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# Influenza and pneumococcal vaccination and COVID-19 in kidney transplant patients

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ABSTRACT

*Background:* This study aims to investigate the effect of recent influenza and pneumococcal vaccines' administration on the development of COVID-19 infection in kidney transplant recipients during the pandemic.
*Methods:* The effect of influenza and pneumococcal vaccines on the clinical course of the disease in COVID-positive (COVID group, n: 105) and COVID-negative (control group, n: 127) recipients has been examined. The control group included patients with negative rRT-PCR test results. At the time of the study, no patient was vaccinated with COVID-19 vaccine. The patients' influenza and/or pneumococcal vaccination rates in 2019 and 2020 were determined. In 2019 and 2020, 32 and 33 people in the COVID-positive group and 61 and 54 people in the COVID-negative group had received influenza and/or pneumococcal vaccines, respectively. The median study follow-up times of the COVID-negative and COVID-positive groups were 13.04 and 8.31 months, respectively.
*Results:* Compared with the COVID-negative group, the patients in the COVID-positive group were younger and had a longer post-transplant time. In addition, the rate of transplantation from a living donor and the rate of COVID positivity in family members were also higher. The influenza vaccination rates in the COVID negative group were significantly higher than the COVID-positive group in 2020 (23.8% vs 37%, $p = 0.031$). Multivariate logistic regression analysis revealed that the presence of COVID-19 in family members and lack of pneumococcal vaccination in 2020 increased the risk of being positive for COVID-19. There was no significant difference in the hospitalization rates, the need for dialysis and intensive care, the hospital stay, and the graft dysfunction in the COVID-positive patients with and without influenza and pneumococcal vaccines.
*Conclusion:* The observations made throughout this study suggest that influenza and pneumococcal vaccination in transplant patients may reduce the risk of COVID-19 disease and provide additional benefits during the pandemic period.

## 1. Introduction

The COVID-19 pandemic has resulted in morbidity and mortality worldwide and educational, economic, and socio-cultural issues. While some promising experimental antiviral drugs (i.e., molnupiravir and paxlovid) are currently being tested in clinical trials, researchers still have not found an effective treatment. Clinicians began administering several COVID-19 vaccines, with consecutive emergency use approvals from December 2020. As of December 9$^{th}$2021, a total of 8,158,815,265 vaccine doses have been administered, including inactivated or attenuated virus vaccines, protein-based vaccines, viral vector vaccines, RNA and DNA vaccines (Pfizer/BioNtech Comirnaty vaccine, SII/Covishield and AstraZeneca/AZD1222 vaccines, Janssen/Ad26.COV 2.S Moderna COVID-19 vaccine [mRNA 1273], Sinopharm COVID-19 vaccine and Sinovac-CoronaVac) [1,2]. The current vaccines are the primary resort against COVID-19, however, vaccination rates and the number of double-dose vaccines remained low in most countries due to low socioeconomic status, anti-vaccination, or spread of vaccine hesitancy about the side effects of vaccines. Continuing transmission, especially among the unvaccinated, constantly leads to new COVID-19 mutations. Thus, the more contagious delta variant caused the 4th wave of pandemic globally and recently, WHO also identified the severe acute

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respiratory syndrome coronavirus 2 (SARS-CoV-2) variant (B.1.1.529, omicron) that could initiate a new wave. Widespread debates continue about the efficacy of current vaccines and the necessity of a reminder dose (3rd dose) for variants, and countries take different approaches on this issue. The inability of individuals in the community to be vaccinated to a level sufficient for herd immunity also raises concerns about the fate of the pandemic.

Primary or secondary immunocompromised patients may be exposed to some vaccine-preventable diseases. Among the main risk groups for COVID-19 infection are some chronic diseases (chronic kidney disease, obesity, diabetes mellitus, etc.) and immunocompromised patient groups (dialysis and kidney transplant patients). The safety and effectiveness of vaccines in immunocompromised patients depend on the nature and severity of immunosuppression. Although the physicians continue to apply vaccine immunization such as influenza and pneumococcal vaccines in uremic patients and kidney transplant recipients, responses to vaccines are deteriorating due to their favorable safety profile and high infection rates in these patients [3]. Many kidney transplant patients have been regularly vaccinated against influenza and/or pneumococcus before the pandemic and strictly take seasonal personal protection measures. Few observational studies have claimed that the influenza vaccine may reduce the risk of contracting COVID-19 infection or the severity of disease and the risk of death in persons vaccinated with the influenza vaccine [4,5]. After the emergency use approval in Turkey, the vaccination program with the CoronaVac vaccine started with healthcare workers on January 14th 2021. Then vaccination continued with the most at-risk groups with chronic diseases, such as the elderly and organ transplants. On April 2nd 2021, the Ministry of Health started to apply the BioNTech vaccine. Consequently, this study aims to investigate the relationship of influenza and/or pneumococcal vaccine administration with the development and course of COVID-19 infection and the factors affecting disease risk in kidney transplant recipients before the COVID-19 vaccination era.

