Monitoring of patients with concomitant diseases post coronavirus infection

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ARTICLE INFO	ABSTRACT
	This survey study presents data on the prevalence of, and the risk factors associated with post-COVID-19 complications for surviving patients with concomitant diseases during and after months of infection by coronavirus. A prospective, questionnaire-based study was conducted from May 2021 to June 2022. Patients who recovered from COVID-19 in 62 countries completed the online survey or did so during visits to hospitals and health centers. Individuals who recovered from COVID-19 were asked about their symptoms, adverse effects and adverse drug reactions. They were also asked if their concomitant diseases (diabetes, cardiovascular illness, asthma and GIT diseases) were affected after infection and if they had an uncontrolled treatment regimen. The severity of COVID was studied and the correlation coefficient to uncontrolled concomitant diseases was analyzed. Overall, 844 patients (44% female, 56% male) were assessed, and the highest percentage were suffering from long-term cough, dyspnea, constipation and uncontrolled concomitant diseases. A high significantly positive correlation between the severity of COVID infection and uncontrolled concomitant diseases was recorded. Many patients with mild to severe disease presentation reported persistent symptoms months later. Long-term complications to the lungs, heart, vascular system, kidneys, as well as metabolic disruption appear as uncontrolled treatment regimens for surviving COVID-19 patients.

INTRODUCTION

Post-acute COVID symptoms vary widely. Mild COVID may be associated with long-term symptoms, mostly cough, fever and fatigue – all of which may relapse and remit [1]. Other symptoms include shortness of breath, chest pain, headaches, neurocognitive difficulties, muscle pain and weakness, gastrointestinal upset, rashes, metabolic disruption (such as poor control of diabetes), thromboembolic conditions, depression and other mental health conditions [2].

Coronaviruses belong to a group of enveloped, single-stranded, positive-sense RNA viruses [3,4] that can spread so widely and rapidly that the World Health Organization (WHO), in the case of COVID, declared a global pandemic called 'coronavirus disease-2019' [5].

SARS CoV 2 manipulates the host's receptor ACE-2 and serine protease TMPRSS2 to activate viral S protein and enter into the host cell [6-8]. SARS CoV 2 infection, with a heavy viral load in the body, damages the human lungs through cytokine storming because of the overreaction of the body's immune system [9].

Among the risk factors that can increase the likelihood of becoming ill from SARS-CoV2 are diabetes, high blood pressure and other respiratory conditions. These conditions can also cause complications and increase the risk of death [10-13]. Indeed, Guo and colleagues reported that, statistically, in general, patients with comorbidities had an enhanced susceptibility to COVID-infection [11]. The development of multiorgan failure in COVID-19 is believed to be caused by damage to the endothelium, which could be caused through either immune cell activity or direct virus infection [14].

After acute respiratory failure following COVID-19, persistent symptoms such as shortness of breath, fatigue and fibrotic changes are common. These are multifactorial. Some of the abnormalities that can be found in lung function are low diffusion capacity and restrictive patterns. These are usually stable and can improve with time [15]. The clinical features of this disease vary, extending from an

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asymptomatic state to acute respiratory distress syndrome to septic shock and multi-organ dysfunction [16].

MATERIAL AND METHODS

Design of questionnaire

This was a prospective, multisite study designed to evaluate coronavirus patients with concomitant diseases during infection and after being cured of infection by assessing the impact on their general health. Of note, the questionnaire was in English only.

Demographic data collection

Data on the following were collected:
1. The safety and tolerability of the medication regimen of strategies to prevent COVID infection, as measured by adverse effects, adverse drug reactions and serious adverse events, were reported on a weekly questionnaire.
2. The efficiency of treatment regimens to prevent and cure COVID.
3. Any new or persistent symptoms.
4. Any change in the condition of concomitant diseases (asthma, chronic lung disease, chronic heart disease, diabetes, chronic kidney disease, immunosuppressive condition, gastrointestinal tract problems).

