

Long-Term Exposure to PM₁₀ Above WHO Guidelines Exacerbates COVID-19 Severity and Mortality

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Abstract

A retrospective observational study with patients suffering COVID-19 was performed to assess the underlying effect of long-term exposure to NO₂ and PM₁₀ on the COVID-19 outcomes. We built multivariate predictive models to assess the relationship between the long-term exposure to NO₂ and PM₁₀ and COVID-19 outcomes. The probability of either death or severe COVID-19 outcome and the percentage of dead or severe patients were predicted, while odds ratios and effects estimates were calculated. Whilst the long-term exposure to NO₂ is a variable with a rather low importance in the prediction of COVID-19 health outcomes, the long-term exposure to PM₁₀ is a more important variable than some stated comorbidities. PM₁₀ showed the highest effects estimates (1.65, 95% CI 1.32-2.06) on COVID-19 severity. For mortality, the highest effect estimates corresponded to age (3.59, 95% CI 2.94-4.40), followed by PM₁₀ (2.37, 95% CI 1.71-3.32). Finally, an increase of 1 µg/m³ in PM₁₀ concentration causes an increase of 3.06% (95% CI 1.11%-4.25%) and 2.68% (95% CI 0.53%-5.58%) of patients suffering COVID-19 as a severe disease and deaths, respectively. These results demonstrate that long-term PM₁₀ burdens above WHO guidelines exacerbate COVID-19 outcomes, while it must be considered for an accurate medical prognosis of COVID-19.

Introduction

COVID-19 is caused by the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2). Age, sex, race, as well as a number of comorbidities, including hypertension, cardiovascular diseases, obesity and diabetes have been reported as determinants to overcome COVID-19 (Ejaz et al., 2020; Grasselli et al., 2020; Richardson et al., 2020). However, these factors have been insufficient to explain the high heterogeneity of the infection course. Other known causes are genetic factors of the host are pointed out as individual risk factors (Hu et al., 2021), while the potential role of environmental stressors is currently being explored (Bashir et al., 2020; Tian et al., 2021).

Exposure to air pollution is associated with an increased oxidative stress, which in turn, is the primary cause for respiratory and cardiovascular morbidity and premature mortality (Khafaie et al., 2016; Yang et al., 2017; World Health Organization, 2020; Hahad et al., 2021). In addition, exposure to air pollutants might lead to more severe and lethal forms of respiratory viruses, including SARS-CoV-2 (Domingo and Rovira 2020; Paital and Kumar Agrawal 2021). This topic is being explored by means of ecological studies focused on the impact of the typical environmental pollutants from urban areas (i.e.: PM₁₀, PM_{2.5}, NO₂, O₃) on the incidence, mortality and/or lethality of COVID-19 (Copat et al., 2020; Frontera et al., 2020; Marquès et al., 2020; Meo et al., 2020; Sciomer et al., 2020; Maleki et al., 2021; Zheng et al., 2021). According to Barnett-Itzhaki and Levi (2021), long-term exposure to air pollutants concentrations exceeding WHO guidelines might exacerbate morbidity and mortality rates from COVID-19.

To date, the severity and mortality of COVID-19 considering the long-term exposure to environmental pollution in addition to the individual clinical variables has not been addressed yet. The present study was aimed at assessing the underlying effect of long-term exposure to NO₂ and PM₁₀ on the severity and mortality of COVID-19. Clinical variables of individuals admitted to various hospitals in Catalonia (Spain) due to COVID-19 infection have been examined together with the clinical histories and the estimated long-term exposure to NO₂ and PM₁₀.

Methods

Study design

A retrospective observational study was conducted with 2112 patients with COVID-19 infection admitted to Catalan hospitals between April and June 2020. Patients aging at least 18 years and staying at the hospital for a minimum of 24 hours were invited to join the cohort (Cohort registration code NCT04407273-STACOV). Hospitals participating in the study were the following: Pius Hospital de Valls, Hospital Verge de la Cinta (Tortosa), Hospital Universitari Sant Joan (Reus), Hospital Universitari de Joan XXIII (Tarragona), Hospital Sant Pau i Santa Tecla (Tarragona), Hospital del Vendrell, Hospital del Mar (Barcelona), Hospital HM Delfos (Barcelona), Hospital Universitari Vall d'Hebron (Barcelona), Hospital Santa Creu Sant Pau (Barcelona), Hospital de Santa Caterina (Girona), Althaia (Manresa), Hospital Comarcal de Blanes, Consorci Sanitari de Terrassa, Hospital Moisès Broggi (Sant Joan Despí) (Figure 1).

Clinical Data

An *ad hoc* database with data on anthropometry, personal medical antecedents and clinical outcomes during the stay in the hospitals was built. All data were anonymized and recorded in accordance with legal provisions of the protection of personal data in Spain and European Union Regulations (EU) 2016/6799 on the physical protection of the treatment of personal data. The study was compliant with the Declaration of Helsinki. The Ethics Committee of the Pere Virgili Health Research Institute approved the study, including the exemption of the requirement for informed consent (Ref. CEIM: 106/2020). More details on confidentiality are already described elsewhere (Masana et al., 2020).

Long-term exposure to environmental pollution

The closest cabin from the Catalan Atmospheric Pollution Monitoring and Forecasting Network was allocated to each hospital participating in the study (Figure 1). The cities of Tarragona and Barcelona count with several atmospheric pollution monitoring cabins as well as several hospitals included in the study. In those cases, we averaged the measurements of all cabins and allocated them to all the hospitals in each city. The only cabin from Terrassa was allocated to the two hospitals from this city. Time series data of hourly average NO₂ and PM₁₀ from the air monitoring cabins were obtained from the open data portal from the Government of Catalonia (Generalitat de Catalunya, 2021). The average long-term exposure to PM₁₀ and NO₂ was estimated by calculating the median concentration with data from January 1, 2014 to March 13, 2020. This selected time-period is linked to data availability, the COVID-19 outbreak, and that exposure of a year or more can be considered as a long-term exposure (Hoek et al., 2013). The WHO air quality guideline values for

PM₁₀ (20 µg/m³ annual mean) and NO₂ (40 µg/m³ annual mean) were considered as thresholds to determine low and high long-term exposures in the multivariate predictive models (World Health Organization, 2020).

Statistical analysis

Continuous variables were tested for normality using the Shapiro–Wilk test. Data are presented as medians and 25th and 75th percentiles for continuous variables with a non-normal distribution or as the means and standard deviations (SDs) for those variables with a normal distribution. Unless indicated otherwise, categorical variables are reported as percentages. Differences between groups were analysed using the non-parametric Mann–Whitney test or the Student’s parametric t test for continuous variables, and the chi-square test or Fisher’s exact test for categorical variables. All continuous variables were standardized and normalized when necessary.

Two sets of multivariate predictive models were carried out in order to assess the relationship between the pollutants and COVID-19 outcome. Firstly, we built two regularized logistic regressions where the probability of either death or severe COVID-19 outcome was predicted as a function of all the clinical variables together with the exposure to high concentrations of pollutants. These show the harmful effect of PM₁₀ but not the importance of this variable *versus* the rest of variables under analysis. Therefore, a series of random forest models with the same setup as the regressions were carried out to assess the relative importance of each variable by determining the out-of-bag accuracy before and after variable permutation.

