Research Article

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

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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. With respect to A), 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

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(31%), hoarseness (21%), eye soreness (8%) and brain fog (6%). With respect to B), homeopathic symptoms related to cough and fever were particularly prevalent.

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.

Short title: COVID-19 Omicron symptoms in Chinese patients

Keywords: Covid-19; SARS-COV-2; Omicron variant; Clinical Case registry.

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[2]. The lack of information on the nature of Omicron variant symptoms is compounded by the -usually- milder nature of infections with the Omicron variant, leading to fewer interactions between patients and their healthcare providers.

By December 2021, the Omicron variant was involved in almost all of the Chinese patients testing positive for COVID-19. Despite stringent public health measures, including contact tracing and quarantine not only of close contacts but also close contacts of close contacts, the outbreak of BA.2.2

was not controlled and this strain was responsible for the large epidemic that occurred. Virus sequencing has been done throughout the epidemic, and the last local BA.1 cases and Delta cases were detected in mid-January and early February, respectively, with one sporadic local Delta detection in late March[3].

Whilst information is available on symptoms reported by Chinese patients during the first COVID-19 wave[4] [5], little is know to date on symptoms reported by Chinese patients infected with the Omicron variant.

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. Such knowledge is important for the identification of suitable 'test-triggering' symptoms[2]. 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[2], and one from France[6]. No such studies from China were identified, leading us to conclude that there is a knowledge gap in this regard.

Apart from this, we were interested in 'homeopathic' symptoms reported in Chinese patients infected with the Omicron variant. Homeopathic symptoms are all abnormal sensations experienced by a person as a whole, or in a part of the body. While clinical symptoms are pathophysiologically related to the functioning of the organ system(s) involved in the disease, this is not required for homeopathic symptoms[7]. In homeopathic practice, including in the treatment of COVID-19 patients[8], both clinical and homeopathic symptoms are used in the selection process of the appropriate homeopathic medicine.

The primary aim of this study was to explore in detail reported clinical symptoms of Chinese patients infected by the Omicron variant. In addition, we compared our findings with the available data from other countries and we looked at reported homeopathic symptoms.

Materials and Methods

Prospectively collected, questionnaire based, COVID-19 clinical case data were analysed. 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. For children, the questionnaires were completed with the parents. 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 COVID-19 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[9]: 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. On the 25th of February 2022, the Hong Kong government recognised the rapid antigen test as a valid test for COVID-19 (https://www.info.gov.hk/gia/general/202202/25/P2022022500816.htm). From that time onwards, antigen positive cases were also considered as suspected Omicron cases in this study.

A 171-item paper-based 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. Some of the questions were further fine-tuned based on the initial responses received. It contained a mandatory assessment of a number of clinical (diagnostic) 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'). Homeopathic symptoms and their modalities were categorized in so-called ‘homeopathic repertory’ rubrics using a special software program (ZeusSoft 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	
	Brain fog (memory / concentration problems)		
		Mental restlessness	
		Pain aggravated by cough	
		Ameliorated from open air	
Head	Headache	Headache worse during fever Headache at temples	
Eyes, nose, mouth and throat	Eye soreness		
	Runny nose		
	Loss of smell		
	Loss of taste		
	Hoarse voice	Dryness of mouth	
	Sore throat		
Respiratory	Cough Chest constriction	Dry cough	
Gastro intestinal		Appetite, poor/wanting Thirst for large quantities	
Musculoskeletal	Unusual muscle pains	Restlessness of limbs Bone pain, worse 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 pathophysiologically related to the clinical diagnosis. Both types of symptoms can be used in the selection process of an individualized Homeopathic Medicinal Product.

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

Demographic characteristics such as age and sex were also 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.

Completed questionnaires were converted into clinical symptoms and repertory rubrics according to a standardized protocol. Members of the Hong Kong team entered the data into the Clificol database, which is a cloud-based, General Data Protection Regulation (GDPR) and Health Insurance Portability and Accountability Act (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 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 are outlined in figure 1.

