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Preliminary study: nutrigenomics analysis results of COVID-19 survivors

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Abstract

Background Numerous attempts have been made at both prevention and treatment of COVID-19. Specific genotypes carry a risk of causing clinical symptoms that can be beneficial or detrimental. We performed nutrigenomics testing on COVID-19 survivors who were on ventilators during their treatment and mild COVID-19 survivors who did not require ventilators to determine the risk of genetic variation through nutrigenomic testing regarding COVID-19 incidence. DNA was isolated from saliva and genotyped for genetic markers using a commercially available nutrigenomics test. We compared genotype frequencies between those with severe symptoms (cases) and those with mild symptoms (controls).

Result Sequencing results showed that the distribution from pattern of the Sankey diagram included an ultra risk category in the control group, but not in the case group. None of the subjects in the case group were in the ultra risk category for resilience. A descriptive pattern of risk-level distribution was observed in both the control and case groups. One subject in the ultra risk category was in the control group, indicating a lower risk factor for severe COVID-19.

Conclusion From this study, a uniqueness begins to emerge, revealing the discovery of ultra-category patterns in the endurance of the control group. The vitamin E risk deficiency is significantly higher in the severe COVID-19 group compared to the mild group, categorized as "typical."

Keywords Nutrigenomics, COVID-19, Endurance genomic, Risk of genetic variation, Vitamin E

Introduction

The SARS-CoV-2 virus causes severe acute respiratory distress syndrome and has resulted in numerous deaths around the world. Several explanations for this phenomenon have emerged, some of which were related to specific age groups and the presence of certain comorbid diseases or viral strains. As a result, several preventive measures have been implemented in communities to avoid further negative consequences. However, these efforts have not yielded convincing results. According to previous research, social factors significantly influence the COVID-19 transmission route, which involves patterns of daily habits [1]. Other side effects of COVID-19 include psychological depression and distress. Depression causes people to ignore their responsibilities to maintain cleanliness or engage in other preventive measures [2].

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Recent advances in molecular biology, combined with the wealth of data generated by the Human Genome Project, have resulted in the emergence of nutrigenomics, a new discipline within the field of nutritional research. The new era of molecular nutrition, known as nutrigenomics, unlocks the mystery of gene-nutrition interactions [3]. Nutrigenomics is the study of the effects of nutrition or dietary elements on the transcriptome of cells and tissues. It is a broad term for the study of how nutrition or dietary elements affect the structure, integrity, and function of the genome. It is a branch of genomics science that is influenced by powerful and rapidly developing genomic technology, and it has the potential to become one of the strategies used in the prevention and treatment of various diseases, including COVID-19.

The COVID-19 pandemic is one of the most pressing issues confronting the nutrition research community. We conducted research using a nutrigenomics approach on COVID-19 cases, and each piece of data we obtained will provide new insights into the mechanisms of nutrient-gene interactions. Based on previous research demonstrating that food components not only provide fuel to the body but also participate in modulating gene expression, nutrigenomics can be used as a reference for nutrition research [4]. This chapter will discuss the feasibility of a nutrigenomics approach in COVID-19 research, and the data from each of these studies will provide new insights into the mechanism of nutrient-gene interaction to identify risk factors for COVID-19.

The nutrigenomics testing in this research consists of nutrient metabolism, food intolerance and sensitivities, cardiometabolic health, weight management and body composition, eating habits, exercise physiology, fitness, and injury risk. Several genes have effects other than the effect on the nutrition's stimulation, for example, the response to pain, it turns out that pain is related to the COMT rs 4680 which is a gene related to vitamin E. Vitamin E, an essential antioxidant, plays a crucial role in the immune system by protecting cells from oxidative stress and modulating gene expression related to immune responses. Previous studies have suggested that vitamin E risk deficiency can lead to severe health issues, including increased susceptibility to infections.

The GC gene encodes the vitamin D binding protein, which binds vitamin D and then transports it to various tissues. Since vitamin D is needed for the absorption of calcium, this binding protein can impact calcium levels in the body and, therefore, bone fracture risk. Research shows that two variations in the GC gene are associated with an increased risk of bone fractures when calcium intake is low.

In 1959, Hirschfield initially named vitamin D binding protein as the 'group-specific component' (Gc) following its isolation from the α2-globulin fraction of plasma [5]. Following the discovery of its ability to bind and transport vitamin D analogues, the protein was named DBP. Upon uncovering its macrophage-stimulating properties, DBP was subsequently renamed as the macrophage-activating factor (GcMAF/DBP-MAF). The name of VDBP has undergone several changes due to the discovery of various biological functions associated with it. VDBP binds to both fatty acids and actin monomers, and it also possesses immune functions that are separate from its role in transporting vitamin D, this includes the binding to leukocyte membrane proteoglycans and the activation of the complement C5 system. VDBP is renowned for its single nucleotide polymorphisms (SNPs), with the most prevalent ones being rs7041 and rs4588, situated within exon 11 of the VDBP gene. SNPs are the predominant genetic variations found in genomes. SNPs have the potential to influence various aspects of protein behaviour, including stability, folding, flexibility, and aggregation. They can also impact functional sites, reaction kinetics, and sensitivity to environmental factors such as pH, salt concentration, and temperature. Additionally, SNPs may affect protein expression, subcellular localization, and interactions with small molecules, other proteins, DNA, and membranes [6]. Numerous studies have demonstrated connections between single nucleotide polymorphisms (SNPs) and the concentration of proteins, specifically about the transport of substances via VDBP in this particular case [7]. Al-Daghri et al. studied vitamin D supplementation effects based on vitamin D binding protein polymorphisms. They found higher 25[OH]D levels in individuals with major homozygous rs7041 genotype. After supplementation, those with major genotypes in rs4588 and rs7041 showed higher levels 25[OH]D compared to other genotypes [8, 9].

In this study, we isolated DNA from saliva, a non-invasive and efficient method for genetic testing, to identify genetic markers associated with severe and mild COVID-19 symptoms. Saliva collection is less invasive than blood collection and can improve study participation rates. Therefore, this research aimed to determine the risk of genetic variation in COVID-19 survivors through nutrigenomics testing.

Methods

This research received ethics approval from Dr Soetomo General Academic Hospital under ethics protocol number 0458/KEPK/VIII/2022. We conducted a case–control study with 10 subjects in each group. We did not use a large number of samples due to funding limitations provided. Based on several sources we obtained, sample size calculations can be done using the rule of thumb method, in which we took 10% of the total population of

COVID-19 cases in the ICU of Dr. Soetomo General Academic Hospital who used ventilators during treatment and survived [10, 11]. The total population of COVID-19 cases with ventilators that survived at Dr. Soetomo General Academic Hospital was 75 cases. Another method for calculating sample size is the formula:

$$n > \frac{(Z\alpha + Z\beta)^2 \Sigma^2}{d^2}$$

The result was 7 subjects each group [12]. Calculation of the sample size using the online platform select-statistics.co.uk also shows that the minimum sample used is 19 samples for the entire group. So, we decided that the sample size for each group was 10 subjects.

