RESEARCH PAPER

Preparing for future pandemics: frailty associates with mortality in hospitalised older people during the entire COVID-19 pandemic, a Dutch multicentre cohort study

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Key summary points

Aim   We aim to investigate how associations of frailty with in-hospital mortality changed throughout the pandemic in older people hospitalised for COVID-19.

Findings   Older hospitalised COVID-19 patients with frailty had a higher in-hospital mortality risk over the entire course of the pandemic. Older hospitalised COVID-19 patients had a lower in-hospital mortality risk in each subsequent wave, which reflects the effects of improved prevention and treatment options.

Message   Frailty is a relevant risk factor in all stages of a pandemic, which indicates that frailty is important to consider in prevention and treatment guidelines for future pandemics.

Abstract

Purpose   Viral mutations and improved prevention or treatment options may have changed the association of frailty with mortality throughout the COVID-19 pandemic. We investigated how associations of frailty with in-hospital mortality changed throughout the pandemic in older people hospitalised for COVID-19.

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Methods The COVID-OLD study included COVID-19 patients aged ≥ 70 years hospitalised during the first (early 2020), second (late 2020), third (late 2021) or fourth wave (early 2022). Based on the clinical frailty scale, patients were categorised as fit (1–3), pre-frail (4–5) or frail (6–9). Associations of frailty with in-hospital mortality were assessed with pairwise comparisons with fit as reference category and modelled using binary logistic regression adjusted for age and sex.

Results This study included 2362 patients (mean age 79.7 years, 60% men). In the first wave, in-hospital mortality was 46% in patients with frailty and 27% in fit patients. In-hospital mortality decreased in each subsequent wave to 25% in patients with frailty and 11% in fit patients in the fourth wave. After adjustments, an overall higher risk of in-hospital mortality was found in frail (OR 2.26, 95% CI: 1.66–3.07) and pre-frail (OR 1.73, 95% CI: 1.27–2.35) patients compared to fit patients, which did not change over time (p for interaction = 0.74).

Conclusions Frailty remained associated with a higher risk of in-hospital mortality throughout the entire COVID-19 pandemic, although overall in-hospital mortality rates decreased. Frailty therefore remains a relevant risk factor in all stages of a pandemic and is important to consider in prevention and treatment guidelines for future pandemics.

Keywords Frailty · COVID-19 · In-hospital mortality

Abbreviations

IL-6	Interleukin-6
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
PCR	Polymerase chain reaction
CCI	Charlson comorbidity index
SD	Standard deviation
IQR	Interquartile range
CRP	C-reactive protein

Introduction

During the first two years of the pandemic, approximately one-third of patients hospitalised for COVID-19 in the Netherlands was aged 70 years or older, while they only make up one-seventh of the population [1]. The high rate of hospitalisations placed a high burden on the healthcare systems with a significant pressure on hospital bed occupancy. Older age and frailty were risk factors for severe infection and mortality, both contributing to the large proportion of older people in the number of hospitalisations [2, 3]. Frailty is characterised by decreased physiological reserve and increased biological vulnerability to internal and external stressors [4]. It is currently unknown if the occurrence of viral mutations, improved diagnosis and treatment options and the introduction of vaccinations altered the association of frailty with in-hospital mortality over the course of the pandemic.

Since the start of the COVID-19 pandemic, different government policies were introduced in the Netherlands to prevent and reduce the spread of infection, improved diagnostics, treatment options and vaccinations became available and different viral variants arose. Policies regarding protection of public health introduced by the Dutch government included the vaccination program, a lockdown with limitation of contact moments, obligation to wear a facemask in public places and a variety of hygienic rules. The Dutch

vaccination program for COVID-19 started in January 2021 with initial priority for older people due to limited initial supply. In addition to vaccinations, important new treatment options incorporated in treatment guidelines were dexamethasone and interleukin 6 (IL-6) inhibitors. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mutated rapidly since the start of the pandemic which led to different viral variants [5, 6]. Viral mutagenesis increases efficiency of viral transmission, cell tropism and evasion of recognition by the immune system, all which enhance pathogenicity [7]. It is currently unknown to what extent all these factors affected the association of frailty with in-hospital mortality and disease severity of older people hospitalised for COVID-19 over the course of the pandemic. Understanding these associations may provide insights in the benefits of prevention, timely hospitalisation and treatment in frail older people, which is relevant for guidelines in future pandemics.

