Clinical outcomes associated with long-term exposure to airborne particulate pollution in kidney transplant recipients

Yong Chul Kim, Ejin Kim, Jiyun Jung, Jae Yoon Park, Hajeong Lee, Dong Ki Kim, Yon Su Kim, Chun Soo Lim, Jung Pyo Lee, and Ho Kim

Abstract

Background: Researchers have yet to investigate the specific association between 10-μm particulate matter (PM10) levels and the risk of graft failure, kidney disease, or the functional decline of transplanted kidneys, in kidney transplant recipients (KTRs). Furthermore, we know very little about the association between PM10 levels and the development of allograft rejection in transplanted kidneys. Identification of air pollution as a potential contributor to kidney disease could help reduce future disease burden, stimulate policy discussions on the importance of reducing air pollution with respect to health and disease, and increase public awareness of the hazards of air pollution. We aimed to evaluate the relationship of PM10 with the risk of graft failure, mortality, and decline of graft function in KTRs.

Methods: Air pollutant data were obtained from the Korean National Institute of Environmental Research. We then investigated potential associations between these data and the clinical outcomes of 1532 KTRs who underwent kidney transplantation in a tertiary hospital between 2001 and 2015. Survival models were used to evaluate the association between PM10 concentrations and the risk of death-censored graft failure (DCGF), all-cause mortality, and biopsy-proven rejection (BPR), over a median follow-up period of 6.31 years.

Results: The annual mean PM10 exposure after kidney transplantation was 27.1 ± 8.0 μg/m³. Based on 1-year baseline exposure, 1 μg/m³ increase in PM10 concentration was associated with an increased risk of DCGF (hazard ratio (HR): 1.049; 95% confidence interval (CI): 1.014–1.084) and BPR (HR: 1.053; 95% CI: 1.042–1.063). Fully adjusted models showed that all-cause mortality was significantly associated with 1-year average PM10 concentrations (HR, 1.09; 95% CI, 1.043 to 1.140).

Conclusions: Long-term PM10 exposure is significantly associated with BPR, DCGF, and all-cause mortality in KTRs.

Keywords: Long-term PM10 exposure, Kidney transplant recipients, Outcomes
Background
Exposure to outdoor air pollution is a leading cause of global disease burden and accounts for over four million deaths each year [1]. Increased concentrations of daily fine particles that are 10 μm in aerodynamic diameter (PM10) are associated with an increased risk of cardiovascular disease [2, 3], stroke [4], heart failure [5, 6], death [7], and reduced life expectancy, as well as a host of other adverse health outcomes [1].

In a large cohort of veterans in the United States [8, 9], higher amounts of fine particulate matter were associated with an increased risk of incident chronic kidney disease (CKD), a reduction in estimated glomerular filtration rate (eGFR), and end-stage renal disease (ESRD). Experimental laboratory evidence also indicates that long-term exposure to micro-particles leads to disturbances in renal hemodynamics, thus promoting oxidative stress and systemic inflammation in the renal tissue; these factors exacerbates acute kidney injury and further promotes chronic renal injury in murine models [10, 11].

Previous studies have focused only on evaluating the association between PM10 and the outcomes of kidney diseases in native kidneys. However, researchers have yet to investigate the specific association between PM10 levels and the risk of graft failure, kidney disease, or the functional decline of transplanted kidneys, in kidney transplant recipients (KTRs). Furthermore, we know very little about the association between PM10 levels and the development of allograft rejection in transplanted kidneys. The identification of air pollution as a potential contributor to kidney disease could help reduce future disease burden, stimulate policy discussions on the importance of reducing air pollution with respect to health and disease, and increase public awareness relating to the hazardous nature of air pollution.

In the present study, we developed a longitudinal national cohort of KTRs and investigated the relationship between PM10 levels and the risk of biopsy-proven rejections (BPR), death-censored graft failure (DCGF), and mortality.

Methods
Study population
This was a retrospective cohort study involving data generated between January 2001 and December 2015 at the Seoul National University Hospital and Seoul National University Boramae Medical Center. Initially, a total of 1531 adult participants (> 18 years) were included. However, a number of patients were then excluded for the following reasons: (1) multiple organ transplantation (n = 61) and double kidney transplantation (n = 85); (2) graft failure within 3 months of transplantation (n = 7), and (3) mortality within 3 months of transplantation (n = 16). Only the participants whose data included a zip code were included in the final analysis.

We also collected a range of baseline information, including recipient/donor age, gender, the relationship between donor and recipient, smoking status, body mass index (BMI), the incidence of diabetes and hypertension, chronic glomerulonephritis as a cause of ESRD, the duration of renal replacement therapy (RRT) prior to transplantation, and the type of previous RRT. We also collated data relating to a range of immunological factors, including preemptive transplantation (defined by the absence of dialysis prior to transplantation), donor status (living or deceased), ABO incompatibility, and a number of HLA-A, -B, and -DR mismatches.

