

Persistent cough and asthma-like symptoms post COVID-19 hospitalization in children

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Abstract

Backgrounds: Respiratory viruses are the main triggers of asthma. Coronavirus is shown to contribute to infections of the respiratory tract that can lead to prolonged cough and asthma. **Objectives:** Present study aimed to determine the risk of developing Persistent cough and asthma-like symptoms in hospitalized children due to COVID-19.

Methods: This prospective study was carried out in a tertiary referral center. During the COVID-19 pandemic, 69 hospitalized pediatric patients admitted with COVID-19 were observed from February 2020 to January 2021. Clinical and laboratory data were recorded, and after discharge, patients were followed and visited for cough and asthma evaluation in one, 2 and 6 months later. Patients with asthma-like diagnosis in follow-up defined as asthma-like group and patients without any sign of asthma categorized as the non-asthma group. Asthma-like co-morbidities and risk factors were evaluated and compared between two groups.

Results: Most of the COVID-19 hospitalized patients (N=42) (58.5%) were not affected by asthma-like symptoms in follow-up. 60.9% of the COVID-19 patients were male. The asthma-like group cases had a significantly familial history of asthma (63.0%), past medical history of asthma (33.3%), and Allergic rhinitis (85.2%). Rates of signs and symptoms during hospitalization were significantly higher in patients with COVID-19 and past medical history of asthma.

Conclusions: We found an asthma-like prevalence of 41.5% in the cohort of COVID-19 hospitalized children. Family history of asthma and previous history of asthma and allergic rhinitis are risk factors for asthma-like after COVID-19 hospitalization. COVID-19 presentations are more severe in the asthma-like group.

What Is Known:

- Asthma is one of the most common childhood diseases and the most important trigger of asthma is viral infection.
- During the COVID-19 pandemic, airway inflammation has been a presentation of COVID-19 in children

What Is New:

- We found an asthma prevalence of 41.5% in the cohort of COVID-19 hospitalized children
- Our study indicates that family history of asthma and previous history of asthma and allergic rhinitis are risk factors for asthma after COVID-19 hospitalization

Background:

As a new beta coronavirus, the severe acute respiratory syndrome coronavirus 2 first identified in December 2019. Coronavirus disease 2019 (COVID-19) rapidly spread throughout the world, characterized by severe pneumonia and some other complications, such as a death in highly severe cases. The diseases spread rapidly in the community due to the easy transmission of the virus, even from asymptomatic patients. Moreover, the causing agent survives in respiratory droplets and fomites [1]. Three months following the first emergence, about 2.6 million cases were reported globally due to high community transmission. Some comorbidities exacerbate COVID-19 outcomes, namely hypertension, chronic obstructive pulmonary disease, diabetes mellitus, cardiovascular disease, obesity, and asthma [2, 3].

In the United States, asthma is among the most prevalent chronic diseases affecting 8–9 % of the population, and its acute exacerbations are considered as a common reason for hospitalizations and/or visits to the emergency rooms [4]. Respiratory viruses usually regarded as the triggers of asthma [5–7]. Therefore, coronaviruses, which are respiratory viruses, have been shown to contribute to the infections of the respiratory tract and asthma exacerbations [8].

Currently, asthma risk factors in children induced by COVID-19 are not clear. The studies performed in China and the United States reported $\leq 1\%$ and 7.4%-17% prevalence for asthma in patients with COVID-19, respectively [9, 10]. Another study claimed the asthma prevalence of 1.82% among COVID patients [11].

The CDC currently classifies uncontrolled moderate to severe asthma as a high-risk group susceptible to severe COVID-19. The signs of COVID-19 in patients with asthma include cough, breath shortness, and chest tightness. The differentiation of these symptoms from severe asthma exacerbation is difficult. It is especially true about children with a lower ability to recounting their signs and possibly varying symptoms than adults are.