The study population in this case control study comprises 20 cases which were classified into two groups: the case group were 17–70 years old, confirmed with COVID-19, during the treatment a ventilator was installed, the patient was declared to have survived after being extubated and tested negative one time from the SARS-COV-2 PCR examination; the control group were age 17–70 years, not hospitalized, not using a ventilator, and mild symptoms for upper respiratory infection. In general, patients were declared severe COVID-19 by intensivists working in the ICU according to the Ministry of Health's criteria [13], likewise in the control group based on criteria from the Ministry of Health. The exclusion criterion for the two groups was if the patient refused to be examined.

The researchers began by collecting medical record data from post-COVID-19 patients who had used a ventilator in the ICU and survived. After obtaining the patient's address, cellphone number, gender, and age, we collected them into one group of cases (A) and used randomization to select ten subjects. The control group (B) consisted of COVID-19 survivors who had mild symptoms at the time of COVID-19 diagnosis. Only male patients were included in this study, and their BMI and ages were recorded. The saliva of each subject was collected for DNA isolation and genotyping after the research was explained to them and they signed the consent form.

The basis for selecting the gene along with the rs number in Table 1 is the result of a literature study which proves that certain genes contribute to disease emergence and response to nutrition and drugs.

In our study, nutrigenomics testing was conducted using the Oragene-One ON 600 DNA collection kit (A product by Kalbe Industries, manufactured in Canada in collaboration with Nutrigenme). This comprehensive test analyses genetic markers across several categories relevant to nutrition and health outcomes, particularly in the context of COVID-19 susceptibility and severity. The genetic markers were selected based on their known associations with nutrient metabolism, food intolerances, cardiometabolic health, weight management, body composition, eating habits, exercise physiology, fitness, and injury risk.

The test specifically included the analysis of genes and SNPs (single nucleotide polymorphisms) associated with the metabolism of crucial vitamins and minerals (e.g., Vitamin A, B12, C, D, and E), which have been implicated in immune function and the body's response to infections. For instance, the vitamin E metabolism gene COMT rs4680 was analysed due to its relevance in antioxidant defence mechanisms critical for viral infection resilience.

Furthermore, the test covered markers related to food intolerances (e.g., lactose intolerance linked to MCM6 rs4988235 and gluten sensitivity associated with several HLA genes), as well as genes influencing cardiometabolic health (e.g., CYP1A2 rs2472300 for caffeine metabolism and its impact on cardiovascular health). For each analysed SNP, we evaluated the allele frequencies and their distribution across our study population, comparing COVID-19 survivors with severe symptoms requiring ventilation to those with mild symptoms.

A risk analysis was conducted for certain genotypes using the above DNA data. The risk categories are classified into seven categories: typical (average population health) is normal or for control; elevated means that it increases towards a negative risk (for example, the emergence of a disease or tissue damage); medium means that the risk is slightly above typical but below elevated; low means it decreases in a negative direction (the opposite is elevated, for example, the ability of an enzyme to physiological activity has decreased); diminished means it decreases in a positive direction (the opposite is enhanced, for example, the amount of energy burned during an important process/resting metabolic rate is lower than the general population); enhanced means it increases towards a positive risk (for example, exercising can significantly increase HDL levels in the blood); ultra means that it increases above enhanced (genetically already has higher muscle endurance than the general population); high means slightly below ultra (requires regular exercise efforts to gain muscle endurance).

The classification of research subjects to be included in one of the above categories is based on the nutrigenomic examination database owned by the company NutriGENME (supported by Nutrigenomix). The reference to these words is based on the research literature on their respective characteristics and SNPs. This literature study provides data on people with certain SNP variations that cause interference with certain gene traits so that in simplification the vocabulary is made unique (for

Table 1 Gene and the rs number which referred to the nutrition component examination

Groups	Component	Gene, rs Number	References
Nutrient metabolism	Vitamin A	BCMO1, rs11645428	[14]
	Vitamin B_{12}	FUT2, rs601338	[15–18]
	Vitamin C	GSTT1, rs2266633	[19]
	Vitamin D	CYP2R1, rs10741657	[20–23]
		GC, rs2282679	[24]
	Vitamin E	COMT, rs4680	[25–27]
	Folate	MTHFR, rs1801133	[28–31]
	Choline	MTHFD1, rs2236225	[32, 33]
		PEMT, rs12325817	[34]
	Calcium	GC, rs7041	[20, 24, 35]
		GC, rs4588	[20, 24]
	Iron Overload	SLC17A1, rs17342717	[36]
		HFE, rs1800562	[37]
		HFE, rs1799945	[38]
	Low Iron Status	TMPRSS6, rs4820268	[36, 39]
		TFR2, rs7385804	[36, 40]
		TF, rs3811647	[40]
Food intolerances and sensitivities	Lactose	MCM6, rs4988235	[41]
	Gluten	HLA, rs2395182	[42]
		HLA, rs7775228	[43]
		HLA, rs2187668	[44]
		HLA, rs4639334	[45]
		HLA, rs7454108	[46]
		HLA, rs4713586	[46]
	Caffeine	ADORA2A, rs5751876	[47]
Cardiometabolic health	Caffeine	CYP1A2, rs2472300	[48, 49]
	Glycaemic Index	TCF7L2, rs12255372	[50–56]
	Sodium	ACE, rs4343	[33, 57, 58]
	Omega-6 and Omega-3 Fat	FADS1, rs174547	[59–61]
	Physical activity	LIPC, rs1800588	[62, 63]
Weight management and body composition	Physical activity	FTO, rs9939609	[64, 65]
		ADRB2, rs1042713	[66]
	Energy balance	UCP1, rs1800592	[67]
	Protein	FTO, rs9939609	[64, 65]
	Total Fat	TCF7L2, rs7903146	[50, 51, 56]
	Saturated fat	APOA2,rs5082	[68]
	Saturated and unsaturated fat	FTO, rs9939609	[64, 65]
	Monounsaturated FAT	PPARy2, rs1801282	[69]
Eating habits	Fat taste perception	CD36, rs1761667	[70–72]
	Sugar preference	GLUT2, rs5400	[73]
	Eating between meals	MC4R, rs17782313	[74]

Table 1 (continued)

Groups	Component	Gene, rs Number	References
Exercise physiology, fitness and injury risk	Motivation to exercise	BDNF, rs6265	[75]
	Exercise Behaviour	CYP19A1, rs2470158	[76]
		LEPR, rs12405556	[77]
	Power and strength	ACTN3, rs1815739	[78–81]
		NFIA-AS2, rs1572312	[82]
		ADRB3, rs4994	[83]
		NRF2, rs12594956	[84, 85]
		GSTP1,rs1695	[86]
		PGC1a, rs8192678	[87]
	Muscle damage	ACTN3, rs1815739	[78, 79, 88–90]
	Pain	COMT,rs4680	[27, 91]
	Bone mass	WNT16, rs2707466	[92, 93]
	Achilles tendon injury	COL5A1, rs12722	[94–96]

wild type), high, medium, low, reduced, enhanced, ultra, and high (variants other than wild type) [20]. In addition, recommendations are based on evidence-based scientific research that has been reviewed by experts in the fields that we have mentioned above (basic explanation of gene selection in Table 1).

