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RESEARCH PAPER

Characteristics and outcomes of older patients hospitalised for COVID-19 in the first and second wave of the pandemic in The Netherlands: the COVID-OLD study

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Abstract

Background: as the coronavirus disease of 2019 (COVID-19) pandemic progressed diagnostics and treatment changed.
Objective: to investigate differences in characteristics, disease presentation and outcomes of older hospitalised COVID-19 patients between the first and second pandemic wave in The Netherlands.
Methods: this was a multicentre retrospective cohort study in 16 hospitals in The Netherlands including patients aged ≥ 70 years, hospitalised for COVID-19 in Spring 2020 (first wave) and Autumn 2020 (second wave). Data included Charlson comorbidity index (CCI), disease severity and Clinical Frailty Scale (CFS). Main outcome was in-hospital mortality.
Results: a total of 1,376 patients in the first wave (median age 78 years, 60% male) and 946 patients in the second wave (median age 79 years, 61% male) were included. There was no relevant difference in presence of comorbidity (median CCI 2) or frailty (median CFS 4). Patients in the second wave were admitted earlier in the disease course (median 6 versus 7 symptomatic days; $P < 0.001$). In-hospital mortality was lower in the second wave (38.1% first wave versus 27.0% second wave; $P < 0.001$). Mortality risk was 40% lower in the second wave compared with the first wave (95% confidence interval: 28–51%) after adjustment for differences in patient characteristics, comorbidity, symptomatic days until admission, disease severity and frailty.
Conclusions: compared with older patients hospitalised in the first COVID-19 wave, patients in the second wave had lower in-hospital mortality, independent of risk factors for mortality. The better prognosis likely reflects earlier diagnosis, the effect of improvement in treatment and is relevant for future guidelines and treatment decisions.

Keywords: frailty, COVID-19, in-hospital mortality, second pandemic wave

Key Points

- Older hospitalized COVID-19 patients in the first and second pandemic wave had similar frailty and comorbidity.
- Older hospitalized COVID-19 patients presented earlier in the disease course in the second pandemic wave in the Netherlands.
- Older hospitalized COVID-19 patients had a lower in-hospital mortality in the second pandemic wave, independent of other risk factors.
- These findings suggest earlier diagnosis and more effective in-hospital treatment of older COVID-19 patients in the second pandemic wave.

Introduction

Older patients hospitalised for coronavirus disease of 2019 (COVID-19) infection during the first wave of the worldwide pandemic had a high risk of in-hospital mortality [1–3]. Moreover, frailty was independently associated with an increased risk for in-hospital mortality [4–6]. Since the start of the first pandemic wave, the diagnostics and treatment of patients with COVID-19 infection has gradually changed, for example in testing strategies, early detection of pulmonary embolisms and treatment regimens. However, as far as we know, no comparisons of patient characteristics and in-hospital mortality of older patients in the first and second pandemic wave have been published yet.

At the start of the first wave, COVID-19 diagnosis was mostly based on clinical symptoms. Over time, it became possible to test more people in the community and earlier in the disease course due to increased testing capacity and rapid PCR tests as standard diagnostic tools. Moreover, frailty in older patients was increasingly incorporated in decision-making on treatment at home versus hospital admission [7] and may have influenced referral to the hospital. Treatment regimens also changed in time with the introduction of, for instance, high dose corticosteroids [8] and early prevention and screening for coagulopathy, which may lead to complications such as pulmonary embolisms [9]. It is unknown whether these developments in diagnosis and treatment have led to better outcomes specifically for older patients hospitalised with COVID-19 infection in the second wave.

Therefore, the aim of the present study was to investigate differences in patient characteristics, disease presentation and outcomes of older patients hospitalised for COVID-19 infection between the first and second COVID-19 waves in The Netherlands.

Methods

Study design

This was a retrospective multicentre cohort study among patients aged 70 years and older who were hospitalised for COVID-19 infection from 27th February until 14th May 2020 (first wave) and from 1st September until 31st December 2020 (second wave) in The Netherlands. Data were collected from 16 Dutch hospitals, listed in Supplemental Table 1, Supplementary data are available in *Age and Ageing* online. The medical ethics committees of all hospitals waived the necessity for formal approval of the study, as data collection followed routine practice and was executed until

hospital discharge. Details on the study design can be found in an earlier publication on the first pandemic wave [4].

