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Comorbidities, symptoms, and end-of-life medication use in hospitalized decedents before and during the COVID-19 pandemic: a retrospective regional cohort study

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ABSTRACT

Objective: To compare comorbidities, symptoms, and end-of-life (EoL) palliative medication (antisecretories, opioids, antipsychotics and sedatives) use among decedents before and during the COVID-19 pandemic.

Design: In a retrospective cohort study, decedent records in 3 acute care hospitals were abstracted, generating a pre-pandemic (November 2019-February 2020) group (Pre-COVID) and 2 intra-pandemic (March-August 2020, Wave 1) groups, one without (COVID-ve) and one with COVID-19 infection (COVID+ve). Control group decedents were matched 2:1 on age, sex and care service (Medicine/Intensive Care Unit (ICU)) with COVID+ve decedents.

Setting: One quaternary and two tertiary adult regional acute care hospitals

Participants: Decedents (N=425): COVID+ve (n=85), COVID-ve (n=170) and Pre-COVID (n=170).

Main outcome measures: Data were abstracted regarding demographics, admission comorbidities and symptoms, and EoL medication use; opioid doses were standardized to parenteral morphine equivalent daily dose (MEDD), and the predictors of upper quartile MEDD in the last 24 hours of life were examined in multivariable logistic regression with adjusted odds ratios (aORs) and 95% confidence intervals (CIs).

Results: The prevalence of dementia (41% vs 28% and 26%, p=0.03), breathlessness (63.5% vs 42% and 47%, p<0.01), cough (40% vs 27% and 19%, p<0.01) and fever (54% vs 9% and 13.5%) was higher in COVID+ve vs Pre-COVID and COVID-ve groups, respectively. The median (interquartile range) of MEDD over the last 72 hours of life was 16.7, (9-36.5) vs 13.5 (5.7-21.8) and 10.5 (5.3-23.8) for COVID+ve vs PreCOVID and COVID-ve groups, respectively, (p=0.007). Male sex, COVID+ve grouping, ICU death, and high-flow nasal cannula use predicted upper quartile MEDD dose, aORs (CIs): 1.84 (1.05-3.22), 2.62 (1.29-5.3), 5.14 (2.47-10.7) and 1.93 (1.05-3.52), respectively. COVID+ve group decedents used highest lorazepam and propofol doses.

Conclusions: COVID-19 decedents, particularly those in ICU, required higher EoL opioid and sedating medication doses than matched pre- or intra-pandemic controls. These findings should inform and guide clinical practice.

Abstract: 300 words

Main manuscript: 3795 words

Tables: 4 (plus 2 Supplementary, Appendix 1 and 3)

Figures: 1 (plus 1 Supplementary, Appendix 2)

Keywords: COVID-19, adult palliative care, adult intensive & critical care, sedation, medications, opioid, morphine equivalent daily dose

Strengths and limitations of this study

- The decedent cohort was representative of the source population in all adult acute care hospitals in a large urban region, and use of control groups from within and prior to the COVID-19 pandemic facilitated valid and unique comparisons.
- This study relates to Wave 1 of the pandemic. It is possible that symptom burden, and thus use of symptom control medications, has changed with subsequent waves.
- Although rigorous training and accuracy checks were conducted in relation to data abstraction, abstractors were not blinded in relation to the study hypothesis, posing a potential source of bias.
- The study's retrospective design and recording of admission symptom assessment and comorbidity data without similar data, including medication efficacy and side-effects, from within the more immediate end-of-life period are obvious limitations.
- The generalizability of our study findings is largely limited to end-of-life care for hospitalized decedents, whereas many of the COVID-19 related deaths in Wave 1 of the pandemic occurred in nursing homes.

INTRODUCTION

Globally, by mid-January 2023, over six million deaths due to COVID-19 (Coronavirus 2019) are reported to have occurred.[1] However, a bigger picture estimate of overall excess mortality due to the COVID-19 pandemic suggests a figure of just over 18 million deaths by the end of 2021.[2] These estimates highlight the need for effective integration of specialist palliative care within hospitals,[3 4] and adoption of a palliative care approach to ensure end-of-life care provision in the COVID-19 pandemic.[5-7] Although the uptake of vaccines has helped to reduce COVID-19 disease severity and mortality,[8] the mortality risk remains higher with chronic medical conditions, socioeconomic deprivation, and in certain ethnic groups.[9 10] Prior to vaccination uptake, earlier in the pandemic, infection with COVID-19 posed a greater risk of hospitalization, Intensive Care Unit (ICU) admission and subsequent death, particularly for older people, those with frailty and chronic medical comorbidities.[11-13]

Among those hospitalized with severe COVID-19 infection, dyspnoea, cough, fatigue, delirium, agitation and myalgia are the most prevalent symptoms.[14-18] Both pharmacological and respiratory support interventions are often required for symptom control.[12 19 20] In caring for those dying of COVID-19 infection, clinicians, particularly those with limited palliative expertise, are often faced with urgent need for information and support,[21 22] and are guided in their use of pharmacological interventions by expert publications and specific guidelines.[6 7 23 24]

Palliative medications used in severe COVID-19 infection include: opioids for pain and dyspnoea; benzodiazepines for anxiety, agitation and dyspnoea; antipsychotics for refractory delirium symptoms; and antisecretory medications for airway secretions.[20] Phenobarbitone and propofol are also used for sedation,[25 26] the latter mainly in ICU settings. However, higher-level evidence derived directly from COVID-19 infected study populations for the efficacy and safety of pharmacological interventions in targeting symptom control is limited.[27 28] Furthermore, guidelines addressing end-of-life symptom management in the COVID-19 context, for example dyspnoea, are largely informed by primary studies conducted pre-pandemically in patients with either cancer or COPD,[29] raising potential generalizability concerns. There is also a paucity of real world reported data on palliative medication use during the pandemic.[30 31] Although most reports suggest that opioid requirements for end-of-life symptom management in COVID-19 infection are similar to other end-of-life conditions,[28 30 31] some report higher

requirements.[32 33] Based on clinical experience, we hypothesized that higher opioid and sedative doses are needed to control symptoms in hospitalized patients dying of COVID-19 infection.

We conducted a study with the primary objective of comparing palliative medication use in the last 72 hours of life among three hospitalized decedent groups: a pre-pandemic group and two groups from Wave 1 of the pandemic, one who died of COVID-19 infection, and the other who died of other causes without COVID-19 infection. Group comparisons of admission comorbidity and symptom prevalence, and respiratory/circulatory support use were additional objectives.

METHODS

Study design

As part of a larger project on grief and bereavement in the COVID-19 pandemic,[34 35] we conducted a retrospective multicentre matched cohort study of decedents' documented end-of-life care in acute care hospitals. The study is reported according to the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) criteria.[36]

Setting

The study population source consisted of inpatients in Ottawa (city and catchment area population 1.4 million), Canada, who died in the city's three adult acute care hospital sites between November 1, 2019 and August 31, 2020. Site 1, Hôpital Montfort is a tertiary hospital with 289 inpatient beds. Site 2, Queensway-Carleton Hospital is a tertiary hospital with 264 inpatient beds. Site 3, The Ottawa Hospital is a quaternary hospital with 1271 inpatient beds. All sites used established electronic health records (EHR) software systems, MEDITECH (Medical Information Technology, Inc.) at Sites 1 and 2, and Epic (Epic Systems Corporation) at Site 3, in documenting patient care.

Key exposures

Between March 1 and August 31, 2020, a total of 85 people died of COVID-19 infection in the region's three acute care hospitals. The study's key exposures related to COVID-19 infection status during decedents' last hospital admission and when the admission occurred in relation to the pandemic. Three decedent study groups were

identified on the basis of these exposures: a Pre-COVID group who died between November 1st 2019 and February 29th 2020; and 2 groups who died between March 1st 2020 and August 31st 2020, within Wave 1 of the pandemic, one who died of COVID-19 infection, and the other, without any record of COVID-19 during their hospital admission, designated COVID+ve and COVID-ve, respectively.

Participants

Adult (≥ 18 years old) decedents were included if they died in ICU or under the care of internal medicine in the designated study period. Both Emergency Department decedents and those primarily under surgical care were excluded. The index study group was COVID+ve (n=85), and each of these decedents was included. Using a 2: 1 ratio, the control Pre-COVID (n=170) and COVID-ve (n=170) group members were matched with COVID+ve members at each site on the basis of age (± 5 years), sex and care service (Medicine or ICU) at the time of death.

Data sources/measurement

Anonymized EHR data, including study variables were abstracted by teams of internal/palliative medicine physicians and two research assistants at each site, and entered into a common electronic study database. All abstractors received training regarding abstraction requirements. A senior study team member conducted a duplicate data abstraction of 154 (35%) of the patient records to confirm accuracy of details.

Variables

Study group designation was based on EHR documentation of COVID-19 infection status, date of death and death certification. Demographic variables included age, sex, admission referral source, acute care site, care service at death, and admission duration (days). Based on EHR documentation, comorbidities and symptoms at admission, and respiratory/circulatory support use during admission, were recorded (Yes/No) by abstractors, **Supplemental Table, Appendix 1**. Abstractors recorded medications prescribed (yes/no) and administered (yes/no) in the last 72 hours of life. Administered doses were totalled for each 24-hour interval (T3: > 48 and ≤ 72 hours, T2: > 24 and ≤ 48 hours, and T1: the last 24 hours of life) within this period, where available, and recorded for the following: opioids (morphine, fentanyl, hydromorphone), antisecretory medications

(glycopyrrolate and hyoscine hydrobromide), antipsychotics (haloperidol and methotrimeprazine), benzodiazepines (lorazepam and midazolam), other sedating medication (phenobarbitone and propofol). Opioid doses were recorded in parenteral equivalent using a standard oral to parenteral ratio of 2:1.[37]

Patient and public involvement

Decedents' study data were retrospectively acquired and are part of a project involving the prospective evaluation of grief in decedents' bereaved family members. Although there was no direct patient or public involvement in the project's retrospective component, the study team engaged with three knowledge user organizations (Bereaved Families of Ontario, Canadian Virtual Hospice and Champlain Hospice Palliative Care Program), whose representatives collaborated with the study planning team and were co-applicants in funding applications for the overall project.

Ethics

Each hospital's Research Ethics Board (REB) approved the study: Ottawa Health Science Network-REB (20200653-01H, December 18th 2020); Montfort REB (20-21-10-032, December 2nd 2020) and Queensway Carleton Hospital REB (20-06, December 1st 2020).

Bias

Data abstractors were not blinded to the study objectives and consequently there was potential for misclassification bias.

Study size

The sample size (N=425) was predetermined, based on the inclusion of all known Wave 1 deaths due to COVID-19 in the index group (COVID+ve, n=85), and subsequent 2:1 matching to generate the other two study groups.

Quantitative variables

The administered opioid doses abstracted for each 24-hour period in the last 72 hours of life were used to calculate the parenteral morphine equivalent daily dose (MEDD) in mg using standard equianalgesic ratios.[37]

An individual mean total 24-hour medication dose was calculated for palliative medications administered to each patient who had data for one or more of the 24-hour periods in their last 72 hours of life; the median (interquartile, Q1-Q3 range) of these individual mean doses was used as an aggregate summary measure in relation to both opioids (MEDD) and non-opioid medications administered in this period. Also, the maximum 24-hour dose of opioid, midazolam and propofol within the last 72 hours of life were determined for study group comparison. Continuous variables were expressed as mean ± standard deviation (SD) unless otherwise indicated.

Statistical methods

Demographic characteristics, palliative care consultation, comorbidities, symptoms, occurrence of medication use, median group values for individual mean 24-hour doses and MEDD values, and maximum MEDD, midazolam and propofol doses within the last 72 hours of life were compared among study groups, using a chi-square test for categorical variables, and an ANOVA or Kruskal-Wallis test for continuous variables, as appropriate. Subgroup analyses for MEDD at TI were conducted in relation to site and care service at death. The association of variables with the upper quartile of MEDD at T1 was examined in unadjusted bivariable and adjusted multivariable logistic regression analyses, reporting odds ratios and confidence intervals (CIs). Based on clinical relevance and/or having a p value <0.25 in bivariable analyses, variables were selected for a forced entry multivariable model with adjusted odds ratios (aORs). Terms were tested in the model for study group, age, sex and care service interactions. Statistical significance, using Stata (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP.) for analyses, was set at p<0.05.

