The symptomatic expression of infection with the Omicron variant in Chinese patients; findings from the Clificol COVID-19 clinical case registry

Alexander Tournier[1], Yvonne Fok, Robbert van Haselen, Aaron To[2]

1 University of Berne
2 Hong Kong Association of Homeopathy

Potential competing interests: The author(s) declared that no potential competing interests exist.

Abstract

Background

Little systematic research has been conducted into the symptomatic expression of COVID-19 infections in patients. It is known that symptomatic expression varies between patients, but the nature and extent of this variability is poorly understood. This paper elaborates on the symptoms reported by Chinese patients infected with the Omicron variant, and compares this with available data from other countries.

Methods

Observational clinical case registry study of Chinese patients with confirmed Omicron variant COVID-19 infection. Symptoms were prospectively collected via a 171-item questionnaire and entered into the Clificol COVID-19 Clinical Case Registry. Two types of symptoms were distinguished: A) common clinical symptoms as identified by a search of available/published data, and B) homeopathic symptoms, used for the selection of the most suitable homeopathic medicine. Data were mainly analysed descriptively. Additionally, we compared the prevalence of the reported symptoms with available symptom data from the UK and France.

Results

Twenty one Chinese practitioners collected questionnaires on 388 cases that received a first homeopathic prescription between 5 December 2021 and 8 April 2022. The most frequently reported Clinical symptoms were respectively cough (71%), fever (65%), extreme tiredness (58%), headache (51%), sore throat (46%), runny nose (34%), Unusual muscle pains (31%), hoarseness (21%), eye soreness (8%) and brain fog (6%).

Conclusions

This is the first study which systematically investigated the reported symptoms of Chinese COVID-19 patients infected with the Omicron variant. Whilst the overall clinical symptom expression was similar to those reported for other countries, cough and fever related symptoms appeared to be particularly prevalent.

Introduction

The first COVID-19 cases in China were reported in December 2019. Since then, there were multiple infection waves

around the world, the latest being attributable largely to the Omicron variant. The official death toll attributed to COVID-19 is over 6 million people (https://www.worldometers.info/coronavirus/), but the true toll is likely to be significantly higher [1].

Despite the success of vaccination programs and slowly rising herd immunity, the pandemic is still ongoing, and currently China is struggling to contain case numbers infected with the milder, but highly contagious, Omicron variant.

Whilst anecdotal data abounds, little systematic research has been conducted on the symptoms reported by patients infected with COVID-19. For the Omicron variant, the most reliable identifiable data seems to come from hundreds of thousands of UK citizens reporting their symptoms on their smartphone as part of the ZOE COVID Study (https://joinzoe.com/learn/omicron-symptoms), the results of which were recently published in the Lancet. This situation is compounded by the -usually- milder nature of infections with the Omicron variant, leading to fewer interactions between patients and their healthcare providers.

Initial observations, focusing on the homeopathic clinical features of 18 Chinese patients during the first COVID-19 wave, were reported in 2020[2], and this was followed by a paper on the reported symptoms by 359 Chinese patients during the first COVID-19 wave in early 2020 (paper in press[3]).

In order to improve the management of the pandemic, there is a need to better understand variability in the clinical manifestations of COVID-19 infections. Whilst there is knowledge on patient factors (such as co-morbidity) on the likelihood of developing severe symptoms, little is known about virus-strain related symptom variability, and even less about geography related symptom variability. At the time of submission, we were able to identify only two studies that reported in detail on the prevalence of clinical symptoms in Omicron cases, one from the UK[4], and one from France[5]. We therefore used these two studies for a comparative symptom prevalence analysis.

In this study we report in detail on the symptoms of Chinese patients infected by the Omicron variant, and we compare our findings with the available data from other countries.

Materials and Methods

Retrospective analysis of prospectively collected, questionnaire based, COVID-19 clinical case data. The recruitment and treatment of patients was organised by the Living Homeopathy Clinic in Hong Kong, which offers treatment to a large number of patients in Mainland China as well as to the Hong Kong and Macau Special Administrative Region populations. A team of 21 practitioners was involved in the co-ordination of the recruitment, questionnaire administration and treatment of patients. Most recruitment of patients took place online using videoconferencing or other appropriate means of communication. Acute COVID-19 cases from China, who had tested positively for the Omicron variant that received a first homeopathic prescription between 5 December 2021 and 8 April 2022, were eligible. Eligible patients needed to have at least one of the following diagnostic criteria as described in the 7th edition of the diagnosis and treatment protocol in China[6]: 1) Reverse transcription polymerase chain reaction (RT-PCR) positive for 2019-novel Coronavirus (2019-nCoV); 2) Serology test positive for IgM/IgG (immunoglobulin M/immunoglobulin G) specific for COVID-19; 3) Suspected COVID-19, defined as follows: fever, chills, or respiratory symptoms related to an outbreak cluster* (* three or more symptomatic patients, identified in a 2-week period in a small unit such as family, office or school class in which one or more cases were RT-PCR positive). In February 2022, the Hong Kong government recognised the rapid antigen test as a valid test for COVID-19, antigen positive cases were therefore also considered as confirmed cases in this study.

