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COVID-19 mRNA vaccine effectiveness against hospitalisation and death in veterans according to frailty status during the SARS-CoV-2 delta (B.1.617.2) variant surge in the USA: a retrospective cohort study

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Summary

Background Studies have shown that COVID-19 vaccination is effective at preventing infection and death in older populations. However, whether vaccination effectiveness is reduced in patients with frailty is unclear. We aimed to compare vaccine effectiveness against hospitalisation and death after COVID-19 during the surge of the delta (B.1.617.2) variant of SARS-CoV-2 according to patients' frailty status.

Methods In this retrospective cohort study, we used data derived from the US Veterans Health Administration (VHA) facilities and the US Department of Veterans Affairs (VA) COVID-19 Shared Data Resource, which contains information from the VA National Surveillance Tool, death certificates, and National Cemetery Administration. We included veterans aged 19 years or older who tested positive for SARS-CoV-2 using RT-PCR or antigen tests between July 25 and Sept 30, 2021, with no record of a previous positive test. Deaths were identified through VHA facilities, death certificates, and National Cemetery Administration data available from VA databases. We also retrieved data including sociodemographic characteristics, medical conditions diagnosed at baseline, frailty score, and vaccination information. The primary outcomes were COVID-19-associated hospitalisations and all-cause deaths at 30 days from testing positive for SARS-CoV-2. The odds ratio (OR) for COVID-19-associated hospitalisation and hazard ratio (HR) for death of vaccinated patients compared with the unvaccinated patients were estimated according to frailty categories of robust, pre-frail, or frail. Vaccine effectiveness was estimated as 1 minus the OR for COVID-19-associated hospitalisation, and 1 minus the HR for death.

Findings We identified 57 784 veterans (mean age 57.5 years [SD 16.7], 50 642 [87.6%] males, and 40 743 [70.5%] White people), of whom 28 497 (49.3%) were categorised as robust, 16 737 (29.0%) as pre-frail, and 12 550 (21.7%) as frail. There were 2577 all-cause deaths (676 [26.2%] in the vaccinated group and 1901 [73.8%] in the unvaccinated group), and 7857 COVID-19-associated hospitalisations (2749 [35.0%] in the vaccinated group and 5108 [65.0%] in the unvaccinated group) within 30 days of a positive SARS-CoV-2 test. Vaccine effectiveness against COVID-19-associated hospitalisation within 30 days of a positive SARS-CoV-2 test was 65% (95% CI 61–69) in the robust group, 54% (48–58) in the pre-frail group, and 36% (30–42) in the frail group. By 30 days of a positive SARS-CoV-2 test, the vaccine effectiveness for all-cause death was 79% (95% CI 74–84) in the robust group, 79% (75–83) in the pre-frail group, and 68% (63–71) in the frail group.

Interpretation Compared with non-frail patients (pre-frail and robust), those with frailty had lower levels of vaccination protection against COVID-19-associated hospitalisation and all-cause death. Future studies investigating COVID-19 vaccine effectiveness should incorporate frailty assessments and actively recruit older adults with frailty.

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Introduction

Older adults have been disproportionately affected by the COVID-19 pandemic. Studies have documented higher risk of morbidity, hospital admission, admission to care homes, and death among the older population than in younger people with COVID-19.1 The delta (B.1.617.2) variant of SARS-CoV-2 became dominant in the USA between June and August, 2021, and was characterised by even higher transmissibility, more severe clinical presentation, and higher mortality in unvaccinated individuals than the preceding alpha (B.1.1.7) variant.2 Older adults stand to benefit the most from interventions aimed at preventing infection or mitigating the effects of COVID-19. Studies have shown that COVID-19 vaccination is effective at preventing infection, symptomatic disease, severe complications, and death in older populations, but their responses to vaccines are lower than those of younger adults.3 Post-clinical trial data show
Articles

Research in context

Evidence before this study
We searched PubMed, Embase, Cochrane Library, Google Scholar, and Web of Science for research articles published between March 1, 2020, and March 1, 2022, using the search terms and keywords [“COVID”] OR [“SARS-CoV-2,”] OR [“novel human coronavirus”] OR [“coronavirus disease 2019”] AND [“vaccines, vaccination, inoculation, immunization”] AND [“frail, frailty”] AND [“mortality, mortalities”] OR [“death”] OR [“survivor, survival”] OR [“hospital, hospitalization, hospitalizations”]. No language restrictions were applied. Reference lists from identified articles were also analysed for additional studies. We included articles that evaluated the effects of mRNA COVID-19 vaccines on hospitalisation and all-cause death according to frailty status. Evidence shows that COVID-19 vaccination is effective at preventing severe complications and all-cause death in older populations; however, their responses to vaccines are lower than those of younger adults. Furthermore, current research reveals a heterogeneity in the responses to vaccination in older adults, although the reasons for this are not well understood. The existing evidence suggests that chronological age might not be an optimal criterion when evaluating the effectiveness of COVID-19 vaccines. Frailty, a state of reduced reserves and increased vulnerability to stressors resulting from multisystemic dysfunction, can be considered a surrogate marker of biological age. Frailty is common in older populations and is responsible for many negative clinical outcomes. It is associated with age-related immune dysregulation characterised by low-grade chronic inflammation and immunosenescence, which are factors that might contribute to decreased vaccine protection. Although vaccine effectiveness has not been well studied in relation to frailty or underlying health status, some studies investigating the efficacy or effectiveness of vaccines in older adults with frailty have shown mixed results.

