INTRODUCTION
Viral respiratory infections are an important cause of increased pulmonary symptoms in children and adults with pre-existing asthma. The prevalence and severity of viral exacerbations vary by patient age and season. Viral infection is responsible for around three-quarters of asthma exacerbations in children and prevalent respiratory pathogens. Human rhinovirus (HRV) primarily affects the upper respiratory tract, causing common colds. The majority of persons with HRV infections exhibit no or mild symptoms, as HRV typically causes a short self-limiting illness in the majority of persons with HRVs infection exhibit no or mild symptoms, as HRV typically causes a short self-limiting illness in immunocompetent hosts. However, HRV infections can have serious consequences in asthmatic immunocompromised and elderly patients and have also been linked to asthma as well as chronic obstructive pulmonary disease (COPD) exacerbations, wheezing, and pneumonia. As a result, strategies enabling the management and control of viral-induced events are a priority for preventing disease exacerbations.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that leads to coronavirus disease 2019 (COVID-19) is spreading widely among humans all over the globe. The symptoms of COVID-19 can vary from mild symptoms to severe pneumonia requiring mechanical ventilation, and the clinical characteristics of HRV infection might be similar to those of COVID-19. COVID-19 may be more severe in patients with chronic lung diseases, such as asthma. Biological factors may influence an asthmatic patient's susceptibility to SARS-COV-2 or the severity of COVID-19.

In many countries, including the United States and Canada, asthma hospitalizations during viral infections, particularly with HRV, are the main cause of increased asthma hospitalization rates that are consistently found in late summer and early fall. These findings underscore the crucial role of viral infection in respiratory disease morbidity and mortality. Patients with asthma were at a higher risk of hospitalization and respiratory morbidity. During the 2009 H1N1 influenza pandemic, children with asthma were at an elevated risk of ICU stays and pneumonia.

A recent study in Australia and South-eastern Wisconsin have demonstrated that HRV is the highest frequent SARS-CoV-2 co-infection, representing 63.2% and 41.51%, respectively. In Turkey, HRV was reported in 14.2% and 10.0% of the COVID-19 cases in men and women, respectively. However, a study performed in Brazil reported a relatively normal frequency of HRV detection from March to December 2020.

Keywords: Asthma exacerbation; COVID-19; Rhinovirus; Co-infection
The susceptibility to asthma exacerbations were linked with asthma severity and co-morbidities in a recent study based in Jordan. However, no regional studies were performed to examine the role of HRV and COVID-19 in asthma exacerbations. Understanding these principles is critical for public health practice in terms of reducing seasonal respiratory virus outbreaks and informing response to potential respiratory virus pandemics.

We can learn more about the pathophysiology and clinical manifestations of COVID-19 and polymicrobial infection associated with COVID-19 by examining the link between COVID-19 and asthma and by looking at HRV co-infections in SARS-CoV-2 patients. The present research is therefore aimed, first, to determine the prevalence of HRV during and 14-days following asthma exacerbation in COVID-19 patients to specify if any may be implicated in asthma exacerbations. Second, to investigate the prevalence of acute asthma exacerbation before and during the COVID-19 pandemic on a matched basis and examine whether hand washing, face masks, and social/physical distancing during COVID-19 decreased the prevalence of asthma exacerbations in Jordanian patients.

**METHODS**

**Study design and participants**

This cohort study, a branch of a prospective observational project, took place over an 8-month period from March 10, 2021, to November 15, 2021. Based in Jordan, the participants in this study were with suspected COVID-19 aged 18 years and above with a history of breathing problems characterized as asthma (excluding severe persistent asthma) at the time of informed consent. Having more than 12% reversibility in FEV1 (forced expiratory volume in one second) and more than 200 ml increase in FEV1 following the administration of salbutamol (200 μg) as documented in the medical report was the used criteria to confirm the presence of asthma. Exclusion criteria included those under the age of 18 and those who had any other pulmonary disease, like COPD or cystic fibrosis. The study participants were gathered from a respiratory consultant clinic or were recommended by primary care workers.

