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Symptom control and survival for people severely ill with COVID-19: a multicentre cohort study --Manuscript Draft--

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Abstract:	<p>Context Evidence of symptom control outcomes in severe COVID-19 is scant.</p> <p>Objective To determine changes in symptoms among people severely ill or dying with COVID-19 supported by palliative care, and associations with treatments and survival.</p> <p>Methods Multicentre cohort study of people with COVID-19 across England and Wales supported by palliative care services, during the pandemic in 2020 and 2021. We analysed clinical, demographic and survival data, symptom severity at baseline (referral to palliative care, first COVID-19 assessment) and at three follow-up assessments using the Integrated Palliative Outcome Scale – COVID-19 version (IPOS-COV).</p> <p>Results We included 572 patients from 25 services, mostly hospital support teams; 496 (87%) were newly referred to palliative care with COVID-19, 75 (13%) were already supported by palliative care when they contracted COVID-19. At baseline, patients had a mean of 2.4 co-morbidities, mean age 77 years, a mean of five symptoms, and were often bedfast or semiconscious. The most prevalent symptoms were: breathlessness, weakness/lack of energy, drowsiness, anxiety, agitation, confusion/delirium, and pain. Median time in palliative care was 46 hours; 77% of patients died. During palliative care, breathlessness, agitation, anxiety, delirium, cough, fever, pain, sore/dry mouth and nausea improved; drowsiness became worse. Common treatments were low dose</p>

morphine and midazolam. Having moderate to severe breathlessness, agitation and multimorbidity were associated with shorter survival.

Conclusion

Symptoms of COVID-19 quickly improved during palliative care. Breathlessness, agitation and multimorbidity could be used as triggers for timelier referral, and symptom guidance for wider specialities should build on treatments identified in this study.

Symptom control and survival for people severely ill with COVID: a multicentre cohort study (CovPall-Symptom)

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Abstract

Context

Evidence of symptom control outcomes in severe COVID is scant.

Objective

To determine changes in symptoms among people severely ill or dying with COVID supported by palliative care, and associations with treatments and survival.

Methods

Multicentre cohort study of people with COVID across England and Wales supported by palliative care services, during the pandemic in 2020 and 2021. We analysed clinical, demographic and survival data, symptom severity at baseline (referral to palliative care, first COVID assessment) and at three follow-up assessments using the Integrated Palliative Outcome Scale – COVID version (IPOS-COV).

Results

We included 572 patients from 25 services, mostly hospital support teams; 496 (87%) were newly referred to palliative care with COVID, 75 (13%) were already supported by palliative care when they contracted COVID. At baseline, patients had a mean of 2.4 co-morbidities, mean age 77 years, a mean of five symptoms, and were often bedfast or semiconscious. The most prevalent symptoms were: breathlessness, weakness/lack of energy, drowsiness, anxiety, agitation, confusion/delirium, and pain. Median time in palliative care was 46 hours; 77% of patients died. During palliative care, breathlessness, agitation, anxiety, delirium, cough, fever, pain, sore/dry mouth and nausea improved; drowsiness became worse. Common treatments were low dose morphine and midazolam. Having moderate to severe breathlessness, agitation and multimorbidity were associated with shorter survival.

Conclusion

Symptoms of COVID quickly improved during palliative care. Breathlessness, agitation and multimorbidity could be used as triggers for timelier referral, and symptom guidance for wider specialities should build on treatments identified in this study.

Keywords: Symptom Treatment, Symptom Management, COVID, Palliative care, Integrated Palliative Outcome Scale, Specialist Palliative Care, Acute Hospital Ward, Hospice

Key message of paper:

In this multicentre cohort study of 572 patients with COVID the symptoms of breathlessness, agitation, anxiety, delirium, cough, fever and pain were quickly improved during palliative care. This supports the role of palliative care for people with rapidly deteriorating disease. Triggers to prioritise future referrals include multimorbidity and severe breathlessness.

Running title: Symptoms and survival in severe COVID

Background

Patients with COVID can experience rapid deterioration, may die, and often suffer severe symptoms, including breathlessness, cough, agitation and delirium.^{1,2} Because COVID was a new disease, early symptom management guidance and referral practices were initially based on evidence from conditions such as cancer, emerging clinical observations and audit.¹ There is scant evaluation of symptom treatment effectiveness in severe COVID, nor an understanding of patient trajectories over time, especially for patients who are sick enough to die.³⁻⁷ Information on optimal symptom management and timing of referral to palliative care, including factors associated with worse symptoms or shorter survival, are vital to improve clinical management in COVID and in SARS and similar respiratory illnesses. Differences between pandemic waves in presenting symptoms, infectivity and other epidemiological characteristics are described, probably influenced by prevention, SARS-CoV-2 variants, treatments and population characteristics.⁸⁻¹⁰ However, we do not know whether these lead to differences among patients severely ill or dying with COVID. Characterisation of the cohorts of patients severely affected by COVID is needed to target clinical guidelines and care.

This multicentre study aimed to determine the prevalence and severity of symptoms, using validated measures, among cohorts of patients severely ill or dying with COVID referred to palliative care. In United Kingdom, palliative care is provided across several settings (i.e. hospital, hospice, inpatient units, nursing home, home) and include different healthcare professionals – generalists (General Practitioners or community nurses) as well specialists (consultants trained in palliative medicine, specialist palliative care nurses, or occupational therapists or physiotherapists). We wanted to determine whether symptoms changed during palliative care and which treatments were used in instances where symptom control appeared most effective. Our null hypotheses were that there would be no differences between symptom severity scores between baseline and subsequent assessments. In addition, we explored whether there were differences between COVID waves, and by length of time receiving palliative care. We also identified factors associated with rapid deterioration to help target future interventions and referrals.

Methods

Design: Multicentre cohort study of people with severe COVID seen and treated by palliative care services, focusing on hospital-based palliative care. The study received Health Research Authority (HRA, England) and Health and Care Research Wales (HCRW) approval (REC reference: 20/NW/0259); study co-sponsors: King's College Hospital NHS Foundation Trust and King's College

London, registered ISRCTN 16561225. It is reported according to STROBE¹¹, and MORECARE¹² statements. Patient, public and stakeholders informed the aims, methods, analysis plan and conclusions.¹³

Settings: Palliative care services within England and Wales were recruited via an earlier multinational survey.³ We actively sought services from areas with different cultural/ethnic, geographic, and socioeconomic diversities. The initial survey included a wide range of inpatient and community services; it was mainly hospital services who offered to collect the required individual outcomes data for this study.

Palliative care services were defined as: multi-professional teams of dedicated staff trained in palliative care, comprising doctors, nurses, and often social workers and therapists who specialised in palliative care.¹⁴ In England and Wales these professionals provide active holistic care to individuals with serious health-related suffering due to severe illness and especially to those near the end of life.¹⁵ Services supported patients and those important to them, and advised colleagues, in one or more of the following settings: hospital palliative care team, inpatient palliative care unit (this could be a ward within a hospital, or a free-standing building), home palliative care team, home nursing.³ These services work together to support patients and those important to them where they want to be cared for, working across boundaries and settings.

Inclusion criteria: We included consecutive patients with COVID who were seen and treated by each participating palliative care service (hospital, community, voluntary hospice settings, including remote consultations). Patients were ≥ 18 years and had clinically diagnosed and/or test confirmed COVID. We included two distinct patient groups: A) those newly referred to palliative care because of illness due to COVID, and; B) those already supported by palliative care who developed COVID. Services aimed to provide a consecutive series of 10 or more patients.

Assessment timing: Data were collected at baseline and then up to three further time points, after 12-24 hours, 36-48 hours, and at discharge or death (supplementary figure S2). Baseline for our patient groups was either:

- A) their first assessment in palliative care, referred because of illness due to COVID, therefore, not previously known to palliative care;
- B) their first palliative care assessment after they became ill with COVID, this group was already supported by palliative care (having been referred earlier, e.g. due to advanced cancer).

Data and outcomes: Data about the participating services was extracted from the multinational survey database.³ For data about individual patients: at baseline we collected socio-demographic information, including gender, ethnicity, age, and deprivation based on patient's usual address, clinical details including co-morbidities, dates of first COVID symptoms, diagnosis and referral to palliative care.

All assessments recorded: date and time of assessment, place of care, performance status according to the Australian Modified Karnofsky Performance Scale (AKPS), and phase of illness (a clinician-completed assessment of whether patients are clinically stable, unstable, deteriorating, or dying).¹⁶ Medicinal treatments were reported in free text fields for opioids and other medicines. Symptom severity was recorded according to the Integrated Palliative care Outcome Scale (IPOS)¹⁷ COVID specific version, the IPOS-COV. The IPOS is validated in many illnesses, multi-morbidities, cultures and settings.¹⁸⁻²³ IPOS-COV comprises all IPOS physical symptoms, the IPOS anxiety item, plus symptoms relevant to COVID (fever, cough, shivering, confusion/delirium, diarrhoea) using definitions from the longer POS precursor measures,²⁴ selected based on prior evidence and clinical review.^{25,26} Items were rated on a 4 point scale from no problem/patient not affected (0) to overwhelming (4) using set definitions for each point. Open text comments about other symptoms, treatment or care were invited. In this study, professionals completed the assessments based on patient symptom severity, as part of standard clinical practice.

At final assessment, additional data on whether the patient was still in care, discharged or died, and dates, times and places associated with outcome of care such as the place of death, were collected.

Procedures: Clinical teams entered anonymised data into a REDCap database using a standardised case report form. Data were collected about patients cared for between February 2020 and February 2021, and entered between May 2020 until February 2021. Standard Operating Procedures, virtual training, anonymised and dummy case reviews and troubleshooting meetings ensured consistency and confidentiality. Due to waiting for UK health research authority approvals, data were extracted from routinely collected clinical and administrative records until summer 2020,

and entered prospectively during care where possible thereafter. Each participating site was allocated randomly generated REDCap codes, sent via secure NHS email, as an additional anonymity procedure.

Analysis:

We analysed patient data according to the two different baseline groups described above, because the clinical circumstances of those already supported by palliative care may be different from those newly referred due to COVID illness. We conducted sensitivity analysis according to diagnosis of cancer or non-cancerous conditions, because of the high cancer prevalence in palliative care populations. We compared the characteristics of patients referred during UK pandemic wave 1 and wave 2. We followed widely used approaches to define the UK pandemic waves as reported by the King's Fund and the Office for National Statistics:^{27,28} wave 1 (February to end August 2020), and wave 2 (September 2020 to February 2021).

We inspected missing data patterns in symptom assessments; missing data were expected due to the sickness of the population. Summary statistics explored baseline symptom prevalence, severity and changes during palliative care. Symptom data were skewed, therefore we plotted radar graphs of the prevalence (%) of common moderate to overwhelming symptoms (scores 2- 4) according to three time periods between baseline and final assessment: <2 days (46 hours being the median time in palliative care), 2-4 days or >4 days. We also compared the scores on four subscales identified in factor analysis of IPOS-COV: BreathAg (sum of 3 symptoms, Breathlessness, Anxiety, Agitation, possible score ranges 0 - 12), Drow-Del (sum of 3 symptoms, Drowsiness, Weakness / Lack of energy, Confusion/Delirium, possible score ranges 0 - 12), Flu (sum of 5 symptoms, Sore or dry mouth/throat, Cough, Fever, Shivering, Pain, possible score ranges 0 - 20) and GI (sum of 2 symptoms, Nausea and Vomiting, possible score ranges 0 - 8).²⁹ The original IPOS validation found that 5 point change on total IPOS score was a moderate clinical difference¹⁷ which on these subscales would translate to: 0.9 in BreathAg, 0.9 in Drow-Del, 1.5 in Flu and 0.6 in GI.

Wilcoxon signed-rank test using all data points was used to identify significant differences between baseline, T1 and final scores for individual items and subscales. To avoid type I errors from multiple statistical testing, and balance for type II errors due to attrition, we used Hochberg's correction for multiple testing (procedures, www.multipletesting.com), based on unadjusted $p < 0.05$, determined $p \leq 0.001$ as significant.³⁰ In sensitivity analysis, mean symptom scores were calculated and compared. Sample size calculations were based on follow up data from 80 patients in subgroups to

detect a difference of ~5 points on IPOS total score (SD=6) between two groups (80 percent power, two-sided 0.05 significance level, mean Minimum Clinical Important Difference, SD based on previous research¹⁷), allowing for 50-60% attrition from those who die before a second assessment. We were aware that the IPOS-COV and this population would be different from earlier research and so we aimed to exceed this sample size to allow for different score distributions.

To understand more about which medicines and doses were beneficial, we identified a subgroup of patients whose scores for breathlessness and agitation both improved by ≥ 1 point on each POS item, and had data at baseline, T1 and final assessment. We focus on these two symptoms here as they were the most commonly very distressing. We collated the free text information on symptom treatments used after baseline assessment up to final assessment for these patients.

Using Cox proportional hazards modelling, we estimated multivariate-adjusted hazard ratios (HRs) of multiple risk factors on the survival function (short survival used to indicate rapid deterioration), censored when cases were still in care or discharged. Here the censoring was noninformative, where censoring times of the patients are not influenced by their times of their death³¹. We tested whether the proportional hazard assumption stands with inspection of Kaplan–Meier survival curves.³² Parallel survival curves are an evidence that hazards in groups of cases are proportional over time.³¹ We took into consideration the time-dependent covariates in the Cox model by including interactions of predictors as a function of survival time. We inspected whether any of the interaction terms were significant, which would suggest that the corresponding predictor is not proportional. $P < 0.05$ was taken as significant. Sensitivity analyses excluding cases from the largest site ($n=181$) were carried out.

Results

Across England and Wales, 25 palliative care services provided data about 572 patients in their care; 7 to 181 (median 10) consecutive patients per service (table 1, supplementary table S2). This was sufficient for planned subgroup analysis. Four sites who originally agreed to take part and were sent anonymised codes were unable to collect data due to staffing pressures. Of the 25 services, 10 were managed by charities/not for profit organisations, 14 by the public sector (national health service) and 1 private (supplementary table S1). Sixteen were primarily hospital palliative care teams offering advisory support to (of these 4 had home palliative care as well), 13 had in-patient palliative care units, of these 4 provided home palliative care team support as well (see table S1, and figure

S1). All cared for patients with COVID, had staff infected with COVID, and many experienced shortages of essential equipment or medicines (table S1).

