

FRAILITY AND MORTALITY ASSOCIATION IN PATIENTS WITH COVID-19 : A SYSTEMATIC REVIEW

Yenny Frida Setiawan*

**Faculty of Medicine, Maranatha Christian University*

***Corresponding Author:-**

yenny31fs@gmail.com

Abstract

When a person's physiological reserve is low, they are more susceptible to the negative effects of stress, which can lead to poor health outcomes. This condition is known as frailty. This condition is linked to a number of chronic conditions, many of which are risk factors for the outcomes of SARS-COV-2 infections in elderly patients. This review aims to describe frailty as a physiological vulnerability agent during the Covid-19 pandemic in elderly patients. It will do so by providing a summary of the direct and indirect effects caused by the SARS-COV-2 infection, as well as its prognosis in frail individuals, as well as the interventions and recommendations that can be used to reduce the effects of these infections. However, other scales have also associated frailty with longer hospital stays and more severe forms of the disease. Cohort studies have shown that patients with a Clinical Frailty Scale that is higher than five have a higher risk of mortality and use of mechanical ventilation after Covid-19. In addition, the pandemic's indirect effects have a negative impact on the health status of people who are older in age. As a result of the aforementioned, a holistic intervention is proposed. This intervention is based on a comprehensive geriatric assessment for frail patients and places an emphasis on physical activity and nutritional recommendations. If successful, this intervention could serve as a potential preventive intervention in viral infections caused by Covid-19. One of the primary contributors to a precarious state of life as a result of the gradual loss of physiological functions and a key factor in the development of pathological aging is simply getting older. In this particular study, the overall mortality rate for patients was found to be 38.3% on average.

Keyword: Covid-19; Frailty; Inflammation; Mortality

INTRODUCTION

The outbreak was reported to the World Health Organization by China on the 31st of December, 2019, and the Huanan sea food market was shut down on the 1st of January, 2020. On January 7th, the virus was determined to be a coronavirus that shared greater than 95% homology with the coronavirus found in bats and greater than 70% similarity with the SARS-CoV. There is a wide range of clinical manifestations associated with COVID-19, from asymptomatic states to acute respiratory distress syndrome and multiple organ dysfunction. The common clinical manifestations include fever (not at all), cough, sore throat, headache, fatigue, myalgia, and breathlessness. Other manifestations include headache, breathlessness, and myalgia. By the end of the first week, the disease can progress to pneumonia, respiratory failure, and death in some patients. This can happen in a subset of patients.^{1,2}

There have been more than one hundred million confirmed cases of Covid-19 over the world. The older adults were the demographic segment that was most affected by Covid-19 in terms of hospitalization, poor outcomes, and mortality. This was the case in all four countries.³ The high frequency of comorbidities, a weakened immune system, and, most significantly, frailty in this specific community contribute to a high risk of mortality and poor outcomes among older persons who have been diagnosed with Covid-19. This is a natural effect of the unique demographic.^{4,5}

Frailty is defined as an age-related clinical disorder that is typically accompanied by a decline in the physiological ability of multiple organ systems. It is also characterized by a higher degree of vulnerability to what appears to be a minor stressor, which places frail older adults at a greater risk of poor health outcomes, such as dependence and disability.^{6,7} Frailty is caused by an underlying mechanism that is not related to the process of aging, but it is highly likely to progress along with the aging process. Nevertheless, frailty is not an essential component of becoming older, and many persons live to a ripe old age without ever becoming feeble.⁸

The fact that frailty is a prevalent clinical symptom seen in older persons makes it particularly relevant in the context of the ongoing Covid-19 epidemic. The overall prevalence of frailty was found to be 12% across the board in a recent meta-analysis that included 1,750,000 persons aged 50 years from 62 different countries. The prevalence of frailty among Europeans aged 65 years is believed to be 15%, and these findings are consistent with that estimation. In addition, over three quarters of those who are fragile have multiple health conditions.⁹⁻¹¹

Frail older persons have a larger chance of having severe Covid-19 than pre-frail or non-frail older adults, according to a recent study. This is despite the fact that the presence of frailty or multimorbidity was not found to be related with an increased risk of SARS-CoV-2 infection. In point of fact, the existence of frailty makes it necessary for complex medical care demands to be met, including admission to an intensive care unit, despite the limited resources of healthcare systems in the current environment of the SARS-CoV-2 pandemic.¹²

In patients diagnosed with Covid-19, the purpose of this article is to illustrate the connection that exists between frailty and mortality.

