SMER
Society of Medical Education & Research

2022, Volume 2, Issue 1, Page No: 1-8
ISSN: 3108-4826

Society of Medical Education & Research

Journal of Medical Sciences and Interdisciplinary Research

Exploring the Role of CRP Analysis and Obesity in the Disparities of COVID-19 Outcomes

Leonidas Palaiodimos[1,2*], Ryad Ali[3], Hugo O. Teo[1], Sahana Parthasarathy[1,2*], Dimitrios Karamanis[3], Natalia Chamorro-Pareja[1,2], Damianos G. Kokkinidis[1], Sharanjit Kaur[1], Michail Kladas[1,4], Jeremy Sperling[1,2], Michael Chang[1], Kenneth Hupart[1], Colin Cha-Fong[1,2], Shankar Srinivasan[3], Preeti Kishore[1,2], Nichola Davis[1,5], Robert T. Faillace[1,2]

[1] NYC Health + Hospitals, New York, NY 10461, USA.
[2] Jacobi Medical Center, Albert Einstein College of Medicine, Bronx, NY 10461, USA.
[3] Department of Health Informatics, Rutgers School of Health Professions, Newark, NJ 07107, USA.
[4] Division of General Internal Medicine, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA.
[5] Department of Population Health, NYU Grossman School of Medicine, New York, NY 10016, USA.

***E-mail** ✉ leonidas.palaiodimos@gmail.com

Abstract

Obesity has now become a global concern and contributes to various risk factors, especially in Western countries, where its prevalence has increased sharply. This surge has led to a significant increase in cardiovascular diseases in the general population. Inflammatory proteins, such as C-reactive protein (CRP), play an important role in the acute phase response to inflammation. This study aimed to investigate the impact of obesity on inflammation, as measured by CRP levels, in obese patients who exhibit frequent inflammatory responses. These patients may be at an elevated risk of contracting COVID-19 due to the effects of obesity on the immune system, with variations observed based on gender, ethnicity, and age. Our findings emphasize the importance of obese individuals maintaining low CRP levels to mitigate the risk of COVID-19 infection.

Keywords: C-reactive protein analysis, COVID-19 pandemic, Obesity, Immune system, SARS-CoV-2 infection

Introduction

In Western countries, the rise of economic growth and industrialization has coincided with a notable increase in obesity rates. This growing prevalence of obesity has led to serious health consequences, especially an uptick in cardiovascular diseases, which now stand as the leading cause of death in these regions [1, 2]. Research has indicated that the duration of obesity may be more impactful on health than its severity, with excessive intake of dietary fats—particularly saturated fats and cholesterol—being a key factor contributing to obesity's rise due to an imbalanced diet [3, 4]. Obesity is now recognized as a condition that fosters chronic inflammation, evidenced by heightened production of pro-inflammatory cytokines (such as TNF-α and IL-6) and increased levels of systemic inflammation markers like CRP [5]. Some studies suggest that this ongoing inflammation could lead to cardiometabolic disturbances, such as endothelial dysfunction and insulin resistance, which are common in obese individuals [6].

Humans, along with other higher mammals, are born with an inherent response to food stimuli [7, 8]. Over time, this innate response is shaped through unconscious Pavlovian conditioning, where the sensory attributes of food become linked to its physiological effects. As a result, individuals can predict the nutritional consequences of what they eat and adjust their consumption accordingly.

Access this article online https://smerpub.com/

Received: 18 November 2021; **Accepted:** 07 January 2022

How to cite this article: Palaiodimos L, Ali R, Teo HO, Parthasarathy S, Karamanis D, Chamorro-Pareja N, et al. Exploring the Role of CRP Analysis and Obesity in the Disparities of COVID-19 Outcomes. J Med Sci Interdiscip Res. 2022;2(1):1-8. https://doi.org/10.51847/GnA3T0sCP1

However, in obese individuals, this adaptive mechanism appears to be disrupted, particularly concerning a heightened preference for foods rich in fats [9, 10].