Of the 572 patients, most (496, 87%) were newly referred to palliative care with their COVID illness, 75 (13%) were already supported by palliative care when they contracted COVID and entered the study (table 1). Of our sample, 61% were in wave one, and 39% in wave two, with the dates of study entry clustering around the wave peaks (Supplementary Figure S3). Just under half were women, mean age was 77 years, median 80, range 32 to 102 years, most were supported by hospital palliative care teams. Around 80% were from white (British or other) ethnic groups, 20% from other ethnic groups; the proportions from non-white ethnic groups were higher in wave 2 than wave 1 (Supplementary table S1), possibly due to the inclusion of more patients from ethnically diverse inner city areas during wave 2 (Supplementary Table S2).

[table 1 ~here]

On average patients had 2.4 co-morbidities alongside COVID, range 0 to 7 (table 1). The most prevalent co-morbidities were: hypertension (46%), metastatic solid tumour (27%), diabetes (26%), chronic obstructive pulmonary disease (25%), renal disease (23%), dementia (22%), cerebrovascular disease (16%), congestive cardiac failure (15%), myocardial infarction (11%), and non-metastatic solid tumour (11%). Co-morbidities of hypertension, dementia, renal disease and cerebrovascular disease were significantly more prevalent in the group newly referred to palliative care with COVID; whereas tumours (metastatic or not) were significantly more prevalent in the group already supported by palliative care (figure 1). There were no significant differences in morbidities between waves, except for hypertension (42% wave 1, v 53% wave 2) and metastatic cancer (32% wave 1 v 18% wave 2). The proportion of patients with baseline oxygen saturations level below 90% were lower in patients already supported by palliative care and those with cancer. Litres of oxygen received in the last 12 hours ranged from 0.3 to 89, where most patients (42%) received 15 litres (Table S3).

[figure 1 ~here]

Patients were newly referred to palliative care after a median of 144 hours (6 days) following their diagnosis of COVID. Compared with patients already supported by palliative care, newly referred patients with COVID had greater functional impairment according to the AKPS (Supplementary

Figure S4), were in the dying phase of illness at referral (44% versus 17%, chi squared = 21.6, df=3. $p < 0.001$), died during the study (77 v 48%) and had shorter survival (1.9 v 3.1 days following baseline assessment).

Symptoms at baseline and in follow-up

Of the 572 patients, 7 (1%) had no IPOS-COV assessments recorded. There were some missing data for individual items when these could not be assessed by the teams, often because patients were unconscious. Baseline individual assessments were missing for <5% patients for breathlessness, 5-10% patients for fever, cough, pain, vomiting, agitation, drowsiness, weakness, diarrhoea, vomiting and 11-15% for shivering, sore or dry mouth, anxiety, confusion/delirium and nausea.

At baseline the most prevalent moderate to severe symptoms were: weakness/lack of energy (79%), breathlessness (63%), drowsiness (46%), anxiety (36%) and agitation (34%), each with moderate to overwhelming levels for more than one third of patients (table 2), and present in almost half of the patients (supplementary table S3). Patients had a median of 5 symptoms overall, with few differences between referral groups (tables 1,2). The 'Drow-Del' (3 symptoms, Drowsiness, Weakness / Lack of energy, Confusion/Delirium) and 'BreathAg' subscales (3 symptoms, Breathlessness, Anxiety, Agitation), had the highest scores, despite 'Flu' being a sum of five symptoms. Scores for 'GI' were low, indicating this was rarely a problem. Mean scores showed similar patterns (supplementary table S6). Symptoms across settings and subgroups of patients appeared similar (table 1), although some subgroups were small and the study was not designed to test for differences between subgroups. The improvement in BreathAg mean score was of moderate clinical difference.

[table 2 ~here]

Between baseline and final assessments during palliative care the severity of nine symptoms: breathlessness, cough, pain, anxiety, confusion/delirium, agitation, fever, sore/dry mouth and nausea significantly reduced (Wilcoxon standardised (Z) test statistics were respectively: -10.3, -8.5, -7.7, -7, -5.6, -5.4, -5.4, -5.3, -4.4, p ranged < 0.0001 to < 0.001 , supplementary table S7). During palliative care support fewer patients experienced moderate to severe symptoms (table 2, supplementary table S2, figure 2). Improvements in these symptoms were apparent even when patients had <2 days in care, although longer time in care (>2 days) appeared to have a pattern of lower final symptoms, for example for breathlessness (figure 2). Drowsiness significantly deteriorated

over time (Wilcoxon standardised (Z) test statistic = 5.6, $p < 0.001$); vomiting, shivering and diarrhoea showed trends towards improvement that did not meet our thresholds for significance, and weakness/lack of energy was unchanged (supplementary table S7). Three subscales (BreathAg, Flu and GI) also showed significant improvements (Wilcoxon Z respectively = -8.4, -9.4, -3.9, p ranging < 0.001 to < 0.0001), while Drow-Del (sum of 3 symptoms, Drowsiness, Weakness/Lack of energy, Confusion/Delirium) showed no significant change (supplementary table S7). Sensitivity analysis found similar changes (supplementary tables S10-12, figure S6-7).

Inspection of treatments used in patients with ≥ 1 point improvements for both breathlessness and agitation and three assessments, identified that at baseline 8/23 patients were on regular opioids, and by final assessments all patients were on regular opioids. Morphine sulphate and midazolam in small doses (e.g. 10mg in continuous subcutaneous infusion of each over 24 hours) were most commonly used. This was supplemented as required by low dose morphine and midazolam (table 3). Similar doses and medicines were seen among patients with shorter periods of time in care.

[table 3, figure 2 ~here]

Factors associated with more rapid deterioration / shorter survival

Having, at baseline, more moderate to severe symptoms, more co-morbidities, moderate to severe levels of breathlessness and agitation were significantly associated with shorter survival (table 4). A clear dose-response of shorter survival with more severe breathlessness and agitation can be seen (figure 3). There was no difference in survival between waves. A similar pattern was seen on survival with breathlessness prevalence. (supplementary figure S7) Sensitivity analyses produced similar results to the main analyses (supplementary tables S7-12, figure S6-7)

[table 4, figure 3 ~here]

Discussion

This is the first study to quantify the complexity, severity of, and changes in symptoms experienced by patients supported by palliative care teams across multiple settings during two waves of the COVID-19 pandemic. Patients were referred with a complex myriad of symptoms, in particular breathlessness, weakness, anxiety, agitation, and often severe illness, with short survival (average time in care 46 hours). Despite this nine symptoms (breathlessness, cough, pain, anxiety, confusion/delirium, agitation, fever, sore/dry mouth and nausea) improved whilst receiving

palliative care; drowsiness became more severe. Having longer than two days supported by palliative care seemed to offer greater benefits in terms of final symptom outcomes. Breathlessness, agitation and multimorbidity were significantly associated with shorter survival.

Analysis of cohorts of patients indicates that the usual course for individuals severely ill or dying with COVID results in increasing symptom severity and suffering over time.^{2,33,34} Therefore, our findings of symptom improvements during palliative care for these nine symptoms are very encouraging and suggest that symptoms can be ameliorated. Little is known about effectiveness of therapeutics for symptoms in COVID,^{34,35} so this is an important contribution for the many clinicians who care for patients with COVID, both within, and perhaps even more crucially outwith specialist palliative care. These improvements were achieved in the context of relatively small doses (compared to, for example, doses used in cancer patients)³⁶ of commonly used medicines, such as morphine and midazolam. This provides the first multicentre, outcome-based data on symptom treatments in severely ill COVID patients.^{1,25,37} We did not find differences between pandemic waves in symptoms or survival.

During the pandemic, palliative care services responded rapidly to provide symptom support and care, including at the end of life. In areas of high COVID prevalence palliative care became extremely stretched with staff and other shortages.³ We found that the duration in palliative care was very short (less than 2 days), which meant that they had to work in this complex situation very quickly,⁵ contributing to pressures on staff. Despite this, our findings show that palliative care support can make a major difference even in little time. Our data suggest that longer periods in care could lead to even greater symptom improvements. This finding is supported by research in other conditions, where early palliative care is associated with improved quality of life and survival.^{38,39} We found that three factors (multimorbidity, breathlessness and agitation) could identify patients with shorter survival (more rapid deterioration). These should be available in clinical records and could be employed as clinical triggers for referral to palliative care in COVID.

Our study has several limitations. We conducted a cohort study, without a randomly allocated control, and so cannot say that improvements in symptoms were caused by the treatments prescribed or the interventions of palliative care. However, we present the highest level of evidence currently available on the effective management of symptoms in people severely affected by or dying from COVID, with data from multiple sites, in an ethnically diverse population and in the largest study to our knowledge. In addition, because of the condition of many patients, 30%

unstable, 37% deteriorating, 40% dying, we had to rely on staff assessments; families or friends also often being absent due to infection control measures. This may have caused some biases, staff may have reported differently than patients, and may have sought evidence of improvements, aware of the treatments given, or been influenced by burden of care, burnout, and resource limitations.⁴⁰ However, research into IPOS has found acceptable or good agreement between most patient self-reported and staff proxy-reported physical symptoms, suggesting that our data are sound.¹⁷ Furthermore, staff reported that some symptoms worsened, for every symptom studied there were some patients who did not improve or deteriorated, and overall drowsiness deteriorated, as might be expected as patients approach the end of life. In addition, staff assessments were consistently used for all patients, and at all time points, so there was no switching between patient and proxy data which would have risked additional biases. Patient assessments at the end of life are often limited, impossible or unreliable because of patient illness and/or cognitive impairment. In our study, training and reviews were carried out to harmonize ratings and improve validity and reliability. Nonetheless, there were some missing symptom data. Finally, when modelling survival, lead time bias may have led to a superficial increase in patient's survival, as some patients such as those known to palliative care may have tested positive for COVID and referred to palliative care before onset of severe symptoms. However, as the patients referred to palliative care were presenting with severe symptoms, we believe that lead bias is minimised.

Conclusions

In this large multicentre study of people with severe COVID supported by palliative care, people had complex morbidities and symptoms. Despite this, nine symptoms improved during palliative care, breathlessness, cough, pain, anxiety, confusion/delirium, agitation, fever, sore/dry mouth and nausea; drowsiness became more severe. Common low dose medicines were used, such as morphine and midazolam, which can inform future guidance. Breathlessness, agitation, multiple symptoms and multimorbidity could be used as triggers for earlier referral, which could be helpful given the short time in palliative care (median 46 hours) and the pressures on services.

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Author contributions

IJH is the grant holder and chief investigator; KES, MM, FEM, CW, NP, LKF, SB, MBH and AO are co-applicants for funding. IJH and CW with critical input from all authors wrote the protocol for the CovPall study. MBH co-ordinated data collection and liaised with centres, with input from AO, RC, CW, NP, FM and SB. IJH and MBH analysed the data, with input from LKF. All authors had access to all study data, discussed the interpretation of findings and take responsibility for data integrity and analysis. IJH and MBH drafted the manuscript. All authors contributed to the analysis plan and provided critical revision of the manuscript for important intellectual content. IJH is the guarantor.

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York Teaching Hospital NHS Foundation Trust : York Hospital, Scarborough Hospital

The CovPall study group

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Table 1 Demographic and clinical characteristics of the total sample of patients (n=572), and total sample by status at baseline assessment (not previously known or already supported by palliative care)

Characteristics/Variable	Status at Baseline Assessment		
	Total Sample	Not previously known to Palliative Care	Already supported by Palliative Care
		n=496 (86.7%)	n=75 (13.1%)
n =572^a			
Age, Mean (Median, Range)	77.2(80, 32 to 102)	78.1 (80, 32 to 102)	71.4(72, 38 to 96)
Sex, Women n (%)	264(46.2)	227(45.8)	36(48)
Ethnicity, n (%)			
White (British and Other)	436(79.9)	372 (79)	64(86.5)
Other ^c	110(20.1)	99(21)	10(13.5)
Index of Multiple Deprivation Deciles, Mean (Median, Range)	5(4, 1 to 10)	4.9 (4, 1 to 10)	5.7 (6, 1 to 10)
Number of symptoms recorded at Baseline Mean (Median, Range)	4.9(5, 0 to 12)	4.9(5, 0 to 12)	5 (5, 0 to 10)
Numbers of Moderate to Overwhelming Symptoms at Baseline Mean (Median, Range)	3.5 (3, 0 to 9)	3.6 (3, 0 to 9)	3.2 (3, 0 to 7)
Numbers of Comorbidities Mean (Median, Range)	2.4(2, 0 to 7)	2.4(2, 0 to 7)	2.1(2, 0 to 6)
Place of Care on admission/baseline, n (%)			
Hospital-based Specialist Palliative Care Teams (Acute Hospital Ward, ICU and ED)	402(72)	370(76.6)	31(41.9)
Inpatient Hospice/Palliative Care Ward	146(26.2)	104(21.5)	42(56.8)

Care Home including own home and sheltered housing	10(1.8)	9(1.9)	3≥
Baseline Integrated Palliative Outcome Scale - COVID (IPOS-COVID19^b) subscales, Mean (Median, Range)			
Breathlessness and Agitation	3.9 (3, 0 to 12)	4 (4, 0 to 12)	2.7 (2, 0 to 10)
Drowsiness and Delirium	4.4 (4, 0 to 12)	4.6 (4, 0 to 12)	3.4 (3, 0 to 8)
Flu-like Symptoms	2.4 (2, 0 to 12)	2.4 (2, 0 to 12)	3.1 (3, 0 to 7)
Gastro-Intestinal	0.2 (0, 0 to 5)	0.2 (0, 0 to 5)	0.2 (0, 0 to 4)
Symptom Burden (Baseline IPOS-COVID19Scores^f) Mean (Median, Range)			
Breathlessness	1.8(2, 0 to 4)	1.9(2, 0 to 4)	1.3(1, 0 to 4)
Weakness / Lack of energy	2.4(3, 0 to 4)	2.4(3, 0 to 4)	2.1(2, 0 to 4)
Drowsiness	1.4(1, 0 to 4)	1.5(1.5, 0 to 4)	0.8(0, 0 to 4)
Anxiety	1.1(1, 0 to 4)	1.1(1, 0 to 4)	1.1(1, 0 to 4)
Agitation	1(0, 0 to 4)	1(0, 0 to 4)	0.5(0, 0 to 4)
Confusion/Delirium	0.9(0, 0 to 4)	0.9(0, 0 to 4)	0.7(0, 0 to 3)
Pain	0.8(0, 0 to 4)	0.7(0, 0 to 4)	1.1(1, 0 to 3)
Sore or dry mouth/throat	0.7(0, 0 to 4)	0.7(0, 0 to 4)	0.5(0, 0 to 3)
Cough	0.6(0, 0 to 4)	0.6(0, 0 to 4)	1.1(1, 0 to 3)
Fever	0.5(0, 0 to 4)	0.5(0, 0 to 4)	0.8(0, 0 to 4)
Shivering	0.1(0, 0 to 3)	0 (0, 0 to 3)	0.1(0, 0 to 1)
Diarrhoea	0.1(0, 0 to 3)	0(0, 0 to 3)	0.2(0, 0 to 3)
Nausea	0.2(0, 0 to 3)	0.2(0, 0 to 3)	0.2(0, 0 to 2)
Vomiting	0.1(0, 0 to 4)	0.1(0, 0 to 4)	0.1(0, 0 to 2)
Baseline AKPS Score, Mean (Median, Range)	24.3 (20, 10 to 90)	22.9 (20, 10 to 90)	33.3 (30, 10 to 60)

