global prevalence of frailty is not yet known, predominantly due to the fact that studies have only been carried out in high-income countries [7]. Collard et al. found that in community-dwelling elderly, the prevalence of frailty was 10.7%. This increased with age and was higher in women [8]. Kojima et al. studied 1,373 nursing home residents and found that 52.3% of the subjects were frail, and 40.2% were pre-frail [9].

Frailty is often measured by the Clinical Frailty Scale (CFS) [10]. Several study found a significant association between frailty and mortality to support its use as a mortality predictor [4, 11, 12]. However, other studies found otherwise [13, 14]. In the general population, frailty and mortality risk were highly influenced by gender, as men and women are different in terms of type of comorbidities, self-awareness of disability and biologically (e.g. hormones) [15]. Studies regarding the differences of mortality risk on frail COVID-19 patients based on gender are scarce but are often needed by a clinician to make decision in daily clinical practice.

Objectives

Given that frailty is prevalent in elderly patients, especially with COVID-19, and could be associated with a higher risk of complications, severe manifestation and death, we believe

studies regarding its effect on mortality are highly beneficial. Moreover, studies highlighting gender to mortality risk in frail COVID-19 patients are still limited. Therefore, studies regarding this matter are still very much needed. We aimed to investigate the association of frailty to mortality risk and the dose-response relationship of CFS in elderly with COVID-19 as reported in available literature. We would further group patients into five frail groups (fit, pre-frail, mild frail, moderate frail, severe frail). We also investigated the association of gender to mortality risk in frail elderly with COVID-19.

Material and methods

Eligibility criteria

We included all research articles analysing the prevalence of frailty or the association of frailty with mortality risk in older adults with COVID-19. We excluded non-research articles (e.g. case reports or series, review articles, letters to editors, study protocols, editorials or commentaries), studies with insufficient data, non-English articles and those not using CFS as an assessment tool for frailty.

Search strategy and study selection

This meta-analysis was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [16]. We systematically searched Pubmed, Europe PMC and the Directory of Open Access Journal (DOAJ) with the following search terms: (”Coronavirus Disease 2019” OR “COVID-19” OR ”novel coronavirus pneumonia” OR “2019-nCoV” OR “SARS-CoV-2”) AND (“frailty” OR “frail”) AND (“ARDS” OR “critically ill COVID-19” OR “Mortality” OR ”outcome” OR “ICU”) on 9 July 2021. The search results were not limited to date. Duplicate results were initially removed. Authors independently screened remaining articles for relevance by their abstracts. These articles were thoroughly read, and those that fulfilled our criteria were included in the study. The final inclusion of studies was based on the agreements of all authors. Any disagreement was resolved by consensus. The full text of residual articles was assessed according to the inclusion and exclusion criteria.

Data extraction

Data extraction was performed independently by the authors using standardised forms that included author, year of study, study design, country of study, gender, location of study, number of frail patients, number of samples, age and outcome. The outcomes of the studies were 14-day mortality, 28-day mortality, 30-day mortality, 60-day mortality, 90-day mortality and in-hospital mortality. The quality of observational cohort studies was assessed using the Newcastle-Ottawa quality assessment scale (NOS). The quality of studies was defined as poor (score 0–3), fair (score 4–6) or high (score 7–9) [17].

Definition of frailty

Frailty is defined as an age-related clinical condition, typically with deterioration in the physiological capacity of several organ systems characterised by an increased susceptibility to sudden, disproportionate functional decline following stressor events [18]. Frailty was assessed with CFS. The clinical frailty scale scores ranging from 1 to 9 based on clinical judgement. We further classified frailness in COVID-19 patients into five groups as presented in Table 1: CFS 1–3 was labelled as fit, CFS 4 was labelled as pre-frail, CFS 5 was labelled as mild frail, CFS 6 was labelled as moderate frail, and CFS 7–9 was labelled as severe frail [4, 19]. More than five point in the CFS score was labelled as frail.

Statistical analysis

To perform a meta-analysis, Review Manager 5.4.1 (Copenhagen: The Cochrane Collaboration, 2020) and Stata version 16 (StataCorp LP, Texas 77845, USA) were used. The effects of frailty to mortality in COVID-19 patients were presented as Odds Ratio (OR). Dichotomous variables were calculated using the Mantel-Haenszel formula. The OR was reported with a 95% Confidence Interval (CI) for dichotomous variables. The *p*-value was two-tailed, and statistical significance was set at < 0.05.

Heterogeneity was assessed with the Q-statistic test and I^2 test. The I^2 statistic measured the percentage of total variation across the studies due to clinical or methodological heterogeneity instead of chance. If significant Q statistics ($p < 0.1$) indicated heterogeneity across the studies, a random-effect model was utilised. Otherwise, a fixed-effect model was utilised. Substantial heterogeneity was represented by I^2 for > 50% [20]. We analysed the effect of pre-frailty, mild frailty, moderate frailty, severe frailty and frailty to mortality in COVID-19 patients. A dose-response analysis was then performed to generate OR per 1-unit increment of CFS.

To assess the small-study effect and publication bias, we performed the regression-based Egger test. We also performed a qualitative assessment for publication bias by using funnel plot analysis, and an asymmetrical shape indicated publication bias.

