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Joint impact of key air pollutants on COVID-19 severity: prediction based on toxicogenomic data analysis

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Considering that some researchers point to a possible influence of air pollution on COVID-19 transmission, severity, and death rate, the aim of our *in silico* study was to determine the relationship between the key air pollutants [sulphur dioxide (SO_2), carbon monoxide (CO), particulate matter (PM_x), nitrogen dioxide (NO_2), and ozone (O_3)] and COVID-19 complications using the publicly available toxicogenomic analytical and prediction tools: (i) Comparative Toxicogenomic Database (CTD) to identify genes common to air pollutants and COVID-19 complications; (ii) GeneMANIA to construct a network of these common and related genes; (iii) ToppGene Suite to extract the most important biological processes and molecular pathways; and (iv) DisGeNET to search for the top gene-disease pairs. SO_2, CO, PM_x, NO_2, and O_3 interacted with 6, 6, 18, 9, and 12 COVID-19-related genes, respectively. Four of these are common for all pollutants (*IL10*, *IL6*, *IL1B*, and *TNF*) and participate in most (77.64 %) physical interactions. Further analysis pointed to cytokine binding and cytokine-mediated signalling pathway as the most important molecular function and biological process, respectively. Other molecular functions and biological processes are mostly related to cytokine activity and inflammation, which might be connected to the cytokine storm and resulting COVID-19 complications. The final step singled out the link between the *CEBPA* gene and acute myelocytic leukaemia and between *TNFRSF1A* and TNF receptor-associated periodic fever syndrome. This indicates possible complications in COVID-19 patients suffering from these diseases, especially those living in urban areas with poor air quality.

KEY WORDS: carbon monoxide; cytokines; disease complications; *in silico*; nitrogen dioxide; ozone; particulate matter; SARS-CoV-2; sulphur dioxide

With the appearance of the SARS-CoV-2 pandemic, numerous complications of COVID-19 disease followed, raising suspicion that severe forms of the disease and even deaths could partly be associated with air pollution (1). Some authors have even suggested that atmospheric factors can influence COVID-19 transmission and death rate (why is it so different around the world, even in the same country?) (2). As the World Health Organization's (WHO) new Global Air Quality Guidelines (AQGs) provide convincing evidence of the harm caused by air pollution to human health, especially with regard to sulphur dioxide (SO_2), carbon monoxide (CO), particulate matter (PM_x), nitrogen dioxide (NO_2), and ozone (O_3) (3, 4), the aim of our study was to determine the relationships between these key air pollutants and COVID-19 complications using *in silico* models based on currently available toxicogenomic software tools and databases.

Toxicogenomics combines the measurement of different biological molecules with both bioinformatics and traditional toxicology to find the exact relationships between genes and environmental stress in disease pathogenesis (5–7). As a result, it may be used to predict gene functions and genomic biomarkers in specific biochemical pathways (8, 9). It also provides combined evaluation methodologies that take into account all the conceivable chemical-gene-disease interactions that may be essential in generating combined toxicities (5).

METHODS

In this study we used four freely available tools, each with a specific purpose: Comparative Toxicogenomic Database (CTD) to obtain a set of genes interrelated with air pollutants and COVID-19 complications, GeneMANIA to construct a network between the obtained gene set and related genes, ToppGene Suite to identify the most important biological processes and molecular pathways, and DisGeNET to search for the top gene-disease pairs. Figure 1 shows a flow chart detailing each step of our analysis.

The CTD database (http://CTD.mdibl.org) records information on chemicals, genes, and molecular mechanisms that cause chemically induced disorders but also contains data about chemical-exposure statements and chemical-phenotype interactions (10, 11). We used it to obtain a set of genes affected by the selected air pollutants (SO_2, CO, PM_{10}/$_{2.5}$, NO_2, and O_3). CTD gene cards provide information about chemical interactions with various genes, most of which are binary (involving one chemical and one gene or protein), but the database also contains complex interactions (12,

