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

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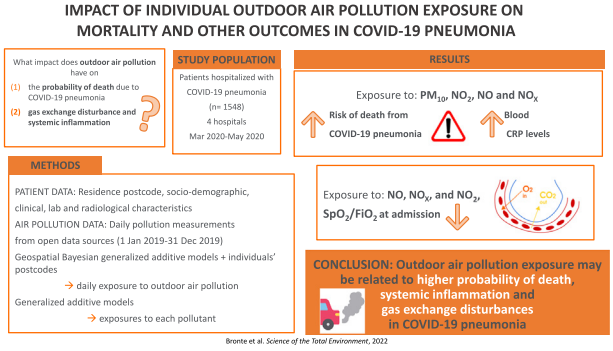
HIGHLIGHTS

- 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.

GRAPHICAL ABSTRACT



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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

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.

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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.

1. 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 374,000 premature deaths attributable to particles with an aerodynamic diameter <2.5 μm ($PM_{2.5}$), 68,000 to nitrogen dioxide (NO_2) and 14,000 to ozone (O_3) in Europe in 2018 (European Environment Agency (EEA), 2019).

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., 2007; 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 and Martelletti, 2020; Dutheil et al., 2020; Zhu et al., 2020; Frontera et al., 2020a, 2020b; Conticini et al., 2020; Wang et al., 2020; Setti et al., 2020; Adhikari and Yin, 2020; Copat et al., 2020; Fattorini and Regoli, 2020; Wu et al., 2020; Zoran et al., 2020; Bourdrel 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 and Regoli, 2020; Ogen, 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., 2020a, 2020b; 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) (Du et al., 2020b). 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 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 (Du et al., 2020; Zhou 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 <60 mmHg (among others), have been postulated as risk factors associated with COVID-19 pneumonia mortality in hospitalised patients (Du et al., 2020b; Ali et al., 2023; Nieto-Codesido et al., 2022; Choi et al., 2022; Muñoz-Rodríguez 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.

2. Material and methods

2.1. 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 (<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 sociodemographic, 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.

2.2. 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 et al., 2020). 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 et al., 2022). Finally, in the Community of Valencia, at this moment, there are 65 operating samplers (Estarlich 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.

2.3. 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, Gaoken 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).

2.4. Outcomes

The main objective of our study was to examine the relationship between exposure to outdoor air pollution and the risk of death in hospitalised 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.

2.5. 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 and Feinn, 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., 2018; Umlauf et al., 2018) [Eqs. (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:

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

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 Eq. (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^{Mort}_{Pollut}) and keeping constant the rest of the variables:

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

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

being β the parameters corresponding to the fixed effects, f univariate smoothing P-splines, g univariate smoothing P-splines estimated by hospital and **1**Female, **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/m^3 increases in exposure (β^{CRP}_{Pollut} and $\beta^{SpO_2/FiO_2}_{Pollut}$) and keeping constant the rest of the variables.

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

where, likewise in Eq. (5), with the same form of effect modelling:

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

and

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

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

2.6. 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.

3. Results

3.1. 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.

3.2. 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 μg/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 Fig. 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). Fig. 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 (Fig. S1, a-l).

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

3.3. 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 % (Fig. 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 (Fig. 4b, and Table S1 in the online supplementary material).

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 [71, 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]	2 [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 χ^2 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 χ^2 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 correlation, respectively. Subsequently, effect sizes were categorized by magnitude into negligible, small, medium, or large as in Cohen (2013). Num. valid: number of valid participating patients. N/A: not applicable. PSI: calculated as Fine et al. (1997).

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 (Fig. 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 ($p \geq 0.05$).

4. Discussion

4.1. 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 μg/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.

4.2. 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

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	32.0	59.8	6.2	20.3	58.1
NO	1.6	4.7	23.6	1.6	4.3	18.3	2.7	9.7	44.5	2.3	5.5	41.7
NO_X	9.8	23.4	65.4	8.8	21.0	52.1	18.6	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.

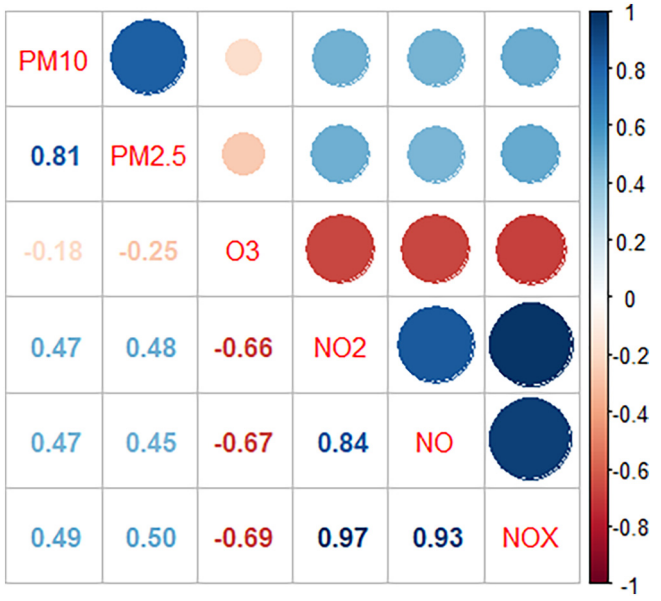


Fig. 1. Spearman's rank correlations between pairs of air pollutants, across geographical locations.
Spearman's rank correlation coefficients close to ±1 indicate strong positive/negative correlations; whereas values close to 0 indicate a lack of correlation.

