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RESEARCH ARTICLE

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Short-term exposure to ambient air pollution and COVID-19 severity during SARS-CoV-2 Delta and Omicron waves: A multicenter study

Barbara Poniedziałek[1] | Piotr Rzymski[1,2] | Dorota Zarębska-Michaluk[3] | Magdalena Rogalska[4] | Marta Rorat[5] | Piotr Czupryna[6] | Dorota Kozielewicz[7] | Marcin Hawro[8] | Justyna Kowalska[9] | Jerzy Jaroszewicz[10] | Katarzyna Sikorska[11,12] | Robert Flisiak[4]

[1]Department of Environmental Medicine, Poznan University of Medical Sciences, Poznań, Poland
[2]Integrated Science Association (ISA), Universal Scientific Education and Research Network (USERN), Poznań, Poland
[3]Department of Infectious Diseases, Jan Kochanowski University, Kielce, Poland
[4]Department of Infectious Diseases and Hepatology, Medical University of Białystok, Białystok, Poland
[5]Department of Forensic Medicine, Wrocław Medical University, Wroclaw, Poland
[6]Department of Infectious Diseases and Neuroinfections, Medical University of Białystok, Bialystok, Poland
[7]Department of Infectious Diseases and Hepatology, Faculty of Medicine, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University, Toruń, Poland
[8]Department of Infectious Diseases and Hepatology, Medical Center in Łańcut, Łańcut, Poland
[9]Department of Adult's Infectious Diseases, Hospital for Infectious Diseases, Medical University of Warsaw, Warsaw, Poland
[10]Department of Infectious Diseases and Hepatology, Medical University of Silesia in Katowice, Bytom, Poland
[11]Division of Tropical Medicine and Epidemiology, Faculty of Health Sciences, Medical University of Gdańsk, Gdańsk, Poland
[12]Division of Tropical and Parasitic Diseases, Faculty of Health Sciences, Medical University of Gdańsk, Gdańsk, Poland

Correspondence
Piotr Rzymski.
Email: rzymskipiotr@ump.edu.pl

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Abstract

Air pollution may affect the clinical course of respiratory diseases, including COVID-19. This study aimed to evaluate the relationship between exposure of adult patients to mean 24 h levels of particulate matter sized <10 µm (PM_{10}) and <2.5 µm ($PM_{2.5}$) and benzo(a)pyrene (B(a)P) during a week before their hospitalization due to SARS-CoV-2 infection and symptomatology, hyperinflammation, coagulopathy, the clinical course of disease, and outcome. The analyses were conducted during two pandemic waves: (i) dominated by highly pathogenic Delta variant (*n* = 1440) and (ii) clinically less-severe Omicron (*n* = 785), while the analyzed associations were adjusted for patient's age, BMI, gender, and comorbidities. The exposure to mean 24 h B(a)P exceeding the limits was associated with increased odds of fever and fatigue as early COVID-19 symptoms, hyperinflammation due to serum C-reactive protein >200 mg/L and interleukin-6 >100 pg/mL, coagulopathy due to D-dimer >2 mg/L and fatal outcome. Elevated PM_{10} and $PM_{2.5}$ levels were associated with higher odds of respiratory symptoms, procalcitonin >0.25 ng/mL and interleukin >100 pg/mL, lower oxygen saturation, need for oxygen support, and death. The significant relationships between exposure to air pollutants and the course and outcomes of COVID-19 were observed during both pandemic waves. Short-term exposure to elevated PM and B(a)P levels can be associated with a worse clinical course of COVID-19 in patients requiring hospitalization and, ultimately, contribute to the health burden caused by SARS-CoV-2 variants of higher and lower clinical significance.

KEYWORDS
air quality, benzo(a)pyrene, clinical severity, particulate matter, respiratory disease

1 | INTRODUCTION

Exposure to air pollutants can affect vulnerability to respiratory viral infections and increase their severity.[1–3] This is predominantly due to damage induced in airway epithelial cell cilia and adverse impact on immune responses through stimulation of proinflammatory cytokine production and increased levels of reactive oxygen species, as well as changes of function of dendritic cells, lymphocytes, neutrophils, and macrophages.[4–8] Such effect has been documented for infections with influenza viruses, rhinoviruses, and respiratory syncytial virus[9–11] and more recently in relation to SARS-CoV-2.[12–16] The association between respiratory disease and air pollutants is particularly relevant for regions where coal and wood combustion continues to play a substantial role in domestic heating and contribute to the emission of particulate matter <10 µm (PM_{10}) and <2.5 µm ($PM_{2.5}$), and PM-bound polycyclic aromatic hydrocarbons such as benzo(a)pyrene (B(a)P). These regions include Poland, where air pollution in nearly all areas exceeds air standards, particularly during the autumn-winter season.[17]

