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DOCTORAL THESIS

**IMPACT OF INDIVIDUAL AND ENVIRONMENTAL FACTORS
ON THE DYNAMICS AND EVOLUTION OF COVID-19**

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T i m i s o a r a

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INTRODUCTION

Human respiratory viruses encompass a wide array of viruses that target the cells lining the respiratory tract, provoking a spectrum of respiratory and other symptoms. These viruses primarily spread through respiratory secretions from infected individuals. Clinically, distinguishing between respiratory virus infections can be challenging due to their overlapping symptoms. These viruses belong to diverse virus families, each characterized by distinct viral and genomic structures, affected populations, disease severity, seasonality of circulation, transmissibility, and modes of transmission. Together, respiratory viruses impose a significant global burden, contributing to substantial morbidity, mortality, and economic losses annually, with occasional pandemics, such as the ongoing COVID-19 pandemic, causing unprecedented societal and economic disruptions.

In the absence of effective treatments or vaccines for COVID-19, the control of transmission relies heavily on population-based and individual-based public health measures, collectively referred to as non-pharmaceutical interventions (NPIs). The suitability and efficacy of NPIs for mitigating transmission hinge significantly on the ease of transmission (transmissibility) and the specific modes of transmission associated with a particular virus. NPIs can target some, but not all, potential modes of transmission. Consequently, understanding how to assess transmissibility and the supporting evidence for various modes of transmission is essential in devising effective strategies to control respiratory virus transmission.

Understanding the multifaceted modes of transmission employed by respiratory viruses is crucial for devising comprehensive strategies for transmission control. As these viruses can utilize various routes independently or simultaneously, it is essential to consider all potential modes of transmission when implementing preventive measures. This knowledge not only informs infection control practices in healthcare settings but also aids in the development of effective public health interventions for managing respiratory virus outbreaks.

As we delve into the aims of this PhD study, "Impact of individual and environmental factors on the dynamics and evolution of covid-19," it becomes clear that investigating the intricate relationships between these factors is not only crucial for expanding our knowledge of respiratory virus transmission but also for developing effective strategies to mitigate the spread of respiratory diseases. By gaining deeper insights into these interactions, we can work towards more targeted interventions and public health measures to reduce the burden of respiratory pathology on individuals and communities alike.

AIMS OF THE STUDY

The coronavirus disease (COVID-19) represents a pervasive global pandemic characterized by millions of documented cases and hundreds of thousands of fatalities on a worldwide scale. This ongoing crisis imposes a substantial strain on healthcare infrastructures globally. This study aimed to evaluate impact of individual and environmental factors on the dynamics and evolution of COVID-19.

GENERAL PART

The paper is organized into 99 pages, 217 bibliographic references, and 9 figures. In the general part, which comprises four chapters, the basic theoretical elements are introduced, representing the theoretical support of the special part.

In **Chapter 1, "SARS-CoV-2 Pandemic - A global threat,"** an overview of the COVID-19 pandemic is provided, including information about the pathogen's structure, its epidemiology, data regarding SARS-CoV-2 infection, its dynamic evolution, as well as individual and environmental factors that play an essential role in the transmission of the SARS-CoV-2 virus.

Chapter 2, "Air pollution", describing the composition of the air and the pollutants found in the atmosphere, which are consequently inhaled. Suspended particulate matter, including PM₁₀ (particles with a diameter ranging between 2.5 and 10 $\mu\text{g}/\text{m}^3$) and PM_{2.5} (particles with a diameter less than 2.5 $\mu\text{g}/\text{m}^3$), plays a significant role. Additionally, other types of atmospheric pollutants such as nitrogen oxides, primarily represented by nitrogen dioxide, are discussed. Nitrogen dioxide poses a substantial concern in air quality management, as it exhibits a toxicity level approximately four times higher than nitrogen monoxide. Sulfur dioxide is also addressed, noting that short-term exposure to elevated concentrations can lead to severe respiratory distress, while prolonged exposure increases susceptibility to respiratory tract infections.

Chapter 3, "Ozone (O₃)" is dedicated to the description of ozone, a pungent gas with strong reactivity and oxidizing properties. Ozone plays a dual role in Earth's atmosphere. While it serves as a protective shield against harmful ultraviolet (UV) radiation when present at altitudes ranging from 15 to 40 kilometers above the Earth's surface, ground-level ozone poses a significant environmental pollutant.

Chapter 4: "Preventive strategies and public health policies", is dedicated in exploring the link between socioeconomic gradients and health is reinforced by disparities in both social and health outcomes, particularly impacting those with lower incomes. These

inequalities are evident across multiple facets, such as variations in living standards, job prospects, rates of concurrent health conditions, and economic security. Together, these factors heighten the vulnerability of low-income individuals to the risks associated with COVID-19.

Recognizing and mitigating the factors that contribute to the increased risk among these populations are essential steps in controlling the spread of COVID-19 and improving health outcomes for all societal segments.

