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The ZNF717-rs2918520 genotype contributes to COVID-19 severity: a Taiwanese cohort study

Yang-Hsiang Lin[1†], Jen Yu[2†], Yu-Chuan Teng[3†], Chung-Guei Huang[4,5], Siew-Na Lim[6,7], Ming-Wei Lai[1,7,8] and Wey-Ran Lin[1,7,9*]

Abstract

Background Coronavirus disease 2019 (COVID-19) has been a challenging pandemic since late 2019 and patients with COVID-19-related severe respiratory failure associated with high mortality rates worldwide. Genetic information such as single nucleotide polymorphisms (SNPs) serves as a predictor or prognostic factor in disease development and cancer progression. This study aimed to explore the clinical associations of SNPs with mild and severe COVID-19 symptoms in the Taiwanese population.

Methods SARS-CoV-2-infected patients in pilot cohort study (cohort 1, $n=39$) and validation cohort (cohort 2, $n=71$) were enrolled. The clinical significance of SNPs in those patients with mild and severe symptoms was investigated by whole exon sequencing, polymerase chain reaction and Sanger sequencing.

Results The current study investigated Taiwanese patients with COVID-19. We found that clinical parameters such as age, aspartate aminotransferase, blood urea nitrogen, C-reactive protein, ferritin, and segment were positively associated with severe COVID-19 symptoms but that albumin, lymphocytes, and basophils correlated negatively with severe symptoms in two independent cohorts. By conducting whole-exome sequencing, we identified a novel SNP, ZNF717-rs2918520, the GG genotype of which was significantly associated with severe symptoms in COVID-19 patients.

Conclusions Our findings highlight that the ZNF717-rs2918520 GG genotype may serve as a predictor for evaluating the severity of COVID-19 in Taiwan.

Keywords COVID-19, SNP, ZNF717-rs2918520, Predictor, Severity

†Yang-Hsiang Lin, Jen Yu and Yu-Chuan Teng contributed equally to this work.

*Correspondence:
Wey-Ran Lin
t12360@adm.cgmh.org.tw
[1]Liver Research Center, Linkou Chang Gung Memorial Hospital, Taoyuan, Taiwan
[2]Department of internal medicine, Linkou Chang Gung Memorial Hospital, Taoyuan, Taiwan
[3]Genomic Medicine Core Laboratory, Chang Gung Memorial Hospital, Linkou, Taiwan
[4]Department of Laboratory Medicine, Chang-Gung Memorial Hospital, Taoyuan, Taiwan
[5]Department of Medical Biotechnology and Laboratory Science, Chang-Gung University College of Medicine, Taoyuan, Taiwan
[6]Department of Neurology, Chang Gung Memorial Hospital, Taoyuan, Taiwan
[7]Chang Gung University College of Medicine, Taoyuan, Taiwan
[8]Department of Pediatrics, Chang Gung Memorial Hospital, Taoyuan, Taiwan
[9]Department of Hepatology and Gastroenterology, Linkou Chang Gung Memorial Hospital, 5, Fu-Shin Street, Taoyuan 333, Taiwan

Introduction

Patients with severe acute respiratory syndrome coronavirus (SARS-CoV-2) infection developing severe acute respiratory syndrome were first identified in late 2019, followed by the coronavirus disease 2019 (COVID-19) pandemic. The transmittable SARS-CoV-2, a positive strand RNA virus, is identified as the member of Coronaviridae family [1]. The in vitro experiments supported that angiotensin-converting enzyme 2 (ACE2) could associate with spike protein of SARS-CoV-2, indicating that ACE2 was a receptor for SARS-CoV-2-transferred into target cells [2]. The clinical manifestations of the disease include asymptomatic infection, mild symptoms or severe respiratory failure [3]. Patients with severe respiratory failure have high mortality rates worldwide [4]. It is crucial to understand the potential progression of SARS-CoV-2 infection from mild to severe symptoms. Such insight can reduce mortality and prevent long-term sequelae of COVID-19, and it can guide patients to a rapid recovery. Multiples COVID-19 vaccines have been developed [5]. The vaccine development contributes to limit the virus transmission and reduce the severity of COVID-19, which may prolong the survival outcome of COVID-19 patients. Although the underlying mechanism remains unclear, scientists are dedicated to uncovering such associations, leading to improved patient survival outcomes with appropriate treatment.

Several dysregulated genes in healthy controls and patients with mild or severe COVID-19 have been characterized using gene expression profiling analysis [6], revealing dysregulated gene-mediated immune responses associated with COVID-19 development. Genetic information such as single-nucleotide polymorphisms (SNPs) in COVID-19 patients has also been characterized. Hu and coworkers demonstrated that eight genetic pieces of information correlate significantly with death caused by SARS-CoV-2 infection in the United Kingdom [7]. In the Chinese population, the loci 11q23.3 and 11q14.2 (rs1712779 and rs10831496) correlate with severe COVID-19 symptoms [8]. A study by Fares and co-workers showed that the genotype of hemoxygenase 1 (HMOX-1) rs13057211 (A > G) within its promoter region was associated with high mortality rate in COVID-19 patients via PCR and Sanger sequencing [9]. Another study revealed that the genotype of interferon alpha and beta receptor subunit 2 (IFNAR2) rs2236757 A was associated with illness of COVID-19 in Palestine [10]. Recent study demonstrated that the polymorphism of interferon-induced transmembrane protein 3 (IFITM3) rs12252 and transmembrane serine protease 2 (TMPRSS2) rs12329760 were correlated with risk of SARS-CoV-2 infection [11]. The individual SNP information may help to be used as a biomarker for patients with SARS-CoV-2 infection who are susceptible to progression to severe symptoms. This would allow doctors to diagnose and intervene quickly to reduce patient suffering. In addition, identification of a suitable predictor intervened patient's therapeutic outcome was an important study in the different regions. The risk factors for the severity of COVID-19 may depend on an individual's genetic information, environment and geography. In this study, we determined associations between genetic variants and COVID-19 symptoms in the Taiwanese population using whole-exome sequencing (WES). We found that ZNF717 rs2918520 GG genotype was positively associated with severity of COVID-19 in two independent cohorts. It may serve as a predictor for evaluating the severity of COVID-19 and improving survival outcomes of SARS-CoV-2-infected patients in Taiwan.

Materials and methods

Patients

Informed consent of all individuals was collected before performing experiments. All assays were approved by the Medical Ethics and Human Clinical Trial Committee at Chang Gung Memorial Hospital (IRB No. 202101285B0C501). A total of 39 SARS-CoV-2-infected patients (cohort 1) were randomly included. COVID-19 was confirmed using real-time reverse transcriptase polymerase chain reaction (RT-PCR) at Chang Gung Memorial Hospital. Notably, the Wuhan ($n = 6$), Epsilon ($n = 4$), and Beta ($n = 1$) strains were identified in clinical samples (Supplementary Table 1). The sequencing results in two clinical samples cannot be used to define which strain of SARS-CoV-2 belongs to. In addition, which strain of COVID-19 in other samples was missing (no sequencing results). To verify the results obtained from cohort 1, the independent validation cohort (cohort 2, $n = 71$) was also randomly collected and subjected for further investigation, including WES analysis and clinical association analysis.