Results

Baseline characteristics and study selection

A total of 16,438 patients from 15 studies were included in qualitative and quantitative synthesis (meta-analysis) (Figure 1) [1, 2, 4, 5, 10–13, 21–27]. The study characteristics of the included studies are presented in Table 1. All of the studies were cohort studies, with 46.67% of the studies being retrospective cohort studies. Most of the countries were located in Europe, with one study from Brazil. Most of the study patients were male. All of the patients were hospitalised. Frailty was found in 52.67% of the patients. The lowest mean age was 65.4 ± 15.8 years of age [24].

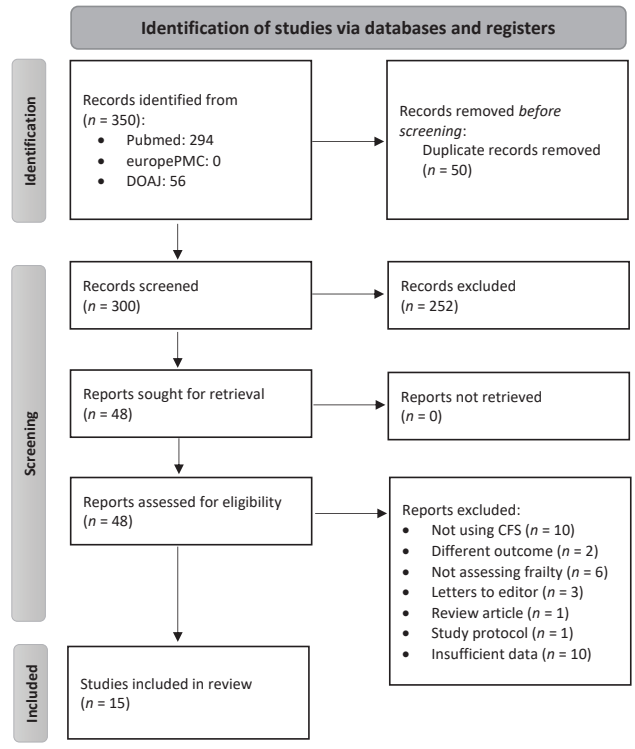

Figure 1. Prisma study flow diagram

Table 1. Demographic and clinical characteristics of included studies

Author	Design	Country	Male (%)	Setting	Frailty (%)	Sample (*n*)	Age (year)	Outcome	NOS
Aliberti 2021	PCS	Brazil	58	Hospital	27	1,830	66	30-days mortality	7 (good)
Andrés-Esteban 2021	PCS	Spain	61.02	Hospital	17.32	254	> 65	In-hospital mortality	8 (good)
Aw 2020	PCS	UK	54	Hospital	70.7	677	81.1 ± 8.1	In-hospital mortality	8 (good)
Bavaro 2020	RCS	Italy	48	Hospital	N/A	206	80 (72–86)	In-hospital mortality	6 (fair)
Blomaard 2021	RCS	Netherlands	60.4	Hospital	N/A	1,376	76 (74–84)	In-hospital mortality	6 (fair)
Chinnadurai 2021	PCS	UK	61.9	Hospital	51.2	215	71 (60–82)	In-hospital mortality	7 (good)
Dres 2021	PCS	France, Switzerland and Belgium	73	Hospital	49.33	1,199	74 (72–78)	90-day mortality	7 (good)
Hewitt 2020	PCS	UK and Italy	58	Hospital	51.25	1564	74 (64–83)	In-hospital mortality	8 (good)
Mendes 2020	RCS	Switzerland	43	Hospital	78.72	235	86 ± 6.5	In-hospital mortality	6 (fair)
Neradova 2021	RCS	UK	57.5	Hospital	58.62	174	65.4 ± 15.8	28-day mortality	7 (good)
Osuafor 2021	RCS	UK	56.07	Hospital	66.4	214	80 (75–87)	In-hospital mortality until 14-day mortality	6 (fair)
Owen 2021	RCS	UK	54	Hospital	53.3	206	78.8 ± 8.3	In-hospital mortality	6 (fair)
Sablerolles 2021	RCS	11 countries in Europe	61	Hospital	28.38	2434	68 (55–77)	In-hospital mortality	7 (good)
Tehrani 2021	PCS	Sweden	N/A	Hospital	30	143	66 ± 17	60-day mortality	8 (good)
Welch 2021	PCS	12 countries in Europe	55.2	Hospital	54.12	5,711	74	In-hospital mortality	8 (good)

PCS – prospective cohort study, RCS – retrospective cohort study, N/A – not available, NOS – Newcastle Ottawa Scale.

Frailty and mortality

Frailty was observed in 52.67% of elderly patients with COVID-19. Frailty increases mortality risk in elderly with COVID-19 (OR 2.50 [1.10–5.69]; $p = 0.03$; I^2 : 98%; $p < 0.00001$) (Figure 2).

