Polytechnic Journal

Polytechnic Journal

Volume 14 | Issue 1 Article 8

April 2024

The Healing Power Of Dietary Supplements To Prevent Long-Term Covid-19; A Prospective Observation Study

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How to Cite This Article

Mohammad, Hadi; Sadeq, Tariq; Ismail, Media; Ahmed, Swar O; and Ameen, Zana (2024) "The Healing Power Of Dietary Supplements To Prevent Long-Term Covid-19; A Prospective Observation Study," *Polytechnic Journal*: Vol. 14: Iss. 1, Article 8.
DOI: https://doi.org/10.59341/2707-7799.1804

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Abstract

The novel coronavirus which emerged from Wuhan, China, in December 2019, was first described as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and affects different systems in the body resulting in different symptoms and severity. The role of macro and micro nutrients plus gut microbiome (gut-lung axis) to boost the immune system is well documented. Therefore, this study aims to boost the immune system particularly the lung immunity to shorten the infection course and prevent post-covid complications. The study strategy depends on maintaining the maximum nutritional status for well-functioning immune system, directing immune system to focus on viral infection by minimizing all the other oxidative stress pathways that cause further damage and put the body immune system under pressure. Furthermore, this study exploits all the possible mechanisms that could promote lung immunity via boosting healthy microbiome. This study includes 183 patients with positive PCR test and typical COVID-19 symptoms from Feb 2020 to Jun 2022. The patients were guided to follow a designed protocol which includes food supplements and healthy diet and nutrition. After 3 days of the protocol initiation, the covid score reduced by 1.14 (p

Keywords

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ORIGINAL ARTICLE

The Healing Power of Dietary Supplements to Prevent Long-term COVID-19; A Prospective Observation Study

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Abstract

The novel coronavirus which emerged from Wuhan, China, in December 2019, was first described as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and affects different systems in the body resulting in different symptoms and severity. The role of macro and micro nutrients plus gut microbiome (gut—lung axis) to boost the immune system is well documented. Therefore, this study aims to boost the immune system particularly the lung immunity to shorten the infection course and prevent post-covid complications. The study strategy depends on maintaining the maximum nutritional status for well-functioning immune system, directing immune system to focus on viral infection by minimizing all the other oxidative stress pathways that cause further damage and put the body immune system under pressure. Furthermore, the protocol exploits all the possible mechanisms that could promote lung immunity via boosting healthy microbiome. This study includes 183 patients with positive PCR test and typical COVID-19 symptoms from Feb 2020 to Jun 2022. The patients were guided to follow a designed protocol which includes food supplements and healthy diet and nutrition. After 3 days of the protocol initiation, the covid score reduced by 1.14 ($p < 0.005$) then by 0.97 per day in classified study groups. The designed protocol showed a significant impact to shorten the infection course and complete recover within 10—13days and prevent long term symptoms and post-covid complications. The participants involved in this study did not receive any medications apart from pain killers. This protocol, which combined many factors to maximize the body immune system, is not restricted to covid infection but could be applicable for other viral infections.

Keywords: COVID-19, Dietary supplements, Probiotics, Pneumonic covid infection, Post-covid complications

1. Introduction

The novel coronavirus which emerged from Wuhan, China, in December 2019, was first described as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), as the respiratory system was the most prominent target [1]. However, later studies reported different systems in the body affected by the virus resulting in different symptoms and severity [2]. In the other hand, long COVID-19 symptoms were reported in infected patients which include anosmia, parosmia, pulmonary fibrosis, post Intensive therapy Unit (ITU) psychosis, cognitive dysfunction, anxiety or depression and chronic fatigue syndrome [3,4].

Symptoms severity and mortality rate varies widely from one group to another. People with metabolic syndrome, including diabetes, obesity and hypertension, and elderly are considered to be high-risk groups and vulnerable to severe COVID-

Received 27 August 2023; revised 11 December 2023; accepted 15 February 2024.
Available online 18 April 2024

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https://doi.org/10.59341/2707-7799.1804

19 infection [5−7]. Most of these groups suffer from one or more of nutrition deficiency. As an example, but not limited to, most of the diabetic patients suffer from vitamin D, zinc and selenium deficiency [8]. Vitamin D deficiency has been reported in 80−90% of obese individuals [9], while other reported low level of vitamin E in this group [10]. Malabsorption of many nutrients in elderly people is well documented. Both macro- and micronutrients malabsorption has been described in elderly. These nutrients include vitamin D, zinc, folic acid, iron, B12 and proteins [11,12]. These studies may explain the reason for the viral infection severity in aged groups which may related with nutrients deficiency.