Secondly, two regularized linear regressions were constructed to predict the percentage of dead or severe patients in each of the hospitals involved in the study. Since our “*n*” was small (16), we maintained only the most relevant clinical variables (age, sex, smoking, cancer and diabetes) and environmental pollutants (PM₁₀).

Finally, we provide odds ratios for the logistic regressions and estimates for the linear regressions, both with 95% confidence intervals and p-values.

All continuous variables were normalized when needed prior to model training. Missing data was imputed by multiple imputation by chained equations with a random forest based method (White et al., 2011).

All statistical analyses were performed using the R software package version 4.0. (R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing. 2020. Vienna, Austria. URL: [https:// www.R-project.org/](https://www.R-project.org/)).

Results

The demography, anthropometry and clinical characteristics of the studied population, together with the long-term exposure to NO₂ and PM₁₀ are summarized in Table 1. Additional clinical details, such as clinical inflammation and respiratory biomarkers, as well as drug therapies, are described elsewhere (Masana et al., 2020). The cohort participants were mainly men (57.1%). The average age of the infected individuals was 66 years old, being slightly older (72 years) those admitted to Hospital del Vendrell and Althaia (Manresa). Most of the individuals hereby assessed underwent mild COVID-19 (67.1%). Specifically, the highest rates of mild COVID-19 corresponded to Hospital Comarcal de Blanes (76.0%) and Hospital Moisès Broggi (81.0%), Pius Hospital de Valls (81.5%) and Hospital del Vendrell (86.6%). In contrast, the highest rates of mortality were found in Hospital de Santa Caterina (20.5%), Hospital Sant Joan de Reus (21.7%) and Althaia (30.2%). In turn, Reus, Girona and Manresa were above the WHO guideline value for PM₁₀ (20 µg/m³), while Valls, El Vendrell, Mataró and Sant Joan Despí were below this reference concentration. In addition, those individuals affected by COVID-19 in Girona and Manresa had a previous high rate of one or more respiratory and cardiovascular diseases, which in turn, might be related to long-term exposure to PM₁₀ (Henderson et al., 2011; Zhu et al., 2021). Finally, up to 31.4% of patients infected with COVID-19 in Terrassa suffered severe COVID-19, or even died. Furthermore, a high rate of individuals showed high blood pressure, stroke and COPD/asthma. The population living in Terrassa had the highest long-term exposure to PM₁₀, while they were the only group exposed to a NO₂ concentration above the reference value (40 µg/m³). Finally, similar rates of mild, severe and death patients were found in Barcelona and Amposta. Surprisingly, Barcelona was above the PM₁₀ WHO threshold and close to the NO₂ guideline level, while Amposta is one of the localities with the lowest concentrations of NO₂ and PM₁₀. Table 2 summarizes the characteristics of the cohort according to the COVID-19 severity (mild, severe and death). The average age of mild, severe and death patients was 64, 62 and 80 years old, respectively. COVID-19 severity increased as the incidence of history and chronic diseases (high blood pressure, coronary heart disease, stroke, COPD/Asthma, as well as chronic liver, kidney and rheumatologic diseases, and cancer) increased. In contrast, the clinical outcomes (Intensive Care Unit hospitalization, fever, cough, dyspnea, bilateral alteration thorax X ray, Acute respiratory distress syndrome, high-flow mechanical ventilation and tracheal intubation) occurred more frequently in those patients suffering severe COVID-19 than in those who died. Finally, the exposure to NO₂ and PM₁₀ did not differ among COVID-19 severity groups. Unfortunately, long-term exposure of each individual depends only on the city of hospitalization, and consequently, only 11 average long-term exposures to NO₂ and PM₁₀ for all the 2112 individuals have been estimated.

Table 1
Demography, anthropometry, clinical characteristics and long-term exposure to NO2 and PM10 of the population included in the study.

	Pius Hospital de Valls	Hospital Verge de la Cinta (Tortosa)	Hospital Universitari Sant Joan (Reus)	Hospital Universitari Joan XXIII Hospital Sant Pau i Santa Tecla (Tarragona)	Hospital del Vendrell	Hospital Santa Creu Sant Pau	Hospital de Santa Caterina (Girona)	Althaia (Manresa)	Hospital Comarcal de Blanes	Consorti Sanitari de Terrassa
N	81	62	143	172	112	572	220	248	100	302
Sex (female)	28 (34.6%)	27 (43.5%)	57 (39.9%)	58 (33.7%)	47 (42.0%)	282 (49.3%)	76 (34.5%)	102 (41.1%)	42 (42.0%)	153 (50.7%)
Age	64.0 [51.0;76.0]	69.0 [57.0;75.8]	64.0 [55.0;77.0]	70.0 [57.0;78.2]	72.0 [56.8;82.0]	65.5 [53.0;79.0]	66.0 [53.0;81.0]	72.0 [61.0;80.0]	62.0 [53.8;74.2]	70.0 [59.0;80.0]
Smoker	4 (14.8%)	2 (3.39%)	6 (4.65%)	7 (4.27%)	7 (7.37%)	32 (5.68%)	16 (7.66%)	12 (4.84%)	6 (6.59%)	8 (2.68%)
Personal history of diseases										
High Blood Pressure	34 (42.0%)	36 (58.1%)	73 (51.0%)	93 (54.1%)	60 (53.6%)	293 (51.4%)	107 (48.6%)	131 (52.8%)	47 (47.5%)	158 (52.3%)
Diabetes	16 (19.8%)	21 (33.9%)	37 (25.9%)	47 (27.3%)	21 (18.8%)	127 (22.2%)	54 (24.5%)	71 (28.6%)	30 (30.0%)	54 (17.9%)
Obesity	9 (45.0%)	23 (42.6%)	16 (26.7%)	47 (28.8%)	16 (22.5%)	179 (32.7%)	59 (28.5%)	40 (16.8%)	30 (41.1%)	80 (30.9%)
Coronary Heart Disease	2 (2.50%)	5 (8.06%)	6 (4.20%)	22 (12.8%)	11 (9.82%)	67 (11.7%)	25 (11.4%)	17 (6.85%)	13 (13.0%)	26 (8.61%)
Stroke	1 (1.23%)	3 (4.84%)	10 (6.99%)	10 (5.81%)	3 (2.68%)	44 (7.69%)	14 (6.36%)	15 (6.05%)	8 (8.00%)	24 (7.95%)
Peripheral Arterial Disease	2 (2.47%)	1 (1.61%)	5 (3.50%)	12 (6.98%)	1 (0.89%)	29 (5.07%)	17 (7.73%)	19 (7.66%)	4 (4.00%)	9 (2.98%)
Heart Failure	0 (0.00%)	2 (3.23%)	8 (5.59%)	16 (9.30%)	10 (8.93%)	50 (8.74%)	36 (16.4%)	21 (8.47%)	9 (9.00%)	27 (8.94%)
COPD/Asthma	8 (9.88%)	6 (9.68%)	13 (9.09%)	28 (16.3%)	25 (22.3%)	102 (17.9%)	50 (22.7%)	42 (16.9%)	17 (17.0%)	61 (20.2%)
Chronic Liver disease	0 (0.00%)	0 (0.00%)	8 (5.59%)	8 (4.65%)	0 (0.00%)	12 (2.10%)	4 (1.82%)	10 (4.03%)	2 (2.00%)	11 (3.64%)
Chronic Kidney disease	5 (6.17%)	2 (3.23%)	14 (9.79%)	12 (6.98%)	14 (12.5%)	57 (9.98%)	26 (11.8%)	40 (16.1%)	9 (9.00%)	32 (10.6%)
Rheumatologic disease	4 (4.94%)	2 (3.23%)	6 (4.20%)	6 (3.51%)	4 (3.57%)	34 (5.95%)	5 (2.27%)	12 (4.84%)	1 (1.00%)	25 (8.28%)
Cancer	11 (13.6%)	5 (8.06%)	16 (11.2%)	28 (16.3%)	17 (15.2%)	48 (8.42%)	27 (12.3%)	41 (16.5%)	7 (7.00%)	37 (12.3%)
Clinical outcomes										
Intensive Care Unit Hospitalization	9 (11.1%)	18 (29.0%)	32 (22.4%)	43 (25.0%)	1 (0.89%)	72 (12.6%)	38 (17.4%)	55 (22.2%)	11 (11.0%)	30 (9.93%)
Fever	77 (95.1%)	55 (88.7%)	126 (88.1%)	147 (85.5%)	91 (82.0%)	446 (78.0%)	190 (86.4%)	207 (84.5%)	87 (87.9%)	251 (83.1%)
Cough	49 (60.5%)	50 (80.6%)	108 (75.5%)	117 (68.0%)	89 (80.2%)	395 (69.2%)	127 (62.9%)	178 (72.7%)	71 (71.0%)	196 (64.9%)
Dyspnea	25 (30.9%)	39 (62.9%)	96 (68.1%)	106 (61.6%)	80 (71.4%)	312 (54.6%)	159 (72.6%)	138 (56.3%)	67 (68.4%)	150 (49.7%)