METHODS

The full-text papers written in English were used as the source material for the data that was gathered for the purpose of conducting this systematic review. This review was carried out for the purpose of determining whether or not a particular treatment is more effective than another. The goal of the review was to establish whether or not there was a connection between frailty and mortality in patients diagnosed with Covid-19. During the process of producing this essay, the online databases Pubmed and Google Scholar were utilized extensively throughout the duration of the research phase. The following was mentioned among the conditions for eligibility: (1) A cohort study, cross-sectional study, or case-control study that reported between frailty and mortality in patients with Covid-19; (2) A relative risk, hazard ratio, incidence ratio (IR), or standardized IR with 95% confidence intervals (CIs), or sufficient data to calculate those ratios were provided.

The keywords used in the search were “frailty”; “Covid-19”; and “mortality”. We include study conducted above in 2020-2022. This analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) paradigm, in which the researchers originally entered keywords into each database. The phrases: (*"frailty"[MeSH Terms] OR "frailty"[All Fields] OR "frailties"[All Fields]*) AND (*"covid 19"[All Fields] OR "covid 19"[MeSH Terms] OR "covid 19 vaccines"[All Fields] OR "covid 19 vaccines"[MeSH Terms] OR "covid 19 serotherapy"[All Fields] OR "covid 19 serotherapy"[Supplementary Concept] OR "covid 19 nucleic acid testing"[All Fields] OR "covid 19 nucleic acid testing"[MeSH Terms] OR "covid 19 serological testing"[All Fields] OR "covid 19 serological testing"[MeSH Terms] OR "covid 19 testing"[All Fields] OR "covid 19 testing"[MeSH Terms] OR "sars cov 2"[All Fields] OR "sars cov 2"[MeSH Terms] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR ("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "cov"[All Fields])*) AND (*2019/11/01:3000/12/31[Date - Publication]*) AND (*"mortality"[MeSH Terms] OR "mortality"[All Fields] OR "mortalities"[All Fields] OR "mortality"[MeSH Subheading]*) used in this study. We received six articles, which will be discussed during the discussion (**Table 1**).

RESULT

Smet *et al*¹³ showed no correlation between death and staying in a long-term care facility, having dementia or delirium, or taking multiple medications. In multivariable logistic regression analyses, CFS, LDH, and RT-PCR Ct remained independently associated with mortality; however, age was not one of the variables considered. Both old age and frailty were poor survival predictors due to their lack of specificity. Mortality was significantly but weakly associated with age (Spearman $r = 0.241$, $P = .03$) and CFS score ($r = 0.282$, $P = .011$), baseline lactate dehydrogenase (LDH; $r = 0.301$, $P = .009$), lymphocyte count ($r = -0.262$, $P = .02$), and RT-PCR cycle threshold (Ct, $r = -0.285$, $P = .015$).

Hewitt *et al*¹⁴ showed frailty was found to be a more accurate predictor of disease outcomes in a large population of Covid-19 patients admitted to the hospital than age or the presence of other medical conditions. Frailty was assessed using clinical frailty scale (CFS) and patients were grouped according to their score (1–2=fit; 3–4=vulnerable, but not frail; 5–6=initial signs of frailty but with some degree of independence; and 7–9=severe or very severe frailty). Compared with CFS 1–2, the adjusted hazard ratios for time from hospital admission to death were 1.55 (95% CI 1.00–2.41) for CFS 3–4, 1.83 (1.15–2.91) for CFS 5–6, and 2.39 (1.50–3.81) for CFS 7–9, and adjusted odds ratios for day-7 mortality were 1.22 (95% CI 0.63–2.38) for CFS 3–4, 1.62 (0.81–3.26) for CFS 5–6, and 3.12 (1.56–6.24) for CFS 7–9.