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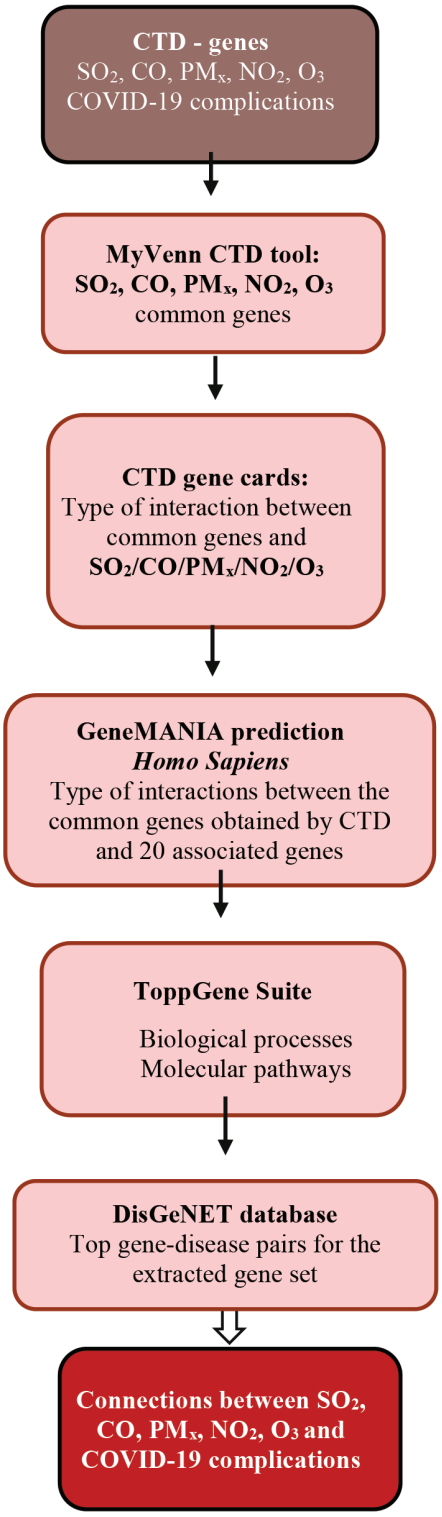

Figure 1 Flow chart of toxicogenomic analysis to identify relationships between air pollutants and COVID-19. CTD – Comparative Toxicogenomic Database (http://CTD.mdibl.org)

13). We limited our study to binary interactions alone. The total number of genes affected by each investigated pollutant (SO_2, CO, PM_x, NO_2 and O_3) and connected to COVID-19 was obtained from the disease data cards individually. After that, we used the MyVenn CTD tool (http://ctdbase.org/tools/myVenn.go) to identify common genes for all the investigated pollutants.

GeneMANIA is one of the most reliable free online tools (with its Cytoscape plugin available at https://apps.cytoscape.org/apps/genemania) that identifies 20 genes most closely related to a specified gene set and determines the type of interactions between them. It includes around 800 networks across six different species, and each of the retrieved genes can be traced back to the source network from which the prediction was derived (14, 15). If two genes are in *physical interaction*, this means that they interact on a protein-protein level. *Co-expression* means that two genes have similar expression. *Predicted interactions* means that two genes/proteins are expected to interact if their orthologues have been reported to interact in another organism. *Co-localisation* means that genes are expressed in the same tissue or their proteins found in the same location. If two genes are in a *genetic interaction* and functionally associated, this means that the effects of perturbing one gene are modified by perturbations to a second gene. *Pathway interaction* means that two genes share the same pathway. They can also *share* the same *protein domain* (14–16).

The ToppGene Suite is a publicly available online tool (https://toppgene.cchmc.org/) that uses protein-protein interaction networks to prioritise candidate genes for exploration of new disease genetic markers (17). To further elucidate molecular mechanisms behind disease progression under the influence of the investigated air pollutants, we used this online tool to obtain the most important biological processes (gene ontology) and molecular pathways associated with the identified set of common genes.

DisGeNET (http://www.disgenet.org) is one of the largest databases of genes and variants associated with human diseases (18), containing information from expert-curated repositories, Genome-Wide Association Studies (GWAS) libraries, animal models, and scientific literature. It can be used to investigate the molecular bases of specific human diseases and their comorbidities, analyse disease gene properties, generate hypotheses on drug therapeutic action and adverse effects, validate computationally predicted disease genes, and evaluate the performance of text-mining methods (19, 20). We used it to search for the top gene-disease pairs for the extracted set in order to predict sensitive individuals who might additionally be affected by air pollutants in case of SARS-CoV-2 infection.

