Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Impact of outdoor air pollution on severity and mortality in COVID-19 pneumonia

O. Bronte, F. García-García, D.-J. Lee, I. Urrutia, A. Uranga, M. Nieves, J. Martínez-Minaya, J.M. Quintana, I. Arostegui, R. Zalacain, L.A. Ruiz-Iturriaga, L. Serrano, R. Menéndez, R. Méndez, A. Torres, C. Cilloniz, P.P. España, COVID-19 and Air Pollution Working Group

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TITLE: IMPACT OF OUTDOOR AIR POLLUTION ON SEVERITY AND MORTALITY IN COVID-19 PNEUMONIA

AUTHORS:

Bronte O.[1,8]*, García-García F.[2], Lee D.-J.[2], Urrutia I.[1,8], Uranga A.[1,8] Nieves M.[1,8], Martínez-Minaya, J. [9], Quintana JM[3], Arostegui I.[4,2], Zalacain R.[5,8], Ruiz-Iturriaga L.A.[5,8], Serrano L.[5,8], Menéndez R.[6], Méndez R.[6], Torres A.[7], Cilloniz C.[7,10], España P.P.[1,8] and the COVID-19 & Air Pollution Working Group

* Corresponding author.

E-mail address: obronte001@ikasle.ehu.eus

1. Galdakao-Usansolo University Hospital, Pulmonology Department, Galdakao, Spain.

2. Basque Center for Applied Mathematics (BCAM), Bilbao, Spain.

3. Galdakao-Usansolo University Hospital, Research Unit, Galdakao, Spain.

4. University of the Basque Country (UPV/EHU), Department of Applied Mathematics, Statistics and Operative Research, Leioa, Spain.

5. Cruces University Hospital, Pulmonology Department, Baracaldo, Spain.

6. Hospital Universitari i Politècnic La Fe de Valencia, Pulmonology Department, Valencia, Spain.

7. Hospital Clínic i Provincial de Barcelona, Pulmonology Department, University of Barcelona, Barcelona, Spain.

8. BioCruces Bizkaia Health Research Institute, Baracaldo, Spain.

9. Universitat Politècnica de València, Valencia, Spain.

10. Faculty of Health Sciences, Continental University, Huancayo, Peru

Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus type 2; ARDS, acute respiratory distress syndrome; OAPE: outdoor air pollution exposure; NO_2: nitrogen dioxide, NO; nitrogen monoxide, O_3: ozone; $PM_{2.5}$: particulate matter <2.5 µm, PM_{10}: particulate matter <10 µm; 95% CI, 95% confidence interval.

HIGHLIGHTS:

- In COVID-19 pneumonia patients, the probability of death rises significantly with exposure to PM_{10}, NO_2, NO, NO_X, and CO.
- Systemic inflammatory response increases with exposure to PM_{10}, NO_2, NO and NO_X.
- Gas exchange disturbance is associated with exposure to NO, NO_X, and NO_2.

ABSTRACT:

The relationship between exposure to air pollution and the severity of coronavirus disease 2019 (COVID-19) pneumonia and other outcomes is poorly understood. Beyond age and comorbidity, risk factors for adverse outcomes including death have been poorly studied. The main objective of our study was to examine the relationship between exposure to outdoor air pollution and the risk of death in patients with COVID-19 pneumonia using individual-level data. The secondary objective was to investigate the impact of air pollutants on gas exchange and systemic inflammation in this disease. This cohort study included 1548 patients hospitalised for COVID-19 pneumonia between February and May 2020 in one of four hospitals. Local agencies supplied daily data on environmental air pollutants (PM_{10}, $PM_{2.5}$, O_3, NO_2, NO and NO_X) and meteorological conditions (temperature and humidity) in the year before hospital admission (from January 2019 to December 2019). Daily exposure to pollution and meteorological conditions by individual postcode of residence was estimated using geospatial Bayesian generalised additive models. The influence of air pollution on pneumonia severity was studied using generalised additive models which included: age, sex, Charlson comorbidity index, hospital, average income, air temperature and humidity, and exposure to each pollutant. Additionally, generalised additive models were generated for exploring the effect of air pollution on C-reactive protein (CRP) level and SpO_2/FiO_2 at admission. According to our results, both risk of COVID-19 death and CRP level increased significantly with median exposure to PM_{10}, NO_2, NO and NO_X, while higher exposure to NO_2, NO and NO_X was associated with lower SpO_2/FiO_2 ratios. In conclusion, after controlling for socioeconomic, demographic and health-related variables, we found evidence of a significant positive relationship between air pollution and mortality in patients hospitalised for COVID-19 pneumonia. Additionally, inflammation (CRP) and gas exchange (SpO_2/FiO_2) in these patients were significantly related to exposure to air pollution.

KEYWORDS:

SARS-CoV-2; COVID-19; Pneumonia; Mortality; Air pollution; Individual-level data.

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INTRODUCTION

In late 2019, an outbreak of the novel severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) spread rapidly around the world and led to the declaration of a public health emergency of international concern on 30th January 2020. Shortly afterwards, on 11th February, it was declared a pandemic. Despite the implementation of numerous control measures, the global pandemic persists and continues to cause cases and deaths worldwide. Therefore, it is critical to identify the key modifiable risk factors that may affect COVID-19 fatality (Tian et al., 2021).

Air pollution is the world's leading environmental cause of illness and premature death (GBD, 2018; WHO, 2018). According to the World Health Organization (WHO), about seven million deaths a year across the world are attributable to air pollution (WHO, 2018). According to the European Environment Agency, there were 417,000 premature deaths attributable to particles with an aerodynamic diameter <2.5 μm ($PM_{2.5}$), 55,000 to nitrogen dioxide (NO_2) and 20,600 to ozone (O_3) in Europe in 2018 (EEA,2020).

Air pollution is a complex mixture of gaseous and particulate components that vary both temporally and spatially. Outdoor air pollution exposure (OAPE) has been associated with marked detrimental effects on respiratory health (GBD, 2018; Dick et al. 2014; Raji et al., 2020; Fukuda et al., 2011; Huang et al., 2016; Huh et al. 2020; Liang et al., 2020; Somayaji et al., 2020; Jaligama et al., 2017; Cai et al., 2017; Cui et al., 2003). In line with this, OAPE has been identified as a cause of higher morbidity and mortality in viral and bacterial lower respiratory tract infections and pneumonia (Fukuda et al., 2011; Huang et al., 2016; Huh et al., 2020; Liang et al., 2020; Somayaji et al., 2020; Jaligama et al., 2017).

Epidemiological studies have previously investigated impacts of particulate matter (PM) and gaseous pollutants such as nitrogen oxides (NO_X) and ozone (O_3) on COVID-19 outcomes. In most cases, the results have linked mean air pollution levels to COVID-19 severity and mortality (Martelletti et al., 2020; Dutheil et al., 2020; Zhu et al., 2020; Frontera et al., 2020; Conticini et al., 2020; Wang et al., 2020; Setti et al., 2020; Adhikari et al., 2020; Copat et al., 2020; Fattorini et al., 2020; Wu et al., 2020; Zoran et al., 2020; Bourdel et al., 2021; Andersen et al., 2021; Borro et al., 2020). Among the pollutants studied, COVID-19 mortality appears to be most closely related to $PM_{2.5}$ (Copat et al., 2020) and NO_2 (Copat et al., 2020; Fattorini et al., 2020; Ogen et al., 2020; Guan et al., 2020). Recently, specific mechanisms by which air pollution could

increase the severity and mortality risk of COVID-19 infection have been described (Frontera et al., 2020; Andersen et al., 2021; Borro et al., 2020; Guan et al., 2020, Bourdrel et al., 2021).

