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Research Article

Evaluating Persistent Symptoms of SARS-CoV-2 Infection by Precision Medicine

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ABSTRACT

During these two years, the SARS-CoV-2 pandemic spread fast, killing people as surely as the global war. Step by step, research revealed several aspects of this plague. Understanding the essential etio-pathological characteristics of SARS-CoV-2 infection is necessary to outline discuss and assess its pathogenic mechanism and proceed with proper viral behaviours assessment. Coronaviruses are enveloped by positive-sense and negative-sense RNA viruses. Their characteristic is a characteristic long spike protein projecting from the surface. These viruses have an unusual huge RNA genome (that is up to 33.5 kilobases). These viruses are the largest Noroviruses; the order includes Coronaviridiae and includes the order which includes the Coronaviridae, Arteriviridneae, Mesoniviridieae, and Roniviridieae families. Coronaviruses have two subfamilies, Corinaviridea Orthocoronavirinae and Torviridiae Letovirinae. The taxonomy subdivides Orthocoronavirinae Coronaviridiae into different genera, e.g., the alfa, the beta, and gamma Coronaviruses. The coronavirus virion structure of coronaviruses is spherical with a diameter of 125 nm.

Keywords: Viral pathogenesis, Precision medicine, Persistent symptoms, Biomarkers, Polymorphism, Personalized medicine.

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ABBREVIATIONS

SARS-CoV-2: Severe Acute Respiratory Syndrome Corona Virus 2; OR: Odds Ratio; CI: Confidence Interval.

INTRODUCTION

Viral activity is determined based on the replication and transportation of viral RNA, its synthesis and assimilation of viral replication complexes. Coronaviruses cause a large variety of diseases in mammals as well as other companion animals. In humans, they cause 15%-20% of annual respiratory infections. Even though SARS-CoV-2 has inefficient transmission, it still spreads widely during the pandemic. It spreads directly through the hosts during the onset of transmission by becoming aerosolised. Tailoring of treatments to patient dates to at least the time of Hippocrates. Therefore, personalised medicine is the most appropriate approach for developing a targeted therapy for patients suffering from long COVID-19 and other chronic issues stemming from having had COVID-19 [1].

Coronavirus particles contain four proteins: the spike, membrane, envelope and nucleocapsid. The spike protein (150 kDa) starts and initiates the signal sequence once the N-terminal accesses the Endoplasmatic reticulum. The homodimer encoding the spike protein then make forms a structure on the viruses' surface. Most coronavirus infect the host cell with two separate polypeptides of furan-like protease proteases into two separate polypeptides, spike-1 (S1) and spike-2 (S2). While S1 is the receptor for the binding domain, S2 forms the stalk of the spike molecule. The membrane protein causes the virus to exist as a virion dimer of the virion [2]. It promotes the membrane curvature as well as binds the nucleocapsid. The envelope protein is a small (approximately 8-12 kDa) with a divergent structure. It plays a crucial role in releasing the release of the virus virions, and so it plays a key role during therefore in the pathogenesis of SARS-CoV-2 pathogenesis. The nucleocapsid protein just constitutes itself the nucleocapsid. It comprises two separate domains, an N-terminal and C-terminal domain. Heavy phosphorylation of this protein results in structural changes, enhancing its affinity for nonviral RNA. The interaction between nucleoside transport proteins and other packaging proteins constitutes is a component of the replicate replication complex. These protein interactions help the viral genome to replicate three gene transcriptase and package the genome into the viral particles. The initial virion attachment to the host cell starts with the spike protein and receptor. The receptor site binding is within the S1 receptor part. Coronaviruses have a receptor-binding domain at the C-terminus of spike-1 (S1). This path is the primary interaction derivation by which the virion starts hosting RNA and infects the host. It is the call initial action that results in starting virus tropism into the cell and thus infection of the host cell, leading to viral by protein replication in the cytosol and the exposition in the cytosol release of virions. Generally, in Coronaviruses, the replicase gene encodes two wide ORGF Open Reading Frames (ORFs), rep1a and rep1b, which express two polyproteins, pp1a and pp1ab. These two last polyproteins contain the serine proteases 1-11 and 1-16. The polyprotein pp1ab, along with the protein nsp11 derived from pp1qa becomes serine protease-12 following the extension of pp1a into pp1b. The neutrophil serine protease's protease function includes RNA replication and immune response blocking. Viral activity is determined based on the replication and transportation of viral RNA. It synthesises and also helps in assimilation of viral replicase replication complexes. Viral replication starts with 16-neutrophil serine proteases non-structural proteases non-structural proteins. Virion assembly and release follow the replication [3]. The subgenomic RNA, as also it Sub genomic RNA inserted

