Brief Report

A Multi-Centre COVID-19 Study Examining Symptoms and Medication Use in the Final Week of Life

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Abstract

Context. Guidelines exist to direct end-of-life symptom management in COVID-19 patients. However, the real-world symptom patterns, and degree of concordance with guidelines on medication use, and palliative care involvement has received limited attention.

Objectives. To describe the evolution of COVID-19 symptoms, medication used to alleviate these, and degree of palliative care involvement in the final week of life.

Methods. This retrospective study reviewed all COVID-19 inpatient deaths across five metropolitan hospitals in Australia from January 1 to December 31, 2020. Outcome measures were collected at day of death, and days one, two, five and seven before death. These were COVID-19 symptom severity (measured by the Palliative Care Outcome Scale), and use of supportive pharmacological and non-pharmacological therapies. Palliative care referral timepoint was also collected.

Results. Within the sample of 230 patients, commonest symptoms were breathlessness, agitation, pain, and respiratory secretions. On day of death, 79% ($n = 181$) experienced at least one symptom, and 30% ($n = 68$) experienced severe/extreme symptoms. The use of midazolam, glycopyrrolate, and infusions for symptom management occurred late, less frequently, and at lower doses than suggested in guidelines and other studies. Palliative care referrals were made late, at median three days before death (IQR 1-6 days), and for only half of people dying from COVID-19 (51%; $n = 118$).

Conclusion. Symptoms peaked in final three days of life. Earlier use of in fusional and breakthrough medications should be considered in anticipation of symptoms given high likelihood of dying in discomfort. Earlier palliative care referral for high-risk patients should be considered at hospital admission.   J Pain Symptom Manage 2022;64:e139−e147. *Crown Copyright © 2022 Published by Elsevier Inc. on behalf of American Academy of Hospice and Palliative Medicine. All rights reserved.*

Key Words
COVID-19, Palliative care, Death, Infectious diseases, Signs and symptoms

Key Message

This multi-center longitudinal study describes symptoms and medication use to alleviate these in the final week of life of COVID-19 decedents. The results indicate that symptoms are highly prevalent and uncontrolled. The use of symptom management medications occurred late, less frequently, and at relatively lower doses than suggested in guidelines.

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Introduction

As of May 2022, there have been 6.24 million deaths worldwide due to COVID-19 (Coronavirus Disease 2019).[1] In Australia, the state of Victoria has been most heavily affected, accounting for 90% of Australia's COVID-19 deaths in 2020.[1,2] This death rate had been relatively low until October 2021, but has increased more than five-fold in the past short months.[1] With more transmissible variants and increasing prevalence of disease, this is likely to rise.[1]

It is known that COVID-19 decedents commonly suffer from breathlessness, pain, and agitation, with concordant local and international guidelines to guide management.[3−8] However, the real-world symptom patterns, and degree of concordance with guidelines on medication use, and palliative care involvement in Australia and overseas has received limited attention. This multi-site study aims to describe the evolution of COVID-19 symptoms, medication used to alleviate these, and degree of palliative care involvement in the final week of life amongst COVID-19 decedents in hospitals in Victoria, Australia in 2020. Given that in the past 24 months total COVID-19 deaths worldwide have increased by almost 20-fold,[1] the likely ongoing rise in COVID-19 deaths mean there is benefit in the characterization of these elements, with exigency for quality improvement in the management of COVID-19 deaths.

Methods

Design: This retrospective study reviewed all COVID-19 inpatient deaths across five metropolitan hospitals in Melbourne, Australia, expanding upon the outcomes of a single center study.[9]

The study was approved by the institutional research ethics committees of each hospital (The Royal Melbourne Hospital (QA2020141), Austin Health (Audit 18/384), Western Health (QA2021.41), Werribee Mercy Health (2021−031), and Northern Health (21.2021)).