Data analysis

The nutrigenomics analysis of each sample yielded data in the form of gene and risk variants for each subject. After we analysed all the gene components for the magnitude of the risk of COVID-19's severity, we also performed a Chi-square (X^2) analysis used to determine the genotype between the two groups. The R statistic was used to conduct the statistical analysis. Statistical analysis was performed using open-source R statistics 4.0.3 version software.

Results

We analysed 20 subjects (10 cases and 10 controls), and we depicted them in bar plots in Fig. 1. The genotyping results revealed significant differences in the vitamin E risk deficiency between the severe and mild COVID-19 groups. Specifically, the severe COVID-19 group had a higher prevalence of the typical risk category for vitamin E risk deficiency compared to the mild group. The distribution of other genetic markers, such as those related to calcium and low iron status, was also analysed and presented in bar plots and a Sankey diagram.

Based on the results above, there was no difference between cases and controls in the elevated and Typical risk categories for specific genes. However, in terms of Vitamin C case groups appeared more in the elevated risk category than group control (all subjects in the group case in the elevated risk category are the type of gene deletion). This is the type of deletion that prevents optimal vitamin C absorption.

This was also the case for the Achilles tendon injury risk, with group A (cases) appearing more frequently in the elevated risk category than group B (control); the same was true for the Calcium and Eating between Meals risk categories. It is also interesting that there is one patient in group B (control) in the low risk category on calcium and low iron status.

The detailed description of the above bar plot is as follows:

Vitamin A: Only one subject in the control group and one subject in the case group were in the typical risk category and had the AG genotype. Except for these two subjects, all of them have an elevated risk category, which means they have a reduced catalytic function of the enzyme produced by the BCMO 1 gene with the genetic variation rs 11,645,428 with all GG genotype patterns.

Vitamin B12 (FUT2, rs601338): All subjects in the control and case groups had an elevated risk category with all GG genotype patterns. Only one subject in the case group had the GA genotype.

Vitamin C (GSTT1, rs2266633): There were three subjects in the case group with genotype deletion in elevated risk category and six subjects in typical risk category. In the control group, there was only one

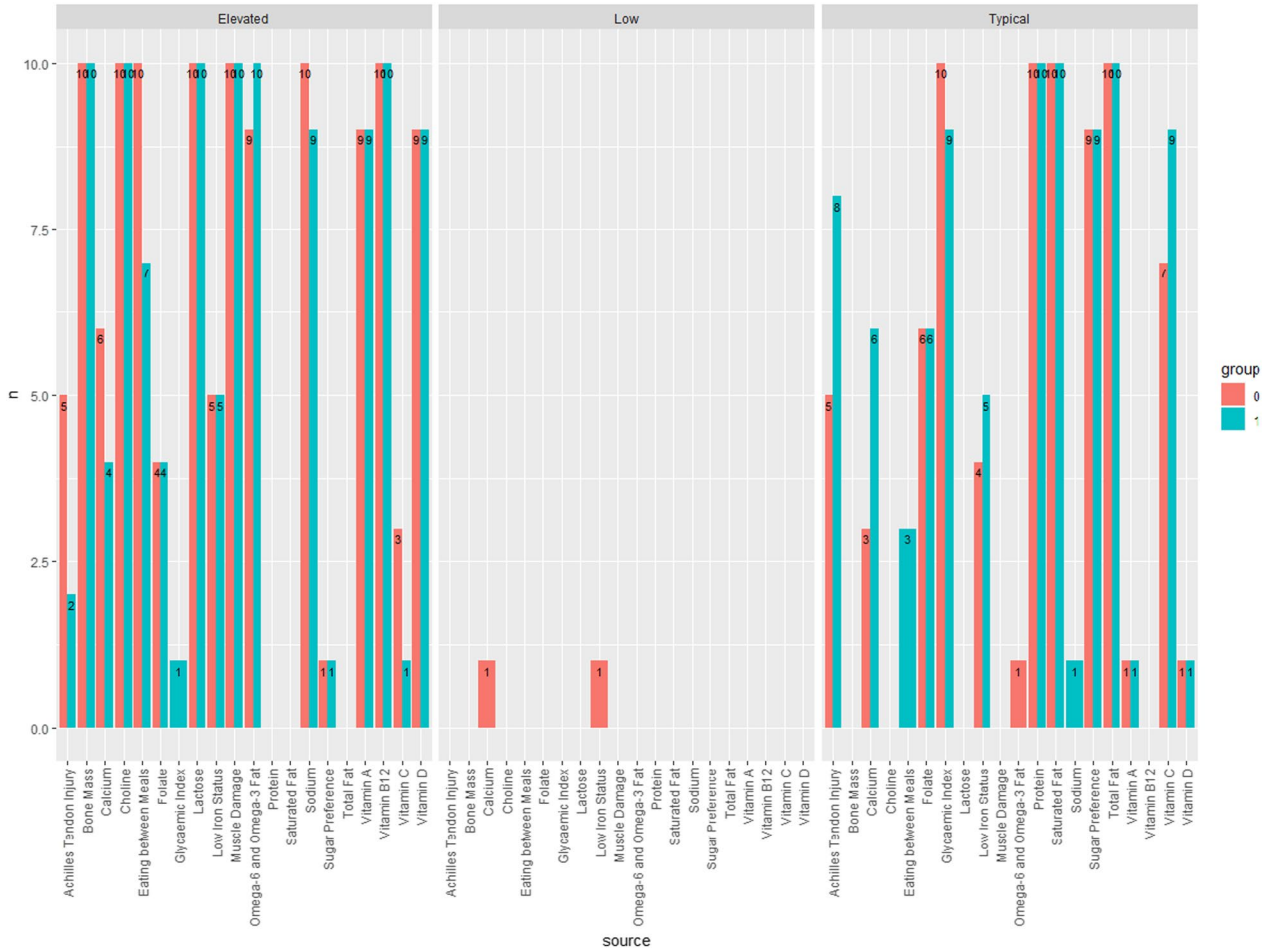

Fig. 1 A descriptive visualization of nutrigenomics risk categories for the case and control groups in bar plot format. *Note* The red chart represents the case groups, while the blue chart represents the control groups

subject with an elevated risk category of deletion and nine subjects in typical risk category.

Vitamin D (CYP2R1, rs10741657; GC, rs2282679): We chose two genes according to the previous research that facilitate vitamin D screening, namely CYP2R1 and GC [22]. We found no difference in genotype risk between the control and case groups. In the case group, one subject was in typical risk category, and nine subjects were in elevated risk category. The same thing happened to the control group.

Vitamin E (COMT, rs4680): In the case group, three subjects were in elevated risk category (GG genotype), and seven subjects were in typical risk category. Meanwhile, all subjects in the control group had an elevated risk category in the GG genotype.

Folate (MTHFR, rs1801133): In the case group, four subjects were in elevated risk category (CT genotype), whereas the remaining six subjects were in typical risk category (CC genotype). Four subjects from the control group also were in elevated risk category (three subjects with the CT genotype, and one subject with the TT genotype). The limitation of this study is that we did not collect data on comorbidities in both the case and control groups. Based on the existing literature, the MTHFR gene, rs1801133 with CC, CT, and TT genotypes contributes to many diseases such as diabetes mellitus, cardiovascular diseases, and even COVID-19 [29, 30, 97, 98]. However, the results of our study did not reveal any TT genotype in the case group, whereas in the control group, the TT genotype was found. This may be due to comorbidities in the control group subjects, for which we did not collect data.

