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Can atmospheric pollution be considered a co-factor in extremely high level of SARS-CoV-2 lethality in Northern Italy?☆

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ABSTRACT

This paper investigates the correlation between the high level of Severe Acute Respiratory Syndrome CoronaVirus 2 (SARS-CoV-2) lethality and the atmospheric pollution in Northern Italy. Indeed, Lombardy and Emilia Romagna are Italian regions with both the highest level of virus lethality in the world and one of Europe's most polluted area. Based on this correlation, this paper analyzes the possible link between pollution and the development of acute respiratory distress syndrome and eventually death. We provide evidence that people living in an area with high levels of pollutant are more prone to develop chronic respiratory conditions and suitable to any infective agent. Moreover, a prolonged exposure to air pollution leads to a chronic inflammatory stimulus, even in young and healthy subjects. We conclude that the high level of pollution in Northern Italy should be considered an additional co-factor of the high level of lethality recorded in that area.

1. Introduction

Severe Acute Respiratory Syndrome CoronaVirus 2 (SARS-CoV-2) (Lu et al., 2020) is the pathogenic agent of Covid-19, a disease first reported in a small cluster in Wuhan, Hubei Province, China, in December 2019, and subsequently spread all over the world. Due to its high contagiousness and aggressive course, it has been declared by World Health Organization (WHO) a Public Health Emergency of International Concern (A public health emergency, 2019). The course of the disease is often mild, undistinguishable from a common flu, but in a considerable number of cases may require hospitalization, eventually leading to an acute respiratory distress syndrome (ARDS) and death.

Due to the high variability of political and sanitary decisions taken by the different Governments, data about incidence, lethality and mortality are notably different among countries and even among regions of the same country. Starting from the end of February 2020, contagious has rapidly spread in Italy, particularly in the North (Lombardy, Veneto and Emilia-Romagna), apparently sparing central and southern regions. After a delay of a few days, Covid-19 is now widely diffuse in many other European countries, particularly Spain and Germany, nevertheless with evident international dissimilarities which cannot be explained only by different health policies and systems. In particular, since the virus began to spread in Italy, Lombardy and Emilia Romagna recorded a substantial high level of lethality if compared with other countries but also than other Italian regions. Despite the difficulty in assessing the reasons of such differences in the middle of this enormous health emergency, researchers all around the world have linked this unexpected surplus of lethality in North Italy with two main co-factors i) the different way to report the number of deaths and infects among countries; ii) the old age of Italian population. Few or no hypothesis have identified the atmospheric pollution as potential and additional co-factor of lethality. Although a study conducted by Sima (http://www.simaonlus.it/w, 2020) has showed that pollution has played a key role in the propagation of SARS-CoV-2 there is no evidence about if pollution may have had an impact on communities exposed to toxic air in terms of worsening of initial health status in order to be considered an additional co-factor of SARS-CoV-2 lethality.

According to data from Italian Civil Protection on March 21st 2020, lethality in Lombardy and Emilia Romagna was about 12% whereas in the rest of Italy was about 4.5% (Protezione Civile Italian). A team of researchers at the Royal Netherlands Meteorological Institute by using data from the Ozone Monitoring Instrument on NASA's Aura satellite, revealed that Northern Italy is one of

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Europe's most polluted areas in terms of smog and air pollution also due to its climatic and geographic conditions, which cause the stagnation of pollutants (Earth Observatory. A, 1590). The European Environment Agency (EEA) has recently introduced an aggregated index named as Air Quality Index (AQI), index reflecting the potential impact of air quality on health, driven by the pollutants in geographical regions. It is calculated hourly for more than two thousand air quality monitoring stations across Europe, using up-to-date data reported by EEA member countries (European Air Quality Inde). The AQI is based on concentration values for up to five key pollutants, including: PM_{10}, $PM_{2.5}$, O_3, SO_2 and NO_2. According to the AQI the area covering Lombardia and Emilia Romagna results to be the most polluted area in Italy (and one of the most polluted in Europe) (Indice di qualitá dell'ar). Qin et al., 2020

Based on this direct and evident correlation between high level of lethality and atmospheric pollution, the overreaching question addressed from this paper is: are communities living in polluted area such as Lombardy and Emilia Romagna more predisposed to die of Covid-19 due to their health status?

2. Analysis

As previously mentioned, the physio pathological event leading to intensive care unit (ICU) and to death is an ARDS, a dramatic event whose treatment is usually only supportive, requiring mechanical ventilation. Regardless of the etiology (Aisiku et al., 2016), a hyper-activation of immune innate system is thought to have a paramount role in this condition: inflammatory cytokines and chemokines, such as tumor necrosis factor (TNF) α, interleukin (IL) 1β, IL-6, IL-8, IL-17 and IL-18, as well as several growth factors, are overexpressed in ARDS, triggering apoptotic cascade and epithelial-mesenchymal transition (Gouda et al., 2018). Moreover, their high serum and bronchoalveolar lavage level seem related to a poorer prognosis (Butt et al., 2016). These findings, although not validated and not available in the common clinical practice, make them suitable as potential biomarkers and targets for the therapy.