Participants: The study cohort included patients of all ages who died from January 1 to December 31, 2020 due to COVID-19, with diagnosis determined by DRG (diagnosis-related group) coding identified from the patients' discharge summary performed post-death. Deaths not directly caused by COVID-19 were excluded.

Data collection: All daily clinical notes in patients' health records were interrogated and collected systematically by medical and palliative care teams across the five participating sites, which involved in total 10 hospital doctors and three research nurses. De-identified outcome data were extracted from the medical records of eligible cases using an electronic standardized case report form (REDCap, Vanderbilt University). A detailed data dictionary was available, with standardization and data quality checks completed by a senior palliative care consultant and research nurse for each site, and separately conducted centrally by a senior palliative care research consultant and senior research nurse. Data collected included:

- *Demographic and clinical characteristics*, including the Australian-modified Karnofsky Performance Status (AKPS)[10] and the Charlson Comorbidity Index[11];
- *Final admission characteristics* including treating unit, length of stay, palliative care referral, goals of care documentation, and place of death;
- *Symptom severity in the final eight days of life* as measured by the Palliative Care Outcome Scale Staff Questionnaire[12], a validated, clinician-rated assessment of common end-of-life symptom domains measured on a five-point categorical scale (absent, slight (observed only, not requiring intervention), moderate (relieved by primary intervention used on that day), severe (requiring change to different intervention), overwhelming/extreme (unrelieved by any intervention)));
- *Use of supportive pharmacological and non-pharmacological therapies in the final 8 days of life* as measured by background and breakthrough opioid use converted into oral morphine equivalent daily dose (oMEDD)[13], sedative use, and anti-secretory use, and suction of respiratory secretions.

Analyses: Descriptive statistics were utilized to summarize each variable collected. Continuous variables were expressed as median with interquartile range (IQR) and categorical variables as number (percentage). We assessed the relationship between patient demographic and clinical factors with the outcome measures using Pearson's Chi-squared test (for categorical variables) or the Wilcoxon rank-sum (for continuous non-normally distributed variables) as appropriate. A *P*-value of < 0.05 was considered significant. All analyses were performed using Stata version 15.1 (Stata Corp, College Station, Texas, United States of America). Ventilated patients ($n = 13$) were excluded from the analysis of morphine and midazolam use on the basis that it would not reflect usual dose titration against symptom intensity in this cohort. Patients from one center ($n = 38$) were excluded from analyses for palliative care involvement because by default they were seen by a senior doctor who was dual-trained in palliative care, rather than formally referred to the palliative care consult service.

Results

A total of 230 COVID-19 deaths were recorded. Patient demographics and admission characteristics are summarized in Table 1. The median age of patients

Patient Demographics, Admission Characteristics, and Goals of Care

	N = 230
Gender	N (%)
Female	101 (44%)
Male	129 (56%)
Age (median; IQR)	86 (79−90)
Place of residence	
Home	82 (36%)
Residential Aged Care Facility	141 (61%)
Other	7 (3%)
Unit of death	
Dedicated Covid ward	82 (36%)
Acute medical ward	72 (31%)
Aged care ward/Rehabilitation	66 (29%)
Intensive care unit	9 (4%)
Palliative Care Ward	1 (0.04%)
Patients referred to Palliative Care[a]	118 (51%)
	Median (IQR)
Days from symptom onset to diagnosis	1 (0−3)
Days from symptom onset to admission	2 (0−5)
Days from symptom onset to death	11 (6−16)
Days from Palliative Care referral to death	3 (1−6)
Days from first goals of care to death	6 (3−12)
Days from last goals of care to death	3 (1−6)

[a]Patients from one centre (n = 38) were excluded on basis that the senior doctor in charge was dual-trained in palliative care.

who died from COVID-19 was 86 years (IQR 79−90 years). Most were male (56%, n = 129), lived in a Residential Aged Care Facility (62%, n = 141), and 54% (n = 123) had dementia, with median Charlson Comorbidity Score of 7 (IQR 6−8). Most people died in designated COVID (36%; n = 82), and Acute Medical Wards (31%; n = 72). Few people died in the Intensive Care Unit (4%; n = 9), and only 1 person died in a palliative care ward. Approximately half (51%; n = 118) of the cohort was referred to palliative care, at median 3 days before death (IQR 1−6).