The genetic variants of SARS-CoV-2 can significantly influence the clinical severity of COVID-19. As shown, mutations accumulated by the Delta lineage, which emerged in October 2020 in India, increased viral fusogenicity, translating into a higher risk of severe disease and death.[18–20] On the other hand, the subsequent Omicron lineage, first identified in November 2021 in Africa, was highly transmissible due to the effective evasion of antibodies induced by previous infections or vaccination.[21–23] This feature allowed it to rapidly replace the Delta variant in various world regions in late 2021 and early 2022.[24] At the same time, it was characterized by lower clinical severity resulting from lower fusion activity, preference to infect cells via the endocytic pathway, and limited ability to replicate in the lower respiratory tract.[25–27] Various epidemiological studies have confirmed a lower risk of hospitalization and death due to infection with Omicron.[28–32]

Whether air pollution could influence the severity of infections with highly pathogenic Delta variant and clinically less severe Omicron variant was not a subject of any study. Therefore, the present multicenter research aimed to evaluate the association between exposure to air pollution (PM_{10}, $PM_{2.5}$, and B(a)P levels) estimated during the viral incubation period and further clinical course of COVID-19 in patients hospitalized in Poland during two pandemic waves dominated by different variants of SARS-CoV-2. In this regard, assessed exposure had to be considered short-term, contrary to other studies in which air quality data taken into account corresponded to annual or longer intervals.[33–36] Specifically, we examined the relationship between increased levels of air pollutants and early COVID-19 symptoms, the concentration of inflammatory and coagulopathy markers at admission, oxygen saturation, the need for oxygen supplementation and mechanical ventilation, and fatal outcome. Such a study design allowed an understanding of whether exposure around the time of viral infection and incubation may be an additional factor associated with an additional risk of more severe COVID-19 in the specific population of patients already characterized by increased risk for severe SARS-CoV-2 infection.

2 | MATERIALS AND METHODS

2.1 | Clinical data

The clinical patient data were retrieved retrospectively from the SARSTer, the largest national database of patients hospitalized with COVID-19 in Poland, run under the hospices of the Polish Association of Epidemiologists and Infectiologists. Patients whose data were collected in the SARSTer database were treated in 20 Polish clinical centers spread across the country (Białystok–2 units, Busko-Zdrój, Bydgoszcz, Bytom, Chorzów, Gdańsk–2 units, Gdynia, Kielce, Łańcut, Ostrołęka, Puławy, Racibórz, Warsaw–4 units, Wrocław) and located in eight different voivodeships (Kuyavia-Pomerania, Lower Silesia, Lublin, Masovia, Pomerania, Podlasie, Silesia, Świętokrzyskie). Overall, 2225 records of adult patients hospitalized due to SARS-CoV-2 infection were obtained and divided into two pandemic phases: wave dominated by the Delta variant (Delta wave; from August 1, 2021 to December 31, 2021) and dominated by the Omicron variant (Omicron wave; from January 1, 2022 to April 30, 2022). These two periods were distinguished based on sequences submitted to the GISAD database.[37] All individuals were diagnosed and treated according to the Polish recommendations for managing COVID-19 enforced during the study period.[38,39]

The demographic patients' data included age, BMI, gender, and comorbidities. The clinical data included early COVID-19 symptoms, serum inflammatory markers (C-reactive protein [CRP], interleukin-6 [IL-6], procalcitonin [PCT]), serum D-dimer, oxygen saturation (SpO_2) at admission, need for oxygen therapy and mechanical ventilation, length of oxygen therapy and hospitalization, and outcome (survival or death). Three types of early COVID-19 symptoms were considered: (1) respiratory symptoms (cough, dyspnea), (2) fever, and (3) fatigue. A hyperinflammatory state was defined when CRP > 200 mg/L, IL-6 > 100 pg/mL, or PCT > 0.25 ng/mL.[40,41] D-dimer >2 mg/L was used as a marker of coagulopathy as previous studies reported it has a value in COVID-19 prognosis at this threshold.[42]

The present study had a retrospective, non-interventional nature; therefore, it did not require written consent from participants. The SARSTer study was approved by the Ethics Committee of the Medical University of Bialystok, Poland (APK.002.303.2020) and conducted per the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments, while patients' data were protected according to the European Union General Data Protection Regulation.

2.2 | Air pollution data

Data on air quality were retrieved from the Chief Inspectorate for Environmental Protection in Poland, which is legally responsible for the national air pollution monitoring program. The following parameters were considered for this study: PM_{10}, $PM_{2.5}$, and B(a)P. Stations were equipped with instruments using the gravimetric method for PM measurement, which is considered the most accurate method.[43] Mean 24 h levels of PM_{10}, $PM_{2.5}$, and B(a)P during the week preceding hospitalization were calculated for each patient. If more than one air quality monitoring station was available in a particular area, the data were collected from all of them and averaged. Due to the strict regionalization of COVID-19 health services in Poland, the medical units taking part in this study admitted patients from specific residence areas for which the air quality data was collected.