The role of macro and micro nutrients to boost the immune system is well documented. High blood sugar level has negative impact on immune system elements in different ways. Simple carbohydrate ingestion reduces neutrophil phagocytic index for 5 hours after consuming 75 gram of sugar [13]. Fructose, the most common sugar in fruits, negatively regulates innate immune system against influenza A virus and *S. aureus* through Mannose-binding lectin (MBL) mechanism [14]. Induced short term hyperglycemia for 2 hours impairs immune system by reducing IL-6 which is important for both innate and adaptive immune response [15]. This may explain the severity of COVID-19 infection in diabetes patients. Thus, nutritional change including low carb diet, even for non-diabetic, may boost immune system against COVID-19 infection.

Generally, vitamin D play a vital role in both innate and acquired immune system to reduce the risk of infection [16]. Specifically, vitamin D directly affects the immune system in respiratory system. Systematic review and meta-analysis study showed that vitamin D protect against acute respiratory tract infection [17]. The possible mechanism of this was proposed by Chen group who showed that vitamin D and vitamin D receptor reduce inflammation in lung and maintaining pulmonary barrier integrity [18].

Zinc plays an important role in production of IFN-γ and IL-12 which are essential for phagocytic activity of macrophage against bacterial and viral infection. Zinc deficiency may induce inflammatory cytokines by monocytes and macrophage and also increase the oxidative stress markers [19]. Studies reveal the role of zinc in reducing the risk of respiratory tract infection and pneumonia in nursing home elderly [20].

Cell-based, preclinical and clinical studies emphasized the role of vitamin E in modulating the function immune response particularly in the respiratory infection. Vitamin E affect the cell membrane integrity and signal transduction of T cell, the cell that play a significant role in viral infection particularly in lung [21].

Antioxidants play a vital role in reducing the cellular damage during infection diseases. Understanding the way that viral infection effect the host cell state including ROS (reactive oxygen species) production and antioxidant balance, direct the protocol in this study to include appropriate antioxidants such as vitamin E, C, glutathione, N-acetylcysteine and selenium that minimize cellular damage. During viral infection, activated phagocytic cells release ROS, tumor necrosis factor (TNF) and interleukin-1 which play important role in the pathogenesis of RNA viral infection [22]. TNF inhibits mitochondria respiration and increases superoxide production by infected cells and this can be inhibited by using vitamin E [20]. RNA viral infection induces apoptotic cytotoxicity which can be encountered by antioxidants such as glutathione peroxidase and N-acetylcysteine [23,24]. In animal model study, RNA viral infection resulted in low concentration of vitamin C, E and glutathione which indicates that oxidative stress is associated with the pathogenesis [25]. In addition, antioxidants not only reduce the oxidative stress but also decrease viral replication and reduce the incidence of viral mutations [26] which is the common feature of the RNA viruses such as coronavirus.

Gut microbiome, which recently become an area of interest in human health, plays a significant role on immune system particularly lung immunity. Ichinohe co-workers found that gut microbiota regulates the production of virus-specific CD4 and CD8 T cells and antibody response against respiratory viral infection [27]. Furthermore, gut microbiota produce metabolites such as short-chain fatty acids (SCFAs) that influence hematopoietic precursors in the bone marrow. This affects both innate and adaptive immune response in lung during viral infection [28]. Dietary adjustment could be useful to combat lung conditions as gut microbiome population is affected by diet profile, simple carbohydrates and refine sugar consumption. Studies showed that consumption of gluten free foods and foods rich in fibers, non-digestible carbohydrates and unsaturated fats increase the production of SCFAs and fecal butyrates. In contrast, foods rich in animal proteins and saturated fats reduce SCFAs production [29]. Simple sugar such as fructose and glucose that reach large intestine reduce the gut colonization by beneficial bacteria [30].