Experimental studies have shown that air pollution can decrease immune response and, in the respiratory tract, facilitate viral entry through angiotensin-converting enzyme 2 by increasing protease activity, which might facilitate SARS-CoV-2 infection. Most severe forms of COVID-19 and deaths associated with the disease have been related to a disproportionate systemic inflammatory response. In relation to this, air pollution exposure can increase respiratory mucosal permeability leading to impaired gas exchange, oxidative stress and systemic acute inflammatory reactions, observed in severe forms of COVID-19 with multiorganic failure and pulmonary complications such as acute respiratory distress syndrome (ARDS). Air pollution plus SARS-CoV-2 infection, may have a multiplicative effect on inflammatory response exacerbating the cytokine storm. Consequently, inferring more severe respiratory epithelium damage and immune dysregulation, pulmonary vascular endothelial cell apoptosis, inflammation and activation of prothombotic state, leading to alveolar edema, ARDS, multiple organ failure and death (Boyd S. et al 2022, Nieto-Codesido et al 2022, Bronte- Moreno et al 2023) . The impact of acute phase reactants and related blood cellularity seems to be highly relevant as mortality predictor in COVID 19 pneumonia (Nieto-Codesido et al 2022) and respiratory comorbidities (Bronte-Moreno et al 2023). However, neutrophil count relationship with mortality from COVID-19 is not consistent in the current literature (RH Du, et al 2020, Zhou F. et al 2020). Air pollutants can also reduce antioxidant levels and modify surfactant antimicrobial properties. Additionally, air pollution is associated with the decompensation of pre-existing comorbidities, increasing COVID-19-related morbidity and mortality (Guan et al., 2020, Bourdrel et al., 2021). Furthermore, age older than 65 years, coexistence of cardiovascular comorbidities, lymphopenia and arterial oxygen pressure less than 60 mmHg (among others), have been postulated as risk factors associated with COVID-19 pneumonia mortality in hospitalized patients (Rong-Hui et al. 2020, Shebl Ali et al. 2023, Nieto-Codesido et al. 2022, Jung Choi et al. 2022, Muñoz-Rodriguez et al. 2021). Finally, it should be taken into account that air pollution exposure can predispose individuals to chronic diseases, in particular, respiratory and cardio-metabolic conditions, which are comorbidities that have been found to increase the risk of hospitalisation or death due to COVID-19 (Zoran et al., 2020; Guan et al., 2020).

Nonetheless, most of these studies have been ecological, that is, their design has not been appropriate for evaluating possible associations between air pollution and COVID-19 (Liang et al., 2020; Wu et al., 2020; Borro et al., 2020). Their main limitation is that they are based on aggregated data, and hence, lack detailed information at the individual level (Zoran et al., 2020).

In this context, the main objective of our study was to examine the relationship between exposure to outdoor air pollution and the risk of death in patients with COVID-19 pneumonia using individual-level data. The secondary objective was to investigate the impact of personal exposure to air pollutants on gas exchange and host inflammatory response in COVID-19 pneumonia.

MATERIAL AND METHODS

1.- Study population

Our study is retrospective, observational and multicentric cohort study. It was carried in Respiratory department of four public Spanish hospitals. The participating hospitals were: Hospital Universitari i Politècnic La Fe de Valencia (Valencia, Region of Valencia), Hospital Clínic i Provincial de Barcelona (Barcelona, Catalonia), Cruces University Hospital (Baracaldo, Biscay, Basque Country) and Galdakao-Usansolo University Hospital (inland region of Biscay and parts of Araba, Basque Country). The catchment populations of these hospitals in 2020 were 300, 540, 330 and 309 thousand, respectively.

We included all patients admitted in hospital with COVID-19 pneumonia diagnosis. All patients included in our cohort were older than 18 years and were admitted to one of the four participating hospitals for COVID-19 pneumonia between 1st March 2020 and 31st May 2020. The requirements for the diagnosis of COVID-19 pneumonia were: having a positive microbiological test for SARS-CoV-2, involving DNA amplification by polymer chain reaction, as well as compatible chest imaging findings on chest radiography and/or chest computer tomography. Inclusion criteria were: hospital admission with COVID-19 pneumonia diagnosis, accepted to participate and give written informed consent. We excluded patients with non-inclusion criteria, subsequent admissions, hospitalised for SARS-CoV-2 infection without a diagnosis of pneumonia, duplicates for the same patient, padiatric patient patient (< 18 years old) or who declined to

participate and/or give written informed consent. The protocol was approved by the research ethics committees of the autonomous region of the Basque Country, Hospital Universitari i Politècnic La Fe de Valencia, and Hospital Clínic i Provincial de Barcelona (reference codes: PI 2019090, PI 2020083, 20-122-1, and HCB/2020/0273 respectively).

Data were gathered on place of residence (postcode), and socio-demographic, clinical, laboratory and radiological characteristics and entered into an *ad hoc* database. The respiratory physician of the research group in charge of each patient reviewed the corresponding case from hospital admission up to 3 months after discharge.

2.- Air pollution exposure

We obtained daily pollution data from open sources, from 1st January 2019 to 31st December 2019, as published by the corresponding air quality agencies of the regional authorities (see supplementary material, data sources). Such data were only available for specific locations, namely, the sites of monitoring stations, which form the air quality surveillance networks.

In Spain, each autonomous community has its own network to monitor air quality. In our study, the air quality networks from which we have collected pollution data have been: (1) the Basque Country, for the Galdakao and Baracaldo hospitals, and their respective areas of influence; (2) Barcelona, for the Hospital Clínic and its area of influence (3) Valencia, for the Hospital la Fe de Valencia and its area of influence.

The Air Quality Control Network of the Basque Country includes 55 stations that are located throughout all the territory which is subdivided in eight zones, in accordance with the requirements of current regulations. This division is calculated based on aerial basis of similar orography in which the levels of pollutants are fundamentally influenced by the same sources, and by the same transport processes of the aerial mass of the aforementioned sources. The zoning of the territory also depends on the pollutant (Alberdi E, Alvarez I, Hernández H, Oyarbide-Zubillaga A, Goti A. Analysis of the Air Quality of the Basque Autonomous Community Using Spatial Interpolation. Sustainability. 2020; 12(10):4164. https://doi.org/10.3390/su12104164). In Barcelona, 11 stations make up the Atmospheric Pollution

Monitoring and Forecasting Network and they measure the air concentration of the main environmental pollutants that are harmful to people's health. (Rodriguez-Rey, D. et al 2022). Finally, in the Community of Valencia, at this moment, there are 65 operating samplers. (Estarlich M, et al. 2013).

The maximum mean levels of outdoor air pollutants recommended by the World Health Organization (WHO) in the most recent air quality guidelines (AQGs) published in 2021 (WHO, 2021) were taken as a reference for this study.

3.- Covariates

As well as OAPE measurements, we considered meteorological conditions (temperature and humidity), since evidence in the literature indicates that they have an impact on mortality due to respiratory diseases (Song et al., 2017). For this, we used data published by the meteorology agencies in each geographical area (see supplementary material, data sources).

In addition, we assessed the socioeconomic status of the patients. Most of the articles that have analyzed the impact of socioeconomic status on community-acquired pneumonia (CAP) point out that adults residing in low-deprivation areas, they have a higher incidence, severity, and mortality of CAP compared to adults residing in high-deprivation areas (Wiemken et al. 2020). As the collection of such data at an individual level was not feasible due to data protection concerns, we decided to use the mean net personal income at each individual's postcode of residence, compared to the average net income in the province. For this, we used data published by the Spanish National Institute of Statistics, in its 2019 census report (see supplementary material, data sources).

4.- Outcomes

The main objective of our study was to examine the relationship between exposure to outdoor air pollution and the risk of death in hospitalized patients for COVID-19 pneumonia using individual postcode-level air pollution exposure data. The secondary objective was to investigate the impact of personal exposure to air pollutants on gas exchange and host inflammatory response in COVID-19 pneumonia.

5.- Statistical analysis

For a descriptive analysis of the cohort, we performed univariate statistical comparisons: using the chi-squared test for discrete variables and the non-parametric Mann-Whitney U test for continuous variables. Effect size, which quantifies the magnitude of the difference between groups (Sullivan et al., 2012), was assessed using Cramer's V statistic and rank-biserial correlation. For the sake of exploring inter-group differences, effect sizes were categorized by magnitude into negligible, small, medium, or large attending to the methodology proposed by Cohen (2013).

For each pollutant, we estimated daily OAPE at postcode level, using Bayesian spatial statistical models. In particular, we used Bayesian generalised additive models (BGAMs) (Umlauf et al., 2018; Alas et al., 2021) to compute the distribution of pollutant values as a function of latitude, longitude and elevation with respect to the location of the monitoring stations. Calculations were carried out for each of the six pollutants under consideration here, namely: PM_{10}, $PM_{2.5}$, O_3, NO_2, NO, and NO_X. To assess OAPE, we took into account daily levels over 2019 and obtained four percentile values to summarise this exposure: per-year 50, 90, 95 and 99% percentiles.