RESULTS

As expected, of the five investigated air pollutants PM_x interacted with the highest number of genes (11,573), followed by O_3 (3,578). Eighteen from the first group (*ACE2, AGT, BSG, CCL2, CCL3, CRP, CSF3, CXCL10, CXCL8, IL10, IL1B, IL2, IL2RA,*

IL6, IL7, LZTFL1, TMPRSS4, TNF) and 12 (BSG, CCL2, CCL3, CSF3, CXCL10, CXCL8, IL10, IL1B, IL2, IL6, TMPRSS2, TNF) from the second are related to COVID-19 complications. The remaining three pollutants interact with fewer genes (148, 138, and 104 for NO_2, SO_2, and CO, respectively), of which nine (*CCL2*, *CCL3*, *CRP*, *CXCL8, IL10, IL1B, IL6, LZTFL1, TNF*), six (*CCL2*, *IL10, IL1B, IL2, IL6, TNF*), and six (*AGT*, *CRP, IL10, IL1B, IL6, TNF*) are related to COVID-19 complications, respectively. Genes common to all the tested air pollutants include *IL10*, which encodes interleukin 10 (IL-10), *IL1B*, which encodes interleukin 1 beta (IL-1β), *IL6*, which encodes interleukin 6 (IL6), and *TNF*, which encodes tumour necrosis factor α and ß (TNF-α and TNF-β).

Table 1 shows how each pollutant interacts with each of the genes from the common set. To better understand the obtained set of shared genes (*IL10*, *IL6*, *IL1B*, and *TNF*), in the next step we generated a network of interactions between them and 20 additional genes (*A2M*, *TNFRSF1A*, *IL1R1*, *CASP1*, *TNFAIP3*, *IL6ST*, *TNFRSF1B*, *IL1R2*, *IL10RA*, *SQSTM1*, *IL1RAP*, *IL10RB*, *IL10*, *TRADD*, *HRH1*, *IL1A*, *IL6R*, *IL19*, *CEBPA*, *IL20*, and *MAP3K3*) predicted with the GeneMANIA tool to identify the types of interactions by percentages (Figure 2). Physical interactions dominate with 77.64 % of genes involved, followed by co-expression (8.01 %), interactions predicted by the server (5.37 %), co-localisation (3.63 %), genetic interactions (2.87 %), shared pathway (1.88 %), and shared protein domain (0.60 %) (Figure 2A). Figure 2B shows separate interaction networks constructed for each interaction type.

The ToppFun function at the ToppGene Suite identified top 10 molecular functions behind resulting COVID-19 complications that are connected to the investigated set of 24 genes (molecular functions and biological processes) as follows: cytokine binding, cytokine receptor binding, growth factor receptor binding, growth factor binding, cytokine receptor activity, immune receptor activity, interleukin-1 binding, signalling receptor binding, cytokine activity, and interleukin-6 receptor binding. The top 10 biological processes included cytokine-mediated signalling, cellular response to cytokine stimulus, response to cytokine, inflammatory response, defence response, regulation of inflammatory response, interleukin-6 production, cytokine production, regulation of defence response, and regulation of cytokine production.

The DisGeNET database provided the linkage between various diseases and genes from the set (Table 2). The highest score was obtained for the link between *CEBPA* and acute myelocytic leukaemia and between *TNFRSF1A* and *TNF* receptor-associated periodic fever syndrome (TRAPS), followed by *TNFAIP3* and the familial Behcet-like autoinflammatory syndrome.

DISCUSSION

Our study has singled out cytokine binding and activation as the most important molecular functions for the extracted gene set. Cytokine release caused by air pollutants could, among other factors, lie behind the so-called "cytokine storm" (21), an excessive production of proinflammatory cytokines found to induce acute respiratory distress syndrome which has also been reported after SARS-CoV-2 infects the upper and lower respiratory tract (22, 23). A significant concentration of cytokines has also been reported in the plasma of severely sick patients infected with SARS-CoV-2, probably due to the "cytokine storm" (24).