Baseline Oxygen Saturation (%) Mean (Median, Range)	90.4(93,48 to 100)	90(92, 48 to 100)	93.4(95, 75 to 100)
Proportion of patients with baseline oxygen saturation below 90% n(%)	136(23.8)	128(25.8)	8(10.7)
Baseline Oxygen Therapy n(%)			
Room Air	192(33.6)	147(29.6)	45(60)
Oxygen via Nasal Prongs	116(20.3)	96(19.4)	19(25.3)
Oxygen via Hudson Mask	83(14.5)	81(16.3)	3≥
Rebreather Mask	113(19.8)	108(21.8)	5(6.7)
BiPAP or CPAP	25(4.4)	24(4.8)	3≥
High Flow Nasal Prongs	40(7)	39(7.9)	3≥
Ventilated	0(0)	0	0
Treatment reported at Baseline, yes n (%)			
Regular Opioids prescribed <i>before</i> referral to palliative care	245(42.9)	202(40.8)	43(57.3)
PRN Opioids prescribed	335(58.6)	298(60.1)	37(49.3)
Outcome at the end of the study observation and follow-up period, n (%)			
Died	417(73)	381(77)	36(48)
Discharged or Still in Care	154(27)	114(23)	39(52)
Survival Time in Hours, Median (Mean, Range)	45.9(98.6, 0.5 to 1825.9)	45.4(86.9, 0.5 to 1825.9)	73.4(222.2, 8.3 to 1536)
Time periods of COVID waves, n (%)			
Wave 1 (February - August 2020)	316(61.4)	269(60.9)	47(64.4)
Wave 2 (September 2020 - February 2021)	199(38.6)	173(39.1)	26(35.6)
Hours between first presentation of COVID symptoms and referral to palliative care^e, Median (Mean, Range)	144(146.9, - 8352 to 8352)	192(250.9, 0 to 8352)	-192(-481, -24 to - 8352) ^d

Deaths, n (%)	417(73)	381 (77)	36(48)
Place of Death, n (%)			
Hospital-based Specialist Palliative Care Teams (Acute Hospital Ward, ICU and ED)	316(76.9)	300(80)	16(44.4)
Inpatient Hospice/Palliative Care Ward	86(20.9)	67(17.9)	19(52.8)
Care Home including own home and sheltered housing	9(2.2)	8(2.1)	3≥
^a 1 case is missing most of the demographic and clinical information, most present findings from n=571 Survival Time is calculated from the date and time of the baseline assessment to time and date of death. ^b <i>IPOS-COVID 19 subscales - higher scores indicate worsening impact on the patient's wellbeing</i> ^c includes Asian/Asian British, Black/African/Caribbean/Black British, Arab, Mixed/Multiple ethnic groups ^d is negative because these patients were supported by palliative care before contracting COVID, and so this indicates time in palliative care before contracting COVID. ^e Negative values indicate that the patient presented COVID symptoms after their referral to palliative care, whereas positive values indicate that patients presented COVID symptoms and were then referred to palliative care ^f Possible scores range from 0-4, higher scores indicating higher levels of burden			

Table 2 Prevalence^a of moderate to overwhelming symptoms and IPOS COVID subscale scores at baseline, time 1, time 2 and final assessments

IPOS -COVID 19 Symptoms	Baseline (T0)		Time 1 (T1)		Time 2 (T2)		Final (TF)	
	Assessment		Assessment		Assessment		Assessment	
	%	n/N ^b	%	n/N ^b	%	n/N ^b	%	n/N ^b
Breathlessness	62.7	340/542	45.8	192/419	38.0	111/292	36.1	177/490
Weakness / Lack of energy	79.4	402/506	76.6	298/389	77.3	208/269	72.6	310/427
Drowsiness	46.3	242/523	49.9	201/403	47.9	134/280	57.2	259/453
Anxiety	35.5	167/471	27.6	102/369	21.3	57/268	16.8	70/416
Agitation	33.6	170/506	27.6	109/395	17.6	48/272	19.3	92/476
Confusion/Delirium	29.8	145/486	26.6	102/383	20.6	55/267	13.6	58/428
Pain	26.0	137/527	23.5	96/408	19.4	56/288	11.9	57/479
Sore or dry mouth/throat	20.6	101/490	18.2	71/391	14.9	41/275	11.0	49/445
Cough	23.5	121/515	13.4	54/402	14.2	41/288	5.2	24/464
Fever	17.8	94/529	8.5	33/387	3.3	9/276	6.3	28/448
Nausea	5.1	25/492	4.2	16/383	3.0	8/269	1.4	6/424
Diarrhoea	3.3	17/518	3.0	12/395	2.5	7/278	2.1	10/471
Shivering	1.0	5/498	1.0	4/390	0.7	2/273	0.0	0
Vomiting	1.9	10/530	1.2	5/409	2.1	6/285	0.6	3/482
Integrated Palliative Outcome Scale - COVID (IPOS-COVID19) Mean (Median, Range) ^c								
Breathlessness and Agitation (BreathAg)	3.9 (3, 0 to 12)		2.9 (2, 0 to 12)		2.4 (2, 0 to 10)		2.3 (2, 0 to 12)	
Drowsiness and Delirium (Drow-Del)	4.4 (4, 0 to 12)		4.6 (4, 0 to 12)		4.4 (4, 0 to 11)		4.6 (5, 0 to 12)	
Flu-like Symptoms (Flu)	2.4 (2, 0 to 12)		2 (2, 0 to 9)		1.6 (1, 0 to 9)		1.1 (0, 0 to 10)	
Gastro-Intestinal (GI)	0.2 (0, 0 to 5)		0.2 (0 to 6)		0.2 (0, 0 to 6)		0.1 (0, 0 to 4)	
ⁱPrevalence expressed as percentage (%) of total cases with valid data								
ᵇDenominators exclude cases whose symptoms could not be assessed								
ᶜIPOS-COVID 19 subscale scores presented from the total sample								

Table 3 Common medicines prescribed for patients whose breathlessness and agitation showed greatest improvements over time.

Regular medicines	As required medicines
<p>Opioids given in Continuous Subcutaneous Infusion (CSCI) via a syringe driver over 24 hours</p> <p>Morphine Sulphate, doses ranging 5 to 40mg, median dose 10mg (13/23 patients, the last 24 hours of life for 1 -2 patients had the higher doses in this range)</p> <p>Oxycodone, doses ranging 7.5 to 50mg (3/23 patients, the patient on 50mg had been on oxycodone prior to contracting COVID)</p> <p>Fentanyl, doses ranging 100 to 200mcg s/c (3/23 patients)</p> <p>Fentanyl 12 microgram patch (1/23 patient)</p> <p>Oral opioids</p> <p>Morphine Sulphate MR 50mg twice daily (1/23 patient, already receiving when contracted COVID)</p> <p>Oxycodone 5mg PO twice daily (1/23 patient)</p> <p>Other medicines given CSCI over 24 hours</p> <p>Midazolam, doses ranging 2.5 to 30mg, median dose 10mg, (10/23 patients, the last 24 hours of life for 1 -2 patients had the higher doses in this range)</p> <p>Levomepromazine, 12.5mg (4 patients)</p> <p>Other medicines given regularly for some patients included:</p> <p>Paracetamol, Dexamethasone, Salbutamol, Saline nebuliser Glycopyrronium, Hyoscine butylbromide Gabapentin, Pregabalin, Amitriptyline Senna, Sodium Docusate, Metoclopramide, Omeprazole, Nystatin</p>	<p>Opioids prescribed as required subcutaneously, doses and medicine chosen were concordant with usual practice alongside regular opioids</p> <p>Morphine sulphate, doses ranging 1 to 2.5mg s/c (14/23, also prescribed for the one patient not on regular CSCI opioids)</p> <p>Oxycodone, doses ranging 1.25 - 8mg (3 patients)</p> <p>Fentanyl, doses ranging 12.5 to 25mcg (4 patients)</p> <p>Other medicines prescribed as required subcutaneously</p> <p>Midazolam, doses ranging 2 to 5mg Levomepromazine, doses ranging 6.25 to 12.5mg Haloperidol, doses ranging 0.5-1.5mg</p> <p>Other medicines prescribed as required for some patients included:</p> <p>Glycopyrronium, 400 mcg subcutaneously Hyoscine butylbromide, 20mg subcutaneously Lorazepam, doses ranging 0.5 to 1mg sublingually</p> <p><i>Note that it is often reported that the as required medicines were not used or needed only occasionally</i></p>

Table 4 Cox Proportional Hazards Model (n=361^a) of multiple risk factors on the survival function (short survival used to indicate rapid deterioration)

Independent Variables	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
Numbers of moderate to overwhelming symptoms the patient presented with at baseline	-0.10	0.04	5.79	1	0.016	0.91	0.84	0.98
Do the patients have cancer? (Y/N)	-0.31	0.14	5.01	1	0.025	0.74	0.56	0.96
Gender	-0.09	0.12	0.56	1	0.455	0.92	0.72	1.16
Age	0.00	0.01	0.38	1	0.538	1.00	0.99	1.01
Number of Comorbidities of COVID patients	0.08	0.04	3.76	1	0.053	1.08	1.00	1.16
Baseline Breathlessness (Not at all)			35.52	4	<0.001			
Reference								
Baseline Breathlessness (Slightly)	0.01	0.24	0.00	1	0.956	1.01	0.64	1.61
Baseline Breathlessness (Moderately)	0.49	0.21	5.16	1	0.023	1.63	1.07	2.47
Baseline Breathlessness (Severely)	0.79	0.22	12.60	1	<0.001	2.21	1.43	3.42
Baseline Breathlessness (Overwhelming)	1.37	0.28	24.04	1	<0.001	3.93	2.27	6.79
Baseline Agitation (Not at all)			19.40	4	<0.001			
Reference								
Baseline Agitation (Slightly)	0.39	0.18	4.84	1	0.028	1.48	1.04	2.10
Baseline Agitation (Moderately)	0.57	0.17	11.62	1	<0.001	1.77	1.27	2.46
Baseline Agitation (Severely)	0.50	0.21	5.99	1	0.014	1.65	1.11	2.47
Baseline Agitation Overwhelming)	1.28	0.39	10.69	1	0.001	3.61	1.67	7.79
Waves of COVID (Wave1: January - August 2020, Wave 2: September 2020 - January 2021)	-0.04	0.12	0.08	1	0.772	0.97	0.76	1.22

^aData for the independent variables in the model are only complete for these cases, therefore the sample size is smaller than the original sample

Figure 1 Co-morbidities in our sample, according to whether patients were supported by palliative care before contracting COVID or were newly referred to palliative care because of COVID

^a significant difference between groups with referred due to covid group higher, Pearson chi-squared >4.68, df=1, $p<0.031$,

^b significant difference between groups with supported by palliative care higher, Pearson chi-squared >9.16, df=1, $p<0.002$)

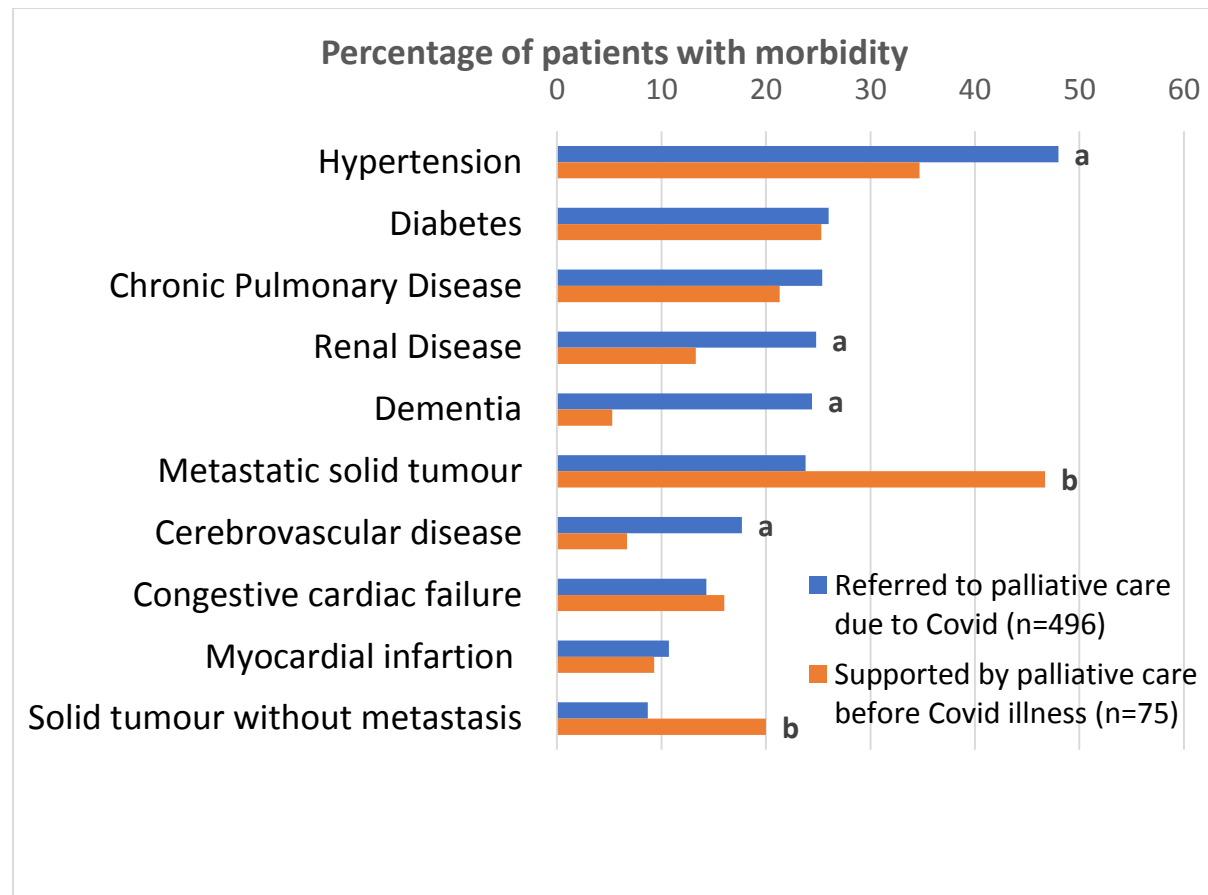


Figure 2 (a-c) Radar plots showing baseline and final moderate to severe symptom prevalence according to days in palliative care before death (supplementary table S5, shows the test results)