Table 1. The literature include in this study

Author	Origin	Method	Sample Size	Result
Smet, 2020 ¹³	Belgium	Retrospective study	81	There was no correlation between death and staying in a long-term care facility, having dementia or delirium, or taking multiple medications. In multivariable logistic regression analyses, CFS, LDH, and RT-PCR Ct remained independently associated with mortality; however, age was not one of the variables considered. Both old age and frailty were poor survival predictors due to their lack of specificity. There was a significant correlation between survival and the use of a multivariable model that included age, CFS, LDH, and viral load.
Hewitt, 2020 ¹⁴	UK	Prospective study	1,559	Compared with CFS 1–2, the adjusted hazard ratios for time from hospital admission to death were 1.55 (95% CI 1.00–2.41) for CFS 3–4, 1.83 (1.15–2.91) for CFS 5–6, and 2.39 (1.50–3.81) for CFS 7–9, and adjusted odds ratios for day-7 mortality were 1.22 (95% CI 0.63–2.38) for CFS 3–4, 1.62 (0.81–3.26) for CFS 5–6, and 3.12 (1.56–6.24) for CFS 7–9.
Owen, 2021 ¹⁵	UK	Retrospective study	1,071	Mean ED age was 79.7 and 49.4% were women. All-cause mortality (by 30 days) rose from 9 (not frail) to 33% (severely frail) in the COVID-negative cohort, but was around 60% in the COVID-positive cohort. In adjusted analyses, the death hazard ratio for Covid-19 was 7.3 (95% CI: 3.00, 18.0), with age, comorbidities, and illness severity making small contributions.
Marengoni, 2020 ¹⁶	Italy	Retrospective study	91	72% of hospitalized patients with delirium died, compared to 31.8% without. Patients with delirium were four times more likely to die during hospitalization than those without (OR = 3.98; 95%CI = 1.05–17.28; p = 0.047).
Aw, 2020 ¹⁷	UK	Retrospective study	664	Worse baseline frailty was associated with increased mortality risk (p = 0.004). CFS 4 and 5 patients had non-significantly higher mortality risks than CFS 1–3 patients. CFS 6 patients had a 2.13-fold (95% CI 1.34–3.38) increased mortality risk compared to CFS 1–3 patients (p = 0.001 and 0.016, respectively).
Rawle, 2020 ¹⁸	UK	Retrospective study	134	Mortality was more likely with increasing frailty (OR 1.25, 95% CI 1.00, 1.58, P = .049) and those presenting with anorexia (OR 3.20, 95% CI 1.21, 10.09, P = .028).

Even after taking into account all of the variables, a worse baseline frailty was associated with an increased risk of mortality (p = 0.004). Patients diagnosed with CFS 4 and CFS 5 had increased mortality risks, but these increases were not statistically significant when compared to patients diagnosed with CFS 1–3. Patients diagnosed with CFS 6 had an increased mortality risk of 2.13 times (95% confidence interval [CI]: 1.34–3.38), while those diagnosed with CFS 7–9 had an increased mortality risk of 1.79 times (95% confidence interval [CI]: 1.12–2.88) (p = 0.001 and 0.016, respectively).¹⁷