Air pollution data
Across the South Korea, there are eleven different types of monitoring sites operated by the Ministry of Environment and local governments. These monitoring sites are situated across 584 locations in 114 cities and counties. This study used data arising from 373 monitoring stations situated in both urban and roadside positions.

PM10 concentration data for 2001 and 2015 were provided by the Korean National Institute of Environmental Research (https://www.airkorea.or.kr/web). We collated hourly PM10 data from each of our 373 national monitoring sites. In addition, we used daily mean PM10 concentrations for individual study populations according to the respective district of each enrolled patient, as determined by the residential address stated on medical records.

In this study, we were interested in the effects of long-term exposure. To examine the effect of the amount of exposure at the time of outcome, rather than at the time of kidney transplantation, the exposure concentration was varied from 1 to 5 years before the clinical outcomes. We analyzed the effects of exposure by applying the average concentration values for each of these periods.

Laboratory measurements and study outcomes
Graft function was assessed by determining serum creatinine levels after transplantation. The eGFR was calculated using the MDRD GFR equation [12]. Graft failure was defined as an irreversible loss of graft function with the need to restart dialysis or to undergo re-transplantation. DCGF data were also analyzed. Surveillance biopsies were routinely performed 1–2 weeks after transplantation in almost all patients. Additional biopsies were performed when renal graft function was impaired, or when there was a considerable reduction in urine output. Rejection was determined according to the diagnostic criteria proposed at the 2007 Banff Conference [13], while BPRs involved acute T-cell
mediated rejection (TCMR) and acute antibody-mediated rejection (ABMR), and chronic rejections.

**Statistical analysis**

Demographic and clinical characteristics of the overall cohort are presented as frequencies (percentages) for categorical variables and as means (with standard deviation, SD) for continuous variables.

To investigate the association between the clinical outcomes of transplantation patients and PM10 concentration, we calculated Kaplan-Meier estimates of survivor functions and compared survival curves between groups of patients according to a pre-determined cut-off value, which was defined as the median annual mean PM10 concentration.

Next, the median PM10 concentration was used to divide PM10 data into two groups, and a log rank test was used to test the null hypothesis. We then used the Cox proportional hazards survival model to investigate the association between the 1-year mean PM10 concentrations (for the 5-year study period) before the events occurred, along with the individual and clinical outcomes. Finally, we adjusted our data to take account of covariates. As the definition of exposure was dependent on the annual mean obtained from an air monitoring station in each district, we also collated data from the year prior to the event. Additionally, subgroup analysis was performed for two groups of TCMR and ABMR according to the mechanism of occurrence of the biopsy-proven rejection event, one of the outcomes.

To explore whether this association was non-linear or linear, we considered a non-linear relationship via smoothing splines. Splines are mathematical constructs made of fragments of polynomial functions that are stitched together to form a smooth curve. In order to identify a smoothing spline, we used the penalized partial likelihood method; this is known to be an effective method for survival analysis.

We used models that incorporated subject-specific random effects to account for unmeasured subject characteristics that influenced the hazard of the occurrence of the outcome. In our research, these models were then extended to models that incorporated cluster-specific random effects to account for within-cluster homogeneity in outcomes. Moreover, we investigated whether different concentrations of PM10 affected the health of kidney transplant patients using the two-pollutant model of PM10 with adjustment for SO2, CO, NO2, and O3 and whether these effects differed by regions. All statistical analyses were performed using R (3.6.0) and SAS version 9.4.

**Results**

Initially, we recruited a total of 1532 individuals. However, we then excluded 240 patients aged < 19 years, 61 patients who underwent multiple organ transplantation, and 85 patients who underwent kidney transplantation more than twice. Consequently, our final analysis featured 1146 eligible KTRs (Fig. 1). The demographic characteristics of the final study participants are presented in Table 1. The mean age of the recipients at the time of kidney transplantation was 45.0 ± 12.5 years and that of the donors was 42.6 ± 13.0 years. The majority of the study population were males (60.12%), and 11.61% were smokers. Overall, 91.97% of our patients were hypertensive and 34.12% had diabetes mellitus. When measured 6 months after transplantation, the eGFR was 56.0 ± 17.5 ml/min/1.73 m2. The incidence of preemptive kidney transplantation was 29.8%, while that of ABO incompatible kidney transplantation was 5.9%. The geographic locations of the participants are shown in Figure S1. Figure 2 shows the annual mean PM10 concentrations for each year during the entire study period. The overall mean PM10 concentration was 52.68 ± 30.49 \( \mu g/m^3 \). The mean PM10 exposure showed a slight increase compared to the overall mean PM10 concentration between 2001 and 2009 (yearly mean PM10 exposure was 60.22, 59.19, 58.05, 58.85, 57.83, 55.9, 56.8, 54.22, and 53.1 \( \mu g/m^3 \), respectively), but then a slight decrease from 2010 to 2015 (yearly mean PM10 exposure was 51.11, 49.84, 44.96, 48.89, 48.94, and 47.63 \( \mu g/m^3 \), respectively).

