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Research

Characteristics, treatment and delirium incidence of older adults hospitalized with COVID-19: a multicentre retrospective cohort study

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Abstract

Background: The COVID-19 pandemic has affected older adults disproportionately, and delirium is a concerning consequence; however, the relationship between delirium and corticosteroid use is uncertain. The objective of the present study was to describe patient characteristics, treatments and outcomes among older adults hospitalized with COVID-19, with a focus on dexamethasone use and delirium incidence.

Methods: We completed this retrospective cohort study at 7 sites (including acute care, rehabilitation and long-term care settings) in Toronto, Ontario, Canada. We included adults aged 65 years or older, consecutively hospitalized with confirmed SARS-CoV-2 infection, between Mar. 11, 2020, and Apr. 30, 2021. We abstracted patient characteristics and outcomes from charts and analyzed them descriptively. We used a logistic regression model to determine the association between dexamethasone use and delirium incidence.

Results: During the study period, 927 patients were admitted to the acute care hospitals with COVID-19. Patients' median age was 79.0 years (interquartile range [IQR] 72.0–87.0), and 417 (45.0%) were female. Most patients were frail (61.9%), based on a Clinical Frailty Scale score of 5 or greater. The prevalence of delirium was 53.6%, and the incidence was 33.1%. Use of restraints was documented in 20.4% of patients. In rehabilitation and long-term care settings (n = 115), patients' median age was 86.0 years (IQR 78.5–91.0), 72 (62.6%) were female and delirium occurred in 17 patients (14.8%). In patients admitted to acute care during wave 2 of the pandemic (Aug. 1, 2020, to Feb. 20, 2021), dexamethasone use had a nonsignificant association with delirium incidence (adjusted odds ratio 1.38, 95% confidence interval 0.77–2.50). Overall, in-hospital death occurred in 262 (28.4%) patients in acute care settings and 28 (24.3%) patients in rehabilitation or long-term care settings.

Interpretation: In-hospital death, delirium and use of restraints were common in older adults admitted to hospital with COVID-19. Further research should be directed to improving the quality of care for this population with known vulnerabilities during continued waves of the COVID-19 pandemic.

The COVID-19 pandemic has affected older adults disproportionately. Older age is a risk factor for morbidity and mortality related to COVID-19 because of impaired immune response, multimorbidity and higher risk of institutionalization.[1] In Ontario, Canada, during the early stages of the pandemic, outbreaks in long-term care homes allowed the SARS-CoV-2 virus to spread rapidly,[2] and residents with COVID-19 were often transferred to hospital for acute care management. Later in the pandemic, rapid vaccination led to a dramatic reduction in SARS-CoV-2 infections in long-term care residents, but infections rose among community-dwelling older adults, who also often required hospitalization.[3]

Evolution of the SARS-CoV-2 virus led to the dominance first of the Alpha (B.1.1.7) strain, and later the Beta (B.1.351) and Gamma (P.1) strains.[4] These variants increased the transmissibility of the virus by up to 58% in Ontario.[4] In response, stricter and more prolonged periods of community lockdown

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were required to reduce the reproduction number of the virus.[5] The Alpha variant was associated with increased virulence and risk of death, particularly in older adults.[6] Hospitalizations continued to rise during wave 2 of the pandemic (Aug. 1, 2020, to Feb. 20, 2021[7]) in Ontario.

Advances in the treatment of COVID-19 have enabled clinicians to augment supportive care. Therapies found to be effective in wave 2 for the treatment of hospitalized patients with COVID-19 have included dexamethasone,[8] remdesivir[9] and tocilizumab.[10] The use of dexamethasone has led to concerns about increased risk of delirium in older adults,[11] but delirium has not been measured in randomized trials.[8] Other drugs such as azithromycin,[12] lopinavir–ritonavir[13] and hydroxychloroquine[13] were no longer used in wave 2 because of a lack of efficacy. In terms of nonpharmacologic treatment, proning[14] was found to be helpful in improving oxygenation and was used commonly in wave 2.

A better understanding of the transmission of the SARS-CoV-2 virus led to improved treatment protocols in wave 2, including broader testing for SARS-CoV-2 in hospitalized patients; improved disease surveillance among health care staff and patients; protocol-guided hospital outbreak management;[15] and prioritizing the vaccination of health care staff. Still, despite these efforts, the evolution of SARS-CoV-2 suggests that the virus will persist even if populations reach high levels of vaccination.[16] It is essential that we understand hospital management and outcomes in older adults with COVID-19, so that we can prepare for potential future waves of the pandemic.

