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Symptom burden and clinical profile of COVID-19 deaths: a rapid systematic review and evidence summary

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ABSTRACT

The spread of pandemic COVID-19 has created unprecedented need for information. The pandemic is the cause of significant mortality and with this the need for rapidly disseminated information for palliative care professionals regarding the prevalence of symptoms, their intensity, their resistance or susceptibility to symptom control and the mode of death for patients.

Methods We undertook a systematic review of published evidence for symptoms in patients with COVID-19 (with a specific emphasis on symptoms at end of life) and on modes of death. Inclusion: prospective or retrospective studies detailing symptom presence and/or cause or mode of death from COVID-19.

Results 12 papers met the inclusion criteria and gave details of symptom burden: four of these specifically in the dying and two detailed the cause or mode of death. Cough, breathlessness, fatigue and myalgia are significant symptoms in people hospitalised with COVID-19. Dyspnoea is the most significant symptom in the dying. The mode of death was described in two papers and is predominantly through respiratory or heart failure.

Conclusions There remains a dearth of information regarding symptom burden and mode of death to inform decisions regarding end-of-life care in patients dying with COVID-19. Rapid data gathering on the mode of death and the profile of symptoms in the dying and their prevalence and severity in areas where COVID-19 is prevalent will provide important intelligence for clinicians. This should be done urgently, within ethical norms and the practicalities of a public health, clinical and logistical emergency.

INTRODUCTION

Since first reported in December 2019 in Wuhan, China, coronavirus disease

2019 (COVID-19) has spread rapidly, with over 2 million confirmed cases globally. Originally, it was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) due to phylogenetic and clinical similarities to the severe acute respiratory syndrome coronavirus. The pathogen has now been identified as highly contagious novel enveloped RNA betacoronavirus. Most experience mild symptoms, yet 6% of cases will be critically ill.¹ Mortality rates vary regionally, but the WHO estimates a global mortality of about 3% of confirmed cases.²

The COVID-19 pandemic has created unprecedented need for information. It is the cause of significant mortality, and there is a need for rapidly disseminated information about symptom prevalence and intensity, resistance or susceptibility to symptom control and mode of death. We undertook a symptomatic literature review to inform palliative and end-of-life care.

METHODOLOGY

A rapid literature review was completed over a 3-month period in 2020. Rapid reviews streamline systematic review methods to synthesise evidence in a short timeframe, particularly in understudied topics. As with systematic reviews, a rapid review follows a structured approach to search and evaluate the literature, but the review steps may vary in comprehensiveness due to the timeframe.³ Our approach was comprehensive and only differed from a systematic review in simplified data presentation and elimination of marginal or grey literature.^{4 5} Symptom prevalence was rounded in data extraction and presentation.

Literature search

Relevant publications in English were located through a literature search from 1 January to 23 March 2020 and subsequent weekly autosearches in PubMed (to 21 April 2020). To address symptom burden and clinical profile in those dying from COVID-19, a combination of database-specific subject headings and keywords was used in the search. We used the following search terms: [COVID* [OR] CORONAVIRUS* [OR] SARS-CoV2] AND [SYMPTOM*]. This covered the symptom burden associated from COVID-19 and care of the dying. No date limits were applied. Specific study types (case reports, case-control studies, cohort studies, clinical trials and systematic reviews) were incorporated into the searches of Embase, Ovid MEDLINE, Journals@Ovid, NHS Scotland Journals@Ovid and the Cochrane Library. A second search of the same databases adopted wide search criteria to capture symptom prevalence and management data. This second search was to capture data on cause and mode of death and used the search terms: [COVID* [OR] CORONAVIRUS* [OR] SARS-CoV2] AND [DEATH* [OR] DYING* [OR] PALLIATIVE [OR] HOSPICE [OR] END OF LIFE].

In addition, a hand search of original and review articles was conducted as an additional measure to ensure quality and comprehensiveness.

Study selection

Two independent assessors (PWK and SIRN) screened results by review of titles and abstract and applied inclusion/exclusion criteria. After that, weekly auto-searches continued for a further 4 weeks. A further paper was identified as an article in press. Prospective or retrospective cohort studies were included of adult patients with COVID-19, SARS-CoV-2 or coronavirus. Study outcomes: symptoms on all patients (survivors or those dying), mode of death and symptoms of patients who died. We included only studies published in English. Paediatric studies were excluded.