Choline (MTHFD1, rs2236225 and PEMT, rs12325817): There was no distinction between the two groups. Elevated risk category was recorded for both the case and control groups. The genotypes that played a substantial role in the case group were CG in five subjects, CC in four subjects, and GG in one subject. In the

control group, the genotypes that played a substantial role were CC in six subjects, and CG in four subjects.

Calcium (GC, rs7041; GC, rs4588): In the case group, there was one subject in low risk category and six subjects in elevated risk category. Meanwhile, in the control group, only four subjects were in elevated risk category (CC genotype), with the remainder being in typical risk category (five subjects with the CC genotype, and one subject with the CA genotype).

Iron overload (SLC17A1, rs17342717; HFE, rs1800562; HFE, rs1799945): There was no discernible difference between the two groups. All subjects in both groups had a low risk category. The CC genotype was present in both groups.

Low iron status (TMPRSS6, rs4820268; TFR2, rs7385804; TF, rs3811647): In the case group, there was one subject in low risk category, five subjects in elevated risk category, and two subjects in typical risk category. In the control group, five subjects were in elevated risk category and the remainder were in typical risk category.

Lactose (MCM6, rs4988235): All subjects in both groups had an increased risk of developing lactose intolerance, with an elevated risk category. The genotype that played a role in both groups was CC.

Gluten (HLA, rs2395182; HLA, rs7775228; HLA, rs2187668; HLA, rs4639334; HLA, rs7454108; HLA, rs4713586): In the case group, there were five subjects in low risk category, one subject in high risk category, and four subjects in medium risk category. In the control group, three subjects were in low risk category, one subject was in high risk category, and the remaining six were in medium risk category.

Caffeine (ADORA2A, rs5751876): In the case group, there were two subjects in elevated risk category (TT genotype), and the other eight were in typical risk category (CT genotype). In the control group, four subjects were in elevated risk category (TT genotype), and the remaining six were in typical risk category (five subjects with the CT genotype, and one subject with the CC genotype).

Caffeine (CYP1A2, rs2472300): In the case group, five subjects had an elevated risk category of being slow caffeine metabolizers (GA genotype), whereas the other five had the GG genotype (fast caffeine metabolizers) with a typical risk category. In the control group, only two subjects were slow metabolizers and were in elevated risk category. The remaining subjects had the GG (fast metabolizer) genotype and a typical risk category.

Glycaemic index (TCF7L2, rs12255372): All subjects in the case group had the GG genotype with typical risk category. Meanwhile, one subject in the control group had the GT genotype and was in elevated risk category, whereas the other nine subjects had the GG genotype and a typical risk category.

Sodium (ACE, rs4343): All subjects in the case group were in elevated risk category, whereas one subject in the control group was in typical risk category, and the rest were included in elevated risk category. Five subjects in the case group had the GA genotype, and the other five had the AA genotype. Five subjects in the control group had the GA genotype, four had the AA genotype, and one had the GG genotype.

Omega-6 and Omega-3 Fat (FADS1, rs174547): One subject in the case group had the TT genotype and a typical risk category, whereas the remaining nine had the CC and CT genotypes and were in elevated risk category. In the control group, all subjects were elevated risk category (CC and CT genotypes).

Physical activity (LIPC, rs1800588): Physical activity influences the LIPC gene (HDL-C is an abbreviation for high-density lipoprotein C). In the case group, seven subjects were in elevated risk category (four subjects with the CT genotype and three subjects with the TT genotype), and the other three had the CC genotype and were in typical risk category. In the control group, six subjects were in elevated risk category (five subjects with the CT genotype and one subject with the CC genotype), and the remaining four subjects were in typical risk category (CC genotype).

Physical activity (FTO, rs9939609; ADRB2, rs1042713): In the case group, two subjects were in enhanced risk category, and the remaining eight subjects were in typical risk category. Meanwhile, one subject in the control group was in enhanced risk category, and the remaining nine subjects were in typical risk category.

Energy balance (UCP1, rs1800592): In the case group, nine subjects were in diminished risk category (GA genotype), and one subject was in typical risk category (AA genotype). In the control group, eight subjects were in diminished risk category (GA genotype), and the other two were in typical risk category (AA genotype).

Protein (FTO, rs9939609): All subjects in both groups appeared to be in typical risk category. In the case group, one subject had the AA genotype, three subjects had the TT genotype, and six subjects had the TA genotype. In the control group, four subjects had the TT genotype, five subjects had the TA genotype, and one subject had the AA genotype.

Total Fat (TCF7L2, rs7903146): There was no difference between the two groups; all subjects were in typical risk category. In both the case and control groups, nine subjects had the CC genotype, and one subject had the TC genotype.

Saturated Fat (APOA2, rs5082): There was no difference between the two groups, with all subjects in typical

risk category. In the case group, nine subjects had the TT genotype and one subject had the TC genotype. The control group had nine subjects who had the TT genotype, and one subject had the TC genotype.

Saturated and unsaturated fat (FTO, rs9939609): In the case group, six subjects had the TA genotype and one subject had the AA genotype; three subjects had the TT genotype and were in typical risk category. In the control group, there were six subjects with enhanced risk categories, six subjects had 5 TA genotypes and one AA subject. Meanwhile, four subjects in the control group were in typical risk category and had the TT genotype.

Mono-unsaturated Fat (PPARy2, rs1801282): In the case group, there was one subject in enhanced risk category (GC genotype), and the other nine were in typical risk category 0 (genotype CC). In the control group, three subjects were in enhanced risk category (GC genotype), and seven subjects were in typical risk category (CC genotype).

Fat Taste Perception (CD36, rs1761667): There was no difference between the two groups; all subjects were in enhanced risk category. In the case group, six subjects had the GG genotype and four subjects had the GA genotype. In the control group, six subjects had the GA genotype and four subjects had the GG genotype.

Sugar Preference (GLUT2, rs5400): In both the case and control groups, one subject was in elevated risk category (CT genotype). All subjects had the CC genotype.

Eating between Meals (MC4R, rs17782313): One subject in the case group had genotype CC and was in elevated risk category, whereas the other nine had genotype TT and were in elevated risk category. There were genotype variations in the control group; seven subjects had the TT genotype and three subjects had CT genotype.

Motivation to Exercise (BDNF, rs6265): In the case group, eight subjects had the AG genotype, one subject had the AA genotype, and one subject had the GG genotype. In the control group, six subjects had the AG genotype, two subjects had the GG genotype, and two subjects had the AA genotype.

Exercise Behaviour (CYP19A1, rs2470158; LEPR, rs12405556): Both groups were in typical risk category.

Power and Strength (ACTN3, rs1815739): Two subjects in the case group were in elevated risk category (CC genotype), six subjects were in enhanced risk category (TC genotype), and two subjects were in typical risk category (TT genotype). Eight subjects in the control group had the TC genotype and were in enhanced risk category, and the other two had the CC genotype were in elevated risk category.

