Report 8: Symptom progression of COVID-19

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Summary

The COVID-19 epidemic was declared a Public Health Emergency of International Concern (PHEIC) by WHO on 30th January 2020 [1]. As of 8 March 2020, over 107,000 cases had been reported. Here, we use published and preprint studies of clinical characteristics of cases in mainland China as well as case studies of individuals from Hong Kong, Japan, Singapore and South Korea to examine the proportional occurrence of symptoms and the progression of symptoms through time.

We find that in mainland China, where specific symptoms or disease presentation are reported, pneumonia is the most frequently mentioned, see figure 1. We found a more varied spectrum of severity in cases outside mainland China. In Hong Kong, Japan, Singapore and South Korea, fever was the most frequently reported symptom. In this latter group, presentation with pneumonia is not reported as frequently although it is more common in individuals over 60 years old. The average time from reported onset of first symptoms to the occurrence of specific symptoms or disease presentation, such as pneumonia or the use of mechanical ventilation, varied substantially. The average time to presentation with pneumonia is 5.88 days, and may be linked to testing at hospitalisation; fever is often reported at onset (where the mean time to develop fever is 0.77 days).

1. Methods

We collated published papers and preprints on the clinical progression of cases of COVID-19 within China. Studies included are shown in Table 1 summarising the paper and cohort size included.

Box 1: Definition of onset used in our analysis.

> ***Onset**
> the first occurrence of *any* symptom. The symptoms reported at onset varied. We calculated the time from onset to each symptom as:
>
> time from onset to symptom = (date that a symptom is first reported) – (onset date).

We also extracted information from detailed case reports on cases reported in Hong Kong, Japan, Singapore and South Korea, up to 29 February 2020. These case reports provide detailed information on the date of disease presentation and the date that symptoms were first recorded. As such, we can examine the average time from onset* to first symptom occurrence or disease presentation. A summary of case reports included from each country/region is shown in Table 2 and the data are publicly available from the relevant ministries of health. For specific case reports, see attached data file for links.

Table 1: Clinical studies included in current analysis of symptom progression in China for COVID-19 [2–14].

First author	Peer reviewed	Cohort size
Cai	No	298
Chan	Yes	6
Chen	Yes	99
Chen	No	21
Guan	Yes	1099
Huang	Yes	41
Wang	Yes	138
Wei	Yes	9
Li	Yes	425
Phan	Yes	2
Wang	No	2745
Yang	No	4021
Yang	Yes	51

Table 2: Summary information for case reports included in analyses.

Country/ region	Number of cases	Last included report
HK SAR	93	2020-02-27
Japan	245	2020-02-29
Singapore	81	2020-02-18
South Korea	29	2020-02-16

For both the clinical studies in mainland China and the case reports from Hong Kong, Japan, Singapore and South Korea, we group the symptoms into common conditions, detailed in the following figures. Where proportional symptom presentation is calculated (figure 1), only studies where specific symptoms or disease presentation are recorded are included. Additionally, as individuals may exhibit more than one symptom, the proportions do not necessarily sum to one.

