Clin. Lab. 2024;70:XXX-XXX

ORIGINAL ARTICLE

Contributing Factors Affecting the Length of Hospital Stay among Febrile Patients with Omicron Reported in Suzhou

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SUMMARY

Background: **Coronavirus disease 2019 (COVID-19) has had global attention with regard to the urgent challenging threat to global public health. Currently, the novel Omicron variant is showing rapid transmission across the world, which appears to be more contagious than the previous variants of COVID-19. Early recognition of disease is critical for patients' prognosis. Fever is the most common symptom. We evaluated the clinical characteristics of febrile patients with COVID-19 reported in Suzhou and explored the predictors for a longer duration of hospitalization in febrile patients.**
Methods: **This retrospective study was carried out in 146 Omicron variant infected patients confirmed by nucleic acid tests in the Affiliated Infectious Hospital of Soochow University between February 13, 2022 and March 2, 2022. Data of febrile and afebrile laboratory-confirmed patients on hospital admission in Suzhou were collected and compared. According to the median length of stay (LOS), febrile cases were divided into short and long LOS groups. Then the predictive factors for a prolonged duration of hospitalization were analyzed using logistic regression methods. Receiver Operating Characteristic (ROC) Curve analysis was used to analyze the effectiveness of the risk factors for prolonged duration of hospitalization in febrile COVID-19 patients.**
Results: **Of the 146 discharged patients in our study, 112 patients (76.7%) caught a fever. Compared to afebrile Omicron patients, febrile patients showed a significantly longer duration of hospitalization (15.00 (5.80) vs. 13.00 (6.00), $p = 0.002$). Taking the median LOS (15 days) as the dividing point, 64 febrile cases were assigned to the short LOS group and the rest to the long LOS group. The long LOS group had a longer virus shedding duration than the short LOS group (18.42 ± 2.86 vs. 11.94 ± 2.50 days, $p < 0.001$). Compared to short LOS febrile patients, long LOS patients were older (44.88 ± 21.36 vs. 30.89 ± 17.95 years, $p < 0.001$) and showed a higher proportion of greater than 60 years old (33.3% vs. 9.4%, $p = 0.002$; Supplemental Table S2). Febrile patients with long LOS also showed a higher proportion of hypertension (25% vs. 6.3%, $p = 0.005$) and higher levels of cTnI (5.00 (3.00) vs. 4.00 (2.00) µg/L, $p = 0.025$). The multivariate analysis indicated that virus shedding duration (OR 2.369, 95% CI 1.684 - 3.333, $p < 0.001$) was the independent risk factor associated with long-term hospital stay in febrile patients with Omicron. Furthermore, ROC Curve analysis revealed that the area under the curve (AUC) for virus shedding duration to diagnose prolonged duration of hospitalization in febrile COVID-19 patients was 0.951 (95% CI 0.913 - 0.989). The cutoff point was set at 14.5 days.**
Conclusions: **More than half of the non-severe patients exposed to the new Omicron variant had symptoms of fever. In total, 42.86% of the febrile patients were discharged within 15 days since hospital admission. Febrile Omicron cases took a longer duration of hospitalization compared to afebrile patients, and virus shedding duration (OR 2.369, 95% CI 1.684 - 3.333, $p < 0.001$) was probably a predictive factor for long-term hospital stays.**
(Clin. Lab. 2024;70:xx-xx. DOI: 10.7754/Clin.Lab.2023.231104)

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Manuscript accepted November 22, 2023

KEYWORDS

COVID-19, Omicron, fever, length of stay, predictive factor, non-severe

LIST OF ABBREVIATIONS

COVID-19 - coronavirus disease 2019
LOS - length of stay
ROC - Receiver Operating Characteristic
SARS-CoV-2 - severe acute respiratory syndrome coronavirus 2
IL-6 - interleukin-6
PCT - procalcitonin
CRP - C-reactive protein
cTnI - troponin I
NT-proBNP - N-terminal pro-brain natriuretic peptide
CK-MB - creatine kinase isoenzyme
ALT - alanine aminotransferase
AST - aspartate aminotransferase
CT - chest computed tomography
SD - standard deviation
ACE - angiotensin-converting enzyme
ARBs - angiotensin receptor blockers
TCM - Traditional Chinese Medicine

INTRODUCTION

During the two years since the unpredictable emergence of coronavirus disease 2019 (COVID-19), a communicable disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has widely spread around the world, creating a wide range of public health concerns, and causing extreme pressure on medical resources internationally [1-3]. As enormous efforts by scientific researchers and health care workers to struggle with this global pandemic are ongoing, a variety of variants have arisen in succession. In the last November, a novel variant of coronavirus detected firstly in South Africa appeared, designated as Omicron presently by World Health Organization (WHO), which induced a rapid rise in new cases within a short span across the world [4-6]. It is reported that the risk of severe or lethal cases exposed to Omicron is lower; however, the growing transmissibility could put another highly challenging strain on global health care systems, which raised a thorny problem of whether herd immunity could be achieved with universal vaccination coverage [4-7]. Therefore, it is urgent to block transmission of Omicron, identify severe cases early, develop more effective therapies and expedite booster vaccination projects for health care staff worldwide in the event of a new wave of Omicron happening.
On February 13, 2022, the health authority reported the first Omicron case in Suzhou. Since then, the Omicron cases spread rapidly in Suzhou city, particularly in mass gatherings. To control COVID-19 as soon as possible,

