

**Pandemic Covid 19: Symptom Burden and Clinical Characteristics of Patients at End of Life
with COVID-19: A Systematic Review and Rapid Evidence Summary**

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Introduction

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 regarding the prevalence of symptoms, their intensity, their resistance or susceptibility to symptom control and the mode of death for patients. With this in mind, a systematic review was undertaken of the literature available from the outbreak.

Method

A systematic review was undertaken using the following databases:

Embase , Ovid MEDLINE(R), Journals@Ovid, NHS Scotland Journals@Ovid and the Cochrane Library all from Jan 1 to March 23 2020. The following search terms were used: [COVID* [OR] CORONAVIRUS*] AND [SYMPTOM*] a second search was undertaken using the same databases using the terms [COVID* [OR] CORONAVIRUS*] AND [DEATH* OR DYING* OR PALLIATIVE]

Searches were limited to adult human studies with an abstract or full text available and in English.

In addition, a hand search of original and review articles was undertaken for additional articles which may not have appeared in the literature search as additional measure to ensure the quality of the search.

Inclusion criteria: clinical studies – prospective or retrospective of cohorts of patients hospitalised with COVID-19, with details of symptoms on all patients (survivors or those dying), data on mode of death or symptoms in a proportion of patients who died.

Results

The search revealed a total of 117 papers and reports of which 10 fitted the criteria for inclusion as giving data on symptoms overall, three papers gave discrete data for symptoms in patients who died and two studies gave data about the cause or mode of death. Data was heterogeneous in collection and largely related to presentation but gave some indication of the likely problems encountered at the end of life. The data on symptoms was collated as below. One paper published in *The Lancet* giving useful data on symptoms in patients with COVID19 had simply disappeared from its original publication site.¹ No answer as to why it had disappeared has been forthcoming from the publishers. Ghostly traces of its presence remain on Google Scholar.

The details of the data in pooled patients (studies in which patients died or survived) are given are given in Table 1, below.

Table 1: Symptoms in surviving and dying patients presenting and in the course of their illness with COVID19

	Chang et al ² n=13	Deng et al ³ n=225	Guan et al ⁴ n=1099	Huang et al ⁵ n=41	Kui et al ⁶ n=137	Wang et al ⁷ n=138	Xu et al ⁸ n=62	Yang et al ⁹ n=52	Zhou et al ¹⁰ n=191	ISS (Italy) ¹¹ n=6801
Cough	46.3%	37.7%	67.8%	76%	48.2%	59.4%	81%	77%	79%	40%
Breathlessness/Dyspnoea	No data	44%	18.7%	55%	19%	31.2%	No data	63.5%	No data	71%
upper airway congestion	61.5%	No data	5.1%	No data	No data	No data	No data	6%	No data	No data
myalgia	23.1%	25.3%%	14.9%	44%*	32.1%	34.8%	52%*	11.5%	15%	No data
headache	23.1%	5.7%	13.6%	0	9.5%	6.5%	34%	6%	No data	No data
Diarrhoea	7.7%	14.6%	3.8%	3%	8.0%	10.1%	8%	No data	5%	6%
Expectoration	No data	21.7%	33.7%	38%	4.4%	26.8%	56%	No data	23%	No data
Palpitations	No data	10.6	No data	No data	7.3%	No data	No data	No data	No data	No data
Haemoptysis	No data	3%	0.9%	8%	5.1%	No data	3%	No data	No data	1%
Fatigue	No data	No data	38.1%	44%*	32.1%	69.6%	52%*	20%***	23%	No data
Nausea/vomiting	No data	No data	5.0%	No data	No data	13.7%**	No data	4%	4%	No data