(https://www.info.gov.hk/gia/general/202202/25/P2022022500816.htm).

A 171-item questionnaire for collecting Omicron-wave related symptoms was developed by our team. It was based on the questionnaire utilized in previous flu seasons, and then modified in line with the information available on COVID-19, including any reports on Omicron symptoms available at the time. It contained a mandatory assessment of a number of clinical symptoms such as fever, chills, weakness, cough, headache, sore throat, etc, as well as further homeopathic symptoms such as thirst, dryness of mouth, poor appetite etc. as well as factors that modify (i.e. ameliorate or aggravate) symptoms, e.g. warm drinks, open air, motion, etc (called 'modalities'). Symptoms and their modalities were categorized in so-called 'homeopathic repertory' rubrics, which aid homeopathic practitioners in the selection process of the appropriate homeopathic medicine. Repertory rubrics therefore represent a standardized way of categorizing and analysing symptoms. For this purpose, use was made of one the world's major repertory software programs (RadarOpus, version 3.0.16). Rubrics of homeopathic symptoms and their modalities are referred to in this paper as 'homeopathic symptom rubrics'.

An overview of the symptom assessment is given in table 1.

System / organs concerned	Common Clinical* symptoms	Homeopathic* symptoms	Comment
General / mental	Fever	Fever, alternating with chills	
	Extreme tiredness / fatigue	Worse after physical exertion Worse from motion Sleepiness Weakness during chill	
	Brain fog (memory / concentration problems)		
		Mental restlessness	
		Desire for company	
		Better after perspiration	
		Pain aggravated by cough	
		Ameliorated from open air	
		Ameliorated by warm drinks	
		Aggravated by cold air	
Head	Headache	Headache at temples Headache on forehead above the eyes Constriction as if band or hoop Headache worse during fever Headache worse by coughing Headache better by lying with the head high.	
Eyes, nose, mouth and throat	Eye soreness	Difficult to keep the eyelids open	
	Runny nose		
	Hoarse voice	Dryness of mouth	
	Sore throat	Throat pain worse by empty swallowing Throat pain worse by coughing	
Respiratory	Cough Chest constriction Chest pain	Dry cough Cough due to tickling in larynx Cough better by warm drinks Cough better in open air Dry Cough, only in morning Expectoration, infrequent Expectoration, copious Chest pain, worse during cough	Extent of expectoration was assessed in both directions: infrequent or copious

Gastro intestinal		Appetite, poor/wanting Thirst, worse during fever • for large quantities • for small quantities (frequently) Absence of thirst during fever	Thirst during fever was assessed in both directions: absence or excessive
Musculoskeletal	Unusual muscle pains	Restlessness of limbs Bone pain, worse during fever Pain in muscles during fever	

* 'Clinical' symptoms are clinically and/or pathophysiologically related to the COVID-19 diagnosis. 'Homeopathic' symptoms are experienced by some patients, but not necessarily related to the clinical diagnosis. Both types of symptoms can be used in the process of selecting the appropriate HMP.

Table 1: Overview of the symptom questionnaire that was completed by the patients

Apart from these symptoms, demographic characteristics such as age and sex were recorded, as well as, if available, the following COVID specific baseline data: Date when symptoms started; results of any PCR, antibody tests and/or antigen tests, CT (computed tomography) status, need for oxygen and/or ICU care if hospitalized.

The full questionnaire is available as appendix 1.

After screening of patients by a study team member, the questionnaire was administered to consenting eligible patients. Only patients who provided informed consent to completing the questionnaire were eligible for inclusion in the data analysis.

After converting the questions into repertory rubrics in line with a standardized protocol, members of the Hong Kong team entered the data into the Clificol database, which is a cloud-based, GDPR/HIPAA compliant international Clinical Case Registry (https://www.clificol.net/). All data were fully anonymised in compliance with GDPR/HIPAA standards during uploading to the online platform.

The analysis team would download the data periodically from the platform as excel sheets. Any errors detected were resolved via discussion in the database team. Data were stored on password-protected databases, and accessible only by members of the analysis team.

The data collected in the Clificol Case Registry also included information on the homeopathic medicine(s) prescribed and outcomes. However, for the purpose of this paper, we focused on the reported symptoms prior to receiving homeopathic treatment, and not on treatment outcomes.

The data analysis was primarily descriptive. Analyses were conducted in SPSS (version 27) and Microsoft Excel (version 16.56).

