

Air Pollution Alleviation During COVID-19 Pandemic is Associated with Renal Function Decline in Stage 5 CKD Patients

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Introduction: Air pollution is a novel environmental risk factor for chronic kidney disease (CKD). Air quality improved during COVID-19 lockdowns; however, the effects of these lockdowns on PM_{2.5} concentrations and renal function remain unclear.

Methods: We conducted a retrospective cohort study to compare air pollution and estimated glomerular filtration rate (eGFR) decline in patients with stage 5 CKD between a year-long period of lockdown (2020; n = 724) and a similar period before lockdown (2019, n = 758).

Results: Compared with 2019, a 17.5% reduction in the average PM_{2.5} concentration (from 17.36% to 14.32%; $P < 0.001$) and a 45.1% reduction (from 20.56% to 11.25%; $P < 0.001$) in cumulative days with PM_{2.5} concentration $>35 \mu\text{g}/\text{m}^3$ were noted in 2020. Moreover, a 93% reduction in PM_{2.5} air quality index >150 per station-day (from 0.43% to 0.03%) was observed in 2020. From 2019 to 2020, the yearly incidence of eGFR decline $\geq 5 \text{ mL}/\text{min}/1.73 \text{ m}^2$ decreased by 33.7% (24.6% vs 16.3%; $P < 0.001$). Similarly, the proportion of patients who started undergoing regular dialysis also decreased by 32.7% in 2020 (from 20.8% to 14.0%; $P = 0.001$).

Conclusion: Our findings suggest that fewer events of renal function decline during the COVID-19 pandemic may be associated with a decline in PM_{2.5} concentrations, supporting the global strategy of reducing air pollution to prevent CKD progression.

Keywords: COVID-19 pandemic, chronic kidney disease, air pollution, PM_{2.5}, air quality index

Introduction

According to recently published World Health Organization (WHO) data, 99% of the global population breathes air that exceeds WHO air quality limits, thereby causing several diseases.¹ Particulate matter (PM), one of the air pollutants, is a complex mixture of solid and liquid particles that are contributed by various sources, including industrial manufacturing processes, fossil fuel burning, road dust, and other natural sources.²⁻⁴ Breathing fine PM with a diameter $<2.5 \mu\text{m}$ (PM_{2.5}) causes detrimental health effects, because these particles reach the distal alveoli and trigger a systemic inflammatory response and oxidative stress. Moreover, they enter the systemic circulation and damage distal organs,^{5,6} such as the heart, blood vessels, and kidneys.⁶⁻¹⁷

Chronic kidney disease (CKD) is recognized as a global public health issue because of the increasing number of cases.¹⁸ The overall CKD mortality increased by 31.7% over the last 10 years, making it one of the fastest rising causes of death, alongside diabetes and dementia.¹⁹ Air pollution is the second leading cause of death from noncommunicable diseases (NCDs) after tobacco smoking.¹⁸ The third United Nations high-level meeting on NCDs in 2018 recognized indoor and outdoor air pollution as a risk factor for NCDs.²⁰ Several traditional metabolic risk factors and modifiable behaviors have been identified for CKD. Moreover, several studies have reported the association between CKD and air

pollution, specifically PM_{2.5} pollution. Therefore, air pollution is considered a novel environmental risk factor for the development and progression of CKD.^{15–17}

COVID-19, which emerged in early 2020, continues to threaten the lives of people worldwide. Pandemic lockdowns are known to improve air quality.^{21–24} Studies based in a Chinese megacity have reported an association between the improved air quality during COVID-19 lockdown and reduced mortality.^{24,25} Similar to other countries, Taiwan has made considerable efforts to combat COVID-19. The food, hospitality, transportation, and manufacturing industries were hit hard by the pandemic. In 2020, a marked reduction in air pollution was also reported in Taiwan.²⁵ Chiu et al noted the high prevalence and incidence of CKD in Taiwan²⁶ and conducted a study to report an association between high PM_{2.5} concentrations and an increased risk of acute lung edema in patients with stage 5 CKD who were not undergoing dialysis.²⁷ Few studies have focused on the effect of reduced PM_{2.5} concentrations on the renal function of patients with CKD. Therefore, we evaluated the association between air pollutant concentrations and renal function in patients with stage 5 CKD during the 2-year COVID-19 period.