local government and health authorities implemented strict public health measures, including case tracing, active detection, and restrictions on outdoor activities, traveling, and gatherings. Personal preventive behaviors (wearing masks, practicing social distancing, washing hands frequently, etc.) were encouraged. Due to these positive anti-epidemic measures, the daily number of new cases in Suzhou began to drop steadily. By March 15, 2022, the fight against COVID-19 had achieved a phased success. However, despite the declining trend in Suzhou, the spread of COVID-19 in peripheral cities accelerated beginning in late March. Since then, Suzhou experienced a second wave of the COVID-19 pandemic. Meanwhile, the diagnosis and treatment plan for COVID-19 (trial version 8 revision) was updated with trial version 9 on March 14, 2022. Subsequently, Fangcang hospitals started to receive patients.

To date, researchers found that the Omicron virus seemed to produce a relatively milder infection compared to the previous variants [7,8]. It was observed that the Omicron variant cases showed flu-like symptoms, including fever, chills, cough, expectoration, sore throat, congestion or runny nose, headache, muscles aches, generalized myalgia, diarrhea, vomiting, etc., a few of which might develop pneumonia, ARDS, or even multiple organ failure [9]. Fever, as the most common sign of acute upper respiratory infection, is widely employed as a screening symptom monitoring for early-warning cases with COVID-19 in many places, including hospital out-patient departments, communities, supermarkets, schools, public transportation systems, and so on [10]. Previous studies have shown that more than 90% of COVID-19 patients experienced fever [10-12]. The latest research reported that adult febrile COVID-19 patients were more likely to develop into severe events before the emergence of the Omicron variant [13]. So far, there are few data about the differences in clinical characteristics and short-term prognosis between Omicron febrile and afebrile cases, and the relationship between fever and the hospitalization time of Omicron cases remains unknown. The proper early diagnosis would help the medics in identifying severe cases for special treatment thus sparing resources for mild ones.

In this study, we aimed to retrospectively evaluate the clinical characteristics of hospitalized patients with laboratory-confirmed COVID-19 and analyze the risk factors with a long length of hospital stay (LOS) in febrile COVID-19 patients.

MATERIALS AND METHODS

Study design and setting

The retrospective study was carried out at the designated hospital for COVID-19 patient clinical treatment in Suzhou. Inclusion criteria: all laboratory-confirmed COVID-19 patients with pharyngeal swab samples who tested positive by RT-PCR test for SARS-CoV-2 RNA by Suzhou Center for Disease Control and admitted to the affiliated infectious hospital of Soochow University, China, from February 13, 2022 and March 2, 2022, were enrolled. The virus RNA was isolated from samples harboring SARS-CoV-2. The genome sequences of the virus were performed by Illumina sequencing methods, which were confirmed corresponding to the existing detection of Omicron in China. Exclusion criteria were as follows: (a) patients with incorrect contact information (the failure of follow-up); (b) pregnant women (no record on CT scan and blood test due to the unusual nature of pregnancy). The diagnosis of COVID-19 was performed according to the Diagnosis and Treatment plan for COVID-19 (trial version 8 revision) established by the General Office of National Health Commission of the Peoples' Republic of China in 2021. Asymptomatic type of COVID-19 was presented below: 1) a positive result of RT-PCR testing for nasopharyngeal and oropharyngeal swab samples; 2) no typical COVID-19-related clinical symptoms (fever, dry cough, shortness of breath, sore throat, fatigue, etc.) prior to the diagnosis; 3) no apparent pulmonary pathological changes on the chest CT scan at the time of diagnosis. Mild COVID-19 infected cases had fever and mild respiratory symptoms without pneumonia in chest CT imaging. General cases had fever and respiratory symptoms with pneumonia manifestations on the chest CT scan.

Data collection

We reviewed the medical records of all patients and extracted all the related data. The demographic information, exposure history, clinical characteristics (symptoms onset, the time from illness onset to admission, vital signs on admission and comorbidities), laboratory results (white blood cell (WBC), lymphocyte count, interleukin-6 (IL-6), procalcitonin (PCT), C-reactive protein (CRP), D-dimer, fibrinogen, troponin I (cTnI), N-terminal pro-brain natriuretic peptide (NT-proBNP), creatine kinase isoenzyme (CK-MB), myoglobin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, albumin and creatinine), and chest computed tomography (CT) imaging data during hospitalization were recorded and analyzed.

The temperature fluctuations prior to hospital admission were collected based on the patients' descriptions. On admission, the axillary temperature measured by a mercury thermometer for 10 minutes was performed at least once a day, which was assisted and recorded by professional nursing management. The axillary temperature of 37.3℃ or higher was defined as fever.