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 et 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 (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.

4.3. 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. (2022), 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, Tahery 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

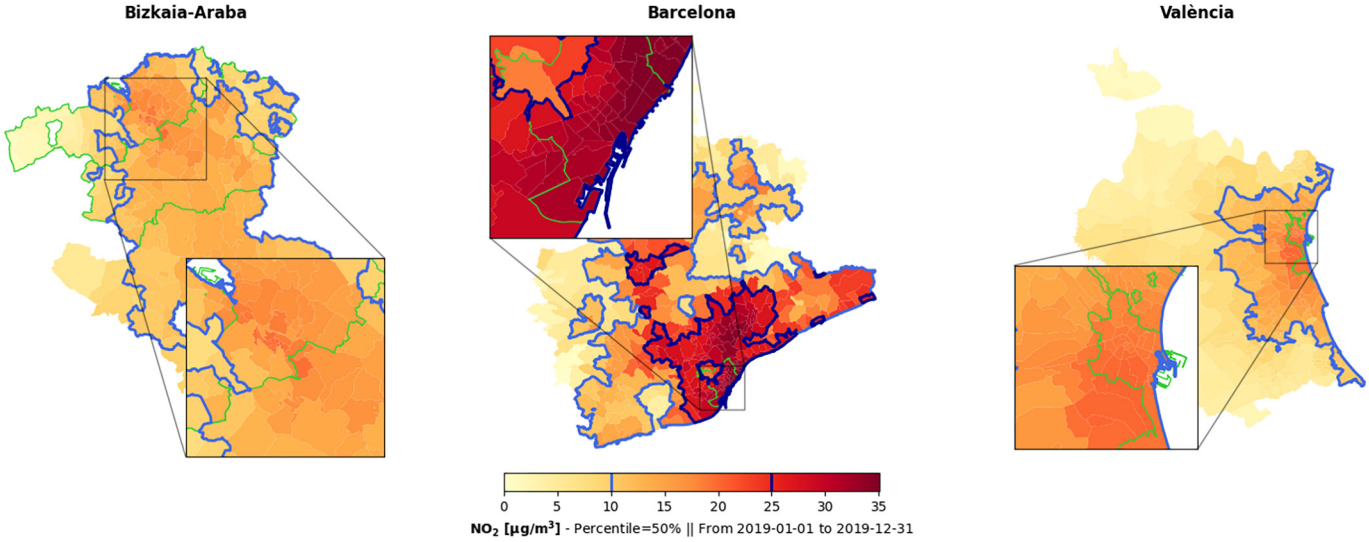
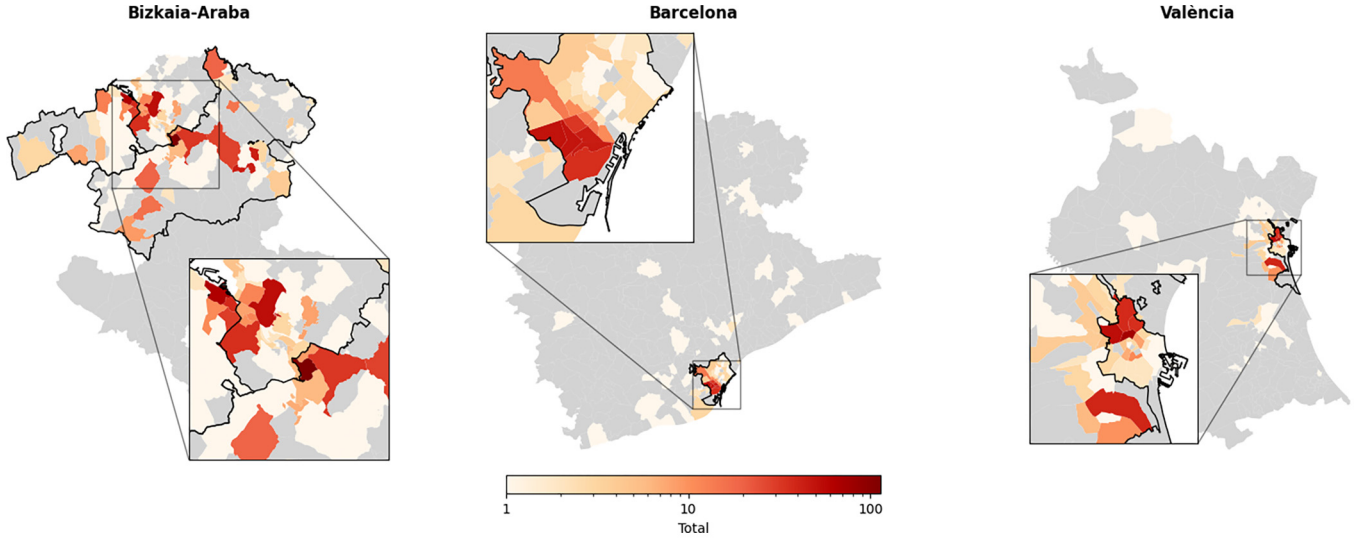
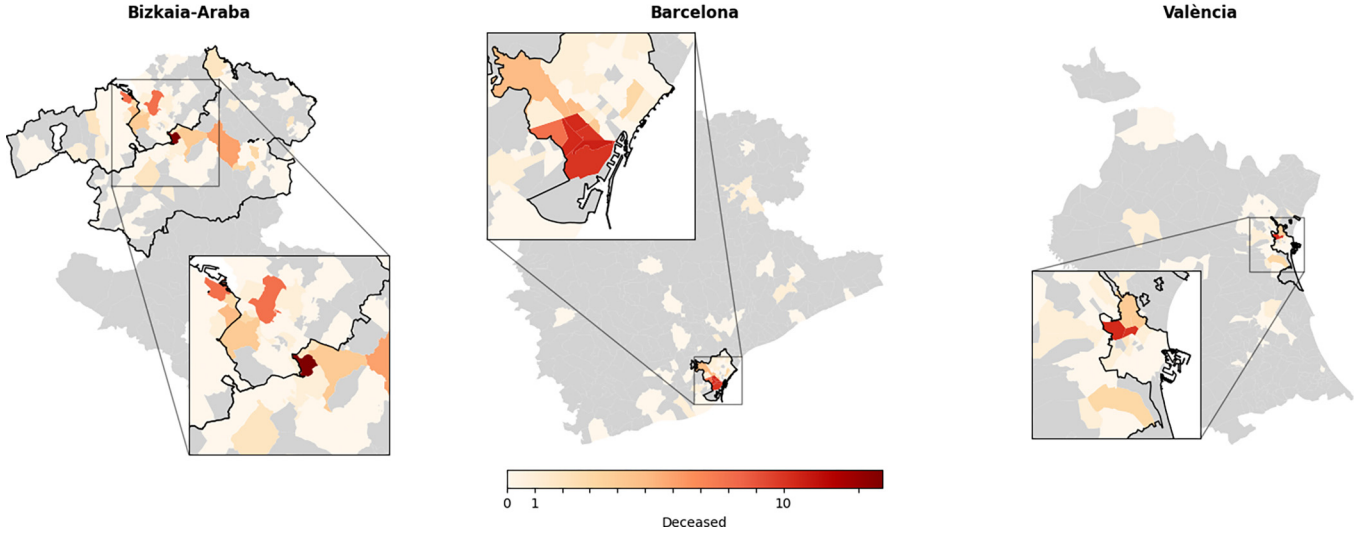