Relative to symptom onset, patients were diagnosed with COVID-19 within 1 day (IQR 0−3), admitted within two days (IQR 0−5), and died 9 days later (IQR 4−16).

All patients had Goals of Care documented, completed a median of 6 days (IQR 3−12) prior to death. Most patients were identified as not for resuscitation (74%; n = 170) at that time. Goals of Care were updated for 51% (n = 117) of patients, and subsequently for another 18% (n = 42) of patients, with very few remaining at full/limited resuscitation (6.5%; n = 15, and 4.4%; n = 10 respectively). The median number of days between final Goals of Care documentation and death was three.

Symptoms and Medications

Severe/extreme symptoms doubled in final three days of life (30-31%; n = 63−68) compared to days five (17%; n = 30) and 7 (14%; n = 19). This peaked at one day before death, where almost half (47%; n = 32) had to or more severe/extreme symptoms. Most of these

symptoms were breathlessness, agitation, pain, and respiratory secretions.

Of recorded symptoms at any severity, the prevalence of breathlessness and respiratory secretions peaked on day of death (64% (n = 146) and 27% (n = 63) respectively), whereas agitation and pain peaked on day before death (49% (n = 109) and 38% (n = 85) respectively) (Table 2). Although patients were least symptomatic on day of death, 79% (n = 181) still had at least one symptom.

Most patients who experienced the four commonest symptoms (breathlessness, agitation, pain, respiratory secretions) were not referred to palliative care until one day before death. Most patients with fever and cough were not referred to palliative care.

Breathlessness and respiratory secretions were the only symptoms that increased closer to death. On the day of death, the proportion of patients with each symptom was less in the palliative care cohort, except for breathlessness (64 vs. 63%) and respiratory secretions (27% vs. 27%), where the proportion was similar or equal across both groups.

Opioids were administered for the large majority of patients (Table 3), with 44% (n = 53) given at least one dose of opioid at seven days before death, increasing to almost every patient (98%; n = 213) on day of death (Fig. 1). Median total opioid doses doubled (25 mg to 57 mg), and median breakthrough frequency tripled in this period.

Of non-ventilated patients, most who were prescribed a sedative received midazolam (94%; n = 165). Midazolam use increased 11-fold in the in the final week (7% (n = 9) to 76% (n = 165)), with greatest use in the final 3 days of life. The mean daily dose and breakthrough frequency remained similar throughout (10 mg; 1−2 breakthroughs/day).

Glycopyrrolate was the commonest antisecretory agent used; only one patient was prescribed hyoscine butyl bromide instead. Its use increased daily to every patient experiencing secretions receiving glycopyrrolate on day of death. Fig. 1 demonstrates the use of opioids, midazolam, and glycopyrrolate, relative to their respective symptoms.

Discussion

This study is one of the first multisite studies to explore the evolution of symptoms and the medication management of COVID-19 deaths. In our cohort, the median age of decedents was 86 years, reflective of worldwide data on higher death rates with age.[14]

Breathlessness was the commonest observed symptom, matching reports from other centres.[9,15−17] Although it is noted that breathlessness is ideally a patient-reported subjective measure, clinician

