Frailty and comorbidity in predicting community COVID-19 mortality in the UK

Biobank: the effect of sampling

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Abstract

Frailty has been linked to an increased risk of coronavirus disease 2019 (COVID-19)-associated mortality, but evidence has been inconclusive and limited to hospitalized older individuals. Using data from the UK Biobank, we assessed whether frailty and comorbidity predict COVID-19 mortality in the overall community population (n=437,555) and in a selected COVID-19 positive sample (n=2,059). Frailty was assessed using the Rockwood Frailty Index (FI) and the Hospital Frailty Risk Score (HFRS), whereas comorbidity was assessed by the Charlson Comorbidity Index (CCI). Overall, 408 individuals died of COVID-19, as ascertained from the death register data. In the full sample, HFRS (odds ratio [OR] 1.07; 95% confidence interval [CI] 1.06–1.07) and CCI (OR 1.14; 95% CI 1.08–1.20) were associated with increased risk of COVID-19 mortality, while FI was not statistically significantly different from null in the multivariable logistic regression model. Adding HFRS or CCI to a model with only age and sex resulted in significantly larger areas under the receiver operating characteristic curves. Nevertheless, when restricting the analyses to COVID-19 positive cases, which is a sample with over-representation of frail individuals, neither of the frailty measures or CCI added meaningful predictive accuracy on top of age and sex. Besides, we observed stronger associations between HFRS categories and COVID-19 mortality in relatively younger (<75 years) than older individuals (≥75 years). Our results suggest that HFRS and CCI, which could be readily derived from medical records, may be useful for COVID-19 mortality risk stratification in the community.

Keywords: COVID-19, mortality, frailty, comorbidity, ageing
Introduction

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has led to a global pandemic, affecting more than 41 million individuals and causing ~1.1 million deaths worldwide as of 22nd October 2020 [1]. Accumulating evidence has shown that older age, male sex, comorbidities (e.g. diabetes, hypertension), social deprivation, black ethnicity, and laboratory indicators such as elevated levels of d-dimer and interleukin 6 are risk factors for mortality associated with COVID-19 [2–6]. However, there are relatively few data available for risk stratification in community samples compared to hospitalized patients.

Frailty, characterized as a state of increased vulnerability due to cumulative decline in multiple physiological systems [7], has consistently shown to be a strong predictor of mortality in the general population [8–10]. Various tools have been developed for measuring frailty. Some of which require assessment by physicians, such as the Clinical Frailty Scale (CFS) [11], which is more suitable in clinical settings. Another widely used measure is the Rockwood frailty index (FI), which is defined as a ratio of accumulated deficits over the total number of deficits considered [12]. The Hospital Frailty Risk Score (HFRS), constructed based on the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) coding system [13], was developed for frailty risk stratification among older hospitalized patients and has been validated for its ability to predict adverse outcomes in various settings [14,15].

A growing number of studies have investigated the association between frailty, frequently measured using the CFS in hospital settings, and mortality among COVID-19 patients, but findings remain inconclusive. While there is evidence that frailty may add to the risk prediction in hospitalized patients [16–19], some studies have observed weak [20,21], or
 even null associations [22]. Heterogeneity in the prior results may partly be owing to the COVID-19 patients being a non-random, selected sample with a particularly high prevalence of frailty [23], potentially causing selection bias [24]. With the continuing spread of the SARS-CoV-2 across the world, it is of importance to assess whether COVID-19 mortality can be predicted using other frailty and comorbidity measures, such as the HFRS and CCI that can be readily derived from medical records, in community samples.

Using a large population cohort from the UK Biobank study, we aimed to investigate the predictive ability of frailty, measured using the HFRS and FI, and the Charlson Comorbidity Index (CCI) as a measure of comorbidity, for COVID-19 mortality among (a) the overall community population and (b) COVID-19 positive individuals. Our goal was to assess whether an easily accessible frailty and/or comorbidity measure could aid in COVID-19 mortality risk stratification in community settings. In keeping with the observations that higher levels frailty carry a relatively greater risk of all-cause mortality in younger than older ages [9,10,25], we additionally assessed whether the same holds true for COVID-19 mortality. As excess mortality due to COVID-19 may be more pronounced in younger and fitter individuals compared to old and frail [22], it is essential to identify the factors contributing to this risk.