Since the pandemic outbreak, many different protocols and medicines were subjected to different clinical trials to treat COVID-19 patients worldwide.

Some of these did not show any significant outcome and were rejected by WHO such as remdesivir [31] others did not showed significant effect such as ivermectin [32], hydroxychloroquine [33], azithromycin and doxycycline [34,35]. However, research and clinical trials still underway to develop an active and safe drug for COVID-19 treatments.

In attempt to control the outbreak, many vaccines were invented which provide varying levels of protection [36]. In spite of COVID-19 vaccines considered to be a great achievement in tackling the pandemic, however, some complications associated with the vaccines were reported such as blood clotting [37], low antibody production in individual suffering from chronic diseases [38], neurological complication [39] cardiac complication [40] and ocular complication [41]. In addition, many new variants of coronavirus have been emerged which may make the vaccine not fully protective and effective [42].

Therefore, in the absence of effective therapeutic agents, or even in presence of different available vaccines, body immune system remains the top priority that could be boosted against COVID-19 infection to prevent, or at least reduce, long term infection. Thus, in this study a safe supportive protocol was designed to maintain the maximum nutritional status for well-functioning immune system, directing immune system to focus on viral infection by minimizing all the other oxidative stress pathways that cause further damage and put the body immune system under pressure. The protocol also exploited all the possible mechanisms that could promote good metabolic health such as healthy diet and boosting healthy microbiome. One hundred and eighty-three patients from different countries with positive PCR test and typical COVID-19 symptoms were involved in our study. The designed protocol showed significant effect within a couple of days to decrease the symptoms and complete recover within 10–14 days without any medications apart from pain killers. Furthermore, we didn't report any long term complications after recovery. This protocol shortens the infection course, prevents long-term symptoms and likely prevents the virus to get mutations. Boosting immune system could also help as a preventive measure to reduce hospitalization rate.

2. Patients and methods

This prospective observation study was carried out between Feb 2020 and Jun 2022 and includes 183 patients (23–65 y) from different countries with positive PCR test and typical COVID-19 symptoms. The mean age was 43, 106 male and 77 female. The patients were self-referred or referred by physicians and were contacted via phone to record and fill up the data form (Table S1) for each patient. The following up was conducted in daily bases for first two weeks then every week, two weeks and every month afterward for six months to monitor long term consequences.

The participants were classified into two groups; healthy group (n = 132) and group with metabolic syndromes (MS) such as diabetes type 2, hypertension and obesity (n = 51). Furthermore, the participants were subclassified into a group of pneumonic covid (LRS: n = 96) and a non-pneumonic covid (GS: n = 87). This categorization helps to compare the effectiveness of the designed protocol between different groups. The patients were suffered from different symptoms with variable severity. The reported symptoms include fever and chills, loss of appetite, severe headache, fatigue, cough, body ache, nausea, difficult breathing, anosmia, diarrhea and insomnia. By the end of the report, each patient obtains a score which represents the overall symptom and severity. The COVID score was measured according to the 12 symptoms listed in Table S1. The score was obtained by multiplying number of the symptom by factor 10 and divided by 12 (*Covid score* = *n*10/12*).

The scores were recorded before and after the protocol initiation. Therefore, covid scores further stratified the participants into three groups; mild (covid score <5), moderate [6,7] and severe [8–10]. The supportive protocol in this study was designed based on published scientific literature [16,29,43–47]. This includes low carb diet program and administration of probiotic, vitamins, minerals and food supplements such N-acetylcysteine and quercetin [48]. The complete protocol is outlined in the supplementary information (Table S2). The rational target of this study is to investigate whether the suggested protocol is able to reduce hospitalization rate, shorten the infection course, accelerate the recovery process and prevent or reduce post-covid complications.

The statistical analysis was performed using IBM SPSS Statistics, version 23.0 (SPSS Inc., Chicago, IL, USA). Costume tables were used to indicate the frequency and percentage in the population. Moreover, descriptive non-parametric survival analysis such as Kaplan Meier survival curve was used for the estimation mean of recovery time and illustrates the recovery time for each group. Days were used as time scale to calculate mean time for recovery. A cox proportional hazards regression model was used to determine factors associated with recovery time. Factors associated with recovery time at *p*-value <0.05 in bivariable cox regression were selected for multivariable cox regression analysis. Adjusted Hazard Ratios (AHR) with 95% confidence intervals was computed and statistical significance was declared at 5% level (*p*-value < 0.05). A comparative analysis was conducted using paired t-test to investigate the protocol effect before and after application in the same group.