Added value of this study
Our study showed that COVID-19 vaccine effectiveness against COVID-19-associated hospitalisation and all-cause death varied by frailty status. So far, this is the first retrospective cohort study evaluating the effects of mRNA vaccines on COVID-19-associated hospitalisation or all-cause death after documented SARS-CoV-2 infection according to frailty status. The results of this study are important to build our understanding of frailty as an influential factor in the variability of responses to vaccination in older populations.

Implications of all the available evidence
Although individuals with frailty benefit from COVID-19 mRNA vaccination, the degree of protection against COVID-19-associated hospitalisation and all-cause death seems to be lower than in people without frailty. The evidence from this study suggests that future research design, development, and evaluation of COVID-19 vaccine effectiveness should consider baseline frailty assessments. The findings of reduced vaccine protection in patients with frailty underscore the need to optimise vaccine effectiveness for these patients, with the goal of preventing severe SARS-CoV-2-related outcomes. Future large cohort studies and randomised controlled trials that consider frailty status are essential to gain more information about the effects of COVID-19 vaccination in older adults according to frailty status.

The US veteran population is older and predominantly male, and has a high prevalence of chronic medical and mental health multimorbidity, substance abuse, obesity, disability, and frailty, all of which are known risk factors for worse outcomes after SARS-CoV-2 infection. Although COVID-19 mRNA vaccines were effective at reducing clinical outcomes in older people. Two mechanisms could lead to the decline in vaccine responsiveness in older individuals with frailty: immunosenescence, which refers to the age-related dysregulation in humoral and cellular immunity, and inflammaging, which describes low-grade chronic inflammation. Mounting research suggests that inflammaging and immunosenescence do not invariably occur in all older adults and might account for the variability in vaccine responses seen in individuals with frailty. More research examining the effects of frailty on COVID-19 vaccination responsiveness in patients with previous SARS-CoV-2 infection is needed. Frailty in older adults might be an important factor to consider when designing, developing, and evaluating COVID-19 vaccines. The US veteran population is older and predominantly male, and has a high prevalence of chronic medical and mental health multimorbidity, substance abuse, obesity, disability, and frailty, all of which are known risk factors for worse outcomes after SARS-CoV-2 infection. Although COVID-19 mRNA vaccines were effective at reducing
death in veterans during the delta variant wave, protection was lower for veterans older than 65 years than those aged 65 years or younger, and veterans’ frailty status was not assessed.\(^\text{19}\) As one in three veterans older than 65 years have frailty,\(^\text{16}\) the determination of frailty status might identify a group at higher risk of both worse clinical outcomes and lower vaccine responsiveness. Our primary aim was to compare vaccine effectiveness against COVID-19-associated hospitalisation and all-cause death after SARS-CoV-2 infection according to patients’ frailty status. Our hypothesis was that vaccine effectiveness against COVID-19-associated hospitalisation and all-cause death during the delta variant wave will be lower in patients with frailty than in robust and pre-frailty groups.

Methods

Study design and population

This retrospective cohort study was done at the Veterans Health Administration (VHA), the largest integrated health-care system in the USA. Data were extracted from the US Department of Veterans Affairs (VA) COVID-19 Shared Data Resource (which was created by the VHA in 2020 to facilitate research into SARS-CoV-2\(^2\)), the VA National Surveillance Tool (NST; which is the authoritative data source for positive and negative COVID-19 cases in the veteran population),\(^3\) and the VA Corporate Data Warehouse. We included US veterans aged 19 years or older who tested positive for SARS-CoV-2 on RT-PCR or antigen tests between July 25 and Sept 30, 2021, a period during which the prevalence of COVID-19 resulting from antigen tests between July 25 and Sept 30, 2021, a period during which the prevalence of COVID-19 resulting from