Methods

Study population

This is a population-based cohort study using data from the UK Biobank. Between 2006 and 2010, more than 500,000 participants completed a touch-screen questionnaire, had physical measurements taken, and provided biological samples at one of the 22 assessment centres in England, Wales or Scotland [26]. The UK Biobank study was approved by the North West Multi-
Centre Research Ethics Committee. All participants provided written informed consent for data collection, analysis, and record linkage.

We excluded participants who died before 1st March 2020, requested to withdraw from the study prior to August 2020, and had missing data on frailty and comorbidity measures. This resulted in a sample size of \( n = 437,555 \), which we referred to as the “full sample”. The subgroup of “COVID-19 positive sample” \( n = 2,059 \) consisted of those being tested positive, diagnosed as COVID-19 patients in hospitals, and/or died of COVID-19. Analyses were performed in both samples (Fig. 1).

COVID-19 diagnosis and mortality

Information on COVID-19 was obtained from three data sources linked to UK Biobank: laboratory test results, inpatient medical records, and death register. SARS-CoV-2 PCR test results were provided by Public Health England [27], with data available in England only, between 16th March and 24th August 2020. Hospital inpatient data were sourced from the Hospital Episode Statistics (HES), containing electronic medical records (i.e., ICD-10 diagnostic codes) for all hospital admissions to National Health Service (NHS) hospitals in England up to 30th June 2020. Death register data included all deaths up until 24th August 2020 in England, Wales and Scotland, containing ICD-10 codes assigned as individuals’ primary and contributory causes of death.

Participants were considered “COVID-19 positive” when meeting at least one of the following criteria: (i) being positive in at least one of the PCR tests; (ii) shown as COVID-19 inpatients, with ICD-10 code U07 in hospital admission; and (iii) died of COVID-19, defined as those with COVID-19 (ICD-10 code U07) as the primary or contributory causes of death. COVID-19 mortality was used as the main outcome in the analyses.
Among the COVID-19 positive individuals, we compared characteristics of those diagnosed as patients (i.e., with positive test result or was a COVID-19 inpatient; n=1,970) and those died of COVID-19 but without positive test record (n=89), and found that both groups were generally comparable except that individuals in the latter group were more likely to be older, with lower income and with higher HFRS (Appendix Table S1).

Frailty and comorbidity measures

Frailty was assessed using the FI and HFRS, and comorbidity was measured using the CCI (timeline of data collection is shown in Appendix Fig. S1). The FI has previously been created and validated by us for the UK Biobank participants, using 49 self-reported frailty items assessed at baseline during 2006–2010 that cover a wide range of items for physical and mental well-being (Appendix Table S2) [10]. The FI was calculated as the sum of the items (deficits) present in an individual divided by the total number of deficits, for instance, an individual with 7 deficits from 49 items would receive an FI of 7/49=0.14. The FI was used as both continuous and categorical variable, the latter being categorized into four groups: relatively fit (≤0.03), less fit (>0.03–0.1), least fit (>0.1–0.21) and frail (>0.21) [28]. HFRS and CCI were computed based on the ICD-10 codes from hospital records [13,29]. Only medical records before 1st March 2020 were included so that diagnoses due to or associated with COVID-19 would not bias the results. The HFRS was derived based on 109 frailty-related ICD-10 codes, as previously described by Gibert et al (Appendix Table S3) [13]. While it was originally developed for older individuals (≥75 years) who had been admitted to hospital during the prior 2 years, we utilized all available ICD-10 codes for each individual for calculation. Each of the 109 codes were assigned a weight ranging from 0.1 to 7.1, depending on its strength of association with frailty. HFRS was then calculated by summing all the...
weighted codes, and used both as continuous and categorical measures, the latter being categorized into low (<5), intermediate (5–15) and high (>15) risk of frailty [13]. Similarly, CCI was derived by summing weighted ICD-10 codes, based on 17 comorbidities with weights from 1 to 6 depending on disease severity and mortality risk (Appendix Table S4) [29], and was treated as a continuous variable in all analyses. Individuals who had missing hospital data were those who had not been hospitalized or resided outside England (these data were only available for England). To maximize data utilization, we first excluded individuals who attended baseline assessment in Wales or Scotland and with missing hospital data, and then coded the remaining individuals with missing hospital data as 0 for HFRS and CCI. As a sensitivity analysis, we assessed whether including diagnoses from long ago would affect the results by calculating 2-year HFRS and CCI scores using diagnoses assigned only during the past two years (i.e., between 1st March 2018 and 29th February 2020). The FI, HFRS and CCI correlated moderately with each other (Appendix Table S5).