The questionnaire (in English only) enabled monitoring during COVID infection and, after being cured, tracking patient health and progress, side effects, adverse drug reactions, and any disruption of the condition of the patients' concomitant diseases.

Demographic data, laboratory results, management and treatment methods and results, clinical signs and symptoms of COVID patient post-cure concomitant diseases, including disruptions in their conditions, were studied. The type and number of doses of vaccine and the history of infection were also recorded. The severity of COVID infection was assessed and the participants were categorized into five severity groups based on their symptoms and disease history. The five groups are asymptomatic (no symptoms), mild (no shortness of breath, mild symptoms displayed, among others, cough, fever, sore throat, headache, aches, upset stomach), moderate (minor shortness of breath, possibly cough, fever, sore throat, headache, aches, upset stomach), severe (moderate shortness of breath and signs of respiratory distress, possibly cough, fever, sore throat, headache, aches, upset stomach) and critical (severe shortness of breath, respiratory failure, shock and multi-organ failure). The severity of the disease was then used as a statistical factor in analyses and correlated to uncontrolled concomitant diseases.

Inclusion Criteria

1. Participant is willing and able to provide informed consent.
2. The participants are 18-75 years of age.
3. The participant is willing to provide blood samples for the study.
4. The subject agrees with all aspects of the study.

Exclusion Criteria

1. Does not meet inclusion criteria.
2. Participants are unable or unwilling to provide informed consent.
3. The participant is currently enrolled in a study to evaluate an investigational drug.
4. The participant has a known allergy/hypersensitivity or has a medication or co-morbidity (including a history of gastric bypass, epilepsy or renal failure).

Ethical approval

A questionnaire was shared on social networks and by email by the authors or was distributed at health centers. The study was approved by the ethical committee (No.: IU.FA. FR.137E) of the University.

Statistical Analysis

The data were analyzed using the Statistical Package for Social Sciences (SPSS) version 24.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics, such as percentage, and standard deviation (SD), were employed for the presentation of categorical and continuous variables. Pearson's correlation coefficient was applied to assess the strength of the correlation between two numerical variables. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 844 patients from 62 countries were enrolled in this study and completed an online survey, while others did so during visits to hospitals and health centers. Characteristics, such as the sociodemographic status, pre-COVID-19 comorbidities and COVID-19 course of the enrolled patients, are listed in Table 1. Most of the respondents in this survey study were male (56%); 44% were female. The age group with the most participants was 25-34 years old (22.49%), and the race/ethnicity with the highest representation was Asians (38.76%). Most of the participants were university-educated (79%) and the rest completed high school.

The diseases and preexisting comorbidities reported by the patients were asthma – 2.53%, chronic lung disease – 16.76%, chronic heart disease – 11.74%, diabetes – 31.43%, chronic kidney disease – 13.03%, immunosuppressive condition – 4.51%, and gastrointestinal tract problems – 20.00%.

The highest percentage of patients followed the recommended COVID safety instructions (mask, gloves and social distance) – 92.2%. Responses on uncontrolled symptoms for concomitant diseases after being cured of COVID were as follows: gastrointestinal tract problems – 32.62%, diabetes – 19.37%, and asthma – 11.32%.

Of the enrolled patients, 75% were vaccinated, and, regarding then known side effects of being vaccinated for COVID-19, 26.33% were very concerned, while 21.26% were moderately concerned, 18.81% were slightly concerned, and 33.60% were not concerned at all. Most patients received antiviral treatment (40.33%) or vitamins (39.33%), and 49.30% were treated for a 2 week period. The recorded symptoms during the COVID infection were fever/feverish – 60.95%, cough – 10.33%, sore throat – 9.20%, runny or

stuffy nose – 8.15%, difficulty breathing – 5.66%, no sense of smell or taste – 3.61%. Of the enrollees, 1.10% reported no symptoms.