Study design

The study design was as follows. The patients were divided into two groups based on disease severity: a mild group and a severe group. The definition of the mild disease group was not requiring supplemental oxygen and corresponding to non-severe cases according to WHO guidelines, asymptomatic or pre-symptomatic infection, mild to moderate illness according to NIH guidelines, and mild or moderate disease according to Taiwan CDC guidelines. The severe group consisted of patients who required supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation and corresponded to severe or critical COVID-19 cases according to WHO guidelines, severe or critical illness according to NIH guidelines, or severe to critical disease according to Taiwan CDC guidelines [12, 13]. The symptoms

of COVID-19 patients in this study were assessed and defined by the Chang Gung Memorial Hospital physician. The definition of hospital length of stay (days) was the patient's period from admittance to discharge. Once clinical specimens were collected, samples were subjected to DNA extraction and WES analysis.

DNA extraction

Peripheral blood mononuclear cells (PBMCs) were collected from COVID-19 patients and isolated [14]. The DNA in the samples was extracted using a DNeasy Blood & Tissue Kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions.

WES analysis

The WES procedure was described previously [15]. Briefly, the quality and concentration of the DNA were assessed using an Agilent Bioanalyzer (Agilent Technologies, CA, USA) and Qubit® DNA assay kit (Thermo Fisher Scientific, Waltham, USA). A SureSelect Library Prep Kit (Agilent Technologies) was used to establish a DNA library (approximately 150–200 bp). WES was performed using the Illumina NovaSeq 6000 platform with a 150 bp read length (Illumina, USA). The sequencing reads were converted to fastq format using bcl2fastq2 (version 2.17) and analyzed by Illumina DRAGEN Bio-IT platform including reads mapping, position sorting, duplicate marking and joint variant calling. To obtain functional relevance of the variants, we focused on the SNV and indel detection results from above were determined annotations after using by ANNOVAR and RefSeq [16]. We used the general population from Genome Aggregation Database (gnomAD) v2.1.1 and selected the East Asia strains included 9197 exomes to perform the case-control association study [17]. We conducted the statistical analysis for the association by comparing the allele and genotype frequencies between cases and controls. The genetic associations were examined by logistic-regression analysis and rank-ordered according to the lowest *P* value. A false discovery rate (FDR) correction was applied for the multiple comparisons and adjusted the *P* values using the numbers of tests [18]. The linkage disequilibrium (LD) analysis of the SNPs within the ZNF717, FCGBP, MUC5AC and MUC12 locus was analyzed by LDBlockShow (version 1.39) [19].

Genotype of ZNF717 rs2918520 detection

To determine the genotypes of ZNF717 rs2918520 in SARS-CoV-2-infected patients, PCR assay was performed. This assay was conducted in a 20 μl containing 10 μl of 2x PCR matser mix, 2 μl of 2.5 mM dNTPs, 1 μl of ZNF717 rs2918520 forward and reverse primer and 6 μl of ddH2O. The primers used in this study were described as follow: ZNF717 rs2918520 forward primer: 5'-ACTggCAAgTTTCACTCACCCAAT-3'; ZNF717 rs2918520 reverse primer: 5'-TggAgACCTACAA-CAgCCTggTATCA-3'. The PCR product was subjected to Sanger sequencing. The sequences of ZNF717 rs2918520 genotypes in those samples were analyzed via Vector NTI software, compared to the reference sequences of ZNF717 rs2918520. The information of ZNF717 rs2918520 genotype in this study has been deposited in clinVAR (https://www.ncbi.nlm.nih.gov/clinvar) with accession number SCV004697464.

Statistical analysis

Clinical information was recorded and is shown as the mean ± standard deviation (SD). The associations between clinical parameters, genotype and symptoms of COVID-19 were analyzed by Mann-Whitney U test. Clinical associations between SNPs and the severity of COVID-19 were evaluated using Fisher's exact test. The statistical analyses in this study were conducted using SPSS software version 20 (SPSS, Chicago, IL, USA).

Results

Demographic information of enrolled patients

A total of 39 SARS-CoV-2-infected patients in cohort 1 were enrolled. Their demographic characteristics, including the normal range of biochemistry tests, are shown in Table 1. To determine associations between clinical manifestations and symptoms of COVID-19, data were analyzed using SPSS software with the Mann−Whitney U test. The results showed that age ($P = 0.0016$), aspartate aminotransferase (AST, $P = 0.0030$), blood urea nitrogen (BUN, $P = 0.0002$), potassium ($P = 0.0189$), C-reactive protein (CRP, $P = 0.0019$), ferritin ($P = 0.0078$), IL-6 ($P = 0.0098$), and white blood cell (WBC, $P = 0.0443$) and segment ($P = 0.0004$) were significantly higher in COVID-19 patients with severe symptoms than in patients with mild symptoms (Table 1). As expected, COVID-19 patients with severe symptoms stayed at the hospital longer than those with mild symptoms. Conversely, albumin ($P = 0.0003$), platelets ($P = 0.0365$), lymphocytes ($P = 0.0004$), eosinophils ($P = 0.0037$) and basophils ($P = 0.0010$) were significantly lower in patients with severe symptoms than in those with mild symptoms (Table 1). In addition, using a respirator, ICU stay and antiviral drug treatment were associated with the severity of COVID-19 symptoms (Table 1). However, the results showed no significant associations with BMI, ALT, total bilirubin, creatinine, sodium, red blood cells (RBCs), hemoglobin, monocytes, erythrocyte sedimentation rate (ESR), prothrombin time, sex or overall survival. These findings suggest that SARS-CoV-2 modulates several clinical manifestations, leading to different consequences of COVID-19.

