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Disease burden from coronavirus disease 2019 symptoms among inpatients at the temporary military hospitals in Wuhan: A retrospective multi-center cross-sectional study

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Ethics approval

The research ethics committee of the No. 900 Hospital of Joint Logistics Troop of People's Liberation Army (PLA) gave ethical approval (The approval number: 2020-001).

Conflict of interest

None declared.

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Authors' contributions

Conceived and designed the studies: Xiao-xiao Li and Mai-hong He

Literature search and review: Mai-hong He and Xiao-xiao Li

Conducted questionnaire and PTO processes: Xiao-xiao Li, Jian-ping You, and Yong Chen

Collected and extracted the data: Xian Lin, Qing Zheng, and Ying Lin

Contributed materials: Maihong He, Qing Tan and Yue Kong

Analyzed and interpreted the data: Xiao-xiao Li, Jianping You, and Yong Chen

Drafted the article and revised it: Xiao-xiao Li and Mai-hong He

All authors gave approval before submission.

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ABSTRACT:

Aim: We aimed to establish a set of disability weights (DWs) for COVID-19 symptoms, evaluate the disease burden of inpatients, analyze the characteristics, and influencing factors of the disease.

Methods: DWs of COVID-19 symptoms were determined by the person-trade-off approach. The extracted medical records data of 2,702 randomly selected at three temporary military hospitals in Wuhan, China, were analyzed and used to calculate the disability adjusted life years (DALY). Means DALY between gender and age groups were tested. The relationship between DALY and age, gender, body mass index, length of stay, symptom duration before admission, and native place was determined by multiple line regression.

Results: For the DALY of each inpatient, severe expiratory dyspnea and mild cough and sore throat had the highest (0.399) and lowest (0.004) weights, respectively. The average synthetic DALY and daily DALY were 2.29±1.33 and 0.18±0.15 days, respectively. Fever and fatigue contributed the largest DALY at 31.36%; nausea and vomiting, and anxiety and depression contributed the least at 7.05%. There were significant differences between gender and age groups in both synthetic and daily DALY. Age, body mass index, length of stay, and symptom duration before admission were strongly related to both synthetic and daily DALY.

Conclusions: Although the disease burden was higher among females than in the males; however, their daily disease burdens were similar. The disease burden in the younger population was higher than that in the older population. Treatment at the hospitals relieved the disease burden efficiently, while delay in hospitalization could worsen it.

Keywords: COVID-19; Wuhan; Burden of disease; Bio-security; Symptom; Inpatient; Disability adjusted life years

Strengths and limitations

Our work firstly proposed the COVID-19 disability weights by each main symptom of COVID-19, and calculated the inpatient burden of disease caused by the symptoms.

The validity of the symptoms of COVID-19 inpatient's data obtained from the military medical units are likely to be high.

To determine the pure burden of disease caused by COVID-19 symptoms, this study excluded the inpatients with comorbidity, which makes the results more reliable.

The PTO method has been questioned for having a lower test-retest reliability than the time-tradeoff technique, which is another common technique used in DALYs studies; and cultural differences may affect the determination of PTO values.

Death cases are excluded, due to the reluctance of some family members to allow the use of their family members' death for a public study. By doing this, this study handled DALYs in the same way that we handled YLD.

Background

The coronavirus disease (COVID-19) pandemic is both a global public health emergency and a major bio-security event; it brings pain and loss to individuals and families, and a heavy burden to countries and societies [1, 2]. Scientific evaluation of the social and economic impact of the public health incident provides an important way to determine the therapeutic effectiveness in medical institutions and an important basis for the government to formulate relevant rescue policies and recovery measures. The economic burden of disease (BOD) and injury include treatment costs as well as various forms of losses in life (e.g., death and loss of the quality of life due to temporary or sustained decline in the quality of life) [3,4].

There are several new features of COVID-19 compared with those of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) [5]. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection can cause symptoms such as fever, fatigue, cough, dyspnea, headache, nausea, vomiting, abdominal pain, and diarrhea; in severe cases, it can lead to severe acute respiratory syndrome, multiple organ failure, and even death [6-9]. As it is an emerging disease, the BOD caused by COVID-19 is yet to be fully explored. Studying the BOD of COVID-19 and its symptoms will be helpful to further deepen the understanding of the disease, its harm, and severity and to predict the developing trend of the disease. Thus, public health authorities could improve the treatment and rehabilitation programs, renew relief measures, and adjust public health policies appropriately.

Since the 1990s, the World Health Organization (WHO) and the World Bank have proposed indicators to evaluate the BOD, that is, the disability-adjusted life years (DALY) measure. This single-utility measure used to determine the burden attributable to a specific disease is calculated using the standard method proposed by Murray and Lopez [10]. The DALY is a summary measure of population health that accounts for both the years of life lost (YLLs) and years lost due to disability (YLDs). The DALY was first developed for the primary purpose of quantifying the global burden of disease (GBD), expressed in terms of the relative

magnitude of losses of healthy life associated with different causes of disease and injury [11]. Since then, the DALY has been widely used globally to estimate the BOD at the national, international, and regional levels.

In recent years, the DALY has been used to evaluate the BOD caused by some specific diseases. Qi et al. comprehensively evaluated the direct and indirect BOD caused by Asian Lineage Avian Influenza A (H7N9) public health emergencies [12]. Zhang et al. evaluated and analyzed the BOD and related factors in hospitalized patients with coal workers' pneumoconiosis and provided the basis for improving relevant medical policy [13]. Bacellar et al. used similar method to assess the BOD in hospitalized elderly patients with neurological disorders in Brazil, and recommended measures to improve the treatment plan [14]. Adopting the WHO approach, Pei and Li et al. formulated the disability weights (DWs) for chronic mountain disease, which was used to calculate the BOD among soldiers stationed at Tibet, and provided an important basis for evaluating the ability of troops to carry out tasks [15].

The DALY method could provide important insights into public health studies and practice regarding COVID-19. This year, series of researches were conducted worldwide to estimate the BOD of COVID-19 in different regions, from multiple perspectives, and using different methods. Jo et al. adopted DW from previous similar causes to calculate the BOD due to COVID-19 in Korea including YLDs and YLLs [16]. Oh et al. estimated the YLLs due to COVID-19 in 30 high-incidence countries using the WHO-provided data [17]. To assess the socio-economic burden of COVID-19 pandemic in Italy, Nurchis et al. estimated YLLs and YLDs along with the productive YLL and the comparable DW of lower respiratory tract infection was adopted to estimate the YLDs [18]. Mohanty et al. examined COVID-19 impact in the USA, Italy, Germany, and Sweden's longevity, years of potential life lost, and DALY, and also adopted similar diseases DW as proxy [19]. Furthermore, Ortiz-Prado et al. also assessed the BOD caused by COVID-19 in Ecuador by adopted other similar diseases DW [20].

These researches not only contributed greatly to the understanding of COVID-19 BOD, but also

provided the basis for the global COVID-19 public health services and related policy-making. However, in recent reports, the assessment of COVID-19 BOD remained at the macro level and relatively unclear. The challenge here relates to the fact that only the DWs from similar diseases were adopted, leaving COVID-19 with a singular DW, which ignored the complexity of COVID-19 symptoms. Until now, limited reports exist on China's COVID-19 BOD, especially BOD based on each COVID-19 symptom, in detail. Thus, this study aimed to establish the DW for COVID-19 symptoms, to estimate the BOD among inpatients in Wuhan, China, and to analyze the characteristics and potential influencing factors. To design this technical approach, in this study we referred to the previous studies' methods to design this technical approach. The BOD caused by COVID-19 symptoms was evaluated according to the data from existing medical records.

Method

Selection of the population groups

To counter the public health disaster and bio-security crisis caused by COVID-19 in Wuhan, PLA performed a series of non-combat military operations. These included the deployment of three temporary military hospitals: Huoshenshan Hospital (from March 2, to April 15, 2020), Taikang-Tongji Hospital (March 13, to April 16, 2020), and Guanggu Woman and Child Hospital (March 13, to April 16, 2020). The first hospital was a newly built one while the other two were civil medical facilities temporarily utilized by the PLA medical staff. While in operation, all the hospitals were designated as COVID-19 special hospitals used to hospitalize COVID-19 patients only.

All the analyzed inpatient data were selected randomly from the three temporary military hospitals' medical records using the same recording standard. The included inpatients' hospitalization period ranged from February 5 to April 5, 2020. The selection process conducted from May 25 to June 5, 2020 after the closure of the temporary hospitals is shown in Fig. 1. Data for 2,702 inpatients from the medical records were included in this study. All the inpatients treated by the military medical staff were from the military

hospitals affiliated to the PLA.

<Insert Fig. 1 here>

The diagnosis and treatment method were according to the "Diagnosis and treatment standard of COVID-19 (7th edition)" published by the PRC central government [21]. All patients were hospitalized before the release of the 7th edition was reconfirmed according to the diagnostic criteria. The inclusion criteria were having been diagnosed of COVID-19 at the hospitals according to the standard guideline and been hospitalized and treated continuously at the hospitals. To determine the BOD caused by COVID-19, inpatients with records of any other morbidity (other infectious disease, other respiratory disease, psychiatric disease, tumor, pregnant and lactating women, chronic cardiac, liver, kidney, and neurological diseases) were excluded from the study. We also excluded cases of COVID-19 inpatient deaths, due to the reluctance of their family members to allow the use of their family members' data for a public study. Similarly, cases with incomplete medical records were also excluded.

Establishment of the disability weights for COVID-19 symptoms

DW is a key component of BOD analysis that represents the severity of an illness. DW ranges from 0 to 1, where 0 represents healthy life and 1 represents death [4]. The WHO has been conducting GBD studies for several years, with series of DWs derived for different health states that are the outcomes of different diseases [22-26].

Because COVID-19 is a new infectious disease, no DWs existed for COVID-19 symptoms in the WHO's DWs' list; thus, we attempted to establish customized DWs for COVID-19 symptoms. First, COVID-19 symptoms were listed following the literature review of a series of newly published COVID-19 clinical reports. Based on these, three rounds of questionnaires were completed by front-line medical staffs in the three military field hospitals in Wuhan to derive a raw list of COVID-19 symptoms for DWs establishment (questionnaire sample is shown in Additional file 1).

Then, we convened a nine-expert panel composed of three senior respiratory physicians, two senior infectious disease physicians, one epidemiologist, one public health management expert, and two nursing experts. Based on the raw list of COVID-19 symptoms, the panel performed Delphi process to finally determine the symptom list for DWs creation [27].

Then, the panel members performed the Person-Trade-Off (PTO) exercise to derive each symptom's DW by three levels of severities (health stages) [15, 28, 29]. The health stages were described on an A4-sized vignette that contained disease-specific information in simple terminologies. As a reference framework for this task, the panel members were provided with a WHO-GBD framework table, which displayed 7 disability classes and 22 anchoring example conditions. The coefficient of variation (CV) was calculated to determine the need for additional rounds of discussion and reassignment of values.

Data extraction

Basic information for the confirmed cases included the identification number (ID), age, gender, weight, height, native place, date of onset reported by patient, diagnostic conclusion, all the symptoms recorded by the medical staff, and inpatient and outpatient time. Nine age groups were created: <10, 10-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, and >80 years. Body mass index (BMI) was calculated from each patient's weight and height, while duration of symptoms was determined as the length of stay + symptom duration before hospitalization (by self-report in the medical record).

To accurately extract the medical data from the records, we trained six staffs to standardize the criteria of how to judge an inpatient with one or more symptoms in a day and how severe the symptoms were according to the medical records. During the data extraction, the six staffs were divided into three groups of two in each group and a cross-check was conducted when data were extracted from the records. The extraction process was conducted from May 29 to August 7, 2020.

Calculation of DALY for COVID-19 symptoms

The DALY was used to estimate the disease burden due to COVID-19 symptoms. The DALY for a disease

or health condition were calculated as the sum of the YLLs due to premature mortality in the population and the equivalent 'healthy' YLDs for incident cases of the health condition [4, 11, 30]. However, this study did not consider the death cases of COVID-19. Therefore, the DALY due to COVID-19 was equal to the YLDs. Thus, a patient's individual DALY was calculated case-by-case using the following formula [15]:

$$\mathrm{DALY} = \int_{x=\alpha}^{x=\alpha+L} DC\, xe^{-\beta x} e^{-\gamma(x-\alpha)} dx \qquad (1.0)$$

In this formula, *D* represents DW, *K* is an age weighting factor, *C* is a constant, *r* is the discount rate, *a* is age at the beginning, β is a parameter from the age weighting function, and *L* is life time with disability. We used the base case recommended by Murray and Lopez, with C = 0.1658, r = 0.03, K = 1, and β = 0.04 [15, 31].

Considering that the COVID-19 inpatient's hospitalization time was relatively short, *L in* the formula (1.0) is shorter than 1 year, thus the age of each inpatient was treated as fixed. Accordingly, the formula was simplified into:

$$\mathrm{DALY} = DCxe^{-\beta x} \qquad (2.0)$$

In formula 2.0, $Cxe^{-\beta x}$ reflects the life value discounted by age. This function is based on the hypothesis that life value is different for different age groups: a person's life value increases after he/she is born and reaches the peak in one's youth; after that, the life value `declines with age (Fig. 2). As a result, in calculating the DALY, although the symptoms are all the same, the DALY will differ for the different age groups.

<**Insert Fig. 2 here**>

In this study, a person's DALY was calculated as follows: 1) the cumulative duration (in days) of each health condition (a health condition is one type of symptom severity); 2) the health condition's duration was multiplied by the corresponding DW to get the DALY of each health condition; 3) all the health conditions' DALY was summed up into an inpatient's synthetic DALY for COVID-19; 4) the synthetic

DALY was divided by the patient's length of stay to get an inpatient's daily DALY. Considering that the inpatient's length of stay was relatively short, the unit of DALY was set as days.

Statistical analysis

The demographic characteristics of the hospitalized patients by hospital, gender, and native place, were calculated. The distribution of each symptom by each hospital, gender, and overall population, were calculated. The means of signal symptom's DALY, synthetic DALY, DALY per day (daily DALY), age, BMI, and symptoms course (including symptom duration before hospitalization, length of stay, and overall duration) by hospital, gender, and age groups were calculated and compared by analysis of variance (ANOVA) or t-test (for two groups only). The ratio difference of the cumulative duration (in days) of the symptom severity levels (mild, moderate, and severe) was tested by chi-square test. The proportions of BOD caused by each symptom by gender and age group, and in the entire sample population were computed. DALY per 1,000 capita was also calculated by age group and gender. Besides, the proportion of each symptom's duration in the whole study population was also calculated.

To test the relationship between the DALY and age, gender, BMI, and symptom duration, separate linear regression analyses were performed using the DALY as the dependent variable and age, gender, BMI, native place, symptom duration before hospitalization, and length of stay as the independent variables. In the regression models, gender and native place were set as categorical variables while the others were continuous variables. Synthetic DALY and daily DALY were analyzed, and each hospital's study population and overall study population were also analyzed separately. IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, N.Y., USA) was used to perform ANOVA and linear regression analyses. In all the analyses, a P-value <0.05 was considered statistically significant.

Patient and public involvement

This was a multi-center retrospective cross-sectional descriptive study of COVID-19 inpatients in Wuhan,

the People's Republic of China (PRC). The study was performed after the closure of the three temporary military hospitals. None of the inpatients were involved in any health intervention. All individual data were anonymized prior to retrieval and analysis. Because the study only analyzed the data, the study design has no patient involved.

Results

Patient characteristics

The total number of included cases was 2,702 (that is 872, 921, and 909 selected cases from Taikang-Tongji, Huoshenshan, and Guanggu Woman and Child Hospitals, respectively). Table 1 shows the inpatients' demographic characteristics.

They were all Chinese: 1,326 female and 1,376 male inpatients; 2,618 were natives of Hubei province, while 84 were not. The mean age was 55.52±16.09 years and 54.18±15.85 years for female and male populations, respectively. The mean age for the male population was significantly lower (P=0.03). No significant difference was found in symptoms duration before hospitalization, length of stay, and overall duration of symptoms between female and male populations.

For age groups, there were significant difference in symptoms duration before hospitalization, length of stay, and overall duration of symptoms according to the ANOVA test (P>0.05). The least significant difference (LSD) test showed that in symptoms duration before hospitalization, age group 20-29 years had the lowest duration, whereas the group 60-69 years had highest age duration, with a significant difference between the groups (P<0.05).

Table 1: Demographic characteristics of inpatients

Characteristics	Number of patients	Proportio

		n
Hospital		
Taikang-Tongji	872	32.27%
Huoshenshan	921	34.09%
Guanggu Woman and Child	909	33.64%
Gender		
Female	1326	49.07%
Male	1376	50.93%
Native place		
Hubei province	2618	96.89%
Outside Hubei province	84	3.11%

Duration of symptoms

Table 2 shows the means for the inpatients age, BMI, symptoms duration before hospitalization, length of stay, and overall duration of symptoms by hospital, gender, and age group. There were no significant differences in age, symptoms duration before hospitalization, length of stay, and overall duration of symptoms among the three hospitals according to the ANOVA test (P>0.05). The inpatients' age ranged from 11 to 94 years, with a mean of 54.84±15.98 years, while BMI ranged from 16.23 to 28.7, with a mean of 22.11±1.94. The length of stay ranged from 5 to 50 days, with a mean of 17.88±7.38 days; the self-reported symptom duration before hospitalization ranged from 2 to 72 days, with a mean of 24.11±15.66 days. By combining the duration of inpatient and self-reported symptom duration before hospitalization, we obtained the duration of the symptoms, which ranged from 7 to 94 days, with a mean of

41.99±16.37 days.

Table 2: Means of age, body mass index, symptoms duration before hospitalization, length of stay, and overall duration of symptoms by hospital, gender, and age group of the inpatients

	Age	Body mass index	Symptoms duration before hospitalization	Length of stay	Overall duration of symptoms
Hospital					
Taikang-Tongji (n=872)	54.76±15.75	22.25±1.92	24.36±15.92	17.92±7.42	42.28±16.57
Huoshenshan (n=921)	55.21±15.88	22.02±2.00	24.65±15.65	17.91±7.34	42.55±16.33
Guanggu Woman and Child (n=909)	54.53±16.29	22.07±1.90	23.34±15.40	17.80±7.39	41.15±16.21
Gender					
Female (n=1326)	55.52±16.09	22.14±1.92	24.11±15.40	18.11±7.34	42.22±16.04
Male (n=1376)	54.18±15.85	22.08±1.96	24.12±15.92	17.66±7.41	41.77±16.69
Age group (years)					
<20 (n=49)	15.59±2.53	21.79±2.19	24.61±14.01	13.22±5.67	37.84±13.16
20-29 (n=116)	25.35±2.53	21.95±1.76	16.28±12.36	14.91±5.69	31.20±14.32
30-39 (n=305)	34.87±2.84	22.21±1.98	23.77±16.68	15.79±6.71	39.56±17.44
40-49 (n=529)	44.84±2.96	22.10±1.97	21.56±14.29	17.24±6.93	38.80±14.31
50-59 (n=592)	54.68±2.80	22.13±1.97	23.83±15.81	17.98±7.20	41.81±16.15
60-69 (n=635)	64.16±2.72	22.2±1.910	27.63±16.08	18.49±7.12	46.12±16.39
70-79 (n=306)	73.96±2.88	21.99±1.84	25.12±15.95	20.34±8.09	45.46±16.04
>79 (n=170)	84.49±3.35	21.97±2.04	23.94±14.37	19.86±8.96	43.79±17.55
Overall (n=2702)	54.84±15.98	22.11±1.94	24.11±15.66	17.88±7.38	41.99±16.37

To further analyze the course of the disease (duration of symptom before hospitalization, length of stay, and overall duration of symptom), we drew line diagrams of the means by age group and gender (Figs. 3 to 5). We also performed two-way ANOVA to test for the difference in the mean course of disease by age group and gender. The results showed that age was significantly associated with the three course of disease variables ($P<0.05$), whereas gender was not associated, and two factors had no significant interaction effect

(*P*>0.05).

<Insert Fig. 3, 4, and 5 here>

We also calculated each symptom's cumulative duration (in days) by three levels of severity in the overall sample population (Table 3). Fever and fatigue had the longest duration, with a cumulative duration of 26,863 days. The lowest cumulative duration occurred with anxiety and depression, which had 4,565 days. By chi-square test, the proportion of severity differed significantly among different symptoms (*P*<0.05). Anxiety and depression had the highest proportion of severe conditions (30.54%), whereas cough and sore throat had the highest proportion of mild conditions (10.63%). Based on these findings, composition proportions of the cumulative duration (in days) by symptom in the whole study population are shown in Fig. 6a. Cough and sore throat contributed the largest part of the symptom duration, with a proportion of 32.06%, whereas anxiety and depression contributed the least, with a proportion of 3.72%.

<Insert Fig. 6 here>

Table 3: Each COVID-19 symptom's cumulative duration (in days) in the study population

Symptoms	Mild		Moderate		Severe		Overall duration
	Day	%	Day	%	Day	%	(days)
Fever and fatigue	2,231	8.31	20,846	77.60	3,785	14.09	26,863
Muscular soreness	334	3.08	8,220	75.71	2,303	21.21	10,858
Dizziness and headache	92	1.68	3,864	70.51	1,524	27.81	5,481
Expiratory dyspnea	104	1.83	4,096	72.23	1,471	25.94	5,672
Cough and sore throat	4,180	10.63	30,172	76.75	4,959	12.61	39,312
Palpitations and chest tightness	862	5.86	11,232	76.34	2,620	17.81	14,715
Nausea and vomiting	387	4.40	6,434	73.19	1,970	22.41	8,792

Abdominal pain and diarrhea	150	2.36	4,534	71.30	1,675	26.34	6,360
Anxiety and depression	35	0.77	3,135	68.69	1,394	30.54	4,565
Overall	8,375	6.83	92,533	75.47	21,701	17.70	122,610

COVID-19, coronavirus disease 2019.

DWs of COVID-19 symptoms

After two rounds of the Delphi process by the panel, we developed a 9-item COVID-19 symptoms' list with six categories. Each symptom included three levels of severity (mild, moderate, and severe), thereby representing 27 health stages. Based on these, we derived the DWs for each health stage by the PTO exercise; along with the expert panel, a consensus was reached at the fifth round of the Delphi process (CV <0.5). Thus, the DWs of 27 COVID-19 health stages were derived; severe expiratory dyspnea had the highest weight of 0.399, while mild cough and sore throat had the lowest weight of 0.004, as shown in Table 4.

Table 4: Disability weights for the symptoms of COVID-19

Category	Symptom categories	Health stages	DWs	95% CI
Systemic symptoms	Fever and fatigue	Mild	0.006	(0.004-0.008)
		Moderate	0.051	(0.036-0.066)
		Severe	0.133	(0.089-0.177)
	Muscular soreness	Mild	0.015	(0.012-0.018)
		Moderate	0.054	(0.041-0.067)
		Severe	0.110	(0.059-0.113)
Neurological symptoms	Dizziness and headache	Mild	0.028	(0.019-0.037)

		Moderate	0.083	(0.055-0.111)
		Severe	0.163	(0.109-0.217)
Respiratory symptoms	Expiratory dyspnea	Mild	0.045	(0.040-0.050)
		Moderate	0.108	(0.085-0.131)
		Severe	0.399	(0.293-0.505)
	Cough and sore throat	Mild	0.004	(0.003-0.005)
		Moderate	0.011	(0.008-0.014)
		Severe	0.034	(0.023-0.045)
Cardiovascular symptoms	Palpitations and chest tightness	Mild	0.041	(0.029-0.053)
		Moderate	0.072	(0.048-0.096)
		Severe	0.179	(0.120-0.238)
Gastrointestinal symptoms	Nausea and vomiting	Mild	0.009	(0.006-0.012)
		Moderate	0.057	(0.038-0.076)
		Severe	0.130	(0.089-0.171)
	Abdominal pain and diarrhea	Mild	0.011	(0.008-0.014)
		Moderate	0.091	(0.062-0.120)
		Severe	0.194	(0.128-0.260)
Psychological symptoms	Anxiety and depression	Mild	0.030	(0.021-0.039)
		Moderate	0.120	(0.084-0.156)
		Severe	0.366	(0.243-0.489)

COVID-19, coronavirus disease 2019; DWs, disability weights; CI, confidence interval

DALY of inpatients

According to the formula and DWs, the DALY of each inpatient for each symptom was calculated, as well

as their synthetic DALY and DALY per day. The composition proportion of DALY in the study population is shown in Fig. 6b. Among these, fever and fatigue contributed the largest part of the DALY, with a proportion of 31.36%, whereas nausea and vomiting and anxiety and depression contributed the smallest part, at 7.05%.

The mean and standard deviation of DALY by symptom by hospital, gender, and overall study population are shown in Table 5, and those by age group are shown in Table 6. The mean overall DALY in the overall study population was 2.29±1.33 days, whereas the mean DALY per day was 0.18±0.15 days. Among the three hospitals, no significant difference occurred with each symptom's DALY, the synthetic DALY, or the DALY per day in ANOVA test (P>0.05). However, in the LSD test of the ANOVA, synthetic DALY in Huoshenshan Hospital was significantly lower than that in Taikang-Tongji (P =0.048) and Guanggu Woman and Child (P =0.031) Hospitals, respectively. The DALY per day in Huoshenshan Hospital was significantly lower than that in Guanggu Woman and Child Hospital (P =0.023). The DALY for fever and fatigue, muscular soreness, palpitations and chest tightness, nausea and vomiting, and synthetic DALY was significantly lower for the male population than for the female population by t-test (P>0.05). In the inpatient population the overall DALY per 1,000 capita was 6.28, in female and male population the overall DALY per 1,000 capita was 6.07 and 6.51 years respectively.

Table 5: The mean DALY of COVID-19 inpatient by symptoms in each hospital, gender, and overall study population

Symptom	Taikang-Tongji (n=872)	Huoshenshan (n=921)	Guanggu Woman and Child (n=909)	Female (n=1326)	Male (n=1376)	Overall (n=2702)
Fever and fatigue	0.72±0.60	0.70±0.59	0.73±0.63	0.75±0.61	0.69±0.60‡	0.72±0.61

Muscular soreness	0.19±0.18	0.18±0.17	0.18±0.17	0.19±0.18	0.18±0.17‡	0.18±0.17
Dizziness and headache	0.14±0.18	0.13±0.17	0.14±0.20	0.13±0.17	0.14±0.19	0.14±0.18
Expiratory dyspnea	0.18±0.31	0.18±0.32	0.21±0.38	0.19±0.34	0.19±0.33	0.19±0.34
Cough and sore throat	0.18±0.12	0.18±0.12	0.18±0.13	0.18±0.12	0.18±0.13	0.18±0.12
Palpitations and chest tightness	0.41±0.45	0.37±0.40	0.39±0.43	0.42±0.44	0.36±0.41‡	0.39±0.43
Nausea and vomiting	0.16±0.24	0.16±0.23	0.17±0.24	0.17±0.25	0.15±0.23‡	0.16±0.24
Abdominal pain and diarrhea	0.18±0.30	0.16±0.26	0.17±0.24	0.17±0.26	0.16±0.28	0.17±0.27
Anxiety and depression	0.16±0.23	0.15±0.21	0.17±0.24	0.16±0.23	0.17±0.23	0.16±0.23
Total DALY	2.33±1.33	2.21±1.26*	2.34±1.38	2.38±1.33	2.21±1.32‡	2.29±1.33
DALY per day	0.19±0.14	0.18±0.14*†	0.19±0.16	0.19±0.14	0.18±0.15	0.18±0.15

* $P<0.05$ vs. Guanggu Woman and Child Hospital; † $P<0.05$ vs. Taikang-Tongji Hospital; ‡ $P<0.05$ vs. female.

DALY, Disability-adjusted life years.

Table 6: COVID-19 inpatient DALY by symptoms and age group

Symptom	<20 years (n=49)	20-29 years (n=116)	30-39 years (n=305)	40-49 years (n=529)	50-59 years (n=592)	60-69 years (n=635)	70-79 years (n=306)	>79 years (n=170)
Fever and fatigue	0.75±0.58	0.79±0.73	0.99±0.89	0.88±0.70	0.73±0.54	0.60±0.42	0.55±0.38	0.39±0.28
Muscular soreness	0.14±0.12	0.16±0.19	0.25±0.23	0.22±0.20	0.19±0.16	0.16±0.13	0.15±0.12	0.11±0.09
Dizziness and headache	0.15±0.18	0.13±0.16	0.17±0.22	0.16±0.22	0.16±0.21	0.11±0.13	0.10±0.11	0.08±0.09
Expiratory dyspnea	0.19±0.24	0.11±0.15	0.18±0.28	0.21±0.43	0.25±0.45	0.17±0.24	0.13±0.19	0.18±0.25
Cough and sore throat	0.20±0.09	0.25±0.13	0.26±0.15	0.21±0.14	0.18±0.12	0.15±0.09	0.14±0.08	0.09±0.06
Palpitations and chest tightness	0.33±0.43	0.54±0.54	0.51±0.61	0.47±0.5	0.37±0.35	0.37±0.34	0.31±0.33	0.17±0.17

Nausea and vomiting	0.21±0.28	0.25±0.36	0.21±0.30	0.17±0.23	0.18±0.25	0.15±0.22	0.10±0.12	0.06±0.07
Abdominal pain and diarrhea	0.10±0.11	0.25±0.31	0.22±0.43	0.22±0.36	0.15±0.20	0.13±0.17	0.13±0.17	0.10±0.16
Anxiety and depression	0.21±0.25	0.18±0.24	0.21±0.28	0.20±0.28	0.19±0.25	0.14±0.16	0.09±0.12	0.06±0.08
Synthetic DALY	2.28±0.93	2.65±1.46	2.98±1.87	2.74±1.52	2.41±1.12	1.98±0.92	1.70±0.79	1.24±0.69
DALY per day	0.21±0.11	0.21±0.15	0.25±0.18	0.22±0.17	0.20±0.16	0.15±0.10	0.11±0.06	0.09±0.06

COVID-19, coronavirus disease 2019.

DALY, Disability-adjusted life years.

According to the ANOVA test, the mean DALY by age groups differed significantly for each symptom and also for the synthetic DALY and DALY per day (P<0.05). The DALY for both single symptoms and synthesized DALY had the tendency of an inverse U-shaped curve. The DALY increased with age, reached a peak in the prime of life, and then slowly decreased with age. In this study, the 40-49 years age group had the highest DALY for expiratory dyspnea; while the 20-29 years group had the highest DALY for palpitations and chest tightness, nausea and vomiting, and abdominal pain and diarrhea. DALY for the other symptoms, synthetic DALY, and DALY per day peaked in those aged 20-29 years.

The composition of synthetic DALY for each symptom by hospital is shown in Fig. 7, and the composition of the synthetic DALY by gender and age group are shown in Fig. 8 and Fig. 9, respectively.

To visualize each symptom's DALY by age group and gender, we drew a thermal map for each subgroup's DALY per 1,000 capita (in days), as shown in Fig. 10. Fever and fatigue were in the most intense (red) area, while palpitations and chest tightness were the next intense area, for both female and male populations. Female population aged 30-39 years had the highest DALY score of 1,115 DALY (in days) per 1,000 capita. On the contrary, in the female population above 79 years, the lowest DALY

temperature of 50 DALY (in days) per 1,000 capita was found.

