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 (Khabaie et al., 2016; Yang et al., 2017; World Health Organization, 2020; Haddad et al., 2021). In addition, exposure to air pollutants might lead to more severe and lethal forms of respiratory viruses, including SARS-CoV-2 (Domínguez-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, PM₂.₅, NO₂, O₃) on the incidence, mortality and/or lethality of COVID-19 (Copat et al., 2020; Frontera et al., 2020; Marquès et al., 2020; Moo et al., 2020; Sciomer et al., 2020; Maleki et al., 2021; Zheng et al., 2021). According to Barnett-Izhaki 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) 2016/679 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
PM$_{10}$ (20 µg/m$^3$ annual mean) and NO$_2$ (40 µg/m$^3$ 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 PM$_{10}$ 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 (PM$_{10}$).

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/).

Results

The demography, anthropometry and clinical characteristics of the studied population, together with the long-term exposure to NO$_2$ and PM$_{10}$ 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 PM$_{10}$ (20 µg/m$^3$), 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 PM$_{10}$ (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 PM$_{10}$, while they were the only group exposed to a NO$_2$ concentration above the reference value (40 µg/m$^3$). Finally, similar rates of mild, severe and death patients were found in Barcelona and Amposta. Surprisingly, Barcelona was above the PM$_{10}$ WHO threshold and close to the NO$_2$ guideline level, while Amposta is one of the localities with the lowest concentrations of NO$_2$ and PM$_{10}$. 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 NO$_2$ and PM$_{10}$ 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 NO$_2$ and PM$_{10}$ 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.

| Demography | Anthropometry | Clinical outcomes |
|-------------|---------------|-------------------|
| N           | Sex (female)  | Age              |
| 81          | 28 (34.6%)    | 64.0 [51.0;76.0] |
| 62          | 27 (43.5%)    | 69.0 [57.0;75.8] |
| 143         | 57 (39.9%)    | 64.0 [55.0;77.0] |
| 172         | 58 (33.7%)    | 70.0 [57.0;78.2] |
| 112         | 47 (42.0%)    | 72.0 [56.8;82.0] |
| 572         | 282 (49.3%)   | 65.5 [53.0;79.0] |
| 220         | 76 (34.5%)    | 66.0 [53.0;81.0] |
| 248         | 102 (41.1%)   | 72.0 [61.0;80.0] |
| 100         | 42 (42.0%)    | 62.0 [53.8;74.2] |
| 302         | 153 (50.7%)   | 70.0 [59.0;80.0] |

| Personal history of diseases | N | Sex (female) | Age | Smoker | Sex (female) | Age | Smoker | Sex (female) | Age |
|------------------------------|---|--------------|-----|--------|--------------|-----|--------|--------------|-----|
| High Blood Pressure          | 34| 34 (42.0%)   | 61 (19.8%) | 64 (45.0%) | 2 (2.47%) | 1 (1.23%) | 0 (0.00%) | 0 (0.00%) |
| Diabetes                     | 16| 16 (19.8%)   | 61 (19.8%) | 64 (45.0%) | 2 (2.47%) | 1 (1.23%) | 0 (0.00%) | 0 (0.00%) |
| Obesity                      | 9 | 9 (45.0%)    | 16 (26.7%) | 22 (12.8%) | 2 (2.50%) | 1 (1.23%) | 0 (0.00%) | 0 (0.00%) |
| Coronary Heart Disease       | 2 | 2 (2.50%)    | 16 (26.7%) | 22 (12.8%) | 1 (1.23%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |
| Stroke                       | 1 | 1 (1.23%)    | 16 (26.7%) | 22 (12.8%) | 1 (1.23%) | 1 (1.23%) | 1 (1.23%) | 1 (1.23%) |
| Peripheral Arterial Disease  | 2 | 2 (2.50%)    | 16 (26.7%) | 22 (12.8%) | 1 (1.23%) | 1 (1.23%) | 1 (1.23%) | 1 (1.23%) |
| Heart Failure                | 0 | 0 (0.00%)    | 16 (9.30%) | 2 (2.32%)  | 1 (1.61%) | 5 (3.50%) | 12 (6.98%) | 1 (0.89%) |
| COPD/Asthma                  | 8 | 8 (9.88%)    | 28 (16.3%) | 28 (16.3%) | 28 (16.3%) | 16 (9.30%) | 10 (8.93%) | 8 (9.59%) |
| Chronic Liver disease        | 0 | 0 (0.00%)    | 8 (4.65%)  | 8 (4.65%)  | 8 (4.65%)  | 12 (2.10%) | 4 (1.82%)  | 4 (1.82%) |
| Chronic Kidney disease       | 5 | 5 (6.17%)    | 28 (16.3%) | 28 (16.3%) | 28 (16.3%) | 16 (9.30%) | 10 (8.93%) | 8 (9.59%) |
| Rheumatologic disease        | 4 | 4 (4.94%)    | 28 (16.3%) | 28 (16.3%) | 28 (16.3%) | 16 (9.30%) | 10 (8.93%) | 8 (9.59%) |
| Cancer                       | 11| 11 (13.6%)   | 28 (16.3%) | 28 (16.3%) | 28 (16.3%) | 16 (9.30%) | 10 (8.93%) | 8 (9.59%) |