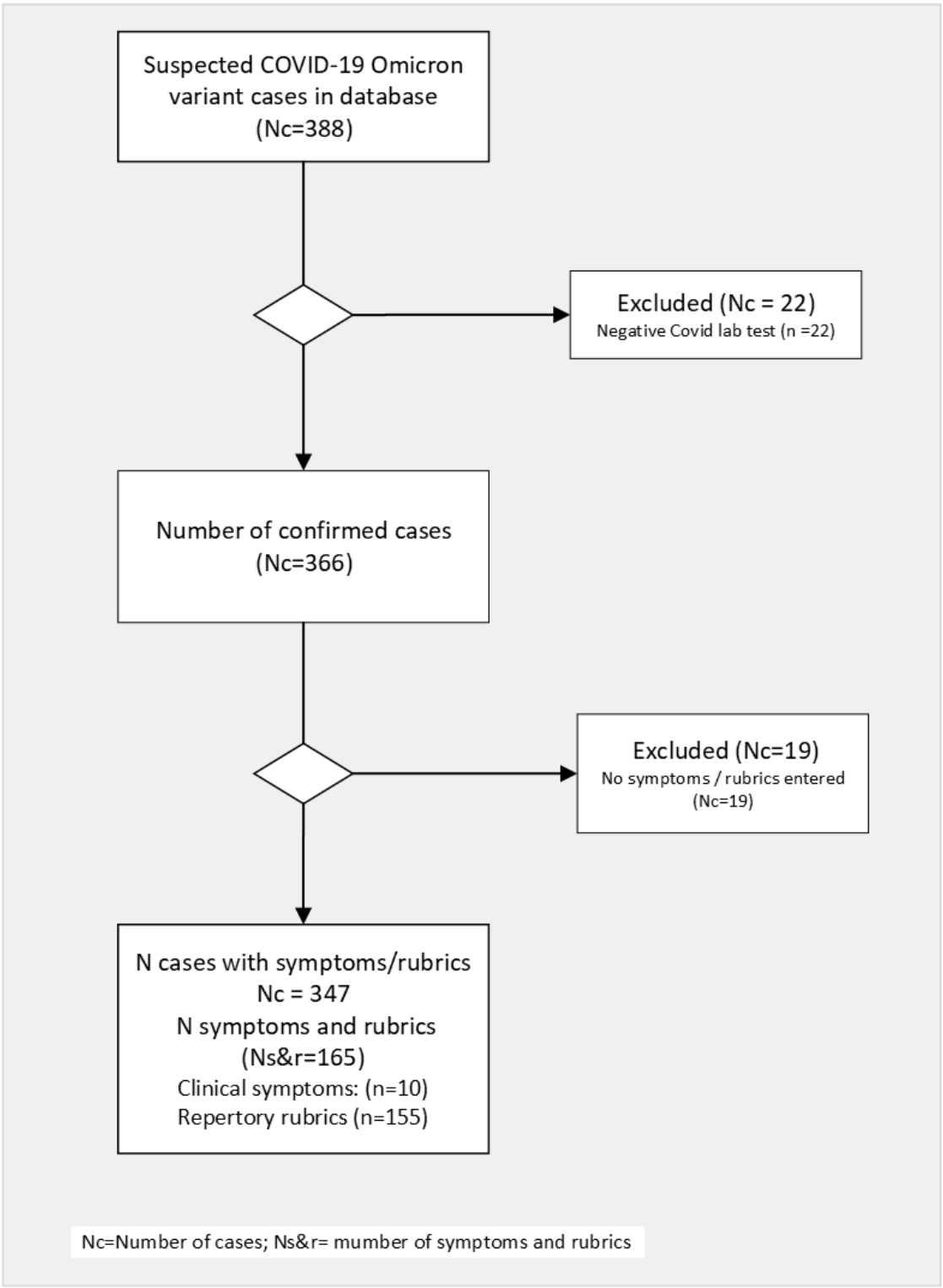

Figure 1. *Patient and symptom selection flowchart*

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.

