

ORIGINAL RESEARCH

Mortality in hospitalized older adults with COVID-19 during three waves: A multicenter retrospective cohort study

Eric Kai Chung Wong^{1,2,3} | Jennifer Watt^{1,2,3} | Hanyan Zou⁴ |
Arthana Chandraraj¹ | Alissa W. Zhang⁵ | Richard Norman^{3,4} |
Katrina Lynn Piggott^{3,5} | Sharon E. Straus^{1,2,3} | Barbara Liu^{3,5}

¹Li Ka Shing Knowledge Institute, St. Michael's Hospital, Unity Health Toronto, Toronto, Canada

²Division of Geriatric Medicine, Department of Medicine, St. Michael's Hospital, Unity Health Toronto, Toronto, Canada

³Division of Geriatric Medicine, Department of Medicine, University of Toronto, Toronto, Canada

⁴Division of Geriatric Medicine, Department of Medicine, Sinai Health and University Health Network, Toronto, Canada

⁵Division of Geriatric Medicine, Department of Medicine, Sunnybrook Health Sciences Centre, Toronto, Canada

Correspondence

Barbara Liu, Department of Medicine, University of Toronto, Sunnybrook Health Sciences Centre, 2075 Bayview Ave, Room H4 79, Toronto, ON M4N 3M5, Canada.
Email: barbara.liu@sunnybrook.ca

Funding information

Sinai Health/University Health Network Healthy Ageing and Geriatrics Program; Baycrest Health Sciences Academic Health Science Centre Alternate Funding Plans (AFP) Innovative Funds; Division of Geriatric Medicine and General Internal Medicine, Sunnybrook Health Sciences Centre; Unity Health Toronto Academic Health Science Centre Alternate Funding Plans (AFP) Innovative Funds

Abstract

Background: The waves of COVID-19 infections in Ontario, Canada, were marked by differences in patient characteristics and treatment. Our objectives were to (i) describe patient characteristics, treatment, and outcomes of hospitalized older adults with COVID-19 between waves 1, 2, and 3, (ii) determine if there was an improvement in in-hospital mortality in waves 2 and 3 after adjusting for covariates.

Methods: This retrospective cohort study was done in five acute care hospitals in Toronto, Ontario. Consecutive hospitalized older adults aged ≥ 65 years with confirmed COVID-19 infection were included. Wave 1 extended from March 11 to July 31, 2020, wave 2 from August 1, 2020 to February 20, 2021, and wave 3 from February 21 to June 30, 2021. Patient characteristics and outcomes were abstracted from charts. A logistic regression model was used to determine the association between COVID-19 and in-hospital mortality in waves 2 and 3 compared with wave 1.

Results: Of the 1671 patients admitted to acute care, 297 (17.8%) were admitted in wave 1, 751 (44.9%) in wave 2, and 623 (37.3%) in wave 3. The median age of our cohort was 77.0 years (interquartile range: 71.0–85.0) and 775 (46.4%) were female. The prevalence of frailty declined in progressive waves. The use of dexamethasone, remdesivir, and tocilizumab was significantly higher in waves 2 and 3 compared with wave 1. In the unadjusted analysis, in-hospital mortality was unchanged between waves 1 and 2, but it was lower in wave 3 (18.3% vs. 27.4% in wave 1). After adjustment, in-hospital mortality was unchanged in waves 2 and 3 compared with wave 1.

Conclusion: In-hospital mortality in hospitalized older adults with COVID-19 was similar between waves 1 and 3. Further research should be done to determine if COVID-19 therapies have similar benefits for older adults compared with younger adults.

KEYWORDS

aging, epidemiology, geriatrics, healthcare management

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1 | INTRODUCTION

The COVID-19 pandemic was marked by multiple waves as the infection waxed and waned. In Ontario, Canada, the waves of COVID-19 infection were related to seasonality,¹ changes in public health measures,² and the emergence of new COVID-19 strains.³ Little was known about the treatment of COVID-19 during the first wave, which predominantly affected older adults.⁴ When the second wave started on August 1, 2020,⁵ there was more familiarity with isolation measures and more treatments available (Figure S1).⁶ A third wave started in February 2021. Variants of COVID-19 in waves 2 and 3 included predominantly alpha (B.1.1.7), but later included beta (B.1.351) and gamma (P.1).⁷ These variants increased the transmissibility and virulence of the infection in Ontario.⁷