The approval of the study was sought and gained from the Research Ethics Board of Applied Science Private University (ASU), Amman in Jordan (2021-PHA-35), in accordance with the Research Ethics and Governance Policies and Procedures at the Al-Rayhan Medical Center (2021-IRB-9-1). Informed consent was obtained from every participant.

**Data collection**

The case report form consisted of demographic and clinical variables such as gender, age, number of years since diagnosis of asthma, co-morbidity, previously inhaled corticosteroid (ICS) uses and other asthma medications, and asthma severity. The frequency of exacerbation, unscheduled physician visits, emergency room (ER)/hospitalization visits, treatment for exacerbation, hospital and intensive care unit (ICU) admission during three years (2019-2021) were reported. The clinical variables also include presenting complaints (for example, rhinorrhea, wheezing, cough and fever). Additionally, the extent of the application of precaution measures during the COVID-19 pandemic such as face masks, hand washing, and social or physical distancing were reported. The study included the proportion of patients who received the COVID-19 vaccine. Data security was maintained by encrypting data before transmission with the only date and subject ID as identifiers.

Acute asthma exacerbation is an episode of deteriorating asthma symptoms and lung function in patients with a documented asthma diagnosis, requiring a change in treatment. This exacerbation occurs as a result of a viral respiratory infection, noncompliance with controller medication, irritant or allergen exposure, or other triggers. Asthma severity was assessed using the Global Initiative for Asthma (GINA) standards based on the frequency of symptoms and controller treatments employed categorized as intermittent, mild persistent, moderate persistent, or severe persistent asthma.

**Clinical samples and detection of SARS-CoV-2 and HRV**

During the first visit, the health care provider requested SARS-CoV-2 testing for those with suspected COVID-19. After 14 days, another nasopharyngeal swab was taken from those with confirmed COVID-19. The samples were processed by a research nurse. The samples were immediately transferred to the Regional Laboratory, in Amman, Jordan on dry ice and tested for SARS-CoV-2 according to a previous study. The fully automated total nucleic acid extraction was performed by BIOBASE Kit from 200-μl samples using the magnetic beads method (Biobase Biodustry (Shandong) co. ltd). Following extraction, the 100-μl eluted nucleic acid samples were used for SARS-CoV-2 detection. Then, the remaining volume of samples were transferred to 1.5-ml conical tubes and deeply frozen at -80°C for HRV retrospective detection at the end of the study.

SARS-CoV-2 RT-qPCR assay was performed in the TIANLONG: Real-Time PCR System with 48-well block equipment using LiliF™ COVID-19 Multi Real-time RT-PCR Kit depending on the CDC protocol. A SARS-CoV2 assay result was registered positive if the ribonuclease P (RNP) and either the N1 or N2 gene were identified, and negative if only the RNP gene was identified. Samples were tested for RNP, a gene that maintains essential cellular function, to identify PCR inhibition and evaluate the quality of the samples. HRV detection was performed according to a recent publication.

The absolute quantification / second derivative maximum strategy was used to analyze the samples. A positive result was registered for Cç values less than or equal to 40 cycles, while a negative result was registered in the absence of a Cç value and for Cç values were greater than 40 cycles. A further criterion was a positive RNP value with Cç ≤ 37 cycles. In the case of RNP, Cç values greater than 37 cycles, the sample had been frozen, thawed, re-extracted, and tested again. Samples having RNP Cç values greater than 37 cycles for the second test had eliminated from the analysis because they were either poor quality or include a component that inhibits the PCR.
Al-Dulaimi A, Alsayed AR, Maqbali MA, Alzihlif M. Investigating the human rhinovirus co-infection in patients with asthma exacerbations and COVID-19. Pharmacy Practice 2022 Apr-Jun;20(2):2665. https://doi.org/10.18549/PharmPract.2022.2.2665

Statistical analysis
Data were analyzed using SPSS Statistics v.25 (IBM Corporation, New York, NY, USA). All data are presented as numbers (%) unless otherwise noted. The Shapiro-Wilk test for normality was used. The statistically significant p value was considered if it is less than 0.05.

