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Indian food habit & food ingredients may have a role in lowering the severity & high death rate from COVID-19 in Indians: findings from the first nutrigenomic analysis

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***Background & objectives*: During the COVID-19 pandemic, the death rate was reportedly 5-8 fold lower in India which is densely populated as compared to less populated western countries. The aim of this study was to investigate whether dietary habits were associated with the variations in COVID-19 severity and deaths between western and Indian population at the nutrigenomics level.**

***Methods*: In this study nutrigenomics approach was applied. Blood transcriptome of severe COVID-19 patients from three western countries (showing high fatality) and two datasets from Indian patients were used. Gene set enrichment analyses were performed for pathways, metabolites, nutrients, *etc*., and compared for western and Indian samples to identify the food- and nutrient-related factors, which may be associated with COVID-19 severity. Data on the daily consumption of twelve key food components**

[#] Equal contribution

across four countries were collected and a correlation between nutrigenomics analyses and per capita daily dietary intake was investigated.

***Results*: Distinct dietary habits of Indians were observed, which may be associated with low death rate from COVID-19. Increased consumption of red meat, dairy products and processed foods by western populations may increase the severity and death rate by activating cytokine storm-related pathways, intussusceptive angiogenesis, hypercapnia and enhancing blood glucose levels due to high contents of sphingolipids, palmitic acid and byproducts such as CO_2 and lipopolysaccharide (LPS). Palmitic acid also induces ACE2 expression and increases the infection rate. Coffee and alcohol that are highly consumed in western countries may increase the severity and death rates from COVID-19 by deregulating blood iron, zinc and triglyceride levels. The components of Indian diets maintain high iron and zinc concentrations in blood and rich fibre in their foods may prevent CO_2 and LPS-mediated COVID-19 severity. Regular consumption of tea by Indians maintains high high-density lipoprotein (HDL) and low triglyceride in blood as catechins in tea act as natural atorvastatin. Importantly, regular consumption of turmeric in daily food by Indians maintains strong immunity and curcumin in turmeric may prevent pathways and mechanisms associated with SARS-CoV-2 infection and COVID-19 severity and lowered the death rate.**

***Interpretation & conclusions*: Our results suggest that Indian food components suppress cytokine storm and various other severity related pathways of COVID-19 and may have a role in lowering severity and death rates from COVID-19 in India as compared to western populations. However, large multi-centered case–control studies are required to support our current findings.**

Key words Caffeine - COVID-19 - death rate - diet- iron - palmitic acid - severity - sphingolipid - tea - transcriptome - turmeric - zinc

Variation in the rate of deaths due to COVID-19 has been detected in different countries (*https://covid19.who.int/table*; accessed on May 30, 2022). Since COVID-19 is an infectious disease, presumably more cases and higher death rates should be found in densely populated countries. The population density varies between 36/km² to 92/km² in the USA, Spain and Greece, whereas, in India, it is 428/km² (*https//www.worldpopulationreview.com*; accessed on May 18, 2022). Therefore, in principle, India should have had a higher number of COVID-19 cases and deaths. However, in reality, these western countries have shown five to eight times higher death rates compared to India (*https://covid19.who.int/table*; accessed on May 30, 2022). Therefore, identifying factors that could explain such differences remain important.

Existing comorbid conditions and their risk related to COVID-19 severity and death have been well established[1]. Host genetic polymorphisms are also associated with severe symptoms and deaths from COVID-19[2]. Plant-based foods, pescatarian and Mediterranean diets and low consumption of red and processed meat have been shown to lower the susceptibility to moderate-to-severe COVID-19 disease[3,4]. Reported diets supplemented with vitamins and zinc may reduce COVID-19 severity[5]. On the other hand, higher consumption of a western diet was found to be associated with increased COVID-19 risk and severity[4,6].

Gene expression profiles of SARS-CoV-2-infected individuals have been used to identify susceptibility, symptoms, severity, disease pathways and drugs for COVID-19 patients[7-10]. In this study, we aimed to identify specific foods, diets, metabolites or nutrients associated with the observed differences in severity and death rates due to COVID-19 in the western and Indian populations using available transcriptome data and nutrigenome approaches.

Material &Methods

Selection of datasets: RNA sequencing (RNA-Seq) data from COVID-19 patients' blood were obtained from public domain through Gene Expression Omnibus (GEO; *https://www.ncbi.nlm.nih.gov/geo/*) and PubMed (*https://pubmed.ncbi.nlm.nih.gov*) databases and were grouped into two categories based on the country-specific death rates (death/100,000 people) from COVID-19. The USA, Greece and Spain were the selected countries with high death rates representing western samples, whereas data from India was used for a country with a low COVID-19 death rate. For the USA, 29 severe COVID-19 samples and nine healthy controls were collected from Bioproject: PRJNA634489[7] and GSE189990[11]. For Greece, the GSE152641 dataset of 62 cases and 24 controls were included[12], and for Spain, the GSE180594 dataset (18 cases and 7 controls)[13] was used. Two datasets were chosen for India; the south Indian (Karnataka) dataset (GSE196822) of 49 expression profiles of four distinct COVID-19 conditions including asymptomatic (n=8), mild (n=9), moderate (n=10), severe (n=7) and control (n=9) and the north Indian (Haryana) dataset (GSE181439) had asymptomatic (n=9) and severe (n=9) cases.

Obtaining differentially expressed genes (DEGs) from RNA-Seq data: The GO2R tool (*https://www.ncbi.nlm.nih.gov/geo/geo2r*; accessed on May 16, 2022) was used for differentially expressed gene (DEG) profiles of cases *vs*. control for GSE180594 and for the south Indian dataset GSE196822. The Limma-Voom package version 4.2 (Bioconductor, Victoria, Australia) was used in R Studio[14] to analyze asymptomatic *vs*. control, mild *vs*. control, moderate *vs*. control and severe *vs*. control. Other DEGs were obtained from the corresponding publications[7,11,12,15]. In all cases, the fold change (Log_2) >1 was considered upregulated and <1 was considered downregulated at adjusted $P<0.05$.

DEG analysis for metabolites and pathways: A modified method of our previously established DEG analysis using only the upregulated gene sets was applied which gave us >90 per cent accuracy[8-10]. DEGs of each country sample were separately analyzed using Enrichr (release March 29, 2021; New York, USA)[16]. However, two USA samples and two Indian datasets were clubbed to make combined USA and Indian samples, respectively. Since for the other countries, only one sample was used, the two Indian samples were combined to make one combined sample for India and the two USA samples were combined to make one combined USA samples for our analysis. All western country samples were also combined for an integrated and comparative analysis with the combined Indian samples. Some analyses with the downregulated genes were also considered to cross verify the reliability of data sets. For example, while using the ‘COVID-19 Related Gene Sets 2021’ database in the Enrichr for upregulated gene sets, it required first to be enriched by giving n number of genes upregulated by SARS-CoV-2 infection. In our cross verification of data set reliability, it was found that all these DEGs were associated with SARS-CoV-2 infection and influenza. Therefore, we proceeded with our DEGs for further analysis.

In Enrichr, the ‘COVID-19 Related Gene Sets 2021’ database was first used to validate if our applied gene set was up or downregulated in COVID-19. In addition, ‘Disease perturbations from GEO up’ and ‘Disease perturbations from GEO down’ were also used to cross-verify the reliability of datasets. In the second step, the human metabolites database (HMDB) was used to identify the metabolites associated with the given gene set. Three pathway databases, WikiPathway 2021 Human, KEGG 2021 Human, and Reactome 2016 were used to identify pathways commonly enriched by at least two databases to interpret our results. The ‘Drug perturbations from GEO up’ and ‘Drug perturbations from GEO down’ databases were also used to correlate the results with identified pathways. In all enrichment analyses, top 10 enrichment results were only considered for interpretation.

Nutrigenomics analysis of DEG: NutriGenomeDB (release November 21, 2021; Madrid, Spain)[17] and its phenotype-centered analysis was used for nutrigenomics analysis and selected *Homo sapiens* as organism. Each dataset was analyzed individually and in combination with complete DEGs (up + downregulated genes). Only the blood based gene expression signatures of different foods, nutrients and bioactive compounds from this database were considered. Furthermore, net enrichment score (NES) were used to predict the final results as NES typically gives better accuracy compared to the number of overlapping gene (NOS) calculations.

Analyses of western and Indian foods and diet: Data and literature mining approaches were used to understand the food consumption among western and Indian populations. Furthermore, various databases and corporate reports were used to understand the differences between dietary habits in the western and Indian populations (Supplementary Table I).

A flow diagram of overall study design is given in Figure 1.

Results

Differences between Indian and western dietary intakes: Twelve key food components were found in the Indian diet, which were considerably different from that in the western populations (Supplementary Table I). At the national level (mean intake per capita, g/day), western populations consumed 10-25 times more red meat, 8-12 times more processed foods, 5-7 times more dairy products, 3-8 times more fish, 10-12 times more coffee and two times more alcohol than Indians. On the other hand, Indians used 1.5 times more legumes and

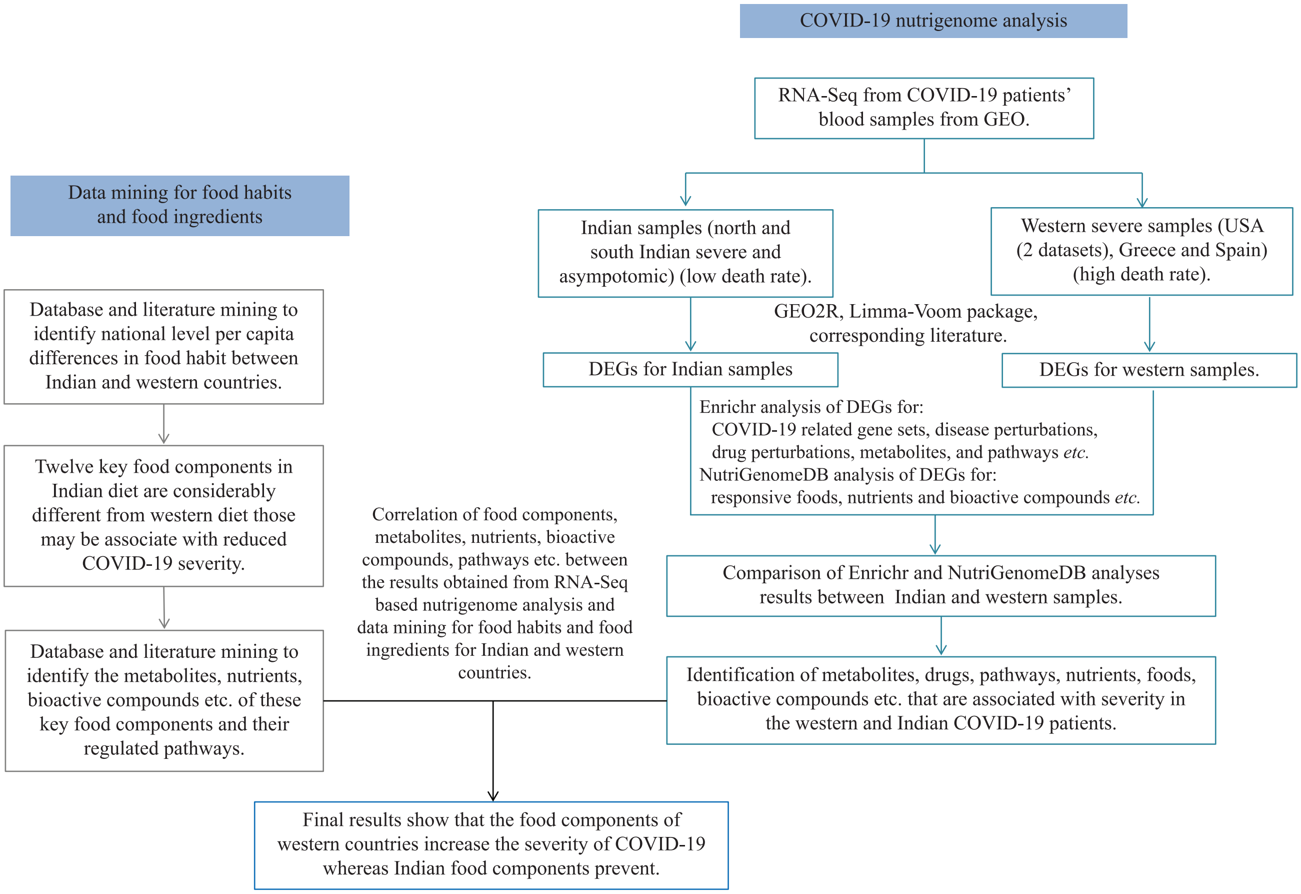

Fig. 1. Schematic flow chart of overall methodology or study design.

vegetables and four times more whole grains than western populations. Most importantly, while western populations used nil or negligible amounts of tea and turmeric, Indians consumed an average 1.2 and 2.5 g tea and turmeric per person per day, respectively (Table I and Supplementary Figure). In south India, the main staple foods were *Idli* and *Dosa* (fermented food, rice and black gram 2:1 ratio) with *Sambar* (lentil-based stew) and rice with *Rasam* (spicy soup)[18]. *Sambar* and *Rasam* contain several spices including turmeric, chili pepper, cumin, curry leaves, mustard, coriander, asafoetida, sea salt, *etc*.[19,20]. Similarly, in north India, kidney bean (*Rajma*), chickpea, legumes, wheat, corn, rice and several spices such as turmeric, chili, cumin, mustard, coriander *etc*. were used as daily foods[21]. When the raw values of per capita daily consumptions of the identified twelve key food components were plotted against COVID-19-associated deaths to create a column chart, a distinct food habit of Indians was found which may be associated with low death rate in Indian populations (Fig. 2 and Supplementary Table I).

Cytokine storm and complement related pathways are upregulated in western and Indian severe COVID-19 samples, respectively: Two pathway databases showed upregulation of interferon (IFN) (type I and II), tumour necrosis factor (TNF), cytokine, chemokine and NOD-like receptor signalling pathways in severe COVID-19 patients from Spain and Greece (Supplementary Table IIE and G). The USA samples displayed over expression of the VEGFA-VEGFR2 signaling pathway (Supplementary Table IIF). The up regulated DEG of combined western populations was associated with IFN, TNF, cytokine, chemokine, VEGFA-VEGFR2 and NOD-like receptor signalling pathways (Supplementary Table IIH). The upregulated genes of combined western countries were also associated with lipopolysaccharide (LPS) and IFN-beta responses (Supplementary Table IIE-H). In contrast, the cell cycle and vitamin D metabolism related pathways were over represented in north Indian severe and south Indian asymptomatic cases (Supplementary Table IIA and C). South Indian severe COVID-19 samples showed upregulation

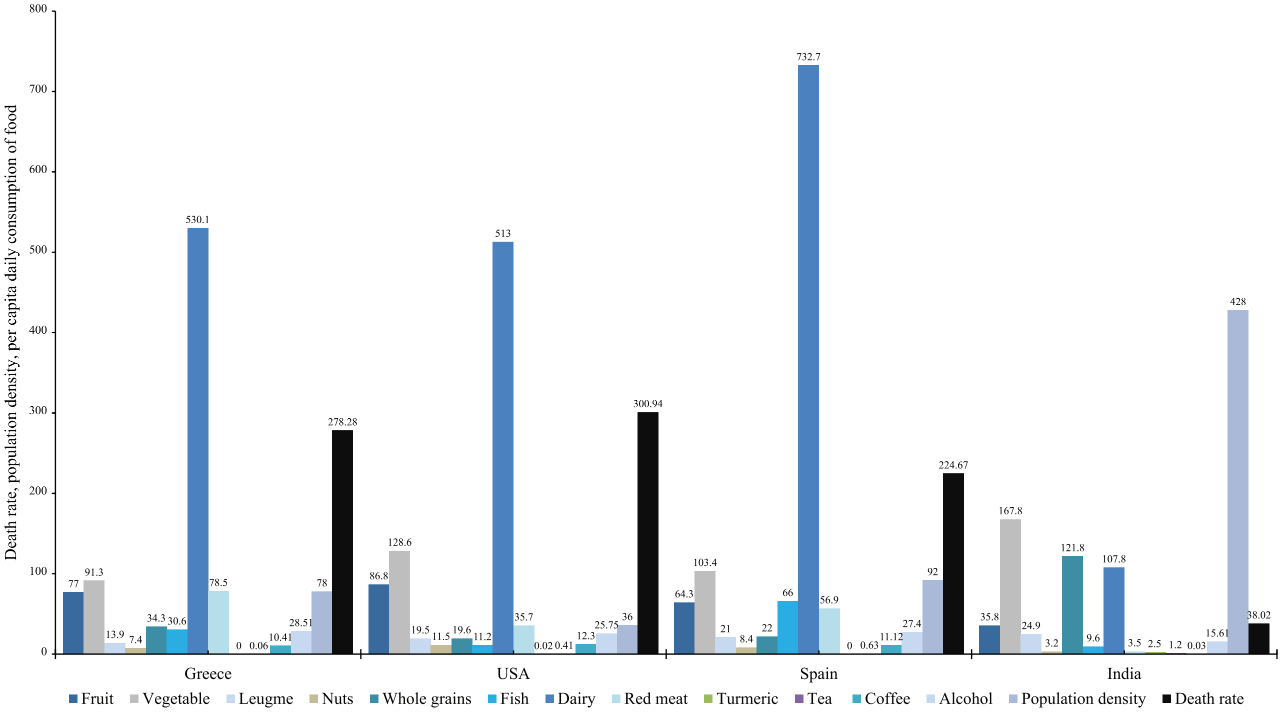

Fig. 2. Dietary habits in Indian and western populations. Per capita daily consumption of 12 key foods and nutrients (variables) along with the population density and death rates (person/100,000) in India and three western countries (Also shown in Supplementary Table 1)**.**

of complement and coagulation cascades (Supplementary Table IIB). The combined Indian severe cases showed similar results to those found for cases from south India (Supplementary Table IIB and D).

Atorvastatin, lipopolysaccharide (LPS), and interferon (IFN)-β responsive genes are differentially upregulated in Indian and western populations: In Using Drug perturbations from GEO up analysis, it was found that the cholesterol lowering drug atorvastatin ranked at 3rd position among severe COVID-19 cases in the USA, 2nd amond severe Indian and 3rd asymptomatic Indian cases. Atorvastatin was not enriched in any other western country (Supplementary Table IIA-H). Therefore, atorvastatin itself, or metabolites or nutrients that act as atorvastatin may have a role in regulating the severity of COVID-19. In contrast, LPS and IFN-β-1a were enriched in all samples except in severe Indian cases. The ranks of LPS and INF-β in asymptomatic Indian cases and in severe USA cases were lower as compared to other severe cases from western countries (Supplementary Table IIA-H).

Palmitic acid (PA) and CO_2 responsive genes upregulated in western severe COVID cases and zinc, iron and carbohydrate responsive genes are enriched in Indian patients: The HMDB-based metabolite analysis showed that carbon dioxide (CO_2), hexadecanoyl-CoA, dermatan sulfate, arachidonic acid and palmitic acid (PA) were differentially enriched for individual western country samples (Supplementary Table IIE-G). However, for combined western samples, CO_2, hexadecanoyl-CoA and PA were enriched (Supplementary Table IIH). In contrast, upregulation of zinc and glucose responsive genes (Supplementary Table IIB) was observed in severe south Indian samples and upregulation of iron, sodium, ammonia, folic acid, riboflavin *etc*. responsive genes in asymptomatic south Indian samples (Supplementary Table IIA). Importantly, the combined severe Indian samples gave a result similar to the south Indian samples. We found that zinc, iron and glucose responsive genes were over represented (Supplementary Table IIB and D). Based on the enrichment ranks, our results indicated that blood iron levels might be associated with COVID-19 severity[22]. Taken together, there were distinct metabolic processes and metabolites governing the severity of COVID-19 between western and Indian populations and they could potentially be linked to the dietary habits of these populations.

PA and CO_2 responsive genes were associated with increased sphingolipid metabolism and PPAR signaling: In a separate Enrichr analysis, we found that the CO_2 responsive genes were associated with the TCA cycle, sphingolipid metabolism, proximal tubule transport and O_2/CO_2 exchange in erythrocyte pathways in western samples. Upregulation of these genes was associated with chronic obstructive pulmonary disease (COPD)-like conditions and metabolic acidosis. In addition, we found curcumin and iron having some association with CO_2 (Supplementary Table IIIA and B). On the other hand, a separate nutrigenomics analysis of the CO_2 responsive genes showed that curcumin negatively regulated CO_2 production (Supplementary Table IIIA and C). Conversely, the PA responsive genes were associated with fatty acid beta-oxidation, PPAR signalling and sphingolipid metabolism. Furthermore, the PA responsive genes also had indicative association with hypertension and obesity like comorbid conditions in COVID-19 (Supplementary Table IIIA and D).

Curcumin determines COVID-19 severity: In NutriGenome DB analyses, three datasets were found to be related to blood based gene expression in response to *Lactobacillus rhamnosus*, curcumin and docosahexaenoic acid. Based on NOG calculation, the number of response genes (RG) for these three nutrients were higher in severe cases as compared to asymptomatic COVID-19 in south Indian samples. The number of RGs was higher in severe western samples than in severe Indian cases (Fig. 3A and Supplementary Table IIIE). The NES analysis yielded positive scores for curcumin, which was higher in cases of asymptomatic Indian samples as compared to severe cases from both north and south India. The NES of curcumin RGs was negative for all western samples. Importantly, we found that the negative NES of curcumin RGs of all severe western samples was lower after treatment with curcumin for 4 h than 18 h (Fig. 3B and Supplementary Table IIIE).

