Thrombocytopenia in COVID-19 and vaccine-induced thrombotic thrombocytopenia

STYLIANI A. GERONIKOLOU[1,2], IŞIL TAKAN[3,4], ATHANASIA PAVLOPOULOU[3,4], MARINA MANTZOURANI[5*] and GEORGE P. CHROUSOS[1,2*]

[1]Clinical, Translational and Experimental Surgery Research Centre, Biomedical Research Foundation Academy of Athens; [2]University Research Institute of Maternal and Child Health and Precision Medicine, and UNESCO Chair on Adolescent Health Care, National and Kapodistrian University of Athens, Aghia Sophia Children's Hospital, 11527 Athens, Greece; [3]Izmir Biomedicine and Genome Center (IBG); [4]Izmir International Biomedicine and Genome Institute, Dokuz Eylül University, 35340 Izmir, Turkey; [5]First Department of Internal Medicine, Laiko Hospital, National and Kapodistrian University of Athens Medical School, 11527 Athens, Greece

Received October 21, 2021; Accepted December 28, 2021

DOI: 10.3892/ijmm.2022.5090

Abstract. The highly heterogeneous symptomatology and unpredictable progress of COVID-19 triggered unprecedented intensive biomedical research and a number of clinical research projects. Although the pathophysiology of the disease is being progressively clarified, its complexity remains vast. Moreover, some extremely infrequent cases of thrombotic thrombocytopenia following vaccination against SARS-CoV-2 infection have been observed. The present study aimed to map the signaling pathways of thrombocytopenia implicated in COVID-19, as well as in vaccine-induced thrombotic thrombocytopenia (VITT). The biomedical literature database, MEDLINE/PubMed, was thoroughly searched using artificial intelligence techniques for the semantic relations among the top 50 similar words (>0.9) implicated in COVID-19-mediated human infection or VITT. Additionally, STRING, a database of primary and predicted associations among genes and proteins (collected from diverse resources, such as documented pathway knowledge, high-throughput experimental studies, cross-species extrapolated information, automated text mining results, computationally predicted interactions, etc.), was employed, with the confidence threshold set at 0.7. In addition, two interactomes were constructed: i) A network including 119 and 56 nodes relevant to COVID-19 and thrombocytopenia, respectively; and ii) a second network containing 60 nodes relevant to VITT. Although thrombocytopenia is a dominant morbidity in both entities, three nodes were observed that corresponded to genes (AURKA, CD46 and CD19) expressed only in VITT, whilst ADAM10, CDC20, SHC1 and STXBP2 are silenced in VITT, but are commonly expressed in both COVID-19 and thrombocytopenia. The calculated average node degree was immense (11.9 in COVID-19 and 6.43 in VITT), illustrating the complexity of COVID-19 and VITT pathologies and confirming the importance of cytokines, as well as of pathways activated following hypoxic events. In addition, PYCARD, NLP3 and P2RX7 are key potential therapeutic targets for all three morbid entities, meriting further research. This interactome was based on wild-type genes, revealing the predisposition of the body to hypoxia-induced thrombosis, leading to the acute COVID-19 phenotype, the 'long-COVID syndrome', and/or VITT. Thus, common nodes appear to be key players in illness prevention, progression and treatment.

Correspondence to: Dr Styliani A. Geronikolou, Clinical, Translational and Experimental Surgery Research Centre, Biomedical Research Foundation Academy of Athens, 4 Soranou Ephessiou Street, 11527 Athens, Greece
E-mail: sgeronik@bioacademy.gr; sgeronik@gmail.com

*Contributed equally

Key words: SARS-CoV-2, COVID-19, thrombocytopenia, vaccine-induced thrombotic thrombocytopenia, interactions network, HLA system, enzymes, lymphocytes, autoimmunity, artificial intelligence, cytokine storm, natural language processing

Introduction

The current SARS-CoV-2-induced pandemic has raised a number of public health policy and scientific queries, related to the virus origin, transmission, activity, contamination, pathophysiologic effects and treatment. As of May 3, 2021, almost 188 million cases had been confirmed, while 4.05 million deaths had been registered under the cause of death: 'COVID-19'. Although this may underline an apogee of the third phase of the pandemic in some countries, or may have been the result of certain interventions. Public health policy approaches, communication campaigns, pharmacological approaches, surveillance, and prevention practices have been suggested.

The highly varying symptomatology and the unpredictable global progress of COVID-19 have triggered an

unprecedentedly intensive activity in biomedical research and public policy decisions. Furthermore, although the pathophysiology of the disease is being progressively clarified, its complexity remains vast, and preventive care approaches or treatments, although both have significantly improved, remain unsatisfactory.

Notably, the extremely rare yet highly unpredictable and occasionally lethal vaccination-induced thrombotic thrombocytopenia (VITT) syndrome has emphasized the gaps in the current knowledge of certain unsuspected pathophysiological pathways. The VITT morbid entity is of particular importance given the generally mild and to a certain extent expected vaccination side-effects, namely chills, fever, diarrhea, fatigue, muscle pain, headache and mildly increased blood coagulability (1,2). As of April 2021, 16 vaccination options were available: Two RNA vaccines [BNT162b2 (Comirnaty) by Pfizer-BioNTech, mRNA.1273 (Spikevax) by Moderna], seven conventional inactivated ones (CoronaVac, Covaxin, BBIBP-CorV, WIBP-CorV, Minhai-Kangtai, QazVac, CovIran Bakerat), five viral vector-employing ones (Covishield and Vaxzevria by Oxford Astra-Zeneca, the Janssen COVID-19 vaccine by Johnson & Johnson, the Sputnik V and Sputnik Light by the Gamaleya Research Institute of Epidemiology and Microbiology in Russia, and the AD5-nCOV-Convidencia by CanSino Biologics Inc.), and two protein subunit vaccines (EpiVacCorona and RDB-dimer). Vaccination programs have been implemented so as to reach 'herd immunity', in every country. According to national health authority reports, as of August 30, 2021, 5.27 billion doses had been administered globally. This is equal to 39.7% of the population on the planet (where, however, only 1.6% of individuals in the low-income countries had received at least one dose), having been fully vaccinated (3). As of August 30, 2021, 55.15% of the Greek population had been fully vaccinated (3).

The aim of the present study was to illustrate the signaling pathways implicated in SARS-CoV-2 infection, including those of the extremely rare, yet severe VITT syndrome.

Data and methods

The scientific literature database, MEDLINE/PubMed (https://pubmed.ncbi.nlm.nih.gov/), was searched thoroughly for genes or gene products implicated in COVID-19 infection and VITT syndrome. Searches were conducted in the PubTator article collection (4) (https://www.ncbi.nlm.nih.gov/research/pubtator/) from the LitCovid database (5), using i) ('COVID19' OR 'SARS-CoV-2') AND ('VITT' OR 'vaccine-induced thrombotic thrombocytopenia'); ii) ('COVID19' OR 'SARS-CoV-2') AND ('thrombocytopenia' OR 'thrombopenia') key words to obtain relevant articles. Of the 495 candidate articles, 190 met the inclusion criteria which were as follows: i) written in English; ii) include an abstract; and iii) contain adequate information in their text for processing (Fig. 1).

The natural language toolkit (NLTK: https://www.nltk.org/), a freely accessible Python platform, was used for text processing, including tokenization, parsing and stemming. Word2vec embeddings module in the open-source Python library Gensim (https://pypi.org/project/gensim/) was implemented to train word vectors of processed text. A list of all word-to-word distances was extracted. To calculate the similarity distances between each word pair, the *Word2Vec.most_similar* function in Gensim Word2vec model was used. The top 50 detected entries were included in the present study. The work flow is presented in Fig. 1. The search results are illustrated in Fig. 2.

Furthermore, the interactions among the retrieved genes/proteins were investigated by employing the Search Tool for Retrieval of Interacting Genes/Proteins (STRING) database v11.0 (6,7), a database containing both primary and predicted, physical and functional association data among genes or proteins. These data are collected from diverse resources, such as documented pathway knowledge, high-throughput experimental studies, cross-species extrapolated information, automated text mining results, computationally predicted interactions, etc. The confidence threshold value for displaying interactions was set to 'high' (i.e., 0.7). The interactions in the generated network were manipulated and visualized through Cytoscape (http://www.cytoscape.org/) (8), a software platform for network processing and statistical analyses; the Edge Betweenness mode was used to detect the number of the shortest paths that pass-through a given edge in the COVID-19 network.