Statistical analysis

The primary outcomes were COVID-19-associated hospitalisations and all-cause death within 30 days after testing positive for SARS-CoV-2 infection.
Continuous variables are presented as means with SDs and medians with IQRs; categorical variables are presented as numbers with proportions. A Cox proportional-hazards model was used to estimate the hazard ratios (HRs) of death at 30 days from testing positive for SARS-CoV-2 among vaccinated compared with unvaccinated patients, controlling for covariates that are known risk factors for severe infection: age (as a continuous variable), BMI, race, ethnicity, sex, smoking status, being an active patient in the VHA system in the past 12 months, rurality, and treatment with monoclonal antibodies. Multiple imputation by chained equations was used to impute missing values of BMI using the MICE package in R. When information on race, ethnicity, and smoking status was not available, we reported the data as “unknown”. The proportional-hazards assumption was assessed and verified by testing the correlation between the Schoenfeld residuals and survival time. A log–log plot was generated to show the proportional hazards of the robust, pre-frail, and frail groups (appendix p 9). As the proportional-hazards assumption does not hold for COVID-19-associated hospitalisation (p<0·001), we used logistic regression to estimate the odds ratio (OR) of COVID-19-associated hospitalisation within 30 days from testing positive for SARS-CoV-2, controlling for the same covariates as in the Cox model. Vaccine effectiveness was defined as 1 minus the HR for all-cause death and 1 minus the OR for COVID-19-associated hospitalisation. The 95% CI for vaccine effectiveness was calculated as 1 minus the lower end of the 95% CI of the HR or OR to 1 minus the upper end of the 95% CI of the HR or OR. We stratified the analysis according to frailty status (robust, pre-frail, and frail groups). Vaccine effectiveness was calculated according to frailty status for the two mRNA vaccines (mRNA-1273 and BNT162b2) combined and also separately for each vaccine. Since the date of COVID-19 vaccination was not available for unvaccinated participants, we used the date of testing as the index date for both vaccinated and unvaccinated individuals. The time to event (all-cause death) was calculated from the date of a documented positive SARS-CoV-2 test. As patients with frailty were more likely to be vaccinated earlier based on vaccination policies, we did an additional analysis to de-confound the effects from time of vaccination and frailty status by comparing the OR for COVID-19-associated hospitalisation and HR for all-cause death at 30 days for patients vaccinated less than 4 months, 4–6 months, and more than 6 months before infection with unvaccinated patients, according to frailty status. We created a variable indicating vaccination status and time from vaccination to a positive SARS-CoV-2 test: not vaccinated, less than 4 months from vaccination, 4–6 months from vaccination, and longer than 6 months from vaccination. We report adjusted HRs for all-cause death and adjusted ORs for COVID-19-associated hospitalisation at less than 4 months, 4–6 months, and longer than 6 months from vaccination compared with the unvaccinated patients, adjusting for the covariates. We tested whether an interaction between frailty and age existed by adding an interaction term of frailty status and age (as a binary variable indicting whether a patient is 65 years or older) to the model. We report adjusted ORs for COVID-19-associated hospitalisation and adjusted HRs for death in individuals younger than 65 years and those 65 years or older according to frailty status. We also used the same Cox model and logistic regression model to compare the effectiveness of mRNA-1273 versus BNT162b2, adjusting for the covariates and frailty status. In addition, we calculated ORs and HRs for vaccination stratified by age group (<65 years and ≥65 years) and sex. All the statistical analyses were done with R (version 4.0.5).
Role of the funding resource
The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results
Between July 25 and Sept 30, 2021, 62 213 SARS-CoV-2-positive veterans were identified. 57 784 patients (mean age 57·5 years [SD 16·7], 50 642 [87·6%] males, and 40 743 [70·5%] White people) were included in the analysis (figure). The final cohort consisted of 28 497 (49·3%) patients in the robust group, 16 737 (29·0%) in the pre-frail group, and 12 550 (21·7%) in the frail group. Baseline characteristics of patients according to frailty status are shown in table 1. Patients with frailty were older and more likely to have the common chronic comorbidities diabetes, hypertension, chronic obstructive pulmonary disease, cardiovascular disease, and kidney disease than patients in the robust group. 45 282 (36·1%) of 125 500 patients in the frail group and 12 950 (45·4%) of 28 497 patients in the robust group had asymptomatic COVID-19. Compared with robust patients, those with frailty were more likely to have abdominal pain and dyspnoea as COVID-19-presenting symptoms. Patients in the frail group were more likely to be fully vaccinated (76 103 [60·6%]) than patients in the pre-frail group (64 432 [38·5%]) and robust group (72 234 [25·4%]).

The mean time between the date of vaccination and the date of a positive SARS-CoV-2 test was 4·9 months (SD 1·4) in the robust group, 5·2 months (1·3) in the pre-frail group, and 5·4 months (1·2) in the frail group. The time between the date of vaccination and the date of a positive SARS-CoV-2 test was more than 6 months for 16 395 (22·6%) of 72 234 patients in the robust group, 17 888 (27·8%) of 64 432 patients in the pre-frail group, and 25 644 (33·7%) of 76 103 patients in the frail group (appendix p 3). The number of COVID-19-associated hospitalisations and all-cause deaths in vaccinated and unvaccinated groups by age group and frailty status are shown in the appendix (p 4).

Within 30 days of a positive SARS-CoV-2 test, there were 7 857 COVID-19-associated hospitalisations (2749 [35·0%] in the vaccinated group and 5 108 [65·0%] in the unvaccinated group) and 2 577 all-cause deaths (676 [26·2%] in the vaccinated group and 1 901 [73·8%] in the unvaccinated group; table 2). Vaccination effectiveness against 30-day COVID-19-associated hospitalisation was 51% (95% CI 48·5–53%) and all-cause death was 74% (71·7–76%; table 2). ORs for COVID-19-associated hospitalisation and HRs for all-cause death for all the covariates included in the models are in the appendix (p 5).

When comparing the two mRNA vaccines directly, mRNA-1273 was more effective than BNT162b2 (reference) in protection against 30-day COVID-19-associated hospitalisation (OR 0·71, 95% CI 0·65–0·77), but not significantly different against 30-day all-cause death (HR 0·89, 95% CI 0·77–1·04).