SPECIAL PART

STUDY OBJECTIVES

To accomplish the main purpose, the study propose several objectives as follows:

1. To systematically review and analyze the current body of literature to assess the impact of some important environmental factors, such as fine particulate matter, nitrogen dioxide, and ozone, factors who might increase susceptibility to respiratory infections, including COVID-19, thereby worsening disease outcomes. These pollutants are well-established inducers of respiratory tract inflammation and damage, potentially rendering individuals more vulnerable to viral infections. A special focus will be on the short-term ozone exposure to COVID-19 transmission dynamics and disease evolution. Such a comprehensive review is necessary to improve our understanding of COVID-19 in the context of air pollution, with potential implications for public health strategies, policy-making, and preventive measures during current or future pandemics.

The potential influence of environmental factors, particularly air pollutants such as ozone (O₃), on the dynamics and progression of COVID-19 remains a significant concern. This study aimed to systematically review and analyze the current body of literature to assess the impact of short-term ozone exposure on COVID-19 transmission dynamics and disease evolution. A rigorous systematic review was conducted in March 2023, covering studies from January 2020 to January 2023 found in PubMed, Web of Science, and Scopus. We followed the PRISMA guidelines and PROSPERO criteria, focusing exclusively on the effects of short-term ozone exposure on COVID-19. The literature search was restricted to English-language journal articles, with the inclusion and exclusion criteria strictly adhered to. Out of 4674 identified studies, 18 fulfilled the inclusion criteria, conducted across eight countries. The findings showed a varied association between short-term ozone exposure and COVID-19 incidence, severity, and mortality. Some studies reported a higher association between

ozone exposure and incidence in institutional settings (OR: 1.06, 95% CI: 1.00–1.13) compared to the general population (OR: 1.00, 95% CI: 0.98–1.03). The present research identified a positive association between ozone exposure and both total and active COVID-19 cases as well as related deaths (coefficient for cases: 0.214; for recoveries: 0.216; for active cases: 0.467; for deaths: 0.215). Other studies also found positive associations between ozone levels and COVID-19 cases and deaths, while fewer reports identified a negative association between ozone exposure and COVID-19 incidence (coefficient: -0.187) and mortality (coefficient: -0.215). Conversely, some studies found no significant association between ozone exposure and COVID-19, suggesting a complex and potentially region-specific relationship. The relationship between short-term ozone exposure and COVID-19 dynamics is complex and multifaceted, indicating both positive and negative associations. These variations are possibly due to demographic and regional factors.

2. To construct a prediction model for COVID-19 unfavourable outcome, based on patient clinical and paraclinical profiles, that could separate them between high-risk and low-risk groups. In this way we intended to scrutinize easy to obtain available factors, like demographic characteristics of the patient, comorbidities, and blood metrics like white blood count (WBC), absolute neutrophil count (ANC), C-reactive protein (CRP), and utilize them to generate a simple straightforward forecasting model to differentiate whether the disease progression is likely to be favourable or unfavourable. Using this kind of prediction approach empowers resource-constrained hospitals to make timely referrals of their patients to larger, more resource-equipped hospitals.

Purpose: Coronavirus disease is a global pandemic with millions of confirmed cases and hundreds of thousands of deaths worldwide that continues to create a significant burden on the healthcare systems. The aim of this study was to determine the patient clinical and paraclinical profiles that associate with COVID-19 unfavourable outcome and generate a prediction model that could separate between high-risk and low-risk groups.

Patients and Methods: The present study is a multivariate observational retrospective study. A total of 483 patients, residents of the municipality of Timișoara, the biggest city in the Western Region of Romania, were included in the study group that was further divided into 3 sub-groups in accordance with the disease severity form.

Results: Increased age (cOR=1.09, 95% CI: 1.06–1.11, $p<0.001$), cardiovascular diseases (cOR=3.37, 95% CI: 1.96–6.08, $p<0.001$), renal disease (cOR=4.26, 95% CI: 2.13–8.52, $p<0.001$), and neurological disorder (cOR=5.46, 95% CI: 2.71–11.01, $p<0.001$) were all independently significantly correlated with an unfavourable outcome in the study group. The severe form increases the risk of an unfavourable outcome 19.59 times (95% CI: 11.57–

34.10, $p < 0.001$), while older age remains an independent risk factor even when disease severity is included in the statistical model. An unfavourable outcome was positively associated with increased values for the following paraclinical parameters: white blood count (WBC; cOR=1.10, 95% CI: 1.05–1.15, $p < 0.001$), absolute neutrophil count (ANC; cOR=1.15, 95% CI: 1.09–1.21, $p < 0.001$) and C-reactive protein (CRP; cOR=1.007, 95% CI: 1.004–1.009, $p < 0.001$). The best prediction model including age, ANC and CRP achieved a receiver operating characteristic (ROC) curve with the area under the curve (AUC) = 0.845 (95% CI: 0.813–0.877, $p < 0.001$); cut-off value = 0.12; sensitivity = 72.3%; specificity = 83.9%.