Other study variables

Demographic characteristics (e.g. birth year, sex, ethnicity, smoking status) and socioeconomic indicators (e.g. education, income, Townsend deprivation index) were collected at baseline during 2006–2010. Education was assessed by the highest self-reported qualification and categorized into low (no relevant qualifications), intermediate (A levels, O levels/GCSEs, CSEs, NVQ/HND/HNC, other professional qualifications) and high (college or university degree). Annual household income was self-reported and categorized into four groups (<£18,000, £18,000–30,999, £31,000–51,999, ≥£52,000). Townsend deprivation index was derived from national census data regarding unemployment, car ownership, home
ownership, and household overcrowding; higher scores correspond to higher level of socioeconomic deprivation.

Statistical analyses

Descriptive statistics were calculated for the full sample and COVID-19 positive sample. Due to the apparent over-representation of frail individuals in the COVID-19 positive sample, we performed logistic regression to formally ascertain if frailty and comorbidity were determinants for being COVID-19 positive.

In both samples, multivariable logistic regression models were applied to investigate the associations of frailty and comorbidity (FI, HFRS, CCI, as continuous measures) with COVID-19 mortality, adjusted for age (as linear effect, after confirming that the age-mortality relationship was approximately linear) and sex. Ethnicity, smoking status, and socioeconomic variables were subsequently added into the models to test whether they had an effect on the associations. Areas under the receiver operating characteristic curves (AUROC) were used to assess the predictiveness of the different measures. Because the HFRS was originally designed for individuals older than 75 years and previous studies have reported age-varying risks for frailty [9,10,25], we additionally stratified the analysis by age <75 and ≥75 years, as well as performed an analysis with an interaction term between HFRS (continuous) and age group.

We further performed a series of sensitivity analyses to assess the robustness of our findings, which included (i) using categorical instead of continuous FI and HFRS variables; (ii) using 2-year HFRS and CCI, constructed by ICD-10 codes from the past 2 years only; and (iii) performing multinomial logistic regression models to account for non-COVID-19 deaths as competing risk, where mortality due to COVID-19 or other causes than COVID-19 were compared to those who were alive as of 24 August 2020.
To account for multiple comparisons, the Benjamini-Hochberg false discovery rate method was applied [30]. All analyses were performed using Stata v16.0 (Stata Corp, College Station, TX) and R v3.6.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Sample characteristics

Table 1 shows the characteristics of participants in the full sample and COVID-19 positive sample. In the full sample of 437,555 participants, the mean age as of the year 2020 was 68.1 (standard deviation [SD] 8.1) and 55.3% were women. The proportions of men, Black ethnicity, previous or current smokers, low education, lowest income and most deprived groups were higher in the COVID-19 positive sample than the full sample. Frailty appeared to be over-represented among COVID-19 positive individuals, with 21.6% being “frail” (assessed by FI) and 22.4% being “high frailty risk” (assessed by HFRS), compared to 12.1% and 2.9% in the full sample. Logistic regression models for COVID-19 positivity showed that FI, HFRS, and CCI were all associated with higher risk of being COVID-19 positive, after adjusting for age and sex (Appendix Table S6).