Materials and Methods

Study Participants

This retrospective cohort study included patients with pre-end-stage renal disease (pre-ESRD) presenting to the Taichung Veterans General Hospital. In Taiwan, the nationwide pre-ESRD pay-for-performance program was implemented in 2006 to improve the care quality of patients with CKD stages 3B, 4, and 5. The program is coordinated by the Taiwan Society of Nephrology and Taiwan Health Promotion Administration, Ministry of Health and Welfare.^{28,29} Nephrologists, along with a multidisciplinary kidney care team consisting of renal nurses, renal pharmacists, and dietitians, play the central role in the pre-ESRD program. Enrollment in the program can only be initiated by the nephrologist. Follow-up and education on a regular 3-month basis are mandated for case payment.^{30,31} According to the 2020 annual report, 63.9% of all patients undergoing dialysis were enrolled in the pre-ESRD program before dialysis initiation.³²

We included patients with stage 5 CKD who were not undergoing dialysis presenting in 2019 and 2020. Patients aged <20 years; without complete residential address; who were enrolled in the pre-ESRD program before January 1, 2019, and after December 31, 2020; not residing in Taichung City, Changhua County, or Nantou County; and without eGFR records for both baseline and advanced CKD stages were excluded. To protect patient privacy, all personal identification data were encrypted and anonymized before the database was analyzed. The study protocol was approved by the Research Ethics Committee of Taichung Veterans General Hospital, Taichung, Taiwan (CE19222B-1), and the protocol complies with the Declaration of Helsinki principles. The institutional review board waived the requirement to obtain informed consent due to the minimal risk of harm to participants. Data was acquired from the Taichung Veterans General Hospital Research Database with the permission of the hospital's Clinical Informatics Research and Development Center. We first collected clinical information from electronic medical records and laboratory reports, including data on the *International Classification of Diseases* diagnosis code, body mass index, blood urea nitrogen, serum creatinine, estimated glomerular filtration rate (eGFR), hemoglobin, albumin, sodium, potassium, phosphate, uric acid, cholesterol, low-density lipoprotein (LDL), triglyceride, fasting sugar, hemoglobin A1c (HbA1c), systolic blood pressure, and diastolic blood pressure. Patients were stratified into two groups on the basis of their presentation year, that is, 2019 or 2020.

eGFR Outcomes of Patients with Pre-ESRD

The Modification of Diet in Renal Disease-4 equation was used to calculate eGFR levels. Data on eGFR decline occurring during the observation period for patients with pre-ESRD who were not receiving dialysis were obtained. According to the Patient Care and Health Education Plan criteria of the Taiwan Society of Nephrology, an eGFR decrease of ≥ 5 mL/min/1.73 m² in 1 year is defined as an event of eGFR decline. The percentages of eGFR decline in the observation period of 6 months and 12 months were calculated for each of the two groups. Data on patients who were initiated to receive regular dialysis were also collected.

Calculation of PM_{2.5} Concentrations and Air Quality Index

Air pollution data were extracted from official records of the Taiwan Air Quality Monitoring Network (<https://airtw.epa.gov.tw/CHT/Themes/LinkOut.aspx>) and the Air Quality Report of Environmental Protection Bureau of Taichung City Government (<https://www.epb.taichung.gov.tw/1714222/post>). Data are recorded at hourly intervals for the pollutants, NO₂, NO, PM_{2.5}, PM₁₀, CO, SO₂, and O₃. We selected data collected at remote stations, as they were more accurate and were relatively free of local pollutants and changes due to COVID-19-related restrictions.

Statistical Analysis

Data are presented as percentage for categorical variables and mean \pm standard deviation for continuous variables. A chi-squared test was used for comparing categorical variables, and continuous variables were compared using the analysis of variance and post hoc Bonferroni test. Statistical analyses were performed using SAS software 9.4 (SAS Institute, Cary, NC, USA). The significance level for all statistical tests was set at a two-sided *P* value of <0.05 .