## 2. Materials and methods

This study included patients with real-time reverse transcriptase-polymerase chain reaction test (RT-PCR) results for COVID-19 followed at two kidney transplant centers in Bursa between March 2020 and July 2021.None of the patients included in the study had received COVID-19 vaccines. Bursa is an industrialized province in the southern Marmara region of Turkey and is the fourth largest province by population density (2020 population: 3,101,833 people) [6]. The Ministry of Health announced the first detected COVID-19 case in Turkey on March 11th 2020 [7].According to the hospital COVID-19 case records, the peaks of COVID-19 waves in Bursa between March 2020 and July 2021 were as follows: the peak of the first wave was in April 2020, the peak of the second wave was in November 2020 (original alpha variant, October–December 2021) and the peak of the third wave (delta variant) was in April 2021 (March–May 2021). The study started in March 2020. The study follow-up period ended in July 2021, when widespread vaccination was administered to all risk group patients and the community in Turkey. Patients whose hospital records did not have any data of hospitalization, COVID-19, influenza or pneumococcal vaccine, or definite or suspected COVID-19 diagnosis (COVID-PCR test or hospitalization history) during the study period were excluded from the study. The primary endpoints for this longitudinal study were identified as being diagnosed with COVID-19 infection, receiving the first dose of COVID-19 vaccine, or being the last outpatient admission by July 2021. Kidney transplant recipients were divided into two groups: COVID-positive and COVID-negative (Fig. 1). The characteristics of the patients with and without COVID-19 infection and the clinical course of the disease (hospitalization, need for intensive care, and death) in COVID-19-positive patients with and without a vaccination history of influenza and/or pneumococcus were compared.

Patient data were obtained from hospital medical records:

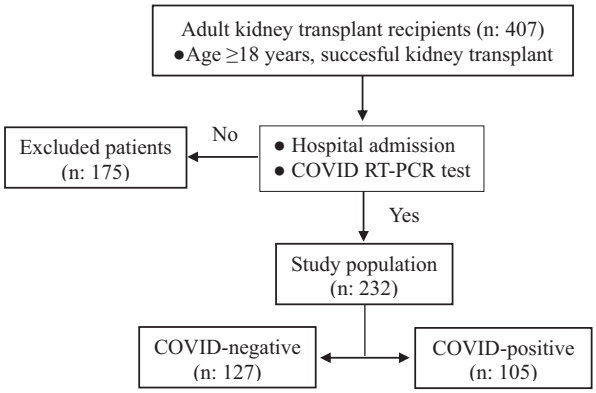


**Fig. 1.** Flow chart of the study.

characteristics, comorbidities, height, body weight, smoking history, medical treatments, transplant and dialysis information, blood group, Rh status, family history of COVID-19, and pre-pandemic laboratory values. The status of Influenza (Fluarix tetra 0.5 mL [GlaxoSmithKline] and Vaxigrip tetra 0.5 mL [Sanofi Pasteur], split virion, inactivated quadrivalent influenza vaccine) and/or pneumococcal (23-valent pneumococcal polysaccharide vaccine [PPV23: Pneumo 23 0.5 mL, Sanofi Pasteur or Pneumovax 23 0.5 mL, Merck Sharp Dohme] or 13-valent pneumococcal protein-conjugate vaccine [PCV13: Prevenar 13/0.5 mL, Pfizer]) vaccines in 2019 and 2020 and whether the patients had these vaccinations regularly were recorded.

All the patients admitted were diagnosed with findings suggestive of COVID-19 disease and a RT-PCR positivity for SARS-CoV-2 in nasopharyngeal and oropharyngeal swabs. The tests were repeated in patients whose initial tests were negative, considering that they might be positive later. The patients with clinical symptoms were screened with a chest computed tomography (CT). They were diagnosed as a possible case of COVID-19 in the presence of radiological evidence according to the Ministry of Health's COVID-19 Diagnosis and Treatment Guidelines [8]. The control group consisted of patients with a negative RT-PCR test for a history of contact with an infected case, suspected COVID-19 or screening. They did not have findings consistent with COVID-19 infection on chest X-rays and/or CT scans.