| Intensive Care Unit Hospitalization | N | Sex (female) | Age | Smoker | Sex (female) | Age | Smoker | Sex (female) | Age |
|------------------------------------|---|--------------|-----|--------|--------------|-----|--------|--------------|-----|
| Fever                              | 77| 77 (95.1%)   | 126 (88.1%) | 147 (85.5%) | 91 (82.0%) | 446 (78.0%) | 190 (86.4%) | 207 (84.5%) |
| Cough                              | 49| 49 (60.5%)   | 108 (75.5%) | 117 (68.0%) | 89 (80.2%) | 395 (69.2%) | 127 (62.9%) | 178 (72.7%) |
| Dyspnea                            | 25| 25 (30.9%)   | 96 (68.1%)  | 106 (61.6%) | 80 (71.4%) | 312 (54.6%) | 159 (72.6%) | 138 (56.3%) |

Page 4/14
| Hospital | Bilateral alteration Thorax X ray | Acute Respiratory Distress Syndrome | Respiratory Failure | High-Flow Mechanical Ventilation | Invasive Mechanical Ventilation. Tracheal Intubation | Disseminated Intravascular Coagulation | Acute Renale Failure | Liver alterations | Shock | Severity |
|----------|----------------------------------|------------------------------------|-------------------|---------------------------------|-----------------------------------------------|-------------------------------------|-------------------|------------------|-------|---------|
| Pius Hospital de Valls (Tortosa) | 58 (71.6%) | 11 (13.6%) | 14 (17.3%) | 2 (2.47%) | 7 (8.64%) | 1 (1.23%) | 15 (18.5%) | 2 (2.47%) | 1 (1.23%) | Mild |
| Hospital Verge de la Cinta (Reus) | 52 (83.9%) | 14 (22.6%) | 10 (38.5%) | 4 (6.45%) | 12 (19.4%) | 1 (1.61%) | 11 (17.7%) | 1 (1.61%) | 5 (8.06%) | Severe |
| Hospital Universitari Sant Joan XXIII (Tarragona) | 105 (73.9%) | 61 (43.0%) | 62 (43.4%) | 12 (19.4%) | 25 (17.5%) | 7 (4.93%) | 29 (20.3%) | 5 (3.52%) | 23 (16.1%) | Death |
| Hospital Universitari Joan XXIII Sant Pau i Santa Tecla (Tarragona) | 128 (80.2%) | 68 (39.5%) | 43 (28.1%) | 47 (27.3%) | 35 (20.3%) | 5 (2.92%) | 33 (19.2%) | 9 (5.23%) | 15 (8.72%) | Long-term exposure to environmental pollutants |
| Hospital del Vendrell | 81 (72.3%) | 15 (13.4%) | 37 (33.0%) | 1 (0.89%) | 2 (1.79%) | 0 (0.00%) | 30 (26.8%) | 1 (0.89%) | 2 (1.79%) | Alcover |
| Hospital Sant Pau | 362 (63.4%) | 122 (21.4%) | 73 (26.1%) | 68 (11.9%) | 58 (10.1%) | 2 (0.35%) | 65 (11.4%) | 11 (1.92%) | 18 (3.16%) | Amposta |
| Hospital Universitari Vall d’Hebron | 162 (73.6%) | 70 (31.8%) | 80 (37.9%) | 62 (28.2%) | 36 (16.4%) | 4 (1.82%) | 41 (16.5%) | 6 (2.73%) | 12 (5.45%) | Reus |
| Hospital de Santa Caterina | 215 (87.8%) | 136 (54.8%) | 92 (41.1%) | 70 (28.2%) | 41 (16.5%) | 9 (3.63%) | 11 (11.0%) | 22 (8.91%) | 30 (12.1%) | Tarragona |