2. Results

Figure 1 shows that pneumonia is the most commonly reported clinical presentation in studies from mainland China, followed by fever and cough and/or sore throat (both of which are themselves possible symptoms of pneumonia).
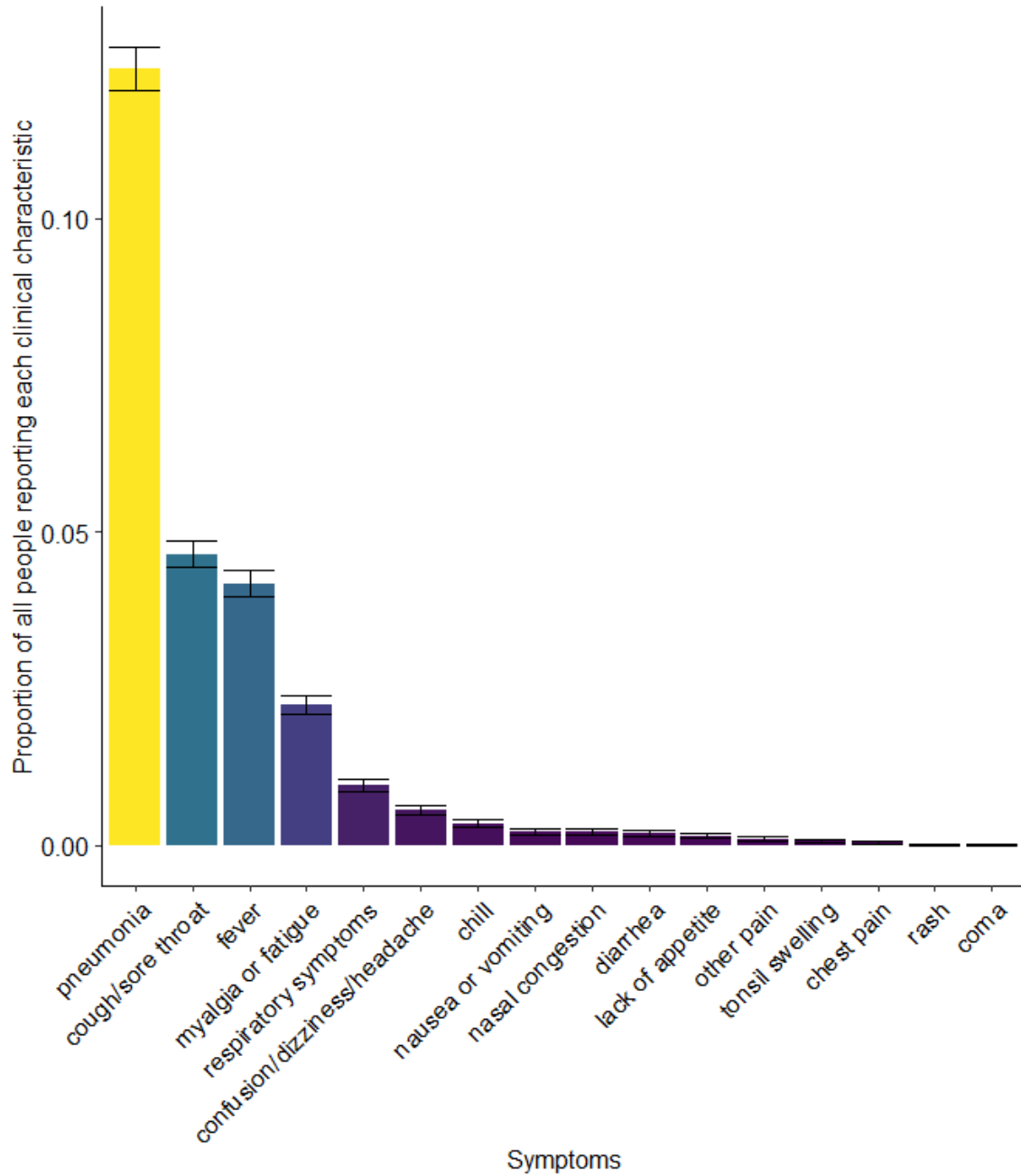
Figure 1: Clinical characteristics of cases in mainland China.

