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RESEARCH ARTICLE

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Delirium in older patients with COVID-19: Prevalence, risk factors and clinical outcomes across the first three waves of the pandemic

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Abstract

Objectives: Delirium is a serious condition, which poses treatment challenges during hospitalisation for COVID-19. Improvements in testing, vaccination and treatment might have changed patient characteristics and outcomes through the pandemic. We evaluated whether the prevalence and risk factors for delirium, and the association of delirium with in-hospital mortality changed through the pandemic.

Methods: This study was part of the COVID-OLD study in 19 Dutch hospitals including patients ≥70 years in the first (spring 2020), second (autumn 2020) and third wave (autumn 2021). Multivariable logistic regression models were used to study risk factors for delirium, and in-hospital mortality. Differences in effect sizes between waves were studied by including interaction terms between wave and risk factor in logistic regression models.

Results: 1540, 884 and 370 patients were included in the first, second and third wave, respectively. Prevalence of delirium in the third wave (12.7%) was significantly lower compared to the first (22.5%) and second wave (23.5%). In multivariable-adjusted analyses, pre-existing memory problems was a consistent risk factor for delirium across waves. Previous delirium was a risk factor for delirium in the first wave (OR 4.02), but not in the second (OR 1.61) and third wave (OR 2.59, *p*-value interaction-term 0.028). In multivariable-adjusted analyses, delirium was not associated with in-hospital mortality in all waves.

Conclusion: Delirium prevalence declined in the third wave, which might be the result of vaccination and improved treatment strategies. Risk factors for delirium

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remained consistent across waves, although some attenuation was seen in the second wave.

KEYWORDS
COVID-19, delirium, frailty, metabolic encephalopathy, older adults, SARS-CoV-2

Key points

- Prevalence of delirium in the third COVID-19 wave was significantly lower compared to the first and second wave
- Risk factors for delirium remained consistent across waves
- Delirium was not independently associated with in-hospital mortality

1 | INTRODUCTION

A delirium is a serious condition frequently observed in patients during hospitalisation.[1] It mainly affects frail older adults and severely ill patients and is associated with increased risk on adverse clinical outcomes.[2] Delirium also plays a significant role in the context of older patients hospitalised for Coronavirus disease 2019 (COVID-19) and its estimated prevalence is between 14.2% and 54.9%.[3,4] Severe Acute Respiratory Syndrome Coronovirus-2 (SARS-CoV-2) can induce the onset of metabolic encephalopathy in patients with COVID-19 by a cytokine storm, hypoxemia and the direct effect on the central nervous system.[5,6] Delirium during COVID-19 hospitalisation poses several specific challenges.[7] Medication that is often prescribed for COVID-19 such as morphine for dyspnoea and/or pain and dexamethasone are known to increase the risk for delirium.[8] When patients are isolated, contacts are minimised and healthcare professionals look all the same in isolation clothes potentially provoking disorientation. Furthermore, agitation can complicate treatment with for example, invasive devices such as airflow or the use of catheters and intravenous infusions.[9]

Additionally, over time, the severity of disease in COVID-19 patients decreased.[10] Over the course of the pandemic there have been many developments in areas such as vaccination and treatment. After the introduction of COVID-19 vaccinations, the most frail older adults were vaccinated first, which could have decreased disease severity in this specific patient population.[11] Besides, treatment strategies became more effective on limiting severity of disease over time, for example, with the introduction of corticosteroid treatment.[12] We know that compared to the first wave, in-hospital mortality decreased in the second wave, whereas no differences in prevalence of comorbidities or frailty were observed.[13] It is likely that because of the aforementioned developments, the prevalence of delirium changed in the second and third wave.

The aim of this study was to compare the prevalence of delirium among older hospitalised COVID-19 patients through the first, second and third wave of the COVID-19 pandemic. Furthermore, we aimed to compare risk factors for delirium, and the possible association of delirium with in-hospital mortality through different waves of the pandemic.

2 | MATERIALS AND METHODS

2.1 | Study design

The COVID-OLD study is a retro- and prospective, multicentre observational cohort study among patients ≥70 years who were hospitalised for a COVID-19 infection.[14] In this study, we included patients admitted between February 27th 2020—May 14th 2020 (first wave), September 1st 2020—December 31st 2020 (second wave) and September 1st 2021—December 31st 2021 (third wave) in the Netherlands. During the first wave, the wild-type virus variant was dominant, in the second wave the Alpha variant and in the third wave the Delta variant.[15] Data for the first wave was collected in 19 hospitals, for the second wave in 10 hospitals and for the third wave in 5 hospitals (Supplemental Table S1). An opt-out procedure was applied for data collection of the first and second wave. The medical ethics committees of all hospitals waived the necessity for formal approval of the study, as data collection followed routine practice and took place until hospital discharge. When applicable, informed consent has been asked for patients included in the third wave. All data were treated according to the European privacy regulations and the study was performed in accordance with the declaration of Helsinki.