RESULTS

Study sample

The derivation of the study groups is summarized in **Supplemental Figure, Appendix 2.** Data from all COVID+ve decedents (n=85) and all Pre-COVID (N=170) and COVID-ve (n=170) matched groups were used in comparison of admission comorbidity and symptom prevalence, and use of respiratory or circulatory support. To enable valid group comparisons, decedents who died < 24 hours of admission (n=14) were excluded in medication analyses. Demographic characteristics are summarized in **Table 1.**

Table 1 Demographic characteristics of study groups according to COVID-19 status and time periods

Demographic characteristics	Time periods and designated study groups			P values
	Nov 2019-Feb 2020	Mar 2020 – Aug 2020 (Wave 1)		
	Pre-COVID Group N=170 (%)*	COVID-ve Group N=170 (%)*	COVID+ve Group N=85 (%)*	
Age				
Years, mean ± SD	79.5 ± 12.3	79.2 ± 12.3	78.9 ± 12.2	0.942
Sex				
Male	100 (58.8)	100 (58.8)	50 (58.8)	1.0
Hospital location				
Site 1, n=155, (row %)	62 (40)	62 (40)	31 (20)	1.0
Site 2, n=100, (row %)	40 (40)	40 (40)	20 (20)	
Site 3, n=170, (row %)	68 (40)	68 (40)	34 (20)	
Care service at death				
Medicine service/unit	118 (69.4)	122 (71.7)	62 (72.9)	0.814
Intensive Care Unit	52 (30.6)	48 (28.2)	23 (27.1)	
Admission referral source				
Home	99 (58.2)	109 (64.1)	31 (36.5)	**<0.001**
Retirement Home	36 (21.2)	34 (20.0)	11 (11.8)	
Nursing Home	22 (12.9)	8 (4.7)	43 (50.6)	
Complex Continuing Care	2 (1.2)	2 (1.2)	0 (0.0)	
Other	11 (6.5)	17 (10.0)	1 (1.2)	
Admission duration category				
< 24 hours	7 (4.1)	7 (4.1)	0 (0)	0.061
≥ 24 and < 48 hours	26 (15.3)	18 (10.6)	6 (7.1)	
≥ 48 hours and < 72 hours	16 (9.4)	8 (4.7)	5 (5.9)	
≥ 72 hours	121 (71.2)	137 (80.6)	74 (87.1)	

Palliative care involvement				
Consult requested	70 (41.2)	71 (41.8)	26 (30.6)	0.184
Consult completed	67 (39.4)	67 (39.4)	25 (29.4)	0.234
Days from consult completion to death (median, Q1-Q3)	4 (1-9)	3 (1-6)	3 (2-12)	0.577

*** Column numbers refer to number of persons (%) in respective study groups unless stated otherwise**

There were no study group differences in age, sex, and care service at death, reflecting effective matching across study sites. Referral from nursing homes was highest (50.6%) in the COVID+ve group, compared to 12.9% and 4.7% in the Pre-COVID and COVID-ve groups, respectively (p<0.001). Palliative care consultation rates were similar across study groups but lowest (29.4%) in the COVID+ve group.

Clinical characteristics

Admission comorbidities and symptoms in addition to use of respiratory or circulatory support are summarized in **Supplemental Table, Appendix 3.** Atrial fibrillation was less prevalent in the COVID+ve group (15.3%) compared to the Pre-COVID (26.5%) and COVID-ve (32.4%) groups (p=0.015). However, dementia and miscellaneous other comorbidities occurred more frequently (41.2% and 77.7%, p=0.032 and 0.018, respectively) in the COVID+ve group compared to the Pre-COVID (27.7% and 63.5%, respectively) and COVID-ve groups (25.9% and 60.0%, respectively). In the COVID+ve group compared to other groups, pain occurred less frequently (10.6% vs 29.4% and 28.8%, p=0.002), but breathlessness, (63.5% vs 42.4% and 47.1%, p=0.006), cough (40.0% vs 27.1% and 19.4%, p=0.002) and fever (54.1% vs 9.4% and 13.5%, p<0.001) occurred more frequently. High-flow nasal cannula use was more frequent in the COVID+ve group vs PreCOVID and COVID-ve groups (54.1% vs 37.1% and 28.8%, respectively, p<0.001)

Medication use at end-of-life

Opioids were prescribed for 92.4%, 91.2% and 95.3% of the Pre-COVID, COVID-ve and COVID+ve groups (including those who died < 24 hours of admission, respectively. The median and interquartile MEDD values for study groups in relation to each 24-hour interval (T3, T2 and T1) in which decedents received an opioid, is presented in **Figure 1,** illustrating a progressive increase according to proximity to death, in both the proportion of decedents receiving

opioids and in doses administered. Group comparison of opioid use within the last 72 hours of life is summarized in **Table 2.**

Table 2 Comparative inpatient opioid use within the last 72 hours of life among decedent study groups

Opioid use in last 72 hours of life	Decedent reference periods and study groups			P values
	Nov 2019-Feb 2020	Mar 2020 – Aug 2020 (Wave 1)		
	Pre-COVID Group N=163 (%)*	COVID-ve Group N=163 (%)*	COVID+ve Group N=85 (%)*	
Type of opioid administered†				
Any opioid, n (%)	145 (89.0%)	146 (89.6%)	81 (95.3%)	0.236
Morphine, n (%)	63 (38.7%)	65 (39.9%)	40 (47.1%)	0.418
Hydromorphone, n (%)	92 (56.4%)	93 (57.1%)	52 (61.2%)	0.758
Fentanyl, n (%)	25 (15.3%)	15 (9.2%)	6 (7.1%)	0.085
Total MEDD‡ for each 24-hour period (T3-T1) within last 72 hours of life§				
T3: mg (Q1-Q3)	**10.0 (5.0-18.5)**	**10.0 (4.4-20.0)**	**14.5 (7.5-48.0)**	**0.041**
No. of decedents: n (%)	**83 (50.9%)**	**90 (55.2%)**	**58 (68.2%)**	**0.032**
T2: mg (Q1-Q3)	**8.5 (4.3-18.8)**	**10.0 (5.0-24.0)**	**18.3 (11.5-46.0)**	**<0.001**
No. of decedents: n (%)	104 (63.8%)	105 (64.4%)	63 (74.1%)	0.220
T1: mg (Q1-Q3)	**15.0 (6.5-29.8)**	**12.5 (6.3-25.0)**	**20.0 (12.0-50)**	**0.011**
No. of decedents: n (%)	137 (84.1%)	143 (87.7%)	79 (92.9%)	0.133
T1 MEDD by care service at death				
Internal Medicine: mg (Q1-Q3)	12.3 (5.8-24.5)	10.0 (5.0-20.5)	14.5 (8.0-26.3)	0.140
No. of decedents: n (subgroup %)	96/117 (82.1%)	104/119 (87.4%)	56/62 (90.3%)	0.265
Intensive Care Unit: mg (Q1-Q3)	**25.0 (14.4-49.5)**	**23.8 (10.5-45.0)**	**52.5 (31.5-80.0)**	**0.014**
No. of decedents: n (row %)	41/46 (89.1%)	39/44 (88.6%)	23/23 (100%)	0.245
T1 MEDD by hospital site				
Site 1: mg (Q1-Q3)	15.0 (9.0-27.5)	11.3 (5.0-25.0)	16.5 (10.0-45.0)	0.199
No. of decedents: n (subgroup %)	55/60 (91.6%)	49/57 (86.0%)	26/31 (83.9%)	0.480
Site 2: mg (Q1-Q3)	**11.0 (5.8-32.5)**	**16.8 (8.0-28.4)**	**31.7 (12.8-63.8)**	**0.019**
No. of decedents: n (subgroup %)	32/38 (84.2%)	36/39 (92.3%)	20/20 (100.0%)	0.130

Site 3: mg (Q1-Q3)	16.5 (8.0-33.8)	10.5 (6.0-22.5)	18.0 (9.0-35.0)	0.105
No. of decedents: n (subgroup %)	**50/65 (76.0%)**	**58/67 (86.6%)**	**33/34 (97.1%)**	**0.026**
Patient groups for aggregate MEDD summary measures estimation‖				
Decedent administered opioid n (%)	145 (89.0%)	146 (89.6%)	81 (95.3%)	0.236
Internal Medicine: n (subgroup %)	102/117 (87.2%)	105/119 (88.2%)	58 (93.6%)	0.414
Intensive Care: n (subgroup %)	43/46 (93.5%)	41/44 (93.2%)	23/23 (100%)	0.444
Aggregate MEDD measures				
Maximum MEDD: mg (Q1-Q3)	**16.5 (7.5-30.0)**	**15.0 (7.5-30.0)**	**21.0 (12.0-54.5)**	**0.012**
Internal Medicine: mg (Q1-Q3)	13.4 (6.0-27.5)	11.3 (6.8-22.5)	15.7 (8.0-30.0)	0.172
Intensive Care: mg (Q1-Q3)	**25.0 (14.4-55.0)**	**24 (11.3-54.5)**	**59.5 (44.8-120.0)**	**0.005**
Individual mean MEDD: mg (Q1-Q3)	**13.5 (5.7-21.8)**	**10.5 (5.3-23.8)**	**16.7 (9.0-36.5)**	**0.007**
Internal Medicine: mg (Q1-Q3)	10.3 (5.0-17.3)	9.4 (4.5-15.0)	13.6 (6.7-24.7)	0.072
Intensive Care: mg (Q1-Q3)	**20.9 (11.5-38.5)**	**19.8 (10.0-44.8)**	**40.0 (24.9-64.2)**	**0.009**

* Column proportions expressed as percentages in parentheses unless otherwise specified.

†Opioid administered to decedents in a minimum of one complete 24-hour admission period within the last 72 hours of life; data were excluded for 7 decedents each in the Pre-COVID and COVID-ve groups whose admission duration was < 24 hours.

‡MEDD: Morphine Equivalent Daily Dose, parenteral, mg; summarized as a median (interquartile range, Q1-Q3) value for each of the three decedent study groups.

§Designation based on hours before death: T3, > 48 and ≤ 72 hours; T2, > 24 and ≤ 48 hours; T1, last 24 hours as an inpatient

‖ Based on exposure to a minimum of one complete inpatient 24-hour admission period (T3, T2 or T1) for opioid dose administration. Aggregate measures are reported as median group values (interquartile range, Q1-Q3)

Although more COVID+ve group patients (68.2% vs 50.9% and 55.2%, p=0.032) received opioids in the T3 period, there were no other significant study group differences in opioid administration as a binary (yes/no) outcome, specifically in comparisons based on opioid type, T2 or T1 period MEDDs, care service at death, hospital site, or with reference to the 72-hour aggregate summary measures (individual mean and maximum dose). However, the

median MEDD in the COVID+ve group at T1 was 20.0 (12.0-50.0) compared to 15.0 (6.5-29.8) and 12.5 (6.3-25.0) in the Pre-COVID and COVID-ve groups, respectively (p=0.011). This group difference in MEDD was consistent at each time point (T3-T1) and in relation to 72-hour aggregate summary measures. A site subgroup analysis at T1 revealed higher median MEDD in the COVID+ve group at Site 2. An additional subgroup analysis at T1 revealed a higher median MEDD in the COVID+ve group decedents who died in ICU but not in those who died in Medicine units/wards; a similar difference was also found in relation to the aggregate measures of opioid administration over the last 72 hours of life. The independent association of variables with MEDD was examined in multivariable logistic regression.

The logistic regression analyses examining the predictors of the T1 MEDD upper quartile (≥ 30mg of parenteral morphine) are summarized in **Table 3.**

Table 3 Logistic regression analyses examining the association of variables with parenteral MEDD ≥ 30mg (upper quartile) in the last 24 hours of life in those who received opioids (n=359)

Variables examined	Proportion of patients* (%)	Unadjusted OR† (95% CI)		P value		Adjusted OR† (95% CI)		P value
Age of decedent‡	…	**0.951**	**(0.93-0.97)**	**<0.001**		0.99	(0.96-1.01)	0.313
Sex								
Female	31/155 (20.0)	1				1		
Male	**64/204 (31.4)**	**1.82**	**(1.12-2.99)**	**0.016**		**1.84**	**(1.05-3.22)**	**0.034**
Study group								
Pre-COVID	34/137 (24.8)	1				1		
COVID-ve	30/143 (21.0)	0.804	(0.46-1.41)	0.445		0.95	(0.51-1.76)	0.866
COVID+ve	**31/79 (39.2)**	**1.96**	**(1.08-3.55)**	**0.027**		**2.62**	**(1.29-5.32)**	**0.008**
Hospital site								
Site 1	32/130 (24.6)	1				1		

Site 2	27/88 (30.7)	1.36	(0.74-2.48)	0.323		0.83	(0.40-1.72)	0.617
Site 3	36/141 (25.5)	1.05	(0.61-1.82)	0.862		0.51	(0.25-1.05)	0.067
Care service at death								
Medicine	45/256 (17.6)	1				1		
ICU	**50/103 (48.5)**	**4.42**	**(2.68-7.31)**	**<0.001**		**5.14**	**(2.47-10.70)**	**<0.001**
High-Flow Nasal Cannula								
No	46/219 (21.0)	1						
Yes	**49/140 (35.0)**	**2.03**	**(1.26-3.26)**	**0.004**		**1.93**	**(1.05-3.52)**	**0.033**
Palliative Care Consult								
No	61/211 (28.9)	1				1		
Consult completed	34/148 (23.0)	0.733	(0.45-1.19)	0.210		1.51	(0.80-2.86)	0.205
Admission assessment[§]								
Cognitive status								
Not impaired	71/229 (31.0)	1				1		
Impaired	**24/130 (18.5)**	**0.504**	**(0.30-0.85)**	**0.010**		0.85	0.46-1.57	0.606
Documented pain								
No	69/264 (26.0)	1				1		
Yes	26/95 (27.4)	1.07	(0.63-1.81)	0.815		1.48	(0.80-2.74)	0.209
Active cancer								
No	67/275 (24.4)	1				1		
Yes	28/84 (33.3)	1.55	(0.91-2.64)	0.104		1.68	(0.88-3.18)	0.114
Chronic Kidney disease								
No	75/283 (26.5)	1						
Yes	20/76 (26.3)	0.991	(0.56-1.76)	0.974				
Agitation								

No	89/330 (27.0)	1						
Yes	6/29 (20.7)	0.706	(0.28-1.79)	0.464				

*Proportion of patients in upper quartile MEDD (≥ 30 mg of parenteral morphine) for T1 period (last 24 hours of life); †OR = Odds Ratio; ‡Treated as a continuous variable or covariate; §Documented on admission assessment.