Table 1 Clinical information of COVID-19 patients in cohort 1

Parameters (normal range[a], unit)	All patients		Symptoms of COVID-19				
			Mild		Severe		*P* value[b]
	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	
Age (year)	34	55.79 ± 21.00	26	49.85 ± 20.1	8	75.13 ± 8.13	**0.0016**
BMI (18.5–24.9, kg/m2)	25	24.02 ± 4.360	17	23.66 ± 4.15	8	24.76 ± 4.97	0.6205
AST (≦ 34 U/L)	34	34.94 ± 22.53	26	28.27 ± 13.6	8	55.63 ± 32.0	**0.0030**
ALT (≦ 36 U/L)	34	37.94 ± 31.82	26	36.35 ± 34.5	8	43.13 ± 21.6	0.1380
Albumin (3.5–5.4 g/dL)	32	3.758 ± 0.612	24	3.968 ± 0.54	8	3.130 ± 0.25	**0.0003**
Total bilirubin (0.2–1.1 mg/dL)	33	0.493 ± 0.229	25	0.488 ± 0.24	8	0.512 ± 0.18	0.5932
BUN (7–25 mg/dL)	34	17.62 ± 13.16	26	12.09 ± 5.39	8	35.58 ± 15.1	**0.0002**
Creatinine (Male: 0.64–1.27 mg/dL Female: 0.44–1.03 mg/dL)	34	0.781 ± 0.393	26	0.683 ± 0.17	8	1.099 ± 0.68	0.2080
Sodium (136–146 mEq/L)	34	135.2 ± 23.96	26	133.9 ± 27.2	8	139.6 ± 4.95	0.7132
Potassium (3.4–4.1 mEq/L)	34	3.674 ± 0.442	26	3.569 ± 0.36	8	4.013 ± 0.51	**0.0189**
CRP (< 5 mg/L)	34	33.02 ± 57.28	26	18.04 ± 32.4	8	81.69 ± 90.4	**0.0019**
Ferritin (Male: 30–400 ng/mL Female: 13–160 ng/mL)	26	445.4 ± 366.7	19	328.0 ± 320	7	764.1 ± 300	**0.0078**
IL-6 (< 7 pg/ml)	17	29.25 ± 52.38	14	9.470 ± 8.49	3	121.5 ± 77.2	**0.0098**
WBC (3.9–10.6, 1000/ul)	34	6.671 ± 2.995	26	6.200 ± 3.01	8	8.200 ± 2.53	**0.0443**
RBC (4.5–5.9 million/uL)	34	4.574 ± 0.732	26	4.708 ± 0.683	8	4.138 ± 0.75	0.0773
Hemoglobin (13.5–17.5 g/dL)	34	13.19 ± 1.726	26	13.31 ± 1.53	8	12.81 ± 2.33	0.5558
Platelet (150–400, 1000/uL)	34	255.3 ± 113.9	26	274.8 ± 106	8	191.9 ± 120	**0.0365**
Segment (42–74%)	34	65.96 ± 16.19	26	60.37 ± 13.5	8	84.14 ± 9.16	**0.0004**
Lymphocyte (20–56%)	34	25.02 ± 13.73	26	29.67 ± 11.8	8	9.912 ± 7.06	**0.0004**
Monocyte (0–12%)	34	6.632 ± 2.479	26	6.985 ± 2.21	8	5.488 ± 3.08	0.0997
Eosinophil (0–5%)	34	1.788 ± 2.964	26	2.312 ± 3.22	8	0.087 ± 0.24	**0.0037**
Basophil (0–1%)	34	0.308 ± 0.338	26	0.392 ± 0.34	8	0.037 ± 0.05	**0.0010**
ESR (Male: 0–20 mm/hr, Female: 0–30 mm/hr)	25	30.48 ± 25.67	19	25.95 ± 21.3	6	44.83 ± 34.6	0.3892
PT (10–13 s)	30	12.39 ± 1.173	22	12.10 ± 0.78	8	13.19 ± 1.69	0.0822
Hospital length of stay (days)	34	32.94 ± 32.90	26	21.08 ± 13.8	8	71.50 ± 46.8	**0.0007**
Parameters	All patients (n)		Mild (n)		Severe (n)		*P* value[c]
Gender							
Male	16		11		5		0.4290
Female	18		15		3		
Respirator							
without	28		26		2		**< 0.0001**
with	6		0		6		
ICU stay							
without	27		26		1		**< 0.0001**
with	7		0		7		
Antiviral drug							
without	15		14		1		**0.0352**
with	15		8		7		
Death							
No	33		26		7		0.2353
Yes	1		0		1		

a: The normal ranges of clinical parameters were defined by the Chang Gung Memorial Hospital

b: Mann-Whitney U test for two groups. Bold values indicate statistical significance $p < 0.05$

c: Fisher's exact test

Significance of SNPs in SARS-CoV-2-infected patients is determined via WES analysis

As shown in Table 1, COVID-19 correlated with abnormal blood indicators, inflammation-related factors and biochemical parameters. WES analysis was then conducted to characterize the clinical significance of SNPs in SARS-CoV-2-infected patients with mild and severe symptoms ($n = 39$). Data in gnomAD were used as a reference panel (control group). A Manhattan plot showed that ten loci on chromosomes 1,

3, 7, 9, 10, 11, 13, 19, 21 and 22 (rs4915494 in immunoglobulin like and fibronectin type III domain containing 1 (IGFN1), $p = 4.22 \times 10^{-150}$, rs2918520 in zinc finger protein 717 (ZNF717), $p = 4.22 \times 10^{-150}$, rs111576591 in mucin 12 (MUC12), $p = 4.22 \times 10–^{150}$, rs62561230 in ZNF658, $p = 5.55 \times 10^{-141}$, rs3127817 in G protein regulated inducer of neurite outgrowth 2 (GPRIN2), $p = 7.65 \times 10^{-149}$, rs1028705525 in MUC5AC, $p = 4.22 \times 10^{-150}$, rs376589131 in poly(a) binding protein cytoplasmic 3 (PABPC3), $p = 5.55 \times 10^{-141}$, rs782103783 in Fc gamma binding protein (FCGBP), $p = 7.65 \times 10^{-149}$, rs212146 in transmembrane phosphatase with tensin homology (TPTE), $p = 4.22 \times 10^{-150}$, rs5748622 in XK related 3 (XKR3), $p = 4.22 \times 10^{-150}$) correlated significantly with SARS-CoV-2 infection (Fig. 1). The top SNPs (rs4915494 in IGFN1, rs2918520 in ZNF717, rs111576591 in MUC12, rs1028705525 in MUC5AC, rs212146 in TPTE, and rs5748622 in XKR3) were selected for further clinical investigation. Of note, LD analysis revealed that the R^2 value for ZNF717-rs2918520, FCGBP-rs782103783, MUC5AC-rs1028705525 and MUC12-rs111576591 is 1, 0.210, 0.831 and 0.267, respectively (Fig. 2A-D). Accordingly, these observations indicated that ZNF717-rs2918520 was the perfect LD.

