Clinical Frailty Scale (CFS) Indicated Frailty is Associated with Increased In-Hospital and 30-Day Mortality in COVID-19 Patients: A Systematic Review and Meta-Analysis

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Research

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Abstract

Background: The concept of frailty provides an age-independent, easy-to-use tool for risk stratification. We aimed to summarize the evidence regarding the use of frailty tools in COVID-19, assessing the risk of frail patients for in-hospital and 30-day mortality, intensive care unit (ICU) admission, and length of hospitalization (LOH).

Methods: The protocol was prospectively registered via PROSPERO (CRD42021241544). Studies reporting on frailty in COVID-19 patients were eligible. We compared in-hospital and 30-day mortality, lengths of stay and ICU admission in frail and non-frail COVID-19 patients. We also compared average frailty in COVID-19 survivors and non-survivors. MEDLINE (via PubMed), EMBASE, Scopus, CENTRAL, and Web of Science were searched up to 3 February 2021 with terms related to COVID-19 and frail*. Search, selection, data extraction and risk of bias assessment were conducted in duplicate by two independent review authors. The QUIPS tool was used for the risk of bias assessment. Odds ratios (OR) and weighted mean differences (WMD) were calculated with 95% confidence intervals (CI) using a random effect model. Heterogeneity was assessed using the I^2 and χ^2 tests.

Results: From 1693 records identified, 27 were included in the qualitative and 21 in the quantitative synthesis. Clinical Frailty Scale (CFS) was used in 24 studies, the Hospital Frailty Risk Score (HFRS) by one and the Frail Non-Disabled questionnaire by another one. One study reported both CFS and HFRS. We found that frail patients (CFS 5–9) compared to non-frail patients (CFS 1–4) have a higher risk for both in-hospital (OR: 2.77; CI: 1.86–4.15) and 30-day mortality (OR: 1.47; CI: 1.05–2.06). Frail patients (CFS 5–9) were less likely to be admitted to ICU (OR 0.05, CI: 0.01–0.16). Statistical heterogeneity was not present for CFS 5–9 30-day mortality OR and ICU admission OR (CFS 1–3 vs 4–9), and was moderate for in-hospital mortality WMD. Quantitative synthesis for LOH was not feasible. Most studies carried a high risk of bias.

Conclusions: As determined by CFS, frailty is strongly associated with in-hospital and 30-day mortality; hence, investigating its use in deciding on ICU admission further in COVID-19 is warranted.

Background

Since the outbreak of the SARS-CoV-2 pandemic, healthcare systems around the world face shortage of resources; therefore, identifying factors that predict negative outcomes in COVID-19 is essential. The use of risk stratification tools for protocolized admission and determination of ceiling of care could help the decision-making and create transparency in these uncertain times.

Clinical frailty describes a state of reduced physical, physiologic, and cognitive reserve [1]. The concept of frailty provides an age-independent measure for risk stratification in the form of fast, easy-to-use tools. However, the wide variety of frailty tools makes frailty assessment heterogenous. The clinical frailty scale (CFS) was created by Rockwood et al. in 2005 to provide a simple approach with good predictive value [2]. The original 7-point scale was later upgraded to 9-points, one for the "severely frail", "very severely frail", and one for the "terminally ill" [3]. In the terminology used until 2020, points 1 to 4 covered patients described as "very fit", "well", "managing well", and "vulnerable". The revision published by Rockwood and Theou classified formerly "well" patients to "fit" and "vulnerable" patients to "living with very mild frailty" [4]. The score also assesses comorbidities, physical and cognitive abilities.

The CFS is widely used in different clinical settings [5]. CFS outperformed the Charlson comorbidity index and age in predicting in-hospital mortality of patients older than 75 years with emergency hospital admission [6] and is an independent predictor of short- and long-term mortality in patients over 70 admitted to the ICU [7]. The Hospital Frailty Risk Score (HFRS) was developed to assess frailty in older individuals automatically from routinely collected data (using ICD codes).