	Pius Hospital de Valls	Hospital Verge de la Cinta (Tortosa)	Hospital Universitari Sant Joan (Reus)	Hospital Universitari Joan XXIII Hospital Sant Pau i Santa Tecla (Tarragona)	Hospital del Vendrell	Hospital Santa Creu Sant Pau Hospital Universitari Vall d'Hebron Hospital del Mar Hospital HM Delfos (Barcelona)	Hospital de Santa Caterina (Girona)	Althaia (Manresa)	Hospital Comarcal de Blanes	Consorti Sanitari de Terrassa
Bilateral alteration Thorax X ray	58 (71.6%)	52 (83.9%)	105 (73.9%)	138 (80.2%)	81 (72.3%)	362 (63.4%)	162 (73.6%)	215 (87.8%)	77 (77.0%)	224 (74.9%)
Acute Respiratory Distress Syndrome	11 (13.6%)	14 (22.6%)	61 (43.0%)	68 (39.5%)	15 (13.4%)	122 (21.4%)	70 (31.8%)	136 (54.8%)	19 (19.2%)	77 (25.6%)
Respiratory Failure	14 (17.3%)	10 (38.5%)	62 (43.4%)	43 (28.1%)	37 (33.0%)	73 (26.1%)	80 (37.9%)	92 (41.1%)	19 (20.2%)	65 (25.5%)
High-Flow Mechanical Ventilation	2 (2.47%)	4 (6.45%)	12 (8.39%)	47 (27.3%)	1 (0.89%)	68 (11.9%)	62 (28.2%)	70 (28.2%)	29 (29.0%)	58 (19.3%)
Invasive Mechanical Ventilation. Tracheal Intubation	7 (8.64%)	12 (19.4%)	25 (17.5%)	35 (20.3%)	2 (1.79%)	58 (10.1%)	36 (16.4%)	41 (16.5%)	11 (11.0%)	24 (7.97%)
Disseminated Intravascular Coagulation	1 (1.23%)	1 (1.61%)	7 (4.93%)	5 (2.92%)	0 (0.00%)	2 (0.35%)	4 (1.82%)	9 (3.63%)	4 (4.04%)	2 (0.67%)
Acute Renale Failure	15 (18.5%)	11 (17.7%)	29 (20.3%)	33 (19.2%)	30 (26.8%)	65 (11.4%)	36 (16.4%)	68 (27.5%)	11 (11.0%)	41 (13.6%)
Liver alterations	2 (2.47%)	1 (1.61%)	5 (3.52%)	9 (5.23%)	1 (0.89%)	11 (1.92%)	6 (2.73%)	22 (8.91%)	5 (5.00%)	5 (1.67%)
Shock	1 (1.23%)	5 (8.06%)	23 (16.1%)	15 (8.72%)	2 (1.79%)	18 (3.16%)	12 (5.45%)	30 (12.1%)	4 (4.00%)	22 (7.33%)
Severity										
Mild	66 (81.5%)	43 (69.4%)	90 (62.9%)	102 (59.3%)	97 (86.6%)	390 (68.2%)	133 (60.5%)	132 (53.2%)	76 (76.0%)	207 (68.5%)
Severe	8 (9.88%)	12 (19.4%)	22 (15.4%)	39 (22.7%)	9 (8.04%)	94 (16.4%)	42 (19.1%)	41 (16.5%)	19 (19.0%)	40 (13.2%)
Death	7 (8.64%)	7 (11.3%)	31 (21.7%)	31 (18.0%)	6 (5.36%)	88 (15.4%)	45 (20.5%)	75 (30.2%)	5 (5.00%)	55 (18.2%)
Long-term exposure to environmental pollutants	Alcover	Amposta	Reus	Tarragona	Vilafranca del Penedès	Barcelona	Girona	Manresa	Mataró	Terrassa
NO ₂ (µg/m ³)	9.89	14.73	18.72	21.05	16.88	38.25	29.55	30.22	24.36	40.77
PM ₁₀ (µg/m ³)	19.55	19.12	21.98	19.08	19.25	24.18	23.98	23.09	19.29	24.38

Table 2
Demography, anthropometry, clinical characteristics and long-term exposure to environmental pollutants of the population according to COVID-19 severity

