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REVIEW ARTICLE

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Association of frailty with outcomes in individuals with COVID-19: A living review and meta-analysis

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Abstract

Background and Objectives: Frailty leaves older adults vulnerable to adverse health outcomes. Frailty assessment is recommended by multiple COVID-19 guidelines to inform care and resource allocation. We aimed to identify, describe, and synthesize studies reporting the association of frailty with outcomes (informed by the Institute for Healthcare Improvement's Triple Aim [health, resource use, and experience]) in individuals with COVID-19.

Design: Systematic review and meta-analysis.

Setting: Studies reporting associations between frailty and outcomes in the setting of COVID-19 diagnosis.

Participants: Adults with COVID-19.

Measurements: Following review of titles, abstracts and full text, we included 52 studies that contained 118,373 participants with COVID-19. Risk of bias was assessed using the Quality in Prognostic studies tool. Our primary outcome was mortality, secondary outcomes included delirium, intensive care unit admission, need for ventilation and discharge location. Where appropriate, random-effects meta-analysis was used to pool adjusted and unadjusted effect measures by frailty instrument.

Results: The Clinical Frailty Scale (CFS) was the most used frailty instrument. Mortality was reported in 37 studies. After confounder adjustment, frailty identified using the CFS was significantly associated with mortality in COVID-19 positive patients (odds ratio 1.79, 95% confidence interval [CI] 1.49–2.14; hazard ratio 1.87, 95% CI 1.33–2.61). On an unadjusted basis, frailty identified using the CFS was significantly associated with increased odds of delirium and reduced odds of intensive care unit admission. Results were generally consistent using other frailty instruments. Patient-reported, cost and experience outcomes were rarely reported.

Conclusion: Frailty is associated with a substantial increase in mortality risk in COVID-19 patients, even after adjustment. Delirium risk is also increased. Frailty assessment may help to guide prognosis and individualized care

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planning, but data relating frailty status to patient-reported outcomes are urgently needed to provide a more comprehensive overview of outcomes relevant to older adults.

KEYWORDS
COVID-19, frailty, living review, outcomes

INTRODUCTION

Advanced age and comorbidity have both emerged as key predictors of adverse outcomes in the setting of SARS-COV-2 infection and its clinical syndrome, COVID-19. Individuals over the age of 65 make up 17% of the population of the United States; however, older people accounted for 31% of COVID-19 infections, 45% of hospitalizations, 53% of intensive care unit (ICU) admissions, and 80% of deaths caused by COVID-19.[1] Similar findings have been reported internationally.[2] The presence of any comorbidity more than doubles the risk of COVID-19 mortality, while certain comorbidities such as cardiovascular, pulmonary, and diabetic diagnoses more than quadruple risk.[3]

Frailty is a multidimensional syndrome related to accumulation of age- and disease-related deficits that leaves people vulnerable to adverse health outcomes.[4,5] The prevalence of frailty increases exponentially with age; half of people 85 years and older live with substantial frailty.[6] Although distinct concepts, comorbidity and frailty are closely linked; 70% of people with frailty have one or more comorbidities.[7] Not surprisingly, the prognostic value of frailty in helping to guide to care planning for people with COVID-19 is increasingly recognized.[8] Guidelines from the United Kingdom suggest that frailty assessment be incorporated into COVID-19 care pathways.[9] However, the association of frailty with the breadth of outcomes relevant to patients, clinicians, and the healthcare system in the setting of COVID-19 has not been robustly synthesized and evaluated.

During a global pandemic, where both challenges and new insights are ever-evolving, up to date knowledge is essential. As such, we undertook a living review of frailty and COVID-19. Informed by this ongoing review, the objective of the current study was to identify, describe, and synthesize studies reporting he association between frailty and outcomes (informed by the Institute for Healthcare Improvement's Triple Aim (health, resource use, and experience[10]) in individuals with COVID-19. As specified in our preregistered protocol, adequate data allowed us to progress from a scoping review design to a systematic review and meta-analysis, which is reported herein.

Key Points

- There is consistent evidence that the presence of frailty is associated with mortality in COVID-19 patients, even after adjustment for covariates.
- Included studies also reported associations between frailty and delirium, critical illness, and resource use.
- Patient experience and functional outcomes were not reported, which represents a substantial and patient-important knowledge gap that should be addressed.