Results

A total of 1482 patients meeting the inclusion criteria were enrolled and classified into two year-based groups: the 2019 group (*n* = 758) and 2020 group (*n* = 724). In the 2019 and 2020 groups, 50.4% and 51.2% of participants, respectively, were men. At baseline, participants' overall mean age was 69.4 ± 14.3 years, and the mean eGFR was 10.4 ± 3.8 mL/min/1.73 m². Participants' demographic characteristics, biochemistry data, and underlying diseases are listed in Table 1. No statistically significant difference in these aspects was observed between the two groups.

Table 1 Demographic and Health Characteristics of Patients with Stage 5 Chronic Kidney Disease Presenting in 2019 and COVID-19 Pandemic Year 2020

| | Year 2019 | Year 2020 | P value |
|---|------------------|------------------|---------|
| Number of patients | 758 | 724 | |
| Mean age | 69.4 \pm 14.4 | 69.3 \pm 14.1 | 0.571 |
| Men | 50.4% | 51.2% | 0.825 |
| Diabetes mellitus | 30.2% | 31.7% | 0.554 |
| Hypertension | 17.3% | 16.1% | 0.611 |
| Dyslipidemia | 19.6% | 18.1% | 0.523 |
| Smoking | 9.5% | 9.7% | 0.982 |
| Body mass index | 24.0 \pm 6.3 | 24.3 \pm 5.2 | 0.801 |
| Systolic blood pressure | 136.3 \pm 16.6 | 136.4 \pm 18.2 | 0.893 |
| Diastolic blood pressure | 71.8 \pm 11.7 | 72.2 \pm 12.5 | 0.626 |
| Hemoglobin (g/dL) | 10.0 \pm 1.5 | 10.1 \pm 1.4 | 0.781 |
| Blood urea nitrogen (mg/dL) | 71.9 \pm 24.7 | 72.5 \pm 26.2 | 0.710 |
| Serum creatinine (mg/dL) | 5.1 \pm 2.5 | 5.2 \pm 2.7 | 0.871 |
| Estimated glomerular filtration rate [#] | 10.5 \pm 3.8 | 10.2 \pm 3.7 | 0.788 |
| Uric acid (mg/dL) | 6.3 \pm 2.1 | 6.5 \pm 2.3 | 0.259 |
| Serum sodium (mEq/L) | 138.6 \pm 4.1 | 138.7 \pm 3.6 | 0.553 |
| Serum potassium (mEq/L) | 4.7 \pm 0.6 | 4.7 \pm 0.7 | 0.763 |
| Serum calcium (mg/dL) | 8.7 \pm 0.8 | 8.7 \pm 0.7 | 0.430 |
| Serum phosphate (mg/dL) | 4.7 \pm 1.0 | 4.8 \pm 1.0 | 0.141 |
| Serum Albumin (g/dL) | 4.0 \pm 0.5 | 3.9 \pm 0.5 | 0.716 |
| Total Cholesterol (mg/dL) | 158.4 \pm 39.9 | 166.1 \pm 41.8 | 0.168 |
| Triglyceride (mg/dL) | 138.1 \pm 69.3 | 127.4 \pm 87.9 | 0.086 |
| LDL cholesterol (mg/dL) | 93.3 \pm 32.6 | 94.6 \pm 5.2 | 0.273 |
| HbA1c (%) | 6.5 \pm 1.3 | 6.5 \pm 1.1 | 0.669 |
| Fasting sugar (mg/dL) | 110.0 \pm 33.2 | 114.0 \pm 41.1 | 0.267 |

Notes: Quantitative data are presented as mean \pm standard deviation. [#]mL/min/1.73 m².

Abbreviation: LDL, low-density lipoprotein.