Therefore, we aim to investigate how associations of frailty with in-hospital mortality in hospitalised older people changed over the course of the COVID-19 pandemic.

Methods

Study design

The COVID-OLD study [8, 9], a retrospective multicentre cohort study, included older people hospitalised for COVID-19 during one of the four pandemic waves between February 2020 and April 2022 in the Netherlands. The 19 participating hospitals are listed in Appendix 1 and the number of inclusions per hospital for each pandemic wave are shown in Appendix 2. The necessity for formal approval of the study was waived by each local medical ethics committee, as data collection followed routine clinical practice. This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

The COVID-19 pandemic in the Netherlands

We identified four pandemic waves based on peaks in hospital admission rates of patients aged 70 years and older, viral variants and important treatment implementations (Fig. 1). Occurrence of SARS-CoV-2 variants was evaluated by the National Institute for Public Health and the Environment Ministry of Health (Rijksinstituut over Volksgezondheid en Milieu, RIVM), in the Netherlands [1]. The waves were: first (February 27–May 15, 2020 [wild-type/Wuhan variant-dominant]), second (September 1–December 31, 2020 [Alpha variant-dominant]), third (September 1–December 31, 2021 [Delta variant-dominant]) and fourth (February 1–April 30, 2022 [Omicron variant-dominant]).

Each of the participating hospitals had a specific treatment protocol for COVID-19 of which most followed the treatment recommendations from the national guideline of the Dutch Working Party on Antibiotic Policy (Stichting Workgroups AntibioticaBeleid, SWAB). These recommendations changed over time as evidence changed and new treatment options emerged. The Dutch vaccination program for COVID-19 started on 6 January 2021, shortly after the end of the second wave and well before the start of the third wave. In other words, all patients included in this study had the opportunity of being vaccinated in the third and fourth wave. The vaccination coverage of the first series of COVID-19 vaccinations in people aged 70 years and older ranged from 92 to 93% in the Netherlands [10].

Patient population

Patients aged 70 years and older were eligible for inclusion if they were admitted during one of the four defined waves and were not transferred from another hospital, because transferred patients had incomplete data. Patients with another primary diagnosis than COVID-19 at the time of admission, defined as a polymerase chain reaction (PCR) test conducted > 1 day after admission, were excluded, because they possibly lacked a COVID-19-related indication for hospitalisation. In addition, patients discharged to another hospital and patients in whom both a trained researcher and geriatrician could not retrospectively determine the frailty status were excluded because their data were incomplete. Diagnosis of COVID-19 was confirmed with a positive PCR test result from a nasal or oropharyngeal swab in all patients except for patients in the first wave when PCR was not always rapidly available. The included patients in the first wave without a positive PCR test result were diagnosed
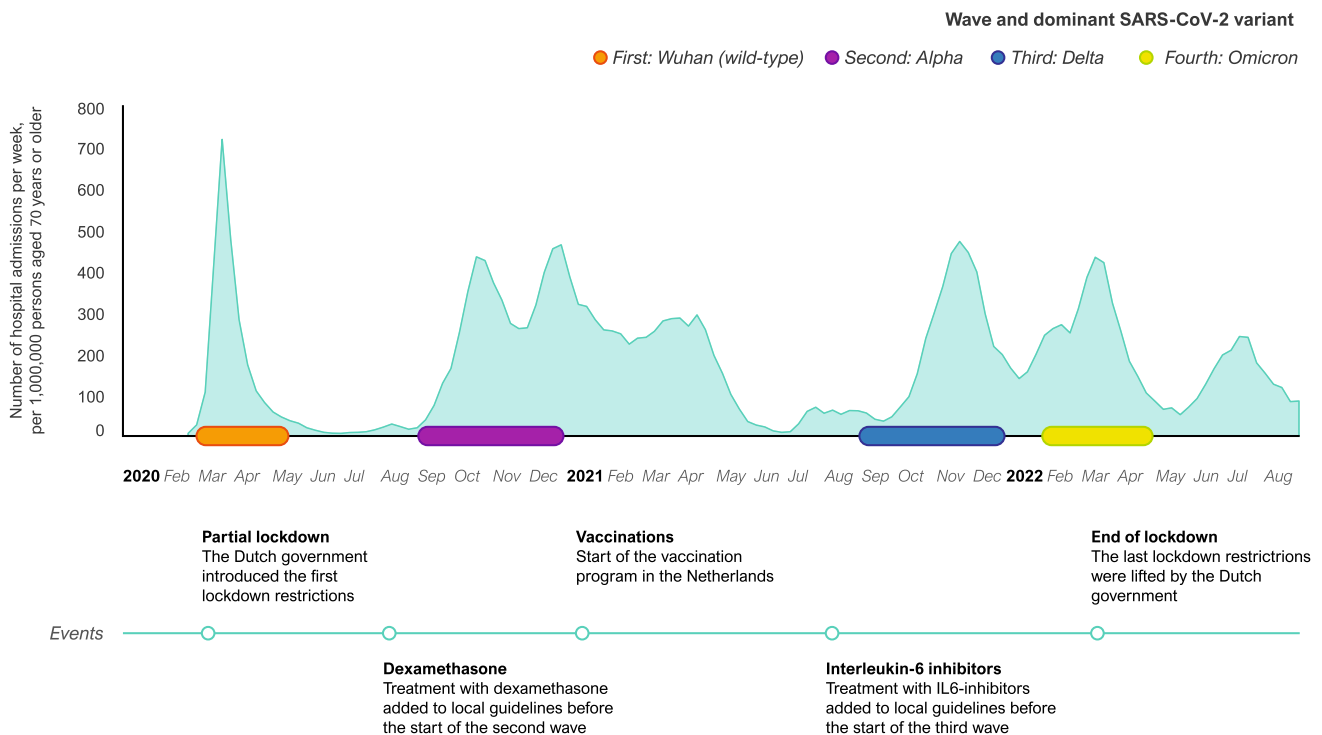