Several therapies were demonstrated to be effective for hospitalized COVID-19 patients in waves 2 and 3, including dexamethasone,⁸ remdesivir,⁹ and tocilizumab,¹⁰ but data on older adults were limited. Vaccinations in long-term care (LTC) homes reduced hospitalizations in wave 2, but community-dwelling older adults were not vaccinated until late in the second wave.¹¹ Despite vaccinations, some older adults continue to be at risk for severe disease and hospitalization.¹²

Given the improvement in pharmacologic and nonpharmacologic treatment of COVID-19, we wanted to determine if mortality was improved in hospitalized older adults with COVID-19 in waves 2 and 3 compared to wave 1. Our objectives were (i) to describe patient characteristics, treatment, and mortality of hospitalized older adults with COVID-19 between waves 1 and 3; and (ii) to determine if there was an improvement in mortality in waves 2 and 3 after adjusting for covariates.

2 | METHODS

2.1 | Study design

This is a substudy in a multicenter retrospective cohort study. The original study investigated atypical COVID-19 presentations and the protocol was published in Open Science Framework (<https://osf.io/k4g7a/>). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement guided this report.¹³ Research ethics approval was obtained through Clinical Trials Ontario (3186-OPIA-Apr/2020-38044) and consent was not required.

2.2 | Setting and timing

The study took place at five acute care hospitals (Mount Sinai Hospital, St. Michael's Hospital, Sunnybrook Health Sciences Centre, Toronto General Hospital, and Toronto Western Hospital). Cases were included from March 11, 2020 to June 30, 2021. Wave 1 of the pandemic occurred from March 11, 2020 to July 31, 2020 as defined by Toronto Public Health.¹⁴ Wave 2 cases were included from August 1, 2020 to February 20, 2021. Wave 3 started on February 21, 2021,

defined by the nadir of total daily case counts between waves 2 and 3 in Toronto.¹⁴ There is no public health-defined start date for wave 3. Data collection ended on June 30, 2021, so that was the last date for wave 3 case inclusion in our study. Vaccinations in LTC homes started on December 23, 2020.¹⁵

2.3 | Participants

We included consecutive adults aged ≥ 65 years with COVID-19 infection confirmed with viral polymerase chain reaction (PCR), admitted to one of the included hospitals. We excluded (i) those who were readmitted to hospital after an index admission for COVID-19 and (ii) those with a false positive swab or recovered COVID-19 infection as defined by the site's infection control team.

2.4 | Data sources

Eligible patients were identified by the data analytics service at each site, using the same case detection protocol for public health reporting. A trained chart assessor abstracted data using standardized data abstraction form hosted on a REDCap database.¹⁶ Each chart assessor was trained by a physician investigator at the hospital site (Barbara Liu, Jennifer Watt, Eric Wong, Katrina Piggott, and Richard Norman). The first five charts were extracted in duplicate with the physician investigator, and additional charts were reviewed as needed by the physician investigator when questions arose.

We extracted patient characteristics from the chart, including age at diagnosis, sex (as documented on chart), baseline functional status (as documented by physician consultation notes or occupational therapist note), place of residence, clinical frailty scale (CFS),¹⁷ past medical history, and COVID-19 vaccination status (as documented on the admission consultation note). Functional status was documented using items of activities of daily living (ADLs) and instrumental activities of daily living (IADLs).¹⁸ The CFS was a frailty measure that used clinical phenotypes.¹⁷ Pharmacologic treatment for COVID-19 was recorded. Delirium was assessed using a validated chart review tool.¹⁹ Prevalent delirium was defined as identifying delirium keywords on the emergency medicine records or admission consultation. Incident delirium was defined as delirium keywords occurring in later notes during the hospital stay. Recorded outcomes included in-hospital mortality, intensive care unit (ICU) admission, and length of stay.