	Mild	Severe	Death	p.overall
N	1417	344	351	< 0.001
Age	64.0 [52.0;77.0]	62.0 [53.0;71.0]	80.0 [73.0;87.0]	< 0.001
Sex (female)	646 (45.6%)	117 (34.0%)	143 (40.7%)	< 0.001
Smoker	64 (4.83%)	23 (7.06%)	18 (5.39%)	
Personal history of diseases				
High Blood Pressure	649 (45.9%)	156 (45.5%)	248 (70.7%)	< 0.001
Diabetes	296 (20.9%)	84 (24.4%)	114 (32.5%)	< 0.001
Obesity	320 (26.9%)	108 (36.4%)	90 (29.6%)	0.005
Coronary Heart Disease	120 (8.47%)	29 (8.43%)	47 (13.4%)	0.014
Stroke	78 (5.50%)	18 (5.23%)	36 (10.3%)	0.003
Peripheral Arterial Disease	51 (3.60%)	15 (4.36%)	33 (9.40%)	< 0.001
Heart Failure	98 (6.92%)	14 (4.07%)	67 (19.1%)	< 0.001
COPD/Asthma	212 (15.0%)	59 (17.2%)	90 (25.6%)	< 0.001
Chronic Liver disease	37 (2.61%)	7 (2.03%)	14 (3.99%)	0.250
Chronic Kidney disease	118 (8.33%)	20 (5.81%)	73 (20.8%)	< 0.001
Rheumatologic disease	64 (4.52%)	19 (5.52%)	20 (5.70%)	0.549
Cancer	137 (9.68%)	37 (10.8%)	64 (18.2%)	< 0.001
Clinical outcomes				
Intensive Care Unit Hospitalization	11 (0.78%)	230 (67.1%)	81 (23.1%)	< 0.001
Fever	1152 (81.5%)	313 (91.0%)	296 (84.8%)	< 0.001
Cough	946 (67.3%)	277 (81.2%)	224 (65.5%)	< 0.001
Dyspnea	707 (50.1%)	283 (82.3%)	248 (71.3%)	< 0.001
Bilateral alteration Thorax X ray	949 (67.3%)	317 (92.2%)	295 (84.5%)	< 0.001
Acute Respiratory Distress Syndrome	96 (6.79%)	257 (74.9%)	257 (73.6%)	< 0.001
Respiratory Failure	215 (20.9%)	141 (43.3%)	150 (54.7%)	< 0.001
High-Flow Mechanical Ventilation	26 (1.84%)	224 (65.1%)	120 (34.2%)	< 0.001
Invasive Mechanical Ventilation. Tracheal Intubation	1 (0.07%)	188 (54.7%)	73 (20.8%)	< 0.001
Disseminated Intravascular Coagulation	5 (0.35%)	13 (3.80%)	18 (5.16%)	< 0.001
Acute Renale Failure	119 (8.42%)	78 (22.7%)	144 (41.1%)	< 0.001
Liver alterations	19 (1.35%)	23 (6.69%)	25 (7.14%)	< 0.001
Shock	3 (0.21%)	55 (16.0%)	74 (21.2%)	< 0.001
Long-term exposure to environmental pollutants				
NO ₂ (µg/m ³)	30.2	30.2	30.2	
PM ₁₀ (µg/m ³)	24.0	24.0	24.0	

The multivariate analysis indicates that along with the age, sex and obesity, long-term exposure to NO₂ and PM₁₀ are significant variables for COVID-19 severity (Fig. 2). In turn, the effect estimates for NO₂ and PM₁₀ are 0.75 (95% CI 0.57–0.99) and 1.65 (95% CI 1.32–2.06), respectively. Albeit the significance and the effect estimate of NO₂ is < 1, the random forest model demonstrates that long exposure to NO₂ is a variable with a rather low importance on COVID-19 severity outcomes (Fig. 3). For that reason, it was discarded from the subsequent analysis. On the contrary, long-term exposure to PM₁₀ is within the top 4 important variables determining COVID-19 severity. Regarding mortality, age, sex, cancer and PM₁₀ are significant variables (Fig. 4). COVID-19 infected males are more prone to die than females, while the effect estimates of cancer and PM₁₀ are 1.47 (95% CI 1.03–2.06) and 2.37 (95% CI 1.71–3.32), respectively.

Furthermore, long-term exposure to PM₁₀ is the second most important variable for COVID-19 mortality (Fig. 5). Hence, exceeding the WHO guideline value for PM₁₀ (20 µg/m³) is a risk factor for a fatal health outcome after COVID-19 infection. Based on the regularized linear regressions built for this purpose, an increase of 1 µg/m³ in PM₁₀ concentration causes an increase of 3.06% (95% CI 1.11% – 4.25%) of patients suffering COVID-19 as a severe disease, and in addition, an increase of 2.68% (95% CI 0.53% – 5.58%) of deaths.

Discussion

We investigated the relationship between long-term exposure to the air concentrations of NO₂ and PM₁₀ and COVID-19 severity and mortality by means of a retrospective study. Using multivariate predictive models, this retrospective study provided evidence of a link between long-term exposure to PM₁₀ and the severity and mortality of COVID-19. However, the importance of NO₂ was low.

Almost 70% of the study participants suffered mild COVID-19. However, the highest rates of mild COVID-19 occurred in localities where the average PM₁₀ concentration was below the PM₁₀ WHO guideline value. In contrast, the highest rates of mortality were found in localities above this PM₁₀ reference limit. Hence, geographical differences in COVID-19 severity after infection can be linked to the already demonstrated long-term exposure to PM₁₀ and related harmful effects on health (Renzi et al., 2019; Zhou et al., 2015). In addition to COVID-19 severity outcomes, those cities above the WHO guideline of PM₁₀ presented higher mortality than those below such reference.

The PM₁₀ effects estimates were 1.67 and 2.38 for severity and mortality of COVID-19. An increase of 1 µg/m³ in long-term exposure to PM₁₀ means an increase of 3.06% of patients suffering severe COVID-19, as well as an increase of 2.68% of the number of deaths.

Our random forest model showed the importance of the long-term exposure to PM₁₀ on the COVID-19 severity and mortality prognosis versus other clinical variables clearly stated as comorbidities, such as COPD/asthma, cancer, diabetes and obesity, among others (Cardamone and Donatiello 2020; Kong et al., 2021; McGunaghan et al., 2020; Mohammad et al., 2021; Oh and Song, 2021). Notwithstanding, we also found that age, sex (male) and obesity significantly increased the severity of COVID-19, which is in agreement with other studies (Elezkurtaj et al., 2021). In turn, cancer significantly increased the COVID-19 mortality due to the depressed immune system of cancer patients (Cavalcanti and Soares 2020, Vahabi et al., 2021). Nonetheless, long-term exposure to PM₁₀ showed the highest effect estimates, being the second most important variable determining the severity of COVID-19. Moreover, even though PM₁₀ was in the fourth position of importance in the ranking of mortality, its value was higher than that of severity. Furthermore, the effect estimate was only slightly lower than that of the age, showing the great importance of the long-term exposure to PM₁₀ on COVID-19 fatality.

To the best of our knowledge, this is the first study where the impact of long-term exposure to air pollutants (NO₂ and PM₁₀) on COVID-19 severity and mortality has been assessed by means of a retrospective study counting with clinical variables of 2112 individuals. To date, most of the assessments carried out are epidemiological studies performed with public data on environmental pollutants and COVID-19 morbidity and mortality.

The infection risk is not addressed in the present study. However, PM₁₀ and NO₂ have shown strong correlations with the risk of COVID-19 infection (Wu et al., 2020; Zhang et al., 2021; Hutter et al., 2021). In this sense, PM has been pointed out as a potential carrier of SARS-CoV-2 (Setti et al., 2020), but high concentrations of PM are necessary (Linillos-Padrillo et al., 2021). Lembo et al. (2021) analyzed public available databases from 33 European countries, concluding that high levels of pollution in Europe should be considered as a potential risk for severe COVID-19 and SARS-CoV-2 related deaths. That study found remarkable correlations for PM_{2.5} and nitrogen oxides with the cumulative number of COVID-19 deaths. Although Hutter et al., (2021) also demonstrated a significant association between NO₂ and death from COVID-19, our results are in disagreement with the relevant role of nitrogen oxides. On the other hand, an ecological association of city-level COVID-19 case fatality rate with PM₁₀ and PM_{2.5} exposure was reported by Ran et al., (2020), while Hou et al., (2021) also observed that air pollutants such as PM_{2.5} may assist with the prediction of COVID-19 death. Yao et al., 2020 determined that for every 10 µg/m³ increase in PM_{2.5} and PM₁₀ concentrations, the COVID-19 case fatality rate increased by 0.24% and 0.26%, respectively. This increase in the number of deaths is much lower than that found for PM₁₀ in the present study.

