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ASSOCIATION OF SEVERITY OF COVID-19 WITH CO-INFECTIONS WITH INFLUENZA AND OTHER RESPIRATORY VIRUSES

Clinical Microbiology

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ABSTRACT

Objectives: Co-infections with viral, bacterial, and fungal pathogens have been reported in Corona virus disease 2019 (COVID-19) patients. A new concern is presence of co-infections with other respiratory viruses, which could complicate diagnosis, treatment, and disease outcomes. This study aimed to detect Influenza and other respiratory viruses in COVID-19 patients and assess the association between co-infections and severity of COVID-19. **Materials And Methods:** A nested case-control study was conducted with 760 real-time polymerase chain reaction (RT-PCR) positive COVID-19 patients of all ages and sexes, enrolled over two consecutive years (January-March 2021 and 2022). Nasopharyngeal or oropharyngeal swabs were tested for 13 respiratory viruses using polymerase chain reaction (PCR). Association of co-infection with respiratory viruses and severity of illness was calculated. **Statistical Analysis:** The chi-square test was used to analyze the relationship between respiratory virus positivity and disease severity/mortality. Data analysis was performed using Statistical Package for Social Sciences (SPSS) Version 21.0. **Results:** Co-infections with other respiratory viruses were observed in 87 (11.44%) of the 760 COVID-19 patients. The majority of co-infections were with Influenza A (42, 5.53%), followed by Parainfluenza virus 3 (12, 1.58%) and Rhinovirus (10, 1.32%). No co-infections were observed with Respiratory Syncytial Virus (RSV) A and B, Parainfluenza 2, and Bocavirus. Co-infections were most common in patients aged 60-80 years. Significant association between co-infection and severity of disease was observed in patients having co-infection with Influenza virus. Poor outcome was also associated with advanced age, patients with one or more comorbidities and patients who required Intensive Care Unit (ICU) admission. **Conclusion:** Increased severity, mortality and higher rates of hospitalisation was seen in COVID-19 patients having co-infection with Influenza viruses.

KEYWORDS

COVID-19, co-infections, Influenza, respiratory viruses

INTRODUCTION

Every year, the world observes high morbidity and fatality rates due to the seasonal occurrence of viral respiratory tract infections. Wuhan, China, in December 2019 saw the onset of respiratory illness caused by novel coronavirus, which, within last three years has claimed hundreds of millions of lives and has destabilized the foundation of global healthcare system.[1] The spectrum of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) illness can range from asymptomatic infection to severe pneumonia progressing to acute respiratory distress syndrome and death.[2] The emergence of the novel virus during pandemics may result in under reporting of other infections that may be the etiological agent enhancing the severity of the disease. In fact, 44.3% of patients during Influenza A (H1N1 pdm 09) pandemic had undocumented co-infection with other respiratory viruses.[3] Due to paucity of testing resources in early wave of pandemic and the perception that co-infections were rare, many clinical laboratories opted not to conduct any further tests on SARS-CoV-2 positive cases or only tested for other respiratory pathogens on SARS-CoV-2 negative specimens. This testing algorithm resulted in incomplete understanding of co-infections in corona virus disease 2019 (COVID-19) patients and their contribution to disease severity and outcome. In comparison to a mono-infection, co-infections can be associated with increased duration of treatment, increased rate of ICU admission, increased risk of complications, and mortality.[4,5] Contrarily, some studies suggest that co-infection with other respiratory pathogens does not exacerbate disease severity and outcome.[6] The association of severity of COVID-19 disease with co-morbidities has already been proven in many studies, [7] whereas the clinical role of respiratory virus co-infection in association with disease severity and outcome in COVID-19 patients still remains unclear. This study aimed to test the association of severity of COVID-19 with co-infections with Influenza and other respiratory viruses.

MATERIALS AND METHODS

Study Population-

The study was conducted and cases were enrolled at the Virology Laboratory of Post Graduate Department of Microbiology, King George's Medical University (KGMU) , Lucknow, a tertiary care referral centre where testing of suspected COVID-19 cases was done for district Lucknow and other adjoining districts of Uttar Pradesh, India. A total of 760 COVID-19 positive patients of any age/sex who were willing to give consent for the study were enrolled over a period of two years from January-March in 2021 and January-March 2022 too. Often peak of Influenza is seen during winter in Northern India.[8] Cases were collected during two consecutive flu season to rule out the chances of co-infection being a random event. The study protocol was approved by the Institutional Ethics Committee, KGMU, Lucknow (Reference code: 107th ECM II B-Thesis/P15). At the time of the enrollment, clinical history including patient's signs and symptoms, hospital admission details and oxygen requirement was recorded from the patients or their attendants in a predesigned questionnaire. Cases were classified into mild, moderate and severe categories according to Indian Council Of Medical Research (ICMR) criteria (clinical management protocol COVID-19, version 5).[9] Patients with uncomplicated upper respiratory tract infection, without shortness of breath or hypoxia and managed at home were placed in mild category. Patients with breathlessness, respiratory rate ≥ 24/min, and SpO2 of <94% on room air who were admitted to hospital wards but did not require Intensive Care Unit (ICU) admission were in moderate category and, patients having severe respiratory distress with respiratory rate >30 breaths/min and SpO2 <90%, admitted to ICU or required ventilatory support placed in severe category.