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

**Wang et al list nausea and vomiting separately

*** Listed as 'malaise' in Yang et al

Three papers give data regarding symptoms discretely as in non-surviving patients, though in two of these (Deng et al and Yang et al) it is unclear whether these are presenting symptoms or symptoms at the end of life.^{3,9} No data are given about their management or persistence. As one might expect, dyspnoea, cough and fatigue feature. More minor symptoms look to be more likely to be presenting features given their consistency throughout the data supplied above across all symptom reporting (surviving and dying patients). Reassuringly pain does not appear to be a feature that is consistently reported, either in surviving or dying patients. Worrying, however, there is no reporting of delirium in patients at the end of life. Given that this is a consistent feature in acutely unwell patients, especially the elderly, whether likely to recover, or dying, its absence raises questions about the extent of data collection and the focus on presenting rather than continuing or terminal symptoms.

Table2: Symptoms in dying patients

	Deng et al ³ n=109	Yang et al ⁹ n=20	ISS (Italy) ¹¹ n=6801
Cough	43.1%	75%	40%
Dyspnea	70.6%	60%	71%
Expectoration	32.1%	No data	No data
Headache	5.5%	5%	No data
Hemoptysis	4.6%	No Data	1%
Diarrhea	17.4%	No data	6%
Palpitations	10.1%	No data	No data
Vomiting	No data	5%	No data
Headache	No data	5%	No data
Pain	No data	10%*	No data
Myalgia	No data	5%	No data

*arthralgia and chest pain

The prevalence of cough and dyspnoea in patients dying with COVID19 is evident from the data above (the more from the palliative focus of the Italian data and the size of the sample)

Mode of death

Only two papers (Deng et al, Ruan et al) appear to give useful data regarding the mode of death in patients, though given the relative paucity of papers and the focus of research on treatment this may be unsurprising.^{3,12} Deng et al list a number of complications in patients who died which one assumes contributed to or were the mode of death.

Table 2: Modes of death listed in Deng et al³

Acute respiratory distress syndrome	98 (89.9%)
Acute cardiac injury	65 (59.6%)
Acute kidney injury	20 (18.3%)
Shock	13 (11.9%)
Disseminated intravascular coagulation	7 (6.4%)

Ruan et al¹² list the modes of death in 68 patients with COVID19 and these are given in Table 4

Table 4: Cause or mode of death listed in Ruan et al¹²

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

As might be expected the majority of patients die with or of either respiratory failure 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.

Discussion

There are clearly limitations to this review. The focus of rapid information gathering from those 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 12 weeks and 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* AND palliative yields no relevant results for the period. It is not evident the setting of the deaths of the patients under review – whether they are being managed on intensive care units, high dependency units or general wards. There is no data evident from settings other than secondary or tertiary care. What will also be evident is the glaring lack of data for some symptoms, the most obvious being delirium.¹³ It may be that there are cultural limitations to the collection of data. The first and most obvious point to be made is the fact that particularly in China and Italy, this has been a public health and medical emergency and the protection and treatment of patients has been the primary concern for services and for clinicians. In this situation the collection of data regarding patients is difficult both ethically and practically. Reporting may also bound by the medical culture in different parts of the world. While there is a well-developed palliative care service in Italy, this is not the case in China. In addition, the reporting of health data in an authoritarian state is very different from the reporting of such data in a liberal democracy (which may, or may not, explain the disappearance within a week of the data from Du et al, that had previously been available from The Lancet).

Rapid data gathering on the mode of death and the nature of symptoms in dying patients (their prevalence and where possible data on how refractory, or not they may be) in areas where COVID19 is becoming will provide important intelligence for clinicians managing COVID19 at the end of life. This should be undertaken as a matter of urgency, within ethical norms, and the practicalities of dealing with a public health, clinical and logistical emergency.