Results

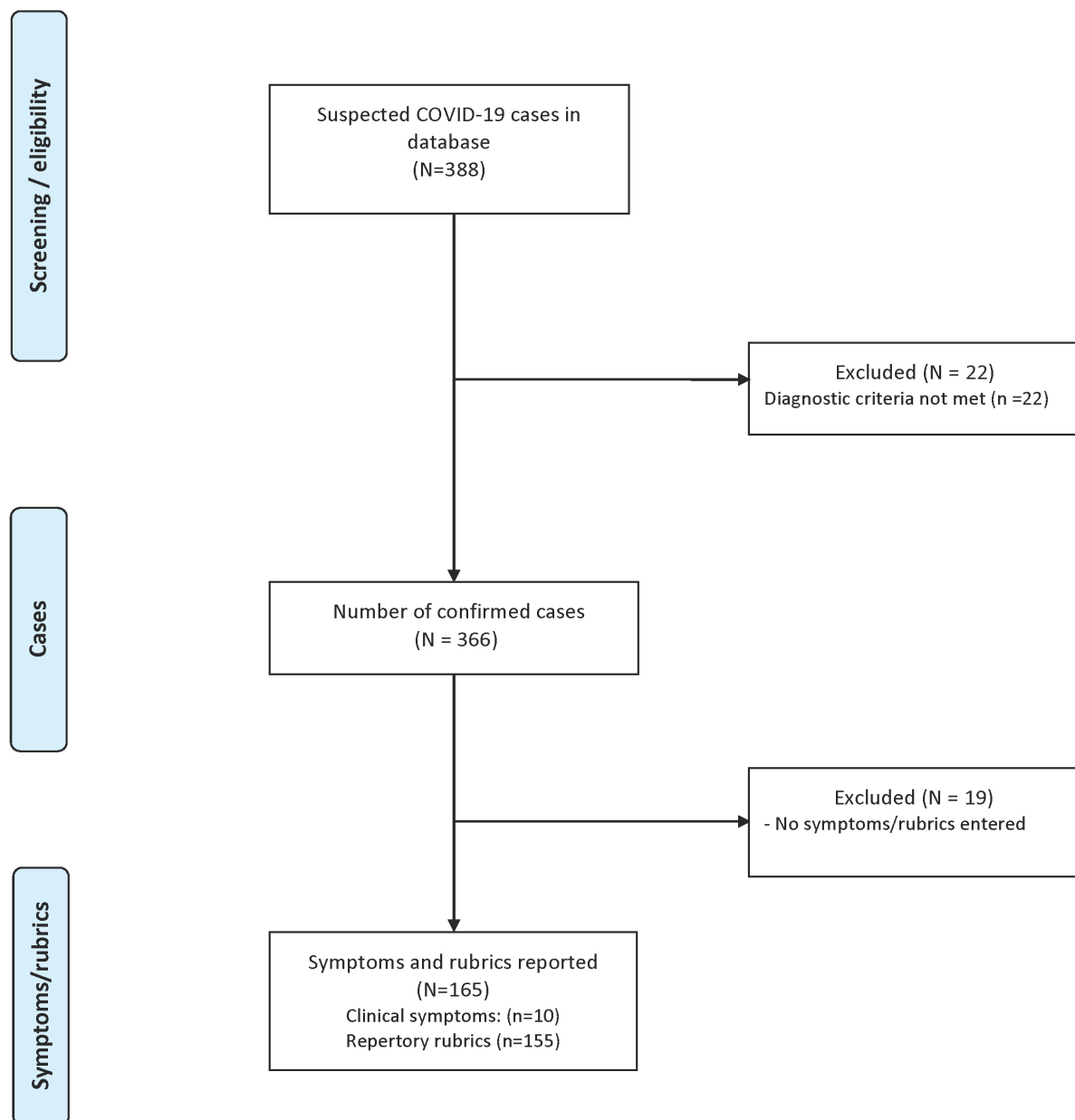The patient recruitment and data selection process as outlined in figure 1.

Figure 1: Patient and symptom selection flow chart

The 366 eligible cases with completed questionnaires reported in total 165 symptoms and/or rubrics.

Some demographic and clinical characteristics are given in table 2.

Table 2: Main demographic and clinical characteristics of the patients.

| Characteristics	(N=366)
Sex; n (%)	
Female	239 (65%)
Male	127 (35%)
Age [years] (mean [min, max])	42.6 [1, 96]
0-14 n (percentage of column total)*	51 (14%)
15-29	29 (8%)
30-44	124 (34%)
45-59	93 (25%)
60-74	49 (13%)
>= 75	19 (5%)
Duration of symptoms; n (%)	
< 24 hours	237 (65%)
1 day	45 (12%)
2 days	30 (8%)
3 days	22 (6%)
4-6 days	23 (6%)
7-9 days	4 (1%)
10-14 days	4 (1%)
15-30 days	1 (0%)
Accuracy COVID-19 diagnosis; n (%)	
PCR / Ab / Ag confirmed	366 (100%)
Severity of COVID-19; n (%)	
Mild	358 (98%)
Moderate	8 (2%)
Comorbidity¶	85 (23%)
Hypertension	28 (8%)
Respiratory diseases	22 (6%)
Auto-immune diseases	18 (5%)
Cardiovascular diseases	13 (4%)
Diabetes	13 (4%)
Cancer and malignancies	8 (2%)
Obesity	5 (1%)
Immunosuppressive treatment	2 (1%)

* Percentages were rounded to the nearest integer
¶ Patients could have more than one Comorbidity

Analysis of symptoms

In total, 10 clinical symptoms and 155 distinct homeopathic symptom rubrics were reported.