To assess temperature and humidity at postcode level, we developed the same type of spatial statistical models using BAMLSS as for pollution exposure (Stauffer et al., 2017; Umlauf et al., 2018) [Equations (1)-(2)]. Temperature *t* was modelled via a normal distribution, whereas humidity *h* (in the range 0-100%) corresponded to a Beta distribution parametrized in terms of the mean and the standard deviation of the distribution:

$$\begin{aligned} t_j &\sim Normal(\mu_j, \sigma_j) \\ h_j &\sim Beta(\mu_j^*, \sigma_j^*) \end{aligned} \tag{3}$$

for the *j*-th location; and where their respective mean distribution parameters μ_j and μ_j^* were explained as a function of latitude, longitude and elevation (*x,y* and *z*) as in [Equation (2)]. Again, no covariates and effects were included in the linear predictor of the standard deviation.

For each patient, we computed the median of the values over the three days before each patient's admission.

A model estimating the quantitative impact of differences in air pollution exposure on the *n*-th patients' mortality *m* was fitted using a generalised additive model approach (GAM, Wood 2017), which makes it possible to explore the effect of pollutant exposures *e* on the probability of death. The model assumed a binomial distribution, linking the probability for death π to the predictors using a logit link function, and it was fitted for: each patient's age *a*, sex *s* and Charlson comorbidity index *c*, hospital, net income *i*, temperature *t* (Celsius) and relative humidity *h* (percentage) in the days leading up to admission (median of the previous 3 days). The GAM was used to estimate the odds ratio (OR) for death per 1 μg/m^3 increase in the corresponding air pollutant exposure (β_{Pollut}^{Mort}) and keeping constant the rest of the variables:

$$m_n \sim Binomial(\pi_n^{Mort}) \tag{4}$$

$$\begin{aligned} logit(\pi_n^{Mort}) &= \beta_0^{Mort} + \beta_{Pollut}^{Mort} e_n + g_{Pollut,hospital}^{CRP}(e_n, hospital) \\ logit(\pi_n^{Mort}) &\sim + \beta_{Sex}^{Mort} s_n + 1_{Female(n)} \beta_{Age,F}^{Mort} a_n + 1_{Male(n)} \beta_{Age,M}^{Mort} a_n \\ logit(\pi_n^{Mort}) &\sim + 1_{Female(n)} f_{Charlson,F}^{Mort}(c_n) + 1_{Male(n)} f_{Charlson,M}^{Mort}(c_n) \\ logit(\pi_n^{Mort}) &\sim + f_{Income}^{Mort}(i_n) + g_{Income,hospital}^{CRP}(i_n, hospital) \\ logit(\pi_n^{Mort}) &\sim + f_{Temp}^{Mort}(t_n) + g_{Temp,hospital}^{Mort}(t_n, hospital) \\ logit(\pi_n^{Mort}) &\sim + f_{Humid}^{Mort}(h_n) + g_{Humid,hospital}^{Mort}(h_n, hospital), \end{aligned} \tag{5}$$

being β the parameters corresponding to the fixed effects, f univariate smoothing P-splines, g univariate smoothing P-splines estimated by hospital and $\mathbf{1}_{Female}$, $\mathbf{1}_{Male}$ are indicator functions for sex.

In addition, we proposed equivalent GAMs to explain the impact of pollution exposure on C-reactive protein (CRP) level and the ratio between the partial pressure of arterial oxygen and the fraction of inspired oxygen (SpO_2/FiO_2), measured at admission with a pulse oximeter. CRP levels are positive and skewed to the right, whereas pO_2/FiO_2 ratios are positive and skewed to the left. Hence, for the GAM, a gamma family model parametrized in terms of the mean and the scale was used. Logarithmic and negative logarithmic functions were employed as link functions in the mean, meanwhile, the logarithm was used for the dispersion parameter (Wood 2017). In these cases, the model estimates a multiplicative factor indicating

the expected change in those clinical markers due to the effect of 1 μg/m³ increases in exposure (β_{Pollut} and $\beta_{Pollut}^{SpO_2/FiO_2}$) and keeping constant the rest of the variables.

$$\begin{aligned} l_n^{CRP} &\sim Gamma(\mu_n^{CRP}, \varphi_n^{CRP}), \\ l_n^{SpO_2/FiO_2} &\sim Gamma\left(\mu_n^{SpO_2/FiO_2}, \varphi_n^{SpO_2/FiO_2}\right), \end{aligned} \tag{6}$$

where, likewise in [Equation (5)], with the same form of effect modelling:

$$\begin{aligned} log(\mu_n^{CRP}) &= \beta_0^{CRP} + \beta_{Pollut}^{CRP} e_n + g_{Income,hospital}^{CRP}(e_n, hospital) \\ \log(\alpha_n^{CRP}) &\sim + \beta_{Sex}^{CRP} s_n + 1_{Female(n)} \beta_{Age,F}^{CRP} a_n + 1_{Male(n)} \beta_{Age,M}^{CRP} a_n \\ \log(\alpha_n^{CRP}) &\sim + 1_{Female(n)} f_{Charlson,F}^{CRP}(c_n) + 1_{Male(n)} f_{Charlson,M}^{CRP}(c_n) \\ \log(\alpha_n^{CRP}) &\sim + f_{Income}^{CRP}(i_n) + g g_{Income,hospital}^{CRP}(i_n, hospital) \\ \log(\alpha_n^{CRP}) &\sim + f_{Temp}^{CRP}(t_n) + g_{Temp,hospital}^{CRP}(t_n, hospital) \\ \log(\alpha_n^{CRP}) &\sim + f_{Humid}^{CRP}(h_n) + g_{Humid,hospital}^{CRP}(h_n, hospital) \\ log(\varphi_n^{CRP}) &= \gamma_0^{CRP} \end{aligned} \tag{7}$$

and

$$\begin{aligned} -log\left(\mu_n^{SpO_2/FiO_2}\right) &= \beta_0^{SpO_2/FiO_2} + \beta_{Pollut}^{SpO_2/FiO_2} e_n + g_{Pollut,hospital}^{SpO_2/FiO_2}(e_n, hospital) \\ -\log(\alpha_n^{SpO_2/FiO_2}) &\sim + \beta_{Sex}^{SpO_2/FiO_2} s_n + 1_{Female(n)} \beta_{Age,F}^{SpO_2/FiO_2} a_n + 1_{Male(n)} \beta_{Age,M}^{SpO_2/FiO_2} a_n \\ -\log(\alpha_n^{SpO_2/FiO_2}) &\sim + 1_{Female(n)} f_{Charlson,F}^{SpO_2/FiO_2}(c_n) + 1_{Male(n)} f_{Charlson,M}^{CRP}(c_n) \\ -\log(\alpha_n^{SpO_2/FiO_2}) &\sim + f_{Income}^{SpO_2/FiO_2}(i_n) + g_{Income,hospital}^{SpO_2/FiO_2}(i_n, hospital) \\ -\log(\alpha_n^{SpO_2/FiO_2}) &\sim + f_{Temp}^{SpO_2/FiO_2}(t_n) + g_{Temp,hospital}^{SpO_2/FiO_2}(t_n, hospital) \\ -\log(\alpha_n^{SpO_2/FiO_2}) &\sim + f_{Humid}^{SpO_2/FiO_2}(h_n) + g_{Humid,hospital}^{SpO_2/FiO_2}(h_n, hospital) \\ log\left(\varphi_n^{SpO_2/FiO_2}\right) &= \gamma_0^{SpO_2/FiO_2}, \end{aligned} \tag{8}$$

being β the parameters corresponding to the fixed effects, f univariate smoothing P-splines, g univariate smoothing P-splines estimated by hospital and $\mathbf{1}_{\text{Female}}$, $\mathbf{1}_{\text{Male}}$ are indicator functions for sex.

5.1.- Data Management.

Data were available at census tract level, and we re-interpolated them to postcode level. To do so, the number of census tract (geographical) polygons within the postcode polygons was computed, as well as the proportion of the area they occupied within each polygon. Subsequently, we calculated a weighted sum for each variable of interest.

RESULTS

- **Study population**

During the study period, 1548 patients were included. Among them, 243 (15.7%) died during hospitalisation within 30 days after admission. The demographic and clinical characteristics of the study sample are summarised in Table 1.

