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BRIEF REPORT

# Nationwide Implementation of Nonpharmaceutical Interventions During the Coronavirus Disease 2019 Pandemic Is Associated With Decreased Incidence of *Pneumocystis jirovecii* Pneumonia in Kidney Transplant Recipients

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This study aimed to investigate the impact of nationwide nonpharmaceutical interventions against coronavirus disease 2019 (COVID-19) on the incidence of *Pneumocystis jirovecii* pneumonia (PCP) in kidney transplant recipients. The monthly incidence of PCP during the COVID-19 period decreased significantly compared to that of the pre–COVID-19 period in kidney transplant recipients.

**Keywords.** nonpharmaceutical interventions; COVID-19; kidney transplant recipients; *Pneumocystis jirovecii* pneumonia.

Kidney transplantation is the ideal modality for improving the survival and quality of life in patients with end-stage kidney disease. The patient and graft survival after kidney transplantation has remarkably improved during the past decades with advances in surgical techniques and immunosuppressive agents. However, concerns regarding infections remain since the use of immunosuppressive agents inevitably increases the risk of opportunistic infections such as *Pneumocystis jirovecii* pneumonia (PCP) [1]. *Pneumocystis jirovecii* is an opportunistic pathogen that causes severe pulmonary infection in immunocompromised hosts and spreads from person to person through the air.

The World Health Organization declared the outbreak of the coronavirus disease 2019 (COVID-19) a global pandemic on 11 March 2020 [2]. Since the first report of severe acute respiratory syndrome coronavirus 2 emerging in December 2019, many countries have implemented nonpharmaceutical interventions (NPIs) to reduce transmission of this virus. In South Korea, NPIs that include mandatory mask-wearing in public, social distancing, hand hygiene, testing of asymptomatic individuals, and isolation of symptomatic individuals have been implemented since February 2020.

With this background, this study aimed to investigate whether the implementation of nationwide NPIs against COVID-19 was associated with a change in the incidence of PCP in kidney transplant recipients (KTRs).

## METHODS

### Study Design and Study Population

This study was a retrospective, dynamic cohort study investigating the change in the incidence of PCP in KTRs after the implementation of NPIs against COVID-19. The study period was divided into a pre–COVID-19 period, designated as January 2018–January 2020, and an COVID-19 period, designated as February 2020–June 2021 based on the Google Trends search for the Korean word for mask to analyze the public interest. Patients who underwent kidney transplantation at the Yonsei University Health System (YUHS), a tertiary medical center in Seoul, South Korea, between April 1979 and June 2021 were screened. Patients who met the following criteria were excluded: (1) graft failure requiring maintenance kidney replacement therapy, and (2) lost to follow-up before January 2018. A total of 3083 patients were included in the final analysis (Supplementary Figure 1). All patients were prescribed trimethoprim-sulfamethoxazole (TMP-SMX) for 3–6 months after kidney transplantation according to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines.

The study protocol was approved by the Institutional Review Board (IRB) of YUHS (IRB number 4-2021-1146). The need for informed consent was waived by the IRB due to the retrospective study design.

### Data Collection

Data from all the KTRs were collected from the hospital's electronic medical records. Clinical data included all-cause mortality, dialysis after graft failure, all-cause hospitalizations, development of PCP, demographic information (age and sex), medication use (immunosuppressive agents and TMP-SMX), and the date of kidney transplantation.