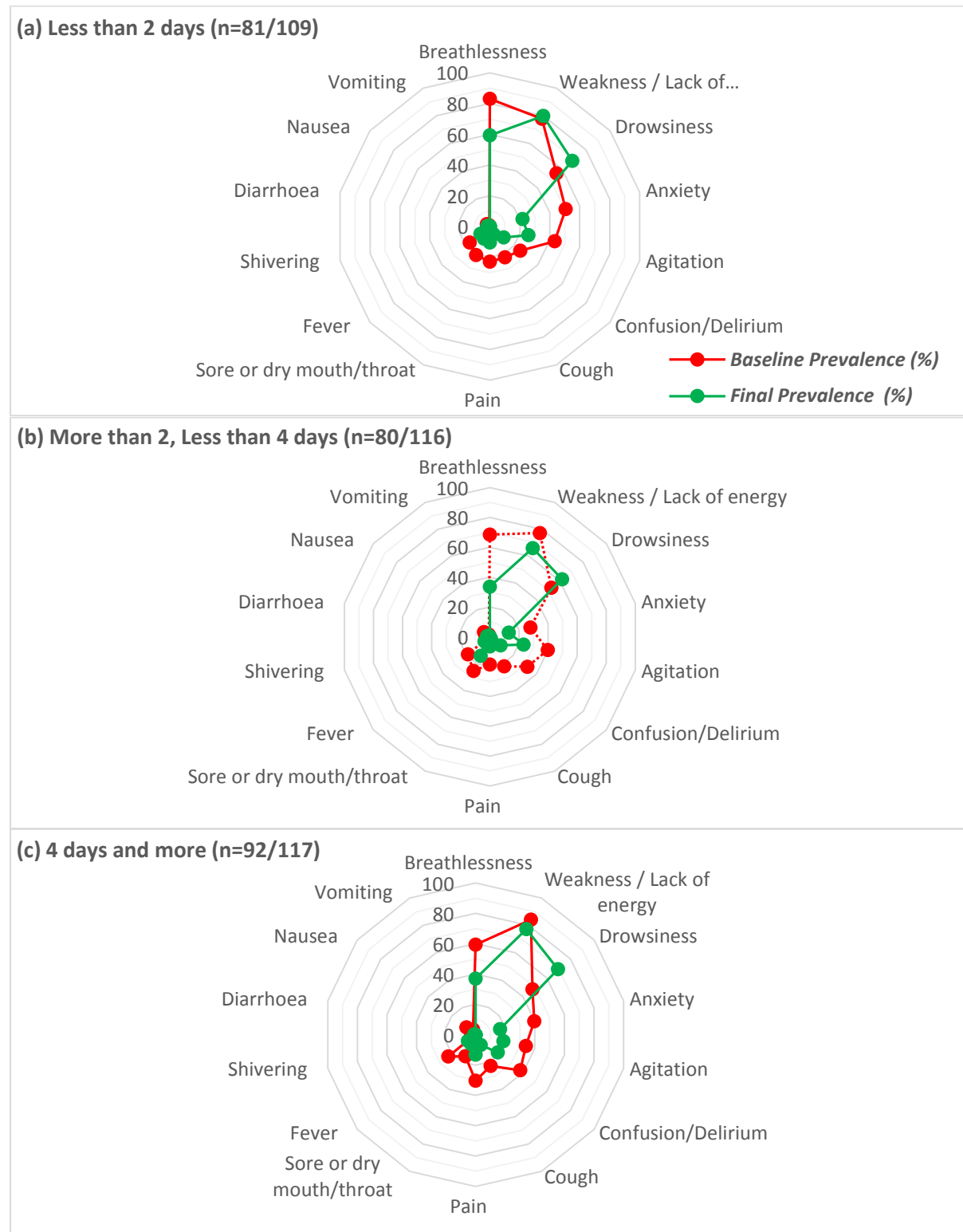
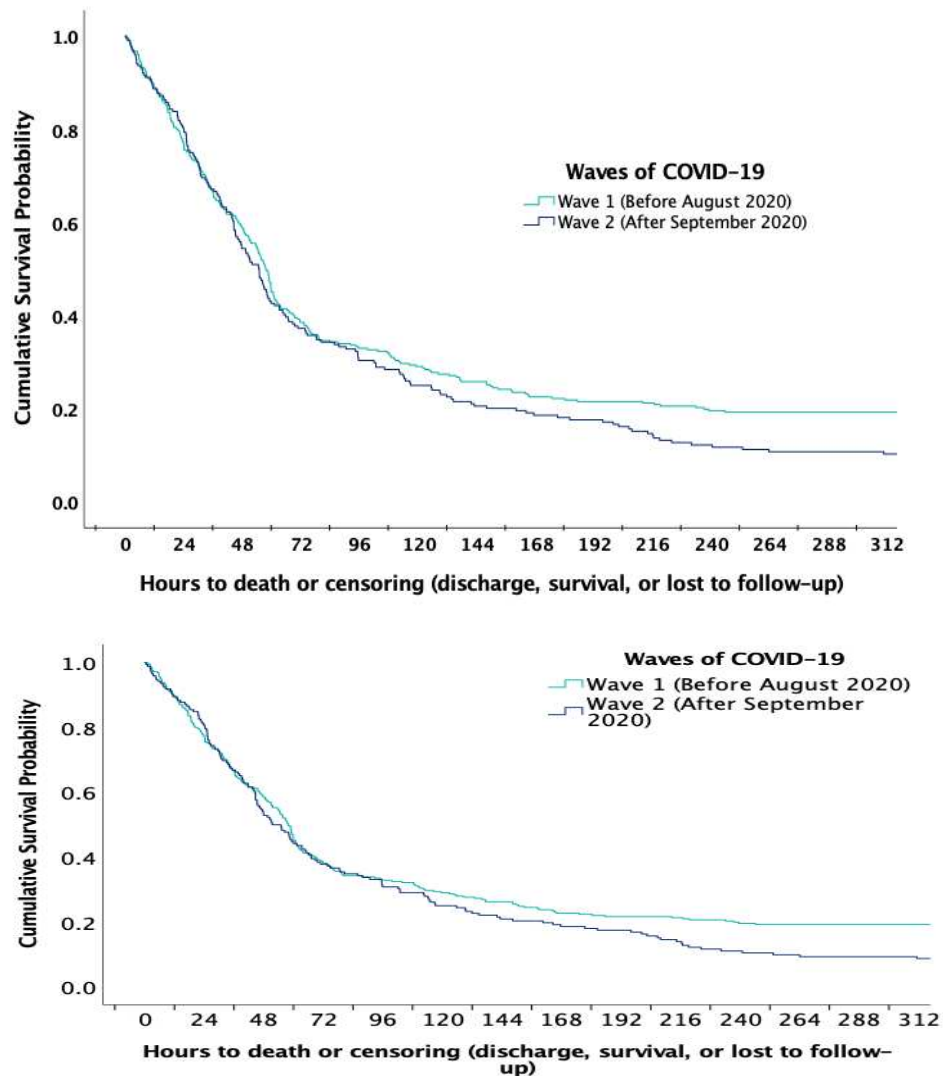
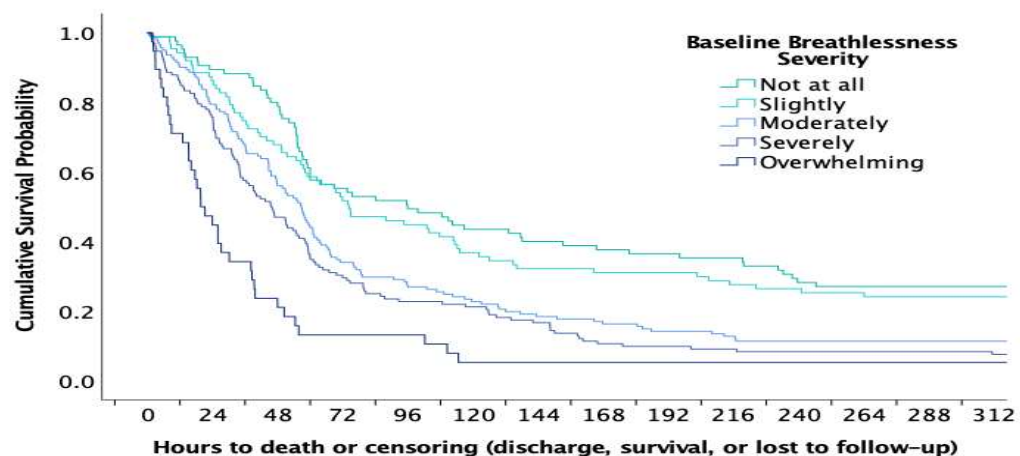


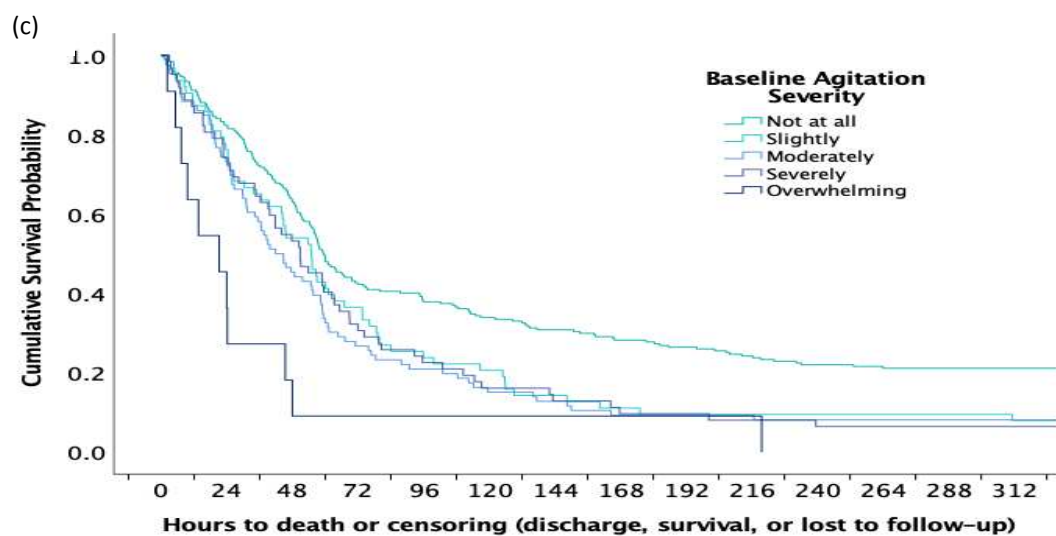
Figure 3 (a-c) Kaplan-Meier Survival Curve of patients referred to palliative care with (a) different waves of the pandemic (n=458), (b) different levels of baseline breathlessness (n=483) and (c) different levels of agitation (n=449)

(a)



(b)





Supplementary File

List of Tables

Table S 1 Details of Services Provided by the Participating 25 Palliative Care Services.....	2
Table S 2a and b (a) Demographic and clinical characteristics of the total sample of patients (n=572), sample divided according to their status at baseline assessment (new or already known to palliative care), and sample divided according to their condition based on co-morbidity data (cancer versus non-cancer), sample divided according to the wave based on their date of referral to palliative care services and (b) sample divided according to place of care (hospital, hospice versus home)	5
Table S 3 the litres of oxygen received in the last 12 hours.....	9
Table S 4 Number and proportion (%) of recruited participants according to region and country (n=572), darker colour indicating higher number of participants	10
Table S 5 Prevalence symptoms any severity from mild up as a percentage of all cases (%) at baseline and final assessments	12
Table S 6 Sensitivity analysis: mean baseline and final scores for patients with complete scores at both assessments, with sample size shown for each symptom of cases seen less than 2, 2 to 4, and more than 4 days and more before their death	13
Table S 7 Related-Samples Wilcoxon Signed Rank Test Summary for the overall sample.....	13
Table S 8 Sensitivity Analysis: Paired Samples t-test of baseline and final IPOS-COVID subscales scores of the overall sample	14
Table S 9 Related-Samples Wilcoxon Signed Rank Test Summary according to their days in palliative care before they died	14
Table S 10 Sensitivity Analysis - Cox Proportional Hazards Model (n=268 ^a) of multiple risk factors on the survival function (short survival used to indicate rapid deterioration) excluding cases from the largest site	15
Table S 11 Sensitivity Analysis - Related-Samples Wilcoxon Signed Rank Test Summary for the overall sample excluding the cases from the largest site	18
Table S 12 Sensitivity Analysis - Paired Samples t-test of baseline and final IPOS-COVID subscales scores of the sample excluding cases from the biggest site	19

List of Figures

Figure S 1 Venn Diagram showing configuration of different services provided by the 25 palliative care services.....	3
Figure S 2 Assessment schedule in the CovPall Symptom study.....	4
Figure S 3 Date of baseline assessment for patients in the CovPall Symptom study, and the UK pandemic wave periods.	11
Figure S 4 Australian Modified Karnofsky Performance Scale (AKPS) Scores at baseline for patients according to baseline group.....	12
Figure S 5 Kaplan-Meier Survival Curve of patients referred to palliative care with no to slight levels compared to moderate to overwhelming levels of baseline breathlessness (n=483)	15
Figure S 6 Sensitivity Analysis – Kaplan-Meier Survival Curve of patients referred to palliative care excluding the larger site with (a) different waves of the pandemic (n=328) , (b) different levels of baseline breathlessness (n=342) and (c) different levels of agitation (n=298)	17
Figure S 7 Sensitivity Analysis - Kaplan-Meier Survival Curve of patients referred to palliative care with no to slight levels compared to moderate to overwhelming levels of baseline breathlessness (n=342)	18

Table S 1 Details of Services Provided by the Participating 25 Palliative Care Services