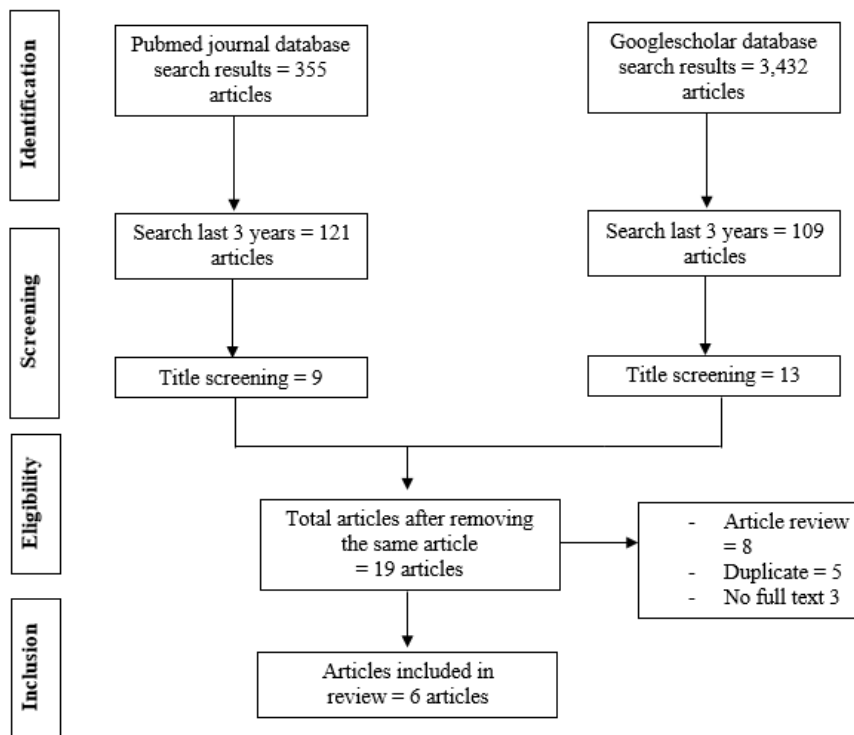


Figure 1. Article search flowchart

Residents of care homes were significantly less likely to cough (46.9% vs. 72.9%, $P = 0.002$) but significantly more likely to present with delirium (51.6% vs. 31.4%, $P = 0.018$), in particular hypoactive delirium (40.6% vs. 24.3%, $P = 0.043$). Mortality was more likely to occur with increasing frailty (odds ratio 1.25, 95% confidence interval [CI] 1.00, 1.58, $P = 0.049$) and with those presenting with anorexia (odds ratio 3.20, 95% confidence interval [CI] 1.21, 10.09, $P = 0.028$). There was no correlation between residential status and either the rate of mortality or the length of stay.¹⁸

The patients' mean age when they arrived at the ED was 79.7 years old, and 49.4% of them were female. In the COVID-negative cohort, the all-cause mortality rate (by 30 days) increased from 9 (not frail) to 33% (severely frail), whereas in the COVID-positive cohort, the all-cause mortality rate was around 60% for all frailty categories. When adjusted for age, comorbidities, and illness severity, the hazard ratio for death in those with Covid-19 compared to those without Covid-19 was 7.3 (95% confidence interval: 3.00, 18.0). This was significantly higher than the hazard ratio for death in those without Covid-19.¹⁵

Marengoni, *et al* (2020) showed 72% of patients who were hospitalized with delirium passed away during their stay, in comparison to only 31.8% of patients who did not have delirium. The odds ratio for patients with delirium was 3.98, with a 95% confidence interval ranging from 1.05 to 17.28, according to a multivariate logistic regression model that took into account potential confounding factors. Patients without delirium had a risk of death during their hospital stay that was only 0.047 times higher.¹⁶

DISCUSSION

The deterioration of physiological functions that comes with getting older is one of the primary causes of a vulnerable state of life, and aging itself is one of the primary factors that determines pathological aging. "Progressive age-related decline of body functions resulting in vulnerability and reduced resilience to physical and mental stressors with an increased risk of negative health outcomes" is how the World Health Organization (WHO) defines frailty. In addition to this, frailty has been defined as an accumulation of deficits in a variety of physiological systems. At the moment, there is no one particular method that is considered to be the gold standard for determining frailty; rather, a variety of methods are required to diagnose this condition. We need a clinical picture that is more comprehensive than just looking at chronological age.^{19,20}

The term "frailty" refers to "a medical syndrome with multiple causes and contributors that is characterized by diminished strength, endurance, and reduced physiologic function that increases an individual's vulnerability for developing increased dependency and/or death." This definition describes frailty as "a medical syndrome with multiple causes and contributors that is characterized by diminished strength, endurance, and reduced physiologic function."^{19,20}