Results

Main findings. The constructed networks presented in Fig. 2 provide noteworthy information on how diverse terms are closely interlinked within the context of thrombocytopenia induced by SARS-CoV-2 infection or through vaccination. The term thrombocytopenia appears with a rather high frequency in the COVID-19/VITT network (Fig. 2A). Similarly, the term VITT is included in the COVID-19/thrombocytopenia network (Fig. 2B). COVID-19 and VITT share several comorbidities implicating vascular and epithelial dysfunction and thrombocytopenia. The nodes represent the top 50 words with a cosine similarity score of each word vector >0.9.

Interactome construction. Subsequently, two interactomes were constructed: The first one involving 119 nodes is described in Table I and illustrated in Fig. 3. Collectively, 119 nodes are involved in COVID-19, while 57 are implicated in thrombocytopenia [the latter profits from an unpublished work of ours (unpublished data). Of these, 14 nodes were common in both entities (Figs. 3 and 4), namely AIM2, IFI16, NOD2, CD8A, IL-1B, 1L-6, JAK2, NCAM1, HLA-DRB1, SERPINE1, TGFB1, TLR2, TNF and VWF. The major hubs detected are displayed in the center of the constructed circular network, while the less connected nodes are shown at the periphery of the circle (Fig. 3). The thrombocytopenia-related nodes are represented in square bullets, and the COVID-19-related ones are presented in circles, whilst the common nodes are depicted in rhomboids. The calculated average node degree of the entire interactome was extremely high (11.9).

The second one including 61 molecules, is described in Table I and illustrated in Fig. 5. Of these, 47 are common with thrombocytopenia (indicated by a polygon), and 16 with COVID-19 (represented by circles). The VITT-related molecules are denoted with triangles.

Venn diagrams were further created to illustrate the nodes that are common between thrombocytopenia and COVID-19

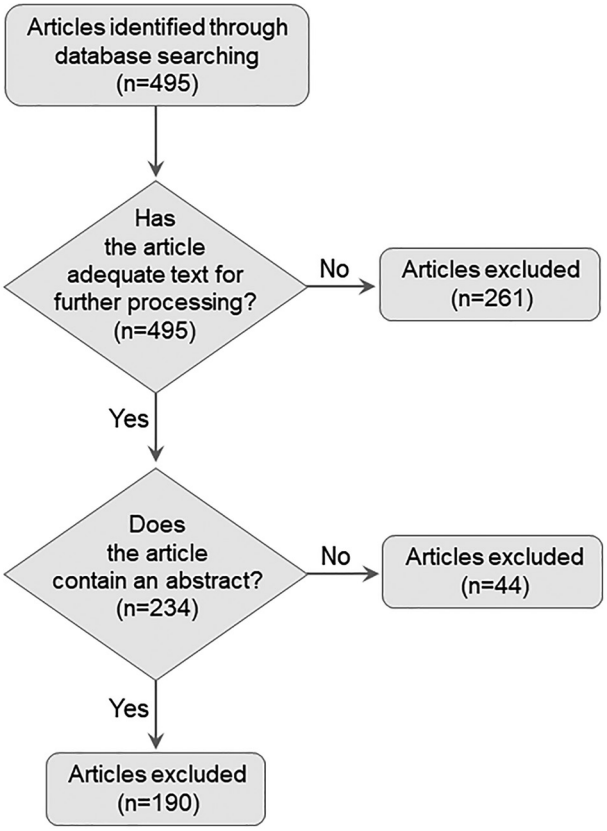

Figure 1. Flowchart of the process followed for the acquisition of eligible articles containing relevant data.

or VITT (Fig. 4A and B, respectively), between COVID-19 and VITT (Fig. 4C), and amid the three morbid entities (Fig. 4D). The common nodes are listed in each diagram in detail.

All included molecules herein are listed in Table I. The figure (network) in which each molecule is implicated is also noted in a separate column in Table I.

Discussion

Epidemics were already identified as entities in antiquity by Hippocrates and named by him in his Treatises '*On Epidemics*' (9,10). Viral epidemics were described therein and in other works of the Hippocratic Corpus (11,12). On the other hand, Aristotle, the ancient Greek physician and philosopher (4th century B.C.) wrote that '*the creativeness of nature focuses on qualities rather than quantities and description rather than measurements*' (13,14). This concept was rejected by Newton's determinism and reductionism and was since forgotten, until it was re-established by Wulff in 1999 (15). Indeed, subtle change in qualities may trigger phase shift alterations with unpredictable consequences, as the Chaos theory of dynamic systems recently confirmed (16). According to this concept, the systems theory was coined as representing a rapid, cost and time-effective method of research (17). It may integrate basic, preclinical and clinical research, and both human and animal results to unravel new insights in complex and often unpredictable issues. In the case of the COVID-19 pandemic, the urgency, and certain ethical issues, make such an *in silico* approach a *sine qua non* research method.

The human-to-human transmission of SARS-CoV-2 is either mediated by respiratory droplets via sneezing/coughing or even just breathing, while the disease demonstrates an incubation period of 5-7 days (18). The clinical outcomes range from asymptomatic to influenza-like, or to even pneumonia and severe acute respiratory distress syndrome (ARDS) (19), and thromboembolic events (20,21), pointing to the lung tropism of this virus. Dissimilarities in patients' profiles are attributed to genetic and/or epigenetic variations and underlying pathologies. Dissimilarities in severity may be attributed to the aforementioned factors, but also to the size of the viral inoculum and/or viral mutations.

COVID-19 and the thrombocytopenia interactions network. Ariadne's thread appears to be the angiotensin I converting enzyme 2 (ACE2), which clearly plays a crucial role. SARS-CoV-2, via its spike S protein, a surface glycoprotein that surrounds the spherical virus, is attached to ACE2 and this is followed by entry into cells of the host (22-27). ACE2 is expressed in cells of a number of human organs (including the skin, nasal and oral mucosa, lung, nasopharynx, brain, lymph nodes, thymus, stomach, small intestine, colon, bone marrow, spleen, liver and kidneys). Additionally, its expression in lung alveoli (type 2 pneumonocytes) and small intestine endothelium, as well as in the arterial and other tissue smooth muscle epithelium (28), may trigger the release of anaphylatoxin (29). There is clinical evidence to confirm the aforementioned knowledge of COVID-19 (29).

In the generated network illustrated in Fig. 2, ACE2 interacts with CYP11B2 and with IL-6. The latter is the greatest hub in this vastly interconnected network, with 63 interactions, confirming that the progress of SARS-CoV-2-induced infection would profit from therapeutic blockade of IL-6. As noted by Mazzoni *et al* (24), blocking this mechanism would '*suppress noxious systemic inflammation but also restore the protective antiviral potential*'. It has been established that innate immunity via natural killer (NK) cells exerts the frontline defense, with $CD8^+$ T-lymphocytes being important for the long-term surveillance against viruses, while adaptive immune responses play a key role in the control of viral infections (28). Both responses are mediated either via cytotoxicity or by IF-γ, IL-12 and IL-18. Virus-induced cytotoxicity is primarily moderated by perforin and granzymes. Increased severity in viral infections may lead to dysregulated immunity and tissue/organ damage (30). Clinical evidence in SARS-CoV-2 infection has demonstrated that high IL-6 levels in patients in intensive care units, are inversely associated with the concentration of NK cells (24,31).

The network included dense interactions illustrating clearly that SARS-CoV-2-specific T-cells are critical for the extended damage caused by the 'cytokine storm' (or 'cytokine release syndrome') (30,32) (Fig. 3). This excessive inflammatory response may be lethal for some patients (29,33). Although the phenomenon may manifest in other inflammatory conditions, including bacterial sepsis, pneumonia, sterile inflammation, etc., the extent in the secretion of several specific cytokines is different in COVID-19-related storm (29). Of note, COVID-19 infection has been associated with changes in the blood coagulation mechanisms, with differing manifestations in different patients, in distinct phases of the disease, and independently of disease severity.