Table 1. Demographic data of enrolled COVID patients

Item	Percentage
Gender	
Male	56%
Female	44%
Age	
18-24	20.14%
25-34	22.49%
35-44	21.81%
45-54	18.39%
55-64	10.62%
65+	6.55%
Race/Ethnicity	
Asian/Pacific Islander	38.76%
White/Caucasian	33.75%
Black or African American	9.43%
Hispanic	9.23%
Multiple ethnicity/Other	6.64%
American Indian or Alaskan Native	2.19%
Region	
Pacific	23.22%
South Atlantic	18.45%
East South Central	17.87%
East North Central	12.67%
Middle Atlantic	12.04%
West North Central	6.52%
Mountain	5.43%
New England	3.80%
Disease state	
Diabetes	31.43%
Gastrointestinal tract problems	20.00%
Chronic lung disease	16.76%
Chronic kidney disease	13.03%
Chronic heart disease	11.74%
Immunosuppressive condition	4.51%
Asthma	2.53%
None	0
Follow safety from COVID instructions (mask, gloves, social distance)	
Yes	92.2%
No	7.8%
Uncontrolled symptoms for the following concomitant diseases after curing from COVID?	
Gastrointestinal tract problems	32.62%
None	25.70%
Diabetes	19.37%
Asthma	11.32%
Chronic heart disease	5.75%
Chronic lung disease	2.32%
Chronic kidney disease	1.47%
Immunosuppressive condition	1.45%

Fifty-four patients in the survey believed that they were at risk of being re-infected with COVID. After weeks or months of COVID infection, 61.80% of the enrolled patients suffered from uncontrolled symptoms (uncontrolled diabetes

|	Percentage
COVID vaccination	
Vaccinated	75%
Not vaccinated	25%
Side effects from a COVID-19 vaccination?	
Not at all concerned	33.60%
Very concerned	26.33%
Moderately concerned	21.26%
Slightly concerned	18.81%
Medication used for COVID treatment	
Antiviral	40.33%
Vitamins	39.33%
Antibiotic	11.86%
Analgesics	8.48%
None	0.00
Duration of COVID treatment	
Days	9.88%
2 weeks	49.30%
1 month	15.60%
More than 1 month	15.30%
Other	9.92%
Symptoms during COVID infection	
A fever/feverish	60.95%
Cough	10.33%
Sore throat	9.20%
Runny or stuffy nose	8.15%
Difficulty breathing	5.66%
No smell or taste	3.61%
None	1.10%
Vaccination types	
Pfizer	69.67%
Moderna	17.89%
AstraZeneca	6.52%
Johnson & Johnson	5.92%
Number of Vaccination doses	
One dose	3%
Two Doses	97%
None	0.00
Date from previous infection with COVID	
Days–1 month	2%
1-2 Months	4%
2-4 Months	7%
4-6 Months	21%
6-8 Months	23%
8-10 Months	21%
10-12 Months	22%

Values are presented as percentages (%)

– 38.70%, uncontrolled gastrointestinal problems – 33.53%, uncontrolled asthma symptoms – 27.77%) (Figure 1).
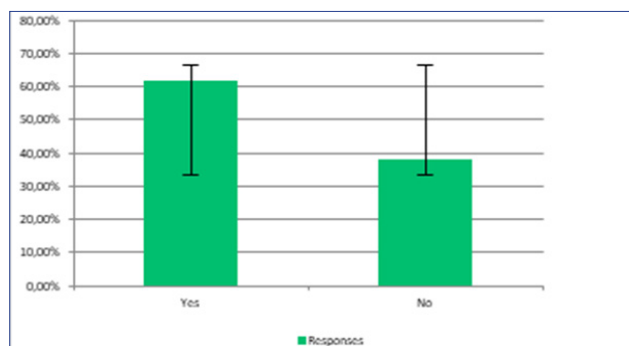

Figure 1. Uncontrolled symptoms (e.g. uncontrolled diabetic, uncontrolled gastrointestinal problems, uncontrolled asthma symptoms, etc.) after weeks to months of COVID infection

Among the patients, 33.64% were concerned about the side effects of treatment, 15.75% suffered from adverse drug reactions (Figures 2A and 2B), while 13.27% still had persistent symptoms. The significant long-term symptoms were cough, dyspnea and constipation.