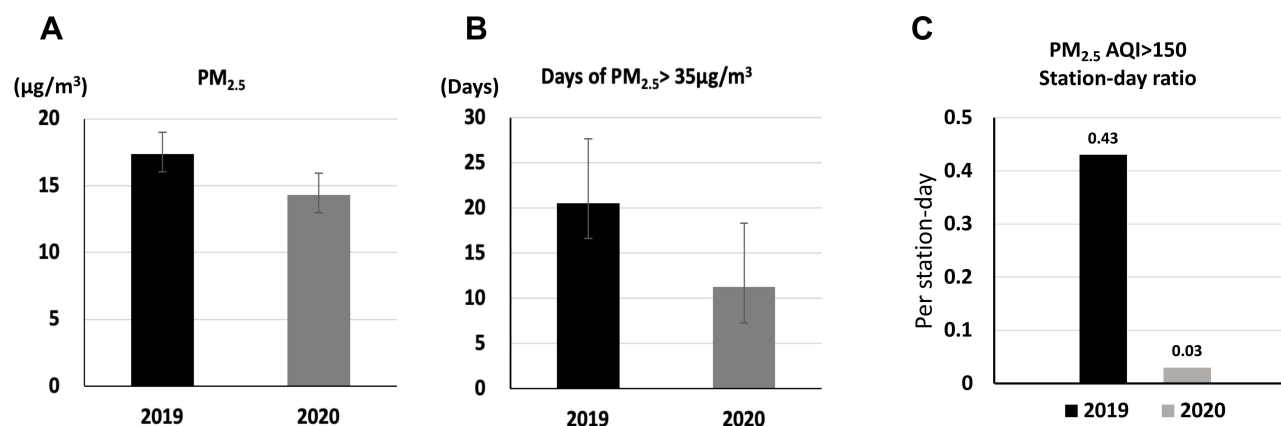


Figure 1 Comparison of PM_{2.5} concentrations in 2019 and 2020 in Taichung area. The average annual concentration of PM_{2.5} (A), Cumulative days with PM_{2.5} concentration >35 µg/m³ (B), the percentages of PM_{2.5} air quality index >150 per station-day (C) in 2019 and 2020.

The average annual concentration of PM_{2.5} was 17.36 ± 1.63 µg/m³ in 2019 and 14.32 ± 1.34 µg/m³ in 2020, revealing a 17.5% decrease in PM_{2.5} concentration in 2020 ($P < 0.001$, Figure 1A). Cumulative days with PM_{2.5} concentration >35 µg/m³ were 20.56 ± 7.07 days (range 11–32 days) in 2019 compared with 11.25 ± 3.96 days (range 4–17 days) in 2020, corresponding to a 45.1% reduction in 2020 ($P < 0.001$, Figure 1B). Moreover, the percentage of PM_{2.5} air quality index >150 was 0.43% per station-day in 2019 compared with only 0.03% per station-day in 2020, corresponding to a 93% reduction in 2020 (Figure 1C).

In the study period (2019 and 2020), 259 (17.5%) patients started undergoing regular dialysis. Sixty-seven (4.5%) patients exhibited an eGFR decline ≥ 5 mL/min/1.73 m² in 6 months, whereas 305 (20.6%) patients exhibited an eGFR decline ≥ 5 mL/min/1.73 m² in 12 months. Table 2 lists the outcomes of patients with stage 5 CKD in 2019 and 2020. Regarding renal function, the mean eGFR decline was 0.41 ± 0.14 mL/min/1.73 m² in the 2019 group and 0.30 ± 0.11 mL/min/1.73 m² in the 2020 group ($P = 0.043$). Given that the event of eGFR decline is defined as an eGFR decrease of ≥ 5 mL/min/1.73 m² in 1 year, the event of eGFR decline in 6 months was 6.1% in the 2019 group versus 2.9% in the 2020 group ($P = 0.002$). Moreover, the event of eGFR decline in 12 months was 24.6% in the 2019 group versus 16.3% in the 2020 group ($P < 0.001$). The proportion of patients who started undergoing regular dialysis in 1 year was 20.8% in the 2019 group versus 14.0% in the 2020 group ($P = 0.001$). Figure 2 compares the percentage of patients with eGFR decline ≥ 5 mL/min/1.73 m² between the two groups ($P = 0.002$).