Frailty and comorbidity in predicting COVID-19 mortality

In total, 408 individuals died of COVID-19 between 1st March and 24th August 2020. Results for the logistic regression models for COVID-19 mortality are presented in Table 2. In the full sample, when each of the measures – FI, HFRS, and CCI were tested separately, they were significantly associated with higher odds of COVID-19 mortality after controlling for age and sex (models 2–4). AUROC for the model including only age and sex was 0.76 (95% confidence interval [CI] 0.74–0.78); adding FI into the model resulted in a slightly larger AUROC of 0.78.
(95% CI 0.76–0.80), while adding HFRS and CCI yielded significantly larger AUROCs of 0.83 (95% CI 0.81–0.86) and 0.82 (95% CI 0.80–0.84) respectively (Fig. 2A). In the multivariable model with both frailty measures and the CCI included (model 5), HFRS (odds ratio [OR] 1.07; 95% CI 1.06–1.07) and CCI (OR 1.14; 95% CI 1.08–1.20), but not FI, predicted statistically significantly higher risk of COVID-19 mortality. AUROC of the multivariable model (0.84; 95% CI 0.83–0.87) was similar to the age and sex-adjusted univariable models of HFRS and CCI (Fig. 2A). After restricting the sample to COVID-19 positive individuals, all of these associations were attenuated, and the predictive accuracies were decreased. In the fully adjusted model (model 5), only CCI was marginally associated with COVID-19 mortality (OR 1.09; 95% CI 1.01–1.14). Frailty and comorbidity did not add predictive value on top of age and sex, as indicated by similar AUROCs across all models (Fig. 2B). We subsequently adjusted for ethnicity, smoking and socioeconomic variables in both samples; associations of frailty and comorbidity with COVID-19 mortality were not affected by these variables (Appendix Table S7).

In both samples, compared with older individuals (≥75 years), relatively younger individuals (<75 years) had higher ORs for COVID-19 mortality across HFRS categories (Fig. 3); there was also significant interaction between HFRS and age in the COVID-19 positive sample (Pinteraction<0.001), but not in the full sample (Appendix Table S8). We also tested the interaction between HFRS and sex, yet it was not statistically significant and thus we did not further perform subgroup analysis by sex.

Sensitivity analyses

The predictive abilities of frailty and comorbidity for COVID-19 mortality were largely similar compared to the main analyses when (i) using FI and HFRS as categorical instead of continuous variables (Appendix Table S9), (ii) using the 2-year HFRS and CCI variables instead of the
original scores (Appendix Table S10), and (iii) accounting for competing risk by deaths due to other causes than COVID-19 (Appendix Table S11).

Discussion

Using data from the UK Biobank, we found that HFRS and CCI, measures of frailty and comorbidity respectively, were viable predictors of COVID-19 mortality and added predictive value on top of age and sex in the overall community population. The associations persisted even after adjusting for ethnicity, smoking and socioeconomic variables. Nonetheless, among COVID-19 positive individuals who were already more likely to be frail, HFRS and CCI did not improve predictive accuracy for COVID-19 mortality in addition to age and sex. Stronger associations between HFRS and COVID-19 mortality were seen among younger (<75 years) than older individuals (≥75 years), indicating that the HFRS may be applicable for predicting mortality risk in younger adults as well.

To the best of our knowledge, this is the first study that has assessed the associations between frailty and COVID-19 mortality in the community population. We showed that frailty was associated with an elevated risk of COVID-19 mortality, and that a HFRS constructed based on ICD-10 codes was a stronger predictor than an FI calculated using self-reported data at baseline. The CCI, a measure of comorbidity computed by ICD-10 codes, likewise predicted COVID-19 mortality, which is in line with prior research showing a positive association between comorbidity and COVID-19 deaths [18,21,31]. Together, our results imply that frailty and comorbidity measures available in routinely collected medical records may be applied for risk stratification of COVID-19 mortality in the overall community population.