Table 2
Symptom Prevalence in Final 8 Days of Life

Symptom/Timepoint	Day of Death n (%)			Day+1 Before Death n (%)			Day+2 Before Death n (%)			Day+5 Before Death n (%)			Day+7 Before Death n (%)		
	Total Sample	PC Involved	No PC	Total Sample	PC Involved	No PC	Total Sample	PC Involved	No PC	Total Sample	PC Involved	No PC	Total Sample	PC Involved	No PC
Breathlessness	146 (64)	75 (64)	71 (63)	130 (58)	65 (63)	65 (54)	126 (59)	47 (59)	79 (60)	66 (41)	21 (54)	45 (37)	50 (37)	11 (46)	39 (36)
Agitation	91 (40)	44 (37)	47 (42)	109 (49)	54 (52)	55 (46)	96 (45)	35 (44)	61 (46)	63 (39)	14 (36)	49 (40)	46 (34)	8 (33)	38 (35)
Pain	68 (29)	34 (29)	34 (30)	85 (38)	45 (43)	40 (33)	68 (32)	27 (34)	41 (31)	52 (32)	11 (28)	41 (33)	33 (25)	5 (21)	28 (26)
Respiratory secretions	63 (27)	32 (27)	31 (27)	38 (17)	18 (17)	20 (17)	40 (19)	12 (15)	28 (21)	19 (12)	2 (5)	17 (14)	16 (12)	2 (8)	14 (13)
Fever	28 (12)	9 (8)	19 (17)	40 (18)	14 (14)	26 (22)	37 (17)	11 (14)	26 (20)	29 (18)	5 (13)	24 (20)	19 (14)	1 (4)	18 (16)
Cough	27 (11)	8 (7)	19 (17)	38 (17)	10 (10)	28 (23)	54 (25)	15 (19)	39 (30)	61 (38)	8 (21)	53 (43)	47 (35)	6 (25)	41 (37)
Shivering	3 (1)	0 (0)	3 (3)	5 (2)	3 (3)	2 (2)	9 (4)	5 (6)	4 (3)	2 (1)	0 (0)	2 (2)	3 (2)	1 (4)	2 (2)
Nausea	3 (1)	1 (1)	2 (2)	5 (2)	5 (5)	0 (0)	3 (1)	1 (1)	2 (2)	7 (4)	3 (8)	4 (3)	3 (2)	0 (0)	3 (3)
Sore throat	2 (1)	0 (0)	2 (2)	1 (0.4)	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)	3 (2)	1 (3)	2 (2)	4 (3)	1 (4)	3 (3)
Total, n	230	118	112	223	104	120	211	80	132	163	39	125	136	24	112

PC = Palliative Care.

assessment was utilized in our cohort of poorly communicative terminal patients. We observed that breathlessness increased closer to death (64% on day of death).

Opioid use increased closer to death, appearing to follow the trend of prevalence of breathlessness (rather than pain) at each day. It seems likely that opioid prescribing was instituted and escalated in response to worsening breathlessness. Nevertheless, despite the significant increases in opioids (by two-fold) and sedatives (by 11-fold) in the final week, breathlessness remained the most prevalent severe/extreme symptom observed on day of death (24%), meaning that in a quarter of patients, breathlessness did not appear to be relieved by those interventions administered, or required a change to a different intervention.

Similarly, more patients experienced respiratory secretions closer to death (27% on day of death). Severe/extreme secretions were experienced by 5% of the cohort. Secretions have been reported in 12% −47% of COVID-19 decedents,[16,17] but interestingly, this is less common compared to reported prevalence in a cohort dying from non-COVID causes.[17,18] Local and international guidelines encourage the use of antisecretory medications.[4,6,8,19] A recent randomized controlled trial in non-covid palliative care patients have revealed that the prophylactic use of antisecretory agents for those patients at risk of secretions led to significantly less likelihood of developing secretions than a control group who received an as required approach (6% vs. 61%).[20] A large Swedish study found that complete relief from secretions was obtainable in a third of COVID-19 decedents, similar to the general dying cohort, and referenced the use of antisecretory medications in their guidelines.[17] However, our cohort saw a 60% increase in patients with secretions on the final day of life. Although the use of glycopyrrolate increased six-fold in the final week, not every patient with secretions received glycopyrrolate until the day of death. Up to 12% of patients received suctioning, although this is discouraged by guidelines as being ineffective as secretions are below the glottis, in addition to potentially being distressing. These data would suggest that for patients dying from COVID-19 the early introduction of antisecretory medications prophylactically should be adopted.