Endurance (NFIA-AS2, rs1572312; ADRB3, rs4994; NRF2, rs12594956; GSTP1, rs1695; PGC1a, rs8192678): In the case group, there were three subjects in enhanced risk category, and seven subjects in typical risk category. In the control group, one subject was in ultra risk category, one subject was in enhanced risk category, and the remaining eight were in typical risk category.

Muscle Damage (ACTN3, rs1815739): All case and control groups were in elevated risk category. In the case group, six subjects had the TC genotype, two subjects had the TT genotype, and two subjects had the CC genotype. In the control group, eight subjects had the TC genotype, and two subjects had the CC genotype.

Pain (COMT, rs4680): All subjects in the control group were in enhanced risk category (GG genotype). Two subjects in the case group were in typical risk category (AA genotype), eight subjects were in enhanced risk category, with four subjects having the GG genotype and four subjects having the GA genotype.

Bone Mass (WNT16, rs2707466): All subjects in both the case and control groups were in elevated risk category. In the case group, five subjects had the TC genotype, and five subjects had the CC genotype. In the control group, six subjects had the CC genotype, four subjects had the TC genotype.

Achilles Tendon Injury (COL5A1, rs12722): In the case group, five subjects were in elevated risk category (three subjects had the CT genotype; two subjects had the TT genotype), and five subjects were in typical risk category and had the CC genotype. In the control group, only two subjects were in elevated risk category (CT genotype), and eight subjects were in typical risk category (six subjects had the CC genotype, one subject had the CT genotype, and one subject had the CC genotype).

The Sankey diagram (Fig. 2) is a vital tool in our study for illustrating the flow of genetic variations across different risk levels among COVID-19 survivors. It visually represents which genetic markers are associated with higher or lower risks of severe symptoms. The thickness of the lines in the diagram indicates how common specific genetic risk patterns are in our study groups, making it easier to spot key differences between those with severe and mild cases.

The following is the pattern of risk category distribution for each genotype between the case and control groups (groups A and B, respectively). This relationship pattern is described by following the paths from the left side of the chart (genotypes) to the other side (risk categories). Pay attention to connecting bands, the wider the connecting bands, the greater the chance that a genotype will be classified in a certain risk category. Both groups had comparable results. The Sankey diagram indicated that the highest number of risk genotypes for components in the "Typical" category in the control group are Exercise Behaviour, Protein, Saturated Fat, Total Fat, and Glycaemic Index, respectively. Then the five most

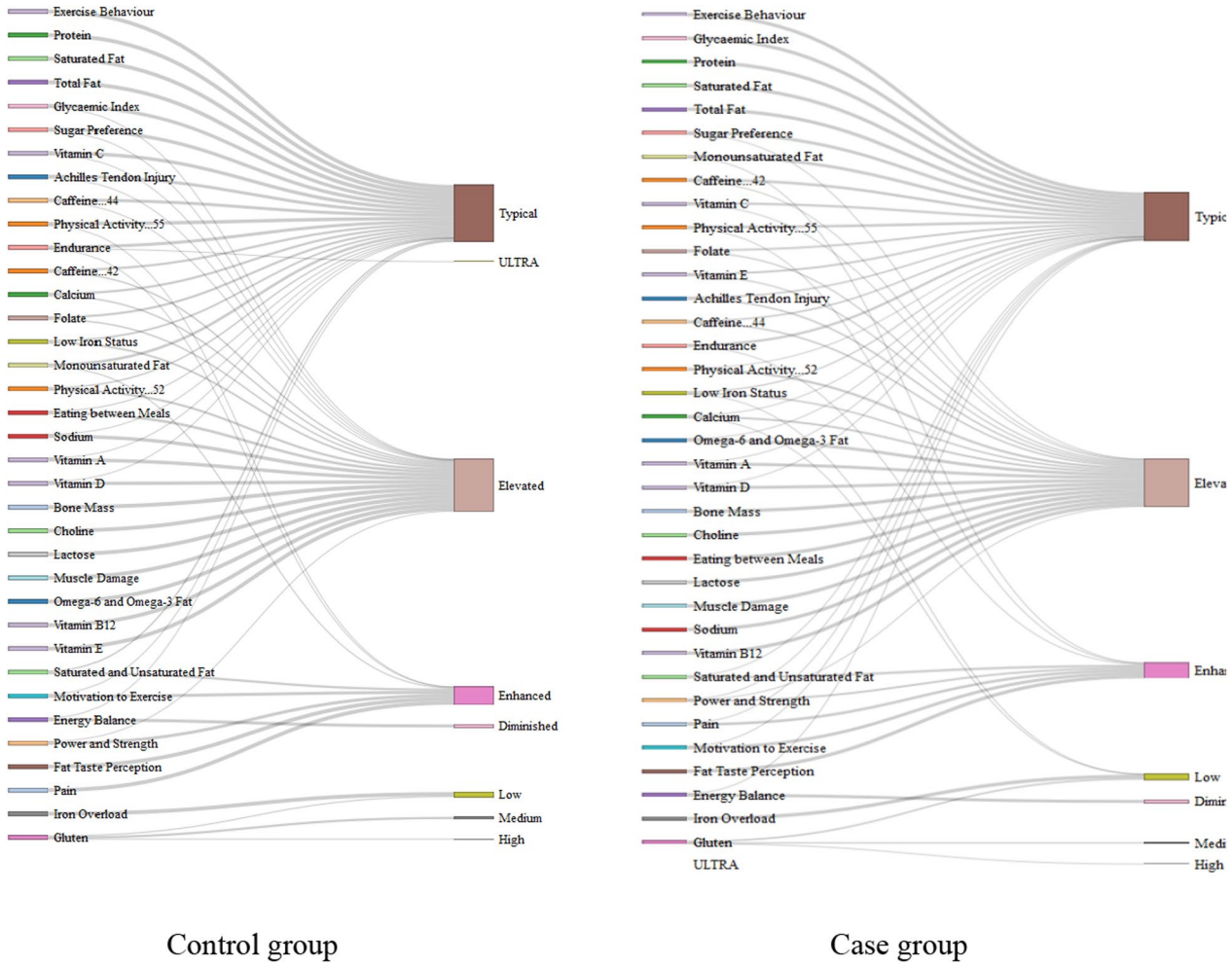

Fig. 2 Distribution pattern with Sankey diagram. *Note* the line thickness of the Sankey diagram shows the most dominant distribution

genotypes at risk for components in the risk category typical in the case group were Exercise Behaviour, Glycaemic Index, Protein, Saturated Fat, and Total Fat. Even though, at first glance, the patterns of both groups do not show many differences, we have found several interesting points here. In the control group, the Glycaemic Index is distributed in the Typical and Elevated categories, whereas in the case group, the Glycaemic Index is only found in the Typical category.

Additionally, in the control group, Endurance is distributed across the Typical, Enhanced, and Ultra categories, while in the case group, Endurance is only distributed in the Typical and Enhanced categories. It was also found that in the control group, Calcium, Low Iron Status, Eating Between Meals, and Sodium are distributed in the Typical and Elevated categories, whereas in the case group, Calcium and Low Iron Status are distributed in the Typical, Elevated, and Enhanced categories, but Eating Between Meals and Sodium are only found in the Elevated category.