The objective of the present study was to describe patient characteristics, treatments and outcomes among hospitalized older adults with COVID-19, with a focus on dexamethasone use and delirium incidence. We investigated the relationship between dexamethasone use and delirium because of concerns about their association in older adults and a lack of delirium outcomes reported in randomized trials.

Methods

Study design and setting

This was a multicentre, retrospective cohort study that describes a cohort of older adults who were hospitalized for COVID-19 between Mar. 11, 2020, and Apr. 30, 2021. The study took place in Toronto at 5 acute care hospitals (Mount Sinai Hospital, St. Michael's Hospital, Sunnybrook Health Sciences Centre, Toronto General Hospital and Toronto Western Hospital) and 2 rehabilitation and long-term care facilities (Baycrest Health Sciences and Providence Healthcare). Overall, we included cases from Mar. 11, 2020, to Apr. 30, 2021, but for the analysis of treatments, we included cases only from wave 2, because treatment evidence became available then.[8–10] As defined by Toronto Public Health,[7] wave 2 began on Aug. 1, 2020, and ended on Feb. 20, 2021, but data were collected until Apr. 30, 2021.

The study protocol is available on Open Science Framework (https://osf.io/k4g7a/), and a study description has been posted on Clinical Trials Ontario (www.ctontario.ca). The study was originally designed to investigate atypical presentations of COVID-19 in older adults, but we expanded it to include all treatment and outcomes data continuously from the start of the pandemic. This paper summarizes the treatment, outcomes and delirium characteristics of this cohort within the stated time frame. We used the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for reporting this cohort study.[17]

Participants

We included adults aged 65 years and over with SARS-CoV-2 infection, consecutively admitted to one of the included hospitals. SARS-CoV-2 infection was confirmed by viral polymerase chain reaction (PCR) test results, available from hospital health records. We limited PCR test results to those conducted in hospital because we were unable to use the provincial health portal (Connecting Ontario) for our research.

Exclusion criteria were as follows: readmission after an index admission for COVID-19 (only records from initial admissions were included); false-positive SARS-CoV-2 results, as defined by infection control procedures or by treatment team assessment and removal of isolation precautions; and positive results because of a recovered SARS-CoV-2 infection, as defined by infection prevention and control procedures or by treatment team assessment and removal of isolation precautions.

If patients were diagnosed with SARS-CoV-2 infection at a rehabilitation or long-term care home but later transferred to acute care, we included only the acute care admission to avoid double-counting patients admitted to multiple facilities. If patients were diagnosed with COVID-19 in acute care and later transferred to a rehabilitation or long-term care home, we included only data from the acute care stay. We did not distinguish between patients admitted with SARS-CoV-2 infection and patients who had a positive test for SARS-CoV-2 infection but had another admission diagnosis, because medical management was similar at that point in the pandemic. Those who received treatments specific to COVID-19 were diagnosed with COVID-19 pneumonia regardless of their admission diagnosis.

Data sources

Patients who met the inclusion criteria were identified by decision support (data analytics) at each site, using the same case-detection protocol as is used for public health reporting. A trained chart assessor abstracted data using a standardized data abstraction form hosted on a REDCap database.[18] Each chart assessor was trained by a physician investigator at the hospital site (E.K.-C.W., J.W., A.V., K.P., T.I. and B.L.). The first 5 charts were extracted in duplicate with the physician investigator, and the physician investigator reviewed additional charts when the chart assessor had questions. We used an online procedure manual for consistent data collection across sites.

We extracted patient characteristics from the charts, including age at diagnosis, date of diagnosis, sex (as documented on chart), baseline functional status (as documented

by internal medicine consultation notes or occupational therapist notes), place of residence, frailty (measured using the Clinical Frailty Scale)[19] and medical history. We recorded treatments for COVID-19, including dexamethasone, remdesivir, tocilizumab, hydroxychloroquine and antibiotics. We also documented enrolment in any clinical trials related to COVID-19.

We assessed delirium using a validated chart review tool,[20] which is based on the occurrence of key words (e.g., agitation, confusion) when a diagnosis of delirium is not documented. We recorded whether delirium occurred upon presentation at hospital (delirium prevalence) or during hospitalization (delirium incidence). If delirium was present, we abstracted characteristics such as predominant motor subtype, documentation of agitation, use of restraints and use of medication.

We recorded outcomes, including in-hospital mortality, intensive care unit (ICU) admission, length of stay and in-hospital complications. Complications were defined as events associated with SARS-CoV-2 infection, such as venous thromboembolism, respiratory failure and cardiovascular events.[21] We also recorded geriatric complications such as in-hospital falls and use of restraints.