Missing data were reviewed by the site physician investigator. Missing CFS was imputed as 6 (severe frailty) for LTC residents and 5 (moderate frailty) for retirement home residents based on local LTC admission criteria and published frailty estimates.^{20,21}

2.5 | Statistical analysis

Patient characteristics and outcomes were analyzed descriptively with counts (proportions), means (standard deviation), and medians

(interquartile range [IQR]), where appropriate. Statistical comparisons involved the use of the Chi-squared test (categorical variables), ANOVA test (normally distributed variables), and Kruskal–Wallis test (nonnormally distributed variables). Two multivariable logistic regression models were used to identify the independent association of waves 2 and 3 with mortality. The model adjusted for clinically relevant covariates that were selected a priori for the relationship between waves 2 and 3 and mortality, including age, sex, number of comorbidities, ICU admission, CFS, and prevalent delirium. Any records missing ICU admission status or CFS were excluded from the regression analysis (listwise deletion). A supplementary analysis was done to compare wave 3 to wave 2 to demonstrate any differences between the latter waves. Another supplementary analysis was done with the addition of vaccination status to demonstrate the impact of vaccination on in-hospital mortality (see Supporting Information Appendix for details). Statistical significance was defined at $p < 0.05$. Model discrimination was tested using the c-statistic. The analysis was done in R version 4.0.3.²²

3 | RESULTS

3.1 | Baseline characteristics

Of the 1671 patients admitted to an acute care hospital during the study period (Table 1), 297 (17.8%) were admitted in wave 1, 751 (44.9%) were admitted in wave 2, and 623 (37.3%) were admitted in wave 3. In the entire cohort, the median age was 77.0 years (IQR: 71.0–85.0) and 775 (46.4%) were female. Compared to the first and second COVID-19 waves, patients admitted in wave 3 were younger (median age 75.0 vs. 78.0 years in wave 1) and fewer were from LTC (1.5% in wave 3 vs. 25.3% in wave 1). The mean CFS decreased across waves 1–3 (5.10 in wave 1, 4.78 in wave 2 [$p = 0.005$], and 4.09 in wave 3 [$p < 0.001$]). The prevalence of several comorbidities including dementia, falls, and stroke declined with each wave (Table 1). The prevalence of hypertension and diabetes remained similar across waves. Nine patients (1.2%) received at least one dose of a COVID-19 vaccine in the wave 2 group and 134 patients (21.5%) in wave 3.

3.2 | Treatment and outcome differences

Some medications were used empirically in wave 1. Significantly more patients received dexamethasone (71.5% vs. 3.0%, $p < 0.001$), remdesivir (16.8% vs. 0%, $p < 0.001$), and tocilizumab (2.4% vs. 0.3%, $p = 0.046$) in wave 2 than wave 1. The use of these medications increased in wave 3 (Table 2).

There was no difference in the proportion of in-hospital deaths between waves 1 and 2 (26.2% in wave 2 vs. 27.4% in wave 1, $p = 0.774$), but unadjusted mortality was lower in wave 3 (18.3% vs. 27.4% in wave 1, $p = 0.003$). Delirium prevalence, delirium incidence, and ICU admissions were similar between waves 1 and 2 (Table 2). In wave 3, delirium prevalence (32.9% vs. 55.7% in wave 1, $p < 0.001$)

and incidence (22.1% vs. 35.4% in wave 1, $p < 0.001$) were lower, but the proportion of ICU admissions remain unchanged. The median length of stay was reduced in wave 3 (10.0 days [IQR 5.0–18.0] vs. 13.0 days [IQR 5.0–25.3] in wave 1, $p = 0.002$).

3.3 | Association of waves 2 and 3 and mortality

Using a multivariable model (Table 3), we determined that having a COVID-19 infection during wave 2 was not associated with decreased in-hospital mortality in older adults (adjusted odds ratio [aOR]: 0.98, 95% confidence interval [CI]: 0.69–1.39) compared to having a COVID-19 infection during wave 1, after adjusting for age (aOR: 1.29 for each 5 years increase, 95% CI: 1.11–1.42), female sex (aOR: 0.74, 95% CI: 0.57–0.97), CFS (aOR: 1.19, 95% CI: 1.07–1.33), number of comorbidities (aOR: 1.16 for each additional comorbidity, 95% CI: 1.07–1.33), ICU admission (aOR: 6.10, 95% CI: 4.48–8.38), and delirium (aOR: 1.83, 95% CI: 1.38–2.42). Although unadjusted mortality was lower in wave 3, the association was not significant after adjustment with the same variables (aOR: 0.89, 95% CI: 0.61–1.30). A comparison between waves 2 and 3 yielded similar estimates (Table S1). A supplementary analysis including vaccination status did not significantly change model estimates (Table S2).