Fig. 2. Geographical distribution of the median daily NO_2 concentration.
Postcodes delimited with light blue lines experienced pollution levels above the annual air quality guideline [AQG] recommended by the World Health Organization (WHO, 2021) [i.e., 10 μg/m^3 for NO_2]; whereas postcodes outlined 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.



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



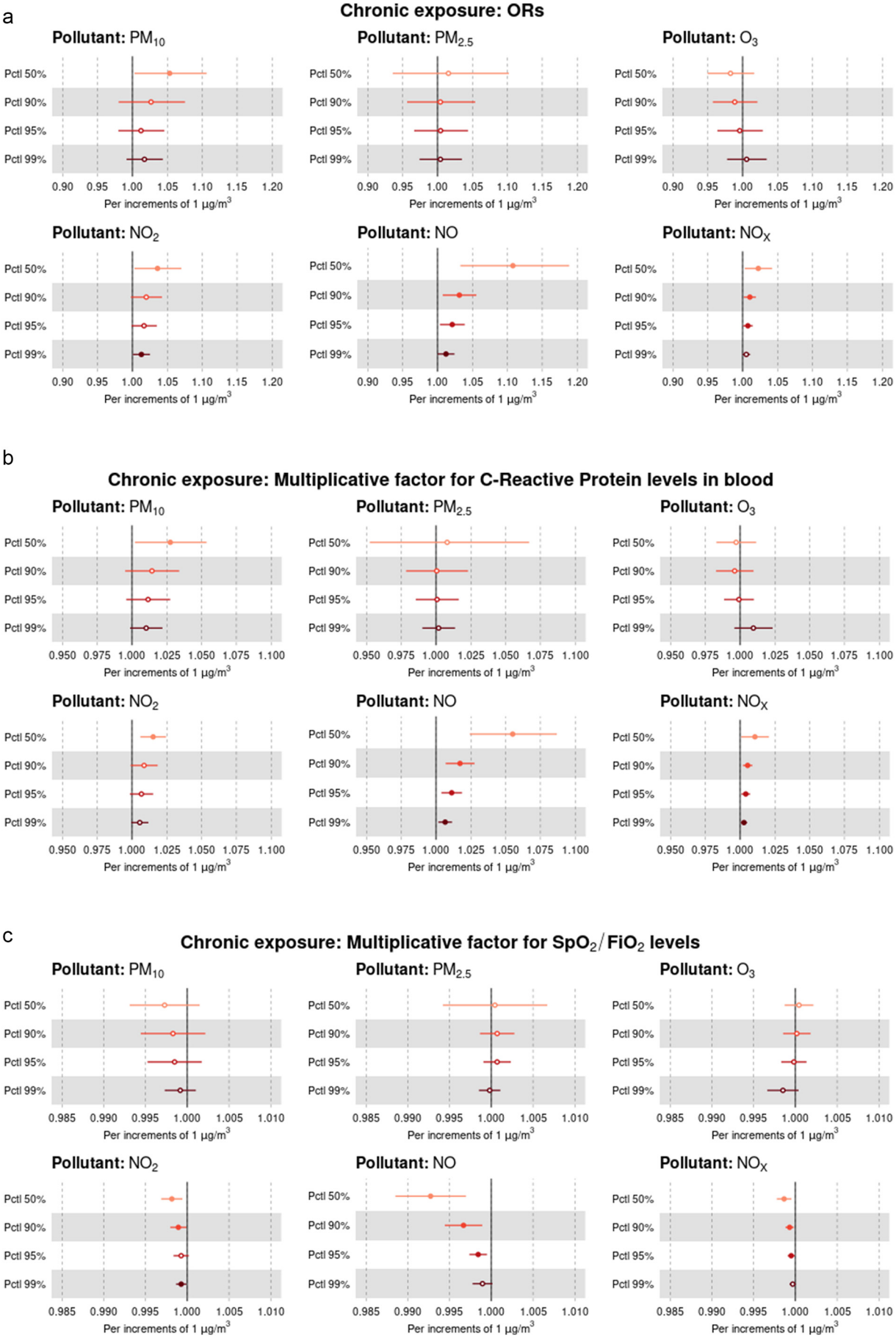
b: Number of deaths among the COVID-19 pneumonia patients enrolled.

Fig. 3. Number of patients in our cohort, by postcode.
a: Number of individuals hospitalised for COVID-19 pneumonia.
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.

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 (Pope et al., 2016). 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., 2022) 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


a
Chronic exposure: ORs
Pollutant: PM10
Pollutant: PM2.5
Pollutant: O3
Pollutant: NO2
Pollutant: NO
Pollutant: NOX
Pctl 50%
Pctl 90%
Pctl 95%
Pctl 99%
0.90 0.95 1.00 1.05 1.10 1.15 1.20
Per increments of 1 µg/m3
b
Chronic exposure: Multiplicative factor for C-Reactive Protein levels in blood
Pollutant: PM10
Pollutant: PM2.5
Pollutant: O3
Pollutant: NO2
Pollutant: NO
Pollutant: NOX
0.950 0.975 1.000 1.025 1.050 1.075 1.100
Per increments of 1 µg/m3
c
Chronic exposure: Multiplicative factor for SpO2/FiO2 levels
Pollutant: PM10
Pollutant: PM2.5
Pollutant: O3
Pollutant: NO2
Pollutant: NO
Pollutant: NOX
0.985 0.990 0.995 1.000 1.005 1.010
Per increments of 1 µg/m3

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.

4.4. 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 et al., 2021; Pegoraro et al., 2021; Bozack et al., 2022; López-Feldman et al., 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 Fig. 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) (Wiemken et al., 2020) and in COVID-19 disease (Gao et al., 2021; Khanijahani et al., 2021; *Agència de Qualitat i Avaluació Sanitàries de Catalunya*, 2020). However, the evidence of the impact of air pollution 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. Moreover, 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.

4.5. 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.

5. 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 analyzed ($PM_{2.5}$, 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}.

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Fig. 4. Forest plot – Effects of increases in air pollution exposure on different clinical outcomes, by pollutant and percentile.
a: Odds ratio for COVID-19 pneumonia mortality (in-hospital or within 30 days after admission), per 1 $\mu g/m^3$ 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 ($p < 0.05$).
b: Multiplicative factor affecting blood CRP levels, per 1 $\mu g/m^3$ 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 is statistically significant ($p < 0.05$).
c: Multiplicative factor affecting SpO_2/FiO_2, per 1 $\mu g/m^3$ 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.

