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The effects of lymphocytopenia over the next three to eight months in patients who experience COVID-19 persistent symptoms

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Abstract. Severe Acute Respiratory Syndrome Coronavirus 2 is a new coronavirus that causes the illness COVID-19. Researchers have established via relevant data that multi-organ destruction, cytokine storm, and lymphocytopenia induced by SARS-CoV-2 are the primary causes of severe illness and patient mortality in COVID-19 patients. And now, as we pass into a new phase, regulatory changes in many nations will cause there to be a shift in the focus of additional research input from the clinical period to the numerous challenges encountered by patients following recovery. We must cope with the growing number of COVID-19 patients who, even after the infection has healed, continue to face functional impairment in their day-to-day life as well as a wide range of long-term symptoms. Their sickness may seriously affect their capacity to carry out the activities of daily living, which will have a detrimental influence on their quality of lives. In addition, lymphopenia has been found to be equally present in these patients recovering from COVID-19 who have undergone the effects of Long-Covid. This study aims to evaluate if the existence of lymphopenia in COVID-19-recovering patients impacts the durability of COVID-19 symptoms by examining individuals with lymphopenia and post-COVID-19 conditions. The purpose of the study is to assess if individuals with lymphocytopenia are more likely than those without lymphocytopenia to be exposed to long-COVID symptoms after eight months.

Keywords: COVID-19 pandemic, post COVID-19 condition, long-covid, lymphocytopenia, SARS-CoV-2.

1. Introduction

In December 2019, local health facilities in Wuhan, Hubei Province, China, reported clusters of patients with pneumonia of unknown etiology [1]. On January 11, 2020, WHO isolated a novel coronavirus from the respiratory tract of local patients with atypical severe viral pneumonia as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [2]. And the SARS-CoV-2 outbreak was declared a public health emergency of international concern on January 28. In a relatively short period of time, the healthcare system and society were severely challenged by this emerging virus. The Chinese government responded to the outbreak promptly and introduced relevant policies to prevent it. However, the virus spread rapidly to different parts of the world and was declared a pandemic by the World Health

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Organization (WHO) on March 11, 2020 [3]. The COVID-19 pandemic has had a highly devastating impact on the health and economy of most parts of human civilization.

Without a doubt, the pandemic brought on by the COVID-19 virus and the accompanying public health initiatives have thrown off the normal cadence of people's lives all around the world. In addition, there are still a considerable number of new cases and hospitalizations in certain regions of the world, despite the fact that the epidemic has been going on for more than two years [4]. At first, researchers focused their attention on the short-term adverse effects that COVID-19 was known to cause. On the other hand, it is becoming more and more obvious that some individuals may continue to have a range of chronic symptoms even after the acute stage of COVID-19 sickness has passed. This is something that is becoming more apparent [5]. Shortness of breath, trouble focusing, cognitive impairment, post-labor fatigue, anxiety, and depression are some of the most prevalent symptoms [6]. Patients who have COVID-19 have a greater chance of having a disorder known as long COVID, which is defined by symptoms that linger for an extended period of time. Patients who have COVID-19 also have an increased risk of developing a condition known as long COVID [7]. Patients who have recovered from an acute COVID-19 infection have described being left with a lingering set of symptoms that have a major and detrimental impact on their day-to-day life after the illness has cleared up. In addition, while an increasing number of people achieve a full recovery from COVID-19, there is rising evidence of symptoms that continue even after recovery [6, 7, 8]. In addition to this, it was shown that these people displayed characteristics consistent with lymphocytopenia [9].

Since the current COVID-19 pandemic, the public debate on COVID-19 has focused on illnesses that can be life-threatening or lethal, as well as the more clinical symptoms [2, 10]. It has been determined that the syndrome coronavirus 2 is the cause of the sickness. The signs and symptoms of this condition include fatigue, a dry cough, fever, and dyspnea [11]. Despite the fact that eighty percent of people with COVID-19 make a full recovery without requiring hospitalization. Up to 5–10% of patients may develop a major illness condition that might be potentially life-threatening, and 5% of patients may become critically ill and require immediate medical attention. Five percent of the population is in a serious condition and requires extensive medical attention [11, 12]. Several investigations have found that the SARS-CoV-2 virus generates lymphocytopenia by inducing systemic inflammation and direct neutralization. Studies have also found that there are connections between the severity of the disease and the presence of lymphocytopenia [2, 5, 13]. The researchers used relevant data to prove that the main causes of death in patients with severe COVID-19 were SARS-CoV-2-mediated multiorgan damage, cytokine storm, and lymphopenia. Patients with severe COVID-19 are also at higher risk of developing lymphocytopenia [2]. Additionally, in situations that were not severe, 80.4% of patients exhibited hematological abnormalities, the majority of which consisted of lymphocytopenia [13]. The patient's immune effector cells may develop dysfunction as a result of the condition [4]. Thus, the circumstances of chronic lymphocytopenia can be used to detect potentially very unwell COVID-19 patients. There is limited follow-up evidence on the effects of lymphocytopenia and COVID-19, despite the fact that researchers in a variety of nations have extensively researched the clinical aspects that characterize COVID-19 at the outset today [14].

