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ORIGINAL RESEARCH

# Epidemiological Evidence That Air Pollutants May Accelerate or Delay Breast Cancer Mortality: A Retrospective Cohort Study

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**Purpose:** To explore the effects of long-term exposure to air pollutants on risk of death and survival time of breast cancer patients.

**Methods:** We retrospectively collected data of 4,438 primary breast cancer patients treated at the Affiliated Tumor Hospital of Xinjiang Medical University between January 1, 2014, and May 31, 2023. We analyzed the effects of single and multiple pollutants on mortality risk using both univariate and multivariate Cox proportional hazard models. Meanwhile, we employed the Cox model to investigate the interaction between pairs of air pollutants. Then, an accelerated failure time (AFT) model was used to quantify the effects of air pollutants on the survival time of breast cancer patients, quantifying whether they accelerate or delay survival.

**Results:** The multivariate Cox model revealed that the highest quartile ($Q_4$) of $SO_2$ (HR=11.96, 95% CI: 4.68–30.55), CO (HR=4.58, 95% CI: 2.82–7.44), $NO_2$ (HR=3.83, 95% CI: 2.50–5.86), $PM_{2.5}$ (HR=2.67, 95% CI: 1.88–3.80), and $PM_{10}$ (HR=2.67, 95% CI: 1.88–3.80) significantly increased the risk of breast cancer mortality. In contrast, $O_3$ showed a dose-dependent protective effect (HR=0.19, 95% CI: 0.08–0.21). $NO_2$ significantly increased risk of death in breast cancer patients after introduction of particulate matter. The accelerated failure time model further revealed that $SO_2$ ($Q_4$-TR=0.18, 95% CI: 0.08–0.41) and CO ($Q_4$-TR=0.20, 95% CI: 0.12–0.33) reduced survival time to 18%-20% of the reference group ($Q_1$). $O_3$ demonstrated a dose-dependent reduction in mortality risk ($Q_4$-TR=7.29, 95% CI: 4.51–11.78); Notably, $NO_2$ and particulate matter ($PM_{2.5}$, $PM_{10}$) had a bidirectional effect—low concentrations ($Q_2$-$Q_3$) extended survival time (TR: 1.47–2.64), while high concentrations ($Q_4$) accelerated death (TR: 0.26–0.39).

**Conclusion:** Air pollution collectively impacts breast cancer mortality, with complex pollutant interactions modulating risk. This highlights the need for holistic environmental health strategies.

**Keywords:** air pollution, breast cancer, survival time, accelerated failure time model

## Introduction

Breast cancer is the most common cancer among women globally, posing a significant threat to women's health.[1] According to the latest estimates from the International Agency for Research on Cancer, the global female breast cancer mortality rate reached 6.9% in 2022.[2] From 1993 to 2020, the breast cancer mortality rate in China increased by 5.3% annually, and by 2020, the standardized breast cancer mortality rate for Chinese women was 4.06 per 100,000, with this rate continuing to rise.[3,4] In Xinjiang Uygur Autonomous Region, the breast cancer mortality rate is relatively high, with a standardized rate of 5.35 per 100,000 in 2019, and the average breast cancer mortality rate for women in Urumqi, China, from 2015 to 2019 was 6.35 per 100,000.[5,6]

Breast cancer, a highly prevalent malignant tumor among women, is characterized by the interaction of multiple factors in its pathogenesis. Besides the well-established risk factors such as hormone receptor subtypes, obesity, and family history,[7–9] the association between environmental exposure, particularly air pollutants, and the development of breast cancer

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has gained significant attention in recent years.[10,11] Air pollutants, a complex mixture of components including $SO_2$, $NO_2$, CO, $PM_{2.5}$, $PM_{10}$, and $O_3$, pose a unique risk as they serve as carriers for various confirmed or potential carcinogens and endocrine disruptors. These substances can affect breast tissue through multiple biological pathways. On one hand, they can induce the abnormal accumulation of reactive oxygen species within cells, leading to DNA oxidative damage, increasing genomic instability, and directly driving cancer development.[12,13] On the other hand, they can interfere with the synthesis, metabolism, receptor binding, and signaling pathways of estrogen, causing an abnormal increase in estrogen activity, which promotes the abnormal proliferation of breast epithelial cells and tumor progression.[14,15]

The epidemiological evidence supporting the impact of air pollutants on breast cancer is accumulating. Multiple studies have shown that long-term exposure to high concentrations of air pollution is significantly associated with an increased risk of breast cancer.[16,17] For example, Kayyal[18] found through an exposure gradient analysis that for every one-quarter percentile (IQR) increase in $PM_{2.5}$ concentration, the risk of breast cancer increases by 150%, with a more significant contribution to the risk compared to nitrogen oxides. Perry[19] revealed that $NO_2$ exposure levels have a significant dose-response relationship with the incidence of breast cancer in premenopausal women. More importantly, the effects of air pollutants extend beyond disease onset to influence patient prognosis and survival. A 10-year prospective follow-up study by Li[20] provided crucial evidence showing that continuous exposure to $PM_{2.5}$ and $NO_2$ environments is significantly associated with an increased risk of all-cause mortality in breast cancer patients. These studies collectively suggest that assessing the impact of long-term air pollutant exposure on the survival outcomes of breast cancer patients is essential for understanding disease progression and improving patient outcomes.[21,22]

Although existing research has enhanced our understanding of the link between air pollution and breast cancer, several significant limitations remain to be addressed. The previous studies have focused on the impact of air pollutants on breast cancer incidence, but we focused on survival risk and tried to explore whether there are complex interactions between air pollutants. While the traditional Cox model estimates the relative risk (hazard ratio, HR) of exposure, it does not directly quantify its absolute impact on patient survival time. The AFT model can provide a "Time Ratio (TR)", which intuitively reflects how much the exposure factor shortens or extends survival time compared to the reference group, thus addressing the limitations of HR in conveying absolute effects.[23] Finally, Urumqi, the capital of Xinjiang, is situated in a central basin and is a typical coal-heating city. The area experiences frequent winter temperature inversions, with air pollution primarily consisting of $SO_2$ and particulate matter, giving it distinct regional characteristics.[24,25] Therefore, studying the link between pollution and health here holds particular significance.