Diets and nutrients correlated with pathways and metabolites related to COVID-19 severity: A linear correlation was observed between diet or nutrients and molecular mechanisms of COVID-19 severity. The cytokine storm, intussusceptive angiogenesis and respiratory acidosis related pathways, which were exclusively upregulated in severe western samples, were positively associated with PA and CO_2 but were negatively correlated with curcumin. The sources of the PA and CO_2 were red meat, processed food and dairy products. PA also increased the expression of ACE2 leading to more severe COVID-19. The low iron and zinc levels in red meat and dairy products of western diets had the probability of increasing the severity and death from COVID-19. In contrast, south Indian *Idli* and other food components are high in iron and zinc content. Curcumin also reduces respiratory acidosis and blood glucose levels (Fig. 4)[18,22,23-75]. Therefore, regular intake of an Indian diet rich in zinc, iron, curcumin, fibre, catechins and EGCG have the potential to reduce the severity and death due to COVID-19. However, consumption of regular western diet, mainly red meat, processed food, dairy products, coffee and alcohol could activate the pathways and factors associated with COVID-19 severity, which may therefore contribute to the increased deaths observed in western countries.

Discussion

Low serum iron and zinc levels are associated with increased severity and death rates in COVID-19[22] (Fig. 4). Zinc is used for treatment of COVID-19[23]. Dairy products are low in iron contents and alcohol consumption decreases plasma zinc levels. Notably, *Idli* (zinc 23.4 mg/g, iron 46.4 mg/g, 3-4% fibre)[18] contains higher amount of zinc and iron than meat and its zinc content is twice the amount available from vitamin tablets containing zinc which were consumed (10 mg), commonly during the COVID-19 pandemic. Similarly, rice, legumes, wheat, chickpeas and *Rajma*, which are daily used ingredients in north Indian diet[21], are rich in vitamins, minerals, zinc and iron. Hence, Indian foods, in contrast to the western diet are able to maintain high blood zinc and iron levels, which can lower the COVID-19 severity and death rates in India (Fig. 4)[18,22-75].

Low plasma HDL-C and high triglyceride levels increase COVID-19 severity[24]. High alcohol consumption in western countries, increases plasma triglyceride and atorvastatin, a triglyceride lowering medicine and increases HDL-C in the blood is enriched in the Indian samples. Atorvastatin reduces COVID-19 severity, contributes to shortening hospitalization and reduction in COVID-19 mortality[25]. Catechins present in tea are the natural substitutes of statin. Catechin and EGCG in tea block SARS-CoV-2 Spike RBD and ACE2 interactions and prevent initiation of SARS-CoV-2 infection. India is the largest tea consumer (Supplementary Table I), where >64 per cent of Indians drink tea[26]. Furthermore, curcumin, consumed in India, enhances the permeability and lipid-lowering effect of EGCG. In contrast, caffeine in coffee reduces statin function, decreases zinc levels, and also inhibits iron absorption[27] (Fig. 4). Coffee is the main source of caffeine and is consumed in large quantities per capita

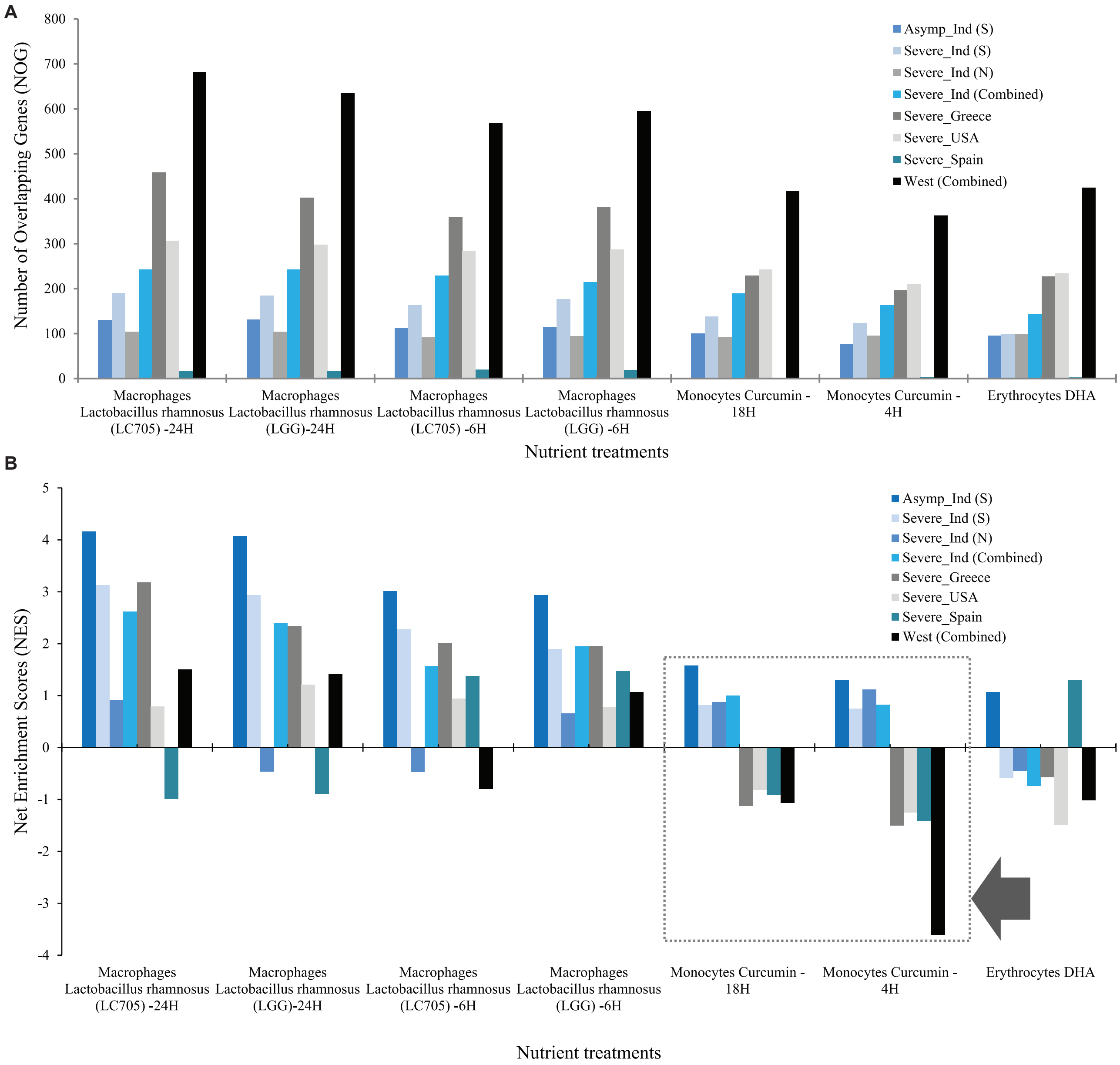

Fig. 3. Blood nutrigenomics profiles of samples from western and Indian populations. (**A**) Number of *L. rhamnosus*, curcumin, and DHA responsive genes increased with increased disease severity in India and the USA and Greece, but not in Spain. (**B**) The NES-based analysis shows that the curcumin response score is positive and highest in samples from asymptomatic cases in India compared to the severe cases in India. In contrast, the NES is negative for curcumin in all samples in western countries (Black arrow). NES, net enrichment score.

in western countries, whereas the consumption is negligible in India (Supplementary Table 1). Therefore, while coffee consumption contribute to COVID-19 severity in western countries; high consumption of tea is potentially associated with less severe form of COVID-19 and lower death rates in India.

Low zinc and high PA-containing western food induces pro-inflammatory activity of PPAR signalling and enhances SARS-CoV-2 pathogenesis by activating pro-inflammatory cytokines, chemokines, NF-κB and ACE2[28]. Western foods also contain high amounts of sphingolipids which activate the SphK1/S1P/S1PR (S1P) hyperinflammatory response pathway and increased COVID-19 severity[29] (Fig. 4). We found that PA and sphingolipids, the two key metabolites of western foods, were associated with the activation of COVID-19 severity pathways and higher death rates in western countries (Fig. 4)[18,22-75].

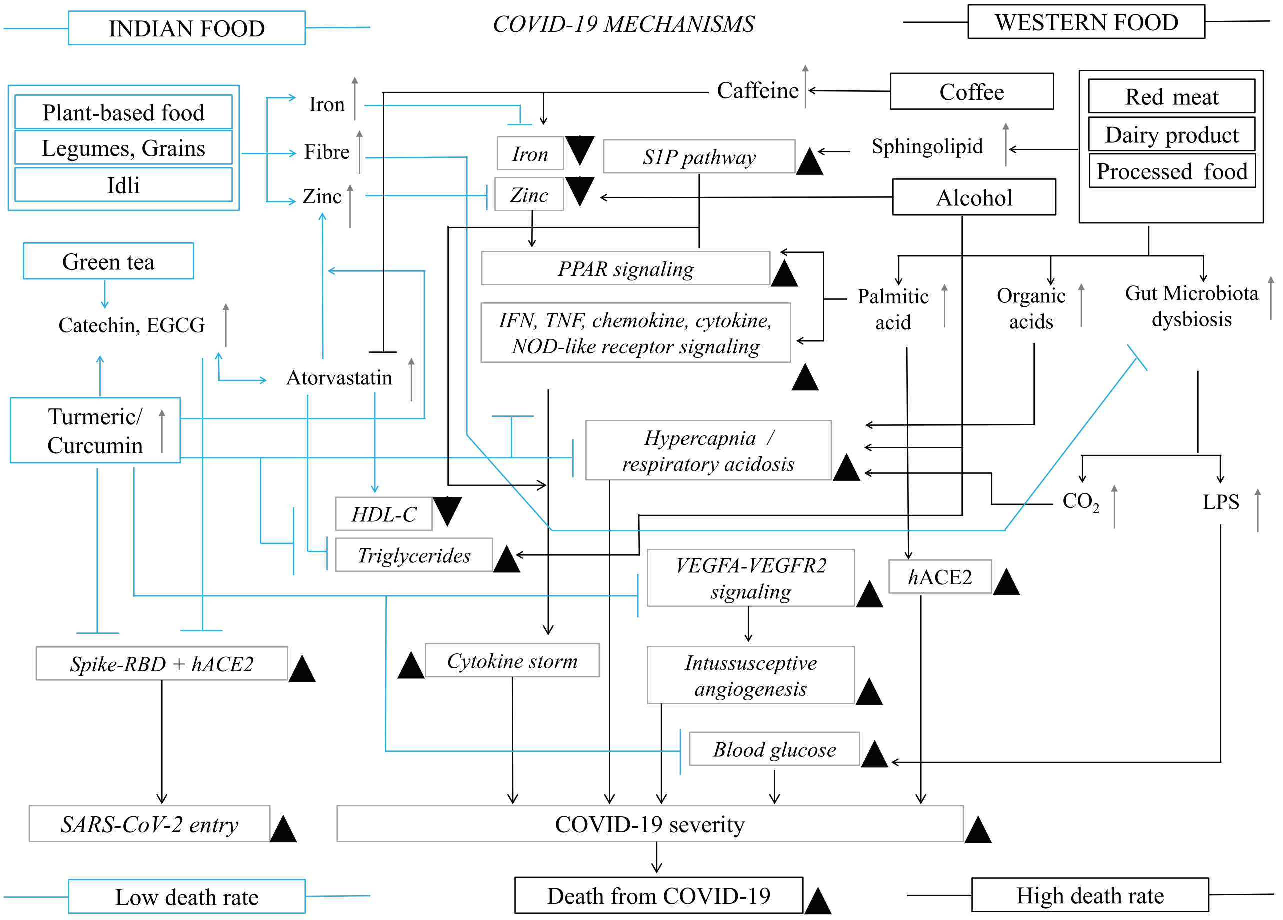

Fig. 4. Key dietary and nutrient interactions with COVID-19 pathways at molecular level that determines COVID-19 severity and fatality rates in Indian and Western populations. The figure is developed based on our results, available literature[18,22-75].↑ and ▲ indicate upregulation or increase, ← is activation, and Tdenotes inhibition.

Meat, fish, eggs, cheese and alcohol induce hypercapnia and respiratory acidosis[30]. Furthermore, high animal fat and protein diets, which are low in fibres, are known to cause gut microbiota dysbiosis leading to increased CO$_2$ and hypercapnia and LPS-induced increased blood glucose levels[31]. Both the hypercapnia and increased blood glucose levels are associated with COVID-19 severity (Fig. 4)[18,22-75]. CO$_2$ RGs are highly enriched in patients with severe COVID-19 in western countries, but not in India. Therefore, the western diet might be associated with hypercapnia and increased blood glucose levels contributing to increase the severity and death during COVID-19 in western populations.

Curcumin, the active compound of turmeric is a prophylactic agent[9] and treatment with curcumin reduces the severity and mortality from COVID-19[32]. Curcumin increases serum zinc levels[33] and it blocks the Spike RBD interaction with ACE2, decreases cholesterol and triglyceride levels, and inhibits hypercapnia, IFN, TNF, chemokine, cytokine, VEGFA-VEGFR2-mediated intussusceptive angiogenesis and NOD-like receptor signaling pathways, which are associated with cytokine storm leading to severity and deaths from COVID-19[34,35] (Fig. 4).

We found that all these pathways were exclusively upregulated in western but not in Indian samples (Supplementary Table II). Further, we identified curcumin to be inversely associated with COVID-19 severity (Fig. 3 and Supplementary Table IIIE). Curcumin is the active compound of turmeric and turmeric is regularly consumed (>2 g/day/capita) spice/condiment in India, but not in western countries (Fig. 2 and Supplementary Table I). Therefore, daily intake of turmeric in India maintains high concentration of body curcumin that inhibits almost all molecular mechanisms associated with SARS-CoV-2 infection and COVID-19 severity, leading to less severe disease outcome and lower death rates in India as compared to western countries (Fig. 4)[18,22,23-75].

Although our findings are significant from the nutrigenomics point of view, there are some limitations. Our study does not represent a precise case-control study where specific foods were used as treatment. Rather, we considered population-specific dietary habits and transcriptomes of patients. We also did not consider factors such as major clinical determinants of health outcomes, co-morbid conditions, age, gender, vaccination status, nutrition index, food habit diversity, smoking status and other biological and socio-economic factors. Our sample sizes were small and hence establishing statistically significant correlation is not possible.

In conclusion, our results suggested that Indian dietary habits and food ingredients could possibly be associated with reduced severity and death rates from COVID-19 in India. While the western diet and food components seemed to contribute to severity of COVID-19, Indian dietary habits and food ingredients might play a role in reduction of severity of COVID-19 disease. Regular consumption of plant-based foods, *Idli*, whole grains, legume, vegetables, tea and turmeric (curcumin) diets were probably the key elements behind reduced severity and lower death rates from COVID-19 in India, despite the much higher population density in the country as compared to western countries. However, additional large scale and intervention trial are required for drawing definitive inference in this direction.

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***Conflicts of Interest*:** None.

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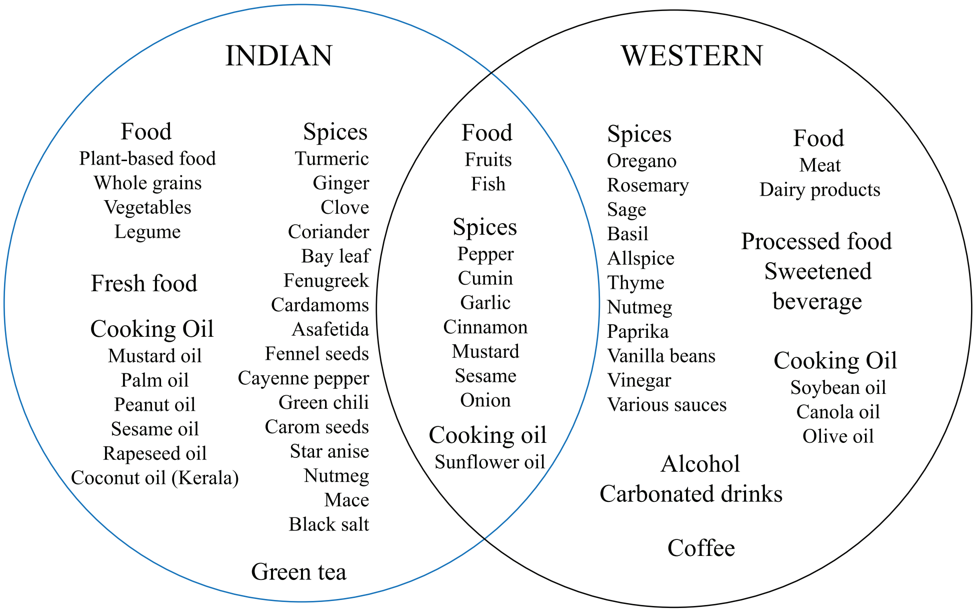

Supplementary Figure. Differences between Indian and western food and spices. The figure is developed based on Supplementary Table 1, several web portals, following literature[1-13].

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Supplementary Table I. Dietary intakes of key foods and nutrients in adults aged 20 yr, national data, per capita g/day

Country	Dietary intakes of key foods and nutrients in adults aged 20 yr, national data, per capita g/day								Per capita g/day, for alcohol ml/day				Population de	Death from COVID-19/100,000 people
	Fruit[a]	Vegetable[a]	Legume[a]	Nuts[a]	Whole grains[a]	Fish[a]	Dairy[a]	Red meat[a]	Turmeric[b]	Tea[c]	Coffee[d]	Alcohol[e]	Population de[f]	Death rate[g]
Greece	77	91.3	13.9	7.4	34.3	30.6	530.1	78.5	0	0.06	10.41	28.51	78	278.28
USA	86.8	128.6	19.5	11.5	19.6	11.2	513	35.7	0.02	0.41	12.3	25.75	36	300.94
Spain	64.3	103.4	21	8.4	22	66	732.7	56.9	0	0.63	11.12	27.4	92	224.67
India	35.8	167.8	24.9	3.2	121.8	9.6	107.8	3.5	2.5	1.2	0.03	15.61	428	38.02

a *https://globalnutritionreport.org/resources/nutrition-profiles/*, accessed on May 30, 2022

b *https://www.statista.com/statistics/798717/india-turmeric-consumption-share-by-region/*, accessed on 30 May, 2022

b *https://oec.world/en/profile/hs/turmeric-curcuma*, accessed on May 30, 2022
Daily intake of turmeric/curcumin in India is very high (>2 g/day) (PMID: 21338207, NBK92752)

c *https://www.statista.com/statistics/507950/global-per-capita-tea-consumption-by-country/*, ccessed on May 30, 2022

d *https://www.helgilibrary.com/indicators/coffee-consumption-per-capita/*, accessed on May 30, 2022

e https://apps.who.int/iris/bitstream/handle/10665/274603/9789241565639-eng.pdf (Accessed on May 30, 2022

f *https://worldpopulationreview.com/*, accessed on May 30, 2022

g *https://covid19.who.int/table*, accessed on May 30, 2022

Supplementary Table IIA. Gene set enrichment analysis of asymptomatic South Indian samples

Up-regulated genes						Down-regulated genes					
Index	Name	*P*	Adjusted *P*	OR	Combined score	Index	Name	*P*	Adjusted *P*	OR	Combined score
COVID-19 Related Gene Sets 2021						COVID-19 Related Gene Sets 2021					
1	COVID-19 patients PBMC up	7.57E-38	3.35E-35	8.89	760.03	1	COVID-19 patients PBMC down	3.00E-33	1.26E-30	11.92	892.72
2	Top 500 up genes for SARS-CoV-2 infection in Rhesus macaqu	1.16E-35	2.56E-33	8.98	721.99	2	SARS perturbation; 220 Down Genes from GEN3VA; Hu	7.36E-17	1.55E-14	6.51	242.02
3	500 genes up-regulated by SARS-CoV-2 in human lung cells fr	3.31E-28	4.88E-26	7.36	465.81	3	Top 500 down genes for SARS-CoV-2 infection in Rhesu	1.49E-16	2.10E-14	4.29	156.42
4	Top 500 up genes for SARS-CoV-2 infection in Rhesus macaqu	4.38E-27	4.84E-25	7.42	450.49	4	Top 500 down genes for SARS-CoV-2 infection in Rhesu	1.11E-12	1.17E-10	3.72	102.45
5	500 genes upregulated by SARS-CoV-2 in human lung tissue f	4.51E-26	3.32E-24	7.2	420.01	5	Top 500 up genes for SARS-CoV-2 infection in Rhesus m	1.83E-12	1.55E-10	3.55	95.93
6	Healthy human lung biopsy versus COVID-19-infected human lung	4.51E-26	3.32E-24	7.2	420.01	6	Top 500 up genes for SARS-CoV-2 infection in Rhesus m	9.49E-12	6.68E-10	3.42	86.86
7	Top 500 up genes for SARS-CoV-2 infection in Rhesus macaque	2.68E-24	1.69E-22	6.99	379.62	7	Top 500 up genes for SARS-CoV-2 infection in Rhesus m	6.36E-10	3.84E-08	3.15	66.79
8	Top 500 upregulated genes for SARS-CoV-2 infection in human	6.90E-23	3.81E-21	6.46	329.42	8	Top 500 up genes from control versus Ad5-hACE2 for SARS-	3.08E-08	1.625E-06	3.09	53.45
9	SARS Perturbation 430 Up Genes from GEN3VA Mouse Lung	6.65E-22	3.27E-20	6.86	334.5	9	Top 500 up genes for SARS-CoV-2 early infection in hum	5.32E-07	0.00002495	2.6	37.55
10	SARS perturbation; 280 Up Genes from GEN3VA; Human PBM	8.91E-22	3.94E-20	8.7	421.92	10	Top 500 up genes for SARS-CoV-2 infection in Rhesus m	8.25E-07	0.00003483	2.62	36.73
HMDB (human metabolome database) metabolites											
1	Iron (HMDB00692)	0.000211	0.2749	3.48	29.43	1	Ubiquinol 8 (HMDB01060)	2.09E-07	0.0007313	25.95	399.09
2	Sodium (HMDB00588)	0.00255	0.2749	2.88	17.2	2	Ubiquinone Q1 (HMDB02012)	0.00381	0.3541	3.83	21.36
3	Ammonia (HMDB00051)	0.006083	0.2749	4.66	23.77	3	Sulfide (HMDB00598)	0.02993	0.3541	3.07	10.78

Contd...