Comparison of proportions of positive samples for the SARS-CoV-2 and HRV between the exacerbation (recruitment) and 14-days follow-up states was conducted with the McNemar’s test for related samples (the chi-squared distribution) with continuity correction.31 A Friedman test was applied to uncover the differences in the number of asthma exacerbations during 2019, 2020, and 2021 years. Pairwise comparisons were conducted with a Bonferroni correction for multiple comparisons.

Viral Ct values were assessed by ANCOVA and post-hoc analysis with a Bonferroni adjustment to determine any significant difference by viral type.

RESULTS
Study population and their clinical characteristics
Of the 223 individuals with suspected COVID-19, 212 (95.1%) continued participation in the study and provided nasopharyngeal swabs for SARS-CoV-2 detection. Overall, 175 (82.5%) positive cases of SARS-CoV-2 were reported, among them, 47 (26.9%) have already diagnosed with asthma. The majority of the included asthmatic patients (n = 29, 61.7%) showed positivity only to SARS-CoV-2. Interestingly, 38.3% (n = 18) patients were infected with both SARS-CoV-2 and HRV. Two weeks following the initial real-time qPCR, only 3 samples (from 3 participants) remained positive to SARS-CoV-2 alone, one sample was positive to both SARS-CoV-2 and HRV, and three samples with HRV detection alone (1/3 was HRV-positive at recruitment and 2/3 were HRV-negative becoming positive after two weeks) (Figure 1).

Table 1 represents the demographics and clinical data for the study participants. Among those 47 asthmatic patients, 17 (36.2%) were male and 30 (63.8%) were females. The mean age (SD) was 42.53 (±16.02) years. Overall, 8 (17.0%) had comorbidity; 4 (8.5%) diabetes mellitus and 4 (8.5%) cardiovascular disease. Around three quarters were non-smokers (76.6%). More than one-half of the included asthmatic patients were second-hand smokers (66.0%). The majority (72.3%) of participants did not take two doses of the COVID-19 vaccine at the time of recruitment. Family history of lung diseases (asthma, COPD), allergic rhinitis and eczema, was 15 (31.9%), 14 (29.8%), and 10 (21.3%), respectively. The ICS/LABA was the most frequent used medications (n = 43, 91.5%) followed by LTRA (n = 32, 68.1%). During the study period for every patient (day 0 until day 14), supplemental oxygen was used for 18 patients (38.3%), 10/18 (55.6%) were HRV-positive (p = 0.055) (Table 1). None of the study participants required hospitalization during the 14 days follow-up.

The most frequently reported symptoms at the initial visit were shortness of breath and cough, 40 (85.1%) and 38 (80.9%), respectively. Although sputum production does not always accompany asthma exacerbation, the frequency of sputum production was high (n = 31, 66.0%).

Suspected COVID-19 cases
N = 223
Follow-up loss, n = 11

Positive SARS-CoV-2
N = 175/212

Non-asthmatic cases, n = 128
Asthmatic patients, n = 47

SARS-CoV-2 alone
n = 29 (61.7%)
SARS-CoV-2 and HRV
n = 18 (38.3%)

SARS-CoV-2 alone
n = 3
SARS-CoV-2 and HRV
n = 1
HRV alone
n = 1 (old) and 2 (new)

Follow-up after 14 days
Figure 1. Flow chart of the study participants.