Based on the above research background, we used large-scale retrospective cohort data from a single center in Urumqi, China, and air pollutant concentration data from the China National Environmental Monitoring Center. Conventional Cox model was used to analyze the effects of air pollutants and their pairwise interactions on the risk of mortality among breast cancer patients. Then, AFT model was used to quantify the absolute accelerated or delayed effects of different exposure levels of pollutants on the survival time of breast cancer patients. We not only revealed the association between air pollution and breast cancer prognosis in a representative sample of cities in northwest China, but also provided a more clinically meaningful quantitative assessment of survival time beyond the traditional hazard ratio through the innovative combination of Cox model and AFT model.

# Materials and Methods

## Study Population

This study retrospectively collected patients diagnosed with breast cancer by pathological examination in the Affiliated Cancer Hospital of Xinjiang Medical University from January 1, 2014 to May 31,2023 as the research subjects. The main data collected were the demographic characteristics, clinical and pathological characteristics and survival outcomes of patients.

Inclusion criteria: ① The age at diagnosis ≥18 years; ② Diagnosed with primary breast cancer (i.e., not recurrent or metastatic disease from other origins); ③ Complete documentation of pathological features. Exclusion criteria: ① Non-Urumqi residents; ② Male patients; ③ Missing basic and clinical information; ④ Patients who did not sign the informed consent form or patient admission form. As shown in Figure 1, based on these inclusion and exclusion criteria, 4,438 subjects were ultimately included in the study. The collected patient information includes age, clinical stage (I, II, III, IV), T stage ($T_1$, $T_2$, $T_3$, $T_4$), N stage ($N_0$, $N_1$, $N_2$, $N_3$), M stage ($M_0$, $M_1$), presence of carcinoma in situ (yes, no,

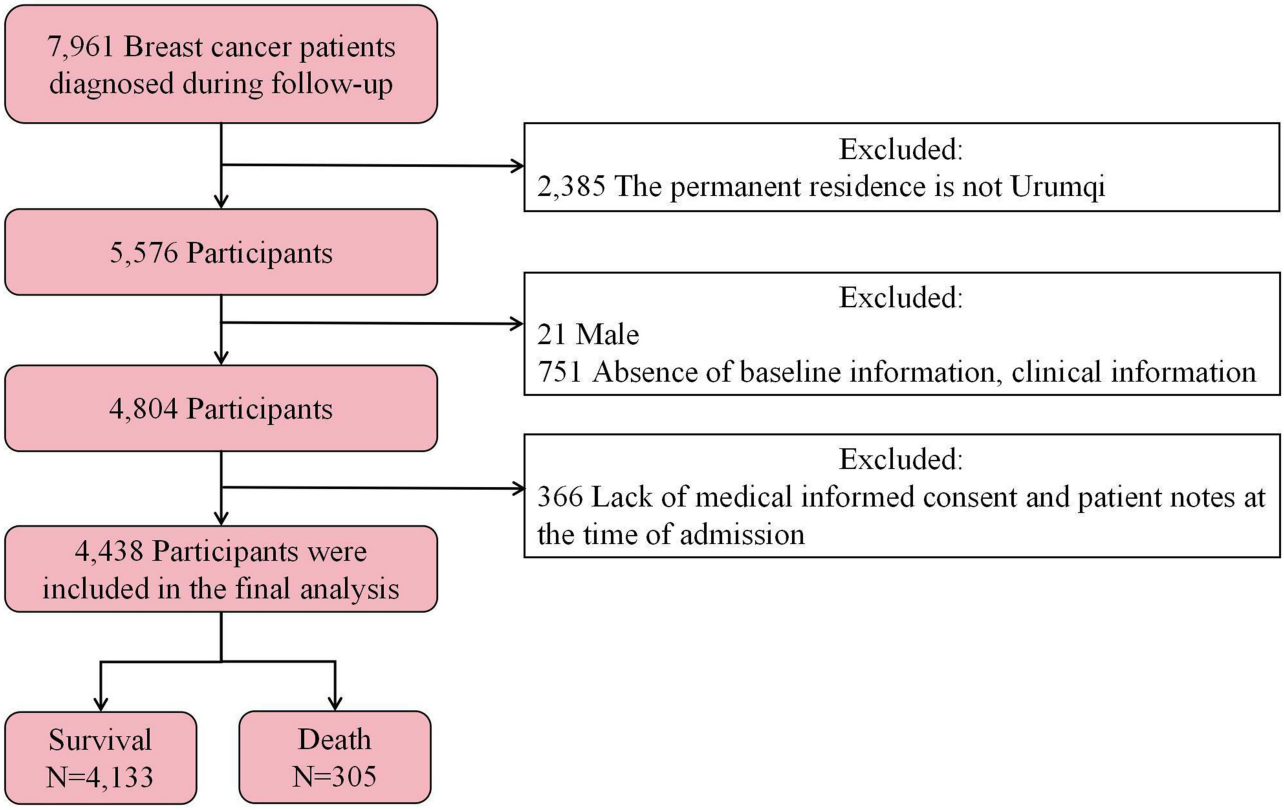


**Figure 1** Flowchart of study population screening and grouping.

unknown), ductal carcinoma (yes, no, unknown), chemotherapy (yes, no), radiotherapy (yes, no), and follow-up information (including outcomes and duration). The median follow-up time was 46.07 months.

## Air Pollutant Assessment

This study refers to the basic items of air pollutants specified in the Ambient Air Quality Standards (GB 3095–2012) and its amendments, using data on six pollutants: $SO_2$, $NO_2$, CO, $O_3$, $PM_{2.5}$, and $PM_{10}$. Daily air pollution data were obtained from the National Urban Air Quality Real-time Release Platform (https://www.cnemc.cn/) of the China National Environmental Monitoring Center. The data included 24-hour average concentrations of $PM_{2.5}$ and $PM_{10}$, $SO_2$, $NO_2$, CO, and the daily maximum 8-hour moving average concentration of $O_3$. The resolution of particulate matter data is 1km×1km, while that of gas data is 10km×10km. The 24-hour average values are calculated based on hourly measurements from 11 monitoring stations in Urumqi.