Our study has some limitations. Firstly, we assumed the long-term exposure to NO₂ and PM₁₀ for each individual taking into account the hospital of admission and the closest atmospheric pollution monitoring cabin. Hence, it was considered that each individual was admitted to the corresponding reference hospital. Consequently, the long-term exposure to PM₁₀ was that of the allocated atmospheric pollution monitoring cabin. This assumption is usually valid, but some patients could have been transferred between hospitals according to the severity of the individual and the capacity of the intensive care unit. In addition, we also assumed that participants lived in the locality of the hospital where they were admitted, and therefore, they underwent the allocated long-term exposure. On the other hand, even though our cohort counts with more than 2000 individuals, as the long-term exposure depends only on the location of the hospital, many individuals would be subjected to the same exposure. Thus, it was impossible to estimate the long-term exposure to PM₁₀ according to the severity group. Finally, the air contaminants here assessed were limited to those regularly monitored by the Catalan Atmospheric Pollution Monitoring and Forecasting Network.

In conclusion, the current findings highlight the urgent need to protect the population against long-term exposure to PM₁₀, and all toxic air pollutants in general. Our results demonstrate that the current guideline concentration of PM₁₀ fixed by the WHO in 20 µg/m³, the air quality standard established by the Directive 2008/50/EU in 40 µg/m³, and that of the US-EPA in 50 µg/m³, are not safe. It is well established that the long-term exposure to these PM₁₀ concentrations is likely to enhance the development of cardiovascular and respiratory diseases (Rovira et al., 2020; Polichetti et al., 2009; Beelen et al., 2014; Elbarbary et al., 2021; Bodor et al., 2021; Tahery et al., 2021). In addition, subjects infected with respiratory viruses such as SARS-CoV-2 and exposed to PM₁₀ above the present legal thresholds are more prone to develop a severe COVID-19 - or even to die - after SARS-CoV-2 infection. In the current study, individuals

living in the metropolitan area of Barcelona, as well as in Manresa, Girona and Reus, are at risk of suffering a more lethal form of COVID-19 due to long-term exposure to PM₁₀.

This is a crucial issue of public health, the WHO and worldwide air quality regulators are called to update the guideline values and air quality standards of PM₁₀. Regulations must be revised without delay to protect the health of the population. Therefore, it is necessary to urgently reduce long-term exposure to PM₁₀ in those locations above the reference limits in order to: i) decrease the incidence of cardiovascular and respiratory diseases; ii) reduce the severity and mortality due to respiratory viruses infection, including SARS-CoV-2; iii) reduce the healthcare costs derived from a sick population.

Finally, present findings mark a turning point to start considering the place of residence - and the related exposure to PM₁₀ - for a proper prognosis of respiratory viral infections.

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Author contributions:

M.M.: Contributed to conception and design of the work; analysis of data; wrote the manuscript; approved the final version. E.C.: Contributed to conception and design of the work; performed the statistical analyses; wrote the manuscript; approved the final version. D.I., E.A., J.A.A., C.J., R.M.B, M.Ia.M., S.N., A.P., V.P., R.P.B., R.R.M., M.R., C.S., M.U.P., A.Z., J.P.B.: Contributed to acquisition and interpretation of data; reviewed the manuscript approving the final version. L.M.: Contributed to conception and design of the work; reviewed the manuscript; approved the final version. J.L.D.: Contributed to conception and design of the work; reviewed the manuscript; approved the final version. All authors agreed to be personally accountable for their own contributions and to ensure the accuracy or integrity of any part of the work.

References

1. Barnett-Itzhaki, Z. & Levi, A. Effects of chronic exposure to ambient air pollutants on COVID-19 morbidity and mortality - A lesson from OECD countries. *Environ. Res.* **195**, 110723 (2021).
2. Beelen, R. *et al.* Long-term Exposure to Air Pollution and Cardiovascular Mortality, *Epidemiology* **25**, 368-378 (2014).
3. Cardamone, C. & Donatiello, I. Management of COVID-19 in comorbidities. *Ital. J. Med.* **14**, 223-227 (2020).
4. Copat, C. *et al.* The role of air pollution (PM and NO₂) in COVID-19 spread and lethality: a systematic review. *Environ. Res.* **191**, 110129 (2020).
5. Bashir, M. F. *et al.* Correlation between climate indicators and COVID-19 pandemic in New York, USA. *Sci. Total Environ.* **728**, 138835 (2020).
6. Bodor, K. *et al.* Effects of PM₁₀ and weather on respiratory and cardiovascular diseases in the Ciuc Basin (Romanian Carpathians). *Atmosphere* **12**, 289 (2021).
7. Cavalcanti, I. D. L. & Soares, J. C. S. Impact of COVID19 on cancer patients: A review. *Asia-Pac. J. Clin. Oncol.* **1**, 7 (2020).
8. Domingo, J. L. & Rovira J. Effects of air pollutants on the transmission and severity of respiratory viral infections. *Environ. Res.* **187**, 109650 (2020).
9. Ejaz, H. *et al.* COVID-19 and comorbidities: Deleterious impact on infected patients. *J. Infect. Public Health.* **13**, 1833-1839 (2020).
10. Elbarbary, E. *et al.* Systemic inflammation (C-Reactive Protein) in older Chinese adults is associated with long-term exposure to ambient air pollution. *Int. J. Environ. Res. Public Health* **18**, 3258 (2021).
11. Elezkurtaj, S. *et al.* Causes of death and comorbidities in hospitalized patients with COVID-19. *Sci. Rep.* **11**, 4263 (2021).
12. Frontera, A., Cianfanelli, L., Vlachos, K., Landoni, G. & Cremona, G. SARS-CoV-2 spread in Northern Italy: what about the pollution role?. *J. Infect.* **81**, 255-259 (2020).