The prevalence of the 53 most common homeopathic symptom rubrics with a prevalence greater than 10%, is given in figure 2.
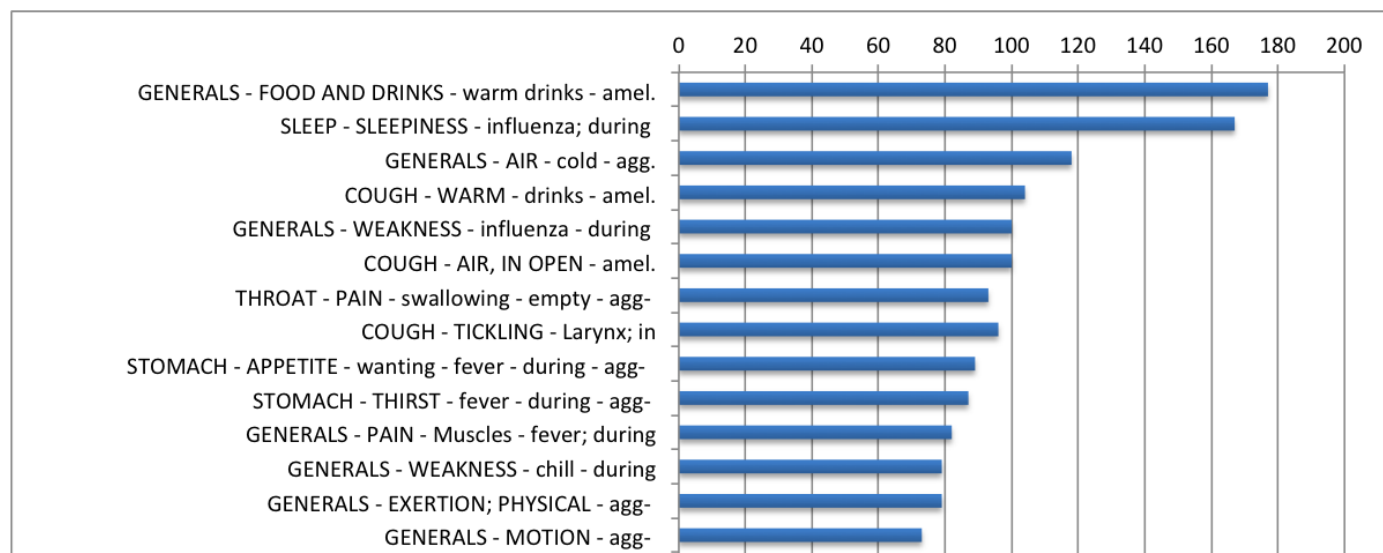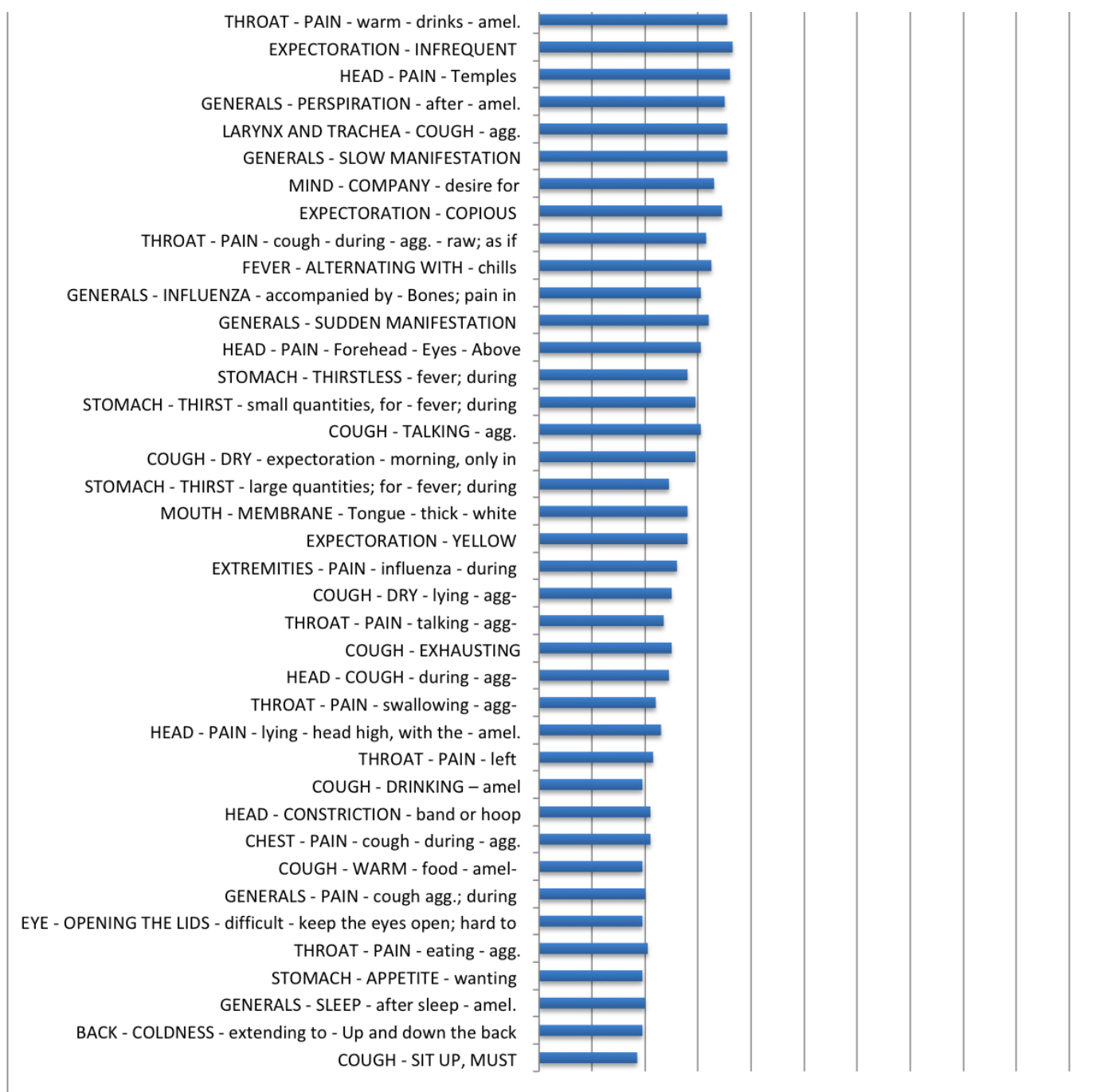
Figure 2: Homeopathic symptom rubrics with a prevalence greater than 10%