Up-regulated genes						Down-regulated genes					
Index	Name	*P*	Adjusted *P*	OR	Combined score	Index	Name	*P*	Adjusted *P*	OR	Combined score
HMDB (human metabolome database) metabolites											
4	C34H34N4O4.Fe (HMDB03178)	0.009033	0.2749	2.68	12.64	4	A3P (HMDB00061)	0.03442	0.3541	4.65	15.67
5	C10H13N2O7P (HMDB01570)	0.02097	0.2749	10.51	40.61	5	QH2 (HMDB01304)	0.04188	0.3541	2.78	8.83
6	L-Carnitine (HMDB00062)	0.02482	0.2749	9.46	34.95	6	Coenzyme Q (HMDB06709)	0.04456	0.3541	2.73	8.49
7	Folic acid (HMDB00121)	0.02482	0.2749	9.46	34.95	7	Flavin Mononucleotide (HMDB01520)	0.05798	0.3541	3.68	10.48
8	Riboflavin (HMDB00244)	0.02482	0.2749	9.46	34.95	8	PPS (HMDB01134)	0.06906	0.3541	3.4	9.08
9	D-Mannose (HMDB00169)	0.02893	0.2749	8.6	30.45	9	DG (14:0/14:0/0:0) (HMDB07008)	0.08197	0.3541	2.56	6.41
10	TMP (HMDB01227)	0.02893	0.2749	8.6	30.45	10	DG (14:0/14:1 (9Z)/0:0) (HMDB07009)	0.08197	0.3541	2.56	6.41
Disease perturbations from GEO up						Disease perturbations from GEO down					
1	H1N1 DOID-0050211 human GSE27131 sample 514	2.33E-98	1.95E-95	23.96	5386.87	1	H1N1 DOID-0050211 human GSE27131 sample 514	4.82E-69	3.92E-66	27.2	4278.41
2	Septic shock C0036983 human GSE9692 sample 307	2.80E-75	1.17E-72	16.41	2816.19	2	sJIA DOID-848 hu	1.39E-36	5.66E-34	11.1	916.33
3	sJIA DOID-848 human	8.04E-46	2.25E-43	12.87	1336.25	3	Acute myeloid leukaemia DOID-9119 human GSE9476 sa	2.86E-26	7.78E-24	5.8	341.3
4	Sickle-cell anaemia DOID-10923 human GSE16728 sample 505	3.97E-36	8.31E-34	9.57	780.39	4	Multiple sclerosis DOID-2377 human GSE23832 sample	3.07E-23	6.25E-21	7.18	372.18
5	Sickle-cell anaemia DOID-10923 human GSE16728 sample 506	7.65E-33	1.28E-30	8.62	637.43	5	Schizophrenia DOID-5419 human GSE27383 sample 54	2.41E-19	3.93E-17	5.89	252.43
6	Dengue disease DOID-12205 human GSE51808 sample 556	1.03E-29	1.43E-27	8.95	597.51	6	Schizophrenia DOID-5419 human GSE27383 sample 54	5.70E-19	7.75E-17	5.61	235.76
7	SARS C1175175 human	7.34E-24	8.78E-22	11.57	616.54	7	sJIA (subgroup-ex	3.36E-18	3.91E-16	6.38	256.76
8	Autism-spectrum disorder DOID-0060041 human GSE25507 s	7.43E-23	7.79E-21	8.18	417.05	8	Septic shock C0036983 human GSE9692 sample 307	5.97E-16	5.55E-14	9.89	346.66

Contd...

Up-regulated genes						Down-regulated genes					
Index	Name	*P*	Adjusted *P*	OR	Combined score	Index	Name	*P*	Adjusted *P*	OR	Combined score
Disease perturbations from GEO up						Disease perturbations from GEO down					
9	Monoclonal gammopathy of uncertain significance DOID-744	8.90E-23	8.29E-21	8.41	427.1	9	Sarcoidosis DOID-11335 human GSE19314 sample 708	6.13E-16	5.55E-14	5	175.04
10	Dengue haemorrhagic fever DOID-12206 human GSE51808 sa	1.83E-22	1.53E-20	7.3	365.33	10	Ankylosing Spondylitides C0038013 human GSE11886 s	1.47E-11	1.15E-09	4.05	100.98
WikiPathway (WP) 2021 human											
1	Retinoblastoma gene in cancer WP2446	3.10E-09	0.000001018	9.31	182.35	1	TCR signalling pathway WP69	1.10E-12	3.15E-10	9.19	253.12
2	Vitamin D Receptor Pathway WP2877	0.00002883	0.004293	4.02	42.08	2	Modulators of TCR signalling and T-cell activation WP50	8.23E-11	1.17E-08	10.67	247.76
3	Cell cycle WP179	0.00004208	0.004293	4.85	48.9	3	Pathogenesis of SARS-CoV-2Mediated by nsp9-nsp10 C	3.58E-10	3.40E-08	27.08	588.92
4	G1 to S cell cycle control WP45	0.00005235	0.004293	6.84	67.4	4	TCR and Co-stimulatory Signalling WP2583	9.22E-10	6.57E-08	18.22	379.12
5	Photodynamic therapy-induced HIF-1 survival signalling WP36	0.0001052	0.006898	9.23	84.55	5	T-cell antigen Receptor (TCR) pathway during Staphylo	9.02E-08	5.139E-06	7.92	128.53
6	Nuclear Receptors Meta-Pathway WP2882	0.0001358	0.007422	2.9	25.8	6	Selective expression of chemokine receptors during T-c	3.095E-06	0.000147	11.31	143.42
7	Fluoropyrimidine Activity WP1601	0.000558	0.02288	8.5	63.65	7	Cancer immunotherapy by PD-1 blockade WP4585	6.316E-06	0.0002404	12.97	155.25
8	Nucleotide Metabolism WP404	0.0005581	0.02288	12.67	94.88	8	Allograft Rejection WP2328	6.748E-06	0.0002404	5.1	60.74
9	Spinal Cord Injury WP2431	0.0008116	0.02958	3.95	28.12	9	Arrhythmogenic Right Ventricular Cardiomyopathy WP	0.00002896	0.0009171	5.19	54.28
10	Glycolysis and Gluconeogenesis WP534	0.002343	0.07684	5.94	36	10	Development and heterogeneity of the ILC family WP38	0.00006699	0.001909	8.3	79.73

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Up-regulated genes						Down-regulated genes					
Index	Name	*P*	Adjusted *P*	OR	Combined score	Index	Name	*P*	Adjusted *P*	OR	Combined score
KEGG (Kyoto encyclopedia of genes and genomes) 2021 human											
1	Cell cycle	0.00005693	0.01412	4.68	45.74	1	Th17 cell differentiation	5.93E-13	1.40E-10	8.29	233.4
2	p53 signalling pathway	0.0008011	0.09933	5.06	36.09	2	Haematopoietic cell lineage	7.93E-12	9.36E-10	8.13	207.77
3	Transcriptional misregulation in cancer	0.002353	0.143	2.91	17.62	3	T-cell receptor signalling pathway	1.64E-10	1.29E-08	7.18	161.68
4	Toxoplasmosis	0.002372	0.143	3.67	22.2	4	Th1 and Th2 cell differentiation	1.00E-09	5.92E-08	7.31	151.49
5	Mitophagy	0.002884	0.143	4.61	26.95	5	Primary immunodeficiency	2.45E-08	1.155E-06	12.14	212.82
6	Cellular senescence	0.005448	0.1907	2.92	15.24	6	Graft-versus-host disease	7.72E-08	3.036E-06	10.57	173.17
7	Pyrimidine metabolism	0.006083	0.1907	4.66	23.77	7	Natural-killer cell-mediated cytotoxicity	3.06E-07	0.00001032	4.78	71.67
8	FoxO signalling pathway	0.006151	0.1907	3.1	15.79	8	Cell adhesion molecules	4.25E-07	0.00001254	4.42	64.87
9	Pantothenate and CoA biosynthesis	0.008995	0.2479	7.9	37.2	9	Antigen processing and presentation	1.475E-06	0.00003867	5.97	80.13
10	Ferroptosis	0.01018	0.2525	5.13	23.53	10	Inflammatory bowel disease	0.00000811	0.0001914	6.06	71.07
Reactome 2016											
1	G1/S-Specific Transcription Homo sapiens R-HSA-69205	2.60E-08	0.00002118	33.5	585.07	1	Generation of second messenger molecules Homo sapi	1.36E-16	7.29E-14	28.43	1038.62
2	E2F-mediated regulation of DNA replication Homo sapiens R-	0.000004287	0.001468	12.87	159.13	2	Translocation of ZAP-70 to Immunological synapse Hom	7.67E-15	2.06E-12	48.63	1580.63
3	Mitotic G1-G1/S phases Homo sapiens R-HSA-453279	0.000005409	0.001468	5.1	61.9	3	Immunoregulatory interactions between a Lymphoid an	3.71E-14	6.65E-12	6.91	213.68
4	Erythrocytes take up oxygen and release carbon dioxide Homo sapiens	0.00001209	0.00246	47.52	538.13	4	Phosphorylation of CD3 and TCR zeta chains Homo sapiens	2.79E-12	3.76E-10	29.87	794.8
5	Cell Cycle, Mitotic Homo sapiens R-HSA-69278	0.0000413	0.005818	2.68	27.02	5	PD-1 signalling Homo sapiens R-HSA-389948	9.39E-12	1.01E-09	25.6	650.14
6	Transport of glucose and other sugars, bile salts and organic	0.00004847	0.005818	5.28	52.42	6	Costimulation by the CD28 family Homo sapiens R-HSA	1.01E-08	8.02E-07	7.88	145.06

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Up-regulated genes						Down-regulated genes					
Index	Name	*P*	Adjusted *P*	OR	Combined score	Index	Name	*P*	Adjusted *P*	OR	Combined score
Reactome 2016											
7	SLC-mediated transmembrane transport Homo sapiens R-HS	0.00005004	0.005818	3.28	32.5	7	TCR signalling Homo sapiens R-HSA-202403	1.04E-08	8.02E-07	5.77	106.04
8	Cell Cycle Homo sapiens R-HSA-1640170	0.00006012	0.006117	2.45	23.84	8	Adaptive Immune System Homo sapiens R-HSA-128021	2.59E-07	0.00001743	2.3	34.86
9	Erythrocytes take up carbon dioxide and release oxygen Hom	0.00008	0.006512	23.76	224.11	9	Chemokine receptors bind chemokines Homo sapiens R	1.765E-06	0.0001055	7.28	96.43
10	O2/CO2 exchange in erythrocytes Homo sapiens R-HSA-1480	0.00008	0.006512	23.76	224.11	10	Downstream TCR signalling Homo sapiens R-HSA-20242	4.441E-06	0.0002389	4.92	60.6
DisGeNET											
1	Juvenile psoriatic arthritis	4.59E-08	0.0001598	5.75	97.19	1	Autoimmune diseases	1.18E-12	4.71E-09	2.63	72.19
2	Juvenile-Onset Still Disease	8.61E-08	0.0001598	5.48	89.2	2	Sezary syndrome	5.79E-12	1.15E-08	6.21	160.79
3	Neoplasm Metastasis	0.000003009	0.002982	1.68	21.41	3	Peripheral T-cell Lymphoma	1.27E-11	1.69E-08	6.96	174.57
4	Malignant neoplasm of prostate	0.000003841	0.002982	1.73	21.52	4	Lymphoma, T-cell, cutaneous	1.51E-10	1.50E-07	4.28	96.76
5	Breast carcinoma	0.000004016	0.002982	1.62	20.15	5	Lupus Erythematosus, Systemic	2.82E-09	2.245E-06	2.26	44.58
6	Juvenile arthritis	0.000005257	0.003253	3.36	40.85	6	T-cell lymphoma	1.02E-08	6.787E-06	3.45	63.5
7	Liver Cirrhosis, Experimental	0.0000131	0.00695	2.33	26.2	7	Celiac disease	1.45E-08	8.242E-06	3.47	62.72
8	Hereditary spherocytosis	0.00001996	0.008697	13.01	140.82	8	Lymphoma	2.70E-08	0.00001347	2.07	36.08
9	Ovarian carcinoma	0.00002108	0.008697	1.77	19.1	9	Multiple sclerosis	5.46E-08	0.00002418	2.14	35.72
10	Carcinogenesis	0.00004708	0.01622	1.57	15.63	10	Graft-versus-Host Disease	1.30E-07	0.00005168	3.75	59.55
Drug perturbations from GEO up						Drug perturbations from GEO down					
1	Estradiol DB00783 human GSE46924 sample 2487	3.04E-18	1.82E-15	6.14	247.48	1	Methotrexate DB00563 human GSE41831 sample 2601	3.71E-17	3.19E-14	5.2	196.83
2	Estradiol DB00783 human GSE8597 sample 2731	4.02E-18	1.82E-15	6.08	243.65	2	5-aminosalicylic acid 4075 human GSE38713 sample 31	3.06E-15	1.15E-12	4.75	158.74

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Up-regulated genes						Down-regulated genes					
Index	Name	*P*	Adjusted *P*	OR	Combined score	Index	Name	*P*	Adjusted *P*	OR	Combined score
Drug perturbations from GEO up						Drug perturbations from GEO down					
3	Atorvastatin DB01076 human GSE11393 sample 3196	2.74E-14	8.25E-12	6.08	189.71	3	Azathioprine DB00993 human GSE38713 sample 3194	4.01E-15	1.15E-12	5.64	186.84
4	IFN beta-1a DB00060 human GSE26104 sample 3187	5.26E-13	1.19E-10	4.92	139.09	4	IFN beta-1a DB00060 human GSE26104 sample	8.19E-12	1.76E-09	5.19	132.58
5	Nilotinib DB04868 human GSE19567 sample 2528	1.24E-12	2.25E-10	6.56	179.85	5	LMP-420 497668 human GSE20211 sample 3222	1.29E-08	0.00000221	3.67	66.72
6	Bleomycin DB00290 mouse GSE25640 sample 3121	3.70E-12	5.27E-10	4.69	123.37	6	Atorvastatin DB01076 human GSE11393 sample 3196	2.58E-08	3.696E-06	3.46	60.47
7	Atarax DB00557 human GSE31773 sample 2485	4.08E-12	5.27E-10	5.28	138.51	7	Resveratrol DB02709 human GSE36930 sample 3497	2.11E-07	0.00002593	3.19	49.02
8	Lipopolysaccharide 11970143 human GSE40885 sample 2475	9.79E-12	1.10E-09	5.08	128.83	8	Atorvastatin DB01076 human GSE11393 sample 3401	3.77E-07	0.00003923	3.24	47.98
9	Mesalazine DB00244 human GSE38713 sample 3289	3.12E-11	3.13E-09	5.84	141.33	9	Calcitriol 5280453 human GSE52819 sample 3129	4.11E-07	0.00003923	3.51	51.59
10	Adenosine triphosphate 5957 human GSE30903 sample 3219	3.82E-11	3.45E-09	5.54	132.82	10	IFN beta-1b DB00068 human GSE26104 sample	2.934E-06	0.0002523	3.11	39.65
DSigDB											
1	Retinoic acid CTD 00006918	2.48E-16	6.25E-13	2.39	85.76	1	1 AGN-PC-0JHFVD BOSS	3.64E-07	0.0008624	3.92	58.09
2	COPPER CTD 00005706	3.90E-15	4.92E-12	2.93	97.05	2	2 Isoguanine BOSS	0.00002064	0.02448	3.29	35.49
3	tretinoin HL60 UP	2.65E-14	2.23E-11	6.85	214.07	3	3 diphenylpyraline BOSS	0.00004182	0.03306	3.37	33.93
4	LUCANTHONE CTD 00006227	5.86E-14	3.70E-11	7.24	220.55	4	4 methyprylon BOSS	0.0002915	0.1728	3.39	27.63
5	etoposide MCF7 DOWN	5.79E-13	2.92E-10	20.02	564.27	5	5 ARSENIC CTD 00005442	0.0004146	0.1967	1.77	13.75
6	estradiol CTD 00005920	9.24E-13	3.89E-10	2.14	59.35	6	6 Prestwick-983 HL60 UP	0.0005429	0.2146	2.76	20.73
7	calcitriol CTD 00005558	2.25E-12	8.11E-10	2.54	68.16	7	7 ajmaline HL60 UP	0.001871	0.6209	2.18	13.68
8	resveratrol CTD 00002483	2.74E-12	8.65E-10	2.69	71.66	8	8 staurosporine TTD 00011086	0.0022	0.6209	2.97	18.16

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Up-regulated genes						Down-regulated genes					
Index	Name	*P*	Adjusted *P*	OR	Combined score	Index	Name	*P*	Adjusted *P*	OR	Combined score
DSigDB											
9	fludroxycortide HL60 UP	4.32E-12	1.21E-09	31.26	818.05	9	9 ZIRAM CTD 00007014	0.002356	0.6209	6.15	37.23
10	benzo[a] pyrene CTD 00005488	4.85E-12	1.22E-09	2.09	54.34	10	10 ionomycin BOSS	0.004986	0.951	3.63	19.26

IFN, interferon; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; OR, odd's ratio; GEO, gene expression omnibus; PD, Parkinson's disease; sJIA, systemic juvenile idiopathic arthritis; TCR, T-cell receptor; PBMC, peripheral blood mononuclear cells; HIF, hypoxia-inducible factor; ILC, innate lymphoid cell; TMP, thymidine monophosphate; DG, diglyceride; R-HSA, R-HSA reactome pathway ID

Supplementary Table IIB. Gene set enrichment analysis of severe South Indian samples

Up-regulated genes						Down-regulated genes					
Index	Name	*P*	Adjusted *P*	OR	Combined score	Index	Name	*P*	Adjusted *P*	OR	Combined score
COVID-19-related gene sets 2021											
1	SARS perturbation; 280 Up Genes from GEN3VA; Human PBM	4.17E-77	1.92E-74	19.5	3430.03	1	COVID-19 patients PBMC down	3.91E-26	1.70E-23	9.78	572.46
2	500 genes up-regulated by SARS-CoV-2 in human lung cells fr	3.37E-69	7.76E-67	10.99	1731.92	2	Top 500 down genes for SARS-CoV-2 infection in Rhesu	2.01E-21	4.18E-19	5.04	240.15
3	500 genes upregulated by SARS-CoV-2 in human lung tissue f	4.02E-68	4.62E-66	11.29	1752.26	3	SARS perturbation; 220 Down Genes from GEN3VA; Hu	2.89E-21	4.18E-19	7.74	366.11
4	Healthy human lung biopsy versus COVID-19-infected human lung	4.02E-68	4.62E-66	11.29	1752.26	4	Top 500 down genes for SARS-CoV-2 infection in Rhesu	7.70E-16	8.35E-14	4.24	147.65
5	COVID-19 patients PBMC up	1.61E-46	1.48E-44	7.75	817.02	5	Top 500 down genes for SARS-CoV-2 infection in Rhesu	1.47E-10	1.27E-08	3.38	76.45
6	Top 500 up genes for SARS-CoV-2 infection in Rhesus macaque					6	Top 500 up genes for SARS-CoV-2 infection in Rhesus m	2.85E-09	2.06E-07	3.03	59.64
7	Top 500 up genes for SARS-CoV-2 infection in Rhesus macaque					7	Top 500 up genes for SARS-CoV-2 infection in Rhesus m	3.00E-08	1.86E-06	2.89	50.12
8	Top 500 down genes for SARS -CoV-2 infection in Rhesus mac					8	Top 500 down genes for SARS-CoV-2 infection in Rhesus	3.90E-08	2.114E-06	2.91	49.6
9	Top 500 up genes for SARS-CoV-2 infection in Rhesus macaque					9	Top 500 down genes for SARS-CoV-2 infection in Rhesus	5.02E-07	0.00002422	2.68	38.91
10	Top 500 up genes from control versus Ad5-hACE2 for SARS-CoV-					10	Top 500 down genes for SARS-CoV-2 early infection in h	1.29E-06	0.00005583	2.53	34.35
HMDB (human metabolome database) metabolites											
1	Zinc (HMDB01303)	0.0004604	0.5249	3.98	30.61	1	I3P (HMDB01498)	0.127	0.4455	3.49	7.2
2	C6H12O6 (HMDB03345)	0.0005829	0.5249	8.92	66.46	2	PC (16:0/16:0) (HMDB00564)	0.224	0.4455	1.89	2.83
3	C6H12O6 (HMDB00516)	0.0007451	0.5249	12.68	91.3	3	PC (18:1 (9Z)/18:1 (9Z)) (HMDB00593)	0.224	0.4455	1.89	2.83