Furthermore, in the control group, Omega-6 and Omega-3 Fat and Vitamin E are distributed only in the Elevated category, whereas in the case group, they are distributed in the Typical and Elevated categories. Lastly, in the control group, Pain is only in the Enhanced category, while in the case group, it is distributed in the Typical and Enhanced categories. It could be a finding or indication that the mentioned genotypes become distinguishing factors between the behaviour of the control and case groups for COVID-19.

From this Sankey diagram, there is an order of risk categories from two study groups. In both the control and case groups, there is no difference in exercise behaviour risk between mild and severe COVID-19. However, in the case group, it can generally be said (typical risk category) that the Glycaemic Index is a decisive factor in becoming

severe COVID-19. Unlike the control group, typically, there are not many issues with the Glycaemic Index.

Furthermore, in the risk category Elevated, the five most genotypes at risk of components in the control group are Vitamin E, Vitamin B12, Omega-6 and Omega-3 Fat, Muscle Damage, and Lactose. The five most genotypes at risk for components in group A (cases) were Vitamin B12, Sodium, Muscle Damage, Lactose, and Eating between meals. Similarly, in the risk category Enhanced, the five most genotypes at risk of components in the control group are Pain, Fat Taste Perception, Power and Strength, Motivation to Exercise, and Saturated and Unsaturated Fat. Then the five most genotypes at risk for components in the case group were Fat Taste Perception, Motivation to Exercise, Pain, Power and Strength, and Saturated and Unsaturated Fat. Unsaturated fat intake is associated with increased mortality from COVID-19. Unsaturated fatty acids cause injury, and organ failure resembling COVID-19. Early albumin and calcium can bind unsaturated fatty acids, and reduce injury [99].

The most noticeable difference between the two groups was that the Endurance phenotype did not include Ultra risk category in the case group and that it was more frequent in risk category Typical in the case group than in the control group. Furthermore, when compared to the case group, the Pain and Fat Taste Perception phenotypes in the control group were the most prominent in risk category Enhanced.

Data analysis

The analysis was conducted to determine genotype differences among patients who successfully recovered from Corona Virus Disease 2019 (COVID-19) infection. In this study, patients were categorized into two groups. The first group consist of patients with severe degrees of infection and require ventilators and the group of patients with moderate and mild degrees of infection. In each group, the number of subjects observed was 10 individuals. The data analysis used to determine the genotype between the two groups was Chi-Square analysis. In addition, the study also aimed to determine the difference in body mass index (BMI) and age between the two groups of patients. The analysis used to achieve the above objectives is an independent statistical analysis of the *T* test. The level of accuracy used in this study was 95% ($\alpha = 0.05$). The differences in genotype, body mass index (BMI), and age between the two groups were considered significant if the calculated *p* value was smaller than the α ($p < \alpha$ value). The tabulation of the results of data analysis is presented in full in Table 2.

Based on Table 2, it is known that the average age of patients in the group of COVID-19 patients with severe infection and requiring ventilators is older than the group

Table 2 Genotype, BMI, and age analysis

Variable	COVID-19 patients		*p*
	Severe infection with ventilator	Moderate & mild Infection	
BMI			
Mean	25.40	28.32	0.15
Standard deviation	10.07	8.25	
Age			
Mean	50.40	42.70	0.08
Standard deviation	2.55	5.49	
Vitamin A			
Typical	1	1	1.00
Elevated	9	9	
Vitamin C			
Typical	7	9	0.58
Elevated	3	1	
Vitamin D			
Typical	1	1	1.00
Elevated	9	9	
Vitamin E			
Typical	6	0	0.01*
Elevated	4	10	
Folate			
Typical	6	6	1.00
Elevated	4	4	
Calcium			
Typical	3	6	0.30
Elevated	6	4	
Low	1	0	
Low iron status			
Typical	4	5	0.57
Elevated	5	5	
Low	1	0	
Gluten			
Medium	4	6	0.64
Low	5	3	
7	1	1	
Caffeine			
Typical	8	6	0.63
Elevated	2	4	
Glycaemic Index			
Typical	10	9	1.00
Elevated	0	1	
Sodium			
Typical	0	1	1.00
Elevated	10	9	
Omega 3 & 6			
Typical	1	0	1.00
Elevated	9	10	
Physical activity			
Typical	3	4	1.00

Table 2 (continued)

Variable	COVID-19 patients		*p*
	Severe infection with ventilator	Moderate & mild Infection	
Elevated	7	6	
Energy balance			
Typical	1	2	1.00
Diminished	9	8	
Saturated & unsaturated fat			
Typical	3	4	1.00
Enhanced	7	6	
Monosaturated fat			
Typical	9	7	
Enhanced	1	3	0.58
Sugar Preference			
Typical	9	9	1.00
Elevated	1	1	
Eating between meals			
Typical	0	3	0.21
Elevated	10	7	
Motivation to exercise			
Typical	1	2	
Enhanced	9	8	1.00
Power & strength			
Typical	2	0	0.22
Elevated	2	2	
Enhanced	6	8	
Endurance			
Typical	7	8	0.36
Enhanced	3	1	
Ultra	0	1	
Pain			
Typical	2	0	0.47
Enhanced	8	10	
Achilles Tendon Injury			
Typical	5	8	0.35
Elevated	5	2	

* = Significance at 0.05 level. We calculated the standard deviation for age and BMI parameters, as both are parametric. Meanwhile, the other data are considered nonparametric

of COVID-19 patients with mild and moderate infection. It can be inferred that age is one of the factors correlated with the severity of infection. It aligns well with a study conducted by Starke et al. on the best possible quantification of the increase in COVID-19 disease severity due to age [100].

It can lead to the conclusion that the older the patient, the risk of experiencing severe COVID-19 infection, will increase. In addition, the group of patients with moderate and mild COVID-19 infection had a higher BMI compared to the group of patients with severe COVID-19 infection who needed a ventilator.

Genotype analysis showed that there were differences in Vitamin E genotypes between the two groups of COVID-19 patients. Based on data tabulation, it is known that COVID-19 patients with moderate and mild degrees of infection have Vitamin E genotypes in the elevated category. While the group of COVID-19 patients with severe infection rates and requiring ventilators, most (60%) have Vitamin E genotypes in the typical category.

In addition, it's known that there are some differences in calcium genotype, eating between meals, and power and strength, in each patient category. Although statistically, the *p-value* is still above the α value ($p > 0.05$), it is known that COVID-19 patients with severe infection rates and require ventilators, have a higher proportion of calcium genotypes in the low and elevated categories compared to COVID-19 patients with moderate and mild degrees of infection.

The results of the analysis also showed that patients with severe COVID-19 infection and requiring ventilators had eating between meals behaviour with genotypes in the elevated category. Meanwhile, patients infected with COVID-19 in moderate and mild degrees of infection have power & strength conditions with enhanced and elevated genotypes.

Discussion

Table 1 shows the phenotypes (component) and genotypes (gene and rs number) selected in this study. There is an objection that the components examined above will affect the handling of COVID-19 in the ICU. Providing proper nutrition is the main goal, but the other data we get from this nutrigenomic examination support the selection of drugs in the ICU, although it is more accurate if pharmacogenomic examinations are carried out on each patient in the ICU. In addition, data regarding endurance, muscle damage, and pain, can also help in the post-ventilator rehabilitation process. The handling of COVID-19 is very complex and multifactorial, so we also carry out examinations that do not only involve physical problems but also psychological elements. For example, the LEPR gene, rs12405556 which are related to various physiological processes in the body, including growth, metabolism, and appetite regulation [101–103].