By 30 days after a positive SARS-CoV-2 test, 2 635 (9·2%) of 28 497 (405 vaccinated and 2 230 unvaccinated) patients in the robust group, 2 094 (12·5%) of 16 737 (606 vaccinated and 1 488 unvaccinated) patients in the pre-frail group, and 3 128 (24·9%) of 12 550 (1 738 vaccinated and 1 390 unvaccinated) patients in the frail group had a
COVID-19-related symptoms (Continued from previous page)

| COVID-19-related symptoms | Total (n=57 784) | Robust group (n=28 437) | Pre-frail group (n=16 737) | Frail group (n=12 550) |
|--------------------------|------------------|-------------------------|--------------------------|------------------------|
| Abdominal pain           | 2076 (3·6%)      | 788 (2·8%)              | 587 (3·5%)               | 701 (5·6%)             |
| Chills                   | 8792 (15·2%)     | 4834 (16·9%)            | 2347 (12·8%)             | 1611 (16·4%)           |
| Cough                    | 21 820 (3 78%)   | 10 457 (36·7%)          | 6296 (37·6%)             | 5067 (40·4%)           |
| Diarrhoea                | 8317 (14·4%)     | 3866 (13·6%)            | 2359 (14·1%)             | 2092 (16·7%)           |
| Dyspnoea                 | 12 883 (22·3%)   | 5390 (18·9%)            | 3639 (21·7%)             | 3854 (30·7%)           |
| Fatigue                  | 12 870 (22·3%)   | 6063 (21·3%)            | 3522 (21·0%)             | 3285 (26·2%)           |
| Fever                    | 15 830 (27·4%)   | 7815 (44·9%)            | 4528 (36·1%)             | 7815 (27·4%)           |
| Headache                 | 11 840 (20·5%)   | 6394 (22·4%)            | 3294 (19·7%)             | 2152 (17·1%)           |
| Loss of smell            | 936 (1·6%)       | 468 (1·6%)              | 252 (1·5%)               | 216 (1·7%)             |
| Loss of taste            | 6221 (10·8%)     | 3390 (11·9%)            | 1733 (10·4%)             | 1098 (8·7%)            |
| Myalgia                  | 8681 (15·0%)     | 4769 (16·7%)            | 2334 (13·9%)             | 1578 (12·6%)           |
| Nausea                   | 7622 (13·3%)     | 3662 (12·9%)            | 2123 (12·7%)             | 1887 (15·0%)           |
| Rhinorrhoea              | 6979 (12·1%)     | 3580 (12·6%)            | 1953 (11·7%)             | 1446 (11·5%)           |
| Sore throat              | 7391 (12·8%)     | 3942 (13·8%)            | 2068 (12·4%)             | 1381 (11·0%)           |
| Asymptomatic             | 25 000 (43·3%)   | 12 950 (45·4%)          | 7522 (44·9%)             | 4528 (36·1%)           |

Table 1: Baseline characteristics according to frailty status

COVID-19-associated hospitalisation (table 2). 705 (2·5%; 89 vaccinated and 616 unvaccinated) patients in the robust group, 760 (4·5%; 144 vaccinated and 616 unvaccinated) in the pre-frail group, and 1112 (8·9%; 443 vaccinated and 669 unvaccinated) in the frail group died within 30 days of a positive SARS-CoV-2 test (table 2). Although vaccination provided protection against COVID-19-associated hospitalisation and all-cause death within 30 days after a positive SARS-CoV-2 test for all patients, the protection was lower in the frail group than in the robust and pre-frail groups. By 30 days after a positive SARS-CoV-2 test, vaccination effectiveness against COVID-19-associated hospitalisation was 65% (95% CI 61–69) for the robust group, 54% (48–58) for the pre-frail group, and 36% (30–42) for the frail group, and vaccine effectiveness against all-cause death was 79% (74–84) for the robust group, 79% (75–83) for the pre-frail group, and 68% (63–71) for the frail group. The survival curve shows the lowest probability of survival in the unvaccinated individuals with frailty (appendix p 10). The reduction of vaccine effectiveness for patients with frailty was similar for mRNA-1273 and BNT162b2 vaccines (appendix pp 6–7).

The frail group had lower vaccine effectiveness than the robust and pre-frail groups against COVID-19-associated hospitalisation and all-cause death at 30 days from a positive SARS-CoV-2 test at time intervals from vaccination to a positive SARS-CoV-2 test of less than 4 months, 4–6 months, and longer than 6 months (table 3; appendix p 11).

Discussion

In this study, patients with frailty had the highest rates of vaccination and were more likely to receive a vaccine earlier in the delta variant wave compared with the robust and pre-frail groups. We showed that vaccines were effective against COVID-19-associated hospitalisation and all-cause death in veterans within 30 days of a positive SARS-CoV-2 test. However, and consistent with our hypothesis, vaccine effectiveness varied according to age and frailty status. After adjusting for covariates, vaccine effectiveness against COVID-19-associated hospitalisation and all-cause death at 30 days from testing positive for SARS-CoV-2 was lower in patients who were 65 years or older than in those who were younger than 65 years. Moreover, patients with frailty had lower levels of protection against COVID-19-associated hospitalisation and all-cause death at 30 days after testing positive for SARS-CoV-2 than patients in the robust group. Notably, the reduction in effectiveness in frail, compared with robust, patients was greater in patients younger than 65 years than in those who were 65 years or older. Our results add to the evidence that although frailty is often associated with old age, it is a distinct condition that also occurs in younger individuals. These results suggest that frailty should be an important consideration in the design, development, and testing of efficacy and safety of vaccines.