| Hospital Sant Pau i Santa Tecla (Tarragona) | 77 (77.0%) | 19 (19.2%) | 65 (25.5%) | 29 (29.0%) | 11 (11.0%) | 4 (4.04%) | 58 (19.3%) | 5 (5.00%) | 4 (4.00%) | Barcelona |
| Hospital del Mar | 224 (74.9%) | 77 (25.6%) | 65 (25.5%) | 58 (19.3%) | 24 (7.97%) | 2 (0.67%) | 65 (25.5%) | 65 (19.3%) | 22 (7.33%) | Girona |
| Hospital HM Delfos (Barcelona) | | | | | | | | | | Mataró |
| Hospital Santa Creu Sant Pau | | | | | | | | | | Manresa |
| Hospital Universitari Vall d’Hebron | | | | | | | | | | Mataró |
| Hospital del Vendrell | | | | | | | | | | Terrassa |

**NO\(_2\) (µg/m\(^3\))**
- Alcover: 9.89
- Amposta: 14.73
- Reus: 18.72
- Tarragona: 21.05
- Vilafrana del Penedès: 16.88
- Barcelona: 38.25
- Girona: 29.55
- Manresa: 30.22
- Mataró: 24.36
- Terrassa: 40.77

**PM\(_{10}\) (µg/m\(^3\))**
- Alcover: 19.55
- Amposta: 19.12
- Reus: 21.98
- Tarragona: 19.08
- Vilafrana del Penedès: 19.25
- Barcelona: 24.18
- Girona: 23.98
- Manresa: 23.09
- Mataró: 19.29
- Terrassa: 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 Intravenous 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 |            |            |            |           |
| NO₂ (µg/m³)             | 30.2       | 30.2       | 30.2       |           |
| PM₁₀ (µg/m³)            | 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 PM\textsubscript{10} is the second most important variable for COVID-19 mortality (Fig. 5). Hence, exceeding the WHO guideline value for PM\textsubscript{10} (20 \text{\mu}g/m\textsuperscript{3}) 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 \text{\mu}g/m\textsuperscript{3} in PM\textsubscript{10} 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 NO\textsubscript{2} and PM\textsubscript{10} 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 PM\textsubscript{10} and the severity and mortality of COVID-19. However, the importance of NO\textsubscript{2} 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 PM\textsubscript{10} concentration was below the PM\textsubscript{10} WHO guideline value. In contrast, the highest rates of mortality were found in localities above this PM\textsubscript{10} reference limit. Hence, geographical differences in COVID-19 severity after infection can be linked to the already demonstrated long-term exposure to PM\textsubscript{10} and related harmful effects on health (Renz et al., 2019; Zhou et al., 2015). In addition to COVID-19 severity outcomes, those cities above the WHO guideline of PM\textsubscript{10} presented higher mortality than those below such reference.