See Appendix 1, available at www.cmajopen.ca/content/10/3/E692/suppl/DC1, for details of the variables collected and additional data processing.

Statistical analysis

We analyzed data for the acute care and rehabilitation and long-term care cohorts separately because they differed in terms of disease severity and patient characteristics. We limited the analysis of treatment-specific (i.e., dexamethasone, remdesivir and tocilizumab) characteristics and outcomes to patients in wave 2 of the COVID-19 pandemic because evidence-based treatments were not available in wave 1. We analyzed patient characteristics and outcomes descriptively using counts (proportions), mean ± standard deviation (SD) and median (interquartile range [IQR]), where appropriate. We used statistical tests to compare data, including χ^2 tests (categorical variables), analysis of variance (continuous variables) and Kruskal–Wallis tests (variables with skewed distribution).

Missing or erroneous data (e.g., dates that were outside of the study range or temperatures that were outside of physiologic range) were reviewed by the site physician investigator. We imputed missing Clinical Frailty Scale scores as 6 (severe frailty) for residents of long-term care homes and 5 (moderate frailty) for residents of retirement homes, based on local long-term care admission criteria and published frailty estimates.[22,23]

We used a multivariable logistic regression model to explore the association between dexamethasone use (primary predictor) and delirium incidence (dependent variable) in wave 2 of the COVID-19 pandemic, because dexamethasone was widely used only at that time. The model adjusted for clinically relevant covariates that we selected a priori for the relationship between dexamethasone and delirium, including age, presence of dementia, ICU admission and Clinical Frailty Scale score. Later, we added use of remdesivir and tocilizumab as covariates. Any records missing ICU admission status or Clinical Frailty Scale score were excluded from the regression analysis.

Statistical significance was defined at $p < 0.05$. We tested the model fit using the Hosmer–Lemeshow test and discrimination using the C statistic. We avoided model overspecification by ensuring an appropriate number of variables (1 variable per 10 events).[24] We conducted analyses in R (version 4.0.3).

Ethics approval

Research ethics approval was obtained through Clinical Trials Ontario (3186-OPIA-Apr/2020-38044).

Results

Baseline characteristics (both cohorts)

During the study period, 927 patients who met our inclusion criteria were admitted to an acute care hospital with COVID-19 (Table 1). Their median age was 79.0 years (IQR 72.0–87.0), and 417 (45.0%) were female. Impairment in at least 1 instrumental activity of daily living was documented in 497 patients (53.6%), and impairment in at least 1 activity of daily living was documented in 359 patients (38.7%). The mean (± SD) Clinical Frailty Scale score was 4.95 ± 1.55, and 552 patients (61.9%) were classified as frail (Clinical Frailty Scale score ≥ 5).[25] In terms of mobility, 371 patients (41.0%) walked independently, 245 (27.1%) walked with a walker, 90 (9.9%) used a wheelchair and 44 (4.9%) were bed-bound.

In the acute care setting, the most common comorbidities were hypertension (n = 637, 69.0%), diabetes (n = 369, 40.0%) and coronary artery disease (n = 220, 23.9%). Dementia was present in 212 patients (23.1%), and 132 had a history of falls (14.3%). Overall, 463 patients (55.6%) had documented full code resuscitation status on admission, and 329 patients (39.5%) had a documented do not resuscitate order. At admission, 632 patients (68.2%) had infiltrate on chest x-ray, and the median (IQR) maximum temperature was 37.7°C (37.0–38.4°C).

In the 2 facilities that provided rehabilitation and long-term care services, 115 patients were admitted (Table 2). At baseline, patients in these facilities were older than those in acute care (median age 86.0 years v. 79.0 years in acute care) and more were female (62.6% v. 45.0% in acute care). They were also more frail (94.8% classified as frail v. 61.9% in acute care) and more likely to have dementia (48.7% v. 23.1% in acute care) and falls (46.1% v. 14.3% in acute care).

Treatments, outcomes and delirium characteristics

Acute care

In acute care hospitals, dexamethasone was used in 460 patients (49.6%), remdesivir was used in 99 (10.7%) and tocilizumab was used in 25 (2.7%; Table 3). Eighty patients (8.6%) took part in a clinical trial, and 44 (4.7%) had surgery in hospital.