ZNF717 serves as a determinant of susceptibility to COVID-19

Based on our results (in cohort 1), 39 patients (100%) carried homozygous variants for rs1028705525 in MUC5AC (C > T) and rs212146 in TPTE (A > G) (Table 2). Thirty-nine cases of heterozygous SNPs (100%) for rs4915494 in IGFN1 (T > C) were identified in COVID-19 patients (Table 2). Twenty-seven specimens (69%), 23 specimens (59%) and 28 specimens (72%) showed homozygous variants for rs2918520 in ZNF717 (A > G), rs111576591 in MUC12 (A > G) and rs5748622 in XKR3 (G > T), respectively (Table 2). Specifically, ZNF717 rs2918520 was identified in 18 and 9 samples from the mild and severe symptom groups, respectively, MUC12 rs111576591 in 19 and 4 samples, respectively, MUC5AC rs1028705525 in 30 and 9 samples, respectively, TPTE rs212146 in 30 and 9 samples, respectively, and XKR3 rs5748622 in 22 and 6 samples, respectively. On the other hand, twelve patients with mild symptoms showed heterozygous genotypes of ZNF717 rs2918520. There were 11 and 5 heterozygous genotypes of MUC12 rs111576591 in the mild and severe symptom groups, respectively, and 8 and 3 heterozygous genotypes of XKR3 rs5748622, respectively. Furthermore, the clinical significance of these SNPs in COVID-19 was analyzed by Fisher's exact test. In comparison with the ZNF717 rs2918520 AG genotype, only the ZNF717 rs2918520 GG genotype

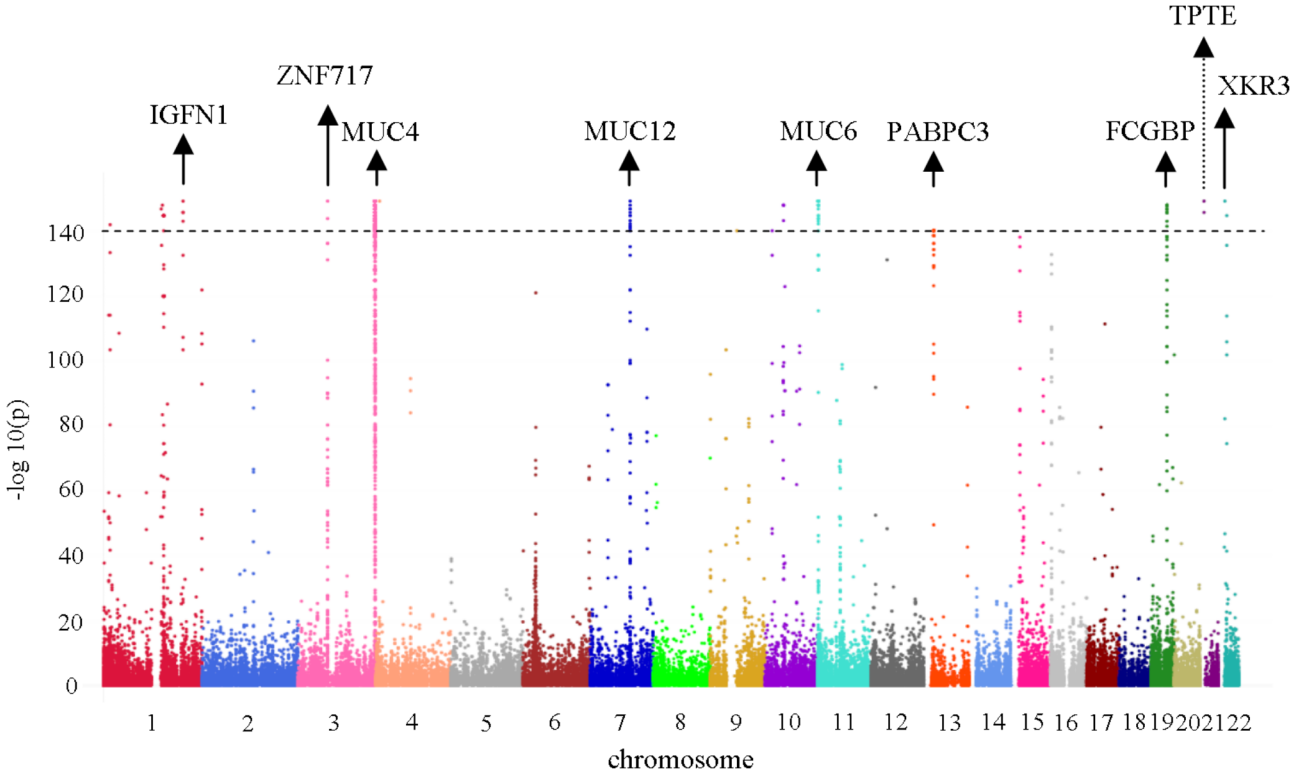

Fig. 1 A Manhattan plot represents the WES analysis for susceptibility loci in COVID-19 patients. The plot indicates associations between SNPs/mutations and SARS-CoV-2 infection. The black dashed line marks the statistical significance threshold of the *P* value