Discussion

Our principal finding is that the events of eGFR decline in patients with stage 5 CKD who were not undergoing dialysis were significantly fewer in the COVID-19 pandemic year 2020 than in 2019. The PM_{2.5} concentration was also lower in 2020 than in 2019. However, we are yet to provide evidence to support the causal relationship between declines in PM_{2.5} concentration and such renal events. The etiology of renal function decline is multifactorial; high PM_{2.5} concentration

Table 2 Outcomes of Patients with Stage 5 Chronic Kidney Disease Presenting in 2019 and COVID-19 Pandemic Year 2020

| | Year 2019 | Year 2020 | P value |
|-------------------------|------------------|------------------|---------|
| Number of patients | 758 | 724 | |
| eGFR/month | -0.41 ± 0.14 | -0.30 ± 0.11 | 0.043 |
| Event within 6 months* | 46 (6.1%) | 21 (2.9%) | 0.002 |
| Event within 12 months* | 187 (24.6%) | 118 (16.3%) | <0.001 |
| Start regular dialysis | 158 (20.8%) | 101 (14.0%) | 0.001 |

Note: *Event of eGFR decline is defined by an eGFR decrease of ≥ 5 mL/min/1.73 m².

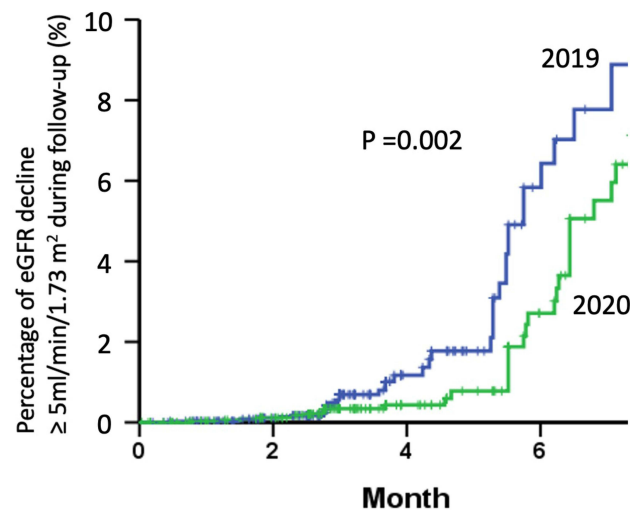


Figure 2 Comparison of patients with eGFR decline ≥ 5 mL/min/1.73 m^2 in 2019 and 2020.

may be a risk factor for eGFR decline as it induces systemic inflammatory responses. Severe air pollution (air quality index > 150) results in prominent unhealthy consequences. Several experimental and clinical findings have indicated such a biologic plausibility, supporting the hypothesis that environmental exposure to air pollutants, especially high concentrations of $PM_{2.5}$, is associated with an increased risk of systemic diseases affecting several organs, including the kidneys.^{2,3,5-9}