Mean follow-up time was 6.3 ± 4.2 years and a total of 51 deaths (4.5%), 78 cases of DCGF (6.8%), and 549 cases of BPR (47.9%) were recorded. The Kaplan-Meier survival curves for BPR, DCGF, and mortality were significantly worse in the group exposed to higher

![Fig. 1 Flow diagram showing patient enrollment and application of exclusion criteria](image-url)
concentrations of PM10 than in the group exposed to lower concentrations (Fig. 3).

Overall, our data indicated that a 1 μg/m³ increase in PM10 concentration was associated with an increased risk of BPR (hazard ratio [HR]: 1.053; 95% confidence interval [CI]: 1.042–1.063), graft failure (HR: 1.049; 95% CI: 1.014–1.084), and mortality (HR: 1.090; 95% CI: 1.043–1.140) in our analyses considering exposure over a 1-year period with regards to prospective clinical outcome (Table 2). In addition, we performed analyses of various PM10 exposure values, from 2-year to 5-years (S1-S3 Tables). According to the results of this sensitivity analysis, the effect of PM10 on the clinical outcome of kidney transplant patients consistently showed a significant effect according to the concentration value of PM10 over various periods. Spline analyses suggested a linear relationship between PM10 concentration and the risk of BPR (P-value for nonlinearity < 0.031), DCGF (P-

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**Table 1 Demographic and baseline characteristics of the overall study population**

| Variables                      | Category                | Median                                   | Total |
|--------------------------------|-------------------------|------------------------------------------|-------|
|                                |                         | Low[26.26 ~ 53.00)] (663 [57.85)]        |       |
|                                |                         | High[53.00 ~ 120.19)] (483 [42.15)]      |       |
|                                | N (%)                   | N (%)                                    |       |
| **Recipient characteristics**  |                         |                                         |       |
| Age at transplantation, years  | 45.12 ± 12.92           | 44.92 ± 11.86                            | 45.0 ± 12.5 |
| Sex                            | male                    | 405 (35.34)                              | 689 | 60.12 |
|                                | female                  | 258 (22.51)                              | 457 | 39.88 |
| Smoking                        | yes                     | 66 (5.76)                                | 133 | 11.61 |
|                                | no                      | 597 (52.09)                              | 1013 | 88.39 |
| Body mass index, kg/m³         | 22.74 ± 3.35            | 22.56 ± 3.25                             | 26.2 ± 70.5 |
| Hypertension                   | yes                     | 588 (51.31)                              | 1054 | 91.97 |
|                                | no                      | 75 (6.54)                                | 92 | 8.03 |
| Diabetes mellitus              | yes                     | 229 (19.98)                              | 391 | 34.12 |
|                                | no                      | 434 (37.87)                              | 755 | 65.88 |
| Preemptive                     | yes                     | 208 (18.15)                              | 342 | 29.84 |
|                                | no                      | 455 (39.70)                              | 804 | 70.16 |
| RRT duration before KT, months | 36.93 ± 45.44           | 39.78 ± 48.28                            | 38.13 ± 46.65 |
| Phosphorus, mg/dl              | 5.11 ± 6.16             | 4.91 ± 1.62                              | 5.02 ± 4.82 |
| Albumin, g/dl                  | 5.27 ± 38.66            | 3.90 ± 0.61                              | 4.69 ± 29.40 |
| eGFR at 6 months, ml/min/1.73m²| 55.30 ± 18.45           | 57.06 ± 16.02                            | 56.0 ± 17.5 |
| Diseases causing ESRD          | DM                      | 119 (10.38)                              | 189 | 16.49 |
|                                | HTN                     | 29 (2.53)                                | 48 | 4.19 |
|                                | GN                      | 250 (21.82)                              | 422 | 36.82 |
|                                | others                  | 81 (7.07)                                | 154 | 12.43 |
|                                | unknown                 | 184 (16.06)                              | 333 | 29.06 |
| HLA mismatch                   | 2.98 ± 1.76             | 3.01 ± 1.60                              | 2.99 ± 1.69 |
| **Donor characteristics**      |                         |                                         |       |
| Donor age, years               | 43.1 ± 13.14            | 41.80 ± 12.70                            | 42.6 ± 13.0 |
| Donor sex                      | male                    | 368 (32.11)                              | 651 | 56.81 |
|                                | female                  | 295 (25.74)                              | 495 | 43.19 |
| Donor type                     | Living                  | 452 (39.44)                              | 777 | 67.8 |
|                                | Deceased                | 211 (18.41)                              | 369 | 32.2 |
| ABO                            | compatible              | 621 (53.40)                              | 1078 | 94.07 |
|                                | incompatible            | 51 (4.45)                                | 68 | 5.93 |

Data are presented as means with standard deviation unless otherwise indicated. Covariates are given as measured at the time of kidney transplantation. *RRT* renal replacement therapy, *KT* kidney transplantation, *eGFR* estimated glomerular filtration rate, *ESRD* end stage renal disease, *DM* diabetes mellitus, *HTN* hypertension, *GN* glomerulonephritis, *HLA* human leukocyte antigen
value for nonlinearity = 0.2), and all-cause mortality ($P$-value for nonlinearity = 0.7; Fig. 4). The slope of the mortality plot showed a linear trend. For BPR, we observed a significant increasing trend in nonlinearity with a slight flat turn after the 1-year moving average PM10 concentration of 70 $\mu$g/m$^3$. However, only a limited amount of data was acquired at these higher concentrations, as reflected by the wide CI; this confirms our observation that a departure from linearity cannot be established.