Our cohort was generally frail, identified to be not for resuscitation on admission, and were at risk of death from COVID-19, yet midazolam use was comparatively low. Not all patients suffering agitation received midazolam, and for many who did, this did not occur until the day before death. This is despite midazolam use being recommended as best practice in COVID-19 patients who are expected to die.[4-6,8] This finding correlates with the literature, with a multi-center study in the United Kingdom also reporting that only one-third of COVID-19

Table 3
Medication Use in the Final 8 Days of Life

Oral Morphine Equivalent Daily Doses[a]			
Day of death	No of Participants	mg, Median (IQR)	Breakthrough Frequency, median (IQR)
Background	159	45 (30−75)	-
Breakthrough	166	30 (15−45)	3 (1−4)
Total	213	57 (30−90)	-
1 Day Before Death			
Background	122	45 (30−60)	-
Breakthrough	144	22.5 (15−45)	3 (1−4)
Total	181	45 (22.5−75)	-
2 Days Before Death			
Background	104	30 (17.5−45)	-
Breakthrough	118	15 (7.5−37.5)	2 (1−3)
Total	154	32.5 (15−60)	-
5 Days Before Death			
Background	46	20 (15−60)	-
Breakthrough	57	15 (7.5−22.5)	2 (1−2)
Total	74	23.75 (10−50)	-
7 Days Before Death			
Background	36	20 (15−30)	-
Breakthrough	38	15 (7.5−15)	1 (1−3)
Total	53	20 (14.5−35)	-
Midazolam Daily Doses[a]			
Day of death	No of Participants	mg, Median (IQR)	Breakthrough Frequency, median (IQR)
Background	126	10 (7.5−20)	-
Breakthrough	105	5 (2.5−10)	2 (1−3)
Total	165	12.5 (7.5−20)	-
1 Day Before Death			
Background	78	10 (10−15)	-
Breakthrough	70	5 (2.5−10)	2 (1−3)
Total	114	10 (5−15)	-
2 Days Before Death			
Background	52	10 (7.25−11.5)	-
Breakthrough	54	5 (2.5−7.5)	1 (1−2)
Total	82	10 (3−15)	-
5 Days Before Death			
Background	11	7.5 (5−10)	-
Breakthrough	14	5 (2.5−7.5)	2 (1−2)
Total	21	7.5 (2.5−10)	-
7 Days Before Death			
Background	6	8.75 (5−10)	-
Breakthrough	7	5 (5−7.5)	1 (1−3)
Total	9	10 (5−12.5)	-
Glycopyrrolate Daily Doses			
Day of death	No of Participants	mg, Median (IQR)	Breakthrough Frequency, median (IQR)
Background	23	.8 (.6−1.2)	-
Breakthrough	57	.4 (.2−.6)	1 (1−2)
Total	70	.4 (.4−1)	-
1 Day Before Death			
Background	11	1 (.8−1.2)	-
Breakthrough	26	.4 (.2−.6)	2 (1−3)
Total	33	.6 (.2−1)	-
2 Days Before Death			
Background	5	1 (.6−1.2)	-
Breakthrough	15	.4 (.2−.6)	1 (1−2)
Total	19	.4 (.2−.8)	-
5 Days Before Death			
Background	2	.8 (.4−1.2)	-
Breakthrough	2	.3 (.2−.4)	1 (1- 1)
Total	4	.4 (.3−.8)	-
7 Days Before Death			
Background	1	.4 (.4−.4)	-
Breakthrough	2	.3 (.2−.4)	1 (1−1)
Total	3	.4 (.2−.4)	-

