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.

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 (Spirevax) by Moderna], seven conventional inactivated ones (CoronaVac, Covaxin, BBIBP-CorV, WIBP-CorV, Minhai-Kangtai, QazVac, Covfran 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 PubMed 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 ‘thrombocytopenia’) 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, IIF16, NOD2, CD8A, IL-18, IL-6, JAK2, NCAM1, HLA-DRB1, SERPINE1, TGFBI, 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.
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, lead to dysregulated immunity and tissue/organ damage (30).

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.

**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.

**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.
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, TGFBI, CD8A, and VWF) (Fig. 3), most of which serve as major hubs (IL-6, TNF, JAK2, IL-1B, SERPINE1, TGFBI, CD8A and VWF) in the herein presented interactome (Figs. 1 and 2).

Cytokines, such as IL-1B, IL-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 cytokotoxic 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 athrogenesis (40).

TGFBI 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 TGFBI, so as to inhibit cytokotoxicity 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.
| Gene symbol | Gene name | Main function with brief description (Refs.) | Figure(s) | Entitya |
|-------------|-----------|-------------------------------------------------|-----------|---------|
| 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 thrombospondin type I 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       |
| Gene symbol | Gene name                       | Main function with brief description (Refs.)                                                                 | Figure(s) | Entitya |
|-------------|---------------------------------|---------------------------------------------------------------------------------------------------------------|-----------|---------|
| 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/ternal 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) | Entitya |
|-------------|-----------|---------------------------------------------|-----------|--------|
| 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) | 3,4 | 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           |
| Gene symbol | Gene name | Main function with brief description (Refs.) | Figure(s) | Entity |
|-------------|-----------|---------------------------------------------|-----------|--------|
| 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   |
| Gene symbol | Gene name | Main function with brief description (Refs.) | Figure(s) | Entity<sup>a</sup> |
|-------------|-----------|-----------------------------------------------|-----------|-----------------|
| 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-cytophilic 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        |

<sup>a</sup>Entities: C, COVID-19; V, vaccine-induced thrombotic thrombocytopenia; T, thrombocytopenia.
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 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.
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, FGFR7, 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-1B, 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
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

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.
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 TBPI). 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.

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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.

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Not applicable.

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Competing interests
The authors declare that they have no competing interests.

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