However, the predictive accuracies of frailty and comorbidity for COVID-19 mortality were reduced after restricting the sample to only those with the disease. It has been argued
that using non-random samples may induce selection bias in COVID-19-related studies [24]. In our COVID-19 positive sample, there was an over-representation of the most frail individuals, with even greater proportion of the “high frailty risk” group in our sample than in the cohort of older hospitalized individuals in the original HFRS study (22.1% vs 20.0%) [13]. Consistent with a previous study [32], we confirmed that frailty and comorbidities are determinants of being COVID-19 positive in the UK Biobank sample. Such over-representation of frailty may partly explain the inconsistencies in the frailty-mortality associations among hospitalized COVID-19 patients [16–22]. In a relatively frail sample, COVID-19 mortality risk may in fact be more related to other factors, such as viral load and host immune characteristics [20,33]. Indeed, none of our models in the COVID-19 positive sample yielded a good predictive accuracy of AUROC>0.8, even when smoking, ethnicity and socioeconomic variables were included. More research is warranted to identify the most accurate predictors for mortality among COVID-19 patients.

Given that the HFRS was initially developed for older individuals, we stratified the analysis by age and observed a more pronounced association between HFRS and COVID-19 mortality among the younger individuals (<75 years). A similar pattern has also been reported in the literature, in which frailty has shown to be more strongly associated with mortality at younger old ages than the oldest ages [9,25]. Our findings thus highlight the importance of frailty screening in younger individuals in prevention for COVID-19 related mortality.

The large sample of UK Biobank participants with linkage to COVID-19 data enabled us to study the associations among the overall population and to examine the potential effects of sample selection. Nevertheless, there are several caveats to this study. Firstly, demographic variables, socio-economic indicators and the deficits for construction of FI were assessed during baseline in 2006–2010. In particular, the FI, calculated by self-reported data ~10 years...
ago, may not fully reflect participants’ current physiological status. Future research may utilize an FI based on routine primary care data, such as the electronic FI [34], for assessing its predictive ability for COVID-19 mortality among the general population. Secondly, with the limitation of data availability, we were not able to retrieve test results and hospital inpatient data for people living in Scotland or Wales. Thirdly, during the earlier periods of the epidemic, COVID-19 testing in the UK was largely restricted to hospitalized individuals, who have more severe course of the diseases. As such, mild or asymptomatic COVID-19 cases may conceivably be missed, leading to an underestimation of COVID-19 positive cases. Fourthly, we modelled the outcome, COVID-19 mortality, as a binary variable rather than a time-to-event or survival outcome because we could not ascertain the exact date of confirmed COVID-19 infection for several individuals in the COVID-19 positive subsample. However, as the follow-up time was limited, it could be considered essentially complete for most participants (i.e., minimal censoring due to migration and other deaths). Finally, UK Biobank is not a nationally representative sample, with generally healthier and less socioeconomically deprived participants than the UK average [35], thereby reducing the generalizability of our findings.

Conclusions and implications

In conclusion, HFRS and CCI, measures of frailty and comorbidity respectively, constructed using routinely collected medical records, predicted COVID-19 mortality in the overall community sample and added predictive value on top age and sex. However, similar effects were not seen in those who already have the disease. Our findings suggest that identification of frail individuals in the general population may be a viable strategy for COVID-19 mortality risk stratification.
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Declarations

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Conflicts of interest: The authors declare that they have no conflict of interest.

Ethical approval: Ethical approval for this study is covered by the general ethics review for the UK Biobank, conducted by North West Multi-Centre Research Ethics Committee (Reference: 16/NW/0274, 13 May 2016).

Consent to participate: Informed consent was obtained from all individual participants included in the study.

Consent to publish: Not applicable.

Availability of data and material: UK Biobank is an open access resource. All bona fide researchers can apply to use its data for health-related research that is in the public interest (http://www.ukbiobank.ac.uk/register-apply).

Code availability: Not applicable.