The period of the week preceding hospitalization was chosen as it most likely represented a time of transition of infection from the incubation phase to the symptomatic stage, a time window during which the innate response constitutes a substantial line of the antiviral defense.[12,44–47] In turn, its alterations can lead to hyperinflammation, resulting in a more severe clinical course of COVID-19 and a worse prognosis.[48–51] Air pollutants such as PM and B(a)P were shown to reveal proinflammatory action and adversely influence innate immune responses, also following short-term exposures.[6,52–54] The following air quality limits were considered in the present research: mean 24 h $PM_{10} > 50\ \mu g/m,^3$ mean 24 h $PM_{2.5} > 20\ \mu g/m,^3$ and mean 24 h B(a)P > 1.0 ng/m.[355,56]

2.3 | Statistical analyses

The data were analyzed with Statistica v. 13.1 (StatSoft) and MedCalc 15.8 (MedCalc Software). The differences in hospitalization length and length of oxygen therapy between groups exposed to air pollutants exceeding and not exceeding threshold levels and the difference in air pollution levels between the Delta and Omicron waves were analyzed with the Mann–Whitney *U* test. Multiple logistic regression models were used to evaluate the association between air pollution exposure and COVID-19 characteristics and outcomes. The independent variables included in each model were exceedances of mean PM_{10}, $PM_{2.5,}$ and B(a)P levels (yes/no) and confounding variables known well to modify the severity and of COVID-19 and mortality risk: age, BMI, gender, and comorbidities (present/not present).[57–62] The dependent variable in subsequent models included: the presence of early symptoms (respiratory symptoms, fever, or fatigue), hyperinflammation (CRP > 200 mg/L, IL-6 > 100 pg/mL, or PCT > 0.25 ng/mL), serum D-dimer >2 mg/L, $SpO_2 <$ 90%, need for oxygen therapy, need for mechanical ventilation, and death. A *p*-value below 0.05 was deemed statistically significant.

3 | RESULTS

3.1 | General characteristics of the studied group

Overall, 2225 patients were included in the study, among which 1440 and 785 were hospitalized during the domination of the Delta and Omicron variants of SARS-CoV-2, respectively. Their general demographic and clinical characteristics are summarized in Table 1. The mean ± SD concentrations of PM_{10}, $PM_{2.5}$, and B(a)P throughout the studied period were $24.3 \pm 11.1\ \mu g/m,^3$ $17.6 \pm 7.5\ \mu g/m,^3$ and 3.4 ± 7.2 ng/m,^{3} respectively, with higher B(a)P levels observed during the Omicron wave compared to a period dominated by Delta variant (3.7 ± 6.5 vs. 3.1 ± 7.6 ng/m,^{3} $p < 0.001$).

3.2 | Association between air pollution and early COVID-19 symptoms

Patients exposed to mean 24 h PM_{10} and 24 h $PM_{2.5}$ levels exceeding the threshold limits of 50 and 20 μg/m,^{3} respectively, were characterized by increased odds of early respiratory COVID-19 manifestations in both pandemic waves (Figure 1). However, the values were higher in the case of $PM_{2.5}$ and during the dominance of the Delta variant. In turn, individuals exposed to mean 24 h B(a)P levels exceeding the threshold limit of 1 ng/m^3 were characterized by increased frequency of fever and fatigue during both considered waves of the pandemic, with higher values of odds ratio observed during the Delta dominance (Figure 1).

3.3 | Association between air pollution and inflammatory and coagulopathy markers at admission

Exposure to elevated mean 24 h B(a)P levels within a week preceding the hospitalization was associated with increased odds of CRP > 200 mg/L, IL-6 > 100 pg/mL, and dimer >2 mg/L at admission during both pandemic waves, with higher values observed under Delta dominance. In turn, patients exposed to mean 24 h PM_{10} and 24 h $PM_{2.5}$

TABLE 1 Demographic and basic clinical characteristics of the studied group of adult patients hospitalized due to COVID-19 during pandemic waves dominated by Delta and Omicron variants of SARS-CoV-2.

	Delta wave (*n* = 1440)	Omicron wave (*n* = 785)
Age, mean ± SD	63.1 ± 17.4	68.6 ± 18.1
BMI, mean ± SD	28.2 ± 5.3	26.9 ± 5.3
Women/men, *n* (%)	687/753 (47.7/52.3)	407/378 (51.8/48.2)
Comorbidities, *n* (%)	1092 (75.8)	735 (93.6)
Exposed to air pollution exceeding the limits		
Mean 24 h PM_{10} > 50 µg/m,^{3} *n* (%)	33 (2.3)	74 (9.4)
Mean 24 h $PM_{2.5}$ > 20 µg/m,^{3} *n* (%)	438 (33.5)	238 (30.4)
Mean 24 h B(a)P > 1 ng µg/m,^{3} *n* (%)	950 (66.0)	644 (82.0)
Hospital stay (days), mean ± SD	13.0 ± 7.9	11.7 ± 8.3
Requiring oxygen therapy, *n* (%)	1086 (75.6)	372 (47.5)
Length of oxygen therapy (days), mean ± SD	11.6 ± 8.1	10.4 ± 7.4
Requiring mechanical ventilation, *n* (%)	103 (7.2)	24 (3.1)
Fatal cases, *n* (%)	214 (14.9)	102 (13.0)

Abbreviations: B(a)P, benzo(a)pyrene; PM, particulate matter.