Variable	Management Type		
	Charitable/Non-profit n=10	Public n=14	Private n=1
Charitable / non-profit			
Public			
Other			
Setting (n/N, %)			
Inpatient PC unit	9/10(90)	3/14(21.4)	1/1(100)
Hospital PC team	1/10(10)	14/14(100)	1/1(100)
Home PC team	9/10(90)	4/10(28.6)	0
Home nursing	4/10(40)	1/14(28.6)	0
Experience with suspected or confirmed COVID			
Services with confirmed or suspected COVID cases (n/N, %)a	10/10(100)	14/14(100)	1/1(100)
Use of virtual technologies with patients and families during the pandemic compare to before COVID pandemic Yes (n/N, %)			
A lot more	6/10(60)	6/14(42.9)	1/1(100)
Slightly more	3/10 (30)	4/14(28.6)	-
About the same	1/10(10)	4/14(28.6)	-
Severity of disease in patients with suspected or confirmed COVID (n/N, %)			
Severely ill or dying due mainly to COVID	1/10(10)	12/14(85.7)	1/1(100)
Pre-existing illnesses/co-morbidities as well as COVID who are severely ill or dying	6/10(60)	13/14(92.9)	0
Patients known to service already who now have COVID	5/10(50)	10/14(71.4)	0
Services with staff with suspected or confirmed COVID (n/N, %)	10/10(100)	14/14(100)	1/1(100)
Type of staff with suspected or confirmed COVID (n/N, %)			
Nurses	10/10(100)	14/14(100)	1/1(100)
Physicians	9/10(90)	10/14(71.4)	1/1(100)
Others (Allied Health Professionals, Managers, Receptions etc)	8/10(80)	7/14(50)	0
Services that have encountered patients or families with COVID who are from black and minority ethnic groups (n/N, %)	3/10 (30)	9/14(64.3)	1/1(100)
Shortages Yes (n/N, %)			
Personal Protective Equipment (PPE) shortages	8/10(80)	4/13(30.8)	0
Key medicines shortages	0	3/13(23.1)	0
Equipment shortages (e.g. syringe drivers)	0	5/13(38.5)	0
Staff shortages	4/10(40)	4/13(30.8)	0
Overall Busyness Levels during the pandemic compared to before the COVID pandemic			
More busy	2/10(20)	8/14(57.1)	1/1(100)
About the same	3/10(30)	1/14(7.1)	-
Less busy	5/10(50)	5/14(35.7)	-

Figure S 1 Venn Diagram showing configuration of different services provided by the 25 palliative care services

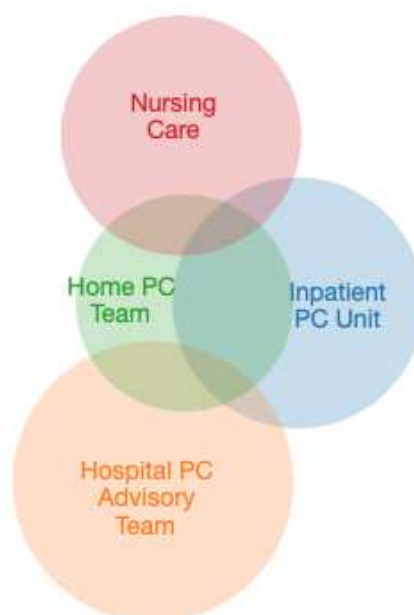


Figure S 2 Assessment schedule in the CovPall Symptom study

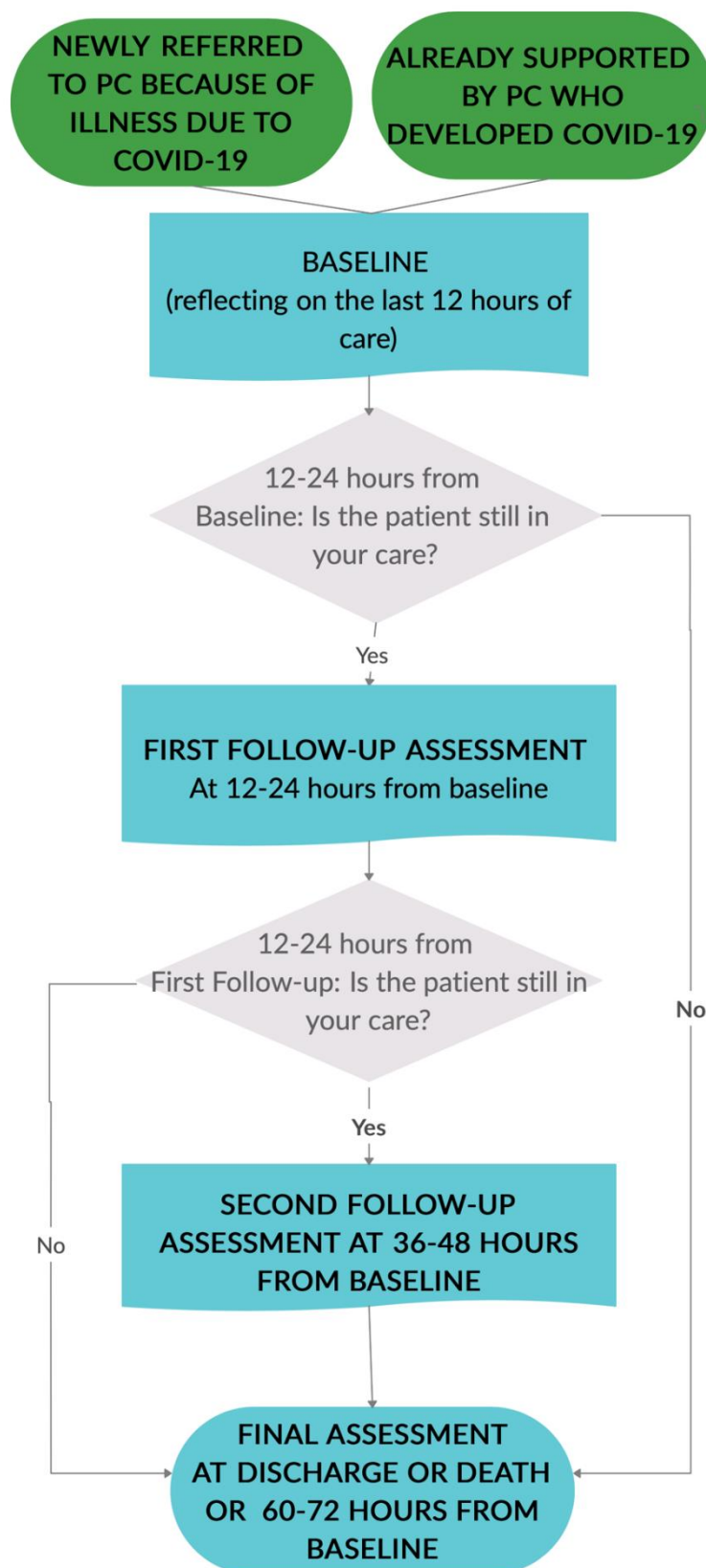


Table S 2a and b (a) Demographic and clinical characteristics of the total sample of patients (n=572), sample divided according to their status at baseline assessment (new or already known to palliative care), and sample divided according to their condition based on co-morbidity data (cancer versus non-cancer), sample divided according to the wave based on their date of referral to palliative care services and (b) sample divided according to place of care (hospital, hospice versus home)

a)

Characteristics/Variable	Total Sample	Status at baseline assessment		Underlying Conditions (cancer or not)		Waves	
		New to Palliative Care	Already supported by Palliative Care	Cancer	Non-Cancer	1 (February - August 2020)	2 (September 2020 - February 2021)
	n =572 ^a	n=496 (86.7%)	n=75 (13.1%)	n=227 (39.7%)	n=345 (60.3%)	n=337(58.9%)	n=199(38.6%)
Age, Mean (Median, Range)	77.2(80, 32 to 102)	78.1 (80, 32 to 102)	71.4(72, 38 to 96)	73.4(75, 32 to 102)	79.7(81, 36 to 100)	76.5(79, 34 to 99)	78.9(81, 36 to 102)
Sex, Women n (%)	264(46.2)	227(45.8)	36(48)	102(44.9)	162(47)	152(45.1)	98(49.2)
Ethnicity, n (%)							
White (British and Other)	436(79.9)	372 (79)	64(86.5)	192 (88.9)	244(73.9)	282(89.2)	129(65.5)
Other	110(20.1)	99(21)	10(13.5)	24(11.1)	86(26.1)	34(10.8)	68(34.5)
Index of Multiple Deprivation Deciles, Mean (Median, Range)	5(4, 1 to 10)	4.9 (4, 1 to 10)	5.7 (6, 1 to 10)	5.4 (5, 1 to 10)	4.7 (4, 1 to 10)	5.4(5, 1 to 10)	5.5 (5, 1 to 10)
Number of symptoms recorded at Baseline Mean (Median, Range)	4.9(5, 0 to 12)	4.9(5, 0 to 12)	5 (5, 0 to 10)	5(5, 0 to 12)	4.9(5, 0 to 11)	5(5,0 to 11)	4.9(5, 0 to 12)
Numbers of Moderate to Overwhelming Symptoms at Baseline Mean (Median, Range)	3.5 (3, 0 to 9)	3.6 (3, 0 to 9)	3.2 (3, 0 to 7)	3.4 (4, 0 to 9)	3.5 (3, 0 to 9)	3.5(3.5, 0 to 9)	3.5(3, 0 to 9)
Numbers of Comorbidities Mean (Median, Range)	2.4(2, 0 to 7)	2.4(2, 0 to 7)	2.1(2, 0 to 6)	2.4(2, 1 to 7)	2.3(2, 0 to 7)	2.5(2, 0 to 7)	2.2(2, 1 to 3)
Place of Care (Current) on admission/baseline, n (%)							
Hospital-based Specialist Palliative Care Teams (Acute Hospital Ward, ICU and ED)	402(72)	370(76.6)	31(41.9)	124(55.6)	278(83)	217(66.6)	165(83.3)
Inpatient Hospice/Palliative Care Ward	146(26.2)	104(21.5)	42(56.8)	96(43)	50(14.9)	102(31.3)	30(15.2)
Care Home including own home and sheltered housing	10(1.8)	9(1.9)	3≥	3≥	7(2.1)	7(2.1)	3≥
Integrated Palliative Outcome Scale - COVID (IPOS-COVID) ^b Mean (Median, Range)							
Breathlessness and Agitation (BreatAg)	3.9 (3, 0 to 12)	4 (4, 0 to 12)	2.7 (2, 0 to 10)	3.2 (3, 0 to 11)	4.4 (4, 0 to 12)	3.5 (3, 0 to 11)	3.6 (3, 0 to 11)
Drowsiness and Delirium (Drow-Del)	4.4 (4, 0 to 12)	4.6 (4, 0 to 12)	3.4 (3, 0 to 8)	4.1 (3, 0 to 12)	4.7 (5, 0 to 11)	4.3 (4, 0 to 12)	4.3 (4, 0 to 12)
Flu-like Symptoms (Flu)	2.4 (2, 0 to 12)	2.4 (2, 0 to 12)	3.1 (3, 0 to 7)	2.9 (3, 0 to 12)	2.1 (2, 0 to 10)	2.8 (2, 0 to 12)	2.9 (3, 0 to 12)
Gastro-Intestinal (GI)	0.2 (0, 0 to 5)	0.2 (0, 0 to 5)	0.2 (0, 0 to 4)	0.3 (0, 0 to 5)	0.1 (0, 0 to 4)	0.2 (0, 0 to 4)	0.2 (0, 0 to 4)
Symptom Burden (Baseline IPOS-COVID19Scores ^c) Mean (Median, Range)							
Breathlessness	1.8(2, 0 to 4)	1.9(2, 0 to 4)	1.3(1, 0 to 4)	1.6(2, 0 to 4)	2(2, 0 to 4)	1.8(2, 0 to 4)	2.1(2, 0 to 4)
Weakness / Lack of energy	2.4(3, 0 to 4)	2.4(3, 0 to 4)	2.1(2, 0 to 4)	2.4(3, 0 to 4)	2.3(3, 0 to 4)	2.4(3, 0 to 4)	2.3(3, 0 to 4)
Drowsiness	1.4(1, 0 to 4)	1.5(1.5, 0 to 4)	0.8(0, 0 to 4)	1.3(1, 0 to 4)	1.6(2, 0 to 4)	1.4(1, 0 to 4)	1.4(1, 0 to 4)
Anxiety	1.1(1, 0 to 4)	1.1(1, 0 to 4)	1.1(1, 0 to 4)	0.9(0, 0 to 4)	1.2(1, 0 to 4)	1(0, 0 to 4)	1.3(1, 0 to 4)