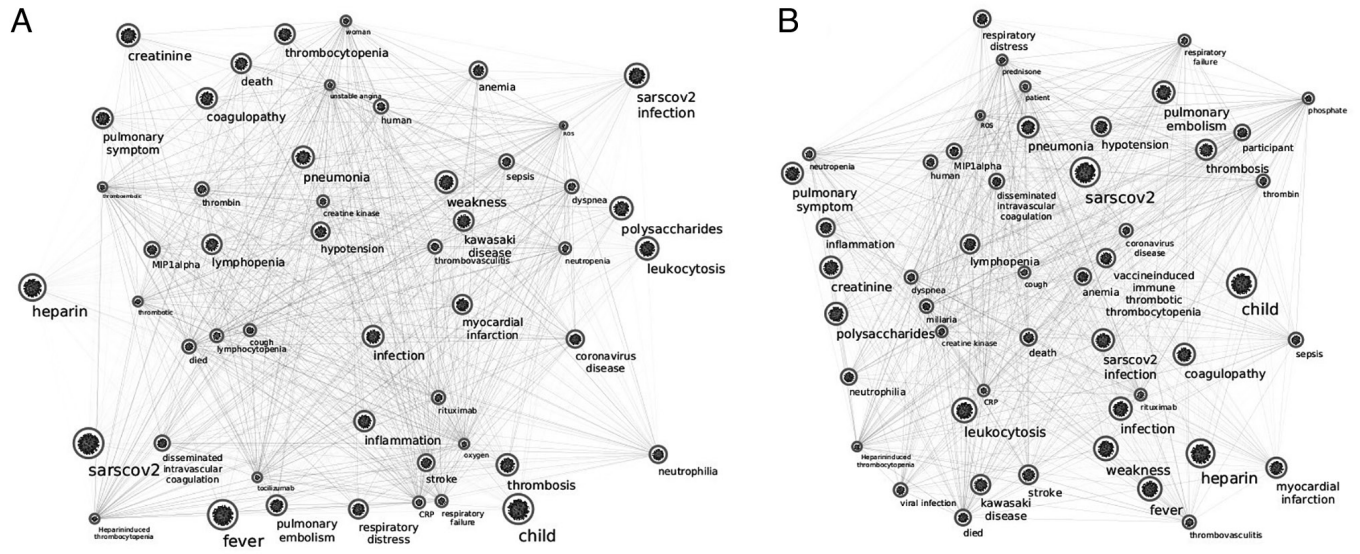

Figure 2. Networks depicting the semantic relations of the top 50 most similar words to the query (A) COVID-19 or VITT, and (B) thrombocytopenia. Only those word pairs with a cosine similarity score of each word vector >0.9 are shown. The nodes represent the words and the edges denote the semantic associations between them. The size of the nodes indicates the frequency of occurrence of the given term. VITT, vaccine-induced thrombotic thrombocytopenia.

Autoimmune destruction of platelets, cytokine release and high consumption of coagulation factors and platelets have been observed in patients with SARS-CoV-2 infection (Geronikolou *et al*, unpublished data) and initial hypercoagulability (34). Thromboembolic events increase by 31% in patients with COVID-19 admitted in intensive care units (35,36); the phenomenon may be interpreted by the 'two way activation theory' (20,37), i.e., thrombogenesis via inflammation-relevant pathways, with parallel occurrence of release of VWF large polymers. The coagulation and platelet profiles of patients with COVID-19 are then rather normal, unlike in patients with sepsis where platelets are activated and consumed, with the occurrence of thrombocytopenia (38). Only a few patients may then survive, particularly of those with extensive disseminated intravascular coagulation (38). Thrombosis has been observed *in situ* in the lungs, as well as in a systemic manner, in a similar fashion with classic sepsis and acute respiratory distress syndrome. Reported thromboembolic complications include mostly venous pulmonary embolism (38), aortic graft thrombosis, and mesenteric ischemia; coronary and cerebral thrombosis cases have been reported, although these are rare. The so-called 'COVID toe' is a sign of thrombosis accompanied by arterial and venous clots, urgent oxygen demand and multiple organ dysfunction (20,36,39).

COVID-19 and thrombocytopenia interactomes share only 14 nodes (AIM2, IFI16, TLR2, NOD2, NKAM1, IL-6, TNF, JAK2, IL-1B, SERPINE1, HLA-DRB1, TGFB1, CD8A, and VWF) (Fig. 3), most of which serve as major hubs (IL-6, TNF, JAK2, IL-1B, SERPINE1, TGFB1, CD8A and VWF) in the herein presented interactome (Figs. 1 and 2).

Cytokines, such as IL-1B, 1L-6 and TNF contribute to the so-called cytokine storm, as aforementioned. Moreover, JAK2 is a kinase suspected to be implicated in thrombocytopenia via reduced levels of thrombopoietin or via decreased expression levels of their cognate receptors (cMpl receptors). JAK2 mutations (V617F) that are present in the majority of patients with myeloproliferative disease, may increase hematopoietic cell sensitivity to erythropoietin and thrombopoietin. NKAM1 or CD56 is a homophilic binding glycoprotein expressed on the surface of neurons, glia cells and skeletal muscles. NKAM1 is a prototypic marker of NK cells, also present in $CD8^+$ T-cells. These cell types exhibit diminished antiviral ability and cytotoxic impairment during COVID-19 infection (24). CD8A1 is a cytotoxic marker for T-cell populations. SERPINE1 or plasminogen activator inhibitor-1 is a protein encoded by the *SERPINE1* gene, which participates in both thrombosis and atherogenesis (40).

TGFB1 is a multifunctional peptide, with diverse activities, including the control of cell growth, proliferation, differentiation, and apoptosis. It can also down-regulate the activity of immune cells via decreasing the expression levels of cytokine receptors, such as that of IL-2. Several types of T-cells secrete TGFB1, so as to inhibit cytotoxicity and the secretion of certain cytokines, such as interferon-γ, TNF-α and various interleukins, such as IL-6. This makes this molecule a potential target of therapeutic value. On the other hand, the hemostatic VWF is detected in blood plasma, endothelium and megakaryocytes, as well as in subendothelial connective tissue. This factor appears to be also increased and implicated in autoimmune diseases, such as thrombotic thrombocytopenic purpura, as well as in stroke and atrial fibrillation, due to the platelet clots that are potentially formed when its levels are elevated.

Recent literature has further revealed that an HLA class I and II molecule, that is, HLA-DRB1, which is common in COVID-19 and in thrombocytopenia networks (Fig. 2), may play a role in the observed COVID-19 individual and ethnic diversity in clinical severity and/or response to therapy or vaccination (41-44). Of note, HLA-DRB1 is interconnected with the lymphocyte function markers CD3D, CD3E, CD3G, CD4, lymphocyte regulation positive FCGR1A, FCGR1B, HLA class I and II molecules, such as HLA-A, HLA-B, similar to the NCAM1, PTPN1, SHC1 and VCAM1 molecules that have been implicated in thrombosis and atherosclerosis.

Table I. Genes included in the molecular networks depicted in Figs. 3 and 4.

