

Characteristics, symptom management and outcomes of 101 patients with COVID-19 referred for hospital palliative care

Natasha Lovell MBChB BSc MRCP^{1,2}, Matthew Maddocks BSc MCSP PhD¹, Simon N Etkind MB BChir BA MRCP DTMH^{1,3}, Katie Taylor BA (Hons)Oxon MSc MBBS MRCP³, Irene Carey MB BCh BAO MSc FRCP³, Vandana Vora MBBS FRCP³, Lynne Marsh BM MSc MRCP¹, Irene J Higginson BMedSci BMBS PhD FMedSci FRCP FFPHM^{1,2}, Wendy Prentice MBBS MA FRCP¹, Polly Edmonds MBBS FRCP¹, Katherine E Sleeman BSc MBBS FRCP PhD^{1,2}

1 King's College Hospitals NHS Foundation Trust

2 King's College London, Cicely Saunders Institute, Bessemer Road, London, SE5 9PJ

3 Guy's and St Thomas' NHS Foundation Trust

Corresponding author:

Dr Katherine E Sleeman

King's College London

Cicely Saunders Institute

Bessemer Road, London, SE5 9PJ

Katherine.Sleeman@kcl.ac.uk

Number of tables: 2

Number of figures: 0

Number of references: 11

Word count: 1196 / 1500

Abstract

Hospital palliative care is an essential part of the COVID-19 response but data are lacking. We identified symptom burden, management, response to treatment, and outcomes for a case series of 101 in-patients with confirmed COVID-19 referred to hospital palliative care. Patients (64 male, median [IQR] age 82 [72-89] years, Elixhauser Comorbidity Index 6 [2-10], Australian-modified Karnofsky Performance Status 20 [10-20]), were most frequently referred for end of life care or symptom control. Median [IQR] days from hospital admission to referral was 4 [1-12] days. Most prevalent symptoms (n) were breathlessness (67), agitation (43), drowsiness (36), pain (23) and delirium (24). Fifty-eight patients were prescribed a subcutaneous infusion. Frequently used medicines (median-maximum dose/24h) were opioids (morphine, 10-30mg; fentanyl, 100-200mcg; alfentanil 500-1000 mcg) and midazolam (10-20mg). Infusions were assessed as at least partially effective for 40/58 patients, while 13 patients died before review. Patients spent a median [IQR] of 2 [1-4] days under the palliative care team, who made 3 [2-5] contacts across patient, family and clinicians. At March 30 2020, 75 patients had died, 13 been discharged back to team, home or hospice, and 13 continued to receive inpatient palliative care. Palliative care is an essential component to the COVID-19 response, and teams must rapidly adapt with new ways of working. Breathlessness and agitation are common but respond well to opioids and benzodiazepines. Availability of subcutaneous infusion pumps is essential. An international minimum dataset for palliative care would accelerate finding answers to new questions as the COVID-19 pandemic develops.

Key words: COVID-19, coronavirus, palliative care, symptom management, hospice, end of life

Key message

In this first case series of 101 patients with COVID-19 referred to palliative care, input was brief; most patients died in <3 days. The most common symptoms were breathlessness and agitation, controlled in most cases using relatively small doses of opioid and benzodiazepine, delivered by subcutaneous infusion. To meet the rapidly growing need for palliative care, services must adapt with training and guidance for non-specialists will help ensure symptoms are addressed promptly.

Journal Pre-proof

Introduction

People diagnosed with COVID-19 have an estimated mortality of 1–3%, with those with multimorbidity most at risk of dying.¹ Estimates vary widely, but COVID-19 could directly cause up to 510,000 deaths in the UK and 2.2 million in the USA.² Although the clinical characteristics of COVID-19 patients have been described, the focus has been on risk factors for ICU admission and death.³ Data are lacking on the palliative care needs of people with COVID-19, including symptom burden and response to treatment; to help inform service planning for palliative care and hospice services in the UK and elsewhere. Here we describe the symptom burden, management, response to treatment, and outcomes for COVID-19 patients referred to the palliative care teams in two large NHS hospital trusts in London, UK.

Method

Design and setting: Case series of 101 inpatients with confirmed COVID-19 infection, referred to the hospital palliative care teams at two large acute NHS Hospital Trusts in London, UK. The two trusts comprise four hospitals and include a Highly Communicable Infectious Disease Unit. They serve populations with among the highest prevalence of COVID-19 in the UK.