Agitation	1(0, 0 to 4)	1(0, 0 to 4)	0.5(0, 0 to 4)	0.7(0, 0 to 4)	1.1(1, 0 to 4)	0.9(0, 0 to 4)	1.1(1, 0 to 4)
Confusion/Delirium	0.9(0, 0 to 4)	0.9(0, 0 to 4)	0.7(0, 0 to 3)	0.6(0, 0 to 4)	1(0, 0 to 4)	0.8(0, 0 to 4)	0.9(0, 0 to 4)
Pain	0.8(0, 0 to 4)	0.7(0, 0 to 4)	1.1(1, 0 to 3)	1.1(1, 0 to 4)	0.6(0, 0 to 4)	1(1, 0 to 4)	0.5(0, 0 to 3)
Sore or dry mouth/throat	0.7(0, 0 to 4)	0.7(0, 0 to 4)	0.5(0, 0 to 3)	0.7(0, 0 to 4)	0.6(0, 0 to 4)	0.7(0, 0 to 4)	0.6(0, 0 to 4)
Cough	0.6(0, 0 to 4)	0.6(0, 0 to 4)	1.1(1, 0 to 3)	0.8(0, 0 to 4)	0.6(0, 0 to 3)	0.7(0, 0 to 4)	0.6(0, 0 to 3)
Fever	0.5(0, 0 to 4)	0.5(0, 0 to 4)	0.8(0, 0 to 4)	0.6(0, 0 to 4)	0.4(0, 0 to 4)	0.7(0, 0 to 4)	0.3(0, 0 to 3)
Shivering	0.1(0, 0 to 3)	0(0, 0 to 3)	0.1(0, 0 to 1)	0.1(0, 0 to 3)	0(0, 0 to 2)	0.1(0, 0 to 4)	0.1(0, 0 to 2)
Diarrhoea	0.1(0, 0 to 3)	0(0, 0 to 3)	0.2(0, 0 to 3)	0.1(0, 0 to 3)	0.1(0, 0 to 3)	0.1(0, 0 to 4)	0.1(0, 0 to 3)
Nausea	0.2(0, 0 to 3)	0.2(0, 0 to 3)	0.2(0, 0 to 2)	0.2(0, 0 to 3)	0.1(0, 0 to 3)	0.2(0, 0 to 3)	0.1(0, 0 to 3)
Vomiting	0.1(0, 0 to 4)	0.1(0, 0 to 4)	0.1(0, 0 to 2)	0.1(0, 0 to 3)	0(0, 0 to 4)	0.1(0, 0 to 4)	0(0, 0 to 2)
Phase of Illness at Baseline Assessment n (%)							
Stable	17(3)	11(2.2)	5(6.9)	10(4.5)	7(2)	11(3.3)	3≥
Unstable	171(30.3)	142(28.9)	29(40.3)	74(33.2)	97(28.4)	75(22.5)	86(43.2)
Deteriorating	151(26.7)	125(25.4)	26(36.1)	75(33.6)	76(22.2)	105(31.5)	39(19.6)
Dying	226(40)	214(43.5)	12(16.7)	64(28.7)	162(47.4)	142(42.6)	70(35.2)
Baseline AKPS Score, Mean (Median, Range)	24.3 (20, 10 to 90)	22.9 (20, 10 to 90)	33.3 (30, 10 to 60)	29.8 (20, 10 to 70)	20.7 (20, 10 to 90)	25.2 (20, 10 to 90)	25.9 (20, 10 to 90)
Baseline Oxygen Saturation (%) Mean (Median, Range)	90.4(93.48 to 100)	90(92, 48 to 100)	93.4(95, 75 to 100)	91.7(94, 52 to 100)	89.7(92, 48 to 100)	90.5(93, 52 to 100)	89.8(92, 48 to 100)
Proportion of patients with baseline oxygen saturation below 90% n(%)	136(23.8)	128(25.8)	8(10.7)	33(14.5)	103(29.9)	74(22)	59(29.6)
Baseline Oxygen Therapy n(%)							
Room Air	192(33.6)	147(29.6)	45(60)	108(47.6)	84(24.3)	128(38)	48(24.1)
Oxygen via Nasal Prongs	116(20.3)	96(19.4)	19(25.3)	54(23.8)	62(18)	77(22.8)	34(17/1)
Oxygen via Hudson Mask	83(14.5)	81(16.3)	3≥	22(9.7)	61(17.7)	59(17.5)	22(11.1)
Rebreather Mask	113(19.8)	108(21.8)	5(6.7)	25(11)	88(25.5)	54(16)	52(26.1)
BiPAP or CPAP	25(4.4)	24(4.8)	3≥	6(2.6)	19(5.5)	10(3)	14(7)
High Flow Nasal Prongs	40(7)	39(7.9)	3≥	8(3.5)	32(9.3)	6(1.8)	29(14.6)
Ventilated	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
Treatment reported at Baseline, yes n (%)							
Regular Opioids prescribed before referral to palliative care	245(42.9)	202(40.8)	43(57.3)	123(54.2)	122(35.5)	171(50.7)	66(33.2)
PRN Opioids prescribed	335(58.6)	298(60.1)	37(49.3)	133(58.6)	202(58.6)	211(62.6)	110(55.3)
Outcome at the end of the study observation and follow-up period, n (%)							
Died	417(73)	381(77)	36(48)	139(61.2)	278(80.8)	240(71.2)	156(78.4)
Discharged or Still in Care	154(27)	114(23)	39(52)	88(38.8)	66(19.2)	97(28.8)	43(21.6)
Survival Time (Hours) Median (Mean, Range)	45.9(98.6, 0.5 to 1825.9)	45.4(86.9, 0.5 to 1825.9)	73.4(222.2, 8.3 to 1536)	51.4 (133.4, 1.7 to 1825.9)	41.8(81.3, 160.7 to 1536)	45.6(112.9, 1.3 to 1825.9)	47.7(83.2, 0.5 to 900.4)
Patients admitted at waves of COVID, n (%)							
Wave 1 (February - August 2020)	316(61.4)	269(60.9)	47(64.4)	148(65.5)	189(54.9)	-	-
Wave 2 (September 2020 - February 2021)	199(38.6)	173(39.1)	26(35.6)	78(34.4)	155(45.1)	-	-
Hours between first presentation of COVID symptoms and referral to palliative care, Median (Mean, Range)	144(146.9, - 8352 to 8352)	192(250.9, 0 to 8352)	-192(-481, - 24 to - 8352)	72(33.1, - 8352 to 1512)	192(220.6, -8112 to 8352)	144(179.9, - 1008 to 8352)	168(94.8, - 8352 to 1032)
Guideline Availability^d at admission, yes, n (%)	503(88.2)	451(91.3)	51(68)	192(85)	311(90.4)	269(80.1)	199(100)
Deaths, n (%)	417(73)	381 (77)	36(48)	139(61.2)	278(80.8)	240(71.2)	156(78.4)

Place of Death, n (%)							
Hospital-based Specialist Palliative Care Teams (Acute Hospital Ward, ICU and ED)	316(76.9)	300(80)	16(44.4)	86(62.8)	230(83.9)	164(70.1)	136(87.2)
Inpatient Hospice/Palliative Care Ward	86(20.9)	67(17.9)	19(52.8)	47(34.3)	39(14.2)	63(26.9)	18(11.5)
Care Home including own home and sheltered housing	9(2.2)	8(2.1)	3≥	4(2.9)	5(1.8)	7(3)	3≥
Number of Participants with Assessment Data ^c (%)							
Baseline	567(99.1)	493(99.4)	73	223(98.2)	344(99.7)	334(99.1)	199(100)
Time 1 (12-24 hours following baseline assessment)	444(77.6)	376(75.8)	67	191(84.1)	253(73.3)	264(78.3)	152(76.4)
Time 2 (12-24 hours later from T1)	308(53.8)	251(50.6)	56	147(64.8)	161(46.7)	186(55.2)	101(50.8)
Final Assessment (following discharge, death, or completion of T2)	571(99.8)	495(99.8)	75	227(100)	344(99.7)	337(100)	199(100)
^a 1 case is missing most of the demographic and clinical information, most present findings from n=571 Survival Time is calculated from the date and time of the baseline assessment to time and date of death. ^b IPOS-COVID 19 subscales - higher scores indicate worsening impact on the patient's wellbeing ^c These figures are based on the compulsory field that was asked to be entered on the date of assessments and not any other variables, except for the final assessment, compulsory first question on whether the patient has died, transferred/discharged or still in care was used. All the participants should have baseline and final assessments. ^d Referral to palliative care before or after online publication of 'Managing the supportive care needs of those affected by COVID-19' in April 2020 (https://erj.ersjournals.com/content/early/2020/04/07/13993003.00815-2020) ^f Possible scores range from 0-4, higher scores indicating higher levels of burden							

b)

Characteristics/Variable	Place of Care		
	Hospital (Acute, Community, ICU, ED) n=402	Hospice (Inpatient Hospice/Palliative Ward) n=146	Home (Care home, own home and sheltered housing) n=4
Age, Mean (Median, Range)	78.5(80, 37 to 100)	75(76, 32 to 102)	70(NA)
Sex, Women n (%)	185(46)	70(47.9)	NA
Ethnicity, n (%)			
White (British and Other)	295(74.9)	121(92.2)	NA
Other	99(25.1)	8(1.6)	NA
Index of Multiple Deprivation Deciles, Mean (Median, Range)	4.9(4, 1 to 10)	5.2(5, 1 to 10)	3.3(4, 1 to 5)
Number of symptoms recorded at Baseline Mean (Median, Range)	4.8(5, 0 to 11)	121(5, 0 to 12)	4.3(5, 2 to 6)
Numbers of Moderate to Overwhelming Symptoms at Baseline Mean (Median, Range)	3.4(3, 0 to 9)	3.7(4, 0 to 9)	1(1, 1 to 1)
Numbers of Comorbidities Mean (Median, Range)	2.3(2, 0 to 7)	2.6(2, 0 to 7)	1.3(1, 1 to 2)
Integrated Palliative Outcome Scale - COVID (IPOS-COVID) ^b Mean (Median, Range)			
Breathlessness and Agitation (BreatAg)	4.3(4, 0 to 12)	2.8(2, 0 to 11)	3(2, 1 to 6)
Drowsiness and Delirium (Drow-Del)	4.2(4, 0 to 11)	4.9(4, 0 to 12)	3.5(3.5, 3 to 4)
Flu-like Symptoms (Flu)	2.1(2, 0 to 12)	3.5(4, 0 to 11)	1(1, 0 to 2)

Gastro-Intestinal (GI)	0.2(0, 0 to 5)	0.2(0, 0 to 3)	0.8(0.5, 0 to 2)
Symptom Burden (Baseline IPOS-COVID19Scores¹) Mean (Median, Range)			
Breathlessness	2(2, 0 to 4)	1.4(1, 0 to 4)	1.5(1, 0 to 4)
Weakness / Lack of energy	2.3(3, 0 to 4)	2.5(3, 0 to 4)	2.5(2.5, 2 to 3)
Drowsiness	1.4(1, 0 to 4)	1.5(1, 0 to 4)	0.3(0, 0 to 1)
Anxiety	1.2(1, 0 to 4)	0.8(0, 0 to 4)	0.8(0.5, 0 to 2)
Agitation	1.1(0, 0 to 4)	0.8(0, 0 to 4)	0.3(0, 0 to 1)
Confusion/Delirium	0.8(0, 0 to 4)	1(1, 0 to 4)	0.7(1, 0 to 1)
Pain	0.6(0, 0 to 4)	1.3(1, 0 to 4)	0.3(0, 0 to 1)
Sore or dry mouth/throat	0.6(0, 0 to 4)	1(1, 0 to 4)	0(0, 0 to 0)
Cough	0.5(0, 0 to 3)	0.9(0, 0 to 4)	0.7(1, 0 to 1)
Fever	0.5(0, 0 to 4)	0.5(0, 0 to 4)	0(0, 0 to 0)
Shivering	0.1(0, 0 to 3)	0(0, 0 to 1)	0(0, 0 to 0)
Diarrhoea	0.1(0, 0 to 3)	0.2(0, 0 to 3)	0(0, 0 to 0)
Nausea	0.1(0, 0 to 3)	0.2(0, 0 to 3)	0.8(0.5, 0 to 2)
Vomiting	0.1(0, 0 to 4)	0(0, 0 to 2)	0(0, 0 to 0)
Phase of Illness at Baseline Assessment n (%)			
Stable	6(1.5)	9(6.4)	NA
Unstable	137(34.2)	32(22.7)	NA
Deteriorating	76(19)	63(44.7)	NA
Dying	182(45.4)	37(26.2)	NA
Baseline AKPS Score, Mean (Median, Range)	22.2(20, 10 to 90)	29.6(20, 10 to 60)	45(NA)
Baseline Oxygen Saturation (%) Mean (Median, Range)	90(92, 48 to 100)	91.9(94, 52 to 99)	-
Proportion of patients with baseline oxygen saturation below 90% n(%)	115(28.6)	16(11)	0
Baseline Oxygen Therapy n(%)			
Room Air	100(24.9)	67(45.9)	4(100)
Oxygen via Nasal Prongs	75(18.7)	38(26)	0(0)
Oxygen via Hudson Mask	62(15.4)	17(11.6)	0(0)
Rebreather Mask	106(26.4)	4(2.7)	(0)
BiPAP or CPAP	24(6)	3≥	(0)
High Flow Nasal Prongs	39(9.7)	3≥	(0)
Ventilated	0(0)	0(0)	(0)
Treatment reported at Baseline, yes n (%)			
Regular Opioids prescribed <i>before</i> referral to palliative care	142(35.4)	92(63)	NA
PRN Opioids prescribed	238(59.2)	80(54.8)	NA
Outcome at the end of the study observation and follow-up period, n (%)			
Died	329(81.8)	72(49.3)	NA
Discharged or Still in Care	73(18.2)	74(50.7)	NA
Survival Time (Hours) Median (Mean, Range)	94.6(44.8, 0.5 to 1825.9)	115.4(55.3, 2.1 to 747.7)	43.9(NA)
Patients admitted at waves of COVID, n (%)			
Wave 1 (February - August 2020)	217(54.1)	102(69.9)	NA
Wave 2 (September 2020 - February 2021)	184(45.9)	44(30.1)	NA
Hours between first presentation of COVID symptoms and referral to palliative care, Median (Mean, Range)	179(192, -8352 to 8352)	36.1(0, -1008 to 1248)	228(NA)
Guideline Availability^d at admission, yes, n (%)	362(90.3)	120(82.2)	NA
Deaths, n (%)	329(81.8)	72(49.3)	NA
Place of Death, n (%)			

Hospital-based Specialist Palliative Care Teams (Acute Hospital Ward, ICU and ED)	308(95.4)	0(0)	NA
Inpatient Hospice/Palliative Care Ward	11(3.4)	72(100)	-
Care Home including own home and sheltered housing	4(1.2)	0(0)	NA
Number of Participants with Assessment Data^c (%)			
Baseline	401(99.8)	144(98.6)	NA
Time 1 (12-24 hours following baseline assessment)	297(73.9)	130(89)	NA
Time 2 (12-24 hours later from T1)	186(46.3)	112(76.7)	NA
Final Assessment (following discharge, death, or completion of T2)	402(100)	146(100)	4(100)
NA: Not appropriate to present for disclosure control consideration due to small sample size.			

Table S 3 the litres of oxygen received in the last 12 hours

Litres of Oxygen^a	Number of Patients	%
0.3	3	0.9
0.4	3≥	-
0.5	≥3	-
0.6	3	0.9
1	15	4.3
2	43	12.3
3	16	4.6
4	38	10.9
5	13	3.7
6	6	1.7
8	10	2.9
10	19	5.4
12	3≥	0.6
14	3≥	0.3
15	147	42
16	3≥	-
19	3	0.9
40	3≥	-
60	22	6.3
70	3≥	-
89	3≥	-

^aMode of delivery varied, and for 2 patients the range of litres of oxygen was noted and the lower value is noted here (data from 350 participants)

Table S 4 Number and proportion (%) of recruited participants according to region and country (n=572), darker colour indicating higher number of participants

Country	Regions	Total n (%)	Wave 1 (n)	Wave 2 (n)	Wave Unknown
England	North East (England)	20 (3.5)	20	0	-
	North West (England)	10 (1.7)	10	0	-
	Yorkshire and The Humber	90 (15.7)	66	15	9
	East Midlands (England)	82 (14.3)	67	11	4
	West Midlands (England)	27 (4.7)	11	7	9
	London	243 (42.5)	75	137	31
	South East (England)	39 (6.8)	20	18	1
	South West (England)	18 (3.1)	6	11	1
Wales	West Wales	43 (7.5)	41	-	2

Figure S 3 Date of baseline assessment for patients in the CovPall Symptom study, and the UK pandemic wave periods.