Frailty assessment was adopted in many guidelines in the triage of COVID-19 patients to aid decision-making regarding intensive care admission or the commencement of mechanical ventilation [8]. Recent studies and a meta-analysis reported higher odds and hazard ratios for mortality in frail COVID-19 patients [9–11].

We aimed to provide a detailed summary on the use of frailty tools in COVID-19, assessing the odds of frail patients for in-hospital and 30-day mortality, ICU admission, and length of hospitalization (LOH).

Methods

Protocol registration and reporting

The protocol was prospectively registered via PROSPERO under registration number CRD42021241544. There was no deviation from the protocol. We report our results following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations [12].

Eligibility And Definitions

We formulated our clinical question using the PECO format. Based on preliminary searches, we chose to use two PECO's. We selected studies reporting on adult hospitalized patients with COVID-19, comparing frail (or frailer) patients to not frail (or less frail) patients. The assessed outcomes were all-cause in-hospital and 30-day mortality, ICU admission, and LOH. In our other analysis, the average frailty score of deceased COVID-19 patients was compared to survivors'.

COVID-19 positivity was defined as clinical, radiological, or laboratory diagnosis [13]. Any validated frailty scores and indexes were included, as well as non-validated ones, if the record contained sufficient information on the used index.

Studies with original data reporting on at least ten patients were eligible independently of study design. Abstracts and full-texts were both accepted.

Search And Selection

We searched MEDLINE (via PubMed), EMBASE, Scopus, The Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science on the 3rd of February 2021 for eligible articles. We used "Title, Abstract, Keywords" filter in Scopus. No other filters or restrictions were applied. We also scanned the reference lists of the included studies and their citations in Google Scholar. The following search key was used: ("covid 19" OR "Wuhan virus" OR coronavirus OR "2019 nCoV" OR SARS-cov-2) AND frail*.

After removing duplicates using a reference management software (EndNote X9, Clarivate Analytics), two review authors (MR and TL) independently screened titles, abstracts, and then full-texts against predefined eligibility criteria. Discrepancies were resolved by a third review author (ZM). Inter-rater reliability was determined at every phase by Cohen's kappa coefficient, where values 0.01–0.20 indicate slight, 0.21–0.40 indicate fair, 0.41–0.60 indicate moderate, 0.61–0.80 indicate substantial and 0.81–1.00 indicate almost perfect or perfect agreement, respectively [14].

Outcomes reported by at least three studies using the same frailty score comparing identical frailty subgroups were included in the meta-analysis. All other eligible studies were incorporated into the qualitative synthesis.

Data Collection

Data on the first author, publication year, countries, study design, number of patients in each comparison group, their baseline characteristics (sex, age), type of frailty score used, and available primary and secondary outcome parameters were extracted by two independent review authors (MR and LT) in duplicate using our standardized data collection form in Microsoft Excel. Disagreements were resolved by a third independent investigator (KO). Data from studies reporting individual patient data or raw data were regrouped if statistically feasible. Overlapping populations were identified, and the study with the largest sample size was included in the analyses.

Risk Of Bias

Following the recommendations of the Cochrane Collaboration, the Quality in Prognosis Studies (QUIPS) tool was used by MR and TL independently [15]. Disagreements were resolved by ZM. In the study participation domain, gender, age, ethnicity, and comorbidities were taken into account. Study attrition was not judged for retrospective studies. In the prognostic factor measurement domain, the specification of the frailty assessor, information about their training, and missing data on frailty were considered. Less than 10% missing data were considered low risk, 10–20% some concerns, and more than 20% resulted in high risk for the whole domain. Outcome measurement and statistical analysis domains carried low risk in most cases because mortality is a hard outcome, and we mostly used raw data. In the case of ICU admission, a detailed protocol for ICU admission was needed. In the study confounding domain, studies separately reporting baseline information for the frailty groups were judged low risk if no clinically significant differences were seen, some concerns if some differences were seen, and high risk if no data was reported. The overall risk of bias was calculated using the suggestions of Grooten et al. [16].

Statistical analysis

Our primary aim was to investigate the differences between the two groups (Frail group vs Not frail group). We only included studies using the same cut-off in each analysis; therefore, multiple analyses were performed with slightly different frailty cut-offs.