Table 2 Symptoms in the dying

| | ISS (Italy) ⁷ n=6801 | Deng et al ⁸ n=109 | Yang et al ⁹ n=20 | Lovell et al ¹⁰ n=101 |
|--------------------------|------------------------------------|----------------------------------|---------------------------------|-------------------------------------|
| Agitation | No data | No data | No data | 43% |
| Cough | 40% | 43% | 75% | 4% |
| Delirium | No data | No data | No data | 24% |
| Diarrhoea | 6% | 17% | No data | 3% |
| Dyspnoea | 71% | 71% | 60% | 67% |
| Expectoration/secretions | No data | 32% | No data | 11% |
| Fatigue | No data | 20%* | No data | 9% |
| Haemoptysis | 1% | 5% | No data | No data |
| Headache | No data | 6% | 5% | No data |
| Pain | No data | No data | 10%† | 23% |
| Palpitations | No data | 10% | No data | No data |
| Vomiting | No data | No data | 5% | No data |

*Listed as 'malaise' in Yang et al.

†Arthralgia and chest pain.

RESULTS

The search found a total of 118 papers and reports of which 12 met the inclusion criteria: 10 had data on overall symptoms, 4 had discrete symptom data for those who died and 2 had data about the cause or mode of death. The paucity of studies, all produced for rapid publication, most within 2 months of data collection and the limited scope of the data meant meta-analysis was impossible. Data were heterogeneous in collection and mostly at presentation but gave some information about the dying. One paper with useful data on COVID-19 symptoms disappeared from the original publication site, withdrawn by the authors.⁶

The data are presented in tables 1–4 below.

Four papers^{7–10} give data about symptoms discretely as in non-surviving patients, though in three of these it is unclear whether these are presenting symptoms or in the dying^{4 10 11} (see table 2). The symptoms are ordered in order of their prevalence. No data were given in the papers about chronicity or intensity of

Table 1 COVID19 symptoms in decedents and survivors

| | ISS (Italy) ⁷ n=6801 | Guan et al ¹¹ n=1099 | Deng et al ⁸ n=225 | Zhou et al ¹⁴ n=191 | Wang et al ¹⁵ n=138 | Liu et al ¹⁶ n=137 | Xu et al ¹⁷ n=62 | Yang et al ⁹ n=52 | Huang et al ¹⁸ n=41 | Chang et al ¹⁹ n=13 |
|-------------------------|------------------------------------|------------------------------------|----------------------------------|-----------------------------------|-----------------------------------|----------------------------------|--------------------------------|---------------------------------|-----------------------------------|-----------------------------------|
| Breathlessness/dyspnoea | 71% | 18% | 45% | No data | 31% | 19% | No data | 64% | 55% | No data |
| Cough | 40% | 68% | 38% | 79% | 59% | 48% | 81% | 77% | 76% | 46% |
| Diarrhoea | 6% | 4% | 15% | 5% | 10% | 8% | 8% | No data | 3% | 8% |
| Expectoration | No data | 34% | 22% | 23% | 27% | 4% | 56% | No data | 38% | No data |
| Fatigue | No data | 38% | No data | 23% | 70% | 32% | 52%* | 20%† | 44%* | No data |
| Haemoptysis | 1% | 1% | 3% | No data | No data | 5% | 3% | No data | 8% | No data |
| Myalgia | No data | 15% | 25% | 15% | 35% | 32% | 52%* | 12% | 44% | 23% |
| Nausea/vomiting | No data | 5% | No data | 4% | 14%‡ | No data | No data | 4% | No data | No data |
| Palpitations | No data | No data | 11% | No data | No data | 7% | No data | No data | No data | No data |
| Upper airway congestion | No data | 5% | No data | No data | No data | No data | No data | 6% | No data | 62% |

*Huang et al, Liu et al and Xu et al list myalgia or fatigue.

†Listed as 'malaise' in Yang et al.

‡Wang et al list nausea and vomiting separately.

Table 3 Modes of death

| Modes of death | n=109 | % |
|----------------------------------------|-------|----|
| Acute respiratory distress syndrome | 98 | 90 |
| Acute cardiac injury | 65 | 60 |
| Acute kidney injury | 20 | 18 |
| Shock | 13 | 12 |
| Disseminated intravascular coagulation | 7 | 6 |

Deng *et al.*⁸

symptoms. Dyspnoea, cough and fatigue feature most prominently as common symptoms. Other symptoms (e.g., myalgia or headache) appear to be presenting features given their consistency across all symptom reporting survivors and deaths.

The prevalence of cough and dyspnoea in the dying is evident from the data above (more from the palliative focus of the Italian data and the size of the sample). Symptom classification more familiar to palliative physicians is found in the most recent retrospective study by Lovell *et al.*¹⁰

Mode of death

Only two papers give useful data about the mode of death.^{8,12} One study lists several complications in those who died, which perhaps contributed to or were the mode of death⁸ (see table 3). The second gives data on the cause of death¹² (see table 4).