3. Results and discussion

The demographic and clinical characteristics of the 183 participants are reported in Table 1. The mean age of the participants was 43 (SD ± 9.75). In order to investigate the symptom severity and response to the protocol, the participants were categorized according to their age into 4 groups (Table 1). The age factor plays a role in COVID-19 infection severity. Therefore, majority of the participants (42%) mean age was 45.1 (SD ± 2.63) reflects a good population study. A male to female ratio was 1.38:1, 106 patients (57.9%) were male and 77 (42.1%) were female. Healthy participants (i.e without underlying conditions) accounted 72.1%, while 27.9% were suffering from underlying conditions (metabolic syndrome) prior to COVID-19 infection. The severity of the symptoms were distributed as 7.1% mild, 31.1% moderate and 61.74% severe with mean score of 5, 6.63, and 8.48 respectively. Ninety-six (52.5%) patients were suffered from pneumonic COVID-19 (Lower Respiratory Symptom LRS) and 87 (47.5%) patients from non-pneumonic COVID-19 (General symptom GS).

All patients were improved after 72 hours of the protocol initiation. The covid score mean reduced from 7.66 (SD ± 1.26) on the first day to 6.39 (SD ± 1.12) on the third day of protocol application (P < 0.005) (Fig. 1a). Simple linear regression (Fig. 1b), showed a significant (p < 0.0001) reduction of the mean score over time ($R2 = 0.97 \pm 0.029$) with the score of 0.97 decrease per day. It seems that the protocol is effective in reducing the clinical symptoms in different groups. No statistically significant difference was found between different age groups and between male and female in term to the protocol response and recovery time (Fig. 1c and d, Fig. 2a). However, the findings of the main Cox regression analysis in Table 2 showed some statistically differences in the variables. The patients with age group (≤30) recover quicker than patients with age group (50–65) P- value < 0.001 (Fig. 1c and Table 2). However, since the hazard rate are (0.963) so the difference is below the significant level. Previous studies reported mild symptoms and shorter recovery time in young patients than older patients [49–52]. This is not contradictory rather than the designed protocol in this study might have worked effectively in both age groups. Healthy and MS patients responded to the protocol in the similar way. However, on the 5th day and onward healthy patients mean score reduced quicker than MS patients (Fig. 1e). This is consistent with other studies which reported that metabolic syndrome such as obesity, diabetes and hypertension is associated with severe COVID-19 infection and need more recovery time [6,7,53]. Infected patients with metabolic syndrome suffer from nutrients deficiency such as vitamin D, E, zinc and selenium. Low level of these nutrients exacerbates the symptoms and causes more cellular damage which prolongs the infection course. In addition, the high level of glucose in blood in diabetic patients impairs the immune system. Replenishment of these important nutrients or controlling the blood sugar is the key role of the designed protocol in this study. This may explain the effectiveness of the protocol in covid patients.

Table 1. Demographic and clinical characteristics of the participants.

Variable	Category	Number	Mean	SD	%	Ratio	*P* value[b]
Age	20–30	18	26.9	2.68	9.8	1:3:4.3:2	<0.001
	31–40	55	35.7	2.28	27.3		<0.001
	41–50	77	45.1	2.63	42		<0.001
	51–65	37	57.9	3.40	20.2		<0.005
Gender	Male	106	7.81[a]	1.228[a]	57.9	1.38:1	<0.001
	Female	77	7.44[a]	1.282[a]	42.1		<0.001
Comorbidities	Healthy	132	7.45[a]	1.34[a]	72.1	2.5:1	<0.001
	MS	51	8.20[a]	0.8[a]	27.9		<0.005
Severity	Mild	13	5.0[a]	0.0[a]	7.1	1:4.4:8.7	<0.001
	Moderate	57	6.63[a]	0.52[a]	31.1		<0.001
	Severe	113	8.48[a]	0.67[a]	61.74		<0.005
Symptoms	LRS	96	8.37[a]	0.79[a]	52.5	1.1:1	<0.05
	GS	87	6.86[a]	1.2[a]	47.5		<0.001