SARS-CoV-2 nucleic acid was collected for at least two consecutive mensuration at an interval of one day or above since disease in relief period, amid which sampling results that had been negative for two consecutive tests was identified as virus negative conversion. For symptomatic cases, the duration of virus shedding was recorded as the time from symptoms' onset to the first negative sampling result with no positive thereafter. For asymptomatic cases, the duration of virus shedding was calculated from the day of diagnosis. Hospitalized cases were approved discharged according to the following criteria: 1) Temperature normalization for at least three consecutive days; 2) Significant improvement of respiratory symptoms; 3) Marked absorption of acute exudative lesions displayed on chest CT scan; 4) Two consecutive respiratory tract samples tested by RT-PCR test for SARS-CoV-2 RNA with negative results, with the time gap between sampling more than 24 hours. According to the median length of stay (LOS), patients enrolled were divided into two groups: short LOS group and long LOS group.

Statistical analysis

The data in this research were analyzed using SPSS 27.0 software. A two-sided p-value < 0.05 was regarded as statistically significant. According to the normality assessment using the Shapiro-Wilk test, continuous data were presented as mean ± standard deviation (SD) or median and interquartile range (IQR), and compared using Student's *t*-test and Mann-Whitney U-test, respectively. Categorical variables were shown as frequency (n) and percentage (%). The χ^2 test or Fisher's exact test was employed to analyze the categorical variables. The primary endpoint of the study was LOS, which was evaluated as the hospitalization days from admission to discharge. Logistic regression analyses were applied to identify the risk factors for long LOS in febrile Omicron patients, and Receiver Operating Characteristic (ROC) curve analysis to analyze the effectiveness of the risk factors for prolonged duration of hospitalization in febrile COVID-19 patients.

RESULTS

Baseline characteristics of the study population

A total of 147 hospitalized patients diagnosed with COVID-19 on admission between February 13, 2022 and March 2, 2022 were recruited initially. Of these, one pregnant woman was excluded, and then we enrolled 146 patients in our study, of whom 22 were children younger than 18, with the youngest case aged 1 month. In total, 72 (49.3%) patients were fully vaccinated and 40 (27.4%) had received a booster dose after full vaccination. No patients had a history of previous SARS-CoV-2 infection. On admission, 28 (19.2%) patients were regarded as asymptomatic. As shown in supplemental Table S1, the average age was 37.1 ± 19.84 years. The number of COVID-19 patients below the age of 18 years, between 18 and 60 years, and above the age of 60 years were 22 (15.1%), 97 (66.4%), and 27 (18.5%), respectively. Among these patients, 47.3% (n = 69) were female. Hypertension (22/146, 15.1%) and chronic respiratory disease (10/146, 6.8%) were the most common comorbidities, and eighteen (12.3%) patients had at least one coexisting condition. Besides the 13 patients (8.9%) who gave incomplete exposure histories, most of the cases (n = 63, 43.2%) had close contact with their confirmed family members, 44 patients (30.1%) with their confirmed friends/colleagues, and 13 (8.9%) at mass gatherings. No patients had resided or traveled to medium- and high-risk areas outside Suzhou within 14 days. Antiviral therapy was given to 57 cases during hospitalization; 33 (22.6%) and 88 patients (60.3%) received anticoagulation and immunity-boosting interventions, respectively, and 31 (21.1%) cases were subjected to the prone position for at least 12 hours every day. Furthermore, almost everyone in this study was treated with traditional Chinese medicine after admission (The details are shown in Supplemental Table S1). Thanks to these effective and comprehensive treatments, there were no severe cases in this first wave in Suzhou, and no patients developed into severe cases or died during hospitalization. As of March 15, 2022, all the patients were discharged without mortality and subsequently restored to health smoothly in the rehabilitation center.

Characteristics of febrile and afebrile Omicron cases

One hundred and forty-six discharged patients were included in our study, including 112 febrile patients (76.7%) and 34 non-febrile patients (23.3%). The demographic and clinical characteristics of the febrile and afebrile cases were summarized in Supplemental Table S1. There was no significant difference in age (p = 0.816), BMI (p = 0.298), and gender (p = 0.675) between febrile and afebrile patients. No statistical significance could be observed in exposure history and vaccination status between febrile and afebrile patients (p > 0.05). We found that 56 (50.0%) febrile patients and 16 (47.1%) afebrile patients were fully vaccinated, while 30 (26.8%) febrile patients and 10 (29.4%) afebrile patients had taken boosters following full vaccination. Compared with afebrile cases, febrile patients showed a higher incidence of cough (60.7 vs. 29.4%, p = 0.001; Supplemental Table S1), phlegm (33.0 vs. 14.7%, p = 0.039; Supplemental Table S1), and myalgia (18.8 vs. 0%, p = 0.014; Supplemental Table S1). There was no significant difference in onset symptoms between the febrile and afebrile patients as details below: fatigue (8.9% vs. 2.9%, p = 0.431), nasal congestion (17.0% vs. 5.9%, p = 0.182), runny nose (8.0% vs. 0%, p = 0.194), pharyngalgia (33.0% vs. 23.5%, p = 0.293), chills (10.7% vs. 0%, p = 0.102), headache (16.1% vs. 2.9%, p = 0.089), diarrhea (3.6% vs. 0%, p = 0.573), and vomit (6.3% vs. 0%, p = 0.300) (Supplemental Table S1). The mean time from illness onset to admission in the febrile group was 1.0 (2.0) days, which was not statistically significant compared with afebrile group (p > 0.05). In this study, 8.0% (n = 9) of febrile patients and 55.9% (n = 19) of afebrile patients were regarded as asymptomatic, 69.6% (n = 78) of febrile patients and 26.5% (n = 9) of afebrile patients were regarded as mild type, 22.3% (n = 25) of febrile patients and 17.6% (n = 6) of afebrile patients were regarded as general type, among which the difference was significant (p <