Conclusion: This model and risk profiling may contribute to a more precise allocation of limited healthcare resources in a clinical setup and can guide the development of strategies for disease management.

3. A comparison of the COVID-19 morbidity among hospital staff and that in general population, with an exhaustive analysis of the factors predicting non-vaccination and reinfection. The healthcare workers are the main actor in fighting the COVID-19 pandemic and their maintaining their health and professional capacity is a very important element. The COVID-19 pandemic has severely impacted healthcare workers, a professional category at risk of infection in both hospital and community settings. The present study followed the analysis of COVID-19 infection cases in medical staff members of the administrative-territorial units of Western Romania, highlighting certain predictor factors for non-vaccination and reinfection, respectively.

Purpose: The COVID-19 pandemic has severely impacted healthcare workers, a professional category at risk of infection in both hospital and community settings. The aim of the study was to compare morbidity among hospital staff and that in general population, as well as the factors predicting non-vaccination and reinfection.

Patients and Methods: The present study is a retrospective, cross-sectional study. It was conducted by including all the confirmed COVID-19 infection cases in medical staff members during the period 01.01.2021–31.03.2022 that were reported to the Public Health Authority of Timis County, Timisoara, Western Romania.

Results: Direct, strong, statistically significant correlations were found between the incidence of COVID-19 recorded in all categories of medical personnel and the community pandemic trend, with maximum values for auxiliary and medium medical staff ($\rho = 0.852/0.821$, $p < 0.001$). The high socio-economic level, as well as the advanced medical education level, were predictor factors for antiSARS-COV-2 vaccination among the personnel. The non-vaccinated status as well as incomplete vaccination or even the 2-dose

vaccination represented independent risk factors for reinfection in 2022. Conversely, receiving a higher number of vaccine doses emerged as the primary protective factor. Notably, reduced adherence to the administration of the following doses was observed particularly among medium and auxiliary staff, leading to additional risks of infection with the Omicron variant.

Conclusion: Despite over 70% vaccination coverage among all studied medical personnel categories, there was low adherence to repeat doses of vaccination, particularly among medium and auxiliary staff. The study highlighted a distinct necessity for enhanced training on preventive behaviours and targeted prevention/control strategies for all professional groups interacting with patients, including caretakers, ambulance workers, receptionists, physiotherapists, and psychologists.

FINAL CONCLUSIONS AND ORIGINAL CONTRIBUTIONS

- The urgent, uncertain, and perilous situation of the COVID-19 pandemic makes any research related to the etiology and dynamics of SARS-CoV-2 viral infection a significant contribution, both in managing the current pandemic and, especially, in the prevention and management of future pandemics. In this context, investigating the impact of the increasingly widespread and aggressive pollution in the environment is a key element in the transmission process of the viral agent and particularly in the response to it.
- The selection of pollutants such as particulate matter, carbon monoxide, nitrogen dioxide, ammonia, and sulfur dioxide was not arbitrary, given their widespread distribution and their interaction with ozone (a highly reactive form of oxygen), resulting in pollutants with enhanced aggressive potential.
- Although our study had global coverage of information, the lack of standardization regarding the assessment standards of environmental impact did not allow for firm and unified conclusions. However, it has imperatively highlighted the need for international legislative instruments and standardized procedural guidelines for the uniform evaluation of the impact of pollutants from the environment on human health, especially concerning pollution involved in the transmission of viral factors.
- For the first time in Romania, a clinical predictive model based on identifying the clinical and paraclinical characteristics of patients associated with unfavorable outcomes of COVID-19 and developing a predictive model capable of distinguishing between high-risk and low-risk groups has been developed and constructed.

- This predictive model was selected as the optimal version out of three developed variants, each utilizing clinical and paraclinical parameters easily obtained through a set of basic biological investigations. The common idea behind the development of these predictive models was their utility, ease of use, and minimal requirement of data used as determining parameters. The model was designed for any type of healthcare facility, with the necessary data for its development being basic and the usual biological parameters easily obtainable in any healthcare setting.
- The performance of the predictive model is exceptional, with the most effective prediction model incorporating age, ANC and CRP the model's sensitivity was 72.3%, and the specificity was 83.9%.
- This is the first study in Romania to evaluate the impact of the COVID-19 pandemic on healthcare workers in connection with their professional activities and extraprofessional community interactions.
- It was found that the etiology of infection is predominantly linked to professional activity, which carries a significantly higher risk factor compared to contact with the local community. However, this risk factor has been largely mitigated by a higher vaccination rate. Among healthcare workers, the level of training and responsibility has proven to be essential in the acceptance and adherence to antiviral preventive measures.
- Future research should focus on differentiating the effects of short-term versus long-term exposure to ozone. Additionally, it is imperative to explore the biological mechanisms through which ozone may influence COVID-19, as this knowledge is crucial for developing targeted public health interventions.
- Future research should refine this predictive model and validate its effectiveness in diverse populations and healthcare settings.