We collected the permanent addresses of all study subjects and geocoded them into latitude and longitude coordinates. For each location, we calculated its distance to 11 monitoring stations. We adopted the "nearest monitoring station assignment method", meaning each address point was matched with data from the closest monitoring station. For each patient, the study uses data from the monitoring station in their residential area to calculate the average daily air pollution exposure from the date of diagnosis to the last follow-up or death. For the missing values at a specific site, a time series autoregressive model was employed for imputation.

## Statistical Analysis

Continuous variables are described using the median (inter-quartile range, IQR). For inter-group comparisons of data with non-normal distributions, Mann–Whitney test is used. Categorical variables are presented as frequencies (percentages), and inter-group comparisons are conducted using either a chi-square test ($\chi^2$) or Fisher's exact test. All statistical tests are two-sided, with a significance level of 0.05. All data were statistically analyzed using R software (version 4.3.1) in this study.

## Cox's Proportional Hazards Regression Model

In this study, the association between air pollutant exposure and breast cancer mortality risk was first evaluated using the Cox proportional risk model. The formula of the Cox model is as follows:

$$h(t) = h_0(t)exp\left(\beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_p X_p\right)$$

Among them, $h(t)$ represents the instantaneous risk of death at time, $h_0(t)$ is the baseline risk function, $X_i$ is the study variable, and $\beta_i$ is the logarithmic risk ratio corresponding to the variable.

Pollutants were grouped into four quartiles ($Q_1$-$Q_4$), with the lowest quartile ($Q_1$) as the reference group. Univariate analysis was used to initially assess the individual effects of each pollutant, and multivariate analysis was conducted after adjusting for confounding factors such as age, TNM stage, clinical stage, chemotherapy, and radiotherapy. In the basic multivariate model, two pollutants were introduced simultaneously, and the changes in effect values between single-pollutant and dual-pollutant models were compared to determine the direction of interaction (synergistic or antagonistic). The results were presented using HR and 95% confidence intervals (95% CI), and statistical analysis was performed using the "survival" package in R 4.3.1.

## Accelerated Failure Time Model

Cox focuses on the risk ratio, which is used to assess the relative risk of an event occurring. For studying the absolute change in survival time, the AFT model is more appropriate. The AFT model is a regression model used in survival analysis, assuming that variables have a proportional effect on accelerating or decelerating survival time. Through the AFT model, the impact of pollutants on survival time can be directly quantified. The formula for the AFT model is:

$$log(T) = \mu + \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_p X_p + \sigma W$$

Here, $T$ denotes the survival time, $\mu$ represents the intercept, $X_i$ is the study variable, $\beta_i$ is the effect coefficient, $\sigma$ is the scale parameter, and $W$ is the error term (which follows a specific distribution, such as the extreme value distribution or normal distribution). The TR can be calculated using $\beta_i$:

$$TR = e^{\beta_i}$$

TR represents the multiplier effect of a variable on survival time. Specifically, the TR of an exposure factor is greater than 1, it means that the exposure will prolong survival. Conversely, if TR is less than 1, it means that exposure reduces survival time.

The Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC) are used to measure the goodness of fit of models under different distributions. Both are calculated based on the maximum likelihood function value, the number of parameters (including regression coefficients and error term variance, etc.), and the sample size. The formulas are as follows:

$$AIC = 2k - 2ln(L)$$

$$BIC = ln(n)k - 2ln(L)$$

Among them, $k$ represents the number of parameters of the model, $L$ is the maximum likelihood function value of the model, and $n$ is the sample size. The AIC and BIC values of each candidate model are compared, and the model with smaller AIC and BIC values is selected as the relatively better model.

# Results

## Basic Characteristics and Differentiation Analysis

This study included 4,438 breast cancer patients from January 1, 2014, to May 31,2023, with a median follow-up of 46.07 months. By the end of the follow-up, 4,133 patients (93.13%) were still alive, while 305 patients (6.87%) had died. There were statistically significant differences between the two groups in age, clinical stage, T, N, M, chemotherapy, radiotherapy, CO, $PM_{2.5}$, $PM_{10}$, $SO_2$, $NO_2$ and $O_3$ levels ($P<0.05$), but no significant differences in carcinoma in situ or

ductal carcinoma (P>0.05). The concentration of five air pollutants (CO, $PM_{2.5}$, $PM_{10}$, $SO_2$, $NO_2$) was significantly higher in the death group compared to the survival group, while the concentration of $O_3$ was significantly lower in the death group (49.03 vs 58.21, p<0.001), see Table 1 for details.