4 | DISCUSSION

This multicenter retrospective cohort of consecutive older patients admitted to hospital with COVID-19 highlighted differences in the patient population, treatment, and mortality between waves 1–3 of the pandemic in Toronto, Ontario. Later waves involved younger patients with less frailty and fewer comorbidities, and they received significantly more evidence-based medications. However, after adjustment, the in-hospital mortality was similar between waves. This finding is in agreement with published studies comparing the survival of ICU patients in waves 1 and 2 in Europe, where no improvement in survival was seen.^{23,24}

Complicating waves 2 and 3 of the pandemic was the rise of SARS-CoV-2 variants.²⁵ In Ontario, Canada, the prevalence of variants increased from 15% of all cases in early February 2021 to 92% in June 2021.²⁶ Variant data was not captured in our study because researchers were not allowed to access the external health portal where variant sequencing results were hosted. The increased virulence of the variants²⁵ may explain the lack of improvement in mortality in the second wave, despite the prevalent use of disease-modifying drugs (e.g., 71%–76% on dexamethasone). Another explanation for the lack of mortality improvement in the latter waves may be related to the efficacy of the drugs in older adults. A systematic review of steroid trials in COVID-19 patients showed that the median age of trial participants ranged from 57 to 67, with few patients aged >80 years.⁸ In contrast, the median age in our wave 2 cohort was 79.0 years (IQR: 71–86) and wave 3 was 75.0 years (IQR: 69–82). In the absence of randomized data, an observational study in France ($n = 267$) showed improved survival for

TABLE 1 Baseline characteristics of older adults aged ≥ 65 admitted to acute care hospital with COVID-19 in waves 1–3

	Cohort	Missing (%)	Wave 1	Wave 2	Wave 3
n (%)	1671 (100)		297 (17.8)	751 (44.9)	623 (37.3)
Age, median (IQR)	77.0 (71.0–85.0)	0	78.0 (71.0–85.0)	79.0 (71.0–86.0)	75.0 (69.0–82.0)**
Female, n (%)	775 (46.4)	0	126 (42.6)	349 (46.5)	299 (48.0)
From long-term care, n (%)	336 (20.2)	5 (0.3)	75 (25.3)	103 (13.8)**	9 (1.5)**
Any impairment in activities of daily living, n (%)	516 (30.9)	60 (3.6)	110 (37.2)	287 (38.2)	119 (19.1)**
Any impairment in instrumental activities of daily living, n (%)	817 (48.9)	60 (3.6)	137 (46.3)	425 (56.6)*	255 (40.9)
Clinical frailty scale (CFS), mean (SD)	4.58 (1.58)	60 (3.6)	5.10 (1.61)	4.78 (1.54)*	4.09 (1.46)**
Frail (CFS ≥ 5), n (%)	859 (53.3)	60 (3.6)	174 (61.9)	433 (58.8)	252 (42.5)**
At least 1 dose vaccine, n (%)	143 (8.6)	0	0	9 (1.2)	134 (21.5)**
Pfizer-Biontech/BNT162b2	112 (66.7)	0	0	5 (25.0)	107 (72.3)**
Moderna/mRNA-1273	43 (25.6)	0	0	15 (75.0)	28 (18.9)**
Astrazeneca/ChAdOx1	13 (7.7)	0	0	0	13 (8.8)**
Days from first dose of vaccine to COVID-19 diagnosis, median (IQR)	14.0 (8.0–35.0)	0	NA	11.0 (6.0–14.0)	14.5 (8.0–35.3)
Comorbidities, n (%)					
Dementia	277 (16.7)	0	64 (21.8)	160 (21.5)	53 (8.5)**
Falls	177 (10.6)	0	54 (18.3)	86 (11.5)*	37 (6.0)**
Heart failure	223 (13.4)	0	48 (16.3)	94 (12.6)	81 (13.0)
Coronary artery disease	351 (21.1)	0	78 (26.5)	160 (21.4)	113 (18.2)*
Chronic kidney disease	318 (19.1)	0	62 (21.1)	156 (20.8)	100 (16.2)
Stroke	248 (14.9)	0	67 (22.9)	122 (16.3)*	59 (9.5)**
Hypertension	1136 (68.1)	0	212 (71.9)	496 (66.1)	427 (68.8)
Diabetes	665 (40.0)	0	125 (42.5)	288 (38.4)	252 (40.7)
Chronic obstructive pulmonary disease	173 (10.4)	0	43 (14.6)	74 (9.9)*	56 (9.0)*
Cancer	376 (22.6)	0	65 (22.2)	181 (24.2)	129 (20.8)
Number of comorbidities, median (IQR)	2.0 (1.0–4.0)	0	3.0 (2.0–4.0)	3.0 (2.0–4.0)	2.0 (1.0–3.0)