Table 1. Multiple logistic regression analysis of risk factors associated with prolonged duration of hospitalization in febrile patients.

Variables	OR (95% CI)	p-value
Age stratification	0.46 (0.079 - 2.676)	0.388
Clinical type on admission	1.095 (0.194 - 6.17)	0.918
Hypertension	0.269 (0.028 - 2.579)	0.255
≥ 1 comorbidity	0.422 (0.019 - 9.166)	0.583
Chest CT scan	1.273 (0.427 - 3.792)	0.665
Virus shedding duration (days)	2.369 (1.684 - 3.333)	< 0.001
cTnI	0.961 (0.879 - 1.051)	0.384
Nasal congestion	5.133 (0.688 - 38.272)	0.111

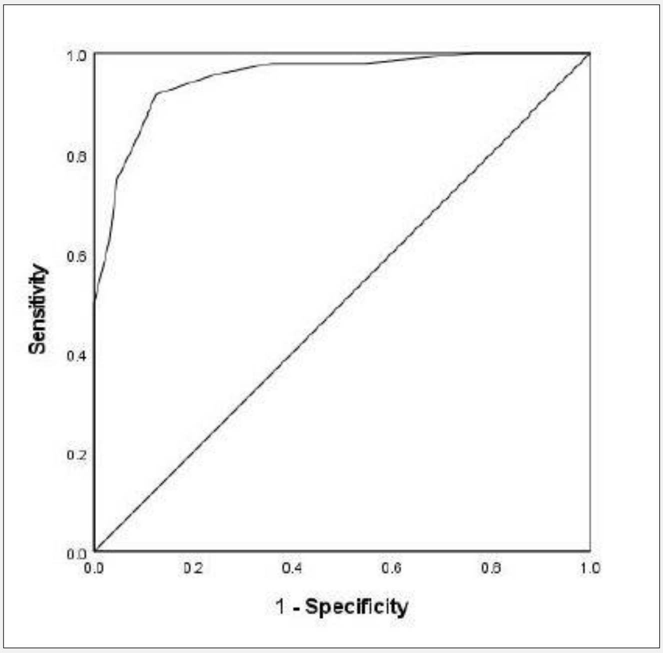

Figure 1. ROC curve of the multivariable model for predicting the possibility of severe events in adult febrile COVID-19 patients.

ROC - Receiver Operating Characteristic, COVID-19 - coronavirus disease 2019.

0.001).
Heart rate (HR) on admission was higher in febrile cases than in afebrile patients ($p < 0.05$). Abnormalities on chest CT scan results were observed among 104 patients (71.2%) after admission, 53 cases had bilateral involvement, and 51 cases had unilateral involvement. The proportions of abnormality on chest CT scan were comparable among the febrile and afebrile cases ($p > 0.05$). No significant difference in WBC and lymphocyte count levels between febrile and afebrile groups was observed ($p > 0.05$). At the time of admission, febrile cases presented more elevated D-dimer and fibrinogen levels than those of afebrile cases, but the differences were not significant ($p > 0.05$). No differences

were found in bilirubin, albumin, ALT, AST, cholesterol, triglyceride, creatinine, myoglobin, CK-MB, and NT-proBNP between the two groups ($p > 0.05$).

In terms of prognostic indicators, febrile cases had longer virus shedding duration than afebrile group (14.71 ± 4.17 vs. 11.68 ± 4.44 days, $p < 0.001$). Moreover, febrile patients had shown a significantly longer duration of hospitalization (15.00 (5.80) vs. 13.00 (6.00) days, $p = 0.002$) compared to afebrile Omicron patients (Supplemental Table S1).

Characteristics of short LOS and long LOS febrile cases

Because of the significant longer duration of hospital stays in febrile patients, a further subgroup analysis of febrile patients based on the LOS was performed. The median LOS was 15.0 (IQR 12.0 - 18.0) days, ranging from 8.0 days to 26.0 days. Taking 15 days as the dividing point, 64 febrile cases discharged ≤ 15 days was considered as the short LOS group and 48 febrile cases discharged > 15 days as the long LOS group. The demographic and clinical characteristics of 112 Omicron cases between the above two groups were compared in Supplemental Table S2. There were no significant differences in HR, MAP, and pulse oximeter O_2 saturation (SpO_2) on admission between the two groups. In addition, no significant differences in BMI, gender, exposure history, vaccination status, the time from illness onset to admission, and the early symptoms were indicated between the two groups. The proportion of abnormality on chest CT scan in the long LOS group was higher than the short LOS group (81.2% vs. 64.1%, $p < 0.05$). No significant differences in WBC, lymphocyte count, D-Dimer, fibrinogen, interleukin-6, PCT, and CRP levels between short LOS and long LOS groups were presented ($p > 0.05$). cTnI in the long LOS group was significantly higher than that in the short LOS group (5.00 (3.00) vs. 4.00 (2.00) μg/L, $p = 0.012$), while no differences were found in bilirubin, albumin, ALT, AST, cholesterol, triglyceride, creatinine, myoglobin, CK-MB, and NT-pro BNP between the two groups ($p > 0.05$).