Table 1 Influence of air pollutants (SO_2, CO, PM_x, NO_2 and O_3) on protein secretion, mRNA expression, and protein expression of genes related to these air pollutants and COVID-19 disease complications (CTD Database; http://CTD.mdibl.org)

Air pollutant	Interaction	*IL10*	*IL6*	*IL1B*	*TNF*
SO_2	Protein secretion				↑
	mRNA expression				
	Protein expression	↑	↑	↑	
CO	Protein secretion		↑		
	mRNA expression	↑			
	Protein expression	↑	↑	↑↓	↑↓
PM_x	Protein secretion	↑↓	↑	↑	↑
	mRNA expression	↑↓	↑↓		↑↓
	Protein expression	↑↓	↑	↑↓	↑↓
NO_2	Protein secretion		↑		↓
	mRNA expression	↑	↑↓	↓	↑
	Protein expression	↑	↑	↑	↑
O_3	Protein secretion		↑		↑
	mRNA expression	↓	↑	↑↓	↓
	Protein expression	↓	↑	↑↓	↑↓

↑ – induction; ↓ – inhibition; ↑↓ – induction/inhibition

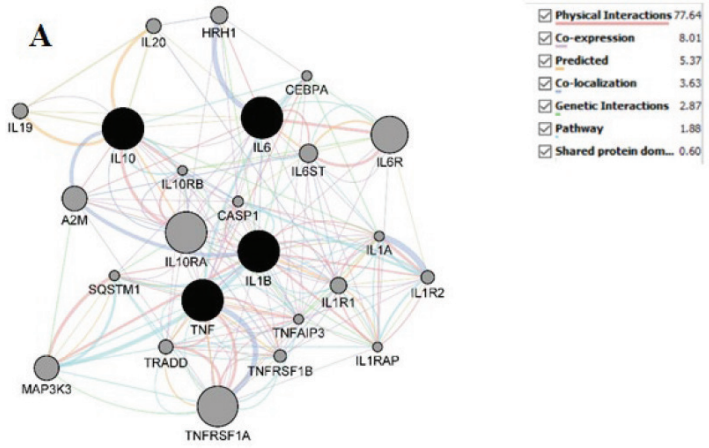

Figure 2 Network of genes associated with SO_2, CO, PM_x, NO_2 and O_3 exposure and COVID-19 disease complications (*IL10*, *IL6*, *IL1B*, and *TNF*) (black circles) and 20 related genes predicted by the GeneMANIA tool (http://geneMANIA.org/plug-in/) (grey circles). Panel **A** shows prevalence of interaction types (in percentages) and panel **B** networks for each interaction type

