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# Impact of viral co-infection on clinical outcomes and mortality of COVID-19 patients: a study from Saudi Arabia

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ABSTRACT

**Background:** In COVID-19 patients undetected co-infections may have severe clinical implications associated with prolonged hospitalization, ICU admission, and mortality. Therefore, we aimed to investigate the impact of viral co-infections on the outcomes of hospitalized patients with COVID-19 in a large tertiary Saudi Arabian Hospital.

**Methods:** A total of 178 adult patients with confirmed SARS-CoV-2 who were hospitalized at the Armed Forces Hospital Southern Region (AFHSR), Saudi Arabia, from March 1st to June 30th 2022, were enrolled. Real-time PCR for the detection of viral co-infections was carried out. Cases (SARS-CoV-2 with viral coinfections) and control (SARS-CoV-2 mono-infection) groups were compared.

**Results:** 12/178 (7%) of enrolled COVID-19 patients had viral coinfections. 82/178 (46%) of patients were males. 58% of patients had comorbidities. During the study period, 4/12 (33%) and 21/166 (13%) cases and control patients died, p=0.047, respectively. Duration of hospitalization was the only significant independent factor associated with SARS-CoV-2 coinfections, OR 1.140, 95% CI 1.020-1.274, p=0.021.

**Conclusions:** The findings of this study from a large tertiary Saudi Arabian Center revealed a prevalence of 7% for SARS-CoV-2 viral coinfections. SARS-CoV-2 coinfected patients had a significantly prolonged duration of hospitalization and higher mortality than those with SARS-CoV-2 alone. Future studies are needed

**Key words:** COVID-19; virus; coinfection; outcomes; clinical; mortality; hospitalization; impact.

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## Introduction

Beyond SARS-CoV-2 pathogenesis, the incidence of infections of other respiratory viruses along with COVID-19 has been observed in different studies worldwide [1]. The impact of viral coinfection on COVID-19 patients is not fully understood but pathologically, respiratory viruses can damage the airway epithelium, decrease mucociliary clearance, and trigger immune system disorders [2]. Therefore, in COVID-19 patients undetected co-infections may have severe clinical implications associated with increased hospitalization, varied treatment approaches and mortality [1,3,4]. Earlier studies have shown that common viral co-infections reported in COVID-19 patients include Influenza viruses, respiratory syncytial virus (RSV), and adenovirus [5].

The novelty of SARS-CoV-2 and the complexity of the profound etiology of co-infection highlight the importance of consideration of associated comorbidities. COVID-19 patients with underlying comorbidities such as diabetes mellitus, hypertension, chronic kidney disease, and heart failure have been associated with COVID-19 disease severity [6]. Moreover, comorbidities were linked with increased hospitalization, prolonged stay in the intensive care unit (ICU), and mortality [7].

Studies found contradictory results concerning the impact of coinfection on the outcomes of COVID-19; one study reported that the prevalence of bacterial infection was nearly 7%, and most secondary infections were associated with compromised patients [8]. On the other hand, a recent meta-analysis found that influenza viral coinfection did not significantly increase the risk of in-hospital mortality, while it significantly reduced the risk of critical illness [9]. Moreover, studies of COVID-19 coinfections from Saudi Arabia have shown different results. Alosaimi *et al.* [4] had shown evidence of co-infection in 71% of COVID-19 patients, and viral coinfections were associated with increased ICU admission and higher mortality compared to bacterial coinfections. On the other hand, Alhoufie *et al.* [10] revealed that seropositivity for influenza A and B and parainfluenza-2 occurred only in 4.2% of COVID-19 patients. All coinfection cases were mild and misdiagnosed during the care period in the hospital. Therefore, in the current study, we aimed to investigate clinical characteristics, impact of comorbidities and the outcomes of respiratory virus co-infections in hospitalized people with COVID-19 in a large tertiary Saudi Arabian Hospital.

## Materials and Methods

### Study population

This was a single-center, retrospective case-control study, including a total of 178 adults (≥14 years) patients with confirmed SARS-CoV-2 who were hospitalized at the Armed Forces Hospital Southern Region (AFHSR), Khamis Mushayt, Saudi Arabia, during the late-stage of the pandemic from March 1st to June 30th 2022. Testing for additional respiratory viruses was done using RT-PCR for influenza virus (A or B) and respiratory syncytial virus (RSV), at the discretion of the treating clinician.