For dichotomous outcomes, odds ratios (ORs) with their 95% confidence intervals (CI) were calculated from the original raw data of the articles. In some cases, crude ORs were extracted and pooled with the calculated ORs. For continuous outcomes, weighted mean differences (WMDs) with 95% CI were calculated from the original raw data of the articles except in some cases when standard deviations (SDs) and means were calculated from the first quartile, median, the third quartile, and sample size according to Wan's method [17].

We used the random effect model by DerSimonian and Laird [18]. We estimated the heterogeneity using the χ^2 test with a significance of $p < 0.1$ and the I^2 indicator. We followed the Cochrane Handbook's recommendations when interpreting heterogeneity (<http://handbook.cochrane.org>, Chapter 10), meaning that I^2 values between 30% and 60% were considered as moderate heterogeneity, between 50% and 90% as substantial heterogeneity and as considerable heterogeneity above 75%. Results of each meta-analysis were displayed graphically using forest plots.

Subgroup analyses were performed for all outcomes where the subgroups were determined by country (United Kingdom; UK and non-UK), by age (older than 65 years and no age restriction), and by mortality (in-hospital mortality and 30-day mortality).

To determine the robustness of an assessment, we performed the leave-one-out sensitivity analysis for all outcomes. Using this method, we could examine whether altering any assumptions may lead to different final interpretations or conclusions [19]. The potential for a "small study effect", including publication bias, was examined by visual inspection of funnel plots. Furthermore, Egger's test was performed for analyses including at least ten studies to indicate significant asymmetry by using a significance of $p < 0.05$.

All data management and statistical analyses were performed with Stata (version 16.0, StataCorp).

Results

Selection and characteristics of included studies

The systematic search yielded 1690 records, and three additional records were identified. After duplicate removal, 678 records were screened by title, 219 by abstract, and 134 by full text. 27 studies were included in the qualitative and 21 in the quantitative synthesis. The detailed selection process and Cohen's kappa values are shown in Fig. 1.

The most important aspects of each included study are presented in Table 1. Only cohort studies were enrolled. From the 27 studies, three collected data prospectively, 24 used the CFS, one the Hospital Frailty Risk Score (HFRS), one both, and one the Frail Non-Disabled (FiND) questionnaire. Most studies enrolled patients over 65 years. In the study of Apea et al., patients over 16 years of age were eligible, but the average age was over 57 in every subgroup; therefore, the study was included in our analysis.