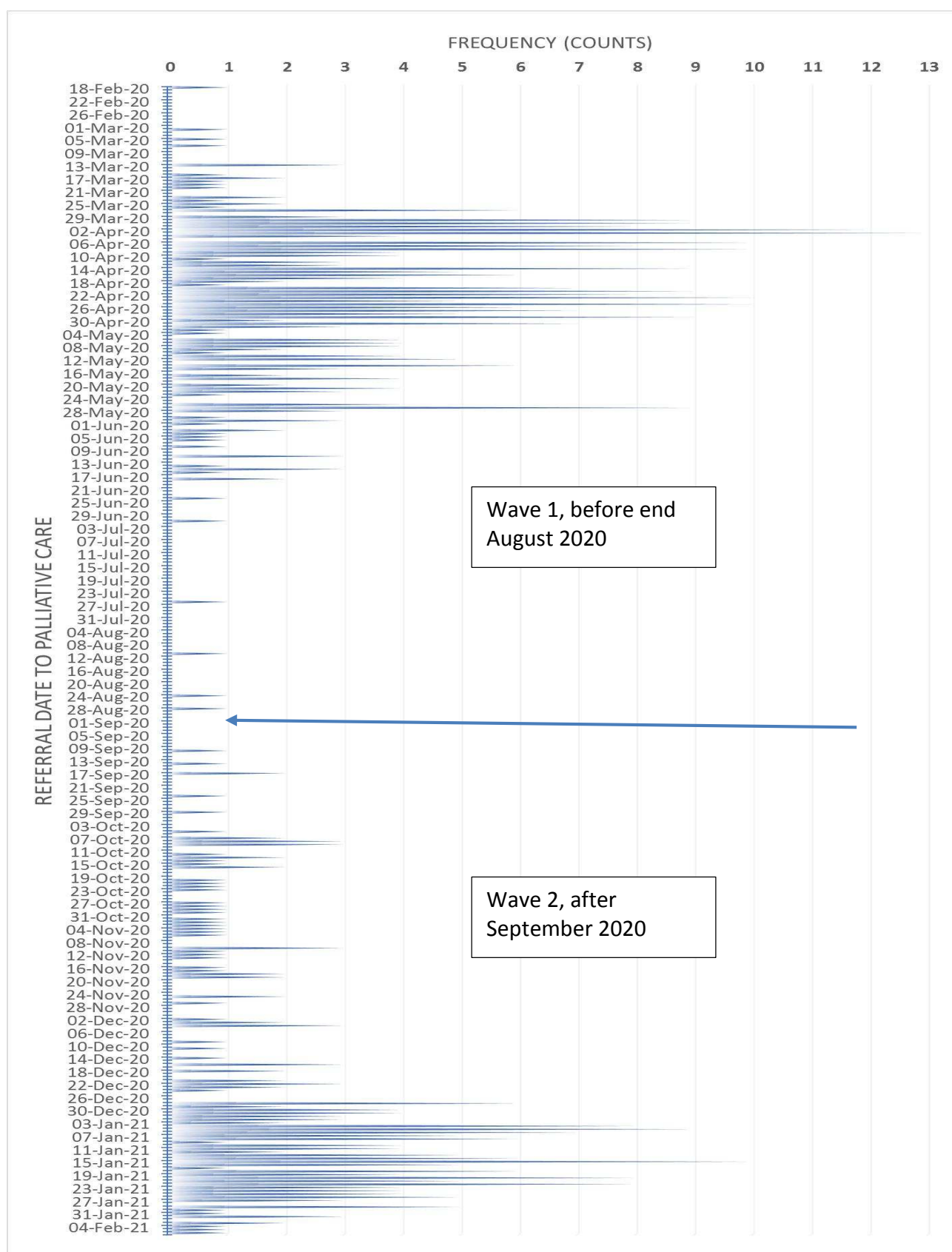


Figure S 4 Australian Modified Karnofsky Performance Scale (AKPS) Scores at baseline for patients according to baseline group

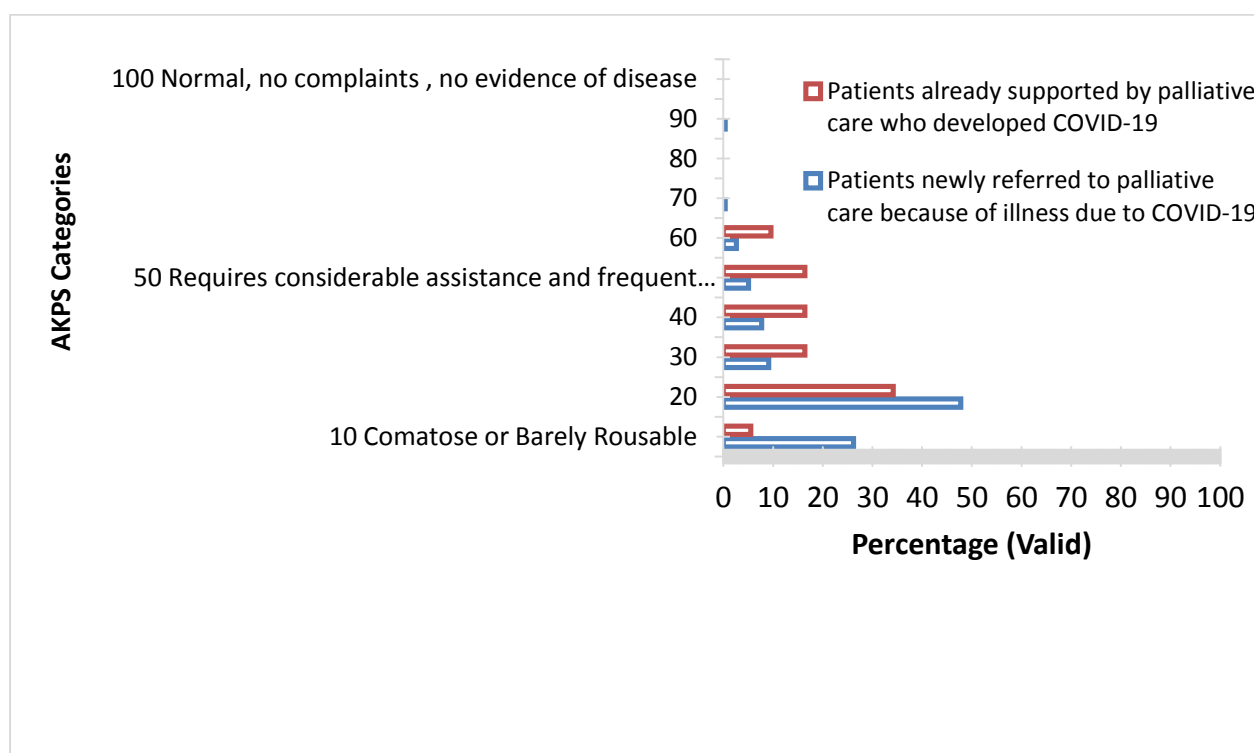


Table S 5 Prevalence symptoms any severity from mild up as a percentage of all cases (%) at baseline and final assessments

IPOS -COVID	Baseline (T0) Assessment		Time 1 (T1) Assessment		Time 2 (T2) Assessment		Final (TF) Assessment	
	Mild to overwhelming symptoms		Mild to overwhelming symptoms		Mild to overwhelming symptoms		Mild to overwhelming symptoms	
Symptoms	%	n/N	%	n/N	%	n/N	%	n/N
Breathlessness	80.6	437/542	69.7	292/419	59.9	175/292	64.5	316/490
Weakness / Lack of energy	87.2	441/506	85.1	331/389	82.9	223/269	77.8	332/427
Drowsiness	63.5	332/523	63.8	257/403	60	168/280	65.6	297/453
Anxiety	54.1	255/471	43.6	161/369	41	110/268	34.1	142/416
Agitation	47.2	239/506	42.8	169/395	34.2	93/272	34.5	164/476
Confusion/Delirium	43.4	211/486	39.9	153/383	36.7	98/267	29.9	128/428
Pain	43.1	227/527	41.9	171/408	35.8	103/288	24.6	118/479
Sore or dry mouth/throat	40.2	197/490	40.2	157/391	31.6	87/275	30.8	137/445
Cough	37.1	191/515	27.1	109/402	24.7	71/288	14	65/464
Fever	25.7	136/529	15.2	59/387	9.8	27/276	11.6	52/448

Nausea	9.3	46/492	7.8	30/383	6.3	17/269	2.8	12/424
Diarrhoea	5.4	28/518	4.8	19/395	4.3	12/278	4.2	20/471
Shivering	3.6	18/560	1.8	7/390	2.2	6/273	1.8	8/450
Vomiting	3.6	19/530	2	8/409	3.2	9/285	1.2	6/482

Prevalence expressed as percentage (%) of total cases with valid data

Denominators exclude cases whose symptoms could not be assessed

Table S 6 Sensitivity analysis: mean baseline and final scores for patients with complete scores at both assessments, with sample size shown for each symptom of cases seen less than 2, 2 to 4, and more than 4 days and more before their death

IPOS -COVID	Referral to Palliative Care before Death (Days)								
	Less than 2 days (n=141)			2 or more, less than 4 days (n=133)			4 Days and more (n=139)		
	Baseline Mean Scores	Final Mean Scores	n	Baseline Mean Scores	Final Mean Scores	n	Baseline Mean Scores	Final Mean Scores	n
Breathlessness	2.5	1.7	109	1.9	1.2	116	1.6	1.2	115
Weakness / Lack of energy	2.6	2.6	90	2.4	2.4	91	2.5	2.6	94
Drowsiness	1.9	2.3	97	1.7	2.2	100	1.4	2.3	100
Anxiety	1.4	0.7	81	0.9	0.4	80	1.2	0.6	92
Agitation	1.3	0.7	107	1.1	0.7	111	1.0	0.7	111
Confusion/Delirium	0.8	0.5	83	1.0	0.4	91	0.9	0.7	99
Pain	0.6	0.3	104	0.6	0.2	105	0.9	0.4	117
Sore or dry mouth/throat	0.6	0.5	83	0.8	0.6	95	0.5	0.3	103
Cough	0.7	0.3	103	0.6	0.2	104	0.6	0.3	113
Fever	0.5	0.4	100	0.4	0.2	103	0.6	0.2	103
Nausea	0.0	0.0	87	0.1	0.0	83	0.3	0.0	96
Diarrhoea	0.0	0.1	107	0.1	0.1	106	0.1	0.1	108
Shivering	0.1	0.0	93	0.0	0.0	103	0.1	0.0	105
Vomiting	0.0	0.0	110	0.1	0.0	111	0.1	0.0	113

Table S 7 Related-Samples Wilcoxon Signed Rank Test Summary for the overall sample

Baseline and Final Scores Compared	n	Standardized Test Statistic	p-value (2 sided)
Breathlessness	475	-10.3	<0.0001
Weakness / Lack of energy	402	-0.4	0.676
Drowsiness	426	5.6	<0.001
Anxiety	377	-7	<0.001
Agitation	460	-5.4	<0.001

Confusion/Delirium	399	-5.6	<0.001
Pain	459	-7.7	<0.001
Sore or dry mouth/throat	404	-5.3	<0.001
Cough	446	-8.5	<0.0001
Fever	433	-5.4	<0.001
Nausea	390	-4.4	<0.001
Diarrhoea	451	-1.3	0.2
Shivering	429	-2.3	0.021
Vomiting	465	-3	0.002
IPOS-COVID			
BreathAg (Breathlessness and Agitation)	342	-8.4	<0.0001
GI (Gastro-intestinal Issues)	384	-3.9	<0.001
Drow-Del (Drowsiness and Delirium)	339	1	0.31
Flu (Flu-like symptoms)	325	-9.4	<0.0001
Note: Significant differences adjusting for Hochberg's correction for multiple testing where $p \leq 0.001$ is determined as significant			

Table S 8 Sensitivity Analysis: Paired Samples t-test of baseline and final IPOS-COVID subscales scores of the overall sample

IPOS-COVID	n	Mean Baseline	Mean Final	Mean Difference	95%CI of the Difference		t	df	p-value (2-tailed)	Cohen's d (point estimate for effect size)
					Lower	Upper				
BreathAg (Breathlessness and Agitation)	342	3.7	2.3	1.4	1.1	1.7	9	341	<0.001	0.5
GI (Gastro-intestinal Issues)	384	0.2	0.1	0.2	0.1	0.2	4	383	<0.001	0.2
Drow-Del (Drowsiness and Delirium)	339	4.7	4.7	-0.1	-0.4	0.3	-0.3	338	0.7	0
Flu (Flu-like symptoms)	325	2.4	1.1	1.3	1	1.5	10.7	324	<0.001	0.6

Table S 9 Related-Samples Wilcoxon Signed Rank Test Summary according to their days in palliative care before they died

Baseline and Final Scores Compared for the items ^a	Referral to Palliative Care before Death (Days)								
	Less than 2 days			2 or more, less than 4 days			4 days and more		
	n	Test Statistic	p-value (2 sided)	n	Test Statistic	p-value (2 sided)	n	Test Statistic	p-value (2 sided)
Breathlessness	109	270	<0.0001	116	564.5	<0.0001	115	764	<0.0001
Weakness / Lack of energy	90	312	0.799	91	647	0.878	94	1129.5	0.396
Drowsiness	97	1007	0.001	100	1409	0.013	100	2170	<0.001
Anxiety	81	108.5	<0.001	80	78.5	<0.001	92	403.5	<0.001
Agitation	107	362	<0.001	111	526	0.002	111	912.5	0.049

Confusion/Delirium	83	162.5	0.031	91	119	<0.001	99	491.5	0.028
Pain	104	101	<0.001	105	80.5	0.001	117	200	<0.001
Sore or dry mouth/throat	83	40	0.012	95	188.5	0.003	103	98.5	0.004
Cough	103	21.5	<0.0001	104	0	<0.0001	113	128	<0.0001
Fever	100	37.5	0.033	103	22	0.001	103	45	<0.001
Nausea	87	0	0.18	83	0	0.066	96	3.5	0.001
Diarrhoea	107	3	0.18	106	10	0.13	108	18	0.305
Shivering	93	5	0.234	103	1	0.655	105	0	0.059
Vomiting	110	0	0.18	111	0	0.038	113	0	0.016
Note: Significant differences adjusting for Hochberg's correction for multiple testing where $p \leq 0.001$ is determined as significant									

Figure S 5 Kaplan-Meier Survival Curve of patients referred to palliative care with no to slight levels compared to moderate to overwhelming levels of baseline breathlessness (n=483)