Fig. 1 Timeline of hospital admissions for COVID-19 of older people (70 years and older) in the Netherlands in relation to inclusions of the COVID-OLD study and important events

based on symptoms, radiological abnormalities and laboratory findings.

Data collection

Demographics, patient and clinical characteristics and outcomes of hospital treatment were collected from electronic medical records. Clinical characteristics included vital signs and laboratory findings on the day of admission as indicators of disease severity. In-hospital mortality was defined as patients who were deceased during admission or discharged to a hospice. Comorbidity was assessed with the Charlson Comorbidity Index (CCI) [11]. Frailty was assessed with the use of the clinical frailty scale (CFS) and patients were categorised in three groups: fit (CFS 1–3), pre-frail (CFS 4–5) or frail (CFS 6–9) [12].

The CFS was recorded during the first day of admission in hospitals that routinely collect frailty according to local guidelines. Otherwise, the CFS was recorded retrospectively by trained researchers based on available data in medical records. Retrospective assessment of CFS has been clinically validated in multiple studies [13, 14]. The researchers were trained by geriatricians and consultations were held in case of ambiguities. The classification of CFS was considered missing if both the researcher and geriatrician were unable to assess frailty.

Statistical analysis

Continuous data are presented with mean and standard deviation (SD) or with median and interquartile range (IQR) depending on the normality of distribution. Categorical data are presented with absolute values and percentages. The associations of frailty with in-hospital mortality and disease severity were analysed for each different wave with pairwise comparisons with a fit classification as reference category to a pre-frail or frail classification. Differences of patient characteristics based on frailty were analysed with an identical method. These pairwise comparisons were performed with an independent t test or Mann–Whitney U test for continuous data depending on the normality of distribution. Categorical data were analysed with a chi-square test or Fisher's exact test depending on the number of expected counts. To explore whether missingness of CFS was random or specific to a given subgroup of older people, we compared baseline characteristics of patients with a recorded CFS to patients with CFS missing. To evaluate whether associations with frailty and indicators of disease severity and outcomes changed over time, linear and binary logistic regressions were performed with an interaction term between CFS and

wave (acting as a time variable). All regression models were corrected for age and sex.

The reported p values are two-sided and values less than 0.05 were considered statistically significant. Statistical analyses were performed with IBM SPSS Statistics, version 25.

Results

In total, 3682 patients hospitalised for COVID-19 met the inclusion criteria (Fig. 2). We excluded 417 (11%) patients who acquired COVID-19 after admission, 198 (5%) patients discharged to another hospital and 705 (19%) patients with a missing frailty status. The remaining 2362 (64%) patients were included in the statistical analyses. A comparison of baseline characteristics between patients with a recorded frailty status that were included in this study and patients with a missing frailty status that were excluded is provided in Appendix 3. Overall, there were no relevant differences between patients with a recorded frailty status and a missing frailty status.