Subjects were included in the co-infected group if they had positive test results registered for influenza virus or RSV, and they were labeled as the "cases' group". Patients were included in the SARS-CoV-2 mono-infected group if they had a negative test result registered for influenza virus or RSV, and they were labeled as the "control group". Demographic and clinical data and laboratory results were collected at the time of hospital admission from the patients' medical records.

Comorbidities were collected individually as well as summarized as an overall comorbidity count, with each comorbidity having the same weight. Included comorbidities were chronic cardiac disease, chronic pulmonary disease, chronic kidney disease, chronic liver disease, diabetes mellitus (type 1 or 2), chronic neurological disease, connective tissue/rheumatological disease, malignant neoplasm, dementia, and HIV/AIDS.

Comparison between the cases and control groups was carried out with regard to demographic, clinical, laboratory data, duration of hospitalization, location of care (ICU or non-ICU), and outcomes.

### Real time PCR for detection of SARS-CoV-2 and viral co-infections

The Xpert Xpress CoV-2/Flu/RSV *plus* test is an automated *in vitro* diagnostic test for the simultaneous qualitative detection and differentiation of RNA from SARS-CoV-2, Flu A, Flu B, and RSV (Cepheid, Sunnyvale, CA, USA). The Xpert Xpress CoV-2/Flu/RSV *plus* test is performed on GeneXpert Instrument Systems (Dx and Infinity Systems). The primers and probes in the Xpert Xpress CoV-2/Flu/RSV *plus* test are designed to amplify and detect unique sequences in the following: nucleocapsid (N) and envelope (E) and RNA-dependent RNA polymerase (RdRP) genes of the SARS-CoV-2 virus genome, influenza A matrix (M), influenza A basic polymerase (PB2), influenza A acidic protein (PA), influenza B matrix (M), influenza B nonstructural protein (NS), and the RSV A and RSV B nucleocapsid.

A nasopharyngeal swab specimen is collected and placed into a transport tube containing 3 mL of viral transport medium. The specimen is briefly mixed by rapidly inverting the collection tube 5 times; 300 uL of the sample is transferred to the sample chamber of the Xpert Xpress SARS-CoV-2/Flu/RSV cartridge (Cepheid). The GeneXpert cartridge is loaded onto the GeneXpert Instrument System platform, which performs hands-off, automated sample processing, and real-time RT-PCR for the detection of viral RNA.

### Ethical considerations

Ethical approval was obtained from the institutional review board of the AFHSR (approval no; AFHSRMREC/2022/PULMONOLOGY-INTERNAL MEDICINE/603). The study participants were fully informed about the study procedures and informed consent was obtained from the study participants.

### Statistical analysis

Significance testing for continuous normally distributed variables was done using the paired *t*-test for 2 groups and a one-way ANOVA for viral co-infections, respectively. Significance testing for continuous non-normally distributed values was done using the Mann Whitney-U test for 2 groups and the Kruskal Wallis test for comparing the viral co-infections, respectively.

A multivariable regression analysis was performed to analyze the effect of viral co-infection independent of other variables. The confounders used were age, gender, presence or absence of comorbidities, duration of hospitalization, location of care, laboratory and radiological findings, and the International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC) 4C mortality score. A p of 0.05 or less was considered to indicate statistical significance. Statistical analysis was performed using the Statistical Package for Social Science (SPSS) Software (version 24).

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## Results

### Demographic and clinical characteristics

Our results showed that 12/178 (7%) of enrolled COVID-19 patients had viral coinfections. Out of these, 8(67%), 2(16.5%), and 2(16.5%), had influenza A, influenza B, and RSV, respectively. Eighty-two out of 178 (46%) patients were males. The patients' average age was 65 years, with a range of 15-109 years. There were no significant differences between the cases and control groups with regard to age, gender, vital signs [temperature, respiratory rate (RR), and oxygen saturation ($O_2$ sat)]. Cases had lower values Glasgow Coma Scale (GCS) than control subjects (p=0.036) (Table 1).

### Comorbidities

One hundred and three patients out of 178 (58%) had comorbidities. These comorbidities included diabetes mellitus (72/178, 40%), hypertension (78/178, 44 %), chronic cardiac (73/178, 41%), chronic respiratory (20/178, 11%), chronic renal (38/178, 21%), and chronic neurological (39/178, 22%) diseases, respectively. Ninety-one (161/178) percent of patients had up to 3 morbidities, while 9% (17/178) had 4 to 6 comorbidities. Characteristically, there was neither a significant difference between cases and controls with regard to the presence or absence of comorbidities nor the number of comorbidities. Also, there was no significant difference between cases and controls with regard to any single comorbidity (Table 1).