Data availability

The data that has been used is confidential.

Declaration of competing interest

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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2023.164877.

References

Adhikari, A., Yin, J., 2020. Short-term effects of ambient ozone, PM2.5, and meteorological factors on COVID-19 confirmed cases and deaths in Queens, New York. Int. J. Environ. Res. Public Health 17. https://doi.org/10.3390/ijerph17114047.

Alas, H.D., et al., 2021. Pedestrian exposure to black carbon and PM2. 5 emissions in urban hot spots: new findings using mobile measurement techniques and flexible Bayesian regression models. J. Expo. Sci. Environ. Epidemiol. 1–11.

Alberdi, E., et al., 2020. Analysis of the air quality of the Basque autonomous community using spatial interpolation. Sustainability 12 (10), 4164. https://doi.org/10.3390/su12104164.

Ali, A.S., et al., 2023. Cardiovascular complications are the primary drivers of mortality in hospitalized patients with SARS-CoV-2 community-acquired pneumonia. Chest 163 (5), 1051–1060. https://doi.org/10.1016/j.chest.2022.11.013.

Andersen, Z.J., et al., 2021. Air pollution and COVID-19: clearing the air and charting a post-pandemic course: a joint workshop report of ERS, ISEE, HEI and WHO. Eur. Respir. J. 58 (2), 2101063. https://doi.org/10.1183/13993003.01063-2021.

Bolaño-Ortiz, T.R., et al., 2020. Spread of COVID-19, meteorological conditions and air quality in the city of Buenos Aires, Argentina: two facets observed during its pandemic lockdown. Atmosphere 11, 1045. https://doi.org/10.3390/atmos11101045.

Borro, M., et al., 2020. Evidence-based considerations exploring relations between SARS-CoV-2 pandemic and air pollution: involvement of PM2.5-mediated up-regulation of the viral receptor ACE-2. Int. J. Environ. Res. Public Health 17, 5573. https://doi.org/10.3390/ijerph17155573.

Bourdrel, T., et al., 2021. The impact of outdoor air pollution on COVID-19: a review of evidence from in vitro, animal, and human studies. Eur. Respir. Rev. 30, 200242. https://doi.org/10.1183/16000617.0242-2020.

Bowe, et al., 2021. Ambient fine particulate matter air pollution and the risk of hospitalization among COVID-19 positive individuals: Cohort study. Environ. Int. 154, 106564 (Sep).

Boyd, S., Nseir, S., Rodriguez, A., Martin-Loeches, I., 2022. Ventilator-associated pneumonia in critically ill patients with COVID-19 infection: a narrative review. ERJ Open Res. 8 (3), 00046-2022 Published 2022 Jul 25 https://doi.org/10.1183/23120541.00046-2022 Published 2022 Jul 25.

Bozack, A., et al., 2022. Long-term air pollution exposure and COVID-19 mortality: a patient-level analysis from New York City. Am. J. Respir. Crit. Care Med. 205 (6), 651–662. https://doi.org/10.1164/rccm.202104-0845OC.

Bronte-Moreno, O., González-Barcala, F.-J., Muñoz-Gall, X., Pueyo-Bastida, A., Ramos-González, J., Urrutia-Landa, I., 2023. Impact of air pollution on asthma: a scoping review. Open Respir. Arch. 5 (2), 100229 Available from: https://www.sciencedirect.com/science/article/pii/S2659663622000753 Available from:.

Cai, Q., et al., 2007. Influence of meteorological factors and air pollution on the outbreak of SARS. Public Health 121, 258–265. https://doi.org/10.1016/j.puhe.2006.09.023.

Choi, Y.J., et al., 2022. Prognostic factors of 30-day mortality in patients with COVID-19 pneumonia under standard remdesivir and dexamethasone treatment. Medicine (Baltimore) 101 (38), e30474. https://doi.org/10.1097/MD.0000000000030474. PMID: 36197235; PMCID: PMC9508954 (Sep 23).

Cohen, J., 2013. Statistical power analysis for the behavioural sciences. Routledge https://doi.org/10.4324/9780203771587.

Conticini, E., et al., 2020. Can atmospheric pollution be considered a co-factor in extremely high level of SARS-CoV-2 lethality in Northern Italy? Environ. Pollut. https://doi.org/10.1016/j.envpol.2020.114465.

Copat, C., et al., 2020. The role of air pollution (PM and NO2) in COVID-19 spread and lethality: a systematic review. Environ. Res. 191, 110129. https://doi.org/10.1016/j.envres.2020.110129.

Cui, Y., Zhang, Z.F., Froines, J., et al., 2003. Air pollution and case fatality of SARS in the People's Republic of China: an ecologic study. Environ. Health 2, 15. https://doi.org/10.1186/1476-069X-2-15.