We further analysed the association between different groups of frailty to mortality. Pre-frailty increase the mortality risk in elderly with COVID-19 (OR 2.07 [1.53–2.79]; $p < 0.00001$; I^2 : 72%; $p = 0.0009$) (Figure 3). Mild frailty increased the mortality risk in elderly with COVID-19 (OR 2.24 [1.48–3.38]; $p = 0.00001$; I^2 : 80%; $p = 0.0001$)) (Figure 4). Moderate frailty increased the mortality risk in elderly with COVID-19 (OR 2.55 [1.75–3.71]; $p < 0.00001$; I^2 : 79%; $p = 0.0007$) (Figure 5). Severe frailty increased the mortality risk in elderly with COVID-19 (OR 3.57 [2.35–5.43]; $p < 0.00001$; I^2 : 83%; $p < 0.0001$) (Figure 6). Based on our analysis, the ORs for mortality risk in each frailty groups increased as CFS increased (Table 2).

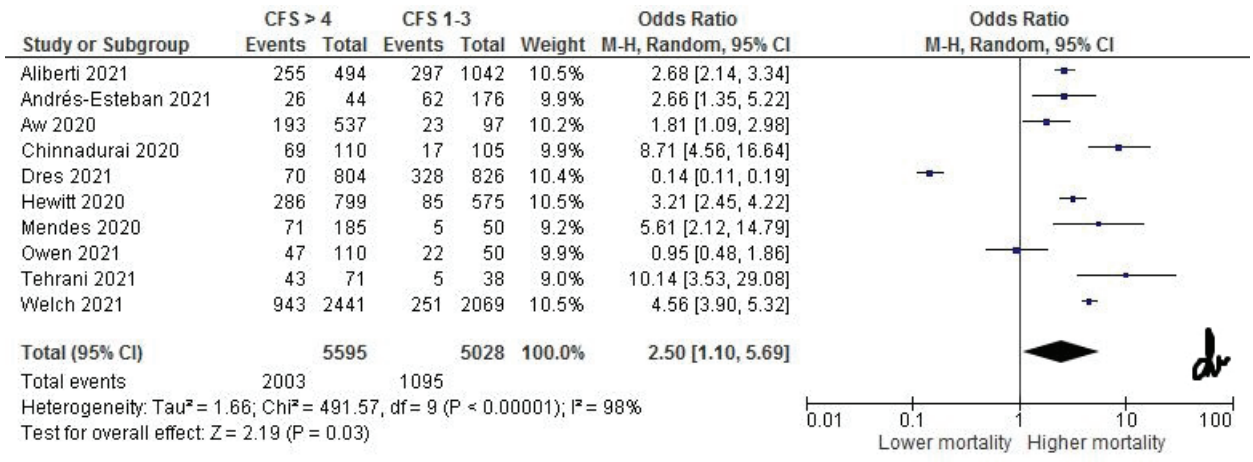

Figure 2. Forest plot and OR for the association of frailty and mortality in elderly with COVID-19

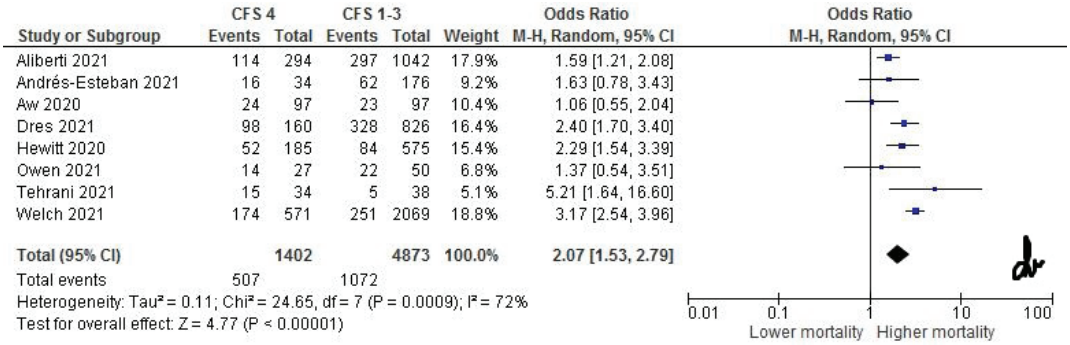

Figure 3. Forest plot and OR for the association of pre-frailty and mortality in elderly with COVID-19

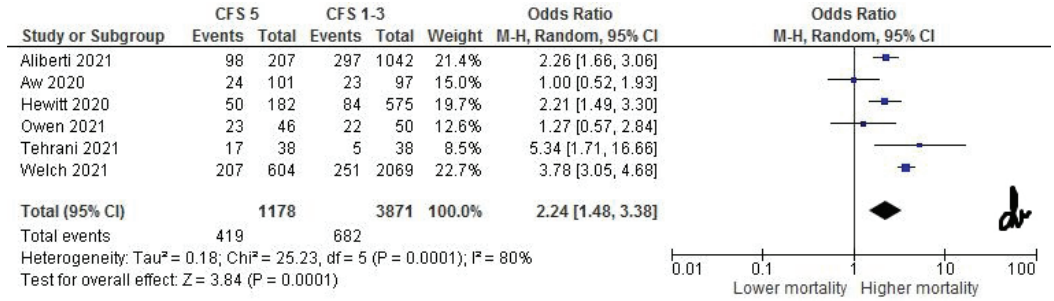

Figure 4. Forest plot and OR for the association of mild frailty and mortality in elderly with COVID-19