Authors’ contributions: J.K.L.M., R.K.-H., and J.J. contributed to the study concept and design; Y.W., S.H. and J.J. were responsible for acquisition of data; J.K.L.M., R.K.-H. and J.J. analysed and interpreted the data; J.K.L.M. and J.J. drafted the manuscript; R.K.-H., Y.W. and S.H. critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.
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## Tables and Figures

### Table 1  Characteristics of UK Biobank participants in the full sample and COVID-19 positive sample

|                               | Full sample  | COVID-19 positive sample |
|-------------------------------|--------------|--------------------------|
|                               | (n=437,555)  | (n=2,059)                |
| Deaths, n (%)                 | 2,146 (0.5)  | 477 (23.2)               |
| Age (years), mean ± SD        | 68.1 ± 8.1   | 68.8 ± 9.0               |
| Sex, n (%)                    |              |                          |
| Women                         | 241,791 (55.3) | 976 (47.4)          |
| Men                           | 195,764 (44.7) | 1,083 (52.6)         |
| Ethnicity, n (%)              |              |                          |
| White                         | 411,094 (94.3) | 1,798 (87.7)         |
| Asian                         | 10,471 (2.4)  | 94 (4.6)                |
| Black                         | 7,608 (1.7)   | 102 (5.0)               |
| Others                        | 6,886 (1.6)   | 57 (2.8)                |
| Smoking status, n (%)         |              |                          |
| Never                         | 242,414 (55.6) | 981 (48.0)             |
| Previous                      | 150,245 (34.5) | 806 (39.5)            |
| Current                       | 43,346 (9.9)  | 256 (12.5)              |
| Education, n (%)              |              |                          |
| Low                           | 70,461 (16.4)  | 512 (25.6)              |
| Intermediate                  | 218,540 (50.9) | 999 (50.0)             |
| High                          | 140,713 (32.8) | 489 (24.5)             |
| Income, n (%)                 |              |                          |
| <£18,000                      | 81,674 (22.0)  | 564 (33.5)              |
| £18,000–30,999                | 94,319 (25.4)  | 438 (25.6)              |
| £31,000–51,999                | 98,079 (26.4)  | 372 (22.1)              |
| ≥£52,000                      | 97,456 (26.3)  | 311 (18.5)              |
| Townsend deprivation quintile, n (%) |          |                          |
| 1 (least deprived)            | 87,712 (20.1)  | 291 (14.1)              |
| 2                             | 88,844 (20.3)  | 334 (16.2)              |
| 3                             | 88,525 (20.3)  | 375 (18.2)              |
| 4                             | 87,596 (20.0)  | 431 (20.9)              |
| 5 (most deprived)             | 84,352 (19.3)  | 627 (30.5)              |
| Frailty Index, median (IQR)   | 0.112 (0.066–0.163) | 0.133 (0.083–0.199) |
| By category, n (%):           |              |                          |
| Relatively fit (≤0.03)        | 26,412 (6.0)   | 78 (3.8)                |
| Less fit (>0.03–0.1)          | 164,761 (37.7) | 604 (29.3)              |
| Least fit (>0.1–0.21)         | 193,409 (44.2) | 933 (45.3)              |
| Frail (>0.21)                 | 52,973 (12.1)  | 444 (21.6)              |
| Hospital Frailty Risk Score, median (IQR) | 0.7 (0–3.2) | 3.2 (0–12.9) |
| By category, n (%):           |              |                          |
| Low risk (<5)                 | 365,958 (83.6) | 1,196 (58.1)            |
| Intermediate risk (5–15)      | 59,046 (13.5)  | 402 (19.5)              |
| High risk (>15)               | 12,551 (2.9)   | 461 (22.4)              |
| Charlson Comorbidity Index, median (IQR) | 0 (0–1) | 1 (0–3) |

IQR, interquartile range; SD, standard deviation
Table 2 Logistic regression models for the associations of age, sex, frailty and comorbidity with COVID-19 mortality in the full sample and COVID-19 positive sample