Our work is a preliminary examination of differences in the nutrigenomics pattern of COVID-19 survivors on a ventilator compared to survivors of mild COVID-19. The checks we performed totalled 35 items, as shown in the results above. In addition to vitamins, several results referred to fat metabolism, as well as several activities that activate gene responses to fat and sugar metabolism.

DNA examination through saliva is deemed satisfactory. Despite lower purity, which potentially leads to variations in the amplification and analysis of genetic markers, saliva DNAs demonstrated excellent performance in microarray genotyping. The previous study aligns with other studies that suggest saliva collection as a viable substitute for blood. The ability to increase study enrollments and minimize subject discomfort is not necessarily compromised by a decrease in genotyping efficiency. Given the convenience of saliva collection, there might be a tendency for certain demographic groups to be more willing or able to participate in the study, leading to sampling bias [104, 105].

Although DNA yield is approximately twofold lower from saliva than from blood and other measures indicate slightly lower quality DNA, the key measure of genotyping quality is comparable on both Taqman and Illumina genome-wide bead chip arrays platforms. Saliva collection is less invasive than blood collection and participants who followed printed instructions, without supervision, provided useful quantities of DNA. The collection of saliva-derived DNA could substantially improve recruitment to translational studies in clinical trials, and reduce costs and logistical problems associated with blood collection within multicentre studies [106]. Demographic and behavioural characteristics of smoking cessation trial participants have significant associations with saliva and DNA metrics, but not with the performance of TaqMan® SNP or VNTR genotyping assays [104, 107].

Genetic codes are interrelated; we cannot interpret the results of one risk category in isolation without involving other genetic codes. For example, we label physical activity with a specific gene code in our results, indicating that physical activity triggers a gene response to fat metabolism. According to Nassef et al., aerobic exercise can affect HDL-C levels in the blood [108]. The synthesis of the hepatic lipase enzyme, which is essential for lipid metabolism, is influenced by the hepatic lipase gene, which is found on chromosome 15 (q21–q23) [109]. Previous research has found that hepatic lipase activity is a major genetic predictor of plasma HDL-C concentrations [63]. A higher level of HDL-C has been linked to the common LIPC gene variant Rs1800588 [108, 110].

Our findings revealed no significant differences in risk categories between the case and control groups. However, certain patterns can be considered and investigated further in research with a large number of samples. Some of the interesting patterns that we discovered included the low category in the case group, notably Calcium and Low iron status. The fact that TMPRSS6 in the case group is related to hepcidin is intriguing and warrants further investigation. How might these be connected to hepcidin biology? The first three factors found to influence hepcidin are anaemia, hypoxia, and inflammation [37]. Anaemia of inflammation can develop from inflammation caused by infections, according to the general knowledge of this regulatory network [111]. Hepcidin is generated more frequently when inflammation is caused by an infection. Hepatic heparan sulphate influences and regulates IL-6-stimulated hepcidin expression (112). Hepcidin is a protein that is produced in the liver that is activated by IL-6 [113, 114], and several studies have found that membrane-associated serine proteinases, in synergy with or in place of TMPRSS2, contribute to the activation of the SARS-CoV-2 spike protein [115].

Calcium is vital in critical case management for reasons other than bone density and vitamin D consumption. It is also related to albumin and saturated and unsaturated fat. According to research on lipotoxicity in COVID-19, unsaturated fatty acids generated by adipose lipolysis cause multisystem organ failure (MSOF), including acute lung injury [116, 117]. Severe acute pancreatitis and severe COVID-19 share obesity as a risk factor, along with lipase elevation, hypoalbuminemia, and hypocalcaemia [118–121].

There is a possibility of suspicion of low iron status with the TMPRSS6 gene, rs4820268 in the AA genotype; TFR2, rs7385804 genotype CA and TF, rs3811647 genotype GG, have a low risk category, which means that people who have this genetic code have an abnormal risk category. We cannot explain whether one of the factors that activate the spike protein of SARS-COV 2 is TMPRSS6 because, in the control group, there was no TMPRSS6 which had the AA genotype variation. As we know, the TMPRSS2 enzyme is a protease enzyme involved in infection with the SARS-COV2 virus. Whether TMPRSS6 with genetic variation in our study is one of the supporting factors that make it easy for someone to fall into severe COVID-19 conditions needs to be explored further. In addition, conditions of low iron status or iron overload can cause iron dysregulation which affects a person's immune system whereas in the case of COVID-19, it can contribute to causing specific clinical symptoms of COVID-19. This dysregulation and iron overload causing ferroptosis may explain other symptomatology of COVID-19 pathogenesis including multiorgan pathology and explain neuroprotection by vitamin E, a known ferroptosis blocker [38].

Our study found a significant association between risk of vitamin E deficiency and the severity of COVID-19 symptoms. The vitamin E risk deficiency was significantly higher in the severe COVID-19 group compared to the mild group, categorized as "typical". This finding aligns with previous research indicating the crucial role of vitamin E in immune function. Vitamin E deficiency can lead to several symptoms, including cardiomyopathy,

anaemia, decreased erythrocyte survival, and ultimately, death [122]. However, there was no significant difference in the analysis of pain response with the same gene code as vitamin E (rs4680). In the pain assessment, there was no difference in the risk of the "enhanced" category between the case and control groups. In the pain response, both groups had a high pain threshold.

Another intriguing finding from our research is that CYP1A2, rs2472300 affects caffeine metabolism, which is divided into slow and fast metabolizer groups. There were five subjects in the case group in the risk category elevated in the slow metabolizer group, compared to the eight subjects in the control group in risk category typical in the fast metabolizer group. This is important because caffeine is often used in pharmaceutical therapy. We are concerned, however, about the slow metabolism group, since slow metabolism can result in unfavourable clinical symptoms. The group of people with slow metabolizer qualifications has a greater risk of myocardial infarction than the fast metabolism group [48]. The rapid metabolizer for rs2472300 is GG, whereas the slow metabolizers are GA and AA [123]. However, Elzupir published an in-silico study on the inhibitory effect of SARS-COV-2–2-chymotrypsin-like protease (3CLpro) on caffeine and caffeine containing pharmaceuticals (3CPs) based on molecular dynamics stimulations and free energy calculations using molecular mechanics Poisson–Boltzmann surface area and molecular mechanics-generalized Born surface area. According to a study conducted by Elzupir, there is a link even with great energy [124]. Based on our nutrigenomics analysis, more research is required to determine which genomes are most suited for achieving optimal results from administering caffeine to reduce the replication of the SARS-COV-2 virus.

In our study, all subjects had a Glycaemic Index in the case group, indicating a typical risk level. TCF7L2, rs12255372, is known to have a risk of single nucleotide polymorphisms within the transcription factor 7-like 2 gene are well established risk variants for type 2 diabetes mellitus. The association between TCF7L2 SNPs and T2DM has been investigated in several studies, but the results have been controversial. The T-allele of the TCF7L2 polymorphisms rs12255372, rs7903146, and rs290487 confer susceptibility to T2DM in the Iranian Kurdish population [50, 56].