In-hospital death occurred in 262 patients (28.4%). ICU admission was required in 215 patients (23.4%). At least 1 complication occurred in 432 patients (46.6%). The most common complications related to COVID-19 were respiratory failure

Table 1: Baseline characteristics of adults aged ≥ 65 years admitted to acute care hospital with COVID-19

Characteristic	No. (%) of patients* n = 927	No. (%) of records missing n = 927
Age, yr, median (IQR)	79.0 (72.0–87.0)	0
Female	417 (45.0)	0
From long-term care	174 (18.8)	2 (0.2)
Any impairment in activities of daily living	359 (38.7)	0
Any impairment in instrumental activities of daily living	497 (53.6)	0
Clinical Frailty Scale		35 (3.8)
Mean score ± SD	4.95 ± 1.55	–
Frail (score ≥ 5)	552 (61.9)	–
Baseline mobility		22 (2.4)†
Walks independently	371 (41.0)	–
Walks with cane	56 (6.2)	–
Walks with walker	245 (27.1)	–
Wheelchair	90 (9.9)	–
Bed-bound	44 (4.9)	–
Undocumented	99 (10.9)	–
Comorbidities		
Dementia	212 (23.1)	10 (1.1)
Falls	132 (14.3)	5 (0.5)
Heart failure	131 (14.2)	6 (0.6)
Coronary artery disease	220 (23.9)	6 (0.6)
Chronic kidney disease	189 (20.5)	5 (0.5)
Stroke	170 (18.5)	6 (0.6)
Hypertension	637 (69.0)	4 (0.4)
Diabetes	369 (40.0)	5 (0.5)
Chronic obstructive pulmonary disease	112 (12.2)	7 (0.8)
Cancer	217 (23.6)	7 (0.8)
Baseline code status		95 (10.2)†
Full code	463 (55.6)	–
Do not resuscitate	329 (39.5)	–
Only intubation	21 (2.5)	–
Other option	8 (1.0)	–
Undocumented	11 (1.3)	–
Presenting characteristics		
Any infiltrate on chest x-ray	632 (68.2)	39 (4.2)
Maximum temperature on presentation, °C, median (IQR)	37.7 (37.0–38.4)	120 (13.0)
Days from prodromal symptoms to COVID-19 diagnosis, median (IQR)	3.0 (1.0–7.0)	115 (12.4)

Note: IQR = interquartile range, SD = standard deviation.
*Unless otherwise indicated.
†Indeterminate.

(n = 154, 16.6%) and acute respiratory distress syndrome (n = 101, 10.9%). Pulmonary embolism occurred in 20 patients (2.2%), and deep venous thrombosis in 9 patients (1.0%). Patients' median length of stay was 11.0 days (IQR 6.0–22.0). A palliative care plan was documented in 199 patients (21.5%).

The prevalence of delirium was 53.6% (497 of 927 patients) and the incidence of delirium was 33.1% (201 of 608 patients who did not have delirium on presentation). Restraints were used in 189 patients (20.4%). Forty-five patients (4.9%) had an in-hospital fall.

Table 2: Characteristics, outcomes and treatments of adults aged ≥ 65 years admitted to rehabilitation or long-term care hospitals with COVID-19*

Characteristic	No. (%) of patients† *n* = 115
Age, yr, median (IQR)	86.0 (78.5–91.0)
Female	72 (62.6)
Rehabilitation hospital	44 (38.3)
Long-term care	71 (61.7)
Clinical Frailty Scale	
Mean score ± SD	6.80 ± 1.17
Frail (score ≥ 5)	109 (94.8)
Comorbidities	
Dementia	56 (48.7)
Falls	53 (46.1)
Heart failure	17 (14.8)
Coronary artery disease	27 (23.5)
Chronic kidney disease	13 (11.3)
Stroke	21 (18.3)
Hypertension	68 (59.1)
Diabetes	38 (33.0)
Chronic obstructive pulmonary disease	9 (7.8)
Cancer	25 (21.7)
Presenting characteristics	
Any infiltrate on chest x-ray	7 (6.1)
Maximum temperature on presentation, °C, median (IQR)	37.5 (36.9–38.0)
Outcomes	
In-hospital death	28 (24.3)
Delirium	17 (14.8)
Any complications	44 (38.3)
Complications	
Fall	19 (16.5)
Pneumonia	16 (13.9)
Aspiration	2 (1.7)
Respiratory failure	8 (7.0)
Acute respiratory distress syndrome	4 (3.5)
Use of restraints	0 (0)
Treatments	
Dexamethasone	25 (21.7)
Azithromycin	7 (6.1)
Other antibiotics	16 (13.9)

Note: IQR = interquartile range, SD = standard deviation.
*No missing data.
†Unless otherwise indicated.