<**Insert Fig. 7, 8, 9, and 10 here**>

We also identified the changing curves of the means synthetic DALY, DALY per day and by age groups and gender, as shown in Fig. 11 and Fig 12. The two-way ANOVA test showed that both age and gender significantly affected synthetic DALY (P<0.05); and there was a significant interaction effect between the two variables (P=0.02). However, when DALY per day was the dependent variable, the significant difference with gender was lost (P=0.08), whereas age remained significant (P<0.05), and the interaction effect between the two variables was also lost (P=0.518).

<**Insert Fig. 11 and 12 here**>

Linear regression analyses

The results of the multiple linear models are shown in Table 7. When synthetic DALY was set as the dependent variable, all of the four models were significant (P<0.05), with R^2 ranging from 0.214 to 0.240. In the four models, symptom duration before hospitalization and length of stay were significantly positively associated with synthetic DALY; while age was significantly negatively associated with the overall synthetic DALY. For gender and BMI, however, the four models showed different results. In the Guanggu Woman and Child Hospital model, gender and BMI were not significant (P=0.098 and P=0.146); in contrast, in the other three models, gender and BMI were significant, indicating that the female population had higher DALY than the male population (P<0.05), and high BMI population had higher DALY (P<0.05).

When DALY per day was set as the dependent variable, all of the four models were significant (P<0.05), with R^2 ranging from 0.153 to 0.188. For age and symptom duration before hospitalization, the level of significance was the same as with model type I. Length of stay remained significant; however, the effectiveness was negatively reversed for DALY. For gender, the overall sample and Huoshenshan Hospital

models were significant (P=0.037 and P=0.022, respectively), and for BMI, the overall sample and Taikang-Tongji Hospital models were significant (P<0.001 and P=0.001, respectively). In all the models, native place was not significant (P>0.05).

Table 7 Linear regression analyses between COVID-19 inpatient's DALY and individual variables

Variable	Model Type I *								Model Type II **							
	Overall sample		Taikang-Tongji		Huoshenshan		Guanggu Woman and Child		Overall sample		Taikang-Tongji		Huoshenshan		Guanggu Woman and Child	
	R^2=0.222		R^2=0.214		R^2=0.224		R^2=0.240		R^2=0.164		R^2=0.188		R^2=0.170		R^2=0.153	
	β	*P*-value	β	*P*-value	β	*P*-value	β	*P*-value	β	*P*-value	β	*P*-value	β	*P*-value	β	*P*-value
Age	-0.415	<0.001	-0.431	<0.001	-0.388	<0.001	-0.429	<0.001	-0.290	<0.001	-0.288	<0.001	-0.269	<0.001	-0.312	<0.001
Gender	0.069	<0.001	0.070	0.020	0.088	0.003	0.048	0.098	0.037	0.037	0.047	0.123	0.070	0.022	-0.002	0.956
Symptom duration before hospitalization	0.166	<0.001	0.169	<0.001	0.206	<0.001	0.133	<0.001	0.208	<0.001	0.207	<0.001	0.251	<0.001	0.180	<0.001
Length of stay	0.312	<0.001	0.265	<0.001	0.334	<0.001	0.338	<0.001	-0.139	<0.001	-0.184	<0.001	-0.134	<0.001	-0.108	0.001
Body mass index	0.048	0.005	0.090	0.003	0.011	0.719	0.042	0.146	0.062	<0.001	0.101	0.001	0.030	0.331	0.056	0.068
Native place	0.015	0.365	0.000	0.987	-0.017	0.549	0.030	0.303	0.003	0.856	-0.005	0.882	-0.002	0.951	0.024	0.437

COVID-19, coronavirus disease 2019; DALY, disability-adjusted life years.

* Dependent variable is overall DALY; ** Dependent variable is DALY per day.

Discussion

BOD caused by COVID-19 and its symptoms in inpatient population is an indirect economic and social burden; however, it is usually ignored by some public health authorities. According to this study, each cured inpatient averagely lost about 2-3 days of healthy life due to COVID-19 symptoms and, on an average, discounted almost 1/5th of the quality of life every day. If viewed from the population's perspective, the indirect life loss per 1,000 inpatients was more than 6 years, even if death was not considered. If we consider the increasing number of COVID-19 inpatients worldwide [32], the indirect life loss could be an enormous figure. Considering pre-hospitalization symptoms and temporary or permanent loss of body function after patients are discharged from the hospital, the cumulative loss of life would be several times more.

In general, inpatient's BOD caused by each symptom of COVID-19 in the three hospitals had a relatively smaller gap; however, when the BOD was added together, inpatients at Huoshenshan Hospital enjoyed a relatively lower overall BOD than the other two hospitals' inpatients. However, the gap was small. This is accounted for by the greater investment of manpower and material resources at Huoshenshan Hospital.

As far as the DWs are concerned, among the main symptoms of COVID-19, severe expiratory dyspnea accounted for the most serious BOD, followed by the negative psychological symptoms such as severe anxiety and depression. In actual cases, however, the prevalence of severe depression and dyspnea among the inpatient population was not high. Although the prevalence and BOD of anxiety and depression were not high, the ratios of their severity were notable and should be taken into consideration in medical care. Among the inpatient population, the most common symptoms were cough and sore throat, but these had low contribution to the BOD. In contrast, fever and fatigue caused most of the BOD. This suggests that to reduce the BOD, the symptomatic treatment should focus on the symptoms that caused higher BOD.

In general, the BOD of female inpatients was higher than that of male inpatients, which is similar to the findings in Korean report [16]; however, when the BOD was shared per day in the hospitals, there were no significant differences. This indicated that the symptoms in female inpatients, in particular, during the period of hospitalization, were more serious (i.e., the symptoms fluctuated dramatically during hospitalization). In terms of the specific symptoms such as fever, fatigue, muscular soreness, palpitations, chest tightness, nausea, and vomiting; these could cause more BOD in female than in male populations. For the other symptoms, there was no significant difference between female and male populations in the BOD. Thus, cardiovascular and respiratory system symptoms in female inpatients were more serious, as were systemic symptoms, in particular, for the disease course. Consequently, more attention should be paid to female patients' cardiovascular and respiratory systems during the acute stage.

Contrary to the general thinking, the BOD of the younger population was found to be higher than that of the older population in our study. Both ANOVA and linear models support this conclusion. The main reason for this trend was that the "value" of life at different age stages was fully accounted for in the BOD evaluation. The illness among the youths and middle-aged could bring about greater personal, social, and economic losses. Although the symptoms in the elderly may be slightly more severe, it is more significant to reduce the disease burden in youths and middle-aged inpatients with COVID-19 from a macro-economic perspective when the medical resources are limited.

Whether for the synthetic DALY or DALY per day, most of the linear models indicated that the BOD for obese people was more serious. Studies have shown that obesity affects the immune function of the body, and burden borne by the organs in obese people is heavier than for in non-obese people. Obese people are not only more likely to suffer from various types of infection including COVID-19 but also experience more serious complications [33, 34]. Therefore, in order to reduce the disease burden of obese people, it is necessary to strengthen the intervention on the symptoms of obese people.

Although the synthetic DALY increased as the hospitalization time, DALY per day decreased significantly with hospitalization. Although the cumulative BOD increased, the BOD shared per day continuously reduced, and the trend of this reduction was very obvious. It indicated that the patients received better treatment during hospitalization, and the symptoms continued to reduce with the medical care process. In contrast, the longer the symptom duration before hospitalization, the heavier the BOD of inpatient time. It indicated that delaying the treatment may aggravate the BOD and lead to consumption of more medical resources. This finding suggests that earlier detection, diagnosis, and treatment of COVID-19 are very important for the medical service system. In addition, teenagers and some older-aged groups, especially those aged above 60 years, exhibited longer duration of symptoms before hospitalization in our study. This suggests that teenagers and the older-aged groups may have difficulties in seeking medical treatment or lack vigilance of their own health, which could result in the consumption of more medical resources. This suggests that relevant social service departments should be strengthened to provide help and support for the teenagers and older ones.

Conclusion

COVID-19 symptoms could cause heavy BOD to inpatients. The BOD for the female population was higher than that for the male population; however, the daily BOD between male and female inpatients were similar. When the changing life value with age was considered, the disease burden of the younger population was higher than that of the older population, except for teenagers. The treatment at the three military hospitals could have efficiently relieved the BOD of the inpatients, despite the similar treatment effect between them. Delay in hospitalization could worsen the BOD for patients with COVID-19. Thus, there is need for the deployment of adequate medical resources for the early hospitalization of patients with moderate or severe symptoms by the public health authority.

List of abbreviations

BOD: burden of disease

COVID-19: coronavirus disease 2019

DALY: disability-adjusted life years

DW: disability weight

PLA: people's liberation army

GBD: global burden of disease

WHO: World Health Organization

YLDs: years lost due to disability

YLLs: years of life lost

Declarations

Ethics approval and consent to participate

The research ethics committee of the No.900 Hospital of Joint Logistics Troop of PLA gave ethical approval (approval number: 2020-001). None of the inpatients were involved in any health intervention. All the individual data were anonymized prior to retrieval and analysis, and they did not contain any individual's private information.

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from Wuhan Huoshenshan Hospital, Tongji Hospital, and Guanggu Womam & Child Hospital. However, restrictions will apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are

however available from the authors upon reasonable request and with permission of the health service authority of Joint Logistics Troop of PLA.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

XXL and MH conceived and designed the studies; MH and XXL did literature search and review; XXL, JY, and YC conducted questionnaire and PTO processes; XL1, QZ, and XL2 collected and extracted the data; MHe, QT and YK contributed materials; XXL, JY, and YC analyzed and interpreted the data; XXL and MH drafted the article and revised it. All the authors gave approval before submission.

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Figure legends

Fig. 1 Flow of inpatient selection

Fig. 2: Curve of weighted life value changing with age

Fig. 3: Duration of symptom before hospitalization changes with age group in female and male populations

Fig. 4: Length of stay changes with age group in female and male populations

Fig. 5: Overall duration of symptom changes with age group in female and male populations

Fig. 6a: The composition proportion of accumulative duration (in day) by symptom in the study population

Fig. 6b: The composition proportion of DALY by symptom in the study population

Fig. 7: Composition of each military temporary hospital's synthetic DALY

Fig. 8: Composition of each gender group's synthetic DALY

Fig. 9: Composition of each age group's synthetic DALY

Fig. 10: Thermal map of COVID-19 inpatient's DALY by gender and age group (DALY per 1000 capita).

Fig. 11: Synthetic DALY changes with age group in female and male populations

Fig. 12: DALY per day changes with age group in female and male populations

Additional file

File name: Additional file 1

File format: DOC

Title of data: questionnaire

Description of data: Text/table

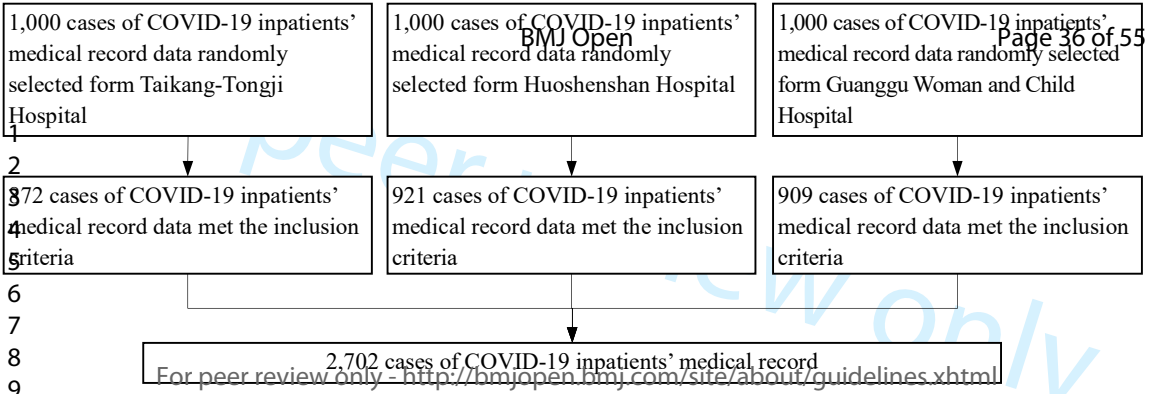


Fig. 1

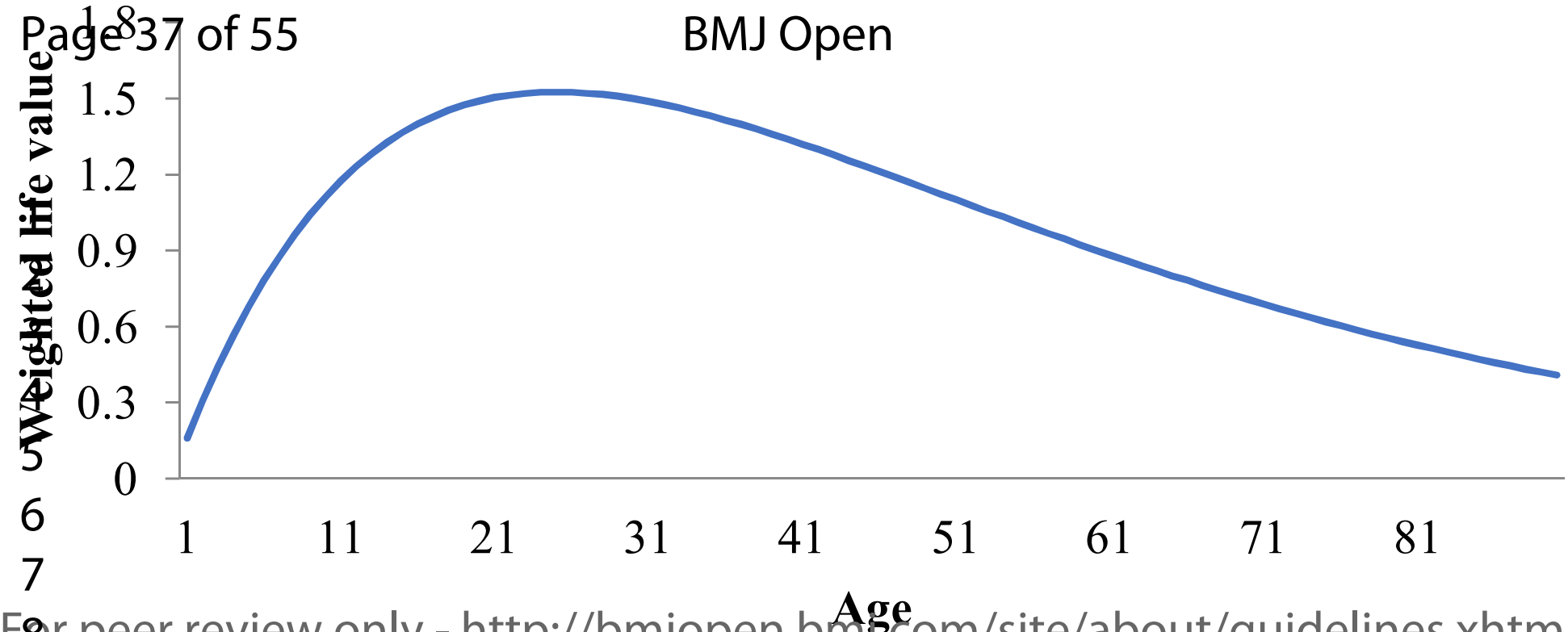
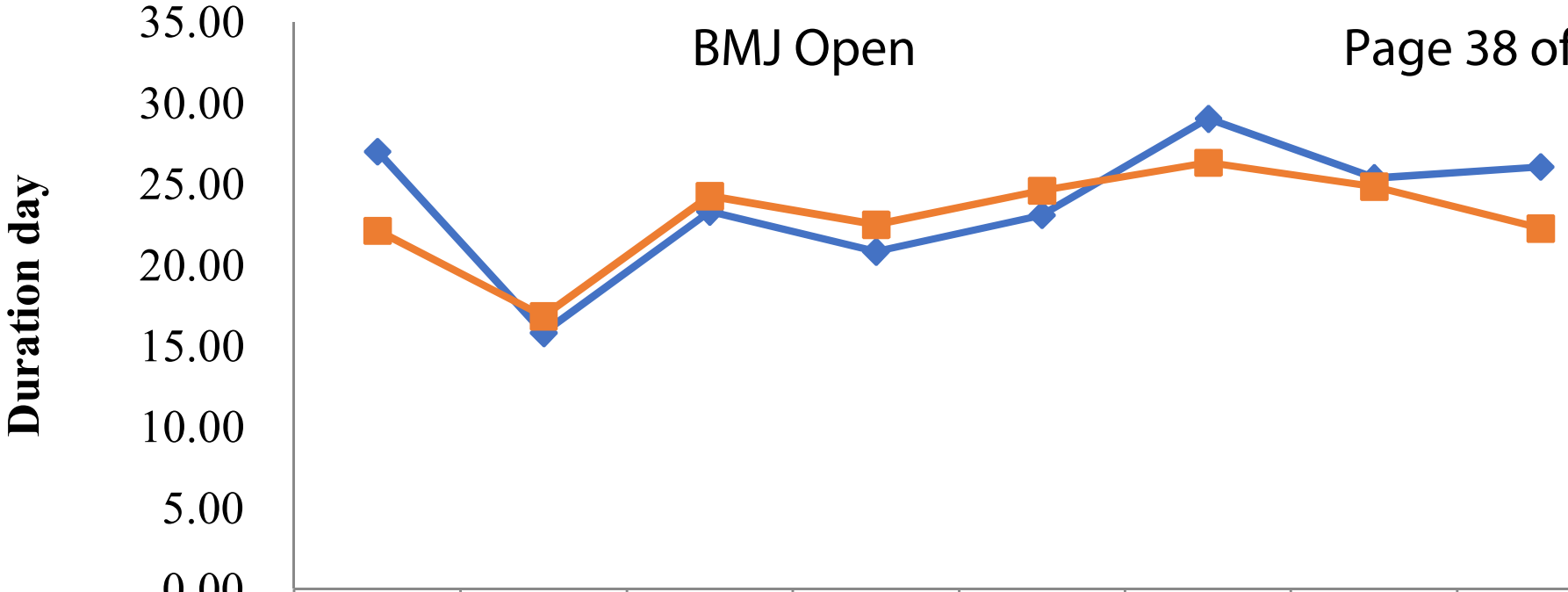


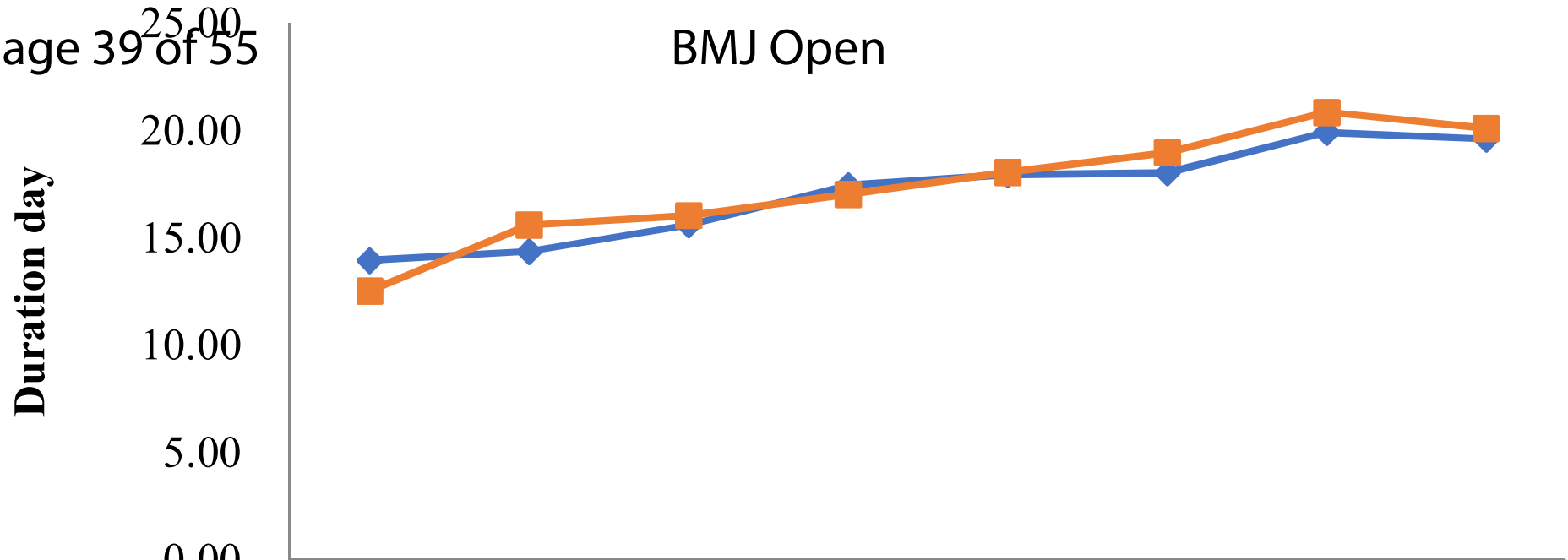
Fig. 2



	<19	20-29	30-39	40-49	50-59	60-69	70-79	>79
Male	27.00	15.81	23.30	20.82	23.08	29.03	25.37	26.07
Female	22.13	16.83	24.26	22.48	24.59	26.32	24.84	22.25

Age group

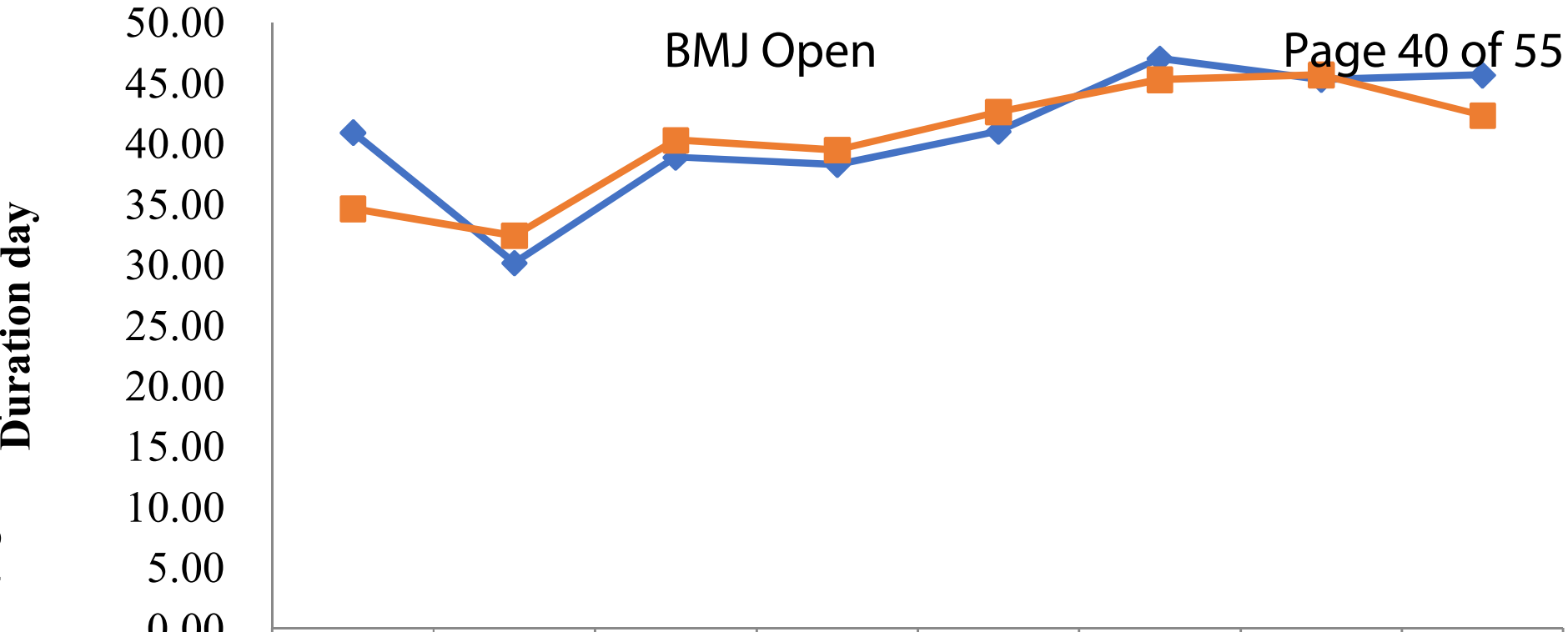
Fig. 3



	<19	20-29	30-39	40-49	50-59	60-69	70-79	>79
Male	13.92	14.34	15.58	17.43	17.93	18.00	19.90	19.59
Female	12.50	15.57	16.02	17.00	18.03	18.95	20.82	20.07

Age group

Fig. 4



	<19	20-29	30-39	40-49	50-59	60-69	70-79	>79
Male	40.92	30.15	38.88	38.26	41.01	47.03	45.27	45.65
Female	34.63	32.41	40.28	39.48	42.62	45.27	45.67	42.33