The results for the gamma frailty model is reported in Table 3. The estimate of the within-cluster correlation

Fig. 2 Distribution of baseline PM10 exposure by year. Boxes display the 25-75th percentiles (interquartile range: IQR); the center line represents the median concentration. Whiskers indicate the most extreme data within 3 IQRs of the box, while circles indicate outlying values

Fig. 3 Survival curves by median value of the annual mean PM10 concentration. (A) Biopsy-proven rejection (BPR), (B) Death-censored graft failure (DCGF), and (C) All-cause mortality. Note: The units for the X-axis “Time” of the Kaplan meier curve are months
of outcomes and the variance of the frailty distribution for clinical outcomes of BPR, DCGF, and all-cause mortality was 0.05304, 0.0001, and 0.03079, respectively. Thus, the within-cluster correlation of survival times was marginally greater than 0.007, 0.012, and 0.186. After adjustment for air pollutants, the associations between PM10 and BPR and between DCGF and all-cause mortality were significant for all outcomes. The estimates of the hazard ratio for BPR with one unit increase in PM10 concentration decreased significantly after adjustment for SO2 (0.2%), CO (0.4%), NO2 (4.1%), and O3 (0.4%). Notably, the hazard ratio for GF with the same increase in PM10 concentration increased by 6.2%, and the hazard ratio for mortality increased by 6.8% after adjustment for O3 (Table 4). As a result of subgroup analysis of two groups according to the BPR mechanism, the hazard ratio of PM10 was 1.053 (95% CI: 1.043–2.895) in the TCMR group, and the HR in the ABMR group was 1.133 (95%CI:1.054–1.219), which were statistically significant (Table 5).

### Discussion

To the best of our knowledge, this is the first study to examine the association between long-term exposure to PM10 and clinical outcomes in KTRs. In this study, we demonstrated that long-term exposure to higher 1-year moving mean PM10 concentration significantly increased the risk of all-cause mortality, DCGF, and BPR in KTRs. We used the observations of the monitoring stations at the local level and applied the average values over several periods to conduct a sensitivity analysis. In addition, by considering the unmeasured confounder, the characteristic of regions, we used models with a random effect term. When considering the within-cluster correlation of survival times, random effects were significant only in DCGF and BPR and not mortality. The results of both models, the model with random effects or not, showed that PM10 had a statistically significant effect on the health of kidney transplant patients.

Several epidemiological studies have reported the association between particulate matter and CKD. For example, a weak acceleration in the progression of