Why Does this Paper Matter?

Knowing that individuals with frailty and COVID-19 are at risk of poor health outcomes can inform care planning and resource allocation. There are no data on the association of frailty and COVID-19 with patient-centered outcomes including function and quality of life.

METHODS

Following protocol registration (Open Science Framework osf.io/2bqnt) we conducted a scoping review according to recommendations from Levac and colleagues.[11] The review was a "living review," as it is continually updated to incorporate new evidence as it becomes available, in keeping with recommendations of the Cochrane Collaboration and the Living Evidence Network.[12] As we met our prespecified criteria to convert to a systematic review (>2 studies reporting outcome data suitable for meta-analysis), we converted the outcome data arm of our scoping review to a systematic review and meta-analysis, which was conducted after uploading a protocol update on July 27, 2020. The methods of our systematic review were informed by Riley and colleagues' guidance on reviews of prognostic factor studies and reporting follows Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance.[13,14]

Search strategy

Until February 15, 2021, researchers searched LitCOVID (the National Library of Medicine's COVID-19-specific portal) using the terms "frailty" OR "frail" OR "fragility," and Google Scholar and Google Web Search (separately) using broad terms for frailty and COVID-19: (Covid | coronavirus | SARS | covid 19) AND (frailty | frail | fragility). These strategies were designed to maximize sensitivity. Searches on Google Scholar and LitCOVID were conducted daily and searches on Google Web Search were conducted weekly.

Inclusion and exclusion criteria

Articles were included in our review if they: (1) were full text (published or preprint) available in English or French, (2) reported data on the association between frailty and outcomes (i.e., health, experience, resource use; as event rates, numbers, or effect sizes) in populations with suspected or confirmed COVID-19; and (3) explicitly defined how frailty assignment was operationalized. Articles were excluded if <50% of participants had confirmed or suspected COVID-19, or if COVID-19 specific data could not be extracted.

Selection of included studies and data extraction

As our living review required daily article screening and valued expediency, all title-abstract screening was initially completed by one reviewer, with a second reviewer independently checking decisions for accuracy. Any discrepancies were advanced to full text review, along with all titles marked as "yes" or "unsure." All reviews identified were reference-checked to identify relevant studies potentially missed by our initial search strategy. Full-text reviews were completed independently and in duplicate. Any disagreements were resolved through consensus or adjudicated by the senior author (Daniel I. McIsaac).

Data were extracted using a form specifically designed for this review after piloting and review by the senior author. Two reviewers were involved in the extraction of each data point: a first reviewer extracted all required data from each included article, and a second reviewer independently verified the accuracy of extracted data. Any inconsistencies were discussed and reviewed by a third reviewer. Data points extracted included: population characteristics (setting, sample size, age, sex or gender, frailty score), COVID diagnosis method(s), type of frailty instrument used, and outcome data (e.g., proportions, effect estimates, measures of central tendency, and variance). As recommended by Riley and colleagues, our primary focus was on effect estimates adjusted for postulated confounders.[14]

Outcomes

Health outcomes (e.g., mortality, hospitalization, delirium, ICU admission, need for ventilation), cost outcomes (e.g., length of stay [LoS], nonhome discharge, costs of care), and experience outcomes (e.g., pain, satisfaction) were eligible for inclusion, based on the Institute for Healthcare Improvement (IHI) Triple Aim Framework.[15] As most studies were expected to report binary frailty exposures, we prespecified that this would be our effect of interest. Where categorical frailty estimates were presented, we focused on the association of the middle or moderate frailty category versus the category with no or lowest degree of frailty. Where continuous frailty scores were used, we used the reported regression coefficient and variance to calculate the relative difference between the scale's lowest and mid-point values.

Risk of bias analysis

Risk of bias was assessed independently and in duplicate by two reviewers (with all studies being assessed by the senior author and a second reviewer) using the Quality in Prognostic Studies (QUIPS) tool.[16] Discrepancies were resolved through consensus.