A

B
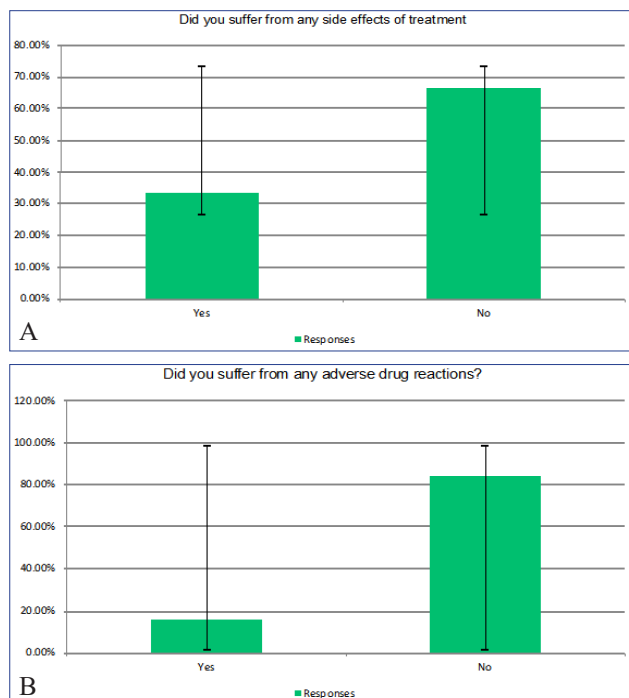
Figure 2. Presence of side effects (A) or adverse drug reaction (B) of COVID treatment

Concerning their treatment regimen, 51.18% were neither satisfied nor dissatisfied, around 8% were dissatisfied or very dissatisfied, and 25.59% were satisfied (Figure 3). Regarding the condition of their chronic diseases (e.g., diabetes, asthma, gastrointestinal issues, metabolic diseases) after COVID infection, about 28.22% said they were the same, 45.18% were worse, and 9.87% declared they were much worse (Figure 4).
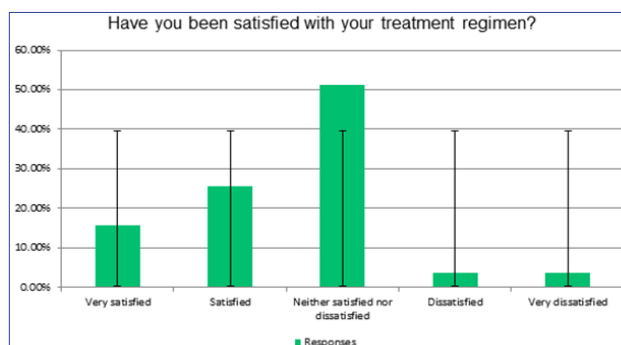

Figure 3. Satisfaction with treatment regimen after COVID treatment
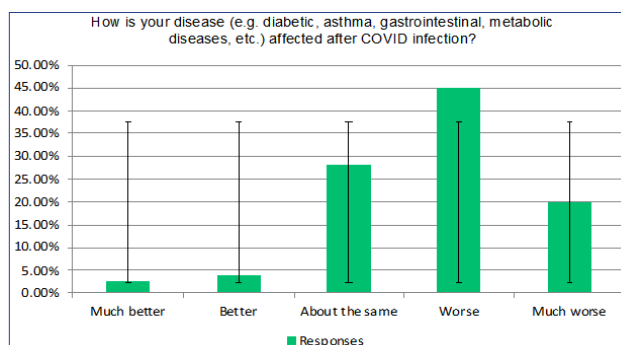
Figure 4. Patients with Concomitant diseases (asthma, chronic lung disease, chronic heart disease, diabetes, chronic kidney disease, immunosuppressive condition, gastrointestinal tract problems) affected after COVID infection