### Laboratory findings

There were significant differences between the cases and control groups with regard to blood urea nitrogen (BUN), C-reactive protein (CRP), and lactate dehydrogenase (LDH), p=0.036, <0.001, and 0.036, respectively. There were no significant differences between the 2 groups with regard to lymphopenia and D-dimer levels (Table 2).

### Outcomes

There was a significant difference between the cases and control groups with regard to days of hospitalization, 12.09±20.29 days *versus* 6.29±5.13 days, p=0.015, respectively. Sixteen percent (29/178) of enrolled patients needed intensive care unit (ICU) admission, with no significant difference between cases (25%) and controls (16%) with regard to ICU admission, p=0.401, respectively. During the study period, 4/12(33%) and 21/166(13%) cases and control patients died, p=0.047, respectively. Among the cases who died, all of them had influenza A coinfection and 3 out of 4 (75%) were admitted to the ICU. There was no significant difference between the cases and control groups with regard to the ISARIC 4C mortality score, p=0.227 (Table 3).

### Logistic regression analysis

The confounders of age, gender, presence or absence of comorbidities, duration of hospitalization, location of care (ICU versus non-ICU), lymphopenia, LDH, D-dimer, the 4C mortality score, and outcome (survived versus died) were pooled into a multivariable regression analysis to analyze the effect of viral co-infection

**Table 1. Demographic and clinical characteristics of the study groups.**

| Baseline variable | All patients (n=178) | Control group (n=166, 93%) | Cases group (n=12, 7%) | p |
|---|---|---|---|---|
| Age (years) | | | | 0.750 |
| Mean±SD | 65.1±23.31 | 65.6±23.49 | 59.5±21.43 | |
| Median | 69.0 | 69.0 | 69.0 | |
| Range | 15-109 | 15-109 | 31-95 | |
| Gender | | | | 0.140 |
| Females | 96 (54%) | 92 (55%) | 4 (33%) | |
| Males | 82 (46%) | 74 (45%) | 8 (67%) | |
| Temperature (°C) | | | | 0.223 |
| Mean ±SD | 37.2±0.8 | 37.11±0.82 | 36.9 ± 5.3 | |
| Median (IQR) | 37.1 (0.7) | 37.15 (0.7) | 36.8 (0.5) | |
| Respiratory rate (Breathes/minute) | | | | 0.055 |
| <20 | 102 (58%) | 98(59%) | 4(33%) | |
| 20-29 | 63 (35%) | 55(33%) | 8 (67%) | |
| >30 | 13 (7%) | 13(8%) | 0 (0%) | |
| $O_2$ saturation (%) | | | | 0.540 |
| <92% | 110 (62%) | 104 (63%) | 6 (50%) | |
| >92% | 68 (38%) | 62 (37%) | 6 (50%) | |
| GCS | | | | 0.036 |
| <15 | 24 (13%) | 20 (12%) | 4 (33%) | |
| 15 | 154 (87%) | 146 (88%) | 8 (67%) | |
| Comorbidities | | | | 0.973 |
| No | 75 (42%) | 70 (42%) | 5 (42%) | |
| Yes | 103 (58%) | 96 (58%) | 7 (58%) | |
| No. of comorbidities | | | | 0.846 |
| Median (IQR) | 2.0 (3.0) | 2.0 (3.0) | 1.0 (3.0) | |
| No. of comorbidities | | | | 0.883 |
| 0-3 | 161 (91%) | 150 (90%) | 11 (92%) | |
| 4-6 | 17 (9%) | 16 (10%) | 1 (8 %) | |

IQR, interquartile ratio; $O_2$, oxygen; GCS, Glasgow Coma Scale.

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independent of these variables. Duration of hospitalization was the only significant independent factor associated with SARS-CoV-2 coinfections, OR 1.140, 95% CI 1.020-1.274, p=0.021 (Table 4).

## Discussion

In this study, we investigated the presence of viral co-infections in COVID-19 patients and analyzed their clinical characteristics and their impacts on outcomes.