[a] *Mean and SD of covid score before protocol application.*
[b] *Paired t-test P value before and after 72 hours of protocol application.*

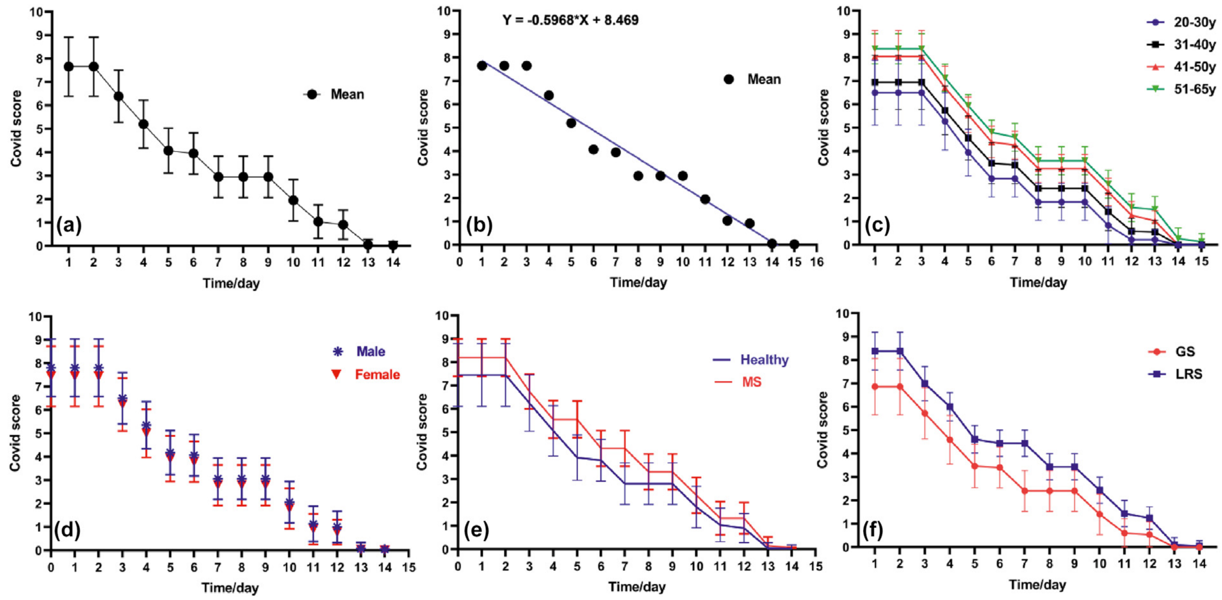

Fig. 1. Covid score means and Std before and after protocol application. Overall means for all participants (a), Simple linear regression for covid score means (b), Different age groups (c), Gender (d), Healthy vs MS (e), and GS vs LRS (f).

The same pattern was observed between GS patients and LRS patients particularly on 7th day (Fig. 1f). Patients with LRS responded to the protocol slower than GS (P value 0.028; the hazard rate 0.668), which means that LRS group needs more time to recover (about %34) than GS group (Table 2). Previous studies reported that involving lung with COVID-19 infection needs longer recovery time. This was explained by elevated IL-6 level and other cytokines, the main possible reasons in lung cellular damage [54,55]. The protocol includes more than one approach to manage and control these cytokines as explained in introduction section. This may explain the quick response and improvement after protocol initiation even in patients with severe illness.

Kaplan–Meier estimation technique was used to estimate the survival time between individual covariates (Fig. 2). There was no statistically significant difference between male and female in recovery rate (Fig. 2a). The same was found for the healthy and MS variable (Fig. 2b). As shown in Fig. 2c, patients with non-pneumonic covid (GS) recover quicker than those with pneumonic covid. Patients with severe symptoms need more time to recovery than patients with moderate and mild symptoms with mean (13.06, 11.965 and 10 days respectively) to recover (Fig. 2d and Table 3).