Baseline characteristics stratified by pandemic wave are listed in Table 1. The median age of patients was 79 (IQR 75–84) years and 60% were men. The mean BMI was 26.9 (SD 5.0) kg/m^2 and 90% of patients lived independently before admission. The median CCI was 2 (IQR 1–3) points and 28% of patients had a history of lung disease. In the first wave, 519 (45%) patients were classified as fit (CFS 1–3), 304 (26%) patients as pre-frail and 331 (29%) patients as frail (CFS 6–9). The percentage of frail patients was higher in the fourth wave (41%) and the percentage of pre-frail patients was higher in the third (34%) and fourth wave (33%) ($p < 0.001$).

In the first pandemic wave, in-hospital mortality was 46% in patients with frailty and 27% in fit patients. In-hospital mortality decreased in each subsequent wave to 25% in patients with frailty and 11% in fit patients in the fourth wave (Fig. 3). Compared to fit patients, patients with frailty had a higher risk of in-hospital mortality in the first (46% vs. 27%, $p < 0.001$), second (36% vs. 18%, $p < 0.001$), third (30% vs. 16%, $p < 0.05$) and fourth (25% vs. 11%, $p > 0.05$) wave.

Overall, after correction for age and sex, a higher risk of in-hospital mortality was found in frail (OR 2.26, 95% CI: 1.66–3.07) and pre-frail (OR 1.73, 95% CI: 1.27–2.35) patients, compared to fit patients (Fig. 4). The association of frailty with in-hospital mortality did not change over time (p for interaction = 0.74). Patients had a lower risk of in-hospital mortality in the second (OR 0.59, 95% CI: 0.42–0.84), third (OR 0.51, 95% CI: 0.30–0.88) and fourth (OR 0.32, 95% CI: 0.12–0.83) wave, compared to patients in the first

Fig. 2 Flowchart of the COVID-OLD study. Number of participating hospitals in the different waves: 19 first wave, 10 second wave, 5 third wave and 4 fourth wave
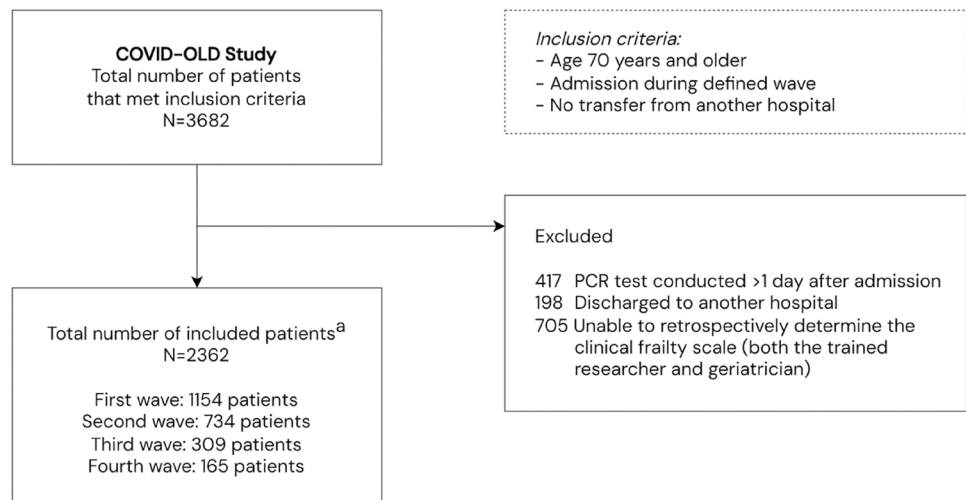
COVID–OLD Study
Total number of patients that met inclusion criteria N=3682

Inclusion criteria:
– Age 70 years and older
– Admission during defined wave
– No transfer from another hospital

Total number of included patients[a]
N=2362

First wave: 1154 patients
Second wave: 734 patients
Third wave: 309 patients
Fourth wave: 165 patients

Excluded

417 PCR test conducted >1 day after admission
198 Discharged to another hospital
705 Unable to retrospectively determine the clinical frailty scale (both the trained researcher and geriatrician)