| Table 2 Risk of outcomes in PM₁₀ concentration for average of 1 year from events day |
|-----------------|-----------------|-----------------|-----------------|
| Variables       | BPR             |                | DCGF             |                | All-cause mortality |
|                 | HR   | 95% CI       | P Value | HR   | 95% CI       | P Value | HR   | 95% CI       | P Value |
| Age at transplantation | 1.099 | 1.009 | 0.9979 | 0.974 | 0.948 | 1.002 | 0.0647 | 1.071 | 1.033 | 1.109 | 0.0001 |
| Smoking         | 1.168 | 0.880 | 1.549 | 0.2828 | 1.091 | 0.507 | 2.350 | 0.8235 | 0.457 | 0.129 | 1.612 | 0.2233 |
| Body mass index | 1.099 | 0.999 | 1.001 | 0.6925 | 0.928 | 0.844 | 1.022 | 0.1279 | 0.905 | 0.801 | 1.022 | 0.1087 |
| Hypertension    | 0.905 | 0.645 | 1.269 | 0.5629 | 1.198 | 0.274 | 5.245 | 0.8108 | 0.926 | 0.116 | 7.369 | 0.9422 |
| Diabetes mellitus | 0.872 | 0.675 | 1.127 | 0.2948 | 0.895 | 0.420 | 1.907 | 0.7731 | 1.167 | 0.502 | 2.710 | 0.72 |
| Sex (male)      | 1.083 | 0.885 | 1.324 | 0.4382 | 2.232 | 1.213 | 4.107 | 0.0098 | 1.772 | 0.834 | 3.767 | 0.1368 |
| HLA mismatch    | 1.213 | 1.145 | 1.285 | <.0001 | 1.182 | 1.006 | 1.389 | 0.0419 | 0.995 | 0.805 | 1.320 | 0.9628 |
| Cause of ESRD (DM) | 1.137 | 0.808 | 1.601 | 0.4602 | 2.404 | 0.958 | 6.035 | 0.0618 | 1.381 | 0.515 | 3.704 | 0.521 |
| Cause of ESRD (HTN) | 0.986 | 0.607 | 1.601 | 0.9532 | 1.663 | 0.471 | 5.868 | 0.4291 | 1.367 | 0.375 | 4.983 | 0.6358 |
| Cause of ESRD (GN) | 0.95 | 0.762 | 1.185 | 0.6504 | 0.682 | 0.374 | 1.243 | 0.2113 | 0.603 | 0.256 | 1.419 | 0.2466 |
| Cause of ESRD (other) | 0.981 | 0.683 | 1.409 | 0.9187 | 1.252 | 1.089 | 1.440 | 0.0016 | 1.2 | 0.995 | 1.447 | 0.0564 |
| Phosphorus      | 1.047 | 0.989 | 1.108 | 0.1147 | 0.444 | 0.323 | 0.611 | <.0001 | 0.669 | 0.440 | 1.015 | 0.0589 |
| Albumin         | 0.885 | 0.781 | 1.012 | 0.0543 | 0.987 | 0.981 | 0.994 | <.0001 | 0.965 | 0.946 | 0.984 | 0.0003 |
| eGFR at 6 months | 0.895 | 0.706 | 1.134 | 0.3579 | 0.815 | 0.445 | 1.494 | 0.509 | 0.992 | 0.438 | 2.247 | 0.9855 |
| preemptive      | 1.053 | 1.042 | 1.063 | <.0001 | 1.049 | 1.014 | 1.084 | 0.0055 | 1.09 | 1.043 | 1.140 | 0.0001 |
| Donor age       | 1.012 | 1.004 | 1.020 | 0.0036 | 0.993 | 0.971 | 1.016 | 0.5561 | 1.005 | 0.978 | 1.033 | 0.0762 |
| Donor sex (male) | 1.146 | 0.944 | 1.392 | 0.1693 | 1.066 | 0.633 | 1.795 | 0.81 | 1.539 | 0.761 | 3.110 | 0.2298 |
| Donor type (Deceased) | 1.355 | 1.074 | 1.709 | 0.0105 | 1.724 | 0.884 | 3.361 | 0.1098 | 1.907 | 0.881 | 4.129 | 0.1015 |
| ABO-incompatible | 1.935 | 1.330 | 2.816 | 0.0006 | 1.897 | 0.549 | 6.558 | 0.3116 | 1.205 | 0.151 | 9.642 | 0.8602 |

Data are presented as mean and standard deviation unless otherwise indicated. Covariates are given as measured at the time of kidney transplantation. BPR biopsy-proven rejection, DCGF death-censored graft failure, HLA human leukocyte antigen, ESRD end stage renal disease, DM diabetes mellitus, HTN hypertension, GN glomerulonephritis, eGFR estimated glomerular filtration rate. The multivariable model was adjusted for age, smoking, BMI, hypertension, DM, sex, HLA mismatch, cause of ESRD, serum phosphorus, albumin, eGFR at 6 months, preemptive, annual mean PM₁₀, donor age, sex, donor type, and ABO-incompatible

*These are unestimable due to the lack of the events
albuminuria was observed during chronic exposure to PM10 in the Multi-Ethnic Study of Atherosclerosis cohort. In China, long-term exposure to PM2.5 was associated with an increased risk of membranous nephropathy in 71,151 native kidney biopsy samples [14]. Another longitudinal observational cohort study of US veterans reported the association between PM2.5 concentration and a higher risk of CKD incidence and progression to ESRD [8]. Among 21,656 Taiwanese adults [15], individual exposure to PM10, coarse particles, or PM2.5 was related to reduced renal function. In a nationwide cohort study [9], Bowe et al. showed that higher concentrations of PM10, NO2, and CO, were associated with increased risks of CKD, renal function decline, and ESRD. In a recent cohort study in the US observed that higher annual PM2.5 exposure was associated the increased albuminuria and a higher risk of CKD [16].

In the present study, we found that elevated levels of PM10 were consistently associated with a significantly higher risk of adverse renal transplantation outcomes, including DCGF, BPR, and all-cause mortality. Our sensitivity analyses indicated that our results were robust, including the examination of various exposure durations and analyses involving fully adjusted models. We found that PM10 affects each outcome even after adjusting for other air pollutants. In addition, the effects of CO and O3, which are other air pollutants that were adjusted, were statistically significant.

Table 3 shows the covariance estimates and associated statistics for fixed effects and the variance of frailty. As shown in the table, the frailty value is significantly greater than zero ($\theta = 0.05$; $p$ value = 0.0078). Furthermore, our result shows that there are factors that influence the hazard of BPR. It is obvious from our results, that the districts were important ($p$ value = 0.0078) and gamma frailty with a covariance estimates of 0.05 shows that there were unmeasured districts effects present in the model.