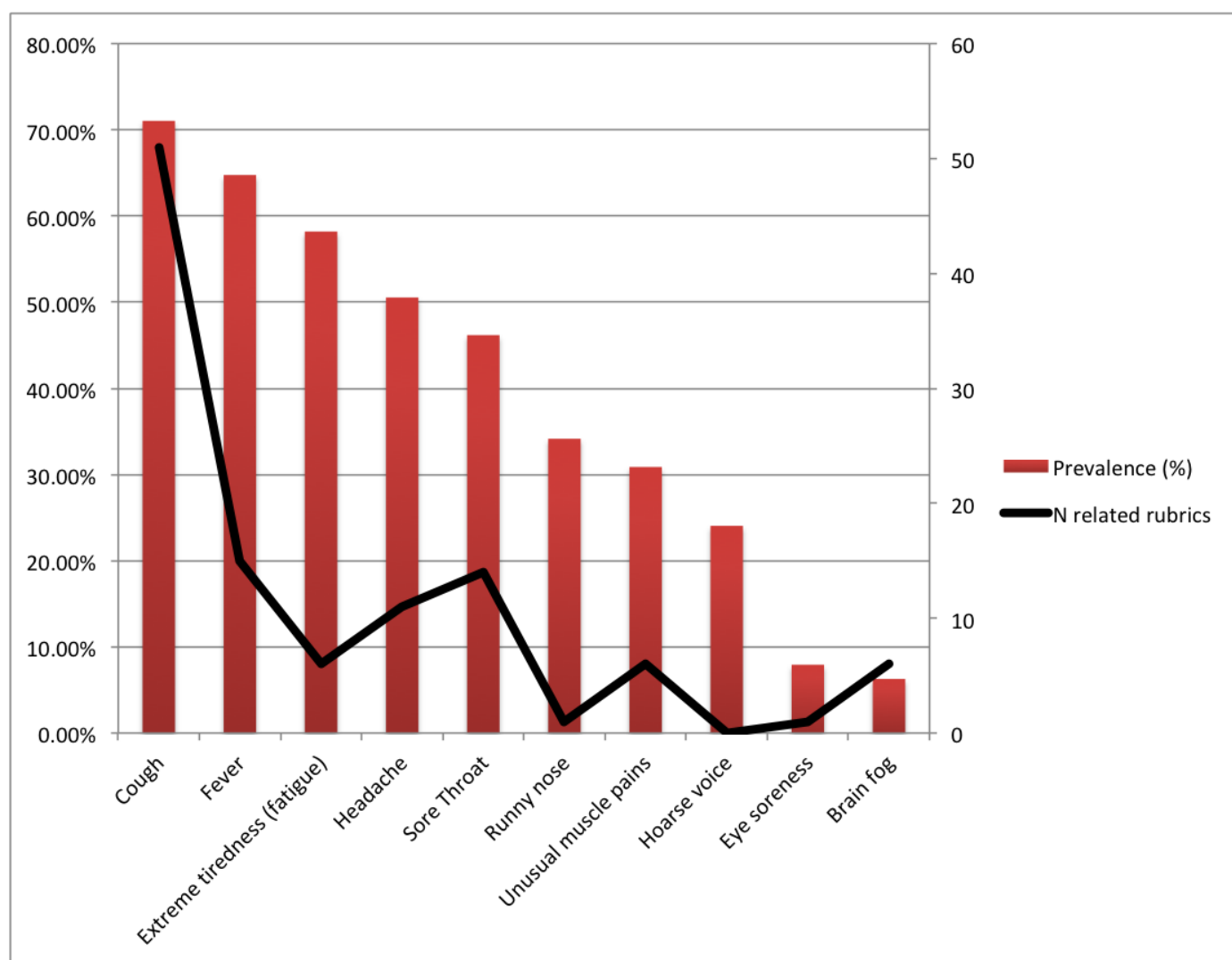The prevalence of the 10 clinical symptoms is depicted in figure 3 (red bars).

