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COVID 19 severity, ICU need and outcome in asthmatic patients

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ABSTRACT

There is insufficient data to definitively establish the link between coronavirus disease 2019 and asthma, despite reports that individuals with comorbidities are more likely to experience unfavorable clinical outcomes. On account of this, the objective of this study is to carefully analyze the clinical traits of asthmatic COVID-19 patients. 18 COVID-19 patients with asthma and 101 COVID-19 patients without asthma were statistically matched in this single-center, retrospective and observational cohort study using propensity scores based on age, sex and comorbidities. In the meantime, data on demographic variables, clinical and laboratory tests and results were gathered and compared between the two groups to identify any differences. According to statistics, patients on the COVID-19 who had asthma had a higher proportion of ICU admissions than those who did not. Additionally, asthma patients showed greater levels of inflammatory responses such as interleukin 6, interleukin 8, procalcitonin, leukocytes, neutrophils, and CD4+ T cells. Additionally, COVID-19 patients with asthma had more significant increases in organ damage markers such D-dimer, lactate dehydrogenase and high-sensitivity cardiac troponin I. In COVID-19 asthma patients, exacerbated inflammatory responses and numerous organ damages were induced, highlighting the need for excessive intense surveillance and supportive care.

Keywords: COVID 19**,** asthma, clinical traits

1. INTRODUCTION

Over 200 countries have been affected by the global pandemic known as COVID-19, which is caused by a coronavirus (WHO updates on the coronavirus disease in real time, 2022). Human health is now seriously at risk

as a result. And to make matters worse, the confirmed cases number keeps growing. Greater preventative measures are essential among high-risk individuals in such situations, especially those with other comorbidities and elderly.

Particularly, corona virus disease patients with underlying illnesses would see poor clinical results (Tian & Miao, 2020). According to reports, people with COVID-19 who have hypertension, diabetes and other concomitant conditions are at a more risk of dying (Zhou et al., 2020). Around 300 million individual worldwide had asthma, and each year about 250,000 people pass away too soon as a result (Bousquet et al., 2020). However, just 5.6% of asthmatics received treatment with inhaled corticosteroids, which is still much less than the rates in major European nations like Italy (17%), the United Kingdom (49%), and others (Janson et al., 1997). As a chronic condition, asthma is distinguished by an innately persistent airway inflammation that involves many different cells, including mast cells and eosinophils. This inflammation is frequently accompanied by an enhanced responsiveness of the airways (Holgate et al., 2015). However, given the scant research demonstrating the link between corona virus disease and asthma, it is critical to investigate the clinical traits and alterations in particular markers of corona virus disease patients with asthma. In order to test our hypothesis, we looked at patients who had both COVID-19 and asthma. Those with both conditions at high risk to have severe clinical features and poorer outcomes than patients without asthma.

The objective of this observational-retrospective cohort study was to compare biological indicators between 18 corona virus disease asthmatic patients and 101 matched COVID-19 patients without asthma in order to clinical characteristics and profile of corona virus disease patients with asthma.

2. METHODS

As a cohort, all corona virus disease patients admitted to KSMC between February 30 and April 5, 2022, were subsequently recruited. The cohort study's primary outcome is death, while its secondary outcomes are hospital duration of stay and ICU admission. The precise hospital electronic records were gathered at the appropriate moment. Patients from the COVID-19 cohort who had been given an asthma diagnosis (N = 18) prior to the start of our trial were enrolled and 101 patients don't had asthma were matched using propensity score at a roughly 1:5 ratio relying on age, sexadditional tocomorbidities. The Ethics Committee of the MOH in Saudi Arabia and KSMC approved this study and waived the requirement for informed permission from study participants.

We obtained demographic, laboratory, clinical and outcome data for all research objects from the KSMC in Riyadh, Saudi Arabia's standard electronic hospital records. A skilled group of doctors gathered, reviewed and validated the in-hospital data for these patients. The correctness of the data was independently examined by two competent investigators and the lead investigators reviewed all charts. The form for development of respiratory infections by the WHO and the International Consortium of emerging Infection served as the basis for the indicators that were extracted, which were designed to reflect COVID-19 conditions as accurately as feasible (WHO, 2016). Laboratory testing including standard blood tests, inflammatory cytokines, immune cell subsets, biomarkers and tests for heart function were collected.