Setting

Organisation of healthcare in The Netherlands

In The Netherlands, basic health insurance is mandatory and covers primary care from general practitioners (GPs) and hospital care. In case of a medical emergency, patients can contact their GP, visit the GP out-of-hours service, call for an ambulance or go to the Emergency Department (ED). During the COVID-19 pandemic, GPs had 24/7 COVID-19 triage units. Special isolation rooms in outpatient clinics and EDs have been organised, together with special trajectories for early admission to special COVID-19 wards in the hospitals [10].

COVID-19 variants and vaccination

In the second wave 99.8–100% of variants found in The Netherlands was Delta. Dutch laboratories only started sequencing COVID-19 variants since 30th November 2020, but the alpha Wuhan variant was dominant in The Netherlands in the first wave [11]. In The Netherlands the vaccination programme started 6th January 2021, starting with residents of nursing homes and people being born before 1931. All patients included in our study were therefore not vaccinated for COVID-19 infection.

Study participants

The inclusion criteria were patients aged ≥ 70 years who were hospitalised for a confirmed COVID-19 infection. Patients were included if they were tested positive for severe acute respiratory syndrome coronavirus 2 on reverse-transcriptase polymerase chain reaction (RT-PCR) from an oropharyngeal and/or nasal swab or if the diagnosis of COVID-19 infection was based on typical findings on computerised tomography scan and/or chest X-ray. Only in the first pandemic wave, we also included patients with a clinical diagnosis of COVID-19 based on review of clinical, laboratory and radiological findings in the absence of PCR testing, which was not always rapidly available in the first wave. Patients diagnosed in the hospital during admission for another illness were excluded, defined as positive PCR test ≥ 1 week after admission. Furthermore, patients who were transferred between hospitals were excluded, because baseline and outcome data were incomplete for these patients.

Outcomes

The main outcome of this study was in-hospital mortality. Other outcomes of interest were the presence of delirium during admission, intensive care unit (ICU) admission (including length of stay and ventilation), hospital length of stay, discharge destination (home, nursing home, other hospital, rehabilitation centre, other) and re-admission at the first hospital of admission. In addition, we collected data on COVID-19 specific medication use during hospital admission. From three hospitals (Gelre Hospitals, Reinier de Graaf Hospital and St Jansdal Hospital) we could not use the data on medication use, therefore the analysis concerning medication use was limited to 13 hospitals.

Data collection

Data were collected from the patients' electronic healthcare records. We collected demographic data on age, sex and living situation (at home or institutionalised). The Charlson comorbidity index (CCI) was used to gain insight in the presence of comorbidity [12]. In addition, data on history of lung disease (interstitial lung disease or lung cancer), presence of hypertension, smoking status and body mass index (BMI) were collected.

Geriatric parameters were routinely collected with the Dutch National Safety Management System (Veiligheidsmanagementsysteem, VMS; [13]). This risk assessment tool was used at hospital admission for all patients aged $\geq$70 years. The instrument consists of 13 questions about four domains: physical impairment, falls, delirium and malnutrition. Physical impairment was evaluated using the Katz activities of daily living (ADL) index [14]. A score ≥ 2 is defined as risk of physical impairment. A fall in the last 6 months is defined as risk of falling. One or more positive answers to questions on memory problems, the need for help with self-care in the last 24 h and previously experienced confusion is defined as a risk for delirium. For evaluation on malnutrition the instruments Short Nutritional Assessment Questionnaire (SNAQ) or Malnutrition Universal Screening Tool (MUST) were used. A score of SNAQ ≥ 3 or MUST ≥ 2 is defined as a risk of malnutrition [15, 16].

Frailty was assessed with the Clinical Frailty Score [17]. The Clinical Frailty Scale (CFS) was prospectively determined at hospital admission according to the implemented guidelines (most of the times by a geriatrics nurse; [7]). If not prospectively assigned, the CFS was determined retrospectively, based on available chart data (which included the geriatric parameters from the VMS) and was scored by a geriatrics specialist (geriatrician or internist-geriatrician) or by a researcher trained by a geriatrics specialist. In most participating hospitals, the CFS was determined retrospectively. Data on CFS were considered missing if information from the health record was not sufficient to determine the CFS score retrospectively. According to the Dutch guidelines, the CFS was categorised in three groups: fit (CFS 1–3), pre-frail (CFS 4–5) and frail (CFS 6–9; [7]).