Fig. 5

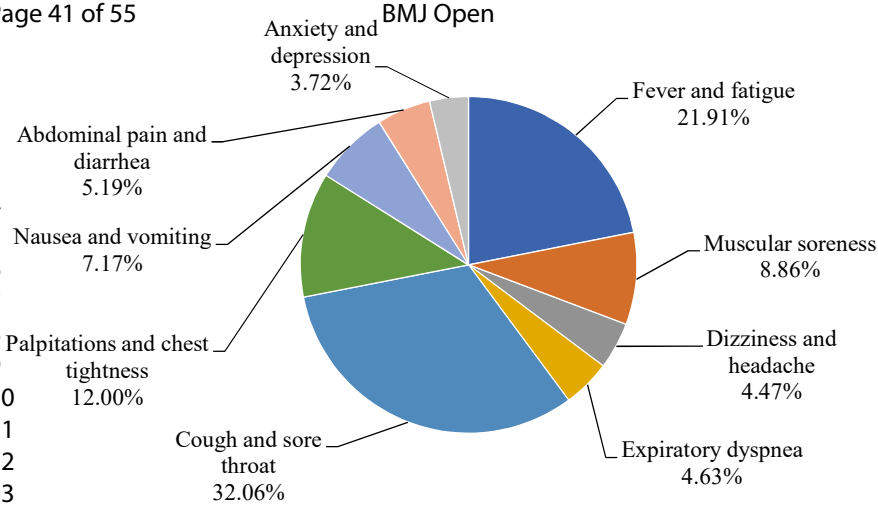


Fig. 6a

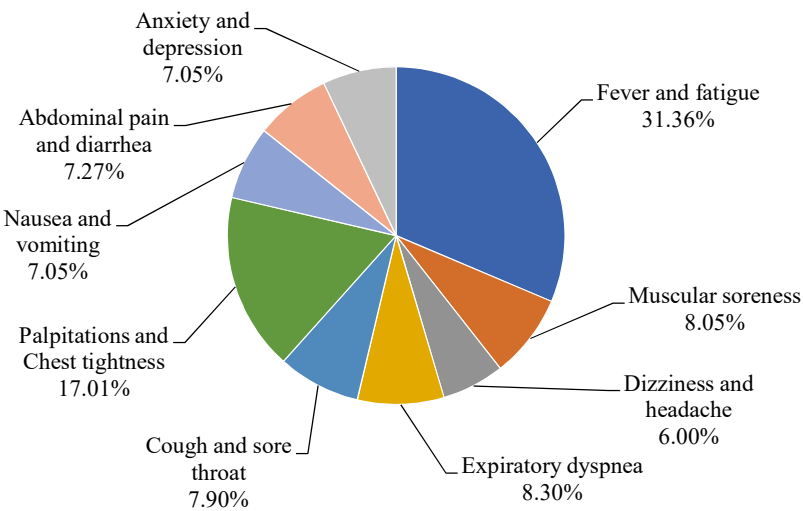


Fig. 6b

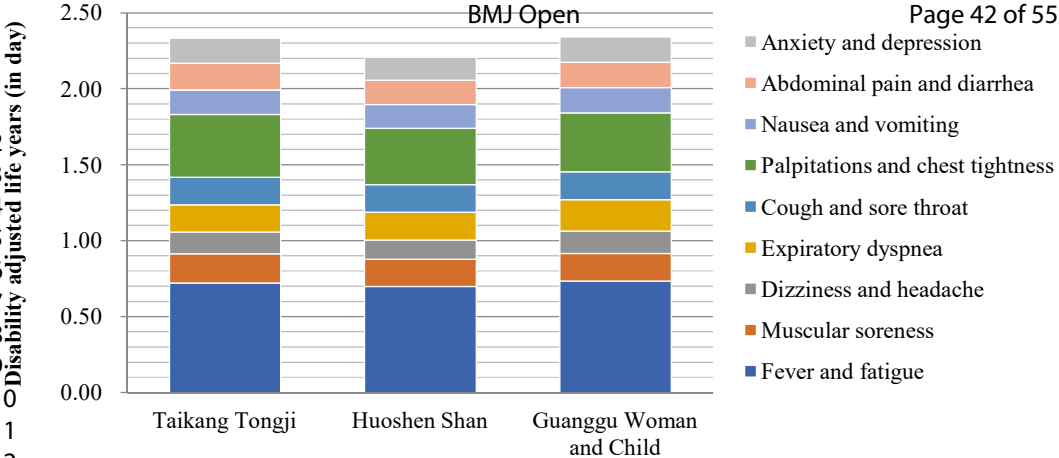


Fig. 7

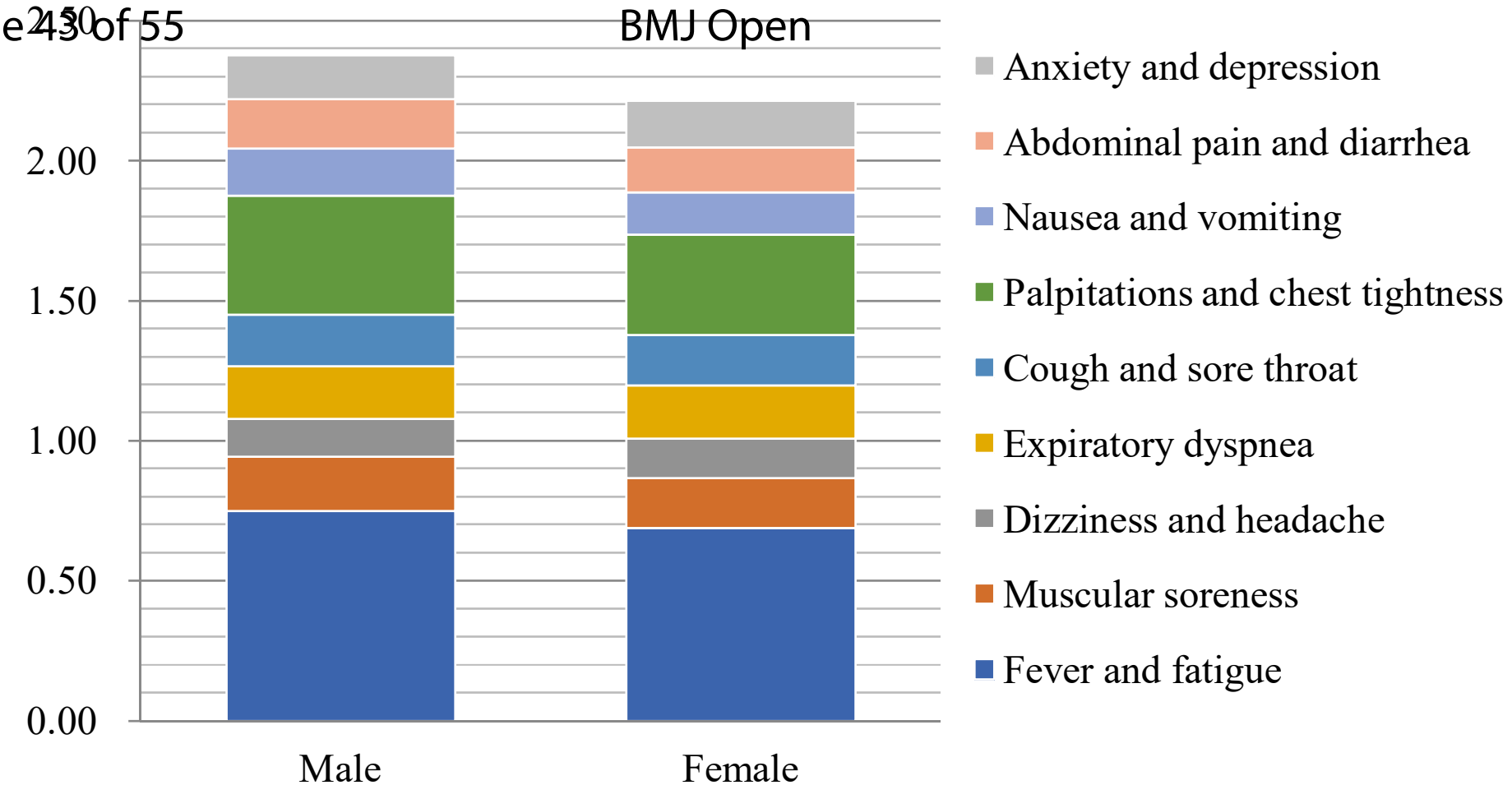


Fig. 8

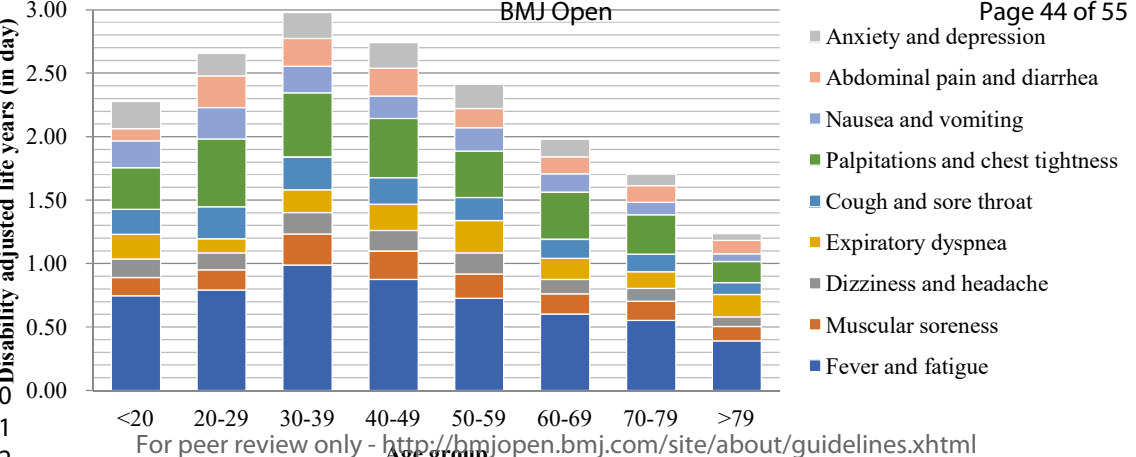
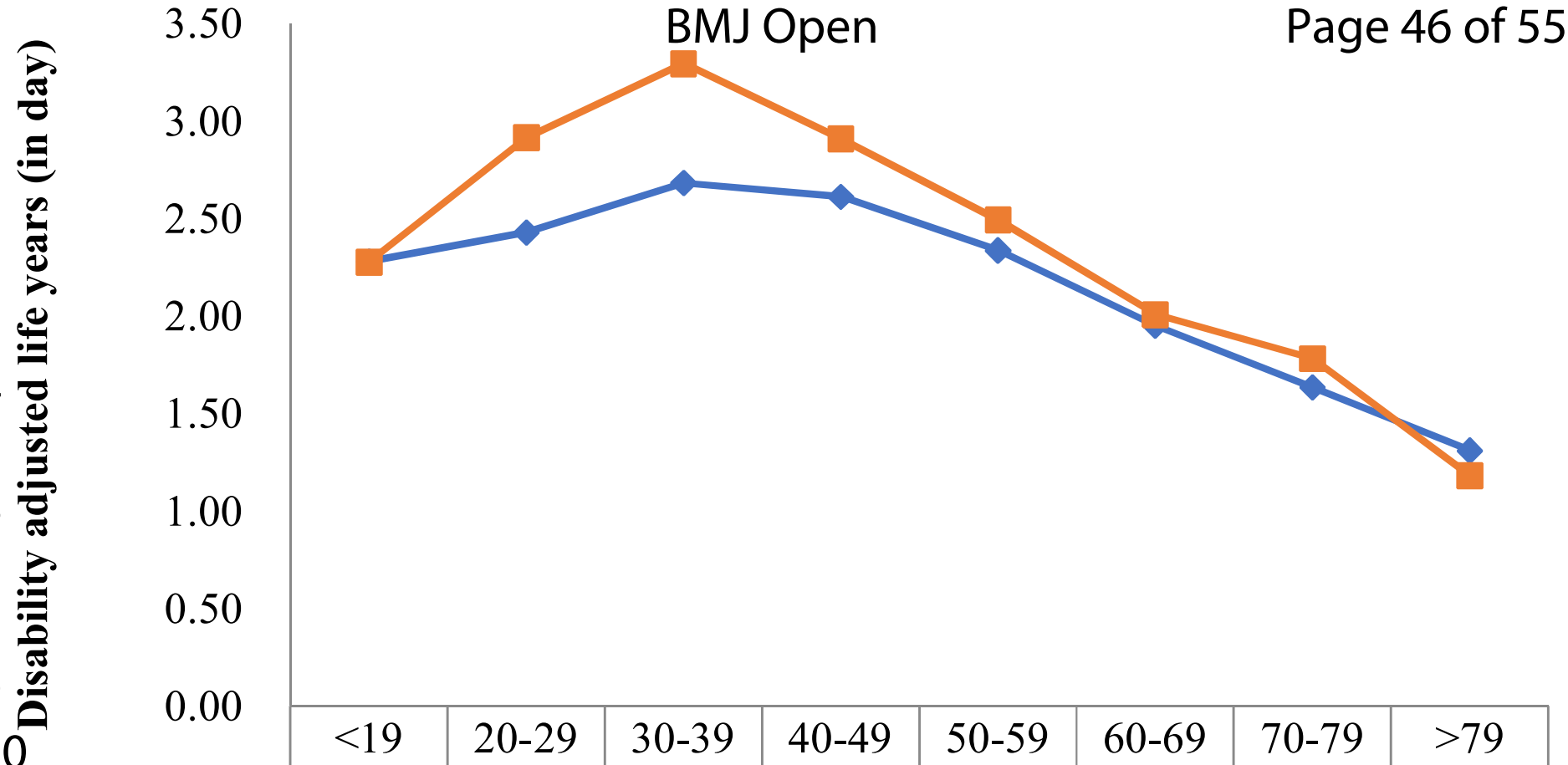


Fig. 9

Male DALY/1000 captia (in days)									Symptoms	Female DALY/1000 captia (in days)								
<19 (n=24)	20-29 (n=54)	30-39 (n=149)	40-49 (n=234)	50-59 (n=295)	60-69 (n=328)	70-79 (n=147)	>79 (n=95)	All age (n=1326)		All age (n=1376)	>79 (n=75)	70-79 (n=159)	60-69 (n=307)	50-59 (n=297)	40-49 (n=295)	30-39 (n=156)	20-29 (n=62)	<19 (n=25)
639	789	1115	947	776	623	547	379	751	Fever and fatigue	689	412	559	584	677	821	868	796	855
162	174	276	233	201	163	157	117	193	Muscular soreness	177	107	145	154	187	215	217	146	121
134	150	176	151	159	109	94	83	134	Dizziness and headache	141	65	107	116	169	169	166	117	161
142	118	181	232	262	160	130	129	190	Expiratory dyspnea	191	236	133	177	247	189	175	108	243
202	275	271	210	183	151	146	87	183	Cough and sore throat	180	101	132	147	182	210	247	229	192
470	626	614	522	360	383	373	168	423	Palpitations and Chest tightness	358	162	252	357	373	423	401	457	193
149	263	238	192	187	151	124	59	171	Nausea and Vomiting	153	62	75	142	178	161	180	236	271
111	316	220	226	179	133	125	108	174	Abdominal pain and Diarrhea	160	100	138	137	126	213	220	187	80
266	203	202	194	184	135	85	50	157	Anxiety and Depression	166	63	92	137	197	210	209	153	164

Fig. 10



	<19	20-29	30-39	40-49	50-59	60-69	70-79	>79
Male	2.28	2.43	2.68	2.61	2.34	1.95	1.63	1.31
Female	2.28	2.91	3.29	2.91	2.49	2.01	1.78	1.18

Fig. 11

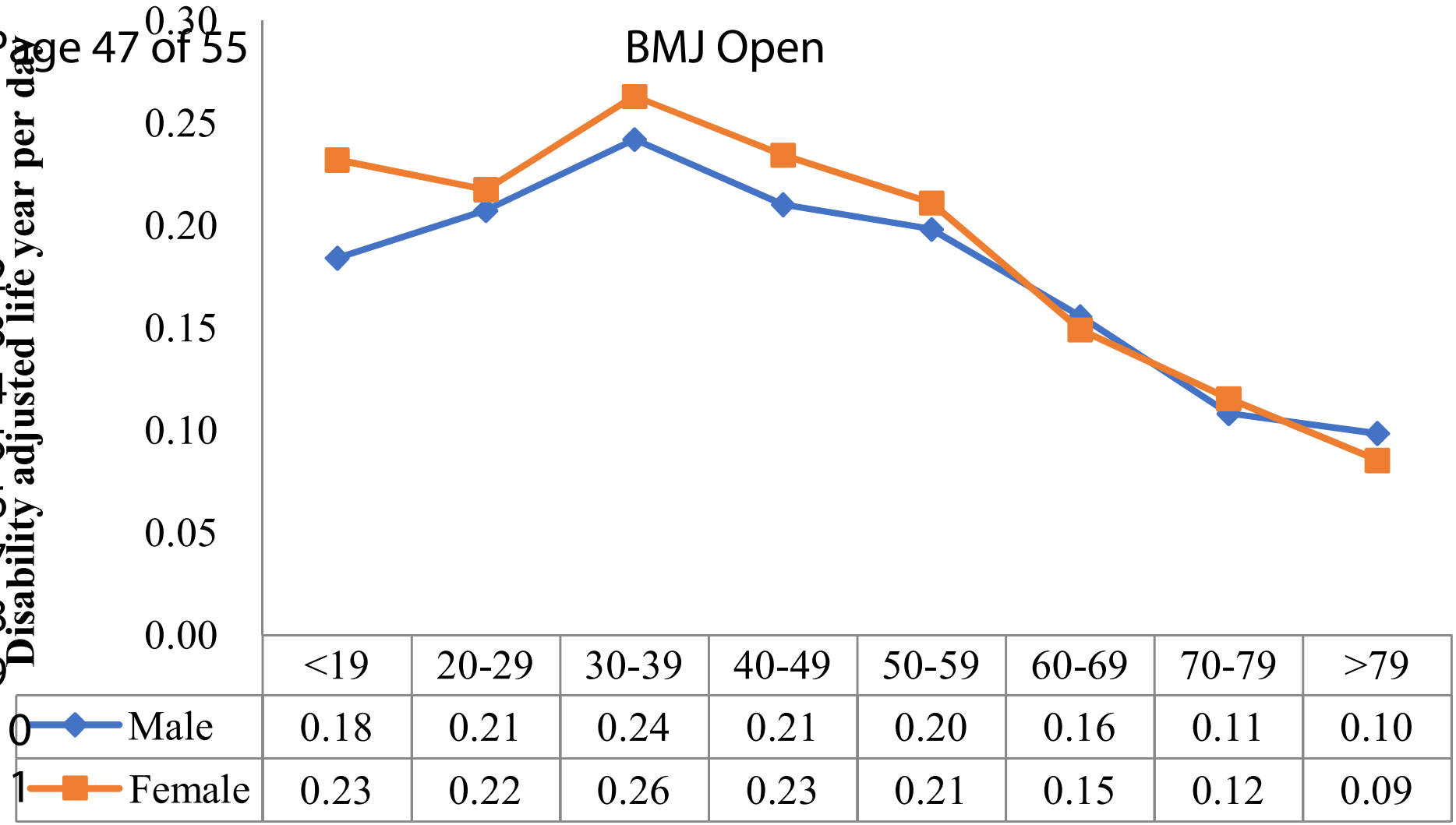


Fig. 12

Additional file 1: Questionnaire

Front-line medical staff questionnaire on symptoms of COVID-19 (The first round)

Dear Sir/Madam:

This is a questionnaire on COVID-19 typical symptom. The aim is to generate a comprehensive list of typical symptoms of inpatient with COVID-19, which can be used to assess the disease burden caused by the symptoms. This study will adopt the method of disability adjusted life years (DALYs) of the World Health Organization (WHO) to evaluate inpatients' burden of disease caused by COVID-19 symptoms.

According to your clinical experience, please judge the raw list of category and symptoms summarized by the literature review (Table 1). The judgment items are included:

For category：

(1) Whether the category should be included in the list;

(2) Whether the name of the category is appropriate.

For symptoms：

(1) Whether the symptom should be listed;

(2) Whether the symptom should be classified into the current category;

(3) Whether the name of the symptom is appropriate.

If you think it is necessary, please supplement the symptom list according to your clinical experience. You can add:

(1) New categories if necessary;

(2) New symptoms if necessary.

As a front-line clinical expert engaged in COVID-19 treatment, your knowledge about the symptoms of the disease is valuable. Therefore, your opinion is very important for this study. Please try your best to fill the list appropriately. All the information you fill in is for academic research only. We will not analyze your responses individually and will keep them anonymous. Please provide responses to the best of your knowledge.

According to the Delphi process, the opinions of each expert in this round will be anonymously submitted to other experts as reference, in the next round of questionnaire survey. You will also see the anonymous opinions of the other experts. This study is expected to be conducted in 2-3 rounds for a more consistent answer.

Thank you for your support and cooperation.

The Research Group on COVID-19 Burden of Disease

Date:_____

Table1: COVID-19 inpatient's symptom list for the burden of disease evaluation (Template)

Category (Code)	Include the item or not (Y/N)	Term appropriate or not (Y/N)	If inappropriate, fill in alternative terms	Symptom	Include the item or not (Y/N)	Term appropriate or not (Y/N)	If inappropriate, fill in alternative terms	Should it be moved to another category? If yes, type the code
Systemic symptoms (01)				Fever				
				Other symptom 1 (if necessary):				
				Other symptom 2 (if necessary):				
Neurological symptoms (02)				Headache				
				Other symptom 1 (if necessary):				
				Other symptom 2 (if necessary):				
Respiratory symptoms (03)				Expiratory dyspnea				
				Cough				
				Other symptom 1 (if necessary):				
				Other symptom 2 (if necessary):				
Cardiovascular symptoms (04)				Palpitations				
				Other symptom 1 (if necessary):				

Category (Code)	Include the item or not (Y/N)	Term appropriate or not (Y/N)	If inappropriate, fill in alternative terms	Symptom	Include the item or not (Y/N)	Term appropriate or not (Y/N)	If inappropriate, fill in alternative terms	Should it be moved to another category? If yes, type the code
				Other symptom 2 (if necessary):				
Gastrointestinal symptoms (05)				Diarrhea				
				Other symptom 1 (if necessary):				
				Other symptom 2 (if necessary):				
Other category (06) (if necessary):				Other symptom 1 (if necessary):				
				Other symptom 2 (if necessary):				
Other category (07) (if necessary):				Other symptom 1 (if necessary):				
				Other symptom 2 (if necessary):				

If you have anything else to explain, please write here:

To confirm the above, please sign (or type here):

Date:

Front-line medical staff questionnaire on symptoms of COVID-19 (The second/third round)

Dear Sir/Madam:

Thank you for your cooperation and hard work in the last round of the questionnaire survey. The anonymous opinions of other experts in the last round have been sent to you as a reference. We retained all the consensus items in the last round of the expert consultation in the list. We also added the most favorite (approval rate > 50%) new items or the items that were proposed for adjustment (Table 1). Please supplement with the necessary items according to your own clinical experience and the opinions of other experts.

According to your clinical experience, please judge the newly added or adjusted category and symptom items:

For category：

(1) Whether the category should be included in the list;

(2) Whether the name of the category is appropriate.

For symptom：

(1) Whether the symptom should be listed;

(2) Whether the symptom should be classified into the current category;

(3) Whether the name of the symptom is appropriate.

Besides, you also can add:

(1) New categories if necessary;

(2) New symptoms if necessary.

According to the Delphi process, the opinion of each expert in this round will be anonymous and submitted to other experts as reference, in the next round of the questionnaire survey. You will also see the anonymous opinions of the other experts. This study is expected to be conducted in 2-3 rounds for a more consistent answer.

Thank you for your support and cooperation.

The Research Group on COVID-19 Burden of Disease

Date：_____

Table1: COVID-19 inpatient's symptom list for the burden of disease evaluation (Template)

Category (Code)	Include the item or not (Y/N)	Term appropriate or not (Y/N)	If inappropriate, fill in alternative terms	Symptom	Include the item or not (Y/N)	Term appropriate or not (Y/N)	If inappropriate, fill in alternative terms	Should it be moved to another category? If yes, type the code
Systemic symptoms (01)				Fever and fatigue *				
				Muscular soreness *				
				Other symptom 1 (if necessary):				
				Other symptom 2 (if necessary):				
Neurological symptoms (02)				Headache				
				Other symptom 1 (if necessary):				
				Other symptom 2 (if necessary):				
Respiratory symptoms (03)				Expiratory dyspnea				
				Cough				
				Other symptom 1 (if necessary):				
				Other symptom 2 (if necessary):				
Cardiovascular symptoms (04)				Palpitations				
				Chest tightness *				
				Other symptom 1 (if necessary):				
				Other symptom 2 (if necessary):				

Category (Code)	Include the item or not (Y/N)	Term appropriate or not (Y/N)	If inappropriate, fill in alternative terms	Symptom	Include the item or not (Y/N)	Term appropriate or not (Y/N)	If inappropriate, fill in alternative terms	Should it be moved to another category? If yes, type the code
Gastrointestinal symptoms (05)				Diarrhea				
				Vomiting *				
				Other symptom 1 (if necessary):				
				Other symptom 2 (if necessary):				
Psychological symptoms * (06)				Anxiety and depression *				
				Other symptom 1 (if necessary):				
				Other symptom 2 (if necessary):				
Other category (07) (if necessary):				Other symptom 1 (if necessary):				
				Other symptom 2 (if necessary):				

* Newly proposed or adjusted item.

If you have anything else to explain, please write here:

To confirm the above, please sign (or type here):

Date:

BMJ Open

Disease burden from COVID-19 symptoms among inpatients at the temporary military hospitals in Wuhan: A retrospective multi-center cross-sectional study

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Primary Subject Heading:	Public health
Secondary Subject Heading:	Health economics
Keywords:	PUBLIC HEALTH, HEALTH ECONOMICS, HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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Disease burden from COVID-19 symptoms among inpatients at the temporary military hospitals in Wuhan: A retrospective multi-center cross-sectional study

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ABSTRACT:

Objectives: We aimed to establish a set of disability weights (DWs) for COVID-19 symptoms, evaluate the disease burden of inpatients, and analyze the characteristics and influencing factors of the disease.

Design: This was a multi-center retrospective cross-sectional descriptive study.

Setting: The medical records generated in three temporary military hospitals in Wuhan were analyzed in Fuzhou.

Participants: Medical records of 2,702 inpatients generated from February 5 to April 5, 2020, were randomly selected for this study.

Primary and secondary outcome measures: DWs of COVID-19 symptoms were determined by the person-trade-off approach. The inpatients' medical records were analyzed and used to calculate the disability-adjusted life years (DALY). The mean DALY was evaluated across sex and age groups. The relationship between DALY and age, sex, body mass index, length of hospital stay, symptom duration before admission, and native place was determined by multiple linear regression.

Results: For the DALY of each inpatient, severe expiratory dyspnea, mild cough, and sore throat had the highest (0.399) and lowest (0.004) weights, respectively. The average synthetic DALY and daily DALY were 2.29±1.33 and 0.18±0.15 days, respectively. Fever and fatigue contributed the most DALY at 31.36%, whereas nausea and vomiting and anxiety and depression contributed the least at 7.05%. There were significant differences between sex and age groups in both synthetic and daily DALY. Age, body mass index, length of hospital stay, and symptom duration before admission were strongly related to both synthetic and daily DALY.

Conclusions: Although the disease burden was higher among women than men, their daily disease burdens were similar. The disease burden in the younger population was higher than that in the older population. Treatment at the hospitals relieved the disease burden efficiently, while a delay in hospitalization worsened it.

Keywords: COVID-19; Wuhan; Burden of disease; Bio-security; Symptom; Inpatient; Disability-adjusted life years

Strengths and limitations of this study

- We calculated the inpatient disease burden according to disability weights of major symptoms of COVID-19.
- The validity of the large sampled medical records from the military medical units was high.
- To determine the pure burden of COVID-19 symptoms, comorbidity and mortality cases were excluded.
- Self-reported bias of symptom duration prior to hospital admission may be high.
- Cultural and ethnic differences and virus variation over time may have affected data comparison.

BACKGROUND

The coronavirus disease (COVID-19) pandemic is both a global public health emergency and a major bio-security event; it brings pain and loss to individuals and families and a heavy burden to countries and societies.[1,2] Scientific evaluation of the social and economic impact of the public health incident provides an important way to determine the therapeutic effectiveness in medical institutions and an important basis for the government to formulate relevant rescue policies and recovery measures. The economic burden of disease (BOD) and injury include treatment costs and various forms of losses in life (e.g., death and poor quality of life due to a temporary or sustained decline in the quality of life).[3,4]

There are several new features of COVID-19 compared with severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS).[5] The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection can cause symptoms such as fever, fatigue, cough, dyspnea, headache, nausea, vomiting, abdominal pain, and diarrhea, and in severe cases, severe acute respiratory syndrome, multiple organ failure, and even death.[6-9] As it is an emerging disease, the BOD caused by COVID-19 remains unclear. Studying the BOD and symptoms of COVID-19 will be helpful to deepen our understanding of the disease, its harm, and severity and to predict the developing trend of the disease. Thus, public health authorities could improve the treatment and rehabilitation programs, renew relief measures, and adjust public health policies appropriately.

Since the 1990s, the World Health Organization (WHO) and the World Bank have proposed indicators to evaluate the BOD, which is a measure of the disability-adjusted life years (DALY).This single-utility measure used to determine the burden attributable to a specific disease is calculated using the standard method proposed by Murray and Lopez.[10] The DALY is a summary measure of population health accounting for both the years of life lost (YLLs) and years lost due to disability (YLDs). The DALY was first developed for quantifying the global burden of disease (GBD), expressed as the relative magnitude of losses

of healthy life associated with different causes of disease and injury.[11] Since then, the DALY has been widely used globally to estimate BOD at the national, international, and regional levels.

Recently, DALY has been used to evaluate the BOD of some specific diseases. Qi et al. comprehensively evaluated the direct and indirect BOD of public emergencies caused by Asian Lineage Avian Influenza A (H7N9) infection.[12] Zhang et al. evaluated the BOD and related factors in hospitalized patients with coal workers' pneumoconiosis and provided the basis for improving relevant medical policies.[13] Bacellar et al. assessed BOD in hospitalized elderly patients with neurological disorders in Brazil and recommended measures to improve the treatment plan.[14] Adopting the WHO approach, Pei and Li et al. formulated the disability weights (DWs) for chronic mountain disease, which was used to calculate the BOD among soldiers stationed in Tibet and helped evaluate the ability of troops to perform tasks.[15]

The DALY method could provide important insights into public health studies and practice regarding COVID-19. This year, a series of research studies were conducted worldwide to estimate the BOD of COVID-19 in different regions, from multiple perspectives, and using different methods. Jo et al. adopted DWs from previous similar causes to calculate the BOD of COVID-19 in Korea, including YLDs and YLLs.[16] Oh et al. estimated the YLLs due to COVID-19 in 30 high-incidence countries using the WHO-provided data.[17] To assess the socio-economic burden of the COVID-19 pandemic in Italy, Nurchis et al. estimated YLLs and YLDs along with the productive YLLs, and the comparable DW of lower respiratory tract infection as adopted to estimate the YLDs.[18] Mohanty et al. examined the impact of COVID-19 on the longevity, years of potential life lost, and DALY in the USA, Italy, Germany, and Sweden, and adopted DWs of similar diseases as proxy.[19] Furthermore, Ortiz-Prado et al. assessed the BOD of COVID-19 in Ecuador by adopting the DWs of other similar diseases.[20]

These studies not only contributed greatly to the understanding of BOD of COVID-19 but also provided the basis for global COVID-19 public health services and related policy-making. However, in recent reports,

BOD assessment of COVID-19 remained at the macro level and relatively unclear, mainly because only the DWs from similar diseases were adopted, leaving COVID-19 with a singular DW, which ignored the complexity of COVID-19 symptoms. Until now, limited reports exist on China's COVID-19 BOD, especially based on each COVID-19. Thus, we aimed to establish the DW for COVID-19 symptoms, to estimate the BOD among inpatients in Wuhan, China, and to analyze the characteristics and potential influencing factors. To design this technical approach, we design a technical approach based on previous studies. The BOD of COVID-19 symptoms was evaluated from existing medical records.

METHOD

Selection of the population groups

To counter the public health disaster and bio-security crisis caused by COVID-19 in Wuhan, People's Liberation Army (PLA) performed a series of non-combat military operations, including the deployment of three temporary military hospitals [Huoshenshan Hospital (from March 2 to April 15, 2020), Taikang-Tongji Hospital (March 13 to April 16, 2020), and Guanggu Woman and Child Hospital (March 13 to April 16, 2020)]. The first hospital was a newly built one, while the other two were civil medical facilities temporarily utilized by the PLA medical staff. While in operation, all the hospitals were designated as specialized COVID-19 hospitals.

All the analyzed inpatient data were randomly selected from the three temporary military hospitals' medical records using the same recording standard. The included inpatients' hospitalization period ranged from February 5 to April 5, 2020. The selection process was conducted from May 25 to June 5, 2020, after the closure of the temporary hospitals (Fig. 1). Data for 2,702 inpatients were included in this study. All the inpatients treated by the military medical staff were from the military hospitals affiliated to the PLA.

<**Insert Fig. 1 here**>

The diagnosis and treatment method were based on the "Diagnosis and treatment standard of

COVID-19 (7th edition)" published by the People's Republic of China's (PRC) central government.[21] The standard detailed laboratory tests for COVID-19, with pathogenic, serological, and chest image criteria, were included. All patients were hospitalized before the release of the 7th edition and were reconfirmed according to the diagnostic criteria. The inclusion criteria were COVID-19 diagnosis at the hospitals according to the standard guideline and continuous treatment at these hospitals. To determine the BOD of COVID-19, inpatients with any other morbidity (other infectious diseases, other respiratory diseases, psychiatric disease, tumor, pregnancy and lactation, and chronic cardiac, liver, kidney, and neurological diseases) were excluded. We also excluded COVID-19 inpatient deaths due to the reluctance of their family members to allow the use of their data for a public study. Similarly, cases with incomplete medical records were excluded.

Establishment of the disability weights for COVID-19 symptoms

DW is a key component of BOD analysis that represents disease severity. It ranges from 0 to 1, where 0 represents healthy life, and 1 represents death.[4] WHO has been conducting GBD studies for several years, with series of DWs derived for different health states that are the outcomes of different diseases.[22-26]

Because COVID-19 is a new infectious disease, no DWs exist for COVID-19 symptoms in the WHO's DWs list; thus, we attempted to establish customized DWs for COVID-19 symptoms. First, COVID-19 symptoms were listed following a literature review of newly published clinical reports on COVID-19. Three rounds of questionnaires were completed by front-line medical staff in the three military field hospitals in Wuhan to derive a raw list of COVID-19 symptoms for DWs establishment (questionnaire sample is shown in Additional file 1).

Then, we convened a nine-expert panel composed of three senior respiratory physicians, two senior infectious disease physicians, one epidemiologist, one public health management expert, and two nursing experts. Based on the raw list of COVID-19 symptoms, the panel performed the Delphi process to

determine the final symptom list for DWs creation.[27]

Then, the panel members performed the Person-Trade-Off (PTO) exercise to derive each symptom's DWs by three levels of severities (health stages).[15, 28, 29] The health stages were described on an A4-sized vignette that contained disease-specific information in simple terminologies. As a reference framework for this task, the panel members were provided with a WHO-GBD framework table, which displayed seven disability classes and 22 anchoring example conditions. The coefficient of variation (CV) was calculated to determine the need for additional rounds of discussion and reassignment of values.

Data extraction

Basic information for the confirmed cases included the identification number (ID), age, sex, weight, height, native place, date of onset reported by the patient, diagnostic conclusion, symptoms recorded by the medical staff, and inpatient and outpatient time. Nine age groups were created: <10, 10-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, and >80 years. Body mass index (BMI) was calculated, while the duration of symptoms was determined as the length of stay + symptom duration before hospitalization (self-reported in the medical record).

To accurately extract the medical data from the records, we trained six staff members to standardize the criteria of judging an inpatient with one or more symptoms in a day and the symptom severity. During data extraction, the six staff members were divided into three groups of two in each group, and a cross-check was conducted when data were extracted from the records. The extraction process was conducted from May 29 to August 7, 2020.

Calculation of DALY for COVID-19 symptoms

The DALY was used to estimate the disease burden of COVID-19 symptoms. The DALY is calculated as the sum of the YLLs due to premature mortality in the population and the equivalent 'healthy' YLDs for incident cases of the health condition.[4,11,30] However, we did not consider COVID-19-related deaths.

Therefore, the DALY due to COVID-19 was equal to the YLDs. Thus, a patient's individual DALY was calculated using the following formula[15]:

$$\mathrm{DALY} = \int_{x=\alpha}^{x=\alpha+L} DC\, xe^{-\beta x} e^{-\gamma(x-\alpha)} dx \quad (1.0)$$

where D represents DW, K is an age weighting factor, C is a constant, r is the discount rate, a is the age at onset, β is a parameter from the age weighting function, and L is life time with disability. We used the base case recommended by Murray and Lopez, with C = 0.1658, r = 0.03, K = 1, and β = 0.04.[15,31]

Considering that the COVID-19 inpatient hospitalization time was relatively short, L *in* the formula (1.0) is shorter than 1 year; thus, the age of each inpatient was treated as fixed. Accordingly, the formula was simplified as follows:

$$\mathrm{DALY} = DCxe^{-\beta x} \quad (2.0)$$

In formula 2.0, $Cxe^{-\beta x}$ reflects the life value discounted by age. This function is based on the hypothesis that life value is different for different age groups: a person's life value increases after they are born and reaches the peak in their youth; next, the life value `declines with age (Fig.2). Hence, in calculating the DALY, DALY will differ for different age groups despite identical symptoms.