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Up-regulated genes						Down-regulated genes					
Index	Name	*P*	Adjusted *P*	OR	Combined score	Index	Name	*P*	Adjusted *P*	OR	Combined score
HMDB (human metabolome database) metabolites											
4	Iron (HMDB00692)	0.0009645	0.5249	2.6	18.07	4	DG (14:0/14:0/0:0) (HMDB07008)	0.224	0.4455	1.89	2.83
5	D-Glucose (HMDB00122)	0.001637	0.5249	6.8	43.6	5	DG (14:0/14:1 (9Z)/0:0) (HMDB07009)	0.224	0.4455	1.89	2.83
6	Glucose 6-phosphate (HMDB01401)	0.002225	0.5249	8.77	53.59	6	DG (14:0/15:0/0:0) (HMDB07010)	0.224	0.4455	1.89	2.83
7	F6P (HMDB03971)	0.002225	0.5249	8.77	53.59	7	DG (14:0/16:0/0:0) (HMDB07011)	0.224	0.4455	1.89	2.83
8	Ammonia (HMDB00051)	0.002802	0.5249	4.08	24.01	8	DG (14:0/16:1 (9Z)/0:0) (HMDB07012)	0.224	0.4455	1.89	2.83
9	C10H13N2O7P (HMDB01570)	0.005285	0.5249	10.68	56	9	DG (14:0/18:0/0:0) (HMDB07013)	0.224	0.4455	1.89	2.83
10	TMP (HMDB01227)	0.008707	0.5249	8.54	40.53	10	DG (14:0/18:1 (11Z)/0:0) (HMDB07014)	0.224	0.4455	1.89	2.83
Disease perturbations from GEO up						Disease perturbations from GEO down					
1	Septic Shock C0036983 human GSE9692 sample 307	3.77E-162	3.16E-159	25.79	9587.69	1	H1N1 DOID-0050211 human GSE27131 sample 514	1.20E-79	1.00E-76	32.69	5940.73
2	H1N1 DOID-0050211 human GSE27131 sample 514	1.87E-83	7.84E-81	14.34	2732.41	2	Acute myeloid leukemia DOID-9119 human GSE9476 sa	3.08E-31	1.29E-28	6.55	460.32
3	SARS C1175175 human	7.04E-74	1.97E-71	25.47	4290.68	3	Huntington's disease DOID-12858 human GSE24250 sa	1.42E-24	3.96E-22	7.02	385.49
4	Overexertion C0161750 human GSE3606 sample 286	2.57E-70	5.40E-68	16.81	2693.84	4	Sarcoidosis DOID-11335 human GSE19314 sample 708	1.02E-23	2.14E-21	6.53	345.69
5	sJIA DOID-848 human	1.50E-66	2.52E-64	13.06	1979.41	5	Autism-spectrum disorder DOID-0060041 human GSE25	1.27E-22	2.13E-20	6.73	339.41
6	Rheumatoid arthritis DOID-7148 human GSE15573 sample 90	1.88E-59	2.63E-57	14.59	1972.98	6	Multiple sclerosis DOID-2377 human GSE23832 sample	3.30E-19	4.60E-17	6.3	268.09
7	Non-sJIA (subgroup-RF)	1.56E-54	1.87E-52	11.15	1380.87	7	sJIA DOID-848 hu	5.59E-18	6.68E-16	6.47	256.83

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Up-regulated genes						Down-regulated genes					
Index	Name	*P*	Adjusted *P*	OR	Combined score	Index	Name	*P*	Adjusted *P*	OR	Combined score
Disease perturbations from GEO up						Disease perturbations from GEO down					
8	Polycystic ovary syndrome DOID-11612 human GSE34526 sa	5.03E-54	5.28E-52	10.58	1298.64	8	JRA - C0553662 human G	2.31E-17	2.41E-15	5.67	217.38
9	Multiple sclerosis DOID-2377 human GSE26484 sample 742	2.44E-50	2.28E-48	12.82	1464.35	9	Rotavirus infection of children C1442797 human GSE27	1.38E-16	1.28E-14	5.23	191.13
10	Huntington's disease DOID-12858 human GSE8762 sample 9	2.97E-49	2.49E-47	9.07	1014	10	Overexertion C0161750 human GSE3606 sample 286	1.66E-15	1.38E-13	4.95	168.59
WikiPathway (WP) 2021 human											
1	Complement system WP2806	9.69E-12	4.30E-09	8.06	204.31	1	Cytoplasmic Ribosomal Proteins WP477	7.22E-15	2.23E-12	10.65	346.72
2	Complement and Coagulation Cascades WP558	6.25E-09	0.000001388	9.19	173.69	2	2 Modulators of TCR signalling and T-cell activation WP50	7.57E-09	8.62E-07	8.98	167.96
3	Microglia Pathogen Phagocytosis Pathway WP3937	6.59E-07	0.00008135	9.58	136.37	3	Pathogenesis of SARS-CoV-2 Mediated by nsp9-nsp10 C	8.37E-09	8.62E-07	22.48	418.13
4	Metabolic reprogramming in colon cancer WP4290	0.000001076	0.00008135	8.98	123.44	4	TCR signalling pathway WP69	2.10E-07	1.39E-05	6.03	92.73
5	Signal transduction through IL1R WP4496	0.000001081	0.00008135	10.77	147.92	5	TCR and Co-stimulatory Signalling WP2583	2.25E-07	0.00001393	13.48	206.37
6	Vitamin D Receptor Pathway WP2877	0.000001099	0.00008135	3.79	51.95	6	Allograft Rejection WP2328	1.104E-06	0.00005685	5.62	77.1
7	Spinal Cord Injury WP2431	0.000002527	0.0001603	4.53	58.42	7	T-Cell antigen Receptor (TCR) pathway during Staphylo	4.685E-06	0.0002068	6.47	79.42
8	IL1 and megakaryocytes in obesity WP2865	0.00001073	0.0005957	11.79	134.93	8	Cancer immunotherapy by PD-1 blockade WP4585	6.008E-06	0.0002321	13.07	157.14
9	Cori Cycle WP1946	0.00001368	0.0006075	15.6	174.74	9	B-Cell receptor Signalling Pathway WP23	0.0003263	0.0112	3.83	30.76
10	Platelet-mediated interactions with vascular and circulating c	0.00001368	0.0006075	15.6	174.74	10	Development and heterogeneity of the ILC family WP38	0.0005237	0.01618	6.88	51.98

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Up-regulated genes						Down-regulated genes					
Index	Name	*P*	Adjusted *P*	OR	Combined score	Index	Name	*P*	Adjusted *P*	OR	Combined score
KEGG (Kyoto encyclopedia of genes and genomes) 2021 human											
1	Neutrophil extracellular trap formation	8.97E-15	2.37E-12	6.26	202.34	1	Hematopoietic cell lineage	5.87E-19	1.38E-16	12.14	509.74
2	Osteoclast differentiation	4.86E-11	6.42E-09	6.46	153.36	2	Th17 cell differentiation	6.23E-15	7.32E-13	9.34	305.42
3	Complement and coagulation cascades	4.33E-10	3.81E-08	7.8	168.19	3	Th1 and Th2 cell differentiation	1.51E-12	1.01E-10	9.01	245.13
4	*S. aureus* infection	1.96E-08	0.000001296	6.32	112.08	4	Inflammatory bowel disease	1.72E-12	1.01E-10	11.62	314.8
5	Legionellosis	4.54E-08	0.000002398	8.53	144.14	5	Primary immunodeficiency	6.52E-12	3.06E-10	17.61	453.6
6	Leishmaniasis	2.85E-07	0.00001253	6.42	96.69	6	Intestinal immune network for IgA production	2.40E-10	9.41E-09	12.43	275.2
7	SLE	7.76E-07	0.00002928	4.46	62.69	7	Ribosome	1.97E-09	6.62E-08	5.19	103.97
8	Phagosome	0.000004399	0.0001348	3.89	47.94	8	Cell adhesion molecules	2.97E-09	8.71E-08	5.31	104.27
9	Lipid and atherosclerosis	0.000004594	0.0001348	3.31	40.66	9	Antigen processing and presentation	2.88E-08	7.31E-07	7.18	124.74
10	Malaria	0.000005876	0.0001551	7.18	86.52	10	Asthma	3.11E-08	7.31E-07	14.29	247.01
Reactome 2016											
1	Hemostasis Homo sapiens R-HSA-109582	4.59E-16	4.06E-13	3.77	133.25	1	Generation of second messenger molecules Homo sapi	1.19E-16	4.61E-14	28.66	1050.67
2	Platelet degranulation Homo sapiens R-HSA-114608	9.76E-15	4.32E-12	9.16	295.66	2	Translocation of ZAP-70 to Immunological synapse Hom	1.31E-16	4.61E-14	60.43	2210.09
3	Response to elevated platelet cytosolic Ca2+Homo sapiens R	3.10E-14	9.16E-12	8.62	268.23	3	Viral mRNA Translation Homo sapiens R-HSA-192823	1.81E-15	2.84E-13	11.52	391.16
4	Platelet activation, signaling and aggregation Homo sapiens R	1.75E-12	3.87E-10	4.75	128.53	4	Peptide chain elongation Homo sapiens R-HSA-156902	1.81E-15	2.84E-13	11.52	391.16
5	Immune System Homo sapiens R-HSA-168256	2.86E-11	5.06E-09	2.21	53.56	5	Phosphorylation of CD3 and TCR zeta chains Homo sapiens	2.02E-15	2.84E-13	42.3	1431.16
6	Cell surface interactions at the vascular wall Homo sapiens R-	1.68E-10	2.34E-08	7.19	161.76	6	Selenocysteine synthesis Homo sapiens R-HSA-2408557	4.20E-15	4.22E-13	10.98	363.52
7	Extracellular matrix organization Homo sapiens R-HSA-14742	1.85E-10	2.34E-08	4.02	90.19	7	Eukaryotic Translation Termination Homo sapiens R-HS	4.20E-15	4.22E-13	10.98	363.52

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Up-regulated genes						Down-regulated genes					
Index	Name	*P*	Adjusted *P*	OR	Combined score	Index	Name	*P*	Adjusted *P*	OR	Combined score
Reactome 2016											
8	Metabolism of carbohydrates Homo sapiens R-HSA-71387	4.42E-07	0.00004891	3.22	47.09	8	Eukaryotic Translation Elongation Homo sapiens R-HSA	7.22E-15	5.64E-13	10.65	346.72
9	Innate Immune System Homo sapiens R-HSA-168249	0.000001824	0.0001796	2.12	28.06	9	NMD independent of the E	7.22E-15	5.64E-13	10.65	346.72
10	Regulation of Complement cascade Homo sapiens R-HSA-977	0.00001922	0.001703	10.55	114.56	10	PD-1 signaling Homo sapiens R-HSA-389948	9.36E-15	6.58E-13	35.24	1138.46
DisGeNET											
1	Sepsis	4.86E-22	2.75E-18	4.62	226.84	1	Autoimmune diseases	1.06E-13	4.45E-10	2.73	81.65
2	Rheumatoid arthritis	1.04E-21	2.89E-18	2.77	133.96	2	Celiac disease	5.51E-11	1.16E-07	4.02	95.08
3	Arteriosclerosis	1.53E-21	2.89E-18	3.32	159.14	3	Immune System Diseases	3.68E-09	5.15E-06	4.02	77.98
4	Atherosclerosis	1.12E-19	1.58E-16	3.12	136.22	4	Chronic Lymphocytic Leukaemia	1.36E-08	1.43E-05	2.2	39.77
5	Arthritis	5.05E-19	5.71E-16	3.91	164.56	5	Peripheral T-cell lymphoma	1.86E-08	0.00001564	5.54	98.53
6	Septicaemia	2.98E-18	2.80E-15	4.39	176.99	6	Sezary syndrome	2.86E-08	0.00002004	4.83	83.87
7	Liver cirrhosis, Experimental	1.30E-17	1.05E-14	3.38	131.44	7	Multiple sclerosis	4.03E-08	0.00002414	2.15	36.69
8	Acute coronary syndrome	1.71E-17	1.21E-14	5.9	227.63	8	Grave's disease	6.52E-08	0.00003421	3.23	53.5
9	Infection	3.23E-17	2.03E-14	4.14	157.1	9	Rheumatoid arthritis	2.14E-07	0.00009531	1.83	28.18
10	Juvenile arthritis	4.72E-17	2.67E-14	5.06	190.18	10	Immunologic deficiency syndromes	2.27E-07	0.00009531	2.44	37.39
Drug perturbations from GEO up						Drug perturbations from GEO down					
1	Etanercept DB00005 human GSE7524 sample 3295	6.65E-45	6.00E-42	13.58	1381.37	1	Azathioprine DB00993 human GSE38713 sample 3194	3.29E-19	1.90E-16	6.67	283.91
2	Atorvastatin DB01076 human GSE11393 sample 3196	5.67E-36	2.56E-33	9.06	735.01	2	IFN beta-1a DB00060 human GSE26104 sample	4.22E-19	1.90E-16	7.28	308.13
3	Soman 7305 rat GSE13428 sample 2635	1.11E-32	3.34E-30	6.25	459.72	3	5-aminosalicylic acid 4075 human GSE38713 sample 31	1.79E-17	5.37E-15	5.2	200.41
4	Soman 7305 rat GSE13428 sample 2639	1.93E-31	4.35E-29	6.04	426.98	4	4 LMP-420 497668 human GSE20211 sample 3222	3.01E-15	6.78E-13	5.23	174.88
5	Soman 7305 rat GSE13428 sample 2633	8.03E-31	1.45E-28	5.89	408.2	5	1,2,4-BENZENETRIOL 10787 human GSE7664 sample 3	1.77E-14	3.19E-12	5.67	179.55

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Up-regulated genes						Down-regulated genes				
Index	Name	*P*	Adjusted *P*	OR	Combined score	Index	Name	*P*	Adjusted *P*	OR	Combined score
Drug perturbations from GEO up						Drug perturbations from GEO down					
6	Soman 7305 rat GSE13428 sample 2640	1.94E-30	2.92E-28	5.65	386.41	6	Methotrexate DB00563 human GSE41831 sample 2601	3.84E-13	5.76E-11	4.42	126.36
7	Promyelocytic leukemia DB00755 human GSE5007 sample 24	2.93E-30	3.78E-28	7.73	525.92	7	Etanercept DB00005 human GSE7524 sample 3295	1.26E-12	1.62E-10	3.98	109.09
8	Soman 7305 rat GSE13428 sample 2637	1.40E-29	1.59E-27	6.12	406.27	8	Resveratrol DB02709 human GSE36930 sample 3497	1.12E-09	1.26E-07	3.72	76.68
9	Mycophenolic acid DB01024 human GSE14630 sample 3302	6.67E-28	6.69E-26	6.89	430.86	9	Estradiol 5757 human GSE12446 sample 3203	2.60E-09	2.60E-07	3.76	74.37
10	Soman 7305 rat GSE13428 sample 2632	1.13E-27	1.02E-25	5.64	349.71	10	Atorvastatin DB01076 human GSE11393 sample 3196	5.94E-09	5.35E-07	3.62	68.59
DSigDB											
1	Tretinoin HL60 UP	3.47E-26	1.14E-22	8.15	477.79	1	AGN-PC-0JHFVD BOSS	0.00001726	0.04434	3.34	36.58
2	Retinoic acid CTD 00006918	1.16E-24	1.90E-21	2.37	130.44	2	2-Fluoroadenosine BOSS	0.00005038	0.06471	4.85	47.99
3	Mebendazole HL60 UP	1.42E-22	1.55E-19	5.88	295.77	3	Fluoride CTD 00005982	0.0003925	0.3361	5.09	39.88
4	Etynodiol HL60 UP	1.78E-19	1.46E-16	18.06	779.66	4	Isoguanine BOSS	0.0005942	0.3816	2.73	20.29
5	Pergolide HL60 UP	2.58E-19	1.70E-16	5.62	240.44	5	Diphenylpyraline BOSS	0.001278	0.6566	2.73	18.16
6	Alprostadil HL60 UP	4.84E-19	2.65E-16	4.81	203.02	6	ALW-II-38-3 LINCS	0.001938	0.8296	6.47	40.43
7	Aspirin CTD 00005447	1.70E-17	7.98E-15	3.93	151.69	7	Orciprenaline HL60 UP	0.002299	0.8438	4.97	30.17
8	Tetryzoline HL60 UP	3.56E-17	1.46E-14	9.5	359.93	8	(-)-isoprenaline HL60 UP	0.002704	0.8684	2.5	14.77
9	Tetradioxin CTD 00006848	4.25E-17	1.55E-14	2.09	78.84	9	Beta-D-allopyranose BOSS	0.004483	1	3.05	16.51
10	Tamibarotene CTD 00002527	2.18E-16	7.16E-14	3.79	136.8	10	Dasatinib TTD 00007441	0.005056	1	4.16	21.98

IFN, interferon; NMD, nonsense-mediated decay; OR, odds ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; GEO, gene expression omnibus; sJIA, systemic juvenile idiopathic arthritis; JRA, juvenile rheumatoid arthritis; TCR, T-cell receptor; *S. aureus, Staphylococcus aureus;* SLE, systemic lupus erythematosus; PD, Parkinson's disease; PBMC, peripheral blood mononuclear cells; DG, diglyceride; TMP, thymidine monophosphate; RF, rheumatoid factor; ILC, Innate lymphoid cell; R-HSA, R-HSA reactome pathway ID; ZAP, zeta-chain-associated protein kinase 70 CTD, comparative toxicogenomics database

Supplementary Table IIC. Gene set enrichment analysis of severe north Indian samples

Up regulated genes (440)						Down regulated genes (490)					
Index	Name	*P*	Adjusted *P*	OR	Combined score	Index	Name	*P*	Adjusted *P*	OR	Combined score
COVID-19-related gene sets 2021											
1	SARS Perturbation; 348 Up Genes from GEN3VA Mouse Lung	0.0622	0.9999	1.7000	4.7100	1	500 genes down-regulated by SARS-CoV-2 in mouse Lu	6.74E-02	1.00E+00	1.55	4.18
2	500 genes down-regulated by MERS-CoV in Calu-3 cells from	0.0664	0.9999	1.5500	4.2100	2	Top 500 downregulated genes in mouse lung with SARS	6.74E-02	1.00E+00	1.55	4.18
3	COVID19-Orf8 protein host PPI from Krogan	0.0844	0.9999	3.0400	7.5300	3	SARS-CoV perturbation; 231 Up Genes from GEN3VA; H	6.94E-02	1.00E+00	1.82	4.87
4	499 genes down-regulated by SARS-CoV-2 in Calu-3 cells from	0.1042	0.9999	1.4900	3.3600	4	SARS-CoV perturbation; 217 up genes from GEN3VA; H	1.03E-01	1.00E+00	1.73	3.94
5	500 genes down-regulated by SARS-CoV-2 in human Calu3 ce	0.1193	0.9999	1.4300	3.0400	5	500 genes downregulated by SARS-CoV-2 in A549-ACE	2.28E-01	1.00E+00	1.27	1.88
6	Top 500 down genes for SARS-CoV-2 infection 48 hpi in huma	0.1297	0.9999	1.4300	2.9200	6	500 genes downregulated by SARS-CoV-1 in human int	2.31E-01	1.00E+00	1.27	1.86
7	7 SARS Perturbation 320 up genes from GEN3VA mouse lung;	0.1373	0.9999	1.5200	3.0200	7	500 genes downregulated by SARS-CoV-2 in human Ca	3.06E-01	1.00E+00	1.19	1.41
8	Top 500 downregulated genes in mouse D1 cardiomyocytes	0.1479	0.9999	1.3900	2.6600	8	Top 500 up genes for SARS-CoV-2 infection in Mesocric	3.20E-01	1	1.2	1.37
9	SARS perturbation; 112 down genes from GEN3VA; human a	0.1571	0.9999	1.9600	3.6300	9	SARS coronavirus formerly known as growth-factor-like	3.28E-01	1	2.66	2.97
10	Top 500 up genes for SARS-CoV-2 infection in Rhesus macaqu	0.1602	0.9999	1.3700	2.5100	10	SARS coronavirus hypothetical protein sars9b from Viru	3.28E-01	1	2.66	2.97
HMDB metabolites											
1	1,4-Naphthalenedione, 2-methyl- (HMDB01892)	0.0091	0.7183	7.8900	37.0600	1	Formyl-CoA (HMDB03419)	0.039	0.724	7.26	23.55
2	L-Proline (HMDB00162)	0.0170	0.7183	6.1000	24.8500	2	1-(1Z-hexadecenyl)-sn-glycero -3-phosphoethanolamine	0.1581	0.724	2.96	5.45
3	Hydroxyproline (HMDB00725)	0.0233	0.7183	9.9200	37.2900	3	1-hexadecyl-2-(9Z-octadecenoyl) -sn-glycero-3-phospho	0.1581	0.724	2.96	5.45
4	Sulfide (HMDB00598)	0.0290	0.7183	3.6500	12.9300	4	PE (P-16:0/14:0) (HMDB11335)	0.1581	0.724	2.96	5.45
5	QH2 (HMDB01304)	0.0387	0.7183	3.3100	10.7800	5	PE (P-16:0/14:1 (9Z)) (HMDB11336)	0.1581	0.724	2.96	5.45