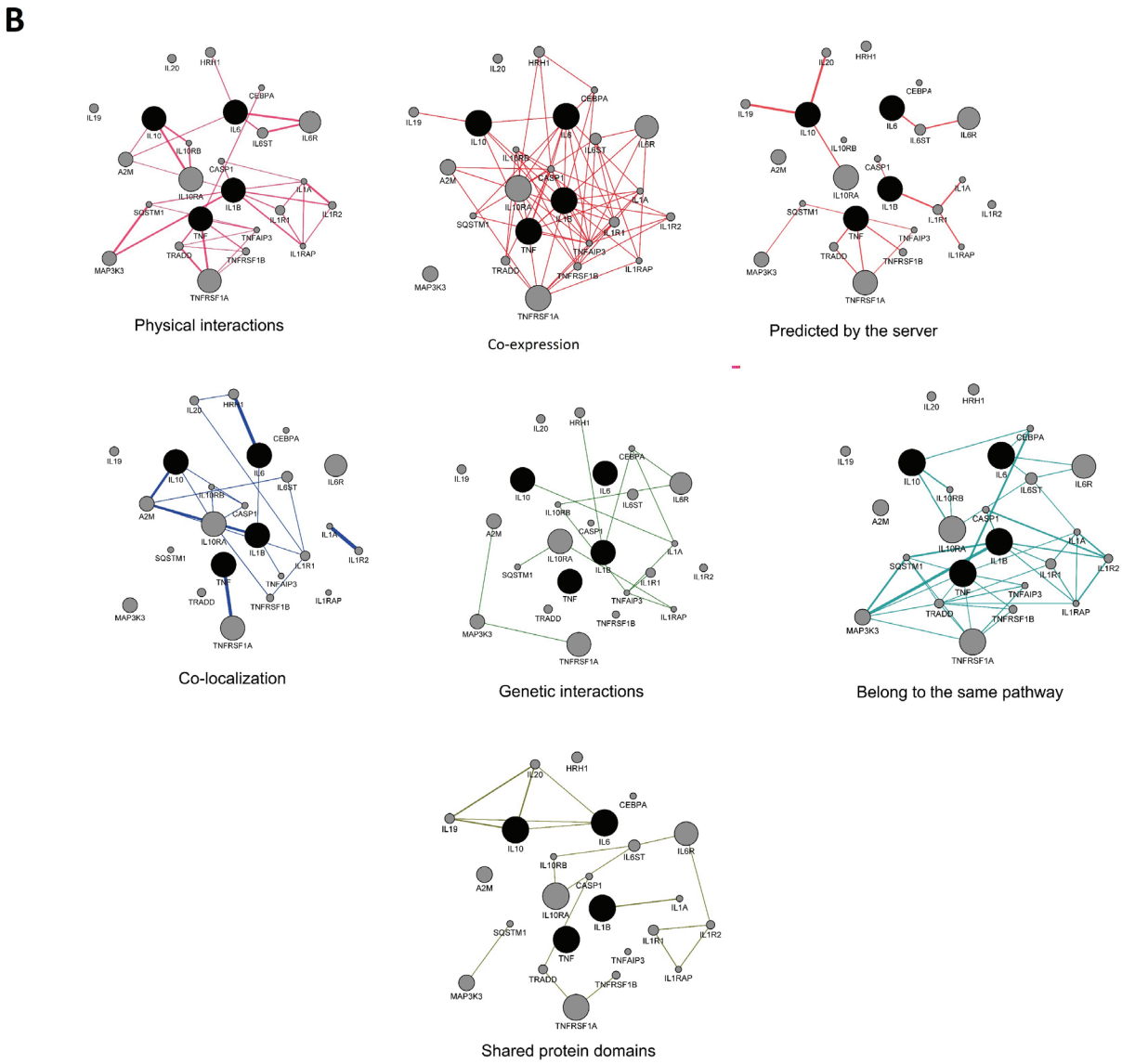

Table 2 Top 10 gene-disease pairs for genes related to both COVID-19 complications and air pollutants, along with the 20 predicted genes (DisGeNET database; http://www.disgenet.org).

Gene	Disease	Disease class (DisGeNET)	Score
CEBPA	acute myelocytic leukaemia	neoplasms	1.000
TNFRSF1A	TNF receptor-associated periodic fever syndrome (TRAPS)	pathological conditions, signs and symptoms; congenital, hereditary, and neonatal diseases and abnormalities; skin and connective tissue diseases	1.000
TNFAIP3	familial Behcet-like autoinflammatory syndrome	/	0.710
TNF	rheumatoid arthritis	skin and connective tissue diseases; musculoskeletal diseases; immune system diseases	0.700
IL10	inflammatory bowel diseases	digestive system diseases	0.700
IL10	systemic lupus erythematosus, systemic	skin and connective tissue diseases; immune system diseases	0.700
IL10	Crohn's disease	digestive system diseases	0.700
IL6	fever	pathological conditions, signs and symptoms	0.700
TNFAIP3	systemic lupus erythematosus	skin and connective tissue diseases; immune system diseases	0.700
SQSTM1	amyotrophic lateral sclerosis	nutritional and metabolic diseases; nervous system diseases	0.700

Inflammatory response and defence mechanisms were also among the identified molecular functions, which was expected, as cytokines and chemokines recruit and mobilise immune cells such as macrophages, neutrophils, and T-cells to the site of infection (25, 26). Pro-inflammatory cytokines such as interleukins like IL-1, IL-6, and TNF play a key part in the early response, whereas anti-inflammatory molecules such as IL-10 are generated during long-term infection to keep inflammation under control and preserve immunological homeostasis (26). We found that all the investigated air pollutants apart from SO_2 are capable of increasing TNF protein expression. Furthermore, all air pollutants increase TNF protein secretion, with the exception of CO. All the investigated air pollutants can also increase protein expression of *IL10*, except for O_3, which decreases it. Additionally, CO, PM_x, and NO_2 increase the mRNA expression of this gene. Furthermore, all air pollutants were found to increase *IL6* expression, while CO, PM_x, NO, and O_3 also increase its secretion. This is in accordance with the literature data, which suggests that the activity of this gene is higher in people living in urban areas but also in patients suffering from COVID-19 (21, 27). A recent clinical study (28) has demonstrated that patients with severe COVID-19 have lower levels of $CD4^+$ and $CD8^+$ T cells and markedly higher plasma IL-6 and IL-10 than patients with mild symptoms. IL-10, the study found, was increased only in severe cases, and suggested its inhibitory function in the immune system and viral control, which means that it might contribute to the severity of the disease.