Our results have shown that 7% of enrolled COVID-19 patients had viral coinfections. In their meta-analysis, Musuuza *et al.* [11] found that the rate of viral coinfections was 10%, in which influenza virus and RSV were the typical pathogens. However, in the meta-analysis by Dadashi *et al.* [12] a total of 11 studies (n=3,070 patients) were pooled to identify the prevalence of influenza virus coinfection in COVID-19 patients which was 0.8%. These similarities and differences could be attributed to different population characteristics, different COVID-19 global distributions, and seasonal influenza variations, and methods of viral testing. Earlier in the pandemic, quarantine, social distancing, self-isolation and the wearing of face coverings have reduced transmission of SARS-CoV-2. These countermeasures have also reduced the transmission and associated disease burden of other endemic respiratory viruses, such as influenza and RSV [13,14]. However, as these countermeasures are less stringently implemented (at the time of the current study, 2022), it is plausible we will see an increase in SARS-CoV-2 viral coinfections [4]. This may explain our findings of a 7% prevalence of viral coinfections among our COVID-19 cohorts.

Our data revealed that 84% of COVID-19 viral coinfections were due to influenza A and B. Influenza has been the predominant cause of severe seasonal respiratory viral disease for decades [15]. Risk factors for severe viral pneumonia are similar in SARS-CoV-2 and influenza [12,16]. Whilst RSV mainly causes bronchiolitis in children, it can cause severe viral pneumonia in the elderly and immunocompromised, both influenza virus and SARS-CoV-2 damage the epithelial cells and cause inflammation [17,18]. Thus, the seasonal influenza virus can cause severe disease leading to ICU admission, the need for mechanical ventilation (MV) and even death [4,18]. Despite that 16% of our enrolled patients needed ICU admission, there was no significant difference between cases and controls with regard to ICU admission.

**Table 2. Laboratory findings of the study groups.**

| Baseline variable | All patients (n=178) | Control group (n=166, 93%) | Cases group (n=12, 7%) | p |
|---|---|---|---|---|
| Lymphopenia (x10⁹/L) | 1.08 (1.07) | 1.09 (1.04) | 1.05 (1.36) | 0.599 |
| BUN (mg/dl) | | | | 0.036 |
| <7 | 94 (53%) | 91 (55%) | 3 (25%) | |
| 7-14 | 48 (27%) | 41 (25%) | 7 (58%) | |
| >14 | 36 (20%) | 34 (20%) | 2 (17%) | |
| CRP | | | | <0.001 |
| <50 | 76 (43%) | 76 (46%) | 0 (25%) | |
| 51-99 | 42 (23%) | 33 (20%) | 9 (75%) | |
| >100 | 60 (34%) | 57 (34%) | 3 (25%) | |
| D-dimer (mg/L FEU) | 2.1 (2.68) | 1.94 (2.71) | 4.0 (5.0) | 0.143 |
| LDH (IU/L) | | | | 0.036 |
| 253.0 (106.0) | 255.0 (105.25) | 295.0 (81.0) | | |

BUN, blood urea nitrogen; CRP, C-reactive protein; LDH, lactate dehydrogenase.

**Table 3. Outcomes of the study groups.**

| Variable | All patients (n=178) | Control group (n=166, 93%) | Cases group (n=12, 7%) | p |
|---|---|---|---|---|
| Hospitalization days | 6.78±7.64 | 6.29±5.13 | 12.09±20.29 | 0.015 |
| Location | | | | 0.401 |
| ICU | 29 (16%) | 26 (16%) | 3 (25%) | |
| Non-ICU | 149 (84%) | 140 (84%) | 9 (75 %) | |
| 4C score | | | | 0.227 |
| 0-3 | 65 (36%) | 63 (38%) | 2 (17%) | |
| 4-8 | 35 (20%) | 31 (19%) | 4 (33%) | |
| 9-14 | 64 (36%) | 60 (36%) | 4 (33%) | |
| ≥15 | 14 (8%) | 12 (7%) | 2 (17%) | |
| 4C score | | | | 0.199 |
| <9 | 165 (93%) | 155 (93%) | 10 (83%) | |
| ≥9 | 13 (7%) | 11 (7%) | 2 (17%) | |
| Outcome | | | | 0.047 |
| Survived | 153 (86%) | 145 (87%) | 8 (67%) | |
| Died | 25 (14%) | 21 (13%) | 4 (33%) | |

ICU, intensive care unit; 4C score, International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC) 4C mortality score.

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**Table 4.** Multivariable logistic regression analysis.

| Variable | Odds ratio | 95% CI | p |
|---|---|---|---|
| Age | 0.967 | 0.923-1.013 | 0.152 |
| Gender (male) | 0.720 | 0.129-4.037 | 0.709 |
| Comorbidities | | | |
| No | 1 | - | - |
| Yes | 0.077 | 0.002-3.090 | 0.174 |
| Location | | | |
| Non-ICU | 1 | - | - |
| ICU | 2.795 | 0.235-33.251 | 0.416 |
| Lymphopenia | 1.160 | 0.952-1.414 | 0.142 |
| LDH | 0.999 | 0.999-1.002 | 0.766 |
| D-dimer | 1.086 | 0.991-1.191 | 0.079 |
| Hospitalization days | 1.140 | 1.020-1.274 | 0.021 |
| Outcome | | | |
| Survived | 1 | - | - |
| Died | 0.113 | 0.009-1.391 | 0.089 |
| 4C score | 1.865 | 0.395-7.198 | 0.481 |

ICU, intensive care unit; 4C score, International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC) 4C mortality score.