Table 1 Characteristics of included studies

Study	Origin	Recruitment period	Study type	Frailty Scale	Inclusion criteria		No. Of Patients		Age (years)		Sex Male n (%)	Outcomes
					Age (years)	COVID-19 diagnosis	Total	Deceased	mean / median	SD / IQ1-3		
Apea, V. J. (2021) [20]	UK	01.01.2020 – 13.05.2020	R/C	CFS, HFRS	> 16	PCR	831	315	n/a	n/a	n/a	30-day mortality
Aw, D. (2020) [21]	UK	01.03.2020 – 30.04.2020	R/C	CFS	> 65	PCR or Clin or Rad	677	271	81.1	8.1	366 (54.1)	in-hospital mortality, ICU admission
Bielza, R. (2021) [22]	Spain	20.03.2020 – 01.06.2020	R/C	CFS	> 70	PCR or Clin	630	282	87	82.9-91.1	223 (35.4)	30-day mortality, frailty diff. for 30-day mort. and severe vs non-severe cases
Blomaard, L. C. (2021) [23]	Netherlands	27.02.2020 – 14.05.2020	R/C	CFS	> 70	PCR or Clin or Rad	1376	499	78	74-84	830 (60.4)	in-hospital mortality, ICU admission, LOH, invasive ventilation, delirium, discharge destination
Bradley, P. (2020) [24]	UK	01.04.2020 – 14.04.2020	R/C	CFS	n/r	PCR	830	300	70	58-80	509 (61.3)	30day mortality, frailty diff. for 30-day mortality and 72 h mortality
Brill, S. E. (2020) [25]	UK	10.03.2020 – 08.04.2020	R/C	CFS	n/r	PCR	450	173	72	56-83	272 (60)	frailty diff. for in-hospital mortality
Burns, G. P. (2020) [26]	UK	13.03.2020 – 22.04.2020	R/C	CFS	n/r	PCR	28	14	81.5	54-91	15 (54)	in-hospital mortality; frailty diff. for in-hospital mortality and duration of respiratory support
Chinnadurai, R. (2020) [27]	UK	13.03.2020 – 30.04.2020	R/C	CFS	n/r	PCR	215	86	74	60-82	133 (61.9)	in-hospital mortality
Davis, P., R. (2020) [28]	UK	18.03.2020 – 20.04.2020	R/C	CFS	n/r	PCR	222	95	82	56-99	74 (33)	30-day mortality
De Smet, R. (2020) [29]	Belgium	12.03.2020 – 30.04.2020	R/C	CFS	n/r	PCR	81	19	85	81-90	33 (41)	in-hospital mortality, frailty diff. for in-hospital mortality
Fagard K. (2021) [30]	Belgium	16.03.2020 – 16.05.2020	R/C	CFS	> 70	PCR or Clin and CT	105	14	82	76-87	55 (52.4)	in-hospital mortality, frailty diff. for in-hospital mortality
Gilis, M. (2020) [31]	France	03.03.2020 – 25.04.2020	P/C	CFS	> 75	PCR	186	56	85.3	5.78	92 (49.5)	30-day mortality, ICU admission, laboratory findings, symptoms, delirium, treatment

Study	Origin	Recruitment period	Study type	Frailty Scale	Inclusion criteria		No. Of Patients		Age (years)		Sex Male n (%)	Outcomes
					Age (years)	COVID-19 diagnosis	Total	Deceased	mean / median	SD / IQ1-3		
Hewitt, J. (2020) [32]	UK, Italy	27.02.2020 – 28.04.2020	P/C	CFS	> 18	PCR or Clin	1564	425	74	61-83	903 (57.7)	in-hospital mortality
Hoek, R. A. S. (2020) [33]	Netherland	27.02.2020 – 30.04.2020	R/C	CFS	n/r	PCR	23	5	n/a	n/a	18 (78.3)	frailty diff. for in-hospital mortality (solid organ transplant recipients)
Knights, H. (2020) [34]	UK	01.03.2020 – 31.03.2020	R/C	CFS	n/r	PCR	108	34	68.7	1.5	63 (58)	frailty diff. for in-hospital mortality
Kundi, H. (2020) [35]	Turkey	11.03.2020 – 22.06.2020	R/C	HFRS	> 65	PCR	18234	3315	74.1	7.4	8498 (46.6)	in-hospital mortality; frailty diff. for in-hospital mortality
Marengoni, A. (2020) [36]	Italy	08.03.2020 – 17.04.2020	R/C	CFS	n/r	PCR or CT	165	42	69.3	14.5	100 (60.6)	in-hospital mortality, ICU admission
McWilliams, D. (2021) [37]	UK	03.2020 – 04.2020	P/C	CFS	> 18	n/a	177	67	n/a	n/a	127 (71.8)	in-hospital mortality, ICU mortality, ICU rehabilitation (only ICU patients)
Mendes, A. (2020) [38]	Switzerland	13.03.2020 – 14.04.2020	R/C	CFS	> 65	PCR or Clin and Rad	235	76	86.3	6.5	102 (43.4)	in-hospital mortality; frailty diff. for in-hospital mortality
Moledina, S. M. (2020) [39]	UK	23.03.2020 – 07.04.2020	R/C	CFS	n/r	PCR	229	75	73	56-81	144 (63)	frailty diff. for 30-day mortality
Moloney, E (2020) [40]	Ireland	17.02.2020 – 24.04.2020	R/C	CFS	> 70	PCR	69	16	79	75-85	40	in-hospital mortality; symptoms, COVID-19 severity, radiological findings, ventilation
Osuafor C.N. (2021) [41]	UK	01.03.2020 – 15.05.2020	R/C	CFS	> 65	PCR or Clin	214	74	80.3	8.3	120 (56.1)	in-hospital mortality, ICU admission, LOH, readmission; delirium, mobility at discharge, prolonged LOH, death within 14 days of discharge
Owen, R. K. (2020) [42]	UK	29.02.2020 – 16.04.2020	R/C	CFS	> 65	PCR	206	92	78.8	8.3	n/a	30-day mortality, ICU admission, ICU mortality
Piers, R. (2021) [43]	Belgium	03.2020 – 04.2020	R/C	CFS	> 80	n/a	711	246	n/a	n/a	n/a	in-hospital mortality, ICU admission
Steinmeyer, Z. (2020) [44]	France	13.03.2020 – 04.05.2020	R/C	FIND	n/r	PCR or Clin and CT	94	17	85.5	7.5	42 (44.6)	in-hospital mortality