Finally, all air pollutants were found to increase the expression of *IL1B*, which encodes IL-1ß. This coincides with the release of pro-IL-1ß resulting from the binding of SARS-CoV-2 to toll-like receptors. This cytokine is cleaved by caspase-1, which activates inflammasome and the generation of active IL-1ß, which, in turn, mediates lung inflammation, fever, and fibrosis (29).

Our results have also revealed strong connections between certain genes affected by the investigated air pollutants and other diseases, namely acute myelocytic leukaemia and TNF receptor-associated periodic fever syndrome. This implies that individuals suffering from these diseases might additionally be affected by air pollutants in case of SARS-CoV-2 infection.

CONCLUSION

Our findings corroborate the assumption that air pollution could aggravate COVID-19 and significantly increase the rate of infection, disease severity, and fatality, most likely by affecting the expression of genes responsible for increased immune response, "cytokine storm" in particular. People living in urban areas, who are constantly exposed to air pollutants, are therefore more susceptible COVID-19 complications. However, it is important to acknowledge that this type of research has some limitations. It does not consider dose-response relationships, duration of exposure, or individual sensitivity. Even so, its application has grown strongly in recent years, as it can generate testable hypotheses and identify knowledge that could guide future *in vitro* and *in vivo* research.

Acknowledgements

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Conflicts of interest

None to declare.

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Zajednički utjecaj ključnih onečišćivača zraka na težinu COVID-a 19 – predviđanje zasnovano na analizi toksikogenomičkih podataka

COVID-19 (engl. *coronavirus disease 2019*) respiratorna je bolest prouzročena infekcijom SARS-CoV-2 virusom (engl. *severe acute respiratory syndrome coronavirus 2*). Pretpostavlja se da postoji utjecaj atmosferskih čimbenika, uključujući i onečišćenje zraka, na prenošenje koronavirusa, njegovu težinu i stopu smrtnosti. Stoga je cilj ovoga *in silico* istraživanja bio utvrditi odnos između ključnih onečišćivača zraka [sumporova dioksida (SO_2), ugljikova monoksida (CO), lebdećih čestica (PM_x), dušikova dioksida (NO_2), ozona (O_3)] i komplikacija COVID-a 19 korištenjem: (i) komparativne toksikogenomičke baze podataka (engl. *Comparative Toxicogenomic Database*, CTD) za dobivanje gena, međusobno povezanih s onečišćivačima zraka i komplikacijama COVID-a 19, (ii) GeneMANIA servera za konstruiranje mreže između dobivenih i srodnih gena, (iii) ToppGene Suite za izdvajanje najvažnijih bioloških procesa/molekularnih puteva i (iv) DisGeNET baze podataka za traženje najvažnijih parova gen-bolest. Za SO_2, CO, PM_x, NO_2 odnosno O_3 utvrđena je interakcija sa 6, 6, 18, 9, odnosno 12 gena povezanih s komplikacijama COVID-a 19. Četiri su zajednička (*IL10*, *IL6*, *IL1B* i *TNF*) i u najvećem postotku (77,64 %) sudjeluju u fizičkim interakcijama. Vezivanje citokina i signalni put posredovan citokinima izdvojeni su kao najvažnija molekularna funkcija i biološki proces. Druge molekularne funkcije i biološki procesi uglavnom su bili povezani s aktivnošću citokina i upalom, što bi se moglo dovesti u vezu s citokinskom olujom i posljedičnim komplikacijama COVID-a 19. Utvrđena je veza između različitih bolesti i ispitivanih gena, posebice između *CEBPA* i akutne mijelogene leukemije (AML) te između *TNFRSF1A* i sindroma periodične vrućice povezanoga s TNF receptorom. To upozorava na moguće komplikacije u osoba zaraženih koronavirusom koje boluju od tih bolesti, poglavito kada su dodatno potaknute poremećajem funkcije spomenutih gena.

KLJUČNE RIJEČI: citokini; dušikov dioksid; *in silico*; komplikacije bolesti; lebdeće čestice; onečišćivači zraka; ozon; poremećaj funkcije gena; SARS-CoV-2; sumporov dioksid; ugljikov monoksid