Figure 3: Prevalence of the clinical symptoms (bars / left axis) and the reported number of related homeopathic symptoms (line / right axis)

The prevalence of the 10 assessed clinical symptoms ranged from 5% for 'brain fog' to 70% for Cough. Cough, fever, tiredness, headache and sore throat were the five most commonly reported clinical symptoms.

We additionally looked if there was a relation between the prevalence of the clinical symptoms, and the reported homeopathic symptom rubrics. The line represents the number of related rubrics and this is quantified in the right vertical axis. Figure 3 indicates that a significant amount of rubrics (as reported in figure 2) were related to the clinical symptoms. This applied particularly to accompanying symptoms and/or modifying factors of the clinical symptoms cough, fever, and sore throat; examples are 'cough, ameliorated by warm drinks', 'thirst, worse during fever' and 'throat pain worse on empty swallowing'. In total 102 rubrics (65% of the total number of rubrics) were related one or more of the 10 clinical symptoms. This illustrates that the majority of the homeopathic rubrics are a more specific, 'granular' expression of several of the clinical symptoms. Differently put, the homeopathic symptoms provide a more detailed 'mapping' of the clinical expression of COVID-19 in individual patients.

Comparison with data from UK and France

The main publication from the UK concerns the ZOE COVID study, which compares symptoms and clinical outcomes reported on the ZOE app in two matched groups (n=4990 each) during periods of the Omicron and Delta variant dominance[4]. The main publication from France was conducted by the EMERGEN consortium[5]. In this study they used a standardized symptom questionnaire and genomic sequencing to confirm the Omicron variant diagnosis.