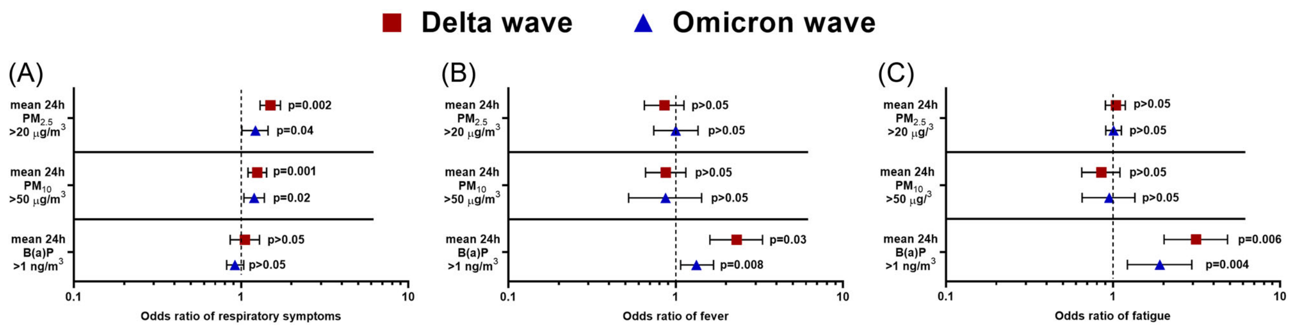

FIGURE 1 The adjusted odds ratio (95% confidence interval) of (A) respiratory symptoms (cough and dyspnea), (B) fever, and (C) fatigue in relation to exposure to air pollution parameters (mean 24 h levels of PM_{10}, $PM_{2.5,}$ and B(a)P) exceeding limits during a week before hospitalization in the studied group of COVID-19 patients hospitalized in Poland during the pandemic waves of the Delta and Omicron variants. The values were adjusted for age, gender, BMI, and comorbidities. B(a)P, benzo(a)pyrene; PM, particulate matter.

at levels exceeding the limits revealed higher odds of PCR > 0.25 ng/mL and IL-6 > 100 pg/mL but not D-dimer >2 mg/L in both COVID-19 waves, although higher odds ratio values were observed during the period dominated by the Delta variant. Higher odds of CRP > 200 mg/L were also found for the group exposed to increased mean 24 h $PM_{2.5}$ levels but only during a period dominated by the Omicron variant (Figure 2).

3.4 | Association between air pollution and the clinical course of COVID-19

During both waves, exposure to air pollutants did not differentiate the hospitalization time of surviving patients, nor did any of them differentiate the time from hospitalization to death ($p > 0.05$ in all cases). Exposure to increased mean 24 h PM_{10} levels was associated with higher odds of $SpO_2 < 90\%$ and oxygen therapy during both waves. In the case of a mean 24 h $PM_{2.5,}$ this effect was seen only during the Delta wave (Figure 3). The length of oxygen therapy did not differ between patients exposed and not exposed to air pollution exceeding threshold levels ($p > 0.05$ in all cases). Air pollution was unrelated to increased odds of mechanical ventilation, except for mean 24 h PM_{10} levels during the Omicron wave study (Figure 3). Fatal cases were more frequently observed in patients exposed to elevated levels of mean 24 h $PM_{2.5}$ and B(a)P during Delta and Omicron waves, although the odds ratio value was higher for the former one (Figure 3).