The duration of symptoms until admission in days was calculated subtracting the date of admission from the date of onset of symptoms. Both dates were collected from health records. Disease severity indicators were the registered vital signs and laboratory results collected within the first 24 h of admission.

Medication use was extracted from the medical records at the first day of admission.

Data were collected using Castor Electronic Data Capture (2019).

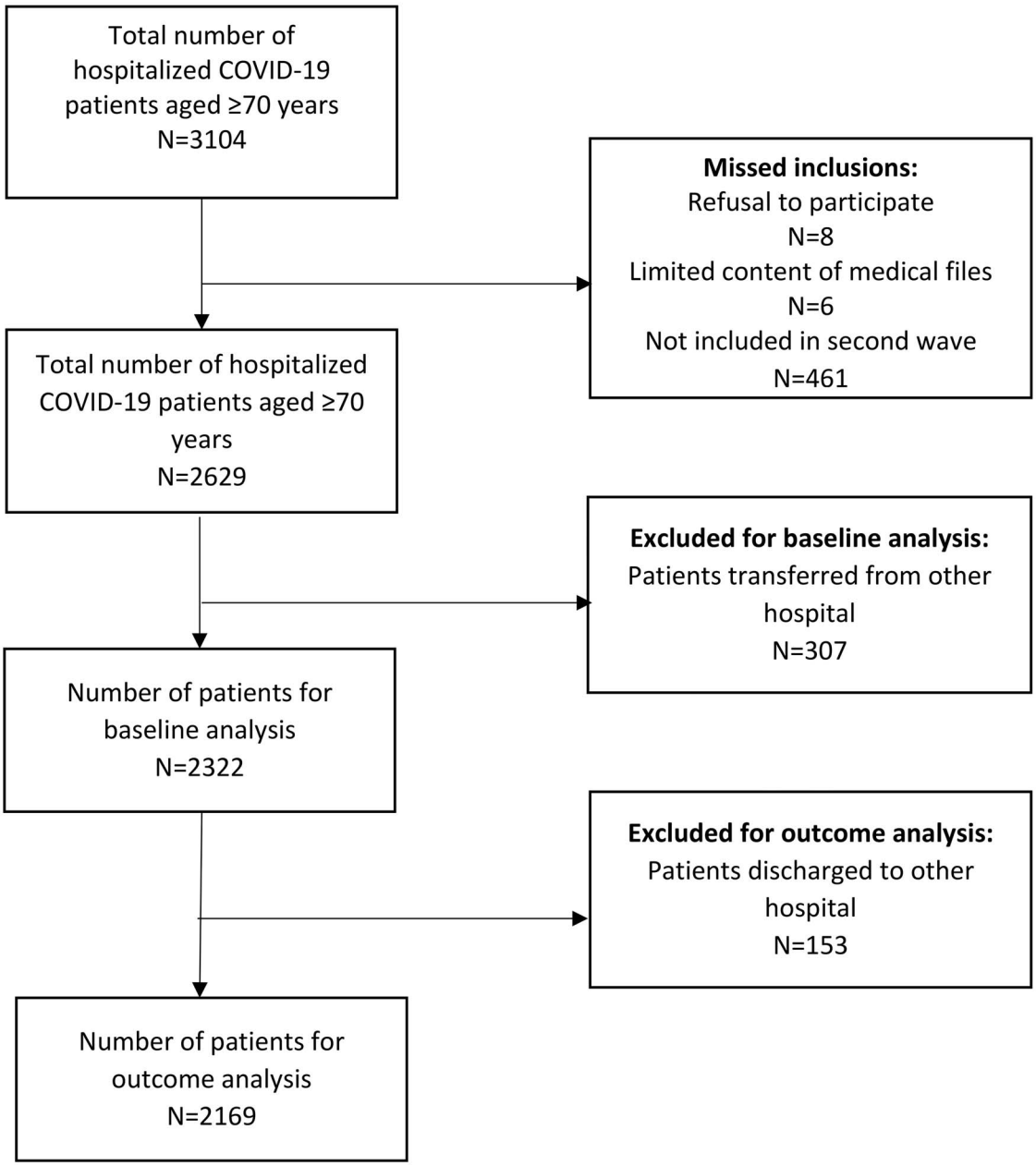

Figure 1. Flowchart patient inclusions.