Of the 497 patients with delirium at any time during their acute care admission (Table 4), 220 (44.3%) were female and the median age was 82.0 (IQR 74.0–89.0). A history of behavioural and psychological symptoms of dementia was documented in 110 patients (22.1%). The predominant delirium motor subtype was hypoactive in 182 patients (36.6%), hyperactive in 142 patients (28.6%) and mixed in 83 patients (16.7%). Sedating medications were used in 335 patients (67.4%); antipsychotics were used in 266 (53.5%) and benzodiazepines in 154 (31.0%). Family were physically present for 101 patients with delirium (20.3%), and virtual technology was used for 278 patients (55.9%) when family could not be present in person.

Rehabilitation or long-term care

In the rehabilitation and long-term care setting (Table 2), dexamethasone was used in 25 patients (21.7%). In-hospital death occurred in 28 patients (24.3%). Delirium occurred in 17 patients (14.8%). Complications occurred in 44 patients (38.3%). The main complications were falls (*n* = 19, 16.5%) and pneumonia (*n* = 16, 13.9%). We found no documented use of restraints.

Dexamethasone, remdesivir and tocilizumab treatment in wave 2 (acute care)

We analyzed patient characteristics and outcomes associated with the use of dexamethasone, remdesivir and tocilizumab only in wave 2 in patients in acute care (*n* = 631; Table 5). Age, frailty and cognitive status were similar for those who received dexamethasone and who did not. Fewer females received drug treatment (42.8% v. 54.4% in males). Patients who received dexamethasone were more likely to have a fever (53.0% v. 33.3%) and have higher mean C-reactive protein levels (109.32 v. 45.15 mg/L). Dexamethasone use was associated with more in-hospital deaths (37.3% v. 7.2%), longer length of stay (11.0 v. 7.0 d), increased ICU admissions (28.4% v. 11.1%), increased delirium prevalence (59.0% v. 36.7%), increased delirium incidence (37.2% v. 21.3%) and increased use of restraints (24.2% v. 9.4%). In a supplementary analysis using the entire cohort (acute care in waves 1 and 2), dexamethasone was similarly associated with these outcomes (Appendix 1, Table S1).

Remdesivir and tocilizumab were not associated with differences in mortality, length of stay, delirium or use of restraints in wave 2. However, both drugs were given to younger, less frail patients who had fewer comorbidities.

Dexamethasone and delirium in wave 2 (acute care)

Because dexamethasone was associated with increased delirium incidence in our unadjusted analysis, we created a multivariable model to test for independent relationships. In the multivariable model (Table 6), the strength of the association between dexamethasone use and delirium incidence in wave 2 was reduced (adjusted odds ratio [OR] 1.38, 95% confidence interval [CI] 0.77–2.50) after adjusting for remdesivir use (adjusted OR 1.56, 95% CI 0.80–3.04), tocilizumab use (adjusted OR 2.53, 95% CI 0.73–9.24), age (adjusted OR 1.21 for each 5-year increase, 95% CI 1.04–1.40), dementia (adjusted OR 3.25, 95% CI 1.67–6.45), ICU admission (adjusted OR 6.82, 95% CI 3.65–13.11) and Clinical Frailty Scale score (adjusted OR 1.53, 95% CI 1.24–1.91).

Table 3: Treatments and outcomes of adults aged ≥ 65 years admitted to acute care hospital with COVID-19

Characteristic	No. (%) of patients* *n* = 927	No. (%) of records missing *n* = 927
COVID-19 treatment		
Dexamethasone	460 (49.6)	0
Azithromycin	203 (21.9)	0
Remdesivir	99 (10.7)	0
Other steroid	56 (6.0)	0
Tocilizumab	25 (2.7)	0
Convalescent plasma	18 (1.9)	0
Lopinavir or ritonavir	6 (0.6)	0
Hydroxychloroquine	4 (0.4)	0
Participation in clinical trial	80 (8.6)	12 (1.3)
Surgery in hospital	44 (4.7)	4 (0.4)
Outcomes		
In-hospital death	262 (28.4)	3 (0.3)
Length of stay, median (IQR)	11.0 (6.0–22.0)	13 (1.4)
Delirium prevalence	497 (53.6)	0
Delirium incidence†	201/608 (33.1)	0
ICU admission	215 (23.4)	8 (0.9)
Any complications	432 (46.6)	0
Palliative care in hospital	199 (21.5)	9 (1.0)
Complications		
Use of restraints	189 (20.4)	0
Respiratory failure	154 (16.6)	0
Acute respiratory distress syndrome	101 (10.9)	0
Other infection	68 (7.3)	0
Aspiration	59 (6.4)	0
Hospital-acquired pneumonia	45 (4.9)	0
In-hospital fall	45 (4.9)	0
Stroke	22 (2.4)	0
Pulmonary embolism	20 (2.2)	0
Heart failure	19 (2.0)	0
Myocardial infarction	18 (1.9)	0
Deep vein thrombosis	9 (1.0)	0

Note: CI = confidence interval, ICU = intensive care unit, IQR = interquartile range.
*Unless otherwise indicated.
†Delirium incidence was calculated by excluding those who presented with delirium, so the denominator was different for this row.