RNA identification of SARS-CoV-2 in throat swab samples by RT-PCR provided confirmation of the COVID-19 patients. The COVID-19 patients included in the study were all adults 18 years old and above. In accordance with the National Lung, Heart and Blood Institute's Diagnosis and Management guidelines of GINA recommendations, the asthma patients were identified through allergen testing, clinical symptoms, lung function examinations and the other interfering diseases exclusion prior to our study (NHLBI, 2022). Fever taken as an axillary temperature of 37.3°C or above (Zhou et al., 2020). Study samplewas clinically categorized into (mild and severe) at the time of admission in accordance with WHO recommendations and the 7th Revised Version of the corona virus disease diagnosis and China Treatment Guidance (WHO, 2022; National Health Commission, 2020).

If continuous variables were not normally distributed, they are described as median with interquartile range, otherwise as mean (SD). Number (%) was used to represent categorical variables. Matching propensity score with a 1:5 was used to find a group of study sample with comparable baseline traits in order to remove any potential confounding effects resulting from sex, age, additional to comorbidities. In order to ensure the homogeneity of age, sex, additional to comorbidities between groups, we matched the differences and then compared them using the appropriate statistical procedures. Positive matching was defined as the statistical disparities' absence between two groups. T-test was employed for variables that were continuous. R 3, 6, 2 and SPSS 23.0 software were used for all statistical analysis. Statistics were deemed significant at p 0.05.

3. RESULTS

According to Table 1, among COVID-19 asthma patients, fever (13/18; 72.2%), cough (8/18; 44.4%), diarrhea (3/18; 16.6), chest tightness (2/18; 11.1%) and dyspnea (2/18; 11.1%) were the most frequently noted symptoms at the admission time. However,

among COVID-19 non asthmatic patients, fever (59/79; 74.6%) was followed by chills (12/79; 15.1%), cough (53/79; 67%), expectoration (34/79; 43%) and dyspnea (24/79; 30.3%). In corona virus disease patients with asthma, expectoration was less common (1/18; 5.5% vs. 34/79; 43%; p = 0.004).

No significant difference in the vital signs was detected between asthmatic and non-asthmatic individuals Table 3. We saw significant disparities in test results between COVID-19 patients who had asthma and those who didn't (Table 2). In COVID-19 individuals with asthma, higher levels of lactate dehydrogenas (252 (210-281) vs. 215 (185-248) U/l, p = 0.036), high-sensitivity troponin I (hs-cTnI, 5.4 (1.2-11) vs. 1.19 (0.59-2.4) pg/ml, p = 0.006) and D-dimer (0.81 (0.40–1.96) vs. 0.42 (0.35–0.74) μg/ml, p = 0.032).

Additionally, we noticed that inflammatory cytokine significant difference, particularly IL-6 (2.35 (1.50–3.61)) vs. 1.62 (1.48–2.32) pg/ml, $p = 0.039$), IL-8(10.98 (8.1–18.88) vs. 6.48 (4.95–10.73) pg/ml, $p = 0.038$) and procalcitonin (0.04 (0.02–0.09) vs. 0.02 (0.01–0.04) ng/ml, $p = 0.035$) were higher in COVID-19 asthma patients. Moreover, increased leukocyte levels (7.1 (5.2–9.5) vs. 5.8 (4.8–7.9) × 10^9/l, $p = 0.032$), neutrophils (4.81 (3.32–6.91) vs. 3.28 (2.52–4.65) × 10^9/l, $p = 0.015$) and neutrophils percentage (70.1 vs. 59.5 $p = 0.009$) were observed in corona virus disease asthmaticpatients. In terms of immune cell subsets, asthmatic COVID-19 patients had considerably lower proportions of lymphocytes and monocytes. (6.96 vs. 8.83 p-value 0.004; 22.1 vs. 29.2, $p = 0.023$; respectively), as well as $CD3^-CD19^+$ B cells (12.9 vs. 22.9, $p = 0.049$). However, $CD3^+CD4^+$ T cells (680.00 (471.00–940.13) vs. 77.51 (70.2–431.49)/μl, $p = 0.009$) was shown at a markedly higher level in COVID-19 asthmatic patients, Table 1.