Consistent with other studies, COVID-19 vaccine effectiveness against hospitalisation and death after SARS-CoV-2 infection was lower in older adults.11 Although overall vaccine effectiveness was high in this
population of veterans, results showed a lower response in the frail group, consistent with our hypothesis. To our knowledge, this study represents the first report of an association of frailty with a decline in COVID-19 vaccine effectiveness against hospitalisation and all-cause death regardless of age in patients who have previously tested positive for SARS-CoV-2. The decline in effectiveness does not appear to be related to earlier time of vaccination in older patients with frailty—who are more likely to be vaccinated overall—because the reduction was persistent when the cohort was divided into defined vaccination periods before infection. The estimated CIs were wide, so our study was not powered to evaluate vaccine waning with frailty, combined with the observation that people so our study was not powered to evaluate vaccine waning with frailty, combined with the observation that people

| Table 2: Vaccination effectiveness against COVID-19-associated hospitalisation and all-cause death within 30 days after a positive SARS-CoV-2 test according to frailty status |
|-----------------------------------------------|
| **COVID-19-associated hospitalisation** |
| **Unvaccinated** | **Vaccinated** |
| Events | Adjusted OR* or HR* (95% CI) | Vaccine effectiveness (95% CI) | Events | Adjusted OR* or HR* (95% CI) | Vaccine effectiveness (95% CI) |
| Unvaccinated | 5108 (14.0%) | 1 (ref) | 1 (ref) | 2220 (19.5%) | 1 (ref) | 1 (ref) |
| Vaccinated | 2749 (12.9%) | 0.47 (0.42-0.52) | 65% (61-69) | 606 (9.4%) | 0.42 (0.42-0.52) | 54% (48-58) |
| **All-cause death** |
| **Unvaccinated** | **Vaccinated** |
| Events | Adjusted OR* or HR* (95% CI) | Vaccine effectiveness (95% CI) | Events | Adjusted OR* or HR* (95% CI) | Vaccine effectiveness (95% CI) |
| Unvaccinated | 1901 (14.0%) | 1 (ref) | 1 (ref) | 1616 (13.5%) | 1 (ref) | 1 (ref) |
| Vaccinated | 676 (3.2%) | 0.42 (0.37-0.49) | 58% (51-63) | 89 (1.2%) | 0.42 (0.16-0.26) | 79% (74-84) |

HR=hazard ratio. OR=odds ratio. *Adjusted for age, BMI, race, ethnicity, sex, smoking status, being an active patient in the Veterans Health Administration system in the past 12 months, rurality, and monoclonal antibody treatment.

| Table 3: Vaccination effectiveness against COVID-19-associated hospitalisation and all-cause death within 30 days after a positive SARS-CoV-2 test according to frailty status and time from vaccination to a positive SARS-CoV-2 test |
|-----------------------------------------------|
| **COVID-19-associated hospitalisation** |
| **<4 months from vaccination to a positive SARS-CoV-2 test** |
| **Robust group** | **Pre-frail group** | **Frail group** |
| Adjusted OR* or HR* (95% CI) | Vaccine effectiveness (95% CI) | Adjusted OR* or HR* (95% CI) | Vaccine effectiveness (95% CI) | Adjusted OR* or HR* (95% CI) | Vaccine effectiveness (95% CI) |
| Unvaccinated patients | 1 (ref) | 1 (ref) | 1 (ref) | 1 (ref) | 1 (ref) |
| Vaccinated patients | OR 0.35 (0.27-0.44) | 65% (54-73) | OR 0.56 (0.45-0.70) | 64% (43-91) | OR 0.70 (0.59-0.83) | 30% (17-41) |
| **4-6 months from vaccination to a positive SARS-CoV-2 test** |
| Unvaccinated patients | 1 (ref) | 1 (ref) | 1 (ref) | 1 (ref) | 1 (ref) |
| Vaccinated patients | OR 0.35 (0.30-0.41) | 65% (59-70) | OR 0.42 (0.37-0.49) | 58% (51-63) | OR 0.58 (0.53-0.64) | 42% (36-47) |
| **All-cause death** |
| **<4 months from vaccination to a positive SARS-CoV-2 test** |
| Unvaccinated patients | 1 (ref) | 1 (ref) | 1 (ref) | 1 (ref) | 1 (ref) |
| Vaccinated patients | HR 0.29 (0.10-0.35) | 81% (65-90) | HR 0.25 (0.16-0.41) | 75% (59-84) | HR 0.37 (0.27-0.50) | 63% (50-73) |
| **4-6 months from vaccination to a positive SARS-CoV-2 test** |
| Unvaccinated patients | 1 (ref) | 1 (ref) | 1 (ref) | 1 (ref) | 1 (ref) |
| Vaccinated patients | HR 0.19 (0.14-0.26) | 81% (74-86) | HR 0.19 (0.15-0.25) | 81% (75-85) | HR 0.29 (0.25-0.34) | 71% (66-75) |