Statistical analyses

In the descriptive analyses, continuous data were presented as means (standard error, SE) if normally distributed, and as medians (interquartile range, IQR) if skewed. Categorical data were presented as numbers (*n*, percentage (%)). Differences in patient characteristics, disease severity indicators and outcomes were assessed using unpaired *T*-tests for normally distributed data, Mann–Whitney *U* test for skewed data and χ^2 test for categorical data.

A Cox regression analysis was performed with the number of admission days as time, discharge as censoring and in-hospital mortality as outcome to investigate the relation between clinical characteristics and in-hospital mortality. Based on prior research of the COVID-OLD Research Group on the first COVID-19 wave [4], we selected seven variables for the multivariable analyses based on their independent association with in-hospital mortality: age, sex, comorbidity (CCI), frailty (CFS), disease severity indicators (duration of symptoms till admission, respiratory rate and CRP level) and pandemic wave. Results are presented as hazard ratios (HRs) with 95% confidence intervals (95% CIs). A *P*-value <0.05 was considered statistically significant.

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, NY, USA).

Results

A total of 2,734 patients were included: 1,530 in the first wave and 1,204 in the second wave (Figure 1). We excluded

Table 1. Baseline characteristics for older hospitalised COVID-19 patients in first and second wave

	First wave *N* = 1,376	Second wave *N* = 946	*P*-value
Demographics			
Age (years), median (IQR)	78 (74–84)	79 (74–85)	0.037
Male, *n* (%)	830 (60.3)	580 (61.3)	0.662
Living at home, *n* (%)	1,186 (89.9)	819 (86.6)	<0.001
Comorbidity			
Charlson comorbidity index, median (IQR)	2 (1–3)	2 (1–4)	0.150
History of chronic lung disease[a], *n* (%)	349 (25.4)	278 (29.4)	0.040
History of hypertension, *n* (%)	776 (56.5)	495 (52.3)	0.048
History of diabetes, *n* (%)	416 (30.2)	300 (31.7)	0.448
History of myocardial infarction, *n* (%)	259 (18.8)	166 (17.5)	0.430
History of dementia, *n* (%)	120 (8.7)	96 (10.1)	0.249
Smoking, *n* (%)			0.005
Never	441 (32.0)	262 (27.7)	
Ex-smoker	507 (36.8)	387 (40.9)	
Current	88 (6.4)	39 (4.1)	
Body mass index, mean (SE)	27.0 (0.19)	27.2 (0.18)	0.468
Geriatric measurements			
Katz ADL score, median (IQR)	0 (0–3)	0 (0–2)	0.189
Risk of physical impairment[b], *n* (%)	424 (30.8)	280 (29.6)	0.483
Risk of falling, *n* (%)	323 (28.5)	244 (25.8)	0.601
Risk of delirium, *n* (%)	475 (34.5)	392 (41.4)	0.004
Risk of malnutrition, *n* (%)	222 (16.1)	184 (19.5)	0.067
Clinical Frailty Scale, *n* (%)			0.881
1–3	515 (46.1)	359 (45.0)	
4–5	288 (25.8)	210 (26.3)	
6–9	313 (28.0)	229 (28.7)	

Abbreviations: ADL, activities of daily living; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; *N*, number; SE, standard error. Analysis: independent *T*-test/Chi square test/Mann–Whitney *U* test. [a]COPD, asthma, interstitial lung disease or lung cancer. [b]Katz ADL score ≥ 2 Missing first wave: 2 sex, 57 living at home, 16 Charlson Comorbidity Index, 2 hypertension, 4 diabetes, 1 myocardial infarction, 2 dementia, 340 smoking, 294 Body Mass Index, 180 Katz ADL, 180 risk of physical impairment, 245 risk of falling, 193 risk of delirium, 322 risk of malnutrition, 260 Clinical Frailty Scale. Missing second wave: 14 living at home, 258 smoking, 162 Body Mass Index, 121 Katz ADL score, 121 risk of physical impairment, 124 risk of falling, 144 risk of delirium, 202 risk of malnutrition, 22 Clinical Frailty Scale.