The symptom prevalence is compared between the countries in Figure 4
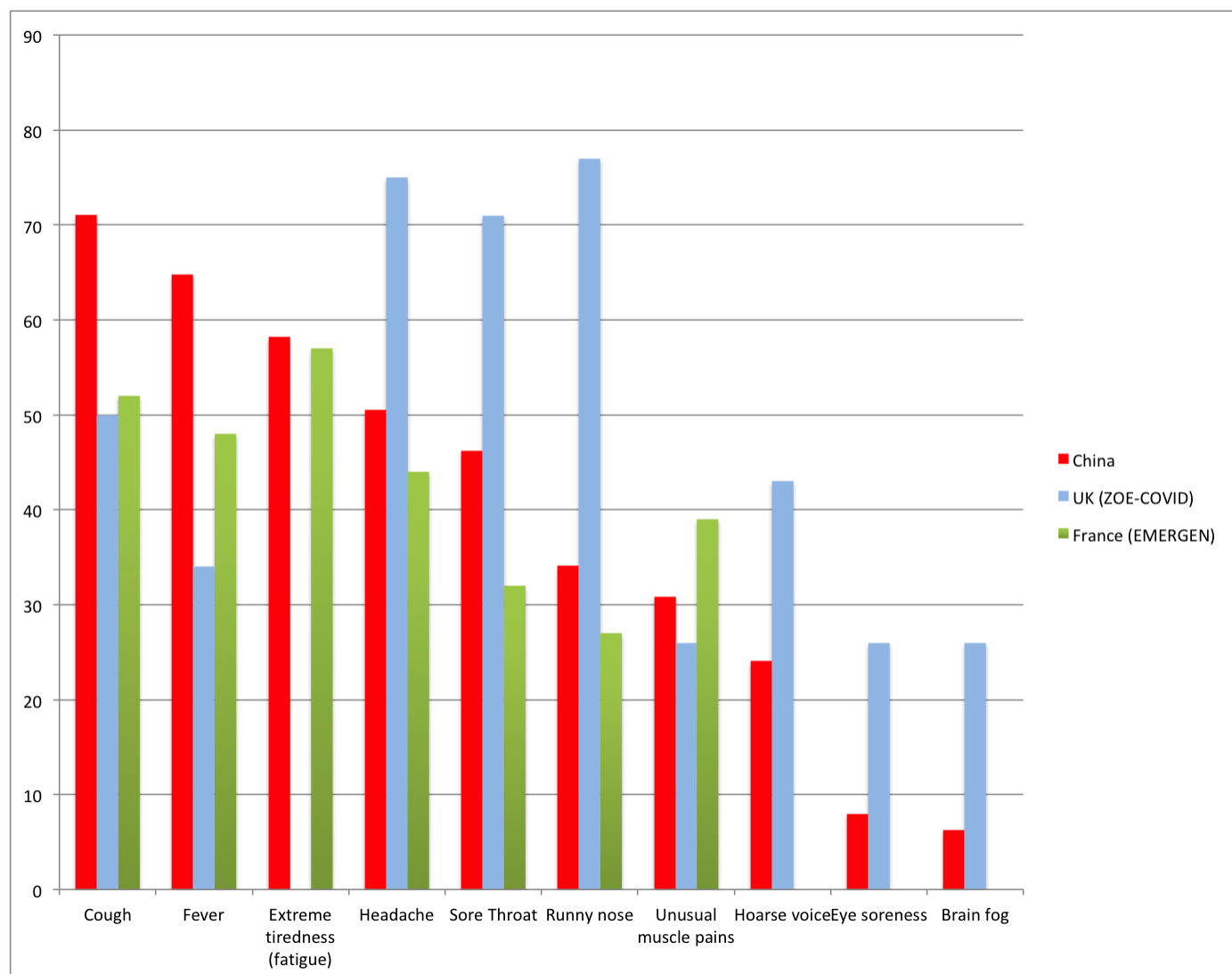

Figure 4: Between country comparison of clinical symptoms. Missing bars are due to no data being available

Figure 4 suggests that there are commonalities as well as differences. Overall, the Chinese data appear to be more similar to the French data than to the UK data. It appears that headache, sore throat, and runny nose were more common in UK cases.

The available studies also confirm the observation that loss of taste and smell is less common in the Omicron cases. The French study reported a respective prevalence of 9% and 8%. The UK study reported that loss of smell was less common (17%) in Omicron patients compared to the reported prevalence in the Delta wave (53%). In our study, the prevalence of these symptoms was low as well, 5% and 4% respectively.

The symptom odynophagia (pain on swallowing), has been reported to be more common in the Omicron variant as

compared to patients infected with other variants[7]. In our study, odynophagia was reported by 13% of the patients. Interestingly, 9% of patients reported that their throat pain was ameliorated by swallowing liquids. This illustrates the variability in the symptomatic expression of COVID-19 in individual patients.

Discussion

This was the first detailed study on the symptomatic expression of Omicron cases in the Chinese population. The most commonly reported clinical symptoms were respectively cough, fever, fatigue, headache and sore throat. The most commonly reported homeopathic symptoms that were related to the clinical symptoms were accompanying symptoms and/or modifying factors of cough, fever and throat pain.

To our knowledge, this is the first study that provides a detailed insight in the symptoms of confirmed Omicron cases in the Chinese population. The study population was relatively homogeneous, and the symptoms were obtained and identified in a standardized way, through the use of a questionnaire.

Many of the more detailed homeopathic symptoms reported by patients clustered around some of the clinical symptoms. A unique feature of this study is that it provides a more detailed, 'granular', perspective on the symptoms reported by infected patients.

A limitation inherent in any case registry is that our analyses are primarily descriptive. Furthermore, this analysis did not focus on the course of, and changes in, symptoms following treatment.

In our population, the patients were not specifically tested (e.g. via sequencing) for the Omicron variant. However, during the inclusion period, the Omicron variant was dominant in the Chinese/Hong Kong population[8].

It should also be pointed out that the distinction between 'clinical' and 'homeopathic' symptoms is not strict nor absolute. For instance, odynophagia, lack of taste and lack of smell are considered to be both 'clinical' and 'homeopathic' symptoms. Clinical symptoms are characterized by a pathophysiological connection between the symptoms and the disease, however this is not necessarily the case for homeopathic symptoms. A further difference is that clinical symptoms are primarily used as a *diagnostic* indicator for the disease under consideration, whilst homeopathic symptoms are primarily used as *prognostic* factor to indicate (together with other homeopathic symptoms) the homeopathic medicine most likely to be effective in that particular patient[9].