The global COVID-19 pandemic has created a serious public health crisis, particularly due to its association with widespread pneumonia. CT scans are crucial for assessing the severity of pneumonia, while CRP levels serve as a reliable indicator for diagnosing this condition early. High CRP levels are often associated with severe cases of pneumonia [11-14]. Similarly, during the 2002 SARS epidemic, CRP overexpression was linked to severe respiratory issues and increased mortality, though the results from different studies were not always consistent [15, 16].

The relationship between high-level BMI and Coronavirus COVID-19 contamination risk is presented in **Figure 1**.

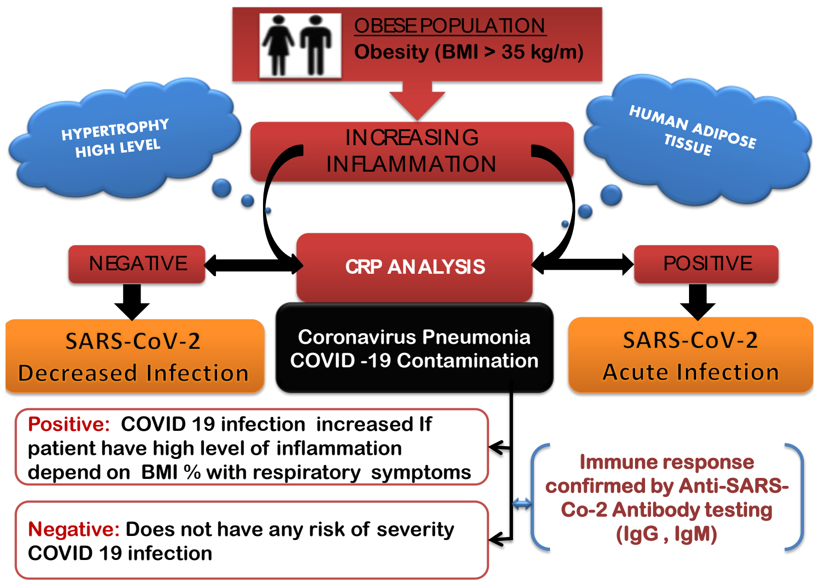

Figure 1. Relationship between high-level BMI and Coronavirus COVID-19 contamination risk.

This study aims to explore the impact of obesity on inflammation, as measured by CRP levels, in obese patients who exhibit frequent inflammatory responses.

Obesity

Definition

Obesity has become a widespread global health issue. In adults, it refers to an excessive accumulation of body fat that leads to various health risks. This condition arises when there is an imbalance between calorie intake and energy expenditure. Obesity is often described as a disorder in which the body's fat mass surpasses the accepted normal range, influenced by factors such as age, gender, body size, and muscle mass. The increase in fat can result from hypertrophy, where individual fat cells increase in size and fat content, or hyperplasia, where the total number of fat cells grows, or a combination of both, particularly in those who are severely obese. The excess fat can be distributed evenly across the body or may be concentrated in specific regions [17-19].

Epidemiology and Classification

Several classification systems have been proposed to categorize obesity:

Obesity Classification by Body Mass Index (BMI)

The World Health Organization (WHO) has identified obesity as a major epidemic of the modern age, recognizing it as a critical public health issue (**Table 1**) [20].

Table 1. Classification of adults according to BMI [21].

Classification (Adults)	BMI category (Kg/m²)
Insufficient weight	< 18.5
Normal weight	18.5–24.9
Overweight	25.0–29.9
Obesity	30.0–34.9
Class I (moderate)	35.0–39.9
Class II (severe)	40 and more
Class III (morbid)	40 and more