Fig. 4 The risk of renal outcomes according to PM10 concentrations. Models were adjusted for age, sex, diabetes mellitus, hypertension, eGFR 6 months after surgery, BMI, HLA Ag Mismatch, the cause of ESRD, albumin, phosphorus, preemptive kidney transplantation, donor age, donor sex, and donor type (deceased). a Risk of incident biopsy-proven rejections (BPR) ($P$ for nonlinearity = 0.000032). b Risk of incident death-censored graft failure (DCGF) ($P$ for nonlinearity = 0.07). c Risk of all-cause mortality ($P$ for nonlinearity = 0.4)
The underlying biological mechanisms that may explain the novel association between long-term PM10 exposure and renal outcomes in KTRs is unclear. Classically, the inhalation of particulate matters activates pulmonary inflammatory cells that may trigger a systemic inflammatory response that triggers a cascade of events, ultimately affecting the body’s cardiovascular system [17]. Recent studies have reported that the inhaled

| Variables                        | BPR HR (95% CI) | P Value | DCGF HR (95% CI) | P Value | All-cause mortality HR (95% CI) | P Value |
|----------------------------------|----------------|---------|-----------------|---------|-------------------------------|---------|
| Age at transplantation           | 1.091 (1.009)  | 0.974   | 1.002           | 0.0647  | 1.07 (1.033)                  | 0.0002  |
| Smoking                          | 1.215 (1.141)  | 1.091   | 2.350           | 0.8235  | 0.463 (0.131)                 | 0.2304  |
| Body mass index                  | 1.099 (1.001)  | 0.928   | 1.022           | 0.1279  | 0.904 (0.800)                 | 0.1077  |
| Hypertension                     | 0.909 (0.647)  | 1.198   | 5.245           | 0.8108  | 0.93 (0.117)                  | 0.9455  |
| Diabetes mellitus                | 0.888 (0.686)  | 0.895   | 1.907           | 0.7731  | 1.159 (0.499)                 | 0.7314  |
| Sex (male)                       | 1.064 (0.870)  | 2.232   | 4.107           | 0.0098  | 1.747 (0.821)                 | 0.3176  |
| HLA mismatch                     | 1.217 (1.149)  | 1.182   | 1.389           | 0.0419  | 1 (0.808)                     | 0.9988  |
| Cause of ESRD (DM)               | 1.158 (0.823)  | 2.404   | 6.036           | 0.0617  | 1.417 (0.528)                 | 3.804   |
| Cause of ESRD (HTN)              | 1.061 (1.262)  | 1.663   | 5.868           | 0.429   | 1.369 (0.375)                 | 4.997   |
| Cause of ESRD (GN)               | 0.955 (0.765)  | 0.682   | 1.243           | 0.2113  | 0.602 (0.255)                 | 1.420   |
| Cause of ESRD (others)           | 1.018 (0.708)  | 1.015   | 1.084           | 0.0016  | 1.204 (0.997)                 | 1.454   |
| Phosphorus                       | 1.051 (0.992)  | 1.252   | 1.440           | 0.0001  | 1.204 (0.997)                 | 1.454   |
| Albumin                          | 0.881 (0.777)  | 0.444   | 0.611           | <0.0001 | 0.67 (0.440)                  | 1.021   |
| eGFR at 6 months                 | 0.987 (0.981)  | 0.965   | 0.984           | 0.0003  | 0.999 (0.977)                 | 1.022   |
| preemptive                       | 0.883 (0.786)  | 0.815   | 1.494           | 0.509   | 0.999 (0.440)                 | 2.266   |
| Annual mean PM10                 | 1.058 (1.047)  | 1.104   | 1.084           | 0.0555  | 1.093 (1.046)                 | 1.142   |
| Donor age                        | 1.012 (1.004)  | 1.091   | 1.084           | 0.0055  | 1.093 (1.046)                 | 1.142   |
| Donor sex                        | 1.16 (0.954)   | 0.993   | 1.056           | 0.5561  | 1.005 (0.978)                 | 1.033   |
| Donor type (Deceased)            | 1.365 (1.080)  | 1.724   | 3.361           | 0.1098  | 1.939 (0.890)                 | 4.223   |
| ABO-incompatible                 | 2.002 (1.374)  | 1.897   | 6.558           | 0.3117  | 1.183 (0.148)                 | 9.467   |
| Random regions                   | 0.05304        | 0.0078  | 0.0001          | 0.0128  | 0.03079                      | 0.1866  |

Data are presented as mean and standard deviation unless otherwise indicated. Covariates are given as measured at the time of kidney transplantation. BPR biopsy-proven rejection, DCGF death-censored graft failure, HLA human leukocyte antigen, ESRD end stage renal disease, DM diabetes mellitus, HTN hypertension, GN glomerulonephritis, eGFR estimated glomerular filtration rate. The multivariable model was adjusted for age, smoking, BMI, hypertension, DM, sex, HLA mismatch, cause of ESRD, serum phosphorus, albumin, eGFR at 6 months, preemptive, annual mean PM10, donor age, sex, donor type, ABO-incompatible and random effect (region).

*These are unestimable due to the lack of the events.