The study is expected to verify whether recovering from COVID-19 infection in lymphocytopenia patients leads to the persistence of COVID-19 symptoms. However, given the lack of knowledge and data on lymphopenia and post-COVID studies, the purpose of this study is to determine whether lymphopenia, which can occur in individuals recovering from COVID-19, effects on the symptoms that remain after recovery. Consequently, this study aimed to answer the question of whether lymphocytopenia affects the persistence of long-term COVID symptoms in patients who recover from COVID-19 over the next three to eight months.

Based on the findings of this study, researchers in the future will be able to explore this issue in more depth and develop treatments that better safeguard patients' health.

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2. Critical appraisal of past research and the gaps

Previous researches have shown that the SARS-CoV-2 virus causes lymphocytopenia in humans by causing a generalized inflammation across the body and by directly neutralizing the virus in the spleen and lymph nodes. In addition, there is a correlation between the severity of COVID-19 illness and a considerable drop in lymphocytes [1, 5, 15]. Monitoring hematologic alterations in COVID-19 patients enables excellent risk classification and the prediction of individuals who will require more care. Monitoring also enables the identification of patients who will require additional care [13, 16]. An admission lymphocytopenia was shown to be related with a poorer outcome in patients who were diagnosed with COVID-19, according to a comprehensive review and meta-analysis [16]. A greater than threefold increase in the risk of severe and deadly COVID-19 is shown in patients who have lymphocytopenia. It is possible that direct cytopathic effects and increased apoptosis as a result of a disrupted cytokine milieu are both involved in the pathophysiology of lymphocytopenia in COVID-19 patients [16, 17].

A retrospective study found that lymphocytopenia was associated with illness severity, that it was a good predictor of COVID-19 severity and recovery [18], and that it could aid in the early identification of critically ill patients and predict COVID-19 clinical progression. This retrospective study sheds some light on several important relationships, including the possibility that the use of corticosteroids by patients while they are hospitalized may have an effect on lymphocyte counts. This eliminates one of the most significant factors that could have contributed to the confusion. On the other hand, the study that was just discussed does have some drawbacks, such as the fact that it is the first study of its kind and that it only had 115 patients, which is a rather low number of participants. Additionally, certain laboratory tests and patient treatment records were missing, including the fact that the majority of patients were not screened for different types of lymphocytes. As a consequence of this, the trial was unable to determine which subpopulation was responsible for the severe lymphocytopenia seen by COVID-19 individuals. In addition, the study did not provide any information on the particular mechanism responsible for lymphocytopenia in individuals with COVID-19.

Early discussions on COVID-19 focused on severe or deadly illnesses, and researchers from a variety of countries conducted extensive studies on the clinical, laboratory, and imaging aspects of COVID-19 [14]. This also encompasses the connection between COVID-19 and lymphocytopenia [9]. However, the majority of research done on lymphopenia has been on determining how severe the condition is and making predictions about how COVID-19 would manifest in clinical settings [19]. It is difficult to find any follow-up evidence about the connection between lymphocytopenia and extended COVID. In addition, a growing number of COVID-19 patients are currently acquiring a variety of long-term symptoms following the beginning of COVID-19, so patients may endure functional impairment in their daily lives with these symptoms. Due to their illness, they are unable to conduct routine tasks, which would have a significant impact on their day-to-day existence.

3. Methods

3.1. Methodology design

This study will employ a prospective cohort study as its experimental design, which will more accurately indicate the temporal relationship between exposure and outcome. Additionally, it will help studies assess the possible impact of atypical or rare events.

Due to the fact that the experiment necessitates a sizable data sample in order to investigate the conclusion of our study more thoroughly, the sample produced by a single hospital may not match all of our criteria, hence this prospective cohort research will be done across an area that may contain numerous hospitals, community clinics, and medical institutions. The study sample will consist of between 1,000 and 2,000 individuals. Patients with COVID-19 infection verified by polymerase chain reaction (PCR) during a certain time period should comprise the research sample. The target population will be contacted by phone and email to enquire about their interest in participating in the study. Patients who require ongoing hospitalization at the time of consultation, patients with preexisting mental and

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associated illnesses that prohibit participation, and patients who do not reply to phone calls or emails following hospital discharge will be excluded from the research. Participants who assent will sign an electronic permission form and complete an online baseline questionnaire and health self-assessment form. The study intends to separate patients into three groups based on whether or not they had lymphopenia at the time of COVID-19, as well as the degree of their lymphopenia: no lymphopenia, mild lymphopenia, and moderate or higher lymphopenia. The participants will thereafter be interviewed by telephone between 12 weeks and 8 months after being discharged from the hospital by trained physicians. At the conclusion of the eight-month trial, participants will get a final online follow-up questionnaire to compare with their self-assessed health condition eight months prior. In addition, the study will employ logistic regression models to investigate the factors of associated with lymphocytopenia symptom persistence and failure to recover to baseline health.