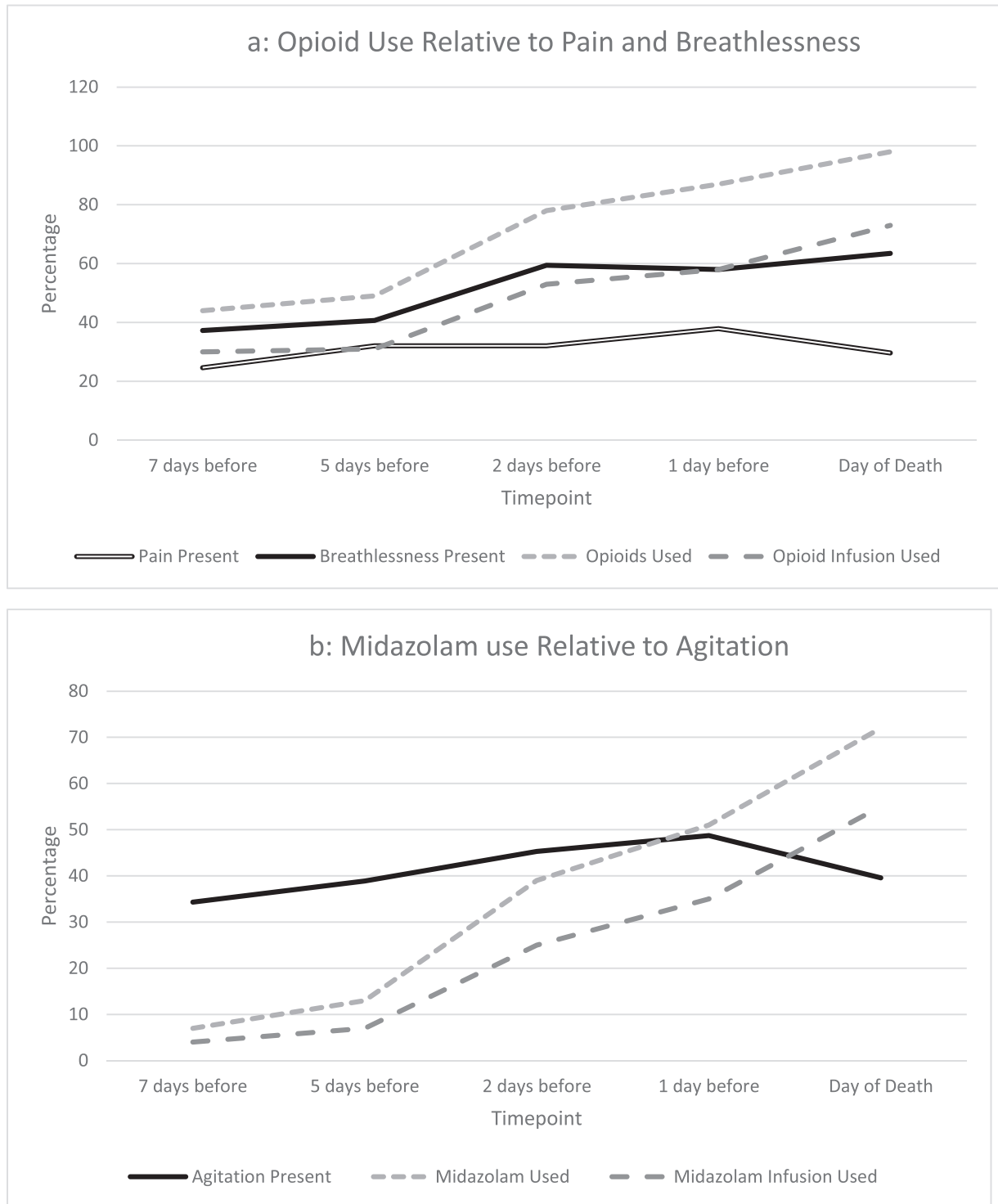[a]Morphine and midazolam doses exclude ventilated patients.

Fig. 1. Medication use relative to symptoms.

decedents received anticipatory medications for comfort.[21] A more vigilant and proactive approach to prescribing should be adopted. We support the suggestions of other authors[22] to consider starting an infusion early and in anticipation of likely symptoms that may arise in COVID-19 end-of-life care.