154 (10.1%) patients in the first wave and 153 (12.7%) patients in the second wave due to incomplete data (mainly due to transferal between hospitals), resulting in a total of 2,322 patients for baseline analysis. In addition, 75 (3.2%) patients in the first wave and 78 (3.4%) patients in the second wave were discharged to other non-participating hospitals and excluded because of incomplete follow-up, resulting in 2,169 patients available for outcome analysis on in-hospital mortality.

Baseline characteristics of the 2,322 included patients in the first and the second wave are shown in Table 1. Compared with the first wave, the median age of the patients in the second wave was minimally but significantly higher (first wave 78 years (IQR 74–84) in the first wave versus 79 years (IQR 74–85) in the second wave; $P = 0.023$) and a similar percentage of the patients was male (60.3% in the first wave versus 61.3% in the second wave; $P = 0.662$). Compared with the first wave, fewer patients were living at home in the second wave (1,186 (89.9%) in the first wave versus 819 (86.6%) in the second wave; $P < 0.001$). The median CCI score was similar in both waves (2 (IQR 1–4) in the first wave versus 2 (IQR 1–3) in the second wave; $P = 0.077$). In the first wave, the median CFS score was similar to the median CFS score in the second wave (4 (IQR 2–6) in the first wave versus 4 (IQR 3–6) in the second wave; $P = 0.847$).

Disease severity indicators in the first 24 h of hospital admission are shown in Table 2. Compared with the first wave, the median duration of COVID-19 symptoms until hospital admission was 1 day shorter in the second wave (median 7 (IQR 3–10) days in the first wave versus median 6 (IQR 3–9) days in the second wave; $P < 0.001$). Compared with the first wave, patients in the second wave needed less oxygen (median 3 (IQR 1–5) litre/minute in the first wave versus median 2 (IQR 0–4) litre/minute in the second wave; $P = 0.001$) and had a lower median CRP level (79 (IQR 40–140) mg/L in the first wave versus 71 (IQR 34–127) mg/L in the second wave; $P = 0.003$) at ED presentation. Mean temperature and respiratory rate were similar in both waves.

COVID-19 specific medication regime was different in both waves (Supplemental Table 2, Supplementary data are available in *Age and Ageing* online). In the first wave, most patients received either chloroquine, hydroxychloroquine or no medical treatment. In the second wave most patients received dexamethasone and/or remdesivir, according to the Dutch treatment guidelines [18]. The use of chloroquine, hydroxychloroquine and ipinavir/ritonavir had stopped completely after the first wave.

Table 2. Disease severity indicators for older hospitalised COVID-19 patients in first and second wave

	First wave $N = 1,376$	Second wave $N = 946$	P-value
Disease severity indicators			
Duration of symptoms until admission (days), median (IQR)	7 (3–10)	6 (3–9)	<0.001
Temperature (°C), mean (SE)	37.7 (0.03)	37.8 (0.03)	0.139
Respiratory rate (breaths/min), mean (SE)	22 (0.23)	22 (0.22)	0.622
Oxygen amount needed (L/min), median (IQR)	3 (1–5)	2 (0–4)	0.001
Lymphocytes (10^9/L), median (IQR)	1.0 (0.6–1.7)	0.8 (0.6–1.1)	<0.001
Creatinine (μmol/L), median (IQR)	93 (74–130)	96 (75–133)	0.324
Lactic Acid Dehydrogenase (U/L), median (IQR)	364 (271–610)	326 (252–431)	<0.001
C-reactive protein (mg/L), median (IQR)	79 (40–140)	71 (34–127)	0.003

Abbreviations: IQR, interquartile range; N, number; SE, standard error. Analysis: independent T-test/Chi square test/Mann–Whitney U test. Missing first wave: 146 duration of symptoms, 64, temperature, 78 respiratory rate, 151 oxygen, 251 lymphocytes, 85 creatinine, 274 Lactic Acid Dehydrogenase, 85 C-reactive protein. Missing second wave: 69 duration of symptoms, 20 temperature, 52 respiratory rate, 58 oxygen, 117 lymphocytes, 19 creatinine, 120 Lactic Acid Dehydrogenase, 21 C-reactive protein.