Similar evidences have been reported in patients affected by severe viral pneumoniae such as SARS (Wong et al., 2004) and MERS (Min et al., 2016) and an immune dysregulation is thought to be responsible of a worse outcome in patients affected by Covid-19. Recently published papers have found an imbalance in T cells, as well as high serum levels of IL-6, IL-1 and TNFα (Qin et al., 2020), in the subjects requiring hospitalization and admitted to ICU: this suggests an intriguing role of the most recent immunosuppressive drugs in the treatment of Covid-19 (Stebbing et al., 2020). This being said, we must remind that an overexpression of the above-mentioned cytokines occurs in many other conditions in addition to viral pneumonia and ARDS.

Air pollution represents one of the most well-known causes of prolonged inflammation, eventually leading to an innate immune system hyper-activation. In a small cohort of mice exposed for three months to particulate matter $\leq$2.5 μm in diameter ($PM_{2.5}$), IL-4, TNF-α and transforming growth factor (TGF)-β1 were significantly increased in both serum and lung parenchyma, as well as leucocytes and macrophages (Yang et al., 2019). Obviously, a high systemic inflammation impairs heart function too, as witnessed in another cohort of mice exposed to $PM_{2.5}$ and PM_{10} (Radan et al., 2019). All these findings have been extensively confirmed in humans too: both $PM_{2.5}$ and PM_{10} lead to systemic inflammation with an overexpression of PDGF, VEGF, TNFα, IL-1 and IL-6 even in healthy, non-smoker and young subjects (Pope et al., 2016), directly related to the length of the exposure to the pollutant (Tsai et al., 2019).

Similarly, an exaggerated inflammatory status is found in airways too: an outdated paper (Ishii et al., 2004) found that alveolar macrophages (AM), exposed *in vitro* to PM_{10}, significantly increased the levels of IL-1β, IL-6, IL-8 and TNF-α, thus underlining the prominent role of AM in cleaning particulates and activating immune response. Such evidences are remarked by a more recent paper, which investigated the effects of Milan city (Lombardy, Italy) winter $PM_{2.5}$ and summer PM_{10}: as expected, human bronchial cells evidenced an *in vitro* elevated production of both IL-6 and IL-8 (Longhin et al., 2018). Also, a high correlation between nitrogen dioxide (NO_2) and particulate in inducing IL-6 hyperexpression was found (Perret et al., 2017), being both responsible of an inflammatory status even in a pediatric population (Gruzieva et al., 2017).

Among the other more common pollutants, ozone (O_3) and sulfur dioxide (SO_2) have also a prominent role in inducing systemic and respiratory system inflammation, particularly via IL-8 (Kurai et al., 2018), IL-17 (Che et al., 2016) and TNF-α (Cho et al., 2007), both *in vitro* and *in vivo* (Knorst et al., 1996). All these modifications are well known to contribute to atherogenesis, chronic respiratory diseases and cardiovascular events, the latter strictly correlated with IL-6 serum levels (Aromolaran et al., 2018). Nevertheless, aside of "classical" pollution-related conditions, several recent studies have pointed out a possible correlation between poor air quality and development and worsening of chronic inflammatory disease, such as systemic lupus erythematous (Alves et al., 2018; Gulati and Brunner, 2018) and rheumatoid arthritis (Sigaux et al., 2019).

3. Conclusions

In conclusion, it is well known that pollution impairs the first line of defense of upper airways, namely cilia (Cao et al., 2020), thus a subject living in an area with high levels of pollutant is more prone to develop chronic respiratory conditions and suitable to any infective agent. Moreover, as we previously pointed out, a prolonged exposure to air pollution leads to a chronic inflammatory stimulus, even in young and healthy subjects.

This, in our opinion, may partly explain a higher prevalence and lethality of a novel, very contagious, viral agent such as SARS-CoV-2, among a population living in areas with a higher level of air pollution, particularly if we consider the relatively high average age of this population. Among elderly living in such a region and affected by other comorbidities, the cilia and upper airways defenses could have been weakened both by age and chronic exposure to air pollution, which, in turn, could facilitate virus invasion by allowing virus reaching lower airways. Subsequently, a dysregulated, weak immune system, triggered by chronic air pollution exposure may lead to ARDS and eventually death, particularly in case of severe respiratory and cardiovascular comorbidities. Moreover, since the prolonged exposure to atmospheric pollution could induce persistent modifications of the immune system (Tsai et al., 2019), short-term changes in the air quality may not be sufficient to break this vicious circle. This might be supported by the persistent high fatality rate, despite the dramatical reduction of air pollution levels in Lombardy since the start of the outbreak. Obviously, our considerations must not let us neglect other critical factors responsible for the high contagiousness and fatality of this rapidly spreading disease. Important factors such as the age structure of the affected population, the wide differences among Italian regional health systems, capacity of the intensive care units in the region, and the prevention policies taken by the Government have had a paramount role in the spreading of SARS-CoV-2, presumably more than the air pollution itself. At the same time, our paper evaluated fatality rate only in two Italian regions: given the pandemic dimension of Covid-19, it will be interesting to evaluate if, similarly, a higher lethality will be also recorded in the most

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polluted regions worldwide.

Finally, experimental and epidemiological studies are urgently needed to evaluate the role of the atmospheric pollution in certain populations: the assessment of bronchial and serological levels of inflammatory cytokines represents the cornerstone for a deeper comprehension of the mechanisms leading to a poorer prognosis.

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Declaration of competing interest

We have no conflict of interests for the paper titled: can atmospheric pollution be considered a co-factor in extremely high level of SARS-CoV-2 lethality in Northern Italy?

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