### 2.1. Immunosuppressive therapy

All patients had undergone the first or the second kidney transplantation. For induction therapy, the patients received 20 mg doses of intravenous basiliximab (on days 0 and 4) or antithymocyte globulin-Fresenius (ATG, now Grafalon® SPC). The maintenance therapy regimens included calcineurin inhibitor (CNI: cyclosporine [CsA] 5 mg/kg/d or tacrolimus [Tac] 0.15 mg/kg/d) or mammalian target of rapamycin (mTOR) inhibitor (everolimus [EVR]) and mycophenolic acid (MPA) (mycophenolate mofetil [MMF] 2000 mg/d or enteric-coated mycophenolate sodium [EC-MPS] 1440 mg/d) or azathioprine (AZA, 100 mg/d) with corticosteroids (500 mg intravenous methylprednisolone, then oral prednisolone). Prednisolone doses were reduced to 20 mg/day at one month, 10 mg/day at two months, and 5 mg/day at six months. The dosages of CNIs were adjusted to reach target trough levels; 200–300 ng/mL in the first three months and then 100–200 ng/mL for CsA, 8–12 ng/mL for the first three months, and then 5–8 ng/mL for Tac and 3–7 ng/mL for EVR. Tac and EVR drug levels were measured by microparticle enzyme immunoassay (MEIA) method (Abbott IMx) and CsA drug levels by fluorescence polarization immunoassay (FPIA) method (Abbott TDx).

### 2.2. Statistical analysis

The conformity of continuous variables to a normal distribution was determined using the Shapiro-Wilk test. Continuous and categorical variables were expressed using median (minimum: maximum) or mean (±standard deviation) values and n (%), respectively. Mann-Whitney *U* test or independent *t*-test was used for intergroup comparisons according to the results of the normality test. Categorical variables were analyzed using the Chi-square test, Fisher's exact chi-square, and Fisher Freeman Halton tests. Logistic regression analysis was used to determine the risk factors affecting COVID-19 positivity. SPSS (IBM Corp. released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) program was used for statistical analysis. The type I error level was accepted as 5% in statistical analysis.

## 3. Results

The data of a total of 407 consecutive patients with regular outpatient follow-up was scanned. The study included 232 (57.0%) kidney transplant recipients who were not vaccinated against COVID-19 and had COVID-19 RT-PCR test results.The median study follow-up period of the patients was 11.81 (1.05:16) months. COVID-19 RT-PCR test result was positive in 93 (45.2%) of 232 recipients. Possible cases of COVID-19 were determined in 12 patients who had multiple negative RT-PCR tests but had radiological evidence. As expected, the study follow-up time of the COVID-negative group was significantly higher than that of the COVID-positive group (13.02 ± 1.94 vs 8.0 ± 2.84 months, $p < 0.001$). In the COVID-positive group, COVID-19 infection developed in a median of 8.31 (1.05:14.98) months after the onset of the pandemic in Turkey. One hundred and twenty-seven patients remained negative or uninfected during the follow-up study (COVID-negative group).

The median age of the COVID-positive group at the start of the study was significantly lower than the COVID-negative group ($p = 0.013$). There was no difference between the gender distribution, body mass index, marital status, blood group distribution, Rh status, the ratios of obesity, diabetes mellitus, hypertension and coronary artery disease in both groups ($p > 0.05$,Table 1). The history of smoking was significantly higher in the COVID-negative group (39.4% vs 21.9%, $p = 0.004$). However, it was determined that a significant proportion of patients (ex-smoker) quit smoking after transplantation.

**Table 1**
Socio-demographic characteristics of the patients.

| Variables | COVID-negative (n = 127) | COVID-positive (n = 105) | p-value |
|---|---|---|---|
| Study age (years) | 46.4 ± 11.1 | 42.6 ± 10.9 | 0.013 |
| Gender (male/female) | 75/52 | 51/54 | 0.111 |
| Body mass index (kg/m$^2$) | 27.0 ± 5.37 | 27.3 ± 5.46 | 0.645 |
| Marital status | | | |
| Single | 24 (18.9) | 17 (16.2) | 0.879 |
| Married | 100 (78.7) | 85 (81) | |
| Divorced | 3 (2.4) | 3 (2.9) | |
| Obesity | 36 (28.3) | 30 (28.6) | 0.970 |
| Diabetes mellitus | 24 (18.9) | 18 (17.1) | 0.730 |
| Hypertension | 89 (70.1) | 71 (67.6) | 0.687 |
| Coronary artery disease | 12 (9.4) | 8 (7.6) | 0.648 |
| Smoking | 18 (14.2) | 17 (16.2) | 0.715 |
| Blood groups | | | |
| 0 | 42 (33.1) | 31 (29.5) | 0.563 |
| A | 57 (44.9) | 53 (50.5) | 0.396 |
| B | 21 (16.5) | 13 (12.4) | 0.373 |
| AB | 7 (5.5) | 8 (7.6) | 0.596 |
| Rh status (positive/negative) | 41/86 | 23/82 | 0.078 |

Data were expressed as mean ± standard deviation and n (%).