2.2 | Study participants

Patients ≥70 years who were hospitalised due to a confirmed COVID-19 infection were eligible to participate. Patients required a positive reverse-transcriptase polymerase chain reaction (RT-PCR) test from an oropharyngeal and/or nasal swab or if the diagnosis of COVID-19 infection was based on typical findings on computerized tomography scan and/or chest X-ray. Patients were excluded if diagnosed with COVID-19 during hospital admission for another illness, defined as a positive RT-PCR test ≥24 h. Additionally, patients were excluded in case they were transferred between hospitals due to missing baseline and outcome data.

2.3 | Data collection

Demographics, clinical parameters and laboratory measurements at hospital admission and hospital outcomes were collected from electronic medical records. The prevalence of delirium during hospitalisation was assessed using the Delirium Observation Screening Scale (DOSS) which was ideally scored three times daily and supplemented with medical record review. A DOSS score >3 suggested the presence of delirium, which was confirmed by a clinical evaluation. Predisposing factors for delirium—age, comorbidities, frailty, previous episode of delirium, history of cognitive problems, and Activities of Daily Living (ADL) dependency—were extracted from the medical records using the Dutch National Safety Management System (Veiligheidsmanagementsysteem; VMS).[16–18] ADL were assessed using the Katz-ADL-scale.[19] Comorbidities were evaluated using the Charlson Comorbidity Index (CCI).[20] Frailty was measured with the Clinical Frailty Scale (CFS) score.[21] The CFS was prospectively assigned during the first day of hospital admission and noted in the medical record. If not prospectively assigned, the CFS was determined retrospectively based on available data about functional status 2 weeks before admission, and was scored by a geriatrician or internist-geriatrician, or researcher trained by a geriatrician or internist-geriatrician.[22] 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 categorized in three groups: fit (CFS 1–3), pre-frail (CFS 4–5) and frail (CFS 6–9).[23] 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 throughout the hospital admission.

Data were collected using Castor Electronic Data Capture (Amsterdam, The Netherlands) (2022).[24]

2.4 | Statistical analyses

Demographics, clinical parameters and laboratory measurements were summarised using descriptive statistics stratified for pandemic wave. Baseline characteristics in patients with and without delirium during hospitalisation were compared using an independent *t*-test for continuous parameters with a normal distribution, a Mann-Whitney U-test for continuous parameters with a non-normal distribution, and a chi-square test for categorical parameters. The association between potential risk factors and delirium was assessed using binary logistic regression analyses. First, a univariable model was built to assess associations between potential risk factors and delirium for each wave separately. Second, in multivariable analyses, associations were adjusted for identified covariates ($p < 0.05$) in univariable analyses (age, frailty, previous episode of delirium and history of memory problems). To determine if the associations between potential risk factors and delirium changed through waves, we used multiplicative interaction terms to provide statistical evidence whether the effect sizes between the waves were different.

The association between delirium and in-hospital mortality was assessed using binary logistic regression analyses. First, a univariable model was built. Second, a multivariable model was built in which was adjusted for sex, age and frailty. To determine if the association between delirium and in-hospital mortality changed through waves, we included a multiplicative interaction term between wave and delirium in the multivariable-adjusted analysis. We used multiplicative interaction terms to provide statistical evidence whether the effect sizes between the waves were different. In-hospital outcomes for patients with and without delirium were compared, also stratified for wave, using an independent *t*-test for continuous parameters with a normal distribution, a Mann-Whitney U-test for continuous parameters with a non-normal distribution and a chi-square test for categorical parameters. A *p*-value <0.05 was considered statistically significant. Statistical analyses were performed using SPSS, version 28.0.1.0.

3 | RESULTS

3461 patients were included: 1874 in the first, 1121 in the second and 466 in the third wave. We excluded 334, 237 and 96 patients per wave respectively, because of a PCR diagnosis >24h after admission and/or missing delirium status and/or because of discharge to another hospital. 2794 patients were available for baseline- and outcome analysis; 1540 in the first, 884 in the second and 370 in the third wave (Figure 1).

Baseline characteristics were stratified by wave and compared between patients with and without delirium in Table 1. Furthermore, comorbidities from the CCI that showed significant differences between patients with and without delirium are presented in Table 1.