Regarding the response to daily treatment of their diseases, 21.33% stated very responsive, 43.13% – somewhat responsive, 6.16% – not so responsive, and 16.59% – not responsive at all (Figure 5).
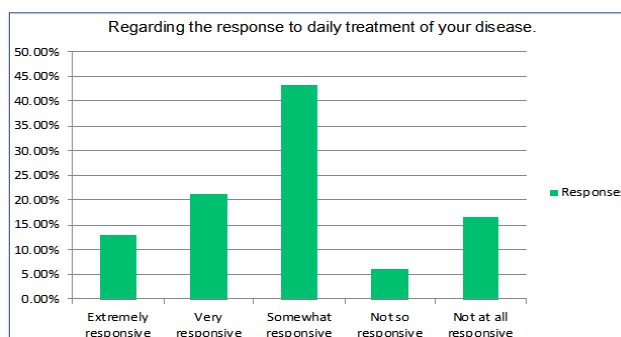

Figure 5. The response to daily treatment of concomitant diseases of COVID patients

The severity of COVID infection was rated according to the medical reports from clinics or hospitals where the patients attended. The relationship between the severity of COVID infection and the uncontrolled concomitant diseases was evaluated, and the highest severity percentages were diabetes – 54%, gastrointestinal tract problems – 51%, chronic heart disease – 47%, immunosuppressive conditions – 46%, asthma – 45%, chronic lung disease – 43%, chronic kidney disease – 35%, $P < 0.01$. Regarding moderate COVID infection, the corresponding figures were chronic kidney disease – 30%, gastrointestinal tract problems – 28%, chronic lung disease – 23%, asthma – 22%,

immunosuppressive condition – 20%, diabetes – 17%, and chronic heart disease – 13%, P<0.02, shown in Figure 6.
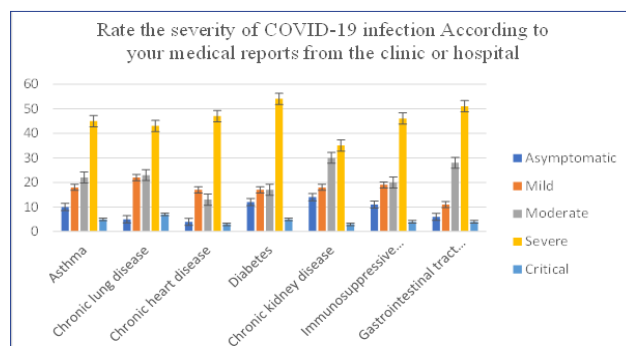
Figure 6. The severity rating of COVID-19 infection according to patients' medical reports from the clinic or hospital

Pearson's correlation analysis showed that there is a high significantly positive correlation between the severity of COVID infection and uncontrolled concomitant diseases, correlation coefficient (r=0.697, P<0.0001), as shown in Figure 7.
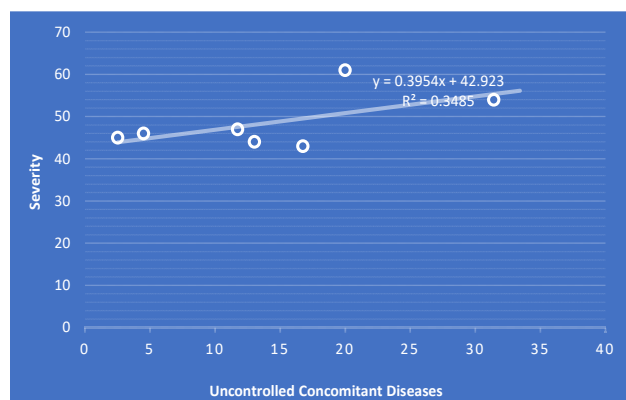
Figure 7. Severity of COVID infection Correlation to uncontrolled concomitant diseases

DISCUSSION

The purpose of this study was to assess and monitor post-coronavirus infection in patients with concomitant diseases. In this study, a statistically significant relationship between the severity of COVID-19 infection and concomitant diseases was observed, and most COVID patients with concomitant diseases suffered from uncontrolled diseases and persistent symptoms. Also, a highly significant positive correlation between the severity of COVID infection and uncontrolled concomitant diseases was recorded.