On the other hand, it has been demonstrated that viral infections, specially severe forms that require hospitalization, activate immunological mechanisms and induce morphological changes such as tissue remodelling that can contribute to the initiation or aggravation of asthma[12, 13]. It is stated that while allergen sensitivity is one of the strongest risk factors for asthma, it rarely directly leads to persistent asthma. Instead, allergies often cause asthma in conjunction with other pre-inflammatory environmental factors, especially respiratory viral infections[14].

Consequently, the present study aimed to describe the association of asthma-like symptoms in hospitalized children affected by COVID-19. In addition, we examined whether hospitalization because of COVID-19 might result in the development persistent cough and asthma-like following COVID-19.

Materials And Methods:

Identifying Patients with COVID-19

This prospective study carried out in Namazi tertiary referral Hospital, Shiraz, as the largest hospital in the south of Iran. Patients identified based on a specialist physician visit. Patient information extracted by reviewing the file data, an electronic repository of the health records of hospitalized patients in the health system. Shiraz University of Medical Sciences, with number of 23556-35-01-99, approved the current study, and the authors took consent from the patient's parents or caregivers.

The inclusion criteria entailed the age of < 18 years old, being evaluated during February 2020 to January 2021, in Shiraz, and having received the diagnosis code of COVID-19 (U07.1) according to the Tenth Revision of the International Classification of Diseases (ICD-10). Presumed COVID-19 patients (U07.2) whom RT-PCR did not confirm were excluded. Moreover, death, the lack of response to call or avoid participating in this cohort study, are affected by other infectious diseases, such as pneumonia, post-infectious cough in 2 months after infection, and patients considered COVID-19 outpatients were the other exclusion criteria.

Asthma-like Diagnosis in Patients with COVID-19

Data of 109 COVID-19 admitted patients confirmed by RT-PCR were collected. Twelve of the subjects died and excluded from the study. The rest of the patients visited one and two months after recovery and discharged, then followed monthly until six months later. We followed the patients by clinic visit at 1,2 and 6 months and by phone in other months and if necessary, the patients asked to come to the clinic. Twenty-eight participants did not respond to our call or did not refer and were excluded from the study resulting in 69 patients (Fig. 1).

For asthma-like diagnosis, patients requested to refer to the clinic for medical history and clinical examination. In addition, the PFT test performed for children aged over five years old. The diagnostic criteria of the Gina guideline [15] included coughs that cause the person to wake up, coughs when exercise or laughing, frequent dry coughs during the day, and changes in PFT in patients over five years old. In PFT, asthma-like was diagnosed if FEV1/FVC was < 80% and elevated by 12% in FEV1 of 200 cc following the administration of a bronchodilator. Coughs behind 2 months registered as persistent cough

Identification of Clinical Characteristics and Comorbidities

Clinical characteristics, such as age, gender, familial history, history of asthma, and Allergic rhinitis and signs evaluated. The symptoms during hospitalization were assessed as a checklist, including fever, cough, dyspnea, sputum, myalgia, headache, diarrhea, vomiting, abdominal pain, cardiac complication, dry cough, waking cough, activity cough, chest tightness, chest wheezing, weight loss, nasal congestion, and smell decrease. Moreover, laboratory test results, past medical history and family history of patients regarding asthma and other allergic disease recorded.

Statistical Analysis

Demographic characteristics and clinical data evaluated for all the patients and compared by the chi-square test. The laboratory test results compared utilizing the Mann-Whitney test. The correlation between asthma-like and COVID-19 hospitalization was examined in these patients.

Results:

Asthma-like Prevalence among COVID-19 patients

One hundred nine patients identified with an ICD-10 diagnosis code of COVID-19 based on patients' medical records referred from February 2020 to January 2021. The following results related to the study of patients two months after discharge. One month after discharge, 30 patients had symptoms, and it seemed to mostly post-infectious of COVID19, and in the 2th month, 20% had no symptoms. During six months following, no new patient added. Out of 109 patients, 97 (88.9%) cases confirmed by RT-PCR and were included in the study. Finally, 69 patients analyzed following excluding those who died or did not respond (Table 1). Most of the COVID-19 patients (N = 42) (58.5%) were not affected by post-hospitalization asthma-like. Among 27 patients with post-COVID-19 asthma-like, 14 (51.9%) participants aged > 5 years old and confirmed as asthma-like using a spirometer (PFT) (Fig. 1). Of the patients, 15.94% had a history of asthma at the time of admission (Table 1), of which 55% had a previous history of childhood asthma that had been stopped medications, and the rest received asthma medications, with 20% having moderate persistent asthma and 30% mild persistent asthma. Also, the patients we diagnosed with asthma-like after discharge had a 20% history of previous hospitalization for asthma attacks, of which only about 45% had active asthma at the time of admission and were taking medication. The rest were patients who had stopped taking their medications.

Demographic and Clinical Characteristics of COVID-19 Patients with and without post-hospitalization Asthma-like

We evaluated and compared diverse demographic characteristics and clinical data between COVID-19 patients with and without post-hospitalization asthma-like (Table 1). The majority of (37.3%) COVID-19 patients were < 5 years regardless of asthma-like status. Slightly over half (60.9%) of the COVID-19 patients were male. The asthma-like group cases had a very high familial history of asthma (63.0%), past medical history of asthma (33.3%), and Allergic rhinitis (85.2%).

Clinical Comorbidities of COVID-19 Patients with and without post-hospitalization Asthma-like

Afterward, we specified the prevalence of diverse comorbidities and symptoms in COVID-19 patients based on post-hospitalization asthma-like status (Fig. 2). Rates of symptoms were significantly elevated in the group of patients with both COVID-19 and asthma-like compared to COVID-19 patients without asthma. However, fever found to be higher in the asthma-like group, and vomiting was not significantly different between patients with and without post-hospitalization asthma-like (Fig. 2).

Laboratory Data at COVID-19 Diagnosis with post-hospitalization Asthma-like Status

We collected the results of different laboratory tests for all hospitalized cases when they were diagnosed with COVID-19 (Fig. 3). Complete blood cell count indicated that White Blood Cell (WBC), Hemoglobin (Hb), Platelet (plt), C-reactive Protein (CRP), Alanine Aminotransferase (ALT), Alkaline phosphatase (ALKP), and eosinophil count were not significantly different between patients with and without post-hospitalization asthma-like (Fig. 3).

Discussion:

This is the first comprehensive cohort study on children with COVID-19 and post-hospitalization asthma-like to the best of our knowledge. In the present study, 41.5% of COVID-19 patients had asthma-like after discharge. Our study population had a higher prevalence of persistent cough and asthma-like symptoms than the US and Chicago population, which were estimated to have an asthma prevalence of 8%-9% and 9.5%, respectively at all [4, 16]. Moreover, recently published papers in the US reported a prevalence of 7.4%-17% for asthma in hospitalized patients with COVID-19 [2, 17–19]. The latter reports are contrary to the low asthma prevalence of $\leq 1\%$ observed in China [9, 10]. These heterogeneous findings could be attributed to genetic, geographically different asthma, screening time (during hospitalization or post-discharge asthma) and frequency or techniques for ascertainment. Given the higher percentage of asthma reported in our study than in other studies, it seems that since most previous articles have screened for asthma during hospitalization since we have examined a longer distance, it turns out that asthma can be a reaction and a delay event after COVID-19, especially in children.

Symptoms, which are clearly established to be associated with COVID-19, existed in patients with post-hospitalization asthma-like (Fig. 2). These symptoms include fever, cough, dyspnea, sputum, myalgia, headache, diarrhea, vomiting, abdominal pain, cardiac complication, dry cough, waking cough, activity cough, chest tightness, chest wheezing, weight loss, nasal congestion, and smell decrease. Which were significantly higher in the post-covid19 asthma-like group. Except for vomiting, which was not significantly different between patients with and without post-hospitalization asthma-like. In addition, Laboratory results demonstrated that WBC, lymphocyte, neutrophil, plt, Hb, ALT, eosinophil, CRP, and ALKP were not significantly different between patients with and without post-hospitalization asthma-like.