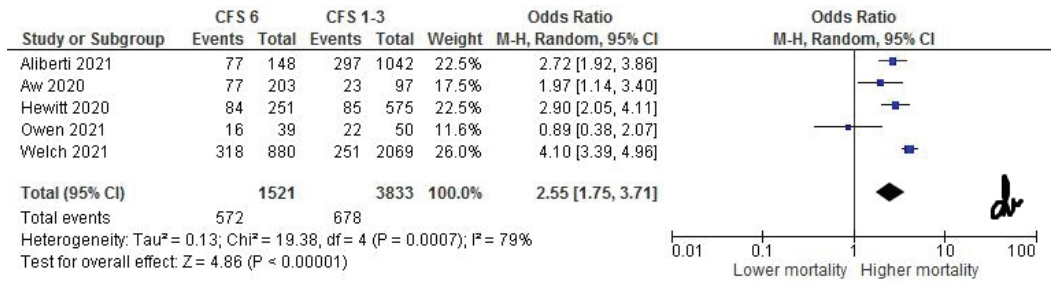

Figure 5. Forest plot and OR for the association of moderate frailty and mortality in elderly with COVID-19

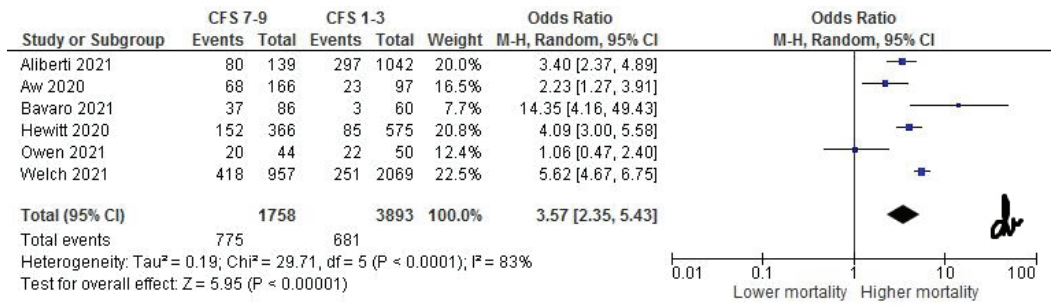

Figure 6. Forest plot and OR for the association of severe frailty and mortality in elderly with COVID-19 patients

Table 2. OR for the association of frailty groups and mortality in elderly with COVID-19

Frailty groups	CFS	OR	95% CI	*p*
Fit	1–3	Reference	–	–
Pre-frailty	4	2.07	1.53, 2.79	< 0.00001
Frailty	> 4	2.50	1.10, 5.69	0.03
mild frailty	5	2.24	1.48, 3.38	0.00001
moderate frailty	6	2.55	1.75, 3.71	0.00001
severe frailty	7–9	3.57	2.35, 5.43	0.00001

OR – odds ratio, CI – confidence interval.

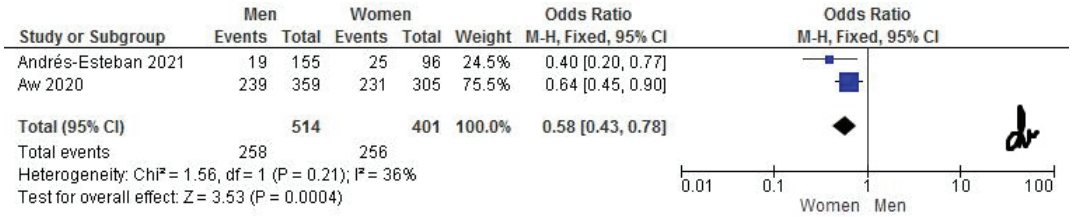

Figure 7. Forest plot and OR for the association of gender and frailty in elderly with COVID-19 patients