The prevalence of delirium in the first, second and third wave was 22.5%, 23.5%, and 12.7%, respectively. There was a significant difference in delirium prevalence between wave 1 and wave 3 ($p < 0.001$), and between wave 2 and wave 3 ($p < 0.001$).

Patients with delirium were older compared to those without delirium in the first (80 vs. 78 years, $p < 0.001$), second (81 vs. 79 years, $p < 0.001$), and third wave (80 vs. 79 years, $p = 0.3$). Patients with delirium had a higher prevalence of previous episode of delirium, (first wave 40.9% vs. 9.0%, $p < 0.001$, second wave 34.3% vs. 12.3%, $p < 0.001$, third wave 27.0% vs. 9.9%, $p = 0.003$) and more often history of memory problems (first 50.7% vs. 16.4%, $p < 0.001$, second 51.0% vs. 15.7%, $p < 0.001$, and third wave 40.5% vs. 18.5%, $p = 0.002$) than patients without. Additionally, patients with delirium were more often frail (first wave 48.5% vs. 23.3%, $p < 0.001$, second wave 47.3% vs. 25.0%, $p < 0.001$, third wave 31.7% vs. 29.9%, $p = 0.8$).

In the first wave and second wave, patients with delirium had lower C-reactive protein (CRP) levels than patients without delirium (first wave 63 vs. 80 mg/L, $p = 0.003$, second wave 59 vs. 73 $p = 0.057$), whereas no numerical difference was seen in the third wave. Furthermore, in the first and second wave, patients with

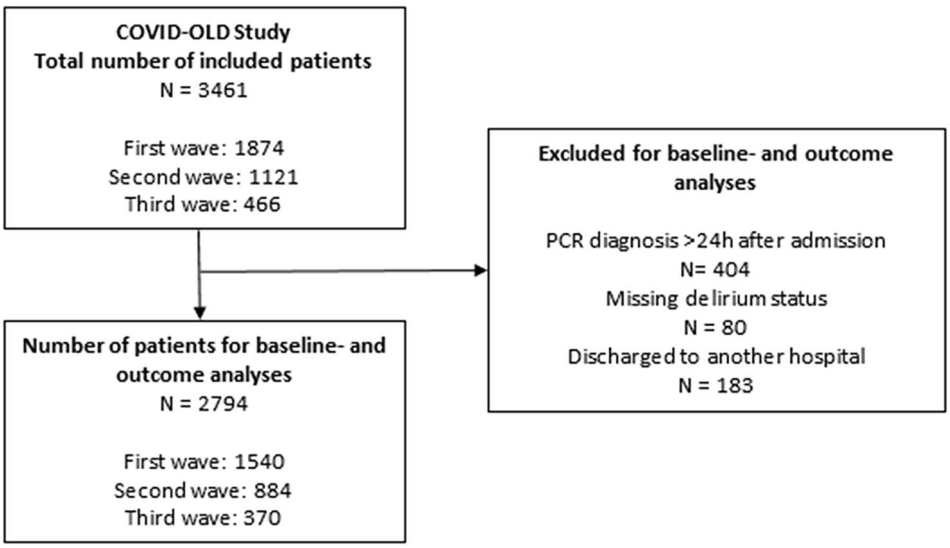

FIGURE 1 Flowchart patient inclusions.

delirium had a shorter duration of symptoms before hospital admission (first wave 5 vs. 7 days, $p < 0.001$, second wave 4 vs. 6 days, $p < 0.001$) than those without. Finally, only relevant in wave 3, patients with delirium were more frequently unvaccinated to COVID-19 compared to those without (64.3% vs. 78.2%, $p = 0.047$).

The association between risk factors and delirium is shown in Table 2. In multivariable-adjusted regression analyses, history of memory problems was associated with delirium in all waves (wave 1 OR 3.26, 95% CI 2.15–4.94, wave 2 OR 3.70, 95% CI 2.34–5.84, wave 3 OR 2.87, 95% CI 1.16–7.14). Furthermore, previous episode of a delirium was associated with delirium in wave 1 (OR 4.02, 95% CI 2.58–6.28), but not in other waves (wave 2 OR 1.61, 95% CI 0.97–2.67, wave 3 OR 2.59, 95% CI 0.91–7.35). The significant multiplicative interaction between previous episode of delirium and wave, showed that the OR of the second wave was significantly lower compared to the OR of the first wave ($p = 0.008$). Frailty was not independently associated with risk of delirium.

The association between delirium and the risk of in-hospital mortality is shown in Table 3. Patients with delirium had an increased risk of in-hospital mortality in the first wave (OR 1.47, 95% CI 1.15–1.87). After adjustment for age, sex and frailty, delirium was no longer associated with the risk of in-hospital mortality. Frailty was independently associated with in-hospital mortality in all waves. The association between risk factors and in-hospital mortality did not change across waves (all multiplicative interaction terms $p > 0.05$).