- **Air pollution exposure**

Table 2 lists the median values (i.e., 50% percentiles) and 95% confidence intervals (CIs, 2.5% to 97.5% percentile ranges) for exposure to air pollutants at the postcode in which the participating hospitals are located, expressed in $\mu g/m^3$. Values marked in light or dark blue exceeded the annual or daily AQGs respectively. Note that AQGs for O_3 are for peak season and 8-hour exposure and that the WHO does not publish any guidelines for either NO or NO_X. Specifically, the median and 97.5% percentile values of PM_{10} exposure respectively exceeded the annual and diary AQGs at hospitals C and D. Moreover, the median and 97.5% percentile values of $PM_{2.5}$ and NO_2 concentrations were higher than the annual and daily AQGs at all hospitals (data on $PM_{2.5}$ was unavailable for hospital C). C and D hospitals are located in more urbanized areas, with more industry and more transport not only by land but also by sea. It is for these reasons that these areas are most polluted. Similarly, for hospitals A and B, the most polluted areas correlate with more polluted locations, mainly by road traffic and industry.

Spearman's correlations between pollutants are shown in Figure 1. In general, there were strong and significant positive correlations between levels of certain pollutants: in particular, NO_2, NO and NO_X. Similarly, PM_{10} and $PM_{2.5}$ concentrations were correlated. On the other hand, levels of ozone (O_3) were significantly negatively correlated with those of nitrogen gases (NO, NO_2 and NO_X). Figure 2 contains maps showing the geographical distribution of median NO_2 exposure (over 2019). Similar figures for other pollutants and percentiles can be found in the online supplementary material (Figure S1, a-l).

Figure 3 depicts the distribution of the numbers of patients who were hospitalised (Fig. 3 a) and who died (Fig. 3 b) by postcode of residence.

- **Modelling the effect of air pollutants:**

We modelled how the OR of death among patients hospitalised for COVID-19 pneumonia changed as exposure levels to air pollution increased by 1 μg/m^3, separately for each of the six air pollutants under consideration. Notably, for 1 μg/m^3 rises in the median exposure to PM_{10}, NO_2, NO and NO_X, the OR for death increased significantly ($p<0.05$): 5.33%, 3.59%, 10.79% and 2.24% (Figure 4a, and Table S1 in the online supplementary material). For the 90% percentile, each 1 μg/m^3 increment in NO and NO_X levels translated to 3.12% and 1.03% higher ORs ($p<0.05$); whereas considering the 95% percentile for these same pollutants, rises of 1 μg/m^3 corresponded to 2.10% and 0.75% higher ORs ($p<0.05$). Finally, each 1 μg/m^3 increment in terms of the 99% percentile exposure to NO_2 and NO implied 1.28% and 1.21% higher ORs for death ($p<0.05$).

Regarding effects on inflammation, each 1 μg/m^3 rise in median PM_{10}, NO_2, NO and NO_X concentration translated to significant increases in CRP ($p<0.05$), levels increasing by 3.39%, 1.52%, 5.50% and 1.06%, respectively (Figure 4b, and Table S1 in the online supplementary material). Moreover, considering 90%, 95% and 99% percentiles, for each 1 μg/m^3 increase in NO and NO_X concentration, CRP levels also rose: 1.72% and 0.54%; 1.12% and 0.40%; and 0.65% and 0.27% respectively ($p<0.05$).

As for the relationship between gas exchange and pollution, each additional 1 μg/m^3 of NO_2, NO and NO_X was significantly associated ($p<0.05$) with decreases in SpO_2/FiO_2: -0.19%, -0.73% and -0.14%, respectively (Figure 4c, and Table S1 in the online supplementary material). For the 90% percentiles of NO_2, NO and NO_X, per 1 μg/m^3 increase, SpO_2/FiO_2 fell by -0.11%, -0.33% and -0.07% ($p<0.05$); while it decreased by -0.16% and -0.05% ($p<0.05$) for the 95% percentiles of NO and NO_X, and by -0.07% ($p<0.05$) for the 99% percentile of NO_2.

The other correlations between air pollutant exposure and the aforementioned clinical outcomes in COVID-19 pneumonia were not statistically significant ($p\geq0.05$).

Discussion

1. Summary of the main results

Our models found that higher exposure to $PM_{10,}$ $NO_{2,}$ NO and NO_X in the year before admission for COVID-19 pneumonia was associated with higher ORs for death. Likewise, each 1 $\mu g/m^3$ increase in the levels of $PM_{10,}$ $NO_{2,}$ NO and NO_X was associated with greater systemic inflammation, as reflected in an elevation of CRP levels in blood, and with greater severity of ARDS, as reflected in a decrease in the SpO_2/FiO_2 ratio.

2. Effect of OAPE on mortality in other studies and comparison with our findings

Numerous studies have linked COVID-19 mortality to exposure to air pollutants, in various locations worldwide (Copat et al. 2020). Among all the known pollutants with negative effects on respiratory health, those that have been most related to COVID-19 mortality are particulates, both PM_{10} (Zhu et al.2020) and $PM_{2.5}$ (Copat et al. 2020; Pozzer et al. 2020) and nitrogen-containing air pollutants (NO_2, NO_X, NO) (Zoran at al., 2020; Copat et al., 2020; Bolaño-Ortiz et al., 2020).

In relation to PM_{10}, in Spain, Culqui-Lévano et al. (2022) have recently found statistically significant associations of PM_{10} and NO_2 with COVID-19 mortality in 41 of the 52 Spanish provinces, with PM_{10} being the variable that showed the strongest associations in most of the areas studied. Furthermore, Magazzino et al. (2020) reported that COVID-19 mortality was associated with exposure to PM_{10} and $PM_{2.5}$ in three French cities.

Regarding NO_2 and COVID-19 mortality in the United States, Liang et al. (2020) found that the mean concentrations of NO_2 were positively associated with the COVID-19 mortality rate, regardless of exposure to O_3 and $PM_{2.5}$. Concerning this gas in Europe, Ogen et al. (2020) found that 78% of deaths were concentrated in five areas located in northern Italy and central Spain with very high levels of NO_2 in the months prior to the COVID-19 pandemic.

Our results are consistent with these and other studies conducted in various locations worldwide. The models used in our study show that exposure to PM_{10}, NO_2, NO and NO_X is significantly associated with a higher probability of death in individuals hospitalised for COVID-19 pneumonia. We also studied potential associations with O_3, but trends did not reach statistical significance.

Levels of O_3, considered one of the most dangerous air pollutants, are correlated with a high risk of respiratory problems, such as asthma exacerbation and lung inflammation, loss of lung function, and idiopathic pulmonary fibrosis (Johannson et al. 2014). The non-statistically significant associations in our study may be explained by the high levels of NO_2 and NO_X. That is, O_3 is an air pollutant that is not directly emitted into the air; rather, it is formed through a series of reactions involving NO_2 and O_2. These reactions depend on the concentration of NO_2 and volatile organic compounds (VOCs) and are facilitated by environmental factors such as solar radiation and atmospheric convection (WHO, 2005; Guarnieri and Balmes, 2014). In our study, O_3 levels were negatively correlated with those of other pollutants.

3. OAPE and COVID-19 pneumonia severity and inflammation

In this study, we found no significant associations between OAPE and the severity of COVID-19 pneumonia, as measured by international Pneumonia Severity Index (PSI) scale. This may be due to the greater weight of the underlying disease in these scales compared to respiratory function, which would underestimate the severity of COVID-19 pneumonia. Unlike Bozack et al. (2021), we have not considered admission or the use of invasive mechanical ventilation as indicators of severity, since such data might have introduced a bias, due to potential overwhelming of resources in the context of the health emergency. Therefore, we decided to evaluate the relationship of PM_{10}, NO_2, NO_X, and NO exposure with the severity of ARDS in COVID-19 as reflected in a measure of gas exchange, namely, SpO_2/FiO_2 (Ranieri et al., 2012). Additionally, CRP is a readily available and widely used inflammatory biomarker, it being both easy and inexpensive to measure. In COVID-19 infection, Taneri et al. (2021) related CRP levels to disease severity and fatality, while Yitbarek et al. (2021) in their systematic review concluded that CRP monitoring can contribute to the early detection of severe manifestations and subsequently improve prognosis. For these reasons, we evaluated the impact of exposure to PM_{10}, NO_2, NO_X, and NO on the level of CRP.