into the endoplasmic reticulum synthesises viral structural protein; inserted into the endoplasmic reticulum. Following the assembly, virions reached are transported to the cell surfaces in vesicles *via* exocytosis. For decades, research has been infusing energy into the molecular aspect of pathogenesis.

MATERIALS AND METHODS

This study aims to assign a proper centric position to patients rather than the etiological phases of the illness. Misunderstanding and misinterpretation due to bio scientific measurements lost in translation made imprecise the treatment of complex illnesses. However, etio-pathogenetic features seem essential in understanding any infectious disease development. The core attention should be on interpreting patients' personal features to optimise efficacy and safety to reduce morbidity and mortality. It is time to reflect on the knowledge advanced for future therapeutic strategies. Nowadays, it is clever to consider the human being in a centric position. Patients' long-term symptom control can start with precision medicine.

Meta-analyses and systematic reviews are preferred due to their quality of evidence. Evidence-based medical criteria were used to appraise the findings reported in the further section [4].

RESULTS

First, the meta-analysis assessed the persistence of more than 50 long-term effects of SARS-CoV-2. The confidence interval was set to 95%, and the PRISMA statement was used to critically appraise the included studies. In the 47,910 included patients (age range: 17-87 years), symptoms persisted 14 to 110 days after infection. Studies have determined that 80% of SARS-CoV-2 patients develop one or more long-term symptoms. The five most common long-term symptoms were fatigue (58%), headaches (44%), attention disorder (27%), hair loss (25%), and dyspnoea (24%). A complete list of persistent COVID-19 symptoms follows, categorised by frequency and variety (Table 1) [5,6].

Table 1: Genetic roots of COVID-19 Biomarkers individual genetics and personal predisposition.

Name/ Gene ID	Description	Location	Aliases
EGFR	Epidermal growth factor receptor *Homo sapiens* (human)	Chromosome 7 7NC_000007.14 (55019017...55211628)	ERBB, ERBB1, ERRP, HER1, NISBD2, PIG61 mENA
TNF	Tumor necrosis factor *H. sapiens* (human)	Chromosome 6 6NC_000006.12 (31575565...31578336)	DIF-alpha, TNFA, TNFSF2, TNLG1F, TNF
VEGF	Vascular endothelial growth factor *Homo sapiens* (human)	Chromosome 6 NC_000006.12 (43770209...43786487)	VEGFA MVCD1, VEGF, VPF
IL-6	Interleukin 6 *Homo sapiens* (human)	Chromosome 7 NC_000007.14 22725889...22732002	IFNB2, BSF-2, BSF2, CDF, HGF, HSF, IFN-beta-2, IFNB2, IL-6
IL-10	Interleukin 10 *Homo sapiens* (human)	Chromosome 1 NC_000001.11 206767602...206772494, complement	CSIF, GVHDS, IL-10A, TGIF, IL10
ACE	Angiotensin-I-converting enzyme *Homo sapiens* (human)	Chromosome 17 NC_000017.11 (63477061...63498373)	ACE1, CD143, DCP, DCP1
STAT3	Signal transducer and activator of transcription 3 *Homo sapiens* (human)	Chromosome 17 NC_000017.11 42313324...42388502, complement	STAT3 ADMIO, ADMIO1, APRF, HIES
CRP	C-reactive protein *Homo sapiens* (human)	Chromosome 1 NC_000001.11 (159712289...159714589, complement)	PTX1
NFKB1	Nuclear factor kappa B subunit 1 *Homo sapiens* (human)	Chromosome 4 NC_000004.12 (102501266...102617302)	NF-kappa-B, CVID12, EBP-1, KBF1, NF-kB, NF-kB1, NF-kappa-B1, NF-kappa beta, NFKB-p105, NFKB-p50
IL-1B	Interleukin 1 beta *Homo sapiens* (human)	Chromosome 2 NC_000002.12 (112829751...112836843, complement)	IL-1-beta IL-1, IL-1-BETA, IL-1F2
TLR4	Toll-like receptor 4 *Homo sapiens* (human)	Chromosome 9 NC_000009.12 (117704403...117724735) ARMD10	TLR-4, TOLL CD284
CXCL8	C-X-C motif chemokine ligand 8 *Homo sapiens* (human)	Chromosome 4 NC_000004.12 (73740569...73743716)	SCYB8, GCP-1, GCP1, IL8, LECT, LUCT, LYNAP, MDNCF, MONAP, NAF, NAP-1, NAP1
MOTR	Mechanistic target of rapamycin kinase *Homo sapiens* (human)	Chromosome 1 NC_000001.11 (11106535...11273497, complement)	FRAP, FRAP1, FRAP2, RAFT1, RAPT1, SKS 601231
INFG	Interferon gamma *Homo sapiens* (human)	Chromosome 12 NC_000012.12 (68154768...68159740, complement	INF GAMMA IFG, IFI, IMD69
JANK2	Janus kinase 2 *Homo sapiens* (human)	Chromosome 9 NC_000009.12 (4984390...5129948)	JNK 2 JTK10
CD4	CD4 molecule *Homo sapiens* (human)	Chromosome 12 NC_000012.12 (6789528...6820799)	CD 4+ CD4mut, IMD79, OKT4D
IL-17A	Interleukin 17A *Homo sapiens* (human)	Chromosome 6 NC_000006.12 (52186375...52190638)	IL-17A, CTLA-8, CTLA8, IL-17, ILA17