Sample Collection And Molecular Testing-

Nasal swabs and throat swabs in viral transport media collected from COVID-19 suspects for real-time polymerase chain reaction (RT-PCR) were tested for COVID-19 virus. Each COVID-19 positive sample was then tested for nucleic acid of following respiratory viruses; Influenza A (Inf A), Influenza B (Inf B), Parainfluenza (PIV) 1,2,3,4, Respiratory Syncytial Virus (RSV) A and B, Rhinovirus, Human Metapneumovirus (HMPV), Adenovirus, Bocavirus and Measles virus by Realtime/Multiplex polymerase chain reaction (PCR) assay.

Nasal and throat swabs in 200 µL of viral transport media (VTM) were subjected to nucleic acid extraction using commercially available fully automated total nucleic acid extraction kit [(MagMax™

Viral/Pathogen II Nucleic Acid Isolation Kit(REF-A48383)] as per the manufacturer's protocol.

Real time PCR detection for amplification of the respiratory viruses under study was carried out on ABI QuantStudio 7 Flex instrument using TaqMan Probe assay. The primer and probe sequences and cycling conditions used in the study were according to the previously published protocol.[10] Briefly for PCR, a 25 µL PCR reaction mixture was prepared in an eppendorf consisting of 12.5 µL of RT-PCR buffer with 1 µL of RT- enzyme (Invitrogen Superscript™ III Platinum™ One-Step qRT-PCR System), 0.5 µL forward primer (40mM), 0.5 µL reverse primer (40 µM), 0.2 µL probe (10 µM), 5 µL of viral template and 5 µL of nuclease free water. Thermal cycling conditions were: reverse-transcription step at 50 °C for 30 min and 95 °C for 2 min, followed by 45 cycles of PCR amplification at 95 °C for 15 sec and 55 °C for 30 sec. For validity of each RT-PCR run negative control, positive control and extraction control were simultaneously run. To test the ribonucleic acid (RNA) extraction procedure, RNaseP gene segments were amplified as internal control for human nucleic acid gene. A specimen was considered positive for a respiratory virus if a sigmoid curve with a cycle threshold (CT) value of 35 or less was detected.

Statistical Analysis-

All continuous variables (age) were expressed as medians (interquartile ranges [IQRs]), and categorical variables (hospital admission, ICU admission and severity) as numbers (percentages). The chi-square test was used to analyse the association between the two categorical variables (Respiratory virus positivity and severity of disease/mortality). Statistical significance was considered at a p-value of <0.05. All statistical analysis was done using SPSS (Statistical Package for Social Sciences) Version 21.0 statistical Analysis Software.

RESULTS

A total of 760 patients with laboratory-confirmed COVID-19 were tested of which 87 patients (11.45%) were co-infected with one or more respiratory viruses. Majority of co-infections were seen with Influenza A virus (42, 5.53%), followed by PIV 3 (12, 1.58%) and Rhinovirus (10, 1.32%). Multiple co-infections were seen in 3 patients [Adenovirus+ Rhinovirus- 1 (0.13%), PIV 1 + PIV 4- 1 (0.13%), PIV 4 + Adenovirus- 1 (0.13%)]. No co-infection was seen from RSV-A, RSV-B, PIV 2 and Bocavirus. With the exception of co-infection with Parainfluenza 3 virus, which was detected only in the year 2022 in 12 (1.57%) COVID-19 patients, no discernible difference was observed between co-infection rates in the year 2021 and 2022 as shown in [Table 1].