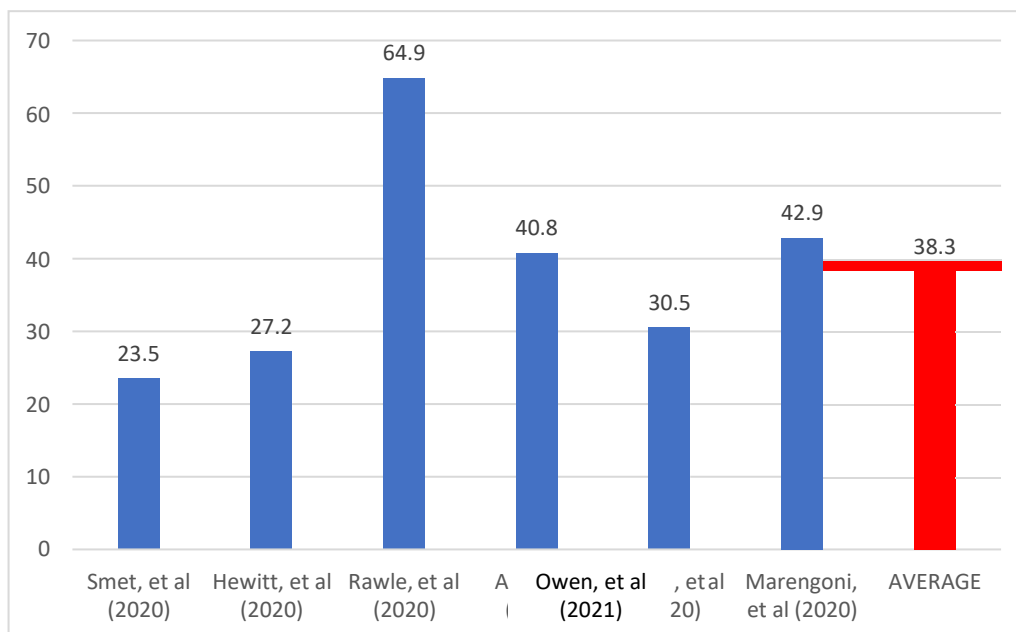


Figure 2. Percentage of patient mortality in all studies

The prevalence of frailty in patients who are middle-aged and older varies depending on the method used to identify frailty as well as the particular population; however, it is estimated to be somewhere around forty percent. The risk of becoming frail increases with age, but it is not impossible for younger adults to experience it. In addition, there is a significant body of evidence suggesting that frailty is associated with worse patient outcomes for those who are admitted to the hospital for medical or surgical reasons, as well as for patients who require intensive care. As a consequence of this, it is gaining popularity as a trigger for the allocation of specialized resources, as an aid in making decisions about pathways, and as a method for collaborative decision making.^{21,22}

During the Covid-19 pandemic, the frailty assessment using the CFS is recommended by the guidelines in the UK. The CFS is a straightforward, speedy, and user-friendly frailty assessment tool; however, it has not been adequately validated for use with individuals under the age of 65 or with those who have learning disabilities. Other frailty measures are available for inpatient frailty assessment; however, completing these measures typically takes more time and/or they rely on data that is routinely collected to determine the frailty score. Despite the fact that other frailty assessments could have been helpful during this pandemic, we did not feel it was appropriate to conduct an analysis of them because there was a lack of research evidence. Additionally, evidence regarding the validated use of the CFS in the frailty assessment of people with Covid-19 is provided by this study.^{22,23}

According to more recent research, an association between an older age and an increased risk of mortality was found to be significant but weak. It has been reported that nonagenarians and centenarians have lived through Covid-19 outbreak.^{24,25} Smet *et al* finding was that frailty was significantly, albeit weakly, associated with a higher risk of mortality in Covid-19 patients. This was the most important finding that we made (multivariate odds ratio for mortality with each higher CFS point: 1.75.) A significant number of patients who were extremely frail were able to survive (72%), and the CFS by itself had poor specificity and no useful cut-off for the prediction of mortality. Frailty, as measured by the Frailty Index, was associated with in-hospital mortality or admission to the ICU in a study that was conducted in Italy not too long ago. The study looked at 105 Covid-19 patients and found that this association held true regardless of the patients' ages or genders.²⁶

This suggests that there is something unique about Covid-19 infection that makes it such a dominant influence over outcomes, especially in comparison to other prognostic indicators that have been well-established for a long time (age, sex, comorbidities and frailty). Even in younger people, it has been reported that Covid-19 infection can cause severe overpowering conditions such as acute respiratory distress syndrome and failure of multiple organs.^{27,28}

These conditions are thought to be mediated by a 'cytokine storm,' which is the uncontrolled systemic inflammatory response that results from the release of large amounts of pro-inflammatory cytokines and chemokines. It should not come as a surprise that the mortality rate of elderly people with frailty is high in relation to Covid-19 because of their susceptibility to functional decline in response to a "apparently innocuous insult," such as a minor infection or the side effect of a medication. Because of this susceptibility, the mortality rate of elderly people with frailty is high in relation to Covid-19.^{29,30}

The decline of physiologic reserve in immune, metabolic, and neuromuscular systems is characteristic of frailty, which can be recognized by an increasing susceptibility to the negative effects of stress. The SARS-COV-2 virus enters the body when it binds to the ACE2 receptor that is located on the surface of host cells. In the meantime, ACE2 is widely expressed in a wide variety of cell types throughout the body in numerous organs, including the lungs, heart, kidneys, and intestines.^{31,32}

Previous research has shown that patients with COVID-19 exhibited severe organ injuries, with 14.0% of them suffering from respiratory distress syndrome, 15.0% of them experiencing cardiac injury, 15.7% of them experiencing hepatic

injury, and 13.7% of them experiencing renal injury. Patients diagnosed with COVID-19, particularly elderly patients, may therefore have a tendency to be frail. According to the findings of Woolford et al., patients who tested positive for COVID-19 had a 1.4-fold increased risk of frailty.¹²