Figure 2. History of asthma exacerbation in the last three years among the study participants.
Figure 2 shows the difference in the number of asthma exacerbations, ER visits, hospital and ICU admissions among the three years 2019, 2020, and 2021. To investigate if there were differences in the number of asthma exacerbations during 2019, 2020, 2021 years, the Friedman test was used. Pairwise comparisons were applied with a Bonferroni correction for multiple comparisons. The number of asthma exacerbations during the three years was significantly different, $\chi^2(2) = 7.987$, $p = 0.018$. Post hoc analysis uncovered a significant difference from 2020 ($\text{Median} = 1.00$) to 2021 ($\text{Median} = 2.00$) ($p = 0.035$) (Figure 3). The mean number of asthma exacerbations was decreased from 2.19 in 2019 to 1.74 in 2020, however, this difference was statistically insignificant. Insignificant differences were observed in the ER visit, hospital, and ICU admissions among the three years.

It is apparent that the face mask, hand washing, and social and physical distancing were not always implemented. The number of patients that wears face mask was 21 (44.7%). As well as, implementation of hand washing and social and physical distancing were reported in 17 (36.2%) and 22 (46.8%), respectively of the included asthmatic patients (Figure 4).

SARS-CoV-2 and HRV detection

Forty-seven patients were investigated, on a matched basis, to compare the proportion of SARS-CoV-2 and HRV detection between the initial presentation (exacerbation) states and after 14 days.

Out of the 47 patients during the exacerbations, a total of 29 patients were positive only to SARS-CoV-2 (CoV-2-group) (61.7%) and three samples (6.4%) remained positive for SARS-CoV-2 at the follow-up (Table 3). The related samples McNemar’s test was performed to conclude whether a difference exists in the proportion of SARS-CoV-2 positivity at the initial presentation (exacerbation) states and after 14 days on a matched basis. The proportion of only SARS-CoV-2-positive (CoV-2-group) reduced at the follow-up to 6.4% of patients from the initial state value of 61.7%, a statistically significant difference, $\chi^2(1) = 15.059$, $p < 0.005$ (Table 3).

On recruitment, 38.3% ($n = 18$) of the patients were HRV-positive. Two weeks following the exacerbation, the number of HRV detection had decreased to 4/47 (8.5%) patients. This change was a consequence of 16/18 HRV-positive patients at the recruitment state becoming HRV-negative in 14 days.

### Table 1. Demographics and clinical data for the study participants (N=47)

| Variables                                              | N (%) or M (±SD)   |
|--------------------------------------------------------|--------------------|
| Age                                                    | 42.53 (±16.02)     |
| Years since diagnosis of asthma                        | 19.52 (±12.19)     |
| Gender                                                 |                    |
| Male                                                    | 17 (36.2%)         |
| Female                                                  | 30 (63.8%)         |
| Smoking                                                 |                    |
| Current smoker                                          | 8 (17.0%)          |
| Previous smoking history                                | 3 (6.4%)           |
| Non-smoker                                              | 36 (76.6%)         |
| Second-hand smoking                                     | 31 (66.0%)         |
| COVID-19 vaccine                                        |                    |
| None                                                    | 34 (72.3%)         |
| One dose                                                | 0 (0%)             |
| Two doses                                               | 13 (27.7%)         |
| Family history of lung diseases (asthma, COPD)          | 15 (31.9%)         |
| Family history of allergic rhinitis                     | 14 (29.8%)         |
| Family history of eczema                                | 10 (21.3%)         |
| Comorbidities                                           |                    |
| Diabetes mellitus                                       | 4 (8.5%)           |
| Allergic rhinitis                                       | 0 (0%)             |
| Eczema                                                  | 0 (0%)             |
| Immunocompromised                                       | 0 (0%)             |
| Cardiovascular disease                                  | 4 (8.5%)           |
| Maintenance medication                                  |                    |
| ICS                                                     | 23 (48.9%)         |
| ICS/LABA                                                | 43 (91.5%)         |
| SABA                                                    | 21 (44.7%)         |
| LTRA                                                    | 32 (68.1%)         |
| LAMA                                                    | 1 (2.1%)           |
| OCS                                                     | 6 (12.8%)          |
| Theophylline                                            | 0 (0%)             |
| Supplemental oxygen (0-14 days)                         | 18 (38.3%)         |
|                                                       | 10/18 (0.56) HRV-positive ($p = 0.055$) |
| Magnesium sulfate                                       | 0 (0%)             |