Dialysis type, dialysis duration and re-transplantation rates were similar in both groups. The transplantation rate from a living donor (49.5% vs 35.4%) in the COVID-positive group and a deceased donor (64.6% vs 50.5%) in the COVID-negative group was significantly higher than in the other group ($p < 0.030$). The COVID-positive group had a considerably higher median post-transplant time (61 vs 38 months, $p = 0.003$) and a lower median transplant age (37.3 vs 44.6 years, $p = 0.001$) than the COVID-negative group. Induction therapy with ATG was used more frequently in the COVID-negative group than in the COVID-positive group (35.4% vs 24.8%, $p > 0.05$). The distribution of immunosuppressive regimen protocols was similar in both groups (Table 2). In addition, the ratios of MPA (MMF [41.9% vs. 43.5%] or EC-MPS [58.1% vs. 56.5%]) and CNI (Tac ([82.3% vs. 82%] or CsA [17.7% vs. 18%]) use in the COVID-positive and the COVID-negative groups were comparable ($p > 0.05$). Similarly, there was no difference between the ratios of patients who received and did not receive EVR (5.5% vs 5.7%) or AZA (3.9% vs 10.5%) in the COVID-positive and the COVID-negative groups, respectively ($p > 0.05$). Some selected laboratory parameters at the start of the study were not different in the two groups (Table 3).

The history of COVID-19 infection in family members of the COVID-19 positive group was significantly higher than in the negative group (66.7% vs. 15%, $p < 0.001$). In 2019 and 2020, 32 (30.5%) and 33 (31.4%) people in the COVID-positive group and 61 (48%) and 54 (42.5%) people in the COVID-negative group had received influenza and/or pneumococcal vaccines, respectively. The 2019 rates of the groups were significantly different (30.5% vs 48%, $p = 0.007$). The rates

**Table 2**
Dialysis and transplantation data.

| Variables | COVID-negative (n = 127) | COVID-positive (n = 105) | p-value |
|---|---|---|---|
| Dialysis duration (month) | 49 (1:276) | 42 (1:264) | 0.702 |
| Dialysis modality | | | |
| Pre-emptive | 18 (14.2) | 17 (16.2) | 0.669 |
| Hemodialysis | 100 (78.7) | 72 (68.6) | 0.078 |
| Peritoneal dialysis | 9 (7.1) | 16 (15.2) | 0.056 |
| Donor type (deceased/living) | 82/45 | 53/52 | 0.030 |
| Transplant age (years) | 42.6 ± 11.4 | 37.2 ± 11.7 | 0.001 |
| Post-transplant time (month) | 38 (1:171) | 61 (3:206) | 0.003 |
| Retransplantation | 10 (7.9) | 8 (7.6) | 1.000 |
| Induction therapy (ATG/IL-2ra) | 45/82 | 25/79 | 0.087 |
| Immunosuppressive therapy | | | |
| Tac + MMF + P | 41 (32.3) | 31 (29.5) | 0.801 |
| EVR + MMF + P | 1 (0.8) | 2 (1.9) | |
| Tac + MMF | 0 | 1 (1.0) | |
| Tac + AZA + P | 5 (3.9) | 8 (7.6) | |
| Tac + EC-MPS + P | 51 (40.2) | 40 (38.1) | |
| CsA + EC-MPS + P | 15 (11.8) | 10 (9.5) | |
| Tac + EVR | 1 (0.8) | 0 | |
| CsA + MMF + P | 7 (5.5) | 6 (5.7) | |
| EVR + AZA + P | 0 | 1 (1.0) | |
| EVR + EC-MPS + P | 2 (1.6) | 2 (1.9) | |
| CsA + AZA + P | 0 | 2 (1.9) | |
| EVR + Tac + P | 3 (2.4) | 1 (1.0) | |
| Tac + P | 1 (0.8) | 1 (1.0) | |
| EC-MPS/MMF | 68/49 | 52/40 | 0.817 |
| CsA/Tac | 22/102 | 18/82 | 0.960 |
| EVR | 7 (5.5) | 6 (5.7) | 1.000 |
| AZA | 5 (3.9) | 11 (10.5) | 0.068 |

ATG: antithymocyte globulin, IL-2ra: anti-interleukin-2 receptor antibody, Tac: tacrolimus, MMF: mycophenolate mofetil, P: prednisolone, EVR: everolimus, AZA: azathioprine, EC-MPS: enteric-coated mycophenolate sodium, CsA: cyclosporine. Data were expressed as median (min:max), mean ± standard deviation and n (%).