The long LOS group had a longer virus shedding duration (18.42 ± 2.86 days) than the short LOS group (11.94 ± 2.50 days) ($p < 0.001$). Compared to short LOS febrile patients, long LOS patients were older (44.88 ± 21.36 vs. 30.89 ± 17.95 years, $p < 0.001$), and showed a higher proportion of aging more than 60 years old (33.3 vs. 9.4%, $p = 0.002$; Supplemental Table S2). Febrile patients with long LOS also showed a higher proportion of hypertension (25.0 vs. 6.3%, $p = 0.005$; Supplemental Table S2) and a higher proportion of multiple comorbidities (22.9 vs. 4.7%, $p = 0.004$; Supplemental Table S2)

Analysis of relative factors associated with long duration of hospitalization in febrile patients

The associations between prolonged duration of hospitalization in febrile patients and the related factors were shown in Table 1. As indicated in the multivariate analysis, virus shedding duration (OR 2.369, 95% CI 1.684 - 3.333, $p < 0.001$) was an independent risk factor associated with long-term hospitalization in febrile COVID-19 patients (Table 1). The Hosmer and Lemeshow test revealed that the variables included in this model could be well predictive for patients with long-term hospitalization in febrile COVID-19 patients ($p = 0.729$). We found strong evidence to demonstrate that febrile patients with longer virus shedding duration were taking 6.5 days (OR 2.369, 95% CI 1.684 - 3.333, $p < 0.001$) longer duration of hospitalization than those with shorter virus shedding cases. Moreover, ROC curve analysis suggested that the AUC for virus shedding duration to diagnose prolonged duration of hospitalization in febrile COVID-19 patients was 0.951 (95% CI 0.913 - 0.989) (Figure 1).

DISCUSSION

After constant containment of recurrent waves of the global coronavirus pandemic, many countries seem to have moved into a mitigation phase. A new highly mutated variant suddenly arrived, which led to surges of infection once again all over the world. This outbreak exhibited a widespread community transmission, bringing out another huge challenge for further epidemic control [7,14,15]. Apart from its greater dissemination capability, it is particularly worrying that Omicron might have produced resistance to the available antibody intervention produced by vaccination. It was reported that, so far, most Omicron cases presented have been relatively mild, including several asymptomatic cases [7,14-16]. In this paper, no severe cases or mortality were detected and 28 patients (19.2%) were regarded as asymptomatic. Therefore, recognizing and isolating infections at an early stage is the critical point to control the development of COVID-19. The research so far has suggested fever is the most common symptom in patients with COVID-19, especially in severe cases. A prior meta-analysis indicated that over ninety percent of COVID-19 patients experienced fever [1,9,17]. In several reports, fever was regarded as a predictor for screening suspected cases of COVID-19 [1,9,17]. In this study, fever was less common in COVID-19 cases, one possible reason for which was that there were no severe cases in our study, and most patients had been vaccinated. It was indicated in this study that there were no significant differences in age, gender, BMI, exposure history, and comorbidities between febrile and afebrile cases, which suggested that the baseline status may not be relative to fever symptoms during the illness.

In line with the previous research, we found that the duration of hospitalization was significantly longer in febrile patients compared to the afebrile cases, which indicated that patients who have caught a fever required prolonged hospital stays [18,19]. According to the previous reports, the median LOS of COVID-19 cases at common hospital wards in China was 14 days (IQR: 10 - 19) [17]. In this paper, the median LOS was 15 days

(IQR: 12 - 18) which was almost the same. In this study, not all febrile patients have long-term hospitalization. Therefore, we performed a further subgroup analysis of febrile patients based on the LOS. We found virus shedding duration (OR 2.369, 95% CI 1.684 - 3.333, $p < 0.001$) was an effective predictive factor for the long-term hospitalization through logistic regression analysis.

A meta-analysis of seven articles reported that hypertension was the most prevalent comorbidity in COVID-19-infected patients [20]. The prevalence of hypertension in our study population was 15.1%, while the total population in China was 23.2% [20-22]. One explanation could be that hypertension was more prevalent in the male population, and the prevalence increased with age. While in our study, more than half (52.7%) were male patients, and only a few cases (18.5%) were older than 60 years old. Although there was weak evidence showing a significant association between hypertension and LOS after adjusting for other variables, we found hypertension was relatively more common in the long LOS patients compared to the short LOS cases (25.0% vs. 6.3%, $p = 0.005$). It could be possible that hypertension is prevalent extremely among the elderly, who appear to be more susceptible to the SARS-CoV-2 viral infection and even progressing into severe COVID-19 cases [23,24].