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

Table 2. Main demographic and clinical characteristics of the patients

Analysis of symptoms

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

Appendix 2: Absolute occurrence of homeopathic symptom rubrics with a prevalence greater than 10%

The prevalence of the 10 clinical symptoms is depicted in figure 2 (red bars).

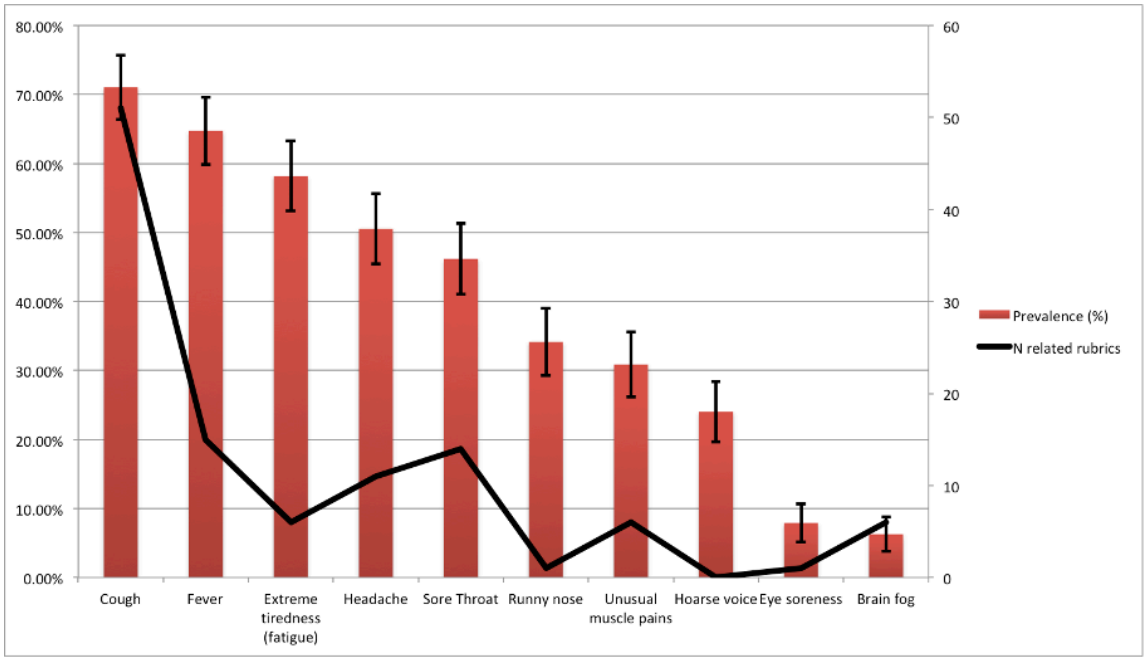

Figure 2. *Prevalence (with 95% CIs) of the clinical symptoms (bars / left axis) and the reported number of related homeopathic symptoms (line / right axis).*

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 to 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 clinical 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[2]. The main publication from France (n=468) was conducted by the EMERGEN consortium[6]. In this study they used a standardized clinical symptom questionnaire and genomic sequencing to confirm the Omicron variant diagnosis.