Waist-to-Hip Ratio and Obesity Classification

The waist circumference (TT) and hip circumference (TH) are measured with a tape measure on a standing individual, and the ratio of TT/TH is used to categorize obesity. If the ratio is under 0.9 in women and under 1 in men, the person is not considered obese. When the ratio exceeds these thresholds, the individual is classified as having gynoid (in women) or android (in men) obesity [22]. While BMI is a widely used tool to assess obesity, it does not provide specific details about body composition, such as the proportions of fat and lean tissue, or fat distribution, which can vary significantly between individuals [23]. It is now acknowledged that abdominal fat (android obesity) poses a greater health risk than fat located in the hips and thighs (gynoid obesity), regardless of BMI. Android obesity is linked to more severe metabolic complications and is therefore considered the more dangerous form of obesity. Studies have shown that within each BMI category, an increased waist-to-thigh ratio, which estimates abdominal fat, is associated with a higher risk of heart attack [24]. Moreover, individuals with lower visceral fat levels show glucose tolerance levels similar to those of normal-weight individuals. The International Day for the Evaluation of Abdominal Obesity (IDEA) study further supports the importance of waist circumference as a significant factor in predicting the risk of cardiovascular disease and type 2 diabetes [25, 26].

Obesity Prevalence

Obesity prevalence tends to rise with age, with the highest rates observed in individuals aged 65 to 69 years. Research suggests that the combination of high-fat diets and sedentary lifestyles contributes to the increasing rates of obesity, particularly in countries experiencing a transition from poverty to wealth [27].

In the United States: 61% of the population is classified as overweight, with this trend steadily increasing across all age groups and genders over the last two decades. Notably, the obesity rate in teenagers has tripled over the past 20 years [28].

In Europe: Obesity rates are generally higher in southern European countries compared to northern Europe, a shift attributed to changes in diet, such as the replacement of traditional Mediterranean foods with those high in fats, sugars, and salts [29].

In France: Data from the Nutritional Surveillance and Epidemiology Unit [USEN, 2007] reveals that the prevalence of obesity has increased from 8.2% in 1997 to 12.4% in 2006, affecting approximately 5.9 million people in France [30].

In Spain: Southern European nations have prioritized addressing food security and malnutrition, and available data indicates that obesity is emerging as a concern, particularly among women [31].

In Algeria (Maghreb Region): Despite some social groups facing undernourishment, recent surveys show that 53% of women and 36% of men in Algeria are overweight or obese [32].

Metabolic Consequences of Obesity

Obesity is a key risk factor for developing insulin resistance and non-insulin-dependent diabetes, especially abdominal obesity. It is also linked to cardiovascular diseases. Metabolic syndrome, which includes a combination of risk factors such as high blood pressure, hypertriglyceridemia, low HDL cholesterol levels, and non-insulin-dependent diabetes, is exacerbated by excess visceral fat [33].

Adipose Tissue and Its Role

Adipose tissue serves as the body's primary energy storage organ, storing triglycerides that can be mobilized through lipolysis to supply energy to other tissues. Besides being a source of energy, it also provides substrates for gluconeogenesis (glycerol) and lipoprotein synthesis (free fatty acids) to support various physiological functions, including those of the liver [34].

Materials and Methods

Subjects and Patients

The present study examined the demographic characteristics of both patients and control groups, which were documented through a questionnaire. Informed consent was obtained from all participants involved in the study. The criteria for selecting obese participants were based on specific characteristics, as shown in **Figure 2**.

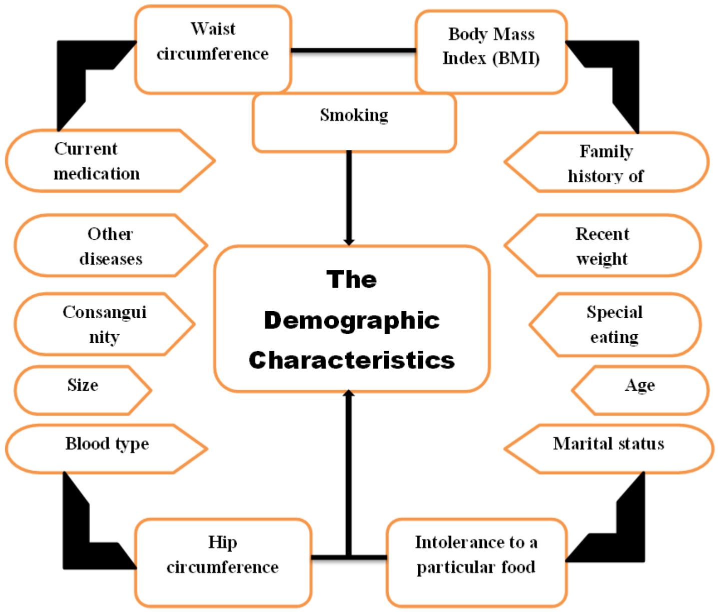

Figure 2. Schematic summary of the demographic characteristics of obese patients.