HR=hazard ratio. OR=odds ratio. *Adjusted for age, BMI, race, ethnicity, sex, smoking status, being an active patient in the Veterans Health Administration system in the past 12 months, rurality, and monoclonal antibody treatment.
with frailty are at high risk of poor outcomes, highlight the importance of considering frailty in vaccine design, evaluation, and programme implementation. Potential approaches to optimally tailor vaccine product design to better stimulate immune responses in older and frailer people could include increasing the dose of antigen, optimising use of adjuvants, or using recombinant antigens. All of these approaches have been used in influenza vaccines. For example, when the immunogenicity (antibody titres) of a high-dose influenza vaccine was measured as part of a clinical trial, the effects of frailty were not apparent, indicating dose as one avenue to mitigate the impact of frailty on vaccine responses. Indeed, consistent with a previous study in a veteran population, the mRNA-1273 vaccine, which has a higher active ingredient, was more effective than the BNT162b2 vaccine in protection against COVID-19-associated hospitalisation. The findings of reduced vaccine protection in patients with frailty underscore the need to optimise vaccine effectiveness for these patients and provide support for considering frailty in COVID-19 vaccine development. Future studies that incorporate measurements of humoral and cellular responses to vaccination in individuals according to frailty status might provide additional insights into the mechanisms of frailty and its effects on vaccination. Prospective cohort studies and randomised controlled trials of COVID-19 vaccines that include baseline assessments of frailty status as risk stratification might clarify the role of frailty in protection against death in older adults.

The data on sex differences in immune responses to viral vaccines are mixed. Our study showed that COVID-19 vaccine effectiveness was higher in females than males. However, these results should be interpreted with caution due to the lower numbers of female participants included in the analyses. Future studies that include a large number of female participants should explore whether the reduction of vaccine effectiveness associated with frailty differs according to sex.

Strengths of our study are the use of a large-scale, national dataset from a large, integrated health-care system with individual-level demographic and clinical data; inclusion of patients who tested positive for SARS-CoV-2 during the specified period; accurate documentation of vaccine type and date, thereby avoiding the potential confounding from US epidemic phases; and determination of frailty status using a validated model predictive of death in US veterans. Even so, the retrospective cohort study design introduces important limitations. Although the deaths within 30 days after a positive SARS-CoV-2 test are probably mostly related to COVID-19, a small number of deaths not related to COVID-19 might have been included because we did not have a detailed record of the cause of death. Veterans are sometimes admitted to hospitals outside the VHA, which might have led to an underestimation of COVID-19-associated hospitalisations. Despite this limitation, the estimated ORs for vaccinated versus unvaccinated patients should not be affected assuming that vaccination status has no effect on whether a patient was admitted to a hospital outside the VHA. We did not consider other factors associated with poor outcomes, such as social determinants of health, symptom duration, and the way that illness might appear in older adults with frailty. Older adults with frailty and COVID-19 might present atypically, thereby delaying diagnosis, which could potentially lead to more deaths despite vaccination. Social isolation due to strict physical distancing might have further amplified the problem by reducing contact with relatives and health-care providers who could identify changes in condition. Failing to recognise these symptoms might delay or even preclude testing, potentially underestimating vaccine effectiveness due to an incorrect estimation of the timing of death in relation to the vaccination date or failing to identify the patient’s death as occurring in the setting of COVID-19. Our study did not consider the effects of concomitant non-invasive or invasive interventions that, in addition to vaccination, might have improved individuals’ survival. Resource allocation issues and more proactive advance care planning might result in the withholding of potentially beneficial treatments for older adults.

Table 4: Vaccine effectiveness against COVID-19-associated hospitalisation and all-cause death according to frailty status and age group (younger than 65 and 65 years or older)

| Frailty status and age group | Unvaccinated | Vaccinated | Unvaccinated | Vaccinated |
|-----------------------------|--------------|------------|--------------|------------|
| Hospitalisation             | Adjusted OR* (95% CI) | Vaccine effectiveness (95% CI) | Adjusted OR* (95% CI) | Vaccine effectiveness (95% CI) |
| Age <65 years               | 1 (ref) | 1 (ref) | 1 (ref) | 1 (ref) |
| Unvaccinated patients       | 1 (ref) | 1 (ref) | 1 (ref) | 1 (ref) |
| Vaccinated patients         | 0.40 (0.36-0.44) | 0.60 (0.56-0.64) | 0.17 (0.12-0.24) | 0.83 (0.76-0.88) |
| Age ≥65 years                | 1 (ref) | 1 (ref) | 1 (ref) | 1 (ref) |
| Unvaccinated patients       | 1 (ref) | 1 (ref) | 1 (ref) | 1 (ref) |
| Vaccinated patients         | 0.56 (0.52-0.60) | 0.44 (0.40-0.48) | 0.31 (0.28-0.34) | 0.69 (0.66-0.72) |
| Robust and age <65 years    | 1 (ref) | 1 (ref) | 1 (ref) | 1 (ref) |
| Unvaccinated patients       | 0.27 (0.22-0.32) | 0.73 (0.68-0.78) | 0.10 (0.05-0.20) | 0.90 (0.80-0.95) |
| Vaccinated patients         | 0.64 (0.54-0.77) | 0.36 (0.23-0.46) | 0.30 (0.19-0.47) | 0.70 (0.53-0.81) |
| Frail and age <65 years     | 1 (ref) | 1 (ref) | 1 (ref) | 1 (ref) |
| Unvaccinated patients       | 0.46 (0.39-0.54) | 0.54 (0.46-0.61) | 0.23 (0.18-0.30) | 0.77 (0.70-0.82) |
| Vaccinated patients         | 0.64 (0.58-0.70) | 0.36 (0.30-0.42) | 0.32 (0.29-0.37) | 0.68 (0.63-0.73) |
| Robust and age ≥65 years    | 1 (ref) | 1 (ref) | 1 (ref) | 1 (ref) |
| Unvaccinated patients       | 0.64 (0.58-0.70) | 0.36 (0.30-0.42) | 0.32 (0.29-0.37) | 0.68 (0.63-0.73) |