The clinical symptom prevalence is compared between the countries in Figure 4

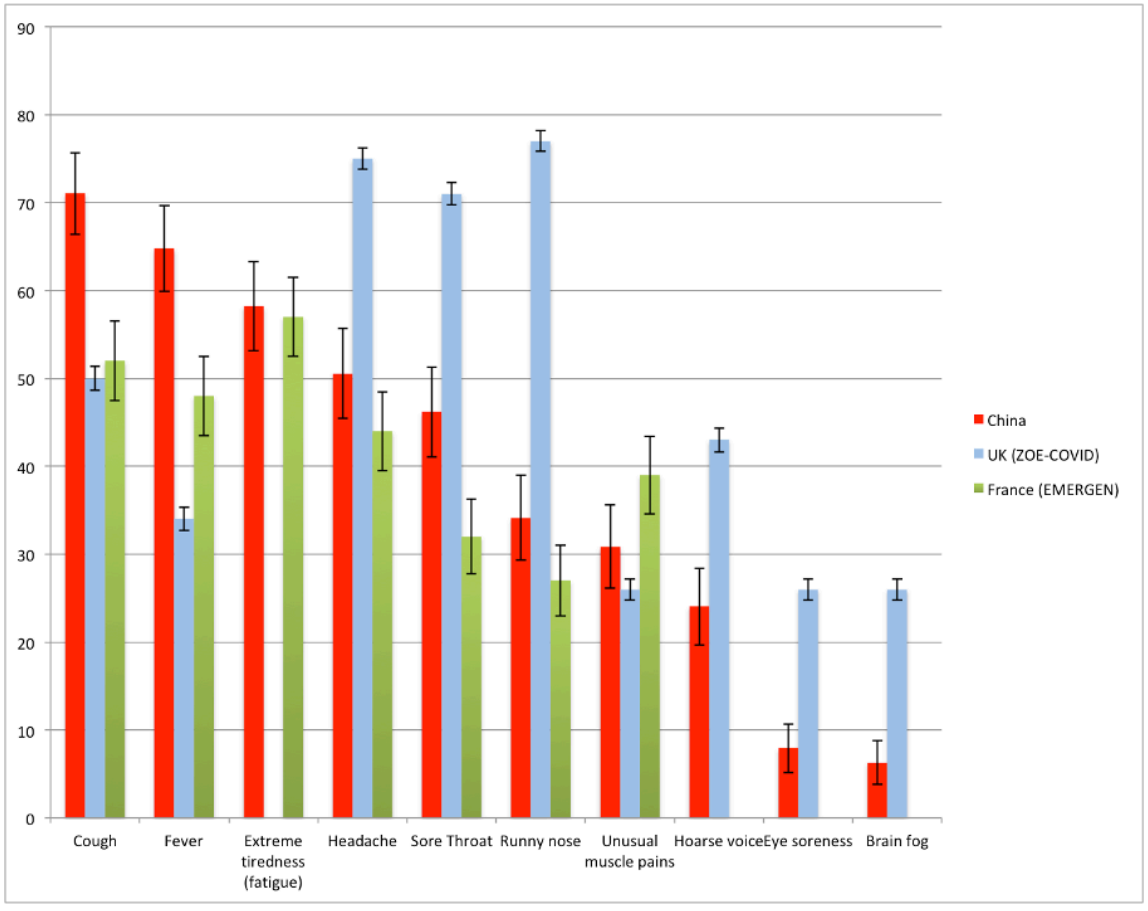

Figure 3. *Between country comparison of clinical symptom prevalence (% with 95% CIs). Missing bars are due to no data being available*

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Figure 3 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. This was also confirmed by a statistical analysis of the ranked symptoms (data not shown). 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 dataset, 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[10]. 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.

We decided to include 'brain-fog' as a clinical symptom in the questionnaire, even though it is a relatively subjective symptom. This was done because it is commonly reported in connection with COVID-19, and because further research suggests that is it a distinct and recognizable symptom cluster which is primarily characterized by fatigue, dizziness, myalgia, word-finding difficulties, and memory impairment[11].

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. Also, the sample size was fairly small (N=366), but still in a similar league compared to the number of cases in the EMERGEN Consortium study by Maisa et al[6] (N=468) as referred to above. In addition, the proportion of females in our sample was higher than that of males. Whilst this is representative of patients that tend to seek complementary and integrative medicine treatments, it makes the sample less representative for the Chinese population at large. Therefore, larger and broader samples would be useful to further substantiate our findings.