The results showed that the highest percentage of enrolled COVID patients continued suffering from uncontrolled disease, despite their treatment regimens. Hypertensive patients, for example, suffered from uncontrolled blood pressure for an extensive period after the coronavirus infection. Moreover, diabetic patients suffered from uncontrolled glucose levels, even with daily treatment, so they had to visit their physicians to control their disease and change the treatment. In addition, those with respiratory problems had long-term coughs, dyspnea, and uncontrolled asthma, and the same was true for patients with GIT problems. Most of the COVID patients suffered from GI upset, and a high

percentage of our study population complained of constipation even a year after the coronavirus infection. Chronic complications that may persist after infection with SARS-CoV-2 have been found to mainly affect the respiratory, cardiovascular, renal and neurological systems [17], and our results agree with that study.

Our results revealed that a significantly higher number of COVID patients with concomitant disease were males who developed persistent post-COVID-19 symptoms. The ACE2 enzyme is commonly found in various organs, such as the heart, lungs, kidney and intestine, and it plays a significant role in the multi-organ dysfunction that can be seen during the SARS-CoV-2 infection [18,19]. According to one study, COVID-19 was linked to an increased risk of dying from cardiovascular diseases [20]. Furthermore, hypertension and Diabetes were found to be more prevalent in severe and fatal cases, and respiratory diseases had a higher prevalence in fatal cases compared to total cases [21].

It has been known that a significant number of COVID-19 patients experience long-term sequelae, such as breathlessness and fatigue. GI symptoms, which include abdominal cramps, diarrhea, anorexia and nausea, can also develop in post-COVID syndrome [22].

The authors agree with aforementioned studies as we noted that the enrolled surviving COVID patients with concomitant diseases continued to suffer from uncontrolled diseases or had treatments that failed. Others had side effects and adverse drug reactions during their treatment regimens.

This worrisome situation has been further aggravated by the potential upregulation of angiotensin-converting enzyme 2 in hypertensive and diabetic patients and, more interestingly, that receiving angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists facilitated the inoculation of lung tissue by COVID-19 [23]. Complications during COVID-19, such as respiratory failure, venous thromboembolism, cardiac injury, myocarditis, cardiogenic shock, and encephalopathy have been studied and helped to alter or augment the management guidelines [24-27].

Regarding satisfaction with their treatment regimen, the highest percentage of enrolled COVID patients were neither satisfied nor dissatisfied. The results of this study indicate that, globally, the preexisting or post-pandemic symptoms of patients with concomitant disease were worse during and after the COVID-19 pandemic. Most of the COVID-19 survivors experienced mild post-recovery symptoms, such as fatigue, poor quality of sleep and anxiety, and a few reported more severe manifestations, such as pulmonary fibrosis, renal failure, diabetes mellitus and stroke. The presence of post-COVID-19 manifestations is related to comorbidities and disease severity [28].

CONCLUSION

Upon analyzing the long-term COVID-19 manifestations of patients with concomitant disease, we found that an overwhelming majority experienced at least one post-COVID-19 symptom or side effect, an adverse drug reaction, or an uncontrolled concomitant disease. This study found that post-pandemic symptoms in patients with concomitant diseases were associated with the highest level of persistent

symptoms and less response to treatment regimens. A positive correlation was observed between the severity of the COVID infection and the development of uncontrolled concomitant conditions. This study showed that an important proportion of infected individuals may develop post-COVID-19 syndrome and that a wide range of healthcare services may be required to support their needs.

LIMITATIONS

The survey tool was mostly provided online and in English, thereby limiting the sample to English-speaking people with internet access who had been infected by COVID. What is more, the study relied on self-reporting.

FUTURE WORK

Randomized clinical studies are required to understand the relationship between COVID-19 and the concomitant diseases of patients.

ABBREVIATIONS

ACE – Angiotensin-converting enzyme,
COVID-19 – Coronavirus Disease 2019,
ICU – Intensive care unit
SARS-CoV – Severe acute respiratory syndrome-coronavirus,
RNA – Ribonucleic acid,
TMPRSS2 – Transmembrane serine protease 2.

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