The percent of deaths in hospital throughout the observation period for the mortality was 5.6% [1/18] for asthma patients and 2% [2/101] for non-asthmatic patients (p = 0.511; Table 1). When it comes to secondary outcomes, asthma patients are statistically more likely to be admitted to the ICU (16.6% [3/18] vs. 1% [1/97]; p = 0.020) than non-asthma patients (Table 1 and Figure 1). On admission, corona virus disease asthmatic patients were divided into mild and severe groups by 66.6% [12/18] and 33.4% [6/18], compared to 65.3% and 34.6 in COVID-19 patients without asthma (p = 0.601).

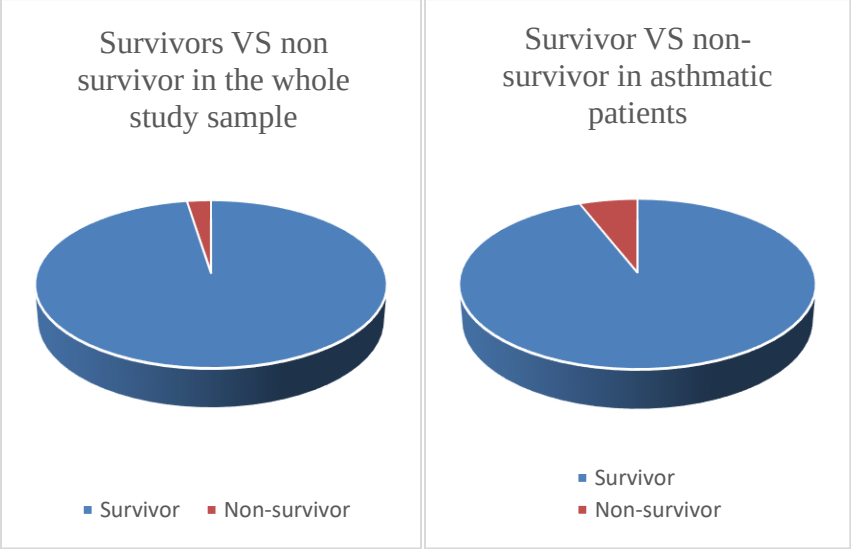

Figure 1 Clinical results and admission to ICU of corona virus disease asthmatic and non-asthmatic patients.

Table 1 COVID-19 patients with and without asthma: demographics, clinical characteristics and outcome.

Indicators	Total		Asthmatic		Non-asthmatic	P-Value
N = 119		N = 18		N = 101		
Characteristics#	N = 119		N = 18		N = 101	
Age(years)	56.61 ± 15.52		54.32 ± 15.17		57.1 ± 13.49	0.501a
Sex (N = 121)						0.711c
Male	39 (32.7%)		7 (38.8%)		32 (31.6%)	
Female	80 (67.2%)		11 (61.2%)		69 (68.3%)	
Early symptoms N = 97	97		18		79	
Fever	75 (77.3%)		13 (72.2%)		59 (74.6%)	0.955
Cough	61 (62.8%)		8 (44.4%)		53 (67%)	0.245