HR=hazard ratio. OR=odds ratio. *Adjusted for age, BMI, race, ethnicity, sex, smoking status, being an active patient in the Veterans Health Administration system in the past 12 months, rurality, and monoclonal antibody treatment.
adults with frailty. The predominantly male population in this study might reduce the generalisability of our findings to women, who are often more frail than men. By contrast, the findings of beneficial effects of vaccination on death are remarkable considering that men are more likely to die from COVID-19.

The clinical implications of our study are that, in addition to age and other factors, we need to consider frailty when evaluating COVID-19 vaccines. If confirmed in future studies, the importance of frailty could have far-reaching implications for COVID-19 vaccine development and evaluation. COVID-19 vaccination represents a key therapeutic strategy for patients with frailty because COVID-19 is associated with higher morbidity and death in this population. As with other vaccines, a wide range of interventions could improve COVID-19 vaccine effectiveness in older and frail adults, including higher dosing, use of adjuvants or recombinant antigens, and earlier and more frequent administration of boosters. The VHA began administering booster shots in late September, 2021. Because our cohort included patients who tested positive between July 25 and Sept 30, 2021, the number of patients who got the booster shot before testing positive for SARS-CoV-2 was exceedingly small.

Future studies should also investigate vaccine reactogenicity and safety in older adults with frailty. Few studies suggest that older patients with frailty might develop more adverse events associated with vaccination, although it is unclear whether these reactions are due to vaccination or to frailty. However, it must be emphasised that if individuals with frailty are excluded from vaccine trials, and if frailty is not explicitly considered in study cohorts, opportunities to identify potential vaccine innovations and to tailor products to generate optimal responses in the context of frailty and older age will be missed. Although the frailty index used in this study was developed in the context of the VHA system, in general when frailty indices conform to prescribed criteria their properties are consistent across settings. Investigators can operationalise frailty using VA-FI variables—ICD 10 and Current Procedural Terminology codes—which are readily available from electronic health records and administrative databases at most health-care institutions worldwide.

Studies comparing the classification and degree of frailty using different scales have shown that although the results are often consistent, there might be variability depending on the emphasis of the scale, so investigation of other commonly used frailty measures in relation to COVID-19 vaccine effectiveness is warranted. In summary, our study shows that although COVID-19 vaccines are effective against hospitalisation and all-cause death after SARS-CoV-2 infection, the effectiveness is lower in patients with frailty. Future observational and experimental studies investigating COVID-19 vaccine effectiveness should incorporate frailty assessments and actively recruit older adults with frailty.

Contributors
FT, ISH, and JGR contributed to the design of the study. FT extracted the data and did the statistical analysis. FT, ISH, and JGR had full access to and verified the data in the study. JGR and FT wrote the first draft. MKA and ISH critically reviewed and edited the manuscript and did the literature search. All authors had full access to the data and accept responsibility for the decision to submit for publication.

Declaration of interests
JGR holds a grant from Longeveron and received consulting fees from Pfizer. MKA reports grants from the Canadian Frailty Network, Canadian Institutes of Health Research, Public Health Agency of Canada, Sanofi, Pfizer, Merck, and GlaxoSmithKline, and payments from Pfizer, Sanofi, and Seqirus outside the submitted work. All other authors declare no competing interests.

Data sharing
Data were obtained from the COVID-19 Shared Data Resource maintained by the Department of Veterans Affairs Informatics and Computing Infrastructure (VINCI). The data are available to approved individuals upon request to VINCI after fulfilling specified requirements.