In the unadjusted analyses, both older age and cognitive impairment were statistically significant negative predictors of the upper quartile MEDD, whereas male sex, COVID+ve group membership, death in ICU, and use of high-flow nasal cannula for oxygen delivery were positive predictors. In the multivariable model, only male sex, COVID+ve group membership, death in ICU, and use of high-flow nasal cannula remained statistically significant, all as positive predictors with aORs of 1.84 (1.05-3.22), 2.62 (1.29-5.3), 5.14 (2.47-10.7) and 1.93 (1.05-3.52), respectively. Potential variable interactions among COVID-19 study group status, age, sex and care service at death were tested in the model, and the interaction terms were not statistically significant.

Comparative non-opioid medication doses (mg) administered within the last 72 hours of life for the study groups are summarized in **Table 4**.

Table 4 Comparative inpatient use of non-opioid End-of-Life medications within the last 72 hours of life among decedent study groups

Non-opioid medications administered in the last 72 hours of life *	**Decedent reference periods and study groups**			**P values**
	Nov 2019-Feb 2020	**Mar 2020 – Aug 2020 (Wave 1)**		
	Pre-COVID Group† N=163 (%)	**COVID-ve Group† N=163 (%)**	**COVID+ve Group N=85 (%)**	
Antisecretory medications				
Glycopyrrolate, n (%)	36 (22.1)	37 (22.7)	12 (14.1)	0.243
Mean 24-hour dose, mg‡	0.5 (0.4-0.9)	0.6 (0.4-1.2)	0.4 (0.4-0.6)	0.570
Scopolamine, n (%)	20 (12.3)	21 (12.9)	14 (16.5)	0.635
Mean 24-hour dose, mg‡	0.4 (0.4-0.9)	0.4 (0.4-0.8)	0.5 (0.4-1.0)	0.909
Antipsychotic medications				

Haloperidol, n (%)	32 (19.6)	25 (15.3)	10 (11.8)	0.257
Mean 24-hour dose, mg‡	1.0 (0.5-1.3)	1.0 (0.5-1.5)	1.4 (0.7-4.5)	0.656
Methotrimeprazine, n (%)	37 (22.7)	40 (24.5)	26 (30.6)	0.389
Mean 24-hour dose, mg‡	10 (6.3-22.5)	11.7 (6.9-24.4)	11.3 (5.0-25.0)	0.947
Benzodiazepines				
Lorazepam, n (%)	19 (11.7)	17 (10.4)	7 (8.2)	0.705
Mean 24-hour dose, mg‡	**1.0 (0.5-1.5)**	**1.5 (1.0-2.3)**	**3.7 (1.5-25.0)**	**0.017**
Midazolam, n (%)	96 (58.9)	100 (61.4)	57 (67.1)	0.454
Mean 24-hour dose, mg‡	3.7 (1.5-12.5)	3.0 (1.5-11.3)	5.7 (2.0-19.0)	0.255
Maximum 24-hour dose, mg‡	4.3 (2.0-13.5)	4.0 (1.7-13.0)	7.0 (2.0-22.0)	0.199
Other sedating medications				
Phenobarbitone, n (%)	4 (2.5)	6 (3.7)	5 (5.9)	0.393
Mean 24-hour dose, mg‡	150.0 (90.0-210.0)	127.5 (90.0-140.0)	150.0 (75.0-180)	0.811
Propofol administered, n (%)	21 (12.9)	28 (17.2)	13 (15.3)	0.555
Mean 24-hour dose, mg‡	1078.5 (692.5-1984.0)	1329.2 (634.0-2811.6)	1887.5 (1337.5-5527.3)	0.080
Maximum 24-hour dose, mg‡	**1444.8 (692.5-2207.0)**	**1624.4 (851.0-3491.5)**	**2665.6 (2119.4-6304.0)**	**0.033**

*Based on exposure to a minimum of at least one full inpatient 24-hour period for mean 24-hour dose determination within the last 72 hours of life.

†Data were excluded for 7 decedents in each of the original Pre-COVID and COVID-ve groups due to admission duration < 24 hours

‡Individual mean 24-hour doses are summarized for the study group as a median (interquartile range) value for each of the three study groups.

Although both mean and maximum 24-hour doses of midazolam were higher in the COVID+ve group, the differences were not statistically different. The median lorazepam COVID+ve group dose, 3.7 (1.5-25.0) was higher than that of the Pre-COVID and COVID-ve groups, 1.0 (0.5-1.5) and 1.5 (1.0-2.3), respectively (p=017). Similarly, the

median of the maximum propofol dose, 2665.6 (2119.4-6304.0) was higher than that of the Pre-COVID and COVID-ve groups, 1444.8 (692.5-2207.0) and 1624.4 (851.0-3491.5), respectively (p=0.033).

DISCUSSION

Study findings and putative explanations

Our study found that COVID+ve decedents received significantly higher opioid doses than matched pre-pandemic or intra-pandemic control patients. This finding was moderately robust: it was consistent in each 24-hour time period within the last 72 hours of life, and further bolstered by finding that dying of COVID-19 was independently associated (aOR=2.6) with a parenteral MEDD ≥30mg in the last 24 hours of life. COVID+ve decedents had significantly higher maximum 24-hour propofol use in ICU compared to control group decedents. Also, higher lorazepam and midazolam doses were used in the COVID+ve group than either of the other groups; the difference was only statistically significant in relation to lorazepam. Collectively, these findings regarding opioid and sedative use support our study hypothesis that the requirement for these medications is higher in hospitalized patients dying of COVID-19 infection. In subgroup analyses, COVID+ve ICU decedents had significantly higher opioid use than ICU decedents in either of the control groups, which was evident in the last 24 hours (T1) and over the last 72 hours of life, suggesting that dying in ICU with COVID-19 infection is particularly associated with increased opioid and propofol requirements. These findings warrant a symptom profile evaluation of those dying of COVID-19.

Although our study patients' comfort in the last 72 hours of life was regularly assessed and documented, there was no formal standardized recording of symptom intensity across sites. For symptom profile comparisons we used the admission documentation of symptoms, which fell within the last 72 hours of life for approximately 20% of the study sample. The COVID +ve group had significantly higher admission prevalence of breathlessness, cough, and fever, and used high-flow nasal cannula oxygen support more frequently during admission. Previous studies have found that breathlessness is a major symptom in patients dying with COVID-19 infection.[15 16 31 38-40] Although myalgic pain is reported in those dying of COVID-19 infection,[15] among our three study groups, pain was least frequent in COVID+ve decedents at admission, but higher prevalence could have occurred closer to death. High-flow nasal cannula use was independently associated (aOR=1.9) with a parenteral MEDD ≥30mg in the last 24

hours of life. Collectively, our results suggest that respiratory distress mediated higher opioid use in the COVID-+ve group, particularly in ICU decedents. Agitation and delirium are reported in patients dying of COVID-19 infection.[14 18 31 33 40] Although the admission prevalence of agitation was largely similar across our groups, subsequent group differences in agitation level could have arisen nearer to death. Furthermore, COVID+ve group decedents had a higher admission prevalence of dementia and other comorbidity burden, both risk factors for delirium.[41] The higher lorazepam and maximum 24-hour propofol doses in our COVID+ve group were possibly due to COVID-19 related respiratory distress in addition to potential contributions of cognitive dysfunction with agitation, and greater comorbidity-related distress.

Study findings in the context of published data

Although atrial fibrillation is a risk factor for mortality in high-risk COVID-19 patients,[42] it was least prevalent in our COVID+ve study group. Meanwhile, the higher COVID+ve group admission prevalence of cognitive impairment and other comorbidities were largely consistent with published data on COVID-19 risk factors.[11 17] Similarly, the higher prevalence of respiratory symptoms and fever is consistent with reported end-of-life prevalence in COVID-19 deaths.[12 14 17] Literature comparison of palliative medication use in patients dying due to COVID-19 infection is limited by paucity of data, particularly on ICU deaths, and further compromised by differences in type of aggregate dose measures reported, time reference, care setting, regional medication formularies, and in the separate reporting of pro re nata (PRN) or "as needed" medication use in addition to continuous infusional use.[28] We reported the total daily medication use which included regularly scheduled and PRN doses, or solely PRN doses in the absence of scheduled dosing. Although antisecretory and antipsychotic medication use was similar across all of our study groups, and comparable to published estimates in COVID-19 deaths,[28 30 31] our findings regarding opioid and benzodiazepine use warrant more detailed evaluation in the context of published data.

A systematic review of symptom management in COVID-19 related deaths, which excluded ICU deaths,[28] concluded that although a higher proportion of those dying with COVID-19 infection required continuous administration of opioid or midazolam than previously reported in pre-COVID-19 palliative care, doses were relatively low (median of 10-15 mg of parenteral morphine, and 10mg of midazolam, in the last 24 hours of life, in an aggregate dose summary of 5 of the studies) and in keeping with published guidelines.[24] A study of COVID-19

deaths in a hospital palliative care unit in New York reported a median parenteral MEDD (range) of 48 (24-144) mg in the last days of life.[33] A Belgian study of hospitalized COVID-19 decedents, excluded ICU deaths, and reported a mean parenteral MEDD of 31.3 (range, 2-120) mg, and mean midazolam dose of 20.4 (range, 1-100) mg in the last 24 hours of life.[32] An Australian study of hospitalized COVID-19 decedents, including 9 (4%) who died in ICU, reported a median (Q1-Q3) oral MEDD of 45 (22.5-75.0) in the last day before death.[31] Our study's higher MEDD findings in the COVID+ve group were comparable to this study; the inclusion of ICU decedents with possibly higher levels of symptom distress in our study could explain the higher opioid and sedative doses than those reported in the systematic review by Heath et al.[28] The progressive MEDD increase in the COVID+ve group over the last 72 hours is consistent with a longitudinal study reporting a doubling of median daily opioid use in the last 7 days of life in COVID-19 decedents.[31] Our finding of an independent association between male sex and higher opioid dosing is difficult to explain, as larger pre-pandemic studies have not reported a sex difference in relation to opioid dosing.[43 44] Although male sex is a recognized mortality-related risk factor in COVID-19 infection,[11 45] a statistically significant interaction between sex and study group status was not detected in the model.

Although 67.1% of the COVID+ve group received midazolam in the last 72 hours of life, the daily midazolam dose estimates in this period were lower than the 10 mg estimate reported in a systematic review.[28] Although palliative care involvement was similar across our study groups, the completion of a consult in only 29.4% of the COVID+ve group is below the 39-51% range reported in other studies of COVID-19 decedents,[3 31] and possibly impacted the prescribing patterns of some medications used for end-of-life symptom control.

Study implications and future research

In addition to informing end-of-life guidelines on medication use for symptom management in COVID-19 infection and in future pandemics, our study findings warrant further research, particularly regarding the use of opioids and sedatives in the ICU setting. Moreover, regarding end-of-life comfort assessment, our study highlights the need for standardized symptom assessment measures such as the palliative version of the Richmond Agitation-Sedation Scale (RASS-PAL),[46] which can be used to evaluate medication efficacy and audit quality of care. Specialist palliative care involvement in end-of-life care of hospitalized individuals warrants further study both in relation to predictors and outcomes.

Study strengths and limitations

Our study's decedent cohort was representative of the source population in all adult acute care hospitals in a large urban region; using matched control groups from within and prior to the COVID-19 pandemic facilitated valid and unique comparisons, which generated some robust findings, particularly regarding opioid use. The retrospective design and use of admission symptom assessment and comorbidity data without similar data, including medication efficacy and side-effects, from within the more immediate end-of-life period are obvious limitations. The role of non-pharmacological interventions was not examined. Although rigorous training and accuracy checks were conducted regarding data abstraction, misclassification bias cannot be excluded, and absence of abstractor blinding to the study hypothesis is a potential source of bias. This study was performed during Wave 1 of the pandemic, and both symptom burden and medication requirements for symptom control could have changed to some extent with subsequent waves. The generalizability of our study findings is largely limited to end-of-life care for hospitalized decedents, whereas many of the COVID-19 pandemic related deaths in Wave 1 of the pandemic occurred in nursing homes.