DISCUSSION

The COVID-19 pandemic has changed how society functions, setting challenges and changes for health services rarely seen outside war time. The prioritisation of emergency care, acute medicine and critical care/intensive care services has resulted in staff of all professions downing the usual tools of their trade to contribute wherever their time is best needed. Many have required additional training and ongoing supervision in new environments. Palliative care is one specialty that has not seen staff deployed elsewhere; as COVID-19 related deaths rise, the need for expertise in symptom control care of the dying has never been more apparent. However, expertise must be responsive, pragmatic and innovative. The harsh reality is that the availability of important drugs, suitable infusion systems and loved one's presence at the time of the death will all become challenges.

Table 4 Cause or mode of death

| Cause or mode of death | n=68 | % |
|----------------------------------------------------|------|----|
| Respiratory failure | 36 | 53 |
| Myocardial damage/failure | 22 | 33 |
| Respiratory failure with myocardial damage/failure | 5 | 7 |
| Unknown | 5 | 7 |

Ruan *et al.*¹²

This rapid review has collated the evidence from the first weeks of the pandemic. The aim is to inform clinical practice with preliminary pointer to the likely symptoms and clinical trajectories encountered that may allow prognostication and effective communication with patients and families. It appears most die with either respiratory or cardiac failure/injury or both. As one might expect in acutely unwell—patients with infection sepsis, liver failure and disseminated intravascular coagulation—there will be elements of multiple organ damage leading to death. This will have implications for the metabolism and clearance of many of the common agents used in end-of-life care.

In many countries this has been a public health and medical emergency and patient protection and treatment the primary concern for services and clinicians. In this situation, the collection of clinical data is difficult, both ethically and practically. Reporting may also be bound by the local medical culture. There are significant differences in the services and culture of palliative care in China, Italy and the UK, the countries from which the papers we report originate. In addition, health data reporting in an authoritarian state is very different from that in a liberal democracy (which may, or may not, explain the disappearance within a week of data from Du *et al.*,⁶ previously available from *The Lancet*).

The review we conducted should prompt urgent prospective data collection in countries where COVID-19 is endemic and patients presenting with symptoms. Given the evident rapidity of the terminal phase, understanding the symptoms in the cohort unlikely to survive and their susceptibility to pharmacological (or other) measures will allow clinicians to direct appropriate management. Similarly, the terminal phase trajectory allows clear communication with relatives and carers to prepare for death.

The focus of rapid information gathering from areas affected by COVID-19 has been on clinical issues related to ventilator support, survival and potential treatments. The rush for data in the short time since the first cases were reported is less than 16 weeks. The emphasis has been anywhere but on palliation in the midst of a public health crisis. Of note is the fact that a search combining CORONAVIRUS or COVID* OR SARS-CoV2 AND palliative yielded no relevant results for the initial period. It is unclear what the setting of the deaths in the review were (intensive care units, high dependency units or general wards). There were no data evident from settings other than secondary or tertiary care. There was a glaring dearth of data for some symptoms, the most obvious being delirium or agitation, given that this is prevalent in acutely illness, especially in the elderly.¹³ The absence raises questions about data collection techniques and the focus on presenting rather than chronic or terminal symptoms. Dyspnoea may be reported as a proxy for delirium, for example. There are evident differences

where data are collected by palliative physicians.¹⁰ Consistency of terms is difficult where studies are heterogeneous, and it may be that there are cultural limitations to data collection. It is noteworthy that no study specially accounted for comorbidities within the symptom groups. We can only surmise that those with pre-existing lung disease experience more dyspnoea and those with heart disease experience more palpitations. Rather than developing risk factors for poorer prognosis, this might help develop risk profiles for symptom load in the dying.

CONCLUSIONS

Our data indicate that cough, breathlessness, fatigue and myalgia are significant symptoms in people hospitalised with COVID-19. Dyspnoea is the most significant symptom in the dying. The mode of death is predominantly through respiratory or heart failure or both. No data are evident on dying trajectories.

Rapid data gathering on the mode of death and the symptoms burden in dying patients (prevalence and where possible data refractions) in areas where COVID-19 is prevalent will provide important intelligence for clinicians. This should be undertaken urgently, within ethical norms, and the practicalities of dealing with a public health, clinical and logistical emergency.

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Contributors PK conceived the study; PK and SN undertook the relevant searches and data extraction; DB, CC, LP and ST had input to the drafting of the text relating to the review.

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