Figure 2 provides a timeline for the clinical progression for COVID-19, where Figure 3 shows the clinical progression for all individuals in our international (i.e. outside mainland China) case study dataset. In this figure, each row represents one case with the age of the case shown on the left-hand side; the cases are arranged by age from youngest (top) to oldest (bottom). There is a broad range of time to hospitalisation and symptoms.
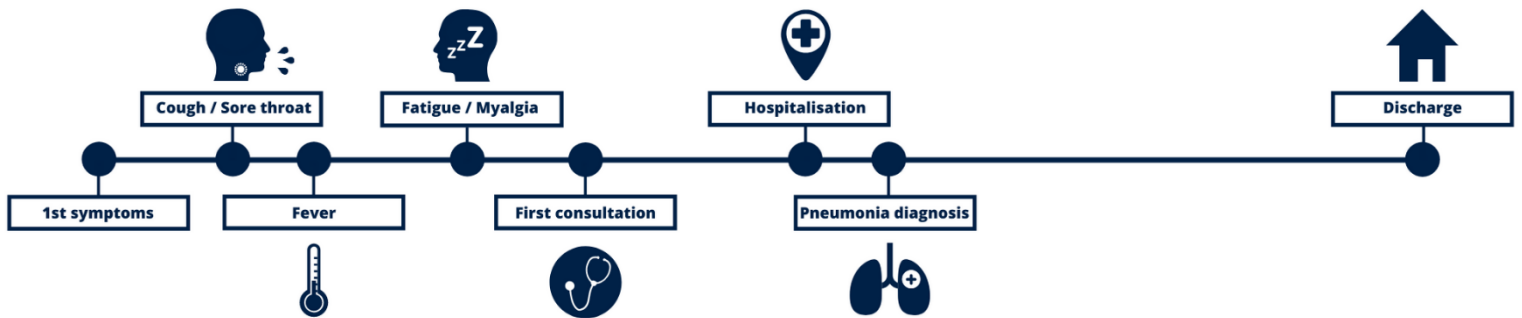

Figure 2: Clinical progression of COVID-19 over time. This progression varies between cases, the most common presentations illustrated (fever and cough followed by fatigue and then, in some cases, pneumonia).
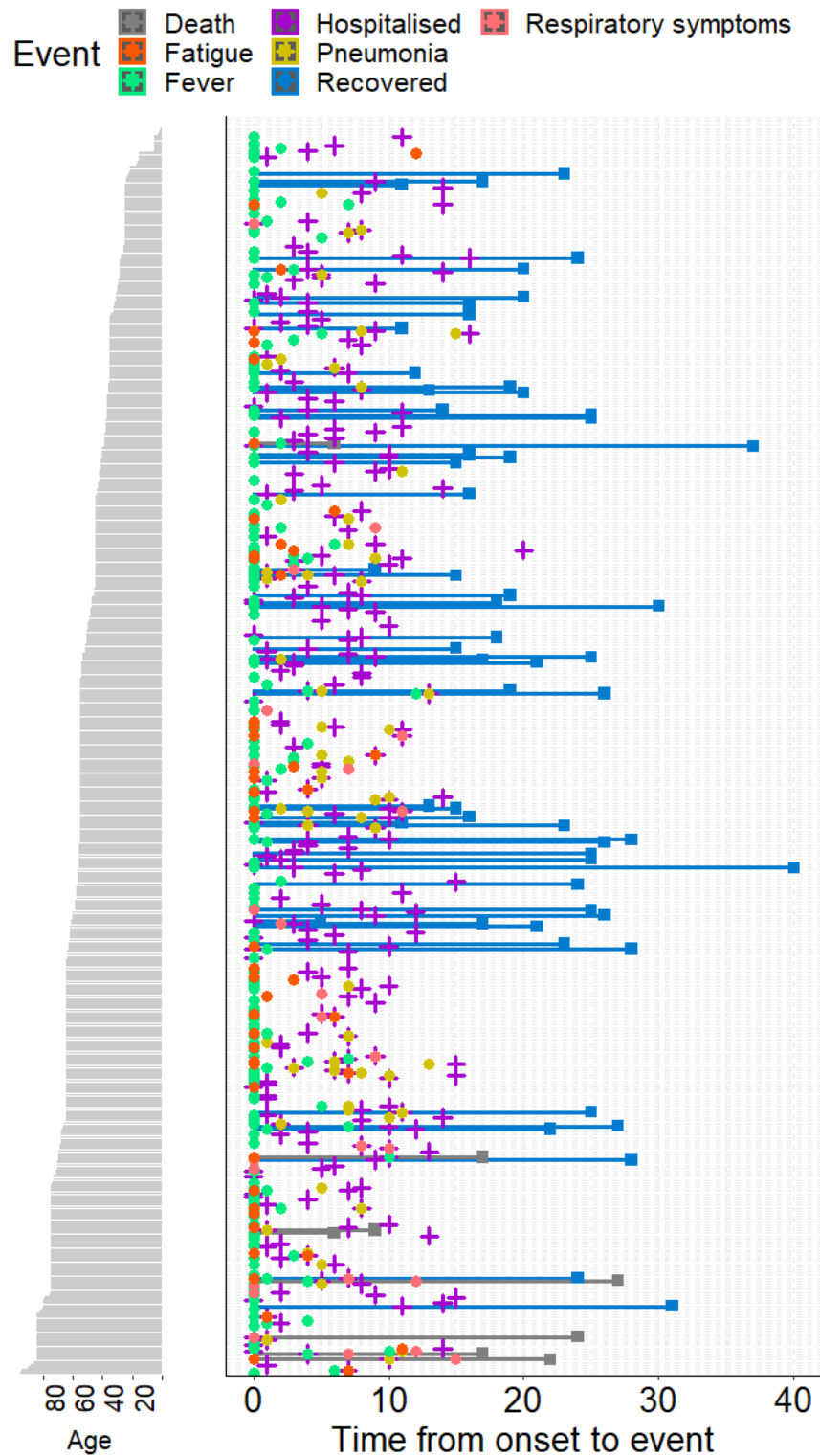
Figure 3: Clinical progression of cases from Hong Kong, Japan, Singapore and South Korea. Each row is an individual case. Dots denote the first reported occurrence of symptom or disease presentation; lines denote durations from onset to recovery/discharge (blue) or death (grey); crosses denote hospitalisation and squares represent recovery/discharge (blue) or death (grey).