SERPINE1	Serpin family E member 1 *Homo sapiens* (human)	Chromosome 7 NC_000007.14 (101127104...101139247)	PAI-1, PAI, PAI1, PLANH1
CCL2	C-C motif chemokine ligand 2 *Homo sapiens* (human)	Chromosome 17 NC_000017.11 (34255285...34257203)	SMC-CF GDCF-2, HC11, HSMCR30, MCAF, MCP-1, MCP1, SCYA2
NPPB	Natriuretic peptide B *Homo sapiens* (human)	Chromosome 1 NC_000001.11 (11857464...11858945, complement)	Iso-ANP, BNP

The percentage of patients experiencing brain sequelae is as follows:

- Headache (44%),
- Attention disorder (27%),
- Anosmia (21%),
- Memory loss (16%),
- Anxiety (13%),
- Depression (11%),
- Fever (11%),
- Sleep disorder (8%),
- Sleep apnoea (8%),
- Healthcare-related and mental health issues (6%),
- Psychiatric illnesses (6%),
- Dizziness (3%),
- Stroke (3%),
- Dysphoria (2%),
- Mood disorder (2%),
- Paranoia (0.3%).

Other symptoms include the following:

- Fatigue (58%),
- Sweating (17%),
- Weight loss (12%),
- Pain (11%),
- Chills (7%),
- New-onset hypertension (1%),
- Ageusia (23%),
- Cough (19%),
- Red eyes (6%),
- Hearing loss/tinnitus (15%),
- Urinary hesitancy (5%),
- Nausea (16%),
- Dyspnoea (24%),
- Pulmonary fibrosis (5%),
- Reduced pulmonary capacity (10%),
- Renal failure (1%),
- Cutaneous signs (12%),
- Joint pain (19%),
- Limb oedema (3%),
- Digestive disorder (12%),
- Diabetes mellitus (4%),
- Arrhythmia (0.4%),
- Myocarditis (1%),
- Palpitation (11%),
- Chest pain discomfort (16%),
- Restring heart rate increase (11%),
- Polypnea (21%).

Second, two further systematic reviews assessed persistent symptoms at the post-viral stage of SARS CoV-2, including the frequency and variety of persistent symptoms. In the first systematic review, among the 145 eligible papers, 30 were on persistent lung symptoms (20.70%), 35 were on persistent neurological and olfactory dysfunctions (24.13%), and 80 were on widespread, persistent symptoms (55.17%).