Culqui-Lévano, D.R., et al., 2022. Mortality due to COVID-19 in Spain and its association with environmental factors and determinants of health. Environ. Sci. Eur. 34, 39. https://doi.org/10.1186/s12302-022-00617-z.

Desigualtats socioeconòmiques en el nombre de casos i la mortalitat per COVID-19 a Catalunya. Agència de Qualitat i Avaluació Sanitàries de Catalunya, Barcelona.

Di Ciaula, A., et al., 2022. Nitrogen dioxide pollution increases vulnerability to COVID-19 through altered immune function. Environ. Sci. Pollut. Res. 29, 44404–44412. https://doi.org/10.1007/s11356-022-19025-0.

Dick, S., et al., 2014. A systematic review of associations between environmental exposures and development of asthma in children aged up to 9 years. BMJ Open 4. https://doi.org/10.1136/bmjopen-2014-006554.

Du, R.H., et al., 2020. Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: a prospective cohort study [published correction appears in Eur Respir J. 2020a Sep 24;56(3):]. Eur. Respir. J. 55 (5), 2000524 Published 2020 May 7 https://doi.org/10.1183/13993003.00524-2020 Published 2020 May 7.

Du, R.H., et al., 2020b. Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: a prospective cohort study. Eur. Respir. J. 55, 000524. https://doi.org/10.1183/13993003.00524-2020.

Dutheil, F., Baker, J.S., Navel, V., 2020. COVID-19 as a factor influencing air pollution? Environ. Pollut., 263 https://doi.org/10.1016/j.envpol.2020.114466.

Estarlich, M., et al., 2013. The spatial distribution of population exposure to outdoor air pollution in Valencia (Spain) and its association with a privation index. Gac. Sanit. 27 (2), 143–148. https://doi.org/10.1016/j.gaceta.2012.05.010 (PMID: 22784779).

European Environment Agency. Air Quality in Europe, 2019. Report. EEA Report No. 10/2019. Publications Office of the European Union, 2019, Luxembourg.

Fattorini, D., Regoli, F., 2020. Role of the chronic air pollution levels in the Covid-19 outbreak risk in Italy. Environ. Pollut. 264, 114732. https://doi.org/10.1016/j.envpol.2020.114732 (Sept.).

Fine, M.J., et al., 1997. A prediction rule to identify low-risk patients with community-acquired pneumonia. N. Engl. J. Med. 336 (4), 243–250 Available from: https://doi.org/10.1056/NEJM199701233360402 Available from:.

Frontera, A., et al., 2020a. Severe air pollution links to higher mortality in COVID-19 patients: the 'double-hit' hypothesis. J. Inf. Secur. 81, 255–259. https://doi.org/10.1016/j.jinf.2020.05.031.

Frontera, A., et al., 2020b. Severe air pollution links to higher mortality in COVID-19 patients: the 'double-hit' hypothesis. J. Inf. Secur. 81, 255–259. https://doi.org/10.1016/j.jinf.2020.05.031.

Fukuda, K., et al., 2011. Including viral infection data supports an association between particulate pollution and respiratory admissions. Aust. N. Z. J. Publ. Health 35, 163–169. https://doi.org/10.1111/j.1753-6405.2010.00620.x.

Gao, Y.D., Ding, M., Dong, X., Zhang, J.J., Kursat Azkur, A., Azkur, D., Gan, H., Sun, Y.L., Fu, W., Li, W., Liang, H.L., Cao, Y.Y., Yan, Q., Cao, C., Gao, H.Y., Brüggen, M.C., van de Veen, W., Sokolowska, M., Akdis, M., Akdis, C.A., 2021. Risk factors for severe and critically ill COVID-19 patients: a review. Allergy 76 (2), 428–455. https://doi.org/10.1111/all.14657 (Epub 2020 Dec 4. PMID: 33185910, Feb).

Gaoken, T.L., et al., 2020. Socioeconomic position and the incidence, severity, and clinical outcomes of hospitalized patients with community-acquired pneumonia. Public Health Rep. 135 (3), 364–371. https://doi.org/10.1177/0033354920912717 (Epub 2020 Mar 31. PMID: 32228396; PMCID: PMC7238712, May/Jun).

GBD, 2018. Global, regional and national risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990–2017: a systematic analysis for the GBD Study. Lancet Lond. Engl. 2017 (392), 1923–1994. https://doi.org/10.1016/S0140-6736(18)32225-6.

Gouda, M.M., Shaikh, S.B., Bhandary, Y.P., 2018. Inflammatory and fibrinolytic system in acute respiratory distress syndrome. Lung 196 (5), 609–616. https://doi.org/10.1007/s00408-018-0150-6.

Guan, W.J., et al., 2020. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. Eur. Respir. J. 55, 2000547. https://doi.org/10.1183/13993003.00547-2020.