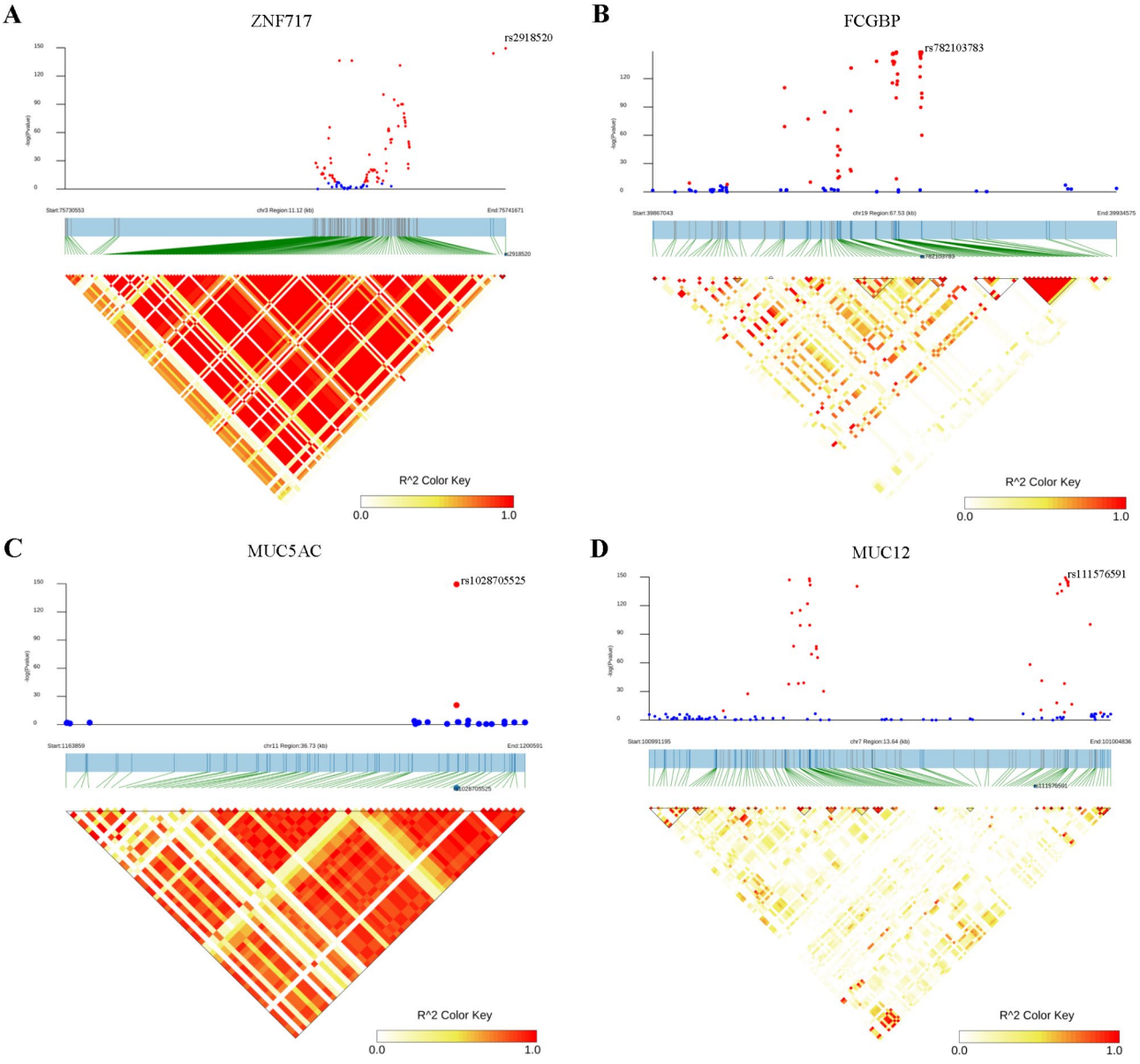

Fig. 2 The LD analysis of the SNPs within the ZNF717, FCGBP, MUC5AC and MUC12 locus. The plot indicated the corresponding region of each SNP within (**A**) ZNF717, (**B**) FCGBP, (**C**) MUC5AC and (**D**) MUC12 locus. Each statistically LD values (R^2) are shown in marker color, which representing the strength of LD within each genes locus (red color: $R^2 = 1$; white color: $R^2 = 0$)

(homozygous) correlated positively with COVID-19 severity (Table 2). Conversely, there were no significant differences observed for IGFN1 rs4915494, MUC5AC rs1028705525, TPTE rs212146 MUC12 rs111576591 or XKR3 rs5748622 and COVID-19 severity (Table 2). Clinical associations between the ZNF717 rs2918520 genotype and clinical manifestations in COVID-19 patients (cohort 1) were also evaluated, but with no correlation (Table 3). To further explore the associations between ZNF717 rs2918520 genotype and clinical manifestations in COVID-19 patients, the independent validation cohort (cohort 2, $n = 71$) was collected and analyzed. We found that in cohort 2, age ($P < 0.0001$), AST ($P = 0.0030$), ALT ($P = 0.0206$), BUN ($P = 0.0003$), CRP ($P = 0.0269$), ferritin ($P = 0.0001$) and segment ($P = 0.0018$) were significantly higher in COVID-19 patients with severe symptoms than in patients with mild symptoms (Table 4). Additionally, COVID-19 patients with severe symptoms stayed at the hospital longer than those with mild symptoms (Table 4). Conversely, albumin ($P = 0.0003$), RBC ($P < 0.0001$), hemoglobin ($P < 0.0001$), lymphocytes ($P = 0.0015$), Monocyte ($P = 0.0073$), and basophils ($P = 0.0146$) were significantly lower in patients with severe symptoms than in those with mild symptoms (Table 4). Most of

Table 2 The association between top hit SNPs and symptoms of COVID-19 in cohort 1

Gene (SNP)	Ref	Alt	Types of SNPs	Symptoms		
				Mild (n)	Severe (n)	*P* value[a]
IGFN1 (rs4915494)	T	C	Heterozygous	30	9	NA
			Homozygous	0	0	
ZNF717 (rs2918520)	A	G	Heterozygous	12	0	**0.0362**
			Homozygous	18	9	
MUC12 (rs111576591)	A	G	Heterozygous	11	5	0.4443
			Homozygous	19	4	
MUC5AC (rs1028705525)	C	T	Heterozygous	0	0	NA
			Homozygous	30	9	
TPTE (rs212146)	A	G	Heterozygous	0	0	NA
			Homozygous	30	9	
XKR3 (rs5748622)	G	T	Heterozygous	8	3	0.6927
			Homozygous	22	6	

a: Fisher's exact test. Bold values indicate statistical significance $p < 0.05$

findings in cohort 2 were similar to results obtain from cohort 1. Notably, the ZNF717 rs2918520 GG genotype was positively associated with COVID-19 severity in cohort 2 (Table 5). Accordingly, we believe that ZNF717 rs2918520 may serve as a predictor for evaluating the severity of SARS-CoV-2-infected patients.

Discussion

Emerging evidence supports that SNPs in genes such as ACE2, Toll-like receptor 7, transmembrane protease serine 2 (TMPRSS2), interferon induced with helicase C domain 1 and angiotensin II type 1 receptor affect the severity of COVID-19 [20–22]. Abdelsattar and coworkers demonstrated that two SNPs, rs2285666 and rs12329760, in ACE2 and TMPRSS2 are significantly associated with the severity of COVID-19 [23]. One study demonstrated that the apolipoprotein E (ApoE) ε4 genotype correlates with delirium and dementia [24], and the ApoE ε4ε4 genotype (homozygous) was shown to be a risk factor in Alzheimer's disease [25]. Another group revealed that the ApoE ε4 genotype was associated with the severity of COVID-19 in the United Kingdom [26]. Lehrer and colleagues reported that in the United Kingdom population, heterozygosity of bridging integrator 1 (BIN1) rs744373 correlates with the lowest mortality in patients with SARS-CoV-2 infection but that homozygosity of BIN1 rs744373 correlates with the highest mortality [27]. These observations suggest that this SNP may function as an important effector to coordinate COVID-19 patient mortality and severity via unknown mechanisms. To date, the effect of ZNF717 on COVID-19 severity remains unclear. In the current study, we found that the ZNF717 rs2918520 GG genotype correlated significantly with severe COVID-19 symptoms in the Taiwanese population. Based on NCBI dbSNP, the frequencies of the G allele or T allele of ZNF717 rs2918520 in the total population ($n = 1486$) are 0.4610 and 0.0000, respectively. Specifically, the frequencies of the G allele or T allele of ZNF717 rs2918520 in the Asian population ($n = 2$) are both zero. However, the sample size in the Asian population only involved two cases. In our study, the frequency of ZNF717 rs2918520 AG genotype or GG genotype was 0.307 and 0.692 in cohort 1 and 0.267 and 0.732 in cohort 2, respectively, suggesting that this SNP has a unique relationship with symptoms of COVID-19. The ZNF717 rs2918520 A > G substitution results in a missense variant. ZNF717 is a transcriptional regulator that is involved in modulating cell growth, cell differentiation, gene expression and viral replication [12, 13]. One study showed a mutation rate of ZNF717 in multifocal hepatocellular carcinoma (HCC) and single-nodular HCC with portal vein tumor thrombus of up to 90% and 72%, respectively [13]. Furthermore, depletion of ZNF717 enhances cell growth, migration and invasive ability via modulation of the signal transducer and activator of transcription 3/matrix metalloproteinase-2/CD44/integrin subunit α3 axis. These observations indicate that high ZNF717 gene mutation frequency and that it plays a tumor-suppressor role in HCC. Chen et al. used PCR and DNA sequencing to show that the ZNF717 gene is commonly mutated in plasma DNA obtained from people with colorectal adenomas (CRAs), a precancerous state [28]. Similar approaches were conducted in the colorectal cancer (CRC) samples. It is worth noting that the mutation frequency of ZNF717 was specific to CRAs and was not seen in CRC samples, indicating that ZNF717 mutations may act as a predictive biomarker in evaluating the CRAs. A distinct study indicated that mutations in MUC3A, RHBG (Rh family B glycoprotein) and ZNF717 genes associated with hypermobility spectrum disorder (HSD) via WES analysis, suggesting potential roles of these mutations may serve as biomarker for HSD [29]. WES of triple-negative apocrine carcinoma (TNAC) identified ZNF717 as a candidate driver gene [30]. In