CONCLUSIONS

Overall, our study evidence suggests that in addition to the association of male sex with higher end-of-life opioid requirements, patients dying of COVID-19 infection required higher daily opioid and lorazepam doses than those dying of other causes both before and during the COVID-19 pandemic. Furthermore, patients who died of COVID-19 infection in ICU required higher maximum 24-hour propofol doses than those who died in ICU without COVID-19 infection. Increased breathlessness and agitation due to COVID-19 and higher underlying comorbidity levels may require higher doses of opioids and sedatives for symptom control. These findings warrant consideration in the context of managing ongoing life threatening COVID-19 infection and in anticipatory preparation for future respiratory virus pandemics.

Data availability statement

No additional data available

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Contributors

JD conceptualized the project and designed the study with assistance from PL, HP, LC, VG, RM, GW, AB, KW, JL, CW, DB, PE, ID, KB, CD, AI, SHB, SI, PT, BV. The study site leads, HP, VG, LC, co-ordinated ethics applications along with PL, JL and DB. Data were abstracted by PL, HP, SRA, EB, LC, RM, GW, AB, KAM, KW, PE, ID, KB and CD. Data verification was coordinated by PL with the assistance of HP, SRA, EB, LC, RM, GW, AB, PE and KB. Statistical analyses were performed by PL with support from LC and CW. All authors, including MK, CN, BH and KA assisted with data interpretation. The original version of the manuscript was drafted by PL and LC and critically reviewed by all authors. All authors approved the final manuscript as submitted.

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Competing interests

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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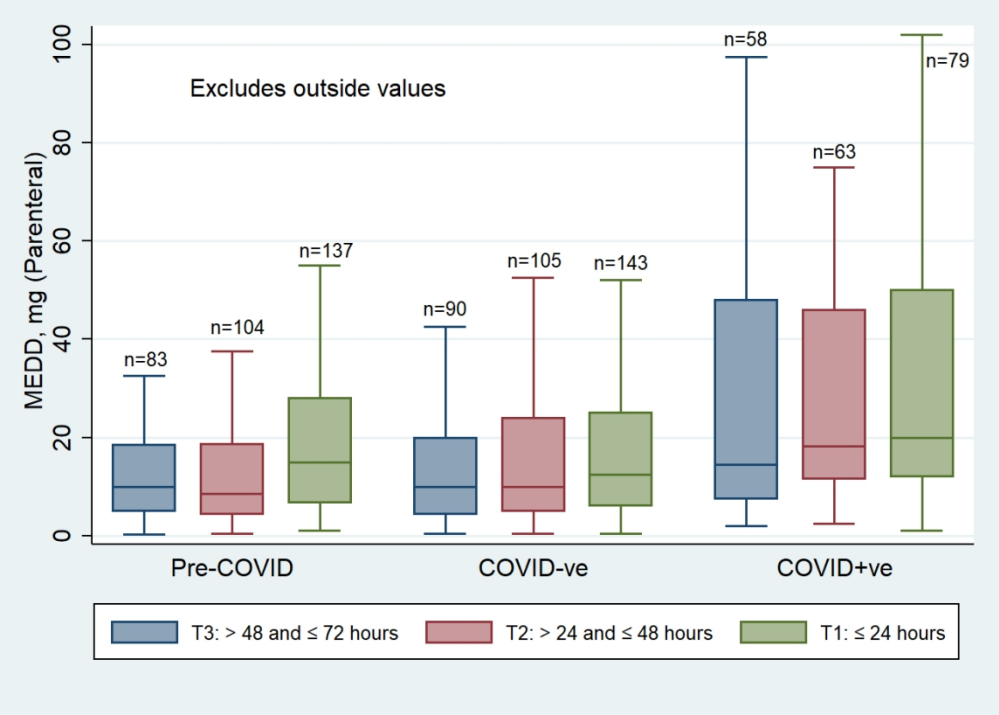


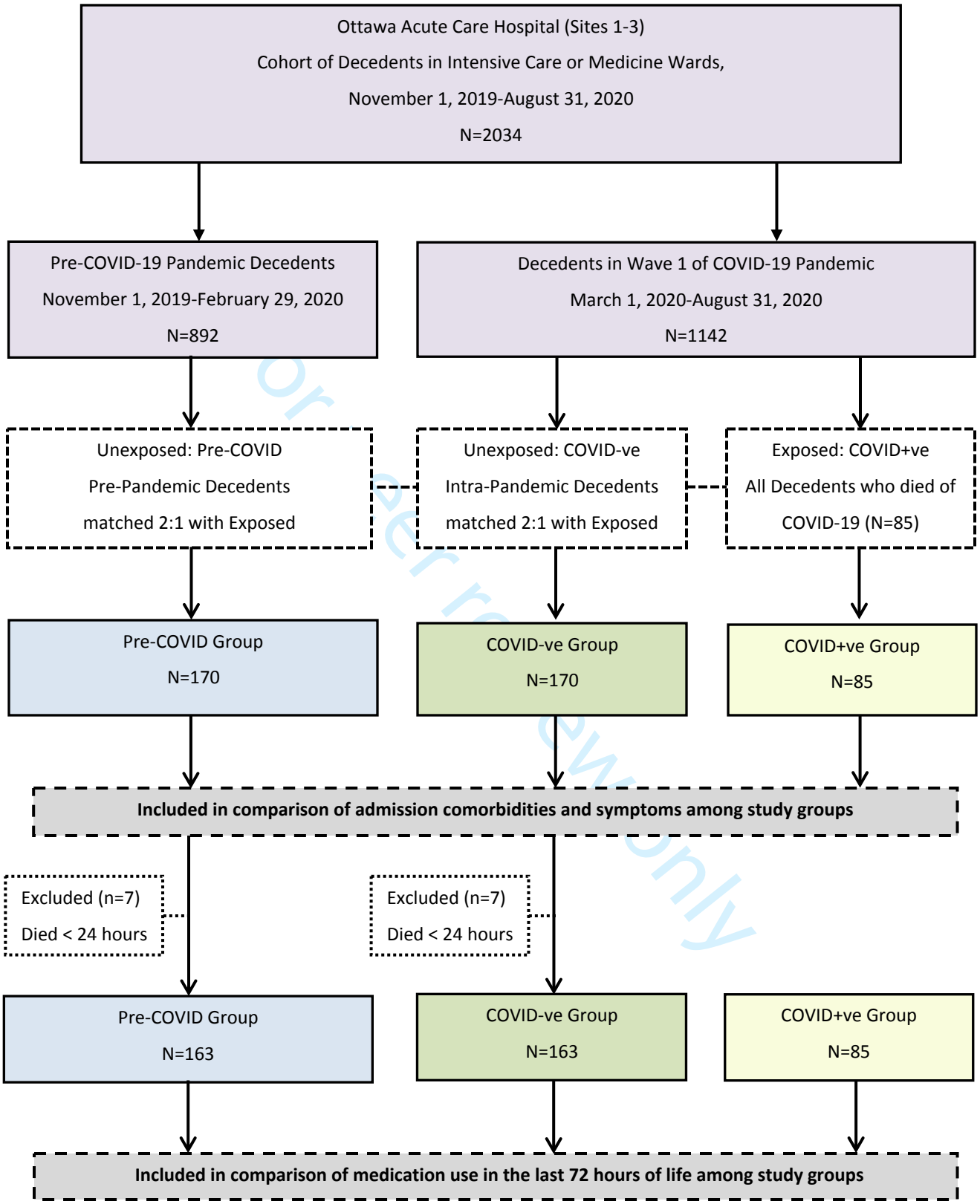
Figure 1 Median MEDD for consecutive 24-hour periods (T3-T1) within the last 72 hours of life

461x329mm (72 x 72 DPI)

Appendix 1 Clinical characteristics as documented at admission, and supportive interventions as documented during admission

Comorbidities at admission
COPD
Asthma
Heart Failure
Hypertension
Atrial fibrillation
Coronary artery disease
Chronic liver disease
Diabetes mellitus
Chronic kidney disease
Obesity
HIV infection
Dementia
Active cancer
Other comorbidity
Symptoms/signs at admission

Breathlessness
Airway secretions
Cough
Agitation
Drowsiness
Pain
Cognitive impairment
Fatigue
Fever
Other symptoms
Respiratory/circulatory support used during admission
BIPAP
High flow nasal cannula
Intubated
Other respiratory support
Vasopressor use



Appendix 3 Supplemental Table Study group comparison of admission clinical characteristics and respiratory/circulatory support use during admission

Clinical characteristics	Time periods and designated study groups			P values
	Nov 2019-Feb 2020	Mar 2020 – Aug 2020 (Wave 1)		
	Pre-COVID Group N=170 (%)	COVID-ve Group N=170 (%)	COVID+ve Group N=85 (%)	
Comorbidities at admission				
COPD	43 (25.3)	49 (28.8)	17 (20.0)	0.312
Asthma	7 (4.1)	9 (5.3)	3 (3.5)	0.780
Heart Failure	40 (23.5)	48 (28.2)	16 (18.8)	0.240
Hypertension	95 (55.9)	104 (61.2)	57 (67.1)	0.217
Atrial fibrillation	**45 (26.5)**	**55 (32.4)**	**13 (15.3)**	**0.015**
Coronary artery disease	52 (30.6)	52 (30.6)	22 (25.9)	0.697
Chronic liver disease	3 (1.8)	11 (6.5)	3 (3.5)	0.084
Diabetes mellitus	48 (28.2)	56 (32.9)	26 (30.6)	0.642
Chronic kidney disease	32 (18.8)	38 (22.4)	19 (22.4)	0.681
Obesity	6 (3.5)	15 (8.8)	4 (4.7)	0.102
HIV infection	0 (0.0)	0 (0.0)	1 (1.2)	0.135
Dementia	**47 (27.7)**	**44 (25.9)**	**35 (41.2)**	**0.032**
Active cancer	44 (25.9)	37 (21.8)	11 (12.9)	0.061
Other comorbidity	**108 (63.5)**	**102 (60.0)**	**66 (77.7)**	**0.018**
Symptoms/signs at admission				
Breathlessness	**72 (42.4)**	**80 (47.1)**	**54 (63.5)**	**0.006**
Airway secretions	28 (16.5)	16 (9.4)	7 (8.2)	0.066
Cough	**46 (27.1)**	**33 (19.4)**	**34 (40.0)**	**0.002**
Agitation	11 (6.5)	14 (8.2)	10 (11.8)	0.350
Drowsiness	68 (40.0)	57 (33.5)	39 (45.9)	0.143
Pain	**50 (29.4)**	**49 (28.8)**	**9 (10.6)**	**0.002**
Cognitive impairment	57 (33.5)	59 (34.7)	35 (41.2)	0.465
Fatigue	88 (51.8)	83 (48.8)	51 (60.0)	0.239
Fever	**16 (9.4)**	**23 (13.5)**	**46 (54.1)**	**<0.001**
Other symptoms	90 (52.9)	79 (46.5)	42 (49.4)	0.490

Respiratory/circulatory support used during admission				
BIPAP	22 (12.9)	17 (10.0)	4 (4.7)	0.121
High flow nasal cannula	**63 (37.1)**	**49 (28.8)**	**46 (54.1)**	**<0.001**
Intubated	45 (26.5)	43 (25.3)	14 (16.5)	0.186
Other respiratory support	50 (29.4)	52 (30.6)	31 (36.5)	0.502
Vasopressor use	43 (25.3)	47 (27.7)	13 (15.3)	0.087

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	6
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	6
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	8
Objectives	3	State specific objectives, including any prespecified hypotheses	9
Methods			
Study design	4	Present key elements of study design early in the paper	9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	9-10
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	10
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	10
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	10-11
Bias	9	Describe any efforts to address potential sources of bias	11
Study size	10	Explain how the study size was arrived at	11
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	12
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	12
		(*b*) Describe any methods used to examine subgroups and interactions	12
		(*c*) Explain how missing data were addressed	12
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	12
		(b) Give reasons for non-participation at each stage	12
		(c) Consider use of a flow diagram	Supplemental Figure
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	12-13
		(b) Indicate number of participants with missing data for each variable of interest	12
		(c) Summarise follow-up time (eg, average and total amount)	12
Outcome data	15*	Report numbers of outcome events or summary measures over time	12-20
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	18-19
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14-15
Discussion			
Key results	18	Summarise key results with reference to study objectives	21
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	21-23
Generalisability	21	Discuss the generalisability (external validity) of the study results	21-24
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	25

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Comorbidities, symptoms, and end-of-life medication use in hospitalized decedents before and during the COVID-19 pandemic: a retrospective regional cohort study in Ottawa, Canada

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Heading:	
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Comorbidities, symptoms, and end-of-life medication use in hospitalized decedents before and during the COVID-19 pandemic: a retrospective regional cohort study in Ottawa, Canada

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ABSTRACT

Objective: To compare comorbidities, symptoms, and end-of-life (EoL) palliative medication (antisecretories, opioids, antipsychotics and sedatives) use among decedents before and during the COVID-19 pandemic.