Since we could not be sure that the reported symptoms are representative of Omicron patients in other geographical regions, we decided to have a closer look at the available literature in this regard. Whilst the overall spectrum of clinical symptoms was similar between the three countries compared, there were variations in the prevalence of specific symptoms. This was more explicit in the comparisons with the UK data than with the French data. Part of this difference could possibly be explained by the different methods of data collection. The UK study made use of an App on smartphones, whilst the Chinese and French data were based on the administration of a questionnaire by symptomatic patients. It is conceivable the ease and accessibility of data entry via a smartphone app could lower the threshold for symptom entry, leading to the reporting of more and milder symptoms. The available data provide some support for this, as the average prevalence of clinical symptoms was distinctly higher in the UK study compared to the French and Chinese data. However, other factors could explain the observed differences as well, so further studies would be needed

to properly assess the influence of the data collection method on symptom prevalence.

Apart from the UK and French studies referred to in detail, we identified two more publications of interest. Lippi et al[10] conducted a Google trends search in Italy, comparing popular search terms during a period with Omicron variant dominance with popular search terms during a period with Alpha variant dominance. They reported a relative predominance of sneezing, sore throat, fever, chills, headache and tiredness during the period of Omicron predominance. This suggests that Google trends can provide early information on changes in experienced symptoms. The other study assessed the symptoms of some of the first confirmed Omicron variant cases in South Korea[11]. Sore throat, fever, cough, headache and runny nose were the most commonly reported symptoms, with a prevalence ranging from 10-25%, which is lower than the reported prevalence of the same symptoms in most other countries.

Overall, our findings suggest that there is a fair amount of geographical stability in terms of the types of clinical symptoms reported, but that at the same time there is some between country variability in the prevalence of these symptoms.

A more detailed understanding of the clinical presentation of COVID-19 variants is important for the selection of test-triggering symptoms. The clinical presentation in response to different variants has shifted significantly and our findings clearly confirm this; a comparison with 'first wave' data from China collected by our team reveals distinct differences with the first wave (data not shown).

Our study provided the first detailed mapping of symptoms reported by Chinese COVID-19 patients infected with the Omicron variant. Whilst the overall clinical symptom expression was similar to those reported for other countries, cough and fever related symptoms appeared to be particularly prevalent in the Chinese population.

References

1.   Estimating excess mortality due to the COVID-19 pandemic: a systematic analysis of COVID-19-related mortality, 2020-21. Lancet (London, England). 2022;399(10334):1513-36.

2.   To KLA, Fok YYY. Homeopathic Clinical Features of 18 Patients in COVID-19 Outbreaks in Hong Kong. Homeopathy. 2020;109:146-62.

3.   Tournier AL, van Haselen R, Fok YYY, To AKL. Searching for the Genus Epidemicus in Chinese patients; findings from the Clificol COVID-19 clinical case registry. Homeopathy. 2022;Accepted for Publication (in Press).

4.   Menni C, Valdes AM, Polidori L, Antonelli M, Penamakuri S, Nogal A, et al. Symptom prevalence, duration, and risk of hospital admission in individuals infected with SARS-CoV-2 during periods of omicron and delta variant dominance: a prospective observational study from the ZOE COVID Study. The Lancet. 2022;399(10335):1618-24.

5.   Maisa A, Spaccaferri G, Fournier L, Schaeffer J, Deniau J, Rolland P, et al. First cases of Omicron in France are exhibiting mild symptoms, November 2021–January 2022. Infectious Diseases Now. 2022.

6.   Diagnosis and Treatment Protocol for COVID-19 (Trial Version 7), National Health Commission of the People's Republic of China. [Available from: http://www.nhc.gov.cn/xcs/zhengcwj/202003/46c9294a7dfe4cef80dc7f5912eb1989.shtml.

7.   Cedro-Tanda A, Gómez-Romero L, de Anda-Jauregui G, Garnica-López D, Alfaro-Mora Y, Sánchez-Xochipa S, et al. Early Genomic, Epidemiological, and Clinical Description of the SARS-CoV-2 Omicron Variant in Mexico City. Viruses.

2022;14(3).

8.   Mefsin Y, Chen D, Bond HS, Lin Y, Cheung JK, Wong JY, et al. Epidemiology of infections with SARS-CoV-2 Omicron BA.2 variant in Hong Kong, January-March 2022. medRxiv. 2022.

9.   Rutten ALB. Prognostic Factor Research in Homeopathy. New Delhi: Central Council for Research in Homeopathy; 2019. ISBN no. 978-93-81458-58-7. 384 p.

10.   Lippi G, Nocini R, Henry BM. Analysis of online search trends suggests that SARS-CoV-2 Omicron (B.1.1.529) variant causes different symptoms. Journal of Infection. 2022;84(5):e76-e7.

11.   Kim MK, Lee B, Choi YY, Um J, Lee KS, Sung HK, et al. Clinical Characteristics of 40 Patients Infected With the SARS-CoV-2 Omicron Variant in Korea. Journal of Korean Medical Science. 2022;37(3).