In the second systematic review, 992 full texts were eligible for assessment out of 52,266. Of 45 studies reporting clinical signs, 30 had a median age younger than 60. In 16 of these studies, the median proportion of individuals who needed hospitalisation was 72.5% (interquartile range: 55.0%-80%). Frequent individual symptoms such as shortness of breath or dyspnoea (the median frequency of these symptoms in 26 studies was 36.0%; interquartile range: 27.6%-50%), fatigue or exhaustion (median in 25 studies: 40.0%, interquartile range: 31.0%-57.0%) and sleep disorders (median in 8 studies: 29.4%, interquartile range: 24.4%-33.0%). Systematic reviews provide a precise assessment of heterogeneous literature findings but do not investigate individual differences in patients' disease characteristics.

Biomarkers associated with COVID-19 symptoms are listed in the following Table 1. Using precision medicine, it is possible to assess the pathogenetic mechanisms that mediate expression. The cumulative effect of pathogenetic factors is due to individual genetics and personal predisposition.

DISCUSSION

An additional step could improve the assessment of long-term symptoms: associating human genetic factors with SARS-CoV-2 infection. Polymorphism, allelic variation, and genetic predisposition improve the assessment of patients' clinical conditions by clarifying the genetic determinants of severity and susceptibility. In this manner, studying long symptoms could assess causality instead of frequency and variety. Similarly, biomarkers should be assessed according to genetic expression. Studies have demonstrated that the factors determining the severity and long-term symptoms of COVID-19 vary according to human chromosomal polymorphisms.

- The human chromosomal polymorphism 3p21.31 (spanning genes *SLC6A20, LZTFL1, CCR9, FYCO1, CXCR6, and XCR1*) has been linked to severe symptoms like respiratory failure (Odds Ratio (OR): 1,77, 95% Confidence Interval (CI): 1,48-2.11 p=1,15 X 10-10).

- The *ABO* gene polymorphism rs657152 on chromosome 9q34.2 is associated with a higher risk of infection in patients with A-type blood (OR: 1.45%-95% CI: 1, 20-1.75% P=1.48%, 10-4), and a lower risk of infection for O-type blood (OR: 0.65%, 95% CI: 0.53-0.79 P=1.06 X 10-5).

- The *ACE2* gene polymorphism p. Arg514-glyn on chromosome XP22.2 indicates the risk of cardiovascular and pulmonary complications in African and African American populations, as it alters the AGT-ACE2 pathway.

- The *ApoE* gene polymorphism rs429358-C-C (e4e4) on chromosome 6p21.33 indicates the risk of vulnerability to disease for patients with HLA-B 46:01 and cross-prospective T-cell-based immunity for HLA-B 15:03.

- The *IFITIM3* gene polymorphism rs12252-C/C on chromosome 11p15.5 indicates the risk of mild to moderate disease requiring hospitalisation.
- The *TLR7* gene polymorphisms g.12905756_129055759del and g.12906010G>T on chromosome Xp22.2 indicate the risk of severe disease.
- The *TMEM189-UBE21V1* gene polymorphism rs6020298-A on chromosome 20Q13.13 also indicates a risk of severe disease.
- TMPRSS2 p. VAL160Met (sr12329760) on chromosome 21q22.3 indicates the risk of increased susceptibility to disease or another risk factor, e.g., cancer.

CONCLUSION

Personalised medicine, also known as precision medicine, is a medical approach that categorises patients according to their genetic differences. Medical decisions, practice, and (primarily) intervention are based on a tailored individual medical approach derived from personal genetic assessment. This leads to a more precise assessment of risk and disease response, intending to improve diagnostic quality as well as efficacy and safety. Stratified medicine aims to treat patients based on coactivity. Long-term symptoms on a large timescale can be accessed *via* stratified approaches. Identifying a characteristic of human susceptibility to COVID-19 could reveal the applications of personalised medicine in treating COVID-19. As personalised assessment provides a more accurate evaluation, it can predict severe disease and prolonged symptomatology in individual patients to offer more efficient personalised and targeted therapy. It will lead to the future of clinical assessment and COVID-19 patients' treatment.

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The author declares no conflicts of interest. He conceived, conceptualized, drafted the article and critically revised the article. The author reviewed the literature and contributed to the outline and writing of the final manuscript.

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The author has no conflicts of interest to declare.

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