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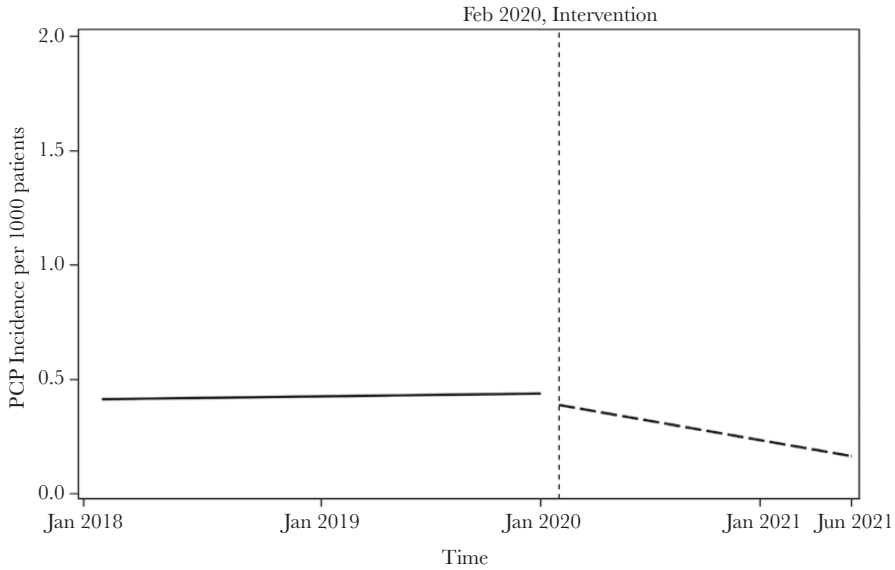


**Figure 1.** Trends of monthly *Pneumocystis jirovecii* pneumonia (PCP) incidence. Regression models were adjusted for age, sex, number of hospitalizations, seasonality, type of immunosuppressive agent, and days after kidney transplantation.

### Study Outcomes

The main outcome of this study was the presence of PCP, defined as a positive real-time polymerase chain reaction (PCR) test result of sputum or bronchoalveolar lavage (BAL).

### Statistical Analysis

Continuous variables are expressed as mean ± standard deviations. Categorical variables are expressed as numbers and percentages. The $\chi^2$ test was used to investigate the general characteristics of the study population. The interrupted time series analysis using Poisson regression with a generalized estimated equation, a log link function, and auto-regression of order 1 was used to evaluate the changes in the outcome variables after NPIs while controlling for other potential confounding variables. Risk ratio (RR) and 95% confidence interval (CIs) were used to estimate the risk of infections. Statistical significance was set at $P < .05$. All data were analyzed using SAS 9.4 software (SAS Institute, Cary, North Carolina).

## RESULTS

### Baseline Characteristics

Baseline characteristics of the patients who were included in the final analysis are presented in Supplementary Table 1. Among the 3083 patients, 1271 (41.2%) were female. During the study period, 59 patients (1.9%) were diagnosed with PCP. Patients diagnosed with PCP had longer times since transplantation and had more all-cause hospitalizations. There was no difference in the use of immunosuppressive agents among the groups.

### Impact of NPIs on Infection

Public interest in the use of face masks began to increase on 1 February 2020 and reached its peak on 1 March 2020 (Supplementary Figure 2). Of the 59 PCP cases, 54 were confirmed by sputum alone, and 5 were confirmed by both sputum and BAL. There was no case confirmed by BAL alone (Supplementary Table 2). After adjusting for confounding demographic factors, including age, sex, number of hospitalization, seasonality, immunosuppressive agents, and days after kidney transplantation, the trends indicated that there was a significant decrease in the incidence of PCP after February 2020 (Figure 1). The adjusted Poisson regression indicated that the incidence of PCP per 1000 patients of the COVID-19 period decreased significantly compared to that of the pre–COVID-19 period (RR, 0.83 [95% CI, .77–.91], $P < .001$; Table 1). Before the implementation of NPIs, the trend of incidence of PCP had no statistically significant change (RR, 1.00 [95% CI, 1.00–1.01], $P = .103$). After the implementation of NPIs, an RR of 0.93 (95% CI, .92–.94, $P < .001$) indicated a marginal decrease in the incidence of PCP.

## DISCUSSION

In this retrospective study, compared to the pre–COVID-19 era, there was a significant decrease in the incidence of PCP in KTRs after the nationwide implementation of NPIs in South Korea during

**Table 1. Results of Poisson Regression of the Effects of Nonpharmaceutical Interventions on *Pneumocystis jirovecii* Pneumonia**

| | PCP | | |
|---|---|---|---|
| Period | RR | (95% CI) | *P* Value |
| Pre–COVID-19 period | 1.00 | (1.00–1.01) | .103 |
| Intervention | 0.83 | (.77–.91) | <.001 |
| COVID-19 period | 0.93 | (.92–.94) | <.001 |

Regression models were adjusted for age, sex, number of hospitalizations, seasonality, type of immunosuppressive agent, and days after kidney transplantation.