We further explore the time from onset* to the initial occurrence of specific symptoms or clinical characteristics amongst the international case reports dataset in Tables 3 and 4. These times are calculated from the date the case first reported illness (of any type). Firstly, we see that the most commonly reported symptom for the included international cases is fever, irrespective of age. The second most common symptom is sore throat and/or cough. Presentation with pneumonia is mentioned in 79 cases but is more generally reported in individuals over 60 years old. We find that cases often present with fever and cough then progress to myalgia or fatigue approximately 1 day later and finally, to pneumonia or respiratory symptoms approximately five days after that. The total number of people reporting a symptom or clinical characteristic was 169.

Table 3: Reported symptoms by age from country/ region cases studies from Hong Kong, Japan, Singapore and South Korea with observed mean time (in days) from onset to symptom occurrence. NA indicates that no symptoms were reported for that cohort. There are 793 symptoms or disease presentation reported in total, with 460 of those in the over 60 year olds.

Symptom	Mean time from onset to symptom	S.D. time from onset to symptom	Proportion of all reported	Proportion of reported in over 60 y.o.	Proportion of reported in under 60 y.o.	Total count of individual symptom
Bronchitis	8.50	6.36	0.00	NA	0.00	1
Chest pain	0.00	NA	0.00	NA	0.00	1
Chill	0.43	1.09	0.02	0.02	0.02	15
Confusion/dizziness/headache	1.18	2.16	0.03	0.01	0.04	20
Cough/sore throat	0.71	2.16	0.27	0.26	0.27	212
Diarrhoea	3.17	3.90	0.01	NA	0.02	9
Difficulty walking	4.25	4.65	0.01	0.01	NA	4
Fever	0.77	1.89	0.36	0.35	0.38	288
ILI	0.00	0.00	0.01	0.01	0.00	4
Lack of appetite	3.12	3.98	0.01	0.02	NA	8
Myalgia or fatigue	1.66	3.03	0.08	0.09	0.07	60
Nasal congestion	0.73	1.49	0.02	0.01	0.03	16
Nausea or vomiting	1.18	1.78	0.02	0.01	0.02	12
Other pain	1.11	1.81	0.03	0.02	0.03	23

Table 4: Reported clinical characteristics and treatment from country/ region cases studies in Hong Kong, Japan, Singapore and South Korea with observed mean time (in days) from onset to occurrence. NA indicates that no symptoms were reported for that cohort. There are 793 symptoms or classifications (i.e. in terms of pneumonia) reported in total, with 460 of those in the over 60 year olds.