Furthermore, the dose of midazolam administered was largely static throughout the final 8 days of life. Regardless of whether it was administered by continuous infusion or by as needed bolus injection, the mean total daily dose was 10 mg. It is likely that the median midazolam dose of 12.5 mg on day of death was not
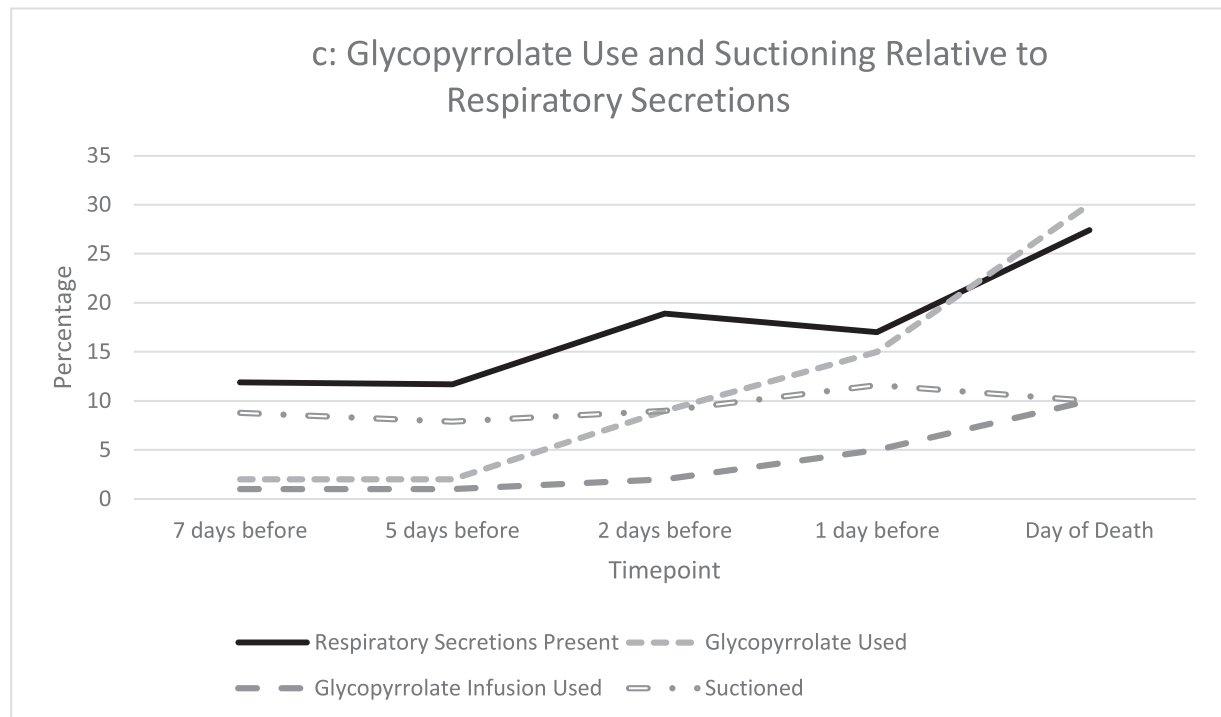
Fig. 1 Continued.

adequate to optimally control agitation, since 40% were reported to have agitation and 10% had severe/extreme agitation on day of death. National Institute for Health and Care Excellence (NICE) guidelines[4] suggest a general minimum starting midazolam infusion dose of 10 mg for agitation, and to titrate its dose to response, and National Health Service (NHS) guidelines suggest a daily dose of up to 60 mg.[5] It is possible that lower doses were used due to our cohort being largely composed of elderly frail patients, however the data indicate that these doses were at the lower end of guideline recommendations, and remained inadequate. An infusion commenced earlier, perhaps in anticipation of symptoms or once symptoms arose, may have provided more time for appropriate dose escalation, and possibly reduced the prevalence and severity of agitation towards death.