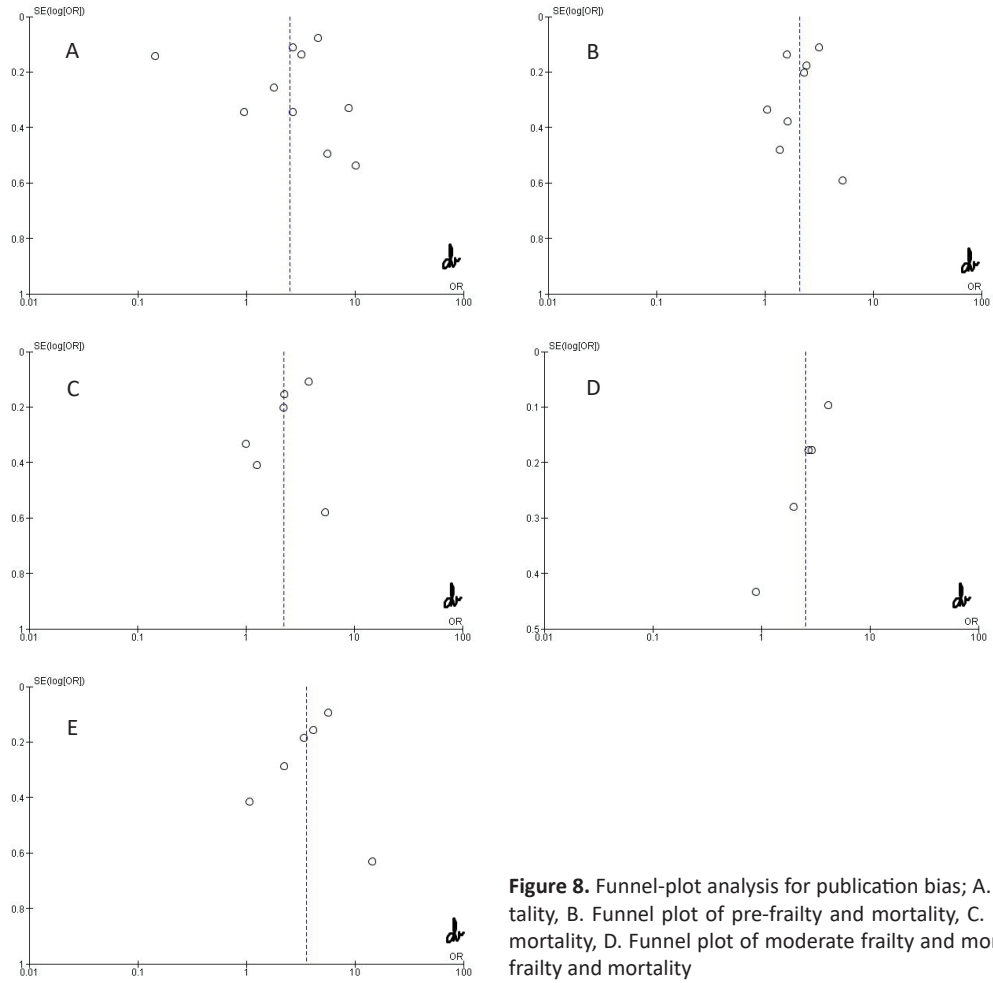

Figure 8. Funnel-plot analysis for publication bias; A. Funnel plot of frailty and mortality, B. Funnel plot of pre-frailty and mortality, C. Funnel plot of mild frailty and mortality, D. Funnel plot of moderate frailty and mortality, E. Funnel plot of severe frailty and mortality

Dose-response analysis

Eleven studies were included in the dose-response analysis (4, 5, 10–13, 21, 24–27). Each 1-point increase in CFS was associated with increased mortality risk by 1.4 [1.3–1.5]; $p = 0.000$; I^2: 98.6%.

Gender

Men had a lower risk of frailty compared to women (OR 0.58 [0.43–0.78]; $p = 0.0004$; I^2=36%; $p = 0.21$) (Figure 7). Owen et al. analysed the difference in mortality between frail COVID-19 male patients and frail COVID-19 female patients. The mortality rate was higher in men compared to women in all frail groups [11].

Comorbidities, clinical symptoms and complication

One study stated that most comorbidities (hypertension, chronic obstructive pulmonary disease (COPD), malignant neoplasm, diabetes mellitus, dementia and mental disorder) have a similar distribution among fit and frail COVID-19 patients, except for heart disease (18.75% vs 40.91%; $p = 0.001$), chronic bronchitis (6.82% vs 22.73%; $p = 0.007$), chronic kidney disease (CKD) (7.95% vs 20.45%; $p = 0.017$) and dementia (0.57% vs 34.09%; $p < 0.001$). Upon arrival to the emergency room, altered behaviour was more common in frail patients than fit patients, 31.82% vs 11.93% ($p < 0.001$), respectively. Altered consciousness was more common frail patients than fit patients, 15.91% vs 3.41% ($p < 0.001$), respectively. Delirium was more common in frail COVID-19 patients compared to fit patients (8.52% vs 43.18%; $p < 0.001$) [5].

Publication bias

The funnel-plot analyses were done to assess publication bias in the included studies. The funnel-plot analysis showed an asymmetrical shape for all outcomes (Figure 8A, B, C, D, E), indicating possible publication bias. We further analysed publication bias with the regression-based Egger test. The regression-based Egger test showed indication of small-study effects only for moderate frail group ($p = 0.000$).

Discussion

We included 16,438 patients from 15 studies in the analysis and found that frailty was prevalent in COVID-19 patients. SARS-CoV-2 enters the body through the Angiotensin Converting Enzyme 2 (ACE2) receptor. This receptor was expressed in extensive cell types in multiple organs, therefore exhibited multiple organ injuries and showed higher rate of frailty [28].

Studies have stated that frail patients were more likely to present with other chronic disease, such as heart disease, CKD and dementia [5, 28]. These comorbidities contribute to a higher risk of frailty and predictors for severe disease [29]. Although often overlapping and acting as confounding factors, disability and comorbidities are do not always accompany by frailty. The main features of frailty are decreased functional reserve, impairment or dysregulation in multiple physiological systems, as well as a reduced ability to regain physiological homeostasis after a stressful and destabilising event. It is important in clinical practice to emphasise that not all disabled persons are frail and not all comorbidities are accompanied with frailty [30].