The underlying biological mechanisms that may explain the novel association between long-term PM10 exposure and renal outcomes in KTRs is unclear. Classically, the inhalation of particulate matters activates pulmonary inflammatory cells that may trigger a systemic inflammatory response that triggers a cascade of events, ultimately affecting the body’s cardiovascular system [17]. Recent studies have reported that the inhaled

| Table 4 Hazard Ratio in association with annual average concentration of PM10 after adjusting for co-pollutants |
|---------------------------------------------------------------|---------------------------------------------------------------|
| BPR HR (95% CI)                                              | DCGF HR (95% CI)                                             | All-cause mortality HR (95% CI) |
| Single pollutant model of PM10                               | 1.053 (1.042)                                               | 1.091 (1.043)                  |
| PM10 with adjustment for SO2 (sulfur dioxide)                | 1.051 (1.040)                                               | 1.084 (1.140)                 |
| Single pollutant model of PM10                               | 1.053 (1.042)                                               | 1.091 (1.043)                  |
| PM10 with adjustment for CO (carbon monoxide)                | 1.049 (1.038)                                               | 1.075 (1.125)                 |
| Single pollutant model of PM10                               | 1.053 (1.042)                                               | 1.084 (1.140)                 |
| PM10 with adjustment for NO2 (Nitrogen dioxide)              | 1.012 (1.004)                                               | 1.091 (1.139)                 |
| Single pollutant model of PM10                               | 1.053 (1.042)                                               | 1.084 (1.140)                 |
| PM10 with adjustment for O3 (Ozone)                          | 1.049 (1.039)                                               | 1.142 (1.201)                 |

BPR biopsy-proven rejection, DCGF death-censored graft failure
Adjusted covariates: age, smoking, BMI, hypertension, DM, sex, HLA mismatch, cause of ESRD, serum phosphorus, albumin, eGFR at 6 months, preemptive, annual mean PM10, donor age, sex, donor type, and ABO-incompatible.
nanoparticles rapidly translocate from the pulmonary tissues into the vascular systemic circulation and subsequently accumulate in various organs, such as the heart, liver, and kidneys; these observations have been made in studies involving both animals and humans [18–21].

These particles have the capacity to induce pulmonary inflammation and oxidative stress; parallel pathways can also be activated in the systemic circulation and organ systems. Research has also shown that inflammatory markers, including C-reactive protein, fibrinogen, white blood cell counts, and IL-6, are positively associated with PM exposure [22, 23], and that short-term changes in PM concentrations cause alterations in these key inflammatory biomarkers [24, 25].

Other studies have investigated kidney damage following sub-chronic exposure to PM2.5 by analyzing the levels of early kidney biomarkers, histological changes, induction of the angiotensin and bradykinin system, and by measuring changes in blood pressure [26, 27]. In a previous study, involving an animal model, long-term exposure to PM2.5 was associated with kidney damage, including inflammatory cell infiltration, tubulo-interstitial fibrosis, and mesangial expansion; collectively, these effects caused an impairment in renal function [28].

Our data showed that prolonged long-term exposure to PM10 was associated with higher risks of transplant kidney rejections in KTRs. However, there is little in the current literature to explain the relationship between PM10 exposure and the risk of graft rejections. However, there is some evidence originating from studies involving the recipients of other transplanted organs, such as lung transplant recipients that suggests that PM may trigger rejection of the transplanted organ. Recent studies have reported that exposure to traffic-related air pollution independently increased the risk of bronchiolitis obliterans syndrome, a condition that is clinically correlated with chronic rejection in lung transplant patients [29], and also associated with the development of chronic lung allograft dysfunction, a condition that is related to both acute and chronic allograft rejections [30, 31]. Acute rejection presents a major problem after organ

Table 5 The results of subgroup analysis by types of BPR

| Variables                  | TCMR | ABMR |
|----------------------------|------|------|
| Age at transplantation     | 0.998| 1.073|
| Smoking                    | 1.148| 3.067|
| Body mass index            | 1    | 0.968|
| Hypertension               | 0.999| 0.624|
| Diabetes mellitus          | 0.884| 0.569|
| Sex (male)                 | 1.152| 0.441|
| HLA mismatch               | 1.219| 1.19  |
| Cause of ESRD (DM)         | 1.153| 0.826|
| Cause of ESRD (HTN)        | 1.065| 0.826|
| Cause of ESRD (GN)         | 0.945| 1.682|
| Cause of ESRD (others)     | 1.032| 0.406|
| Phosphorus                 | 1.042| 0.995|
| Albumin                    | 0.906| 0.652|
| eGFR at 6 months           | 0.989| 1.001|
| preemptive                 | 0.869| 1.062|
| Annual mean PM10           | 1.053| 1.133|
| Donor age                  | 1.014| 0.998|
| Donor sex                  | 1.13 | 2.051|
| Donor type (Deceased)      | 1.348| 0.525|
| ABO-incompatible           | 1.179| 0.525|

Data are presented as mean and standard deviation unless otherwise indicated. Covariates are given as measured at the time of kidney transplantation. TCMR acute T-cell mediated rejection, ABMR acute antibody-mediated rejection, DCGF death-censored graft failure, HLA human leukocyte antigen, ESRD end stage renal disease, DM diabetes mellitus, HTN hypertension, GN glomerulonephritis, eGFR estimated glomerular filtration rate. The multivariable model was adjusted for age, smoking, BMI, hypertension, DM, sex, HLA mismatch, cause of ESRD, serum phosphorus, albumin, eGFR at 6 months, preemptive, annual mean PM10, donor age, sex, donor type, and ABO-incompatible.