Table 3 Associations between ZNF717-rs2918520 genotypes and clinical parameters in cohort 1

Parameters (normal range[a], unit)	**ZNF717-rs2918520 genotypes**				
	AG		**GG**		***P* value[b]**
	n	**Mean ± SD**	**n**	**Mean ± SD**	
Age (year)	9	52 ± 21.49	25	57.16 ± 21.1	0.6389
BMI (18.5–24.9, kg/m2)	7	22.02 ± 1.62	18	24.79 ± 4.86	0.2895
AST (≦ 34 U/L)	9	35.22 ± 17.1	25	34.84 ± 24.5	0.5578
ALT (≦ 36U/L)	9	56.78 ± 51.4	25	31.16 ± 18.1	0.1777
Albumin (3.5–5.4 g/dL)	9	3.831 ± 0.36	23	3.730 ± 0.68	0.6905
Total bilirubin (0.2–1.1 mg/dL)	9	0.488 ± 0.19	24	0.495 ± 0.24	0.9018
BUN (7–25 mg/dL)	9	14.41 ± 7.89	25	18.77 ± 14.6	0.8605
Creatinine (Male: 0.64–1.27 mg/dL Female: 0.44–1.03 mg/dL)	9	0.698 ± 0.15	25	0.811 ± 0.448	0.9533
Sodium (136–146 mEq/L)	9	139.4 ± 2.29	25	133.7 ± 27.9	0.8290
Potassium (3.4–4.1 mEq/L)	9	3.722 ± 0.46	25	3.656 ± 0.44	0.5045
CRP (< 5 mg/L)	9	15.51 ± 16.6	25	39.32 ± 65.2	0.7847
Ferritin (Male: 30–400 ng/mL Female: 13–160 ng/mL)	7	369.0 ± 436.7	19	473.6 ± 346.6	0.3859
IL-6 (< 7 pg/ml)	4	10.81 ± 14.3	13	34.92 ± 58.8	0.3958
WBC (3.9–10.6, 1000/ul)	9	6.578 ± 3.63	25	6.704 ± 2.81	0.6253
RBC (4.5–5.9 million/uL)	9	4.753 ± 0.75	25	4.510 ± 0.72	0.3904
Hemoglobin (13.5–17.5 g/dL)	9	12.98 ± 2.01	25	13.27 ± 1.65	0.9222
Platelet (150–400, 1000/uL)	9	319.9 ± 120	25	232.0 ± 104	0.0665
Segment (42–74%)	9	59.74 ± 17.1	25	68.20 ± 15.5	0.1599
Lymphocyte (20–56%)	9	28.59 ± 14.3	25	23.74 ± 13.5	0.4012
Monocyte (0–12%)	9	7.100 ± 2.59	25	6.464 ± 2.46	0.5064
Eosinophil (0–5%)	9	3.633 ± 4.47	25	1.124 ± 1.91	0.1816
Basophil (0–1%)	9	0.488 ± 0.47	25	0.244 ± 0.25	0.1838
ESR (Male: 0–20 mm/hr, Female: 0–30 mm/hr)	8	23.63 ± 11.1	17	33.71 ± 29.9	0.9534
PT (10–13 s)	8	12.38 ± 0.69	22	12.40 ± 1.31	0.6218
Hospital length of stay (Days)	9	20.44 ± 15.13	25	37.44 ± 36.51	0.0892
Parameters	AG (n)		GG (n)		*P* value[c]
Gender					
Male	4		12		1.0000
Female	5		13		
Respirator					
without	9		19		0.1622
with	0		6		
ICU stay					
without	9		18		0.1506
with	0		7		
Antiviral drug					
without	5		10		0.3898
with	2		13		
Death					
No	9		24		1.0000
Yes	0		1		

a: The normal ranges of clinical parameters were defined by the Chang Gung Memorial Hospital

b: Mann-Whitney U test for two groups. Bold values indicate statistical significance $p < 0.05$

c: Fisher's exact test

addition, another WES study found missense variants in ZNF717 to be associated with non-small-cell lung cancer [31]. Overall, these results underscore ZNF717 genetic variations are robust and important between diseases and cancer.

We observed that genetic changes (SNPs) are involved in the severity of COVID-19. Chu et al. demonstrated that the polypeptide N-acetylgalactosaminyltransferase 14 (GALNT14) rs9679162 GG genotype correlates with a higher expression level of GALNT14 in HCC tissues