Interpretation

Although more than 90% of adults over age 60 years were fully vaccinated in Canada as of Sept. 30, 2021,[26] older adults continue to comprise most of the patients admitted to hospital with COVID-19 in Canada today.[27] As new SARS-CoV-2 variants continue to emerge, we need to continue optimizing the care of older adults in hospital. This multisite cohort study of older patients admitted to hospital with COVID-19 highlighted patient characteristics, treatments used and patient outcomes during the study period. We found a high prevalence of frailty and comorbidities in both the acute care and rehabilitation and long-term care cohorts. In-hospital deaths were common (28.4% in the acute care cohort and 24.3% in the rehabilitation or long-term care cohort). Delirium was prevalent (54.1%) in the acute care setting and was predominantly of the hypoactive motor subtype. Treatment with dexamethasone was associated with poorer outcomes, including a higher incidence of delirium.

Table 4: Delirium characteristics of adults aged ≥ 65 years admitted to acute care hospital with COVID-19

Characteristic	No. (%) of patients* $n = 497$	No. (%) of records missing $n = 497$
Age, yr, median (IQR)	82.0 (74.0–89.0)	0
Female	220 (44.3)	0
History of behavioural and psychological symptoms of dementia	110 (22.1)	14 (2.8)
Motor subtype		13 (2.6)
Hyperactive	142 (28.6)	–
Hypoactive	182 (36.6)	–
Mixed	83 (16.7)	–
No subtype	84 (16.9)	–
Evidence of agitation	283 (56.9)	9 (1.8)
Use of restraints	184 (37.0)	7 (1.4)
Use of any sedating medication	335 (67.4)	22 (4.4)
Use of antipsychotics	266 (53.5)	13 (2.6)
Use of benzodiazepines	154 (31.0)	11 (2.2)
Presence of family or caregivers in person	101 (20.3)	16 (3.2)
Use of virtual technology for family or caregivers who could not be present in person	278 (55.9)	21 (4.2)

Note: IQR = interquartile range.
*Unless otherwise indicated.

We found a high prevalence of frailty in those admitted with COVID-19, similar to studies from other countries.[28,29] In-hospital death was common (28.4%), but it was lower than in cohorts of older hospitalized adults in the Netherlands (38%)[30] and the United Kingdom (60%).[31] The differences may be attributable to severe hospital resource limitations during the initial wave of SARS-CoV-2 infections in those countries.[31]

In-hospital mortality in Canadian adults aged 65 years and older who were hospitalized with pneumonia was consistent at 16.4% to 17.1% from 2004 to 2010.[32] The mortality identified in our study (28.4%) represents nearly double this rate. A Canadian study (median age 65 years) that compared death from COVID-19 or influenza found a threefold increase in mortality in hospitalized adults with COVID-19.[33] Several pathogenic mechanisms explain the susceptibility of older adults to poorer outcomes with COVID-19, including immunosenescence,[34] impaired ciliary clearance in the lungs,[1] impaired physiologic reserve (homeostenosis)[35] and multimorbidity.[36] Still, despite such increased mortality, the median length of stay in this cohort (11.0 d) was similar to that of older adults hospitalized with pneumonia from a historical cohort (11.98 to 13.30 d).[32] This may have been because of an aggressive disease course or because of early discussions about goals of care and palliation.

Delirium was common in this cohort, both in prevalence (53.6%) and incidence (33.1%). These proportions were higher than those from a meta-analysis of published studies (pooled prevalence 28.2% and incidence 25.2%), but in the meta-analysis a wide range of values were reported (e.g., incidence ranged from 4.0% to 80.2%).[37] Differences may have resulted from varying methods of detecting delirium, frailty of the population or illness severity.[37]

In the present study, patients who experienced delirium were frequently restrained (37.0%) and received antipsychotics (53.5%) or benzodiazepines (31.0%). Various organizations[38,39] recommended limiting the use of physical restraints in older hospitalized patients because of increased risk of injuries. However, because of visitor restrictions related to COVID-19, family members were often not allowed to come in person and calm a patient in delirium (only 20.3% had family visit), and this may have increased the prevalence of restraint and medication use. Interestingly, no patients in the rehabilitation or long-term care settings required the use of restraints. Long-term care homes in Ontario undergo routine audits for the use of physical restraints,[40] unlike acute care hospitals. This factor may have encouraged those facilities to have better staff training and policies for patients with agitation. Frequent use of restraints and antipsychotics in hospitalized older adults should prompt further research and staff training.