|                    | Model 1: age + sex OR (95% CI) | Model 2: FI + age + sex OR (95% CI) | Model 3: HFRS + age + sex OR (95% CI) | Model 4: CCI + age + sex OR (95% CI) | Model 5: Multivariable OR (95% CI) |
|--------------------|-------------------------------|-------------------------------------|--------------------------------------|-------------------------------------|----------------------------------|
| (a) Full sample (n=437,555) |                               |                                     |                                      |                                     |                                  |
| Age                | 1.14 (1.12–1.16)*             | 1.13 (1.11–1.15)*                  | 1.11 (1.09–1.13)*                   | 1.11 (1.09–1.13)*                   | 1.10 (1.09–1.12)*               |
| Male sex           | 1.99 (1.63–2.44)*             | 2.12 (1.73–2.59)*                  | 1.93 (1.57–2.36)*                   | 1.77 (1.45–2.17)*                   | 1.86 (1.52–2.29)*               |
| FI (per 10% increase) | 1.70 (1.52–1.90)*            |                                     |                                      |                                     | 1.09 (0.96–1.23)               |
| HFRS               |                               | 1.08 (1.07–1.09)*                  |                                      |                                     | 1.07 (1.06–1.07)*               |
| CCI                |                               |                                     |                                      |                                     | 1.40 (1.35–1.45)*               |
| Area under the ROC curve | 0.76 (0.74–0.78)             | 0.78 (0.76–0.80)                   | 0.83 (0.81–0.86)                    | 0.82 (0.80–0.84)                    | 0.84 (0.83–0.87)               |
| (b) COVID-19 positive sample (n=2,059) |                         |                                     |                                      |                                     |                                  |
| Age                | 1.12 (1.10–1.14)*             | 1.12 (1.10–1.14)*                  | 1.11 (1.09–1.13)*                   | 1.11 (1.09–1.13)*                   | 1.11 (1.09–1.13)*               |
| Male sex           | 1.45 (1.14–1.83)*             | 1.47 (1.16–1.87)*                  | 1.44 (1.14–1.83)*                   | 1.43 (1.13–1.81)*                   | 1.43 (1.12–1.81)*               |
| FI (per 10% increase) | 1.09 (0.96–1.25)             |                                     |                                      |                                     | 1.00 (0.87–1.15)               |
| HFRS               |                               |                                     |                                      |                                     | 1.01 (1.00–1.02)               |
| CCI                |                               |                                     |                                      |                                     | 1.09 (1.04–1.15)*               |
| Area under the ROC curve | 0.74 (0.72–0.77)             | 0.74 (0.72–0.77)                   | 0.75 (0.72–0.77)                    | 0.75 (0.72–0.77)                    | 0.75 (0.72–0.77)               |

CCI, Charlson comorbidity index; CI, confidence interval; FI, Frailty Index; HFRS, Hospital Frailty Risk Score; OR, odds ratio; ROC, receiver operating characteristic curve.

*Significant with a false discovery rate corrected significance level at 0.044

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Fig. 1 Flowchart of selection of study sample from the UK Biobank

UK Biobank participants at baseline (n = 502,631)

- Excluded (n = 65,076)
  - Died before 1st March 2020 (n = 29,301)
  - Requested to withdraw from the UK Biobank study (n = 138)
  - Had missing data on frailty and comorbidity measures (n = 35,637)

Sample included in analyses (n = 437,555)

Outcome (a): COVID-19 mortality among full sample as of 24th August 2020 (n = 408/437,555)

- Excluded non COVID-19 positive individuals (n = 435,496)

Outcome (b): COVID-19 mortality among positive cases as of 24th August 2020 (n = 408/2,059)
Fig. 2 Receiver operating characteristic (ROC) curves for age, sex, frailty and comorbidity in predicting COVID-19 mortality. (A) Analyses performed in the full UK Biobank sample (n=437,555); (B) analyses performed in the COVID-19 positive sample (n=2,059). Model 1 to model 4 are univariable logistic regression models adjusted for age and sex, while model 5 is the multivariable logistic regression model. AUC, area under the receiver operating characteristic curves; CCI, Charlson comorbidity index; FI, Frailty Index; HFRS, Hospital Frailty Risk Score.
Fig. 3 Associations between Hospital Frailty Risk Score and COVID-19 mortality stratified by age into younger (<75 years) and older (≥75 years) individuals in full sample (n=437,555) and in COVID-19 positive sample (n=2,059). Error bars indicate 95% confidence intervals. Models were adjusted for sex.

Note: The point estimates for the stratified analysis can be found in Appendix Table S8