Table 1 Baseline characteristics of all patients and patients stratified by COVID-19 wave

Characteristic	All patients (N = 2362)	Wave			
		First (N = 1154)	Second (N = 734)	Third (N = 309)	Fourth (N = 165)
Age, years	79 [75–84]	79 [74–84]	80 [75–85]	79 [74–85]	79 [75–84]
Sex, men	1421 (60)	689 (60)	446 (61)	194 (63)	92 (56)
BMI, kg/m^2	26.9 ± 5.0	27.2 ± 4.7	26.8 ± 5.1	26.7 ± 5.4	26.1 ± 5.3
Living situation					
Home	2075 (90)	1008 (90)	641 (88)	278 (92)	148 (93)
Nursing home	220 (10)	103 (9)	84 (12)	23 (8)	10 (6)
Other	24 (1)	15 (1)	7 (1)	0 (0)	2 (1)
Vaccinated*	290 (77)	NA	NA	212 (79)	78 (74)
Clinical frailty scale					
Fit, 1–3	986 (42)	519 (45)	313 (43)	110 (36)	44 (27)
Pre-frail, 4–5	660 (28)	304 (26)	196 (27)	106 (34)	54 (33)
Frail, 6–9	716 (30)	331 (29)	225 (31)	93 (30)	67 (41)
Comorbidities					
CCI, total score (0–33)	2 [1–3]	2 [0–3]	2 [1–3]	2 [1–3]	2 [1–3]
Lung disease	661 (28)	297 (26)	211 (29)	96 (31)	57 (35)
Diabetes with medication	727 (31)	360 (31)	231 (32)	93 (30)	43 (26)
Hypertension	1297 (55)	645 (56)	390 (53)	184 (60)	78 (47)
Myocardial infarction	409 (17)	197 (17)	131 (18)	59 (19)	22 (13)
Dementia	220 (9)	111 (10)	81 (11)	21 (7)	7 (4)
Smoking status					
Never	742 (43)	348 (43)	201 (39)	120 (49)	73 (49)
Former	815 (48)	379 (47)	283 (55)	101 (41)	52 (35)
Active	159 (9)	77 (10)	31 (6)	26 (11)	25 (17)

Data are mean ± SD, median [IQR] or n (%). Lung disease includes asthma, chronic obstructive pulmonary disease, interstitial lung disease and lung cancer. Number of missing values: All patients: 2 sex, 440 BMI, 43 living situation, 99 vaccinated, 383 CC, 3 diabetes with medication, 2 myocardial infarction, 2 dementia, 646 smoking status. First wave: 2 sex, 246 BMI, 28 living situation, 180 CCI, 3 diabetes with medication, 2 myocardial infarction, 2 dementia, 350 smoking status. Second wave: 125 BMI, 2 living situation, 117 CCI, 219 smoking status. Third wave: 60 BMI, 8 living situation, 40 vaccinated, 60 CCI, 62 smoking status. Fourth wave: 9 BMI, 5 living situation, 59 vaccinated, 26 CCI, 15 smoking status

BMI body mass index, *CCI* charlson comorbidity index, *NA* not applicable

*Vaccinated is defined as a patient who self-reportedly received at least one dose of a COVID-19 vaccine prior to admission (vaccinations were introduced after the second wave)
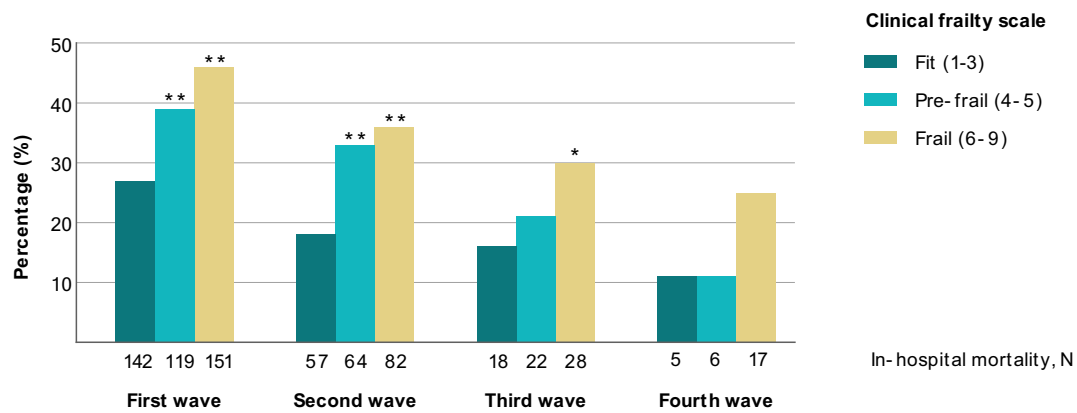
Fig. 3 The association of frailty with in-hospital mortality stratified by COVID-19 wave. Comparisons with fit patients: *p value < 0.05, **p value < 0.001