### Table 2. Presented symptoms at the time of initial visit

| Symptoms                              | N (%) |
|---------------------------------------|-------|
| Shortness of breath                   | 40 (85.1%) |
| Cough                                 | 38 (80.9%) |
| Wheezing                              | 22 (46.8%) |
| Chest tightness                       | 22 (46.8%) |
| Sputum production                     | 31 (66.0%) |
| Runny nose                            | 20 (42.6%) |
| Fever                                 | 37 (78.7%) |
| Headache                              | 30 (63.8%) |
| Myalgia                               | 20 (42.6%) |
| Diarrhea                              | 28 (59.6%) |
| Loss of smell and taste               | 36 (76.6%) |

Abbreviations: Inhaled corticosteroids (ICS), Inhaled corticosteroids /Long-acting beta-agonist (ICS) /LABA, short-acting beta-agonist (SABA), Leukotriene receptor antagonists (LTRA), Long-acting muscarinic antagonists (LAMA), Oral corticosteroids (OCS)
following the initial sampling, and two HRV-negative became positive at the follow-up time. The related samples McNemar’s test\textsuperscript{30} with continuity correction\textsuperscript{31} was used to conclude whether a difference exists in the proportion of HRV-positive at the initial presentation (exacerbation) state and after 14 days. The proportion of HRV-positive decreased from the exacerbation state value of 38.3% to 8.5% at the follow-up, a statistically significant difference, $\chi^2(1) = 5.263$, $p = 0.019$ (Table 3).

To better understand the role of the respiratory virus in asthmatic patients, we investigated the difference in the SARS-CoV-2 $C_T$ values, which refer to the viral load, of the SARS-CoV-2-positive samples. To determine if a significant difference exists between the $C_T$ values of SARS-CoV-2 positive specimens “CoV-2-group” with the SARS-CoV-2 $C_T$ values of those specimens positive to both SARS-CoV-2 and HRV “CoV-2-HRV-group”, analysis of covariance (ANCOVA) and post hoc analysis with a Bonferroni adjustment was applied.

The independent variable had two groups; CoV-2-group versus

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Table 3. Proportions of positive samples for the SARS-CoV-2 and HRV between the exacerbation (recruitment) and 14-days follow-up on a matched basis ($N = 47$ patients)

| Groups            | Exacerbation, n (%) | 14 days following the exacerbation, n (%) | $P$ value (using McNemar’s test) |
|-------------------|---------------------|-------------------------------------------|---------------------------------|
| CoV-2-group       | 29 (61.7%)          | 3 (6.4%)                                  | 0.001                           |
| HRV-group         | 0 (0%)              | 3* (6.4%)                                 | < 0.005                         |
| CoV-2-HRV-group   | 18 (38.3%)          | 1 (2.1%)                                  | < 0.005                         |
| None              | 0 (0%)              | 40 (85.1%)                                | -                               |
| Total             | 47 (100%)           | 47 (100%)                                 | -                               |

*1/3 was HRV-positive at recruitment and 2/3 were HRV-negative becoming positive after two weeks.

CoV-2-HRV-group refers to those samples infected with both SARS-CoV-2 and HRV, CoV-2-group refers to samples infected only with SARS-CoV-2, HRV-group refers to sample infected only with HRV.
CoV-2-HRV-group. In the ANCOVA analysis, positive viral tests’ Ct values are the dependent variable, while the RNP assay Ct values, a function of the sample quality, is the covariate. Preliminary assumptions of ANCOVA were tested and no violations were uncovered. The mean Ct values and 95% CI for each group are shown in Table 4 (CoV-2-group versus CoV-2-HRV-group).

Following adjustment for the RNP Ct values, significant difference was observed between the CoV-2- and CoV-2-HRV-groups, with the CoV-2-HRV-group producing (4.69) lower Ct values than the CoV-2-group, F (1, 34) = 28.22, p < 0.005, partial η²= 0.233.