Determination of CRP via Immuno-Agglutination Method

In this study, CRP levels were measured in serum using the immuno-agglutination technique, where serial two-fold dilutions were used in combination with an antiserum containing anti-CRP antibodies that were fixed on latex particles [35, 36]. The method was utilized in Spain for both qualitative and semi-quantitative CRP testing [37]. The CRP-Latex reagent, which is coated with anti-human CRP antibodies, is calibrated to detect serum CRP levels beginning at 6 mg/L, a value that is considered clinically significant. When the CRP-Latex reagent is mixed with serum, an antigen-antibody reaction occurs, resulting in visible agglutination within approximately two minutes [38]. The presence of agglutination indicates the presence of CRP in the sample [39].

Semi-Quantitative CRP Analysis in the Context of COVID-19 Cases

BMI is commonly used to assess obesity levels. It has been shown that excess adipose tissue increases the expression of ACE2 receptors, which are critical for SARS-CoV-2 virus entry into cells [40, 41]. ACE2 receptors are located in various organs, including the lungs, arteries, heart, kidneys, and intestines, and serve as co-receptors for the virus, thus enhancing the risk of infection. Increased adipose tissue, by boosting ACE2 receptor production, may elevate the risk of contracting SARS-CoV-2 and developing severe COVID-19 symptoms [42-45]. Due to the high viral load in obese individuals, they may also be more likely to transmit the virus to others [46-50].

Effects of Obesity on Body Functions

Obesity can impair lung capacity by limiting diaphragmatic movement, which negatively impacts overall respiratory function and leads to lower oxygen saturation levels [51, 52]. This, in turn, weakens the immune system's ability to respond to viral infections, affecting both the progression of the disease and the effectiveness of vaccines [53]. Higher mortality rates from COVID-19 have been observed in regions with a high prevalence of obesity, particularly in lower socioeconomic populations [54, 55]. Obesity (BMI > 35 kg/m²) has been associated with a greater need for oxygen (OR 3.09), higher rates of intubation (OR 3.87), and an increased risk of in-hospital death (OR 3.78) [56]. Obese individuals are also more likely to exhibit reduced lung function during COVID-19 infection, as seen in the Lille Intensive Care, COVID-19, and Obesity study group in France. The study revealed that 47.6% of ICU-admitted COVID-19 patients were obese (BMI > 30 kg/m²), with 28.2% classified as extremely obese (BMI > 35 kg/m²) [57]. As BMI increased, the severity of illness and the need for mechanical ventilation escalated, reaching almost 90% in patients with a BMI greater than 35 kg/m² [58].

CRP Quantification

To measure CRP levels, serial dilutions (1:2, 1:4, 1:8, 1:16, etc.) were carried out using physiological saline. For each dilution, a qualitative test procedure was performed [59]. The highest dilution that produced a positive result indicated the serum titer, which was used to calculate the CRP concentration based on the visible agglutination [60-62]. The CRP concentration was determined by multiplying the serum titer by the sensitivity threshold of 6 mg/L [63, 64]. Additionally, cholesterol and triglyceride levels were analyzed using Bio Maghreb kits following standardized protocols [65-67].

Results and Discussion

Molecular analyses have shown that certain patients' immune reactivity can serve as a significant marker for the severity of COVID-19. Obesity, which is prevalent among COVID-19 patients, contributes to compromised lung function and lower oxygen levels, ultimately affecting immune responses and leading to chronic low-grade inflammation. This inflammatory state is characterized by the increased secretion of proteins by immune system cells, which exacerbates the condition in obese individuals.