wave. We performed a post hoc analysis of the association of frailty with in-hospital mortality with the selection of patients admitted to one of the four hospitals included in all waves (Appendix 4). The associations of frailty with in-hospital mortality followed a roughly similar pattern compared to our main findings. Discharge to a nursing home or other care facility was more frequent in frail (OR 4.79, 95% CI: 3.20–7.18) and pre-frail (OR 1.98, 95% CI: 1.36–2.89) patients, compared to fit patients. The association of frailty with discharge location did not change over time (p for interaction = 0.24).

To assess whether indicators of disease severity of hospitalised older people changed during the course of the pandemic, associations of frailty with indicators of disease severity were stratified by wave (Appendix 5). Compared to fit patients, frail and pre-frail patients had comparable vital signs (body temperature, respiratory rate, systolic blood pressure and saturation before oxygen therapy) in all four waves. With increasing levels of frailty, the duration of symptoms before admission was shorter in the first three waves (all p < 0.05). In the fourth wave, all patients had a median duration of symptoms before admission of 3 days. Compared to fit patients, frail and pre-frail patients mostly had comparable levels of thrombocytes, leucocytes, lymphocytes and sodium in all the different waves. Compared to fit patients, frail patients had lower levels of haemoglobin, C-reactive protein (CRP) and lactic acid dehydrogenase in the first two waves (all p < 0.001). In the third and fourth wave, frail patients still had lower levels of CRP compared to fit patients, although no longer significantly different. Compared to fit patients, pre-frail patients had higher median levels of creatinine in the first (99 vs. 89 μmol/L, p < 0.001), second (106 vs. 89 μmol/L, p < 0.001) and third (112 vs. 94 μmol/L, p < 0.05) wave. None of the observed associations of frailty with indicators of disease severity changed over time (p for interactions > 0.05).
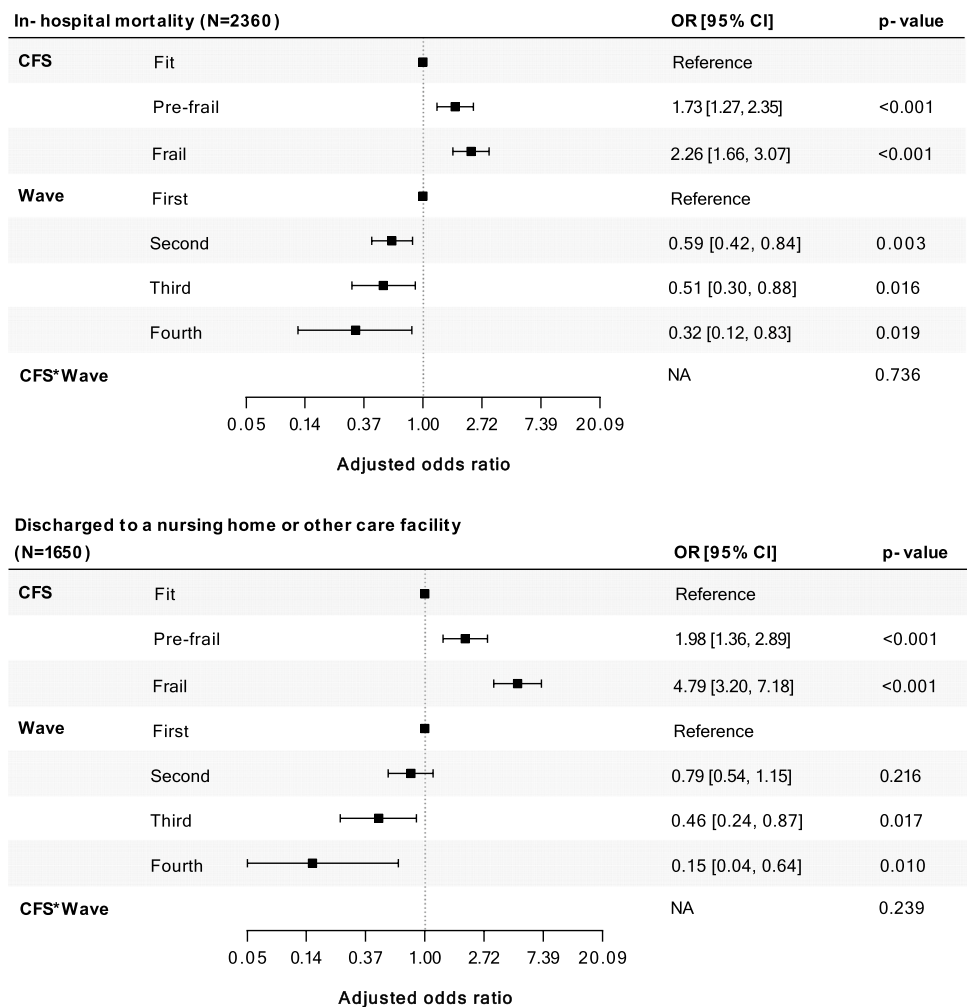
To assess whether patient characteristics of older people with frailty changed during the course of the pandemic, differences in patient characteristics based on frailty were stratified by wave (Appendix 6). The median age of fit patients ranged from 76 to 77 years over the different waves. Compared to fit patients, frail patients were older in all waves with a median age ranging from 80 to 83 years (all p < 0.001). Compared to fit patients, pre-frail patients were older in the first three waves with a median age ranging from 79 to 80 years (all p < 0.001). Compared to fit patients, frail patients had a higher median CCI in the first, second and third wave (2 vs. 1 points, all p < 0.05). In the fourth wave, all patients had a median CCI of 2 points.