Several studies have reported the association between air pollution or $PM_{2.5}$ and CKD. In the United States, long-term exposure to high concentrations of $PM_{2.5}$ in veterans was associated with a higher risk of incident CKD that progressed to ESRD.¹² Among older men, year-long exposure to high concentrations of $PM_{2.5}$ was associated with a lower eGFR.¹³ Similar findings have been reported in the Taiwanese population. Exposure to particulate and acidic gas air pollution is associated with a higher risk of CKD and ESRD.³³ A higher risk of acute lung edema in Taiwanese patients with stage 5 CKD who were not undergoing dialysis was also associated with high concentrations of $PM_{2.5}$.²⁷ These findings are consistent with the results of our study on patients with stage 5 CKD. The effect of the COVID-19 pandemic was higher in 2020 than in 2019, and the lower concentrations of $PM_{2.5}$ and better outdoor air quality are likely to cause fewer events of rapid eGFR decline in patients with advanced CKD. Lockdowns during the COVID-19 pandemic dramatically decreased the social and economic activity worldwide.³⁴ Several studies have reported a significant reduction in air pollution concentrations during lockdowns in most polluted cities, such as New York, Milan, Bangkok, Delhi, and Wuhan;³⁵⁻³⁷ this reduction may be because of less motor vehicle traffic and suspended manufacturing. According to data provided by the Freeway Bureau, Ministry of Transportation and Communications of Taiwan, a decrease in motor vehicle traffic was noted during the lockdown period.³⁸ In addition, the Department of Statistics, Taiwan, revealed a sharp decrease in the numbers of heavily polluting industries, such as chemical, petroleum, and coal industries.³⁹ The above findings are consistent with global trends. However, other possible causes of reduction in pollution readings besides the lockdown may exist. Compared with 2019, 2020 witnessed reduced rainfall. The mean temperature was higher in 2020.⁴⁰ Both decreased rainfall and increased temperature does not cause a negative effect on $PM_{2.5}$ concentrations and is unlikely to confound the results. The main sources of $PM_{2.5}$ pollution in Taiwan are traffic (36%), overseas imports from the mainland (27%), industries (25%), and nature (12%).⁴¹ However, in the Taichung region, where the study was conducted, a large coal-fired power plant with a heavy smokestack is the largest source of air pollution. Moreover, $PM_{2.5}$, sulfur oxides, and nitrogen oxides account for 14.5%, 63.6%, and 39.2%, respectively, of the total emissions of Taichung City.

Our research suggests that controlling air pollution is crucial for reducing the events of renal function decline. In fact, the major finding of our study is not the decrease in average $PM_{2.5}$ concentration or average air quality index but rather the dramatic reduction in cumulative days with critical concentrations of air pollution. The average annual concentration of $PM_{2.5}$ decreased only by 13.0% in 2020; however, cumulative days with $PM_{2.5}$ concentration $> 35 \mu g/m^3$ decreased by

30.4% in 2020. Moreover, the percentage of PM_{2.5} air quality index >150 (unhealthy level) decreased by 93% in 2020. Those fewer days with critical levels of air pollution have more realistic effects as reflected by our study results.

Our study has some limitations. First, our datasets had no information on patients' time spent in traffic or outdoors. Therefore, the accurate determination of patients' exact exposure remains challenging. Second, the majority of all patients undergoing dialysis were enrolled in the pre-ESRD program before dialysis initiation (63.9%). However, currently no data exists between enrolled and unenrolled patients. We cannot be certain if pre-ESRD program enrollees can fully represent patients with advanced CKD. Third, our cohort included only patients with stage 5 CKD who were not undergoing dialysis. Therefore, the findings may not be generalized to patients with other stages of CKD. Because this is a retrospective study, the possibility of unmeasured residual confounding exists. A recently published study revealed both linear and nonlinear associations between PM_{2.5} and NO₂ concentrations and the incidence of eGFR decline in patients with CKD stages 3B, 4, and 5.⁴² More evidence from detailed longitudinal and direct causal research is required to clarify the cause-and-effect relationship between specific types of air pollution and kidney injury.

Conclusion

The COVID-19 pandemic provided a unique opportunity to study the relationship between air pollution and CKD progression. Although we could not demonstrate a cause-and-effect relationship, our findings support the global strategy of reducing air pollution to prevent CKD progression. Our findings can be used as reference in future kidney care.

Data Sharing Statement

Weather data were obtained from official records of the Taiwan Air Quality Monitoring Network of Environmental Protection Administration, and the meteorological conditions can be obtained online at <https://airtw.epa.gov.tw/CHT/Themes/LinkOut.aspx> accessed on January 10, 2022.

Institutional Review Board Statement

This study was approved by the Research Ethics Committee of Taichung Veterans General Hospital, Taichung, Taiwan (CE19222B-1).

Informed Consent Statement

This was a retrospective study, and data were acquired from the Taichung Veterans General Hospital Research Database with the permission of the hospital's Clinical Informatics Research and Development Center.

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Disclosure

Authors declare no competing interests.

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