Furthermore, p-value = 0.000 in Log Rank (Mantel–Cox), Chi-Square = 188.972, suggests that there is statistically significant difference for recover time between these three groups (severe, moderate and mild). The previous recorded recovery time of COVID-19 infection ranged from 12 days to 21 days [51,55–57]. In this study, the overall means and medians recovery time for all participants in different groups was 12.3 and 13 days respectively (Table 3). This is shorter than the recorded recovery time in other previous studies taking into account that our study did not involve any medical treatments apart of the pain killer.

However, there was a difference in mean recovery time between groups. The patients with lower respiratory symptoms (LRS) recovered slower than those without, GS (Means = 13.083 and 11.862 days respectively). As stated in introduction section that particular vitamins, minerals and other nutraceuticals have a potential effect on the immune system. In addition, probiotics also was suggested to have effect on the lung immunity and potential used to flatten COVID-19 curve [58]. The role of the probiotics/microbiome in this respiratory infection may be due to the chemical compounds that produce in the gut and modulate the immune cells in the lung against viral infection. While analyzing the data and writing this manuscript, two article papers were published reporting the potential benefit of ketogenic diet on the COVID-19 consequence [49,50,56]. This supports the designed protocol in this study which includes low carb diet.

Previous studies investigated the effect of individual element at once. However, according to the best of our knowledge, this study is the first study