We attempted to link the UCP1 gene and genetic variation at rs1800592 with BMI profiles in both groups. There were five subjects in the case group with BMIs above the normal range, namely 29.39; 26.35; 28.41; 27.55; and 25,71. There were also five subjects in the control group with BMIs above the normal range, namely 27.4; 34.6; 38.1; 34.66; 25.95; and 28.07. The two groups could not be compared because there was no significant difference in the risk and BMI categories. Although these genes are known to be involved in the regulation of energy metabolism, the role of the polymorphisms in the UCP1 and NPC1 genes concerning obesity is debatable, given the inconsistent findings of research conducted in different ethnic groups [67]. The insignificance of BMI in both case and control groups may become significant if the control group consist of individuals who have never suffered from COVID-19.

We are unable to explain the role of Monounsaturated Fat in cases of COVID-19. However, this genetic variation in rs180282 is strongly associated with the occurrence of metabolic syndrome [69]. Ruggiero et al. explain that the ratio of monounsaturated fat to saturated fat is associated with cardiovascular risk [125]. Likewise, we are unable to adequately explain the role of GLUT2, rs5400 in the incidence of COVID-19. Therefore, GLUT2 might be a candidate susceptibility gene for conditions that affect how much food is consumed [126]. Another interesting finding concerns power and strength, where this gene type may influence the ventilator weaning process in critically ill patients. -Actinin-3, which is generated by the ACTN3 gene, is a structural protein of the muscle fibre that anchors actin filaments to preserve the myofibrillar array and controls muscle length and tension during muscular contraction. Only fast muscle fibres express -actinin-3, indicating that the function of this protein is unique to rapid muscular contractions or those demanding a substantial amount of strength [88]. The R577X polymorphism, which is frequently found in the ACTN3 gene, results in the substitution of an arginine (R) for an early stop codon (X) at amino acid 577. Individuals who are homozygous for the X allele in the R577X polymorphism (XX genotype) generate an inactive form of -actinin-3 and are considered to be -actinin-3 deficient [78]. In contrast, those with the R allele homozygotes (RR genotype) or heterozygotes (RX genotype) express functional -actinin-3, though it has been hypothesized that RR individuals express -actinin-3 at a higher level than RX individuals [90]. Increased expression of -actinin-2, an -actinin isoform that is universally expressed in all muscle fibre types, compensates for the lack of -actinin-3, which is not associated with any disease. However, ACTN3 XX individuals have several undesirable traits, including lower bone mineral density, lower muscular strength, and lower muscle volume [79, 127, 128]. Another area of research focuses on how the ACTN3 R577X polymorphism affects the mechanical ventilation weaning process in the ICU [79].

In terms of pain, we reviewed COMT, rs4680, in this study, but there were no significant differences. It is possible to obtain different findings if we focus on post-COVID-19 pain data. Fernández-de-Las-Peñas et al.

found that four pain-related polymorphisms did not appear to predispose the development of post-COVID pain in previously hospitalized COVID-19 survivors [129]. Furthermore, there was no evidence of a relationship between these SNPs and post-COVID sensory, psychological, or cognitive factors. Cohort studies focusing on particular polymorphisms and in-depth investigations of sex-linked differences should be conducted to better understand the underlying pathophysiology of post-COVID-19 discomfort. This study only included coding variants; however, we cannot rule out that the examined genes may also be associated with post-COVID-19 discomfort through their non-coding regulatory variants. The catechol-O-methyltransferase gene product is affected by the missense variant SNP rs4680, which changes valine (Val) to methionine (Met) [25]. The altered enzyme has reduced activity under physiological conditions because it is synthesized with a less thermostable genotype (Met/Met) [130]. Subjects with the Met/Met genotype typically displayed higher pain sensitivity than those with the a/Val genotype [131]. Therefore, the emergence of chronic pain is linked to the Val158Met rs4680 gene variant [26]. The Met allele has been related to an increased risk of temporomandibular disorders but not migraines, thus this association is debatable [132].

Our initial inquiry into the nexus between nutrition and the incidence of COVID-19 was motivated by emerging evidence suggesting dietary factors could influence the susceptibility and severity of the disease. The core hypothesis posited that specific nutritional patterns and deficiencies might play a critical role in modulating immune responses to SARS-CoV-2 infection. However, as our study unfolded, the data revealed a complex interplay between age, genetic variations related to nutrient metabolism, and COVID-19 risk categories, suggesting a nuanced relationship that extends beyond direct nutritional impacts. One of the most compelling insights from our analysis is the significant modulation of nutritional effects by age, leading to varied risk categories among COVID-19 patients. This observation underscores the complexity of the relationship between diet, genetic predispositions, and the body's response to infectious diseases, including COVID-19. Age significantly influences the genetic response to saturated and unsaturated fat; the older an individual is, the higher the probability of falling into the risk category "Typical." This is related to the hypothesis that as someone ages, there is a decline in metabolic function, including lipid metabolism, and the presence of comorbidities, thereby increasing the severity of COVID-19 [133]. Unsaturated fat intake is associated with increased mortality from COVID-19. Unsaturated fatty acids cause injury, and organ failure resembling COVID-19. Early albumin and calcium can bind unsaturated fatty acids, and reduce injury (99). The conclusion of this study can be used as a reference for understanding how the distribution pattern of specific genes can affect the risk level in COVID-19 patients.

Furthermore, the use of saliva for DNA collection proved effective, consistent with other studies suggesting its viability as an alternative to blood samples. Future research should explore the mechanisms by which these genetic variations affect COVID-19 outcomes and the potential for targeted nutritional interventions.

Conclusion

This preliminary study identified a significant correlation between risk of vitamin E deficiency and severe COVID-19 symptoms. This may relate to the role of vitamin E as an immunomodulator in the innate and adaptive immunity. The presence of an ultra risk category for endurance in the control group suggests potential genetic resilience factors. These findings highlight the importance of further research into genetic predispositions and nutritional factors in COVID-19 severity, paving the way for personalized healthcare solutions. Future research should delve deeper into understanding how genetic predispositions and nutritional factors converge to influence COVID-19 severity, paving the way for personalized healthcare solutions.

Limitation

Several limitations of this study include a small sample size due to cost constraints. Additionally, we did not collect data on comorbidities, demographic information, and behavioural characteristics (especially smoking), which can affect the quantity and quality of DNA. Another limitation is the inability to ensure compliance with saliva collection protocols and to confirm that biospecimen donors were participants in this study. Because the sample size is too small, the bias can be significant.

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Author's contributions
All authors contributed to this research. AN, BP, and AI were involved in collecting the participant data, sample, and laboratory analysis. KI, AK, PH, and RA performed and interpreted the data and manuscript editing. All authors read and approved the final manuscript.

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Availability of data and materials
Data will not be shared publicly. The data sets and materials used and/or analysed during the current study can be made available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study protocol was arranged based on the Helsinki Declaration and had approval from Dr Soetomo General Academic Hospital under ethics protocol number 0458/KEPK/VIII/2022. All subjects who participated signed informed consent forms after receiving detailed information concerning the purpose of the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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