The association between delirium and the risk of other adverse in-hospital outcomes is shown in Table 4. Patients with delirium had a longer length of hospital stay than patients without (8 vs. 6 days, $p < 0.001$) in the first and second wave, but not in the third wave (7 vs. 7 days, $p = 0.094$). Patients with delirium were more often admitted to the Intensive Care Unit (13.8% vs. 10.0%, $p = 0.049$) compared to patients without in the first wave, but not in the second and third wave.

4 | DISCUSSION

This study has three main findings. First, the prevalence of delirium in the third wave was lower compared to the first and second wave. Second, risk factors for delirium remained consistent across waves, except for a previous episode of delirium, which had the highest delirium risk in the first wave and a significantly lower risk in the second wave. Third, delirium did not independently increase the risk for in-hospital mortality.

We found a delirium prevalence of respectively 22.5%, 23.5% and 12.7% in the first three waves of the COVID-19 pandemic. The prevalence in the first wave was similar to a systemic review including 48 studies that estimates delirium prevalence of 28.2% in older COVID-19 patients.[25] The lower delirium prevalence could be explained by improved treatment strategies resulting in decreased disease severity (e.g. anti-IL-6 receptor tocilizumab and corticosteroids). Additionally, the introduction of vaccinations could have decreased disease severity and thus decreased delirium prevalence in the third wave. Another explanation could be that patients in the third wave were less prone to delirium, since the traditional risk factors (previous episode of delirium and earlier memory problems) were less prevalent in the total patient group in the third wave.

Patients with delirium had similar values of vital signs at admission and thus no more severe disease than patients without delirium. We observed slightly lower CRP levels in patients with delirium than without in the first wave. Possible explanations could be that patients with delirium were admitted to the hospital earlier in the disease course compared to patients without, or patients with delirium had a different immune response.

In wave 1 and 2 but not wave 3, patients with delirium were more frequently frail than patients without delirium. Frail patients in the third wave got vaccinated first, which may have led to a decreased disease severity in this group without need for hospitalisation. Additionally, frailty itself was not found to be an independent

TABLE 1 Baseline characteristics compared between patients with and without delirium in the first, second and third wave.

	Wave 1		Wave 2		Wave 3	
	Delirium *N* = 347 (22.5%)	No delirium *N* = 1193 (77.5%)	Delirium *N* = 208 (23.5%)	No delirium *N* = 676 (76.5%)	Delirium *N* = 47 (12.7%)	No delirium *N* = 323 (87.3%)
Patient characteristics						
Age (years), median (IQR)	80 (75.5–85.5)	78 (74–83)***	81 (75–86)	79 (74–84)***	80 (76–85)	79 (74–84)
Man, *n* (%)	217 (62.7)	711 (59.6)	135 (64.9)	412 (60.9)	29 (61.7)	203 (62.8)
BMI (kg/m2), mean (SD)	26.6 (5.0)	27.6 (4.8)**	26.6 (4.9)	27 (5.0)	26.9 (7.4)	26.7 (4.9)
Living situation before admission, *n* (%)						
Living at home	282 (83.4)	1049 (91.5)***	175 (84.1)	590 (88.7)	44 (95.7)	284 (92.2)
Nursing home	49 (14.5)	84 (7.3)	29 (13.9)	68 (10.2)	2 (4.3)	24 (7.8)
Predisposing delirium factors						
Previous episodes of delirium, *n* (%)	117 (40.9)	85 (9.0)***	65 (34.3)	69 (12.3)***	10 (27.0)	26 (9.9)**
History of memory problems, *n* (%)	150 (50.7)	157 (16.4)***	99 (51.0)	90 (15.7)***	15 (40.5)	50 (18.5)**
Comorbidities, *n* (%)						
CVA or TIA	80 (23.1)	231 (19.4)	64 (30.8)	133 (19.7)***	5 (10.6)	62 (19.2)
COPD	59 (17.0)	217 (18.2)	33 (15.9)	152 (22.5)*	5 (10.6)	71 (22.0)
Charlson comorbidity index (CCI), *n* (%)						
CCI 1–3	183 (80.6)	595 (79.3)	98 (74.2)	352 (77.9)	26 (81.3)	165 (81.7)
CCI 4–6	36 (15.9)	124 (16.5)	29 (22.0)	78 (17.3)	4 (12.5)	27 (13.4)
CCI >6	8 (3.5)	31 (4.1)	5 (3.8)	22 (4.9)	2 (6.3)	10 (5.0)
Katz-ADL, median (IQR)	1 (0–4)	0 (0–2)***	1 (0–4)	0 (0–2)***	0 (0–1)	0 (0–2)
Fall in last 6 months, *n* (%)	113 (41.5)	243 (25.2)***	87 (46.5)	156 (26.5)***	13 (37.1)	62 (23.2)
Frailty (CFS score), *n* (%)						
CFS 1–3	74 (27.8)	421 (49.7)***	47 (25.8)	266 (48.3)***	15 (36.6)	95 (35.4)
CFS 4–5	63 (23.7)	229 (27.0)	49 (26.9)	147 (26.7)	13 (31.7)	93 (34.7)
CFS 6–9	129 (48.5)	197 (23.3)***	86 (47.3)	138 (25.0)***	13 (31.7)	80 (29.9)
Vital and laboratory measurements at admission						
Systolic blood pressure (mmHg), median (IQR)	136 (119–152)	137 (122–153)	136 (122–155)	135 (119–151)	136 (120.5–154)	134 (120–154)
Diastolic blood pressure (mmHg), median (IQR)	76 (66–86)	74 (66–84)	74 (64.5–85)	74 (63–83)	75 (65.5–82)	74 (65–84)
Respiratory rate (per minute), mean (SD)	21.9 (6.9)	22.1 (6.4)	23.3 (8.0)	22.7 (7.7)	23 (7.4)	22.6 (7.0)
Oxygen suppletion (L/min), median (IQR)	2 (1–4.5)	2 (1–4.8)	2 (0–4)	2 (0–4)*	3 (2–5)	2 (1–6)