Data analysis

Descriptive statistics were calculated and summarized at the study level. Where adequate data existed (>2 studies reporting the same outcome with appropriate data to support meta-analysis) we performed a formal meta-analysis using the "metafor" package for the R statistical programming language (R Foundation, Vienna, Austria). Random effects models were prespecified (as we expected heterogeneity that would invalidate the assumptions of fixed-effects meta-analysis) to generate pooled effect estimates and associated confidence intervals (a 5% level of significance was prespecified) using Hartung-Knapp approach to estimate confidence intervals, which is demonstrated to improve appropriate confidence interval coverage.[14] Where available, we performed meta-analysis of unadjusted and confounder-adjusted estimates, as

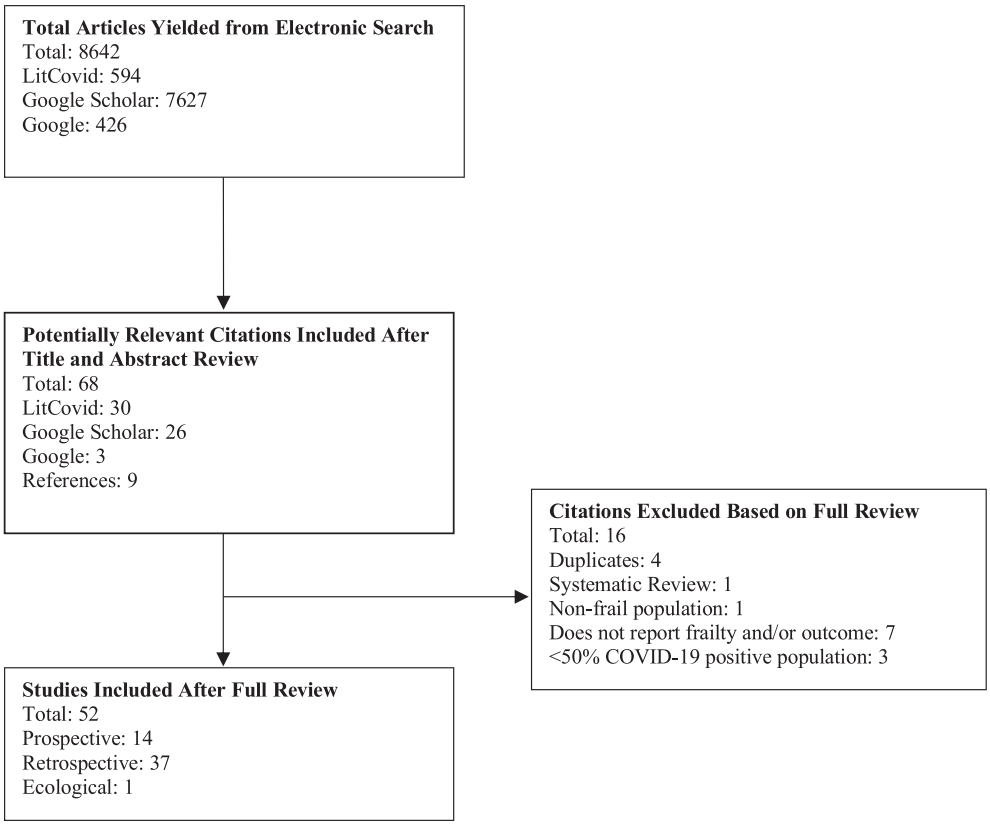

FIGURE 1 Preferred Reporting Items for Systematic reviews and Meta-Analyses flow diagram for study selection and inclusion

recommended.[17] A protocol update was submitted in April 2021 specifying that pooling of studies would occur at the frailty instrument-level where >2 studies reported the same outcome for the same frailty instrument. Binary and time to event outcomes were meta-analyzed separately. Egger's test and funnel plots were used to explore the possibility of publication bias. Where data were not appropriate for meta-analysis, we performed a narrative synthesis.

Exploratory analyses

For the mortality outcome, we completed a trim-and-fill analysis to assess the possible impact of publication bias from studies reporting adjusted associations with mortality.[18]

RESULTS

Of the 8642 titles identified in the search, 52 full-text articles (14 prospective, 37 retrospective, and 1 ecological study) met our inclusion criteria (Figure 1). Included articles were published between May 11, 2020 and February 15, 2021 and none were excluded for language reasons.