Table 4 Clinical information of COVID-19 patients in cohort 2

Parameters (normal range[a], unit)	All patients		Symptoms of COVID-19				
			Mild		Severe		*P* value[b]
	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	
Age (year)	71	55.15 ± 18.73	31	43.68 ± 18.09	40	64.05 ± 13.87	**< 0.0001**
BMI (18.5–24.9, kg/m2)	70	20.51 ± 6.109	30	21.42 ± 6.282	40	19.83 ± 5.964	0.4545
AST (≦ 34 U/L)	62	34.94 ± 22.53	23	21.26 ± 8.269	39	52.51 ± 56.79	**0.0003**
ALT (≦ 36 U/L)	70	40.92 ± 47.59	30	24.07 ± 17.46	40	64.20 ± 115.0	**0.0206**
Albumin (3.5–5.4 g/dL)	60	3.266 ± 0.893	21	4.080 ± 0.800	39	2.828 ± 0.582	**< 0.0001**
Total bilirubin (0.2–1.1 mg/dL)	65	1.009 ± 2.450	26	0.596 ± 0.223	39	1.285 ± 3.144	0.1689
BUN (7–25 mg/dL)	71	32.39 ± 36.50	31	17.00 ± 17.10	40	44.32 ± 42.80	**0.0003**
Creatinine (Male: 0.64–1.27 mg/dL Female: 0.44–1.03 mg/dL)	70	1.665 ± 2.198	30	1.041 ± 1.125	40	2.133 ± 2.662	0.0919
Sodium (136–146 mEq/L)	71	141.3 ± 25.74	31	137.9 ± 3.255	40	143.9 ± 34.14	0.4996
Potassium (3.4–4.1 mEq/L)	71	3.808 ± 0.665	31	3.700 ± 0.371	40	3.893 ± 0.821	0.7275
CRP (< 5 mg/L)	70	43.43 ± 51.47	30	30.71 ± 43.09	40	52.97 ± 55.58	**0.0269**
Ferritin (Male: 30–400 ng/mL Female: 13–160 ng/mL)	37	947.6 ± 1842	18	206.5 ± 152.5	19	1650 ± 2386	**0.0001**
IL-6 (< 7 pg/ml)	27	80.95 ± 196.7	18	81.33 ± 223.0	9	80.18 ± 142.0	0.0506
WBC (3.9–10.6, 1000/ul)	70	8.959 ± 5.782	31	7.395 ± 3.653	39	10.20 ± 6.826	0.1286
RBC (4.5–5.9 million/uL)	71	3.988 ± 1.734	31	4.841 ± 1.933	40	3.328 ± 1.224	**< 0.0001**
Hemoglobin (13.5–17.5 g/dL)	71	12.09 ± 6.468	31	13.90 ± 5.926	40	10.69 ± 6.591	**< 0.0001**
Platelet (150–400, 1000/uL)	71	201.0 ± 106.9	31	212.1 ± 57.25	40	192.5 ± 133.5	0.0565
Segment (42–74%)	71	73.60 ± 15.95	31	68.48 ± 13.23	40	77.57 ± 16.89	**0.0018**
Lymphocyte (20–56%)	71	16.60 ± 14.82	31	20.78 ± 12.45	40	13.36 ± 15.82	**0.0015**
Monocyte (0–12%)	71	7.234 ± 4.093	31	8.406 ± 3.208	40	6.325 ± 4.496	**0.0073**
Eosinophil (0–5%)	71	1.494 ± 2.269	31	1.497 ± 2.037	40	1.493 ± 2.460	0.3131
Basophil (0–1%)	71	0.384 ± 0.509	31	0.4161 ± 0.286	40	0.360 ± 0.634	**0.0146**
ESR (Male: 0–20 mm/hr, Female: 0–30 mm/hr)	25	30.36 ± 31.76	17	13.65 ± 21.3	8	65.88 ± 32.61	**0.0011**
PT (10–13 s)	62	13.42 ± 2.937	25	12.77 ± 2.276	37	13.86 ± 3.267	0.0100
Hospital length of stay (days)	71	38.20 ± 55.11	31	21.94 ± 60.24	40	50.80 ± 47.81	**< 0.0001**
Parameters	All patients (n)		Mild (n)		Severe (n)		*P* value[c]
Gender							
Male	14		14		31		**0.0067**
Female	17		17		9		
Respirator							
without	28		31		19		**< 0.0001**
with	6		0		21		
ICU stay							
without	27		31		18		**< 0.0001**
with	7		0		22		
Antiviral drug							
without	15		21		3		**< 0.0001**
with	15		10		37		
Death							
No	33		30		27		**0.0021**
Yes	1		1		13		

a: The normal ranges of clinical parameters were defined by the Chang Gung Memorial Hospital

b: Mann-Whitney U test for two groups. Bold values indicate statistical significance $p < 0.05$

c: Fisher's exact test

versus noncancerous tissues [32]. Recently, the correlation between tyrosine kinase 2 (TYK2) genotypes/its expression level and severity of COVID-18 was determined based on Sanger sequencing and qRT-PCR, respectively [33]. The results revealed that the TYK2 rs2304255 TT genotype, rs12720354 AA genotype and rs12720207 GG genotype are associated with the severity of COVID-19 through suppression of gene expression, in turn modulating the TYK2-mediated inflammatory response. This evidence revealed that expression of this

Table 5 Associations between ZNF717-rs2918520 genotypes and clinical parameters in cohort 2

Parameters (normal range[a], unit)	**ZNF717-rs2918520 genotypes**				
	AG		**GG**		***P* value[b]**
	n	**Mean ± SD**	**n**	**Mean ± SD**	
Age (year)	19	49.21 ± 17.11	52	57.33 ± 18.98	0.1044
BMI (18.5–24.9, kg/m2)	18	22.48 ± 7.058	52	19.83 ± 5.660	0.1855
AST (≦ 34 U/L)	16	23.81 ± 9.975	46	46.87 ± 53.83	0.0689
ALT (≦ 36U/L)	18	25.22 ± 19.94	52	54.54 ± 102.3	0.1221
Albumin (3.5–5.4 g/dL)	15	3.487 ± 1.054	45	3.193 ± 0.833	0.3933
Total bilirubin (0.2–1.1 mg/dL)	15	0.533 ± 0.303	50	1.152 ± 2.780	0.5205
BUN (7–25 mg/dL)	19	40.54 ± 52.27	52	29.42 ± 28.81	0.9896
Creatinine (Male: 0.64–1.27 mg/dL Female: 0.44–1.03 mg/dL)	18	2.046 ± 2.182	52	1.533 ± 2.209	0.2162
Sodium (136–146 mEq/L)	19	138.7 ± 4.759	52	142.2 ± 29.97	0.7494
Potassium (3.4–4.1 mEq/L)	19	3.868 ± 0.693	52	3.787 ± 0.661	0.7061
CRP (< 5 mg/L)	19	41.88 ± 49.42	51	44.01 ± 52.69	0.7513
Ferritin (Male: 30–400 ng/mL Female: 13–160 ng/mL)	13	697.0 ± 920.7	24	1083 ± 447.8	0.7868
IL-6 (< 7 pg/ml)	9	101.9 ± 284.7	18	70.48 ± 143.9	0.4105
WBC (3.9–10.6, 1000/ul)	19	7.847 ± 4.345	51	9.374 ± 6.221	0.3450
RBC (4.5–5.9 million/uL)	19	3.853 ± 0.953	52	4.038 ± 1.948	0.5330
Hemoglobin (13.5–17.5 g/dL)	19	11.41 ± 2.824	52	12.34 ± 7.373	0.4021
Platelet (150–400, 1000/uL)	19	203.5 ± 96.03	52	200.1 ± 111.5	0.5721
Segment (42–74%)	19	71.50 ± 13.83	52	74.37 ± 16.72	0.3079
Lymphocyte (20–56%)	19	17.99 ± 12.99	52	16.09 ± 15.52	0.3598
Monocyte (0–12%)	19	7.689 ± 3.413	52	7.067 ± 4.333	0.4094
Eosinophil (0–5%)	19	1.411 ± 1.709	52	1.525 ± 2.456	0.9158
Basophil (0–1%)	19	0.310 ± 0.333	52	0.411 ± 0.561	0.7108
ESR (Male: 0–20 mm/hr, Female: 0–30 mm/hr)	7	14.71 ± 11.40	18	36.44 ± 35.19	0.3176
PT (10–13 s)	14	14.08 ± 3.457	48	13.23 ± 2.779	0.8530
Hospital length of stay (Days)	19	32.42 ± 75.02	52	40.31 ± 46.53	0.1318
Parameters	AG (n)		GG (n)		*P* value[c]
Symptom					
mild	13		6		**0.0153**
severe	18		34		
Gender					
Male	11		34		0.5878
Female	8		18		
Respirator					
without	16		34		0.1517
with	3		18		
ICU stay					
without	16		33		0.1468
with	3		19		
Antiviral drug					
without	8		16		0.4054
with	11		36		
Death					
No	14		43		0.5021
Yes	5		9		