<**Insert Fig. 2 here**>

We calculated the DALY as follows: 1) the cumulative duration (in days) of each health condition (a health condition is one type of symptom severity); 2) the duration was multiplied by the corresponding DW to get the DALY of each health condition; 3) all the DALY values were summed up into an inpatient's synthetic DALY for COVID-19; 4) the synthetic DALY was divided by the patient's length of stay to get the daily DALY. Considering that the inpatient's length of stay was relatively short, the unit of DALY was set as days.

Statistical analysis

The demographic characteristics of patients such as hospitalization, sex, and native place, were evaluated.

The distribution of each symptom according to the hospital, sex, and overall population, was calculated. The mean DALY, synthetic DALY, daily DALY, age, BMI, and symptom course (including symptom duration before hospitalization, length of stay, and overall duration) based on the hospital, sex, and age groups were calculated and compared by analysis of variance (ANOVA) or t-test (for two groups only). The ratio difference of the cumulative duration (in days) of symptom severity levels (mild, moderate, and severe) was tested by a chi-square test. The proportions of BOD for each symptom by sex and age group, and in the entire sample population were computed. DALY per 1,000 capita was also calculated by age group and sex. Each symptom's duration in the whole study population was also calculated.

To test the relationship between DALY and age, sex, BMI, and symptom duration, separate linear regression analyses were performed using DALY as the dependent variable and age, sex, BMI, native place, symptom duration before hospitalization, and length of stay as independent variables. In the regression models, sex and native place were set as categorical variables while the others were continuous variables. Synthetic and daily DALY were analyzed, and each hospital's study population and overall study population were analyzed separately. IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, N.Y., USA) was used for statistical analyses. A *P*-value <0.05 was considered statistically significant.

Patient and public involvement

This was a multi-center retrospective cross-sectional descriptive study of COVID-19 inpatients in Wuhan, PRC. The study was performed after the closure of the three temporary military hospitals. None of the inpatients were involved in any health intervention. All individual data were anonymized prior to retrieval and analysis. Because only patient data were used, no patients were directly involved in the study.

RESULTS

Patient characteristics

Data of 2,702 inpatients (872, 921, and 909 from Taikang-Tongji, Huoshenshan, and Guanggu Woman and

Child Hospitals, respectively) were used. Table 1 shows the inpatients' demographic characteristics.

All were Chinese, and 1,326 were woman, whereas 1,376 were man; 2,618 were natives of Hubei province, while 84 were not. The mean age was 55.52±16.09 years and 54.18±15.85 years for female and male populations, respectively. The mean age of men was significantly lower (P=0.03). No significant difference was found in symptom duration before hospitalization, length of stay, and overall duration of symptoms between female and male populations.

For age groups, there were significant differences in the symptom duration before hospitalization, length of stay, and overall duration of symptoms according to the ANOVA test (P>0.05). The least significant difference (LSD) test showed that for 20-29 years age group had the least symptom duration, whereas the 60-69 years age group had the highest duration, with a significant difference between the groups (P<0.05).

Table 1: Demographic characteristics of inpatients

Characteristics	Number of patients	Proportion
Hospital		
Taikang-Tongji	872	32.27%
Huoshenshan	921	34.09%
Guanggu Woman and Child	909	33.64%
Sex		
Woman	1326	49.07%
Man	1376	50.93%

Native place		
Hubei province	2618	96.89%
Outside Hubei province	84	3.11%

Duration of symptoms

Table 2 shows the mean age, BMI, symptom duration before hospitalization, length of stay, and overall duration of symptoms according to hospital, sex, and age group. There were no significant differences in age, symptom duration before hospitalization, length of stay, and overall duration of symptoms among the three hospitals according to the ANOVA test (P>0.05). The inpatients' age ranged from 11 to 94 years (mean, 54.84±15.98 years), while BMI ranged from 16.23 to 28.7 (mean, 22.11±1.94). The length of stay ranged from 5 to 50 days (mean, 17.88±7.38 days), whereas the self-reported symptom duration before hospitalization ranged from 2 to 72 days (mean, 24.11±15.66 days). By combining the inpatient and self-reported symptom duration before hospitalization, we obtained the total duration of symptoms, which ranged from 7 to 94 days (mean, 41.99±16.37 days).

Table 2: Means of age, body mass index, symptom duration before hospitalization, length of stay, and overall duration of symptoms by hospital, sex, and age group of inpatients

	Age	Body mass index	Symptoms duration before hospitalization (days)	Length of stay (days)	Overall duration of symptoms (days)
Hospital					
Taikang-Tongji (n=872)	54.76±15.75	22.25±1.92	24.36±15.92	17.92±7.42	42.28±16.57
Huoshenshan (n=921)	55.21±15.88	22.02±2.00	24.65±15.65	17.91±7.34	42.55±16.33
Guanggu Woman and Child (n=909)	54.53±16.29	22.07±1.90	23.34±15.40	17.80±7.39	41.15±16.21
Sex					
Woman (n=1326)	55.52±16.09	22.14±1.92	24.11±15.40	18.11±7.34	42.22±16.04
Man (n=1376)	54.18±15.85	22.08±1.96	24.12±15.92	17.66±7.41	41.77±16.69

Age group (years)					
<20 (n=49)	15.59±2.53	21.79±2.19	24.61±14.01	13.22±5.67	37.84±13.16
20-29 (n=116)	25.35±2.53	21.95±1.76	16.28±12.36	14.91±5.69	31.20±14.32
30-39 (n=305)	34.87±2.84	22.21±1.98	23.77±16.68	15.79±6.71	39.56±17.44
40-49 (n=529)	44.84±2.96	22.10±1.97	21.56±14.29	17.24±6.93	38.80±14.31
50-59 (n=592)	54.68±2.80	22.13±1.97	23.83±15.81	17.98±7.20	41.81±16.15
60-69 (n=635)	64.16±2.72	22.2±1.910	27.63±16.08	18.49±7.12	46.12±16.39
70-79 (n=306)	73.96±2.88	21.99±1.84	25.12±15.95	20.34±8.09	45.46±16.04
>79 (n=170)	84.49±3.35	21.97±2.04	23.94±14.37	19.86±8.96	43.79±17.55
Overall (n=2702)	54.84±15.98	22.11±1.94	24.11±15.66	17.88±7.38	41.99±16.37

To further analyze the disease course (duration of symptom before hospitalization, length of stay, and overall duration of symptom), we drew line diagrams of the means by age group and sex (Figs. 3 to 5). We also performed a two-way ANOVA to test for the difference in the mean course of the disease by age group and sex. The results showed that age was significantly associated with the disease variables (P<0.05),while sex was not, and that the two factors had no significant interaction (P>0.05).

<Insert Fig. 3, 4, and 5 here>

We also calculated each symptom's cumulative duration (in days) by three levels of severity in the overall sample population (Table 3). Fever and fatigue had the longest duration, with a cumulative duration of 26,863 days. The lowest cumulative duration was for anxiety and depression (4,565 days). By chi-square test, the proportion of severity differed significantly among different symptoms (P<0.05). Anxiety and depression had the highest proportion of severe conditions (30.54%), whereas cough and sore throat had the highest proportion of mild conditions (10.63%). The cumulative durations (in days) by symptoms are shown in Fig. 6a. Cough and sore throat contributed the maximum to symptom duration (32.06%), whereas anxiety and depression contributed the least (3.72%).

<Insert Fig. 6 here>

Table 3: Each COVID-19 symptom's cumulative duration (in days) in the study population

Symptoms	Mild		Moderate		Severe		Overall duration
	Day	%	Day	%	Day	%	(days)
Fever and fatigue	2,231	8.31	20,846	77.60	3,785	14.09	26,863
Muscular soreness	334	3.08	8,220	75.71	2,303	21.21	10,858
Dizziness and headache	92	1.68	3,864	70.51	1,524	27.81	5,481
Expiratory dyspnea	104	1.83	4,096	72.23	1,471	25.94	5,672
Cough and sore throat	4,180	10.63	30,172	76.75	4,959	12.61	39,312
Palpitations and chest tightness	862	5.86	11,232	76.34	2,620	17.81	14,715
Nausea and vomiting	387	4.40	6,434	73.19	1,970	22.41	8,792
Abdominal pain and diarrhea	150	2.36	4,534	71.30	1,675	26.34	6,360
Anxiety and depression	35	0.77	3,135	68.69	1,394	30.54	4,565
Overall	8,375	6.83	92,533	75.47	21,701	17.70	122,610

COVID-19, coronavirus disease 2019.

DWs of COVID-19 symptoms

After two rounds of the Delphi process by the panel, we developed a 9-item COVID-19 symptom list with six categories. Each symptom included three levels of severity (mild, moderate, and severe), thereby representing 27 health stages. Based on these, we derived the DWs for each health stage by the PTO exercise; along with the expert panel, a consensus was reached at the fifth round of the Delphi process (CV <0.5). Thus, the DWs of 27 COVID-19 health stages were derived; severe expiratory dyspnea had the highest weight of 0.399, while mild cough and sore throat had the lowest weight of 0.004 (Table 4).

276 **Table 4: Disability weights for the symptoms of COVID-19**

Category	Symptom categories	Health stages	DWs	95% CI
Systemic symptoms	Fever and fatigue	Mild	0.006	(0.004-0.008)
		Moderate	0.051	(0.036-0.066)
		Severe	0.133	(0.089-0.177)
	Muscular soreness	Mild	0.015	(0.012-0.018)
		Moderate	0.054	(0.041-0.067)
		Severe	0.110	(0.059-0.113)
Neurological symptoms	Dizziness and headache	Mild	0.028	(0.019-0.037)
		Moderate	0.083	(0.055-0.111)
		Severe	0.163	(0.109-0.217)
Respiratory symptoms	Expiratory dyspnea	Mild	0.045	(0.040-0.050)
		Moderate	0.108	(0.085-0.131)
		Severe	0.399	(0.293-0.505)
	Cough and sore throat	Mild	0.004	(0.003-0.005)
		Moderate	0.011	(0.008-0.014)
		Severe	0.034	(0.023-0.045)
Cardiovascular symptoms	Palpitations and chest tightness	Mild	0.041	(0.029-0.053)
		Moderate	0.072	(0.048-0.096)
		Severe	0.179	(0.120-0.238)
Gastrointestinal symptoms	Nausea and vomiting	Mild	0.009	(0.006-0.012)
		Moderate	0.057	(0.038-0.076)

		Severe	0.130	(0.089-0.171)
	Abdominal pain and diarrhea	Mild	0.011	(0.008-0.014)
		Moderate	0.091	(0.062-0.120)
		Severe	0.194	(0.128-0.260)
Psychological symptoms	Anxiety and depression	Mild	0.030	(0.021-0.039)
		Moderate	0.120	(0.084-0.156)
		Severe	0.366	(0.243-0.489)

COVID-19, coronavirus disease 2019; DWs, disability weights; CI, confidence interval

DALY of inpatients

According to the formula and DWs, the DALY of each inpatient for each symptom was calculated, as well as their synthetic DALY and daily DALY. The proportion of DALY in the study population is shown in Fig. 6b. Among these, fever and fatigue contributed the most in DALY (31.36%), whereas nausea and vomiting and anxiety and depression contributed the least (7.05%).

The mean and standard deviation of DALY for each symptom by hospital, sex, and overall study population are shown in Table 5, and those by age group are shown in Table 6. The mean overall DALY was 2.29±1.33 days, whereas the mean daily DALY was 0.18±0.15 days. No significant difference was noted in each symptom's DALY, synthetic DALY, or daily DALY among the hospitals (P>0.05). However, in the LSD test, synthetic DALY in Huoshenshan Hospital was significantly lower than that in Taikang-Tongji (P=0.048) and Guanggu Woman and Child (P=0.031) Hospitals. The daily DALY in Huoshenshan Hospital was significantly lower than that in Guanggu Woman and Child Hospital (P=0.023). The DALY for fever and fatigue, muscular soreness, palpitations and chest tightness, and nausea and vomiting, and synthetic DALY were significantly lower for men than for women (P>0.05). In the inpatient population, the overall DALY per 1,000 capita was 6.28, whereas in the female and male populations, the

overall DALY per 1,000 capita was 6.07 and 6.51 years, respectively.

Table 5: The mean DALY of COVID-19 inpatients or all symptoms, according to hospital, sex, and overall study population

Symptom	Taikang-Tongji Hospital (n=872)	Huoshenshan Hospital (n=921)	Guanggu Woman and Child Hospital (n=909)	Woman (n=1326)	Man (n=1376)	Overall (n=2702)
Fever and fatigue	0.72±0.60	0.70±0.59	0.73±0.63	0.75±0.61	0.69±0.60‡	0.72±0.61
Muscular soreness	0.19±0.18	0.18±0.17	0.18±0.17	0.19±0.18	0.18±0.17‡	0.18±0.17
Dizziness and headache	0.14±0.18	0.13±0.17	0.14±0.20	0.13±0.17	0.14±0.19	0.14±0.18
Expiratory dyspnea	0.18±0.31	0.18±0.32	0.21±0.38	0.19±0.34	0.19±0.33	0.19±0.34
Cough and sore throat	0.18±0.12	0.18±0.12	0.18±0.13	0.18±0.12	0.18±0.13	0.18±0.12
Palpitations and chest tightness	0.41±0.45	0.37±0.40	0.39±0.43	0.42±0.44	0.36±0.41‡	0.39±0.43
Nausea and vomiting	0.16±0.24	0.16±0.23	0.17±0.24	0.17±0.25	0.15±0.23‡	0.16±0.24
Abdominal pain and diarrhea	0.18±0.30	0.16±0.26	0.17±0.24	0.17±0.26	0.16±0.28	0.17±0.27
Anxiety and depression	0.16±0.23	0.15±0.21	0.17±0.24	0.16±0.23	0.17±0.23	0.16±0.23
Total DALY	2.33±1.33	2.21±1.26*	2.34±1.38	2.38±1.33	2.21±1.32‡	2.29±1.33
DALY per day	0.19±0.14	0.18±0.14*†	0.19±0.16	0.19±0.14	0.18±0.15	0.18±0.15

* $P<0.05$ vs. Guanggu Woman and Child Hospital; † $P<0.05$ vs. Taikang-Tongji Hospital; ‡ $P<0.05$ vs. woman.

DALY, Disability-adjusted life years.

Table 6: COVID-19 inpatient DALY by symptoms and age group

Symptom	<20 years	20-29 years	30-39 years	40-49 years	50-59 years	60-69 years	70-79 years	>79 years

	(n=49)	(n=116)	(n=305)	(n=529)	(n=592)	(n=635)	(n=306)	(n=170)
Fever and fatigue	0.75±0.58	0.79±0.73	0.99±0.89	0.88±0.70	0.73±0.54	0.60±0.42	0.55±0.38	0.39±0.28
Muscular soreness	0.14±0.12	0.16±0.19	0.25±0.23	0.22±0.20	0.19±0.16	0.16±0.13	0.15±0.12	0.11±0.09
Dizziness and headache	0.15±0.18	0.13±0.16	0.17±0.22	0.16±0.22	0.16±0.21	0.11±0.13	0.10±0.11	0.08±0.09
Expiratory dyspnea	0.19±0.24	0.11±0.15	0.18±0.28	0.21±0.43	0.25±0.45	0.17±0.24	0.13±0.19	0.18±0.25
Cough and sore throat	0.20±0.09	0.25±0.13	0.26±0.15	0.21±0.14	0.18±0.12	0.15±0.09	0.14±0.08	0.09±0.06
Palpitations and chest tightness	0.33±0.43	0.54±0.54	0.51±0.61	0.47±0.5	0.37±0.35	0.37±0.34	0.31±0.33	0.17±0.17
Nausea and vomiting	0.21±0.28	0.25±0.36	0.21±0.30	0.17±0.23	0.18±0.25	0.15±0.22	0.10±0.12	0.06±0.07
Abdominal pain and diarrhea	0.10±0.11	0.25±0.31	0.22±0.43	0.22±0.36	0.15±0.20	0.13±0.17	0.13±0.17	0.10±0.16
Anxiety and depression	0.21±0.25	0.18±0.24	0.21±0.28	0.20±0.28	0.19±0.25	0.14±0.16	0.09±0.12	0.06±0.08
Synthetic DALY	2.28±0.93	2.65±1.46	2.98±1.87	2.74±1.52	2.41±1.12	1.98±0.92	1.70±0.79	1.24±0.69
DALY per day	0.21±0.11	0.21±0.15	0.25±0.18	0.22±0.17	0.20±0.16	0.15±0.10	0.11±0.06	0.09±0.06

COVID-19, coronavirus disease 2019.

DALY, Disability-adjusted life years.

According to the ANOVA test, the mean DALY by age groups differed significantly for each symptom and for the synthetic DALY and daily DALY (P<0.05). The DALY for both single symptoms and synthesized DALY had the tendency of an inverse U-shaped curve. The DALY increased with age, reached a peak in the prime of life, and then slowly decreased with age. In this study, the 40-49 years age group had the highest DALY for expiratory dyspnea, while the 20-29 years group had the highest DALY for palpitations and chest tightness, nausea and vomiting, and abdominal pain and diarrhea. DALY for the other symptoms, synthetic DALY, and daily DALY peaked in those aged 20-29 years.

The composition of synthetic DALY for each symptom by hospital is shown in Fig. 7, and that by sex and age group is shown in Fig. 8 and Fig. 9, respectively.

To visualize each symptom's DALY by age group and sex, we drew a thermal map for each subgroup's DALY per 1,000 capita (in days; Fig. 10). Fever and fatigue were in the most intense (red) area, while palpitations and chest tightness were in the next intense area, for both female and male populations. The female population aged 30-39 years had the highest DALY score of 1,115 days per 1,000 capita. Contrarily, in the female population above 79 years, the lowest DALY 50 days per 1,000 capita was found.

<**Insert Fig. 7, 8, 9, and 10 here**>

We also identified the changing curves of mean synthetic DALY and daily DALY age groups and sex (Fig. 11 and Fig 12). The two-way ANOVA showed that both age and sex significantly affected synthetic DALY (P<0.05), and there was a significant interaction effect between the two variables (P=0.02). However, when DALY per day was the dependent variable, the significant difference with sex was lost (P=0.08), whereas age remained significant (P<0.05), and the interaction effect between the two variables was also lost (P=0.518).

<**Insert Fig. 11 and 12 here**>

Linear regression analyses

The results of the multiple linear models are shown in Table 7. When synthetic DALY was set as the dependent variable, all four models were significant (P<0.05), with R^2 ranging from 0.214 to 0.240. In the four models, symptom duration before hospitalization and length of stay were significantly positively associated with synthetic DALY, while age was significantly negatively associated with the overall synthetic DALY. For sex and BMI, however, the four models showed different results. In the Guanggu Woman and Child Hospital model, sex and BMI were not significant (P=0.098 and P=0.146); in the other three models, sex and BMI were significant, indicating that the female population had higher DALY than

the male population (P<0.05), and that patients with a high BMI had higher DALY (P<0.05).

When DALY per day was set as the dependent variable, all four models were significant (P<0.05), with R^2 ranging from 0.153 to 0.188. For age and symptom duration before hospitalization, the level of significance was the same as with model I. Length of stay remained significant; however, the effectiveness was negatively reversed for DALY. For sex, the overall sample and Huoshenshan Hospital models were significant (P=0.037 and P=0.022, respectively), and for BMI, the overall sample and Taikang-Tongji Hospital models were significant (P<0.001 and P=0.001, respectively). In all the models, native place was not significant (P>0.05).

Table 7 Linear regression analyses between COVID-19 inpatient's DALY and individual variables

Variable	Model Type I *								Model Type II **							
	Overall sample		Taikang-Tongji		Huoshenshan		Guanggu Woman and Child		Overall sample		Taikang-Tongji		Huoshenshan		Guanggu Woman and Child	
	R^2=0.222		R^2=0.214		R^2=0.224		R^2=0.240		R^2=0.164		R^2=0.188		R^2=0.170		R^2=0.153	
	β	*P*-value	β	*P*-value	β	*P*-value	β	*P*-value	β	*P*-value	β	*P*-value	β	*P*-value	β	*P*-value
Age	-0.415	<0.001	-0.431	<0.001	-0.388	<0.001	-0.429	<0.001	-0.290	<0.001	-0.288	<0.001	-0.269	<0.001	-0.312	<0.001
Sex	0.069	<0.001	0.070	0.020	0.088	0.003	0.048	0.098	0.037	0.037	0.047	0.123	0.070	0.022	-0.002	0.956
Symptom duration before hospitalization	0.166	<0.001	0.169	<0.001	0.206	<0.001	0.133	<0.001	0.208	<0.001	0.207	<0.001	0.251	<0.001	0.180	<0.001
Length of stay	0.312	<0.001	0.265	<0.001	0.334	<0.001	0.338	<0.001	-0.139	<0.001	-0.184	<0.001	-0.134	<0.001	-0.108	0.001
Body mass index	0.048	0.005	0.090	0.003	0.011	0.719	0.042	0.146	0.062	<0.001	0.101	0.001	0.030	0.331	0.056	0.068
Native place	0.015	0.365	0.000	0.987	-0.017	0.549	0.030	0.303	0.003	0.856	-0.005	0.882	-0.002	0.951	0.024	0.437

COVID-19, coronavirus disease 2019; DALY, disability-adjusted life years.

* Dependent variable is overall DALY; ** Dependent variable is DALY per day.

DISCUSSION

The understanding of the symptoms and pathogenic mechanisms of COVID-19 has been updated gradually.[32] In addition to fever and dry cough, COVID-19 patients also have gastrointestinal symptoms such as nausea and vomiting, diarrhea, abdominal discomfort, and abnormal liver function; the viral nucleic acid can be detected in the patients' feces.[33,34] A possible pathogenic mechanism of COVID-19 is the following[7,35]: a cytokine storm caused by viral infection leads to an increase in the neutrophil count, which in turn results in the imbalance and excessive activation of the immune response and immune pathology, focal proliferation of lung cells, and accumulation of multinucleated giant cells; this triggers apoptosis of alveolar epithelial and endothelial cells, and diffuse alveolar injury and interstitial pulmonary fibrosis resulting in progressive hypoxia and injury to the lungs, heart, liver, and other organs. Moreover, the SARS-CoV-2 enters cells primarily through the angiotensin-converting enzyme 2 (ACE2) receptor.[36] ACE2 is not only highly expressed in type II alveolar epithelial cells but also in the small intestine, duodenum, colon, and liver, suggesting that the virus may invade target organs in the digestive tract via the ACE2 receptor, causing primary injury and digestive symptoms.[37] In addition, anxiety, depression, and other psychological stress responses can affect the response of the sympathetic nervous system and increase systemic arterial pressure and heart rate.[38] Anxiety and depression are also common in hospitalized COVID-19 patients. This psychological stress may cause tachycardia and increase the left ventricular after load, thus aggravating pulmonary edema and exacerbating the lung function. The emotional and somatization symptoms caused by psychological stress may also affect the immune system through neuroendocrine pathways, thereby affecting the patient's rehabilitation process and increasing the BOD.[39,40]

The burden of disease of COVID-19 and its symptoms in the inpatient population are an indirect economic and social burden; however, these are ignored by some public health authorities. According to

this study, each cured inpatient averagely loses about 2-3 days of healthy life due to COVID-19 symptoms and discounts almost 1/5th of the quality of life every day. If viewed from the population's perspective, the indirect life loss per 1,000 inpatients was more than 6 years, even if death was not considered. If we consider the increasing number of COVID-19 inpatients worldwide,[41] the indirect life loss could be an enormous figure. Considering pre-hospitalization symptoms and temporary or permanent loss of body function after discharge, the cumulative loss of life would be many-fold higher.Inpatient BOD of each symptom of COVID-19 in the three hospitals had a relatively smaller difference; however, when the BOD was added, inpatients at Huoshenshan Hospital showed a relatively lower overall BOD than the other two hospitals' inpatients. However, the difference was negligible. This can be accounted for by the greater investment of manpower and material resources at Huoshenshan Hospital.

Regarding DWs, among the main symptoms of COVID-19, severe expiratory dyspnea accounted for the most serious BOD, followed by negative psychological symptoms such as severe anxiety and depression. In actual cases, however, the prevalence of severe depression and dyspnea among the inpatient population was not high. Although the prevalence and BOD of anxiety and depression were not high, the ratios of their severity were not able and should be considered in medical care. Among the inpatient population, the most common symptoms were cough and sore throat, but these had a low contribution to the BOD. In contrast, fever and fatigue largely contributed to the BOD. This suggests that to reduce the BOD, symptomatic treatment should focus on symptoms that cause a higher BOD.

The BOD of female inpatients was higher than that of male inpatients, which is similar to the findings in the Korean report[16]; however, when the BOD was shared per day in the hospitals, there were no significant differences. This indicated that the symptoms in female inpatients during hospitalization were more severe (i.e., the symptoms fluctuated dramatically during hospitalization). Specific symptoms such as fever, fatigue, muscular soreness, palpitations, chest tightness, nausea, and vomiting could result in a higher

BOD in female than in male inpatients. For other symptoms, there was no significant difference between female and male populations in the BOD. Thus, cardiovascular and respiratory symptoms in female inpatients were more severe, as were systemic symptoms. Consequently, more attention should be paid to female patients' cardiovascular and respiratory systems during the acute stage.

Contrary to general thinking, the BOD of the younger population was higher than that of the older population. Both ANOVA and linear models supported this conclusion. The main reason for this trend was that the "value" of life at different age stages was fully accounted for in the BOD evaluation. The illness among youth and middle-aged individuals could bring about greater personal, social, and economic losses. Although the symptoms in the elderly may be slightly more severe, it is more significant to reduce the disease burden in youth and middle-aged inpatients with COVID-19 from a macro-economic perspective when the medical resources are limited.

For the synthetic DALY or daily DALY, most linear models indicated that the BOD for obese people was more severe. Obesity affects the immune function of the body, and the burden borne by the organs in obese people is heavier than in non-obese people. Obese people are not only more likely to suffer from various types of infection, including COVID-19 but also experience more serious complications.[42, 43] Therefore, to reduce the disease burden of obese people, it is necessary to strengthen the intervention in this population.

Although synthetic DALY increased with the hospitalization duration, daily DALY decreased significantly. Although the cumulative BOD increased, the BOD shared per day continuously decreased, and the trend of this reduction was very obvious. It indicated that patients received better treatment during hospitalization, and that the symptoms continued to ameliorate with medical care. In contrast, the longer the symptom duration before hospitalization, the heavier the BOD of inpatient duration, indicating that delayed treatment may aggravate the BOD and lead to the consumption of more medical resources. This

finding suggests that earlier detection, diagnosis, and treatment of COVID-19 are very important for the healthcare system. In addition, teenagers and some older age groups, especially those aged above 60 years, exhibited a longer duration of symptoms before hospitalization in our study. This suggests that these individuals may have difficulties in seeking medical treatment or lack vigilance of their own health, which could result in the consumption of more medical resources. Thus, relevant social service departments should be strengthened to provide help and support for teenagers and the elderly.

There are some limitations to this study. First, because this was a retrospective study rather than a prospective study, the data acquired from the medical records may not be fully accurate. The duration of symptoms before admission can only rely on the self-report of the patients, which could cause potential self-reported bias. Notwithstanding, considering the relatively large sample, despite the compromise for potential bias, the macroscopic trend could be detected by statistical analysis.

Second, the medical records were generated in the early stages of the COVID-19 outbreak when the knowledge about COVID-19 was limited. During that time, the diagnosis and treatment protocol of COVID-19 did not include symptoms such as ageusia and anosmia. Thus, there were only a few records of these symptoms in our data. Consequently, we did not include these as the main symptom in this study. However, because inpatients were in the acute stage of the disease, the discomfort from ageusia and anosmia could be clubbed with respiratory and gastrointestinal symptoms. When calculating the disease burden of respiratory and gastrointestinal symptoms, we could make up for the lack of disease burden caused by ageusia and anosmia. Meanwhile, in most cases ageusia and anosmia would more noticeable after discharge, when other acute symptoms gradually disappear. Thus, these symptoms could be treated as sequelae of COVID-19 rather than main symptoms of inpatients in the acute stage.

Third, because this study is based on Chinese cultural and ethnic backgrounds in the early stage of the COVID-19 pandemic, these combined with virus variation over time may affect the comparability of the

results worldwide. The DWs derived from this study may be limited and should consider regional DWs of COVID-19, which could be seen as a pilot study for international BOD study on COVID-19. Notwithstanding, our primary aim was to focus on the regional disease burden and public health management; the cultural difference may therefore not have a great impact on our findings.

Moreover, to determine BOD only caused by COVID-19 symptoms, this study excluded inpatients with comorbidity. When the COVID-19 symptoms superimpose with other diseases, the effect could have been complex and could not have been easily evaluated using simple linear summarization function; moreover, quantitative differentiation of BOD purely caused by COVID-19 symptoms would have been challenging. Because the BOD of COVID-19 comorbidities will be helpful for understanding the COVID-19 burden, it should be considered in future studies. Thus, inpatients with pre-existing medical conditions were excluded, which could have affected the findings in the following two ways: a) the severity and disease duration may have been milder and shorter, respectively, and b) the exclusion of patients with a pre-existing psychiatric disease could have explained the short duration of reported anxiety and depression during hospitalization. Besides, deaths were excluded. Thus, this study evaluated DALY in the same way as YLD caused by symptoms during hospitalization.

CONCLUSION

COVID-19 symptoms could cause heavy BOD in inpatients. The BOD for the female population was higher than that for the male population; however, the daily BOD between male and female inpatients was similar. When the changing life value with age was considered, the disease burden of the younger population was higher than that of the older population, except for teenagers. The treatment at the three military hospitals efficiently relieved the BOD of the inpatients, despite the similar treatment effects. Delay in hospitalization could worsen the BOD for patients with COVID-19. Thus, there is a need for the deployment of adequate medical resources for early hospitalization of patients with moderate or severe

symptoms by the public health authority.

List of abbreviations

BOD: burden of disease

COVID-19: coronavirus disease 2019

DALY: disability-adjusted life years

DW: disability weight

PLA: people's liberation army

GBD: global burden of disease

WHO: World Health Organization

YLDs: years lost due to disability

YLLs: years of life lost

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Authors' contributions: XXL and MH conceived and designed the studies; MH and XXL did literature search and review; XXL, JY, and YC conducted questionnaire and PTO processes; XL, QZ, and YL collected and extracted the data; MH, QT, and YK contributed materials; XXL, JY, and YC analyzed and interpreted the data; XXL and MH drafted the article and revised it. All the authors gave approval before submission.

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Patient consent for publication: Not applicable.