**Table 3**
Laboratory results of the participants.

| Variables | COVID-negative (n = 127) | COVID-positive (n = 105) | p-value |
|---|---|---|---|
| Hemoglobin (g/dL) | 12.8 ± 1.96 | 12.7 ± 1.87 | 0.702 |
| Glucose (mg/dL) | 97.7 ± 23.9 | 99.7 ± 28.9 | 0.555 |
| HbA1c (%) | 6.04 ± 1.68 | 6.28 ± 1.54 | 0.331 |
| Creatinine (mg/dL) | 1.41 ± 0.57 | 1.33 ± 0.50 | 0.243 |
| eGFR (mL/min) | 62.7 ± 24.2 | 64.7 ± 21.7 | 0.516 |
| CRP (mg/L) | 3.11 (0.3:233) | 3.0 (0.1:134) | 0.736 |
| 25OH vitamin D (mcg/L) | 20.14 ± 11.9 | 21.51 ± 10.54 | 0.369 |
| ESR (mm/h) | 13 (1:127) | 15 (2:96) | 0.353 |

eGFR: estimated glomerular filtration rate, ESR: erythrocyte sedimentation rate. Data were expressed as mean ± standard deviation or median (min:max).

of influenza and/or pneumococcal vaccination in 2019 and/or 2020 in the COVID-negative group were significantly higher than in the COVID-positive group (63% vs 42.9%, p = 0.002). There was a statistically significant difference in the only 2020 influenza vaccination rates (37% vs. 23.8%, p = 0.031). Regarding the patients who received both influenza and pneumococcal vaccines in the same year it was determined that the rate of those who received both vaccines in 2020 increased compared to 2019 (Table 4).

A subgroup analysis of 232 patients showed that 62 and 46 in 2019 and 72 and 60 in 2020 received influenza and pneumococcal vaccines, respectively. The COVID RT-PCR positivity rates of patients with influenza (35.3% [n: 23] vs 48.2% [n: 82] in 2019, p = 0.131 and 34.7% [n: 25] vs 50% [n: 80] in 2020, p = 0.031) and pneumococcal (32.6% [n: 15] vs 48.4% [n: 90] in 2019, p = 0.054 and 38.3% [n: 23] vs 47.7% [n: 82] in 2020, p = 0.211) vaccines were lower than those without vaccination.

The risk factors affecting COVID-19 positivity was analyzed with the univariate logistic regression analysis. In the multivariate logistic regression analysis, the variables meeting the p < 0.25 criterion (study age, transplant age, transplantation duration, serum creatinine, gender [male], Rh status [positive], histories of hemodialysis and peritoneal dialysis, donor type [deceased donor], induction therapy [ATG], AZA-based immunosuppression, COVID-19 positivity in family members, influenza and pneumococcal vaccination status [not be vaccinated]) were included. The results of the final step of the analysis were given in Table 5. The logistic regression model created during the analysis phase was significant (p < 0.001) and consistent with the data (p = 0.236). If family members were positive for COVID-19, the risk of COVID-19 positivity was 11.7 times higher. The lack of pneumococcal vaccination in 2020 increased the risk of COVID-19 positivity by 2.4 times.

**Table 4**
The relationship between influenza and pneumococcal vaccination status and COVID-19 positivity.

| Variables n (%) | COVID-negative (n = 127) | COVID-positive (n = 105) | p-value |
|---|---|---|---|
| COVID-19 positivity of family members | 19 (15) | 70 (66.7) | <0.001 |
| Influenza vaccine rates | | | |
| Only 2019 | 39 (30.7) | 23 (21.9) | 0.131 |
| Only 2020 | 47 (37) | 25 (23.8) | 0.031 |
| Both 2019 and 2020 | 32 (25.2) | 19 (18.1) | 0.194 |
| Pneumococcal vaccine rates | | | |
| Only 2019 | 31 (24.4) | 15 (14.3) | 0.054 |
| Only 2020 | 37 (29.1) | 23 (21.9) | 0.211 |
| Both 2019 and 2020 | 2 (1.6) | 4 (3.8) | 0.414 |
| Influenza plus pneumococcal vaccine rates | | | |
| 2019 | 7 (5.5) | 4 (3.8) | 0.758 |
| 2020 | 28 (22) | 15 (14.3) | 0.130 |

Data were expressed as n(%).