Study	Origin	Recruitment period	Study type	Frailty Scale	Inclusion criteria		No. Of Patients		Age (years)		Sex Male n (%)	Outcomes
					Age (years)	COVID-19 diagnosis	Total	Deceased	mean / median	SD / IQ1-3		
Straw, S. (2021) [45]	UK	05.03.2020 – 07.05.2020	R/C	CFS	> 18	PCR	485	159	71.2	16.9	259 (45.8)	frailty diff. for in-hospital mortality
Tehrani, S. (2021) [46]	Sweden	05.03.2020 – 28.04.2020	R/C	CFS	n/r	PCR	255	70	66	17	150 (59)	in-hospital mortality, ventilation

Highlighted studies are included in the quantitative analyses. Age is reported using mean $\pm$ SD, or median (IQ 1–3) except: Davis P.R. where data was reported as mean (range).

Abbreviations: n/a – not available; n/r – no restriction; P/C – prospective cohort; R/C – retrospective cohort; CFS: Clinical Frailty Scale; HFRS: Hospital Frailty Risk Score; FiND: Frail Non-Disabled questionnaire; PCR: polymerase chain reaction; Clin: diagnosis based on clinical suspicion; Rad: radiologically suspected diagnosis; CT: computer tomography based diagnosis; SD: standard deviation; IQ: interquartile; OR: odds ratio; ICU: intensive care unit; LOH: length of hospitalization UK: United Kingdom

Risk of bias

Risk of bias was assessed separately for in-hospital and 30-day mortality, frailty difference for in-hospital and 30-day mortality, ICU admission, and LOH. Most studies did not report detailed baseline data for the frailty groups, therefore carried a high risk of bias (Additional File 1: Fig. S1-6).

Frailty indicated by CFS is associated with an increased chance of in-hospital and 30-day mortality

26 studies reported on mortality, 19 reporting in-hospital mortality, and 7 reporting 30-day mortality. Only two studies reported an OR less than 1 for the frail group.

Quantitative synthesis was performed for studies using CFS as a measure of frailty for in-hospital and 30-day mortality. Frailty significantly increased the chance of mortality in all analyses. Using the original classification (Figure 2, Additional File 1: Fig. S7–S8), where a CFS score greater than 4 indicates frailty, in-hospital mortality was 39% in frail patients compared to 21% in not frail patients (OR: 2.77; CI: 1.86–4.15). 43% of frail individuals died within 30 days compared to 33% in the not frail group (OR: 1.47; CI: 1.05–2.06). The overall odds ratio for mortality was 2.22 (CI: 1.64–3.01). Studies using this classification were regrouped by country and age restriction (Additional File 1: Fig. S7–8). Frailty was significantly associated with higher odds of mortality both in studies from the UK (OR: 2.16; CI: 1.50–3.12) and outside (OR: 2.51; CI: 1.32–4.77). As CFS is only validated for patients older than 65, we examined studies based on age restriction. Studies only enrolling patients over 65 had a smaller, but still significant pooled OR (OR: 1.78; CI: 1.17–2.70) than studies without age restrictions (OR: 2.84; CI: 1.84–4.37). The leave-one-out sensitivity analysis did not identify any influential study that could change the statistical significance (Additional File 1: Fig. S9).