Disease presentation	Mean time from onset to presentation	S.D. time from onset to presentation	Proportion of all reported	Proportion of reported in over 60 y.o.	Proportion of reported in under 60 y.o.	Total count of individual presentation
Pneumonia	5.88	3.65	0.10	0.10	0.10	79
Requiring mechanical ventilation	8.20	5.72	0.01	0.01	0.00	5
Requiring oxygen	11.00	NA	0.00	0.00	NA	1
Respiratory symptoms	5.41	4.71	0.04	0.07	0.02	32

The time from onset to outcome or seeking healthcare is also examined. In Table 4 we see that the average time to seek healthcare is 2.1 days and the average time to hospitalisation is 5.76 days. The average time from onset to recovery or discharge is 20.51 days.

Table 5: Observed time from onset to seeking healthcare or outcome from country/ region cases studies from Hong Kong, Japan, Singapore and South Korea.

Outcome	Mean (days)	S.D. (days)	Number of reports
First consultation	2.10	2.65	172
Hospitalised	5.76	4.22	267
Recovered/Discharged	20.51	6.69	65
Death	16.00	8.21	8
Hospitalised duration	14.51	7.36	57

Using the severity definitions of the WHO-China Joint Mission on COVID-19, we classify each individual as having either mild or severe disease dependant on their reported symptoms [15]. Similarly to that report, we find that 17% of cases are severe.

Finally, in order to understand the relative severity between cases in mainland China and externally, we compare the age distribution in each cohort, (Table 5). We find that the proportion of people who are at least 60 years old is far higher in the mainland China studies compared to the individual cases studies from Hong Kong, Japan, Singapore and South Korea.

Table 6: The proportion of cases (%) that are at least 60 where information on age is available. In some of the clinical studies, the number of individuals over 65 was included rather than 60, therefore this is an underestimate.

Age group	Mainland China clinical studies %	International case studies %
Over 60 year olds	41	33

3. Conclusions

We have examined symptom frequency and clinical progression for a selection of cases from clinical studies in mainland China and individual case reports in Hong Kong, Japan, Singapore and South Korea. There are marked differences in age and severity of cases in mainland China compared to cases reported outside mainland China. We find that, the number of cases presenting with pneumonia is different in mainland China compared to the case studies from Hong Kong, Japan, Singapore and South Korea. This may be due to surveillance outside mainland China detecting milder cases than in mainland China, where pneumonia was a key clinical criterion in the case definition.

There are several caveats to this work. Firstly, our international case studies do not include all cases outside mainland China but a subset in both time and space. As detailed symptom progression data for other countries and more recent cases becomes available, this will be reviewed, and the analysis updated where possible. Secondly, we utilised clinical studies available for cases within mainland China, some of which have not yet been peer-reviewed. Pre-prints optimise the sharing of valuable data and information in outbreak settings; however, the analyses within this report may need to be reviewed as the pre-prints are revised.

We analysed symptom prevalence and clinical progression in cases of COVID-19 within mainland China and internationally in Hong Kong, Japan, Singapore and South Korea. Generally, the age structure and symptom prevalence showed geographic variation, potentially caused by differences in surveillance sensitivity, healthcare-seeking behaviour, population age distributions and the likely characteristics of travellers (*i.e.* younger and with fewer comorbidities). The analyses presented here was made possible by detailed clinical publications and pre-prints as well as the sharing of case characteristics.

4. References

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5. Appendix data sources

We collated data on international travellers from websites and media reports and used a subset of this data for this report. This subset is available from website as subset_international_cases_2020_03_11.csv.