In the present study, data from wave 2 of the pandemic (Aug. 1, 2020, to Feb. 20, 2021) revealed that sicker patients received dexamethasone, leading to poorer outcomes, including increased mortality, length of stay and ICU admission. Female patients were less likely to receive drug treatment, probably because of increased illness severity in male patients.[41] Male sex is hypothesized to predispose patients to more severe disease because of more comorbidities[42] and sex-related differences in the immune system.[43]

In the literature from ICUs, steroid use has been reported to increase delirium risk.[44] Our data showed that

Table 5: Characteristics and outcomes associated with the use of dexamethasone, remdesivir and tocilizumab in acute care patients during wave 2* of the COVID-19 pandemic

	Dexamethasone *n* = 631			Remdesivir *n* = 631			Tocilizumab *n* = 631		
Characteristic	No	Yes	RR or MD (95% CI)†	No	Yes	RR or MD (95% CI)†	No	Yes	RR or MD (95% CI)†
No. (%) of patients	180 (28.5)	451 (71.5)	–	532 (84.3)	99 (15.7)	–	607 (96.2)	24 (3.8)	–
Characteristics									
Age, median (IQR)	79.0 (71.0–86.0)	80.0 (72.0–88.0)	–	81.0 (72.0–88.0)	75.0 (69.5–84.5)	–	80.0 (72.0–88.0)	73.5 (70.0–81.0)	–
Female, no. (%)	98 (54.4)	193 (42.8)	–	253 (47.6)	38 (38.4)	–	281 (46.3)	10 (41.7)	–
Frailty, no. (%)‡	104 (57.8)	274 (60.8)	–	339 (63.7)	39 (39.4)	–	371 (61.1)	7 (29.2)	–
Dementia, no. (%)	42 (23.3)	106 (23.5)	–	137 (25.8)	11 (11.1)	–	147 (24.2)	1 (4.2)	–
Chest x-ray infiltrates, no. (%)	87 (48.3)	354 (78.5)	–	361 (67.9)	80 (80.8)	–	425 (70.0)	16 (66.7)	–
Fever, no. (%)	60 (33.3)	239 (53.0)	–	242 (45.5)	57 (57.6)	–	281 (46.3)	18 (75.0)	–
C-reactive protein, mg/dL, median (IQR)	30.5 (11.0–53.2)	88.6 (49.4–157.5)	–	71.6 (31.1–134.1)	65.0 (48.0–134.0)	–	62.0 (33.0–127.0)	148.7 (88.2–183.9)	–
Outcomes									
In-hospital death, no. (%)	13 (7.2)	168 (37.3)	1.46 (1.35–1.59)	155 (29.1)	26 (26.3)	0.88 (0.58–1.33)	172 (28.3)	9 (37.5)	1.48 (0.66–3.32)
Length of stay, d, median (IQR)	7.0 (3.0–14.0)	11.0 (7.0–21.0)	4.0 (2.0–5.0)	10.0 (5.0–19.0)	11.0 (7.0–22.0)	1.0 (0–3.0)	10.0 (6.0–19.0)	14.0 (7.8–20.0)	2.0 (–2.0 to 6.0)
Delirium prevalence, no. (%)	66 (36.7)	266 (59.0)	1.29 (1.16–1.43)	287 (53.9)	45 (45.5)	0.75 (0.52–1.08)	316 (52.1)	16 (66.7)	1.80 (0.78–4.13)
Delirium incidence, no. (%)§	29/136 (21.3)	103/277 (37.2)	1.26 (1.11–1.43)	109/338 (32.2)	23/75 (30.7)	0.94 (0.60–1.47)	125/399 (31.3)	7/14 (50.0)	2.13 (0.76–5.95)
ICU admission, no. (%)	20 (11.1)	128 (28.4)	1.30 (1.19–1.42)	128 (24.1)	20 (20.2)	0.82 (0.52–1.29)	134 (22.1)	14 (58.3)	4.54 (2.06–10.01)
Complications									
Use of restraints, no. (%)	17 (9.4)	109 (24.2)	1.27 (1.16–1.40)	105 (19.7)	21 (21.2)	1.08 (0.69–1.67)	120 (19.8)	6 (25.0)	1.33 (0.54–3.29)
Falls, no. (%)	12 (6.7)	22 (4.9)	0.90 (0.70–1.16)	31 (5.8)	3 (3.0)	0.55 (0.18–1.64)	33 (5.4)	1 (4.2)	0.76 (0.11–5.48)
Respiratory failure, no. (%)	7 (3.9)	104 (23.1)	1.40 (1.30–1.51)	93 (17.5)	18 (18.2)	1.04 (0.65–1.66)	104 (17.1)	7 (29.2)	1.93 (0.82–4.53)
Acute respiratory distress syndrome, no. (%)	2 (1.1)	74 (16.4)	1.43 (1.34–1.53)	63 (11.8)	13 (13.1)	1.10 (0.65–1.88)	70 (11.5)	6 (25.0)	2.43 (1.00–5.93)