Similarly to our results, multiple logistic regression adjusted for age, sex, respiratory rate, FiO₂, consolidation, and urea resulted in an OR of 2.55 (CI: 1.74–3.74) for 30-day mortality and OR: 2.60 (CI: 1.34–5.06) for 72-hour mortality by Bradley et al. for patients with CFS $\geq$ 5.

We also analysed data comparing CFS 1–5 (from "very fit" to "living with mild frailty") versus CFS 6–9 groups (Figure 3). CFS score 6–9 was associated with increased odds of in-hospital mortality (OR: 3.14; CI: 2.09–4.73). Three studies reported 30-day mortality, the overall OR being 1.62 (CI: 0.96–2.74). All subgroups showed a statistically significantly higher chance for mortality in the CFS 6–9 group regardless of age restriction or the place of data collection (Additional File 1: Fig. S10–11). Although moderate to considerable heterogeneity was observed in all subgroups, no influential study was identified by the leave-one-out sensitivity analysis (Additional File 1: Fig. S12).

12 studies reported the mean or median frailty in survivors and non-survivors, of which 9 were included in quantitative synthesis (Figure 4). Non-survivors generally scored significantly higher using the CFS than survivors (overall WMD: 1.14; CI: 0.70–1.58). Differences were significant for in-hospital and 30-day mortality separately. Regrouping by country also yielded significant results in both subgroups (Additional File 1: Fig. S13). No influential study was identified by the leave-one-out sensitivity analysis (Additional File 1: Fig. S14).

Similarly to the results of the quantitative synthesis, Brill et al. reported, that the median CFS was 4 in discharged patients versus 5 in patients who died (p=0.014).

Hoek et al. provided data on solid organ transplant recipients. The mean CFS was 5.8 points for patients who died, while 1.92 points for survivors (SD was not disclosed).

McWilliams et al. only included COVID-19 patients admitted to the ICU, therefore could not be pooled. ICU mortality and hospital discharge destination were detailed by CFS score categories. 67 patients died in the ICU, who's CFS score was significantly higher than ICU survivors' (p<0.001). Only one patient died in the hospital after ICU discharge, who's CFS score is not detailed.

Kundi et al. and Apea et al. used the HFRS for frailty assessment. Significantly more patients were judged as intermediate and high risk ($\text{HFRS} \geq 5$) among the non-survivors in both publications ($p < 0.001$ in both).

ICU admission

Frail patients had much smaller odds for ICU admission (OR: 0.13; CI: 0.09–0.17) for CFS 4–9 vs CFS 1–3 and (OR: 0.05; CI: 0.01–0.16) for CFS 5–9 vs CFS 1–4 (Figure 5). Only data from countries adopting guidelines with a frailty-based ceiling of care determination were used. Marengoni et al. also reported that all patients admitted to ICU were non-frail.

Length of stay

The average length of stay was only reported in two studies. Neither Blomaard et al. (median 6 vs 6 days; $p = 0.487$) nor Osuafor et al. (median 12 vs 8 days; $p = 0.08$) found significant differences comparing frail to non-frail patients.

Publication bias

Visual examination of funnel plots and Eggers's tests did not show small-study effect for any examined outcomes (Additional File 1: Fig. S15–17). Eggers's test was only conducted where at least 10 studies were included in the analysis. ICU admission could not be examined due to the low number of studies included in the analyses.

Discussion

In this systematic review and meta-analysis on the relationship between frailty and mortality, ICU admission, and LOH in COVID-19 patients, with the inclusion of 27 studies and 28,400 subjects, we found that frail patients have significantly elevated odds for both in-hospital and 30-day mortality in COVID-19. Another important finding of our study is that frail patients are less likely to be admitted to the ICU.