Participants and study characteristics

Study characteristics of included articles are shown in Table S1. The majority of articles (44; 84.6%)[8,19–61] originated from Europe, while two originated from North America,[62,63] two from South America,[64,65] two from Asia,[66,67] and two articles were international.[68,69] Most studies (50; 96.2%) took place in a hospital setting,[8,19–21,23–26,28–62,64–69] while three were community-based (5.8%),[22,58,68] and two took place in a long-term care facility (3.8%).[36,63] Study population sizes were variable (16 to 91,541 participants) and included a total of 118,373 participants across the 50 studies that reported their sample size. Average age ranged from 56–87 years and the percentage of female participants ranged from 21.7% to 66.7%. Five studies (9.4%) were only available in preprint.[22,47,49,50,65]

Frailty instruments

The proportion of people with frailty ranged from 8.3% to 87.2% of the total population in each study. From the 38 studies that specified the number of participants with frailty, 81,568 of the 136,393 (59.8%) participants had frailty. The majority of studies measured frailty using the Clinical Frailty Scale (CFS; 42 [80.7%])[8,19–21,23,25–29,33–44,46,48–55,57–61,64,67–69]; however,

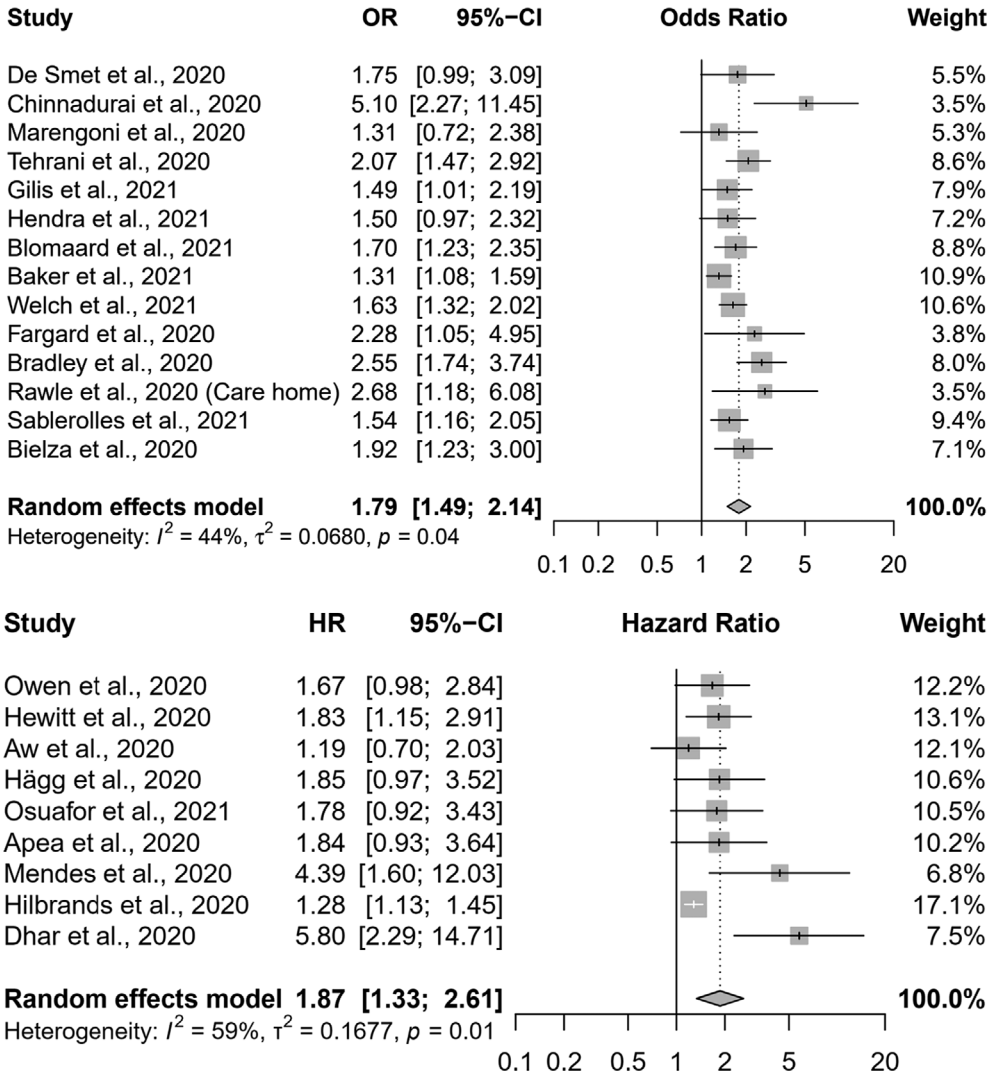

FIGURE 2 (A) Forest plot of adjusted odds ratio (OR) mortality data for frailty based on the Clinical Frailty Scale. Confidence interval (CI) indicates confidence interval. (B) Forest plot of adjusted hazard ratio (HR) mortality data for frailty based on the Clinical Frailty Scale. CI indicates confidence interval

several other frailty assessment tools were also used (Frailty Index [$n = 3$],[30,63,67] PRISMA-7 [$n = 1$],[58] Fried's phenotype [$n = 1$],[24] frailty markers [$n = 1$],[61] the Palliative Performance Scale [$n = 1$],[62] the Frail Nondisabled Survey [$n = 1$],[32] the Hospital Frailty Risk Score (HFRS) [$n = 4$],[27,31,33,45] the Modified Frailty Index [$n = 1$],[65] and the FRAIL Scale [$n = 1$][66]).