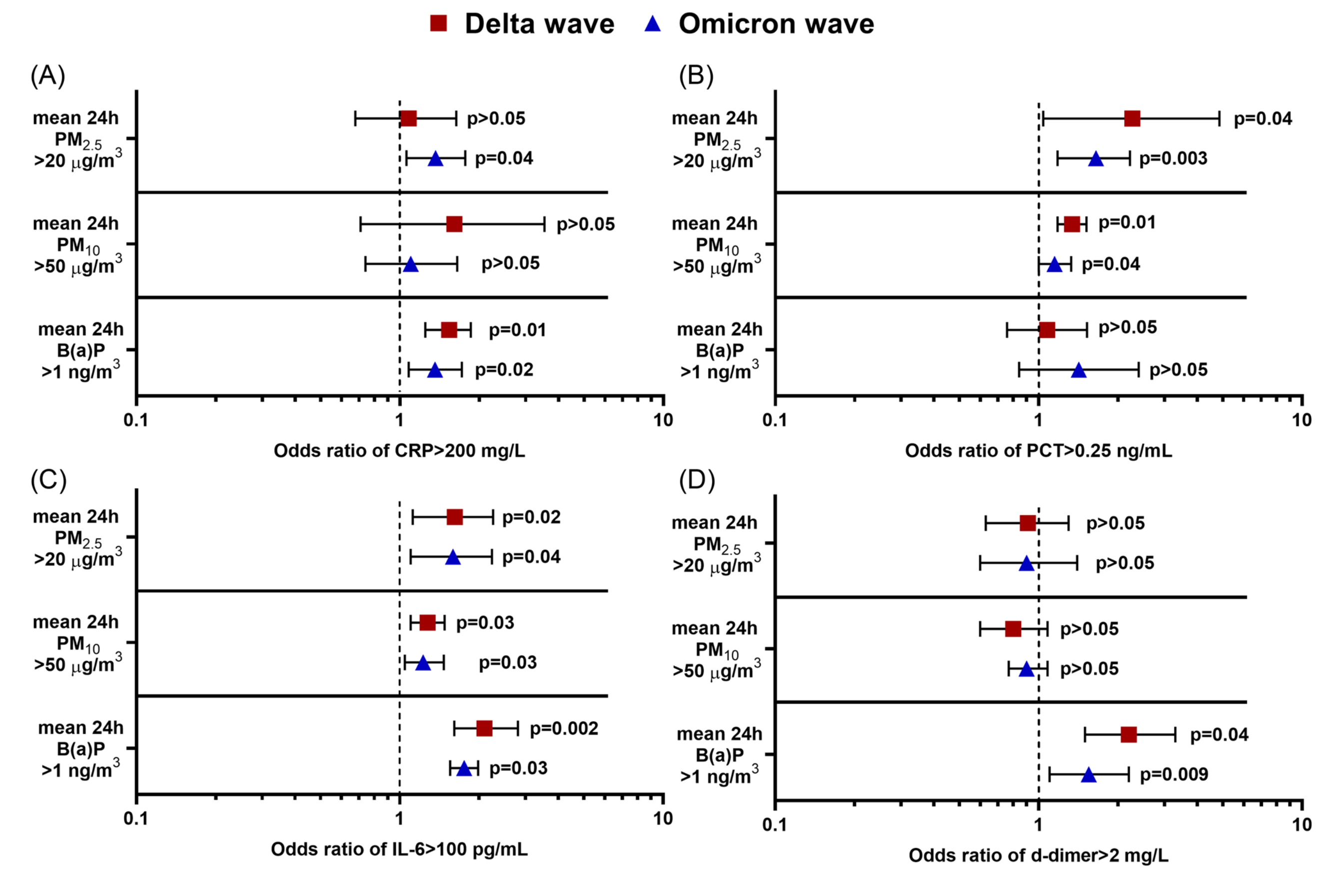

FIGURE 2 The adjusted odds ratio (95% confidence interval) of (A) CRP > 200 mg/L, (B) PCT > 0.25 ng/mL, (C) IL-6 > 100 pg/mL, and (D) D-dimer >2 mg/L in relation to exposure to air pollution parameters (mean 24 h levels of PM_{10}, $PM_{2.5}$, and B(a)P) exceeding limits during a week before hospitalization in the studied group of COVID-19 patients hospitalized in Poland during the pandemic waves of the Delta and Omicron variants. The values were adjusted for age, gender, BMI, and comorbidities. B(a)P, benzo(a)pyrene; CRP, C-reactive protein; IL-6, interleukin-6; PCT, procalcitonin; PM, particulate matter.

4 | DISCUSSION

The present study reports on the potential effects of air pollution on the clinical course of COVID-19 during two periods of the SARS-CoV-2 pandemic dominated by viral variants distinct in risk of clinical severity. Its results indicate that in patients requiring hospitalization, air pollution, that is, PM and B(a)P, was associated with worse outcomes of infection caused by the highly pathogenic Delta variant as well as clinically less severe Omicron. These findings provide important data for public health policy, particularly in regions of low air quality, such as Poland, where the combustion of fossil fuels plays a significant role in domestic heating and substantially contributes to exposure to PM and B(a)P.[63–65]

The strength of our research is the use of individualized exposure levels preceding hospitalization reflecting a time of transition of SARS-CoV-2 infection from incubation phase to symptoms onset, instead of using long-term air quality monitoring or data generalized for the population of a particular region as conducted by numerous other studies.[13–16,33,36,52,66–69] Moreover, we have also included data for B(a)P, for which an association with the clinical course of COVID-19 was only a subject of a few previous investigations during the pandemic.[12,44] Although the pandemic waves included in the present study, dominated by Delta and Omicron SARS-CoV-2 variants, encompassed different periods of the year, each of them also included months characterized by increased emission of PM and B(a)P in Poland, that is, autumn-early winter during the Delta wave and late winter-early spring during Omicron wave.[64,70] Moreover, these analyzes were conducted separately for these waves, enabling an understanding of whether the association between air pollution and COVID-19 is present under the dominance of clinically-distinct viral variants.