Recently, several reported studies have indicated that elderly COVID-19 patients yielded poorer clinical outcomes [25,26]. In our study, the average age was higher and the proportion of febrile patients aging more than 60 years old was significantly higher in the long LOS group compared to the short LOS group ($p < 0.05$). Nonetheless, age was not related to prolonged hospitalization in febrile patients with COVID-19 in our study. One possible explanation could be that fever production in response to infection or inflammatory cytokines was reduced in the elderly [27,28].

Studies have shown that the manifestations of COVID-19 infection range from asymptomatic, mild clinical symptoms to severe pneumonia [29]. In a meta-analysis of 43 reports involving 3,600 patients, over three-quarters of COVID-19 patients presented multiple ground glass opacities on initial CT scan [30]. As reported in a previous study, bilateral pneumonia on chest computed tomography was related to a longer duration of hospitalization [31]. Compared to short LOS febrile patients in our research, long LOS patients had a higher proportion of bilateral pneumonia on chest CT scan, but with no statistical significance (43.8% vs. 29.7%, $p > 0.05$). It is possible that the sample size is not large enough to be significant or skewed in some way. Besides that, we found the proportion of febrile cases with normal CT imaging findings in the short LOS group was significantly higher compared to the long LOS group (35.9% vs. 18.8%, $p = 0.046$; Supplemental Table S2). However, there was no association between LOS and chest CT findings in the multivariable logistic regression. These results may be attributed to the individual differences, various disease severities, and reasonable treatment during hospitalization. Another possible explanation is initial chest CT imaging on admission may demonstrate negative findings, especially in the early stage of infection.

Multiple studies indicated that myocardial injury was common in COVID-19 infection patients, mainly manifested as elevated cTnI levels, which were associated with worse prognosis and increased risk of mortality [32,33]. In this study, febrile patients showed markedly increased cTnI levels compared to the afebrile patients ($p = 0.019$; Supplemental Table S1). Meanwhile, the cTnI levels were elevated significantly in the long LOS group compared to the short LOS group among the febrile cases (5.00 (3.00) vs. 4.00 (2.00) μg/L, $p = 0.012$; Supplemental Table S2). However, there was no association between prolonged duration of hospitalization and increased cTnI levels through logistic regression analysis. A possible explanation could be that there were no severe cases in our study, and all patients recovered well.

Existing evidence has shown that virus shedding duration could be related to the recovery time of COVID-19, especially for non-severe cases [34]. In this study, virus shedding duration in the long LOS group was longer than that of the short LOS group (18.42 ± 2.86 vs. 11.94 ± 2.50 days, $p < 0.001$). Furthermore, it was significantly associated with the prolonged duration of hospital stay in febrile COVID-19 patients (OR 2.369, 95% CI 1.684 - 3.333, $p < 0.001$). According to the latest edition of the COVID-19 Diagnosis and Treatment plan, there are several recommended treatments available besides general intervention, including immunotherapy, anti-viral therapy, anti-inflammatory therapy, anti-coagulation therapy and Traditional Chinese Medicine (TCM) therapy, especially for severe COVID-19 patients [35]. A recent report suggested that anti-viral treatment in the early course of COVID-19 infection could shorten the LOS of non-severe patients and prevent the progression of severe cases [36]. Multiple studies indicated that in China early TCM intervention might shorten the course of the disease, decrease the mortality rate, and improve the prognosis [37,38]. In this study, we did not find a significant difference in LOS between patients who took medicinal treatment and those without medical therapy among febrile patients ($p > 0.05$). Pharmaceutical treatment for COVID-19 needs to be further performed in controlled clinical trials.

As was reported, effective full vaccination could provide protection against COVID-19, nevertheless the virus mutation had created great challenges to the current vaccines. The new variant named Omicron has shown greater human-to-human transmission, but the risk of severe or fatal cases caused by Omicron infection is not correspondingly enhanced [4-8]. In this study, 72 (49.3%) patients took complete vaccination without booster vaccination and 40 (27.4%) received a booster dose after full vaccination. We found that there was no significant difference in the vaccination status between febrile and afebrile patients, and vaccination did not affect the duration of hospitalization in febrile patients. Nevertheless, there was no severity or even mortality in our study. Studies indicate that booster vaccination could augment neutralizing antibody titers, covering the gradually decreasing immunological responses after two doses [39]. Therefore, the acceleration of booster vaccination looms ahead.

We should take into account a few limitations in our research. First, our single-centered study included a limited sample size, which prevented us from conducting more sophisticated analyses to control for potential confounding effects affecting the comparability of the results. Second, information about symptom onset before administration and exposure history supplied by patients might be subject to recall bias. Third, there is a possibility that a small subset of these discharged COVID-19 patients might present positive pharyngeal swab samples tested for SARS-CoV-2 RNA again by RT-PCR test after discharge. In our study, we only analyzed the short-term outcome of these cases, and long-term follow-up after discharge from the rehabilitation center is necessary for further investigations. Fourth, although nobody had past exposure to SARS-CoV-2, it was hard to evaluate the effects of pre-existing immunity from different vaccination programs. In this study, we only evaluated the frequency of vaccination in our paper, and the limited data was insufficient to analyze by vaccine type and time. Lastly, no screening examinations of other conventional respiratory virus infections were performed, so it was unclear whether patients were complicated with other infections.