Guarnieri, M., Balmes, J.R., 2014. Outdoor air pollution and asthma. Lancet 383 (9928), 1581–1592. https://doi.org/10.1016/S0140-6736(14)60617-6.

Huang, L., et al., 2016. Acute effects of air pollution on influenza-like illness in China: a population-based study. Chemosphere 147, 180–187. https://doi.org/10.1016/j.chemosphere.2015.12.082.

Huh, K., et al., 2020. Association of meteorological factors and atmospheric particulate matter with the incidence of pneumonia: an ecological study. Clin. Micr. Infect. Off. Publ. Eur. Soc. Clin. Microbiol. Infect. Dis. https://doi.org/10.1016/j.cmi.2020.03.006.

Jaligama, S., et al., 2017. Regulatory T cells and IL10 suppress pulmonary host defense during early-life exposure to radical containing combustion derived ultrafine particulate matter. Respir. Res. 18, 15. https://doi.org/10.1186/s12931-016-0487-4.

Johannson, K.A., et al., 2014. Acute exacerbation of idiopathic pulmonary fibrosis associated with air pollution exposure. Eur. Respir. J. 43 (4), 1124–1131. https://doi.org/10.1183/09031936.00122213.

Khanijahani, A., Iezadi, S., Gholipour, K., Azami-Aghdash, S., Naghibi, D., 2021. A systematic review of racial/ethnic and socioeconomic disparities in COVID-19. Int. J. Equity Health 20 (1), 248. https://doi.org/10.1186/s12939-021-01582-4 (PMID: 34819081; PMCID: PMC8611382. Nov 24).

Liang, D., et al., 2020. Urban air pollution may enhance COVID-19 case-fatality and mortality rates in the United States. Innovation (New York, NY) 1, 100047. https://doi.org/10.1101/2020.05.04.20090746.

López-Feldman, A., Heres, D., Marquez-Padilla, F., 2021. Air pollution exposure and COVID-19: a look at mortality in Mexico City using individual-level data. Sci. Total Environ. 756, 143929. https://doi.org/10.1016/j.scitotenv.2020.143929.

Magazzino, C., et al., 2020. The relationship between air pollution and COVID-19-related deaths: an application to three French cities. Appl. Energy 279, 115835. https://doi.org/10.1016/j.apenergy.2020.115835.

Martelletti, L., Martelletti, P., 2020. Air pollution and the novel Covid-19 disease: a putative disease risk factor. SN Compr. Clin. Med. 2, 383–387. https://doi.org/10.1007/s42399-020-00274-4.

Muñoz-Rodríguez, J.R., et al., 2021. Characteristics and risk factors associated with mortality in a multicenter Spanish cohort of patients with COVID-19 pneumonia. Arch. Bronconeumol. 57, 34–41. https://doi.org/10.1016/j.arbres.2021.02.021.

Nieto-Codesido, I., et al., 2022. Risk factors of mortality in hospitalized patients with COVID-19 applying a machine learning algorithm. Open Respir. Arch. 4, 100162.

Ogen, Y., 2020. Assessing nitrogen dioxide (NO2) levels as a contributing factor to coronavirus (COVID-19) fatality. Sci. Total Environ. 2020 (726), 138605. https://doi.org/10.1016/j.scitotenv.2020.138605.

Pegoraro, V., et al., 2021. An Italian individual-level data study investigating on the association between air pollution exposure and Covid-19 severity in primary-care setting. BMC Public Health 21 (1), 902 Published 2021 May 12 https://doi.org/10.1186/s12889-021-10949-9 Published 2021 May 12.

Perret, J., et al., 2017. The dose-response association between nitrogen dioxide exposure and serum interleukin-6 concentrations. Int. J. Mol. Sci. 18, 1015. https://doi.org/10.3390/ijms18051015.

Pope 3rd, C.A., et al., 2016. Exposure to fine particulate air pollution is associated with endothelial injury and systemic inflammation. Circ. Res. 119 (11), 1204–1214. https://doi.org/10.1161/CIRCRESAHA.116.309279.

Pozzer, A., et al., 2020. Regional and global contributions of air pollution to risk of death from COVID-19. Cardiovasc. Res. 116 (14), 2247–2253. https://doi.org/10.1093/cvr/cvaa288.

Raji, H., et al., 2020. Acute effects air pollution on hospital admissions for asthma, COPD and bronchiectasis in Iran. Int. J. COPD 15, 501. https://doi.org/10.2147/COPD.S231317.

Ranieri, V., et al., 2012. Acute respiratory distress syndrome the Berlin definition. JAM. 307 (23), 2526–2533.

Rodriguez-Rey, D., et al., 2022. To what extent the traffic restriction policies applied in Barcelona city can improve its air quality? Sci. Total Environ. 807 (Pt 2), 150743. https://doi.org/10.1016/j.scitotenv.2021.150743.