**Table 1** Baseline Characteristics of Participants

| Variables | Total (n = 4438) | Survival (n = 4133) | Death (n = 305) | Statistic | P-value |
|---|---|---|---|---|---|
| Age, (Years) | 51.00 (45.00, 60.00) | 51.00 (45.00, 59.00) | 54.00 (46.00, 66.00) | Z=−4.11 | **<0.001** |
| CO, ($\mu g/m^3$) | 895.90 (813.651067.18) | 883.26 (810.11,1043.644) | 1223.42 (993.51,1381.30) | Z=−18.16 | **<0.001** |
| $PM_{2.5}$, ($\mu g/m^3$) | 47.15 (43.52,53.82) | 46.87 (43.44,53.00) | 59.43 (48.45,68.33) | Z=−13.16 | **<0.001** |
| $PM_{10}$, ($\mu g/m^3$) | 85.13 (79.17,95.43) | 84.59 (79.09,94.21) | 107.41 (87.50,121.30) | Z=−13.74 | **<0.001** |
| $SO_2$, ($\mu g/m^3$) | 7.11 (6.49,8.43) | 7.06 (6.47,8.06) | 10.11 (8.00,12.72) | Z=−20.10 | **<0.001** |
| $NO_2$, ($\mu g/m^3$) | 37.18 (35.39,40.66) | 37.01 (35.28,40.33) | 44.00 (38.89,48.04) | Z=−15.89 | **<0.001** |
| $O_3$, ($\mu g/m^3$) | 57.88 (54.73,61.10) | 58.21 (55.64,61.36) | 49.03 (42.77,55.14) | Z=−18.80 | **<0.001** |
| CO, n (%) | | | | $\chi^2$=334.72 | **<0.001** |
| $Q_1$ | 1110 (25.01) | 1089 (26.35) | 21 (6.89) | | |
| $Q_2$ | 1109 (24.99) | 1086 (26.28) | 23 (7.54) | | |
| $Q_3$ | 1109 (24.99) | 1056 (25.55) | 53 (17.38) | | |
| $Q_4$ | 1110 (25.01) | 902 (21.82) | 208 (68.20) | | |
| $PM_{2.5}$, n (%) | | | | $\chi^2$=244.60 | **<0.001** |
| $Q_1$ | 1110 (25.01) | 1066 (25.79) | 44 (14.43) | | |
| $Q_2$ | 1109 (24.99) | 1087 (26.30) | 22 (7.21) | | |
| $Q_3$ | 1109 (24.99) | 1059 (25.62) | 50 (16.39) | | |
| $Q_4$ | 1110 (25.01) | 921 (22.28) | 189 (61.97) | | |
| $PM_{10,}$ n (%) | | | | $\chi^2$=299.49 | **<0.001** |
| $Q_1$ | 1110 (25.01) | 1068 (25.84) | 42 (13.77) | | |
| $Q_2$ | 1109 (24.99) | 1086 (26.28) | 23 (7.54) | | |
| $Q_3$ | 1109 (24.99) | 1071 (25.91) | 38 (12.46) | | |
| $Q_4$ | 1110 (25.01) | 908 (21.97) | 202 (66.23) | | |
| $SO_2$, n (%) | | | | $\chi^2$=327.40 | **<0.001** |
| $Q_1$ | 1110 (25.01) | 1105 (26.74) | 5 (1.64) | | |
| $Q_2$ | 1109 (24.99) | 1092 (26.42) | 17 (5.57) | | |
| $Q_3$ | 1109 (24.99) | 1023 (24.75) | 86 (28.20) | | |
| $Q_4$ | 1110 (25.01) | 913 (22.09) | 197 (64.59) | | |
| $NO_2$, n (%) | | | | $\chi^2$=318.92 | **<0.001** |
| $Q_1$ | 1110 (25.01) | 1082 (26.18) | 28 (9.18) | | |
| $Q_2$ | 1109 (24.99) | 1083 (26.20) | 26 (8.52) | | |
| $Q_3$ | 1109 (24.99) | 1064 (25.74) | 45 (14.75) | | |
| $Q_4$ | 1110 (25.01) | 904 (21.87) | 206 (67.54) | | |
| $O_3$, n (%) | | | | $\chi^2$=401.54 | **<0.001** |
| $Q_1$ | 1110 (25.01) | 888 (21.49) | 222 (72.79) | | |
| $Q_2$ | 1109 (24.99) | 1070 (25.89) | 39 (12.79) | | |
| $Q_3$ | 1109 (24.99) | 1084 (26.23) | 25 (8.20) | | |
| $Q_4$ | 1110 (25.01) | 1091 (26.40) | 19 (6.23) | | |
| Carcinoma in situ, n (%) | | | | $\chi^2$=5.02 | 0.081 |
| No | 3985 (89.79) | 3700 (89.52) | 285 (93.44) | | |
| Yes | 93 (2.10) | 90 (2.18) | 3 (0.98) | | |
| Unknown | 360 (8.11) | 343 (8.30) | 17 (5.57) | | |
| Ductal carcinoma, n (%) | | | | $\chi^2$=5.27 | 0.072 |
| No | 614 (13.84) | 568 (13.74) | 46 (15.08) | | |
| Yes | 3470 (78.19) | 3225 (78.03) | 245 (80.33) | | |
| Unknown | 354 (7.98) | 340 (8.23) | 14 (4.59) | | |

(*Continued*)

**Table 1** (Continued).

| Variables | Total (n = 4438) | Survival (n = 4133) | Death (n = 305) | Statistic | P-value |
|---|---|---|---|---|---|
| Stage, n (%) | | | | $\chi^2$=512.80 | **<0.001** |
| I | 1554 (35.02) | 1511 (36.56) | 43 (14.10) | | |
| II | 1932 (43.53) | 1853 (44.83) | 79 (25.90) | | |
| III | 744 (16.76) | 649 (15.70) | 95 (31.15) | | |
| IV | 208 (4.69) | 120 (2.90) | 88 (28.85) | | |
| T, n (%) | | | | $\chi^2$=230.98 | **<0.001** |
| T1 | 2004 (45.16) | 1937 (46.87) | 67 (21.97) | | |
| T2 | 1992 (44.89) | 1851 (44.79) | 141 (46.23) | | |
| T3 | 222 (5.00) | 189 (4.57) | 33 (10.82) | | |
| T4 | 220 (4.96) | 156 (3.77) | 64 (20.98) | | |
| N, n (%) | | | | $\chi^2$=243.10 | **<0.001** |
| N0 | 2405 (54.19) | 2326 (56.28) | 79 (25.90) | | |
| N1 | 1315 (29.63) | 1221 (29.54) | 94 (30.82) | | |
| N2 | 375 (8.45) | 329 (7.96) | 46 (15.08) | | |
| N3 | 343 (7.73) | 257 (6.22) | 86 (28.20) | | |
| M, n (%) | | | | $\chi^2$=378.99 | **<0.001** |
| M0 | 4215 (94.98) | 3997 (96.71) | 218 (71.48) | | |
| M1 | 223 (5.02) | 136 (3.29) | 87 (28.52) | | |
| Chemotherapy, n (%) | | | | $\chi^2$=26.25 | **<0.001** |
| No | 3615 (81.46) | 3333 (80.64) | 282 (92.46) | | |
| Yes | 823 (18.54) | 800 (19.36) | 23 (7.54) | | |
| Radiotherapy, n (%) | | | | $\chi^2$=28.24 | **<0.001** |
| No | 3939 (88.76) | 3640 (88.07) | 299 (98.03) | | |
| Yes | 499 (11.24) | 493 (11.93) | 6 (1.97) | | |

**Note**: Z: Mann–Whitney test, $\chi^2$: Chi-square test; $Q_1$: 1st Quartile, $Q_2$: 2st Quartile, $Q_3$: 3st Quartile, $Q_4$: 4st Quartile; Bold values indicate a highly statistically significant effect ($p < 0.01$).