By performing the standard curve of the four concentrations of the standard nucleic acid with five replicates, the mean amplification efficiency (E) of the absolute quantification was 96.37%. The mean (± SD) of the correlation coefficient (r²) was −0.996 (± 0.001).

| Table 4. Descriptive statistics summary of the Ct values of CoV-2-group and CoV-2-HRV-group |
|---------------------------------------------------------------|
| CoV-2-HRV-group (n=18 samples) | CoV-2-group (n=29 samples) |
| Mean (SD) Viral Ct value | 21.48 (4.959) | 25.86 (4.200) |
| 95% CI LB | 19.08 | 24.91 |
| 95% CI UB | 23.88 | 26.8 |
| Minimum value | 14.12 | 16.28 |
| Maximum value | 29.73 | 33.39 |
| Mean (SD) RNP Ct value | 23.91 (2.608) | 23.55 (3.201) |
| 95% CI LB | 22.59 | 22.83 |
| 95% CI UB | 25.23 | 24.27 |
| Minimum value | 20.85 | 20.23 |
| Maximum value | 28.04 | 32.49 |
| ANCOVA adjusted mean Viral Ct value | 21.23 | 25.91 |
| 95% CI LB | 19.65 | 25.16 |
| 95% CI UB | 22.81 | 26.67 |

DISCUSSION

This is the first study, based in Jordan, to investigate the HRV co-infection in COVID-19 asthmatic patients. The main purpose of this study was to investigate the co-infections with HRV among COVID-19 asthmatic patients to determine if any may be implicated in asthma exacerbation and to determine the frequency of asthma exacerbation before and during the COVID-19 pandemic. To better understand the polymicrobial infection associated with COVID-19, we examined HRV co-infection in SARS-CoV-2 individuals. Our study has thoroughly examined the HRV and SARS-CoV-2 roles at asthma exacerbation compared with the stable (14-days following exacerbation) states using nasopharyngeal swab specimens with a particular reference to the Ct values of the SARS-CoV-2.

Evidence from this research displays that HRV and SARS-CoV-2 infections were significantly higher in asthma exacerbation compared with the stable (14-days following exacerbation) states (p < 0.05). These findings suggest that HRV and/or SARS-CoV-2 infections, when presented in this Jordanian patients’ cohort, were potentially cofactors or contributors to the asthma exacerbation. At present, not much is known about how the respiratory virus, particularly HRV and SARS-CoV-2, infection develops and progresses during asthma exacerbation episodes. Despite this knowledge gap, it is clear that asthma progress is a consequence of exacerbations, and HRV and SARS-CoV-2 might be associated with these episodes. The mechanisms that cause some asthma patients to be especially vulnerable to exacerbation episodes are not clear. Collecting more information about the role of the viruses, including HRV and SARS-CoV-2, in asthma exacerbation on a wider scale using molecular methods may aid the development of targeted therapies, potentially reducing the exacerbation severity. This study may suggest the need for effective prevention or therapy for those respiratory viruses. Effective prophylaxis and treatment for the respiratory virus could decrease the length of their infections. Economically, this could decrease the cost of long hospital stays and other healthcare expenses.

The results of the ANCOVA test illustrate that the SARS-CoV-2 Ct values of those samples positive to both SARS-CoV-2 and HRV were smaller than that recorded for the samples positive only to SARS-CoV-2 which shows that HRV might be associated with the greater levels of SARS-CoV-2 shedding than noticed in those samples without HRV. Although the reason for this is unclear and needs further investigation, the results indicate that HRV possibly makes SARS-CoV-2 more able to overcome the immunity in these asthmatic patients. However, this finding has to be confirmed using a large-scale study. Even though it is yet not clear if viral co-infection is associated with more severe COVID-19, this study indicates that detection of HRV with SARS-CoV-2 was associated with a higher tendency to use supplemental oxygen, although this association was not, but close to, statistically significant (p = 0.055).