Table-1 Respiratory Virus Positivity In COVID-19 Positive Patients

Respiratory virus co-infection	JAN- MARCH 2021 (N_1= 380)	JAN- MARCH 2022 (N_2= 380)	TOTAL (N= 760)
INFLUENZA A	24 (6.31%)	18 (4.73%)	42 (5.53%)
PIV 3	0	12 (3.15%)	12 (1.58%)
RHINO VIRUS	5 (1.31%)	5 (1.31%)	10 (1.32%)
PIV 4	5 (1.31%)	2 (0.52%)	7 (0.92%)
MEASLES VIRUS	4 (1.05%)	2 (0.52%)	6 (0.79%)
PIV 1	2 (0.52%)	1 (0.26%)	3 (0.39%)
HMPV	2 (0.52%)	0	2 (0.26%)
INFLUENZA B	1 (0.26%)	0	1 (0.13%)
ADENO VIRUS	1 (0.26%)	0	1 (0.13%)
ADENO + RHINO VIRUS	0	1 (0.26%)	1 (0.13%)
PIV 1+ PIV 4	0	1 (0.26%)	1 (0.13%)
PIV 4 + ADENO VIRUS	1 (0.26%)	0	1 (0.13%)
Total	45 (11.84%)	42 (11.05%)	87 (11.44%)

PIV: Parainfluenza virus, HMPV: Human metapneumovirus

The age range of study population was 1-95 years and the Male: Female ratio was 2.49:1. Median age of patients with co-infection was 38 years (range: 7-78 years) and of patients without co-infection was 36 years (range: 1-95 years). The Male: Female ratio of patients with and without co-infection was 3.14:1 and 2.42:1 respectively. Maximum enrollment of patients was observed in age group >25-60 years, hence cases with co-infection were more in these age groups. Among the 760 COVID-19 positive patients, 623 (82%) were mild cases, 38 (5.00%) patients had moderate infections and 99 (13.02%) patients had severe infections. Total 145 (19.08%) patients were hospitalised, of which 99 had severe COVID-19, 38 cases had moderate COVID-19 and eight patients were admitted due to non COVID-19 disease related complaints (Endocrine surgery-2, Ovarian carcinoma-1, Head injury-1, Road traffic accident-1, lower segment caesarean section-2, prolonged history of abdominal pain-1). Total 91 patients (11.97%) required Intensive care unit (ICU) admission. Total 69 cases (9.08%) died and the rest recovered and were discharged.

Severity of disease showed significant association with the presence of co-infection (p-value= 0.011) by chi-square test as shown in [Table 2]. As expected, statistically significant association was also observed between severity of illness and age >60 years (p-value= 0.000), hospital admission (p-value= 0.000), ICU admission (p-value= 0.000) and presence of comorbidities (p-value= 0.000) [Table 2]. Total 110 patients had one or more comorbidities. The prevalence of Diabetes Mellitus (DM) was 5.39% (41/760), hypertension (HTN) 4.47% (34/760), chronic obstructive pulmonary disease (COPD) 1.18% (9/760), chronic kidney disease (CKD) 0.79% (6/760) and malignancy 0.79% (6/760). Presence of multiple comorbidities was observed in 1.18% (9/760) of the study population. Two patients were pregnant who later had lower (uterine) segment Caesarean section (LSCS) and made a full recovery. DM (p-value= 0.000), HTN (p-value=0.000), COPD (p-value=0.001) and malignancy (p-value= 0.000) had a significant association with severity and mortality as shown in [Table 2].

Table-2 Association Of COVID-19 Severity With Age, Hospital And ICU Admission, Presence Of Co-infection, And Presence Of Comorbidities

Variables	Total cases enrolled (N=760)	Cases with severe illness, n(%)	χ^2 Statistic (p-value)
Age Group			
0-1 years	2	0	211.711 **(0.000)***
>1-5 years	6	0	
>5-18 years	63	2 (3.17)	
>18-25 years	111	1 (0.90)	
>25-40 years	248	8 (3.23)	
>40-60 years	240	35 (14.58)	
>60-80 years	85	49 (57.65)	
>80 years	5	4 (80.00)	
Hospital admission	145	99 (68.28)	472.786 **(0.000)***
Presence of co-infection	87	19 (21.84)	6.735 **(0.010)***
Presence of any comorbidity	110	68 (61.82)	270.258 **(0.000)***
Diabetes Mellitus	41	15 (36.59)	39.723 **(0.000)***
Hypertension	34	3 (67.65)	147.903 **(0.000)***
COPD	9	5 (55.56)	23.833 **(0.001)***
Malignancy	6	5 (83.33)	40.396 **(0.000)***
Others	20	20 (100)	

*Significant at p < 0.05. COPD: chronic obstructive pulmonary disease

On analysing association of individual viral co-infection with severity, significant association was seen in patients coinfected with Influenza virus (p-value= 0.040) as shown in [Table 3]. Total case fatality rate was 9.08%, and all these patients were severely ill (either admitted to ICU or on ventilator), and 23% (16/69) critically ill patients who expired had co-infection. Of all the tested viruses, co-infection with Influenza virus (p-value= 0.011) showed positive association with mortality as shown in [Table 3].