## Relationship Between Environmental Pollutants and Breast Cancer Mortality Risk

The Cox proportional hazards regression analysis revealed a significant association between air pollutant exposure levels and the mortality risk of breast cancer patients, after adjusting for age, TNM stage, clinical stage, chemotherapy, and radiotherapy (Table 2). In the multivariate model, the highest quartile ($Q_4$) of pollutant exposure showed differential risk

**Table 2** Univariate and Multivariate Analyses Were Performed Using the Cox Model

| Pollutants | Univariate Analysis | | Multivariate Analysis | |
|---|---|---|---|---|
| | HR (95% CI) | P-value | HR (95% CI) | P-value |
| CO | | | | |
| $Q_2$ | 0.65 (0.36–1.18) | 0.155 | 0.64 (0.35–1.17) | 0.149 |
| $Q_3$ | 1.07 (0.64–1.78) | 0.803 | 1.00 (0.58–1.71) | 0.997 |
| $Q_4$ | 4.98 (3.15–7.89) | < 0.001 | 4.58 (2.82–7.44) | < 0.001 |
| $PM_{2.5}$ | | | | |
| $Q_2$ | 0.33 (0.19–0.54) | < 0.001 | 0.38 (0.22–0.63) | < 0.001 |
| $Q_3$ | 0.67 (0.45–1.01) | 0.0587 | 0.67 (0.44–1.02) | 0.060 |
| $Q_4$ | 2.75 (1.96–3.86) | < 0.001 | 2.67 (1.88–3.80) | < 0.001 |
| $PM_{10}$ | | | | |
| $Q_2$ | 0.46 (0.28–0.77) | 0.003 | 0.51 (0.22–1.15) | 0.103 |
| $Q_3$ | 0.54 (0.35–0.84) | 0.007 | 0.67 (0.44–1.02) | 0.060 |
| $Q_4$ | 3.45 (2.45–4.86) | < 0.001 | 2.67 (1.88–3.80) | < 0.001 |

(*Continued*)

**Table 2** (Continued).

| Pollutants | Univariate Analysis | | Multivariate Analysis | |
|---|---|---|---|---|
| | HR (95% CI) | P-value | HR (95% CI) | P-value |
| $SO_2$ | | | | |
| $Q_2$ | 1.36 (0.50–3.69) | 0.550 | 1.57 (0.57–4.34) | 0.388 |
| $Q_3$ | 4.96 (2.00–12.30) | < 0.001 | 5.42 (2.11–13.93) | < 0.001 |
| $Q_4$ | 9.93 (4.05–24.36) | < 0.001 | 11.96 (4.68–30.55) | < 0.001 |
| $NO_2$ | | | | |
| $Q_2$ | 0.58 (0.34–1.00) | 0.048 | 0.60 (0.26–1.40) | 0.236 |
| $Q_3$ | 0.70 (0.43–1.13) | 0.143 | 0.51 (0.15–1.78) | 0.293 |
| $Q_4$ | 4.17 (2.78–6.26) | < 0.001 | 3.83 (2.50–5.86) | < 0.001 |
| $O_3$ | | | | |
| $Q_2$ | 0.18 (0.13–0.25) | < 0.001 | 0.17 (0.12–0.24) | < 0.001 |
| $Q_3$ | 0.15 (0.10–0.22) | < 0.001 | 0.18 (0.11–0.27) | < 0.001 |
| $Q_4$ | 0.13 (0.08–0.22) | < 0.001 | 0.19 (0.08–0.21) | < 0.001 |

**Note**: $Q_1$: 1st Quartile, $Q_2$: 2st Quartile, $Q_3$: 3st Quartile, $Q_4$: 4st Quartile; Models were adjusted for age at diagnosis: age, TNM, stage, chemotherapy, and radiotherapy.
**Abbreviations**: HR: Hazard Ratio, CI: Confidence Interval.

effects: CO (HR = 4.58, 95% CI: 2.82–7.44), $PM_{2.5}$ (HR = 2.67, 95% CI: 1.88–3.80), $PM_{10}$ (HR = 2.67, 95% CI: 1.88–3.80), $SO_2$ (HR = 11.96, 95% CI: 4.68–30.55), and $NO_2$ (HR = 3.83, 95% CI: 2.50–5.86) all significantly increased the risk of death ($p<0.001$), with $SO_2$ showing the most pronounced effect. Notably, $O_3$ exposure exhibited a significant protective trend, with the risk ratio decreasing progressively from $Q_2$ to $Q_4$, and all quartiles showed statistical significance. The dose-effect analysis further revealed that there was a risk jump between $SO_2$, CO and $NO_2$ in $Q_3$ and $Q_4$, while $PM_{2.5}$ and $PM_{10}$ only showed a significant increase in risk in $Q_4$; the middle and low exposure group of $PM_{10}$ ($Q_2$-$Q_3$) lost significance after adjusting for confounding factors, indicating that some effects of $PM_{10}$ were mediated by other variables.

Given the potential for complex combined effects among air pollutants, we analyzed the interactions between pairs of pollutants. As shown in Figure 2, after introducing CO and $NO_2$, the relationship between $SO_2$ and breast cancer mortality risk disappeared. $NO_2$ significantly increases risk of death in breast cancer patients after introduction of particulate matter. The introduction of $PM_{10}$ significantly increased the mortality risk due to CO and $NO_2$ exposure. Particulate matter can produce a superimposed risk with $NO_2$. For particulate matter, the effect of CO and $NO_2$ was reduced after their introduction, and the effect of particulate matter disappeared after the introduction of $O_3$. Regardless of which pollutant was adjusted, the effect of $O_3$ was consistently negatively correlated with breast cancer mortality risk.