Abbreviations: CI, confidence interval; IQR, interquartile range; SD, standard deviation.

* $p < 0.05$ versus wave 1; ** $p < 0.001$ versus wave 1.

patients aged >80 years on corticosteroids (hazard ratio: 0.67, 95% CI: 0.46–0.99). This study was done in March 2020, when the wild-type strain was circulating. The benefits were potentially attenuated with the variants.

The lack of improvement in in-hospital mortality in subsequent COVID-19 waves suggests an opportunity to improve the care of older adults hospitalized with COVID-19 and future pandemics. First, clinical trials of therapeutic drugs should include those most impacted by the disease. In COVID-19, frail older adults were known to be most susceptible to death and complications early in the pandemic,⁴ but trials of therapies mainly included younger adults.⁸ When clinical trials of younger patients are applied to older adults, real-world efficacy may be decreased or unanticipated adverse events may occur.²⁷ Second, an aging population requires acute care facilities to be equipped to care for older adults, including an optimal physical

design²⁸ and systems-level policy changes.²⁹ Third, physicians, nurses, and other allied health staff should undergo training for the care of older adults in school. Integrating geriatric training into an undergraduate curriculum allows for early exposure to best practices and person-centered care.³⁰ Strengthening geriatric care in hospitals increases staff resilience when encountering unexpected events, such as a future COVID-19 wave or another pandemic.

5 | LIMITATIONS

There are some limitations to our data. First, we retrospectively collected the data. Second, COVID-19 variants data were not recorded because not all hospitals had this recorded. Third, we did not collect other demographic characteristics such as gender, race,

TABLE 2 Treatment and outcomes of older adults aged ≥ 65 admitted to acute care hospital with COVID-19 in waves 1–3

	Cohort	Missing (%)	Wave 1	Wave 2	Wave 3
n (%)	1671 (100)		296 (31.9)	751 (44.9)	623 (37.3)
COVID-19 treatment, n (%)					
Dexamethasone	1018 (60.9)	0	9 (3.0)	535 (71.2)**	474 (76.1)**
Azithromycin	302 (18.1)	0	70 (23.6)	148 (19.7)	84 (13.5)
Remdesivir	366 (21.9)	0	0 (0.0)	126 (16.8)**	240 (38.5)**
Other steroid	98 (5.9)	0	21 (7.1)	48 (6.4)	29 (4.7)
Tocilizumab	189 (11.3)	0	1 (0.3)	18 (2.4)*	170 (27.3)**
Convalescent plasma	24 (1.4)	0	1 (0.3)	23 (3.1)*	0
Lopinavir/ritonavir	6 (0.4)	0	6 (2.0)	0*	0*
Hydroxychloroquine	4 (0.2)	0	4 (1.4)	0*	0*
Participation in clinical trial, n (%)	123 (7.4)	13 (0.8)	15 (5.1)	91 (12.2)*	17 (2.8)
Surgery in hospital, n (%)	89 (5.3)	5 (0.3)	19 (6.4)	43 (5.7)	27 (4.4)
Outcomes					
In-hospital death, n (%)	390 (23.5)	0	81 (27.4)	196 (26.2)	113 (18.3)*
Length of stay, median (IQR)	11.0 (5.0–20.0)	0	13.0 (5.0–25.3)	11.0 (5.0–20.5)	10.0 (5.0–18.0)*
Delirium prevalence, n (%)	751 (44.9)	0	165 (55.7)	382 (51.1)	204 (32.9)**
Delirium incidence, ^a n (%)	358/1240 (28.8)	0	69/195 (35.4)	175/528 (33.1)	114/516 (22.1)**
ICU admission, n (%)	400 (24.1)	11 (0.7)	67 (22.8)	179 (24.1)	154 (24.8)

Abbreviations: ICU, intensive care unit; IQR, interquartile range.