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Up regulated genes (440)						Down regulated genes (490)					
Index	Name	*P*	Adjusted *P*	OR	Combined score	Index	Name	*P*	Adjusted *P*	OR	Combined score
HMDB metabolites											
6	Coenzyme Q (HMDB06709)	0.0408	0.7183	3.2500	10.4100	6	PE (P-16:0/15:0) (HMDB11337)	0.1581	0.724	2.96	5.45
7	Ubiquinone Q1 (HMDB02012)	0.0452	0.7183	3.1400	9.7200	7	PE (P-16:0/16:1 (9Z)) (HMDB11339)	0.1581	0.724	2.96	5.45
8	Androstenedione (HMDB00053)	0.1874	0.7183	2.6200	4.3900	8	PE (P-16:0/18:0) (HMDB11340)	0.1581	0.724	2.96	5.45
9	FAD (HMDB01197)	0.2171	0.7183	4.4500	6.8000	9	PEP-16:0/18:1 (11Z)) (HMDB11341)	0.1581	0.724	2.96	5.45
10	4’-Phosphopantetheine (HMDB01416)	0.2171	0.7183	4.4500	6.8000	10	PE (P-16:0/18:1 (9Z)) (HMDB11342)	0.1581	0.724	2.96	5.45
Disease perturbations from GEO up						Disease perturbations from GEO down					
1	Simian acquired immune deficiency syndrome C0080151 hu	0.0022	1.0000	2.3000	14.0300	1	ALS C0002736 human G	1.76E-01	1.00E+00	1.47	2.55
2	Squamous cell carcinoma of lung C0149782 human GSE3268	0.0333	1.0000	1.9500	6.6300	2	ALS DOID-332 human GSE833	1.87E-01	1.00E+00	1.44	2.42
3	Ulcerative colitis DOID-8577 human GSE38713 sample 810	0.0506	1.0000	1.8700	5.5800	3	Down syndrome DOID-14250 human GSE19681 sample	2.04E-01	1.00E+00	1.41	2.24
4	Huntington’s disease DOID-12858 mouse GSE3248 sample 72	0.0690	1.0000	1.6300	4.3500	4	Juvenile dermatomyositis UMLS CUI-C0263666 human	2.14E-01	1.00E+00	1.72	2.65
5	Neurofibromatosis DOID-8712 mouse GSE1482 sample 665	0.0692	1.0000	1.7600	4.7000	5	Sjogren’s syndrome DOID-12894 human GSE23117 samples	2.25E-01	1.00E+00	1.34	2
6	Alcohol poisoning C0392620 rat GSE3311 sample 288	0.0719	1.0000	1.7500	4.6000	6	Setleis syndrome C1744559 human GSE16524 sample 2	2.46E-01	1.00E+00	1.4	1.96
7	Turner syndrome C0041408 mouse GSE1606 sample 218	0.0777	1.0000	1.7200	4.3900	7	Mytonic dystrophy Type 1 DOID-11722 human GSE717	2.52E-01	1.00E+00	1.3	1.8
8	Progressive myoclonus epilepsy DOID-891 mouse GSE47516	0.0839	1.0000	1.5200	3.7700	8	Kidney disorder associated with type 2 diabetes mellitus	2.56E-01	1.00E+00	1.32	1.79
9	Huntington’s disease DOID-12858 mouse GSE3248 sample 72	0.0852	1.0000	1.6900	4.1500	9	Rheumatoid arthritis DOID-7148 human GSE15573 samples	2.64E-01	1.00E+00	1.29	1.71
10	Cancer of the intestine C0346627 mouse GSE3915 sample 90	0.0999	1.0000	1.6300	3.7600	10	SLE DOID-9074 human GSE1	2.66E-01	1.00E+00	1.3	1.73
WikiPathway (WP) 2021 Human											
1	Estrogen receptor pathway WP2881	0.0026	0.7006	13.4200	80.0600	1	Mevalonate arm of cholesterol biosynthesis pathway W	2.85E-02	9.98E-01	8.88	31.61

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Up regulated genes (440)						Down regulated genes (490)					
Index	Name	*P*	Adjusted *P*	OR	Combined score	Index	Name	*P*	Adjusted *P*	OR	Combined score
WikiPathway (WP) 2021 Human											
2	ATM signalling pathway WP2516	0.0113	0.8858	4.9800	22.3000	2	Biomarkers for pyrimidine metabolism disorders WP45	5.10E-02	9.98E-01	6.15	18.3
3	ATM signalling network in development and disease WP3878	0.0169	0.8858	4.3700	17.8200	3	Cholesterol biosynthesis pathway WP197	5.10E-02	9.98E-01	6.15	18.3
4	miRNA regulation of DNA damage response WP1530	0.0200	0.8858	3.3900	13.2800	4	Mitochondrial CIV assembly WP4922	5.37E-02	9.98E-01	3.75	10.97
5	Electron transport chain (OXPHOS system in mitochondria)	0.0263	0.8858	2.7700	10.1000	5	Cells and molecules involved in local acute inflammator	6.39E-02	0.998	5.33	14.65
6	MFAP5-mediated ovarian cancer cell motility and invasiveness	0.0321	0.8858	8.1100	27.9100	6	Pyrimidine metabolism and related diseases WP4225	0.06393	0.998	5.33	14.65
7	Mitochondrial complex I assembly model OXPHOS system W	0.0346	0.8858	3.4400	11.5800	7	Small ligand GPCRs WP247	0.07787	0.998	4.7	12
8	p38 MAPK signalling pathway WP400	0.0383	0.8858	4.3200	14.1100	8	8miRNA regulation of DNA damage response WP1530	0.09641	0.998	2.39	5.59
9	Leptin insulin overlap WP3935	0.0528	0.8858	5.9500	17.5000	9	Purine metabolism and related disorders WP4224	0.1003	0.998	3.99	9.18
10	Nsp1 from SARS-CoV-2 inhibits translation initiation in the ho	0.0528	0.8858	5.9500	17.5000	10	Cholesterol metabolism (includes both Bloch and Kandu)	0.1026	0.998	2.79	6.35
KEGG 2021 Human											
1	Non-alcoholic fatty liver disease	0.0558	0.9996	2.1200	6.1200	1	Vibrio cholerae infection	3.38E-02	9.99E-01	3.48	11.8
2	Diabetic cardiomyopathy	0.0805	0.9996	1.8400	4.6300	2	Spliceosome	7.64E-02	9.99E-01	1.96	5.05
3	Glycosaminoglycan biosynthesis	0.1110	0.9996	2.6800	5.8900	3	Vasopressin-regulated water reabsorption	9.27E-02	9.99E-01	2.93	6.96
4	Vitamin B6 metabolism	0.1250	0.9996	8.9100	18.5300	4	Terpenoid backbone biosynthesis	1.00E-01	9.99E-01	3.99	9.18
5	Thermogenesis	0.1409	0.9996	1.6000	3.1300	5	p53 signaling pathway	1.04E-01	9.99E-01	2.32	5.25
6	Sulfur relay system	0.1631	0.9996	6.3600	11.5400	6	Malaria	1.24E-01	9.99E-01	2.55	5.33
7	Tight junction	0.1696	0.9996	1.6500	2.9200	7	Caffeine metabolism	1.38E-01	9.99E-01	7.98	15.78
8	Homologous recombination	0.2278	0.9996	2.2900	3.3800	8	Pyrimidine metabolism	1.58E-01	9.99E-01	2.26	4.18
9	Huntington diseases	0.2337	0.9996	1.3500	1.9700	9	RNA polymerase	1.76E-01	9.99E-01	2.75	4.79
10	Spliceosome	0.2355	0.9996	1.5400	2.2300	10	Mineral absorption	1.82E-01	9.99E-01	2.1	3.58

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Up regulated genes (440)						Down regulated genes (490)					
Index	Name	*P*	Adjusted *P*	OR	Combined score	Index	Name	*P*	Adjusted *P*	OR	Combined score
Reactome 2016											
1	G2/M DNA replication checkpoint R-HSA-69478	0.0046	1.0000	29.7700	160.0600	1	Conjugation Of benzoate with glycine R-HSA-177135	8.42E-03	1.00E+00	19.99	95.48
2	Signaling by leptin R-HSA-2586552	0.0233	1.0000	9.9200	37.2900	2	2 TP53 regulates metabolic genes R-HSA-5628897	1.45E-02	1.00E+00	3.21	13.6
3	Complex I biogenesis R-HSA-6799198	0.0256	1.0000	3.8100	13.9600	3	Phosphate bond hydrolysis by NTPDase proteins R-HSA	1.52E-02	1.00E+00	13.32	55.77
4	Vitamin D (Calciferol) metabolism R-HSA-196791	0.0276	1.0000	8.9300	32.0600	4	Conjugation of salicylate with glycine R-HSA-177128	1.52E-02	1.00E+00	13.32	55.77
5	Tight junction interactions R-HSA-420029	0.0277	1.0000	4.9700	17.8200	5	BB some-mediated cargo-targeting to cilium R-HSA-56	1.80E-02	1.00E+00	6	24.12
6	Citric acid (TCA) cycle and respiratory electron transport	0.0281	1.0000	2.3200	8.2900	6	Amino acid conjugation R-HSA-156587	1.92E-02	1.00E+00	11.42	45.11
7	Respiratory electron transport, ATP synthesis by chemiosmo	0.0374	1.0000	2.5400	8.3400	7	Folding of actin by CCT/TriC R-HSA-390450	2.37E-02	1.00E+00	9.99	37.4
8	Regulation of innate immune responses to cytosolic DNA R-	0.0420	1.0000	6.8700	21.7700	8	Triglyceride biosynthesis R-HSA-75109	4.49E-02	1.00E+00	6.66	20.67
9	Meiosis R-HSA-1500620	0.0448	1.0000	2.7000	8.3800	9	Nucleotide Catabolism R-HSA-8956319	5.37E-02	1.00E+00	3.75	10.97
10	Respiratory electron transport R-HSA-611105	0.0485	1.0000	2.6300	7.9700	10	Cooperation of PDCL (PhLP1) and TRiC/CCT In G-protein	6.15E-02	1.00E+00	3.53	9.84
DisGeNET											
1	Central retinal vein occlusion	0.0026	0.9819	13.4200	80.0600	1	Myeloid metaplasia	5.70E-03	1.00E+00	26.65	137.69
2	Transient ischemic Attack	0.0033	0.9819	2.7800	15.8400	2	Congenital amegakaryocytic thrombocytopenia	8.42E-03	1.00E+00	19.99	95.48
3	Angina, unstable	0.0041	0.9819	4.2800	23.5400	3	Retinoic acid syndrome	1.06E-02	1.00E+00	7.51	34.14
4	Speech sound disorders	0.0046	0.9819	29.7700	160.0600	4	Absence of scalp hair	1.16E-02	1.00E+00	15.99	71.26
5	Familial thrombotic thrombocytopenic Purpura	0.0046	0.9819	29.7700	160.0600	5	Loss of scalp hair	1.16E-02	1	15.99	71.26
6	Haemophilic arthropathy	0.0046	0.9819	29.7700	160.0600	6	Dysglycaemia	1.52E-02	1	13.32	55.77
7	Somnolence	0.0067	0.9819	8.9500	44.7100	7	Hunger	1.59E-02	1	6.32	26.16
8	Spinal muscular atrophy, Jerash type	0.0068	0.9819	22.3200	111.3100	8	Tinnitus	1.59E-02	1	6.32	26.16
9	Cataract and cardiomyopathy	0.0068	0.9819	22.3200	111.3100	9	Ragged-red muscle fibers	1.76E-02	1	4.33	17.49
10	Hypodysfibrinogenaemia	0.0068	0.9819	22.3200	111.3100	10	Xerocytosis	1.92E-02	1	11.42	45.11

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Up regulated genes (440)						Down regulated genes (490)					
Index	Name	*P*	Adjusted *P*	OR	Combined score	Index	Name	*P*	Adjusted *P*	OR	Combined score
	Drug perturbations from GEO up						Drug perturbations from GEO down				
1	Coenzyme Q10 5281915 mouse GSE15129 sample 3454	0.0042	0.9998	2.3600	12.9100	1	Androstanolone 10635 human GSE7868 sample 3411	6.68E-02	1.00E+00	1.72	4.66
2	Sevoflurane DB01236 human GSE4386 sample 2816	0.0061	0.9998	2.0700	10.5500	2	2 imatinib DB00619 human GSE1922 sample 2520	8.52E-02	1.00E+00	1.6	3.95
3	Phosgene 6371 mouse GSE2565 sample 3613	0.0194	0.9998	1.9300	7.6200	3	Soman 7305 rat GSE13428 sample 2633	9.92E-02	1.00E+00	2.11	4.87
4	Rosiglitazone DB00412 mouse GSE2431 sample 2808	0.0229	0.9998	2.1600	8.1700	4	Imatinib DB00619 human GSE1922 sample 2516	1.15E-01	1.00E+00	1.48	3.2
5	Ubiquinol 9962735 mouse GSE15129 sample 3451	0.0236	0.9998	2.1500	8.0700	5	Imatinib DB00619 human GSE1922 sample 2457	1.46E-01	1.00E+00	1.47	2.82
6	Estradiol DB00783 human GSE11352 sample 2729	0.0266	0.9998	1.8100	6.5500	6	3,3',4,4'-Tetrachlorobiphenyl 36187 human GSE6878 sa	1.46E-01	1.00E+00	1.47	2.82
7	Resveratrol DB02709 mouse GSE7111 sample 3496	0.0365	0.9998	1.8100	5.9800	7	Imatinib DB00619 human GSE1922 sample 2512	1.48E-01	1.00E+00	1.46	2.79
8	Bisphenol A 6623 human GSE17624 sample 2658	0.0438	0.9998	1.6500	5.1700	8	EPZ004777 56962336 human GSE29828 sample 2649	1.58E-01	1.00E+00	1.42	2.62
9	Puromycin, EC50, 1 d 439530 human GSE6930 sample 3268	0.0518	0.9998	1.8600	5.5200	9	Imatinib DB00619 human GSE1922 sample 2517	1.60E-01	1.00E+00	1.41	2.59
10	RPI-1 1749978 human GSE49414 sample 3173	0.0525	0.9998	1.8000	5.3000	10	Hypochlorous acid 24341 mouse GSE15457 sample	1.62E-01	1.00E+00	1.5	2.72
						DSigDB					
1	Alvespimycin MCF7 up	0.0117	1.0000	3.9300	17.5000	1	Benzidine CTD 00001406	0.002727	1	13.35	78.81
2	Apigenin MCF7 down	0.0124	1.0000	3.3200	14.6000	2	2-acetamidofluorene CTD 00007023	0.002992	1	7.64	44.39
3	Tanespimycin MCF7 up	0.0124	1.0000	3.3200	14.6000	3	Propanil CTD 00004257	0.005339	1	10.01	52.37
4	Diallyl disulfide CTD 00001321	0.0145	1.0000	4.5900	19.4400	4	2,4-dichlorophenoxyacetic acid CTD 00007028	0.006453	1	9.24	46.59
5	Vitamin B12 BOSS	0.0169	1.0000	4.3700	17.8200	5	2,4-Diisocyanato-1-methylbenzene CTD 00006908	0.007433	1	5.73	28.07
6	2H-1-Benzopyran-2-one, 7-[(3,7-dimethyl-2,6-octadienyl) oxy	0.0170	1.0000	6.1000	24.8500	6	Betamethasone CTD 00005504	0.007695	1	8.58	41.75
7	Geldanamycin PC3 UP	0.0182	1.0000	4.2600	17.0800	7	76180-96-6 CTD 00001374	0.009068	1	8.01	37.65
8	Geldanamycin MCF7 UP	0.0185	1.0000	3.0200	12.0800	8	Tyrphostin AG-825 MCF7 UP	0.01022	1	5.17	23.7
9	0297417-0002B PC3 DOWN	0.0212	1.0000	3.3400	12.9000	9	p-Phenylenediamine CTD 00001400	0.01101	1	4.01	18.09

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Up regulated genes (440)						Down regulated genes (490)					
Index	Name	*P*	Adjusted *P*	OR	Combined score	Index	Name	*P*	Adjusted *P*	OR	Combined score
DSigDB											
10	Okadaic acid CTD 00007275	0.0231	1.0000	2.8600	10.7800	10	Diethyl phthalate CTD 00000348	0.01222	1	7.06	31.11

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; MERS, middle east respiratory syndrome coronavirus; OR, odd's ratio; ALS, amyotrophic lateral sclerosis; SLE, systemic lupus erythematosus; R-HSA, R-HSA Reactome Pathway ID; TCA, citric acid ATP, adenosine triphosphate; PDCL, phosducin-like protein; CCT, chaperonin containing TCP1; CTD, comparative toxicogenomics database

Supplementary Table IID. Gene set enrichment analysis of combined severe North and South Indian samples

Up-regulated genes (1114)						Down-regulated genes (1138)					
Index	Name	*P*	Adjusted *P*	OR	Combined score	Index	Name	*P*	Adjusted *P*	OR	Combined score
COVID-19-related gene sets 2021											
1	SARS perturbation; 280 up genes from GEN3VA; human PBM	3.83E-58	1.77E-55	11.3	1493.62	1	1 COVID-19 patients PBMC down	4.57E-18	2.05E-15	5.64	225.16
2	500 genes up-regulated by SARS-CoV-2 in human lung cells fr	1.34E-47	2.98E-45	6.28	677.82	2	Top 500 down genes for SARS-CoV-2 infection in Rhesu	1.10E-13	2.48E-11	3.09	92.22
3	500 genes upregulated by SARS-CoV-2 in human lung tissue f	2.58E-47	2.98E-45	6.48	695.65	3	SARS perturbation; 220 Down Genes from GEN3VA; Hu	2.26E-13	3.38E-11	4.34	126.48
4	Healthy human lung biopsy versus COVID-19 infected human lun	2.58E-47	2.98E-45	6.48	695.65	4	Top 500 down genes for SARS-CoV-2 infection in Rhesu	1.16E-08	1.30E-06	2.5	45.75
5	COVID-19 patients PBMC up	9.33E-33	8.62E-31	4.76	351.25	5	Top 500 down genes for SARS-CoV-2 infection in Rhesu	9.68E-07	8.69E-05	2.24	31.02
6	Top 500 up genes for SARS-CoV-2 infection in Rhesus macaqu	2.61E-27	2.01E-25	4.46	272.99	6	Top 500 down genes for SARS-CoV-2 infection in Rhesu	2.41E-05	1.81E-03	2.01	21.39
7	Top 500 down genes for SARS-CoV-2 infection in Rhesus mac	1.18E-20	7.77E-19	3.84	176.18	7	7Top 500 up genes for SARS-CoV-2 infection in Rhesus m	6.11E-05	3.92E-03	1.92	18.58
8	Top 500 up genes for SARS-CoV-2 infection in Rhesus macaqu	5.20E-20	3.00E-18	3.77	167.31	8	Top 500 down genes for SARS-CoV-2 infection in Rhesu	1.49E-04	0.008365	1.88	16.54
9	Top 500 up genes for SARS-CoV-2 early infection in human m	2.42E-16	1.24E-14	3.26	117.4	9	Top 500 up genes for SARS-CoV-2 infection in Rhesus m	3.79E-04	0.01892	1.8	14.21
10	Top 500 up genes for SARS-CoV-2 infection in Rhesus macaqu	1.71E-15	7.43E-14	3.28	111.42	10	Top 500 down genes in human lung AT2 cells organoids	2.12E-03	0.09522	1.69	10.43
HMDB metabolites											
1	1,4-naphthalenedione, 2-methyl- (HMDB01892)	0.0005809	0.8304	7.3	54.39	1	1-(1Z-hexadecenyl)-sn-glycero-3-phosphoethanolamine	0.080	0.3953	2.66	6.71
2	Glucose 6-phosphate (HMDB01401)	0.001873	0.8304	7.09	44.54	2	1-hexadecyl-2-(9Z-octadecenoyl)-sn-glycero-3-phospho	0.07995	0.3953	2.66	6.71
3	C10H13N2O7P (HMDB01570)	0.002304	0.8304	9.72	59.03	3	PE (P-16:0/14:0) (HMDB11335)	0.07995	0.3953	2.66	6.71