REFERENCES

- [1] Du Y, Tu L, Zhu P, Mu M, Wang R, Yang P, Wang X, Hu C, Ping R, Hu P, Li T. Clinical Features of 85 Fatal Cases of COVID-19 from Wuhan: A Retrospective Observational Study. *The Lancet* (online, pre-publication, March 2020; no longer available)
See here: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3546088
And here:
https://scholar.google.co.uk/scholar?hl=en&as_sdt=0%2C5&q=Clinical+Features+of+85+Fatal+Cases+of+COVID-19+from+Wuhan%3A+A+Retrospective+Observational+Study&btnG=
- [2] Chang D, Lin M, Wei L, Xie L, Zhu G, Cruz CS, Sharma L. Epidemiologic and clinical characteristics of novel coronavirus infections involving 13 patients outside Wuhan, China. *JAMA*. 2020 Feb 7. <https://jamanetwork.com/journals/jama/article-abstract/2761043>
- [3] Deng Y, Liu W, Liu K, Fang YY, Shang J, Zhou L, Wang K, Leng F, Wei S, Chen L, Liu HG. Clinical characteristics of fatal and recovered cases of coronavirus disease 2019 (COVID-19) in Wuhan, China: a retrospective study *Chinese Medical Journal* (pre-publication, online) March 2020
https://journals.lww.com/cmj/Abstract/publishahead/Clinical_characteristics_of_fatal_and_recovered.99319.aspx
- [4] Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DS, Du B. Clinical characteristics of coronavirus disease 2019 in China. *New England Journal of Medicine*. 2020 Feb 28.
<https://www.nejm.org/doi/full/10.1056/NEJMoa2002032>
- [5] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet* 2020. Doi: 10.1016/S0140-6736(20)30183-5. <https://www.sciencedirect.com/science/article/pii/S0140673620301835>
- [6] Kui L, Fang YY, Deng Y, Liu W, Wang MF, Ma JP, Xiao W, Wang YN, Zhong MH, Li CH, Li GC. Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province. *Chinese Medical Journal*. 2020 Feb 14.
https://journals.lww.com/cmj/Abstract/publishahead/Clinical_characteristics_of_novel_coronavirus.99408.aspx
- [7] Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. *JAMA*. 2020 Feb 7. [10.1001/jama.2020.1585](https://doi.org/10.1001/jama.2020.1585)
- [8] Xu, X.W., Wu, X.X., Jiang, X.G., Xu, K.J., Ying, L.J., Ma, C.L., Li, S.B., Wang, H.Y., Zhang, S., Gao, H.N. and Sheng, J.F., 2020. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. *BMJ*, 368. <https://www.bmj.com/content/368/bmj.m606.full>
- [9] Yang X, Yu Y, Xu J, Shu H, Liu H, Wu Y, Zhang L, Yu Z, Fang M, Yu T, Wang Y. 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 Feb 24. <https://www.sciencedirect.com/science/article/pii/S2213260020300795>

[10] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *The Lancet*. 2020 Mar 11. [https://doi.org/10.1016/S0140-6736\(20\)30566-3](https://doi.org/10.1016/S0140-6736(20)30566-3)

[11] Istituto Superiore di Sanità (ISS). Report sulle caratteristiche dei pazienti deceduti positivi a COVID-19 in Italia Il presente report è basato sui dati aggiornati al 17 Marzo 2020 Istituto Superiore di Sanità, 17th March 2020 (online) (English translation) https://www.epicentro.iss.it/coronavirus/bollettino/Report-COVID-2019_26_marzo_eng.pdf

[12] Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Medicine*. 2020 Mar 3:1-3. <https://link.springer.com/article/10.1007/s00134-020-05991-x?fbclid=IwAR1EbkrPza14lwx-dNFQDrLYG2HRomm-8Lb7NEvWZlqP1Gff8EBDaLmL7lg>

[13] Pandharipande P, Jackson J, Ely EW. Delirium: acute cognitive dysfunction in the critically ill. *Current Opinion in Critical Care*. 2005 Aug 1;11(4):360-8. https://journals.lww.com/co-criticalcare/Abstract/2005/08000/Delirium_acute_cognitive_dysfunction_in_the.14.aspx