Since the pandemic outset, there have been conflicting views on patients’ infectiousness, as a positive RT-PCR test cannot determine whether or not a patient is infectious or when the infection began. In the majority of cases, virus load rapidly decreases following symptom onset, and most patients will no longer have SARS-CoV-2 RNA detected in nasopharyngeal swabs after a median of 14-25 days. However, nasopharyngeal swabs and lower respiratory tract specimens from elderly, critically ill or immunocompromised patients can still be positive for SARS-CoV-2 RNA detection several weeks after symptom onset. Overall, this study specimens have low Ct values, indicating a high virus load. The question was raised as to whether this is infectious virus material or only viral genomic material. Thereby, simply detecting the presence of a viral genome is insufficient. Therefore, some scientists believe that Ct values are an imprecise and low reproducible, laboratory-dependent, and ineffective measure. Several studies, that attempted to quantify the relationship between the Ct and the likelihood of culturing live viruses, indicating that the probability of recovering a live virus from specimens with a Ct higher than 34 is low. While RT-
HRV also in Korea. HRV infection was the most frequently detected virus in adult (n=15/20, 76.4%) and co-infection with SARS-CoV-2 was less frequent (n = 26, 21.7%). In Italy, HRV was reported in 130/583 (22.3%). In Turkey, HRV was reported in 14.2% and 10.0% of the COVID-19 cases in men and women, respectively. However, a study performed in Brazil reported a relatively normal frequency of HRV detection from March to December 2020. After the influenza virus, HRV was the most detected virus in Canada.

The reasons underlying these findings are unknown and could be due to a combination of variables. It is likely that stricter controls on the spread of SARS-CoV-2 resulted in significant reductions in HRV transmission as well. However, the role of SARS-CoV-2-mediated viral displacement and interference is unknown. Furthermore, the hypothesis of a rebound in HRV levels following the relaxation of lockdown measures merits additional examination. It is unknown whether the absence of exposure to non-SARS-CoV-2 respiratory viruses throughout the COVID-19 pandemic resulted in bigger epidemics of other respiratory viral infections in Jordan following the relaxation of existing public health restrictions. Understanding these principles is critical for public health practice in terms of reducing seasonal respiratory virus outbreaks and informing response to potential respiratory virus pandemics.

In spring 2020, anti-SARS-CoV-2 measures in Finland temporarily halted the spread of HRV. HRV incidence quickly returned to normal levels following the lifting of the COVID-19 restrictions. These loosened social restrictions prevented respiratory syncytial virus (RSV) and influenza seasons but did not prevent HRV propagation. In Germany, an almost similar pattern of HRV prevalence was observed in its relation with anti-SARS-CoV-2 measures. South Korea’s widespread use of social distance throughout the COVID-19 pandemic slowed the spread of common respiratory virus infections. In 2020, HRV levels in Korea increased significantly compared to 2019 levels and were negatively related with the confirmed COVID-19 cases in 2020. This could be because the virus is resistant to environmental conditions due to its non-enveloped nature, as well as the protracted period of viral shedding from patients.

In this study, based in Jordan, 38.3% of patients were positive for both SARS-CoV-2 and HRV. In accordance with the present finding, a recent study in Australia and South-eastern Wisconsin have demonstrated that HRV is the highest frequent SARS-CoV-2 co-infection, representing 63.2% and 41.51%, respectively. The most common co-infection was HRV also in Korea. HRV infection was the most frequently encountered additional pathogen in 116 SARS-COV-2-positive specimens, according to Kim and co-workers’ study based in the United States. In Spain, HRV was the most common detected virus in adult (n=18/20, 90.0%) and co-infection with COVID-19 (n=15/20, 83.3%). Also, HRV was predominant in children (n=120/157, 76.4%) but co-infection with SARS-CoV-2 was less frequent (n = 26, 21.7%). In Italy, HRV was reported in 130/583 (22.3%). In Turkey, HRV was reported in 14.2% and 10.0% of the COVID-19 cases in men and women, respectively. However, a study performed in Brazil reported a relatively normal frequency of HRV detection from March to December 2020. After the influenza virus, HRV was the most detected virus in Canada.