Discussion

This study showed that older patients with frailty had a higher risk of in-hospital mortality throughout the entire COVID-19 pandemic, although overall in-hospital mortality risk decreased. Older patients with frailty showed only minor differences in disease severity at admission compared to fit patients reflected by comparable vital signs and minimal differences in laboratory findings.

We found that frailty remained an important risk factor of in-hospital mortality over the course of the COVID-19 pandemic, although in-hospital mortality decreased in each subsequent wave. A previous study of older hospitalised people with COVID-19 over five different waves in France also showed a decline in in-hospital mortality over time. However, mortality rates were 7–10% lower in that cohort in the first and second wave which could have been the reason why a less pronounced decline over time was observed compared to our study [15]. The higher rate of in-hospital mortality during the first two waves in our cohort is likely attributed to an incomparable patient selection because of

Fig. 4 Multivariable adjusted associations of frailty with in-hospital mortality and discharge location. 95% CI = 95% confidence interval. Variables included in both models were: age, sex, clinical frailty scale, wave and clinical frailty scale*wave (interaction term)

In- hospital mortality (N=2360)			OR [95% CI]	p- value
CFS	Fit		Reference	
	Pre-frail		1.73 [1.27, 2.35]	<0.001
	Frail		2.26 [1.66, 3.07]	<0.001
Wave	First		Reference	
	Second		0.59 [0.42, 0.84]	0.003
	Third		0.51 [0.30, 0.88]	0.016
	Fourth		0.32 [0.12, 0.83]	0.019
CFS*Wave			NA	0.736

Adjusted odds ratio

Discharged to a nursing home or other care facility (N=1650)			OR [95% CI]	p- value
CFS	Fit		Reference	
	Pre-frail		1.98 [1.36, 2.89]	<0.001
	Frail		4.79 [3.20, 7.18]	<0.001
Wave	First		Reference	
	Second		0.79 [0.54, 1.15]	0.216
	Third		0.46 [0.24, 0.87]	0.017
	Fourth		0.15 [0.04, 0.64]	0.010
CFS*Wave			NA	0.239

Adjusted odds ratio

differences in the duration of the pandemic waves and differences in organization of healthcare for acute ill older people in the Netherlands, compared to France. The overall observed decrease of in-hospital mortality over the two-year period in our study, likely reflects the previously reported effects of milder variants, such as Omicron, vaccinations and improved treatment options, such as dexamethasone and IL-6 inhibitors [16–20]. The lack of an interaction over time of the association between frailty and in-hospital mortality could indicate that improved treatment and prevention options have no frailty specific effect. Another explanation is that this study lacked statistical power to detect a frailty specific effect over time, as the sample size decreased in each subsequent wave. The lack of an interaction effect over time should be interpreted cautiously as treatment and prevention options were not directly compared between subgroups of patients based on their frailty status and remains a topic of further study. To our knowledge, we are the first to report associations of frailty with in-hospital mortality in hospitalised older people over a two-year period of the COVID-19 pandemic.