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Up-regulated genes (1114)						Down-regulated genes (1138)					
Index	Name	*P*	Adjusted *P*	OR	Combined score	Index	Name	*P*	Adjusted *P*	OR	Combined score
HMDB metabolites											
4	Iron (HMDB00692)	0.002596	0.8304	2.09	12.45	4	PE (P-16:0/14:1 (9Z)) (HMDB11336)	0.07995	0.3953	2.66	6.71
5	C6H12O6 (HMDB00516)	0.004564	0.8304	7.56	40.74	5	PE (P-16:0/15:0) (HMDB11337)	0.07995	0.3953	2.66	6.71
6	TMP (HMDB01227)	0.004564	0.8304	7.56	40.74	6	PE (P-16:0/16:1 (9Z)) (HMDB11339)	0.07995	0.3953	2.66	6.71
7	C6H12O6 (HMDB03345)	0.005115	0.8304	5.32	28.05	7	7PE (P-16:0/18:0) (HMDB11340)	0.07995	0.3953	2.66	6.71
8	Zinc (HMDB01303)	0.005658	0.8304	2.64	13.68	8	PEP-16:0/18:1 (11Z)) (HMDB11341)	0.07995	0.3953	2.66	6.71
9	Hexadecanoyl-CoA (HMDB01338)	0.01111	0.8304	4.25	19.14	9	PE (P-16:0/18:1 (9Z)) (HMDB11342)	0.07995	0.3953	2.66	6.71
10	Ammonia (HMDB00051)	0.01189	0.8304	2.84	12.58	10	PE (P-16:0/18:2 (9Z,12Z)) (HMDB11343)	0.07995	0.3953	2.66	6.71
Disease perturbations from GEO up						Disease perturbations from GEO down					
1	Septic shock C0036983 human GSE9692 sample 307	5.97E-121	5.01E-118	13.71	3794.19	1	H1N1 DOID-0050211 human GSE27131 sample 514	2.59E-60	2.17E-57	17.64	2420.53
2	H1N1 DOID-0050211 human GSE27131 sample 514	1.33E-65	5.58E-63	8.78	1311.73	2	Acute myeloid leukaemia DOID-9119 human GSE9476 sa	4.18E-19	1.75E-16	3.73	157.84
3	SARS C1175175 human	1.39E-55	3.87E-53	14.41	1820.39	3	Huntington's disease DOID-12858 human GSE24250 sa	1.97E-16	5.51E-14	4.16	150.49
4	Overexertion C0161750 human GSE3606 sample 286	3.86E-53	8.09E-51	9.91	1196.61	4	Autism-spectrum disorder DOID-0060041 human GSE25	6.31E-14	1.32E-11	3.83	116.36
5	sJIA DOID-848 human	3.42E-47	5.74E-45	7.5	802.88	5	Sarcoidosis DOID-11335 human GSE19314 sample 708	1.05E-13	1.76E-11	3.61	107.75
6	Rheumatoid arthritis DOID-7148 human GSE15573 sample 90	9.83E-42	1.38E-39	8.25	778.8	6	sJIA DOID-848 hu	1.60E-12	2.03E-10	3.97	107.92
7	Polycystic ovary syndrome DOID-11612 human GSE34526 sa	6.08E-38	7.29E-36	6.23	533.44	7	JRA - C0553662 human G	1.69E-12	2.03E-10	3.63	98.37
8	Multiple sclerosis DOID-2377 human GSE26484 sample 742	2.19E-37	2.29E-35	7.72	651.32	8	Multiple sclerosis DOID-2377 human GSE23832 sample	2.22E-12	2.33E-10	3.72	99.78
9	Non-sJIA (subgroup-RF)	3.65E-37	3.40E-35	6.38	534.97	9	Purpura, Idiopathic Thrombocytopenic C0043117 huma	1.51E-11	1.41E-09	7.89	196.62

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Up-regulated genes (1114)						Down-regulated genes (1138)					
Index	Name	*P*	Adjusted *P*	OR	Combined score	Index	Name	*P*	Adjusted *P*	OR	Combined score
Disease perturbations from GEO up						Disease perturbations from GEO down					
10	Huntington's disease DOID-12858 human GSE8762 sample 9	6.61E-35	5.54E-33	5.48	431.65	10	Septic Shock C0036983 human GSE9692 sample 307	1.59E-10	1.34E-08	5.49	123.84
WikiPathway 2021 human											
1	Complement and coagulation cascades WP558	9.54E-09	4.61E-06	7.12	131.55	1	Cytoplasmic ribosomal proteins WP477	9.56E-11	3.77E-08	6.23	143.73
2	Complement system WP2806	6.60E-08	0.00001595	4.76	78.62	2	Pathogenesis of SARS-CoV-2 mediated by nsp9-nsp10 C	6.78E-08	1.34E-05	15.19	250.78
3	Spinal cord Injury WP2431	7.74E-06	0.0009509	3.5	41.25	3	Modulators of TCR signalling and T-cell activation WP50	1.15E-06	1.51E-04	5.46	74.72
4	Signal transduction through IL1R WP4496	0.000007875	0.0009509	7.43	87.3	4	TCR and Co-stimulatory Signalling WP2583	2.15E-05	1.92E-03	7.51	80.71
5	Vitamin D receptor pathway WP2877	0.00002759	0.0024	2.74	28.75	5	Cancer immunotherapy by PD-1 blockade WP4585	2.44E-05	0.001921	8.9	94.49
6	IL1 and megakaryocytes in obesity WP2865	0.00002981	0.0024	8.53	88.9	6	Allograft Rejection WP2328	0.0001395	0.008935	3.39	30.11
7	Extracellular vesicles in the crosstalk of cardiac cells WP4300	0.00004549	0.003049	9.95	99.44	7	TCR signaling pathway WP69	0.0001587	0.008935	3.35	29.27
8	Microglia pathogen phagocytosis pathway WP3937	0.0000505	0.003049	5.69	56.33	8	T-Cell antigen receptor (TCR) pathway during staphylo	0.0006741	0.0332	3.6	26.29
9	Metabolic reprogramming in colon cancer WP4290	0.00007919	0.00425	5.34	50.4	9	Development and heterogeneity of the ILC family WP38	0.001819	0.07963	4.66	29.42
10	Glycolysis in senescence WP5049	0.0001851	0.008623	14.19	121.93	10	FOXP3 in COVID-19 WP5063	0.008588	0.3384	6.04	28.76
KEGG 2021 human											
1	Neutrophil extracellular trap formation	3.00E-10	8.64E-08	3.95	86.52	1	Hematopoietic cell lineage	1.43E-14	3.89E-12	7.37	235.09
2	Complement and coagulation cascades	5.45E-09	6.23E-07	5.65	107.52	2	Th17 cell differentiation	1.99E-10	2.71E-08	5.42	121.09
3	Osteoclast differentiation	6.49E-09	6.23E-07	4.44	83.8	3	Primary immunodeficiency	8.68E-10	7.87E-08	10.94	228.27
4	*S. aureus* infection	1.01E-06	0.00007269	4.29	59.29	4	Th1 and Th2 cell differentiation	6.75E-09	4.59E-07	5.29	99.57
5	Leishmaniasis	4.22E-06	0.0002432	4.5	55.65	5	Inflammatory bowel disease	1.33E-08	7.23E-07	6.43	116.69
6	Legionellosis	1.14E-05	0.0005492	5.06	57.53	6	Cell adhesion molecules	2.58E-07	1.04E-05	3.59	54.49

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Up-regulated genes (1114)						Down-regulated genes (1138)					
Index	Name	*P*	Adjusted *P*	OR	Combined score	Index	Name	*P*	Adjusted *P*	OR	Combined score
KEGG 2021 human											
7	Malaria	3.69E-04	0.01517	4.27	33.74	7	Intestinal immune network for IgA production	2.68E-07	1.04E-05	6.9	104.36
8	SLE	0.0005069	0.01777	2.63	19.99	8	Ribosome	9.54E-07	3.25E-05	3.32	45.99
9	Coronavirus disease	0.0005552	0.01777	2.17	16.24	9	Asthma	5.05E-06	1.53E-04	7.95	97
10	Starch and sucrose metabolism	0.0006756	0.01946	4.87	35.56	10	Antigen processing and presentation	2.87E-05	7.80E-04	3.99	41.69
Reactome 2016											
1	Neutrophil degranulation R-HSA-6798695	4.79E-38	6.03E-35	5.52	474.74	1	Immunoregulatory interactions between a lymphoid A	1.04E-09	4.94E-07	4.75	98.26
2	Innate immune system R-HSA-168249	4.30E-25	2.71E-22	3	168.22	2	NMD independent of exon	1.21E-09	4.94E-07	5.62	115.38
3	Immune system R-HSA-168256	4.21E-19	1.77E-16	2.18	92.29	3	Peptide chain elongation R-HSA-156902	1.72E-09	4.94E-07	5.79	116.85
4	Hemostasis R-HSA-109582	3.81E-11	1.20E-08	2.56	61.49	4	PD-1 signaling R-HSA-389948	4.01E-09	4.94E-07	18.4	355.74
5	Platelet degranulation R-HSA-114608	9.56E-10	2.41E-07	4.76	98.9	5	Eukaryotic translation elongation R-HSA-156842	4.34E-09	4.94E-07	5.45	104.91
6	Response to elevated platelet cytosolic Ca2+R-HSA-76005	2.39E-09	4.52E-07	4.53	89.92	6	Eukaryotic translation termination R-HSA-72764	4.34E-09	4.94E-07	5.45	104.91
7	Platelet activation, signaling and aggregation R-HSA-76002	2.51E-09	4.52E-07	3.25	64.35	7	Selenocysteine synthesis R-HSA-2408557	4.34E-09	4.94E-07	5.45	104.91
8	Extracellular matrix organization R-HSA-1474244	3.39E-07	0.00004869	2.68	39.96	8	Viral mRNA translation R-HSA-192823	4.34E-09	4.94E-07	5.45	104.91
9	Cell surface interactions at vascular wall R-HSA-202733	3.48E-07	0.00004869	3.76	55.89	9	Response of EIF2AK4 (GCN2) to amino acid deficiency	4.54E-09	4.94E-07	5.17	99.27
10	Transcriptional regulation of granulopoiesis R-HSA-9616222	0.00001705	0.002147	4.84	53.09	10	Translocation of ZAP-70 to immunological synapse R-H	4.61E-09	4.94E-07	23.88	458.36
DisGeNET											
1	Acute coronary syndrome	8.55E-16	5.43E-12	4.42	153.2	1	Autoimmune diseases	1.17E-06	3.17E-03	1.76	23.97
2	Sepsis	7.10E-15	2.26E-11	3.04	98.88	2	Celiac disease	1.22E-06	3.17E-03	2.5	34.04
3	Arteriosclerosis	2.34E-14	4.97E-11	2.31	72.5	3	Sezary syndrome	1.66E-05	2.89E-02	3	32.97
4	Atherosclerosis	4.84E-13	6.33E-10	2.2	62.29	4	Immune system diseases	3.54E-05	4.62E-02	2.39	24.55
5	Arthritis	4.98E-13	6.33E-10	2.66	75.47	5	Peripheral T-cell lymphoma	5.88E-05	0.06137	3.09	30.13
6	Juvenile psoriatic arthritis	2.18E-12	2.30E-09	4.87	130.73	6	Small lymphocytic lymphoma	7.61E-05	0.06622	4.84	45.85

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Up-regulated genes (1114)						Down-regulated genes (1138)					
Index	Name	*P*	Adjusted *P*	OR	Combined score	Index	Name	*P*	Adjusted *P*	OR	Combined score
7	Septicemia	2.74E-12	2.30E-09	2.9	77.29	7	Autoimmune state	1.11E-04	0.08311	5.78	52.57
8	Lung diseases	2.89E-12	2.30E-09	3.12	82.78	8	Graves disease	1.81E-04	0.09854	2.04	17.54
9	Juvenile-onset still disease	8.01E-12	5.66E-09	4.61	117.75	9	9 immunoglobulin deficiency, late-onset	2.05E-04	0.09854	13.87	117.81
10	Liver cirrhosis, experimental	2.45E-11	1.56E-08	2.31	56.47	10	Acute myeloid leukemia, minimal differentiation	2.08E-04	0.09854	7.29	61.82
Drug perturbations from GEO up											
1	Etanercept DB00005 human GSE7524 sample 3295	3.17E-34	2.87E-31	8.32	641.69	1	Azathioprine DB00993 human GSE38713 sample 3194	1.53E-11	1.23E-08	3.74	93.13
2	Soman 7305 rat GSE13428 sample 2635	8.05E-26	3.64E-23	4.26	246.04	2	IFN beta-1a DB00060 human GSE26104 sample	2.73E-11	1.23E-08	3.97	96.63
3	Atorvastatin DB01076 human GSE11393 sample 3196	9.13E-25	2.76E-22	5.4	299.09	3	LMP-420 497668 human GSE20211 sample 3222	2.01E-10	5.61E-08	3.29	73.5
4	Soman 7305 rat GSE13428 sample 2637	9.38E-23	2.12E-20	4.12	208.95	4	5-aminosalicylic acid 4075 human GSE38713 sample 31	2.49E-10	5.61E-08	3.04	67.21
5	Promyelocytic leukemia DB00755 human GSE5007 sample 24	1.35E-21	2.44E-19	4.83	232.18	5	1,2,4-Benzenetriol 10787 human GSE7664 sample 3	5.95E-09	1.07E-06	3.32	62.89
6	Soman 7305 rat GSE13428 sample 2639	3.99E-21	6.02E-19	3.77	177.05	6	Methotrexate DB00563 human GSE41831 sample 2601	1.57E-07	2.36E-05	2.63	41.13
7	Soman 7305 rat GSE13428 sample 2633	1.54E-20	1.99E-18	3.68	167.73	7	Atorvastatin DB01076 human GSE11393 sample 3196	6.20E-07	7.99E-05	2.58	36.83
8	Soman 7305 rat GSE13428 sample 2640	7.23E-20	8.17E-18	3.51	154.72	8	Etanercept DB00005 human GSE7524 sample 3295	2.47E-06	2.79E-04	2.28	29.48
9	Mycophenolic acid DB01024 human GSE14630 sample 3302	1.07E-18	1.08E-16	4.21	174.16	9	Rituximab DB00073 human GSE15490 sample 2577	8.80E-06	8.83E-04	2.33	27.18
10	Soman 7305 rat GSE13428 sample 2632	1.60E-18	1.45E-16	3.55	145.66	10	Resveratrol DB02709 human GSE36930 sample 3497	2.40E-05	2.17E-03	2.25	23.89
DSigDB											
1	Tretinoin HL60 up	3.59E-18	1.26E-14	4.97	199.57	1	2-Fluoroadenosine BOSS	0.0004848	0.8841	3.29	25.12
2	Etynodiol HL60 up	9.10E-17	1.60E-13	12.17	449.66	2	AGN-PC-0JHFVD BOSS	0.000556	0.8841	2.3	17.2
3	Mebendazole HL60 up	3.07E-15	3.59E-12	3.7	123.71	3	Isoguanine BOSS	0.006662	1	1.94	9.74
4	Pergolide HL60 up	3.06E-13	2.68E-10	3.59	103.52	4	Etilefrine HL60 UP	0.006912	1	4.89	24.34
5	Alclometasone HL60 up	4.02E-13	2.82E-10	17.2	490.94	5	Ivermectin CTD 00006182	0.007788	1	3.43	16.64
6	Tetryzoline HL60 up	1.72E-12	1.00E-09	5.85	158.35	6	Orciprenaline HL60 up	0.008898	1	3.33	15.72

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Up-regulated genes (1114)						Down-regulated genes (1138)					
Index	Name	*P*	Adjusted *P*	OR	Combined score	Index	Name	*P*	Adjusted *P*	OR	Combined score
DSigDB											
7	Flumetasone HL60 up	2.65E-12	1.33E-09	19.81	528.17	7	2-Acetamidofluorene CTD 00007023	0.01211	1	4.16	18.35
8	Aspirin CTD 00005447	4.39E-12	1.92E-09	2.68	70.15	8	Fluoride CTD 00005982	0.0134	1	2.77	11.97
9	Troglitazone CTD 00002415	2.20E-11	8.56E-09	2.48	60.79	9	Betamethasone CTD 00005504	0.01368	1	5.11	21.95
10	Beclometasone HL60 up	3.28E-11	1.15E-08	13.09	316.03	10	Diphenylpyraline BOSS	0.01533	1	1.88	7.85

IFN, interferon; *S. aureus, Staphylococcus aureus*; OR, odds ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; sJIA, systemic juvenile idiopathic arthritis; SLE, systemic lupus erythematosus; TCR, T-cell receptor; JRA, juvenile rheumatoid arthritis; IL, interleukin; NMD, nonsense-mediated decay; PD, Parkinson’s disease; PBMC, Peripheral blood mononuclear cells; TMP, thymidine monophosphate

Supplementary Table IIE. Gene set enrichment analysis of severe Greece samples

Upregulated genes						Downregulated genes					
Index	Name	*P*	Adjusted *P*	OR	Combined score	Index	Name	*P*	Adjusted *P*	OR	Combined score
COVID-19 related gene sets 2021											
1	Top 500 up genes for SARS-CoV-2 infection in Rhesus macaqu	1.05E-83	4.87E-81	12.22	2334.57	1	Top 500 up genes for SARS-CoV-2 infection in Rhesus m	6.19E-38	2.88E-35	5.29	453.05
2	Top 500 up genes for SARS-CoV-2 infection in Rhesus macaqu	1.94E-80	4.49E-78	11.94	2190.68	2	500 genes downregulated by MHV-A59 in murine sple	2.32E-27	5.39E-25	4.45	273.14
3	500 genes upregulated by SARS-CoV-2 in human lung cells fr	7.04E-72	1.09E-69	10.53	1725.46	3	500 genes downregulated by MHV-A59 in murine spleen	3.07E-25	4.76E-23	4.19	236.46
4	500 genes upregulated by SARS-CoV-2 in human lung tissue f	4.28E-70	3.96E-68	10.74	1716.11	4	Top 500 up genes for SARS-CoV-2 infection in Rhesus m	1.65E-24	1.91E-22	4.07	223.04
5	Healthy human lung biopsy versus COVID-190-infected human lung	4.28E-70	3.96E-68	10.74	1716.11	5	Top 500 up genes for SARS-CoV-2 late-stage infection in	2.80E-24	2.61E-22	3.9	211.24
6	Top 500 up genes for SARS-CoV-2 infection in Rhesus macaque	1.59E-66	1.23E-64	10.08	1527.33	6	Top 500 down genes for SARS-CoV-2 early infection in h	2.15E-22	1.66E-20	3.72	185.4
7	COVID-19 patients PBMC up	4.71E-66	3.12E-64	9.49	1426.89	7	Top 500 down genes for SARS-CoV-2 infection in Rhesus	6.40E-22	4.25E-20	3.85	187.65
8	Top 500 up genes for SARS-CoV-2 infection in Rhesus macaque	4.52E-65	2.62E-63	9.84	1457.98	8	Top 500 up genes for SARS-CoV-2 infection in Rhesus m	8.06E-21	4.69E-19	3.74	173.03
9	SARS-CoV perturbation; 402 Up Genes from GEN3VA; Human	6.89E-65	3.54E-63	11.79	1742.21	9	500 genes down-regulated by SARS-CoV-2 in human lungs	3.67E-19	1.71E-17	3.45	146.45
10	Top 500 up genes for SARS-CoV-2 infection 48 hpi in human a	4.02E-62	1.86E-60	9.72	1374.45	10	Healthy human lung biopsy versus COVID-19 infected human	3.67E-19	1.71E-17	3.45	146.45
HMDB metabolites											
1	Carbon dioxide (HMDB01967)	0.0006762	0.213	3.51	25.61	1	D-Ribose 5-phosphate (HMDB01548)	0.02627	0.5678	5.74	20.9
2	TMP (HMDB01227)	0.001186	0.213	11.14	75.04	2	CTP (HMDB00082)	0.03035	0.5678	2.79	9.74
3	Hexadecanoyl-CoA (HMDB01338)	0.002348	0.213	6.27	37.95	3	Phosphoric acid (HMDB02142)	0.03164	0.5678	1.56	5.38
4	Coenzyme A (HMDB01423)	0.003889	0.213	2.93	16.23	4	Pyrophosphate (HMDB00250)	0.03288	0.5678	1.55	5.3
5	Hydrochloric acid standard solution (HMDB02306)	0.006482	0.213	6.26	31.55	5	Riboflavin (HMDB00244)	0.03346	0.5678	5.11	17.35
6	C10H13N2O7P (HMDB01570)	0.007466	0.213	9.39	45.96	6	UTP (HMDB00285)	0.03774	0.5678	2.63	8.61
7	Sulfate (HMDB01448)	0.01177	0.213	4.04	17.96	7	D-ribulose 5-phosphate (HMDB00618)	0.04156	0.5678	4.59	14.61