We found that asthma was not a risk factor for admission and hospitalization in COVID-19 patients. We also found that post-discharge asthma-like was higher in patients with a previous history of asthma than in patients without it, and this difference was statistically significant. Therefore, it seems that the background of asthma can be a risk factor for post-discharge asthma-like in COVID-19 patients. Despite the high incidence of asthma, these chronic respiratory conditions have not been reliably reported as major comorbidity for COVID-19, according to a recent report [1]. The evidence presented in this study contradicts the information provided by Lippi and Henry [20] that Severe respiratory disease is associated with severe forms of COVID-19. Such a discrepancy could be because there is no consensus on the severity of COVID-19 patients and all the features of acute respiratory distress syndrome (ARDS) instead of acute lung injury (ALI) [21–23]. It may be difficult or impossible in non-intubated people. However, hospitalized COVID-19 patients with asthma expected to perform worse than patients without. Because

SARS-CoV-2 uses the angiotensin-converting enzyme (ACE-2) as a cellular receptor that suspected to be higher in obstructive respiratory disease, so expected that these individuals would be at higher risk for hospitalization [24]. In fact, reducing the risk of hospitalization in patients with asthma and COVID-19 could be associated with use of inhaled corticosteroids (ICS), which have recently been shown to have a protective effect against infections, specifically those due to coronaviruses [25].

Therefore, asthma appears to be not a primary risk factor to increase the chance of developing COVID19 or more severely admission unless the asthma is uncontrolled. However, background asthma causes recurrent asthma after discharge from the hospital.

Our study had several limitations. Some data were collected retrospectively after discharge of patient, causing limitations for drawing associations rather than causal inferences. Another limitation of the current study was that we assessed the data collected from February 2020-January, 2021, and the findings may alter as the result of collecting more data after the study period. It assumed that the possibility of testing patients affected by asthma was higher due to the chronic nature of this lung disease. Another limitation is that we investigate the development of asthma in hospitalized COVID-19 patients with more severe forms of infection compare to outpatients, which does not represent all COVID-19 patients.

Conclusions:

We found a post-hospitalization persistent cough and asthma-like prevalence of 41.5% in the cohort of COVID-19 hospitalized patients. Our study indicates that post-hospitalization asthma-like risk factors may have a family history of asthma and previous history of asthma and Allergic rhinitis. The incidence of COVID-19 signs and symptoms is higher in the asthma-like group, especially fever. However, in terms of laboratory information, no difference was observed between the two groups. It is necessary to assess post-hospitalization asthma-like in children with a diagnosis of COVID-19.

Abbreviations

COVID-19

coronavirus disease 2019

CDC

Centers for Disease Control and Prevention

ICD

International Classification of Diseases

PFT

Pulmonary Function Tests

WBC

White blood cell

Hb

Hemoglobin Concentration

plt

Platelet Count Test

ESR

Erythrocyte Sedimentation Rate

CRP

C - reactive protein

LDH

Lactate Dehydrogenase

ALT

Alanine transaminase test

ALKP

Alkaline Phosphatase

Declarations

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Conflict of Interest: N/A. The authors declare that they have no conflict of interest.

Ethics approval: The Ethics Committee Shiraz University of Medical Sciences approved the protocol of the study

Consent to participate: Informed consent was obtained from all individual participants included in the study to participate

Consent for publication: Informed consent was obtained from all individual participants and authors included in the study for publication

Availability of data and material : The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability: data analysed with IBM SPSS Statistics version 26

Authors contributions: AS and HE visited COVID-19 patients. HF and NM collected the data and followed the patients. MV analyzed and interpreted the patient data regarding asthma and COVID19. HE was the leading author and guarantor and performed the examination of asthma and was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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Figures