**Table 5**
Risk factors affecting COVID-19 positivity (n = 232).

| Reference category | Wald | p-value | OR | 95% CI | |
|---|---|---|---|---|---|
| | | | | Min | Max |
| Time post-transplant | 2.831 | 0.092 | 1.006 | 0.999 | 1.012 |
| AZA-based regimen | 3.535 | 0.060 | 3.607 | 0.947 | 13.738 |
| COVID-19 positivity in family members | 50.804 | <0.001 | 11.760 | 5.971 | 23.161 |
| No pneumococcal vaccination in 2020 | 5.591 | 0.018 | 2.487 | 1.169 | 5.293 |

Model $\chi^2 = 78.95$, p < 0.001, Hosmer and Lemeshow test: p = 0.236.
OR: odds ratio, CI: confidence interval.

Unlike the COVID-negative group, 46 patients in the COVID positive group were hospitalized. Their median hospital stay was 10 (1:32) days. Hemodialysis was required in 3 patients (2.9%) in the COVID-positive group. Thirty-two (30.8%) patients were treated in the intensive care unit. Graft functions of four (3%) patients worsened by >25%. While there was no patient loss in the COVID-negative group throughout the study, 7 of the patients in the COVID-positive group died. Of these seven patients, three died of causes unrelated to COVID-19. RT-PCR positivity was detected again in 3 patients 65, 68 and 220 days after the first infection during the study period. Three patients had not received influenza and pneumococcal vaccines neither in 2019 nor 2020. Two patients were committed to the hospital for 4 and 13 days. In addition, twelve (9.44%) patients in the COVID-negative group were diagnosed with COVID-19 infection after a median of 4.22 months after the study ended. The study period of ten patients ended because they received the COVID vaccine. The unvaccinated numbers were 9 in 2019 and 7 in 2020 for the pneumococcal vaccine and 7 in 2019 and 6 in 2020 for the influenza vaccine. The other two patients completed their last outpatient visit and did not receive influenza and pneumococcal vaccines in 2019 and 2020.

Significant differences between hospitalization, dialysis and intensive care unit needs, hospital stay duration, and graft dysfunction rates in COVID-positive patients with and without influenza and pneumococcal vaccines (2019, 2020 and 2019 plus 2020) were not found.

## 4. Discussion

Kidney transplant recipients appear to be at extremely high risk for the COVID-19 infection, mainly due to chronic immunosuppression and comorbidities. Angiotensin-converting enzyme 2 (ACE2) is a crucial regulator of the renin-angiotensin system in cardiovascular diseases. It plays an essential role in infections caused by coronaviruses and influenza viruses [9]. Influenza A can facilitate COVID-19 infection by upregulating pulmonary ACE2 receptors [10].In part, high expression of ACE2 in populations at high cardiovascular risk also increases the risk of coronavirus or influenza virus infection. The use of coronavirus and influenza virus vaccines in high cardiovascular risk populations may be a potential strategy to prevent cardiovascular disease and coronavirus or influenza virus infections [9]. The wide distribution of the ACE2 receptor, which is the gateway to the virus, may explain the multi-organ failure [11]. High viral load can spread the infection to various target organs such as the kidney, heart, liver, brain, endothelium, gastrointestinal tract, immune cells, and erythrocytes via ACE2 receptor [12].

Depending on the time of observation and the frequency of infection in the relevant country, different centers have reported COVID-19 infection in kidney transplant patients between 9.5/1000 and 17.7/1000, which is 2 to 5 times higher than the general population rates in the same period [13]. In the study cohort, 45% of patients had COVID-19 infection. The mortality rate among kidney transplant recipients diagnosed with COVID-19 is higher than in the general population and

ranges from 16% to 22% [14–17]. A multicenter study conducted in Turkey reported a mortality rate of 13.2% in 820 kidney patients. However, the mortality rate in kidney transplant patients (11.1%) was lower than in patients with chronic kidney disease (28.4%) and those on hemodialysis patients (16.2%) [18]. In this study, mortality rates (6.66% and 3.01%, respectively) in kidney transplant patients and all cohorts were relatively lower than in other studies.

Influenza infection is associated with higher morbidity and mortality after solid organ transplantation. Therefore, guidelines recommend receiving inactivated influenza vaccines annually [19,20]. The influenza vaccine is used safely in solid organ transplantation candidates and recipients, and a recent analysis reported no association between seasonal influenza vaccine and allograft rejection [21,22]. However, transplant recipients may have a suboptimal immunological response to the influenza vaccine. The vaccine's efficacy has been improved recently with high doses and booster doses of the inactivated influenza vaccination [19]. Although controversial, the influenza vaccine may protect against adverse conditions seen in COVID-19 disease. Although some studies find the influenza vaccine ineffective [23–36], many studies support that the vaccine reduces the risk of morbidity and mortality due to COVID-19 infection [5,27–32].