Availability of data and materials: The data that support the findings of this study are available from Wuhan Huoshenshan Hospital, Tongji Hospital, and Guanggu Woman & Child Hospital. However, restrictions will apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are available from the authors upon reasonable request and with permission of the health service authority of Joint Logistics Troop of PLA.

Ethical Approval Statement: The Research Ethics Committee of the No.900 Hospital of Joint Logistics Troop of PLA gave ethical approval (approval number: 2020-001). None of the inpatients were involved in any health intervention. All the individual data were anonymized prior to retrieval and analysis, and they did not contain any individual's private information.

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Figure legends

Fig. 1 Flow of inpatient selection

Fig. 2: Curve of changes in the weighted life value with age

Fig.3: Duration of symptoms before hospitalization by age group in female and male populations

Fig.4: Length of hospital stay by age group in female and male populations

Fig.5: Overall duration of symptom changes with age group in female and male populations

Fig. 6a: The proportion of accumulative duration (in day) by symptoms in the study population

Fig. 6b: The proportion of DALY by symptoms in the study population

Fig. 7: Composition of each military temporary hospital's synthetic DALY

Fig. 8: Composition of each sex group's synthetic DALY

Fig. 9: Composition of each age group's synthetic DALY

Fig. 10: Thermal map of COVID-19 inpatient's DALY by sex and age group (DALY per 1000 capita).

Fig. 11: Synthetic DALY changes with age group in female and male populations

Fig. 12: DALY per day changes with age group in female and male populations

Additional file

File name: Additional file 1

File format: DOC

Title of data: questionnaire

Description of data: Text/table

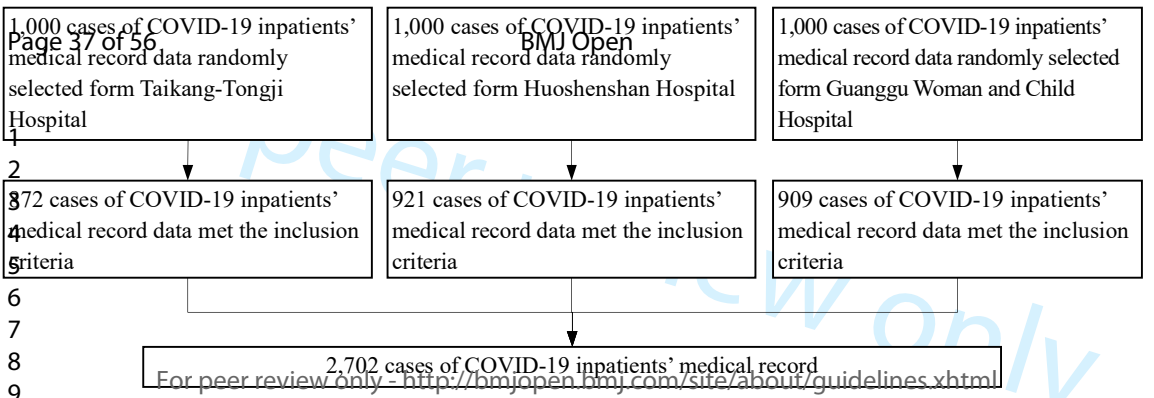
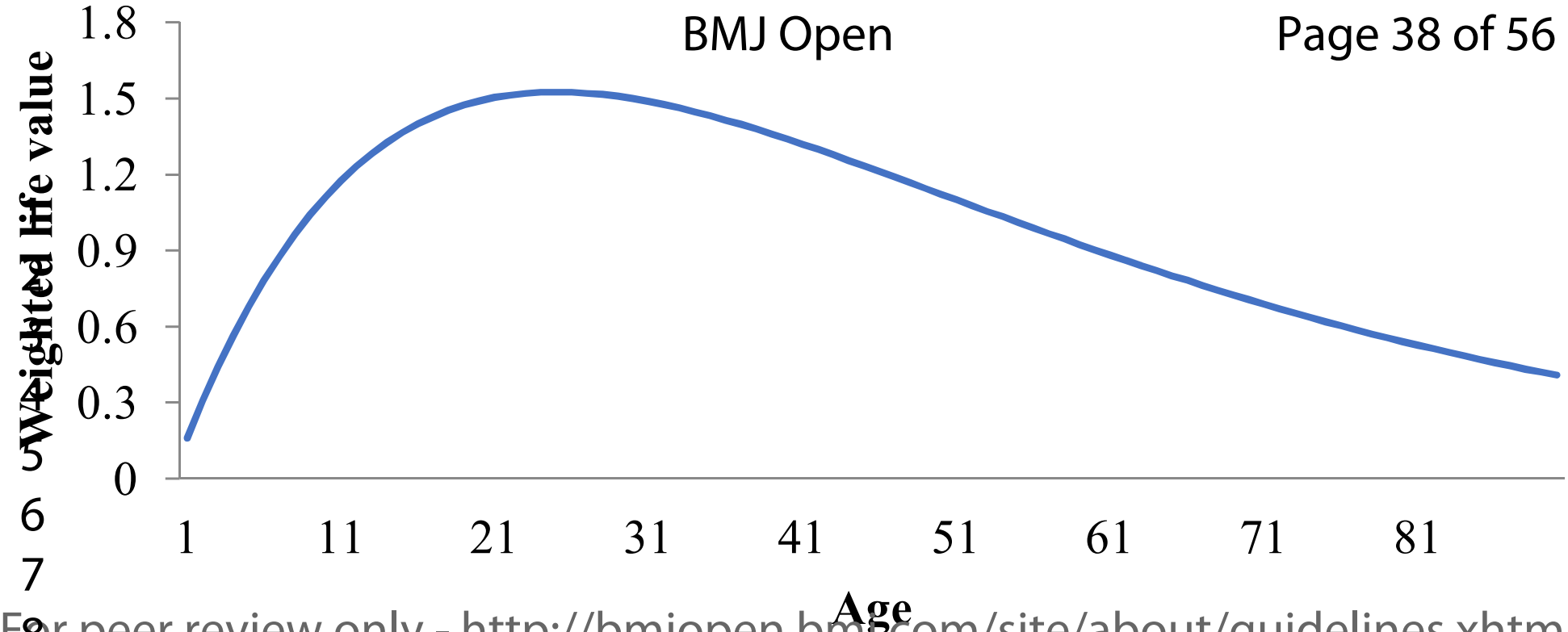


Fig. 1



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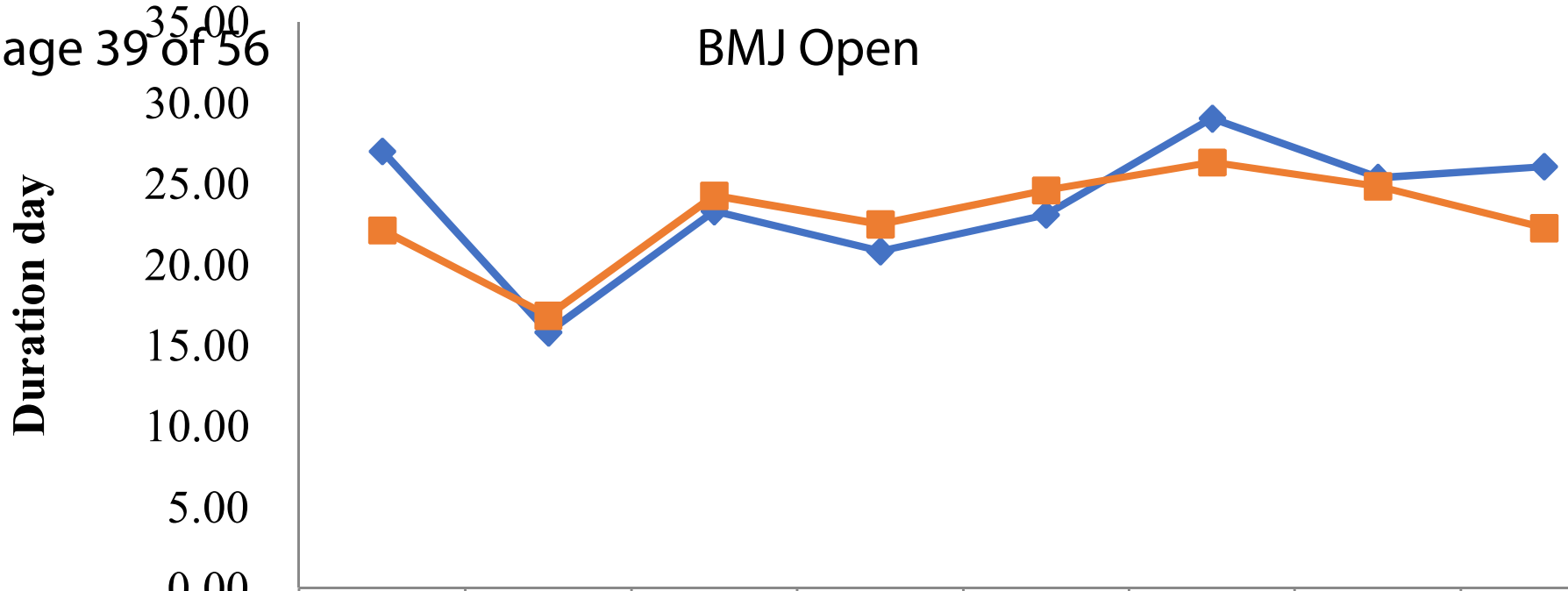
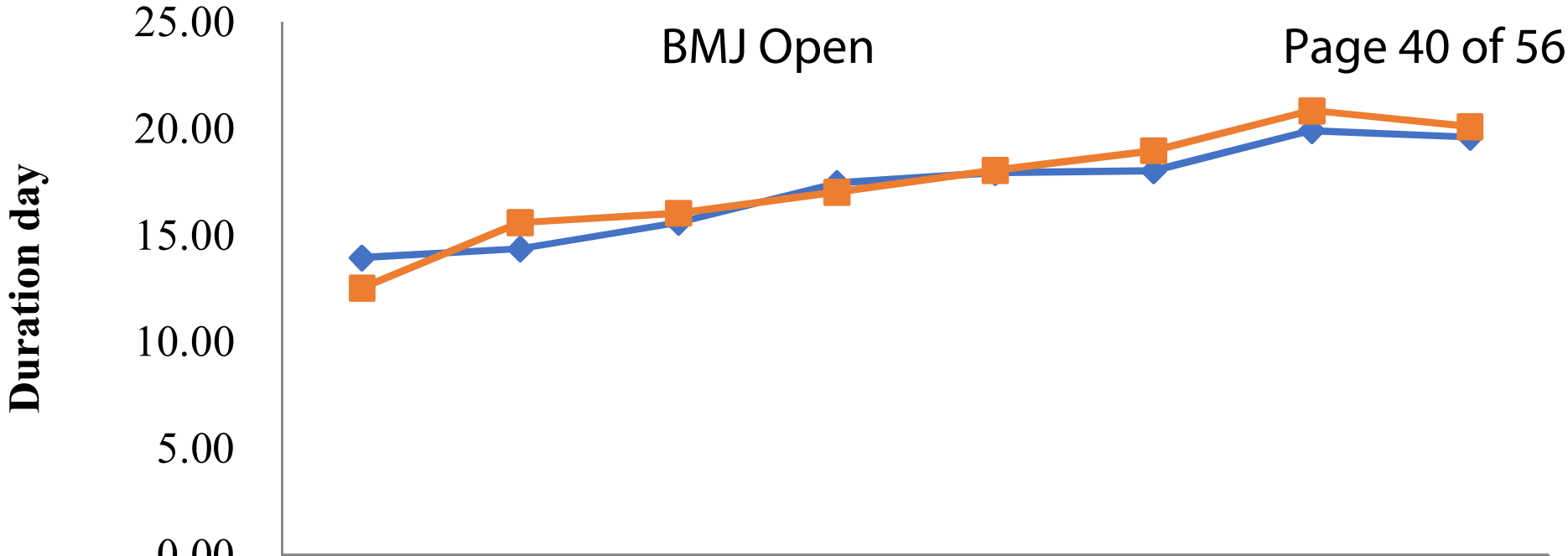


	<19	20-29	30-39	40-49	50-59	60-69	70-79	>79
Male	27.00	15.81	23.30	20.82	23.08	29.03	25.37	26.07
Female	22.13	16.83	24.26	22.48	24.59	26.32	24.84	22.25

Age group

Fig. 3



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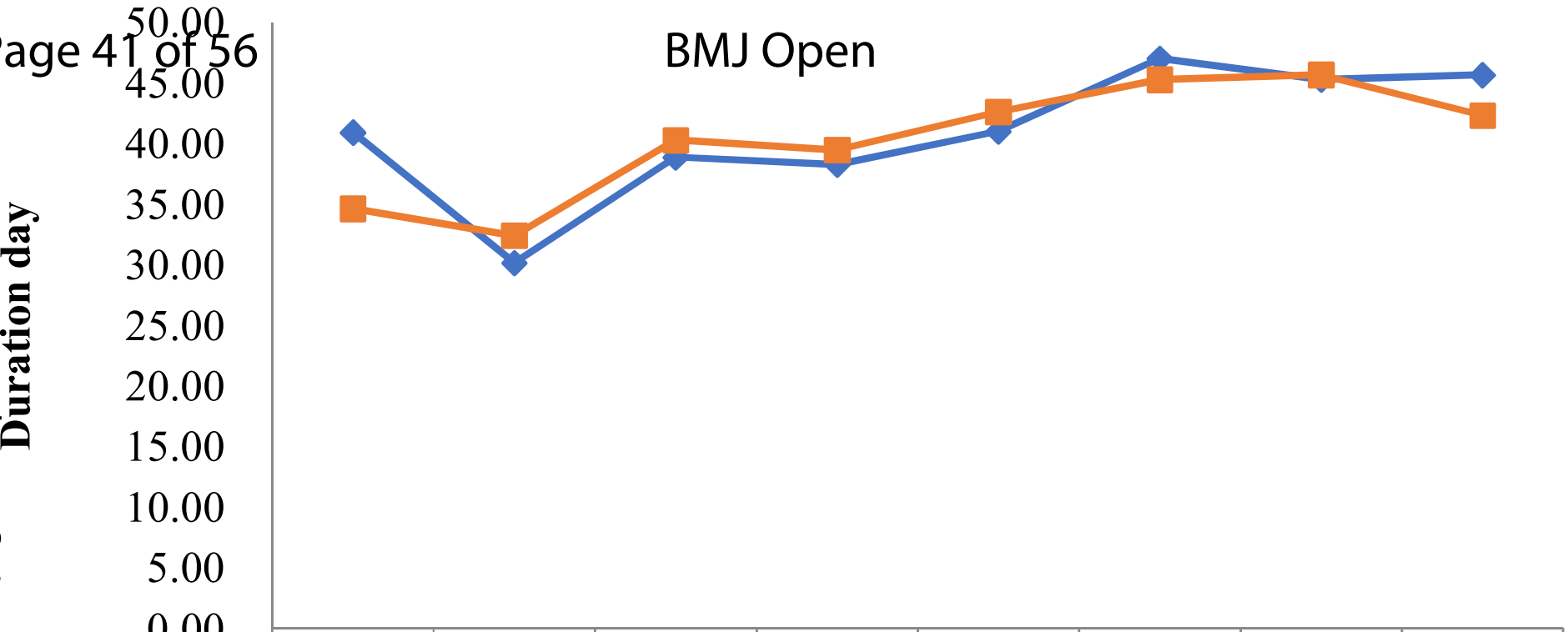
Male	13.92	14.34	15.58	17.43	17.93	18.00	19.90	19.59
Female	12.50	15.57	16.02	17.00	18.03	18.95	20.82	20.07

Age group

Fig. 4



	<19	20-29	30-39	40-49	50-59	60-69	70-79	>79
Male	40.92	30.15	38.88	38.26	41.01	47.03	45.27	45.65
Female	34.63	32.41	40.28	39.48	42.62	45.27	45.67	42.33

Age group

Fig. 5

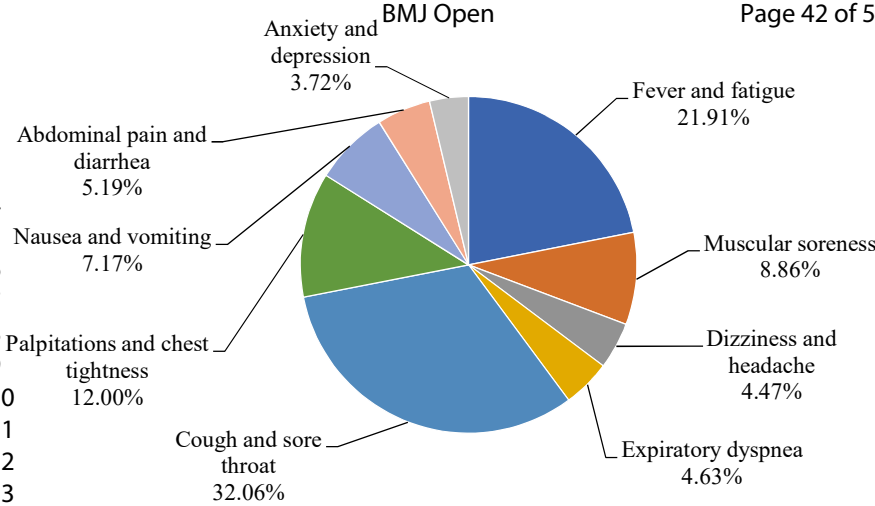
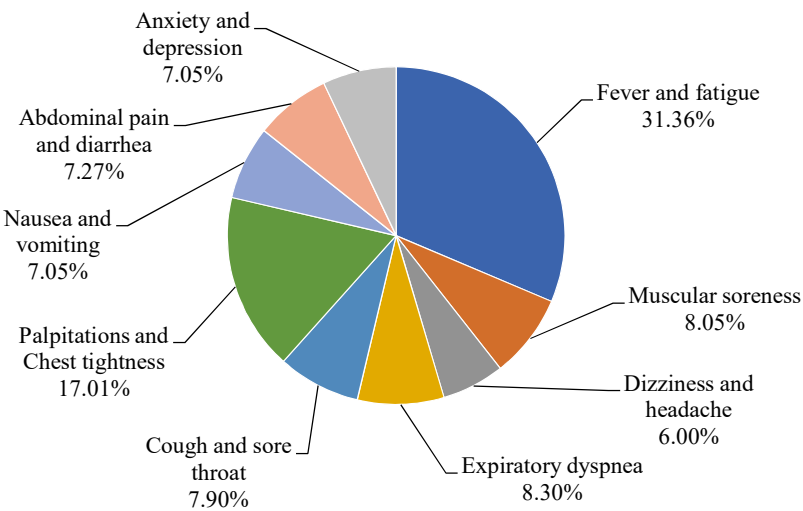


Fig. 6a



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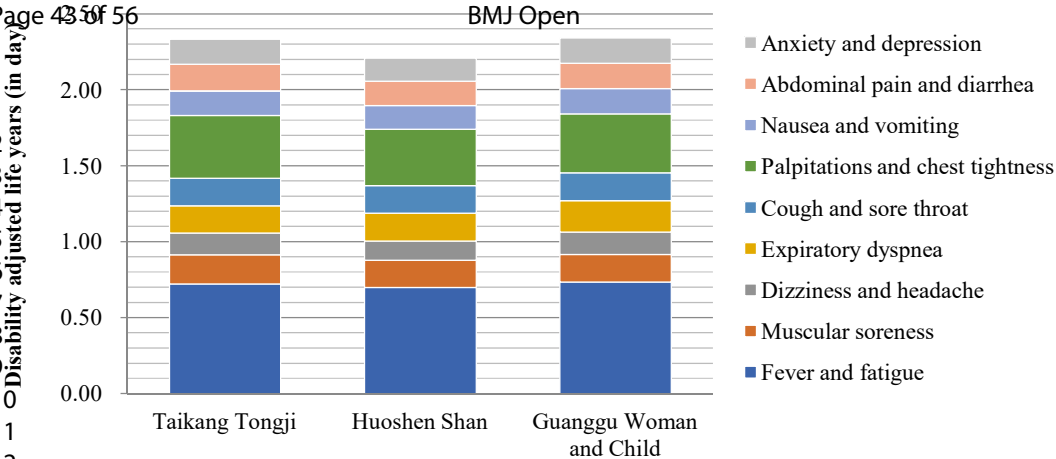


Fig. 7

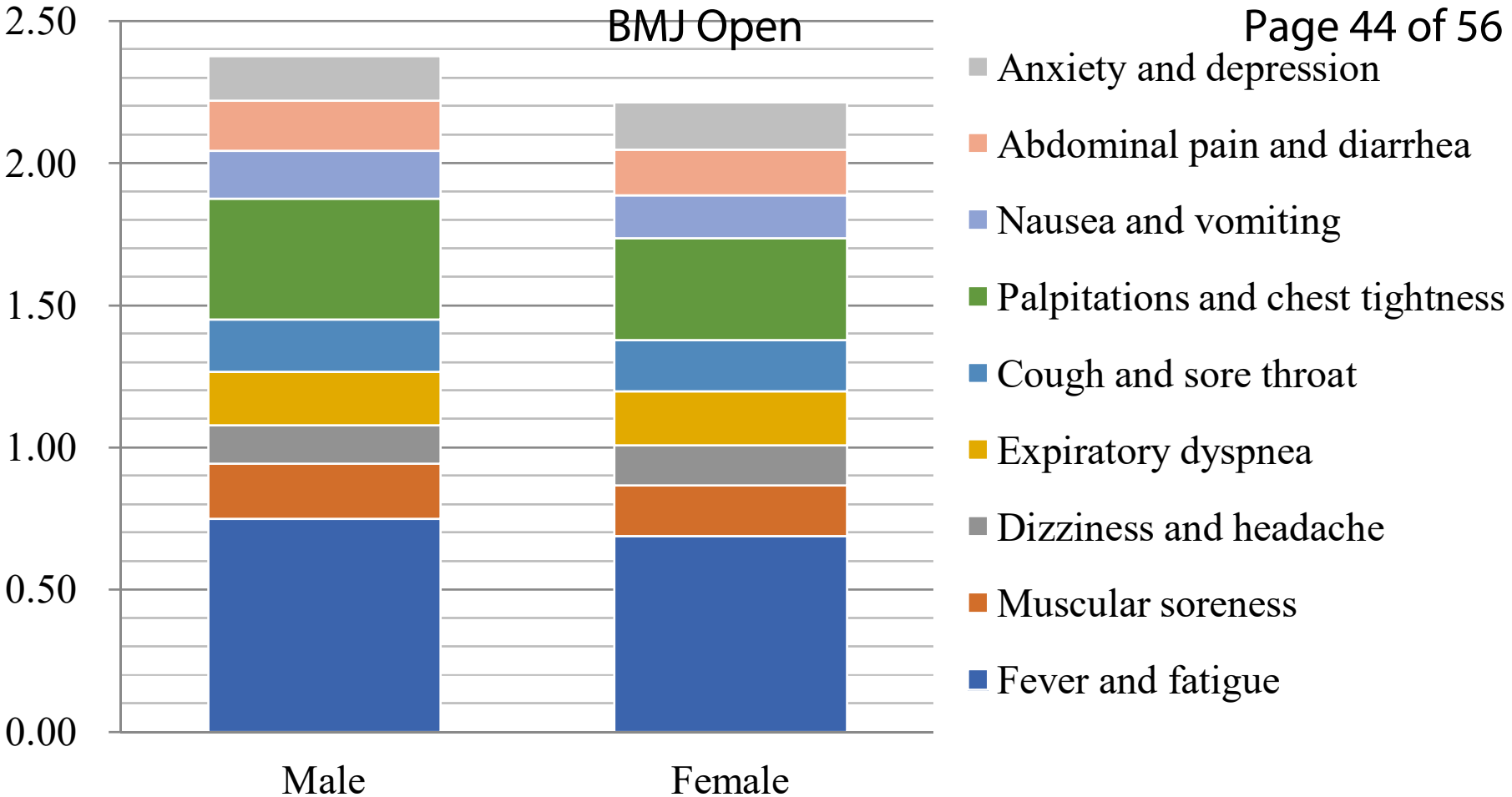


Fig. 8

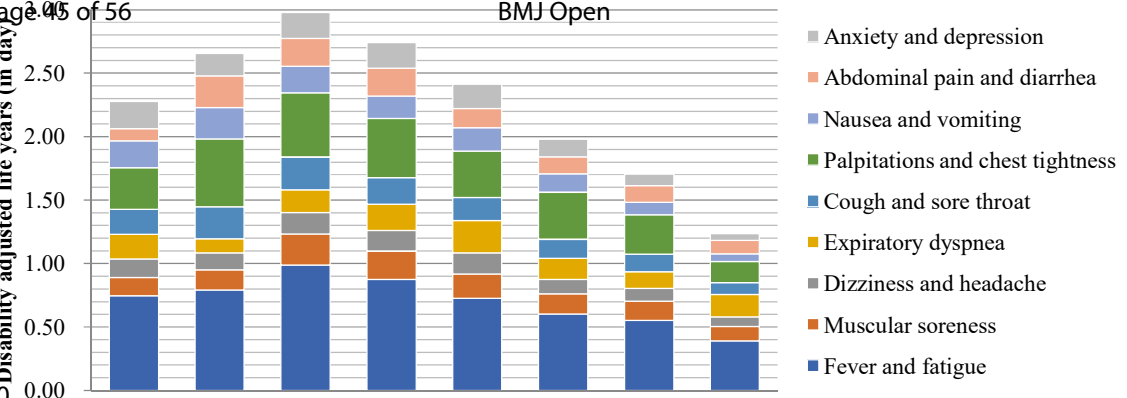
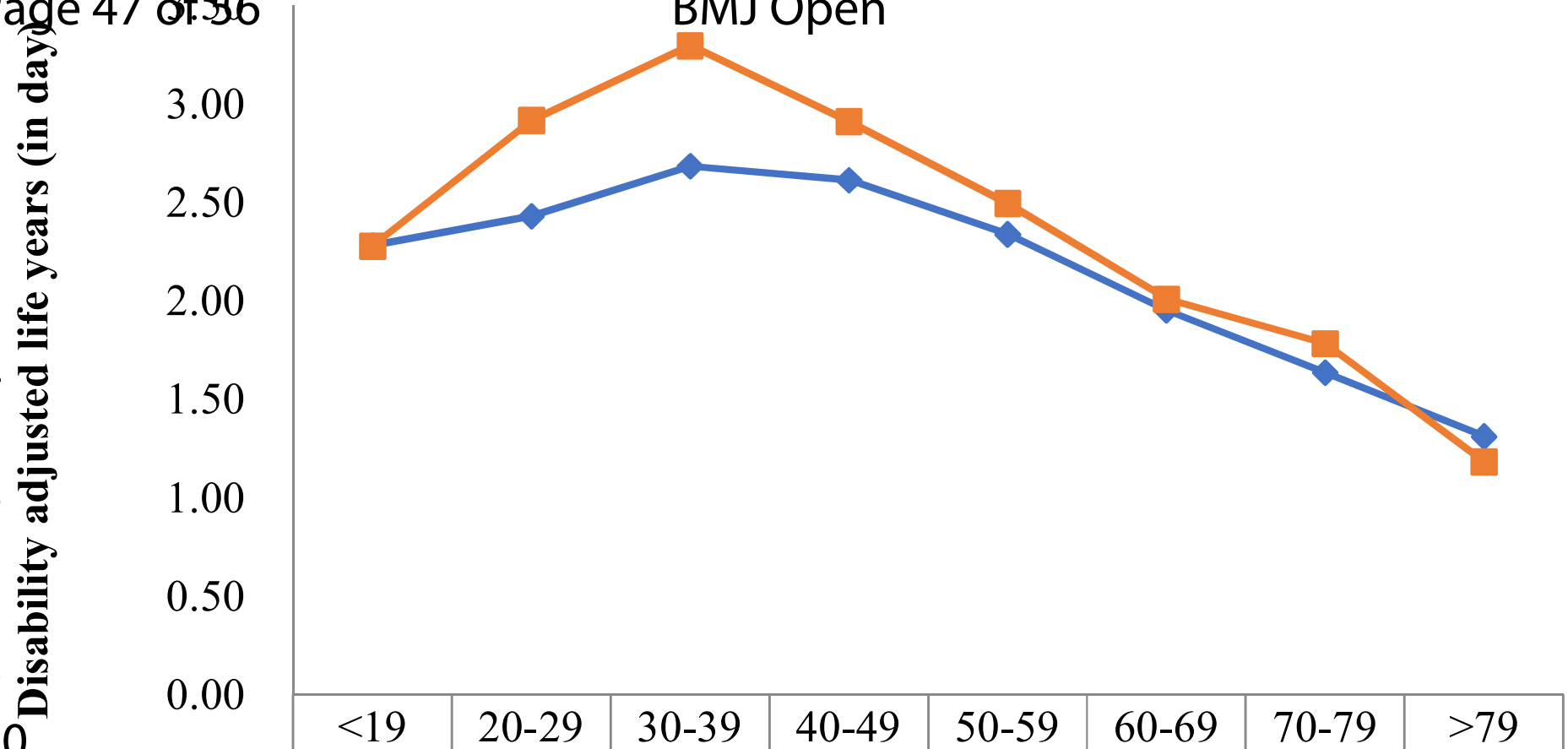


Fig. 9

Male DALY/1000 captia (in days)									Symptoms	Female DALY/1000 captia (in days)								
<19 (n=24)	20-29 (n=54)	30-39 (n=149)	40-49 (n=234)	50-59 (n=295)	60-69 (n=328)	70-79 (n=147)	>79 (n=95)	All age (n=1326)		All age (n=1376)	>79 (n=75)	70-79 (n=159)	60-69 (n=307)	50-59 (n=297)	40-49 (n=295)	30-39 (n=156)	20-29 (n=62)	<19 (n=25)
639	789	1115	947	776	623	547	379	751	Fever and fatigue	689	412	559	584	677	821	868	796	855
162	174	276	233	201	163	157	117	193	Muscular soreness	177	107	145	154	187	215	217	146	121
134	150	176	151	159	109	94	83	134	Dizziness and headache	141	65	107	116	169	169	166	117	161
142	118	181	232	262	160	130	129	190	Expiratory dyspnea	191	236	133	177	247	189	175	108	243
202	275	271	210	183	151	146	87	183	Cough and sore throat	180	101	132	147	182	210	247	229	192
470	626	614	522	360	383	373	168	423	Palpitations and Chest tightness	358	162	252	357	373	423	401	457	193
149	263	238	192	187	151	124	59	171	Nausea and Vomiting	153	62	75	142	178	161	180	236	271
111	316	220	226	179	133	125	108	174	Abdominal pain and Diarrhea	160	100	138	137	126	213	220	187	80
266	203	202	194	184	135	85	50	157	Anxiety and Depression	166	63	92	137	197	210	209	153	164

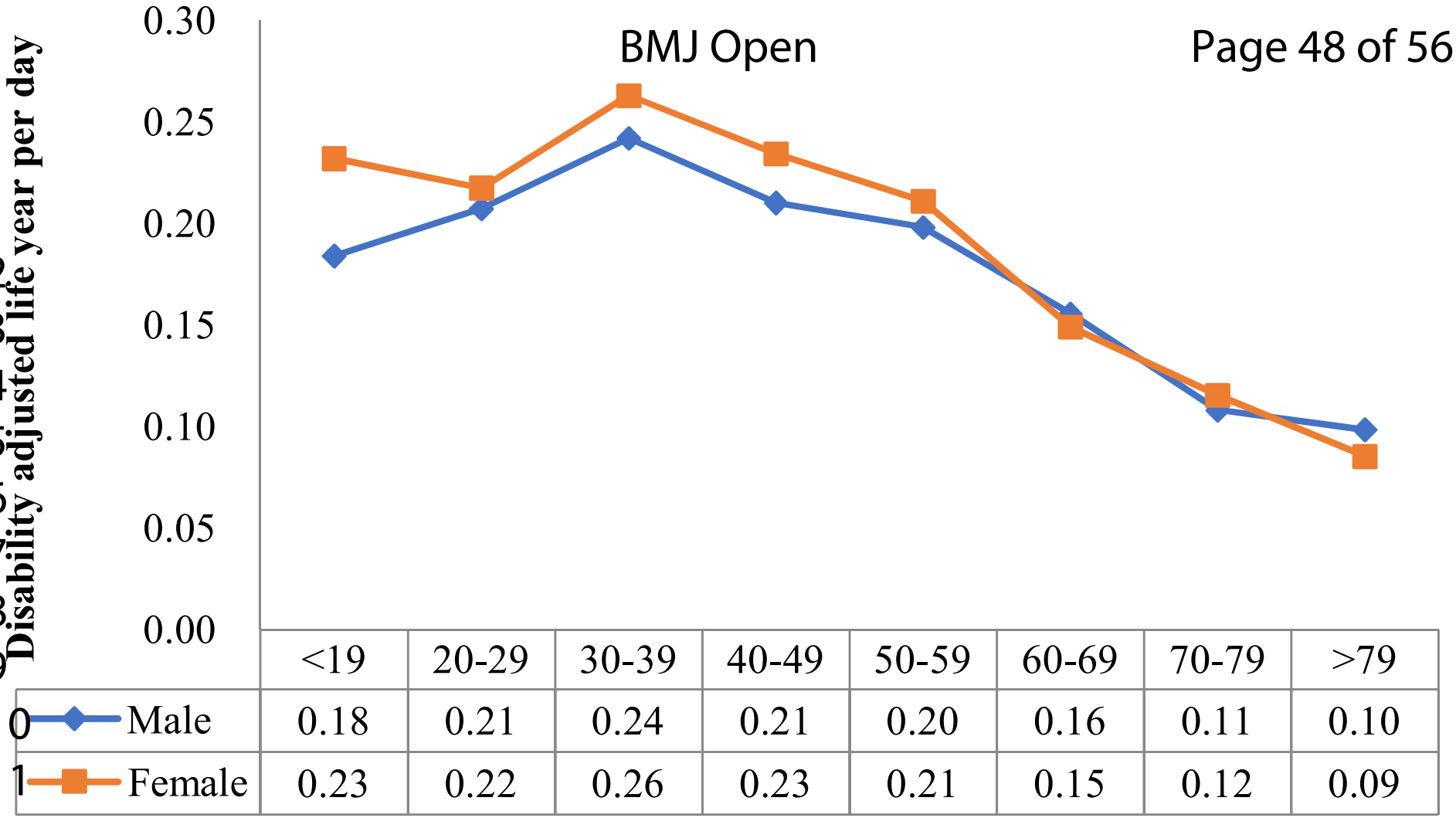
Fig. 10



	<19	20-29	30-39	40-49	50-59	60-69	70-79	>79
Male	2.28	2.43	2.68	2.61	2.34	1.95	1.63	1.31
Female	2.28	2.91	3.29	2.91	2.49	2.01	1.78	1.18

Age group

Fig. 11



	<19	20-29	30-39	40-49	50-59	60-69	70-79	>79
Male	0.18	0.21	0.24	0.21	0.20	0.16	0.11	0.10
Female	0.23	0.22	0.26	0.23	0.21	0.15	0.12	0.09

Fig. 12

Additional file 1: Questionnaire

Front-line medical staff questionnaire on symptoms of COVID-19 (The first round)

Dear Sir/Madam:

This is a questionnaire on COVID-19 typical symptom. The aim is to generate a comprehensive list of typical symptoms of inpatient with COVID-19, which can be used to assess the disease burden caused by the symptoms. This study will adopt the method of disability adjusted life years (DALYs) of the World Health Organization (WHO) to evaluate inpatients' burden of disease caused by COVID-19 symptoms.