Table 3. In-hospital outcomes for older hospitalised COVID-19 patients in first and second wave

	First wave $N = 1,301$	Second wave $N = 868$	P-value
In-hospital mortality, *n* (%)[a]	488 (37.5)	231 (26.6)	<0.001
ICU admission, *n* (%)	142 (10.9)	72 (8.3)	0.025
Invasive ventilation in ICU, *n* (%)	120 (84.5)	46 (63.9)	0.005
ICU length of stay (days), median (IQR)	8 (2–18)	10 (4–21)	0.296
Documented delirium during hospital admission, *n* (%)	305 (23.4)	201 (23.2)	0.408
Hospital length of stay (days), median (IQR)	6 (3–10)	6 (4–11)	0.025
Discharge destination, *n* (%)[b]			<0.001
Home	485 (60.6)	404 (64.1)	
Nursing home	93 (11.6)	76 (12.1)	
Rehabilitation centre	188 (23.5)	137 (21.7)	
Other	34 (4.3)	13 (2.1)	
Readmission[c]	56 (7.0)	90 (14.3)	<0.001

Abbreviations: ICU, Intensive Care Unit; IQR, interquartile range; *N*, number; SE, standard error. Analysis: independent T-test/Chi square test/Mann–Whitney U test. Missing first wave: 48 ICU admission, 73 delirium, 5 discharge destination, 62 re-admission, 5 in-hospital mortality and 2 hospital length of stay. Missing second wave: 5 ICU admission, 4 delirium, 4 discharge destination, 4 re-admission, 4 in-hospital mortality and 3 hospital length of stay. [a]Defined as diseased in hospital and discharge to hospice. [b]First wave $n = 800$, second wave $n = 630$. [c]Documented re-admission in own hospital.

In-hospital outcomes are shown in Table 3. Compared with the first wave, in-hospital mortality was lower during the second wave (37.5% in the first wave versus 26.6% in the second wave; $P < 0.001$). Compared with the first wave, fewer patients were admitted to the ICU ward (142 patients (10.9%) in the first wave versus 72 patients (8.3%) in the second wave; $P = 0.025$) and fewer patients needed intubation (84.5% in the first wave versus 63.9% in the second wave; $P = 0.005$), although there was no difference in median ICU length of stay (8 (IQR 2–18) days in the first wave versus 10 (IQR 4–21) days in the second wave; $P = 0.296$). Compared with the first wave, more patients were discharged to their own home in the second wave (60.6% in the first wave versus 64.1% in the second wave; $P < 0.001$). However, compared with the first wave, more patients needed re-admission in the second wave (4.8% in the first wave versus 10.4% in the second wave; $P < 0.001$).

Univariable and multivariable associations of baseline characteristics, disease severity indicators and in-hospital mortality of all patients are shown in Table 4. After adjustment for other risk factors for in-hospital mortality (age, male sex, comorbidity (CCI), frailty (CFS), duration of symptoms till admission, respiratory rate and CRP level) in-hospital mortality was 40% lower (HR 60, 95% CI: 28–51%) in the second wave compared with the first wave. Compared with patients with CFS 1–3, patients with a higher CFS had a higher risk of death during hospital admission, independent of the other factors mentioned above (CFS 4–5 HR 1.59 (95%CI 1.26–2.01); $P < 0.001$ versus CFS 6–9 HR 1.72 (95%CI 1.34–2.20); $P < 0.001$).

Discussion

The main findings of this study were threefold. Firstly, patients in the first and the second wave showed only small differences in characteristics. Secondly, patients in the second wave were hospitalised somewhat earlier in the disease course and had less severe disease symptoms. Thirdly, in the second wave, risk of in-hospital mortality was lower, independent of other risk factors for in-hospital mortality.

Table 4. Univariable and multivariable Cox regression analysis of in-hospital mortality and patient characteristics per number of admission days for older hospitalised COVID-19 patients in the first and the second pandemic wave