Design: In a retrospective cohort study, decedent records in 3 acute care hospitals were abstracted, generating a pre-pandemic (November 2019-February 2020) group (Pre-COVID) and 2 intra-pandemic (March-August 2020, Wave 1) groups, one without (COVID-ve) and one with COVID-19 infection (COVID+ve). Control group decedents were matched 2:1 on age, sex and care service (Medicine/Intensive Care Unit (ICU)) with COVID+ve decedents.

Setting: Three regional acute care teaching hospitals in Ottawa, Canada

Participants: Decedents (N=425): COVID+ve (n=85), COVID-ve (n=170) and Pre-COVID (n=170).

Main outcome measures: Data were abstracted regarding demographics, admission comorbidities and symptoms, and EoL medication use; opioid doses were standardized to parenteral morphine equivalent daily dose (MEDD), and the predictors of upper quartile MEDD in the last 24 hours of life were examined in multivariable logistic regression with adjusted odds ratios (aORs) and 95% confidence intervals (CIs).

Results: The prevalence of dementia (41% vs 28% and 26%, p=0.03), breathlessness (63.5% vs 42% and 47%, p<0.01), cough (40% vs 27% and 19%, p<0.01) and fever (54% vs 9% and 13.5%) was higher in COVID+ve vs Pre-COVID and COVID-ve groups, respectively. The median (interquartile range) of MEDD over the last 72 hours of life was 16.7, (9-36.5) vs 13.5 (5.7-21.8) and 10.5 (5.3-23.8) for COVID+ve vs PreCOVID and COVID-ve groups, respectively, (p=0.007). Male sex, COVID+ve grouping, ICU death, and high-flow nasal cannula use predicted upper quartile MEDD dose, aORs (CIs): 1.84 (1.05-3.22), 2.62 (1.29-5.3), 5.14 (2.47-10.7) and 1.93 (1.05-3.52), respectively. COVID+ve group decedents used highest lorazepam and propofol doses.

Conclusions: COVID-19 decedents, particularly those in ICU, required higher EoL opioid and sedating medication doses than matched pre- or intra-pandemic controls. These findings should inform and guide clinical practice.

Abstract: 300 words

Main manuscript: 3885 words

Tables: 4 (plus 2 Supplementary, Appendix 1 and 3)

Figures: 1 (plus 1 Supplementary, Appendix 2)

Keywords: COVID-19, adult palliative care, adult intensive & critical care, sedation, medications, opioid, morphine equivalent daily dose

Strengths and limitations of this study

- The decedent cohort was representative of the source population in all adult acute care hospitals in a large urban region, and use of control groups from within and prior to the COVID-19 pandemic facilitated valid and unique comparisons.
- This study relates to Wave 1 of the pandemic. It is possible that symptom burden, and thus use of symptom control medications, has changed with subsequent waves.
- Although rigorous training and accuracy checks were conducted in relation to data abstraction, abstractors were not blinded in relation to the study hypothesis, posing a potential source of bias.
- The study's retrospective design and recording of admission symptom assessment and comorbidity data without similar data, including medication efficacy and side-effects, from within the more immediate end-of-life period are obvious limitations.
- The generalizability of our study findings is largely limited to end-of-life care for hospitalized decedents, whereas many of the COVID-19 related deaths in Wave 1 of the pandemic occurred in nursing homes.

INTRODUCTION

Globally, by mid-January 2023, over six million deaths due to COVID-19 (Coronavirus 2019) are reported to have occurred.(1) However, a bigger picture estimate of overall excess mortality due to the COVID-19 pandemic suggests a figure of just over 18 million deaths by the end of 2021.(2) These estimates highlight the need for effective integration of specialist palliative care within hospitals,(3,4) and adoption of a palliative care approach to ensure end-of-life care provision in the COVID-19 pandemic.(5-7) Although the uptake of vaccines has helped to reduce COVID-19 disease severity and mortality,(8) the mortality risk remains higher with chronic medical conditions, socioeconomic deprivation, and in certain ethnic groups.(9, 10) Prior to vaccination uptake, earlier in the pandemic, infection with COVID-19 posed a greater risk of hospitalization, Intensive Care Unit (ICU) admission and subsequent death, particularly for older people, those with frailty and chronic medical comorbidities.(11-13)

Among those hospitalized with severe COVID-19 infection, dyspnoea, cough, fatigue, delirium, agitation and myalgia are the most prevalent symptoms.(14-18) Both pharmacological and respiratory support interventions are often required for symptom control.(12,19,20) In caring for those dying of COVID-19 infection, clinicians, particularly those with limited palliative expertise, are often faced with urgent need for information and support,(21,22) and are guided in their use of pharmacological interventions by expert publications and specific guidelines.(6,7,23,24)

Palliative medications used in severe COVID-19 infection include: opioids for pain and dyspnoea; benzodiazepines for anxiety, agitation and dyspnoea; antipsychotics for refractory delirium symptoms; and antisecretory medications for airway secretions.(20) Phenobarbitone and propofol are also used for sedation,(25,26) the latter mainly in ICU settings. However, higher-level evidence derived directly from COVID-19 infected study populations for the efficacy and safety of pharmacological interventions in targeting symptom control is limited.(27,28) Furthermore, guidelines addressing end-of-life symptom management in the COVID-19 context, for example dyspnoea, are largely informed by primary studies conducted pre-pandemically in patients with either cancer or COPD,(29) raising potential generalizability concerns. There is also a paucity of real world reported data on palliative medication use during the pandemic.(30,31) Although most reports suggest that opioid requirements for end-of-life symptom management in COVID-19 infection are similar to other end-of-life

conditions,(28,30,31) some report higher requirements.(32,33) Based on clinical experience, we hypothesized that higher opioid and sedative doses are needed to control symptoms in hospitalized patients dying of COVID-19 infection.

We conducted a study with the primary objective of comparing palliative medication use in the last 72 hours of life among three hospitalized decedent groups: a pre-pandemic group and two groups from Wave 1 of the pandemic, one who died of COVID-19 infection, and the other who died of other causes without COVID-19 infection. Group comparisons of admission comorbidity and symptom prevalence, and respiratory/circulatory support use were additional objectives.

METHODS

Study design

As part of a larger project on grief and bereavement in the COVID-19 pandemic,(34,35) we conducted a retrospective multicentre matched cohort study of decedents' documented end-of-life care in acute care hospitals. The study is reported according to the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) criteria.(36)

Setting

The study population source consisted of inpatients in Ottawa (city and catchment area population 1.4 million), Canada, who died in the city's three adult acute care hospital sites between November 1, 2019 and August 31, 2020. Site 1, Hôpital Montfort is a tertiary hospital with 289 inpatient beds. Site 2, Queensway-Carleton Hospital is a tertiary hospital with 264 inpatient beds. Site 3, The Ottawa Hospital is a quaternary hospital with 1271 inpatient beds. All sites used established electronic health records (EHR) software systems, MEDITECH (Medical Information Technology, Inc.) at Sites 1 and 2, and Epic (Epic Systems Corporation) at Site 3, in documenting patient care.

Key exposures

Between March 1 and August 31, 2020, a total of 85 people died of COVID-19 infection in the region's three acute care hospitals. The study's key exposures related to COVID-19 infection status during decedents' last hospital

admission and when the admission occurred in relation to the pandemic. Three decedent study groups were identified on the basis of these exposures: a Pre-COVID group who died between November 1st 2019 and February 29th 2020; and 2 groups who died between March 1st 2020 and August 31st 2020, within Wave 1 of the pandemic, one who died of COVID-19 infection, and the other, without any record of COVID-19 during their hospital admission, designated COVID+ve and COVID-ve, respectively.

Participants

Adult (≥ 18 years old) decedents were included if they died in ICU or under the care of internal medicine in the designated study period. Both Emergency Department decedents and those primarily under surgical care were excluded. The index study group was COVID+ve (n=85), and each of these decedents was included. Using a 2: 1 ratio, the control Pre-COVID (n=170) and COVID-ve (n=170) group members were matched with COVID+ve members at each site on the basis of age (± 5 years), sex and care service (Medicine or ICU) at the time of death.

Data sources/measurement

Anonymized EHR data, including study variables were abstracted by teams of internal/palliative medicine physicians and two research assistants at each site, and entered into a common electronic study database. All abstractors received training regarding abstraction requirements. A senior study team member conducted a duplicate data abstraction of 154 (35%) of the patient records to confirm accuracy of details.

Variables

Study group designation was based on EHR documentation of COVID-19 infection status, date of death and death certification. Demographic variables included age, sex, admission referral source, acute care site, care service at death, and admission duration (days). Based on EHR documentation, comorbidities and symptoms at admission, and respiratory/circulatory support use during admission, were recorded (Yes/No) by abstractors, **Supplemental Table, Appendix 1**. Abstractors recorded medications prescribed (yes/no) and administered (yes/no) in the last 72 hours of life. Administered doses were totalled for each 24-hour interval (T3: > 48 and ≤ 72 hours, T2: > 24 and ≤ 48 hours, and T1: the last 24 hours of life) within this period, where available, and recorded for the following: opioids (morphine, fentanyl, hydromorphone), antisecretory medications (glycopyrrolate and hyoscine

hydrobromide), antipsychotics (haloperidol and methotrimeprazine), benzodiazepines (lorazepam and midazolam), other sedating medication (phenobarbitone and propofol). Opioid doses were recorded in parenteral equivalent using a standard oral to parenteral ratio of 2:1.(37)

Patient and public involvement

Decedents' study data were retrospectively acquired and are part of a project involving the prospective evaluation of grief in decedents' bereaved family members. Although there was no direct patient or public involvement in the project's retrospective component, the study team engaged with three knowledge user organizations (Bereaved Families of Ontario, Canadian Virtual Hospice and Champlain Hospice Palliative Care Program), whose representatives collaborated with the study planning team and were co-applicants in funding applications for the overall project.

Bias

Data abstractors were not blinded to the study objectives and consequently there was potential for misclassification bias.

Study size

The sample size (N=425) was predetermined, based on the inclusion of all known Wave 1 deaths due to COVID-19 in the index group (COVID+ve, n=85), and subsequent 2:1 matching to generate the other two study groups.

Quantitative variables

The administered opioid doses abstracted for each 24-hour period in the last 72 hours of life were used to calculate the parenteral morphine equivalent daily dose (MEDD) in mg using standard equianalgesic ratios.(37)

An individual mean total 24-hour medication dose was calculated for palliative medications administered to each patient who had data for one or more of the 24-hour periods in their last 72 hours of life; the median (interquartile, Q1-Q3 range) of these individual mean doses was used as an aggregate summary measure in relation to both opioids (MEDD) and non-opioid medications administered in this period. Also, the maximum 24-

hour dose of opioid, midazolam and propofol within the last 72 hours of life were determined for study group comparison. Continuous variables were expressed as mean ± standard deviation (SD) unless otherwise indicated.

Statistical methods

Demographic characteristics, palliative care consultation, comorbidities, symptoms, occurrence of medication use, median group values for individual mean 24-hour doses and MEDD values, and maximum MEDD, midazolam and propofol doses within the last 72 hours of life were compared among study groups, using a chi-square test for categorical variables, and an ANOVA or Kruskal-Wallis test for continuous variables, as appropriate. Subgroup analyses for MEDD at TI were conducted in relation to site and care service at death. The association of variables with the upper quartile of MEDD at T1 was examined in unadjusted bivariable and adjusted multivariable logistic regression analyses, reporting odds ratios and confidence intervals (CIs). Based on clinical relevance and/or having a p value <0.25 in bivariable analyses, variables were selected for a forced entry multivariable model with adjusted odds ratios (aORs). Terms were tested in the model for study group, age, sex and care service interactions. Statistical significance, using Stata (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP.) for analyses, was set at p<0.05.