This review highlights that obesity induces an inflammatory effect through elevated CRP levels, emphasizing the importance of immune system activation and the inflammatory status in obese patients. Obesity can thus be categorized as a leading non-infectious "inflammatory" disease. The distribution of adipose tissue plays a crucial role in the inflammatory response, as abdominal fat, in particular, exacerbates the inflammatory state associated with obesity.

Hyperinflammation, indicated by high CRP levels, has also been identified in the pathogenesis of other human coronavirus infections. In this study, elevated CRP levels were associated with higher risks of mortality, underlining the need for careful management of CRP levels and respiratory support to mitigate the risks in COVID-19 patients.

Conclusion

Elevated CRP levels, as indicators of inflammation, are closely linked to an increased risk of severe COVID-19 outcomes in obese individuals. These individuals face a higher risk of infection, severe disease progression, and death due to obesity being an independent risk factor for severe COVID-19. Additionally, excess adipose tissue heightens the risk of spreading the virus to others. This review aims to shed light on the risks faced by obese populations during the COVID-19 pandemic, emphasizing the importance of CRP testing, immune function, and respiratory system protection.

Acknowledgments: None

Conflict of Interest: None

Financial Support: None

Ethics Statement: None

References

1. Lobstein T, Baur L, Uauy R. Obesity in children and young people: a crisis in public health. Obes Rev. 2004;5(1):4-10. doi:10.1111/j.1467-789X.2004.00133.x
2. Whitlock EP, Williams SB, Gold R, Smith PR, Shipman SA. Screening and interventions for childhood overweight: a summary of evidence for the US Preventive Services Task Force. Pediatrics. 2005;116(1):e125-44. doi:10.1542/peds.2005-0242
3. Dietz WH, Bellizzi MC. Introduction: the use of body mass index to assess obesity in children. Am J Clin Nutr. 1999;70(1):123S-5S. doi:10.1093/ajcn/70.1.123s
4. Guo SS, Chumlea WC, Roche AF, Siervogel RM. Age and maturity-related changes in body composition during adolescence into adulthood. The Fels Longitudinal Study. Int J Obes Relat Metab Disord. 1997;21(12):1167-75. doi:10.1093/ajcn/70.1.123s
5. Onis M, Onyango AW, Borghi E, Siyam A, Nishida C, Siekmann J. Development of a WHO growth reference for school-aged children and adolescents. Bull World Health Organ. 2007;85(9):660-70. https://www.who.int/publications/i/item/924154693X
6. Cole T, Bellizzi M, Flegal K, Dietz W. Establishing a standard definition for child overweight and obesity worldwide: international survey. BMJ.