IHI triple aim outcomes

Health outcomes

The most common health outcome reported was mortality (37 studies; 71.2%).[8,19,23,24,26,27,29,31–37,40–45,47–52,54–57,59,62–65,68,69] The pooled odds ratio (OR) for unadjusted data associating frailty based on the CFS with mortality was 2.02 (95% confidence interval [CI] 1.62–2.51; I^2 83%; Figure S1). All studies adjusted for age, a majority controlled for comorbidity and sex, while other factors like COVID severity, laboratory values, and socioeconomic indicators were variably adjusted for. Including only studies with confounder adjustment (see study-level approaches to adjustment in Tables S2–S6), the pooled adjusted OR was 1.79 (95% CI 1.49–2.14; $I^2 = 44\%$; Figure 2A). Egger's test suggested the presence of publication bias for adjusted studies using the CFS ($p = 0.017$); the funnel plot (Figure S2) suggested missing studies would be those with smaller sample sizes reporting effect sizes closer to the null. Imputing missing studies with a trim and fill approach resulted in an adjusted OR 1.54 (95% CI 1.24–1.92).

Unadjusted hazard ratio (HR) data were also consistent with lower survival with CFS frailty present (HR 2.16, 95% CI 1.36–3.43; $I^2 = 87\%$; Figure S3), as was the pooled adjusted HR (1.87, 95% CI 1.33–2.61; $I^2 = 59\%$; Figure 2B). Egger's test suggested publication bias ($p = 0.007$), and the funnel plot (Figure S4) suggested that small studies with small effect sizes were

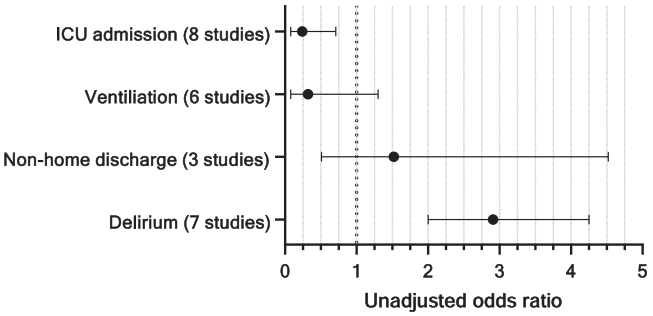

FIGURE 3 Summary of pooled, unadjusted odds ratios for frailty based on the Clinical Frailty Scale

most likely to be missing. The imputed trim and fill pooled adjusted HR was 1.35 (95% CI 0.91–2.01).

Pooled unadjusted mortality data for the HFRS (three studies, pooled OR 3.79, 95% CI 2.05–7.01), as well as adjusted point estimates were directionally consistent and typically significantly associated with increased mortality (Figure S5).