RESULTS

Study sample

The derivation of the study groups is summarized in **Supplemental Figure, Appendix 2.** Data from all COVID+ve decedents (n=85) and all Pre-COVID (N=170) and COVID-ve (n=170) matched groups were used in comparison of admission comorbidity and symptom prevalence, and use of respiratory or circulatory support. To enable valid group comparisons, decedents who died < 24 hours of admission (n=14) were excluded in medication analyses. Demographic characteristics are summarized in **Table 1.**

Table 1 Demographic characteristics of study groups according to COVID-19 status and time periods

Demographic characteristics	Time periods and designated study groups		P values
	Nov 2019-Feb 2020	Mar 2020 – Aug 2020 (Wave 1)	

	Pre-COVID Group N=170 (%)*	COVID-ve Group N=170 (%)*	COVID+ve Group N=85 (%)*	
Age				
Years, mean ± SD	79.5 ± 12.3	79.2 ± 12.3	78.9 ± 12.2	0.942
Sex				
Male	100 (58.8)	100 (58.8)	50 (58.8)	1.0
Hospital location				
Site 1, n=155, (row %)	62 (40)	62 (40)	31 (20)	1.0
Site 2, n=100, (row %)	40 (40)	40 (40)	20 (20)	
Site 3, n=170, (row %)	68 (40)	68 (40)	34 (20)	
Care service at death				
Medicine service/unit	118 (69.4)	122 (71.7)	62 (72.9)	0.814
Intensive Care Unit	52 (30.6)	48 (28.2)	23 (27.1)	
Admission referral source				
Home	99 (58.2)	109 (64.1)	31 (36.5)	**<0.001**
Retirement Home	36 (21.2)	34 (20.0)	11 (11.8)	
Nursing Home	22 (12.9)	8 (4.7)	43 (50.6)	
Complex Continuing Care	2 (1.2)	2 (1.2)	0 (0.0)	
Other	11 (6.5)	17 (10.0)	1 (1.2)	
Admission duration category				
< 24 hours	7 (4.1)	7 (4.1)	0 (0)	0.061
≥ 24 and < 48 hours	26 (15.3)	18 (10.6)	6 (7.1)	
≥ 48 hours and < 72 hours	16 (9.4)	8 (4.7)	5 (5.9)	
≥ 72 hours	121 (71.2)	137 (80.6)	74 (87.1)	
Palliative care involvement				
Consult requested	70 (41.2)	71 (41.8)	26 (30.6)	0.184
Consult completed	67 (39.4)	67 (39.4)	25 (29.4)	0.234

Days from consult completion to death (median, Q1-Q3)	4 (1-9)	3 (1-6)	3 (2-12)	0.577

*** Column numbers refer to number of persons (%) in respective study groups unless stated otherwise**

There were no study group differences in age, sex, and care service at death, reflecting effective matching across study sites. Referral from nursing homes was highest (50.6%) in the COVID+ve group, compared to 12.9% and 4.7% in the Pre-COVID and COVID-ve groups, respectively (p<0.001). Palliative care consultation rates were similar across study groups but lowest (29.4%) in the COVID+ve group.

Clinical characteristics

Admission comorbidities and symptoms in addition to use of respiratory or circulatory support are summarized in **Supplemental Table, Appendix 3.** Atrial fibrillation was less prevalent in the COVID+ve group (15.3%) compared to the Pre-COVID (26.5%) and COVID-ve (32.4%) groups (p=0.015). However, dementia and miscellaneous other comorbidities occurred more frequently (41.2% and 77.7%, p=0.032 and 0.018, respectively) in the COVID+ve group compared to the Pre-COVID (27.7% and 63.5%, respectively) and COVID-ve groups (25.9% and 60.0%, respectively). In the COVID+ve group compared to other groups, pain occurred less frequently (10.6% vs 29.4% and 28.8%, p=0.002), but breathlessness, (63.5% vs 42.4% and 47.1%, p=0.006), cough (40.0% vs 27.1% and 19.4%, p=0.002) and fever (54.1% vs 9.4% and 13.5%, p<0.001) occurred more frequently. High-flow nasal cannula use was more frequent in the COVID+ve group vs PreCOVID and COVID-ve groups (54.1% vs 37.1% and 28.8%, respectively, p<0.001)

Medication use at end-of-life

Opioids were prescribed for 92.4%, 91.2% and 95.3% of the Pre-COVID, COVID-ve and COVID+ve groups (including those who died < 24 hours of admission, respectively. The median and interquartile MEDD values for study groups in relation to each 24-hour interval (T3, T2 and T1) in which decedents received an opioid, is presented in **Figure 1,** illustrating a progressive increase according to proximity to death, in both the proportion of decedents receiving opioids and in doses administered. Group comparison of opioid use within the last 72 hours of life is summarized in **Table 2.**

Table 2 Comparative inpatient opioid use within the last 72 hours of life among decedent study groups

Opioid use in last 72 hours of life	Decedent reference periods and study groups			P values
	Nov 2019-Feb 2020	Mar 2020 – Aug 2020 (Wave 1)		
	Pre-COVID Group N=163 (%)*	COVID-ve Group N=163 (%)*	COVID+ve Group N=85 (%)*	
Type of opioid administered†				
Any opioid, n (%)	145 (89.0%)	146 (89.6%)	81 (95.3%)	0.236
Morphine, n (%)	63 (38.7%)	65 (39.9%)	40 (47.1%)	0.418
Hydromorphone, n (%)	92 (56.4%)	93 (57.1%)	52 (61.2%)	0.758
Fentanyl, n (%)	25 (15.3%)	15 (9.2%)	6 (7.1%)	0.085
Total MEDD‡ for each 24-hour period (T3-T1) within last 72 hours of life§				
T3: mg (Q1-Q3)	**10.0 (5.0-18.5)**	**10.0 (4.4-20.0)**	**14.5 (7.5-48.0)**	**0.041**
No. of decedents: n (%)	**83 (50.9%)**	**90 (55.2%)**	**58 (68.2%)**	**0.032**
T2: mg (Q1-Q3)	**8.5 (4.3-18.8)**	**10.0 (5.0-24.0)**	**18.3 (11.5-46.0)**	**<0.001**
No. of decedents: n (%)	104 (63.8%)	105 (64.4%)	63 (74.1%)	0.220
T1: mg (Q1-Q3)	**15.0 (6.5-29.8)**	**12.5 (6.3-25.0)**	**20.0 (12.0-50)**	**0.011**
No. of decedents: n (%)	137 (84.1%)	143 (87.7%)	79 (92.9%)	0.133
T1 MEDD by care service at death				
Internal Medicine: mg (Q1-Q3)	12.3 (5.8-24.5)	10.0 (5.0-20.5)	14.5 (8.0-26.3)	0.140
No. of decedents: n (subgroup %)	96/117 (82.1%)	104/119 (87.4%)	56/62 (90.3%)	0.265
Intensive Care Unit: mg (Q1-Q3)	**25.0 (14.4-49.5)**	**23.8 (10.5-45.0)**	**52.5 (31.5-80.0)**	**0.014**
No. of decedents: n (row %)	41/46 (89.1%)	39/44 (88.6%)	23/23 (100%)	0.245
T1 MEDD by hospital site				
Site 1: mg (Q1-Q3)	15.0 (9.0-27.5)	11.3 (5.0-25.0)	16.5 (10.0-45.0)	0.199
No. of decedents: n (subgroup %)	55/60 (91.6%)	49/57 (86.0%)	26/31 (83.9%)	0.480
Site 2: mg (Q1-Q3)	**11.0 (5.8-32.5)**	**16.8 (8.0-28.4)**	**31.7 (12.8-63.8)**	**0.019**
No. of decedents: n (subgroup %)	32/38 (84.2%)	36/39 (92.3%)	20/20 (100.0%)	0.130
Site 3: mg (Q1-Q3)	16.5 (8.0-33.8)	10.5 (6.0-22.5)	18.0 (9.0-35.0)	0.105
No. of decedents: n (subgroup %)	**50/65 (76.0%)**	**58/67 (86.6%)**	**33/34 (97.1%)**	**0.026**

Patient groups for aggregate MEDD summary measures estimation‖				
Decedent administered opioid n (%)	145 (89.0%)	146 (89.6%)	81 (95.3%)	0.236
Internal Medicine: n (subgroup %)	102/117 (87.2%)	105/119 (88.2%)	58 (93.6%)	0.414
Intensive Care: n (subgroup %)	43/46 (93.5%)	41/44 (93.2%)	23/23 (100%)	0.444
Aggregate MEDD measures				
Maximum MEDD: mg (Q1-Q3)	**16.5 (7.5-30.0)**	**15.0 (7.5-30.0)**	**21.0 (12.0-54.5)**	**0.012**
Internal Medicine: mg (Q1-Q3)	13.4 (6.0-27.5)	11.3 (6.8-22.5)	15.7 (8.0-30.0)	0.172
Intensive Care: mg (Q1-Q3)	**25.0 (14.4-55.0)**	**24 (11.3-54.5)**	**59.5 (44.8-120.0)**	**0.005**
Individual mean MEDD: mg (Q1-Q3)	**13.5 (5.7-21.8)**	**10.5 (5.3-23.8)**	**16.7 (9.0-36.5)**	**0.007**
Internal Medicine: mg (Q1-Q3)	10.3 (5.0-17.3)	9.4 (4.5-15.0)	13.6 (6.7-24.7)	0.072
Intensive Care: mg (Q1-Q3)	**20.9 (11.5-38.5)**	**19.8 (10.0-44.8)**	**40.0 (24.9-64.2)**	**0.009**

* Column proportions expressed as percentages in parentheses unless otherwise specified.

†Opioid administered to decedents in a minimum of one complete 24-hour admission period within the last 72 hours of life; data were excluded for 7 decedents each in the Pre-COVID and COVID-ve groups whose admission duration was < 24 hours.

‡MEDD: Morphine Equivalent Daily Dose, parenteral, mg; summarized as a median (interquartile range, Q1-Q3) value for each of the three decedent study groups.

§Designation based on hours before death: T3, > 48 and ≤ 72 hours; T2, > 24 and ≤ 48 hours; T1, last 24 hours as an inpatient

‖ Based on exposure to a minimum of one complete inpatient 24-hour admission period (T3, T2 or T1) for opioid dose administration. Aggregate measures are reported as median group values (interquartile range, Q1-Q3)

Although more COVID+ve group patients (68.2% vs 50.9% and 55.2%, p=0.032) received opioids in the T3 period, there were no other significant study group differences in opioid administration as a binary (yes/no) outcome, specifically in comparisons based on opioid type, T2 or T1 period MEDDs, care service at death, hospital site, or with reference to the 72-hour aggregate summary measures (individual mean and maximum dose). However, the median MEDD in the COVID+ve group at T1 was 20.0 (12.0-50.0) compared to 15.0 (6.5-29.8) and 12.5 (6.3-25.0) in the Pre-COVID and COVID-ve groups, respectively (p=0.011). This group difference in MEDD was consistent at each

time point (T3-T1) and in relation to 72-hour aggregate summary measures. A site subgroup analysis at T1 revealed higher median MEDD in the COVID+ve group at Site 2. An additional subgroup analysis at T1 revealed a higher median MEDD in the COVID+ve group decedents who died in ICU but not in those who died in Medicine units/wards; a similar difference was also found in relation to the aggregate measures of opioid administration over the last 72 hours of life. The independent association of variables with MEDD was examined in multivariable logistic regression.

The logistic regression analyses examining the predictors of the T1 MEDD upper quartile (≥ 30mg of parenteral morphine) are summarized in **Table 3.**

Table 3 Logistic regression analyses examining the association of variables with parenteral MEDD ≥ 30mg (upper quartile) in the last 24 hours of life in those who received opioids (n=359)

Variables examined	Proportion of patients* (%)	Unadjusted OR† (95% CI)		P value		Adjusted OR† (95% CI)		P value
Age of decedent‡	**…**	**0.951**	**(0.93-0.97)**	**<0.001**		0.99	(0.96-1.01)	0.313
Sex								
Female	31/155 (20.0)	1				1		
Male	**64/204 (31.4)**	**1.82**	**(1.12-2.99)**	**0.016**		**1.84**	**(1.05-3.22)**	**0.034**
Study group								
Pre-COVID	34/137 (24.8)	1				1		
COVID-ve	30/143 (21.0)	0.804	(0.46-1.41)	0.445		0.95	(0.51-1.76)	0.866
COVID+ve	**31/79 (39.2)**	**1.96**	**(1.08-3.55)**	**0.027**		**2.62**	**(1.29-5.32)**	**0.008**
Hospital site								
Site 1	32/130 (24.6)	1				1		
Site 2	27/88 (30.7)	1.36	(0.74-2.48)	0.323		0.83	(0.40-1.72)	0.617
Site 3	36/141 (25.5)	1.05	(0.61-1.82)	0.862		0.51	(0.25-1.05)	0.067

Care service at death								
Medicine	45/256 (17.6)	1				1		
ICU	**50/103 (48.5)**	**4.42**	**(2.68-7.31)**	**<0.001**		**5.14**	**(2.47-10.70)**	**<0.001**
High-Flow Nasal Cannula								
No	46/219 (21.0)	1						
Yes	**49/140 (35.0)**	**2.03**	**(1.26-3.26)**	**0.004**		**1.93**	**(1.05-3.52)**	**0.033**
Palliative Care Consult								
No	61/211 (28.9)	1				1		
Consult completed	34/148 (23.0)	0.733	(0.45-1.19)	0.210		1.51	(0.80-2.86)	0.205
Admission assessment[§]								
Cognitive status								
Not impaired	71/229 (31.0)	1				1		
Impaired	**24/130 (18.5)**	**0.504**	**(0.30-0.85)**	**0.010**		0.85	0.46-1.57	0.606
Documented pain								
No	69/264 (26.0)	1				1		
Yes	26/95 (27.4)	1.07	(0.63-1.81)	0.815		1.48	(0.80-2.74)	0.209
Active cancer								
No	67/275 (24.4)	1				1		
Yes	28/84 (33.3)	1.55	(0.91-2.64)	0.104		1.68	(0.88-3.18)	0.114
Chronic Kidney disease								
No	75/283 (26.5)	1						
Yes	20/76 (26.3)	0.991	(0.56-1.76)	0.974				
Agitation								
No	89/330 (27.0)	1						
Yes	6/29 (20.7)	0.706	(0.28-1.79)	0.464				

*Proportion of patients in upper quartile MEDD (≥ 30 mg of parenteral morphine) for T1 period (last 24 hours of life); †OR = Odds Ratio; ‡Treated as a continuous variable or covariate; §Documented on admission assessment.