We found that frailty increases the mortality risk in elderly with COVID-19 (OR 2.50 [1.10–5.69]; $p = 0.03$; I^2: 98%; $p < 0.00001$). Compared to the fit group, pre-frailty (OR 2.07 [1.53– 2.79]; $p < 0.00001$), mild frailty (OR 2.24 [1.48–3.38]; $p = 0.00001$), moderate frailty (OR 2.55 [1.75– 3.71]; $p < 0.00001$) and severe frailty (OR 3.57 [2.35–5.43]; $p < 0.00001$) increase mortality risk. Most studies have shown similar results [1, 11, 21]. Inflammation contributes to higher mortality in frail COVID-19 patients. A meta-analysis demonstrated that pre-frailty and frailty were associated with higher inflammatory parameters. Thus, SARS-CoV-2 infection will further exacerbate inflammation state, therefore contributing in forming a cytokine storm, which increases mortality risk [31]. Frailty is associated with a more severe course of some diseases and predisposes patients to the development of additional health problems. In diabetic patients, frailty may lower the effect of reperfusion treatment of chronic limb ischemia [32]. Frailty is also associated with an increased risk of falls, disease progression and ICU admission [18]. It is also associated with loneliness, lower quality of life, depression, cognitive decline, dementia, hospitalisation and nursing home admission [7].

We found that each 1-point increase in CFS was associated with increased mortality risk by 1.4 [1.3, 1.5]; $p = 0.000$. Marengoni et al. found that CFS had an OR of 1.356 [1.145–1.606]; $p < 0.001$). In all patients, CFS was a predictor for mortality with OR 1.2 [1.05–1.62], but in the population more than 70 years old, CFS had higher OR (1.29 [1.03–1.62]) [33]. The association of CFS and mortality is a linear relationship [34]. This provides an insight for clinicians to further highlight the importance of a CFS increase in managing COVID-patients.

The lowest mean age of those included in the studies was 65.4 ± 15.8 years [24]. Frailty is an age-related clinical condition; therefore, age increases the risk of frailty [18]. Aliberti et al. found that frail non-elderly COVID-19 patients tend to have a higher 6-month mortality risk than the elderly. This shows that the prognosis of the older population depends on biological age rather than chronological age itself [4]. It is suggested to use CFS in patients older than 65 years, [35] but studies in the $\geq$ 18 year-old population shows that frailty assessed with CFS was also associated with mortality [22, 27]. It showed that CFS could be used in wider population. The COVID Medication (COMET) Study is a retrospective observational cohort in 63 hospitals in 11 countries for COVID-19 patients. This study stated that CFS is a good mortality predictor for COVID-19 [10]. Other frailty scores, such as the Hospital Frailty Risk Score (HFRS), were used by Hägg et al., but it failed to show a significant association with mortality [36]. Ramos-Rincon et al. compared CFS with HFRS and stated that CFS was more associated with mortality in patients aged $\geq$ 18 years [37].

In COVID-19, men had a lower risk of frailty compared to women but had a higher mortality rate [11]. Studies comparing frailty between men and women in COVID-19 patients are still limited, but meta-analysis in the general population showed that women had a higher frailty score than men but tolerated this frailty better, as demonstrated by a lower mortality rate in frail women compared to men. Both men and women both acquired comorbidities with age, but women usually acquired more deficits overall and had a higher prevalence of non-lethal diseases that negatively impact function and quality of life, hence the higher frailty rate in women [15].

Gender hormones contributed to the severity and mortality of COVID-19. Oestrogen has the ability to modulate RAAS. In RAAS, renin will convert angiotensinogen to angiotensin I. Angiotensin I will be converted to Angiotensin II by ACE. Angiotensin II binds to the Angiotensin 1-Receptor (AT1-R). Activation of AT1-R causes vasoconstriction, sodium retention and oxidative stress. Oestrogen downregulates renin and the Angiotensin 1-Receptor (AT1-R). Another role of oestrogen is to upregulate ACE2 expression levels. Angiotensin Converting Enzyme 2 converts angiotensin II to vasodilatory angiotensin 1–7. Oestrogen upregulates ACE2 expression levels, therefore leading to more vasodilatation. The second protein necessary for SARS-CoV-2 to enter into the cells is cell-surface serine protease (Transmembrane Protease Serine 2 (TMPRSS2)). Testosterone increase activation of TMPRSS2. At the cell membrane, this protein facilitated viral entry and spread [38].

Upon arrival to the emergency room, an altered level of consciousness is common in frail COVID-19 patients compared to fit patients. In line with our findings, Lithander et al. stated that delirium is one of the clinical manifestation in older patients with COVID-19 [39]. This happened due to the high prevalence of dementia in older patient [40]. Andrés-Esteban et al. stated that dementia occurred in 34.09% of frail COVID-19 patients (compared to 0.57% in fit patients; $p < 0.001$) [5]. Saudi et al. stated that 85.69% of frail elderly patients had cognitive impairment [41]. Cognitive decline was associated with mortality in older COVID-19 patients. Cognitive decline is likely to be associated with poorer outcomes because of underlying frailty, less compliance with safety measures and treatments and risk of delirium. Another explanation is that patients with dementia more often have had advance care planning with higher therapeutic restriction codes and that patients with cognitive decline are less often transferred to the Intensive Care Unit (ICU) [42]. Therefore, in managing patients with dementia and delirium, the clinician should further emphasise the need for assessing frailty.