Protection with the influenza vaccine may even provide additional benefits. Innate infection and vaccination induce CD8+ T cell responses capable of killing influenza-infected cells and contribute to heterotypic immunity (cross-protection) against the influenza virus [33,34]. Because influenza impairs host immune defense mechanisms against other pathogens by inducing apoptosis and impairing the cytotoxic effect of natural killer cells [35]. The influenza vaccine may have prevented severe infection in COVID-19 cases by activating natural killer cells [36,37]. Influenza virus and SARS-CoV-2 usually exhibit only limited nucleotide sequence similarity. Influenza vaccines do not induce cross-neutralizing antibodies and T cells, possibly directly targeting viruses such as SARS-CoV-2 [4]. However, the vaccine can lead to T-cell diversity in vaccinated individuals, increasing their chances of fighting viruses such as COVID-19 [38]. The influenza vaccine activates the immune system through Toll-like receptor 7 (TLR7) on the surface of macrophages, dendritic cells and neutrophils, an important binding of single-stranded RNA respiratory viruses such as COVID-19. TLR7 improves innate and adaptive immunity by responding more rapidly to the virus in case of infection via nuclear factor kappa B [27,39].MF59 in the influenza vaccine can strengthen the immune response against COVID-19 variants [40],and protect individuals from COVID-19 disease [41]. Another controversial hypothesis is that antibodies to ACE-2 and tetraspanin can inhibit both coronavirus and low-pathogenic influenza A virus infections [28]. In this study, although influenza and pneumococcal vaccination rates in the COVID-negative group were higher compared to the COVID-positive group, only the influenza vaccine rate in 2020 was statistically significant. However, in the multivariate analysis, not having the influenza vaccine did not increase the risk of COVID-19 infection. In contrast, the absence of the pneumococcal vaccine in 2020 increased the risk of COVID-19 positivity by 2.4 times.

A recent study analyzed data from 53,752 clinically confirmed COVID-19 cases to understand potential associations between the trivalent influenza vaccination and COVID-19 outcomes. The authors found that the intensive care treatment need (7%), the invasive respiratory support (17%) and the death rate (16%) were lower in patients who received a recent influenza vaccine [4]. The influenza vaccine can prevent negative consequences in cases of COVID-19. In a single-centre study of 2005 patients, COVID-positive patients without influenza vaccination within the last year had increased hospitalizations by 2.44 times and intensive care unit admissions by 3.29 times compared with those who had influenza immunization [42]. In 30, 60, 90, and 120 days after the diagnosis, influenza vaccination in COVID-positive patients may be protective against adverse outcomes such as sepsis, stroke, deep vein thrombosis, emergency department admission, and the need for an intensive care unit [5]. A significant difference in the rates of hospitalization, need for dialysis and intensive care, length of stay in the hospital, and graft dysfunction in the COVID-positive patients with and without influenza and pneumococcal vaccines was not found. The influenza vaccine can prevent 20% to 60% of influenza infections, thus potentially preventing COVID-19 morbidity and mortality due to influenza co-infection at a similar rate. The influenza vaccine reduced the risk of hospital admissions and death from COVID-19 for those aged 65 and over [41].A 10% increase in influenza vaccination coverage was associated with a 5% reduction in the COVID-19 mortality rate in the elderly [43].A study of 3370 pregnant and postpartum women in the Brazilian national database found the influenza vaccine effective against COVID-19 infection [44].Healthcare workers with influenza vaccine were 88.9% less likely to develop severe COVID-19 than those without a recent vaccine [45].The 2019 influenza vaccine may protect healthcare workers against COVID-19 [28]. However, another study on healthcare workers failed to show a possible association between the influenza vaccine and COVID-19 infection [23].

The potential protective effect of the influenza vaccine against a severe COVID-19 infection is estimated to last between six months and two years [46]. One small study found that the outcome was independent of the time between the influenza vaccine and COVID-19 testing [31]. In this study, the rate of COVID positivity was lower in those vaccinated for influenza in 2019 (35.3% vs 48.2%) and 2020 (34.7% vs 50%) than in those who did not.

The high number of vaccinations may be one of the reasons why children show a lower susceptibility to SARS-CoV-2 infection and milder severity compared to adults [47].Even existing vaccines other than influenza can reduce the risk of COVID-19 infection. Analysis of data from 137,037 individuals who had COVID-19 PCR testing in the Mayo Clinic electronic health record database between February 15, 2020, and July 14, 2020, consistently showed that many non-COVID-19 vaccines available in the United States (polio, Haemophilus influenza type-B [HIB], measles-mumps-rubella [MMR], varicella, pneumococcal conjugate [PCV13], geriatric influenza and hepatitis A or hepatitis B vaccines) were associated with lower rates of COVID-19 infection at 1, 2 and 5-year periods. The rate of COVID-19 was significantly lower among black individuals who received the PCV13 vaccine [29]. COVID-19 and seasonal influenza are more severe in the elderly, the obese and high-risk groups with chronic comorbidities. Therefore, in high-risk groups such as solid organ transplant recipients, pneumococcal and influenza vaccines are critical to reducing the possibility of influenza infection and co-infection with COVID-19, diagnostic dilemmas, and improper management in terms of antiviral therapy and infection control [48].