(Continues)

TABLE 1 (Continued)

	Wave 1		Wave 2		Wave 3	
	Delirium *N* = 347 (22.5%)	No delirium *N* = 1193 (77.5%)	Delirium *N* = 208 (23.5%)	No delirium *N* = 676 (76.5%)	Delirium *N* = 47 (12.7%)	No delirium *N* = 323 (87.3%)
Temperature (Celsius), mean (SD)	37.8 (1.2)	37.7 (1.2)*	37.9 (1.0)	37.7 (1.1)	38.1 (1.1)	37.6 (1.0)**
Creatinine (μmol/L), median (IQR)	95 (73–135)	91 (74–125)	103 (81–133)	94 (73.5–133.5)	90 (68–115)	101 (77–134)*
CRP (mg/L), median (IQR)	63 (34–121)	80 (40–139)**	59 (27.5–113.1)	73 (35–128)	76 (42–170)	76 (36–140)
Duration of symptoms before admission (days), median (IQR)	5 (3–8)	7 (4–10)***	4 (1–7)	6 (3–9)***	5 (1–8)	6 (2–9)
Vaccinated, *n* (%)					27 (64.3)	223 (78.2)*

Note: Missing values: Wave 1: Missing numbers in patients with a delirium (*N* = 347): 1 Sex, 93 BMI, 9 Living situation before admission, 61 Previous episodes of delirium, 51 History of memory problems, 120 CCI, 75 Fall in last 6 months, 81 Frailty, 21 Systolic blood pressure, 20 Diastolic blood pressure, 24 Respiratory rate, 37 Oxygen suppletion, 17 Temperature, 16 Creatinine, 15 CRP, 35 Duration of symptoms before admission. Missing numbers in patients without a delirium (*N* = 1193): 1 Sex, 248 BMI, 46 Living situation before admission, 251 Previous episodes of delirium, 233 History of memory problems, 2 CVA or TIA, 2 COPD, 443 CCI, 228 Fall in last 6 months, 346 Frailty, 42 Systolic blood pressure, 43 Diastolic blood pressure, 59 Respiratory rate, 113 Oxygen suppletion, 41 Temperature, 49 Creatinine, 57 CRP, 100 Duration of symptoms before admission. Wave 2: Missing numbers in patients with a delirium (*N* = 208): 43 BMI, 19 Previous episodes of delirium, 14 History of memory problems, 76 CCI, 21 Fall in last 6 months, 26 Frailty, 1 Systolic blood pressure, 1 Diastolic blood pressure, 7 Respiratory rate, 11 Oxygen support, 4 Temperature, 3 Creatinine, 5 CRP, 19 Duration of symptoms before admission. Missing numbers in patients without a delirium (*N* = 676): 105 BMI, 11 Living situation before admission, 113 Previous episodes of delirium, 104 History of memory problems, 224 CCI, 88 Fall in last 6 months, 125 Frailty, 13 Systolic blood pressure, 13 Diastolic blood pressure, 35 Respiratory rate, 38 Oxygen support, 17 Temperature, 12 Creatinine, 18 CRP, 47 Duration of symptoms before admission. Wave 3: Missing numbers in patients with a delirium (*N* = 47): 10 BMI, 1 Living situation before admission, 10 Previous episodes of delirium, 10 History of memory problems, 15 CCI, 12 Fall in last 6 months, 6 Frailty, 1 Respiratory rate, 5 Oxygen support, 1 Temperature, 1 Creatinine, 1 CRP, 4 Duration of symptoms before admission, 5 Vaccinated. Missing numbers in patients without a delirium (*N* = 323): 67 BMI, 15 Living situation before admission, 61 Previous episodes of delirium, 53 History of memory problems, 121 CCI, 56 Fall in last 6 months, 55 Frailty, 2 Systolic blood pressure, 2 Diastolic blood pressure, 10 Respiratory rate, 32 Oxygen support, 9 Temperature, 1 Creatinine, 4 CRP, 20 Duration of symptoms before admission, 38 Vaccinated. Significance: * = <0.05, ** = <0.01 *** = <0.001.