The PM\textsubscript{10} effects estimates were 1.67 and 2.38 for severity and mortality of COVID-19. An increase of 1 \text{\mu}g/m\textsuperscript{3} in long-term exposure to PM\textsubscript{10} 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 PM\textsubscript{10} 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; McGunagahan et al., 2020; Mohammad et al., 2021; Oh and Song, 2021). Nonetheless, long-term exposure to PM\textsubscript{10} showed the highest effect estimates, being the second most important variable determining the severity of COVID-19. Moreover, even though PM\textsubscript{10} 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 PM\textsubscript{10} 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 (NO\textsubscript{2} and PM\textsubscript{10}) 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, PM\textsubscript{10} and NO\textsubscript{2} 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\textsubscript{2.5} and nitrogen oxides with the cumulative number of COVID-19 deaths. Although Hutter et al., (2021) also demonstrated a significant association between NO\textsubscript{2} 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 PM\textsubscript{10} and PM\textsubscript{2.5} exposure was reported by Ran et al., (2020), while Hou et al., (2021) also observed that air pollutants such as PM\textsubscript{2.5} may assist with the prediction of COVID-19 death. Yao et al., 2020 determined that for every 10 \text{\mu}g/m\textsuperscript{3} increase in PM\textsubscript{2.5} and PM\textsubscript{10} 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 PM\textsubscript{10} in the present study.

Our study has some limitations. Firstly, we assumed the long-term exposure to NO\textsubscript{2} and PM\textsubscript{10} 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 PM\textsubscript{10} 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 PM\textsubscript{10} 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 PM\textsubscript{10}, and all toxic air pollutants in general. Our results demonstrate that the current guideline concentration of PM\textsubscript{10} fixed by the WHO in 20 \text{\mu}g/m\textsuperscript{3}, the air quality standard established by the Directive 2008/50/EU in 40 \text{\mu}g/m\textsuperscript{3}, and that of the US-EPA in 50 \text{\mu}g/m\textsuperscript{3}, are not safe. It is well established that the long-term exposure to these PM\textsubscript{10} 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 PM\textsubscript{10} 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 PM$_{10}$.

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 PM$_{10}$. Regulations must be revised without delay to protect the health of the population. Therefore, it is necessary to urgently reduce long-term exposure to PM$_{10}$ 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 PM$_{10}$ - for a proper prognosis of respiratory viral infections.

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**Author contributions:**

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\textbf{Figures}
**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

| Variable                  | Odds Ratio | 95% CI     | p    |
|---------------------------|------------|------------|------|
| Age                       | 3.59       | (2.94 - 4.40) | <0.001 |
| Smoking                   | 1.52       | (0.82 - 2.72) | 0.167 |
| Obesity                   | 1.14       | (0.85 - 1.53) | 0.387 |
| Diabetes                  | 1.19       | (0.89 - 1.58) | 0.236 |
| Sex Female                | 0.68       | (0.52 - 0.89) | 0.006 |
| Cancer                    | 1.47       | (1.03 - 2.06) | 0.030 |
| NO₂ High                  | 0.77       | (0.54 - 1.10) | 0.159 |
| PM₁₀ High                 | 2.37       | (1.71 - 3.32) | <0.001 |
| High Blood Pressure       | 1.09       | (0.81 - 1.48) | 0.566 |
| Coronary Heart Disease    | 0.70       | (0.47 - 1.03) | 0.076 |
| Stroke                    | 0.80       | (0.51 - 1.24) | 0.332 |
| Peripheral Arterial Disease | 1.33     | (0.81 - 2.14) | 0.249 |
| Heart Failure             | 1.34       | (0.92 - 1.95) | 0.126 |
| COPD/Asthma               | 1.17       | (0.86 - 1.59) | 0.305 |
| Chronic Liver Disease     | 1.42       | (0.69 - 2.81) | 0.321 |
| Chronic Kidney Disease    | 1.03       | (0.71 - 1.47) | 0.887 |
| Rheumatologic Disease     | 0.92       | (0.52 - 1.57) | 0.772 |
Figure 5

Importance of variables on COVID-19 mortality