People vaccinated with a pneumococcal polysaccharide or influenza vaccine have lower risks of COVID-19 infection. The influenza vaccination rate in COVID-negative patients was higher than in COVID-positive patients (93.9% vs 6.1%) [49]. The use of PPV23 in older adults prevents pneumococcal disease by 33–40% and thus may also prevent COVID-19 morbidity and mortality from the pneumococcal disease [50]. In the cohort, two of the seven patients who died received regular influenza vaccines (both 2019 and 2020). Three had had the pneumococcal vaccine in 2019 and another in 2020. A definitive judgment cannot be made as the number of deaths is low, and probably three died from causes other than COVID-19 infection.In this study, the rate of COVID positivity was lower in those who had pneumococcal vaccination in 2019 (32.6% versus 48.4%) and 2020 (38.3% versus 47.7%) than in those who did not. It is recommended to administer both conjugated (PCV13: Prevenar, single dose) and polysaccharide (Pneumovax 23 and Pneumo-23: booster vaccines at least three to five years after the first dose) in adults. Therefore, the possibility that some patients may have been vaccinated against pneumococcus before 2019 may be a limitation tothis study. If they were vaccinated, the effectiveness of vaccines might have been reduced.

Compared with those in the COVID-negative group, patients in the COVID-positive group had a lower age, a higher living donor transplant rate, and a longer time post-transplant. There was no significant

difference between the two groups' induction and maintenance immunosuppressive regimen protocols. Multivariate analysis showed that a family history of COVID-19 increased the risk of infection by 11.7 times. Transplant patients are aware of the high risk of infection because of immunosuppressive drug use and take all precautions outsidehome. However, this observation confirms that the greatest danger comes from close relatives as in the general population. In this study, the higher contamination rate of the COVID-19 infection in younger transplant patients may be due to less adherence to isolation rules. The longer transplant time in the COVID-positive group may have reduced post-transplant viral monitoring or protective measures over time [51].

COVID-19 infection in patients with renal dysfunction is associated with worse outcomes in the presence of chronic diseases, mainly cardiovascular diseases, compared with the general population [52]. Reducing their doses during infection or withdrawing some immunosuppressive drugs according to the severity of the illness may even increase the risk of rejection. In this study population, the COVID-19 condition adversely affected graft function in a small number of patients.

## 5. Conclusion

In conclusion, this study includes data from two transplant centres in a specific geographic area. Guidelines already recommend influenza and pneumococcal vaccination, but vaccination rates are relatively low in kidney transplant patients. In the cohort, influenza and pneumococcal vaccination ratios in the COVID-negative group were generally higher than those of the COVID-positive group.These vaccines can provide extra benefits associated with COVID-19 infection during the pandemic. These findings suggest that these vaccines (especially the pneumococcal vaccine) may reduce disease risk together with the results of similar studies.The results of many studies, mostly of retrospective designs, support that the influenza vaccine may provide a potential advantage against COVID-19 (lower hospital stay, shorter length of stay, lower mortality, less intensive care and mechanical ventilation needs). Protecting vaccinated patients from influenza and secondary pneumococcal infections during COVID-19 infection would also justify vaccination. In these observations, the increase in the rate of patients who had both influenza and pneumococcal vaccines in the year the pandemic started compared to the previous year shows that patients and physicians took precautions. Debisarun et al. [32] observed a negative association between the incidence of quadrivalent inactivated influenza vaccine and COVID-19 incidence. They showed that the seasonal influenza vaccine could induce a different trained immune program by reducing systemic inflammation and regulating the transcriptional program and cytokine production of circulating immune cells.More studies are required to understand the potential role of trained immunity in the immunological mechanism of the possible protective effects of the influenza vaccine against COVID-19.

The development and availability of the COVID-19 vaccines in a relatively short time during the pandemic saved many lives. At this stage, the fate of mutations in SARS-CoV-2 and the community's vaccination rate will change the pandemic's course. High-risk transplant patients should protect themselves from exposure to COVID-19, and transplant physicians should ensure that they do not neglect their COVID, influenza, and pneumococcal vaccinations.

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