	Univariable model				Multivariable model	
	n=/*N* = 2,169	HR (95%CI)	*P*-value	*n* = 483/ *N* = 1,476	HR (95%CI)	*P*-value
Demographics and comorbidity						
Age (per year)	730/2,160	1.04 (1.03–1.05)	<0.001		1.04 (1.02–1.05)	<0.001
Men	729/2,158	1.29 (1.10–1.51)	0.001		1.34 (1.13–1.70)	0.002
Living at home	730/2,097	0.71 (0.57–0.89)	0.002			
Second wave	730/2,160	0.67 (0.57–0.79)	<0.001		0.60 (0.49–0.72)	<0.001
Charlson Comorbidity Index (per point)	723/2,144	1.06 (1.03–1.10)	<0.001		1.04 (1.00–1.09)	0.058
History of chronic lung disease[a]	725/2,152	1.07 (0.91–1.26)	0.434			
History of hypertension	729/2,158	1.16 (1.00–1.34)	0.054			
History of diabetes	729/2,156	1.25 (1.07–1.45)	0.005			
History of myocardial infarction	729/2,159	1.45 (1.22–1.73)	<0.001			
History of dementia	729/2,158	1.27 (1.01–1.60)	0.041			
Smoking	534/1,605					
Never		Ref	Ref			
Ex-smoker		1.20 (1.00–1.44)	0.057			
Current		1.21 (0.87–1.68)	0.253			
Body mass index	502/1,535					
<25		Ref	Ref			
25–30		1.24 (1.00–1.53)	0.049			
>30		1.31 (1.04–1.67)	0.025			
Geriatric measurements						
Katz ADL score ≥2[b]	611/1,891	1.24 (1.06–1.46)	0.008			
Risk of falling	584/1,826	1.20 (1.01–1.43)	0.036			
Risk of delirium	580/1,805	1.33 (1.13–1.57)	0.001			
Risk of malnutrition	525/1,682	1.00 (0.81–1.22)	0.933			
Clinical Frailty Scale	595/1,793					
1–3		Ref	Ref		Ref	Ref
4–5		1.65 (1.34–2.03)	<0.001		1.59 (1.26–2.01)	<0.001
6–9		1.78 (1.47–2.17)	<0.001		1.72 (1.34–2.20)	<0.001
Disease severity indicators						
Duration of symptoms till admission	662/1,956					
<5 days		1.44 (1.03–2.02)	0.036		1.37 (0.91–2.05)	0.134
5–7 days		Ref	Ref		Ref	Ref
>7 days		1.07 (0.76–1.51)	0.701		1.05 (0.70–1.56)	0.831
Temperature (°C)	707/2,079					
<36.5		0.92 (0.72–1.16)	0.467			
36.5–38.5		Ref	Ref			
>38.5		1.26 (1.06–1.49)	0.010			
Respiratory rate (breaths/min)	684/2,035					
<15		0.81 (0.60–1.09)	0.163		0.96 (0.67–1.39)	0.833
15–20		Ref	Ref		Ref	Ref
21–30		1.29 (1.08–1.55)	0.006		1.36 (1.09–1.69)	0.006
>30		1.96 (1.55–2.48)	<0.001		2.54 (1.92–3.37)	<0.001
Oxygen amount needed (L/min)	665/1,959					
0		Ref	Ref			
1–5		1.72 (1.35–2.20)	<0.001			
>5		3.30 (2.55–4.27)	<0.001			
Lymphocytes (10^9/L)	549/1,685					
<1.0		1.22 (1.00–1.48)	0.052			
1.0–2.0		Ref	0.278			
Lactic Acid Dehydrogenase (U/L)	633/1,903					
0–249		Ref	Ref			
>250		1.42 (1.15–1.75)	0.001			
Creatinine (μmol/L)[c]	698/2,056					
<60		Ref	Ref			
61–100		1.11 (0.79–1.56)	0.544			
101–130		1.44 (1.01–2.05)	0.045			
131–180		1.93 (1.35–2.76)	<0.001			
>180		2.26 (1.57–3.24)	<0.001			

Continued

Table 4. Continued

	Univariable model				Multivariable model	
	n=/*N* = 2,169	HR (95%CI)	*P*-value	*n* = 483/ *N* = 1,476	HR (95%CI)	*P*-value
C-reactive protein (mg/L)	700/2,060					
<10		Ref	Ref		Ref	Ref
10–100		1.75 (1.12–2.71)	0.013		1.62 (0.94–2.79)	0.084
>100		2.41 (1.55–3.75)	<0.001		2.50 (1.44–4.34)	0.001

Abbreviations: ADL, activities of daily living; HR, Hazard Ratio, *N*, number; Ref, reference. [a]Chronic obstructive pulmonary disease, interstitial lung disease or lung cancer. [b]Risk of physical impairment. [c]Divided in chronic kidney disease stages.