The data collected also included information on the homeopathic medicine(s) prescribed and outcomes. However, the primary focus of this article is on the diagnostic role of the clinical symptoms. Therefore, in this paper we only focused on the reported symptoms prior to receiving homeopathic treatment, and *not* on the course of, and changes in, symptoms following treatment. So no statements on the prognostic value of clinical and homeopathic symptoms are made.

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[12].

It should also be pointed out that the distinction between 'clinical' and 'homeopathic' symptoms is neither strict, nor absolute. For instance, odynophagia, lack of taste and lack of smell are considered to be both 'clinical' and 'homeopathic' symptoms. As mentioned, clinical symptoms are characterized by a pathophysiological connection between the symptoms and the disease. For homeopathic symptoms, a pathophysiological connection is possible, but not a requirement. 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* factors to indicate the specific homeopathic medicinal product most likely to be effective in that particular patient[13]. Despite observing an association between reported clinical symptoms and homeopathic symptoms (figure 3), it should be pointed out that for a significant proportion of homeopathic symptoms (36%), there was no association with the clinical symptoms. This is expected, and in line with the homeopathic principle of treating the 'patient', rather than treating the 'disease'.

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. For instance, the distinctly higher prevalence of fever in the Chinese population in comparison with the UK population could be due to the relative predominance in China of the Omicron BA.2 sub-type[13], which has been reported to be associated with more severe symptoms as compared to BA.1 sub-type[14]. Therefore, further studies are needed to properly assess the influence of the data collection method on symptom prevalence.

Our findings confirm reports from other countries that the occurrence of symptoms of chemosensory dysfunction is less common with the Omicron variant as compared to previous variants. This is of importance for better understanding the mechanisms behind these symptoms, which is still not fully understood[15].

Apart from the UK and French studies referred to in detail, we identified two more publications of interest. Lippi et al[16] 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[17]. 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.

Whilst fever was one of the most common symptoms, it should be pointed out that about 35% of the patients were without fever. Therefore, our data suggests that even in the absence of fever, for the Chinese population, testing should be considered for a patient with a cluster of 1 or 2 of the other five most common symptoms (i.e. cough, extreme tiredness, headache, sore throat, runny nose). Whether or not the selection of test-triggering symptoms should vary slightly between countries in order to optimize the predictive diagnostic value of the selected symptoms, would need to be informed by further studies.

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. Even though 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.

The use of test-triggering symptoms is currently less relevant in the context of the mass testing policy in place under China's zero-COVID-19 policy. However, given the inability to fully contain the spread of the highly transmissible Omicron variant, this policy is likely to face challenges in the future[18]. Apart from fever, identifying the most relevant test-triggering symptoms may therefore become more important from a public health point of view.

Supplementary files

- Supplementary file 1: Full version of the questionnaire
- Supplementary file 2: Homeopathic symptoms with a prevalence of more than 10%

Figure Captions

- Figure 1: Patient and symptom selection flowchart

- Figure 2: Prevalence of the clinical symptoms (bars / left axis) with 95% Confidence Intervals and the reported number of related homeopathic symptoms (line / right axis)
- Figure 3: Between country comparison of clinical symptom prevalences, with 95% confidence intervals. Missing bars are due to the absence of available data

Table Legends

- Table 1: Overview of the symptom questionnaire
- Table 2: Main Demographic and clinical characteristics of the patients

Conflict of Interest

None declared

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None

Author Contributions

Alex T and Yvonne F were involved in the planning, conduct, analysis, and writing of the article. Robbert van H and Aaron T were involved in the planning and interpretation of the analyses and writing of the article. All authors agree to the contents of the manuscript.

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* amel. = ameliorates; agg. = aggravates

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Declarations

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