A summary of unadjusted associations of frailty based on the CFS with nonmortality outcomes is provided in Figure 3. Seven studies (13.5%) reported the unadjusted effect of frailty based on the CFS with delirium (OR 2.91; 95% CI 2.00–4.25; $I^2 = 56\%$; Figure S6).[29,40,43,48,58,64,69] Eight studies (15.4%) reported an unadjusted association of frailty based on the CFS with ICU admission[8,23,28,29,39,40,43,69] (OR 0.24, 95% CI 0.08–0.71; $I^2 = 92\%$; Figure S7), and three studies (5.8%) reported the adjusted association[8,67,69] (OR 0.87, 95% CI 0.56–1.35; $I^2 = 69\%$; Figure S8). Six (11.5%) studies reported unadjusted associations between frailty based on the CFS and receipt of mechanical ventilation (OR 0.32, 95% CI 0.08–1.30; $I^2 = 89\%$; Figure S9).[37,40,43,48,60,64] No studies reported data related to functional outcomes, disability, or quality of life.

Cost outcomes

Three (5.7%) studies reported unadjusted data on non-home discharge[43,46,69] (OR 1.52, 95% CI 0.51–4.52; $I^2 = 98\%$; Figure S10). Four articles reported the association of frailty with hospital LoS. One study reported that frailty was significantly associated with longer time to hospital discharge prior to (HR 0.53; 95% CI 0.35–0.80) and after adjustment (adjusted HR 0.55; 95% CI 0.31–0.98).[21] Another study reported the unadjusted HR 0.87 (95% CI 0.71–1.05) and adjusted HR 0.94 (95% CI 0.77–1.16).[19] Two studies investigated the association of frailty with prolonged LoS, defined as a hospital stay >10 days (unadjusted OR 1.71 (95% CI 0.96–3.03); unadjusted OR of 1.27 (95% CI 1.19–1.36) and an adjusted OR of 1.15 (95% CI 1.07–1.24).[29,31]

Patient experience

No studies reported patient experience outcomes.

Risk of bias

QUIPS risk of bias results are presented in Table S7. There were 10 articles with low risk of bias, 27 with moderate risk of bias, and 15 with high or unclear risk of bias included in this review. There was 86.2% between-rater agreement across all domains. The main contributors to high risk of bias were issues of confounding, statistical analysis, and reporting. A high risk of bias of the cofounding domain was typically due to studies not performing or describing an adjusted analysis. A high risk of bias of the statistical analysis and reporting domain was typically due to inconsistencies in reported methods and results.

DISCUSSION

In the first report of a living systematic review and meta-analysis of the association between frailty and outcomes in COVID-19, we found consistent evidence that the presence of frailty was associated with increased mortality, even after adjustment for covariates. Included studies also reported associations between frailty and delirium, critical illness, and resource use. However, patient experience and functional outcomes were not reported, which represents a substantial and patient-important knowledge gap that should be addressed. Future research will also need to address sources of bias identified in many studies about frailty and COVID-19 published to date.

Frailty is described as a health state or syndrome related to accumulation of age- and disease-related deficits that leaves individuals vulnerable to adverse health outcomes.[5,70] Therefore, it is not surprising that in the setting of COVID-19, frailty is associated with adverse outcomes, including mortality. In fact, the adjusted, pooled effect estimates derived from the current study (1.5 to 2-fold increase in risk) are consistent with the relative impact that frailty has on mortality in other acute care and community settings.[71,72] In addition to mortality, our meta-analysis also found a significant association between frailty and a 3-fold increase in the odds of delirium. This suggests that the vulnerabilities inherent in having frailty manifest in the presence of COVID-19

infection, and could further suggest that underlying mechanisms, including poor tolerance of physiologic stressors, likely play a substantial role. We found an inverse directional association between frailty and ICU admission, which appears to be in accordance with current guidelines.[9] For example, National Institute For Health and Care Excellence guidelines state that CFS scores should be considered when deciding whether to admit COVID-19 patients to acute care. Specifically, they suggest that there is uncertainty whether patients with a higher degree of frailty are likely to benefit from critical care admission, which could contribute to the results of our meta-analysis.[9] However, while fit older adults may have the same life expectancy as younger people with frailty,[73] in most cases frailty assessment should be used as part of a larger process to develop a treatment plan for adults with COVID-19. For older patients, such processes should present frailty-related prognostic information in the setting of evidence-based interventions like shared decision-making[74] to ensure alignment of care with patient's values and preferences, not as a strict barrier to access.[73] For younger patients, more data are required.