As demonstrated, in the case of PM_{10} and $PM_{2.5}$, higher odds of respiratory symptoms manifestation during early COVID-19 and increased levels of selected inflammatory markers were observed, ultimately translating into greater odds of low SpO_2 and the need for oxygen therapy during hospitalization. It has been previously demonstrated that exposure to PM can contribute to the cough reflex by activating the transient receptor potential-class ankyrin-1 and vanilloid-1 ion channels.[71–73] The relationship between PM and respiratory symptoms, including cough and dyspnea, has also been evidenced on the epidemiological level.[74–77] Although cough and shortness of breath were common COVID-19 symptoms regardless

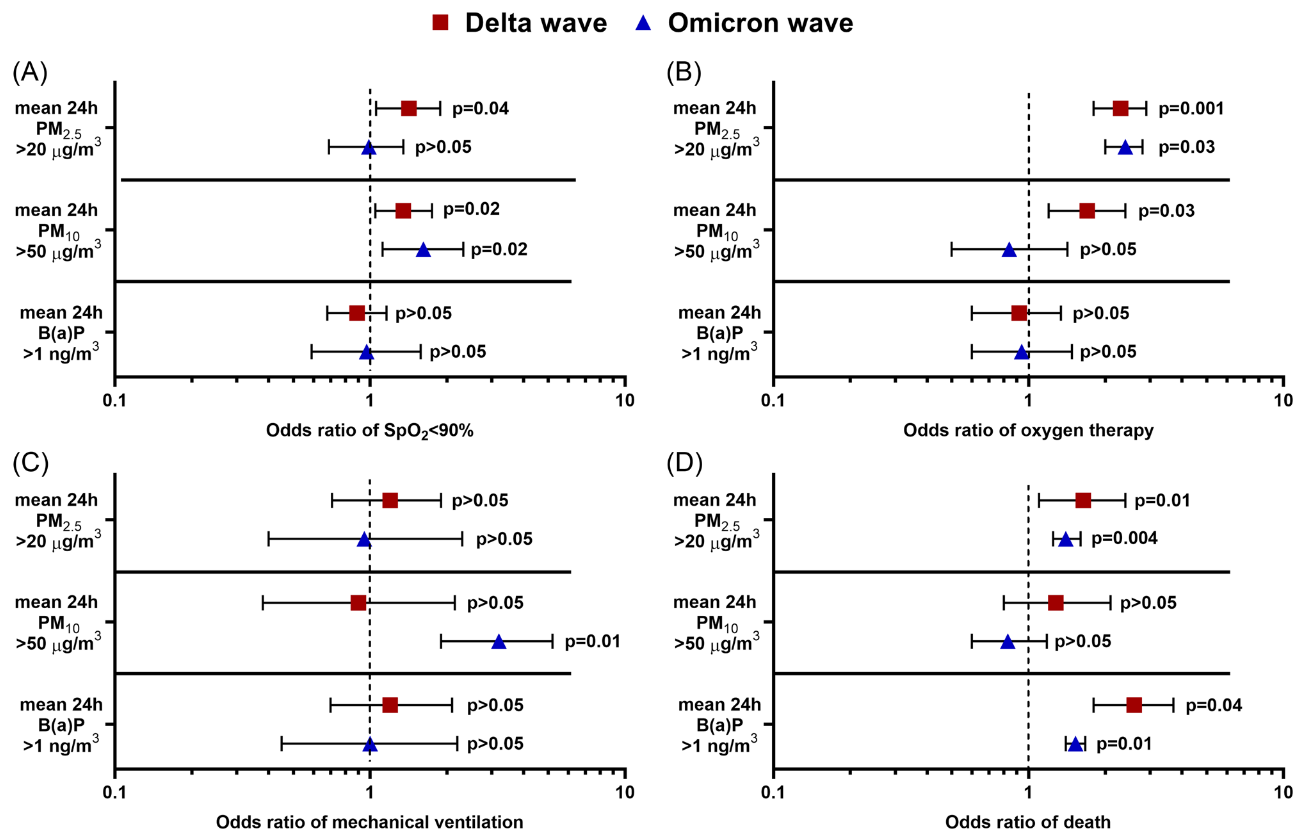

FIGURE 3 The adjusted odds ratio (95% confidence interval) of (A) SpO_2 < 90% at admission, (B) need for oxygen therapy, (C) mechanical ventilation, and (D) death in relation to exposure to air pollution parameters (mean 24 h levels of PM_{10}, $PM_{2.5,}$ and B(a)P) exceeding limits during a week before hospitalization in the studied group of COVID-19 patients hospitalized in Poland during the pandemic waves of the Delta and Omicron variants. The values were adjusted for age, gender, BMI, and comorbidities. B(a)P, benzo(a)pyrene; PM, particulate matter.