13. Generalitat de Catalunya. Departament de Territori i Sostenibilitat. "Dades Meteorològiques de La XEMA." <https://analisi.transparenciacatalunya.cat/Medi-Ambient/Qualitat-de-l-aire-als-punts-de-mesurament-autom-t/taf-thgu> (2021).
14. Grasselli, G. *et al.* Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. *JAMA* **323**, 1574-1581 (2020).
15. Hahad, O., Frenis, K., Kuntic, M., Daiber, A. & Münzel, T. Accelerated Aging and Age-Related Diseases (CVD and Neurological) Due to Air Pollution and Traffic Noise Exposure. *Int. J. Mol. Sci.* **22**, 2419 (2021).
16. Henderson, S.B., Brauer, M., Macnab, Y.C. & Kennedy, S.M. Three measures of forest fire smoke exposure and their associations with respiratory and cardiovascular health outcomes in a population-based cohort. *Environ. Health Perspect.* **119**, 1266-71 (2011).
17. Hoek, G. *et al.* Long-term air pollution exposure and cardio-respiratory mortality: a review. *Environ. Health* **12**, 43 (2013).
18. Hou, C. K. *et al.* 2021. Impact of a long-term air pollution exposure on the case fatality rate of COVID-19 patients-A multicity study. *J. Med. Virol.* **93**, 2938-2946 (2021).
19. Hu, J., Li, C., Wang, S., Li, T. & Zhang H. Genetic variants are identified to increase risk of COVID-19 related mortality from UK Biobank data. *medRxiv* Preprint at <https://doi.org/10.1186/s40246-021-00306-7> (2021)
20. Hutter, H. P. *et al.* Air pollution is associated with COVID-19 incidence and mortality in Vienna, Austria. *Int. J. Environ. Res. Public Health* **17**, 9275 (2020).
21. Khafaie, M., Yajnik, C., Salvi, S. & Ojha, A. Critical review of air pollution health effects with special concern on respiratory health. *J. Air Pollut. Health* **1**, 123-136 (2016).
22. Kong, X. *et al.* Epidemiological and clinical characteristics of cancer patients with COVID-19: A systematic review and meta-analysis of global data. *Cancer Lett.* **508**, 30-46 (2021).
23. Lembo, R., Landoni, G., Cianfanelli, L. & Frontera, A. Air pollutants and SARS-CoV-2 in 33 European countries. *Acta Biomed.* **92**, e2021166 (2021).
24. Linillos-Pradillo, B. *et al.* Determination of SARS-CoV-2 RNA in different particulate matter size fractions of outdoor air samples in Madrid during the lockdown. *Environ. Res.* **195**, 110863 (2021).
25. Maleki, M., Anvari, E., Hopke, P.K., Noorimotlagh, Z. & Mirzaee, S.A. An updated systematic review on the association between atmospheric particulate matter pollution and prevalence of SARS-CoV-2. *Environ. Res.* **195**, 110898 (2021).
26. Marquès, M., Rovira, J., Nadal, M. & Domingo, J. L. Effects of air pollution on the potential transmission and mortality of COVID-19: A preliminary case-study in Tarragona Province (Catalonia, Spain). *Environ. Res.* **192**, 110315 (2020).
27. Masana, L. *et al.* Effect of statin therapy on SARS-CoV-2 infection-related. *Eur. Heart J. Cardiovasc. Pharmacother.* pvaa128; 10.1093/ehjcvp/pvaa128 (2020).
28. McGurnaghan, S. J. *et al.* Risks of and risk factors for COVID-19 disease in people with diabetes: a cohort study of the total population of Scotland. *Lancet Diabetes Endocrinol.* **9**, 82-93 (2021).
29. Meo, S.A., Abukhalaf, A.A., Sami, W & Hoang TD. Effect of environmental pollution PM_{2.5}, carbon monoxide, and ozone on the incidence and mortality due to SARS-CoV-2 infection in London, United Kingdom. *Journal of King Saud University – Science* **33**, 101373 (2020).
30. Mohammad, S. *et al.* Obesity and COVID-19: what makes obese host so vulnerable?. *Immun. Ageing* **18**, 1 (2021).
31. Oh, T. K. & Song, I. A. Impact of coronavirus disease-2019 on chronic respiratory disease in South Korea: an NHIS COVID-19 database cohort study. *BMC Pulm. Med.* **21**, 12 (2021).
32. Paital, B. & Agrawal, P. K. Air pollution by NO₂ and PM_{2.5} explains COVID-19 infection severity by overexpression of angiotensin-converting enzyme 2 in respiratory cells: a review. *Environ. Chem. Lett.* **18**:1-18 (2020).
33. Polichetti, G., Cocco, S., Spinali, A., Trimarco, V. & Nunziata, A. Effects of particulate matter (PM₁₀, PM_{2.5} and PM₁) on the cardiovascular system. *Toxicology* **261**, 1-8 (2009).
34. Ran, J. *et al.* Effects of particulate matter exposure on the transmissibility and case fatality rate of COVID-19: A Nationwide Ecological Study in China. *J. Travel Med.* **27**, taaa133 (2020).
35. Renzi, M. *et al.* Long-term PM₁₀ exposure and cause-specific mortality in the Latium Region (Italy): A difference-in-differences approach. *Environ. Health Perspect.* **127**, 67004 (2019).
36. Richardson, S. *et al.* Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *JAMA* **323**, 2052-2059 (2020).

37. Rovira, J., Domingo, J. L. & Schuhmacher, M. Air quality, health impacts and burden of disease due to air pollution (PM₁₀, PM_{2.5}, NO₂ and O₃): Application of AirQ+ model to the Camp de Tarragona County (Catalonia, Spain). *Sci. Total Environ.* 703, 135538 (2019).
38. Sciomer S *et al.* SARS-CoV-2 spread in Northern Italy: what about the pollution role?. *Environ. Monit. Assess.* **192**, 325 (2020).
39. Setti, L. *et al.* SARS-CoV-2RNA found on particulate matter of Bergamo in Northern Italy: First evidence. *Environ. Res.* **188**, 109754 (2020).
40. Tahery N *et al.* Estimation of PM₁₀ pollutant and its effect on total mortality (TM), hospitalizations due to cardiovascular diseases (HACD), and respiratory disease (HARD) outcome. *Environ. Sci. Pollut. Res.* **28**, 22123-22130 (2021).
41. Tian, T. *et al.* 2021. Risk factors associated with mortality of COVID-19 in 3125 counties of the United States. *Infect Dis Poverty.* **10**, 3 (2021).
42. Vahabi, N., Salehi, M., Duarte, J. D., Mollalo, A. & Michailidis, G. County-level longitudinal clustering of COVID-19 mortality to incidence ratio in the United States. *Sci. Rep.* **11**, 3088 (2021).
43. White, I. R., Royston, P. & Wood, A. M. Multiple imputation using chained equations: Issues and guidance for practice. *Stat Med* **30**, 377-99 (2011).
44. Wu, Y., Zhan, Q. & Zhao Q. Long-term Air Pollution Exposure Impact on COVID-19 Morbidity in China. *Aerosol Air Qual. Res.* **21**, 200143 (2021).
45. World Health Organization. Ambient (outdoor) air pollution. *Fact sheet* available at [https://www.who.int/news-room/fact-sheets/detail/ambient-\(outdoor\)-air-quality-and-health](https://www.who.int/news-room/fact-sheets/detail/ambient-(outdoor)-air-quality-and-health) (2020).
46. Yang, D., Yang, X., Deng, F. & Guo, X. Ambient Air Pollution and Biomarkers of Health Effect. *Adv. Exp. Med. Biol.* **1017**, 59-102 (2017).
47. Yao, Y. *et al.* Association of particulate matter pollution and case fatality rate of COVID-19 in 49 Chinese cities. *Sci. Total Environ.* **741**, 140396 (2020).
48. Zhang, Y. *et al.* Association analysis framework of genetic and exposure risks for COVID-19 in middle-aged and elderly adults. *Mech. Ageing Dev.* **194**, 111433 (2021).
49. Zheng, P. *et al.* Association between coronavirus disease 2019 (COVID-19) and long-term exposure to air pollution: Evidence from the first epidemic wave in China. *Environ. Pollut.* **276**, 116682 (2021).
50. Zhou, M. *et al.* The associations between ambient air pollution and adult respiratory mortality in 32 major Chinese cities, 2006-2010. *Environ. Res.* **137**, 278-286 (2015).
51. Zhu, W. *et al.* Long-term exposure to fine particulate matter relates with incident myocardial infarction (MI) risks and post-MI mortality: A meta-analysis. *Chemosphere* **267**, 128903 (2021).