Gene symbol	Gene name	Main function with brief description (Refs.)	Figure(s)	Entity[a]
ACE2	Angiotensin I converting enzyme 2	Transmembrane protein-entry point of SARS-CoV-2 (22-24,28)	3	C
ADAM10	ADAM metallopeptidase domain 10	Sheddase with strong specificity for peptide hydrolysis reactions (68-70)	3	T
ADAM17	ADAM metallopeptidase domain 17	Sheddase triggering release of cytokines receptors, ligands, etc. (68,69,71)	3,4	V, T
ADAMTS13	ADAM metallopeptidase with throm bospondin type 1 motif 13	Enzyme that cleaves von Willebrand factor (68,69)	3,4	V, T
ADRA2C	Adrenoceptor alpha 2C	Mediators in catecholamine-induced inhibition of adenylate cyclase through the action of G proteins (72)	3	C
ADRB1	Adrenoceptor beta 1	Renin release/lipolysis/Increases heart rate with chrono/inotropic effect (73)	3	C
ADRB2	Adrenoceptor beta 2	Facilitating respiration (74)	3	C
AGER	Advanced glycosylation end-product specific receptor	Mediates interactions of advanced glycosylation end products (75)	3	C
AIM2	Interferon-inducible protein AIM2	AIM2 inflammasome plays a crucial role in the defense against viral infection (76)	3	C, T
ANGPT1	Angiopoietin 1	Receptor of advanced glycosylation end products of proteins, mediating amyloid beta peptide effect on neurons and microglia (77)	3	C
ANGPT2	Angiopoietin 2	Binds to TEK/TIE2, competing for the ANGPT1 binding site, and modulating ANGPT1 signaling (78)	3	C
AURKA	Serine/threonine-protein kinase 6	Orchestrate an exit from mitosis by contributing to the completion of cytokinesis the process through which the cytoplasm of the parent cell is split into two daughter cells (79)	4	V
C4B	Complement C4B (Chido blood group)	Mediator of local inflammatory process, inducing the contraction of smooth muscle, increasing vascular permeability and causing histamine release from mast cells and basophilic leukocytes (80)	3,4	V, T
C5	Complement C5	Involved in the complement system (81)	3,4	V, T
C6	Complement C6	Causes cell lysis (82)	3,4	V, T
C7	Complement C7	Creates a hole on pathogen surfaces leading to cell lysis (82)	3,4	V, T
C9	Complement C9	Cell lysis and death contributor (82)	3,4	V, T
CASP1	Caspase 1	Inflammatory response initiator (83)	3,4	C, V
CASP10	Caspase 10	Cell apoptosis (84)	3	C
CASP9	Caspase 9	Innate immunity, mitochondrial apoptosis (85)	3	C
CCL2	C-C motif chemokine ligand 2	Induces a strong chemotactic response and mobilization of intracellular calcium ions (86,87)	3	C
CCL3	Chemokine (C-C motif) ligand 3	Pyrogenic, attracting macrophages, monocytes and neutrophils (88)	3	C
CCN2	Cellular communication network factor 2	Cell adhesion, apoptosis, migration, proliferation, differentiation, apoptosis, survival and senescence (89)	3	C
CD3D	CD3d molecule	Cell differentiation and adaptive immune response (90)	3	C
CD3E	CD3e molecule	Cell differentiation and adaptive immune response (90)	3	C
CD3G	CD3g molecule	Cell differentiation and adaptive immune response (90)	3	C

Table I. Continued.

Gene symbol	Gene name	Main function with brief description (Refs.)	Figure(s)	Entity[a]
CD4	CD4 molecule	Cell differentiation and adaptive immune response (91)	3	C
CD40LG	CD40 ligand	Acts as a ligand for integrins which have cell-type dependent effects, such as B-cell activation, NF-κB signaling and anti-apoptotic signaling (92,93)	3	T
CD8A	CD8a molecule	Multiple functions in responses against both ex/internal offenses (91)	3	C, T
CD19	B-lymphocyte antigen CD19	Decreases B-cell receptor pathways (94,95)	4	V
CD40LG	Cluster of differentiation 40	Mediates many immune and inflammatory responses including T-cell-dependent immunoglobulin class switching, memory B cell development, and germinal center formation (96)	3,4	T, V
CD46	CD46 complement regulatory protein	Activates T-lymphocytes following vaccination (97,98)	4	V
CDC20	Cell division cycle 20	Regulates the formation of synaptic vesicle clustering at active zone to the presynaptic membrane in post-mitotic neurons; Cdc20-apc/c-induced degradation of neurod2 induces presynaptic differentiation (91)	3,4	V, T
CDCA3	Cell division cycle associated 3	Involves in protein ubiquitination (99)	3,4	V, T
CRP	C-reactive protein	Mitotic initiator (100)	3	C
CSF1R	Colony stimulating factor 1 receptor	Controls the production, differentiation, and function macrophages (93,101)	3,4	V, T
CSF2	Colony stimulating factor 2	Cytokine affecting mostly eosinophils and macrophages (102)	3,4	V, T
CXCL10	C-X-C motif chemokine ligand 10	Chemoattraction for T- and NK cells, monocytes (87,93,103,104)	3	C
CXCL8	C-X-C motif chemokine ligand 8	Neutrophil chemotactic factor increasing respiratory burst (87,105)	3,4	C, V
CYP11B2	Cytochrome P450 family 11 subfamily B member 2	Aldosterone synthesis (87,106)	3	C
CYP2C19	Cytochrome P450 family 2 subfamily C member 19	Part of cytochrome P450, involved in drug and lipid metabolism (107)	3	C
CYP2C9	Cytochrome P450 family 2 subfamily C member 9	Part of cytochrome P450, involved in drug and lipid metabolism (107)	3	C
DDX58	Retinoic acid-inducible gene I	Activates interferon and cytokines production after viral infection (108)	3	C
EDN1	Endothelin 1	Potent vasoconstrictor (106,109)	3	C
EPO	Erythropoietin	Stimulation of erythropoiesis, vasoconstriction, angiogenesis (106)	3,4	V, T
F2	Coagulation factor II, thrombin	Activates the coagulation cascade inhibition (110)	3,4	V, T
FCGR1A	Fc fragment of IgG receptor Ia	Complex activation or inhibitory effects on cell functions (111)	3,4	V, T
FCGR1B	Fc fragment of IgG receptor Ib	Humoral immune response (112)	3,4	V, T
FCGR2A	Fc fragment of IgG receptor IIa	Humoral immune response to pathogens, phagocytosis of opsonized antigens (113)	3,4	V, T
FCGR2B	Fc fragment of IgG receptor IIb	Phagocytosis of immune complexes and regulation of antibody production (114)	3,4	V, T
FCGR3A	Fc fragment of IgG receptor IIIa	Mediates antibody-dependent cellular cytotoxicity and phagocytosis (115)	3,4	V, T
FCGR3B	Fc fragment of IgG receptor IIIb	Captures immune complexes in the peripheral circulation (116)	3,4	V, T
FGF7	Fibroblast growth factor 7	Cell growth, morphogenesis and tissue repair (117)	3,4	C, V

Table I. Continued.

Gene symbol	Gene name	Main function with brief description (Refs.)	Figure(s)	Entity[a]
FKBP1A	FKBP prolyl isomerase 1A	Immunoregulation and basic cellular processes involving protein folding and trafficking (118)	3,4	V, T
FN1	Fibronectin 1	Cell growth, morphogenesis and tissue repair (70)	3	C
FOS	Fos proto-oncogene, AP-1 transcription factor subunit	Signal transduction, cell proliferation and differentiation (119)	3	C
GNB3	G protein subunit beta 3	Integrates signals between receptor and effector proteins (120)	3	C
GZMA	Granzyme A	Common component necessary for lysis of target cells by cytotoxic T-lymphocytes and natural killer cells (24)	3	C
GZMB	Granzyme B	Recognize specific infected target cells (121)	3	C
GZMH	Granzyme H	Suppresses viral replication (122)	3	C
HLA-A	Major histocompatibility complex, class I, A	Sole link between the immune system and what happens inside cells (123)	3,4	C, V
HLA-B	Major histocompatibility complex, class I, B	Helps the immune system distinguish the endo-from exogenous proteins (123)	3,4	C, V
HLA-DRB1	HLA class II histocompatibility antigen, DRB1 beta chain	Triggers response to viral infections (41)	3,4	C, V, T
ICAM1	Intercellular adhesion molecule 1	Signal transduction (92,93)	3,4	V, T
IFI16	Interferon gamma inducible protein 16	Recognizes RNA viral infection, enhancing DDX58 production (124)	3	C, T
IFNA1	Interferon alpha 1	Antiviral and immunomodulator (125)	3	C
IFNG (IFN-γ)	Interferon gamma	Antiviral antibacterial and immunomodulatory effects (104)	3,4	V, T
IFNL1	Interferon lambda 1	Antiviral antibacterial and immunomodulatory effects (126)	3	C
IFNL2	Interferon lambda 2	Antiviral antibacterial and immunomodulatory effects (126)	3	C
IFNL3	Interferon lambda 3	Antiviral antibacterial and immunomodulatory effects (126)	3	C
IFNLR1	Interferon lambda receptor 1	Antiviral antibacterial and immunomodulatory effects (126)	3	C
IKBKG	Inhibitor of nuclear factor kappa B kinase regulatory subunit gamma	Antiviral activity through JAK/STAT signaling activation (127)	3	C
IL10	Interleukin 10	Multiple, pleiotropic effects in immunoregulation, limits excessive infected tissue disruption (92)	3	C
IL10RB	Interleukin 10 receptor subunit beta	JAK1 and STAT2-mediated phosphorylation of STAT3 (128)	3	C
IL12A	Interleukin 12A	Induces IFNG (92)	3	C
IL12B	Interleukin 12B	Induces IFNG by resting PBMC (92)	3	C
IL17A	Interleukin 17A	Mediates protective innate immunity to pathogens or contributes to pathogenesis of inflammatory diseases (87)	3	C
IL18	Interleukin 18	Potent inducer of inflammatory cytokines, especially IFNG (129)	3	C
IL1A	Interleukin 1 alpha	Promotion of intimal inflammation, fever, sepsis and atherogenesis (41)	3	C
IL1B	Interleukin 1 beta	Promotion of fever, development of diabetes mellitus, apoptosis of pancreatic β-cells (87,105)	3,4	C, V, T
IL1RAP	Interleukin 1 receptor accessory protein	Induces synthesis of acute phase and proinflammatory proteins during infection, tissue damage, or stress (130)	3	C
IL3	Interleukin 3	Growth and differentiation of hematopoietic progenitor cells regulator and functional activator of mature neutrophils or macrophages (131)	3,4	V, T