In the unadjusted analyses, both older age and cognitive impairment were statistically significant negative predictors of the upper quartile MEDD, whereas male sex, COVID+ve group membership, death in ICU, and use of high-flow nasal cannula for oxygen delivery were positive predictors. In the multivariable model, only male sex, COVID+ve group membership, death in ICU, and use of high-flow nasal cannula remained statistically significant, all as positive predictors with aORs of 1.84 (1.05-3.22), 2.62 (1.29-5.3), 5.14 (2.47-10.7) and 1.93 (1.05-3.52), respectively. Potential variable interactions among COVID-19 study group status, age, sex and care service at death were tested in the model, and the interaction terms were not statistically significant.

Comparative non-opioid medication doses (mg) administered within the last 72 hours of life for the study groups are summarized in **Table 4**.

Table 4 Comparative inpatient use of non-opioid End-of-Life medications within the last 72 hours of life among decedent study groups

Non-opioid medications administered in the last 72 hours of life *	Decedent reference periods and study groups			P values
	Nov 2019-Feb 2020	Mar 2020 – Aug 2020 (Wave 1)		
	Pre-COVID Group† N=163 (%)	COVID-ve Group† N=163 (%)	COVID+ve Group N=85 (%)	
Antisecretory medications				
Glycopyrrolate, n (%)	36 (22.1)	37 (22.7)	12 (14.1)	0.243
Mean 24-hour dose, mg‡	0.5 (0.4-0.9)	0.6 (0.4-1.2)	0.4 (0.4-0.6)	0.570
Scopolamine, n (%)	20 (12.3)	21 (12.9)	14 (16.5)	0.635
Mean 24-hour dose, mg‡	0.4 (0.4-0.9)	0.4 (0.4-0.8)	0.5 (0.4-1.0)	0.909
Antipsychotic medications				
Haloperidol, n (%)	32 (19.6)	25 (15.3)	10 (11.8)	0.257
Mean 24-hour dose, mg‡	1.0 (0.5-1.3)	1.0 (0.5-1.5)	1.4 (0.7-4.5)	0.656
Methotrimeprazine, n (%)	37 (22.7)	40 (24.5)	26 (30.6)	0.389

Mean 24-hour dose, mg‡	10 (6.3-22.5)	11.7 (6.9-24.4)	11.3 (5.0-25.0)	0.947
Benzodiazepines				
Lorazepam, n (%)	19 (11.7)	17 (10.4)	7 (8.2)	0.705
Mean 24-hour dose, mg‡	**1.0 (0.5-1.5)**	**1.5 (1.0-2.3)**	**3.7 (1.5-25.0)**	**0.017**
Midazolam, n (%)	96 (58.9)	100 (61.4)	57 (67.1)	0.454
Mean 24-hour dose, mg‡	3.7 (1.5-12.5)	3.0 (1.5-11.3)	5.7 (2.0-19.0)	0.255
Maximum 24-hour dose, mg‡	4.3 (2.0-13.5)	4.0 (1.7-13.0)	7.0 (2.0-22.0)	0.199
Other sedating medications				
Phenobarbitone, n (%)	4 (2.5)	6 (3.7)	5 (5.9)	0.393
Mean 24-hour dose, mg‡	150.0 (90.0-210.0)	127.5 (90.0-140.0)	150.0 (75.0-180)	0.811
Propofol administered, n (%)	21 (12.9)	28 (17.2)	13 (15.3)	0.555
Mean 24-hour dose, mg‡	1078.5 (692.5-1984.0)	1329.2 (634.0-2811.6)	1887.5 (1337.5-5527.3)	0.080
Maximum 24-hour dose, mg‡	**1444.8 (692.5-2207.0)**	**1624.4 (851.0-3491.5)**	**2665.6 (2119.4-6304.0)**	**0.033**

*Based on exposure to a minimum of at least one full inpatient 24-hour period for mean 24-hour dose determination within the last 72 hours of life.

†Data were excluded for 7 decedents in each of the original Pre-COVID and COVID-ve groups due to admission duration < 24 hours

‡Individual mean 24-hour doses are summarized for the study group as a median (interquartile range) value for each of the three study groups.

Although both mean and maximum 24-hour doses of midazolam were higher in the COVID+ve group, the differences were not statistically different. The median lorazepam COVID+ve group dose, 3.7 (1.5-25.0) was higher than that of the Pre-COVID and COVID-ve groups, 1.0 (0.5-1.5) and 1.5 (1.0-2.3), respectively (p=017). Similarly, the median of the maximum propofol dose, 2665.6 (2119.4-6304.0) was higher than that of the Pre-COVID and COVID-ve groups, 1444.8 (692.5-2207.0) and 1624.4 (851.0-3491.5), respectively (p=0.033).

DISCUSSION

Study findings and putative explanations

Our study found that COVID+ve decedents received significantly higher opioid doses than matched pre-pandemic or intra-pandemic control patients. This finding was moderately robust: it was consistent in each 24-hour time period within the last 72 hours of life, and further bolstered by finding that dying of COVID-19 was independently associated (aOR=2.6) with a parenteral MEDD ≥30mg in the last 24 hours of life. COVID+ve decedents had significantly higher maximum 24-hour propofol use in ICU compared to control group decedents. Also, higher lorazepam and midazolam doses were used in the COVID+ve group than either of the other groups; the difference was only statistically significant in relation to lorazepam. Collectively, these findings regarding opioid and sedative use support our study hypothesis that the requirement for these medications is higher in hospitalized patients dying of COVID-19 infection. In subgroup analyses, COVID+ve ICU decedents had significantly higher opioid use than ICU decedents in either of the control groups, which was evident in the last 24 hours (T1) and over the last 72 hours of life, suggesting that dying in ICU with COVID-19 infection is particularly associated with increased opioid and propofol requirements. These findings warrant a symptom profile evaluation of those dying of COVID-19.

Although our study patients' comfort in the last 72 hours of life was regularly assessed and documented, there was no formal standardized recording of symptom intensity across sites. For symptom profile comparisons we used the admission documentation of symptoms, which fell within the last 72 hours of life for approximately 20% of the study sample. The COVID +ve group had significantly higher admission prevalence of breathlessness, cough, and fever, and used high-flow nasal cannula oxygen support more frequently during admission. Previous studies have found that breathlessness is a major symptom in patients dying with COVID-19 infection.(15,16,31,38-40) Although myalgic pain is reported in those dying of COVID-19 infection,(15) among our three study groups, pain was least frequent in COVID+ve decedents at admission, but higher prevalence could have occurred closer to death. High-flow nasal cannula use was independently associated (aOR=1.9) with a parenteral MEDD ≥30mg in the last 24 hours of life. Collectively, our results suggest that respiratory distress mediated higher opioid use in the COVID-+ve group, particularly in ICU decedents. Agitation and delirium are reported in patients dying of COVID-19 infection.(14,18,31,33,40) Although the admission prevalence of agitation was largely similar across our groups, subsequent group differences in agitation level could have arisen nearer to death. Furthermore, COVID+ve group

decedents had a higher admission prevalence of dementia and other comorbidity burden, both risk factors for delirium.(41) The higher lorazepam and maximum 24-hour propofol doses in our COVID+ve group were possibly due to COVID-19 related respiratory distress in addition to potential contributions of cognitive dysfunction with agitation, and greater comorbidity-related distress.

Logistical issues associated with the COVID-19 pandemic, particularly the increased healthcare demands that stretched acute care services to and often beyond their limits, also warrant consideration in interpreting our study findings. Fewer COVID+ve group decedents (16.5%) were intubated compared to Pre-COVID (26.5%) or COVID-ve (25.3%) decedents, raising the possibility that greater emphasis was placed on the medication management of dyspnoea with opioids and sedatives for some patients rather than mechanical ventilation per se. It is also possible that more rigorous and prompt assessment of those dying of COVID-19 could have been impeded to some extent by isolation requirements and the need for staff to don burdensome personal protective equipment; this could have resulted in greater reliance on opioids and sedatives for symptom management.

Study findings in the context of published data

Although atrial fibrillation is a risk factor for mortality in high-risk COVID-19 patients,(42) it was least prevalent in our COVID+ve study group. Meanwhile, the higher COVID+ve group admission prevalence of cognitive impairment and other comorbidities were largely consistent with published data on COVID-19 risk factors.(11,17) Similarly, the higher prevalence of respiratory symptoms and fever is consistent with reported end-of-life prevalence in COVID-19 deaths.(12,14,17) Literature comparison of palliative medication use in patients dying due to COVID-19 infection is limited by paucity of data, particularly on ICU deaths, and further compromised by differences in type of aggregate dose measures reported, time reference, care setting, regional medication formularies, and in the separate reporting of pro re nata (PRN) or “as needed” medication use in addition to continuous infusional use.(28) We reported the total daily medication use which included regularly scheduled and PRN doses, or solely PRN doses in the absence of scheduled dosing. Although antisecretory and antipsychotic medication use was similar across all of our study groups, and comparable to published estimates in COVID-19 deaths,(28,30,31) our findings regarding opioid and benzodiazepine use warrant more detailed evaluation in the context of published data.

A systematic review of symptom management in COVID-19 related deaths, which excluded ICU deaths,(28) concluded that although a higher proportion of those dying with COVID-19 infection required continuous administration of opioid or midazolam than previously reported in pre-COVID-19 palliative care, doses were relatively low (median of 10-15 mg of parenteral morphine, and 10mg of midazolam, in the last 24 hours of life, in an aggregate dose summary of 5 of the studies) and in keeping with published guidelines.(24) A study of COVID-19 deaths in a hospital palliative care unit in New York reported a median parenteral MEDD (range) of 48 (24-144) mg in the last days of life.(33) A Belgian study of hospitalized COVID-19 decedents, excluded ICU deaths, and reported a mean parenteral MEDD of 31.3 (range, 2-120) mg, and mean midazolam dose of 20.4 (range, 1-100) mg in the last 24 hours of life.(32) An Australian study of hospitalized COVID-19 decedents, including 9 (4%) who died in ICU, reported a median (Q1-Q3) oral MEDD of 45 (22.5-75.0) in the last day before death.(31) Our study's higher MEDD findings in the COVID+ve group were comparable to this study; the inclusion of ICU decedents with possibly higher levels of symptom distress in our study could explain the higher opioid and sedative doses than those reported in the systematic review by Heath et al.(28) The progressive MEDD increase in the COVID+ve group over the last 72 hours is consistent with a longitudinal study reporting a doubling of median daily opioid use in the last 7 days of life in COVID-19 decedents.(31) Our finding of an independent association between male sex and higher opioid dosing is difficult to explain, as larger pre-pandemic studies have not reported a sex difference in relation to opioid dosing.(43,44) Although male sex is a recognized mortality-related risk factor in COVID-19 infection,(11,45) a statistically significant interaction between sex and study group status was not detected in the model.

Although 67.1% of the COVID+ve group received midazolam in the last 72 hours of life, the daily midazolam dose estimates in this period were lower than the 10 mg estimate reported in a systematic review.(28) Although palliative care involvement was similar across our study groups, the completion of a consult in only 29.4% of the COVID+ve group is below the 39-51% range reported in other studies of COVID-19 decedents,(3,31) and possibly impacted the prescribing patterns of some medications used for end-of-life symptom control.

Study implications and future research

In addition to informing end-of-life guidelines on medication use for symptom management in COVID-19 infection and in future pandemics, our study findings warrant further research, particularly regarding the use of opioids and

sedatives in the ICU setting. Moreover, regarding end-of-life comfort assessment, our study highlights the need for standardized symptom assessment measures such as the palliative version of the Richmond Agitation-Sedation Scale (RASS-PAL),(46) which can be used to evaluate medication efficacy and audit quality of care. Specialist palliative care involvement in end-of-life care of hospitalized individuals warrants further study both in relation to predictors and outcomes.

Study strengths and limitations

Our study's decedent cohort was representative of the source population in all adult acute care hospitals in a large urban region; using matched control groups from within and prior to the COVID-19 pandemic facilitated valid and unique comparisons, which generated some robust findings, particularly regarding opioid use. The retrospective design and use of admission symptom assessment and comorbidity data without similar data, including medication efficacy and side-effects, from within the more immediate end-of-life period are obvious limitations. The role of non-pharmacological interventions was not examined. Although rigorous training and accuracy checks were conducted regarding data abstraction, misclassification bias cannot be excluded, and absence of abstractor blinding to the study hypothesis is a potential source of bias. This study was performed during Wave 1 of the pandemic, and both symptom burden and medication requirements for symptom control could have changed to some extent with subsequent waves. The generalizability of our study findings is largely limited to end-of-life care for hospitalized decedents, whereas many of the COVID-19 pandemic related deaths in Wave 1 of the pandemic occurred in nursing homes.