Figures

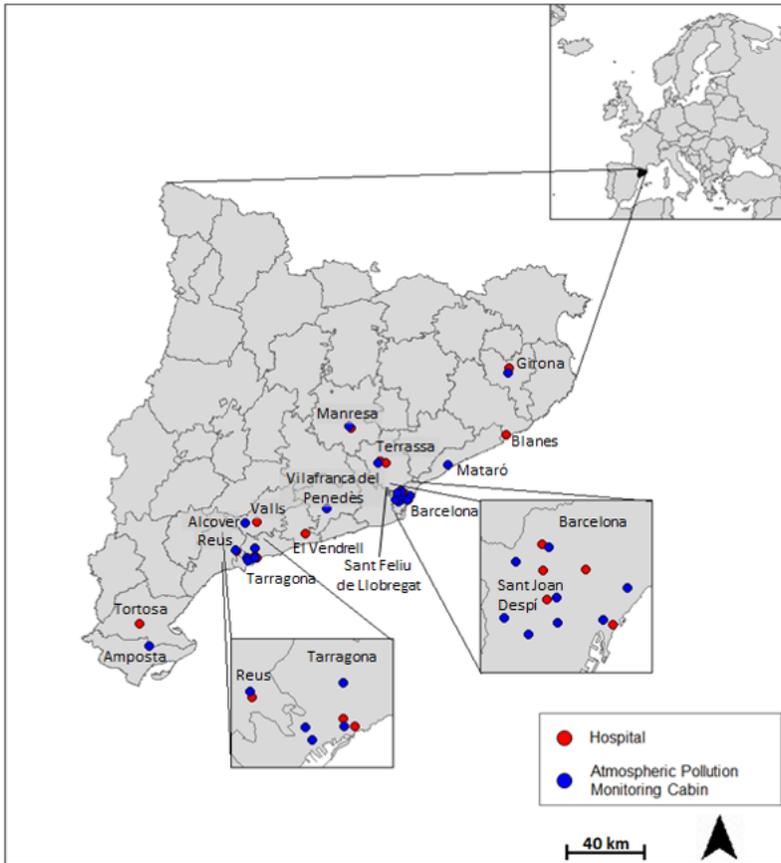


Figure 1
 Location of the hospitals and atmospheric pollution monitoring cabins. Note: The designations employed and the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.

Variable		Odds Ratio	95% CI	p
Age			1.49 (1.32 – 1.68)	<0.001
Smoking			1.41 (0.92 – 2.14)	0.114
Obesity			1.40 (1.13 – 1.73)	0.002
Diabetes			1.14 (0.91 – 1.43)	0.254
Sex	Female		0.64 (0.52 – 0.78)	<0.001
Cancer			1.32 (0.99 – 1.76)	0.055
NO ₂	High		0.75 (0.57 – 0.99)	0.043
PM ₁₀	High		1.65 (1.32 – 2.06)	<0.001
High Blood Pressure			1.02 (0.81 – 1.28)	0.862
Coronary Heart Disease			0.79 (0.57 – 1.10)	0.162
Stroke			0.94 (0.64 – 1.37)	0.757
Peripheral Arterial Disease			1.31 (0.85 – 2.02)	0.213
Heart Failure			1.15 (0.81 – 1.62)	0.434
COPD/Asthma			1.17 (0.92 – 1.50)	0.202
Chronic Liver Disease			0.94 (0.52 – 1.64)	0.822
Chronic Kidney Disease			1.00 (0.72 – 1.38)	0.995
Rheumatologic Disease			1.15 (0.75 – 1.74)	0.528