The reasons underlying these findings are unknown and could be due to a combination of variables. It is likely that stricter controls on the spread of SARS-CoV-2 resulted in significant reductions in HRV transmission as well. However, the role of SARS-CoV-2-mediated viral displacement and interference is unknown. Furthermore, the hypothesis of a rebound in HRV levels following the relaxation of lockdown measures merits additional examination. It is unknown whether the absence of exposure to non-SARS-CoV-2 respiratory viruses throughout the COVID-19 pandemic resulted in bigger epidemics of other respiratory viral infections in Jordan following the relaxation of existing public health restrictions. Understanding these principles is critical for public health practice in terms of reducing seasonal respiratory virus outbreaks and informing response to potential respiratory virus pandemics.
fever may aid in the differentiation of these two illnesses in young and elderly populations, caution should be maintained because fever may be present in other virus-induced asthma exacerbations. Additionally, headache, myalgia, pharyngitis, runny nose, loss of smell and taste, nausea, vomiting, and diarrhoea may help differentiate COVID-19 from asthma. Additionally, travel history, intimate contact with someone infected with COVID-19, and a child’s absence of prior atopic history can aid in the differentiation of asthma exacerbation from COVID-19. COVID-19 testing is indicated for any asthmatic patient experiencing increasing cough or shortness of breath.50

Taken together, the findings of this study, as well as recent research,51 demonstrate significant alterations in the circulation of respiratory pathogens other than SARS-CoV-2, including HRV. The long-term effects of these alterations are unknown, but efforts aimed at mitigating the spread of COVID 19 are predicted to continue to affect many respiratory infections. Understanding current viral circulation enables clinicians to identify the most likely infections that may affect patients, and ongoing surveillance is critical for guiding mitigation methods.

HRV is a collection of genetically heterogeneous non-enveloped, positive-stranded RNA viruses divided into three serotypes: HRV-A, HRV-B and HRV-C.52 It is well established that HRV is highly diverse, with HRV-B infection typically resulting in mild or asymptomatic symptoms, whereas HRV-A or HRV-C infection is typically associated with more severe illness or exacerbation of asthma and hospitalizations.53,54 Therefore, future work will aim to investigate the prevalence of different HRV species and their role in respiratory diseases in Jordan.

With such a large population of asthma patients, it is critical to define the risk of SARS-CoV-2 infection and severity in asthma, which is a major concern during this potentially extended COVID-19 pandemic. A greater knowledge of the link between COVID-19 and asthma may help shed light on the aetiology and clinical characteristics of COVID-19.

CONCLUSION
Our findings indicate that HRV and SARS-CoV-2 were significantly more prevalent in asthma exacerbations than stable asthma. These findings indicate that HRV and/or SARS-CoV-2 infections were potentially cofactors or contributors to the asthma exacerbation in this Jordanian cohort. This is the first study, based in Jordan, to investigate the HRV co-infection in COVID-19 asthmatic patients. HRV could be associated with increasing COVID-19 severity. However, a multi-center research is required.

CONFLICTS OF INTEREST
All Authors declare no conflicts of interest related to this article.

ABBREVIATIONS
COPD  Chronic obstructive pulmonary disease
COVID-19  Coronavirus disease 2019
FEV\textsubscript{1}  Forced expiratory volume in one second
HRV  Human Rhinovirus
SARS-CoV-2  Severe acute respiratory syndrome coronavirus 2

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HIGHLIGHTS
1. The number of asthma exacerbations was higher during 2021 than in 2020 in Jordan.
2. SARS-CoV-2 and HRV were more in asthma exacerbations than in stable states.
3. HRV SARS-CoV-2 and/or HRV infections are cofactors in asthma exacerbation.
4. This is the first study, in Jordan, to examine the HRV and COVID-19 in asthma.
5. HRV could be associated with the more severe form of COVID-19.

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