According to your clinical experience, please judge the raw list of category and symptoms summarized by the literature review (Table 1). The judgment items are included:

For category：

(1) Whether the category should be included in the list;

(2) Whether the name of the category is appropriate.

For symptoms：

(1) Whether the symptom should be listed;

(2) Whether the symptom should be classified into the current category;

(3) Whether the name of the symptom is appropriate.

If you think it is necessary, please supplement the symptom list according to your clinical experience. You can add:

(1) New categories if necessary;

(2) New symptoms if necessary.

As a front-line clinical expert engaged in COVID-19 treatment, your knowledge about the symptoms of the disease is valuable. Therefore, your opinion is very important for this study. Please try your best to fill the list appropriately. All the information you fill in is for academic research only. We will not analyze your responses individually and will keep them anonymous. Please provide responses to the best of your knowledge.

According to the Delphi process, the opinions of each expert in this round will be anonymously submitted to other experts as reference, in the next round of questionnaire survey. You will also see the anonymous opinions of the other experts. This study is expected to be conducted in 2-3 rounds for a more consistent answer.

Thank you for your support and cooperation.

The Research Group on COVID-19 Burden of Disease

Date:_____

Table1: COVID-19 inpatient's symptom list for the burden of disease evaluation (Template)

Category (Code)	Include the item or not (Y/N)	Term appropriate or not (Y/N)	If inappropriate, fill in alternative terms	Symptom	Include the item or not (Y/N)	Term appropriate or not (Y/N)	If inappropriate, fill in alternative terms	Should it be moved to another category? If yes, type the code
Systemic symptoms (01)				Fever				
				Other symptom 1 (if necessary):				
				Other symptom 2 (if necessary):				
Neurological symptoms (02)				Headache				
				Other symptom 1 (if necessary):				
				Other symptom 2 (if necessary):				
Respiratory symptoms (03)				Expiratory dyspnea				
				Cough				
				Other symptom 1 (if necessary):				
				Other symptom 2 (if necessary):				
Cardiovascular symptoms (04)				Palpitations				
				Other symptom 1 (if necessary):				

Category (Code)	Include the item or not (Y/N)	Term appropriate or not (Y/N)	If inappropriate, fill in alternative terms	Symptom	Include the item or not (Y/N)	Term appropriate or not (Y/N)	If inappropriate, fill in alternative terms	Should it be moved to another category? If yes, type the code
				Other symptom 2 (if necessary):				
Gastrointestinal symptoms (05)				Diarrhea				
				Other symptom 1 (if necessary):				
				Other symptom 2 (if necessary):				
Other category (06) (if necessary):				Other symptom 1 (if necessary):				
				Other symptom 2 (if necessary):				
Other category (07) (if necessary):				Other symptom 1 (if necessary):				
				Other symptom 2 (if necessary):				

If you have anything else to explain, please write here:

To confirm the above, please sign (or type here):

Date:

Front-line medical staff questionnaire on symptoms of COVID-19 (The second/third round)

Dear Sir/Madam:

Thank you for your cooperation and hard work in the last round of the questionnaire survey. The anonymous opinions of other experts in the last round have been sent to you as a reference. We retained all the consensus items in the last round of the expert consultation in the list. We also added the most favorite (approval rate > 50%) new items or the items that were proposed for adjustment (Table 1). Please supplement with the necessary items according to your own clinical experience and the opinions of other experts.

According to your clinical experience, please judge the newly added or adjusted category and symptom items:

For category：

(1) Whether the category should be included in the list;

(2) Whether the name of the category is appropriate.

For symptom：

(1) Whether the symptom should be listed;

(2) Whether the symptom should be classified into the current category;

(3) Whether the name of the symptom is appropriate.

Besides, you also can add:

(1) New categories if necessary;

(2) New symptoms if necessary.

According to the Delphi process, the opinion of each expert in this round will be anonymous and submitted to other experts as reference, in the next round of the questionnaire survey. You will also see the anonymous opinions of the other experts. This study is expected to be conducted in 2-3 rounds for a more consistent answer.

Thank you for your support and cooperation.

The Research Group on COVID-19 Burden of Disease

Date：_____

Table1: COVID-19 inpatient's symptom list for the burden of disease evaluation (Template)

Category (Code)	Include the item or not (Y/N)	Term appropriate or not (Y/N)	If inappropriate, fill in alternative terms	Symptom	Include the item or not (Y/N)	Term appropriate or not (Y/N)	If inappropriate, fill in alternative terms	Should it be moved to another category? If yes, type the code
Systemic symptoms (01)				Fever and fatigue *				
				Muscular soreness *				
				Other symptom 1 (if necessary):				
				Other symptom 2 (if necessary):				
Neurological symptoms (02)				Headache				
				Other symptom 1 (if necessary):				
				Other symptom 2 (if necessary):				
Respiratory symptoms (03)				Expiratory dyspnea				
				Cough				
				Other symptom 1 (if necessary):				
				Other symptom 2 (if necessary):				
Cardiovascular symptoms (04)				Palpitations				
				Chest tightness *				
				Other symptom 1 (if necessary):				
				Other symptom 2 (if necessary):				

Category (Code)	Include the item or not (Y/N)	Term appropriate or not (Y/N)	If inappropriate, fill in alternative terms	Symptom	Include the item or not (Y/N)	Term appropriate or not (Y/N)	If inappropriate, fill in alternative terms	Should it be moved to another category? If yes, type the code
Gastrointestinal symptoms (05)				Diarrhea				
				Vomiting *				
				Other symptom 1 (if necessary):				
				Other symptom 2 (if necessary):				
Psychological symptoms * (06)				Anxiety and depression *				
				Other symptom 1 (if necessary):				
				Other symptom 2 (if necessary):				
Other category (07) (if necessary):				Other symptom 1 (if necessary):				
				Other symptom 2 (if necessary):				

* Newly proposed or adjusted item.

If you have anything else to explain, please write here:

To confirm the above, please sign (or type here):

Date:

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Disease burden from COVID-19 symptoms among inpatients at the temporary military hospitals in Wuhan: A retrospective multi-center cross-sectional study

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Disease burden from COVID-19 symptoms among inpatients at the temporary military hospitals in Wuhan: A retrospective multi-center cross-sectional study

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ABSTRACT:

Objectives: We aimed to establish a set of disability weights (DWs) for COVID-19 symptoms, evaluate the disease burden of inpatients, and analyze the characteristics and influencing factors of the disease.

Design: This was a multi-center retrospective cross-sectional descriptive study.

Setting: The medical records generated in three temporary military hospitals in Wuhan.

Participants: Medical records of 2,702 inpatients generated from February 5 to April 5, 2020, were randomly selected for this study.

Primary and secondary outcome measures: DWs of COVID-19 symptoms were determined by the person-trade-off approach. The inpatients' medical records were analyzed and used to calculate the disability-adjusted life years (DALY). The mean DALY was evaluated across sex and age groups. The relationship between DALY and age, sex, body mass index, length of hospital stay, symptom duration before admission, and native place was determined by multiple linear regression.

Results: For the DALY of each inpatient, severe expiratory dyspnea, mild cough, and sore throat had the highest (0.399) and lowest (0.004) weights, respectively. The average synthetic DALY and daily DALY were 2.29±1.33 and 0.18±0.15 days, respectively. Fever and fatigue contributed the most DALY at 31.36%, whereas nausea and vomiting and anxiety and depression contributed the least at 7.05%. There were significant differences between sex and age groups in both synthetic and daily DALY. Age, body mass index, length of hospital stay, and symptom duration before admission were strongly related to both synthetic and daily DALY.

Conclusions: Although the disease burden was higher among women than men, their daily disease burdens were similar. The disease burden in the younger population was higher than that in the older population. Treatment at the hospitals relieved the disease burden efficiently, while a delay in hospitalization worsened it.

Keywords: COVID-19; Wuhan; Burden of disease; Bio-security; Symptom; Inpatient; Disability-adjusted life years

Strengths and limitations of this study

- The validity of the large sampled medical records from the military medical units was high.
- To determine the pure burden of COVID-19 symptoms, comorbidity and mortality cases were excluded.
- Self-reported bias of symptom duration prior to hospital admission may be high.
- Cultural and ethnic differences and virus variation over time may have affected data comparison.

BACKGROUND

The coronavirus disease (COVID-19) pandemic is both a global public health emergency and a major bio-security event; it brings pain and loss to individuals and families and a heavy burden to countries and societies.[1,2] Scientific evaluation of the social and economic impact of the public health incident provides an important way to determine the therapeutic effectiveness in medical institutions and an important basis for the government to formulate relevant rescue policies and recovery measures. The economic burden of disease (BOD) and injury include treatment costs and various forms of losses in life (e.g., death and poor quality of life due to a temporary or sustained decline in the quality of life).[3,4]

There are several new features of COVID-19 compared with severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS).[5] The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection can cause symptoms such as fever, fatigue, cough, dyspnea, headache, nausea, vomiting, abdominal pain, and diarrhea, and in severe cases, severe acute respiratory syndrome, multiple organ failure, and even death.[6-9] As it is an emerging disease, the BOD caused by COVID-19 remains unclear. Studying the BOD and symptoms of COVID-19 will help to deepen our understanding of the disease, its harm, and severity and to predict the developing trend of the disease. Thus, public health authorities could improve the treatment and rehabilitation programs, renew relief measures, and adjust public health policies appropriately.

Since the 1990s, the World Health Organization (WHO) and the World Bank have proposed indicators to evaluate the BOD, which is a measure of the disability-adjusted life years (DALY).This single-utility measure used to determine the burden attributable to a specific disease is calculated using the standard method proposed by Murray and Lopez.[10] The DALY is a summary measure of population health accounting for both the years of life lost (YLLs) and years lost due to disability (YLDs). The DALY was first developed for quantifying the global burden of disease (GBD), expressed as the relative magnitude of losses

of healthy life associated with different causes of disease and injury.[11] Since then, the DALY has been widely used globally to estimate the BOD at the national, international, and regional levels.

Recently, DALY has been used to evaluate the BOD of some specific diseases. Qi et al. comprehensively evaluated the direct and indirect BOD of public emergencies caused by Asian Lineage Avian Influenza A (H7N9) infection.[12] Zhang et al. evaluated the BOD and related factors in hospitalized patients with coal workers' pneumoconiosis and provided the basis for improving relevant medical policies.[13] Bacellar et al. assessed BOD in hospitalized elderly patients with neurological disorders in Brazil and recommended measures to improve the treatment plan.[14] Adopting the WHO approach, Pei and Li et al. formulated the disability weights (DWs) for chronic mountain disease, which was used to calculate the BOD among soldiers stationed in Tibet and helped evaluate the ability of troops to perform tasks.[15]

The DALY method could provide important insights into public health studies and practice regarding COVID-19. This year, a series of research studies were conducted worldwide to estimate the BOD of COVID-19 in different regions, from multiple perspectives, and using different methods. Jo et al. adopted DWs from previous similar causes to calculate the BOD of COVID-19 in Korea, including YLDs and YLLs.[16] Oh et al. estimated the YLLs due to COVID-19 in 30 high-incidence countries using the WHO-provided data.[17] To assess the socio-economic burden of the COVID-19 pandemic in Italy, Nurchis et al. estimated YLLs and YLDs along with the productive YLLs, and the comparable DW of lower respiratory tract infection as adopted to estimate the YLDs.[18] Mohanty et al. examined the impact of COVID-19 on the longevity, years of potential life lost, and DALY in the USA, Italy, Germany, and Sweden, and adopted DWs of similar diseases as proxy.[19] Furthermore, Ortiz-Prado et al. assessed the BOD of COVID-19 in Ecuador by adopting the DWs of other similar diseases.[20]

These studies not only contributed greatly to the understanding of BOD of COVID-19 but also provided the basis for global COVID-19 public health services and related policy-making. However, in recent reports,

BOD assessment of COVID-19 remained at the macro level and relatively unclear, mainly because, only the DWs from similar diseases were adopted, leaving COVID-19 with a singular DW, which ignored the complexity of COVID-19 symptoms. Until now, limited reports exist on China's COVID-19 BOD, especially based on each COVID-19. Thus, we aimed to establish the DW for COVID-19 symptoms, to estimate the BOD among inpatients in Wuhan, China, and to analyze the characteristics and potential influencing factors. To design this technical approach, we design a technical approach based on previous studies. The BOD of COVID-19 symptoms was evaluated from existing medical records.

METHOD

Selection of the population groups

To counter the public health disaster and bio-security crisis caused by COVID-19 in Wuhan, People's Liberation Army (PLA) performed a series of non-combat military operations, including the deployment of three temporary military hospitals (Huoshenshan Hospital [from March 2 to April 15, 2020], Taikang-Tongji Hospital [March 13 to April 16, 2020], and Guanggu Woman and Child Hospital [March 13 to April 16, 2020]). The first hospital was a newly built one, while the other two were civil medical facilities temporarily utilized by the PLA medical staff. While in operation, all the hospitals were designated as specialized COVID-19 hospitals.

All the analyzed inpatient data were randomly selected from the three temporary military hospitals' medical records using the same recording standard. The included inpatients' hospitalization period ranged from February 5 to April 5, 2020. The selection process was conducted from May 25 to June 5, 2020, after the closure of the temporary hospitals (Fig. 1). Data for 2,702 inpatients were included in this study. All the inpatients treated by the military medical staff were from the military hospitals affiliated to the PLA.

<**Insert Fig. 1 here**>

The diagnosis and treatment method were based on the "Diagnosis and treatment standard of

COVID-19 (7th edition)" published by the People's Republic of China's (PRC) central government.[21] The standard detailed laboratory tests for COVID-19, with pathogenic, serological, and chest image criteria, were included. All patients were hospitalized before the release of the 7th edition and were reconfirmed according to the diagnostic criteria. The inclusion criteria were COVID-19 diagnosis at the hospitals according to the standard guideline and continuous treatment at these hospitals. To determine the BOD of COVID-19, inpatients with any other morbidity (other infectious diseases, other respiratory diseases, psychiatric disease, tumor, pregnancy and lactation, and chronic cardiac, liver, kidney, and neurological diseases) were excluded. We also excluded COVID-19 inpatient deaths due to the reluctance of their family members to allow the use of their data for a public study. Similarly, cases with incomplete medical records were excluded.

Establishment of the disability weights for COVID-19 symptoms

DW is a key component of BOD analysis that represents disease severity. It ranges from 0 to 1, where 0 represents healthy life, and 1 represents death.[4] WHO has been conducting GBD studies for several years, with series of DWs derived for different health states that are the outcomes of different diseases.[22-26]

Because COVID-19 is a new infectious disease, no DWs exist for COVID-19 symptoms in the WHO's DW list; thus, we attempted to establish customized DWs for COVID-19 symptoms. First, COVID-19 symptoms were listed following a literature review of newly published clinical reports on COVID-19. Three rounds of questionnaires were completed by front-line medical staff in the three military field hospitals in Wuhan to derive a raw list of COVID-19 symptoms for establishing DWs (questionnaire sample is shown in Additional file 1).

Then, we convened a nine-expert panel composed of three senior respiratory physicians, two senior infectious disease physicians, one epidemiologist, one public health management expert, and two nursing experts. Based on the raw list of COVID-19 symptoms, the panel performed the Delphi process to

determine the final symptom list for creation of DWs.[27]

Then, the panel members performed the Person-Trade-Off (PTO) exercise to derive each symptom's DWs by three levels of severities (health stages).[15, 28, 29] The health stages were described on an A4-sized vignette that contained disease-specific information in simple terminologies. As a reference framework for this task, the panel members were provided with a WHO-GBD framework table, which displayed seven disability classes and 22 anchoring example conditions. The coefficient of variation (CV) was calculated to determine the need for additional rounds of discussion and reassignment of values.

Data extraction

Basic information for the confirmed cases included the identification number (ID), age, sex, weight, height, native place, date of onset reported by the patient, diagnostic conclusion, symptoms recorded by the medical staff, and inpatient and outpatient time. Nine age groups were created: <10, 10-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, and >80 years. Body mass index (BMI) was calculated, while the duration of symptoms was determined as the length of stay + symptom duration before hospitalization (self-reported in the medical record).

To accurately extract the medical data from the records, we trained 6 staffs by same criteria. During the data extraction, the six staff members were divided into three groups of two, and when data were extracted from the records, these were cross-checked. The extraction process was conducted from May 29 to August 7, 2020.

Calculation of DALY for COVID-19 symptoms

The DALY was used to estimate the disease burden of COVID-19 symptoms. The DALY is calculated as the sum of the YLLs due to premature mortality in the population and the equivalent 'healthy' YLDs for incident cases of the health condition.[4,11,30] However, we did not consider COVID-19-related deaths. Therefore, the DALY due to COVID-19 was equal to the YLDs. Thus, a patient's individual DALY was

calculated using the following formula[15]:

$$\mathrm{DALY} = \int_{x=\alpha}^{x=\alpha+L} DC\, xe^{-\beta x} e^{-\gamma(x-\alpha)} dx \quad (1.0)$$

where D represents DW, K is an age weighting factor, C is a constant, r is the discount rate, a is the age at onset, β is a parameter from the age weighting function, and L is lifetime with disability. We used the base case recommended by Murray and Lopez, with C = 0.1658, r = 0.03, K = 1, and β = 0.04.[15,31]

Considering that the COVID-19 inpatient hospitalization time was relatively short, L *in* the formula (1.0) is shorter than 1 year; thus, the age of each inpatient was treated as fixed. Accordingly, the formula was simplified as follows:

$$\mathrm{DALY} = DCxe^{-\beta x} \quad (2.0)$$

In formula 2.0, $Cxe^{-\beta x}$ reflects the life value discounted by age. This function is based on the hypothesis that life value is different for different age groups: a person's life value increases after they are born and reaches the peak in their youth; next, the life value `declines with age (Fig.2). Hence, in calculating the DALY, DALY will differ for different age groups despite identical symptoms.

<**Insert Fig. 2 here**>

We calculated the DALY as follows: 1) the cumulative duration (in days) of each health condition (a health condition is one type of symptom severity); 2) the duration was multiplied by the corresponding DW to get the DALY of each health condition; 3) all the DALY values were summed up into an inpatient's synthetic DALY for COVID-19; 4) the synthetic DALY was divided by the patient's length of stay to get the daily DALY. Considering that the inpatient's length of stay was relatively short, the unit of DALY was set as days.

Statistical analysis

The demographic characteristics of patients such as hospitalization, sex, and native place, were evaluated. The distribution of each symptom according to the hospital, sex, and overall population, was calculated. The mean DALY, synthetic DALY, daily DALY, age, BMI, and symptom course (including symptom

duration before hospitalization, length of stay, and overall duration) based on the hospital, sex, and age groups were calculated and compared by analysis of variance (ANOVA) or t-test (for two groups only). The ratio difference of the cumulative duration (in days) of symptom severity levels (mild, moderate, and severe) was tested by a chi-square test. The proportions of BOD for each symptom by sex and age group, and in the entire sample population were computed. DALY per 1,000 capita was also calculated by age group and sex. Each symptom's duration in the whole study population was also calculated.

To test the relationship between DALY and age, sex, BMI, and symptom duration, separate linear regression analyses were performed using DALY as the dependent variable and age, sex, BMI, native place, symptom duration before hospitalization, and length of stay as independent variables. In the regression models, sex and native place were set as categorical variables while the others were continuous variables. Synthetic and daily DALY were analyzed, and each hospital's study population and overall study population were analyzed separately. IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, N.Y., USA) was used for statistical analyses. A *P*-value <0.05 was considered statistically significant.

Patient and public involvement

This was a multi-center retrospective cross-sectional descriptive study of COVID-19 inpatients in Wuhan, PRC. The study was performed after the closure of the three temporary military hospitals. None of the inpatients were involved in any health intervention. All individual data were anonymized prior to retrieval and analysis. Because only patient data were used, no patients were directly involved in the study.

RESULTS

Patient characteristics

Data of 2,702 inpatients (872, 921, and 909 from Taikang-Tongji, Huoshenshan, and Guanggu Woman and Child Hospitals, respectively) were used. Table 1 shows the inpatients' demographic characteristics.

All were Chinese, and 1,326 were female, whereas 1,376 were male; 2,618 were natives of Hubei Province, while 84 were not. The mean age was 55.52±16.09 years and 54.18±15.85 years for female and male populations, respectively. The mean age of male patients was significantly lower (P=0.03). No significant difference was found in symptom duration before hospitalization, length of stay, and overall duration of symptoms between female and male populations.

By age groups, there were significant differences in the symptom duration before hospitalization, length of stay, and overall duration of symptoms according to the ANOVA test (P>0.05). The least significant difference (LSD) test showed that the 20-29 years age group had the least symptom duration, whereas the 60-69 years age group had the highest duration, with a significant difference between the groups (P<0.05).

Table 1: Demographic characteristics of inpatients

Characteristics	Number of patients	Proportion
Hospital		
Taikang-Tongji	872	32.27%
Huoshenshan	921	34.09%
Guanggu Woman and Child	909	33.64%
Sex		
Female	1326	49.07%
Male	1376	50.93%
Native place		
Hubei province	2618	96.89%

Characteristics	Number of patients	Proportion
Outside Hubei province	84	3.11%

Duration of symptoms

Table 2 shows the mean age, BMI, symptom duration before hospitalization, length of stay, and overall duration of symptoms according to hospital, sex, and age group. There were no significant differences in age, symptom duration before hospitalization, length of stay, and overall duration of symptoms among the three hospitals according to the ANOVA test (P>0.05). The inpatients' age ranged from 11 to 94 years (mean, 54.84±15.98 years), while BMI ranged from 16.23 to 28.7 (mean, 22.11±1.94). The length of stay ranged from 5 to 50 days (mean, 17.88±7.38 days), whereas the self-reported symptom duration before hospitalization ranged from 2 to 72 days (mean, 24.11±15.66 days). By combining the inpatient and self-reported symptom duration before hospitalization, we obtained the total duration of symptoms, which ranged from 7 to 94 days (mean, 41.99±16.37 days).

Table 2: Means of age, body mass index, symptom duration before hospitalization, length of stay, and overall duration of symptoms by hospital, sex, and age group of inpatients

	Age	Body mass index	Symptoms duration before hospitalization (days)	Length of stay (days)	Overall duration of symptoms (days)
Hospital					
Taikang-Tongji (n=872)	54.76±15.75	22.25±1.92	24.36±15.92	17.92±7.42	42.28±16.57
Huoshenshan (n=921)	55.21±15.88	22.02±2.00	24.65±15.65	17.91±7.34	42.55±16.33
Guanggu Woman and Child (n=909)	54.53±16.29	22.07±1.90	23.34±15.40	17.80±7.39	41.15±16.21
Sex					
Female (n=1326)	55.52±16.09	22.14±1.92	24.11±15.40	18.11±7.34	42.22±16.04
Male (n=1376)	54.18±15.85	22.08±1.96	24.12±15.92	17.66±7.41	41.77±16.69

	Age	Body mass index	Symptoms duration before hospitalization (days)	Length of stay (days)	Overall duration of symptoms (days)
Age group (years)					
<20 (n=49)	15.59±2.53	21.79±2.19	24.61±14.01	13.22±5.67	37.84±13.16
20-29 (n=116)	25.35±2.53	21.95±1.76	16.28±12.36	14.91±5.69	31.20±14.32
30-39 (n=305)	34.87±2.84	22.21±1.98	23.77±16.68	15.79±6.71	39.56±17.44
40-49 (n=529)	44.84±2.96	22.10±1.97	21.56±14.29	17.24±6.93	38.80±14.31
50-59 (n=592)	54.68±2.80	22.13±1.97	23.83±15.81	17.98±7.20	41.81±16.15
60-69 (n=635)	64.16±2.72	22.2±1.910	27.63±16.08	18.49±7.12	46.12±16.39
70-79 (n=306)	73.96±2.88	21.99±1.84	25.12±15.95	20.34±8.09	45.46±16.04
>79 (n=170)	84.49±3.35	21.97±2.04	23.94±14.37	19.86±8.96	43.79±17.55
Overall (n=2702)	54.84±15.98	22.11±1.94	24.11±15.66	17.88±7.38	41.99±16.37

To further analyze the disease course (duration of symptom before hospitalization, length of stay, and overall duration of symptom), we drew line diagrams of the means by age group and sex (Figs. 3 to 5). We also performed a two-way ANOVA to test for the difference in the mean course of the disease by age group and sex. The results showed that age was significantly associated with the disease variables ($P<0.05$),while sex was not, and that the two factors had no significant interaction ($P>0.05$).

<Insert Fig. 3, 4, and 5 here>

We also calculated each symptom's cumulative duration (in days) by three levels of severity in the overall sample population (Table 3). Fever and fatigue had the longest duration, with a cumulative duration of 26,863 days. The lowest cumulative duration was for anxiety and depression (4,565 days). By chi-square test, the proportion of severity differed significantly among different symptoms ($P<0.05$). Anxiety and depression had the highest proportion of severe conditions (30.54%), whereas cough and sore throat had the

highest proportion of mild conditions (10.63%). The cumulative durations (in days) by symptoms are shown in Fig. 6a. Cough and sore throat contributed the maximum to symptom duration (32.06%), whereas anxiety and depression contributed the least (3.72%).

<Insert Fig. 6 here>

Table 3: Each COVID-19 symptom's cumulative duration (in days) in the study population

Symptoms	Mild		Moderate		Severe		Overall duration
	Day	%	Day	%	Day	%	(days)
Fever and fatigue	2,231	8.31	20,846	77.60	3,785	14.09	26,863
Muscular soreness	334	3.08	8,220	75.71	2,303	21.21	10,858
Dizziness and headache	92	1.68	3,864	70.51	1,524	27.81	5,481
Expiratory dyspnea	104	1.83	4,096	72.23	1,471	25.94	5,672
Cough and sore throat	4,180	10.63	30,172	76.75	4,959	12.61	39,312
Palpitations and chest tightness	862	5.86	11,232	76.34	2,620	17.81	14,715
Nausea and vomiting	387	4.40	6,434	73.19	1,970	22.41	8,792
Abdominal pain and diarrhea	150	2.36	4,534	71.30	1,675	26.34	6,360
Anxiety and depression	35	0.77	3,135	68.69	1,394	30.54	4,565
Overall	8,375	6.83	92,533	75.47	21,701	17.70	122,610

COVID-19, coronavirus disease 2019.

DWs of COVID-19 symptoms

After two rounds of the Delphi process by the panel, we developed a 9-item COVID-19 symptom list with six categories. Each symptom included three levels of severity (mild, moderate, and severe), thereby

representing 27 health stages. Based on these, we derived the DWs for each health stage by the PTO exercise; along with the expert panel, a consensus was reached at the fifth round of the Delphi process (CV <0.5). Thus, the DWs of 27 COVID-19 health stages were derived; severe expiratory dyspnea had the highest weight of 0.399, while mild cough and sore throat had the lowest weight of 0.004 (Table 4).