2000;320(7244):1240-3. doi:10.1136/bmj.320.7244.1240

7. Jeanrenaud X, Goy JJ, Kappenberger L. Effects of dual-chamber pacing in hypertrophic obstructive cardiomyopathy. Lancet. 1992;339(8805):1318-23. doi:10.1016/0140-6736(92)91961-7
8. Bonora E. The metabolic syndrome and cardiovascular disease. Ann Med. 2006;38(1):64-80. doi:10.1080/07853890500401234
9. Malecka-Tendera E, Mazur A. Childhood obesity: a pandemic of the twenty-first century. Int J Obes. 2006;30(2):S1-3. doi:10.1038/sj.ijo.0803367
10. Ziccardi P, Nappo F, Giugliano G, Esposito K, Marfella R, Cioffi M. Reduction of inflammatory cytokine concentrations and improvement of endothelial functions in obese women after weight loss over one year. Circulation. 2002;105(7):804-9. doi:10.1161/hc0702.104279
11. Sahu BR, Kampa RK, Padhi A, Panda AK. C-reactive protein: a promising biomarker for poor prognosis in COVID-19 infection. Clin Chim Acta. 2020;509:91-4. doi:10.1016/j.cca.2020.06.013
12. Salonen EM, Vaheri A. C-reactive protein in acute viral infections. J Med Virol. 1981;8(3):161-7. doi:10.1002/jmv.1890080302
13. Chen CC, Lee IK, Liu JW, Huang SY, Wang L. Utility of C-reactive protein levels for early prediction of dengue severity in adults. BioMed Res Int. 2015;93:60-2. doi:10.1155/2015/936062
14. Bajwa EK, Khan UA, Januzzi JL, Gong MN, Thompson BT, Christiani DC. Plasma C-reactive protein levels are associated with improved outcome in ARDS. Chest. 2009;136(2):471-80. doi:10.1378/chest.08-2413
15. Seidell JC, Flegal KM. Assessing obesity: classification and epidemiology. Br Med Bull. 1997;53(2):238-52. doi:10.1093/oxfordjournals.bmb.a011611
16. Eisenstein SA, Gredysa DM, Antenor–Dorsey JA, Green L, Arbeláez AM, Koller JM. Insulin, Central Dopamine D2 Receptors, and Monetary Reward Discounting in Obesity. Plos One. 2015;11(1):1-20. doi:10.1371/journal.pone.0133621
17. García-Álvarez A, Serra-Majem L, Ribas-Barba L, Castell C, Foz M, Uauy R. Obesity and overweight trends in Catalonia, Spain (1992–2003): gender and socio-economic determinants. Public Health Nutr. 2007;10(11A):1368-78. doi:10.1017/S1368980007000973
18. World Health Organization. Global Strategy on Diet, Physical Activity and Health, 2003. Available from: http:// www.who.int/hpr/global.strategy.shtml (accessed 15 May 2021)
19. Ahmad N, Adam SI, Nawi AM, Hassan MR, Ghazi HF. Abdominal obesity indicators: Waist circumference or waist-to-hip ratio in Malaysian adults population. Int J Prev Med. 2016;7:82. doi:10.4103%2F2008-7802.183654
20. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet. 2003;362(9386):777-81. doi:10.1016/S0140-6736(03)14285-7
21. Després JP. Abdominal obesity: the most prevalent cause of the metabolic syndrome and related cardiometabolic risk. Eur Heart J Suppl. 2006;8(suppl_B):B4-12. doi:10.1093/eurheartj/sul002
22. Balkau B, Valensi P, Eschwège E, Slama G. A review of the metabolic syndrome. Diabetes Metab. 2007;33(6):405-13. doi:10.1016/j.diabet.2007.08.001
23. Lemieux-Charles L, McGuire WL. What do we know about health care team effectiveness? A review of the literature. Med Care Res Rev. 2006;63(3):263-300. doi:10.1177%2F1077558706287003
24. Delpeuch F, Dop MC. A review of young child feeding practices in Africa and the Middle East: need for improvement. WHO. 1999;1999:27-42.
25. Hurt RT, Kulisek C, Buchanan LA, McClave SA. The obesity epidemic: challenges, health initiatives, and implications for gastroenterologists. Gastroenterol Hepatol. 2010;6(12):780-92. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/pmc3033553/
26. STABLO-BOLTRI, Delphine: Prevalence of sauropods and obesity in young adults in general medicine (the SUPRA study). Gray literature in Europe. 2008;1(27):53-6. Available from: http://hdl.handle.net/10068/804713
27. Maoui A, Bouzid K. Epidemiology of Type 2 Diabetes in the Greater Maghreb. Example of Tunisia. Systematic review of the literature. Tunis Med. 2019;97(2):286-95.
28. Koçak M, Mihalopoulos N, Kubilay N. Chemical composition of the fine and coarse fraction of aerosols in the northeastern Mediterranean. Atmos