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Upregulated genes						Downregulated genes					
Index	Name	*P*	Adjusted *P*	OR	Combined score	Index	Name	*P*	Adjusted *P*	OR	Combined score
	HMDB metabolites										
8	C6H12O6 (HMDB00516)	0.01222	0.213	7.51	33.07	8	Adenosine monophosphate (HMDB00045)	0.05434	0.5678	1.51	4.39
9	NAP (HMDB00217)	0.01467	0.213	2.08	8.8	9	Acetic acid (HMDB00042)	0.09921	0.5678	2.45	5.66
10	Palmitic acid (HMDB00220)	0.01511	0.213	6.82	28.61	10	C11H22O22P4 (HMDB04249)	0.0994	0.5678	1.78	4.1
	Disease perturbations from GEO up						Disease perturbations from GEO down				
1	Septic shock C0036983 human GSE9692 sample 307	1.94E-118	1.62E-115	16.68	4521.5	1	H1N1 DOID-0050211 human GSE27131 sample 514	1.43E-40	1.20E-37	11.23	1030.54
2	Dengue disease DOID-12205 human GSE51808 sample 556	1.20E-97	5.02E-95	17.24	3848.02	2	Huntington's disease DOID-12858 human GSE24250 sa	2.87E-33	1.21E-30	6.41	480.1
3	Dengue haemorrhagic fever DOID-12206 human GSE51808 sa	2.70E-89	7.53E-87	15.78	3218.14	3	Autism-spectrum disorder DOID-0060041 human GSE25	3.35E-30	9.36E-28	6.08	412.86
4	Dengue fever DOID-12206 human GSE51808 sample 447	1.09E-74	2.28E-72	14.55	2478.13	4	Huntington's disease DOID-12858 human GSE24250 sa	6.76E-29	1.42E-26	4.98	323.02
5	H1N1 DOID-0050211 human GSE27131 sample 514	2.74E-72	4.59E-70	11.66	1921.89	5	SLE DOID-9074 human GSE1	4.06E-27	6.82E-25	5.64	342.78
6	Swine influenza DOID-0050211 human GSE48466 sample 498	2.15E-58	3.00E-56	13.13	1743.57	6	PD DOID-14330 human GSE6613 samp	5.25E-26	7.35E-24	5.07	294.89
7	Autism-spectrum disorder DOID-0060041 human GSE25507 s	4.84E-52	5.79E-50	10.97	1296.53	7	Pulmonary hypertension C0020542 human GSE703 sam	3.86E-25	4.63E-23	7.41	416.68
8	West Nile fever DOID-2366 human GSE30719 sample 874	2.92E-51	3.06E-49	7.61	885.62	8	Dengue fever DOID-12206 human GSE51808 sample 4	1.39E-24	1.46E-22	5.5	302.08
9	SLE DOID-9074 human GSE10325	1.15E-43	1.07E-41	8.21	811.35	9	SLE DOID-9074 human GSE6	5.03E-24	4.69E-22	5.1	273.83
10	Dermatomyositis DOID-10223 human GSE48280 sample 705	1.30E-43	1.09E-41	7.71	761.66	10	SARS C1175175 h	3.50E-22	2.82E-20	4.09	201.91
	WikiPathway 2021 Human										
1	Immune response to tuberculosis WP4197	3.01E-13	1.42E-10	32.96	950.33	1	Cytoplasmic Ribosomal Proteins WP477	6.37E-18	3.07E-15	9.23	365.43
2	Type II IFN signalling (IFNG) WP619	2.29E-12	5.39E-10	17.32	464.28	2	Modulators of TCR signalling and T-cell activation WP50	9.14E-08	2.20E-05	5.98	96.84
3	Host-pathogen interaction of human coronaviruses - interfer	5.90E-12	9.27E-10	18.7	483.46	3	VEGFA-VEGFR2 signalling pathway WP3888	5.71E-06	9.16E-04	2.09	25.25

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Upregulated genes						Downregulated genes					
Index	Name	*P*	Adjusted *P*	OR	Combined score	Index	Name	*P*	Adjusted *P*	OR	Combined score
					WikiPathway 2021 Human						
4	Type I IFN induction and signaling during SARS-CoV-2 i	4.08E-11	4.80E-09	18.3	437.9	4	Translation factors WP107	1.11E-05	1.33E-03	5.14	58.64
5	Retinoblastoma gene in cancer WP2446	8.57E-11	8.08E-09	7.62	176.55	5	IL-18 signalling pathway WP4754	2.76E-05	0.002351	2.29	24.09
6	Novel intracellular components of RLR p	6.24E-10	4.90E-08	9.24	195.84	6	TCR signalling pathway WP69	0.00002933	0.002351	3.6	37.53
7	Non-genomic actions of 1,25 dihydroxyvitamin D3 WP4341	8.99E-09	6.05E-07	7.39	136.88	7	TCR and Co-stimulatory signalling WP2583	0.00003932	0.002535	6.92	70.22
8	Hepatitis B infection WP4666	9.23E-08	0.000005432	4.32	69.9	8	Cancer immunotherapy by PD-1 blockade WP4585	0.00004217	0.002535	8.2	82.6
9	Cell cycle WP179	1.64E-07	0.000008578	4.79	74.76	9	Translation inhibitors in chronically activated PDGFRA c	0.00008128	0.004344	4.84	45.57
10	Regulation of toll-like receptor signalling pathway WP1449	3.88E-07	0.00001715	4.28	63.13	10	Pathogenesis of SARS-CoV-2 Mediated by nsp9-nsp10 C	0.0001753	0.008431	7.68	66.44
					KEGG 2021 human						
1	NOD-like receptor signalling pathway	3.42E-16	5.20E-14	6.45	229.57	1	Ribosome	1.81E-09	5.52E-07	3.96	79.71
2	Epstein−Barr virus infection	3.56E-16	5.20E-14	6.03	214.37	2	Hematopoietic cell lineage	4.67E-09	7.13E-07	4.97	95.32
3	Hepatitis B	1.29E-10	1.25E-08	5.13	116.9	3	Coronavirus disease	7.53E-07	7.65E-05	2.77	39
4	Influenza A	2.48E-09	1.81E-07	4.56	90.38	4	Primary immunodeficiency	1.66E-06	1.04E-04	7.12	94.72
5	Measles	3.48E-09	2.03E-07	5.07	98.67	5	Th17 cell differentiation	1.86E-06	0.000104	3.78	49.89
6	RIG-I-like receptor signaling pathway	7.22E-09	3.38E-07	7.53	141.07	6	Herpes simplex virus 1 infection	2.05E-06	0.000104	2.07	27.06
7	Hepatitis C	8.11E-09	3.38E-07	4.61	85.94	7	T-cell receptor signalling pathway	4.50E-06	0.0001961	3.68	45.35
8	TNF signalling pathway	9.50E-09	3.47E-07	5.54	102.33	8	RNA transport	7.28E-05	0.002642	2.52	23.97
9	Cell cycle	5.66E-08	0.000001838	4.9	81.72	9	Human T-cell leukaemia virus 1 infection	0.00007796	0.002642	2.37	22.38
10	Lipid and atherosclerosis	6.99E-08	0.000002042	3.68	60.56	10	Cell adhesion molecules	0.0002816	0.008589	2.55	20.88
					Reactome 2016						
1	Immune system homo sapiens R-HSA-168256	2.76E-25	2.77E-22	3	169.65	1	Gene expression homo sapiens R-HSA-74160	1.68E-32	1.90E-29	2.77	202.72

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Upregulated genes						Downregulated genes					
Index	Name	*P*	Adjusted *P*	OR	Combined score	Index	Name	*P*	Adjusted *P*	OR	Combined score
Reactome 2016											
2	IFN signalling homo sapiens R-HSA-913531	8.04E-21	4.02E-18	7.36	340.75	2	L13a-mediated translational silencing of ceruloplasmin	9.30E-23	3.20E-20	9.94	504.29
3	IFN alpha/beta signaling homo sapiens R-HSA-909733	1.68E-18	5.61E-16	14.95	611.96	3	3’ -UTR-mediated translational regulation homo sapiens	9.30E-23	3.20E-20	9.94	504.29
4	IFN gamma signaling homo sapiens R-HSA-877300	7.17E-14	1.80E-11	8.92	270.02	4	Formation of a pool of free 40S subunits homo sapiens	1.22E-22	3.20E-20	10.77	543.4
5	Cytokine signalling in immune system homo sapiens R-HSA-1	2.28E-13	4.56E-11	3.1	90.18	5	GTP hydrolysis and joining of the 60S ribosomal subunit	1.42E-22	3.20E-20	9.79	492.48
6	Cell cycle, mitotic homo sapiens R-HSA-69278	4.74E-10	7.91E-08	3.02	64.78	6	Cap-dependent translation initiation homo sapiens R-H	2.59E-22	4.17E-20	9.2	457.17
7	Cell cycle homo sapiens R-HSA-1640170	8.83E-10	1.26E-07	2.75	57.4	7	Eukaryotic translation initiation homo sapiens R-HSA-7	2.59E-22	4.17E-20	9.2	457.17
8	Polo-like kinase-mediated events homo sapiens R-HSA-15671	4.60E-08	0.000005756	25.19	425.6	8	Major pathway of rRNA processing in the nucleolus Ho	5.76E-21	8.12E-19	6.63	308.83
9	Activated TLR4 signalling homo sapiens R-HSA-166054	5.27E-08	0.000005857	5.2	87.13	9	rRNA processing homo sapiens R-HSA-72312	6.88E-21	8.62E-19	6.26	290.72
10	NF-kB activation through FADD/ RIP-1 pathway-mediated by c	8.24E-08	0.000007709	35.23	574.64	10	Translation homo sapiens R-HSA-72766	2.20E-20	2.48E-18	6.92	313.17
DisGeNET											
1	Influenza	5.05E-27	3.35E-23	4.67	283.01	1	Chronic lymphocytic leukemia	4.16E-13	2.60E-09	2.15	61.21
2	Breast carcinoma	6.27E-23	2.08E-19	2.14	109.54	2	Malignant neoplasm of breast	1.27E-09	3.97E-06	1.47	30.14
3	Carcinogenesis	2.70E-21	5.97E-18	2.15	101.94	3	Breast carcinoma	8.54E-09	1.78E-05	1.45	26.85
4	Neoplasm Metastasis	6.88E-21	1.14E-17	2.15	99.87	4	Leukaemia	1.24E-08	1.93E-05	1.65	30
5	Malignant neoplasm of breast	2.52E-20	3.33E-17	2.04	92.14	5	Leukaemia, myelocytic, acute	4.11E-08	0.00004293	1.66	28.22
6	Leukemia	7.39E-20	7.72E-17	2.5	110.15	6	Lymphoma	4.12E-08	0.00004293	1.75	29.81
7	Rheumatoid arthritis	8.16E-20	7.72E-17	2.54	111.67	7	B-Cell lymphomas	1.20E-06	0.001069	1.88	25.7
8	Asthma	1.26E-19	1.04E-16	2.82	122.59	8	Diffuse large B-cell lymphoma	1.42E-06	0.001108	2	26.95
9	Lupus erythematosus, systemic	3.59E-19	2.64E-16	2.95	125.46	9	Carcinogenesis	1.83E-06	0.001128	1.38	18.26
10	Leukemia, myelocytic, acute	1.17E-18	7.75E-16	2.53	104.52	10	Hodgkin disease	1.91E-06	0.001128	1.97	25.95
Drug perturbations from GEO up											
1	IFN beta-1a DB00060 human GSE26104 sample 3187	6.88E-92	6.21E-89	15.55	3263.45	1	Mycophenolic acid DB01024 human GSE14630 sample	1.94E-21	1.76E-18	5.07	241.93

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Upregulated genes						Downregulated genes				
Index	Name	*P*	Adjusted *P*	OR	Combined score	Index	Name	*P*	Adjusted *P*	OR	Combined score
Drug perturbations from GEO up											
2	IFN beta-1a DB00060 human GSE26104 sample 3186	6.19E-80	2.80E-77	12.96	2362.8	2	Resveratrol DB02709 human GSE36930 sample 3497	6.86E-19	3.10E-16	4.23	176.71
3	IFN beta-1a DB00060 human GSE26104 sample 3188	8.40E-70	2.53E-67	12.7	2019.4	3	Atorvastatin DB01076 human GSE11393 sample 3196	6.52E-18	1.96E-15	4.18	165.24
4	IFN-Î²-1b (Betaferon) DB00068 human GSE26104 sam	9.37E-63	2.12E-60	11.45	1635.45	4	Estradiol DB00783 human GSE4668 sample 2727	2.75E-16	5.24E-14	4.36	156.2
5	Lipopolysaccharide 11970143 human GSE40885 sample 2475	6.24E-55	1.13E-52	11.23	1401.86	5	Estradiol 5757 human GSE4668 sample 3062	2.90E-16	5.24E-14	4.14	148.21
6	Lipopolysaccharide 11970143 human GSE5504 sample 3485	3.06E-48	4.60E-46	8.34	912.38	6	Zinc acetate 11192 human GSE2964 sample 3589	3.75E-16	5.65E-14	5.07	180.08
7	Quercetin 5280343 human GSE13899 sample 3182	6.80E-48	8.77E-46	10.42	1131.79	7	Estradiol 5757 human GSE4668 sample 3063	1.05E-15	1.35E-13	4.43	152.66
8	Lipopolysaccharide 11970143 human GSE3140 sample 3594	1.43E-47	1.61E-45	9.73	1050.07	8	Promyelocytic leukemia DB00755 human GSE5007 sam	4.05E-15	4.57E-13	3.86	127.79
9	IFN beta-1b DB00068 human GSE26104 sample 3185	7.44E-45	7.46E-43	9.32	947.01	9	Etanercept DB00005 human GSE7524 sample 3295	1.13E-14	1.13E-12	3.35	107.57
10	Lipopolysaccharide 11970143 human GSE5504 sample 3486	3.38E-43	3.05E-41	8.34	815.19	10	Motexafin gadolinium (4 h) DB05428 human GSE2189 s	2.19E-14	1.98E-12	3.68	115.78
DSigD											
1	Suloctidil HL60 up	1.59E-52	5.67E-49	22.52	2685.48	1	8-azaguanine HL60 down	7.21E-22	2.63E-18	2.86	139.37
2	Cyclosporin A CTD 00007121	1.89E-41	3.37E-38	2.8	262.76	2	Methyl methanesulfonate CTD 00006307	2.17E-21	3.96E-18	1.89	90.1
3	Tetradioxin CTD 00006848	7.41E-39	8.83E-36	2.84	249.75	3	Anisomycin HL60 down	2.69E-17	3.26E-14	2.46	93.7
4	Estradiol CTD 00005920	2.84E-36	2.53E-33	2.67	218.75	4	Disodium selenite CTD 00007229	3.77E-14	3.44E-11	2.09	64.52
5	Benzo[a] pyrene CTD 00005488	7.50E-33	5.36E-30	2.54	188.03	5	Vitamin E CTD 00006994	1.06E-13	7.75E-11	2.01	60.08
6	Calcitriol CTD 00005558	1.71E-32	1.02E-29	3.13	229.11	6	Cicloheximide HL60 down	3.17E-13	1.93E-10	2.52	72.55
7	Retinoic acid CTD 00006918	2.15E-30	1.10E-27	2.47	168.85	7	Meclofenoxate HL60 down	3.55E-12	1.85E-09	2.4	63.25
8	Testosterone CTD 00006844	3.59E-29	1.60E-26	3.49	228.76	8	Valproic acid CTD 00006977	4.15E-12	1.89E-09	1.5	39.31
9	Acetaminophen CTD 00005295	3.02E-27	1.20E-24	2.37	144.73	9	Acetaminophen CTD 00005295	6.33E-12	2.56E-09	1.59	40.88
10	Dasatinib CTD 00004330	4.78E-27	1.71E-24	5.08	307.6	10	Etifenin PC3 down	1.41E-11	5.13E-09	2.48	61.9

IFN, interferon; SLE, systemic lupus erythematosus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; IL, interleukin; TNF, tumour necrosis factor; TCR, T-cell receptor; OR, odds ratio; GEO, gene expression omnibus; PD, parkinson's disease; TLR4, toll like receptor 4; RLR, RIG-I-like receptor; HMDB, human metabolome database; TMP, thymidine monophosphate; NAP, Adenine nucleotide phosphate; CTP, chaperonin containing TCP1; UTP, uridine triphosphate; IFNG, interferon gamma; KEGG, Kyoto encyclopedia of genes and genomes; R-HSA, R-HSA reactome pathway ID; NF-kB, nuclear factor kappa B; FADD, fas associated via death domain; GTP, guanosine triphosphate; UTR, untranslated region; CTD, comparative toxicogenomics database

Supplementary Table IIF. Gene set enrichment analysis of severe USA samples

Upregulated genes						Downregulated genes					
Index	Name	*P*	Adjusted *P*	OR	Combined score	Index	Name	*P*	Adjusted *P*	OR	Combined score
COVID-19 related gene sets 2021											
1	Top 500 up genes for SARS-CoV-2 late-stage infection in hum	4.11E-15	1.06E-12	3.23	107.13	1	Top 500 down genes for SARS-CoV-2 middle-stage infe	5.01E-10	2.32E-07	2.37	50.77
2	Top 500 up genes for SARS-CoV-2 early infection in human m	4.57E-15	1.06E-12	3.23	106.53	2	COVID-19 patients PBMC down	3.03E-09	6.99E-07	3.34	65.61
3	SARS perturbation; 280 Up Genes from GEN3VA; Human PB	7.97E-15	1.23E-12	4.26	138.35	3	Top 500 up genes for SARS-CoV-2 infection in Rhesus m	5.69E-09	8.23E-07	2.31	43.84
4	500 genes down-regulated by SARS-CoV-2 in A549-ACE2 cell	2.98E-12	2.87E-10	2.97	78.95	4	SARS perturbation; 220 down genes from GEN3VA; Hu	7.52E-09	8.23E-07	3.11	58.1
5	500 genes down-regulated by SARS-CoV-2 (0.2 MOI) in human	3.09E-12	2.87E-10	2.91	77.24	5	500 genes upregulated by SARS-CoV-2 in A549-ACE2 c	8.91E-09	8.23E-07	2.28	42.26
6	500 genes downregulated by MERS-CoV in Calu-3 cells from	1.07E-11	7.91E-10	2.9	73.32	6	Top 500 downregulated genes in human nasal epithelial cells	1.44E-08	1.11E-06	2.29	41.42
7	500 genes upregulated by SARS-CoV-2 in A549-ACE2 cells fr	1.39E-11	7.91E-10	2.91	72.77	7	Top 500 downregulated genes in human nasal epithelial cells	1.80E-08	1.19E-06	2.3	40.93
8	500 genes upregulated by MHV-A59 in murine liver cells fro	1.51E-11	7.91E-10	3.1	77.34	8	Top 500 down genes for SARS-CoV-2 early infection in	3.92E-08	2.265E-06	2.17	37.01
9	500 genes downregulated by MERS-CoV in Calu-3 cells from	1.54E-11	7.91E-10	2.87	71.56	9	Top 500 up genes for SARS-CoV-2 late-stage infection i	1.59E-07	7.646E-06	2.11	32.97
10	Top 500 downregulated genes in human nasal epithelial cells	3.07E-11	1.43E-09	2.91	70.33	10	Top 500 down genes for SARS-CoV-2 infection in Rhesus	1.66E-07	7.646E-06	2.19	34.14
HMDB metabolites											
1	Glucose 6-phosphate (HMDB01401)	0.001315	0.4271	7.71	51.18	1	N1-Acetylspermine (HMDB01186)	6.53E-04	0.9825	10.62	77.91
2	C18H31NO14S (HMDB00632)	0.004605	0.4271	7.4	39.81	2	UTP (HMDB00285)	0.02737	0.9825	2.62	9.44
3	F6P (HMDB03971)	0.009681	0.4271	5.69	26.39	3	Guanosine triphosphate (HMDB01273)	0.03958	0.9825	1.35	4.38

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Upregulated genes						Downregulated genes					
Index	Name	*P*	Adjusted *P*	OR	Combined score	Index	Name	*P*	Adjusted *P*	OR	Combined score
COVID-19 related gene sets 2021											
4	Sulfatide (HMDB00024)	0.01642	0.4271	6.93	28.48	4	Flavin mononucleotide (HMDB01520)	0.04314	0.9825	2.89	9.1
5	C6H12O6 (HMDB00516)	0.02636	0.4271	5.54	20.16	5	Guanosine diphosphate (HMDB01201)	0.08642	0.9825	1.85	4.54
6	FAD (HMDB01248)	0.02813	0.4271	1.81	6.45	6	CTP (HMDB00082)	0.1521	0.9825	1.87	3.53
7	Iron (HMDB00692)	0.04115	0.4271	1.68	5.35	7	Sulfide (HMDB00598)	0.1874	0.9825	1.62	2.72
8	D-Glucose (HMDB00122)	0.04223	0.4271	3.36	10.64	8	4-Nitrophenol (HMDB01232)	0.1891	0.9825	2.83	4.71
9	Potassium (HMDB00586)	0.04973	0.4271	2.41	7.24	9	C33H56N7O17P3S (HMDB03712)	0.1891	0.9825	2.83	4.71
10	1-(1Z-hexadecenyl)-sn-glycero-3-phosphoethanolamine (HM)	0.05951	0.4271	2.96	8.34	10	Beta-alanine (HMDB00056)	0.2166	0.9825	2.54	3.89
Disease perturbations from GEO up											
1	H1N1 DOID-0050211 human GSE27131 sample 514	1.05E-35	8.78E-33	5.79	466.7	1	H1N1 DOID-0050211 human GSE27131 sample 514	1.26E-36	1.05E-33	9.48	783.45
2	Septic shock C0036983 human GSE9692 sample 307	1.17E-25	4.88E-23	4.34	249.19	2	Huntington's disease DOID-12858 human GSE24250 sa	2.19E-17	9.18E-15	3.9	149.63
3	SARS C1175175 human	2.03E-23	5.67E-21	7.01	366.17	3	Autism-spectrum disorder DOID-0060041 human GSE2	7.61E-17	2.13E-14	3.88	144.12
4	sJIA DOID-848 human	7.13E-20	1.49E-17	4.33	191.1	4	Endometrial cancer DOID-1380 human GSE17025 samples	9.61E-14	2.01E-11	3.53	105.77
5	Hepatocellular carcinoma DOID-684 human GSE58208 samples	1.48E-16	2.48E-14	3.52	128.44	5	Endometrial cancer DOID-1380 human GSE17025 samples	1.27E-13	2.14E-11	3.37	100.06
6	Hepatitis C virus-related hepatocellular carcinoma UMLS CUI-	4.97E-15	6.93E-13	3.35	110.45	6	Endometrial cancer DOID-1380 human GSE17025 samp	4.14E-13	5.78E-11	3.39	96.53
7	Non-sJIA (subgroup-RF	7.08E-15	8.48E-13	3.7	120.71	7	Endometrial cancer DOID-1380 human GSE17025 samples	2.92E-12	3.50E-10	3.13	83