Studies in animals and humans have linked OAPE to systemic and respiratory inflammation. Specifically, the exposure of animal models to air pollutants has shown to be followed by the elevation of inflammatory markers at the systemic and pulmonary levels (Yang et al. (2019). The relationship between exposure to pollutants and inflammation has also been studied in humans. Pollutants that have been most strongly and frequently associated with systemic inflammation are PM_{10}, $PM_{2.5}$ and NO_2, inducing the overexpression of

inflammatory mediators, such as interleukin 6. This inflammation seems to be related to the duration of exposure to pollutants, as observed by Tsai et al. (2019). In line with this, Perret et al. (2017) described an incremental pattern of responses related to exposure to NO_2 and interleukin 6.

In relation to this, recently, studies have been published that relate exposure to air pollutants to oxidative stress and the inflammatory response against SARS-CoV-2. Zhu et al. (2020) suggest that oxidative stress and the inflammatory response are the main mechanisms involved in the adverse effects induced by PM in COVID-19. In addition, among the mechanisms that explain the relationship of pollutants with the immune response associated with SARS-CoV-2, it has been observed that exposure to PM_{10} and NO_2 (Di Ciaula et al., 2021) can weaken and modify the regulation of the immune response. This would reduce the host's defensive capacity to deal with viral invasion, increasing inflammation and tissue damage induced by the virus. For this reason, exposure to air pollutants such as PM_{10} and NO_2 may induce hyperactivation of the innate immune system with overexpression of inflammatory cytokines and chemokines. This systemic proinflammatory state would trigger an apoptotic cascade (Gouda et al., 2018) that, together with immune deregulation, could be responsible for ARDS, resulting in a poorer prognosis in patients with COVID-19, this being the main cause of death. On the other hand, exposure to air pollutants has a deleterious effect on pre-existing respiratory and cardiovascular conditions (comorbidities), in turn, leading to a poorer prognosis in COVID-19 patients.

Our results show a statistically significant relationship between air pollution exposure and both decreases in the SpO2/FiO2 ratio and increases in blood CRP level. On the one hand, 1 $\mu g/m^3$ increases in NO, NO_X, and NO_2 were related to significant reductions in SpO2/FiO2; and on the other, CRP levels rose significantly with each 1 $\mu g/m^3$ increase in PM_{10}, NO_2, NO and NO_X.

4. Strengths

In this study, the participating patients have been individually evaluated and their exposure to PM_{10}, $PM_{2.5}$, O_3, NO_2, NO_X and NO has been estimated by geospatial models, based on their postcode of residence. The first studies to evaluate the impact of pollution on COVID-19 were ecological in nature, that is, they used aggregated data, which cannot be adjusted for individual risk factors for COVID-19-related death. Recently,

individual-level studies have been reported (Travaglio 2020, Pegoraro 2021, Bozack A 2021, Lopez-Feldman A, 2021), but none have been carried out in Spain.

Concerning the methods, daily exposure to pollution and meteorological conditions based on individuals' postcodes were estimated using geospatial BGAMs. Then, the influence of air pollution on pneumonia severity was studied using GAMs which included: age, sex and Charlson comorbidity index, hospital, average income, air temperature and humidity, and exposures to each pollutant. In addition, GAMs were also generated for the effect of air pollution on CRP and SpO2/FiO2 levels at hospital admission.

Assessing the OAPE is challenging to carry out in an individualized manner. The joint report by ERS, ISEE, HEI and WHO (Andersen et al., 2021) identified a single cohort study with individual-level data (Bowe et al., 2021): where the authors employed the annual –i.e. throughout 2018– average PM2.5 exposure, at an approximate 1 km2 resolution, and linked with residential street address in the USA. We performed postcode-based geospatial calculations, because postcode was the most detailed level of information available to researchers about the patients' place of residence, due to privacy legislations. Nonetheless, postcode areas are arguably at a similar geographical resolution to the aforementioned 1 km2 squares, notably at the metropolitan areas, where most of the patients in our cohort came from (see Figure S2, supplementary material). Meteorological covariates, to adjust for the well know effect of meteorology on respiratory diseases (Song et al., 2017), were also computed per postcode in the same manner, but where further particularized to the median of the 3 days prior to each patient's admission. Other covariates adjusted in our statistical GAM models were patient-specific: sex, age, and Charlson comorbidity index.

Socioenonomic inequalities have been found to influence the pneumonia incidence, severity and mortality in community adcquired pneumonia (CAP) (Wiemkem et al.2020) and in COVID-19 disease (Gao et al 2021, Khanijahani A. et al. 2021, Agència de Qualitat i Avaluació Sanitàries de Catalunya; 2020). However, the evidence of the impact of air polllution on the severity and mortality from COVID 19 pneumonia taking into account the socioeconomic level is scarce. Given that socioeconomic inequalities influence many diseases and health outcomes, we believe that having considered this aspect in our study is relevant. Moreoves, socioeconomic position should be considered an important factor for research in air pollution and CAP.

Finally, we are not aware of any studies that have evaluated at an individual level the impact of exposure to air pollutants on the inflammatory response of patients hospitalised for COVID-19 pneumonia, considering either CRP or altered gas exchange as indicators of pneumonia severity and its relationship with air pollution.

5. Limitations

Our study has several limitations. Data from a number of stations were missing for $PM_{2.5}$ and CO, leading to possible errors in the measurement of exposure in the corresponding areas. Additionally, pollutant concentration estimates were made for place of residence only, and therefore they did not capture variability in exposure due to time spent indoors and at locations other than the primary residence. Finally, from 14th March 2020 to 21st June 2020, the Spanish government declared a state of alarm due to the coronavirus pandemic and imposed a lockdown across the country, which reduced exposure to outdoor air pollution. All the aforementioned aspects may explain the observed relatively weak associations of exposure to some pollutants (especially $PM_{2.5}$) with mortality, inflammatory response and decreased oxygen exchange in COVID-19 pneumonia.

In relation to socioeconomic status, we used data published by the Spanish National Institute of Statistics, in its 2019 census report. However, the information of this data is limited to censal data, and we could not register for each subject included in our study.

CONCLUSIONS

In patients hospitalised for COVID-19 pneumonia, we found statistically significant positive associations between death and exposure to certain pollutants, PM_{10}, NO_2, NO and NO_X, independently of the levels of other pollutants analysed ($PM_{2.5}$, and O_3). Further, exposure to PM_{10}, NO_2, NO and NO_X was associated with lower SPO_2/FIO_2 ratios and higher CRP levels.

Therefore, exposure to these pollutants, largely due to vehicle emissions, should be considered an important risk factor for severity and adverse outcomes in COVID-19. These results highlight, in general, the

importance of decreasing air pollution levels, and in particular, the need to implement specific public health measures to address this risk factor by reducing people's exposure, such as cutting emissions from road traffic in areas with high levels of NO_2, NO, NO_X and PM_{10}.

COVID-19 & Air Pollution Working Group

La Fe University and Polytechnic Hospital, Pulmonology Department: Ana Latorre, Paula González Jiménez, Raul Méndez, Rosario Menéndez.

Cruces University Hospital, Pulmonology Department: Leyre Serrano Fernández, Eva Tabernero Huguet, Luis Alberto Ruiz Iturriaga, Rafael Zalacain Jorge.

Hospital Clínic i Provincial de Barcelona, Pulmonology Department: Antoni Torres, Catia Cilloniz.

Galdakao-Usansolo University Hospital, Pulmonology Department: Pedro Pablo España Yandiola, Ana Uranga Echeverría, Olaia Bronte Moreno, Isabel Urrutia Landa.

Galdakao-Usansolo University Hospital, Research Unit: Jose María Quintana, Susana García-Gutiérrez, María Gascón Pérez, Ane Villanueva.

BioCruces Bizkaia Health Research Institute: Mónica Nieves Ermecheo, Pedro Pablo España Yandiola, Ana Uranga Echeverría, Olaia Bronte Moreno, Isabel Urrutia Landa, Leyre Serrano Fernández, Eva Tabernero Huguet, Luis Alberto Ruiz Iturriaga, Rafael Zalacaín Jorge.