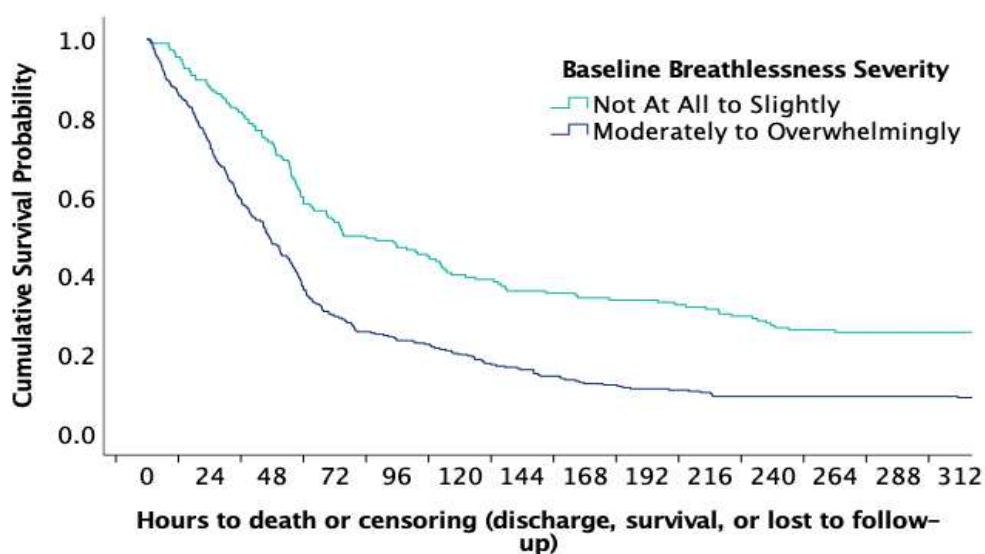


Table S 10 Sensitivity Analysis - Cox Proportional Hazards Model (n=268^a) of multiple risk factors on the survival function (short survival used to indicate rapid deterioration) excluding cases from the largest site

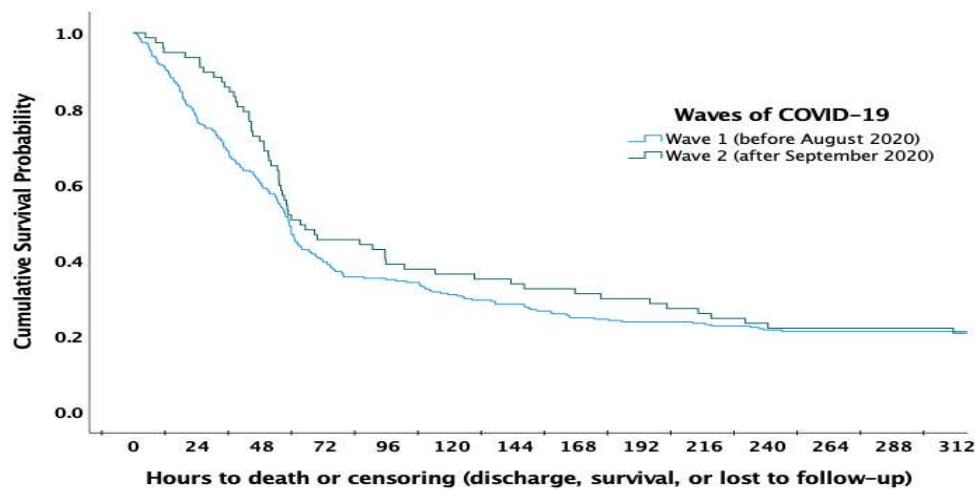
Independent Variables	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper

<i>Numbers of moderate to overwhelming symptoms the patient presented with at baseline</i>	-0.03	0.05	0.30	1	0.582	0.97	0.89	1.07
<i>Do the patients have cancer? (Y/N)</i>	-0.20	0.16	1.62	1	0.204	0.82	0.60	1.12
Gender	-0.29	0.15	3.51	1	0.061	0.75	0.56	1.01
Age	0.01	0.01	1.48	1	0.224	1.01	1.00	1.02
Number of Comorbidities of COVID patients	0.12	0.05	5.56	1	0.018	1.12	1.02	1.24
Baseline Breathlessness (Not at all) Reference			28.42	4	<0.001			
Baseline Breathlessness (Slightly)	-0.09	0.28	0.11	1	0.744	0.91	0.53	1.58
Baseline Breathlessness (Moderately)	0.33	0.24	2.00	1	0.158	1.39	0.88	2.21
Baseline Breathlessness (Severely)	0.70	0.25	8.04	1	0.005	2.02	1.24	3.27
Baseline Breathlessness (Overwhelming)	1.37	0.32	18.70	1	<0.001	3.93	2.11	7.31
Baseline Agitation (Not at all) Reference			13.67	4	0.008			
Baseline Agitation (Slightly)	0.59	0.21	8.00	1	0.005	1.80	1.20	2.71
Baseline Agitation (Moderately)	0.51	0.22	5.63	1	0.018	1.67	1.09	2.56
Baseline Agitation (Severely)	0.52	0.26	4.15	1	0.042	1.68	1.02	2.78
Baseline Agitation Overwhelming)	1.09	0.45	5.72	1	0.017	2.96	1.22	7.22
Waves of COVID (Wave1: January - August 2020, Wave 2: September 2020 - January 2021)	-0.49	0.20	6.37	1	0.012	0.61	0.42	0.90

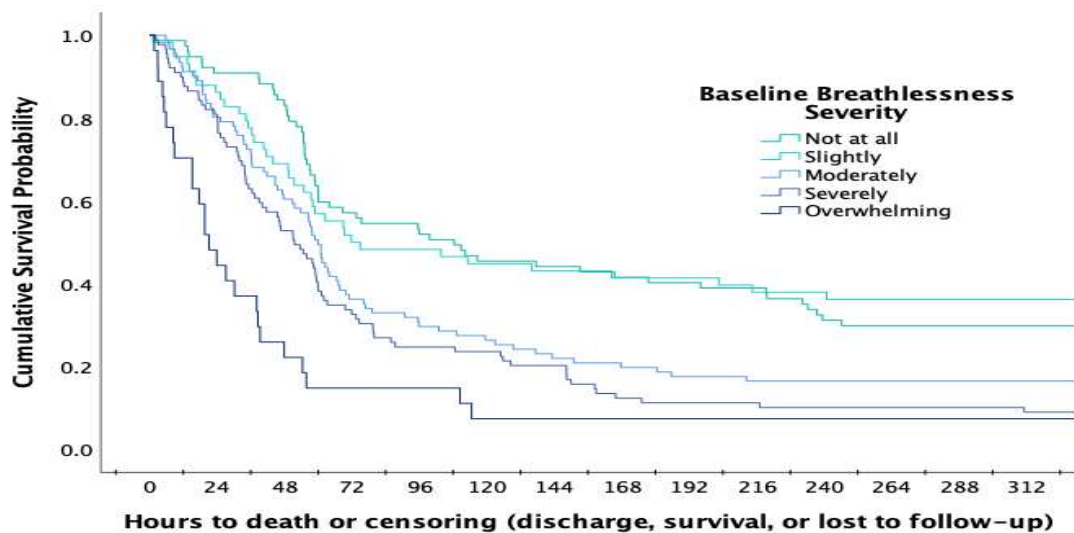
^aData for the independent variables in the model are only complete for smaller number of cases and also the cases from the largest site has not been included in the analysis, therefore the sample size is smaller than the original sample and analysis presented in Table 4 of the main paper

Figure S 6 Sensitivity Analysis – Kaplan-Meier Survival Curve of patients referred to palliative care excluding the larger site with (a) different waves of the pandemic (n=328) , (b) different levels of baseline breathlessness (n=342) and (c) different levels of agitation (n=298)

a)



b)



c)

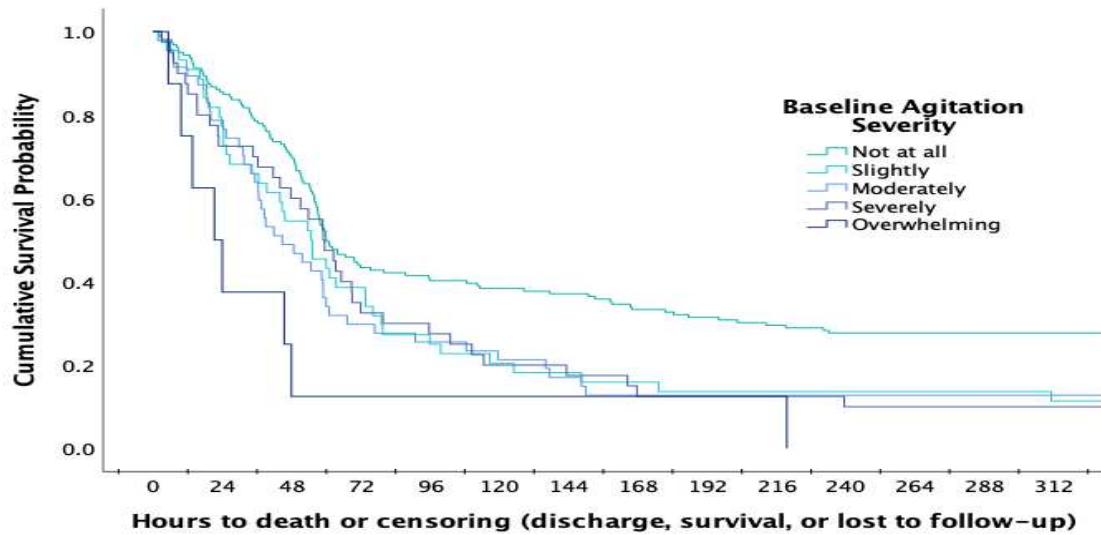


Figure S 7 Sensitivity Analysis - Kaplan-Meier Survival Curve of patients referred to palliative care with no to slight levels compared to moderate to overwhelming levels of baseline breathlessness (n=342)

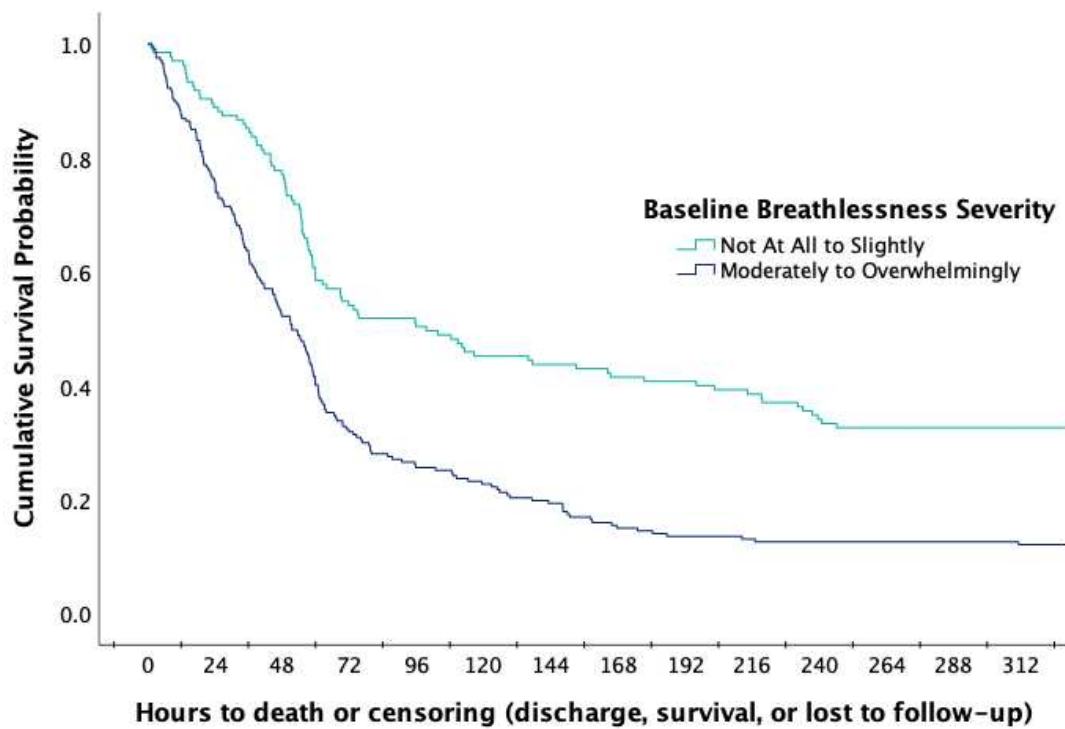


Table S 11 Sensitivity Analysis - Related-Samples Wilcoxon Signed Rank Test Summary for the overall sample excluding the cases from the largest site

Baseline and Final Scores Compared	n	Standardized Test Statistic	p-value (2 sided)
Breathlessness	342	-8.5	<0.0001
Weakness / Lack of energy	287	1.6	0.103
Drowsiness	298	6.9	<0.001
Anxiety	281	-5.1	<0.001

Agitation	308	-3.9	<0.001
Confusion/Delirium	296	-5	<0.001
Pain	325	-7.1	<0.001
Sore or dry mouth/throat	282	-4.5	<0.001
Cough	301	-7.3	<0.001
Fever	291	-4.7	<0.001
Nausea	278	-4.4	<0.001
Diarrhoea	312	-1.5	0.135
Shivering	293	-2.3	0.022
Vomiting	330	-2.9	0.003
IPOS-COVID			
BreathAg (Breathlessness and Agitation)	251	-6.7	<0.001
GI (Gastro-intestinal Issues)	272	-3.8	<0.001
Drow-Del (Drowsiness and Delirium)	249	2.7	0.006
Flu (Flu-like symptoms)	219	-8	<0.001
Note: Significant differences adjusting for Hochberg's correction for multiple testing where $p \leq 0.001$ is determined as significant			

Table S 12 Sensitivity Analysis - Paired Samples t-test of baseline and final IPOS-COVID subscales scores of the sample excluding cases from the biggest site

IPOS-COVID	n	Mean Baseline	Mean Final	Mean Difference	95%CI of the Difference		t	df	p-value (2-tailed)	Cohen 's d (point estimate for effect size)
					Lower	Upper				
BreathAg (Breathlessness and Agitation)	251	3.3	2.1	1.2	0.9	1.6	7.2	250	<0.001	0.5
GI (Gastro-intestinal Issues)	272	0.3	0.1	0.2	0.1	0.3	4	271	<0.001	0.2
Drow-Del (Drowsiness and Delirium)	249	4.7	5.1	-0.5	-0.8	-0.1	-2.5	248	0.013	-0.2
Flu (Flu-like symptoms)	219	2.7	1.3	1.4	1.1	1.7	9.2	218	<0.001	0.6