Table 4: Disability weights for the symptoms of COVID-19

Category	Symptom categories	Health stages	DWs	95% CI
Systemic symptoms	Fever and fatigue	Mild	0.006	(0.004-0.008)
		Moderate	0.051	(0.036-0.066)
		Severe	0.133	(0.089-0.177)
	Muscular soreness	Mild	0.015	(0.012-0.018)
		Moderate	0.054	(0.041-0.067)
		Severe	0.110	(0.059-0.113)
Neurological symptoms	Dizziness and headache	Mild	0.028	(0.019-0.037)
		Moderate	0.083	(0.055-0.111)
		Severe	0.163	(0.109-0.217)
Respiratory symptoms	Expiratory dyspnea	Mild	0.045	(0.040-0.050)
		Moderate	0.108	(0.085-0.131)
		Severe	0.399	(0.293-0.505)
	Cough and sore throat	Mild	0.004	(0.003-0.005)
		Moderate	0.011	(0.008-0.014)
		Severe	0.034	(0.023-0.045)

Category	Symptom categories	Health stages	DWs	95% CI
Cardiovascular symptoms	Palpitations and chest tightness	Mild	0.041	(0.029-0.053)
		Moderate	0.072	(0.048-0.096)
		Severe	0.179	(0.120-0.238)
Gastrointestinal symptoms	Nausea and vomiting	Mild	0.009	(0.006-0.012)
		Moderate	0.057	(0.038-0.076)
		Severe	0.130	(0.089-0.171)
	Abdominal pain and diarrhea	Mild	0.011	(0.008-0.014)
		Moderate	0.091	(0.062-0.120)
		Severe	0.194	(0.128-0.260)
Psychological symptoms	Anxiety and depression	Mild	0.030	(0.021-0.039)
		Moderate	0.120	(0.084-0.156)
		Severe	0.366	(0.243-0.489)

COVID-19, coronavirus disease 2019; DWs, disability weights; CI, confidence interval

DALY of inpatients

According to the formula and DWs, the DALY of each inpatient for each symptom was calculated, as well as their synthetic DALY and daily DALY. The proportion of DALY in the study population is shown in Fig. 6b. Among these, fever and fatigue contributed the most in DALY (31.36%), whereas nausea and vomiting and anxiety and depression contributed the least (7.05%).

The mean and standard deviation of DALY for each symptom by hospital, sex, and overall study population are shown in Table 5, and those by age group are shown in Table 6. The mean overall DALY was 2.29±1.33 days, whereas the mean daily DALY was 0.18±0.15 days. No significant difference was

noted in each symptom's DALY, synthetic DALY, or daily DALY among the hospitals (P>0.05). However, in the LSD test, synthetic DALY in Huoshenshan Hospital was significantly lower than that in Taikang-Tongji (P=0.048) and Guanggu Woman and Child (P=0.031) Hospitals. The daily DALY in Huoshenshan Hospital was significantly lower than that in Guanggu Woman and Child Hospital (P=0.023). The DALY for fever and fatigue, muscular soreness, palpitations and chest tightness, and nausea and vomiting, and synthetic DALY were significantly lower for male than for female patients (P>0.05). In the inpatient population, the overall DALY per 1,000 capita was 6.28, whereas in the female and male populations, the overall DALY per 1,000 capita was 6.07 and 6.51 years, respectively.

Table 5: The mean DALY of COVID-19 inpatients or all symptoms, according to hospital, sex, and overall study population

Symptom	Taikang-Tongji Hospital (n=872)	Huoshenshan Hospital (n=921)	Guanggu Woman and Child Hospital (n=909)	Woman (n=1326)	Man (n=1376)	Overall (n=2702)
Fever and fatigue	0.72±0.60	0.70±0.59	0.73±0.63	0.75±0.61	0.69±0.60‡	0.72±0.61
Muscular soreness	0.19±0.18	0.18±0.17	0.18±0.17	0.19±0.18	0.18±0.17‡	0.18±0.17
Dizziness and headache	0.14±0.18	0.13±0.17	0.14±0.20	0.13±0.17	0.14±0.19	0.14±0.18
Expiratory dyspnea	0.18±0.31	0.18±0.32	0.21±0.38	0.19±0.34	0.19±0.33	0.19±0.34
Cough and sore throat	0.18±0.12	0.18±0.12	0.18±0.13	0.18±0.12	0.18±0.13	0.18±0.12
Palpitations and chest tightness	0.41±0.45	0.37±0.40	0.39±0.43	0.42±0.44	0.36±0.41‡	0.39±0.43
Nausea and vomiting	0.16±0.24	0.16±0.23	0.17±0.24	0.17±0.25	0.15±0.23‡	0.16±0.24
Abdominal pain and diarrhea	0.18±0.30	0.16±0.26	0.17±0.24	0.17±0.26	0.16±0.28	0.17±0.27
Anxiety and depression	0.16±0.23	0.15±0.21	0.17±0.24	0.16±0.23	0.17±0.23	0.16±0.23

Total DALY	2.33±1.33	2.21±1.26*	2.34±1.38	2.38±1.33	2.21±1.32‡	2.29±1.33
DALY per day	0.19±0.14	0.18±0.14*†	0.19±0.16	0.19±0.14	0.18±0.15	0.18±0.15

* P<0.05 vs. Guanggu Woman and Child Hospital; † P<0.05 vs. Taikang-Tongji Hospital; ‡ P<0.05 vs. woman.

DALY, Disability-adjusted life years.

Table 6: COVID-19 inpatient DALY by symptoms and age group

Symptom	<20 years (n=49)	20-29 years (n=116)	30-39 years (n=305)	40-49 years (n=529)	50-59 years (n=592)	60-69 years (n=635)	70-79 years (n=306)	>79 years (n=170)
Fever and fatigue	0.75±0.58	0.79±0.73	0.99±0.89	0.88±0.70	0.73±0.54	0.60±0.42	0.55±0.38	0.39±0.28
Muscular soreness	0.14±0.12	0.16±0.19	0.25±0.23	0.22±0.20	0.19±0.16	0.16±0.13	0.15±0.12	0.11±0.09
Dizziness and headache	0.15±0.18	0.13±0.16	0.17±0.22	0.16±0.22	0.16±0.21	0.11±0.13	0.10±0.11	0.08±0.09
Expiratory dyspnea	0.19±0.24	0.11±0.15	0.18±0.28	0.21±0.43	0.25±0.45	0.17±0.24	0.13±0.19	0.18±0.25
Cough and sore throat	0.20±0.09	0.25±0.13	0.26±0.15	0.21±0.14	0.18±0.12	0.15±0.09	0.14±0.08	0.09±0.06
Palpitations and chest tightness	0.33±0.43	0.54±0.54	0.51±0.61	0.47±0.5	0.37±0.35	0.37±0.34	0.31±0.33	0.17±0.17
Nausea and vomiting	0.21±0.28	0.25±0.36	0.21±0.30	0.17±0.23	0.18±0.25	0.15±0.22	0.10±0.12	0.06±0.07
Abdominal pain and diarrhea	0.10±0.11	0.25±0.31	0.22±0.43	0.22±0.36	0.15±0.20	0.13±0.17	0.13±0.17	0.10±0.16
Anxiety and depression	0.21±0.25	0.18±0.24	0.21±0.28	0.20±0.28	0.19±0.25	0.14±0.16	0.09±0.12	0.06±0.08
Synthetic DALY	2.28±0.93	2.65±1.46	2.98±1.87	2.74±1.52	2.41±1.12	1.98±0.92	1.70±0.79	1.24±0.69
DALY per day	0.21±0.11	0.21±0.15	0.25±0.18	0.22±0.17	0.20±0.16	0.15±0.10	0.11±0.06	0.09±0.06

COVID-19, coronavirus disease 2019.

DALY, Disability-adjusted life years.

According to the ANOVA test, the mean DALY by age groups differed significantly for each symptom and for the synthetic DALY and daily DALY (P<0.05). The DALY for both single symptoms and synthesized DALY had the tendency of an inverse U-shaped curve. The DALY increased with age, reached a peak in the prime of life, and then slowly decreased with age. In this study, the 40-49 years age group had the highest DALY for expiratory dyspnea, while the 20-29 years age group had the highest DALY for palpitations and chest tightness, nausea and vomiting, and abdominal pain and diarrhea. DALY for the other symptoms, synthetic DALY, and daily DALY peaked in those aged 20-29 years.

The composition of synthetic DALY for each symptom by hospital is shown in Fig. 7, and that by sex and age group is shown in Fig. 8 and Fig. 9, respectively.

To visualize each symptom's DALY by age group and sex, we drew a thermal map for each subgroup's DALY per 1,000 capita (in days; Fig. 10). Fever and fatigue were in the most intense (red) area, while palpitations and chest tightness were in the next intense area, for both female and male populations. The female population aged 30-39 years had the highest DALY score of 1,115 days per 1,000 capita. Contrarily, in the female population above 79 years, the lowest DALY 50 days per 1,000 capita was found.

<Insert Fig. 7, 8, 9, and 10 here>

We also identified the changing curves of the mean synthetic DALY and daily DALY by age group and sex (Fig. 11 and Fig 12). The two-way ANOVA showed that both age and sex significantly affected synthetic DALY (P<0.05), and there was a significant interaction effect between the two variables (P=0.02). However, when DALY per day was the dependent variable, the significant difference with sex was lost (P=0.08), whereas age remained significant (P<0.05), and the interaction effect between the two variables was also lost (P=0.518).

<Insert Fig. 11 and 12 here>

Linear regression analyses

The results of the multiple linear models are shown in Table 7. When synthetic DALY was set as the dependent variable, all four models were significant ($P<0.05$), with R^2 ranging from 0.214 to 0.240. In the four models, symptom duration before hospitalization and length of stay were significantly positively associated with synthetic DALY, while age was significantly negatively associated with the overall synthetic DALY. For sex and BMI, however, the four models showed different results. In the Guanggu Woman and Child Hospital model, sex and BMI were not significant ($P=0.098$ and $P=0.146$); in the other three models, sex and BMI were significant, indicating that the female population had higher DALY than the male population ($P<0.05$), and that patients with a high BMI had higher DALY ($P<0.05$).

When DALY per day was set as the dependent variable, all four models were significant ($P<0.05$), with R^2 ranging from 0.153 to 0.188. For age and symptom duration before hospitalization, the level of significance was the same as with model I. Length of stay remained significant; however, the effectiveness was negatively reversed for DALY. For sex, the overall sample and Huoshenshan Hospital models were significant ($P=0.037$ and $P=0.022$, respectively), and for BMI, the overall sample and Taikang-Tongji Hospital models were significant ($P<0.001$ and $P=0.001$, respectively). In all the models, native place was not significant ($P>0.05$).

Table 7 Linear regression analyses between COVID-19 inpatient's DALY and individual variables

Variable	Model Type I *								Model Type II **							
	Overall sample		Taikang-Tongji		Huoshenshan		Guanggu Woman and Child		Overall sample		Taikang-Tongji		Huoshenshan		Guanggu Woman and Child	
	R^2=0.222		R^2=0.214		R^2=0.224		R^2=0.240		R^2=0.164		R^2=0.188		R^2=0.170		R^2=0.153	
	β	*P*-value	β	*P*-value	β	*P*-value	β	*P*-value	β	*P*-value	β	*P*-value	β	*P*-value	β	*P*-value
Age	-0.415	<0.001	-0.431	<0.001	-0.388	<0.001	-0.429	<0.001	-0.290	<0.001	-0.288	<0.001	-0.269	<0.001	-0.312	<0.001
Sex	0.069	<0.001	0.070	0.020	0.088	0.003	0.048	0.098	0.037	0.037	0.047	0.123	0.070	0.022	-0.002	0.956
Symptom duration before hospitalization	0.166	<0.001	0.169	<0.001	0.206	<0.001	0.133	<0.001	0.208	<0.001	0.207	<0.001	0.251	<0.001	0.180	<0.001
Length of stay	0.312	<0.001	0.265	<0.001	0.334	<0.001	0.338	<0.001	-0.139	<0.001	-0.184	<0.001	-0.134	<0.001	-0.108	0.001
Body mass index	0.048	0.005	0.090	0.003	0.011	0.719	0.042	0.146	0.062	<0.001	0.101	0.001	0.030	0.331	0.056	0.068
Native place	0.015	0.365	0.000	0.987	-0.017	0.549	0.030	0.303	0.003	0.856	-0.005	0.882	-0.002	0.951	0.024	0.437

COVID-19, coronavirus disease 2019; DALY, disability-adjusted life years.

* Dependent variable is overall DALY; ** Dependent variable is DALY per day.

DISCUSSION

Principal findings

According to this study, each cured inpatient averagely loses about 2-3 days of healthy life due to COVID-19 symptoms, and discounts almost one-fifth of the daily quality of life. Viewed from the population's perspective, the indirect life loss per 1,000 inpatients was >6 years, even if death was not considered. If we consider the increasing number of COVID-19 inpatients worldwide,[32] the indirect life loss could be an enormous figure. Considering the pre-hospitalization symptoms and temporary or permanent loss of body function after discharge, the cumulative loss of life would be many-fold higher. The difference in inpatient BOD of each COVID-19 symptom in the three hospitals was relatively small; however, when the BOD was added, inpatients at Huoshenshan Hospital showed a relatively lower overall BOD than the other two hospitals' inpatients. However, the difference was negligible. This can be accounted for by the greater investment of manpower and material resources at Huoshenshan Hospital.

Regarding DWs, among the main symptoms of COVID-19, severe expiratory dyspnea accounted for the most serious BOD, followed by negative psychological symptoms such as severe anxiety and depression. In actual cases, however, the prevalence of severe depression and dyspnea among the inpatient population was not high. Although the prevalence and BOD of anxiety and depression were not high, the ratios of their severity were, and these should be considered in medical care. Among the inpatient population, the most common symptoms were cough and sore throat, but these had a low contribution to the BOD. In contrast, fever and fatigue largely contributed to the BOD.

Regarding the symptoms of COVID-19, from which the DWs were derived, in addition to fever and dry cough, COVID-19 patients had gastrointestinal symptoms such as nausea and vomiting, diarrhea, abdominal discomfort, and abnormal liver function; and the viral nucleic acid can be detected in the patients' feces.[33,34] A possible pathogenic mechanism of COVID-19 is as follows[7,35]: a cytokine storm

caused by viral infection leads to an increase in the neutrophil count, which in turn results in the imbalance and excessive activation of the immune response and immune pathology, focal proliferation of lung cells, and accumulation of multinucleated giant cells. These trigger apoptosis of the alveolar epithelial and endothelial cells, and diffuse alveolar injury and interstitial pulmonary fibrosis, resulting in progressive hypoxia and injury to the lungs, heart, liver, and other organs. Moreover, SARS-CoV-2 enters the cells primarily through the angiotensin-converting enzyme 2 (ACE2) receptor.[36] ACE2 is highly expressed not only in type II alveolar epithelial cells but also in the small intestine, duodenum, colon, and liver, suggesting that the virus may invade target organs in the digestive tract via the ACE2 receptor, causing primary injury and digestive symptoms.[37] Anxiety and depression are also common in hospitalized COVID-19 patients. Anxiety, depression, and other psychological stress responses can stimulate sympathetic nervous system response and increase the systemic arterial pressure and heart rate.[38] Therefore, the psychological stress due to anxiety and depression may cause tachycardia and increase the left ventricular afterload, thus aggravating pulmonary edema and exacerbating the lung function. The emotional and somatization symptoms caused by the psychological stress may also affect the immune system through neuroendocrine pathways, thereby affecting the patient's rehabilitation process and increasing the BOD.[39,40]

The BOD of female inpatients was higher than that of male inpatients, which is similar to the findings in the Korean report[16]; however, when the BOD was shared daily between the hospitals, there were no significant differences. This indicated that the symptoms in female inpatients during hospitalization were more severe (i.e., the symptoms fluctuated dramatically during hospitalization). Specific symptoms such as fever, fatigue, muscular soreness, palpitations, chest tightness, nausea, and vomiting could result in a higher BOD in female than in male inpatients. For other symptoms, there was no significant difference between female and male populations in the BOD.

Contrary to general thinking, the BOD of the younger population was higher than that of the older population. Both ANOVA and linear models supported this conclusion. The main reason for this trend was that the "value" of life at different age stages was fully accounted for in the BOD evaluation. The illness among youth and middle-aged individuals could bring about greater personal, social, and economic losses. For the synthetic DALY or daily DALY, most linear models indicated that the BOD for obese people was more severe. Obesity affects the immune function of the body, and the burden borne by the organs in obese people is heavier than in non-obese people. Obese people are not only more likely to suffer from various types of infection, including COVID-19 but also experience more serious complications.[41, 42] Although synthetic DALY increased with the hospitalization duration, daily DALY decreased significantly. Although the cumulative BOD increased, the BOD shared per day continuously decreased, and the trend of this reduction was very obvious. It indicated that patients received better treatment during hospitalization, and that the symptoms continued to ameliorate with medical care. In contrast, the longer the symptom duration before hospitalization, the heavier the BOD of inpatient duration, indicating that delayed treatment may aggravate the BOD and lead to the consumption of more medical resources. In addition, teenagers and some older age groups, especially those aged above 60 years, exhibited a longer duration of symptoms before hospitalization in our study.

Strengths and limitations

Our work firstly proposed the COVID-19 DWs by each main COVID-19 symptom and calculated the inpatient BOD caused by the symptoms. Although the validity of the large sampled medical records from the military medical units was high, there are some limitations to this study. First, because this was a retrospective rather than prospective study, the data acquired from the medical records may not be fully accurate. The duration of symptoms before admission relied on patients' self-report, which could cause potential self-reported bias. Notwithstanding, considering the relatively large sample, despite adjustment

for potential bias, the macroscopic trend could be detected at statistical analysis.

Second, the medical records were generated in the early stages of the COVID-19 outbreak when the knowledge about COVID-19 was limited. During that time, the diagnosis and treatment protocol of COVID-19 did not include symptoms such as ageusia and anosmia. Thus, there were only a few records of these symptoms in our data. Consequently, we did not include these as the main symptom in this study. However, because inpatients were at the acute stage of the disease, the discomfort from ageusia and anosmia could be clubbed with respiratory and gastrointestinal symptoms. When calculating the disease burden of respiratory and gastrointestinal symptoms, we could make up for the lack of disease burden caused by ageusia and anosmia. Meanwhile, in most cases, ageusia and anosmia were more noticeable after discharge, when other acute symptoms had gradually disappeared. Thus, these symptoms could be treated as sequelae of COVID-19 rather than the main symptoms of inpatients in the acute stage. Third, because this study is based on Chinese cultural and ethnic backgrounds in the early stage of the COVID-19 pandemic, these, combined with the virus strain variations over time, may affect the comparability of the results worldwide. The DWs derived from this study may be limited and should be considered as regional DWs of COVID-19, while the study could be considered a pilot for an international COVID-19 BOD study. Notwithstanding, our primary aim was to focus on the regional disease burden and public health management; the cultural difference may therefore not have had a great impact on our findings.

Moreover, to determine BOD caused only by COVID-19 symptoms, this study excluded inpatients with comorbidity. When the COVID-19 symptoms are superimposed on other diseases, the effect might have been complex and may not have been easily evaluated using simple linear summarization function; moreover, quantitative differentiation of BOD purely caused by COVID-19 symptoms would have been challenging. Because the BOD of COVID-19 comorbidities will be helpful for understanding the COVID-19 burden, it should be considered in future studies. Thus, in this study, that inpatients with

pre-existing medical conditions were excluded could have affected the findings in the following two ways: a) the severity and disease duration may have been milder and shorter, respectively, and b) the exclusion of patients with a pre-existing psychiatric disease could have explained the short duration of reported anxiety and depression during hospitalization. Besides, deaths were excluded. Thus, this study evaluated DALY in the same way as YLD caused by symptoms during hospitalization.

Implications for health service

The BOD of COVID-19 and its symptoms in the inpatient population are an indirect economic and social burden; however, these are ignored by some public health authorities. This study suggests that to reduce the BOD, symptomatic treatment should focus on symptoms and behaviors that cause a higher BOD and the BOD for vulnerable populations. For example, since cardiovascular and respiratory symptoms in female inpatients were more severe, as were systemic symptoms, focused attention should be on female patients' cardiovascular and respiratory systems during the acute stage. Although the symptoms in elderly people may be slightly more severe, it is more significant to reduce the disease burden in youth and middle-aged inpatients with COVID-19 from a macro-economic perspective, if the medical resources are limited. It is also necessary to reduce the disease burden of obese people by strengthening the intervention in this population during the treatment. Besides, the findings suggest that earlier detection, diagnosis, and treatment of COVID-19 are very important for the healthcare system. However, the findings also suggest that older individuals may have difficulty seeking medical treatment or may lack vigilance of their health, which could result in the consumption of more medical resources. Thus, relevant social service departments should be strengthened to provide help and support for teenagers and elderly people.

CONCLUSION

COVID-19 symptoms could cause heavy BOD in inpatients. The BOD for the female population was higher than that for the male population; however, the daily BOD between male and female inpatients was

similar. When the changing life value with age was considered, the disease burden of the younger population was higher than that of the older population, except for teenagers. The treatment at the three military hospitals efficiently relieved the BOD of the inpatients, despite similar treatment effects. Delay in hospitalization could worsen the BOD for patients with COVID-19. Thus, there is a need for the deployment of adequate medical resources for early hospitalization of patients with moderate or severe symptoms by the public health authority.

List of abbreviations

BOD: burden of disease

COVID-19: coronavirus disease 2019

DALY: disability-adjusted life years

DW: disability weight

PLA: people's liberation army

GBD: global burden of disease

WHO: World Health Organization

YLDs: years lost due to disability

YLLs: years of life lost

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interpreted the data; XXL and MH drafted the article and revised it. All the authors gave approval before submission.

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Figure legends

Fig. 1 Flow of inpatient selection

Fig. 2: Curve of changes in the weighted life value with age

Fig.3: Duration of symptoms before hospitalization by age group in female and male populations

Fig.4: Length of hospital stay by age group in female and male populations

Fig.5: Overall duration of symptom changes with age group in female and male populations

Fig. 6a: The proportion of accumulative duration (in day) by symptoms in the study population

Fig. 6b: The proportion of DALY by symptoms in the study population

Fig. 7: Composition of each military temporary hospital's synthetic DALY

Fig. 8: Composition of each sex group's synthetic DALY

Fig. 9: Composition of each age group's synthetic DALY

Fig. 10: Thermal map of COVID-19 inpatient's DALY by sex and age group (DALY per 1000 capita).

Fig. 11: Synthetic DALY changes with age group in female and male populations

Fig. 12: DALY per day changes with age group in female and male populations

Additional file

File name: Additional file 1

File format: DOC

Title of data: questionnaire

Description of data: Text/table

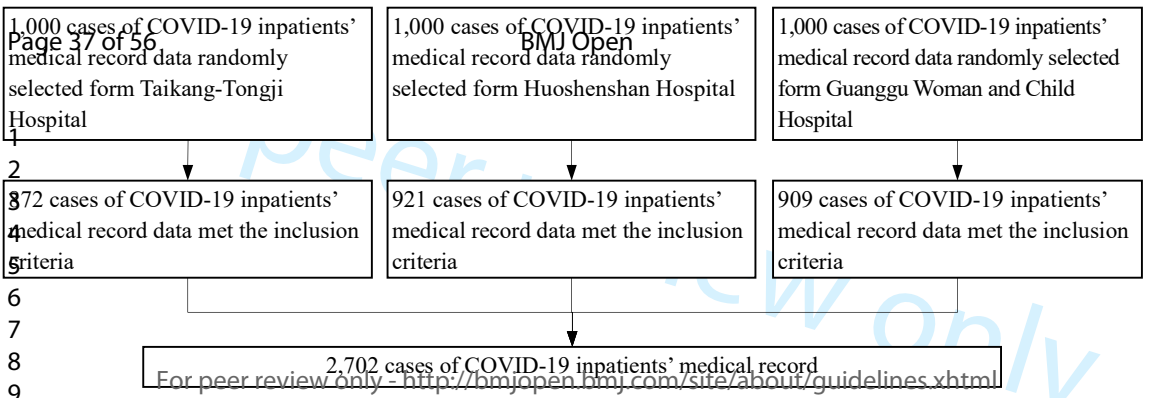
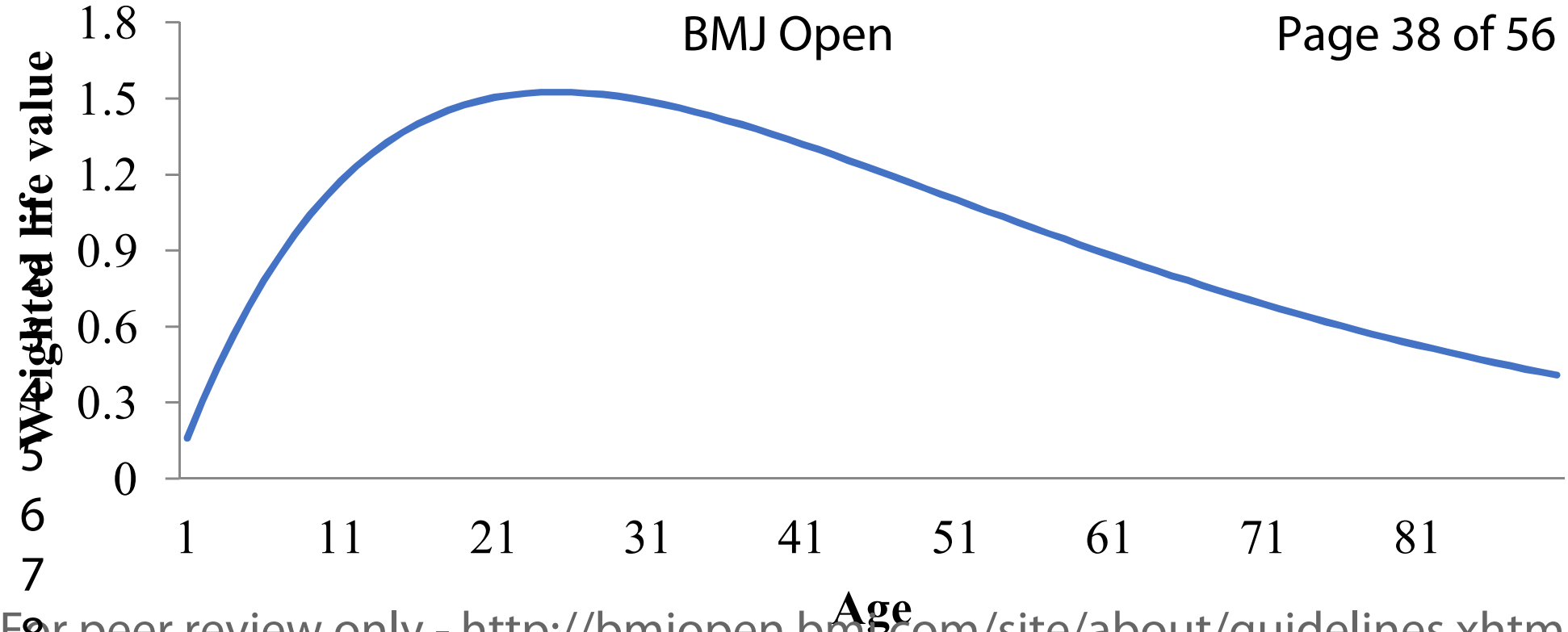


Fig. 1



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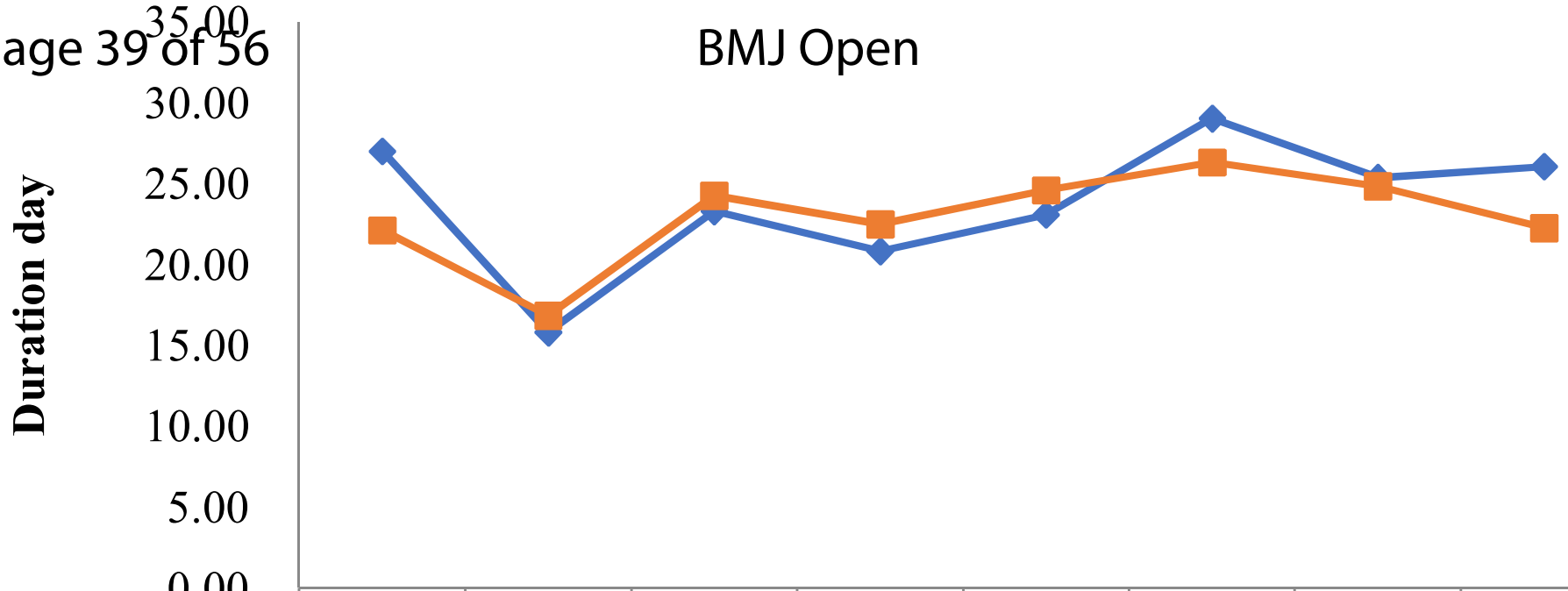
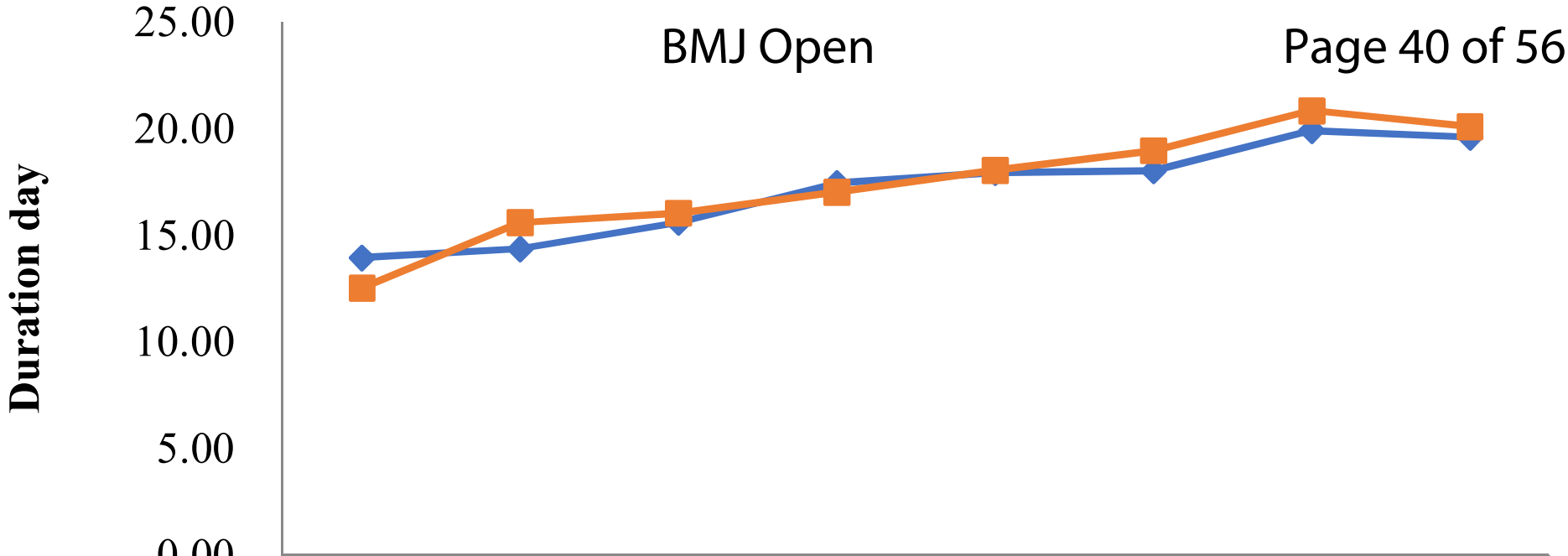