We observed that patients in both waves had roughly similar baseline characteristics; although statistically significant, the difference between both waves in age and the percentage of patients living at home was only small. In the second wave, less people living at home and therefore more care home residents were admitted. There was no difference in national guidelines in both pandemic waves concerning criteria for referral to the hospital [7], although it is possible that GP's and care home physicians tended to refer more care home residents to the hospital in the second wave.

We observed that patients in the second wave were admitted to the hospital in an earlier stage of the disease and were therefore less ill at the time of admission. The most important explanation may be that testing in the second wave was available on a greater scale, which probably has led to earlier detection of COVID-19 patients at home. As a result, there may have been better GP's awareness and possibly also patient and caregiver were more alert for early signs of deterioration and hospital need, leading to earlier ED presentation.

We found that patients in the second wave had lower risk of in-hospital death, independent of other risk factors for mortality. In the second wave the delta variant was dominant, and we know that patients with delta variant have greater risk for hospital admission [19]. One study reports higher mortality in infections in patients with the delta variant [20]. If this study will be confirmed by other studies, it is even more remarkable that in our study patients in the second wave, only dominated by the delta variant, had lower in-hospital mortality. The development in diagnostics and treatment regimens may have been an important factor, for example screening for and early detection of pulmonary embolism (PE). We presume that in the beginning of the first wave cases of pulmonary embolism have been missed, since the final Dutch guideline 'COVID-19 coagulopathy' concerning early diagnostics for PE and thrombosis prophylaxis have been introduced only in April 2020 [21]. The beneficial effects of dexamethasone and low molecular weight heparin on in-hospital mortality have been proved in clinical trials [8, 22, 23]. The use of dexamethasone may also have been a factor that influenced the risk for re-admission in the second wave, since there is some proof that a patient may experience a relapse in COVID-19 symptoms when corticosteroid use is limited [24]. Another explanation is that in the second wave patients were discharged earlier or with more severe disease symptoms, for example persistent oxygen need. Regionally, hospitals and GPs arranged telemonitoring at home for patients with persistent oxygen need, but we did not collect data on this for individual patients. However, we found no difference in length of stay and we have no data on disease severity at discharge. It is also possible that the difference in readmission percentage is a chance finding.

Importantly, besides diagnostics and treatment regimens, clinical knowledge and experience of healthcare workers and awareness of the public were important factors that made a difference between both pandemic waves, influencing in-hospital mortality. Hospital healthcare workers have been exposed to COVID-19 patients for more than a year. Undisputedly, clinical experience has evolved over time, leading to better recognition of early signs of deterioration and need for interventions (e.g. ICU admission, COVID-19 specific medication and diagnostics for pulmonary embolism).

As the COVID-19 pandemic continues to progress, diagnostics and treatment are likely to keep improving. For instance, the effect of vaccination on prevalence of disease and hospital admission is visible in figures on newly reported COVID-19 infections and hospital admission [25]. The resulting further improvement in prognosis, also for older and more frail patients, should guide clinical decision-making and future guidelines and needs to be a continuous subject of study. Further research on other outcomes, such as longer term follow up of functional decline, patient's ability to live at home independently and mortality would make an important contribution.

Our study has some limitations. First, due to the high workload in the ongoing second pandemic wave, some hospitals were not able to include all hospitalised COVID-19 patients, which may have caused selection bias. However, we know from our inclusion numbers that missing patients were randomly spread over the inclusion time period, therefore overall, no essential part of the inclusion period was missed. Second, the CFS was mostly determined retrospectively, which may have caused a bias, although previous studies showed that the value of prospectively and retrospectively determined CFS scores show a good correlation [26]. The study also has several strengths. The large number of patients

included in first and second wave, who were admitted in many different hospitals throughout The Netherlands, forms a representative cohort, at least for The Netherlands. Also, we collected a wide variety of variables including demographics, comorbidity, frailty, symptoms and disease indicators, medication, ICU admission, discharge destination and readmission. Our study is one of the first comparing in-hospital mortality in older hospitalised COVID-19 patients between the first and the second wave of the pandemic.

In conclusion, compared with older patients hospitalised in the first COVID-19 wave, patients in the second wave had lower in-hospital mortality, independent of risk factors for in-hospital mortality.

The better prognosis likely reflects earlier diagnosis and possibly the effect of improvement in treatment and is relevant for future clinical guidelines and treatment decisions.

Supplementary data: Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

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