Despite advances in emergency and intensive therapy, mortality of the critically ill in general and also in COVID-19 remains high [47-49]. Advanced organ support – the cornerstone of intensive care –, may interfere with human dignity. The relatively high mortality and the required work intensity means a burden for the staff and relatives alike, and is, last but not least, costly [50, 51]. Therefore, prolonged, advanced organ support can be regarded as medically futile in those cases, whose chances are extremely limited for survival [52, 53]. Hence predictors of survival have been extensively researched. Due to the unprecedented load on ICUs during the pandemic of COVID-19, implementing a reliable tool to identify those who could not benefit from intensive care would be of utmost help for clinicians, patients, and relatives alike.

It has been known for long that age on its own can be misleading in outcome prediction [54]. A potential alternative is the frailty assessment, a concept that has already been supported during the COVID-19 pandemic by some studies and a recent meta-analysis [9-11]. The results of the current meta-analysis are in line with these findings and provide further support that frailty assessment could serve as a useful tool in predicting outcomes. Our results also suggest that the CSF could potentially help in the selection process of those patients who could not benefit from intensive care.

However, frailty assessment-based decision-making has not been implemented worldwide. According to our literature search (up to February 2021), studies from the UK, the Netherlands, Belgium, and France, COVID-19 guidelines advised the use of CFS in decision-making [55-57]. These countries had high-quality health care and much better resources even before the COVID-19 pandemic as compared to countries with less developed healthcare systems.

As the clinically more aggressive variants are spreading across the world, including Eastern and Central Europe – the home region of the authors –, the effective allocation of resources would be of utmost importance. These countries were more-or-less spared during the first wave and also in the second wave when mortality rates were higher in Western and Northern European countries [58-60]. However, the third wave proved devastating in this region of Europe from both the ICU-burden and the survival perspectives [61].

Although ethical concerns were raised against frailty-based decision-making, this method potentially provides a professional and transparent scaffold for health care providers [62, 63]. It has also been shown that the decision to withhold or withdraw life-sustaining treatment from patients older than 80 years in the ICU correlates with income and religious influence. In countries with lower income and higher religiosity, high-intensity critical care treatments are less frequently withdrawn, and the decision does not depend on age and ICU bed availability [64]. In a recent multicenter, multinational prospective observational study on 1346 elderly (>70) ICU COVID-19 patients, frailty provided relevant prognostic information in addition to age and comorbidities [65]. This data supports our findings that frailty could be a valuable tool in risk stratification in this patient population. Furthermore, an indirect comparison by Kow et al. has indicated that frail individuals may be overrepresented among the COVID-19 patient population and given a rather strong hint that the presence of frailty may lead to a higher risk of acquisition of COVID-19 [66]. In addition to frailty, there are other tools such as the 4C mortality score with good performance [67]; however, they were never directly compared with frailty assessment tools.

Finally, it would be desirable that based on the available scientific evidence, health authorities encouraged and supported the implementation of frailty-based risk assessment into national guidelines.

Strengths And Limitations

To our knowledge, this is the most detailed evaluation of frailty in COVID-19, separately analysing 30-day and in-hospital mortality, studies from and outside of the UK and age groups. We also assessed the relationship between frailty and ICU admission. Another methodological strength is that leave-one-out sensitivity analysis was also performed to identify influential studies. The majority of the included studies were retrospective and carried high risk of bias, therefore could

introduce bias in our analysis. Nevertheless, one of the most important limitations of our study is the considerable heterogeneity that was a common feature in many of the analyses. The explanation could lie in standard medical practice, age distribution, and nurse-to-patient ratio, which can differ between countries and hospitals. Furthermore, studies implementing frailty assessment in COVID-19 were not published from Central and Eastern European countries; therefore, they were not represented in the quantitative analyses.

Conclusion

To the best of our knowledge, this is the largest, most recent and comprehensive meta-analysis of studies in this topic today in COVID-19 patients. Our results show that frailty as determined by CFS is strongly associated with in-hospital and 30-day mortality and may also play an important role in determining eligibility for ICU admission in patients suffering from COVID-19. These findings have implications for research: they render the need for further comparisons of different frailty scores in COVID-19 patients in order to determine the most appropriate. Based on our results, the effects of frailty-based patient management on ICU admission, mortality and hospital readmission rate should also be investigated in the future. Regarding implications for practice, we believe that frailty-based patient management should be included in international COVID-19 treatment guidelines.