Data collection and analysis: Data were extracted from medical and nursing case notes by clinician-researchers (NL, PE, KT, JB and SE). Variables included: Baseline demographic and clinical characteristics; referral ward; comorbidities categorized by the Elixhauser Index;⁴ clinician-assessed Palliative Care Phase of Illness (Stable, Unstable, Deteriorating, and Dying or Deceased) based on care needs and suitability of the current care plan;⁵ and Australia-modified Karnofsky Performance Status (AKPS).⁶ Symptoms were identified from standardised palliative care notes. Symptom control medicines with doses were extracted from drug charts, and clinical impressions of effectiveness were determined based on documentation at follow-up (e.g. improved breathing, agitation,

comfort). Descriptive analyses were performed using SPSS (V.24, IBM, USA). Comparisons between groups were expressed as medians and interquartile ranges (IQR) due to the data distribution.

Ethics approval: The work was registered with the hospital Clinical Effectiveness Teams (registration numbers: PC043, PC044 and 10774).

Results

For full demographic and other details see Table 1. Between March 4 and March 26 2020, 101 patients with COVID-19 were referred to palliative care, most frequently for end of life care or symptom control. Referrals rapidly increased from the first (n=2) to the fourth week (n=51). 64 patients were men, the median age was 82 [72-89]. The Elixhauser Comorbidity Index was 6 [2-10]; the most common comorbidities were hypertension (54), diabetes (36) and dementia (31). 76 patients had been admitted with COVID-19 and 25 were existing inpatients who developed COVID-19; median [IQR] days from admission to referral were 2 [1-6] and 16 [7-30] for these groups respectively. At the time of referral, most patients (n=95) were receiving ward-based care, with six on high-dependency or intensive care units.

For full details of symptoms, drugs prescribed, and outcomes, see Table 2. The most prevalent symptoms were breathlessness, agitation, drowsiness and pain. 24 patients had symptoms of delirium. Ninety-six patients were prescribed 'as needed' medication for symptom relief, and 58 patients were prescribed a subcutaneous infusion for symptom relief. Of the 37 patients who were prescribed morphine by subcutaneous infusion, the median final dose was 10mg/24 hours. Fifty infusions contained midazolam, median final dose 10 mg/24 hours. The infusion was assessed as at least partially effective for 40/58 patients, while 13 patients died before effectiveness could be reviewed.

Patients spent a median [IQR] of 2 [1–4] days under the palliative care team and received 3 [2–5] contacts. As of March 30 2020, patients had died (75), been discharged (13) or continued to receive palliative care input (13).

Discussion

We provide the first report of characteristics, symptom management and outcomes of patients with COVID-19 referred for hospital palliative care. The main symptom experienced by these patients was breathlessness, similar to that found earlier in the disease trajectory.⁷ In addition, we find patients near the end of life commonly experience agitation, while cough is infrequent. Time spent under the palliative care team was brief (median time 2 days), and symptom control with subcutaneous infusion was achieved in most cases using relatively small doses of opioid and benzodiazepine. 74% of patients died.

Many services are currently facing dramatic increases in the number of people severely affected by COVID-19. In this series, the number of patients with COVID-19 referred for palliative care each week increased from 2 to 51 over four weeks. This is likely to necessitate changes in ways of working for palliative care teams such as an increase in remote patient assessment and fewer face to face assessments.

A proactive approach to symptom recognition, assessment, management and escalation for people with COVID-19 is likely to be helpful⁸. Providing brief and accessible ward-base teaching on managing breathlessness and agitation, with a low threshold for prescribing anticipatory medicines for those with prognostic uncertainty, can ensure symptoms are addressed promptly.⁹

Encouragingly, our data indicate that patients' symptoms can be managed using opioids and benzodiazepines at low doses. Subcutaneous infusions were frequently used to achieve symptom control. It is essential that adequate stocks of equipment are available to provide symptom control medication for those affected by COVID-19, both in inpatient and community settings.

Agitation was common among our patients. A high level of psychological distress may result from rapid deterioration and be exacerbated by isolation due to visitor restrictions. Ways to mitigate against this include use of technology such as tablet computers to communicate with carers and friends, though this may not be practical for people near the end of life. Chaplaincy, social work and psychology teams' support is valuable.⁹

The demographic characteristics of patients in this case series, predominantly older men with comorbidities, reflect global data on COVID-19 mortality risk.³ Hypertension and diabetes, the most frequent comorbidities in our patients, were risk factors for poor outcomes in a study of Chinese patients with COVID-19¹⁰. A small proportion of patients in our case series were referred to palliative care for reasons other than COVID-19, but subsequently diagnosed as COVID-19 positive. It is important to acknowledge that their palliative care needs include both COVID-19 and non-COVID-19 related problems. In addition, there are likely to be knock-on impacts on non-COVID-19 patients resulting from the escalation in referrals, many of whom will receive less palliative care input as a result.