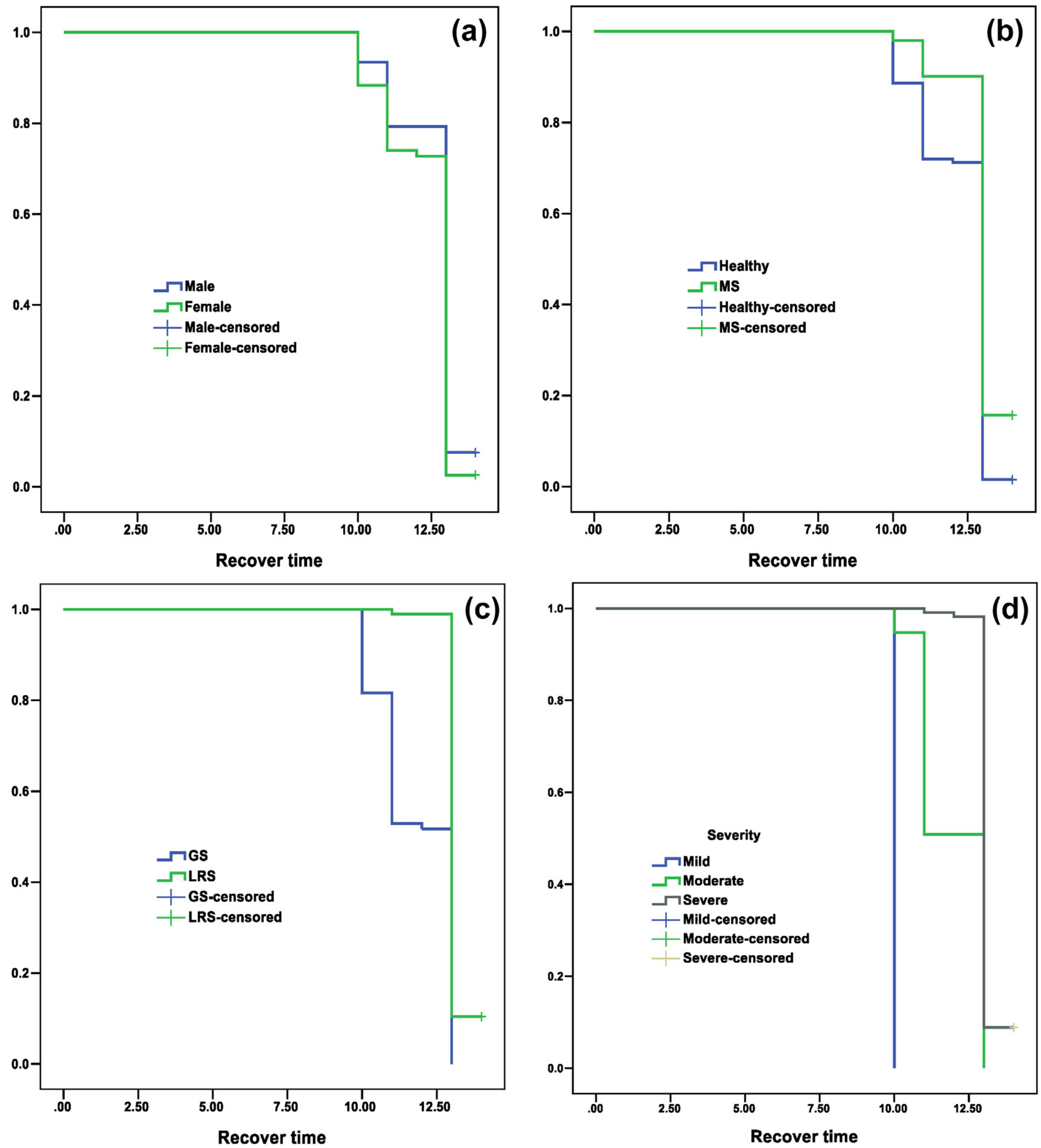

Fig. 2. Kaplan Meier estimates for recover time: Gender (a), Healthy vs MS (b), GS vs LRS (c) and severity (d).

that combined all the approaches in one comprehensive protocol to include diet, nutrition and nutraceuticals in one package. This may create a synergistic effect of the elements used in this protocol. The strategy of this study focused on all the possible mechanisms that promote immune system, lower inflammatory markers and reduce oxidative stress. Therefore, it is expected to find the broad effect of the current protocol on different groups with various conditions.

Table 2. Cox regression analysis.

Variable	SE	*P*	HR	95% CI for HR	
				Lower	Upper
Age	0.010	0.000	0.963	0.944	0.983
Gender	0.156	0.910	0.982	0.723	1.334
MS vs Healthy	0.190	0.988	1.003	0.691	1.455
LRS vs GS	0.170	0.028	0.688	0.493	0.961

Because of the study design and methodology, our study limitations include the lack of blinding and control group, and the small size of the sample. In addition, the starting time of the protocol during the infection course was not similar among the patients. This may result in different outcome as the late stage of illness causes more cellular damage which needs more time to recover and subside the symptoms.

Table 3. Means and median for recovery time for all participant groups.

Variable	Mean[a]				Median			
	Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
Gender								
Male	12.594	0.101	12.397	12.791	13.000	0.072	12.860	13.140
Female	12.377	0.129	12.125	12.629	13.000	0.026	12.949	13.051
Comorbidity								
Healthy	12.333	0.098	12.141	12.525	13.000	0.015	12.970	13.030
MS	12.941	0.112	12.721	13.161	13.000	0.137	12.732	13.268
Symptoms								
GS	11.862	0.133	11.601	12.123	13.000	0.000	–	–
LRS	13.083	0.038	13.009	13.158	13.000	0.070	12.862	13.138
Severity								
Mild	10.000	0.000	10.000	10.000	10.000	–	–	–
Moderate	11.965	0.144	11.683	12.247	13.000	0.000	–	–
Severe	13.062	0.034	12.996	13.128	13.000	0.030	12.941	13.059

4. Conclusion

It can be concluded that the designed protocol played a significant role in reducing the recovery time in all participants with different conditions. Although the patients with severe symptoms or with underlying conditions recovered slower than the others, but the recovery time is still shorter than previous records. The results also showed that the protocol prevented hospitalization and long term infection and post-covid complications. In spite of some limitations associated with this study, the designed protocol is based on solid evidences and safe to be used in patients according to the scientific literature review. Therefore, it can provide a clear evidence for the nutritionist to use it not only for covid 19 infection but in general to boost immune system for other RNA viral infections. Hence, it's worth to expand this study further to investigate more the significant of the current protocol.

Author contributions

Hadi Hussein Mohammad and **Tariq Waece Sadeq**: Conceptualization, Methodology and original draft preparation **Media Khursheed Ismail**: Patient data recording, writing- Reviewing and Editing, **Swar Omer Ahmed**: Formal analysis and statistical applications, Zana Zrar **Ameen**: Patients' referral, follow up and supervision, **Hadi Hussein Mohammad, Zana Zrar Ameen** and **Tariq Waece Sadeq**: Resources. All authors have read and agreed to the published version of the manuscript.

Conflict of interest

All co-authors have seen and agree with the contents of the manuscript and confirm that there is no financial interest to report.

Acknowledgments

We would like to thank all the patients included in this study.

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