CONCLUSION

In the one-center retrospective study, more than half of the non-severe COVID-19 patients, which were identified as Omicron variant cases officially, had symptoms of fever. Of the 112 febrile COVID-19 patients, as many as 42.86% were discharged more than 15 days following hospital admission. Febrile Omicron cases took a longer duration of hospitalization compared to afebrile patients, while virus shedding duration (OR 2.369, 95% CI 1.684 - 3.333, $p < 0.001$) was an effective predictive factor for the long-term hospitalization. Our research might provide some reference for predicting hospital bed demand in the face of Omicron emergence, which could help governors allocate medical resources reasonably and efficiently during the early preparation for the following waves of COVID-19 infection.

Acknowledgment:
We sincerely thank all the medical staff struggling against COVID-19. We also thank the clinical staff for their efforts in this study.

Availability of Date and Materials:
The data employed in this current paper will be available from the corresponding author on qualified application, without inordinate reservation, whereas not available publicly due to protection of patients' privacy.

Ethics Approval and Consent to Participate:
This study was approved and the clinical data used in the research was granted permission by the Ethics Committee of The Affiliated Infectious Hospital of Soochow University (No. 2022009). Experiments were performed in accordance with the Declaration of Helsinki. Written informed consents were not required by the Ethics Committee of The Affiliated Infectious Hospital of Soochow University as this was a retrospective study.

Declaration of Interest:
The authors state that they have no competing interests in this study.

References:

1. Hu B, Guo H, Zhou P, Shi ZL. Characteristics of SARS-CoV-2 and COVID-19. Nat Rev Microbiol 2021 Mar;19(3):141-54. (PMID: 33024307)

2. Safiabadi Tali SH, LeBlanc JJ, Sadiq Z, et al. Tools and Techniques for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)/COVID-19 Detection. Clin Microbiol Rev 2021 May;34(3):e00228-20. (PMID: 33980687)

3. Kevadiya BD, Machhi J, Herskovitz J, et al. Diagnostics for SARS-CoV-2 infections. Nat Mater 2021 May;20(5):593-605. (PMID: 33589798)

4. Thakur V, Ratho RK. OMICRON (B.1.1.529): A new SARS-CoV-2 variant of concern mounting worldwide fear. J Med Virol 2022 May;94(5):1821-4. (PMID: 34936120)

5. Dolgin E. Omicron is supercharging the COVID vaccine booster debate. Nature 2021 Dec 2. (PMID: 34862505)

6. Kannan SR, Spratt AN, Sharma K, et al. Omicron SARS-CoV-2 variant: Unique features and their impact on pre-existing antibodies. J Autoimmun 2022 Jan;126:102779. (PMID: 34915422)

7. Espenhain L, Funk T, Overvad M, et al. Epidemiological characterisation of the first 785 SARS-CoV-2 Omicron variant cases in Denmark, December 2021. Euro Surveill 2021 Dec;26(50): 2101146. (PMID: 34915977)

8. Vaughan A. Omicron emerges. New Sci 2021 Dec;252(3363):7. (PMID: 34876769)

9. Singhal T. A Review of Coronavirus Disease-2019 (COVID-19). Indian J Pediatr 2020 Apr;87(4):281-6. (PMID: 32166607)

10. Jiang F, Deng L, Zhang L, et al. Review of the Clinical Characteristics of Coronavirus Disease 2019 (COVID-19). J Gen Intern Med 2020 May;35(5):1545-9. (PMID: 32133578)

11. Hu M, Zhou Q, Zheng R, et al. Application of high-flow nasal cannula in hypoxemic patients with COVID-19: a retrospective cohort study. BMC Pulm Med 2020 Dec;20(1):324. (PMID: 33357219)

12. Wiersinga WJ, Rhodes A, Cheng AC, et al. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. JAMA 2020 Aug;324(8):782-93. (PMID: 32648899)

13. Wang G, Zhang Q, Wu C, et al. Clinical Characteristics of Adult Fevered COVID-19 Patients and Predictors for Developing Severe Events. Front Med (Lausanne) 2020 Jul;7:324. (PMID: 32719804)

14. Kandeel M, Mohamed MEM, Abd El-Lateef HM, et al. Omicron variant genome evolution and phylogenetics. J Med Virol 2022 Apr;94(4):1627-32. (PMID: 34888894)

15. Torjesen I. Covid-19: Omicron may be more transmissible than other variants and partly resistant to existing vaccines, scientists fear. BMJ 2021 Nov;375:n2943. (PMID: 34845008)

16. Planas D, Saunders N, Maes P, et al. Considerable escape of SARS-CoV-2 Omicron to antibody neutralization. Nature 2022 Feb;602(7898):671-5. (PMID: 35016199)