Abbreviations

ICU: intensive care unit; LOH: length of hospitalization; CENTRAL: The Cochrane Central Register of Controlled Trials; QUIPS: Quality in Prognosis Studies tool; OR: odds ratio; WMD: weighted mean difference; CI: confidence interval; CFS: Clinical Frailty Scale; HFRS: Hospital Frailty Risk Score; ICD: international classification of diseases; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PECO: Patient, Exposure, Control, Outcome; SD: standard deviation; FiND: Frail Non-Disabled questionnaire; IQ: interquartile; UK: United Kingdom; n/a: not available; n/r: no restriction; P/C: prospective cohort; R/C: retrospective cohort; PCR: polymerase chain reaction; Clin: clinical; Rad: radiological; CT: computer tomography.

Declarations

Ethics approval and consent to participate

Given the nature of this study, ethic approval and consent were not required.

Consent for publication

All authors consent to publication of the manuscript and support material.

Availability of data and materials

Original data is available from the corresponding author on reasonable request.

Competing interests

We declare no competing interests.

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Authors' contributions

RM performed the systematic search and selection, data extraction, risk of bias assessment and wrote the methods and results sections of the manuscript. KO provided methodological counsel in all phases from preliminary searches to writing of the manuscript and wrote the introduction and discussion sections of the manuscript. AG performed the statistical analyses. TL performed the systematic search and selection, data extraction, risk of bias assessment and provided expert opinion on the use of frailty in intensive care. MV prepared the figures. PH, TM and BE provided expert opinion during the writing of the manuscript. ZM coordinated the work and provided expert opinion. All authors read and approved the manuscript.

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Figures

Figure 1

PRISMA flowchart of selection. All three additional articles were found in the reference list of eligible articles.

Figure 2

30-day and in-hospital mortality in frail patients indicated by CFS (5–9 vs 1–4). Frail patients (CFS 5–9) have significantly higher odds of 30-day (OR: 1.47; CI: 1.05–2.06) and in-hospital mortality (OR: 2.77; CI: 1.86–4.15), the overall odds ratio being 2.22 (CI: 1.64–3.01). Note that heterogeneity was not significant for 30-day mortality, but significant for in-hospital mortality and overall OR. OR: odds ratio; CI: confidence interval. $P < 0.1$ was considered significant.

Figure 3

30-day and in-hospital mortality for patients with CFS 6–9 compared to CFS 1–5 For the CFS 6–9 group, the overall OR of 30-day mortality was 1.62 (CI: 0.96–2.74). From the study of Bielza et al. a crude OR was pooled with the ORs calculated from raw data. The CFS 6–9 group has significantly higher odds of in-hospital mortality (OR: 3.14; CI: 2.09–4.73). Note significant heterogeneity. OR: odds ratio; CI: confidence interval. $P < 0.1$ was considered significant.

Figure 4

Weighted mean difference of CFS score for 30-day and in-hospital mortality Non-survivors average CFS scores were significantly higher than survivors' (overall WMD: 1.14; CI: 0.70–1.58) in general, and for 30-day (WMD: 0.86; CI: 0.04–1.68) and in-hospital mortality (WMD: 1.33; CI: 0.95–1.71) as well. Please note the significant heterogeneity. WMD: weighted mean difference; SD: standard deviation; CI: confidence interval. $P < 0.1$ was considered significant.

Figure 5

ICU admission in frail patients indicated by CFS. a CFS 1–3 vs CFS 4–9. b CFS 1–4 vs CFS 5–9. Patients with CFS 4–9 (OR: 0.13; CI: 0.09–0.17) and CFS 5–9 (OR: 0.05; CI: 0.01–0.16) had significantly lower chance for ICU admission than non-frail patients. Please note the significant heterogeneity for CFS 5–9 vs CFS 1–4. OR: odds ratio; CI: confidence interval. P<0.1 was considered significant.

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