We found that patients with frailty showed only minor differences in disease severity at admission compared to fit patients reflected by comparable vital signs and minimal differences in laboratory findings. Interpretations of differences in disease severity should be made cautiously as frail patients presented themselves earlier in the course of infection. The earlier moment of presentation could itself be a sign of a more severe disease, but is more likely explained by reduced physical reserve or faster referrals by healthcare professionals for frail patients. Previous studies demonstrated that severe COVID-19 was associated with higher CRP levels in adults [21, 22]. In our study, frail patients had lower levels of CRP compared to fit patients. Frailty is known to be associated with chronic low-grade inflammation (inflammaging) which leads to chronically increased levels of certain biomarkers, such as CRP and IL-6, but may hamper the immune response in case of acute infection [23, 24]. This could explain the lower CRP levels. Frail patients

have an increased susceptibility to infectious diseases, which could contribute to the relative increase of frail patients over time [25]. Another explanation could be a reserved referral policy that was applied for these patients in the Netherlands during the first two waves due to a high mortality risk and high pressure on the number of hospital beds. The observed association of frailty with in-hospital mortality during the entire COVID-19 pandemic, in combination with comparable disease severity and a relative increase of prefrail and frail patients after the second wave, indicates that frail patients have a vulnerability to mortality that cannot be easily remedied despite milder variants and improved prevention and treatment options. A previous study found that frailty had a stronger association with disease outcomes than either age or comorbidities alone, which supports the theory of importance of underlying frailty in the course of COVID-19 infection [26]. Unsurprisingly, this vulnerability of frail patients is also reflected by the observed association of frailty with older age and comorbidities in our cohort. It is postulated that immunosenescence, besides inflammaging, attributes to this vulnerability, but this is currently not fully understood [24, 27].

Our findings indicate that despite milder variants over time and roughly comparable disease severity between frail and fit older patients, frail older people have an intrinsic vulnerability to mortality that cannot be easily remedied with timely initiation of hospitalisation and specific COVID-19 treatment options. These findings show the relevance of frailty as a risk factor in all stages of a pandemic. In the event of a new pandemic, frailty should be considered early on in government communication and policies and in prevention and treatment guidelines. The prognostic value of frailty in decision-making remains subject of further study.

This study has several limitations that need to be considered while interpreting the main findings of this study. The numbers of hospitals that could participate decreased over time, mainly due to increased individual workload for medical professionals during the COVID-19 pandemic and the lack of funding for scientific research. This resulted in a reduction of the sample size in each subsequent wave which affected statistical power over time and could potentially hamper generalizability of results found in the fourth wave. Another limitation is the lack of data on clinical deterioration during admission. Therefore, we could only evaluate disease severity at the time of admission. In addition, details on the numbers of patients with prospective versus retrospective assessment of frailty were not collected. To evaluate possible selection bias introduced by frailty measurements, we compared baseline characteristics between patients with an assessed CFS and CFS missing, which showed no relevant differences, indicating that selection bias was limited at most. Our study had several strengths. To our knowledge, this is the first study with an ongoing data collection during four waves of the COVID-19 pandemic over a 2 year period that systematically analysed associations of frailty in hospitalised older people. Other strengths of this study are the inclusion of both academic and peripheral hospitals across the Netherlands, the large sample size and the collection of a wide variety of variables.

In conclusion, frailty remained associated with a higher risk of in-hospital mortality throughout the entire COVID-19 pandemic, although overall in-hospital mortality decreased. These findings show the relevance of frailty as a risk factor in all stages of a pandemic, which indicates that frailty is important to consider in prevention and treatment guidelines for future pandemics.

Declarations

Conflict of interest The authors have no competing interests.

Ethical approval The necessity for formal approval of the study was waived by each local medical ethics committee as data collection followed routine clinical practice.

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