Table-3 Respiratory Virus Positivity And Its Association With Severity Of COVID-19 Disease And Mortality In COVID-19 Patients.

VIRUS CO-INFECTIONS	Total (N=760)	Severity (%) χ^2 test (p-value)	Mortality (%) χ^2 test (p-value)
INF VIRUS	43	10 (23.26)	9 (20.93)
		4.210 **(0.040)***	7.755 **(0.011)***
PIV VIRUS	23	3 (13.04)	1 (4.35)
		0.000 (1.000)	0.643 (0.713)
RHINOVIRUS	10	2 (20)	2 (20)
		0.435 (0.627)	1.464 (0.228)

MEASLES	6	2 (33.33)	2 (33.33)
		2.201(0.178)	4.31 (0.096)
HMPV	2	0	0
		0.300(1.000)	0.200 (1.000)
ADENOVIRUS	1	1 (100)	1 (100)
		6.686 (0.130)	10.028 (0.091)
ADENOIRUS+ RHINO VIRUS	1	0	0
		0.150 (1.000)	0.100 (1.000)
PIV 1+ PIV 4	1	0	0
		0.150 (1.000)	0.100 (1.000)
PIV 4 + ADENO VIRUS	1	1 (100)	1 (100)
		6.686 (0.130)	10.028 (0.091)

*Significant at $p < 0.05$. Inf : Influenza, PIV: Parainfluenza, RSV: Respiratory Syncytial Virus, HMPV: Human Metapneumovirus.

We applied chi-square test to determine if patient's age, hospital admission, ICU admission and presence of any comorbidity showed any association with the presence of co-infection. It was observed that all the above mentioned variables, except age, were significantly associated with co-infection in COVID-19 patients as shown in [Table 4]. Of all the comorbidities, only hypertension (p-value= 0.010), and malignancy (p-value= 0.022) showed statistically significant association with presence of co-infection.

Table-4 Association Of Co-infection With Age, Hospital And ICU Admission, And Presence Of Comorbidities

Variables	Total (N=760)	Presence Of Co-infections	χ^2 statistic (p-value)
Age Group			
0-1 years	2	0	11.115 (0.179)
>1-5 years	6	0	
>5-18 years	63	6 (9.52)	
>18-25 years	111	7 (6.31)	
>25-40 years	248	34 (13.71)	
>40-60 years	240	24 (10.00)	
>60-80 years	85	16 (18.82)	
>80 years	5	0	
Hospital admission	145	26 (17.93)	7.431 **(0.006)***
ICU admission	91	17 (18.68)	5.337 **(0.021)***
Presence of comorbidities	110	25 (22.73)	16.143 **(0.000)***

*Significant at $p < 0.05$. ICU: Intensive Care Unit

A logistic regression analysis was performed to investigate the odds of poor outcome for different variables, including co-infection with respiratory viruses. No association was seen between poor outcome and presence of respiratory virus co-infection [Table 5].

Table-5: Logistic Regression Model Showing Predictors Of Poor Outcome

Variables	β coefficien	p-value	OR (CI- 95%)
1. Age	0.087	<0.001*	1.09 (1.05-1.13)
2.Presence of comorbidities	1.42	0.003*	4.14 (1.63-10.58)
3.Presence of any co-infection	1.135	0.058	3.11 (0.96-10.06)
4. ICU admission	3.616	<0.001*	37.20 (14.27-96.95)
Constant	-9.108	<0.001	

*Significant at $p < 0.05$. ICU: Intensive Care Unit, OR: odd's ratio, CI: confidence interval

DISCUSSION

In the current study, we investigated the prevalence of co-infections in COVID-19 cases and compared the severity of disease in COVID-19 patients with or without Influenza and other respiratory virus infection. In India, January is usually a period with high Influenza positivity, whereas, the frequency of Influenza cases decreases by March.[8] In order to account for both high and low Influenza prevalence, the study was carried out from January to March. We enrolled cases for two years to observe impact of any seasonal outbreak on positivity of respiratory viruses in COVID-19 cases.

Numerous studies have documented the possible concurrent presence of respiratory pathogens in COVID-19 patients. Case reports, case series, and cohort studies have reported viral co-infections rates ranging from low (0.7%) to high (47.2%).[11,12] Overall co-infection rate in the present study was 11.45%. The latest systematic review by Alhumaid et al., estimated that out of the 31,953 COVID-19 positive patients included in the meta-analysis, the overall pooled proportion of patients with respiratory viral co-infection was 6.6%.[13] Contrarily, a study conducted in USA between December 2019 and October 2021, showed no respiratory virus co-infection in SARS-CoV-2 positive cohort.[14] The differences in reported co-infection rates between various studies may depend upon the population under investigation (hospitalized/outpatients), the duration of the study, testing methods used to diagnose coinfecting pathogens, and range of pathogens targeted.