## Accelerated Failure Time Model Analysis of Different Environmental Pollutants on Breast Cancer Mortality

Figure 3A shows that in the comparison between AIC and BIC, the Log-normal distribution has the lowest AIC and BIC values. This indicates that, after balancing model complexity and fit, the Log-normal distribution model performs best in this data set, making it the optimal choice. Additionally, Figure 3B presents a Q-Q plot, which illustrates the relationship between the sample quantiles and the theoretical quantiles. Ideally, the data points should closely follow the diagonal line. The figure shows that most data points are close to the diagonal, further confirming the Log-normal distribution's excellent fit to the data. Although there may be some deviations at extreme values, the model generally captures the distribution characteristics of the data well.

According to the AFT model results (Figure 4), the impact of different pollutants on survival time shows significant heterogeneity. For $O_3$, the β value is positive across all quantiles ($Q_2$-$Q_4$), and the TR value is significantly greater than 1, indicating that for every one-unit increase in $O_3$ concentration, patients' survival time is extended to 5.91–7.29 times that of the reference group ($Q_1$). For $NO_2$, survival time decreases to 26% of the reference group at Q4, but it becomes a positive

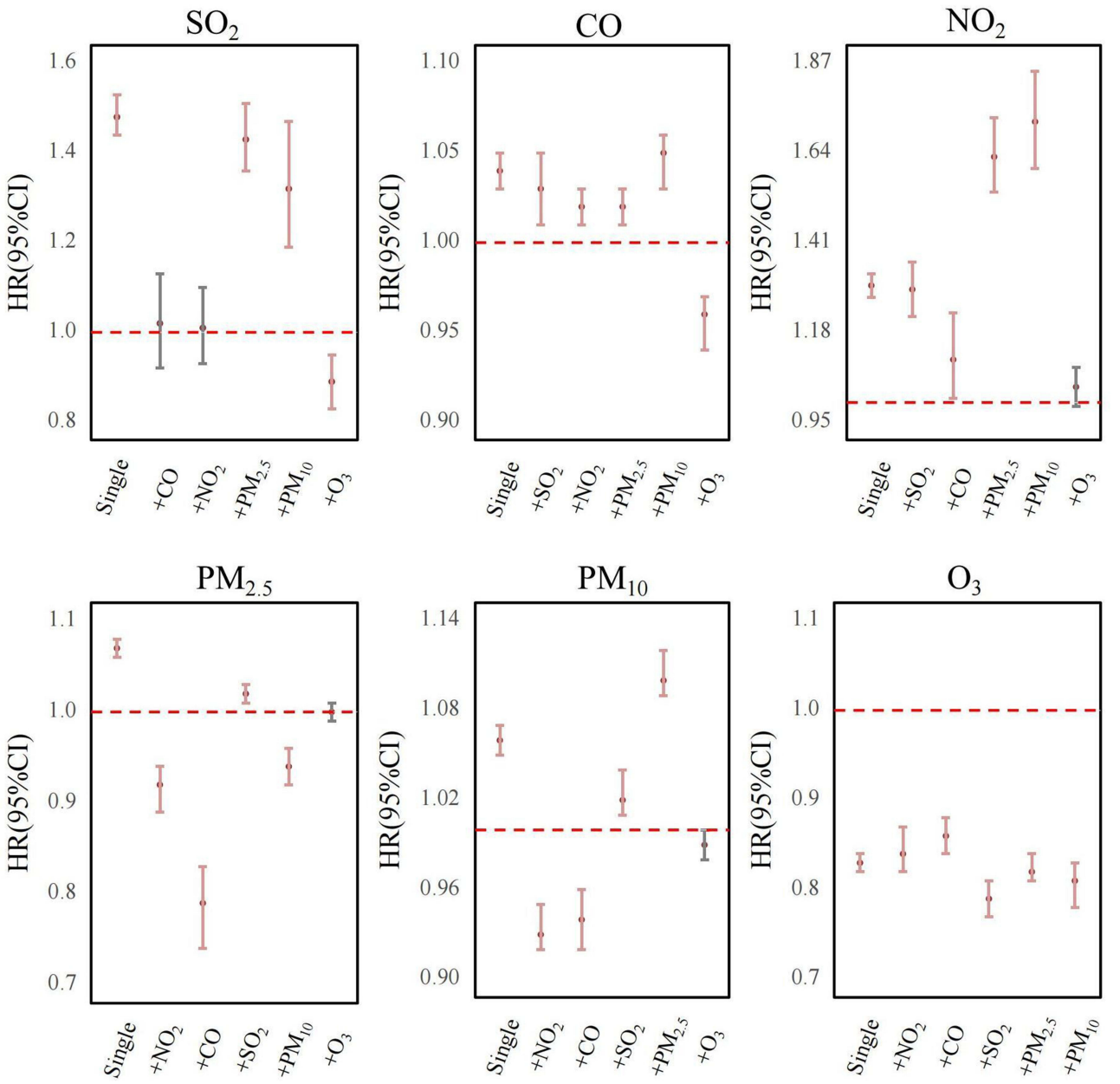


**Figure 2** Impact of each 1-$\mu$ g/m$^3$ increase in single Air Pollutants and their pairwise interactions on breast cancer mortality risk. Models were adjusted for age at diagnosis: age, TNM, stage, chemotherapy, and radiotherapy. Red bars indicate a statistically significant association between the pollutant and mortality risk ($p < 0.05$). Grey bars indicate a non-significant association.

effect at $Q_3$ and $Q_2$ (β=0.39–0.46,TR=1.47–1.59), suggesting a concentration-dependent impact. $SO_2$ shows a strong negative β value (−1.72 to −2.64) and an extremely low TR value (TR=0.07–0.18) at higher quantiles ($Q_3$-$Q_4$), indicating that its concentration increase significantly accelerates mortality, possibly making it the most toxic air pollutant. Particulate matter ($PM_{10}$ and $PM_{2.5}$) shows a significant positive effect (TR=1.78–2.64) at medium and low quantiles ($Q_2$-$Q_3$), while survival time decreases to 32%-39% of the reference group at high quantiles ($Q_4$). CO only shortens survival time to 20% of the reference group at $Q_4$ (β=−1.60, TR=0.20), but has no significant effect at lower quantiles.