CONCLUSIONS

Overall, our study evidence suggests that in addition to the association of male sex with higher end-of-life opioid requirements, patients dying of COVID-19 infection required higher daily opioid and lorazepam doses than those dying of other causes both before and during the COVID-19 pandemic. Furthermore, patients who died of COVID-19 infection in ICU required higher maximum 24-hour propofol doses than those who died in ICU without COVID-19 infection. Increased breathlessness and agitation due to COVID-19 and higher underlying comorbidity levels may require higher doses of opioids and sedatives for symptom control. These findings warrant consideration in

the context of managing ongoing life threatening COVID-19 infection and in anticipatory preparation for future respiratory virus pandemics.

Figure 1 Median MEDD for consecutive 24-hour periods (T3-T1) within the last 72 hours of life

Data availability statement

No additional data available

Ethics statements

Patient consent for publication

Not applicable.

Ethics approval

Each hospital's Research Ethics Board (REB) approved the study: Ottawa Health Science Network-REB (20200653-01H, December 18th 2020); Montfort REB (20-21-10-032, December 2nd 2020) and Queensway Carleton Hospital REB (20-06, December 1st 2020).

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Contributors

JD conceptualized the project and designed the study with assistance from PL, HP, LC, VG, RM, GW, AB, KW, JL, CW, DB, PE, ID, KB, CD, AI, SHB, SI, PT, BV. The study site leads, HP, VG, LC, co-ordinated ethics applications along with PL, JL and DB. Data were abstracted by PL, HP, SRA, EB, LC, RM, GW, AB, KAM, KW, PE, ID, KB and CD. Data verification was coordinated by PL with the assistance of HP, SRA, EB, LC, RM, GW, AB, PE and KB. Statistical analyses were performed by PL with support from LC and CW. All authors, including MK, CN, BH and KA assisted with data interpretation. The original version of the manuscript was drafted by PL and LC and critically reviewed by all authors. All authors approved the final manuscript as submitted.

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Competing interests

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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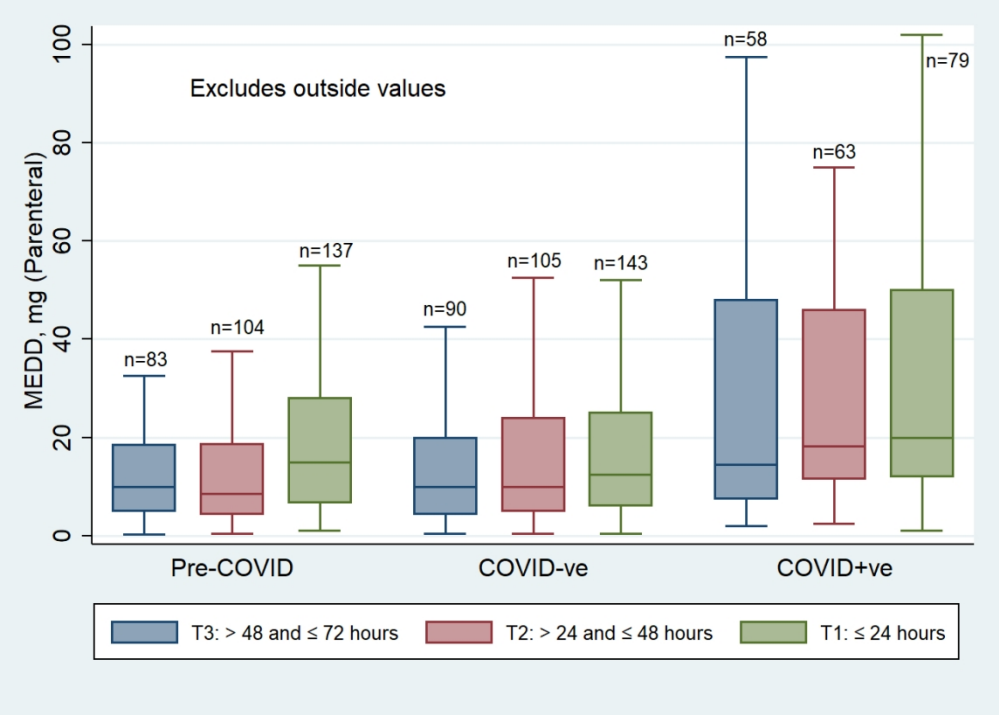


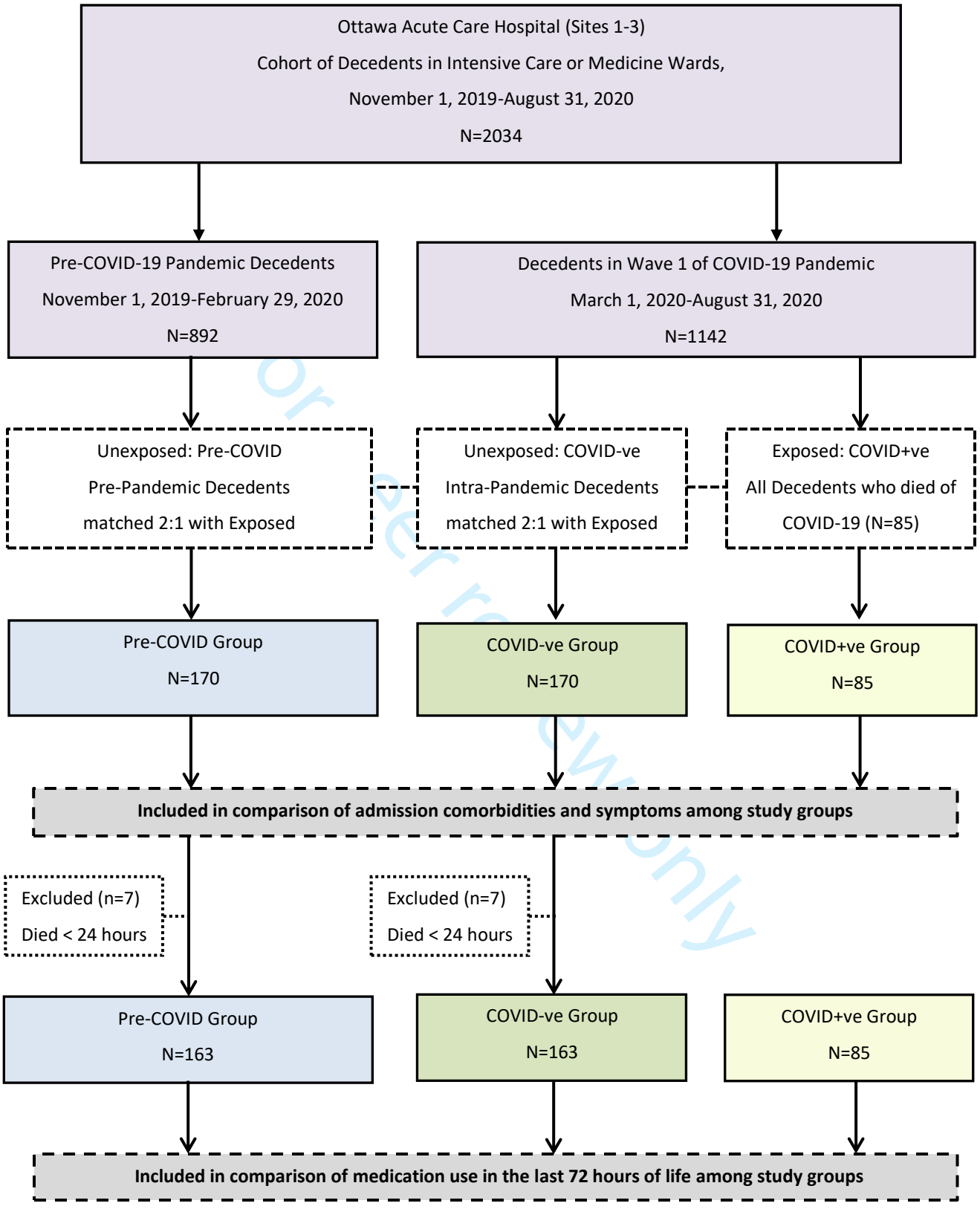
Figure 1 Median MEDD for consecutive 24-hour periods (T3-T1) within the last 72 hours of life

461x329mm (72 x 72 DPI)

Appendix 1 Clinical characteristics as documented at admission, and supportive interventions as documented during admission

Comorbidities at admission
COPD
Asthma
Heart Failure
Hypertension
Atrial fibrillation
Coronary artery disease
Chronic liver disease
Diabetes mellitus
Chronic kidney disease
Obesity
HIV infection
Dementia
Active cancer
Other comorbidity
Symptoms/signs at admission

Breathlessness
Airway secretions
Cough
Agitation
Drowsiness
Pain
Cognitive impairment
Fatigue
Fever
Other symptoms
Respiratory/circulatory support used during admission
BIPAP
High flow nasal cannula
Intubated
Other respiratory support
Vasopressor use



Appendix 2 Supplemental Figure Study Flow Diagram with Study Group Derivation for Comparative Outcomes

Appendix 3 Supplemental Table Study group comparison of admission clinical characteristics and respiratory/circulatory support use during admission

Clinical characteristics	Time periods and designated study groups			P values
	Nov 2019-Feb 2020	Mar 2020 – Aug 2020 (Wave 1)		
	Pre-COVID Group N=170 (%)	COVID-ve Group N=170 (%)	COVID+ve Group N=85 (%)	
Comorbidities at admission				
COPD	43 (25.3)	49 (28.8)	17 (20.0)	0.312
Asthma	7 (4.1)	9 (5.3)	3 (3.5)	0.780
Heart Failure	40 (23.5)	48 (28.2)	16 (18.8)	0.240
Hypertension	95 (55.9)	104 (61.2)	57 (67.1)	0.217
Atrial fibrillation	**45 (26.5)**	**55 (32.4)**	**13 (15.3)**	**0.015**
Coronary artery disease	52 (30.6)	52 (30.6)	22 (25.9)	0.697
Chronic liver disease	3 (1.8)	11 (6.5)	3 (3.5)	0.084
Diabetes mellitus	48 (28.2)	56 (32.9)	26 (30.6)	0.642
Chronic kidney disease	32 (18.8)	38 (22.4)	19 (22.4)	0.681
Obesity	6 (3.5)	15 (8.8)	4 (4.7)	0.102
HIV infection	0 (0.0)	0 (0.0)	1 (1.2)	0.135
Dementia	**47 (27.7)**	**44 (25.9)**	**35 (41.2)**	**0.032**
Active cancer	44 (25.9)	37 (21.8)	11 (12.9)	0.061
Other comorbidity	**108 (63.5)**	**102 (60.0)**	**66 (77.7)**	**0.018**
Symptoms/signs at admission				
Breathlessness	**72 (42.4)**	**80 (47.1)**	**54 (63.5)**	**0.006**
Airway secretions	28 (16.5)	16 (9.4)	7 (8.2)	0.066
Cough	**46 (27.1)**	**33 (19.4)**	**34 (40.0)**	**0.002**
Agitation	11 (6.5)	14 (8.2)	10 (11.8)	0.350
Drowsiness	68 (40.0)	57 (33.5)	39 (45.9)	0.143
Pain	**50 (29.4)**	**49 (28.8)**	**9 (10.6)**	**0.002**
Cognitive impairment	57 (33.5)	59 (34.7)	35 (41.2)	0.465
Fatigue	88 (51.8)	83 (48.8)	51 (60.0)	0.239
Fever	**16 (9.4)**	**23 (13.5)**	**46 (54.1)**	**<0.001**
Other symptoms	90 (52.9)	79 (46.5)	42 (49.4)	0.490

Respiratory/circulatory support used during admission				
BIPAP	22 (12.9)	17 (10.0)	4 (4.7)	0.121
High flow nasal cannula	**63 (37.1)**	**49 (28.8)**	**46 (54.1)**	**<0.001**
Intubated	45 (26.5)	43 (25.3)	14 (16.5)	0.186
Other respiratory support	50 (29.4)	52 (30.6)	31 (36.5)	0.502
Vasopressor use	43 (25.3)	47 (27.7)	13 (15.3)	0.087

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	6
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	6
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	8
Objectives	3	State specific objectives, including any prespecified hypotheses	9
Methods			
Study design	4	Present key elements of study design early in the paper	9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	9-10
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	10
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	10
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	10-11
Bias	9	Describe any efforts to address potential sources of bias	11
Study size	10	Explain how the study size was arrived at	11
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	12
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	12
		(*b*) Describe any methods used to examine subgroups and interactions	12
		(*c*) Explain how missing data were addressed	12
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	12
		(b) Give reasons for non-participation at each stage	12
		(c) Consider use of a flow diagram	Supplemental Figure
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	12-13
		(b) Indicate number of participants with missing data for each variable of interest	12
		(c) Summarise follow-up time (eg, average and total amount)	12
Outcome data	15*	Report numbers of outcome events or summary measures over time	12-20
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	18-19
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14-15
Discussion			
Key results	18	Summarise key results with reference to study objectives	21
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	21-24
Generalisability	21	Discuss the generalisability (external validity) of the study results	22-24
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	26

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.