Managing frailty could be done in home and community settings and through hospital care. It consist of physical activity programmes (resistance-based training, aerobic training or balance and coordination training), nutritional interventions and cognitive training [18, 43]. Combined multidisciplinary treatment is better than sole interventions [43]. Published studies regarding pharmacological intervention for management of frailty are scarce [18].

Limitations of the study

There are some limitations in this meta-analysis. First, some of studies are retrospective observational cohorts, which provide weaker strength of evidence than prospective cohort studies. Second, heterogeneity was high in our study. This may occur due to a significant variation of sample sizes and frailty prevalence.

Conclusions

This meta-analysis showed that pre-frailty and frailty increased the mortality risk in elderly with COVID-19. Every 1-point increase in CFS increased the mortality risk by 1.4. Men had a lower risk of frailty but higher mortality risk.

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References

1. Mendes A, Serratrice C, Herrmann FR, et al. Predictors of In-Hospital Mortality in Older Patients with COVID-19: The COVIDAge Study. *J Am Med Dir Assoc* 2020; 21(11): 1546–1554.e3.
2. Bavaro DF, Diella L, Fabrizio C, et al. Peculiar clinical presentation of COVID-19 and predictors of mortality in the elderly: a multicentre retrospective cohort study. *Int J Infect Dis* 2021; 105: 709–715.
3. Zazzara MB, Penfold RS, Roberts AL, et al. Probable delirium is a presenting symptom of COVID-19 in frail, older adults: a cohort study of 322 hospitalised and 535 community-based older adults. *Age Ageing* 2021; 50(1): 40–48.
4. Aliberti MJR, Szlejf C, Avelino-Silva VI, et al. COVID-19 is not over and age is not enough: using frailty for prognostication in hospitalized patients. *J Am Geriatr Soc* 2021; 69(5): 1116–1127.
5. Andrés-Esteban EM, Quintana-Diaz M, Ramírez-Cervantes KL, et al. Outcomes of hospitalized patients with COVID-19 according to level of frailty. *Peer J* 2021; 9: e11260.
6. Chong E, Chan M, Tan HN, et al. COVID-19: Use of the Clinical Frailty Scale for Critical Care Decisions. *J Am Geriatr Soc* 2020; 68(6): E30–E32.
7. Hoogendijk EO, Afilalo J, Ensrud KE, et al. Frailty: implications for clinical practice and public health. *Lancet* 2019; 394(10206): 1365–1375.
8. Collard RM, Boter H, Schoevers RA, et al. Prevalence of frailty in community-dwelling older persons: a systematic review. *J Am Geriatr Soc* 2012; 60(8): 1487–1492.
9. Kojima G. Prevalence of Frailty in Nursing Homes: A Systematic Review and Meta-Analysis. *J Am Med Dir Assoc* 2015; 16(11): 940–945.
10. Sablerolles RSG, Lafeber M, Kempen JAL van, et al. Association between Clinical Frailty Scale score and hospital mortality in adult patients with COVID-19 (COMET): an international, multicentre, retrospective, observational cohort study. *Lancet Healthy Longev* 2021; 2(3): e163–e170.
11. Owen RK, Conroy SP, Taub N, et al. Comparing associations between frailty and mortality in hospitalised older adults with or without COVID-19 infection: a retrospective observational study using electronic health records. *Age Ageing* 2021; 50(2): 307–316.
12. Geriatric Medicine Research Collaborative, Covid Collaborative, et al. Age and frailty are independently associated with increased COVID-19 mortality and increased care needs in survivors: results of an international multi-centre study. *Age Ageing* 2021; 50(3): 617–630.
13. The COVID-ICU investigators, Dres M, Hajage D, Lebbah S, et al. Characteristics, management, and prognosis of elderly patients with COVID-19 admitted in the ICU during the first wave: insights from the COVID-ICU study: prognosis of COVID-19 elderly critically ill patients in the ICU. *Ann Intensive Care* 2021; 11(1): 77.
14. Miles A, Webb TE, Mcloughlin BC, et al. Outcomes from COVID-19 across the range of frailty: excess mortality in fitter older people. *Eur Geriatr Med* 2020; 11(5): 851–855.
15. Gordon EH, Peel NM, Samanta M, et al. Sex differences in frailty: a systematic review and meta-analysis. *Exp Gerontol* 2017; 89: 30–40.
16. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021; n71.
17. Wells GA, O'Connell D, Peterson J, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses [cited 10.06.2021]. Available from URL: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
18. Dent E, Martin FC, Bergman H, et al. Management of frailty: opportunities, challenges, and future directions. *Lancet* 2019; 394(10206): 1376–1386.
19. Rockwood K, Theou O. Using the Clinical Frailty Scale in Allocating Scarce Health Care Resources. *Can Geri J* 2020; 23(3): 254–259.
20. Deek J, Higgins J, Altman D. *Analysing data and undertaking meta-analysis*. In: *Cochrane handbook for systematic reviews of interventions.* Hoboken, New Jersey: John Wiley & Sons Ltd; 2008.
21. Hewitt J, Carter B, Vilches-Moraga A, et al. The effect of frailty on survival in patients with COVID-19 (COPE): a multicentre, European, observational cohort study. *Lancet Public Health* 2020; 5(8): e444–e451.
22. Tehrani S, Killander A, Åstrand P, et al. Risk factors for death in adult COVID-19 patients: Frailty predicts fatal outcome in older patients. *Int J Infect Dis* 2021; 102: 415–421.
23. Chinnadurai R, Ogedengbe O, Agarwal P, et al. Older age and frailty are the chief predictors of mortality in COVID-19 patients admitted to an acute medical unit in a secondary care setting – a cohort study. *BMC Geriatr* 2020; 20(1): 409.
24. Neradova A, Vajgel G, Hendra H, et al. Frailty score before admission as risk factor for mortality of renal patients during the first wave of the COVID pandemic in London. *G Ital Nefrol* 2021; 38(3): 2021-vol3.
25. Blomaard LC, Linden CMJ van der, Bol JM van der, et al. Frailty is associated with in-hospital mortality in older hospitalised COVID-19 patients in the Netherlands: the COVID-OLD study. *Age Ageing* 2021; 50(3): 631–640.
26. Osuafor CN, Davidson C, Mackett AJ, et al. Clinical Features, Inpatient Trajectories and Frailty in Older Inpatients with COVID-19: A Retrospective Observational Study. *Geriatrics* 2021; 6(1): 11.
27. Aw D, Woodrow L, Ogliari G, Harwood R. Association of frailty with mortality in older inpatients with Covid-19: a cohort study. *Age Ageing* 2020; 49(6): 915–422.
28. Yang Y, Luo K, Jiang Y, et al. The Impact of Frailty on COVID-19 Outcomes: A Systematic Review and Meta-analysis of 16 Cohort Studies. *J Nutr Health Aging* 2021; 25(5): 702–709.
29. Jain V, Yuan J-M. Predictive symptoms and comorbidities for severe COVID-19 and intensive care unit admission: a systematic review and meta-analysis. *Int J Public Health* 2020; 65(5): 533–546.
30. Chen X, Mao G, Leng SX. Frailty syndrome: an overview. *Clin Interv Aging* 2014; 9: 433–441.
31. Soysal P, Stubbs B, Lucato P, et al. Inflammation and frailty in the elderly: a systematic review and meta-analysis. *Ageing Res Rev* 2016; 31: 1–8.
32. Jakubiak GK, Pawlas N, Cieślar G, et al. Chronic Lower Extremity Ischemia and Its Association with the Frailty Syndrome in Patients with Diabetes. *IJERPH* 2020; 17(24): 9339.
33. Marengoni A, Zucchelli A, Vetrano DL, et al. Beyond Chronological Age: Frailty and Multimorbidity Predict In-Hospital Mortality in Patients with Coronavirus Disease 2019. *J Gerontol A Biol Sci Med Sci* 2021; 76(3): e38–e45.
34. Pranata R, Henrina J, Lim MA, et al. Clinical frailty scale and mortality in COVID-19: A systematic review and dose-response meta-analysis. *Arch Gerontol Geriatr* 2021; 93: 104324.
35. Jung C, Flaatten H, Fjølner J, et al. The impact of frailty on survival in elderly intensive care patients with COVID-19: the COVIP study. *Crit Care* 2021; 25(1): 149.
36. Hägg S, Jylhävä J, Wang Y, et al. Age, Frailty, and Comorbidity as Prognostic Factors for Short-Term Outcomes in Patients with Coronavirus Disease 2019 in Geriatric Care. *J Am Med Dir Assoc* 2020; 21(11): 1555–1559.e2.