We included only patients referred to palliative care, and we have no information about the palliative care needs of other inpatients with COVID-19. We had few referrals from Intensive Care Units. Around 50% of patients with COVID-19 who are admitted to ICUs subsequently die and they are likely to have high palliative needs.^{11 12} Information about symptoms was identified from the free-text notes, and we did not collect data on symptom severity. We report only on inpatient hospital patients and did not include community or inpatient palliative care units/hospices. The assessment of response to medication was subjective, and as the length of palliative care involvement was relatively short there was not always sufficient time to assess effectiveness. Last, this is an early case series and patterns are likely to change as the pandemic progresses.

Conclusion

Patients severely affected by COVID-19 frequently experience symptoms and distress, and palliative care is an essential part of the response to this pandemic. Urgent research is needed to understand more about symptom prevalence and management, and how best to deliver palliative care to those dying in ICU and community settings. An international minimum data set for COVID-19 patients receiving palliative care would accelerate finding answers to these questions.

Tables and Figures

Table 1: Demographic and clinical characteristics, palliative care contacts, and outcomes of 101 hospital inpatients with COVID-19 referred to palliative care

Table 2: Symptoms, drugs prescribed, and drug effectiveness in 101 hospital inpatients with COVID-19 referred to specialist palliative care

Contributions

KES and NL conceived the idea for the study and wrote the protocol with input from PE, SNE and WP. NL, KT, SNA, JB and PE extracted data. MM led the analysis, with input from NL, SNE and KES. NL, MM, SNE and KES wrote the paper, with input from all authors. All authors critically reviewed and agreed the final manuscript.

Disclosures and Acknowledgements

The authors have no conflicts of interest to declare. All authors are members of the King's Health Partners Palliative Care Clinical Academic Group. We are grateful to other members of this group including Shaheen Khan, Teresa Beynon, Nick Gough, Rachel Burman, Sabrina Bajwah, Ruth Ting and Richard Towers for supporting this work. We thank Jennifer Brooke for supporting data collection,

and Andrew Wilcock for helpful comments on an early draft. We acknowledge the intense efforts of our clinical colleagues at this time, including those within the palliative care teams and the Highly Communicable Infectious Disease Unit at Guy's and St Thomas NHS Foundation Trust.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. KES is funded by a National Institute of Health Research (NIHR) Clinician Scientist Fellowship (CS-2015-15-005), MM is funded by a NIHR Career Development Fellowship (CDF-2017-10-009), IJH is an NIHR Senior Investigator Emeritus. IJH and MM are supported by the NIHR Applied Research Collaboration South London (NIHR ARC South London) at King's College Hospital NHS Foundation Trust. IJH leads the Palliative and End of Life Care theme of the NIHR ARC South London and co-leads the national theme. SNE and NL are previous Cicely Saunders International PhD training fellows. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, the Department of Health and Social Care or the funding charities.

Table 1: Demographic and clinical characteristics, palliative care contacts, and outcomes of 101 hospital inpatients with COVID-19 referred to palliative care

Age, years	82 [72-89]
Sex, male: female	64:37
Elixhauser Comorbidity Index	6 [2-10]
Comorbidities	
Hypertension	54
Diabetes	36
Dementia	31
Advanced / metastatic cancer	25
Chronic pulmonary disease	22
Renal failure	21
Congestive heart failure	18
Stroke / neurological disorder	12
Peripheral vascular disorder	4
Liver disease	2
AKPS	20 [10-20]
Missing	15
Level of care	
Ward based care	95
High Dependency Unit	5
Intensive Care Unit	1
Reason(s) for referral to palliative care, n (%)	
End of life care	70
Symptom control	41
Care planning	4
Psychological support	1
Phase of illness	
Dying	63
Unstable	24
Deteriorating	7
Stable	1

Missing	6
Days of palliative care involvement	2 [1-4]
Palliative care contacts	3 [2-5]
Contacts by recipient	
Patient	2 [1-3]
Family	1 [0-1]
Hospital staff	2 [1-4]
Contacts by type	
In person	3 [1-4]
Telephone	1 [0-1]
Outcome	
Death	75
Discharged	13
Back to team	10
Home	2
To hospice	1
Remains under palliative inpatient care	13

Data are median [IQR] or n

Table 2: Symptoms, drugs prescribed, and drug effectiveness in 101 hospital inpatients with COVID-19 referred to specialist palliative care