Dyspnea	27 (27.8%)		2 (11.1%)		24 (30%)	0.145
Chest tightness	11 (11.3%)		2 (11.1%)		9 (11%)	
Expectoration	35 (36%)		1 (5.5%)		34 (43%)	0.004*
Diarrhea	14 (14.4%)		3 (16.6%)		11 (13.9%)	0.845
Myalgia	12 (12.3%)		1 (5.5%)		11 (13.9%)	0.881
Fatigue	11 (11.3%)		1 (5.5%)		11 (13.9%)	0.789
Chills	10(10.3%)		1 (5.5%)		12 (13.9%)	0.788
Anorexia	6 (6.1%)		1 (5.5%)		7 (8.8%)	0.321
Treatment						
ICU admission N = 115	4 (3.3%).	N = 18	3 (16.6%)	N = 97	1 (1%)	0.020*,e
Hospital stay duration (N = 119)d	13.00 (7.00–21.00)	N = 18	16.00 (8.00–28.00)	N = 101	13.00 (7.00–20.50)	0.198b
Invasive ventilation (N = 119)	4 (3.3%).	N = 18	1 (5.5%)	N = 101	3 (2.9%)	0.206e
Non-invasive ventilation (N = 119)	9 (7.5%)	N = 18	1 (5.5%)	N = 101	8 (7.9%)	1.000e
High-flow oxygen therapy (N = 119)	79 (66.3%)	N = 18	15 (83.3%)	N = 101	64 (63.3%)	0.298c
High-flow oxygen therapy days (N = 78)d	10.00 (4.00–20.00)	N = 18	13.00 (7.00–26.00)	N = 60	10.00 (4.00–20.00)	0.321b
Glucocorticoid therapy (N = 119)	21 (17.6%)	N = 18	4 (22.2%)	N = 101	17 (16.8%)	0.816d
The glucocorticoid therapy in days (N = 21)d	6.00 (3.50–10.50)	N = 4	10.00 (4.00–11.00)	N = 17	6.00 (3.00–8.00)	0.690b
Severity of Admission	N = 119		N = 18		N = 101	0.601c
Mild	78 (65.5%)		12 (66.6%)		66 (65.3%)	
Severe	41 (34.5%)		6 (33.4%)		35 (34.6%)	
Outcome	N = 119		N = 18		N = 101	0.511e
Survivor	116 (97.5%)		17 (94.4%)		99 (98%)	
Non-survivor.	3 (2.6%)		1 (5.6%)		2 (2%)	

Abbreviation: SD, standard deviation; IQR, Interquartile range, ICU: Intensive Care Unit
[a]indicates Student's *t*-test.
[b]indicates Mann–Whitney U test without parameters.
[c]indicates Pearson χ^2 test.
[d]indicates Using Yates' continuity correction with the Pearson 2 test.
[e]indicates Fisher's test
*Indicated significant p-value < 0.05.
[f]indicatesFactors adjusted in matching of propensity score.

Table 2 asthmatic and non-asthmatic COVID-19 individuals' investigations

Indicators	Total		Patients with Asthma		Non-asthmtic patients	P-Value
	N = 119		N = 18		N = 101	
Laboratory findings						
Biomarkers and Inflammatory cytokines						
IL-6 (N = 108), pg/ml	1.61 (1.49–2.51)	N = 16	2.35 (1.59–3.66)	N = 92	1.62 (1.48–2.32)	0.039*,b
IL-8 (N = 109), pg/ml	7.62 (4.9–11.89)	N = 15	10.98 (8.1–18.88)	N = 94	6.48 (4.95–10.73)	0.038*,b
Procalcitonin (N = 105), ng/ml	0.02 (0.01–0.04)	N = 15	0.04 (0.02–0.09)	N = 90	0.02 (0.01–0.04)	0.035*,b
Subsets of Immune cell						