There have been several other reviews exploring the relationship between frailty and health outcomes for individuals with COVID-19.[75–78] However, the current review is, to our knowledge, the only living review, most up to date, largest and addresses the widest breadth of outcomes (informed by a widely used health outcome framework, the IHI Triple Aim). In contrast, most previously published reviews have focused only on mortality,[75–77] have not considered both unadjusted and confounder adjusted estimates, or have been unable to perform any meta-analysis.[77] The one review that did include nonmortality outcomes was not registered in advance. Overall, estimates across studies were consistent with our findings. Together with previous reviews, our work demonstrates that some high-quality data now exist demonstrating the prognostic value of frailty in COVID-19, but that many studies available suffer from substantial sources of bias (which is consistent with other areas of COVID-19 research[79]), and none focus on measures of experience, function, disability or quality of life that are critically important to older people.[80] This means that future research that accurately captures frailty using a robust multidimensional tool, collects patient-centered outcomes, evaluates the prognostic value of frailty in younger people, and follows prespecified analysis plans consistent with best practices in observational research are still required.

Finally, frailty research has traditionally been challenged by widespread use of diverse and heterogeneous frailty instruments. In the setting of COVID-19, our review found some consistency in instruments, with the CFS being used 80% of studies. As previous research demonstrates that the CFS may be the easiest and most feasible instrument for clinical frailty assessment,[81] with accuracy as good or better than more complicated approaches,[82] continued use of the CFS is likely warranted. Furthermore, the CFS can be validly ascertained even for critically ill patients via proxy interview or chart review.[83]

It is important to note the strengths and limitations of this study. As the COVID-19 literature is rapidly changing and expanding, we used a living review format with daily searches in multiple databases using a strategy intended to maximize sensitivity. This intensive approach required duplicate decision checking, but not duplicate independent review. However, the approach to daily screening and reference checks of all included articles suggests that we were unlikely to miss relevant studies. Furthermore, we preregistered our protocol and transparently set our decision rules for meta-analysis via transparent protocol updates. We also followed best practices for systematic reviews, and specifically reviews of prognostic data.[14] Inclusion of preprint and peer-reviewed articles is likely both a strength and a weakness—preprints were included to maximize the inclusivity and completeness of available data. Future updates to our living review will test the impact of preprints and whether effect estimates change after peer-review. The quality of included studies was variable, as were study settings. While heterogeneity was expected, many pooled estimates had I^2 values over 70%, indicating substantial heterogeneity and the need for cautious interpretation. Our pooled adjusted analyses were routinely included control for age, sex, and comorbidity; however, control for other factors was variable. Publication bias may be present and imputed studies would lead to an attenuation of mortality effect sizes. A lack of reported adjusted data precluded more robust estimation of most outcomes relevant to patients and the healthcare system.

CONCLUSION

In this living systematic review of studies reporting associations between frailty and health, experience and resource use outcomes in COVID-19 patients, we found that frailty was significantly associated with a higher risk of death, even after adjustment for covariates. However, other health outcomes, especially those most relevant to older people, were rarely or never reported. Future studies with a low risk of bias are needed to better establish the association of frailty with functional and quality of life outcomes reflecting recovery from illness.

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CONFLICT OF INTEREST

The authors report no relevant conflicts of interest.

AUTHOR CONTRIBUTIONS

All authors meet the International Committee of Medical Journal Editors requirements for authorship. All authors made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; drafting the manuscript or revising it critically for important intellectual content; and final approval of the version to be published.

SPONSOR'S ROLE

The study had no sponsor.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

Table S1. Study characteristics
Table S2. Summary of outcome: mortality
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Figure S2. Funnel plot of adjusted OR CFS and mortality data
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