of the pandemic phase and dominating viral variant,[62,78,79] their early onset has generally been associated with more severe COVID-19 and increased risk of death.[62,80] Moreover, inhalation of elevated PM levels is known to affect innate immune responses, trigger inflammation in the respiratory tract and subsequently jeopardize its function.[81] It has also been evidenced in humans that even short-term exposure to high airborne PM concentration can induce epigenetic modification leading to higher expression of genes implicated in inflammation (e.g., *CD14*, *NAI3*, *TLR4*, *PREX1*, *TRIM45*).[82–84] These effects are likely more profound following the inhalation of $PM_{2.5}$ than PM_{10} due to the smaller size of this fraction, better penetration of airways, and subsequently more significant irritation of the pulmonic alveolar walls.[81] In addition, $PM_{2.5}$ exposure has been implicated in the upregulation of angiotensin-converting enzyme-2, the cellular receptor for the SARS-CoV-2 entry.[85,86] Furthermore, it can also increase the expression of serine protease TMPRSS2,[87,88] which primes viral S protein following its interaction with the receptor on the cell's surface.[86] Considering that infection with the Omicron variant is not enhanced by TMPRSS2 but is instead preferentially mediated through the endocytic pathway,[25] exposure to $PM_{2.5}$ may, to a lesser extent, influence the clinical course of COVID-19 caused by this variant than in the case of Delta SARS-CoV-2. In summary, overlapping of SARS-CoV-2 infection and PM exposure may act synergistically and aggravate respiratory manifestations, potentially contributing to irritation of airways and worse outcomes—as demonstrated by the present research.

Although the present study shows that PM exposure supported the hypoxic state in COVID-19 patients and subsequently increased the need for oxygen supplementation, in most cases did not translate into higher odds of mechanical ventilation. However, one should note that decision to use it is undertaken only when previous therapeutic measures fail, usually takes place not earlier than in the second week of the disease, and is often influenced not solely by the clinical course of COVID-19 but also by comorbidities and age. Our earlier analyses demonstrated that the frequency of patients requiring mechanical ventilation was generally low and steady throughout the first 17 months of the pandemic (circa 5%), indicating that it is unlikely to be significantly affected by external factors.[62] In addition, in periods of high hospital occupancy, when the availability of mechanical ventilation stations became limited, the qualification criteria had to be tightened. The only association between exposure to air pollutants and mechanical ventilation was observed for PM_{10} for the Omicron wave, during which the hospitals in Poland were not as overwhelmed as in a period dominated by the Delta variant.[89]

On the other hand, exposure to B(a)P levels exceeding the threshold level of 1 ng/m^3 was not associated with increased odds of respiratory COVID-19 symptoms but with early onset of systemic symptoms, that is, fatigue and fever. This significant relationship was seen during both waves considered in the present study. Although various analyses show that increased body temperature does not necessarily predict a worse outcome of SARS-CoV-2 infection,[80] early fever was associated with remarkably lower survival in COVID-19.[90] Moreover, fatigue was demonstrated to be linearly related to infection severity.[80] As further demonstrated in the present study, patients exposed to elevated B(a)P during both pandemic waves had higher odds of the hyperinflammatory state associated with increased levels of CRP and IL-6, which are known to have a significant prognostic value in COVID-19.[91,92] As experimentally evidenced, B(a)P induces CRP in a time-dependent way as well as promotes the release of IL-33, thymic stromal lymphopoietin (a distant paralog of IL-7), tumor necrosis factor-alpha, and nuclear factor kappa B, leading to upregulation of various innate proinflammatory cytokines, including IL-6, through different signaling pathways.[53,93,94] Furthermore, type I interferons, which act as anti-inflammatory mediators and play a role in the initial antiviral response,[95,96] are suppressed by the aryl hydrocarbon receptor (AHR), on which B(a)P is well known to act agonistically.[97] In addition, the proinflammatory state can also be promoted by B(a)P metabolites such as diol epoxides which can also inhibit the activity of interferons alpha and beta.[98] Notably, SARS-CoV-2 infection has also been associated with the diminished activity of these anti-inflammatory cytokines[99] and an increase in AHR activity, leading to impaired regenerative potential of lung epithelial basal cells, ultimately contributing to lung pathogenesis.[100,101]