Basque Center for Applied Mathematics (BCAM): Fernando García-García, Dae-Jin Lee, Joaquín Martínez-Minaya, Miren Hayet-Otero, Inmaculada Arostegui.

University of the Basque Country (UPV/EHU), Department of Mathematics: Miren Hayet-Otero, Inmaculada Arostegui.

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Table 1. *Summary descriptive statistics of the cohort.*

Variable		Total population n=1548	Survived n=1305	Died n=243	p-value	Effect size interpretation
Hospital	A	358	306 (86%)	52 (14%)	<0.001	Small
	B	380	337 (89%)	43 (11%)		
	C	438	338 (77%)	100 (23%)		
	D	372	324 (87%)	48 (13%)		
Sex	Male	952	785	167 (17.6 %)	0.012	Negligible
	Female	596	520	76 (12.8%)		
Age	Median [IQR]	65 [53, 77]	63 [51, 74]	80 [7[illegible], 85]	<0.001	Large
	Num. valid	1548	1305	243		
Lived in a nursing home	No	1274	1117	157	<0.001	Small
	Yes	94	60	34		
	N/A	180	128	52		
Charlson comorbidity index	Median [IQR]	3 [1, 5]	[illegible] [1, 4]	6 [4, 7]	<0.001	Large
	Num. valid	1548	1305	243		
Pneumonia severity score [PSI]	Median [IQR]	70 [53, 92]	65 [50, 84]	105 [86, 128]	<0.001	Large
	Num. valid	1287	1110	177		
SpO_2/FiO_2 [ratio]	Median [IQR]	452.4 [433.3, 461.9]	452.4 [438.1, 461.9]	428.6 [357.3, 452.4]	<0.001	Medium
	Num. valid	1520	1286	234		
C Reactive Protein (CRP) [mg/L]	Median [IQR]	72.13 [32.30, 134.04]	65.9 [30.27, 91.16]	114.62 [59.27, 191.50]	<0.001	Small
	Num. valid	1473	1248	225		
Procalcitonin (PCT) [ng/mL]	Median [IQR]	0.11 [0.06, 0.22]	0.1 [0.06, 0.20]	0.19 [0.11, 0.54]	<0.001	Medium
	Num. valid	1089	929	160		

Univariate statistical comparisons were performed using χ2 tests for discrete variables, and non-parametric Mann–Whitney U tests for continuous variables. Respectively, effect sizes of between-group differences (and their qualitative interpretations) were assessed using Cramer's V statistic and rank-biserial correlation. Univariate statistical comparisons for inter-group differences (survivors vs. deceased) were performed using χ2 tests for discrete variables, and non-parametric Mann–Whitney U tests for continuous variables. Their effect sizes for between-group differences were computed using Cramer's V statistic and rank-biserial

Cohen (2013). Num. valid: number of valid participating patients. N/A: not applicable. PSI: calculated as Fine et al. 1997.

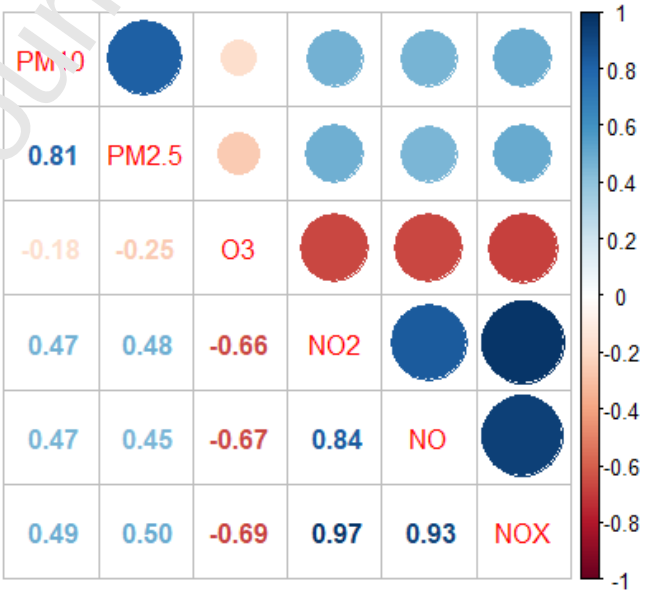
***Table 2*: Exposure throughout 2019 to air pollutants [µg/m^3].**

	A			B			C			D		
	P2.5%	**P50%**	**P97.5%**	**P2.5%**	**P50%**	**P97.5%**	**P2.5%**	**P50%**	**P97.5%**	**P2.5%**	**P50%**	**P97.5%**
PM_{10}	6.2	13.5	30.5	5.8	13.0	29.7	9.9	21.7	47.2	7.1	20.6	48.0
$PM_{2.5}$	3.1	6.9	17.1	2.8	6.8	18.8	*NA*	*NA*	*NA*	3.5	12.7	33.4
O_3	17.5	48.2	75.1	22.7	54.4	79.5	15.5	50.5	82.7	17.3	55.3	86.9
NO_2	7.4	16.4	32.9	6.4	14.5	31.2	13.9	[illegible]	59.8	6.2	20.3	58.1
NO	1.6	4.7	23.6	1.6	4.3	18.3	2.7	[illegible]	44.5	2.3	5.5	41.7
NO_X	9.8	23.4	65.4	8.8	21.0	52.1	[illegible]	46.9	124.2	10.3	28.6	126.9

Abbreviations: *P, percentile; NA, not available.*

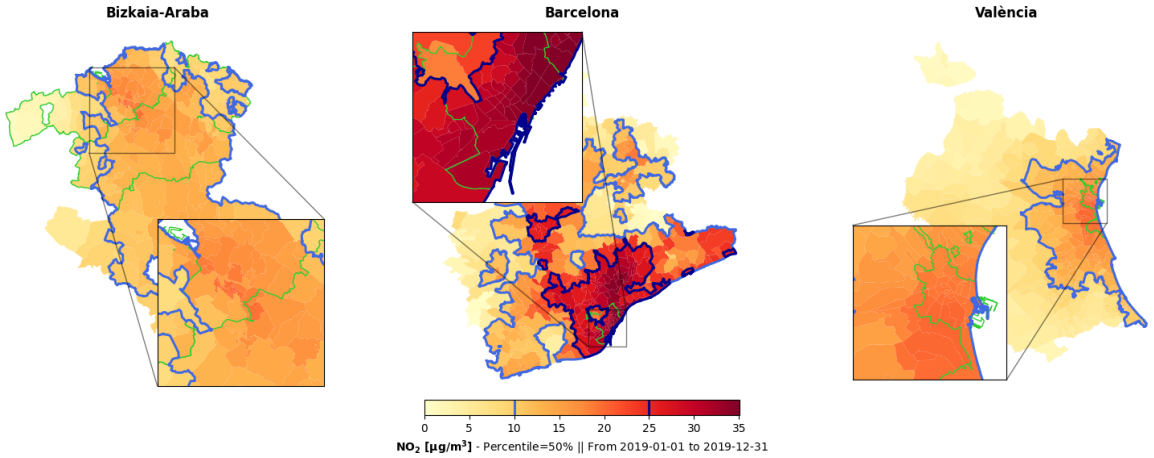
OAPE percentiles throughout 2019, to air PM_{10}, $PM_{2.5}$, O_3, NO_2, NO and NO_x *[µg/m^3]. Marked in light or dark blue, exceeded the annual o daily WHO 2021 air quality guideline recommendations.*

***Figure 1*: Spearman's rank correlations between pairs of air pollutants, across geographical locations.**



Spearman's rank correlation coefficients close to ±1 indicate strong positive/negative correlations; whereas values close to 0 indicate a lack of correlation.

Figure 2: ***Geographical distribution of the median daily NO_2 concentration.***



Postcodes delimited with light blue lines experienced pollution levels above the annual air quality guideline [AQG] recommended by the World Health Organization (WHO, 2021) [i.e., 10 µg/m^3 for NO_2]; whereas postcodes outlined in dark blue experienced levels above the daily AQG [i.e., 25 µg/m^3 for NO_2]. In Bizkaia-Araba (left panel), the green lines delimit the catchment areas of Galdakao and Cruces hospitals; whereas, in the two other panels, green lines delimit the cities of Barcelona and Valencia.