Majority of co-infection in COVID-19 positive cases in the present study was seen with Influenza A virus which agrees with some previous reports.[15,16] In contrast, studies done in early pandemic have reported lower Influenza co-infection rates in 2020-21 flu season,[17,18] which may be attributed to low Influenza activity during the study period due to stringent social distancing and physical measures like masks, sanitization etc. followed during early pandemic. The high prevalence of Influenza A in the present study also suggests concurrent circulation of two viruses, highlighting the significance of screening COVID-19 patients for additional clinically significant respiratory pathogens.

In previously published studies, Rhinovirus and Adenovirus were commonly detected in COVID-19 patients,[6,19,20] however, in our study Rhinovirus was present in 10 (1.32%) patients and Adenovirus co-infection was detected in only 1 patient (0.13%). Parainfluenza virus (PIV) was detected in 22 patients, out of which PIV 1 was present in 3 patients (0.39%), PIV 3 in 12 (1.58%) and PIV 4 in 7 patients (0.92%). Other studies have also revealed a comparably lower prevalence of PIV.[21,22] Co-infection with RSV was not detected in the present study, inspite the fact that majority of our study population belongs to a region which documents high annual rates of RSV transmission.[23] In contrast, certain studies have reported RSV as the most commonly detected respiratory pathogen in SARS-CoV-2 positive patients.[24] Previous studies have established that severity of illness is associated with presence of co-infections by direct and indirect mechanisms as well as through an immune response.[25] In the current study, patients having co-infection with Influenza virus presented with significantly higher disease severity. Similar observations have been reported in previous studies which concluded that SARS-CoV-2 co-infections with Influenza virus are associated with increased disease severity and fatal clinical outcomes as compared to mono-infections.[4, 15, 26] However, on applying logistic regression analysis (adjusted for age, comorbidity etc.), it was clearly seen that co-infection with other respiratory viruses was not associated with adverse outcome. These findings are supported by a large pan-India study conducted by Aggarwal N et al. who showed that SARS-CoV-2 and Influenza virus co-infections were not associated with increased severity of disease.[27] Also, Chekuri et al., reported that no association was seen between co-infection and poor outcomes in either unadjusted analysis or after adjustment was done for age, comorbidities or gender.[6] In contrast to our study, Swets et al., reported that co-infection with both Influenza and adenovirus was associated with higher odds of inhospital mortality.[15] Our study also demonstrated that co-infection with respiratory viruses is more often seen in patients with hospital and ICU admission, and harbouring one or more comorbidities. No significant association between age and presence of co-infection was detected. These findings are corroborated by various studies which reported that COVID-19 patients with co-infections had greater rates of ICU admissions and mechanical ventilation requirement than those with monoinfections.[15,19] A significant association was observed between mortality and co-infection with hypertension. Hypertension related endothelial damage and RAS imbalance leads to release of proinflammatory cytokines, resulting in enhanced disease severity and fatal outcome.[28] Similarly, increased mean age and immunosuppressive states in cancer patients may increase their susceptiblity towards co-infections, thereby increasing their risk of morbidity and mortality.[29]

The case fatality rate in our study was 9.08%, of which 16 patients had co-infection with one or more respiratory virus. Among the respiratory viruses tested, association between co-infection and mortality could be established only with Influenza virus. The odds of mortality were also

increased with age, and hospital and ICU admission. Swets et al., reported a 22% mortality rate and it was observed that hospital and ICU admission, and co-infection with Influenza and adenoviruses increased the odds of fatalities.[15] Alosaimi et al., reported a mortality rate of 19% in which all the expired patients were critically ill, out of which two-third of the patients had a co-infection and higher mortality was reported in case of viral co-infection.[26] Conversely, certain studies reported no significant difference in patient outcome between SARS-CoV-2 monoinfection and co-infection groups.[30,31]

Limitations Of The Study

In the present study, sample and data collection were done from a limited geographical location. We were not able to differentiate between co-infections and superinfections in hospitalised patients. Finally, since symptomatic patients are more likely to visit healthcare facilities to get tested and the study samples were obtained from patients who visited our tertiary care centre, it could have resulted in selection bias.

CONCLUSION

Influenza virus co-infection in COVID-19 cases was found to be associated with increased severity and mortality in these cases.

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Conflicts Of Interest Disclosure

Nil

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