All in all, B(a)P exposure can interfere with similar pathways as SARS-CoV-2 infection, worsening the patient's prognosis. In line with this, the present research found that individuals exposed to elevated B(a)P levels within a week before hospitalization had significantly increased odds of fatality. Even though B(a)P did not impact SpO_2 levels and the need for oxygen supplementation in studied cohorts, one should note that acute inflammatory responses not only promote tissue damage and organ failure but also lead to coagulopathies and a higher risk of thrombotic events, which play a significant role in COVID-19 mortalities.[102–105] In turn, the release of increased CRP and IL-6 concentrations, odds for which were higher in patients exposed to elevated B(a)P, were shown to be a mechanistic link between inflammation and thrombosis.[106–108] In line with this, exposure to B(a)P exceeding the $1\,\mu g/m^3$ limit was associated with high D-dimer concentrations, a biomarker for thrombotic alterations, and an indicator for prognosis in COVID-19 patients.[42,109,110] Notably, the association between B(a)P and higher odds of death persisted also during the wave-dominated Omicron, even though other studies have shown that the risk of in-hospital mortality during this period was 30%–75% lower compared to Delta wave.[111]

Study limitations must be stressed. Our study focused only on the cohort of patients requiring hospitalization due to COVID-19. Therefore, its results cannot be extrapolated to the general population to assess the potential risks arising from air pollution in the context of SARS-CoV-2 infection. COVID-19 patients that require hospitalization suffer from a more severe disease form and are often characterized by risk factors such as increased age, obesity, and comorbidities (e.g., cardiovascular disease, cancer, diabetes, pulmonary disorders), all of which are associated with higher vulnerability to adverse effects of air pollution exposure.[57,112,113] Therefore, although the analyses were adjusted for patient's age, BMI, and comorbidities, we cannot fully exclude the existence of the collider bias.[114] On the other hand, one should note that from the perspective of public health management, hospitalizations due to severe disease, requiring more advanced treatment protocol, longer hospital stays, and often resulting in worse outcomes, introduce a substantial clinical and economic burden. Therefore, the observations of the present study indicate that air pollution may add to this burden by worsening the clinical course of COVID-19 in the group which is already selected for severe disease. In other words, they highlight that air pollution mitigation shall remain a part of the mitigation of health burden, also in the context of respiratory viral infections, such as this caused by SARS-CoV-2. One should also note that the present research did not consider data on vaccination status and history of infections in hospitalized patients as this data was unavailable. However, our study focused exclusively on patients that required hospitalization due to COVID-19, while previous investigations have shown that individuals who suffer from severe disease, despite vaccination, are likely to undergo a comparable clinical course with similar predictors of poor outcomes as reported in unvaccinated patients.[115–117] Similarly, the information on previous SARS-CoV-2 infections was unavailable for patients analyzed in our study. However, one should note that our study focused on hospitalized patients, while the recent meta-analysis indicates that reinfection does not contribute to additional risk of hospitalization, ICU, or death.[118] Moreover, establishing the exact SARS-CoV-2 infection history is challenging since some infected patients, particularly those with milder or asymptomatic clinical course, may not be subject to diagnostic testing, while some of these patients may not generate anti-SARS-CoV-2 antibodies or concentration of these antibodies may decrease over a time to undetectable levels.[119,120] Our study was also not designed to allow comparisons between particular regions of the country, which may differ in industrialization and coal combustion levels. Moreover, meteorological variables such as air temperature and humidity, both shown to potentially influence the clinical course of COVID-19, were not included.[121,122] Although the data on the wind was also not taken into account, changes to its speed had to be reflected in air quality levels since little wind can cause stagnation of air pollutants, while at higher speed, it contributes to their dispersion.[123] Last but not least, the patients included in this study were not stratified according to their smoking status, which may escalate the adverse effects of air pollutants as well as previously diagnosed chronic lung disease that, in some cases, could be a result of or be promoted by prolonged exposure to air pollution.[124,125]

5 | CONCLUSIONS

The present research shows that air pollution is associated with worse clinical course and outcome of COVID-19 in adult patients regardless of the severity of SARS-CoV-2. It indicates that exposures to elevated levels of airborne PM, particularly $PM_{2.5}$, and polycyclic hydrocarbons such as B(a)P, can contribute to health burden caused by more or less clinically significant SARS-CoV-2 variants. Multi-faceted mitigation of air pollution is pivotal in the context of viral respiratory diseases, particularly in regions characterized by highly deteriorated air quality.

AUTHOR CONTRIBUTIONS

Barbara Poniedziałek: Conceptualization, data curation, formal analysis, investigation, methodology, resources. **Piotr Rzymski**: Conceptualization, data curation, formal analysis, investigation, methodology, supervision, writing—original draft. **Dorota Zarębska-Michaluk, Magdalena Rogalska, Marta Rorat, Anna Moniuszko-Malinowska, Dorota Kozielewicz, Marcin Hawro, Justyna Kowalska, Jerzy Jaroszewicz, Katarzyna Sikorska**: Investigation. **Robert Flisiak**: Investigation, methodology, project administration, resources, supervision.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Piotr Rzymski http://orcid.org/0000-0002-4713-0801
Dorota Zarębska-Michaluk http://orcid.org/0000-0003-0938-1084

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