Figure 3: ***Number of patients in our cohort, by postcode.***

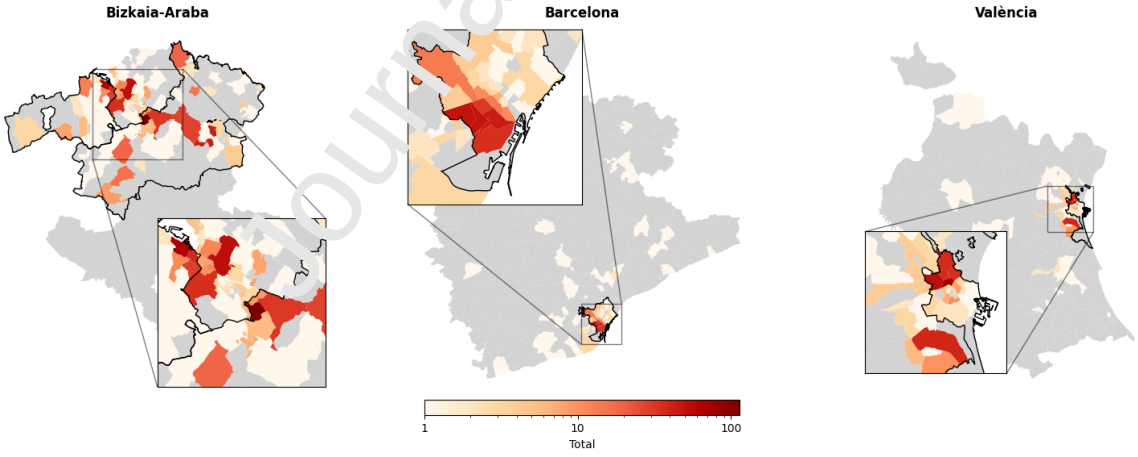


Figure 3 a: Number of individuals hospitalised for COVID-19 pneumonia.

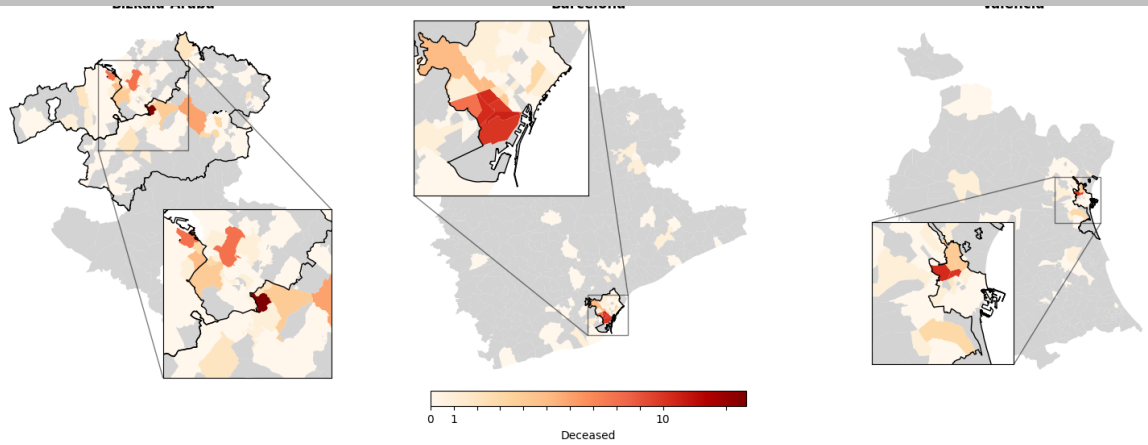


Figure 3 b: Number of deaths among the COVID-19 pneumonia patients enrolled.

Grey areas indicate postcodes without any patients enrolled in our cohort. In Bizkaia-Araba (left panel), the black lines delimit the catchment areas of Galdakao and Cruces hospitals; whereas, in the two other panels, green lines delimit the cities of Barcelona and Valencia.

- ***Figure 4*: Forest plot – Effects of increases in air pollution exposure on different clinical outcomes, by pollutant and percentile.**

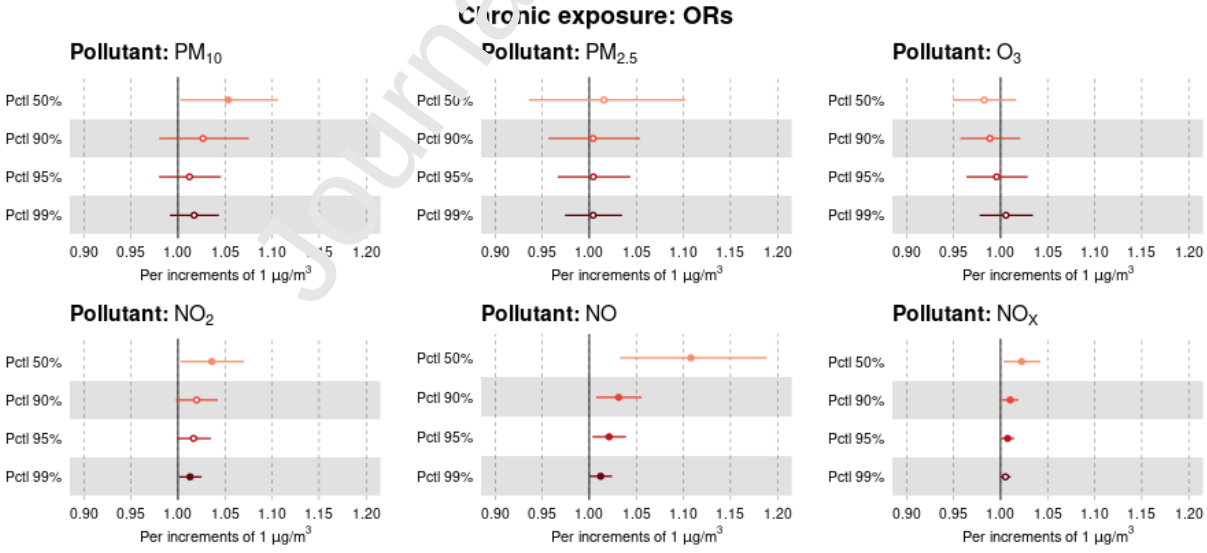


Figure 4 a: Odds ratio for COVID-19 pneumonia mortality (in-hospital or within 30 days after admission), per 1 µg/m^3 increase in air pollution exposure (i.e., throughout 2019) for each pollutant, by yearly percentiles (50-99%). The diagrams show the mean expected value (central dot) and its 95% confidence interval (CI). The dot is solid when the effect was statistically significant (p<0.05).

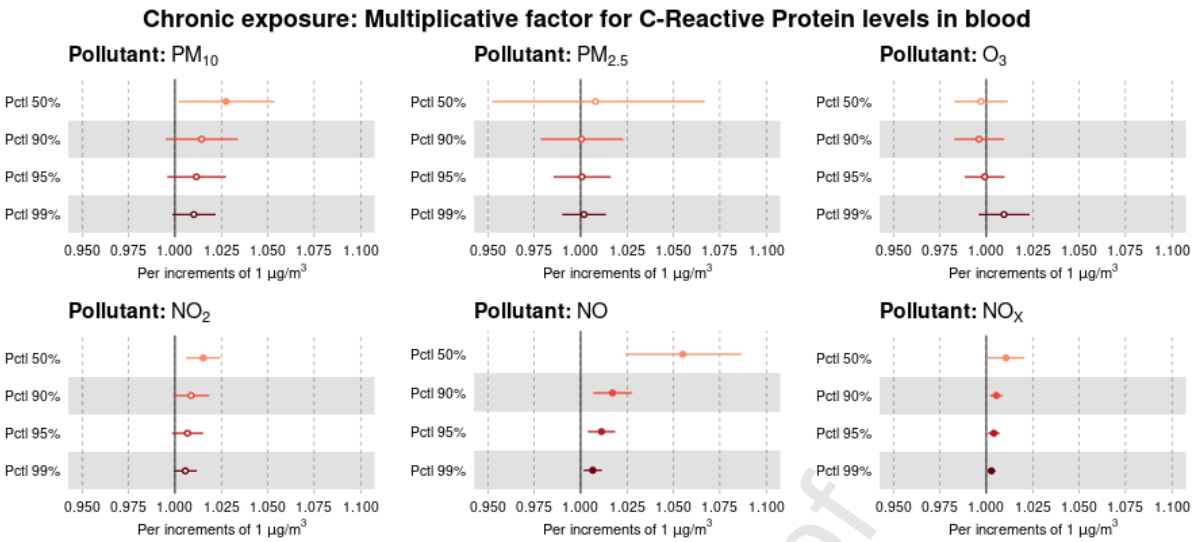


Figure 4 b: Multiplicative factor affecting blood CRP levels, per 1 µg/m^3 increase in air pollution exposure (i.e., throughout 2019) for each pollutant, by yearly percentiles (50-99%). The diagrams show the model-expected value (central dot) and its 95% confidence interval (CI). The dot is solid when the effect is statistically significant (p<0.05).