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; PCP, *Pneumocystis jirovecii* pneumonia; RR, risk ratio.

the COVID-19 pandemic. These findings were independent of relevant sociodemographic factors. These findings suggest that NPI-related factors were associated with PCP in KTRs.

Previous studies have indicated the benefits of NPIs in transplant recipients. Sung et al reported that universal mask usage was associated with a reduction in respiratory viral infections during the most vulnerable period following hematopoietic stem cell transplantation [3]. Abbas et al also reported that vigilant hand washing and other standard precautions such as contact precautions and mask-wearing are the key elements to preventing infectious disease outbreaks in transplant patients [4]. Emerging researches from the COVID-19 pandemic have similarly suggested that NPIs protect against the spread of various viral infections [5, 6]. Two nationwide studies of the South Korean population have suggested that implementation of NPIs was associated with a significant reduction in the incidences of several respiratory infections and Kawasaki disease [7, 8]. The findings of these studies similarly indicate that the benefits of NPIs may also be extended to KTRs. Considering that infections are the most common noncardiac cause of death in KTRs, the implementation of NPIs could improve the clinical outcomes in these patients.

PCP is a serious risk factor for graft failure and mortality in KTRs. The incidence of PCP in KTRs varies from 0.6% to 14% without prophylaxis, with a mortality of up to 50% despite therapy with high-dose antibiotics [9]. In the modern era of prophylaxis with TMP-SMX, the incidence of PCP in KTRs has gradually decreased to 0.4%–7% [1]. However, the occurrence of PCP even >10 years after transplantation has been documented in up to 18% of KTRs [10]. In the current study, the PCP incidence rate in KTRs was 0.064 per person-month before the COVID-19 pandemic. After the implementation of nationwide NPIs, this incidence rate decreased to 0.034 per person-month, suggesting the benefits of NPIs in these patients. Current KDIGO guidelines recommend PCP prophylaxis with daily doses of TMP-SMX for 3–6 months after kidney transplantation. Considering the side effects of TMP-SMX, regular mask-wearing and hand hygiene could be a beneficial inexpensive intervention in KTRs.

This study has some strengths. This study included a large number of KTRs, which allowed us to observe the change in incidence of PCP over time. In addition, the ascertainment of PCP using real-time PCR rather than staining techniques increased the diagnostic yield. Meanwhile, the higher compliance rate of NPIs in Korea than other countries contributed the reliability of this study. However, this study also has several limitations. First, this was a single-center retrospective study; it may be difficult to generalize the results from this study population to other clinical settings. The results should be interpreted with caution when applied to other clinical settings, and further investigation is required to confirm the findings of this study. Second, this study could not identify which NPI was the most effective in reducing the incidence of opportunistic infection in KTRs. It is more likely that, rather than mask-wearing alone, a combination of preventive measures may have contributed to the decrease in the incidence of infection [11]. Third, although this study identified a decline in the incidence of PCP in KTRs, it is possible that patients with PCP chose to avoid visiting the hospital during the COVID-19 pandemic, thus resulting in a sampling bias. Finally, adherence to NPIs may be variable, and not all participants in this study may have complied with the mandatory NPIs. However, the reported rate of compliance with COVID-19 codes of conduct, such as mask-wearing (94%), washing hands frequently (92%), and decreased social interaction (85%), is known to be relatively high in South Korea [12].

In conclusion, this study found a significant decrease in the incidence of PCP in KTRs after the nationwide implementation of NPIs in South Korea. These findings suggest that behavioral changes including mask-wearing, hand hygiene, and social distancing may help prevent opportunistic respiratory infections in KTRs.

## Notes

***Potential conflicts of interest.*** All authors: No reported conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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