The elderly population is a unique subset of the overall population because of the specific characteristics that set them apart from the rest of the population. When compared to the general population, older adults, and especially those who are frail, have a more compromised immune system, less diversity in their gut microbiota, and a longer-standing inflammatory status. These contributing factors help to make Covid-19 as severe as it is, which also contributes to the high mortality rate.¹⁵ In addition, frailty in COVID-19 patients is associated with poor outcomes, mortality while in the intensive care unit (ICU), re-admission, and short survival after being discharged from the ICU. In addition, frailty is associated with a poor response to vaccination as well as an increased risk of side effects; for this reason, it may be reasonable to screen older adults for frailty prior to vaccination as a precautionary measure.^{33,34}

CONCLUSION

One of the primary contributors to a precarious state of life as a result of the gradual loss of physiological functions and a key factor in the development of pathological aging is simply getting older. In this particular study, the overall mortality rate for patients was found to be 38.3% on average.

REFERENCE

- [1]. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* (London, England). Februari 2020;395(10223):497–506.
- [2]. Yang Y, Du L. SARS-CoV-2 spike protein: a key target for eliciting persistent neutralizing antibodies. *Signal Transduct Target Ther*. Februari 2021;6(1):95.
- [3]. Biswas M, Rahaman S, Biswas TK, Haque Z, Ibrahim B. Association of sex, age, and comorbidities with mortality in COVID-19 patients: a systematic review and meta-analysis. *Intervirolgy*. 2021;64(1):36–47.
- [4]. Treçarichi EM, Mazzitelli M, Serapide F, et al. Clinical characteristics and predictors of mortality associated with COVID-19 in elderly patients from a long-term care facility. *Nature*. 2020;10.
- [5]. Salehi S, Abedi A, Balakrishnan S, Gholamrezaezhad A. Coronavirus Disease 2019 (COVID-19): A Systematic Review of Imaging Findings in 919 Patients. *Am J Roentgenol*. Juli 2020;215(1):87–93.
- [6]. Dent E, Martin FC, Bergman H, Woo J, Romero-Ortuno R, Walston JD. Management of frailty: opportunities, challenges, and future directions. *Lancet*. 2019;394(10206):1376–86.
- [7]. Payne M, Morley JE. Editorial: Dysphagia, Dementia and Frailty. Vol. 22, *The journal of nutrition, health & aging*. France; 2018. hal. 562–5.
- [8]. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *Lancet*. 2013;381(9868):752–62.
- [9]. O’Caoimh R, Galluzzo L, Rodriguez-Laso Á, Van der Heyden J, Ranhoff AH, Lamprini-Koula M, et al. Prevalence of frailty at population level in European ADVANTAGE Joint Action Member States: a systematic review and meta-analysis. *Ann Ist Super Sanita*. 2018;54(3):226–38.
- [10]. Vetrano DL, Palmer K, Marengoni A, Marzetti E, Lattanzio F, Roller-Wirnsberger R, et al. Frailty and multimorbidity: a systematic review and meta-analysis. *Journals Gerontol Ser A*. 2019;74(5):659–66.
- [11]. Vetrano DL, Palmer KM, Galluzzo L, et al. Hypertension and frailty: a systematic review and meta-analysis. *Geriatr Med*. 2018;8(12):34–9.
- [12]. Woolford SJ, D’Angelo S, Curtis EM, Parsons CM, Ward KA, Dennison EM, et al. COVID-19 and associations with frailty and multimorbidity: a prospective analysis of UK Biobank participants. *Aging Clin Exp Res*. September 2020;32(9):1897–905.
- [13]. De Smet R, Mellaerts B, Vandewinckele H, Lybeert P, Frans E, Ombelet S, et al. Frailty and Mortality in Hospitalized Older Adults With COVID-19: Retrospective Observational Study. *J Am Med Dir Assoc*. Juli 2020;21(7):928-932.e1.
- [14]. Hewitt J, Carter B, Vilches-Moraga A, Quinn TJ, Braude P, Verduri A, et al. The effect of frailty on survival in patients with COVID-19 (COPE): a multicentre, European, observational cohort study. *Lancet Public Heal*. Agustus 2020;5(8):e444–51.
- [15]. Owen RK, Conroy SP, Taub N, Jones W, Bryden D, Pareek M, 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*. Februari 2021;50(2):307–16.
- [16]. Marengoni A, Zucchelli A, Grande G, Fratiglioni L, Rizzuto D. The impact of delirium on outcomes for older adults hospitalised with COVID-19. *Age Ageing*. Oktober 2020;49(6):923–6.
- [17]. Aw D, Woodrow L, Ogliari G, Harwood R. Association of frailty with mortality in older inpatients with Covid-19: a cohort study. *Age Ageing*. Oktober 2020;49(6):915–22.
- [18]. Rawle MJ, Bertfield DL, Brill SE. Atypical presentations of COVID-19 in care home residents presenting to secondary care: A UK single centre study. *Aging Med (milt)*. Desember 2020;3(4):237–44.
- [19]. Morley JE, Vellas B, van Kan GA, Anker SD, Bauer JM, Bernabei R, et al. Frailty consensus: a call to action. *J Am Med Dir Assoc*. Juni 2013;14(6):392–7.
- [20]. Hanlon P, Nicholl BI, Jani BD, Lee D, McQueenie R, Mair FS. Frailty and pre-frailty in middle-aged and older adults and its association with multimorbidity and mortality: a prospective analysis of 493 737 UK Biobank participants. *Lancet Public Heal*. Juli 2018;3(7):e323–32.
- [21]. Smart R, Carter B, McGovern J, Luckman S, Connelly A, Hewitt J, et al. Frailty Exists in Younger Adults Admitted