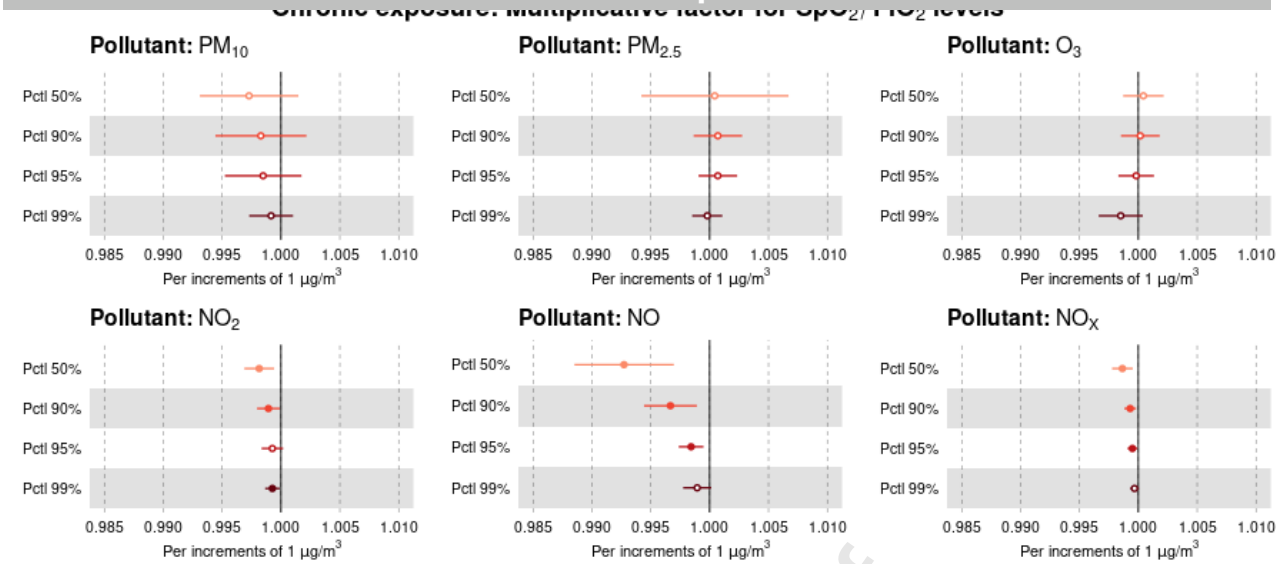


Figure 4 c: Multiplicative factor affecting SpO_2/FiO_2, per 1 µg/m^3 increase in air pollution exposure (i.e., throughout 2019) for each pollutant, by yearly percentiles (50-99%). The diagrams show the mean expected value (central dot) and its 95% confidence interval (CI). The dot is filled when the effect is statistically significant ($p<0.05$).

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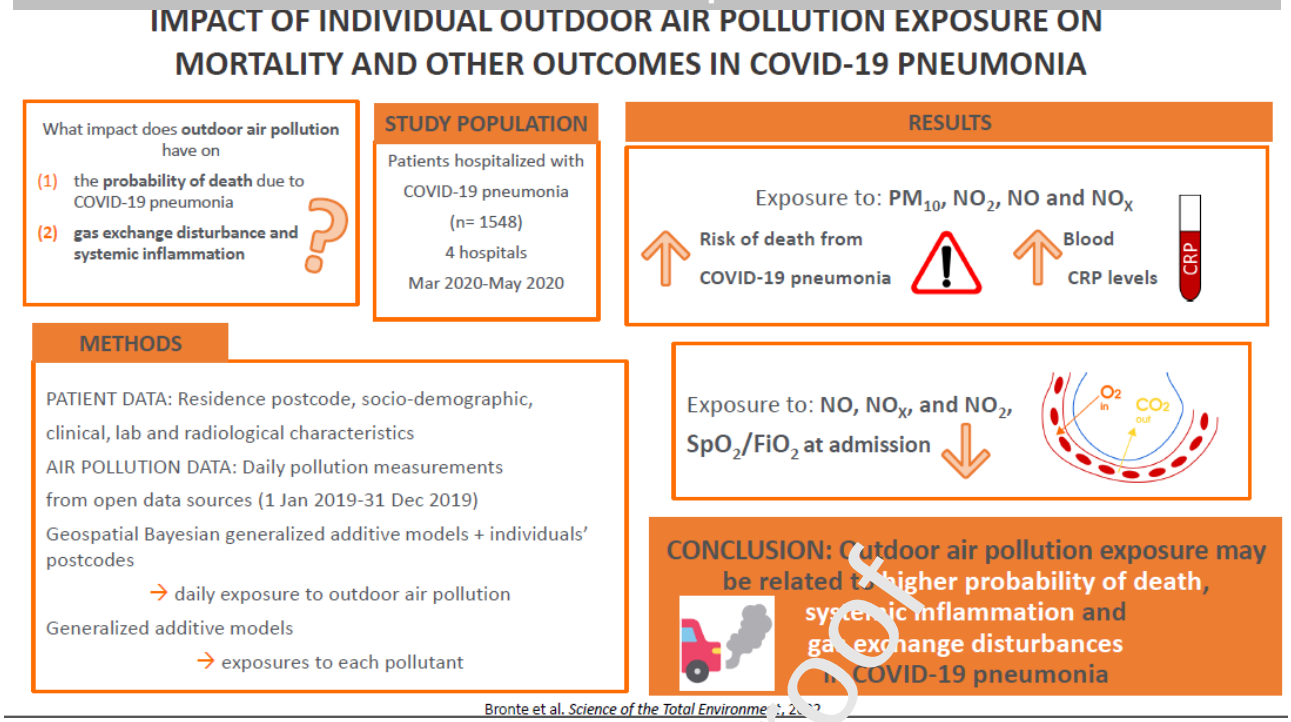
CRediT authorship contribution statement

Olaia Bronte: conceptualization, investigation and resources – clinical data collection, interpretation of data, writing - original draft (lead), review and editing (lead), visualization, supervision. **Fernando García-García:** methodology, software, formal analysis, investigation and resources – air pollution and environmental data, data curation, writing - original draft (methodology), review and editing (supporting). **Dae-Jin Lee:** methodology, software, formal analysis, writing - review and editing (supporting). **Isabel Urrutia:** conceptualization (supporting), investigation and resources – clinical data collection, interpretation of data, writing - original draft, review and editing (supporting). **Ane Uranga:** conceptualization (supporting), investigation and resources – clinical data collection, writing - original draft, review and editing (supporting), interpretation of data. **Monica Nieves:** investigation and resources – air pollution and environmental data collection, data curation, writing - original draft (results), review and editing (supporting). **Joaquin Martínez-Minaya**: methodology, software, formal analysis. **Jose María Quintana:** conceptualization (supporting), methodology, interpretation of data, writing - review and editing (supporting). **Inmaculada Arostegui**: methodology, formal analysis, interpretation of data, writing - review and editing (supporting). **Rafael Zalacaín, Leyre Serrano, Luis Alberto Ruiz-Iturriaga, Rosario Menéndez, Raúl Méndez Antoni Torres, Catia Cilloniz:** investigation and resources – clinical data collection. **Pedro Pablo España**: conceptualization (supporting), investigation and resources – clinical data collection, interpretation of data, writing – original draft, review and editing (supporting), funding acquisition. **All authors** contributed to final approval of the version submitted for publication.

Declaration of interests

☒The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:



Graphical abstract

HIGHLIGHTS:

- In COVID-19 pneumonia patients, the probability of death rises significantly with exposure to PM_{10}, NO_2, NO, NO_X, and CO.
- Systemic inflammatory response increases with exposure to PM_{10}, NO_2, NO and NO_X.
- Gas exchange disturbance is associated with exposure to NO, NO_X, and NO_2.