a: The normal ranges of clinical parameters were defined by the Chang Gung Memorial Hospital

b: Mann-Whitney U test for two groups. Bold values indicate statistical significance $p < 0.05$

c: Fisher's exact test

gene is regulated by its genetic variant (SNP). Moreover, mRNA levels (extracted from blood samples) of the MUC family, including MUC1, MUC2, MUC4, MUC5AC, MUC5B, MUC6, MUC13, MUC16, MUC20, and MUC21, in healthy controls, non-COVID-19 patients with mild symptoms, COVID-19 patients with mild symptoms, and critically ill COVID-19 patients in the ICU have been assessed [34]. The results showed that mRNA levels of MUC1 and MUC2 to be upregulated in the COVID-19 with mild symptom group and the critically ill COVID-19 in the ICU group compared to the healthy control group. Conversely, expression levels of MUC16 were higher in the non-COVID-19 mild symptom group than in the healthy control group and the critically ill COVID-19 ICU group. These findings suggest that different genes of the MUC family may function as important regulators of COVID-19-induced symptoms. Based on transcription level analysis, the MUC family is associated with symptoms of COVID-19 via different mechanisms. Multiple studies have reported that S100A8/A9 is a pivotal regulator of inflammatory processes, such as pulmonary infectious diseases and chronic obstructive pulmonary disorder, and is also involved in mediating the process of COVID-19 pathogenesis [35]. Notably, a group showed that the protein levels of thrombospondin 1 (TSP1) and TSP2 were higher in COVID-19 patients than in healthy controls [36]. Moreover, clinical analysis revealed that these two proteins correlate with clinical parameters and biochemistry factors, including ESR, CRP, procalcitonin, ferritin, ALT, AST, BUN, creatine kinase, and lactate dehydrogenase. By using an antibody microarray with machine learning analysis, Hufnagel and colleagues demonstrated that three combinations at the protein level (1: S100A8/A9, TSP1, FINC, IFNL1, 2: S100A8/A9, TSP1, ERBB2 and 3: S100A8/A9, TSP1, IFNL1) is able to predict the severity of COVID-19 during the early stage [37]. Taken together, previous observations and our investigations revealed that information from DNA (genomic variants) to mRNA (transcription level) to protein (translational level) may act as biomarkers for evaluating the severity of COVID-19. Therefore, the associations of mRNA and protein levels of ZNF717 and COVID-19 need to be elucidated in the future.

Our findings reveal that several parameters, including age, AST, BUN, CRP, ferritin, and segment are significantly associated with symptoms. A systematic meta-analysis reported that older patients with SARS-CoV-2 infection have severe symptoms [38]. Another report showed that mildly elevated AST levels correlate with the severity of COVID-19 [39]. If the level of serum potassium is lower than 3.5 mEq/l, it was considered hypokalemia. The Alfano et al. group demonstrated that hypokalemia was associated with COVID-19 [40]. Furthermore, sex, particularly female sex, and diuretic therapy are major contributors to hypokalemia. CRP serves as an inflammation marker [41]. A clinical association study demonstrated that CRP is a strong indicator of mortality in patients with COVID-19 [42]. Levels of ferritin in the male group with COVID-19 were found to be higher than those in the female group [43]. On the other hand, high levels of ferritin have been associated with the severity of COVID-19, indicating that ferritin may serve as an indicator of COVID-19 severity. Levels of WBCs and lymphocytes also correlate positively and negatively, respectively, with COVID-19 severity [44]. The correlations between clinical parameters and COVID-19 in several studies are mostly consistent with our findings, except for platelet levels. Nevertheless, the ZNF717 rs2918520 genotype was not associated with any clinical parameters. The limitation of this study was that the sample size for determining associations between the ZNF717 rs2918520 genotype and COVID-19 symptoms was small. In addition, little information regarding the SARS-CoV-2 strain in clinical samples was available. Thus, clinical associations between the ZNF717 rs2918520 genotype and SARS-CoV-2 strain should be explored in the future.

Conclusions

Increasing evidence reported that the genetic variance such as SNP of individual has the potential role for developing personalized medicine. This is the first study to uncover the clinical significance of ZNF717 in COVID-19 patients. The ZNF717 rs2918520 GG genotype may be considered a predictor for evaluating the severity of COVID-19 in the Taiwanese population. These findings would allow doctors to diagnose and intervene quickly to reduce patient suffering.

Abbreviations

SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
COVID-19	Coronavirus disease 2019
ACE2	Angiotensin-converting enzyme 2
SNP	Single-nucleotide polymorphisms
WES	Whole-exome sequencing
RT-PCR	Reverse transcriptase polymerase chain reaction
PBMC	Peripheral blood mononuclear cell
FDR	False discovery rate
LD	Linkage disequilibrium
SD	Standard deviation
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CRP	C-reactive protein
WBC	White blood cell
RBC	Red blood cells
ESR	Erythrocyte sedimentation rate (ESR)
IGFN1	Immunoglobulin like and fibronectin type III domain containing 1
ZNF717	Zinc finger protein 717
MUC12	Mucin 12
GPRIN2	G protein regulated inducer of neurite outgrowth 2
PABPC3	Poly(a) binding protein cytoplasmic 3
FCGBP	Fc gamma binding protein (FCGBP)

TPTE	Transmembrane phosphatase with tensin homology
XKR3	XK related 3
TMPRSS2	Transmembrane protease serine 2
ApoE	Apolipoprotein E
BIN1	Bridging integrator 1
HCC	Hepatocellular carcinoma
GALNT14	N-acetylgalactosaminyltransferase 14
TYK2	Tyrosine kinase 2
TSP	Thrombospondin

Supplementary Information

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Supplementary Material 1

Author contributions

Conceptualization, YHL, JY, YCT and WRL; methodology, YHL and JY; formal analysis, YHL, JY, YCT, CGH, SNL and MWL; investigation, YHL, JY, CGH, SNL and MWL; writing-original draft preparation, YHL and JY; writing-review and editing, YHL, JY and WRL; supervision, WRL; funding acquisition, WRL. All authors have read and agreed to the published version of the manuscript. All authors have read and approved the manuscript including content and presentation to the BMC Infectious Diseases.

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Data availability

The information of ZNF717 rs2918520 genotypes has been deposited in clinVAR (https://www.ncbi.nlm.nih.gov/clinvar) with submission ID SUB14253415 (https://www.ncbi.nlm.nih.gov/clinvar/submitters/509452).

Declarations

Ethics approval and consent to participate

Before performing experiments, informed consent of individuals was collected. Our assays were approved by the Medical Ethics and Human Clinical Trial Committee at Chang Gung Memorial Hospital (IRB No. 202101285B0C501). Informed consent was obtained from all subjects involved in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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