Environ. 2007;41(34):7351-68. doi:10.1016/j.atmosenv.2007.05.011
29. Davì G, Guagnano MT, Ciabattoni G, Basili S, Falco A, Marinopiccoli M, et al. Platelet activation in obese women: role of inflammation and oxidant stress. Jama. 2002;288(16):2008-14. doi:10.1001/jama.288.16.2008
30. Dray C, Knauf C, Daviaud D, Waget A, Boucher J, Buléon M. Apelin stimulates glucose utilization in normal and obese insulin-resistant mice. Cell Metabol. 2008;8(5):437-45. doi:10.1016/j.cmet.2008.10.003
31. Dixon JS, Bird HA, Sitton NG, Pickup ME, Wright V. C-reactive protein in the serial assessment of disease activity in rheumatoid arthritis. Scand J Rheumatol. 1984;13(1):39-44. doi:10.3109/03009748409102666
32. Ziegenhagen G, Drahovsky, D. Klinische: Bedeutung des c-reactive proteins. Med Klin. 1983;78:24-35. doi:10.1016/s0065-2776(08)60379-x
33. Hind CR, Pepys PM. The role of serum C-reactive protein (CRP) measurement in clinical practice. Int Med. 1984;5:112-51. doi:10.4070%2Fkcj.2012.42.3.151
34. Carr WP. Acute-phase response. Clin Rheum Dis. 1983;9(1):227-39.
35. Kolb-Bachofen V. A review on the biological properties of C-reactive protein. Immunobiology. 1991;183(1-2):133-45. doi:10.1016/s0171-2985(11)80193-240
36. Cavalli G, De Luca G, Campochiaro C, Della-Torre E, Ripa M, Canetti D. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. Lancet Rheumatol. 2020;2(6):e325-31. doi:10.1016/s2665-9913 (20)30127-2
37. Yang X, Yu Y, Xu J, Shu H, Liu H, Wu Y. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020;8(5):475-81. doi:10.1016/S2213-2600(20)30079-5
38. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054-62. doi:10.1016/S0140-6736(20)30566-3
39. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med. 2020;46(5):846-8. doi:10.1007/s00134-020-05991-x
40. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507-13. doi:10.1016/S0140-6736(20)30211-7
41. Tu WJ, Cao J, Yu L, Hu X, Liu Q. Clinic laboratory study of 25 fatal cases of COVID-19 in Wuhan. Intensive Care Med. 2020;1(1):1-4. doi:10.1016/S0140-6736 (20)30211-7
42. Ruan Q, Yang K, Wang W, Jiang L, Song J. Correction to Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med. 2020;1(1):1-4. doi:10.1016/S0140-6736(20)30211-7
43. Lin C, Ding Y, Xie B, Sun Z, Li X, Chen Z. Asymptomatic novel coronavirus pneumonia patient outside Wuhan: the value of CT images in the course of the disease. Clin Imaging. 2020;63(3):7-9. doi:10.1016/j.clinimag.2020.02.008
44. Zhang J, Yu M, Tong S, Liu LY, Tang LV. Predictive factors for disease progression in hospitalized patients with coronavirus disease 2019 in Wuhan, China. J Clin Virol: Off Publ Pan Am Soc Clin Virol. 2020;(127):104-392. doi:10.1016%2Fj.clinimag.2020.02.008
45. Ørn S, Manhenke C, Ueland T, Damås JK, Mollnes TE, Edvardsen T. C-reactive protein, infarct size, microvascular obstruction, and left-ventricular remodelling following acute myocardial infarction. Eur Heart J. 2009;30(10):1180-6.
46. Wang L. C-reactive protein levels in the early stage of COVID-19. Med Mal Infect. 2020;50(4):332-4. doi:10.1136/bmj.m1091
47. Chen T, Wu DI, Chen H, Yan W, Yang D, Chen G. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ Clin Res Ed. 2020;368:1091. doi:10.1002%2Fehf2.12266
48. Brull DJ, Serrano N, Zito F, Jones L, Montgomery HE, Rumley A. Human CRP gene polymorphism influences CRP levels: implications for the prediction and pathogenesis of coronary heart disease. Arterioscler Thromb Vasc Biol.