3.2. Data collection and study procedures:

During 12 weeks and eight months following discharge, interviewers will contact participants via telephone to collect unresolved symptoms and the duration of unresolved symptoms. The outcome will be the self-reported health state at the last follow-up visit compared to 8 months prior, with patients presenting with lymphocytopenia and COVID-19 as the exposure. Patients with lymphopenia will have their data extracted from their electronic medical records. In contrast, other data will be collected via an online questionnaire.

Patient information will be gathered using a structured interview to guarantee that data are collected and standardized during follow-up. Means and medians for continuous variables will represent demographics, clinical features, and symptoms at follow-up. Possible information bias and inconsistency between interviewers must be avoided and assured by teaching interviewers about fundamental interviewing procedures, how to prevent rejection, and how to respond to the patient's inquiries. Those training should be implemented to prevent the aforementioned issues. Before each follow-up appointment, the questionnaire's content should be reviewed to ensure clarity and consistency.

The study will initially conduct a descriptive analysis of the collected data using univariate logistic regression. Exposure groups were compared using summary statistics or distributions of demographic factors, baseline symptoms, and self-assessed health compared to COVID-19 patients who were healed and discharged from the hospital eight months earlier. Additionally, age, gender, income level, and demographic characteristics with significantly different distributions from the exposure group may serve as confounding variables in this study. We'll utilize these to build adjusted logistic regression models. The final multivariate logistic regression model will incorporate age, gender, chronic illness history, income level, self-reported health state, and test-to-follow-up interval. In addition, the outcome variable will be dichotomized to indicate whether patients were exposed to extended COVID eight months previously or not.

4. Research expected results obtained

The study may be susceptible to information bias, as the researcher is already aware of the exposed participants and may assess the exposed more frequently than the non-exposed during the follow-up period in order to collect accurate data, which may cause undue stress to the exposed participants and even lead to behavioral changes or false information reporting [20]. To prevent observer bias, we should follow the same methodology for both groups, including utilizing the same questionnaires and maintaining the same number and duration of follow-up visits. Therefore, the most effective method for avoiding this prejudice is to blind the observers.

To eliminate any information bias and observer bias in this investigation. Via a hybrid strategy, all data will be collected by the skilled third-party personnel. Before and after observation, data will be gathered at two distinct times: before observation implementation (baseline) and within 72 hours of the conclusion of the 8-month study. Participants are divided into exposed and unexposed groups based on the number of lymphocytes extracted from their electronic medical records prior to the trial. And extra data, including physical symptoms and ratings collected via an online baseline questionnaire and a health

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self-assessment form with categorical factors. Owing to the extended length (8 months) of the prospective cohort research, "lost to follow-up" or "missing data" may occur, and missing values will be reported as "missing." In addition, age, gender, income level, and demographic characteristics with distributions considerably different from the exposed group may be confounding factors in this study. All collected data will be analyzed using Stata 17.0. For categorical variables, proportions and 95% CIs are computed. For continuous data, we determine the median and interquartile range (IQR). In addition, sensitivity analyses are conducted without counting missing data and using parametric and bootstrap approaches to estimate effect sizes and confidence intervals with a confidence level of 95%. We will conduct a descriptive analysis of the collected data using the univariate logistic regression technique, which will be used to develop logistic regression models that account for confounding factors. Age, gender, chronic illness history, income level, self-reported health state, and test-to-follow-up interval will be included in the final multivariate logistic regression model. Also, the outcome variable will be dichotomized to indicate whether the patient was exposed to the long-COVID symptom relative to 8 months ago.

5. Conclusion

On the basis of this study, we expect to be able to make some kind of determination as to whether or not the recovery of COVID-19 individuals who were diagnosed with lymphocytosis will have some kind of influence on the quality of life they experience later in life. We will compare the prognosis status of COVID-19 patients with lymphocytopenia in patients who have been released from the hospital with the prognostic status of COVID-19 patients who have lymphocytopenia. If the findings of the further study necessitate measures to assist patients to recover more quickly, then we will utilize this study as a foundation for additional research and investigate more comprehensive interventions to treat patients more aggressively.

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