## Discussion

Based on a large single-center cohort of breast cancer patients in Urumqi, China, we systematically evaluated the absolute effects of long-term exposure to multiple air pollutants on the risk of death and survival time of patients. By

A

| Distribution | AIC | BIC |
|---|---|---|
| Lognormal | 5976.14 | 6622.34 |
| Weibull | 6013.23 | 6659.42 |
| Logistic | 6332.55 | 6978.75 |

B

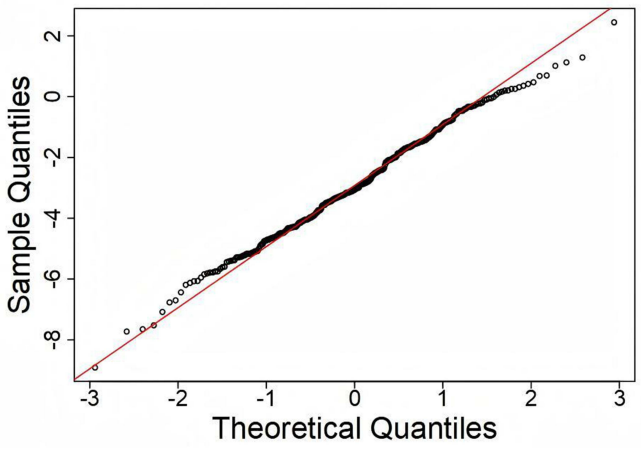


**Figure 3** Model goodness-of-fit comparison and normality verification. (**A**) Comparison of model goodness-of-fit (AIC and BIC values) for three candidate distributions (Lognormal, Weibull, and Logistic); (**B**) Normal Q-Q plot of the residuals from the optimal model (Lognormal distribution).

using the traditional Cox model, we directly assessed significant hazardous or protective effects of specific pollutants on patient survival. These associations were further quantified using the AFT model.

One of the most salient findings of this study is the differential impact of various pollutants on breast cancer survival outcomes and their underlying mechanisms. It was confirmed that high exposure ($Q_4$) to $SO_2$, CO, $NO_2$, and particulate matter significantly increases mortality risk, with $SO_2$ exhibiting a particularly alarming hazard ratio. AFT models further quantified that $SO_2$ exposure reduces patient survival time to just 18% of that in the lowest exposure group. Given its six months of centralized heating annually, Urumqi, China, experiences severe atmospheric pollution during this period, which is further exacerbated by winter inversion layers that trap pollutants.[24] In particular, $SO_2$ adsorbs onto particulate surfaces, carrying polycyclic aromatic hydrocarbons into the respiratory tract. Its derivative can amplify oxidative stress and enhance inflammatory responses downstream of the AhR pathway (eg, elevated IL-22).[26] The activation of AhR pathway may contribute to tumor promotion and immune system disruption. Yoon's multi-pollutant model[27] showed CO exposure increases glioblastoma patient mortality risk by 25.2%.This confirms our finding that long-term exposure to high CO significantly reduced survival in breast cancer patients. On a mechanistic basis, CO itself would not contribute to carcinogenicity, but it may lead to an increase in COHb concentration in the blood, which greatly reduces the oxygen carrying and oxygen releasing capacity of hemoglobin. This activates the HIF-1 alpha pathway and promotes gene expression in tumor development.[28]

We found that $O_3$ demonstrates a protective effect against breast cancer patients at all exposure levels. This conclusion has been corroborated by other studies.[29,30] Multiple studies[31–33] indicate that high-dose $O_3$ induces severe oxidative stress, activating nuclear factor $\kappa$ B and causing tissue inflammation and damage. In contrast, *B* low-dose $O_3$ initiates a "Hormesis" effect (beneficial at low doses, harmful at high doses), triggering cytoprotective antioxidant responses. According to the 2021 WHO Global Air Quality Guidelines,[34] the maximum 8-hour average $O_3$ concentration should not exceed 100 $\mu g/m^3$. In this study, the median $O_3$ concentration was 57.88 $\mu g/m^3$, well below the WHO threshold, further explaining our findings.

In the study of interaction effects, we found that combined exposure to particulate matter and $NO_2$ exhibited a super-additive effect (synergism). Saucy[35] and Weii[36] confirmed that the effect of particulate matter is highly dependent on $NO_2$, and $PM_{2.5}$, $NO_2$, and $O_3$ collectively increase the risk of non-accidental mortality. At the biological mechanism level (eg, amplified inflammation, oxidative stress), these pollutants may still act synergistically, though confirmation through toxicological studies is needed.[37] The discovery of interactions profoundly reflects the complexity of Urumqi's "coal-vehicle composite pollution" (characterized by $SO_2$ and particulates dominated by coal combustion sources and