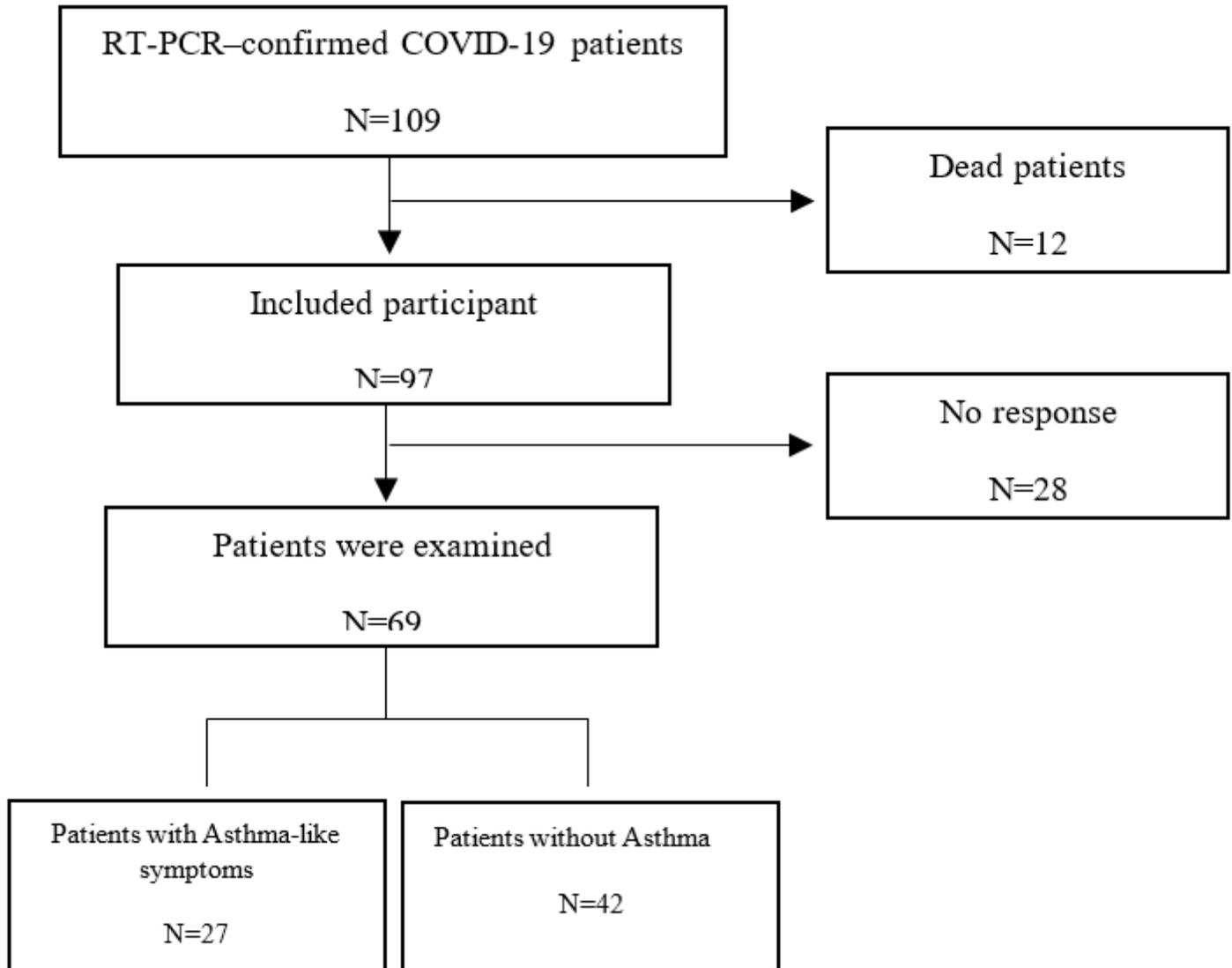


Figure 1

Algorithm of identifying COVID-19 or asthma-like patients

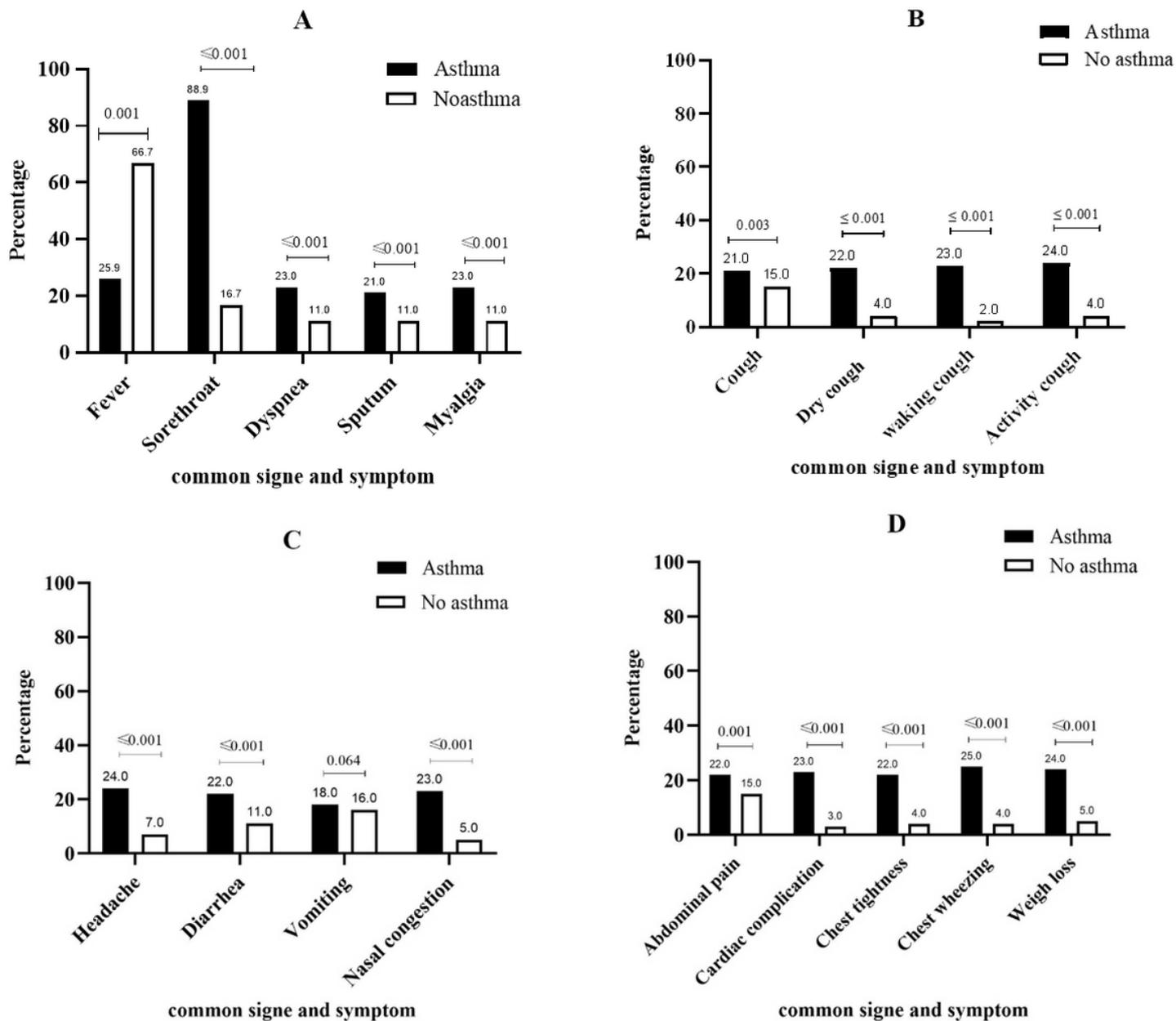


Figure 2

Prevalence of signs and symptoms during hospitalization in COVID-19 patients stratified based on asthma-like status; A total of 69 patients were investigated