Figure 2

Estimates for severity of COVID-19

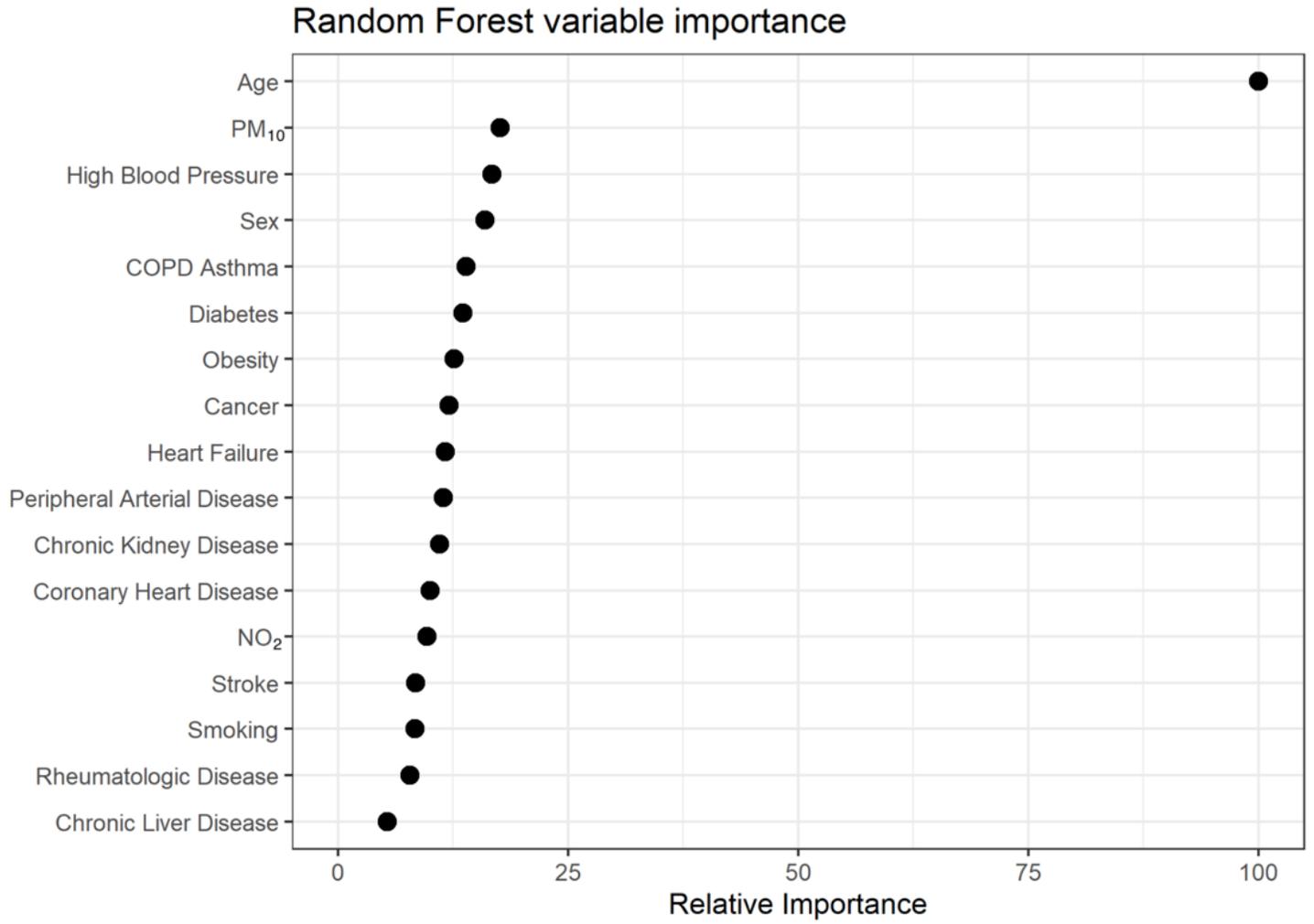


Figure 3

Importance of variables on COVID-19 severity

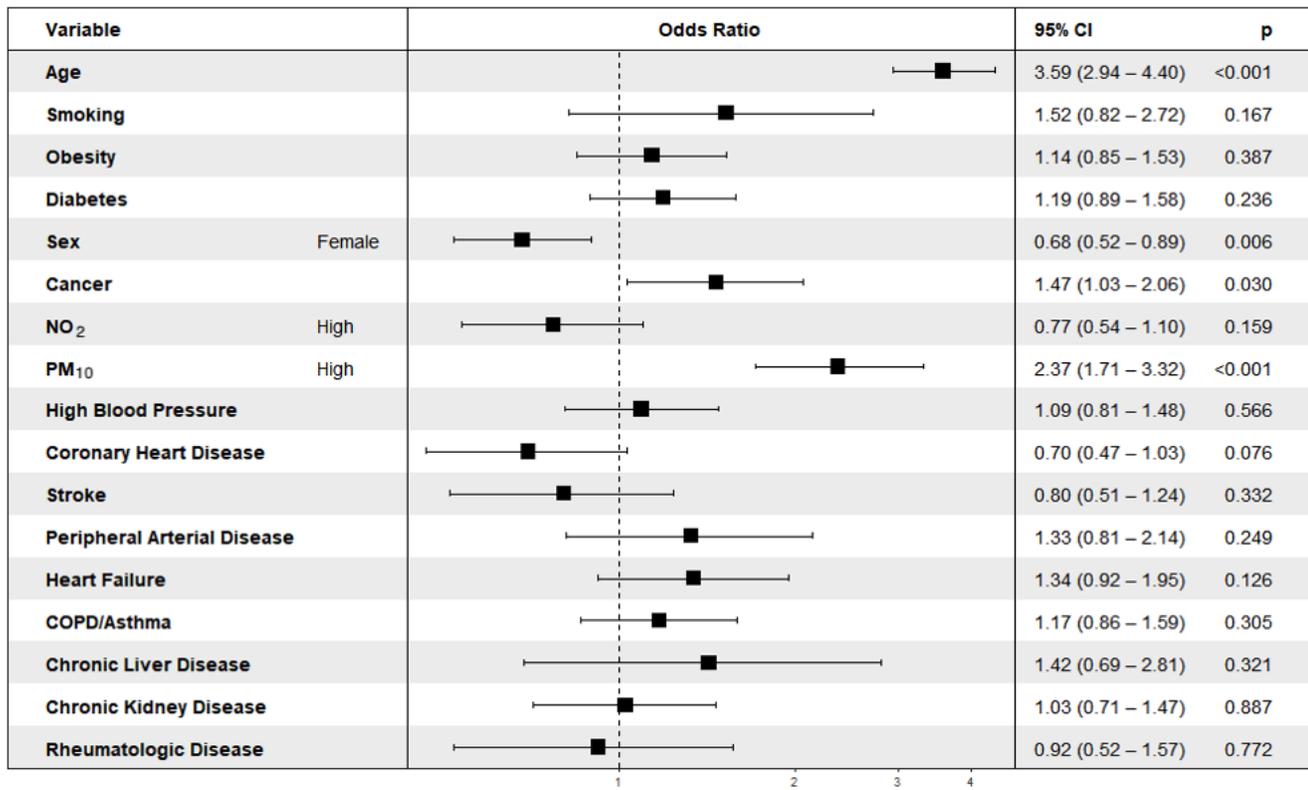


Figure 4

Estimates for mortality of COVID-19

Random Forest variable importance

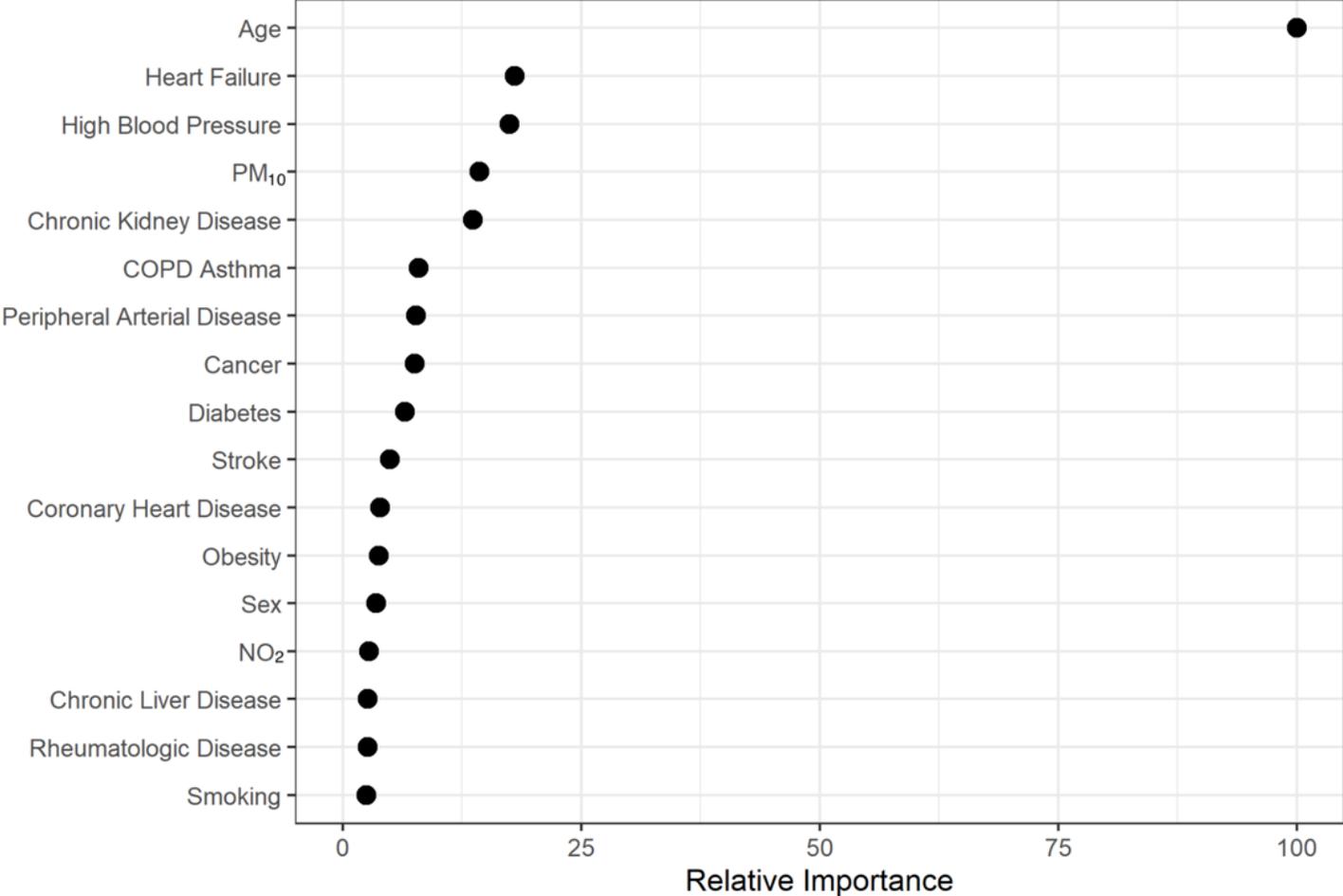


Figure 5
Importance of variables on COVID-19 mortality