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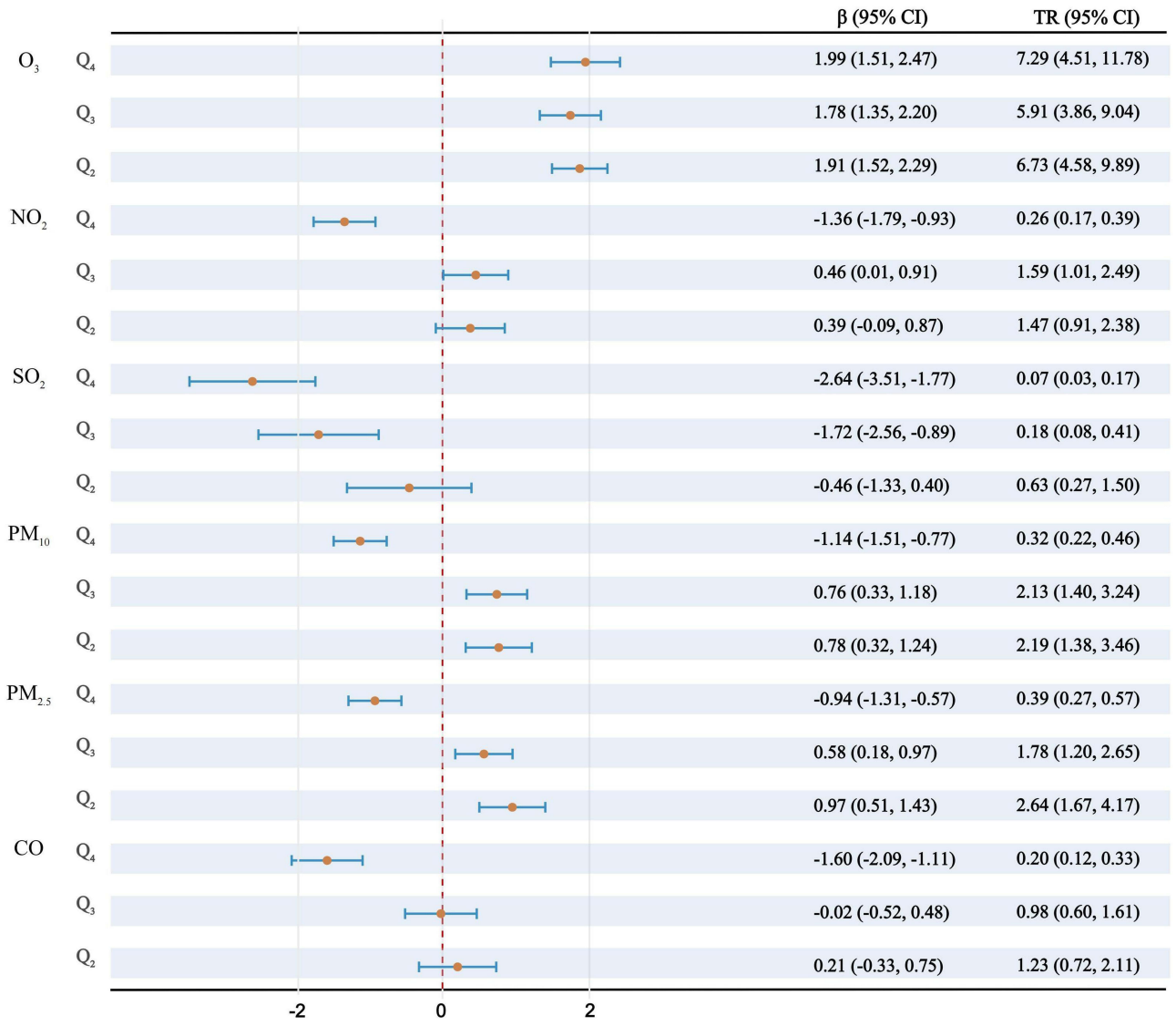


**Figure 4** Association of air pollutant exposure quantiles with time to death among breast cancer patients: an AFT model analysis. Using the $Q_1$ of pollutant exposure as the reference, the AFT model analysis presented β coefficients and time ratios (TR) alongside their 95% confidence intervals for the remaining exposure quantiles. Models were adjusted for age at diagnosis: age, TNM, stage, chemotherapy, and radiotherapy.

$NO_2$ contributed by traffic sources).[38] In the future, we can mitigate health risks based on deeper toxicological mechanisms, integrating environmental management and traditional medical practices.[39,40]

We employed AFT models to quantify the absolute impact of air pollutants on breast cancer survival time, which more intuitively reflects the effect of pollutant exposure on patients' actual survival duration than HR. Based on Urumqi's pollution profile, policies should prioritize strict control of coal combustion sources (especially $SO_2$ and CO) and address traffic-related $NO_2$ emissions and its synergistic effects with particulate matter. While $O_3$ exhibited an apparent protective effect, reflecting lower exposure to primary pollutants, core policies must still focus on reducing primary pollutants such as $SO_2$, $NO_2$, and particulate matter. This provides robust, localized epidemiological evidence for establishing more stringent local emission standards and air quality goals.

Despite the meaningful findings of this study, several limitations exist. First, the research was based on patient data from a single hospital in Urumqi, which may introduce selection bias and limit the generalizability of the results. Second, the assignment of exposure using nearest monitoring station without spatial interpolation. This likely causes non-differential misclassification of exposure, potentially biasing our effect estimates towards the null and underestimating the true associations. Additionally, the study did not thoroughly investigate the differential effects of pollutants on

distinct breast cancer subtypes (eg, hormone receptor subtypes), potentially obscuring underlying biological mechanisms. Future research should expand sample sizes and study scopes, employ refined exposure assessment methods (such as spatiotemporal modeling incorporating personal activity patterns), and conduct in-depth analyses of interactions between pollutants and molecular characteristics of breast cancer. These steps will deepen our understanding of the air pollution-breast cancer relationship and provide stronger scientific support for targeted environmental health interventions.

## Conclusion

Long-term exposure to specific air pollutants significantly impacts breast cancer survival time. High concentrations of $SO_2$, CO, $NO_2$, $PM_{2.5}$, and $PM_{10}$ were strongly associated with increased mortality risk and substantially accelerated death. Conversely, $O_3$ exposure demonstrated a significant dose-dependent protective effect. What's more, there are complex interactions between air pollutants. Critically, the AFT model quantified the absolute acceleration or delay of death, revealing complex impacts of concentration dependence. These findings underscore the urgent need for targeted air pollution control, particularly targeting $SO_2$ and CO from coal combustion and $NO_2$ and particulate matter from traffic. Therefore, local governments should implement stricter emissions standards for industries and vehicles, while also launching public health campaigns to educate citizens about the health impacts of air pollution and effective personal protection measures.

## Data Sharing Statement

The Affiliated Cancer Hospital of Xinjiang Medical University provided data to support the results of this study, but due to the confidentiality of the data, these data are not suitable for public disclosure. If you need to access this dataset, please contact Lei Wang, wlei81@126.com.

## Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the Cancer Hospital affiliated with Xinjiang Medical University (Approval No. K-2023001). All study procedures were performed in accordance with relevant guidelines. This study exclusively enrolled adults aged 18 years or older, all participants were provided with an oral explanation of the purpose and content of the study and gave their written informed consent. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

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## Disclosure

The authors declare that they have no competing interests.

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