Lymphocytes (N = 119), ×109/l	1.51 (1.09–1.92)	N = 18	1.31 (0.89–2.1)	N = 101	1.51 (1.06–1.90)	0.411b
Lymphocytes % (N = 119)	25.96 ± 12.43	N = 18	22.70 ± 12.72	N = 101	27.09 ± 11.92	0.02*,a
CD3 + CD4+ T lymphocytes (N = 24), /µl	388 (70–652)	N = 6	680.00 (471.00–940.13)	N = 18	77.51 (70.2–431.49)	0.009*,b
CD3-CD19+ B lymphocytes (N = 24) /µl	163 (129–209)	N = 6	162 (149–217)	N = 18	159 (131–209)	0.750b
CD3 additional to CD19- T lymphocytes (N = 24) /µl	1110.60 ± 490.01	N = 6	1265.52 ± 520.65	N = 18	1075.78 ± 488.1	0.410a
CD3 additional to CD8+ T lymphocytes (N = 24) /µl	390.71 ± 220.55	N = 6	495 ± 261.89	N = 18	358.85 ± 201.19	0.311a
LDH (N = 109), U/L	211.47 (180.36–251.81)	N = 18	252 (210–281)	N = 91	215 (185–248)	0.036*,b
hs-cTnI (N = 119) pg/ml	1.29 (0.65–3.62)	N = 18	5.4 (1.2–11)	N = 101	1.19 (0.59–2.49)	0.006*,b
Platelet, # (N = 119), ×10^9/l	225 (181–262)	N = 18	233 (181–285)	N = 101	232 (181–265)	0.785b
D-dimer (N = 117) ug/ml	0.41 (0.25–0.90)	N = 17	0.81 (0.40–1.96)	N = 100	0.42 (0.35–0.74)	0.032*,b
Blood routine						
Leukocytes (N = 119) ×10^9/l	5.31 (4.54–8.01)	N = 18	7.1 (5.2–9.5)	N = 101	5.8 (4.8–7.9)	0.032*,b
Neutrophils (N = 119) ×10^9/l	3.31 (2.62–5.01)	N = 18	4.81 (3.32–6.91)	N = 101	3.28 (2.52–4.65)	0.015*,b
Monocytes (N = 119) ×10^9/l	0.51 (0.45–0.65)	N = 18	0.55 (0.32–0.82)	N = 101	0.54 (0.45–0.65)	0.915b

Abbreviations: IL-8, Interleukin 8; IL-6, Interleukin 6; CD, Cluster differentiation; LDH, Lactic dehydrogenase; SD, standard deviation; IQR, Interquartile range; hs-cTnI, High-sensitivity troponin I

Continuous variables were labeled as mean or median (IQR) (SD). For skewedly distributed data, the Mann-Whitney U non-parameter test was used to obtain p values; for normally distributed data, the Student's t-test was applied.

[a]indicate Student's *t*-test.

[b] indicate Mann–Whitney test

*indicate *p- value* < 0.05.

Table 3 vital signs mean, SD and P value for asthmatic and non-asthmatic patients

	Total N= 119	Asthma N=18	Non-asthma N=101	P value
HR bpm	87 (79-97)	83.00(77.00-102.00)	84.00(79.00-95.00)	0.961[b]
RR bpm	19 (19-21)	20.00(18.00-23.50)	18.00(19.00-20.25)	0.657[b]
Temperature	36.6 (36.3-36.8)	35.50(35.20-36.30)	35.50(35.20-35.70)	0.593[b]
MAP mmhg	98.84 ±12.74	94.70±10.31	97.18±11.96	0.370[a]
HR: heart rate, Respiratory rate, T:, mean arterial pressure				

4. DISCUSSION

COVID-19 asthmatic patients were more likely to be admitted to the ICU than those without the condition through our retrospective cohort analysis. Less expectoration was observed as well as increased levels of leukocytes, IL-8, IL-6, PCT, neutrophils, CD4+ T cells, LDH, D-dimer and hs-cTnI. These findings revealed that the inflammatory storm was more worsened and the multiorgan damage were more severe.

Expectoration is a frequent symptom in COVID-19 patients (huang et al., 2020), however in our investigation, COVID-19 patients without asthma did not exhibit expectoration. During the investigation, it was discovered that the rabbit's serum with bronchial asthma caused ciliary dyskinesia (Wilson & Fudenberg, 1977). Asthma-related inflammatory reactions can increase respiratory secretions and thicken sputum, both of which can reduce expectoration. Corona virus disease patients who have asthma tend to have a lot of the intensified inflammatory storm. T cells, especially T helper 2 cells in atopic asthma, have an important role in asthma, which is supported by a wealth of research (Amin, 2016). The model of mouse in asthma infection displayed excessive inflammation and increased replication of virus in the fluid of bronchoalveolar lavage if compared to non-asthma group (Okada et al., 2009). Additional researcheswere required to test the hypothesis that corona virus disease patients with asthma who have elevated inflammatory biomarkers and blood cytokines may share comparable pathways.