These are unestimable due to the lack of the events.
transplantation, and is a recognized risk factor for chronic rejection and all-cause mortality. The authors of these previous papers provided evidence for the increased risk of rejection after lung transplantation with temporal changes in particulate air pollution, and reported this was associated with bronchoalveolar lavage neutrophilia and lymphocytosis. This tissue damage was explained by the novel effect of PM on Th17 polarization via the aryl hydrocarbon receptor [32]. However, the precise biological mechanisms by which exposure to PM10 can trigger kidney rejection is not yet fully understood. One explanation is that the inhaled PM may directly or indirectly induce oxidative stress and inflammation in the transplanted kidney and that this induces endothelial cell dysfunction and exacerbates the production of reactive oxygen species. These complicated processes may be responsible for shifting the immune responses to an effector phenotype, thus leading to the loss of self-tolerance and a shift towards allograft rejection. Further preclinical and epidemiological studies are now required to investigate the association between air pollution and allograft rejection, especially in KTRs.

One particular strength of our study is that we investigated a large contemporary Korean cohort of KTRs with a long-term follow-up of 15 years. Because we had access to comprehensive long-term air pollutant data, we were able to adjust the data for multiple donors and recipient variables. Moreover, this study used BPR data as the chief outcome to evaluate the impact of PM10. However, this study also has several limitations that need to be considered. First, the study participants were mostly South Koreans; therefore, the findings may not be generalizable to other populations. Although we accounted for known confounding factors, and region with frailty survival analysis, we cannot ignore the possibility and potential effects of unknown or non-measured confounders. Therefore, if the sample size of the study was large, and subjects were evenly distributed in the sub-regional unit, it can be carefully assumed that the effect of size on the region may increase.

**Conclusions**

In summary, we demonstrate a significant association between PM10 concentrations and the risk of graft failure development, all-cause mortality, and BPR in KTRs. Continued efforts to improve air quality may help to reduce the burden of renal outcome in KTRs.

**Abbreviations**

PM10: 10-μm particulate matter; KTRs: Kidney transplant recipients; DCGF: Death-censored graft failure; TCVR: Acute T-cell mediated rejection; ABMR: Acute antibody-mediated rejection; BPR: Biopsy-proven rejection; CKD: Chronic kidney disease; eGFR: Estimated glomerular filtration rate; BMI: Body mass index; RRT: Renal replacement therapy; SD: Standard deviation; HR: Hazard ratio; CI: Confidence interval

**Supplementary Information**

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**Authors’ contributions**

Research idea and study design: Y.S.K., E.K., J.P.L., and H.K.; data acquisition: Y.C.K and E.K. J.I., J.Y.P., H.L., and D.K.K.; data analysis/interpretation: Y.C.K., E.K., Y.S.K., C.S.L., and H.K.; drafted and revised the paper: Y.C.K., E.K., and J.P.L. All authors have approved the final version of the manuscript.

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**Availability of data and materials**

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Declarations**

**Ethics approval and consent to participate**

The present study was conducted with the approval of the Research Ethics Committee of the Seoul National University Hospital. All procedures were performed in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The requirement to obtain informed consent was waived by the IRB due to the retrospective nature of this study.

**Consent for publication**

Not applicable.

**Competing interests**

Dr. Yong Chul Kim, Ejin Kim, Jiyoung Jung, Jae Yoon Park, Hajeong Lee, Dong Ki Kim, Yoon Su Kim, Chun Soo Lim, Jung Pyo Lee, and Ho Kim declare that they have no relevant financial and non-financial conflicts of interest.

**Author details**

1Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea. 2Institute of Health and Environment, Graduate School of Public Health, Seoul National University, Seoul, Republic of Korea. 3Department of Public Health Science, Institute of Sustainable Development, Institute of Health and Environment, Graduate School of Public Health, Seoul National University, Room 708, Building 220, Gwanak-Ro Gwanak-Gu, Seoul 08826, Republic of Korea. 4Department of Internal Medicine, Dongguk University Ilsan Hospital, Gyeyonggi-do, Republic of Korea. 5Department of Internal Medicine, Seoul National University College of Medicine, 20 Boramae-ro S-gil, Dongjak-gu, Seoul 07061, Republic of Korea. 6Department of Medical Science, Seoul National University College of Medicine, Seoul, Korea. 7Department of Internal Medicine, Seoul National University Boramae Medical Center, 20 Boramae-ro S-gil, Dongjak-gu, Seoul 07061, Seoul, Republic of Korea.
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