The novelty of SARS-CoV-2 and the complexity of the profound etiology of viral and bacterial coinfections urged clinicians to consider comorbidities. In their systematic review and meta-analysis of 42 studies and 423,117 patients, Dessie and Zewotir [19] concluded that clinical risk factors for a fatal outcome associated with coronavirus are those chronic comorbidities, complications, and demographic variables including acute kidney injury, COPD, diabetes, hypertension, CVD, cancer, increased D-dimer, male gender, older age, current smoker, and obesity [19]. Despite that 58% of our enrolled patients had at least one comorbidity, we could not find a significant difference between cases and controls with regard to the presence or absence of comorbidities or their number. This could be partially explained by the relatively low number of the study cohort.

Given the fact that some demographic data, laboratory markers, and radiological findings are of crucial importance in patients with COVID-19, Izcovich *et al*. [20] had conducted their systematic review to identify those prognostic factors that may be used in decision-making related to the care of patients infected with COVID-19. They found that 49 variables provide valuable prognostic information on mortality and/or severe disease in patients with COVID-19 infectious disease [20]. In concordance with these data, we observed that patients with SARS-Co-V2 viral coinfections had significantly higher BUN, and LDH, in comparison to those with SARS-Co-V2 alone. Interestingly, the average age of the current study population was 65 years, with some patients aged up to 109 years. Identified prognostic factors can help clinicians and policymakers in tailoring management strategies for patients with COVID-19 and improving their outcomes [4,20].

Our data revealed that patients with SARS-Co-V2 viral coinfections had a significantly prolonged duration of hospitalization and higher mortality compared to those with SARS-Co-V2 alone. One-third of SARS-Co-V2 coinfected with influenza A died during the study period. Our results emphasize the importance of screening of viral coinfections in patients with COVID-19. SARS-Co-V2 coinfected patients are more likely to have severe disease, prolonged hospitalization, utilization of health care resources, ICU admission, and more importantly higher mortality. With this regard, our results are in agreement with previous reports [3,4,11,18]. Drake and colleagues [21] found 138 influenza-co-infected patients, including children, in which a prolonged duration of hospital admission was found, although this was not corrected for the likelihood of being tested. Alosaimi and coworkers [4] identified 30 co-infected patients out of 48 hospitalized (14 ICU) SARS-CoV-2 positive patients and found that influenza co-infection was associated with mortality.

The current study highlights an important notification. During the SARS-CoV-2 pandemic, especially in its late stages, focusing on the detection and management of this novel virus may lead to underreporting of other pathogens (like influenza) that could be the etiological agents for severe lung disease. Taking into consideration the natural life cycles of viruses; although respiratory viral co-infections were uncommon during the first two years of the COVID-19 pandemic, as public health guidance changes and social mixing increases, co-circulation of additional respiratory viruses will also increase leading to more co-infections [3,4,11,18,21,22].

The current study emphasizes the importance of preventive measures to reduce the disease burden associated with these viral coinfections, in particular influenza vaccination. The adoption of more widespread testing will identify patients in whom different therapeutic strategies may be more effective and would facilitate the identification of hospital inpatients at high risk of deterioration and death [3,21,22].

Our study has some strength points. First, data are representative of many patients referred to a large tertiary Saudi Hospital. Second, data were collected from in-patients, where close monitoring and easier follow-up could be implemented [10]. On the other hand, our study has some limitations. First, the inherited limitation of being a retrospective analysis. Second, a single-center experience was encountered. Third, the number of cases is relatively low for the number of controls. Lastly, influenza vaccination history was not clear for most of our patients. Further prospective studies are needed to clarify the SARS-Co-V2 viral coinfections.

## Conclusion

The findings of this study from a large tertiary Saudi Arabian Center revealed a prevalence of 7% for SARS-CoV-2 viral coinfections. SARS-CoV-2 coinfected patients had a significantly prolonged duration of hospitalization and higher mortality than those with SARS-CoV2 alone. Future studies are needed.

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