37. Ramos-Rincon J, Moreno-Perez O, Pinargote-Celorio H, et al. Clinical Frailty Score vs Hospital Frailty Risk Score for predicting mortality and other adverse outcome in hospitalised patients with COVID-19: Spanish case series. *Int J Clin Pract* 2021; 75(10): e14599.
38. Gebhard C, Regitz-Zagrosek V, Neuhauser HK, et al. Impact of sex and gender on COVID-19 outcomes in Europe. *Biol Sex Differ* 2020; 11(1): 29.
39. Lithander FE, Neumann S, Tenison E, et al. COVID-19 in older people: a rapid clinical review. *Age Ageing* 2020; 49(4): 501–515.
40. Bielza R, Sanz J, Zambrana F, et al. Clinical Characteristics, Frailty, and Mortality of Residents with COVID-19 in Nursing Homes of a Region of Madrid. *J Am Med Dir Assoc* 2021; 22(2): 245–252.e2.
41. Saudi RA, Tosson EE, Salama HM. Association between frailty status and cognitive performance of elderly patients attending the Family Medicine Outpatient Clinic in Ismailia, Egypt. *Fam Med Prim Care Rev* 2021; 23(2): 232–238.
42. Fagard K, Gielen E, Deschodt M, et al. Risk factors for severe COVID-19 disease and death in patients aged 70 and over: a retrospective observational cohort study. *Acta Clin Belg* 2021; 1–8, doi: 10.1080/17843286.2021.1890452.
43. Bujnowska-Fedak MM, Waligóra J, D'Avanzo B, et al. Approaches to therapy and prevention of frailty in the light of contemporary medicine. *Fam Med Prim Care Rev* 2017; 19(3): 289–297.

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