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References
1. Pujis BG, Jolani S, Atherley A, et al. Demographic risk factors for COVID-19 infection, severity, ICU admission and death: a meta-analysis of 59 studies. BMJ Open 2021; 11: e044640.
2. Del Rio C, Malani PN, Omer SB. Confronting the delta variant of SARS-CoV-2, summer 2021. JAMA 2021; 326: 1001–02.
3. Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on covid-19 related symptoms, hospital admissions, and mortality in older adults in England: test negative case-control study. BMJ 2021; 373: n1088.
4. Chemaitelly H, Tang P, Hasan MR, et al. Waning of BNT162b2 vaccine protection against SARS-CoV-2 infection in Qatar. N Engl J Med 2021; 385: e83.
5. Soiza RL, Scicluna C, Thomson EC. Efficacy and safety of COVID-19 vaccines in older people. Age Aging 2021; 50: 279–83.
6. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001; 56: M146–56.
7. Walston J, Hadley EC, Ferrucci L, et al. Research agenda for frailty in older adults: toward a better understanding of physiology and etiology: summary from the American Geriatrics Society/National Institute on Aging Research Conference on Frailty in Older Adults. J Am Geriatr Soc 2006; 54: 991–1001.
8. Morley JE, Vellas B, van Kan GA, et al. Frailty consensus: a call to action. J Am Med Dir Assoc 2013; 14: 392–97.
9. Collettion J, Martin-Ruiz C, Davies K, et al. Frailty and the role of inflammation, immunosenescence and cellular ageing in the very old: cross-sectional findings from the Newcastle 85+ Study. Mech Ageing Dev 2012; 133: 456–66.
10. Pulop T, Larbi A, Dupuis G, et al. Immunosenescence and inflamm-aging as two sides of the same coin: friends or foes? Front Immunol 2018; 8: 1960.
11. Andrew MK, McElhaney JE. Age and frailty in COVID-19 vaccine development. Lancet 2021; 396: 1942–44.
12. Andrew MK, Shinde V, Ye L, et al. The importance of frailty in the assessment of influenza vaccine effectiveness against influenza-related hospitalization in elderly people. J Infect Dis 2017; 215: 405–14.
13. Andrew MK, Schmader KE, Rockwood K, Clarke B, McElhaney JE. Considering frailty in SARS-CoV-2 vaccine development: how geriatricians can assist. Clin Interv Aging 2021; 16: 731–38.
14 Agha Z, Lofgren RP, VanRuiswyk JV, Layde PM. Are patients at Veterans Affairs medical centers sicker? A comparative analysis of health status and medical resource use. Arch Intern Med 2000; 160: 3252–57.
15 Colhn BA, Cirillo PM, Murphy CC, Krighbaum NY, Wallace AWJS. SARS-CoV-2 vaccine protection and deaths among US veterans during 2021. Science 2022; 375: 131–16.
16 Orkaby AR, Nussbaum L, Ho YL, et al. The burden of frailty among US veterans and its association with mortality, 2002–2012. J Gerontol A Biol Sci Med Sci 2019; 74: 1257–64.
17 Ioannou GN, Locke E, Green P, et al. Risk factors for hospitalization, mechanical ventilation, or death among 10131 US veterans with SARS-CoV-2 infection. JAMA Netw Open 2020; 3: e2022310.
18 Dickerman BA, Gerlovin H, Madenci AL, et al. Comparative effectiveness of BNT162b2 and mRNA-1273 vaccines in US veterans. N Engl J Med 2022; 386: 105–15.
19 Centers for Disease Control and Prevention. COVID Data Tracker. Variant proportions. https://covid.cdc.gov/covid-data-tracker/#variant-proportions (accessed Nov 10, 2021).
20 Sohn MW, Arnold N, Maynard C, Hynes DM. Accuracy and completeness of mortality data in the Department of Veterans Affairs. Popul Health Metr 2006; 4: 2.
21 Rockwood K, Mitnitski A. Frailty in relation to the accumulation of deficits. J Gerontol A Biol Sci Med Sci 2007; 62: 722–27.
22 Walston J, Bandeen-Roche K, Buta B, et al. Moving frailty toward clinical practice: NIA Intramural Frailty Science Symposium summary. J Am Geriatr Soc 2019; 67: 1559–64.
23 Cheng D, DuMontier C, Yildirim C, et al. Updating and validating the US Veterans Affairs Frailty Index: transitioning from ICD-9 to ICD-10. J Gerontol A Biol Sci Med Sci 2021; 76: 1318–25.
24 Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K. A standard procedure for creating a frailty index. BMC Geriatr 2008; 8: 24.
25 Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med 2020; 383: 2603–15.
26 Andrew MK, Bowles SK, Pawelec G, et al. Influenza vaccination in older adults: recent innovations and practical applications. Drug Aging 2019; 36: 29–37.
27 DiazGranados CA, Dunning AJ, Robertson CA, Talbot HK, Landolfi V, Greenberg DP. Efficacy and immunogenicity of high-dose influenza vaccine in older adults by age, comorbidities, and frailty. Vaccine 2015; 33: 4565–71.
28 Klein SL, Jedlicka A, Pekosz A. The Xs and Y of immune responses to viral vaccines. Lancet Infect Dis 2010; 10: 338–49.
29 Hynes DM, Koelling K, Stouppe K, et al. Veterans’ access to and use of Medicare and Veterans Affairs health care. Med Care 2007; 45: 214–23.
30 Gan JM, Kho J, Akhunbay-Fudge M, et al. Atypical presentation of COVID-19 in hospitalised older adults. J Med Sci 2021; 190: 469–74.
31 Maves RC, Downar J, Dichter JR, et al. Triage of scarce critical care resources in COVID-19. An implementation guide for regional allocation: an Expert Panel Report of the Task Force for Mass Critical Care and the American College of Chest Physicians. Chest 2020; 158: 212–25.
32 Izda V, Jeffries MA, Sawalha AH. COVID-19: a review of therapeutic strategies and vaccine candidates. Clin Immunol 2021; 222: 108634.
33 Torjesen I. Covid-19: Norway investigates 23 deaths in frail elderly patients after vaccination. BMJ 2021; 372: n449.
34 Mitnitski A, Song X, Skoog I, et al. Relative fitness and frailty of elderly men and women in developed countries and their relationship with mortality. J Am Geriatr Soc 2005; 53: 2184–89.
35 Rockwood K, Andrew M, Mitnitski A. A comparison of two approaches to measuring frailty in elderly people. J Gerontol A Biol Sci Med Sci 2007; 62: 738–43.