Note: CI = confidence interval, ICU = intensive care unit, IQR = interquartile range, MD = mean difference, RR = relative risk.
*Aug. 1, 2020, to Feb. 20, 2021.
†Where appropriate.
‡Defined as a score on the Clinical Frailty Scale ≥ 5.
§Calculated by excluding those who presented with delirium, so the base population size was different for this row.

dexamethasone use was associated with increased prevalence and incidence of delirium. The strength of its association with delirium incidence was reduced after adjusting for covariates. Our data suggest that dexamethasone use was not independently associated with increased delirium risk, but patients who received dexamethasone likely had increased disease severity, which itself was associated with delirium. It is possible that dexamethasone was associated with increased delirium severity, but we did not evaluate this in the present study. We found a 2.6-fold increase in use of physical restraints in patients who were given dexamethasone, which may suggest increased delirium severity.[45]

Table 6: Multivariable model of dexamethasone as the main predictor of delirium incidence in adults aged ≥ 65 years admitted to acute care hospitals with COVID-19 in wave 2 of the COVID-19 pandemic*

Variable	Unadjusted OR	Adjusted OR†
Dexamethasone use	2.11 (1.32–3.46)	1.38 (0.77–2.50)
Remdesivir use	0.93 (0.53–1.58)	1.56 (0.80–3.04)
Tocilizumab use	2.19 (0.74–6.53)	2.53 (0.73–9.24)
Age, yr‡	1.31 (1.17–1.48)	1.21 (1.04–1.40)
Dementia	4.99 (2.86–8.89)	3.25 (1.67– 6.45)
Clinical Frailty Scale score	1.53 (1.32–1.79)	1.53 (1.24–1.91)
Intensive care unit admission	2.94 (1.82–4.77)	6.82 (3.65–13.11)

Note: OR = odds ratio.
*Number of records in model: 395; Hosmer–Lemeshow test: $p = 0.57$; C statistic: 0.800.
†Adjusted for remdesivir use, tocilizumab use, age, dementia, Clinical Frailty Scale and intensive care unit admission.
‡Each 5-year increase.

Limitations

The present study had several strengths. It was large and included consecutive hospitalized older adults from the beginning of the COVID-19 pandemic in multiple hospitals in Toronto. Each included acute care hospital used an electronic medical record system, making pertinent data readily available. We used a consistent and rigorous chart review process across sites, with close supervision by geriatrician investigators (E.K.-C.W., J.W., A.V., K.P., T.I. and B.L.) at all sites except for one, where charts were directly abstracted by the medical director. We looked at all available medical and allied health documentation to determine frailty and functional status. Identification of delirium was conducted using a validated chart review method.[20]

This study also had some limitations. First, we used a retrospective design, so we could not prospectively collect data on frailty, delirium and functional status. Second, misclassification bias could have occurred because we used a single chart assessor per site, although we used a rigorous training process. Third, we did not capture data on SARS-CoV-2 variants because not all hospitals had access to public health variant sequencing results. Fourth, we did not ascertain whether delirium onset occurred before or after dexamethasone use, because the study was designed before dexamethasone was used widely. This may have led to misclassification of dexamethasone as an exposure if the delirium occurred before the drug was given. Fifth, although we adjusted for clinically relevant variables, residual selection bias was likely given that dexamethasone was used only in sicker patients. Sixth, we did not assess the dosages or clinical context when medications for COVID-19 were administered. Finally, we did not collect other demographic characteristics such as gender, race, language or socioeconomic status.

Conclusion

In-hospital death, delirium and use of restraints were common in older adults admitted to hospital with COVID-19. Future research should explore ways to improve outcomes in hospitalized older adults during pandemics.

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