D-dimer, which is produced during the production and cross-linked fibrin lysis, may serve as a marker for the onset of fibrinolysis. Infection with SARS-Cov-2 can result in systemic responses of pro-inflammatory cytokine, which can lead to endothelial cell dysfunction and then excessive thrombin production, which can promote fibrinolysis and activate platelets (Connors &Levy, 2020). Asthmatic corona virus patients with may have an intensified inflammatory storm that worsens fibrinolysis and raises D-dimer.

Notably, it has been found that viral infection may make asthma patients' conditions worse Up to 30% of asthmatics who died from or were admitted with pH1N1 in California suffered negative clinical outcomes (Mortensen et al., 2009). In addition, a recent study indicated that asthmatic COVID-19 patients have a prolonged incubation period (Mahdavinia et al., 2020), which raises the possibility that asthmatic patients may require additional follow up and care to prevent complications. Leukocyte, neutrophil, and lymphocyte counts were all found to be relatedtobad outcomes in COVID-19 patients (Wei et al., 2020), with elevations in LDH and hs-cTnL indicating, respectively, more severe hepatic and heart damage.

Additionally, COVID-19 asthmatic patients showed greater rates of admission to ICU and more significant inflammatory storms. All of them together give evidence that the asthma comorbidity may exacerbate COVID-19, highlighting the need of monitoring and preventative therapy of heart and liver function. Asthma prevalence varies by country, but is generally higher in industrialized than in undeveloped nations (Global Disease Burden, 2015). While previous research has demonstrated antiviral primary immune responses impaired by corticosteroids and that the use of ICS causes a delay in the clearance of the virus (Southworth et al., 2020), this could worsen COVID-19 infection and result in a bad prognosis. Additionally, a purely observational approach or a non-matched comparison may introduce a number of biases and obfuscate how asthma affects COVID-19. However, the thorough comparison of laboratory parameters in our investigation with adjustments for potential confounding variables might more clearly show this problem.

Limitation

First off, the study sample is small that there is a chance of some false-negative rates and not enough statistical power to detect modest changes. Due to the small sample sizes, we are unable to analyze the risk factors for corona virus diseaseasthmatic patients using the logistic regression. 2nd, because of the nature of the retrospective research, it is unable to gather specific biological markers for asthma and make assumptions about the missing data. 3rd, not all asthmatic patients were included in our study due to a lack of electronic medical records, which could have led to selection bias and reduced samples representativeness. Future research will be required to address these problems.

5. CONCLUSION

We believe that this study is the first to carefully profile the most specific clinical traits of COVID-19 asthma patients, indicating that these individuals may have more aggravated inflammatory reactions and numerous organ impairments. In this situation, more stringent monitoring and supportive care are needed.

Ethical approval

Ethical approval was obtained from Saudi Arabia MOH under IRB number H1RI-25-Oct22-02 we also obtained approval from KSMC authorities.

Author's contribution

Qais zaid Alhamdan: Participated in all steps of the study, starting from proposal writing ending by final editing for submission
Sultan Hudaib Aljaid: Participated in discussion writing and literature collection
Seham Yahya Alzahrani, Abdulrahim Yousef Alomran and Abeer Ishq Alosaimi: Participated in proposal writing, discussion writing and literature collection
Deemah Adnan Alafaliq: Participated in writing introduction, proposal writing and discussion
Fatima Ali Alghanem: Participated in writing results, discussion and introduction
Heba Essam Fahmy: Participated in writing method, introduction and discussion
Khulood Abdullah Bayazeed, Kumail Abdulmonem M Albahrani, Malak Husain Al Ramadhan, Mohammed Ali Radhi Alburi and Zahra Abdullah Ali Al Musa: Participated in writing method, introduction and discussion additional to setting reference in appropriate journal style.
Zainab Ahmed Adnan Alawami & Zainab Ahmed Ali Albetiyan: Participated in writing method, introduction and results additional to setting reference in appropriate journal style.

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Conflict of interest

The authors declare that there is no conflict of interests.

Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

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