- as Surgical Emergency Leading to Adverse Outcomes. *J frailty aging*. 2017;6(4):219–23.
- [22]. Gilbert T, Neuburger J, Kraindler J, Keeble E, Smith P, Ariti C, et al. Development and validation of a Hospital Frailty Risk Score focusing on older people in acute care settings using electronic hospital records: an observational study. *Lancet (London, England)*. Mei 2018;391(10132):1775–82.
- [23]. Hollinghurst J, Fry R, Akbari A, Clegg A, Lyons RA, Watkins A, et al. External validation of the electronic Frailty Index using the population of Wales within the Secure Anonymised Information Linkage Databank. *Age Ageing*. November 2019;48(6):922–6.
- [24]. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054–62.
- [25]. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet (London, England)*. Maret 2020;395(10229):1054–62.
- [26]. Bellelli G, Rebora P, Valsecchi MG, Bonfanti P, Citerio G. Frailty index predicts poor outcome in COVID-19 patients. Vol. 46, *Intensive care medicine*. 2020. hal. 1634–6.
- [27]. Huang C; Wang Y; Li X; et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10334):497–506.
- [28]. Yang W, Sirajuddin A, Zhang X, Liu G, Teng Z, Zhao S, et al. The role of imaging in 2019 novel coronavirus pneumonia (COVID-19). Vol. 30, *European Radiology*. Springer Science and Business Media Deutschland GmbH; 2020. hal. 4874–82.
- [29]. Li X, Geng M, Peng Y, Meng L, Lu S. Molecular immune pathogenesis and diagnosis of COVID-19. *J Pharm Anal*. April 2020;10(2):102–8.
- [30]. McElvaney OJ, McEvoy NL, McElvaney OF, Carroll TP, Murphy MP, Dunlea DM, et al. Characterization of the Inflammatory Response to Severe COVID-19 Illness. *Am J Respir Crit Care Med*. September 2020;202(6):812–21. [31]. Yang Y, Luo K, Jiang Y, Yu Q, Huang X, Wang J, 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):702–9.
- [32]. Yoelekar M, Sukumaran S. Frailty Syndrome: A Review. *J Assoc Physicians India*. 2014;62(7):18–23.
- [33]. Hussien H, Nastasa A, Apetrii M, Nistor I, Petrovic M, Covic A. Different aspects of frailty and COVID-19: points to consider in the current pandemic and future ones. *BMC Geriatr [Internet]*. 2021;21(1):389. Tersedia pada: <https://doi.org/10.1186/s12877-021-02316-5>
- [34]. Pizano-Escalante MG, Anaya-Esparza LM, Nuño K, Rodríguez-Romero J de J, Gonzalez-Torres S, López-de la Mora DA, et al. Direct and Indirect Effects of COVID-19 in Frail Elderly: Interventions and Recommendations. *J Pers Med*. Oktober 2021;11(10).