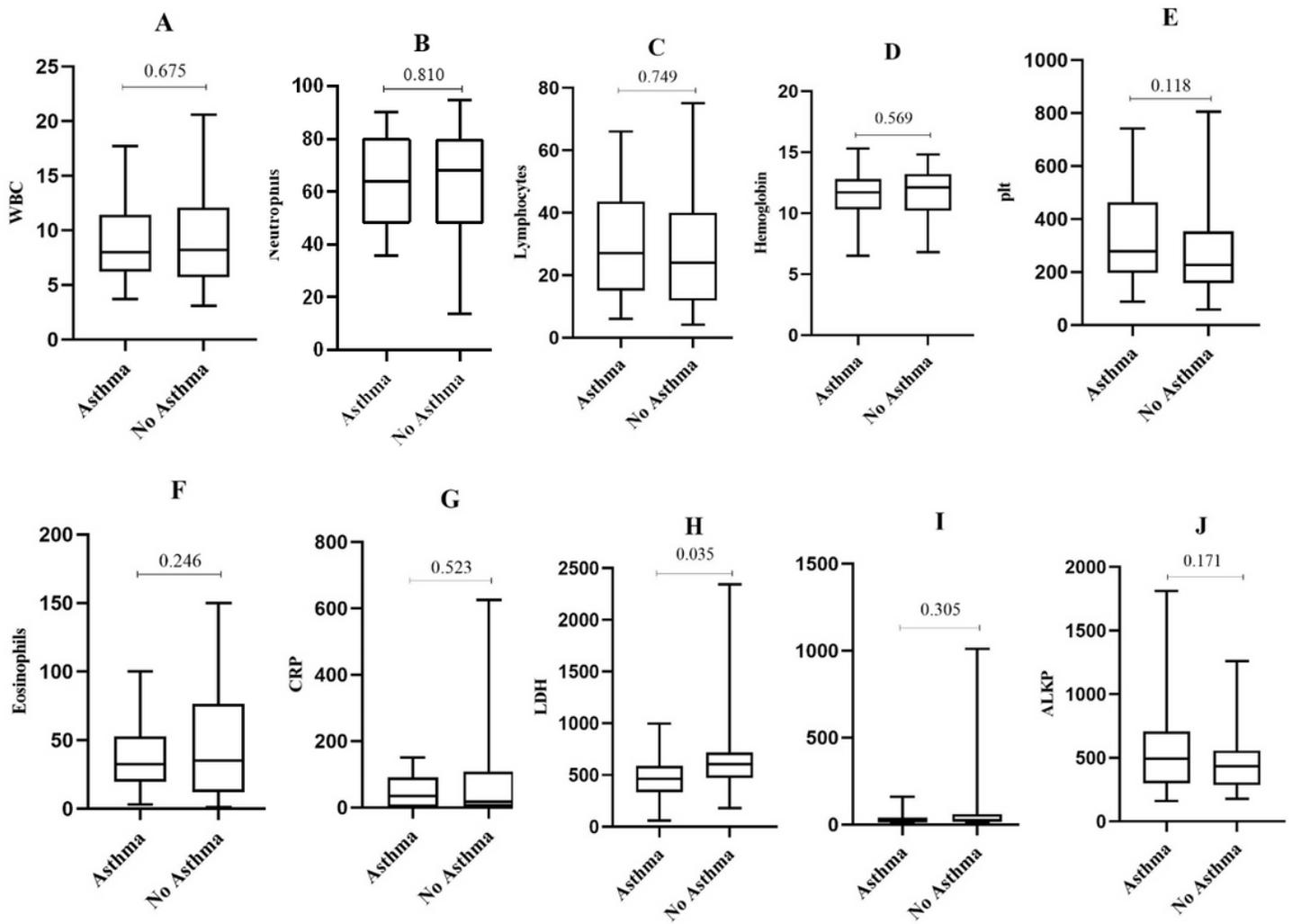


Figure 3

Laboratory results at COVID-19 diagnosis in hospitalized patients with asthma-like, in comparison with patients without asthma. The box is extended from percentiles 25th to 75th. The line in the box represents the median with “1” demonstrated as the mean. Whiskers are the minimum and maximum values. The nonparametric Mann-Whitney 2-tailed test was applied for statistical analysis