2003;23(11):2063-9. doi:10.1161/01.atv.0000084640.21712.9c
49. Tang Y, Huang XR, Lv J, Chung AC, Zhang Y, Chen JZ. C-reactive protein promotes acute kidney injury by impairing G1/S-dependent tubular epithelium cell regeneration. Clin Sci. 2014;126(9):645-59. doi:10.1042/cs20130471
50. Simonnet A, Chetboun M, Poissy J, Raverdy V, Noulette J, Duhamel A. High prevalence of obesity in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) requiring invasive mechanical ventilation. Obesity. 2020;28(7):1195-9. doi:10.1002/oby.22831
51. Liang W, Guan W, Chen R, Wang W, Li J, Xu K. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol. 2020;21(3):335-7.
52. Polamarasetti P, Martirosyan D. Nutrition planning during the COVID-19 pandemic for aging immunity. Bioact Compd Health Dis. 2020;3(7):109-23. doi:10.31989/bchd.v3i7.733
53. Galanakis CM. The food systems in the era of the coronavirus (COVID-19) pandemic crisis. Foods. 2020;9(4):523.
54. Polamarasetti P, Martirosyan D. Dietary deficiencies exacerbate disparity in COVID-19 and nutrition recommendations for vulnerable populations. Bioact Compd Health Dis. 2020;3(11):204-13. doi:10.31989/bchd.v3i11.759
55. Functional Food Center, Martirosyan D. Functional Foods and Viral Diseases. Food Sci Publisher. 2020;(8):229-52. doi:10.31989/ffhd.v10i11.753
56. Pinti M, Appay V, Campisi J, Frasca D, Fülöp T, Sauce D. Aging of the immune system: focus on inflammation and vaccination. Eur J Immunol. 2016;46(10):2286-301.
57. Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. Jama. 2020;323(16):1574-81. doi:10.1001/jama.2020.5394
58. He W, Chen L, Chen L, Yuan G, Fang Y, Chen W. COVID-19 in persons with haematological cancers. Leukemia. 2020;1(1):1-9. doi:10.1038/s41375-020-0836-7
59. Gur J, Mawuntu M, Martirosyan D. FFC's advancement of functional food definition. Funct Foods Health Dis. 2018;8(7):385-97. doi:10.31989/ffhd.v8i7.531
60. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. Jama. 2020;323(20):2052-9. doi:10.1001/jama.2020.6775
61. Liu XH, Lu SH, Chen J, Xia L, Yang ZG, Charles S. Clinical characteristics of foreign-imported COVID-19 cases in Shanghai, China. Emerg Microbes Infect. 2020;9(1):1230-2.
62. Herold T, Jurinovic V, Arnreich C, Lipworth BJ, Hellmuth JC, von Bergwelt-Baildon M. Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19. J Allergy Clin Immunol. 2020;146(1):128-36. doi:10.1016%2Fj.jaci.2020.05.008
63. Sumantri AF, Bashari MH, Tadjoedin H, Atik N. Risk of coronavirus disease 2019 (COVID-19) infection on leukemia patients: basic science to clinical aspect. J Adv Pharm Educ Res. 2022;12(1):38-45. doi:10.51847/qqIktBAHB7
64. Zavalishina SY, Bakulina ED, Eremin MV, Kumantsova ES, Dorontsev AV, Petina ES. Functional changes in the human body in the model of acute respiratory infection. J Biochem Technol. 2021;12(1):22-6. doi:10.51847/F8mofsugnZ
65. Alahmadi YM, Al Thagfan SS. A nationwide study on the knowledge, awareness, and practices towards COVID-19 in Saudi Arabia. Trop J Pharm Res. 2021;20(1):161-7. doi:10.4314/tjpr.v20i1.23
66. Cubeddu LX, de la Rosa D, Ameruoso M. Antiviral and anti-inflammatory drugs to combat COVID-19: Effects on cardiac ion channels and risk of ventricular arrhythmias. BioImpacts: BI. 2022;12(1):9-20. doi:10.34172/bi.2021.23630
67. Yong J, Tian J, Zhao X, Yang X, Zhang M, Zhou Y. Revascularization or medical therapy for stable coronary artery disease patients with different degrees of ischemia: a systematic review and meta-analysis of the role of myocardial perfusion. Ther Adv Chronic Dis. 2022;13:1-12. doi:10.1177/20406223211056713