17. Umakanthan S, Sahu P, Ranade AV, et al. Origin, transmission, diagnosis and management of coronavirus disease 2019 (COVID-19). Postgrad Med J 2020 Dec;96(1142):753-8. (PMID: 32563999)

18. Guo A, Lu J, Tan H, et al. Risk factors on admission associated with hospital length of stay in patients with COVID-19: a retrospective cohort study. Sci Rep 2021 Mar;11(1):7310. (PMID: 33790365)

19. Wu S, Xue L, Legido-Quigley H, et al. Understanding factors influencing the length of hospital stay among non-severe COVID-19 patients: A retrospective cohort study in a Fangcang shelter hospital. PLoS One 2020 Oct;15(10):e0240959. (PMID: 33085709)

20. Yang J, Zheng Y, Gou X, et al. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. Int J Infect Dis 2020 May;94:91-5. (PMID: 32173574)

21. Ma LY, Chen WW, Gao RL, et al. China cardiovascular diseases report 2018: an updated summary. J Geriatr Cardiol 2020 Jan;-17(1):1-8. (PMID: 32133031)

22. Wang Z, Chen Z, Zhang L, et al. Status of Hypertension in China: Results From the China Hypertension Survey, 2012-2015. Circulation 2018 May;137(22):2344-56. (PMID: 29449338)

23. Schiffrin EL, Flack JM, Ito S, et al. Hypertension and COVID-19. Am J Hypertens 2020 Apr 29;33(5):373-4. (PMID: 32251498)

24. Liu J, Liu Z, Jiang W, et al. Clinical predictors of COVID-19 disease progression and death: Analysis of 214 hospitalised patients from Wuhan, China. Clin Respir J 2021 Mar;15(3):293-309. (PMID: 33090710)

25. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020 Mar 28;395(10229): 1054-62. (PMID: 32171076)

26. Grasselli G, Zangrillo A, Zanella A, et al. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. JAMA 2020 Apr 28;323(16):1574-81. (PMID: 32250385)

27. McLay RN, Kastin AJ, Zadina JE. Passage of interleukin-1-beta across the blood-brain barrier is reduced in aged mice: a possible mechanism for diminished fever in aging. Neuroimmunomodulation 2000;8(3):148-53. (PMID: 11124581)

28. Miller D, Yoshikawa T, Castle SC, et al. Effect of age on fever response to recombinant tumor necrosis factor alpha in a murine model. J Gerontol 1991 Sep;46(5):M176-9. (PMID: 1890284)

29. Purohit D, Ahirwar AK, Sakarde A, et al. COVID-19 and lung pathologies. Horm Mol Biol Clin Investig 2021 Aug;42(4):435-43. (PMID: 34333882)

30. Fu L, Wang B, Yuan T, et al. Clinical characteristics of coronavirus disease 2019 (COVID-19) in China: A systematic review and meta-analysis. J Infect 2020 Jun;80(6):656-65. (PMID: 32283155)

31. Chen M, An W, Xia F, et al. Clinical characteristics of rehospitalized patients with COVID-19 in China. J Med Virol 2020 Oct; 92(10):2146-51. (PMID: 32401361)

32. Wibowo A, Pranata R, Akbar MR, et al. Prognostic performance of troponin in COVID-19: A diagnostic meta-analysis and meta-regression. Int J Infect Dis 2021 Apr;105:312-8. (PMID: 33667694)

33. Aboughdir M, Kirwin T, Abdul Khader A, et al. Prognostic Value of Cardiovascular Biomarkers in COVID-19: A Review. Viruses 2020 May;12(5):527. (PMID: 32403242)

34. Lin L, Lu L, Cao W, et al. Hypothesis for potential pathogenesis of SARS-CoV-2 infection-a review of immune changes in patients with viral pneumonia. Emerg Microbes Infect 2020 Dec; 9(1):727-32. (PMID: 32196410)

35. Tsang HF, Chan LWC, Cho WCS, et al. An update on COVID-19 pandemic: the epidemiology, pathogenesis, prevention and treatment strategies. Expert Rev Anti Infect Ther 2021 Jul;19(7):877-88. (PMID: 33306423)

36. Fujii S, Ibe Y, Ishigo T, et al. Early favipiravir treatment was associated with early defervescence in non-severe COVID-19 patients. J Infect Chemother 2021 Jul;27(7):1051-7. (PMID: 33902990)

37. Ren JL, Zhang AH, Wang XJ. Traditional Chinese medicine for COVID-19 treatment. Pharmacol Res 2020 May;155:104743. (PMID: 32145402)

38. Fan AY, Gu S, Alemi SF; Research Group for Evidence-based Chinese Medicine. Chinese herbal medicine for COVID-19: Current evidence with systematic review and meta-analysis. J Integr Med 2020 Sep;18(5):385-94. (PMID: 32792254)

39. Alagheband Bahrami A, Azargoonjahromi A, Sadraei S, et al. An overview of current drugs and prophylactic vaccines for coronavirus disease 2019 (COVID-19). Cell Mol Biol Lett 2022 May; 27(1):38. (PMID: 35562685)

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