Table I. Continued.

Gene symbol	Gene name	Main function with brief description (Refs.)	Figure(s)	Entity[a]
IL33	Interleukin 33	Gene transcription regulator, released after cell necrosis triggering immune response and stress (132)	3	C
IL36G	Interleukin 36 gamma	Inflammasome dependent, involved in systemic inflammation (133)	3	C
IL4	Interleukin 4	Hematopoiesis, antibody production, inflammation response (117)	3,4	V, T
IL5	Interleukin 5	Eosinophil migration, activation survival (134)	3,4	V, T
IL6	Interleukin 6	Innate and adaptive immune response to infections (135)	3,4	C, V, T
INS	Insulin	Blood sugar regulator (136)	3	C
ITGA2B	Integrin subunit alpha 2b	Coagulation (137,138)	3,4	V, T
JAK1	Janus kinase 1	Cell growth survival, development differentiation of various cell types (139)	3	C
JAK2	Janus kinase 2	Cell growth and proliferation (139)	3	C, T
JUN	Jun proto-oncogene, AP-1 transcription factor subunit	Gene expression regulator (92)	3	C
KCNE1	Potassium voltage-gated channel subfamily E regulatory subunit 1	Potassium channels regulator (140,141)	3	C
KCNH2	Potassium voltage-gated channel subfamily H member 2	Electrical signals transmission (141)	3	C
KCNJ2	Potassium inwardly rectifying channel subfamily J member 2	Muscle movement (heart or skeletal) (142)	3	C
KCNQ1	Potassium voltage-gated channel subfamily Q member 1	Electrical signals generation and transmission (143)	3	C
LCN2	Lipocalin 2	Sequesters iron and preventing its use by bacteria, thus limiting their growth (144)	3	C
MMP1	Matrix metallopeptidase 1	Degrades collagen type I and II (145,146)	3	C
MMP2	Matrix metallopeptidase 2	Extracellular matrix (146)	3	C
MPL	MPL proto-oncogene, thrombopoietin receptor	Proliferator of cells involved in blood clotting (147)	3,4	V, T
MS4A1	Membrane spanning 4-domains A1	Regulator of cellular calcium influx necessary for the B-lymphocytes activation (148)	3,4	C, V
MS4A3	Membrane spanning 4-domains A3	Marker of immature circulating neutrophils, a cellular population associated to COVID-19 severe disease (148)	3	C
MUC1	Mucin 1, cell surface associated	High viscosity of airway mucus and sputum retention in the small airway of COVID-19 patients (149)	3	C
MYD88	MYD88 innate immune signal transduction adaptor	Initiates early immune responses (150)	3	C
NCAM1	Neural cell adhesion molecule 1	Molecular mimicry between NCAM-1 and the SARS-CoV-2 envelope protein (151)	3	C, T
NFAT5	Nuclear factor of activated T-cells 5	Protects cells against harmful effects of stress (137)	3	C
NFATC1	Nuclear factor of activated T-cells 1	Transcription factor (137)	3,4	C, V
NFATC2	Nuclear factor of activated T-cells 2	Neuroinflammatory factor (137)	3	C
NFATC3	Nuclear factor of activated T-cells 3	Involved in proliferation of human pulmonary fibroblasts after hypoxic stimulus (137)	3	C
NFATC4	Nuclear factor of activated T-cells 4	Transcriptional regulator in naive T-cells and differentiated effector T-cells, dependent on calcium/PLCγ/calmodulin/calcineurin signaling (137)	3	C

Table I. Continued.

Gene symbol	Gene name	Main function with brief description (Refs.)	Figure(s)	Entity[a]
NFKB1	Nuclear factor kappa B subunit 1	Activated by various intra/extra-cellular stimuli as viruses (92)	3,4	C, V
NLRP3	NLR family pyrin domain containing 3	Intracellular sensor that detects a broad range of pathogen motifs (59)	3,4	C, V
NOD2	Inflammatory bowel disease protein 1	Activates NFKB1, negatively regulates TLR2 (152,153)	3	C, T
NOS1	Nitric oxide synthase 1	Chemical messenger (154,155)	3	C
NOS1AP	Nitric oxide synthase 1 adaptor protein	Inhibitor of Nnos (156)	3	C
NOS3	Nitric oxide synthase 3	Regulating vascular tone, cellular proliferation leucocyte adhesion and platelet aggregation (157,158)	3	C
NTRK1	Neurotrophic receptor tyrosine kinase 1	Development and survival of neurons (159)	3,4	V, T
NTRK2	Neurotrophic receptor tyrosine kinase 2	Development and maturation of the central and the peripheral nervous systems (159)	3,4	V, T
NTRK3	Neurotrophic receptor tyrosine kinase 3	Development of heart and nervous (159)	3,4	V, T
OLFM4	Olfactomedin 4	Facilitates cell adhesion, most probably through interaction with cell surface lectins and cadherin (160)	3	C
P2RX1	Purinergic receptor P2X 1	Ligand-gated ion channel with relatively high calcium permeability (161)	3	C
P2RX7	Purinergic receptor P2X 7	Receptor for ATP that acts as a ligand-gated ion channel (162)	3,4	C, V
PDGFA	Platelet derived growth factor subunit A	Wound healing (163)	3	C
PECAM1	Platelet and endothelial cell adhesion molecule 1	Cell adhesion (164)	3	C
PLAUR	Plasminogen activator, urokinase receptor	Localizing and promoting plasmin formation (165)	3	C
PPP3CB	Protein phosphatase 3 catalytic subunit beta	Transduction of intracellular Ca(2+)-mediated signals (166)	3	C
PRF1	Perforin 1	Defense against virus-infected cells (122)	3	C
PTGS2	Prostaglandin-endoperoxide synthase 2	Role in the inflammatory response (167)	3	C
PTPN11	Protein tyrosine phosphatase non-receptor type 11	Positively regulates MAPK signal transduction pathway (168,169)	3	C
PYCARD	PYD and CARD domain containing	Key mediator in apoptosis and inflammation (170,171)	3,4	C, V
REN	Renin	Angiotensin I from angiotensinogen generator in the plasma, initiating a cascade of reactions that produce an elevation of blood pressure and increased sodium retention by the kidney (172,173)	3	C
SCL11A2	Natural resistance-associated macrophage protein 2	Important in metal transport and their insertion into mitochondria (174)	3,4	V, T
SCN5A	Sodium voltage-gated channel alpha subunit 5	Responsible for the initial upstroke of the action potential in an electrocardiogram (175)	3	C
SELE	Selectin E	Immunoadhesion (176)	3,4	V, T
SELP	Selectin P	Mediates rapid rolling of leukocyte rolling over vascular surfaces during the initial steps in inflammation through interaction with SELPLG (177)	3,4	V, T

Table I. Continued.

Gene symbol	Gene name	Main function with brief description (Refs.)	Figure(s)	Entity[a]
SERPINE1	Serpin family E member 1	Alveolar type 2 cells senescence in the lung (178)	3	C, T
SERPINE2	Serpin family E member 2	Serine protease inhibitor with activity toward thrombin, trypsin, and urokinase (40)	3	C
SFTPC	Surfactant protein C	Lowering the surface tension at the air-liquid interface in the peripheral air spaces (179)	3	C
SFTPD	Surfactant protein D	May participate in the extracellular reorganization or turnover of pulmonary surfactant, regulates immune response (180)	3	C
SHC1	SHC adaptor protein 1	Signaling adapter that couples activated growth factor receptors to signaling pathways (181)	3	T
SIGIRR	Single Ig and TIR domain containing	Inflammation immune, response modulator (182)	3	C
SLC11A2	Solute carrier family 11-member 2	Metal transporter (183)	3	T
SOCS1	Suppressor of cytokine signaling 1	Exerts the viral virulence effect *via* inhibition of type I and type II interferon (IFN) function (184)	3,4	V, T
STXBP2	Syntaxin binding protein 2	Involved in cytolytic pathway (185)	3	T
TBK1	TANK binding kinase 1	Regulator of inflammatory responses to foreign agents (186)	3	C
TF	Transferrin	Transports of iron from sites of absorption and heme degradation to those of storage and utilization (187)	3,4	V, T
TFPI	Tissue factor pathway inhibitor	Anticoagulant protein blocking the initiation of blood coagulation by inhibiting TF-f VIIa and early forms of prothrombinase (188)	3,4	V, T
TFRC	Transferrin receptor	Erythropoiesis and neurologic development (189)	3,4	V, T
TGFB1	Transforming growth factor beta 1	Gene expression proliferation (70)	3	C, T
THPO	Thrombopoietin	Regulates platelets and macrophages differentiation (190)	3,4	V, T
TICAM1	Toll-like receptor adaptor molecule 1	Native immunity against invading pathogens (191)	3	C
TLR2	Toll-like receptor 2	Pathogen recognition-potential therapeutic target (192-194)	3	C, T
TLR4	Toll-like receptor 4	Upregulated after SARS-CoV-2 infection (195)	3	C
TNF	Tumor necrosis factor	Biomarker of COVID-19 severity (104)	3,4	C, V, T
TNFRSF1A	TNF receptor superfamily member 1A	Contributes to the induction of non-cytocidal TNF effects including anti-viral state and activation of the acid sphingomyelinase (93,104)	3	C
TNFRSF1B	TNF receptor superfamily member 1B	Regulates TNF-α function by antagonizing its biological activity (93,104)	3	C
TRAF3	TNF receptor associated factor 3	Regulates pathways leading to a NFKB and MAP kinases activation, and B-cell survival (196)	3	C
TYK2	Tyrosine kinase 2	Antiviral activity (197)	3	C
VCAM1	Vascular cell adhesion molecule 1	Mediates the adhesion of lymphocytes, monocytes, eosinophils and basophils to vascular endothelium (198)	3,4	V, T
VEGFA	Vascular endothelial growth factor A	Dominant inducer to blood vessels growth (increases their permeability) (199)	3	C
VKORC1	Vitamin K epoxide reductase complex subunit 1	Reduces inactive vitamin K 2,3-epoxide to active vitamin K (200)	3	C
VWF	von Willebrand factor	Involved in hemostasis and thrombosis (201)	3,4	C, V, T

[a]Entities: C, COVID-19; V, vaccine-induced thrombotic thrombocytopenia; T, thrombocytopenia.

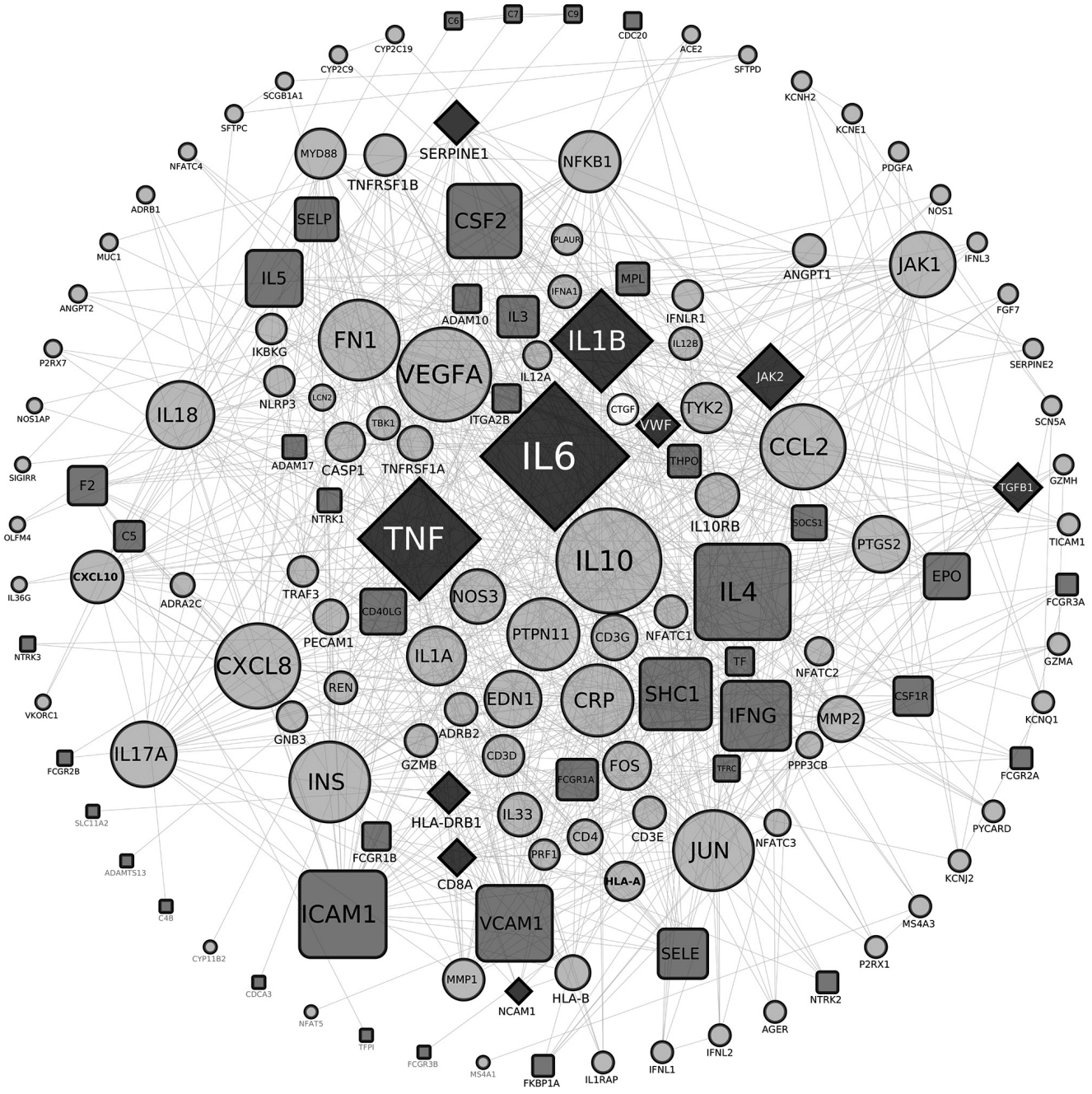

Figure 3. COVID-19 and thrombocytopenia interaction network. COVID-19 molecules are represented by circles; thrombocytopenia-related molecules are represented by squares; common molecules are represented by rhomboids.

NCAM1 is involved in cell-cell adhesion in neural-muscle cells in the embryonic phase and later, and more notably, in the responsiveness to viral infections (rabies virus and papilloma virus) (45). PTPN1 is a potential therapeutic target of obesity and type 2 diabetes mellitus as well (46); SHC1 is implicated in reactive oxygen species regulation, thus, in the oxidative stress response (47), while VCAM1 is directly involved in thrombosis and atherogenesis and acute respiratory syndrome (48-51).

VITT and thrombocytopenia interactome. Various coagulation mechanisms have been implicated in VITT: High levels of D-dimers and low levels of fibrinogen have been observed in patients (2,52,53). On the other hand, early reports of VITT described a higher incidence of the syndrome in young women, exhibiting both age-dependence and sexual dimorphism. VITT, though very rare, is of utmost importance. Yet, in March, 2021, the European Medicines Agency (EMA) issued a statement noting that the thromboembolic events of VITT in vaccinated populations were not higher than in general population (54). Subsequently, the 'risk vs. benefit' equilibrium was weighed by the World Health Organization (WHO), promoting the benefit of the vaccination vs. the extremely low risk of thromboembolic risk of VITT in the general population (55).

VITT is currently termed 'thrombosis with thrombocytopenia syndrome (TTS)' by the Centers for Disease Control and Prevention (CDC) and the US Food and Drug Administration (FDA) (56), and is characterized by arterial and venous thrombosis at unexpected sites (i.e., cerebral venous sinuses,

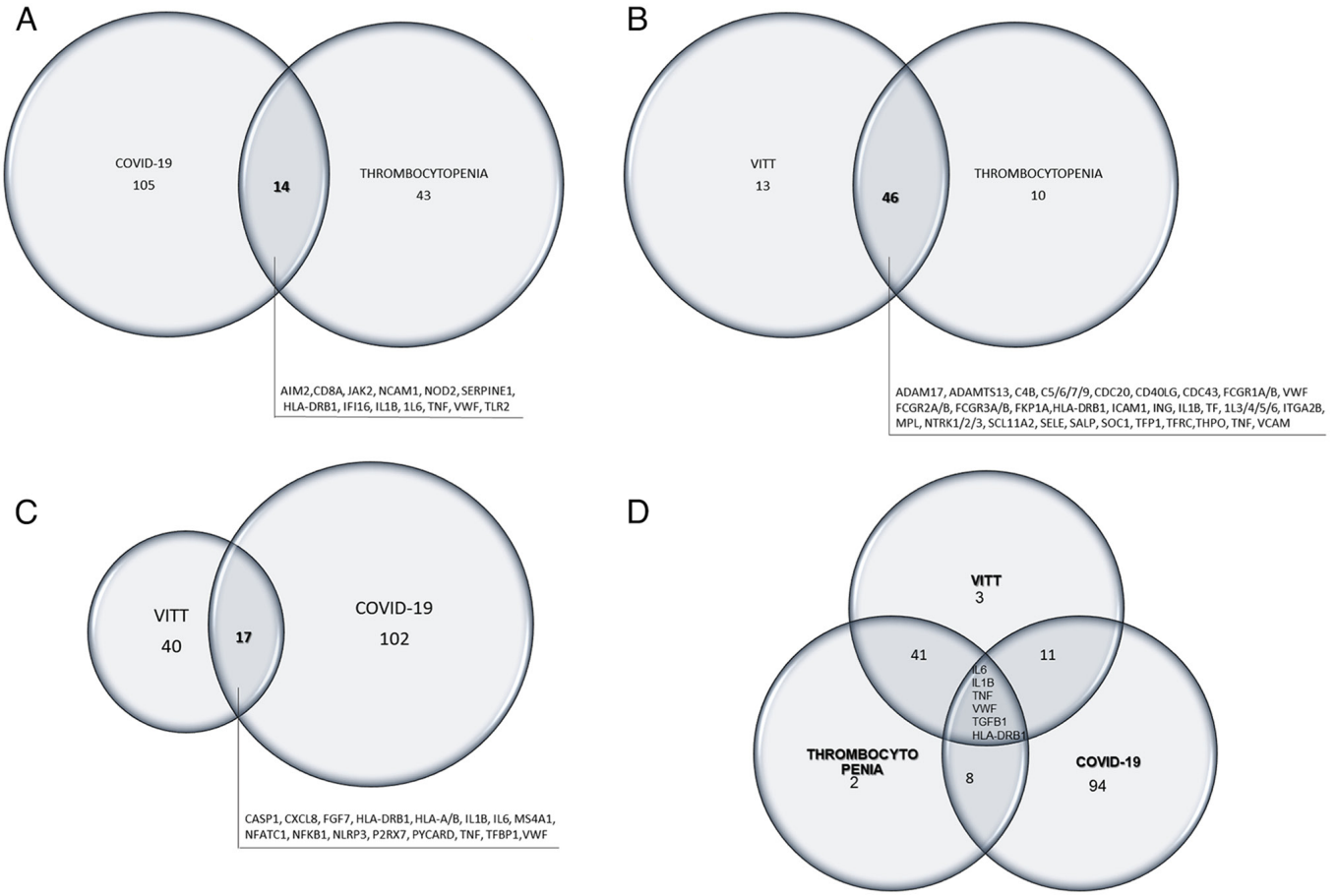

Figure 4. Overlaps between and amid all three morbid entities in Venn diagrams: (A) between COVID-19 and thrombocytopenia, (B) between VITT and thrombocytopenia, (C) between COVID-19 and VITT, and (D) amid all. VITT, vaccine-induced thrombotic thrombocytopenia.

splanchnic vessels of variant severity and/or positive platelet factor (PF) 4-heparin ELISA ('HIT' ELISA) syndrome (52), exhibiting both age dependence and sexual dimorphism (more frequent in individuals <50 years old and of the female sex) (2). The laboratory and clinical features of this syndrome are similar to those of the heparin-induced thrombocytopenia (HIT) syndrome and/or the HIT-like autoimmune thrombosis with thrombocytopenia syndrome (2,52,53), both of which have already been reported following surgery, the uptake of certain pharmaceuticals, or during some infections in patients that are not being treated with heparin. The therapeutic suggestions of this recently coined syndrome include early initiation of non-heparin anticoagulation, high-dose IVIG, and/or prednisolone (57).

The genetic basis of the VITT syndrome appears to be closely intertwined with that of the COVID-19 disease and, as such, they share 16 nodes: CASP1, CXCL8, FGF7, HLA-A, HLA-B, IL1B, IL6, MS4A1, NFATC1, NFKB1, NLP3, P2RX7, PYCARD, TNF, TFP1, VWF (Figs. 3-5). The purpose of the vaccine is to inhibit pathways that mediate this condition (52,58). More importantly, the relevant research is ongoing with the extremely rare cases of this syndrome, as VITT incidence is ~0.74-1 cases per 100,000 vaccinated subjects (52). Of note, the anti-COVID-19 vaccines do not cause illness and the two morbid entities (COVID-19 and VITT) are by no means identical, with the etiopathology of the latter being actually autoimmune, with auto-antibodies against platelet factor 4. More explicitly, COVID-19 network shares 14 nodes with thrombocytopenia (AIM2, CD8A, HLA-DRB1, IFI16, IL1B, IL6, JAK2, NCAM1, NOD2, SERPINE1, TGFB1, TLR2, TNF and VWF), while VITT (which is a type of thrombocytopenia) shares 46 nodes with thrombocytopenia (Figs. 3-5). Notably, SHC1, STXBP2, CDC20 and ADAM10 are silenced in VITT, while AURKA, CD46, CD19 are uniquely expressed following vaccination (apparently not expressed in common thrombocytopenia or in COVID-19) (Figs. 3-5). These molecules were not previously identified as VITT-related and are, thus, a novel finding, at least to the best of our knowledge.

It is known that the NLP3 inflammasome is implicated in both COVID-19 and VITT, apart from its participation in other inflammatory reactions (59). It has also been previously demonstrated that acute thrombotic events may manifest during hypoxia, as shown in COVID-19, due to an early proinflammatory state in the venous milieu, mediated by a HIF-induced NLP3 inflammasome complex (60,61). In the network constructed in the present study, NLP3 connects with CASP1, IL-IB, IL17A, CXCL8, IL-6, MYD88, NFKB1, P2RX7, PYCARD and TNF.

P2RX7 exhibits sexually dimorphic and contrasting roles in the pathogenesis of thrombosis, depending on the pathogen type, the severity of infection, the cell type infected and the level of tissue activation (62). In the thrombocytopenia/COVID-19/VITT cases, the viral load, the cell-type infected

Table II. Common direct connections between 'PYCARD' or 'P2RX7' and 'COVID-19' or 'VITT'.