	<19	20-29	30-39	40-49	50-59	60-69	70-79	>79
Male	27.00	15.81	23.30	20.82	23.08	29.03	25.37	26.07
Female	22.13	16.83	24.26	22.48	24.59	26.32	24.84	22.25

Age group

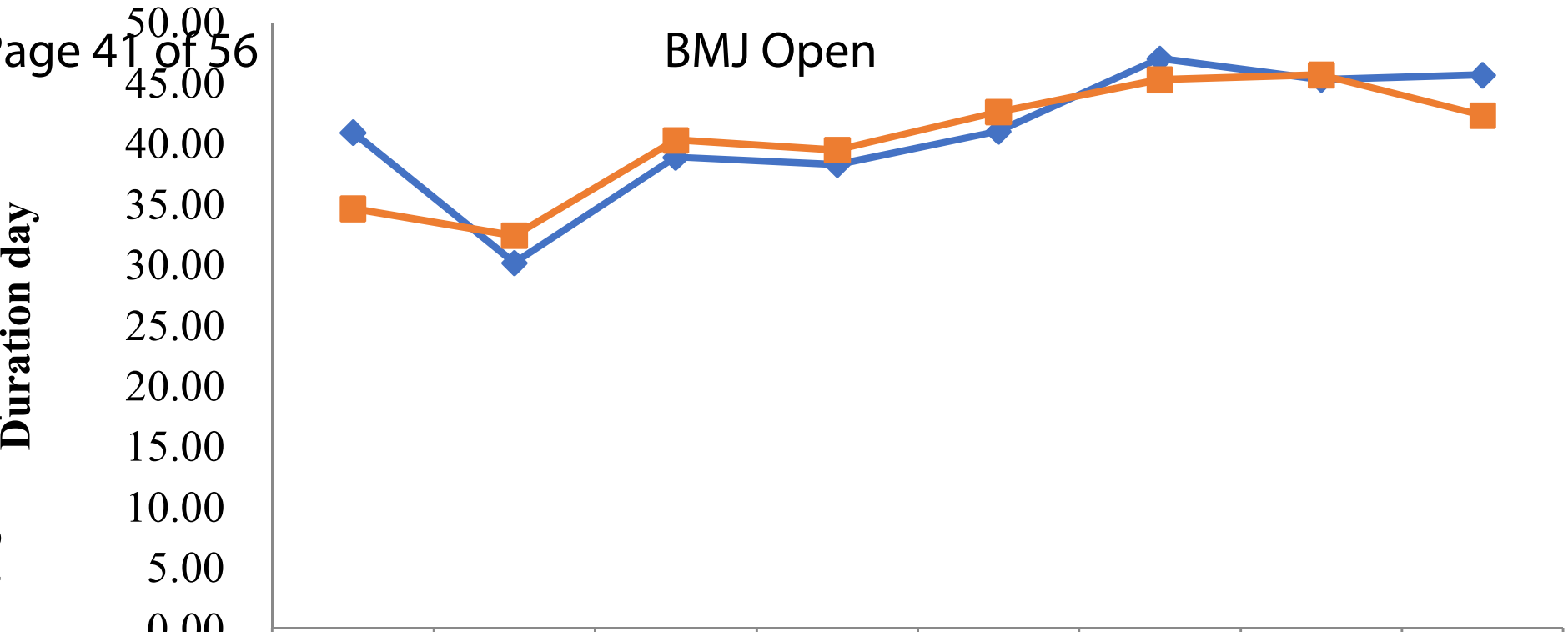
Fig. 3



	<19	20-29	30-39	40-49	50-59	60-69	70-79	>79
Male	13.92	14.34	15.58	17.43	17.93	18.00	19.90	19.59
Female	12.50	15.57	16.02	17.00	18.03	18.95	20.82	20.07

Age group

Fig. 4



	<19	20-29	30-39	40-49	50-59	60-69	70-79	>79
Male	40.92	30.15	38.88	38.26	41.01	47.03	45.27	45.65
Female	34.63	32.41	40.28	39.48	42.62	45.27	45.67	42.33

Age group

Fig. 5

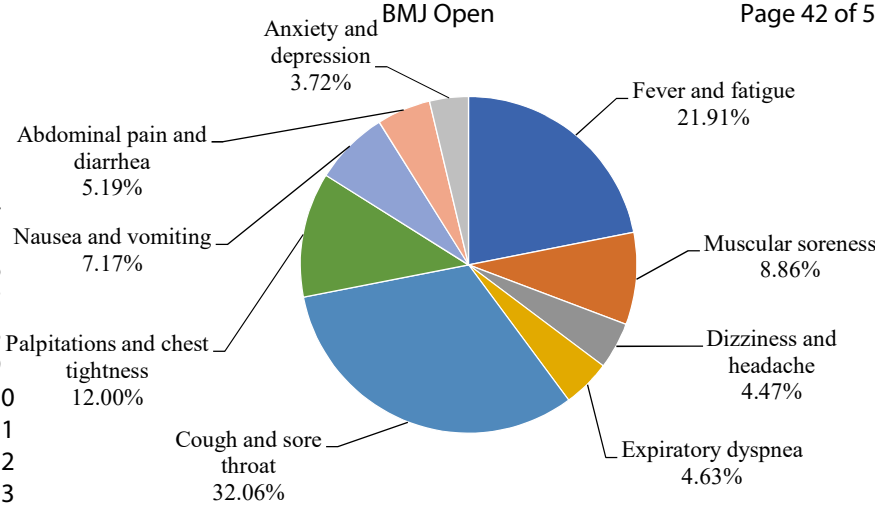


Fig. 6a

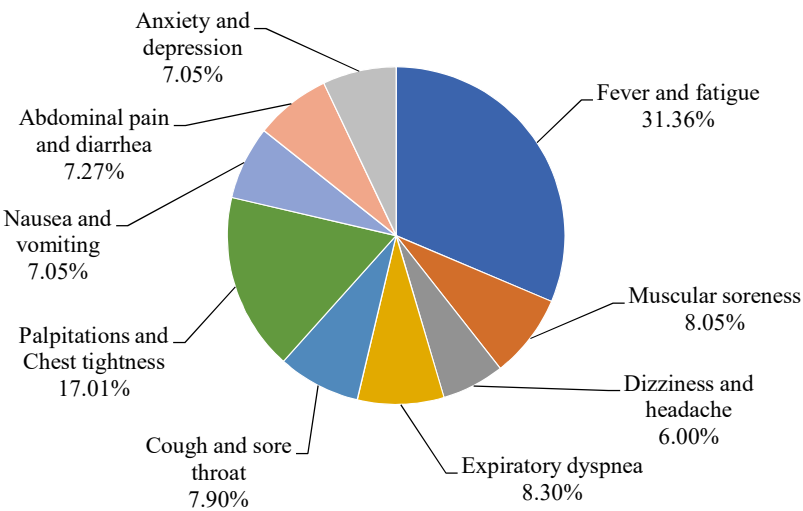


Fig. 6b

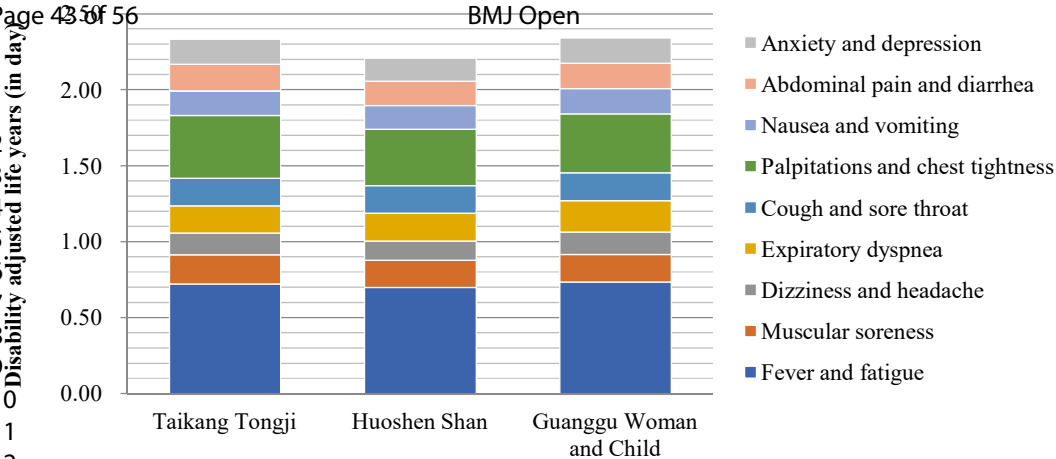


Fig. 7

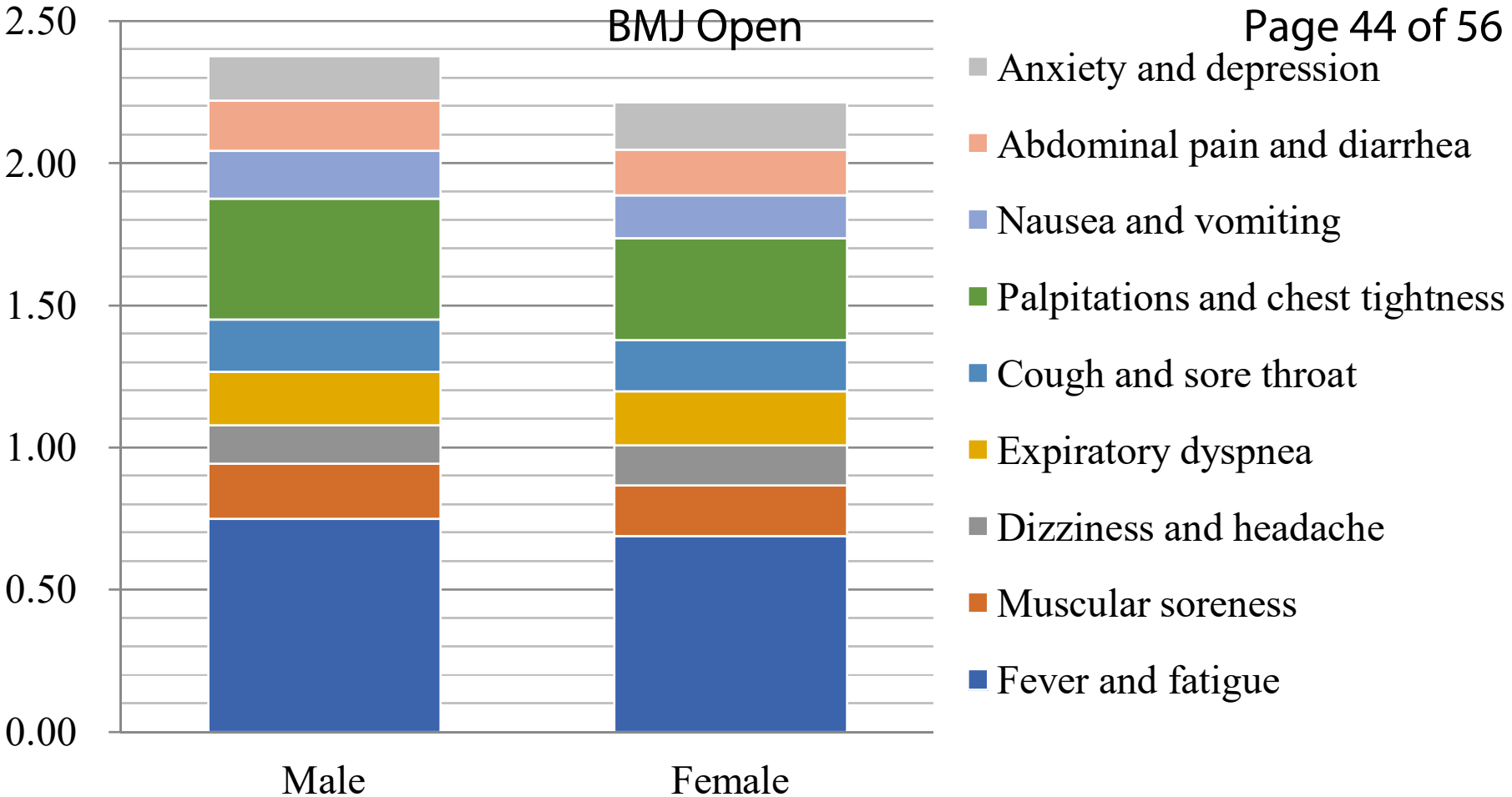


Fig. 8

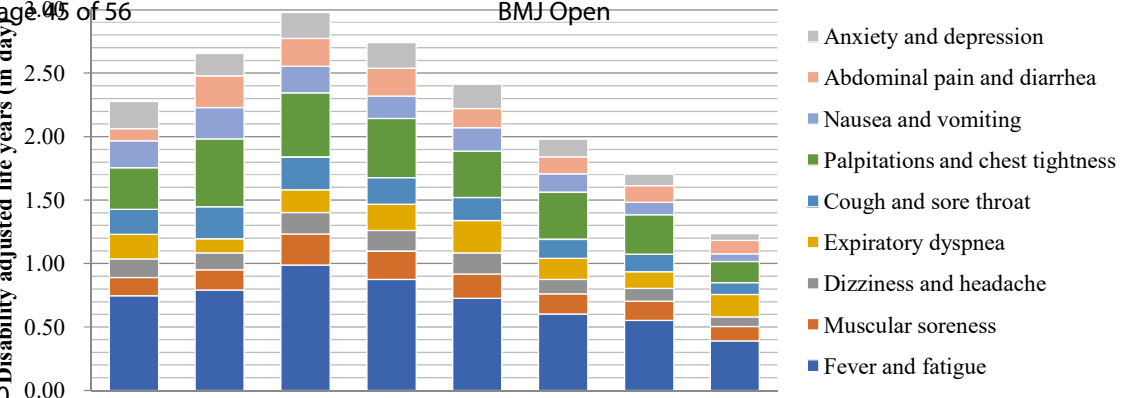
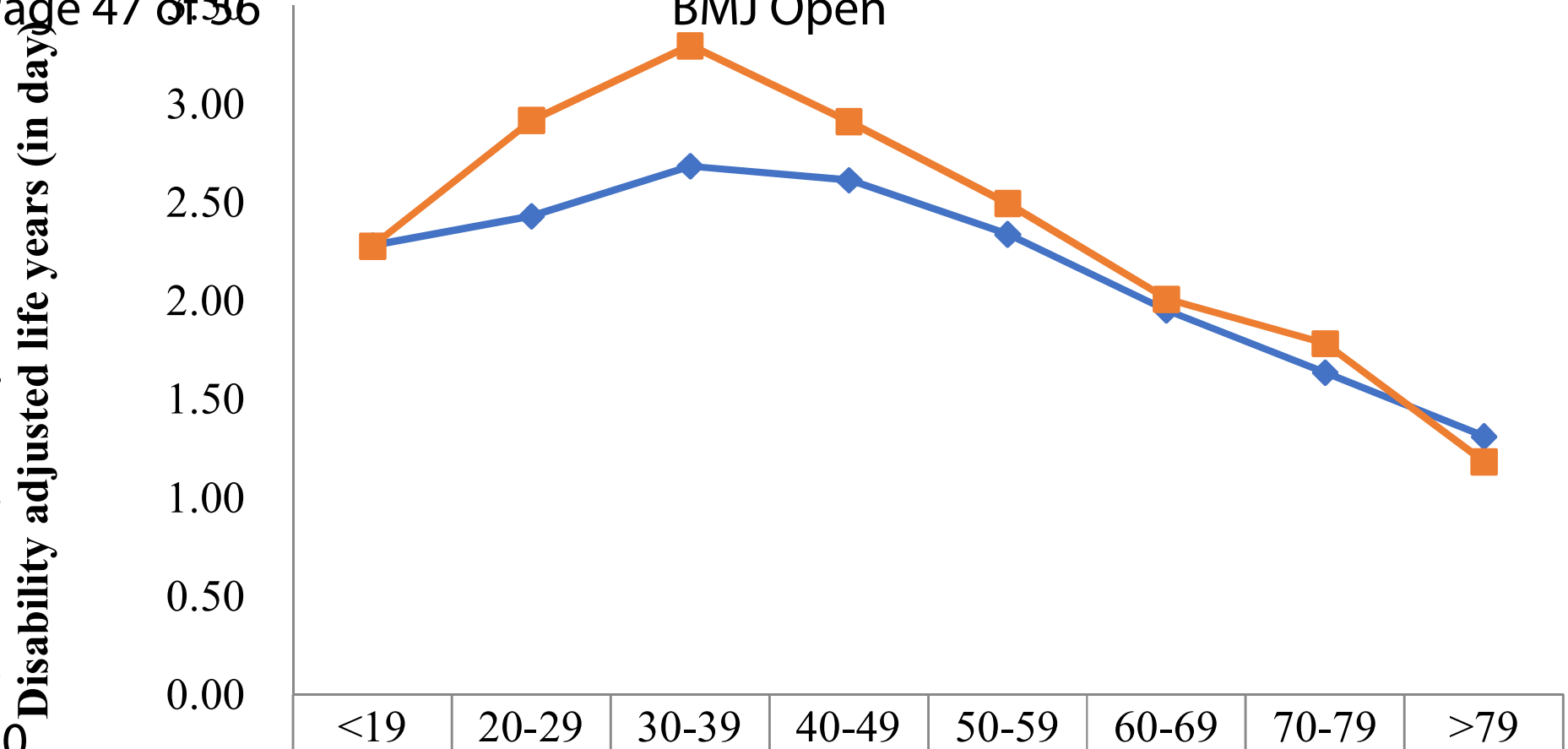


Fig. 9

Male DALY/1000 captia (in days)									Symptoms	Female DALY/1000 captia (in days)								
<19 (n=24)	20-29 (n=54)	30-39 (n=149)	40-49 (n=234)	50-59 (n=295)	60-69 (n=328)	70-79 (n=147)	>79 (n=95)	All age (n=1326)		All age (n=1376)	>79 (n=75)	70-79 (n=159)	60-69 (n=307)	50-59 (n=297)	40-49 (n=295)	30-39 (n=156)	20-29 (n=62)	<19 (n=25)
639	789	1115	947	776	623	547	379	751	Fever and fatigue	689	412	559	584	677	821	868	796	855
162	174	276	233	201	163	157	117	193	Muscular soreness	177	107	145	154	187	215	217	146	121
134	150	176	151	159	109	94	83	134	Dizziness and headache	141	65	107	116	169	169	166	117	161
142	118	181	232	262	160	130	129	190	Expiratory dyspnea	191	236	133	177	247	189	175	108	243
202	275	271	210	183	151	146	87	183	Cough and sore throat	180	101	132	147	182	210	247	229	192
470	626	614	522	360	383	373	168	423	Palpitations and Chest tightness	358	162	252	357	373	423	401	457	193
149	263	238	192	187	151	124	59	171	Nausea and Vomiting	153	62	75	142	178	161	180	236	271
111	316	220	226	179	133	125	108	174	Abdominal pain and Diarrhea	160	100	138	137	126	213	220	187	80
266	203	202	194	184	135	85	50	157	Anxiety and Depression	166	63	92	137	197	210	209	153	164

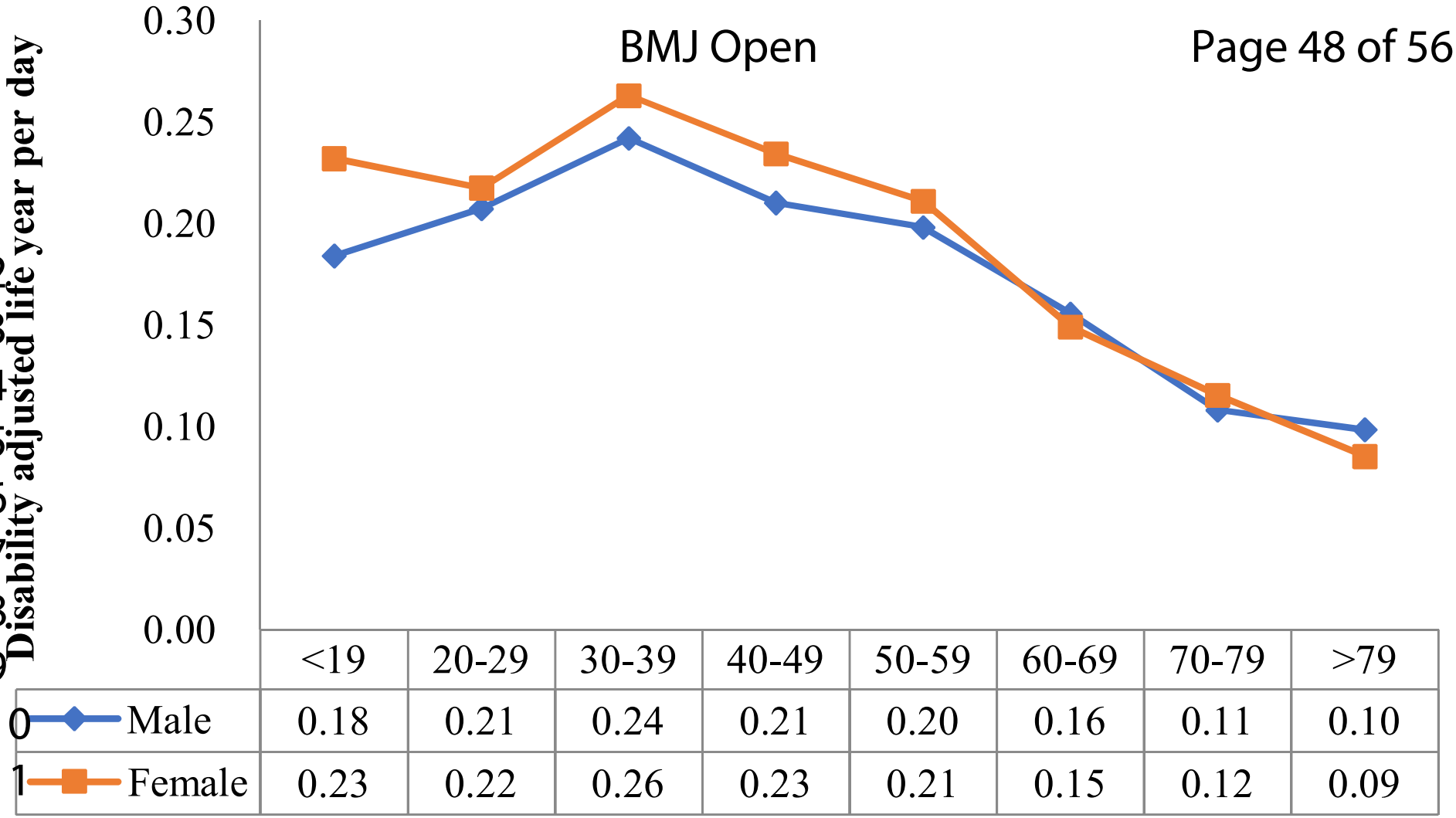
Fig. 10



	<19	20-29	30-39	40-49	50-59	60-69	70-79	>79
Male	2.28	2.43	2.68	2.61	2.34	1.95	1.63	1.31
Female	2.28	2.91	3.29	2.91	2.49	2.01	1.78	1.18

Age group

Fig. 11



	<19	20-29	30-39	40-49	50-59	60-69	70-79	>79
Male	0.18	0.21	0.24	0.21	0.20	0.16	0.11	0.10
Female	0.23	0.22	0.26	0.23	0.21	0.15	0.12	0.09

Fig. 12

Additional file 1: Questionnaire

Front-line medical staff questionnaire on symptoms of COVID-19 (The first round)

Dear Sir/Madam:

This is a questionnaire on COVID-19 typical symptom. The aim is to generate a comprehensive list of typical symptoms of inpatient with COVID-19, which can be used to assess the disease burden caused by the symptoms. This study will adopt the method of disability adjusted life years (DALYs) of the World Health Organization (WHO) to evaluate inpatients' burden of disease caused by COVID-19 symptoms.

According to your clinical experience, please judge the raw list of category and symptoms summarized by the literature review (Table 1). The judgment items are included:

For category：

(1) Whether the category should be included in the list;

(2) Whether the name of the category is appropriate.

For symptoms：

(1) Whether the symptom should be listed;

(2) Whether the symptom should be classified into the current category;

(3) Whether the name of the symptom is appropriate.

If you think it is necessary, please supplement the symptom list according to your clinical experience. You can add:

(1) New categories if necessary;

(2) New symptoms if necessary.

As a front-line clinical expert engaged in COVID-19 treatment, your knowledge about the symptoms of the disease is valuable. Therefore, your opinion is very important for this study. Please try your best to fill the list appropriately. All the information you fill in is for academic research only. We will not analyze your responses individually and will keep them anonymous. Please provide responses to the best of your knowledge.

According to the Delphi process, the opinions of each expert in this round will be anonymously submitted to other experts as reference, in the next round of questionnaire survey. You will also see the anonymous opinions of the other experts. This study is expected to be conducted in 2-3 rounds for a more consistent answer.

Thank you for your support and cooperation.

The Research Group on COVID-19 Burden of Disease

Date:_____

Table1: COVID-19 inpatient's symptom list for the burden of disease evaluation (Template)

Category (Code)	Include the item or not (Y/N)	Term appropriate or not (Y/N)	If inappropriate, fill in alternative terms	Symptom	Include the item or not (Y/N)	Term appropriate or not (Y/N)	If inappropriate, fill in alternative terms	Should it be moved to another category? If yes, type the code
Systemic symptoms (01)				Fever				
				Other symptom 1 (if necessary):				
				Other symptom 2 (if necessary):				
Neurological symptoms (02)				Headache				
				Other symptom 1 (if necessary):				
				Other symptom 2 (if necessary):				
Respiratory symptoms (03)				Expiratory dyspnea				
				Cough				
				Other symptom 1 (if necessary):				
				Other symptom 2 (if necessary):				
Cardiovascular symptoms (04)				Palpitations				
				Other symptom 1 (if necessary):				

Category (Code)	Include the item or not (Y/N)	Term appropriate or not (Y/N)	If inappropriate, fill in alternative terms	Symptom	Include the item or not (Y/N)	Term appropriate or not (Y/N)	If inappropriate, fill in alternative terms	Should it be moved to another category? If yes, type the code
				Other symptom 2 (if necessary):				
Gastrointestinal symptoms (05)				Diarrhea				
				Other symptom 1 (if necessary):				
				Other symptom 2 (if necessary):				
Other category (06) (if necessary):				Other symptom 1 (if necessary):				
				Other symptom 2 (if necessary):				
Other category (07) (if necessary):				Other symptom 1 (if necessary):				
				Other symptom 2 (if necessary):				

If you have anything else to explain, please write here:

To confirm the above, please sign (or type here):

Date:

Front-line medical staff questionnaire on symptoms of COVID-19 (The second/third round)

Dear Sir/Madam:

Thank you for your cooperation and hard work in the last round of the questionnaire survey. The anonymous opinions of other experts in the last round have been sent to you as a reference. We retained all the consensus items in the last round of the expert consultation in the list. We also added the most favorite (approval rate > 50%) new items or the items that were proposed for adjustment (Table 1). Please supplement with the necessary items according to your own clinical experience and the opinions of other experts.

According to your clinical experience, please judge the newly added or adjusted category and symptom items:

For category：

(1) Whether the category should be included in the list;

(2) Whether the name of the category is appropriate.

For symptom：

(1) Whether the symptom should be listed;

(2) Whether the symptom should be classified into the current category;

(3) Whether the name of the symptom is appropriate.

Besides, you also can add:

(1) New categories if necessary;

(2) New symptoms if necessary.

According to the Delphi process, the opinion of each expert in this round will be anonymous and submitted to other experts as reference, in the next round of the questionnaire survey. You will also see the anonymous opinions of the other experts. This study is expected to be conducted in 2-3 rounds for a more consistent answer.

Thank you for your support and cooperation.

The Research Group on COVID-19 Burden of Disease

Date：_____

Table1: COVID-19 inpatient's symptom list for the burden of disease evaluation (Template)

Category (Code)	Include the item or not (Y/N)	Term appropriate or not (Y/N)	If inappropriate, fill in alternative terms	Symptom	Include the item or not (Y/N)	Term appropriate or not (Y/N)	If inappropriate, fill in alternative terms	Should it be moved to another category? If yes, type the code
Systemic symptoms (01)				Fever and fatigue *				
				Muscular soreness *				
				Other symptom 1 (if necessary):				
				Other symptom 2 (if necessary):				
Neurological symptoms (02)				Headache				
				Other symptom 1 (if necessary):				
				Other symptom 2 (if necessary):				
Respiratory symptoms (03)				Expiratory dyspnea				
				Cough				
				Other symptom 1 (if necessary):				
				Other symptom 2 (if necessary):				
Cardiovascular symptoms (04)				Palpitations				
				Chest tightness *				
				Other symptom 1 (if necessary):				
				Other symptom 2 (if necessary):				

Category (Code)	Include the item or not (Y/N)	Term appropriate or not (Y/N)	If inappropriate, fill in alternative terms	Symptom	Include the item or not (Y/N)	Term appropriate or not (Y/N)	If inappropriate, fill in alternative terms	Should it be moved to another category? If yes, type the code
Gastrointestinal symptoms (05)				Diarrhea				
				Vomiting *				
				Other symptom 1 (if necessary):				
				Other symptom 2 (if necessary):				
Psychological symptoms * (06)				Anxiety and depression *				
				Other symptom 1 (if necessary):				
				Other symptom 2 (if necessary):				
Other category (07) (if necessary):				Other symptom 1 (if necessary):				
				Other symptom 2 (if necessary):				

* Newly proposed or adjusted item.

If you have anything else to explain, please write here:

To confirm the above, please sign (or type here):

Date: