Impact of Comorbidity on Severity of Covid-19 Patients: A Network of Target Coding Genes Perspective

Reetu Sharma (sharmar@tech-center.com)
CSIR-Indian Institute of Chemical Technology https://orcid.org/0000-0002-3300-9832

Research Article

Keywords: Covid-19, network, data science, target coding genes, comorbidity

Posted Date: November 13th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-106863/v1

Abstract

Millions of people have been forfeiting their lives due to SARS-CoV-2 infection. Most of them are patients suffering from comorbid complications. However, what makes these patients susceptible to mortality is unknown. For this, we employed a novel network-based approach to Covid-19 associated human target coding genes (TC-genes) overlapping with high relevant diseases to reveal the disease-disease relation. Classification of TC-genes in our study suggests that most of them participate in signal transduction, immune and neuronal systems. The network-based approach provides an insight into the mechanism involving the cascade of the TC-genes action that may drastically increase the reactive oxygen species (ROS). An increase in ROS triggers high oxidative stress and inflammation in the body through the cytokines storm. The cytokines storm set the burden on the comorbid patient by weakening the system that may lead to mortality. Our work highlights the TC-genes that may link Covid-19 to certain diseases. Collectively, the study indicates that selective TC-genes can carry out an overlapping role in seemingly distinct mechanisms. Besides, many mechanisms could independently affect selective targets. Oxidative stress and inflammation are the common processes present in severe Covid-19 patients. The approach demonstrates the potential to elucidate disease-disease relationship that can be applied to other diseases.

1. Introduction

The emergence of a recent health condition, coronavirus-2019 (Covid-19) is rapidly spreading globally[1] and has a detrimental effect on billions of lives and economy[2]. Millions of people have forfeited their life due to it. The mortality rate is higher for inpatients underlying comorbid conditions which include hypertension (HTN), cardiovascular and respiratory diseases[3, 4]. Certain underlying fundamental questions link Covid-19 to mortality; for example: How comorbid conditions relate to Covid-19, what makes these patients more susceptible to mortality and what pathways they share ?.

A disease represents an outcome of perturbed underlying interactions among the target coding genes[5]. Owing to large human functional interactome, the concept of one disease: one gene is failing. Over the years, the former concept is transitioning towards multi-disease: multi-targets in complex sub-networks concept [6-8]. Moreover, a disease comprises a collection of symptoms and many diseases may share overlapping symptoms [9]; therefore, one of the ways to decipher the disease-disease relationship is through the network of associated TC-genes[10, 11]. Network analyses of the genes can reveal the mechanism with which patients suffering from comorbid conditions are severely affected. However, it is a challenge to decipher the disease mechanisms of the Covid-19 owing to the complexity of the proteomics.

Currently, network-based approaches have received tremendous popularity in unravelling diverse objectives [12], for example: in the quantification of the disease-disease [13], drug-disease relationships,

drug efficacy screening [14] and repurposing [8]; therefore, useful to decipher the cell's functional organization [15]. The genes related to the disease are likely to cluster in the same neighbourhood. Network-based functional understanding of a disease can be used to identify the trends associated with it.

Distinct approaches have been recently explored by research groups to predict mortality with Covid-19. For example; univariate and multivariate logistic regression methods investigate the risk factors associated with hospital deaths. Their findings include that nearly 50% of the patients in the Wuhan hospital suffer from HTN, followed by diabetes and heart diseases[16]. A few of the early clinical data indicate that Covid-19 and cardiovascular diseases may be associated [17-19]. Covid-19 may promote the development of various kinds of cardiovascular diseases[20]. Kochi et al [21] have reported the cardiac and arrhythmic complications in Covid-19 patients. However, shreds of evidence indicate the possibility of central nervous system involvement in Covid-19[22, 23]. A study conducted on 1590 hospitalized patients in mainland China, suggests that comorbidity is directly related to adverser clinical outcomes[24]. HTN is the most prevalent comorbidity showing significant mortality if age and smoking status is neglected [24, 25]. A substantial data of 76993 cases reveal that HTN, cardiovascular diseases, pulmonary and chronic kidney diseases remain the prevalent comorbid conditions[26]. In the fatality rate analysis study, the severity of the health deterioration increases those with comorbidity[25]. The critical relation between various diseases to Covid-19 can be further justified by the observation that nearly half of the Covid-19 patients hospitalized had one or more disease[27]. The cardiovascular and lung diseases patients are 12 times (~20%) more prone to mortality than those without the mentioned diseases (~1.6%) [28]. Therefore, decrypting the mechanism of action that causes the co-morbid patients to mortality is interesting in its own right.

Extending our efforts to unravel the trends of diseases [29-32], we employed a novel network-based approach to establish disease-disease relationships. In this approach, Covid-19 associated human target coding genes (TC-genes) are extracted and classified based on the pathways shared by them. The diseases sharing maximum relevance with Covid-19 are considered for the study. The network of common TC-genes among the diseases reveals the possible mechanisms that could cause the comorbid patients towards mortality. The present work provides a powerful approach to analyse the disease-disease relationship.

2. Materials And Methods

2.1 Data mining. The TC-genes were extracted using R from the published literature in PubMed and clinical trials from CHEMBL[33]. PubMed is an archive comprising voluminous citations for biomedical literature from MEDLINE, online books and life science journals. It was text-mined for Covid-19 in the title of the publications. The list of the clinical studies was retrieved from the clinical trials submission resource (https://clinicaltrials.gov/) supported by the U.S. National Library of Medicine. The TC-genes supported by either at least two peer review work or undergoing clinical trial higher than phase I was considered for the study. The collection was sorted and the redundancy was removed.

2.2 Classification of targets and gene ontology (GO). The targets were categorised as per their pathway and systems involved. The maximum populated categories of them were represented using Venn diagrams. GO features like biological processes (BPs), cellular components (CCs) and molecular functions (MFs) were extracted from Open Targets (OT)[34], a public-private initiative tool for target-disease associations. GO features were ranked concerning the descending order of relevance (p-value). BPs and MFs refer to the biological processes and molecular activities of the TC-gene, respectively. CCs represent the location where the targets are active. Lower the p-value; the stronger is the relation. Tables 1-3 mention top 20 BPs, CCs and MFs concerning relevance, respectively.

2.3 Association of Covid-19 with other diseases. OT utilizes evidence from various data sources (e.g. Reactome, SLAPenrich, PROGENy, CRISPR, and SysBio) for the target identification. OT platform integrates evidence to a target using Ensembl stable IDs [35] and the association between diseases by delineating them to experimental factor ontology (EFO) terms [34]. Subsequently, similar data sources were grouped into broader categories, for example; pathways to identify the relation between the target and the diseases. In this manuscript, the word “health condition” and “disease” have been used interchangeably. The definition of it is as according to OT platform.

The diseases relating to TC-genes were distributed assigning to decreasing relevance (p-value). Lowering the p-value indicates a significant possibility that the disease is unassociated with the gene by chance. The linked diseases were arranged in the decreasing order of the relevance and the top 20 of them were extracted. Distinct five diseases were considered with the minimum p-value and the common TC-genes among them were represented using Venn diagrams.

2.4 Network of common TC-genes. The network of TC-genes was extracted using STRING (v11)[36], a database of predicted functional association between the targets. It was employed to identify the relationship between them. The known interactions from curated and experimental databases were collected through text mining, co-expression and protein homology. Interactions were predicted considering gene neighbourhood, their fusions and co-occurrence. The networks were visualized using Cytoscape (v3.6.1)[37], an open-source software platform. The first neighbour and clustering coefficient of the common hub TC-genes were calculated as per the network analyser in Cytoscape. Clustering coefficient is a measure of the degree to which nodes tend to cluster together.

3. Results And Discussion

The goal of the work is to decipher the mechanisms connecting Covid-19 to comorbidity that may lead to mortality. An attempt was committed with the following objectives: (i) Retrieval and classification of TC-genes, (ii) analysing BPs, MPs and CCs of the targets, (iii) determining the selective diseases linking Covid-19, (iv) identifying the common TC-genes among them, (v) elucidating the connection between the disorders through the critical overlapping TC-genes.

3.1 Collection of the TC-genes. Following the search as described in materials and methods, 757 clinical entries were retrieved (Table S1). Text mining of PubMed led to the retrieval of 480 unique PMIDs (Table

S2). PMID is a collection of a unique PubMed reference number issued by the NIH National Library of Medicine. After removing the redundancy, 156 TC-genes associated with Covid-19 are considered for the work.

3.2 Classification of the TC-genes. The 156 targets are classified based on the pathways they are involved in (Table S3). Based on the best relevance, neuronal system heads the list adopted by TC-genes (Fig. 1). Transmission across the chemical synapse, neurotransmitter receptors and postsynaptic signal communication are the characteristics of the neuronal system and are among principal pathways of the targets (Fig. 1). Assembly and cell surface presentation of NMDA (N-methyl-D-aspartate receptor), a glutamate receptor and ion channel present in nerve cells are furthermore among the top relevant ones associated with Covid-19 (Table S4). This suggests that the top relevant p are chiefly connected to nervous system-related functions.

Besides nervous system and SARS-CoV infections, TC-genes encoded for signalling transduction represent the prevalent ones as per relevance. For example; HSP90, MAPK1/MAPK3, P13K/AKT and cytokine function are among the relevant signalling pathways. Cytokine signalling like interleukin (IL)-4, IL-13 and IL-10 are among the top 20 pathways extracted as per relevance. However, certain signalling pathways are part of the immune system as well. Therefore, this sub-section suggests that most relevant pathways assign frequent targets and there are a few selective pathways involved in the process.

Based on the number of TC-genes in the pathways, the majority (> 50%) of them participate in signal transduction (Fig. 2). It is followed by the immune and neuronal system. Within the immune system, more than half of the signalling is related to cytokines, like IL-4, IL-13, IL-6R, 1L6, IL1R and IL-10 (Table S4). A small segment of TC-genes is in infection and metabolism of proteins, which are obvious processes in virus susceptible cells. Nearly half of the signal transduction TC-genes are overlapping with the immune system. Contrarily, only one-fifth (20%) of them are common to the neuronal system. Immune and neuronal systems are connected through signal transduction. These top three pathways share mere one-tenth (~7%) of the TC-genes (Table S5, Fig. 2). Following the analysis, the sub-section suggests that the majority of the TC-genes share certain pathways, irrespective of many possibilities.

3.3 GO analysis. Analysing the top 20 BPs of TC-genes, most of them are related to signalling. Most signalling cascade involves neurons and immune system (Table 1). Therefore, comply with the results gained from the independent study involving the network-based pathway analysis in the previous sub-section. The CCs of the TC-genes include mainly the component of the plasma membrane and are related to neurons (Table 2). Broadly, signal transduction is the most preferred MFs associated with the TC-genes (Table 3). The sub-section suggests that only certain BPs, CCs and MFs are involved in Covid-19 progression, despite multiple likelihoods.

3.4 Association of Covid-19 with diseases. The disease-disease association is deciphered by analysing the network of common genes. Among top 20 diseases; HTN, neurovascular disease, arterial and autoimmune disorders show the maximum number of common Covid-19 associated targets (Table S6 and Fig. 3). They are followed by rheumatic (RC), cerebrovascular and central nervous system disorder

(Fig. 3). Considering the relevance of the association between the diseases and Covid-19, HTN tops the chart (Fig. 3). If both the p-value and number of overlapped targets are considered, then also HTN is most closely related to Covid-19 (Fig. 3). Covid-19 represents the first in the list followed by infections caused by orthocoronavirinae subfamily and nidovirales order viruses, however, are ignored as SARS-CoV-2 is a virus. Therefore, it is not surprising if they are at the top hit diseases.

The five most relevant, diverse diseases considered for the study are Covid-19, HTN, RC, CNS demyelinating autoimmune (CNS_DA) and bone inflammation (BIN). 148 TC-genes are common among the top three health conditions; HTN, RC and Covid-19. However, only 7 TC-genes are overlapping between the Covid-19 and RC but are unassociated with HTN (Table S6, Fig. 4). More than two-third (~80 %) of the TC-genes are also associated with CNS_DA and BIN (Table S6, Fig. 4). The top five relevant diseases concerning Covid-19 suggests that nearly half of them are frequent to HTN, BIN, CNS_DA and ischemic (IC). To our surprise, pairwise relationships between them indicate that more than one-tenth (20) of the TC-genes are common among HTN, BIN and CNS_DA excluding the selective cardiovascular disease. Contrarily, a similar percentage of TC-genes are also present among HTN, BIN and IC but not with the CNS_DA (Fig. 4). This suggests that the BIN and HTN have a relation with IC and CNS_DA, but may additionally include certain targets not associated with each other. The sub-section indicates that more than half of the TC-genes are common among the HTN, BIN, IC and CNS_DA. These TC-genes are listed in Table S7 and Fig. 4.

The network of these common TC-genes is represented in Fig. 5A. The common TC-genes mainly facilitate signalling involving cytokines/chemokines. Top 9 common TC-genes as per the size of the nodes (clustering coefficient in brackets; descending order) are as follows: DRD2 (dopamine receptor 2, 0.85) followed by IL6 (0.75), SLC6A4 (solute carrier family 6 members 4, 0.73), VEGFA (vascular endothelial growth factor A, 0.71), CXCL8 (C-X-C motif chemokine ligand 8, 0.69), OPRM1 (opioid receptor mu 1, 0.67), PIK3CD (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta, 0.72), ACE (angiotensin I converting enzyme, 0.45), and GABR$^{\#}$ (gamma-aminobutyric acid receptor$^{\#}$) (Fig. 6i and Fig. 6ii). The symbol ($^{\#}$) represents types of GABRs. The protein name and Ensembl id of all the TC-genes considered for the study are mentioned in Table S3.

Although the top 9 common TC-genes shown in Fig. 5B, 6i and 6ii are broadly involved in distinct pathways (Table S5) but are connected as first neighbours in general. For example, DRD2 has interactions with PIK3CD, OPRM1, CXCL8, SLC6A4, GABR$^{\#}$ and ACE pathway members (Fig. 6iA). Likewise, the interaction of OPRM1, DRD2, ACE, HTR2A, IL6 and GABR$^{\#}$ with SLC6A4 is highlighted in Fig. 6iiB. The function of IL6 is broadly affected by the expression of SLC6A4, CXCL8, VEGFA, NR3C1, and ACE (Fig. 6iiE). The interaction of most common TC-genes to GABR$^{\#}$ is mainly through DRD2 or SLC6A4 (Fig. 6iiA and 6iiB). The sub-section extracts and constructs networks among common TC-genes from the top hit diseases (HTN, BIN, CNS_DA, and IC diseases).

3.5 Proposed model connecting Covid-19 and comorbidity. The network of selective common TC-genes interplay, extracted in the previous sub-section led to propose the mechanism of how SARS-CoV-2

infection guides the severe condition of the comorbid patients: SARS-CoV-2 enters human cells by binding to ACE2. The network of the first neighbours of ACE2 is represented in Fig. 5B. ACE2 helps modulate the activities of angiotensin II (Ang II). The later can increase inflammation and death of alveoli cells, which are critical for delivering oxygen into the body. ACE2 counters the activity of ACE by reducing the amount of Ang-II and increasing Ang(1-7) (Fig. 7). Ang-II binds to AGTR1 causing an increase of vasoconstriction. The ACE2 expression in hypertensive and cardiovascular disease patients is reported to be higher[38]. However, occupied ACE2 cannot participate in the function leading to enhance blood pressure (Fig. 7). Simultaneously, the infection leads to an increase in TNF-α level as immune cells activation, facilitating its cleavage into a soluble form (sACE2) (Fig. 7). The sACE2 is unable to counteract the AGTR1 to reduce blood pressure.

Disruption of ACE2 drastically reduces the expression of endothelial nitric oxide synthase (eNOS), therefore, a significant reduction in nitric oxide (NO), a vasodilator. NO production is further effected by dysfunctional VEGFA, a homodimer glycoprotein's signalling through PI3K (Phosphatidylinositol 4,5-bisphosphate 3-kinase)/Akt pathway[39]. Deletion of ACE2 function modulates oxidative stress through reactive oxygen species (ROS). ROS imbalance creates oxidative stress that leads to inflammation. Simultaneously, invasion of a pathogen causes nearby inflammation that attracts innate immune cells to act. For example, CXCL8 upregulates during inflammatory conditions and mediates recruitment of neutrophil as a role in innate response[40]. Transcription of certain cytokines/chemokines enhances the adaptive response of the immune system. VEGF dysfunction contributes to inflammation and immune response leading to leukocyte adhesion to endothelial cells; therefore, prevent platelet aggregation and leukocyte rolling, an important step in inflammation initiating immune response[41]. NO also limits the expression of IL-1 induced expression of adhesion molecules, thus affect leukocyte rolling and pro-inflammatory cytokines[42]. Cytokines in the serum are enhanced tremendously, especially IL-1, IL-6, tumour necrosis factor (TNF)-α, and interferon γ. DPP4, a cell surface glycoprotein receptor co-express with ACE2 and is reported to be essential for T-cell activation. T cells play a critical role in antiviral immunity, but their levels are dramatically reduced in Covid-19 patients[43].

Initiating immune response enhances the expression of GABA that mediates neuronal inhibition. Therefore, GABR$^{\#}$, ligand-gated chloride channels are activated by GABA, an inhibitory neurotransmitter[44]. Bhat et al[45] suggest its role in autoimmune inflammation. The network partners of GABR$^{\#}$ are shown in Fig. 6ii suggesting their interaction with DRD2, OPRM1 and SLC6A4. Similar to GABA, the former's depletion increases the inflammatory factors and cytokines/chemokines. Zhang et al[46] suggest that inflammation is the primary impact of decreased DRD2 function and its disruption is associated with increased reactive oxygen species (ROS)[47]. ROS induce oxidative stress which can activate the transcription of some TC-genes involved in inflammatory pathways[48]. CCR5 (C-C chemokine receptor type 5) is a receptor for several inflammatory CC chemokines. Complementing to our findings, IL-6 levels, an indicator of a cytokines storm and inflammation, is elevated in SARS-CoV-2 infected patients[49]. Similar to IL-6, elevated levels of C-reactive protein (CRP), D-dimer and ferritin also suggest the role of the immune system in the Covid-19 [16, 50, 51]. Most of the stated receptors also

express on the nerve cells and are involved in signalling, therefore, are complementing with the GO analyses. The sub-section indicates that the TC-genes may be part of another pathway, but are associated to accomplish one or more broad functions. The cooperative actions of these selective TC-genes increase the oxidative stress causing inflammation that may damage the comorbid system leading to mortality. The findings of work are supported by a few of the experimental observations [52, 53], however, is carried out simultaneously and independently.

Interpretation of the interaction among the TC-genes is challenging due to the complexity of the interactome. The vast research data is characterizing the targets in isolation or reporting the clinical readings, that in general fails to provide an overall mechanism of action. However, we attempted linking the human targets collectively in a simplified yet effective way through the TC-genes. The approach is novel for disease-disease relationships as it considers the common pathways and reports the selective 85 TC-genes. Interpreting the network from limited 85 TC-genes is equally difficult, therefore, the top 9 of them were focused to infer the connection and the mechanism is interpreted. However, the study only considers the TC-genes, but non-coding DNA sequences, post-translational modifications, diet, age or environment could be a few of the factors that may affect the comorbid Covid-19 patient's chances of death.

4. Conclusion

The study provides a network framework to decipher the connection between Covid-19 and top hit diseases through the interaction of TC-genes. The crosstalk among them reveals the relationship between Covid-19 and selective diseases through commonly associated targets, extracted after on-going clinical trials and a literature search. Collectively, the work suggests that most of the illnesses may be associated through a few of the common TC-genes. Certain TC-genes may be involved in responding to many health conditions. Selective pathways can predominantly participate in combating the infection.

Tables

Table 1. Top 20 BFs associated with Covid-19 targets as per relevance.

GO term id	GO term description	Category	Relevance (p-value)
GO:0065008	regulation of biological quality	BP	1.26E-29
GO:0007267	cell-cell signalling	BP	2.29E-28
GO:0042391	regulation of membrane potential	BP	9.58E-28
GO:0007268	chemical synaptic transmission	BP	1.20E-25
GO:0098916	anterograde trans-synaptic signalling	BP	1.20E-25
GO:0023052	signalling	BP	1.29E-25
GO:0099537	trans-synaptic signalling	BP	2.09E-25
GO:0060078	regulation of postsynaptic membrane potential	BP	2.66E-25
GO:0099536	synaptic signalling	BP	6.52E-25
GO:0098660	inorganic ion transmembrane transport	BP	6.26E-23
GO:0007154	cell communication	BP	6.48E-23
GO:0003008	system process	BP	9.16E-23
GO:0006811	ion transport	BP	1.07E-22
GO:0051716	cellular response to a stimulus	BP	1.97E-22
GO:0050896	response to stimulus	BP	3.09E-22
GO:0007165	signal transduction	BP	1.55E-21
GO:0070887	cellular response to chemical stimulus	BP	8.77E-20
GO:0051239	regulation of multicellular organismal process	BP	1.32E-19
GO:0034220	ion transmembrane transport	BP	6.86E-19
GO:0000165	MAPK cascade	BP	1.02E-18

Table 2. Top 20 CCs associated with Covid-19 targets as per relevance.

GO term id	GO term description	Category	Relevance (p-value)
GO:0031226	an intrinsic component of plasma membrane	CC	1.34E-39
GO:0005887	an integral component of plasma membrane	CC	6.10E-39
GO:0043235	receptor complex	CC	8.88E-31
GO:0045211	postsynaptic membrane	CC	6.26E-29
GO:1902711	GABA-A receptor complex	CC	1.10E-25
GO:0097060	synaptic membrane	CC	1.96E-25
GO:1902710	GABA receptor complex	CC	1.53E-24
GO:0034702	ion channel complex	CC	5.66E-23
GO:0005886	plasma membrane	CC	2.32E-22
GO:0071944	cell periphery	CC	3.12E-22
GO:1902495	transmembrane transporter complex	CC	4.86E-22
GO:1990351	transporter complex	CC	1.02E-21
GO:0034707	chloride channel complex	CC	1.67E-21
GO:0098590	plasma membrane region	CC	3.13E-21
GO:0098794	postsynapse	CC	4.26E-20
GO:0099699	an integral component of synaptic membrane	CC	2.74E-17
GO:0016021	an integral component of membrane	CC	6.46E-17
GO:0099055	an integral component of the postsynaptic membrane	CC	6.75E-17
GO:0031224	an intrinsic component of membrane	CC	1.13E-16
GO:0099240	an intrinsic component of synaptic membrane	CC	1.46E-16

Table 3. Top 20 MFs associated with Covid-19 targets as per relevance.

GO term id	GO term description	Category	Relevance (p-value)
GO:0038023	signalling receptor activity	MF	6.63E-44
GO:0060089	molecular transducer activity	MF	1.06E-43
GO:0004888	transmembrane signalling receptor activity	MF	8.08E-38
GO:0098960	postsynaptic neurotransmitter receptor activity	MF	1.06E-30
GO:0030594	neurotransmitter receptor activity	MF	1.14E-30
GO:1904315	transmitter-gated ion channel activity involved in regulation of postsynaptic membrane potential	MF	2.19E-29
GO:0005230	extracellular ligand-gated ion channel activity	MF	3.31E-29
GO:0099529	neurotransmitter receptor activity involved in regulation of postsynaptic membrane potential	MF	9.60E-29
GO:0004890	GABA-A receptor activity	MF	1.98E-28
GO:0022835	transmitter-gated channel activity	MF	5.92E-28
GO:0022824	transmitter-gated ion channel activity	MF	5.92E-28
GO:0016917	GABA receptor activity	MF	1.49E-26
GO:0022851	GABA-gated chloride ion channel activity	MF	4.62E-25
GO:0022836	gated channel activity	MF	5.68E-25
GO:0015276	ligand-gated ion channel activity	MF	2.55E-23
GO:0022834	ligand-gated channel activity	MF	2.55E-23
GO:0099095	ligand-gated anion channel activity	MF	4.01E-23
GO:0005216	ion channel activity	MF	2.28E-21
GO:0005237	inhibitory extracellular ligand-gated ion channel activity	MF	2.64E-20

Declarations

Author Contribution

RS conceived the idea, designed, performed, analysed and drafted the manuscript. RS provided the software and computational systems to conduct the study.

Acknowledgements

RS thanks Department of Biotechnology-BioCARe, New Delhi for the financial assistance through DBT grant (BT/PR18249/BIC/101/390/2016). We are thankful to CSIR-IICT Director for the support. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflict of Interest

None declared.

Declaration of Interest Statement

1. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.
2. The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: NA
3. The manuscript has not been submitted or accepted elsewhere
4. All authors have contributed to, seen, and approved the final, submitted version of the manuscript

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Supplementary Material

The Supplementary Tables are unavailable with this version of the preprint.

Figures

Pathways	Percentage of Covid-19 associated TC-genes
Neuronal System	23.72
Transmission across Chemical Synapses	19.87
Neurotransmitter receptors and postsynaptic signal transmission	17.95
Potential therapeutics for SARS	10.90
Assembly and cell surface presentation of NMDA receptors	9.62
Signal Transduction	55.77
HSP90 chaperone cycle for steroid hormone receptors (SHR)	9.62
Nuclear Receptor transcription pathway	5.13
SARS-CoV Infections	10.90
MAPK1/MAPK3 signaling	13.46
Constitutive Signaling by Aberrant PI3K in Cancer	5.77
Class A/1 (Rhodopsin-like receptors)	17.31
Cytokine Signaling in Immune system	25.64
MAPK family signaling cascades	14.10
Amine ligand-binding receptors	7.69
Signaling by Receptor Tyrosine Kinases	17.31
PI5P, PP2A and IER3 Regulate PI3K/AKT Signaling	6.41
Negative regulation of the PI3K/AKT network	6.41
Interleukin-4 and Interleukin-13 signaling	9.62
Interleukin-10 signaling	6.41

Figure 1

Biological pathways of Covid-19 associated target coding genes (TC-genes). Percentage of TC-genes involved in top 20 pathways. The details of the pathways and related TC-genes are in Table S5.

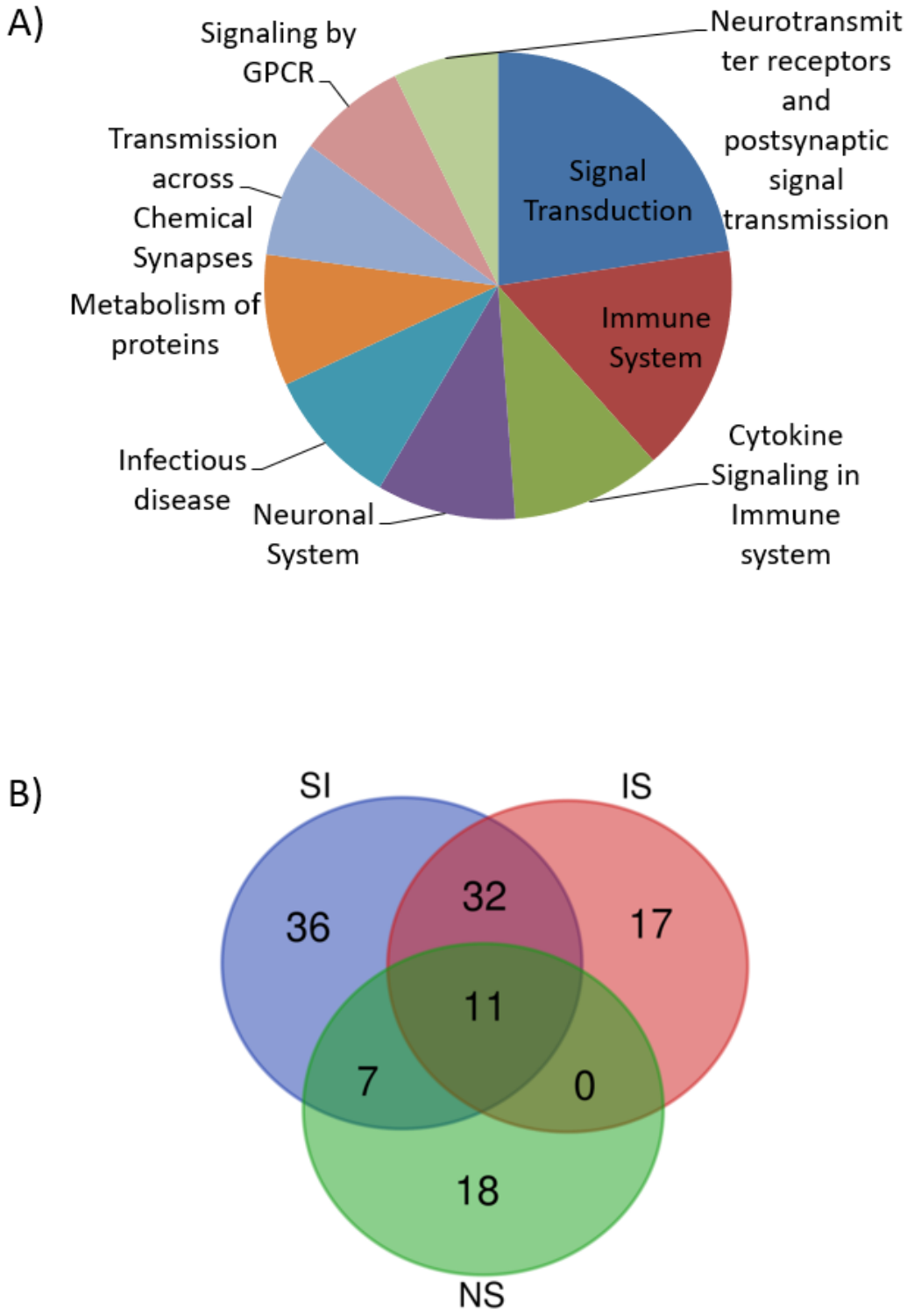

Figure 2

Classification of TC-genes involved in the pathways. A) Pie chart depicting the percentage of TC-genes involved in the pathways. B) Venn diagram showing TC-genes involved in common top 3 systems; namely, signalling (SI), immune system (IS), and neuronal system (NS). The details of the Covid-19 associated human targets involved in SI, IS, MP, NS and H pathways are listed in Table S6.

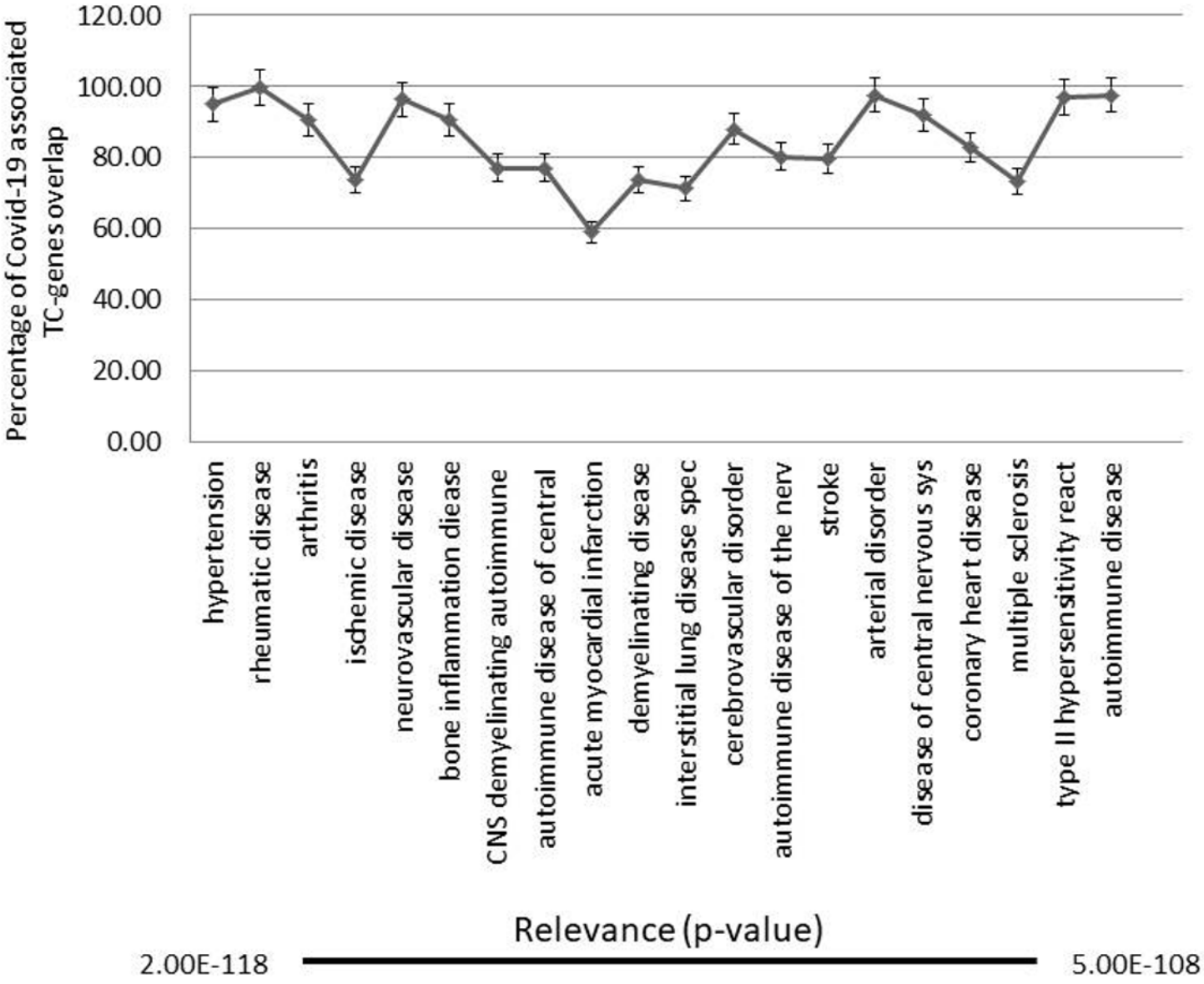

Figure 3

Association of Covid-19 targets with diseases. The percentage of the overlapped TC-genes to top 20 diseases in descending order of relevance. The TC-genes corresponding to the Covid-19 related selective diseases are listed in Table S7.

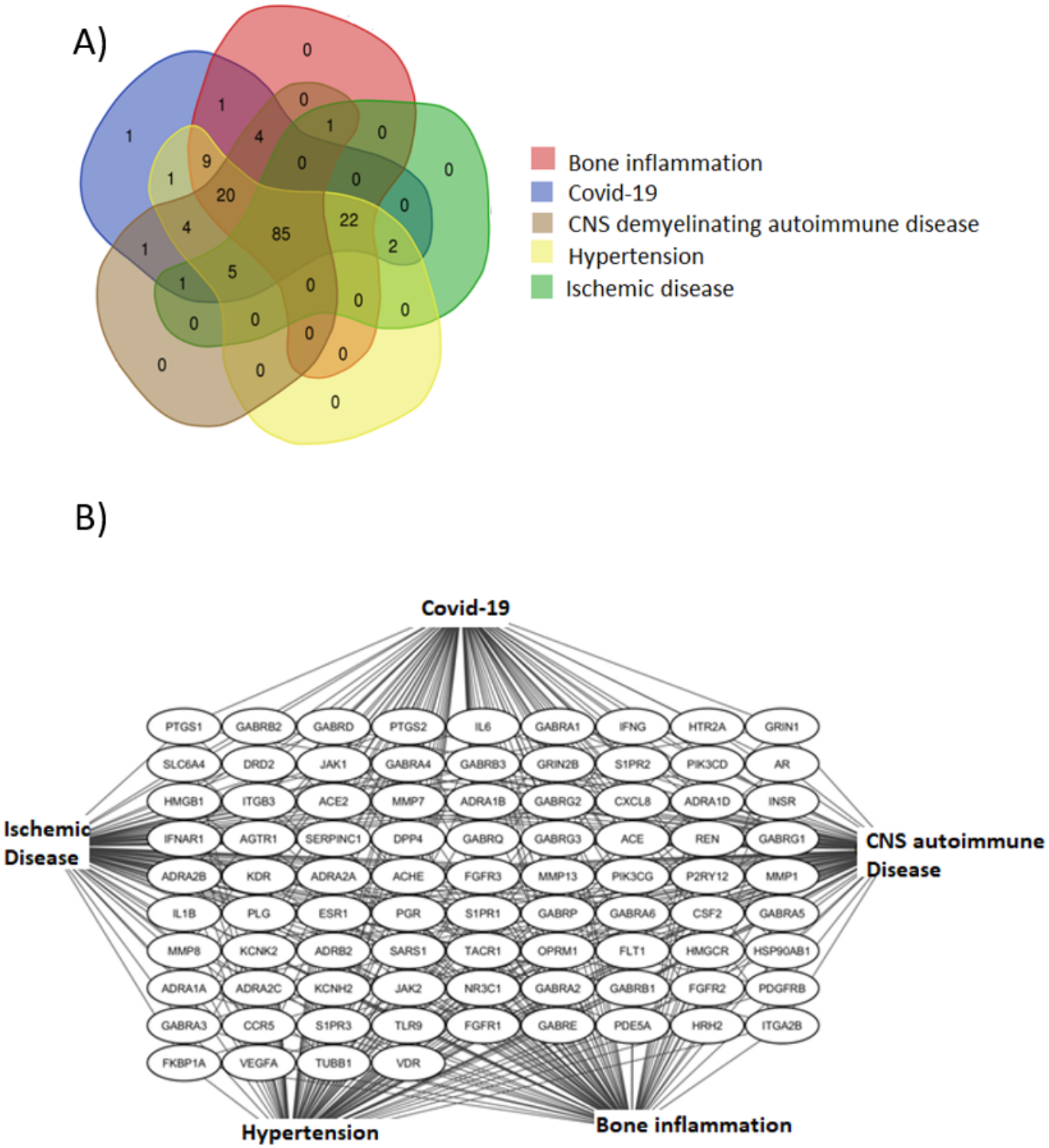

Figure 4

Common TC-genes related to Covid-19 and diseases. A) Venn diagram showing TC-genes involved in top five different diseases. B) The network of 85 common TC-genes associated with the diseases considered for the study. The selective diseases and TC-genes are mentioned in Table S7.

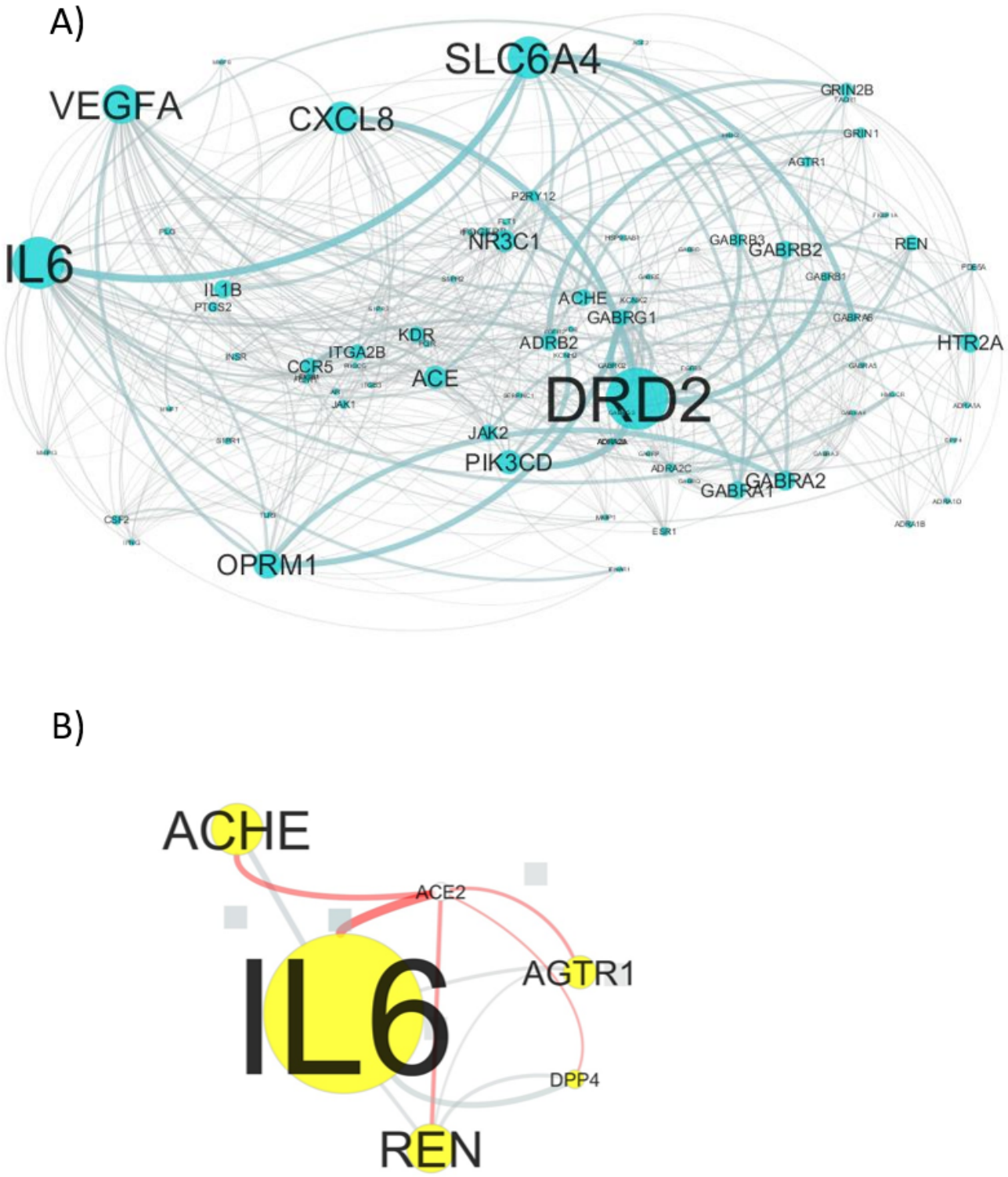

Figure 5

The network of common TC-genes associated with HTN, RC, IC, BIN and CNS_DA. A) The nodes (blue) are the TC-genes and their interaction is represented by edges. The size of the node is directly proportional to the clustering coefficient. B) The first neighbour of ACE2 and the connections are labelled in yellow nodes and red edges, respectively.

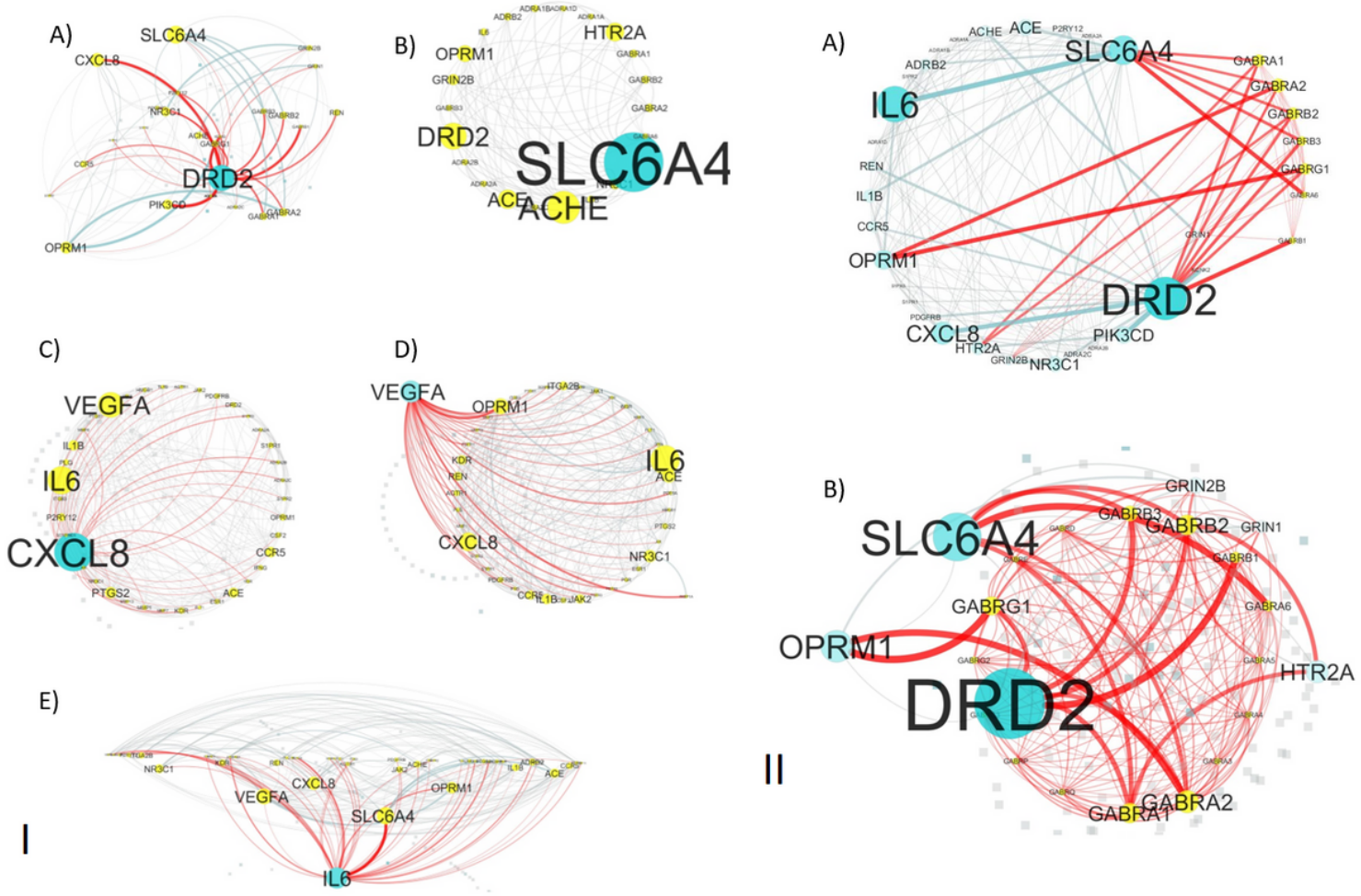

Figure 6

i. Interaction of selective common TC-genes with first neighbours in an undirected network. The network of the first neighbours of A) DRD2, B) SLC6A4, C) CXCL8, D) VEGFA, and E) IL6. The first neighbour nodes are represented in yellow and the edges are in red. ii. The network of the GABR# and the first neighbour TC-genes. A) Interaction of GABR# with first neighbours among 156 TC-genes. B) Extracted network showing the interaction of GABR# with first neighbours of the TC-genes only. The GABR# TC-genes and rest are in yellow and blue nodes, respectively. The red edges represent the relationship between the GABR# are first neighbours.

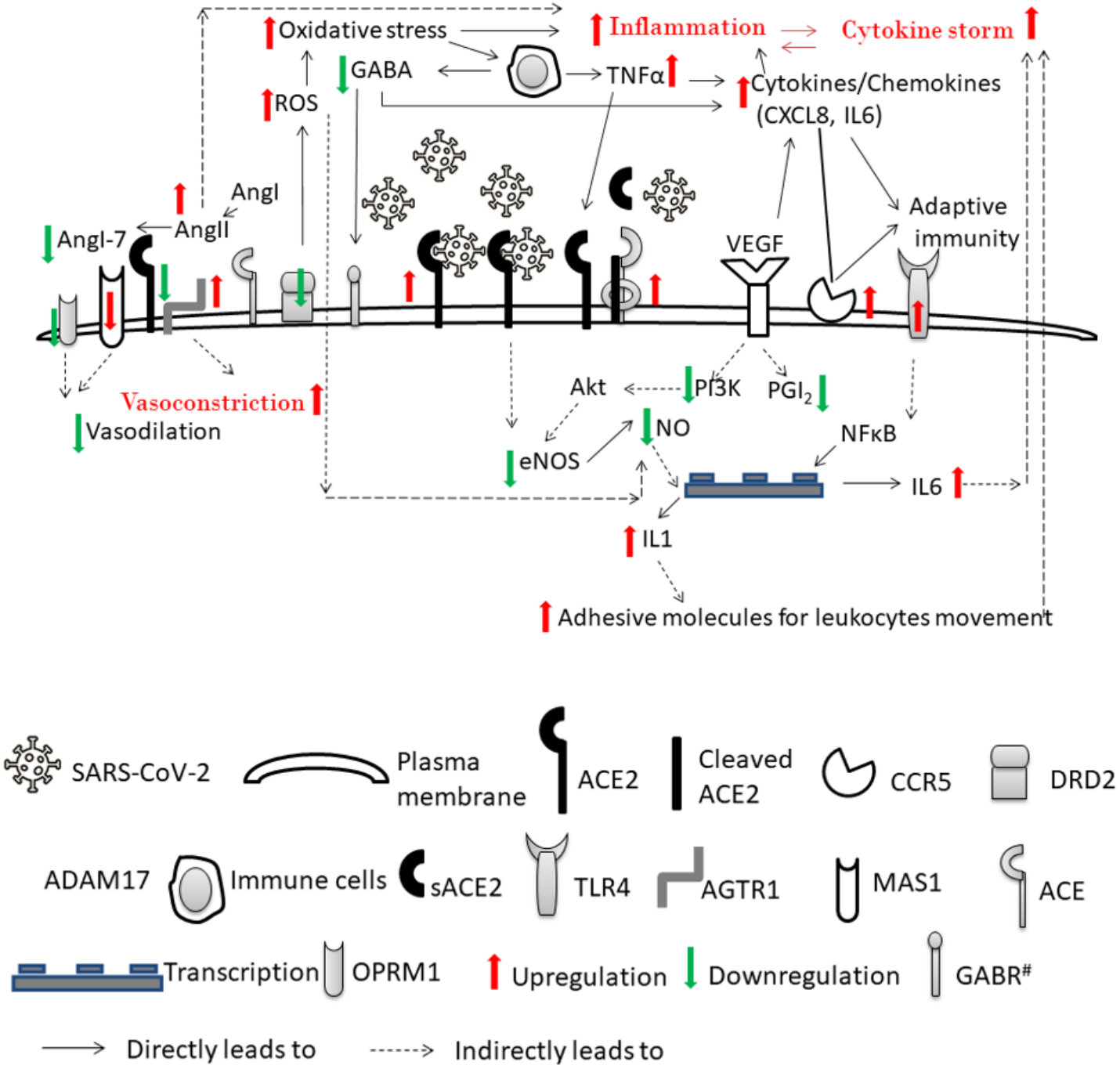

Figure 7

Proposed mechanism of action with SARS-CoV-2 infection in comorbid Covid-19 patients.