Symptoms at time of referral	N=101
Breathlessness	67
Agitation	43
Drowsiness	36
Pain	23
Delirium	24
Secretions	11
Fatigue	9
Fever	9
Cough	4
Other symptoms [§]	12
Symptom relieving drugs given by subcutaneous infusion	58
Morphine + Midazolam	23
Morphine + Midazolam + Glycopyrronium	8
Morphine alone	4
Morphine + Haloperidol	1
Morphine + Midazolam + Haloperidol	1
Fentanyl + Midazolam	9
Fentanyl + Midazolam + Glycopyrronium	3
Alfentanil alone	2
Alfentanil + Midazolam	4
Alfentanil + Cyclizine	1
Alfentanil + Midazolam + Haloperidol	1
Midazolam alone	1
Median (range) dose/24h	
Morphine (mg)	10 (5–30)
Fentanyl (microgram)	100 (100–200)
Alfentanil (microgram)	500 (150–1000)
Midazolam (mg)	10 (5–20)
Glycopyrronium (microgram)	1200 (600–2400)
Haloperidol (mg)	2 (1–2)
Cyclizine (mg)	50

Clinical impression of effectiveness*	
Yes	40
Unclear (patient died prior to follow-up)	13
No	5

\$ diarrhoea (3) reduced oral intake (3), anxiety (2), seizures, ascites, incontinence, dysuria (1 each)

* based on follow up documentation, e.g. improved breathing, agitation, comfort

Journal Pre-proof

References

1. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. *Jama* 2020 doi: 10.1001/jama.2020.2648 [published Online First: 2020/02/25]
2. Neil M Ferguson DL, Gemma Nedjati-Gilani, Natsuko Imai, Kylie Ainslie, Marc Baguelin, Sangeeta Bhatia, Adhiratha Boonyasiri, Zulma Cucunubá, Gina Cuomo-Dannenburg, Amy Dighe, Ilaria Dorigatti, Han Fu, Katy Gaythorpe, Will Green, Arran Hamlet, Wes Hinsley, Lucy C Okell, Sabine van Elsland, Hayley Thompson, Robert Verity, Erik Volz, Haowei Wang, Yuanrong Wang, Patrick GT Walker, Caroline Walters, Peter Winskill, Charles Whittaker, Christl A Donnelly, Steven Riley, Azra C Ghani. Impact of non-pharmaceutical interventions (NPIs) to reduce COVID- 19 mortality and healthcare demand, 2020.
3. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet (London, England)* 2020;395(10223):507-13. doi: 10.1016/s0140-6736(20)30211-7 [published Online First: 2020/02/03]
4. van Walraven C, Austin PC, Jennings A, et al. A modification of the Elixhauser comorbidity measures into a point system for hospital death using administrative data. *Medical care* 2009;47(6):626-33. doi: 10.1097/MLR.0b013e31819432e5 [published Online First: 2009/05/13]
5. Eagar K, Green J, Gordon R. An Australian casemix classification for palliative care: technical development and results. *Palliative medicine* 2004;18(3):217-26. doi: 10.1191/0269216304pm875oa [published Online First: 2004/06/17]
6. Abernethy AP, Shelby-James T, Fazekas BS, et al. The Australia-modified Karnofsky Performance Status (AKPS) scale: a revised scale for contemporary palliative care clinical practice [ISRCTN81117481]. *BMC palliative care* 2005;4:7. doi: 10.1186/1472-684x-4-7 [published Online First: 2005/11/15]
7. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *The Lancet Respiratory medicine* 2020 doi: 10.1016/s2213-2600(20)30079-5 [published Online First: 2020/02/28]
8. Bajwah S WA, Towers R, Costantini M, Bausewein C, Simon ST, Bendstrup E, Prentice W, Johnson MJ, Currow DC, Kreuter M, Wells AU, Birring SS, Edmonds P, Higginson IJ. Managing the supportive care needs of those affected by COVID-19. *ERJ: in press* 2020
9. Etkind SN BA, Lovell N, Cripps R, Harding R, Higginson IJ, Sleeman KE. The role and response of palliative care and hospice services in epidemics and pandemics: a rapid review to inform practice during the COVID-19 pandemic. *Journal of Pain and Symptom Management* 2020 (in press)
10. Guan WJ, Liang WH, Zhao Y, et al. Comorbidity and its impact on 1590 patients with Covid-19 in China: A Nationwide Analysis. *The European respiratory journal* 2020 doi: 10.1183/13993003.00547-2020 [published Online First: 2020/03/29]
11. Intensive Care National Audit & Research Centre. ICNARC report on COVID-19 in critical care.
12. Curtis JR, Kross EK, Stapleton RD. The Importance of Addressing Advance Care Planning and Decisions About Do-Not-Resuscitate Orders During Novel Coronavirus 2019 (COVID-19). *Jama* 2020 doi: 10.1001/jama.2020.4894 [published Online First: 2020/03/29]