risk factor for delirium. This is contrary to findings in literature. Two retrospective cohort studies found an increased delirium prevalence among frail COVID-19 patients, just as a systematic review including 31 other studies.[26–28] In our study, the CFS was used to score frailty which also takes the degree of dementia into account. Hence, the CFS is a combination of both physical and cognitive frailty. Since cognitive frailty yields a larger risk for a new episode of delirium, this might be an explanation for our finding that a previous episode of delirium and history of memory problems representing cognitive frailty were independently associated with delirium risk.

Delirium was associated with increased in-hospital mortality risk in univariable analyses, but not after adjustment for covariates such as frailty. The independent relationship between delirium and in-hospital mortality in COVID-19 patients is still debatable. Some studies did not find an independent relationship between delirium and in-hospital mortality in older COVID-19 patients,[29–31] whereas other studies did.[32–34] Our study implies that delirium is a less accurate predictor for in-hospital mortality compared to frailty, possibly due to the fact that frailty as syndrome is more comprehensive than delirium in itself.

Our study has several limitations. The sample size in each subsequent wave was almost twice as small, which might have affected the power to find significant differences between patients with and without delirium in the second and third wave. Therefore, we used multiplicative interaction terms to test whether associations significantly changed through waves, or whether a non-significant association in the third wave was the result of a smaller sample size. Moreover, there was a decreasing number of participating hospitals through the waves. During the first wave, elective hospital care and educational activities were reduced, whereas limited reduction was observed in the second and especially third wave. Therefore, in the first wave geriatricians had more time to participate in research activities compared to the second and third wave. Since the hospitals participating in the third wave formed a representation of the hospitals in the first and second wave, this most likely did not affect study results. Besides, in the third wave, the ethical procedure changed in one of the participating centres. In this hospital, (Erasmus MC University hospital) only a small proportion of the third wave patients (7 out of 62 (11.3%)), did not give informed consent retrospectively or did not return the informed consent letter. Delirium

TABLE 2 Univariable and multivariable analyses for the possible association of risk factors and delirium.

	Wave 1		Wave 2		Wave 3	
	Univariable	Multivariable	Univariable	Multivariable	Univariable	Multivariable
Age (per year)	1.05 (1.03–1.07)	1.01 (0.98–1.04)	1.05 (1.02–1.07)	1.02 (0.99–1.05)	1.03 (0.98–1.08)	1.02 (0.96–1.08)
Woman	0.88 (0.69–1.13)		0.84 (0.61–1.17)		1.05 (0.56–1.97)	
Frailty (CFS score)						
CFS 1–3	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
CFS 4–5	1.57 (1.08–2.27)	1.04 (0.67–1.63)	1.89 (1.21–2.95)	1.28 (0.77–2.14)	0.89 (0.40–1.96)	0.74 (0.29–1.90)
CFS ≥6	3.73 (2.67–5.19)	1.34 (0.84–2.14)	3.53 (2.34–5.32)	1.63 (0.97–2.74)	1.03 (0.46–2.29)	0.52 (0.18–1.50)
Charlson comorbidity Index (CCI)						
CCI 1–3	Ref.		Ref.		Ref.	
CCI 4–6	0.94 (0.63–1.42)		1.34 (0.83–2.16)		0.94 (0.30–2.91)	
CCI >6	0.84 (0.38–1.86)		0.82 (0.30–2.21)		1.27 (0.26–6.12)	
Previous episodes of delirium	6.98 (5.05–9.66)	4.02 (2.58–6.28)	3.75 (2.54–5.55)	1.61 (0.97–2.67)	3.36 (1.47–7.72)	2.59 (0.91–7.35)
History of memory problems	5.26 (3.95–6.99)	3.26 (2.15–4.94)	5.58 (3.89–8.00)	3.70 (2.34–5.84)	3.00 (1.45–6.19)	2.87 (1.16–7.14)