^aThe denominator for delirium incidence was different from the other characteristics in the table because those presenting with delirium were excluded.

* $p < 0.05$ versus wave 1; ** $p < 0.001$ versus wave 1.

TABLE 3 Multivariable model of waves 2 and 3 as main predictor of mortality in older adults admitted to acute care hospitals with COVID-19 adjusted for age, sex, clinical frailty scale, comorbidities, ICU admission, and delirium

Variables	Unadjusted OR	Adjusted OR	p
Wave 2 versus 1	0.95 (0.70–1.28)	0.98 (0.69–1.39)	0.905
Wave 3 versus 1	0.60 (0.43–0.83)	0.89 (0.61–1.30)	0.538
Age (each 5 year increase)	1.27 (1.19–1.35)	1.29 (1.18–1.40)	<0.001
Sex (female)	0.79 (0.63–0.99)	0.74 (0.57–0.97)	0.030
Clinical frailty scale	1.33 (1.23–1.43)	1.19 (1.07–1.33)	<0.001
Comorbidities (each additional)	1.27 (1.19–1.35)	1.16 (1.07–1.33)	<0.001
ICU	4.00 (3.12–5.12)	6.10 (4.48–8.38)	<0.001
Delirium	3.43 (2.71–4.38)	1.83 (1.38–2.42)	<0.001

Note: Number of records in model: 1573; C-statistic: 0.781.

Abbreviations: ICU, intensive care unit; OR, odds ratio.

language, and socioeconomic status. Fourth, we did not include vaccination status in the final model because most patients tested positive for COVID-19 soon after their first dose (median: 14 days), so the vaccine was not expected to be sufficiently protective yet.³¹

Fifth, we did not collect data on illness severity or supplemental oxygen use, which limited our ability to control for illness severity in the analysis.

There are several strengths to our study. We included consecutive older adults admitted to five academic acute care hospitals in Toronto. A geriatrician investigator supervised the chart review at each site using a consistent process. We abstracted delirium incidence using a validated chart review method.¹⁹ Each patient was assessed until death or discharge from acute care.

6 | CONCLUSION

Older adults hospitalized with COVID-19 did not have improved in-hospital mortality in the latter waves of the pandemic. Future research should explore ways to improve the outcomes of hospitalized older adults during pandemics.

AUTHOR CONTRIBUTIONS

Hanyan Zou: Data curation; formal analysis; investigation; validation; writing—original draft; writing—review and editing. **Arthana Chandraraj:** Data curation; formal analysis; investigation; validation; writing—original draft; writing—review and editing. **Alissa W. Zhang:** Data curation; formal analysis; investigation; validation; writing—original draft;

writing–review and editing. **Katrina Piggott:** Data curation; investigation; project administration; supervision; writing–original draft; writing–review and editing. **Sharon E. Straus:** Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; software; supervision; validation; writing–original draft; writing–review and editing.

ACKNOWLEDGMENTS

The authors thank Dr. George Tomlinson and Dr. Argie Angeliki-Veroniki for providing assistance with our statistical analysis; Dr. Camilla Wong for providing training for chart abstraction; Dr. Samir Sinha and Dr. Rajin Mehta for assistance with funding and site project support. Academic Health Science Centre Alternate Funding Plans (AFP) Innovative Funds from Unity Health Toronto and Baycrest Health Sciences; Sinai Health/University Health Network Healthy Ageing and Geriatrics Program and its Geriatrics Summer Scholars Program; Division of Geriatric Medicine and General Internal Medicine, Sunnybrook Health Sciences Centre. SES is funded by a Tier 1 Canada Research Chair. EKW is funded by the Clinician-Scientist Training Program at the University of Toronto and the Vanier Scholarship from the Canadian Institutes of Health Research.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

ETHICS STATEMENT

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

TRANSPARENCY STATEMENT

The manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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SUPPORTING INFORMATION

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

How to cite this article: Wong E-C, Watt J, Zou H, et al. Mortality in hospitalized older adults with COVID-19 during three waves: A multicenter retrospective cohort study. *Health Sci. Rep.* 2022;5:e603. doi:10.1002/hsr2.603