Gene	COVID-19	VITT	COMMON direct connections
PYCARD	NLP3, CASP1, IL1B, IL18, IKBKG	NLP3, CASP1, IL1B	NLP3, CASP1, IL1B
P2RX7	NLP3, CASP1, P2RX1	CASP1, IL1B	CASP1
COMMON direct connections	NLP3, CASP1	CASP1, IL1B	CASP1

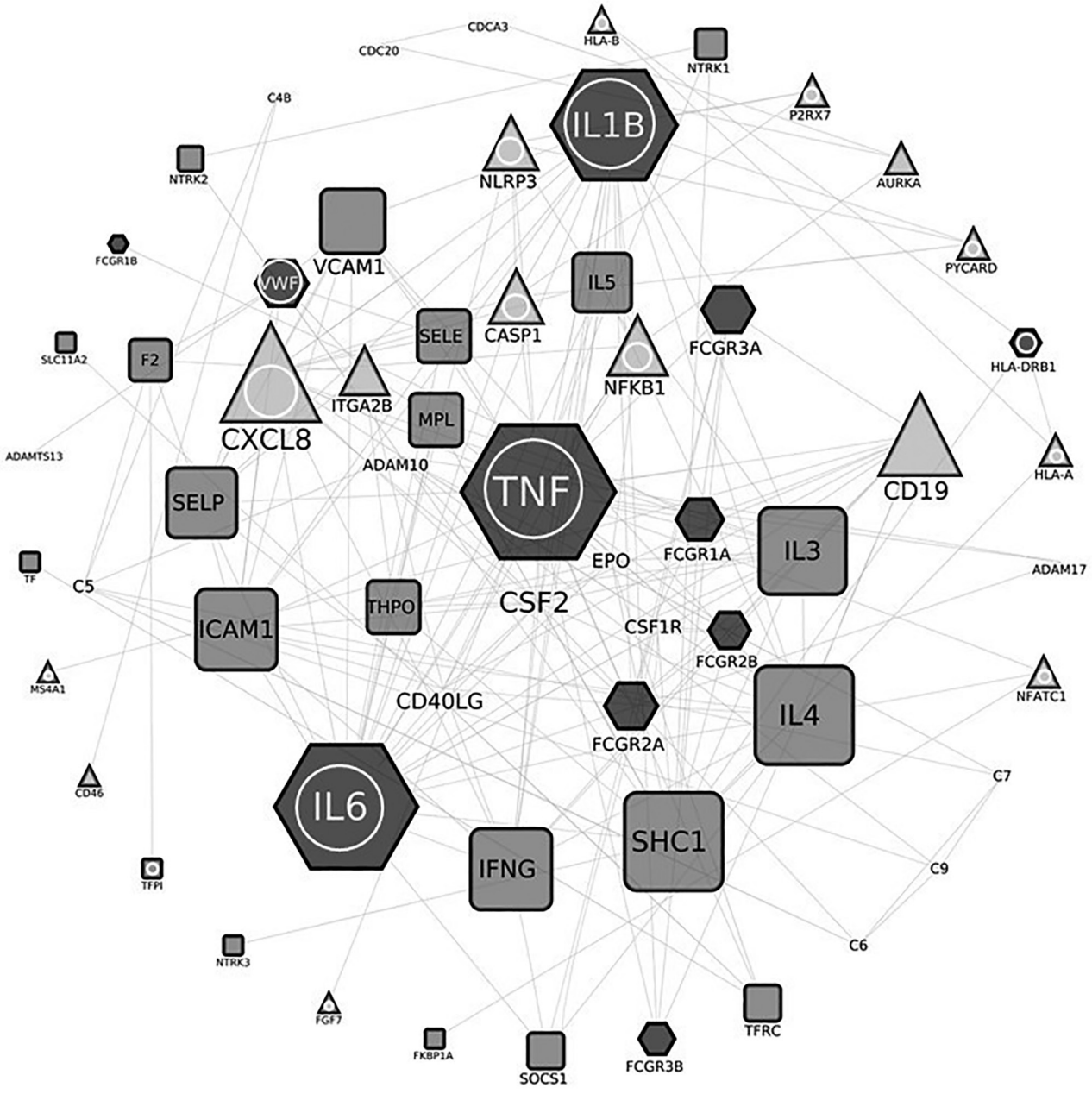

Figure 5. COVID-19 and thrombocytopenia interactions network. VITT-related molecules are depicted by triangles; common with COVID-19 molecules are encircled; thrombocytopenia-related molecules are depicted by squares; VITT common with thrombocytopenia molecules are depicted by polygons.

and the infecting virus strain or certain vaccine types have been associated with NLP3 hyperactivation, which in the presence of comorbidities, such as liver, renal, gut or respiratory tract illnesses, diabetes mellitus, previous infections, exposure to pollutants, and/or lifestyle factors, such as smoking and obesity, may upend the roles of P2RX7 and PYCARD to those of tissue-damaging, or even lethal factors (62,63). More importantly, the persistent neurological effects ('long-COVID-19') observed in a large percentage of patients with COVID-19 may be explained via the activation of these pathways. Thus, P2RX7 antagonists may be promising therapeutics in the management of both VITT and 'long-COVID-19' (62,64), as P2RX7

receptor stimulation has been implicated in lung damage, psychiatric disorders and pathological inflammation (65,66). In the COVID-19 interactome, P2RX7 directly interacts with NLP3, CASP1 and P2RX1. On the contrary, in the VITT network, P2RX7 directly interacts only with NLP3, IL1B and CASP1. Accordingly, PYCARD interacts with NLP3, CASP1, IL1B, IL18 and IKBKG in COVID-19, and with NLP3, CASP1 and IL1B in the VITT syndrome (Table II). The common node in all possible combinations, as shown in Table II, is CASP1, a downstream event of the NLP3 inflammasome; CASP1 activation promotes IL1B production, which may be prevented by a pan-caspase inhibitor or by glyburide treatment (67).

To this end, the present study investigated the aforementioned issues through the construction of molecular networks and the detection of at least one known COVID/VITT/thrombocytopenia molecule that confirmed that endothelial dysfunction and blood thrombosis are the key players of both COVID-19 and VITT morbid entities. One limitation of the present study is that it included only wild-type genes and their products. To the best of our knowledge, however, this is the first effort made at providing a comprehensive network map of the molecules involved in the underlying mechanisms of COVID-19, long COVID-19 and/or VITT pathophysiology.

In conclusion, the interactomes presented herein revealed therapeutic and vaccination modification targets (i.e., SHC1, NCAM1, HLAs, CD8A, PTPN1, VWF and TBP1). It was also demonstrated that: i) NCAM1 is involved in SARS-CoV-2 infection responsiveness, apart from papilloma and rabies virus infections, and may be responsible for relevant vaccination side effects; ii) NLP3, P2RX7 and PYCARD contribution may help explain (partly or mostly) VITT and/or 'long COVID-19 side-effects'; iii) furthermore, the antagonism of these latter nodes should focus on potential pharmacological targets in the context of SARS-CoV-2 infection and/or vaccine immunization responsiveness. In conclusion, network construction is a powerful tool, which may be used to elucidate the physiology and pathophysiology of different states in clinical investigation. The highly interconnected network presented herein highlights the complexity of COVID-19/VITT pathophysiology, mapping the key role of cytokines, enzymes and immune response markers (lymphocyte regulators and human leucocyte antigens) that may be potential drug or vaccine targets. It was constructed using wild-type genes and gene products, revealing the body's predisposition to COVID-19 infection or VITT. Of note, the COVID-19 and thrombocytopenia common nodes appear to be key players in the natural history of the illness.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The datasets used and/or analyzed during the current study are available throughout the manuscript.

Authors' contributions

SAG and MM were involved in the conceptualization of the study. SAG was involved in the study methodology. SAG, AP and MM were involved in data validation. SAG and AP was involved in formal analysis and in the investigative aspects of the study. SAG was involved in the provision of resources (study material). SAG, IT and AP was involved in data curation. IT provided the software used in this study. SAG, IT, GPC and AP were involved in the interpretation of the data, and in the writing and preparation of the original draft. SAG, AP, MM and GPC were involved in the writing, reviewing and editing of the manuscript. MM and GPC supervised the study. SAG and GPC were involved in project administration. All authors confirm the authenticity of the raw data and have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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