Note: Model 1: univariate regression analyses for delirium. Model 2: multivariate regression analyses for delirium in which is corrected for age, frailty, previous episodes of delirium and history of memory problems. Both models are presented with Odds Ratio's and 95% Confidence Intervals. Interaction terms in univariate analyses (variable*wave-categorical, variable, wave-categorical): Age*wave, $p = 0.742$; Sex*wave, $p = 0.833$; CFS*wave, $p = 0.050$; CCI*wave, $p = 0.823$; Previous episodes of delirium*wave, $p = 0.032$; History of memory problems*wave, $p = 0.310$. Interaction terms in multivariate analyses (variable*wave-categorical, variable, wave-categorical, and identified covariates): Age*wave, $p = 0.909$; CFS*wave, $p = 0.437$; Previous episodes of delirium*wave, $p = 0.028$; History of memory problems*wave, $p = 0.862$. Missing values: wave 1: 2 Sex, 427 Frailty, 563 CCI, 312 previous episodes of a delirium, 284 history of memory problems; wave 2: 151 Frailty, 300 CCI, 132 previous episodes of a delirium, 118 history of memory problems; wave 3: 61 frailty, 136 CCI, 71 previous episodes of a delirium, 63 history of memory problems.

TABLE 3 Univariable and multivariable-adjusted binary logistic regression analyses for the possible association of delirium and in-hospital mortality.

	Wave 1		Wave 2		Wave 3	
	Univariable	Multivariable	Univariable	Multivariable	Univariable	Multivariable
Delirium	1.47 (1.15–1.87)	1.10 (0.82–1.49)	1.15 (0.82–1.62)	0.85 (0.57–1.26)	1.24 (0.62–2.48)	1.35 (0.63–2.91)
Woman	0.65 (0.52–0.80)	0.62 (0.48–0.81)	0.49 (0.35–0.67)	0.43 (0.30–0.62)	0.58 (0.35–0.98)	0.48 (0.26–0.88)
Age	1.05 (1.03–1.07)	1.03 (1.01–1.05)	1.04 (1.02–1.07)	1.04 (1.01–1.06)	1.02 (0.98–1.06)	1.00 (0.96–1.05)
BMI	1.01 (0.99–1.04)		1.02 (0.98–1.05)		1.00 (0.95–1.06)	
Frailty						
CFS 1–3	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
CFS 4–5	1.74 (1.28–2.36)	1.70 (1.24–2.33)	2.18 (1.44–3.30)	2.10 (1.37–3.22)	1.34 (0.67–2.67)	1.39 (0.68–2.82)
CFS 6–9	2.17 (1.62–2.91)	2.03 (1.46–2.83)	2.59 (1.75–3.85)	2.57 (1.66–3.98)	2.20 (1.12–4.31)	2.43 (1.21–4.91)
Charlson comorbidity Index (CCI)						
CCI 1–3	Ref.		Ref.		Ref.	
CCI 4–6	1.13 (0.80–1.60)		1.04 (0.65–1.66)		1.07 (0.43–2.65)	
CCI >6	0.74 (0.37–1.48)		0.93 (0.38–2.26)		0.33 (0.04–2.65)	

Note: Model 1: univariate regression analyses for in-hospital mortality. Model 2: multivariate regression analyses for delirium and in-hospital mortality in which is corrected for sex, age and frailty. Both models are presented with Odds Ratio's and 95% Confidence Intervals. Interaction terms in univariate analyses (variable*wave-categorical, variable, wave-categorical): Delirium*wave, $p = 0.518$; Sex*wave, $p = 0.365$; Age*wave, $p = 0.364$; BMI*wave, $p = 0.926$; Frailty*wave, $p = 0.760$; CCI*wave, $p = 0.919$. Interaction terms in multivariate analyses (variable*wave-categorical, variable, wave-categorical, and identified covariates): Delirium*wave, $p = 0.451$; Sex*wave, $p = 0.250$; Age*wave, $p = 0.517$; Frailty*wave, $p = 0.736$. Missing values: wave 1: 2 Sex, 341 BMI, 427 Frailty, 563 CCI; wave 2: 148 BMI, 151 Frailty, 300 CCI; wave 3: 77 BMI, 61 frailty, 136 CCI.