Setti, L., et al., 2020. Searching for SARS-COV-2 on particulate matter: a possible early indicator of COVID-19 epidemic recurrence. Int. J. Environ. Res. Public Health, 17 https://doi.org/10.3390/ijerph17092986.

Somayaji, R., et al., 2020. Effects of air pollution and other environmental exposures on estimates of severe influenza illness. Emerg.Infct.Dis. https://doi.org/10.3201/eid2605.190599.

Song, X., et al., 2017. Impact of ambient temperature on morbidity and mortality: an overview of reviews. Sci. Total Environ. 586, 241–254. https://doi.org/10.1016/j.scitotenv.2017.01.212.

Stauffer, R., et al., 2018. Spatio-temporal precipitation climatology over complex terrain using a censored additive regression model. Int. J. Climatol. 37 (7), 3264–3275. https://doi.org/10.1002/joc.4913.

Sullivan, G.M., Feinn, R., 2012. Using effect size-or why the P value is not enough. J. Grad. Med. Educ. 4 (3), 279–282. https://doi.org/10.4300/JGME-D-12-00156.1.

Tahery, N., et al., 2021. C-reactive protein as a possible marker for severity and mortality of COVID-19 infection. Gastroenterol. Hepatol. Bed Bench 14 (Suppl. 1), S118–S122 (PMID: 35154611; PMCID: PMC8817756, Fall).

Tian, F., et al., 2021. Ambient air pollution and low temperature associated with case fatality of COVID-19: a nationwide retrospective cohort study in China. Innovation 2, 100139. https://doi.org/10.1016/j.xinn.2021.100139.

Travaglio, M., et al., 2021. Links between air pollution and COVID-19 in England. Environ. Pollut. 268 (Pt A), 115859. https://doi.org/10.1016/j.envpol.2020.115859.

Umlauf, N., et al., 2018. BAMLSS: Bayesian additive models for location, scale, and shape (and beyond). J. Comput. Graph. Stat. 27 (3), 612–627. https://doi.org/10.1080/10618600.2017.1407325.

Wang, B., et al., 2020. Is there an association between the level of ambient air pollution and COVID-19? Am. J. Physiol.-Lung Cell. Mol. Physiol. 319 (3), L416–L421. https://doi.org/10.1152/ajplung.00244.2020.

Wiemken, T.L., Wright, M.O., Johnston, KJ., 2020. Association of hospital-area deprivation with hospital performance on health care associated infection rates in 2018. Am J Infect Control 48 (12), 1478–1484. https://doi.org/10.1016/j.ajic.2020.05.038 Epub 2020 Jun 5. PMID: 32512080.

Wood, S.N., 2017. Generalized Additive Models: An Introduction With R. 2nd edition. Chapman and Hall/CRC Press (ISBN 9781498728331).

World Health Organization, 2005. Air Quality Guidelines: Global Update. https://www.euro.who.int/_data/assets/pdf_file/0005/78638/E90038.pdf.

World Health Organization, 2018. Burden of Disease From Ambient Air Pollution for 2016. World Health Organization, Geneva. https://cdn.who.int/media/docs/default-source/air-quality-database/aqd-2018/aap_bod_methods_apr2018_final.pdf?sfvrsn=30ac0d62_3.

World Health Organization, 2021. WHO global air quality guidelines: particulate matter (PM2.5 and PM10), ozone, nitrogen dioxide, sulphur dioxide and carbon monoxide. WHO https://apps.who.int/iris/handle/10665/345329.

Wu, X., et al., 2020. Exposure to air pollution and COVID-19 mortality in the United States: a nationwide cross-sectional study. medRxiv https://doi.org/10.1101/2020.04.05.20054502 (preprint).

Yitbarek, G.Y., Walle Ayehu, G., Asnakew, S., et al., 2021. The role of C-reactive protein in predicting the severity of COVID-19 disease: a systematic review. SAGE Open Med., 9 https://doi.org/10.1177/20503121211050755.

Zhou, F., et al., 2020. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 395 (10229), 1054–1062. https://doi.org/10.1016/S0140-6736(20)30566-3 (Epub 2020 Mar 11. Erratum in: Lancet. 2020 Mar 28;395(10229):1038. Erratum in: Lancet. 2020 Mar 28;395 (10229):1038. PMID: 32171076; PMCID: PMC7270627) (Mar 28).

Zhu, Y., et al., 2020. Association between short-term exposure to air pollution and COVID-19 infection: evidence from China. Sci. Total Environ., 727 https://doi.org/10.1016/j.scitotenv.2020.138704.

Zoran, M.A., et al., 2020. Assessing the relationship between ground levels of ozone (O3) and nitrogen dioxide (NO2) with coronavirus (COVID-19) in Milan, Italy. Sci. Total Environ. 740, 140005. https://doi.org/10.1016/j.scitotenv.2020.140005.