The Australian National COVID-19 Clinical Evidence Taskforce[7] encourages early specialist palliative care involvement for COVID-19 patients who have pre-existing advanced progressive disease, such as that in our cohort. However, only 51% of our frail, high-risk cohort were referred to palliative care. These referrals occurred late (median three days before death), despite patients having been in hospital a median of six days prior. It was also generally less common for patients who experienced any symptom to be referred to palliative care until one day before death. On the day of death, the cohort known to palliative care was proportionally less symptomatic on most

symptoms, providing further rationale for palliative care involvement earlier in the trajectory. Breathlessness and respiratory secretions − the only two symptoms which peaked on day of death − were similarly prevalent in both groups, and possibly reflects the nature of COVID-19. However, as previously highlighted, our sample had used relatively low doses of medications.

Final goals of care documentation were completed three days before death, and the doses of opioids, midazolam, and glycopyrrolate increased significantly in this time (Fig. 1), indicating a possible role of palliative care teams in facilitating goals of care discussions and symptom management. It is possible that earlier palliative care involvement may have resulted in earlier use of glycopyrrolate and midazolam in our cohort, and at higher doses, to manage the problematic respiratory secretions and agitation towards death which remained relatively prevalent in our cohort. Data suggests our international counterparts have been able to control symptoms in people dying of COVID-19 with greater success,[17] perhaps in part due to increased compliance with consensus guidelines and greater involvement of palliative care expertise. A recent scoping review[23] on inpatient COVID-19 deaths showed a large increase in palliative care referrals, whose role was similarly to guide goals of care and symptom management. Other authors have also supported the role of early palliative care in patients at high risk of dying from COVID-19.[8,24] Thus it is likely that earlier palliative care

involvement in a specifically frail cohort likely to die from COVID-19 will be beneficial as well.

Study limitations: This study is limited by the retrospective design and metropolitan setting in one state in 2020; however these were also where most COVID-19 deaths occurred in Australia. We note the more recent spike in deaths has only occurred in the recent 4 months, where data has not matured yet but certainly warrants future exploration and research. A retrospective design was used as it was not possible to prospectively collect data given restrictions on non-clinical personnel attending hospitals. Being the state with the most COVID-19 cases and deaths, it was not reasonable to expect clinical staff to collect extra research data in the overwhelmed health system. As with other studies on critically ill and terminal patients, our data collection is limited to clinician observation, rather than patient-reported data; as such, this may be a reason symptoms such as nausea or sore throat were less apparent in our cohort of terminally ill patients. Although our cohort comprised of largely elderly and frail patients, most COVID-19 decedents remain in this category. As such our results remain translatable to the cohort of patients more likely to die from this illness.

Conclusions

This is one of the largest Australian studies reporting longitudinal patterns of symptom and medication use in the final week of life for patients dying from COVID-19. Symptoms were particularly troublesome in the final three days of life, with 79% decedents experiencing at least one symptom, and 30% experiencing severe/extreme symptoms on day of death. This may be in part due to the fact that the use of midazolam, glycopyrrolate, and infusions for symptom management occurred late, less frequently, and at relatively lower doses than suggested in many guidelines. Palliative care referrals also occurred late, and in only half of this high-risk population.

As the situation evolves, the current climate requires that patients are only admitted if they require hospital care, meaning these patients are likely to be admitted later, if at all. With hospital admissions occurring later in the illness trajectory, routine palliative care referral for this frail cohort should be considered at admission. Low dose medication infusion for symptom management should be considered in anticipation when a patient is expected to die from COVID-19, given the high likelihood of experiencing troublesome and severe symptoms. Midazolam and glycopyrrolate could be used more frequently and at higher doses to reflect need, and to reduce our comparatively higher symptom burden compared to other reports. Future research may address the impact of palliative care involvement and on improving adherence to guidelines on symptom control in this cohort.

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