TABLE 4 In hospital outcomes compared between patients with and without delirium in the first, second and third wave.

	Wave 1		Wave 2		Wave 3	
	Delirium N = 347 (22.5%)	No delirium N = 1193 (77.5%)	Delirium N = 208 (23.5%)	No delirium N = 676 (76.5%)	Delirium N = 47 (12.7%)	No delirium sN = 323 (87.3%)
Length of stay (days), median (IQR)	8 (4–14)	6 (3–9) ***	8 (5–14)	6 (4–11)***	7 (5–18.5)	7 (4–12)
ICU admission, *n* (%)	46 (13.8)	116 (10.0)*	21 (10.1)	57 (8.4)	6 (12.8)	24 (7.4)
Ventilator assisted breathing, *n* (%) of ICU admitted patients	43 (93.5)	94 (81.0)	14 (66.7)	40 (70.2)	4 (66.7)	12 (50.0)
Destination of discharge, *n* (%)						
Home	74 (21.3)	491 (41.2)***	66 (31.7)	341 (50.4)***	18 (38.3)	187 (57.9)*
Nursing home	106 (30.5)	255 (21.4)***	74 (35.6)	140 (20.7)***	13 (27.7)	54 (16.7)
Other	167 (48.1)	477 (37.5)***	68 (32.7)	195 (28.8)	16 (34.0)	82 (25.4)
Readmission, *n* (%)	16 (4.7)	44 (3.8)	18 (8.7)	79 (11.7)	2 (4.3)	14 (4.3)

Note: Missing values: Wave 1: Missing numbers in patients with a delirium (347): 13 ICU admission, 1 Ventilator assisted breathing, 8 Readmission. Missing numbers in patients without a delirium (1193): 30 ICU admission, 44 Readmission. Wave 2: Missing numbers in patients with a delirium (208): n. a. Missing numbers in patients without a delirium (676): 1 ICU admission, 1 Readmission. Wave 3: Missing numbers in patients with a delirium (47): 13 ICU admission. Missing numbers in patients without a delirium (323): 30 ICU admission.

Significance: * = <0.05, ** = <0.01 *** = <0.001.

prevalence was not different in patients who provided informed consent versus patients who did not. Therefore, it is unlikely that this change in ethical procedure affected the results. Additionally, the vaccination programme in the Netherlands started after the end of the second wave—specifically on January 6th, 2021. Therefore, only patients included in the third wave could have been vaccinated which possibly affected disease severity. Furthermore, occasionally the CFS score was collected retrospectively. However, research shows that retrospectively and prospectively collected CFS scores highly correspond.[22] Additionally, delirium is sporadically missed and underdiagnosed. Therefore, the prevalence of delirium could be underestimated. Lastly, data has only been collected in hospitals in the Netherlands. This could make our results less valid for other countries.

This study also has several strengths. 2794 patients were included from 19 different hospitals. This implies that our data forms a representative cohort for older COVID-19 patients in the Netherlands. Besides, a wide variety of baseline variables and in-hospital outcomes were collected. Lastly, this is the first study to compare delirium prevalence and outcomes over the first three waves in older COVID-19 patients.

This study gives a clear view on the role of delirium during the three pandemic waves and its association with mortality. Nevertheless, certain factors remain unclear and further research is needed to investigate long-term outcomes of delirium in COVID-19. Besides, important parameters such as quality of life and patient experiences are not considered, which were suggested by a Seniors Advisory Board. Additionally, more research is needed tailored towards older patients hospitalised for COVID-19. Recent studies predominantly consist of cohorts with mixed age groups, whereas risk stratification and treatment decisions might be even more relevant in older and severely ill patient groups.

To conclude, we observed a decreased prevalence of delirium through COVID-19 waves. This decrease was probably due to differences in virus variant, but also to the start of vaccinations and developments in treatment. These findings suggest that early developments of therapeutic programs can change disease severity and specifically delirium as manifestation. For future potential pandemics and other severe infectious diseases, it remains critical to recognize delirium risk factors in an early stage and diagnose delirium.

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CONFLICT OF INTEREST STATEMENT

None or the authors reported a conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Primary approval by ethical committee of the Leiden University Medical Centre. Furthermore, all participating hospitals acquired approval of their local ethical committees.

PATIENT CONSENT STATEMENT

All medical ethical committees of the local hospitals approved the study and did not ask for written participant consent, except one hospital (Erasmus Medical Centre, Rotterdam, the Netherlands). For the participants of the third COVID-19 wave, hospitalised within the Erasmus Medical Centre, written consent was asked and obtained. For the other hospitals, no written consent was needed as they used an opt-out procedure.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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