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Upregulated genes						Downregulated genes					
Index	Name	*P*	Adjusted *P*	OR	Combined score	Index	Name	*P*	Adjusted *P*	OR	Combined score
Disease perturbations from GEO up											
8	Asthma DOID-2841 human GSE31773 sample 713	5.79E-11	6.06E-09	3.37	79.39	8	Purpura, Idiopathic Thrombocytopenic C0043117 hum	5.57E-12	5.83E-10	7.33	189.92
9	Rheumatoid arthritis DOID-7148 human GSE15573 sample 90	1.09E-10	9.36E-09	3.46	79.42	9	Simian-acquired immune deficiency Syndrome C00801	9.26E-12	8.62E-10	3.39	86.13
10	Ischemic stroke UMLS CUI-C0948008 human GSE22255 samp	1.12E-10	9.36E-09	3.24	74.29	10	Overexertion C0161750 human GSE3606 sample 286	1.38E-11	1.16E-09	3.02	75.56
WikiPathway 2021 human											
1	VEGFA-VEGFR2 signalling pathway WP3888	5.97E-05	0.02911	2.03	19.72	1	Cytoplasmic ribosomal proteins WP477	7.80E-15	3.69E-12	7.27	236.23
2	Host-pathogen interaction of human coronaviruses - MAPK s	0.0003985	0.05925	5.3	41.5	2	TCR and Co-stimulatory Signalling WP2583	3.04E-06	7.18E-04	7.82	99.32
3	Hematopoietic stem cell differentiation WP2849	0.0004395	0.05925	4.13	31.9	3	Proteasome degradation WP183	4.48E-04	7.06E-02	3.39	26.16
4	Effect of progerin on genes involved in Hutchinson-Gilford pr	0.0004857	0.05925	5.12	39.05	4	TNF-related weak inducer of apoptosis (TWEAK) Signalling	7.04E-04	8.32E-02	3.99	28.98
5	Ethanol effects on histone modifications WP3996	0.0008287	0.06794	5.41	38.37	5	T-Cell antigen receptor (TCR) pathway during Staphylo	1.54E-03	0.1257	3.07	19.86
6	Focal adhesion-PI3K-Akt-mTOR-signalling pathway WP3932	0.001007	0.06794	1.98	13.66	6	RANKL/RANK signalling pathway WP2018	0.001813	0.1257	3.19	20.16
7	Leptin and adiponectin WP3934	0.00114	0.06794	12.33	83.6	7	Allograft rejection WP2328	0.00186	0.1257	2.59	16.3
8	Vitamin D receptor pathway WP2877	0.001141	0.06794	2.3	15.59	8	TCR signalling pathway WP69	0.005484	0.3242	2.35	12.25
9	Small cell lung cancer WP4658	0.001254	0.06794	2.91	19.45	9	Angiogenesis WP1539	0.006406	0.3367	4.25	21.46
10	IL-7 signaling pathway WP205	0.001392	0.06794	5.85	38.48	10	Development and heterogeneity of the ILC family WP3	0.007239	0.3424	3.57	17.6
KEGG 2021 human											
1	Hematopoietic cell lineage	0.0000433	0.0129	3.59	36.11	1	Ribosome	2.37E-09	7.12E-07	3.68	73.09
2	Epstein–Barr virus infection	0.0003043	0.03734	2.4	19.44	2	Coronavirus disease	8.08E-07	1.21E-04	2.61	36.63

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Upregulated genes						Downregulated genes					
Index	Name	*P*	Adjusted *P*	OR	Combined score	Index	Name	*P*	Adjusted *P*	OR	Combined score
KEGG 2021 human											
3	Rap1 signalling pathway	0.0005303	0.03734	2.3	17.32	3	Herpes simplex virus 1 infection	4.66E-05	4.66E-03	1.81	18.03
4	Toxoplasmosis	0.0006171	0.03734	2.88	21.27	4	Proteasome	1.49E-03	1.12E-01	3.55	23.08
5	Platelet activation	0.0006265	0.03734	2.76	20.35	5	Th17 cell differentiation	1.87E-03	0.1119	2.42	15.19
6	Small cell lung cancer	0.0008381	0.04162	3.06	21.68	6	Th1 and Th2 cell differentiation	2.60E-03	0.1149	2.49	14.83
7	Leishmaniasis	0.001878	0.07994	3.1	19.43	7	Graft-versus-host disease	2.82E-03	0.1149	3.48	20.43
8	FoxO signalling pathway	0.00304	0.1132	2.4	13.94	8	Natural-killer cell-mediated cytotoxicity	3.06E-03	0.1149	2.17	12.57
9	Focal adhesion	0.0037	0.121	2.06	11.52	9	T-cell receptor signalling pathway	0.003486	0.1162	2.33	13.16
10	Glycerophospholipid metabolism	0.004438	0.121	2.59	14.04	10	Bladder cancer	0.00862	0.2586	3.09	14.7
Reactome 2016											
1	Hemostasis homo sapiens R-HSA-109582	9.62E-06	0.01044	2.01	23.22	1	Eukaryotic translation elongation homo sapiens R-HSA	1.30E-16	7.87E-14	8.02	293.33
2	Asparagine N-linked glycosylation homo sapiens R-HSA-4462	0.0000288	0.01564	2.46	25.7	2	Peptide chain elongation Homo sapiens R-HSA-156902	1.36E-16	7.87E-14	8.39	306.52
3	Extracellular matrix organization homo sapiens R-HSA-14742	0.0001472	0.0533	2.22	19.6	3	NMD independent of the	1.03E-15	2.54E-13	7.64	263.59
4	Chromatin organization homo sapiens R-HSA-4839726	0.0002665	0.05788	2.33	19.14	4	Viral mRNA translation homo sapiens R-HSA-192823	1.13E-15	2.54E-13	7.97	274.44
5	Chromatin modifying enzymes homo sapiens R-HSA-324750	0.0002665	0.05788	2.33	19.14	5	L13a-mediated translational silencing of ceruloplasmin	1.32E-15	2.54E-13	6.68	228.73
6	Platelet activation, signalling and aggregation homo sapiens	0.0006356	0.09438	2.14	15.76	6	3’ -UTR-mediated translational regulation homo sapien	1.32E-15	2.54E-13	6.68	228.73
7	Immune system homo sapiens R-HSA-168256	0.0006633	0.09438	1.43	10.46	7	GTP hydrolysis and joining of the 60S ribosomal subuni	1.85E-15	2.76E-13	6.58	223.27

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Upregulated genes						Downregulated genes					
Index	Name	*P*	Adjusted *P*	OR	Combined score	Index	Name	*P*	Adjusted *P*	OR	Combined score
Reactome 2016											
8	Calnexin/calreticulin cycle homo sapiens R-HSA-901042	0.0006953	0.09438	9.26	67.32	8	Formation of a pool of free 40S subunits Homo sapiens	1.91E-15	2.76E-13	7.11	241.01
9	HDACs deacetylate histones homo sapiens R-HSA-3214815	0.0008981	0.1051	3.71	26.05	9	Selenocysteine synthesis homo sapiens R-HSA-240855	3.67E-15	4.24E-13	7.54	250.53
10	Platelet degranulation homo sapiens R-HSA-114608	0.0009675	0.1051	2.86	19.86	10	Eukaryotic translation termination homo sapiens R-HS	3.67E-15	4.24E-13	7.54	250.53
DisGeNET											
1	Nephrotic Syndrome	2.00E-07	0.001263	3.42	52.72	1	Aase Smith syndrome 2	4.58E-06	2.96E-02	10.46	128.54
2	Platelet mean volume determination (procedure)	1.34E-06	0.004221	3.23	43.69	2	Abnormality of the genital system	2.73E-05	5.87E-02	7.67	80.56
3	Coronary artery disease	0.000009444	0.01986	1.74	20.14	3	Abnormality of the reproductive system	2.73E-05	5.87E-02	7.67	80.56
4	Fetal diseases	0.00003781	0.05458	23.15	235.76	4	Abnormality of the urinary system	1.07E-04	1.59E-01	5.32	48.67
5	Thrombocythemia, essential	0.00005442	0.05458	2.99	29.34	5	Anaemia, macrocytic	1.23E-04	0.1585	4.69	42.21
6	Blood coagulation disorders	0.00006908	0.05458	2.76	26.44	6	Pallor	1.86E-04	0.1997	3.78	32.47
7	Coronary heart disease	0.00007063	0.05458	1.67	16.01	7	T-cell lymphoma	3.98E-04	0.3672	1.87	14.6
8	Severe sepsis	0.00007094	0.05458	3.43	32.75	8	Intermittent migraine headaches	4.71E-04	0.3804	2.79	21.37
9	Bulging forehead	0.00008983	0.05458	3.35	31.22	9	Niemann-Pick disease, Type C	1.23E-03	0.8837	2.84	19.04
10	Prominent forehead	0.00008983	0.05458	3.35	31.22	10	hand deformities	1.78E-03	0.9997	3.45	21.86
Drug perturbations from GEO up						Drug perturbations from GEO down					
1	Oprelvekin DB00038 human GSE8762 sample 3297	1.10E-10	9.92E-08	3.2	73.31	1	Motexafin gadolinium (4 h) DB05428 human GSE2189 s	3.94E-08	2.45E-05	2.58	43.91
2	BPDE 41322 human GSE19510 sample 3378	6.74E-10	2.46E-07	3	63.45	2	Doxycycline DB00254 human GSE2624 sample 3074	5.43E-08	2.45E-05	2.27	37.91
3	Atorvastatin DB01076 human GSE11393 sample 3196	8.15E-10	2.46E-07	3.21	67.26	3	Estradiol 5757 human GSE4668 sample 3063	1.19E-07	3.48E-05	2.76	44.05

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Upregulated genes						Downregulated genes					
Index	Name	*P*	Adjusted *P*	OR	Combined score	Index	Name	*P*	Adjusted *P*	OR	Combined score
4	Methotrexate DB00563 human GSE23687 sample 2541	2.70E-09	5.57E-07	2.9	57.22	4	Apratoxin A 6326668 human GSE2742 sample 3068	1.85E-07	3.48E-05	2.84	44.01
5	IFN beta-1b DB00068 human GSE26104 sample 3185	3.08E-09	5.57E-07	2.97	58.14	5	Fluoxetine DB00472 mouse GSE35765 sample 2500	1.93E-07	0.00003475	2.71	41.85
6	Atarax DB00557 human GSE31773 sample 2485	4.60E-09	6.94E-07	3.01	57.77	6	Neocarzinostatin 5282473 human GSE1676 sample 311	2.35E-07	0.00003533	2.46	37.53
7	Bisphenol A 6623 human GSE17624 sample 2664	1.33E-08	1.71E-06	2.85	51.65	7	Etanercept DB00005 human GSE7524 sample 3295	3.29E-07	0.00003757	2.25	33.6
8	Vemurafenib DB08881 human GSE37441 sample 2561	3.26E-08	3.69E-06	3.07	52.85	8	Arachidonic acid 444899 human GSE3737 sample 3119	3.33E-07	0.00003757	2.68	39.97
9	BPDE 41322 human GSE19510 sample 3379	9.90E-08	9.95E-06	2.82	45.55	9	Promegestone 36709 human GSE67561 sample 3694	4.36E-07	0.00004018	2.33	34.1
10	Bleomycin DB00290 mouse GSE2640 sample 2851	1.51E-07	1.29E-05	2.69	42.28	10	Apratoxin A 6326668 human GSE2742 sample 3070	4.45E-07	0.00004018	2.28	33.41

IFN, interferon; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; IL, interleukin; TCR, T-cell receptor; TNF, tumour necrosis factor; MERS, Middle East respiratory syndrome coronavirus; sJIA, systemic juvenile idiopathic arthritis; OR, odds ratio; GEO, Gene Expression Omnibus; NMD, nonsense-mediated decay

Supplementary Table IIG. Gene set enrichment analysis of severe Spain samples

Up-regulated genes						Down-regulated genes					
Index	Name	*P*	Adjusted *P*	OR	Combined score	Index	Name	*P*	Adjusted *P*	OR	Combined score
COVID-19 related gene sets 2021											
1	500 genes upregulated by SARS-CoV-2 in human Calu3 cells a	5.39E-13	1.38E-10	44.31	1251.61	1	500 genes upregulated by SARS-CoV-2 in human organ	3.14E-12	7.14E-10	47.79	1265.76
2	500 genes upregulated by SARS-CoV-1 in Calu-3 cells from GS	6.52E-12	8.34E-10	41.53	1069.61	2	500 genes upregulated by SARS-CoV-2 in human Calu3	2.40E-10	2.73E-08	36.1	799.63
3	500 genes upregulated by SARS-CoV-2 in human Organoids c	1.15E-11	9.82E-10	39.1	984.76	3	500 genes upregulated by SARS-CoV-2 (0.2 MOI) in hum	4.46E-09	3.38E-07	31.42	604.19
4	SARS perturbation 357 up genes from GEn3va mouse Lung	3.14E-11	2.01E-09	43.58	1053.96	4	500 genes upregulated by SARS-CoV-2 in human Calu3	8.17E-09	4.64E-07	28.99	539.88
5	SARS perturbation; 431 up genes from GEN3VA; human airw	5.70E-11	2.92E-09	40.64	958.68	5	500 genes upregulated by SARS-CoV-2 in Calu-3 cells fr	7.53E-08	3.42E-06	27.3	447.8
6	SARS perturbation 441 up genes from GEN3VA mouse lung	1.45E-10	6.17E-09	36.43	825.44	6	500 genes up-regulated by SARS-CoV-1 in Calu-3 cells fr	9.24E-08	3.50E-06	26.46	428.56
7	500 genes upregulated by SARS-CoV-2 in Calu-3 cells from GS	1.90E-10	6.96E-09	35.27	789.41	7	500 genes up regulated by SARS-COV-2 infection of Calu	1.63E-07	4.62E-06	24.27	379.34
8	500 genes upregulated by SARS-CoV-2 in human cardiomyocy	3.91E-10	1.25E-08	32.4	701.91	8	500 genes up-regulated by SARS-CoV-2 (2 MOI) in huma	1.63E-07	4.619E-06	24.27	379.34
9	500 genes upregulated by SARS-CoV-2 in human hiPSC-CMs c	6.69E-10	1.90E-08	30.4	642.26	9	500 genes up-regulated by SARS-CoV-2 in human Calu3	2.09E-07	5.282E-06	23.35	359.1
10	500 genes upregulated by SARS-CoV-2 in human Calu3 cells a	7.58E-10	1.94E-08	29.96	629.08	10	SARS perturbation; 388 up genes from GEN3VA; human	5.38E-07	0.00001221	26.98	389.54
HMDB metabolites											
1	Arachidonic acid (HMDB01043)	0.001349	0.008094	41.96	277.26	1	Simvastatin (HMDB05007)	2.53E-04	0.001266	102.09	845.42
2	Oxygen (HMDB01377)	0.01042	0.02656	14.3	65.27	2	Butyric acid (HMDB00039)	0.0104	0.02601	110.95	506.56

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Up-regulated genes						Down-regulated genes					
Index	Name	*P*	Adjusted *P*	OR	Combined score	Index	Name	*P*	Adjusted *P*	OR	Combined score
HMDB metabolites											
3	Iron (HMDB00692)	0.01725	0.02656	10.91	44.28	3	Atorvastatin (HMDB05006)	0.01603	0.02672	69.32	286.51
4	Atorvastatin (HMDB05006)	0.01771	0.02656	62.38	251.64	4	Cyclic AMP (HMDB00058)	0.1399	0.1749	7.01	13.79
5	Simvastatin (HMDB05007)	0.02594	0.03112	41.57	151.83	5	Magnesium (HMDB00547)	0.3593	0.3593	2.35	2.4
6	C34H34N4O4.Fe (HMDB03178)	0.1633	0.1633	5.9	10.68						
Disease perturbations from GEO up						Disease perturbations from GEO down					
1	Discoid lupus erythematosus UMLS CUI-C0024138 human GSE	9.32E-13	5.27E-10	50.98	1412.32	1	COPD - C002411	4.10E-10	7.30E-08	59.81	1292.8
2	Acute myocarditis DOID-3951 mouse GSE35182 sample 801	2.59E-12	7.32E-10	38.07	1015.8	2	Pulmonary sarcoidosis DOID-13406 human GSE19976 sa	4.32E-10	7.30E-08	42.78	922.44
3	Acute myocarditis DOID-3951 mouse GSE35182 sample 802	3.09E-11	5.83E-09	35.2	851.81	3	Aplastic anaemia C0002874 human GSE3807 sample 424	4.74E-10	7.30E-08	42.27	907.45
4	Multiple myeloma DOID-9538 human GSE36474 sample 707	1.37E-10	1.93E-08	47.79	1085.39	4	Asthma DOID-2841 human GSE43696 sample 827	7.23E-10	8.35E-08	39.98	841.44
5	Glaucoma associated with systemic syndromes DOID-1686 mo	1.84E-10	1.95E-08	45.96	1030.06	5	Bipolar disorder DOID-3312 human GSE62191 sample 54	7.89E-09	6.79E-07	38.4	716.44
6	Dermatomyositis DOID-10223 human GSE48280 sample 705	2.07E-10	1.95E-08	34.93	778.83	6	Anemia DOID-2355 human GSE4619 sample 792	8.82E-09	6.79E-07	37.76	700.25
7	Swine influenza DOID-0050211 human GSE48466 sample 498	2.67E-10	2.16E-08	43.77	964.85	7	Polycystic ovary syndrome C0032460 human GSE5090 s	1.49E-07	9.00E-06	33.82	531.55
8	Psoriasis DOID-8893 human GSE52471 sample 690	4.34E-10	3.06E-08	41.06	885.22	8	Idiopathic fibrosing alveolitis C0085786 human GSE2136	1.56E-07	9.00E-06	33.57	526.14

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Up-regulated genes						Down-regulated genes					
Index	Name	*P*	Adjusted *P*	OR	Combined score	Index	Name	*P*	Adjusted *P*	OR	Combined score
Disease perturbations from GEO up						Disease perturbations from GEO down					
9	Sendai virus infection C1319860 mouse GSE10211 sample 82	4.94E-10	3.10E-08	40.37	865.01	9	Melanoma DOID-1909 human GSE6887 sample 950	2.17E-07	1.02E-05	31.67	485.93
10	Alzheimer's disease DOID-10652 human GSE36980 sample 52	1.10E-09	6.24E-08	36.31	748.8	10	Anemia DOID-2355 human GSE4619 sample 793	2.22E-07	1.02E-05	31.56	483.58
WikiPathway 2021 Human											
1	SARS-CoV-2 innate immunity evasion and cell-specific immunity	5.34E-11	7.96E-09	132.79	3141.01	1	Cytokines and Inflammatory Response WP530	6.95E-14	1.27E-11	460.64	13956.06
2	p38 MAPK Signalling Pathway WP400	0.000005846	0.0004355	107.25	1292.31	2	IL-18 signalling pathway WP4754	1.14E-12	1.04E-10	67.48	1855.38
3	Lung fibrosis WP3624	0.00003804	0.001889	55.33	563.09	3	Toll-like receptor signaling pathway WP75	3.74E-12	2.27E-10	120.83	3179.24
4	Mammary gland development pathway - puberty (stage 2 of 4	0.00008133	0.002816	191.08	1799.41	4	Lung fibrosis WP3624	2.01E-11	9.15E-10	161.33	3973.56
5	COVID-19 adverse outcome pathway WP4891	0.0001093	0.002816	161.67	1474.57	5	Regulation of toll-like receptor signaling pathway WP14	3.16E-11	1.15E-09	87.72	2120.79
6	MAPK signaling pathway WP382	0.0001134	0.002816	19.19	174.34	6	Allograft rejection WP2328	1.69E-10	5.14E-09	110.65	2489.4
7	Platelet-mediated interactions with vascular and circulating c	0.0001415	0.003011	140.1	1241.77	7	SARS-CoV-2 innate immunity evasion and cell-specific im	3.76E-09	9.78E-08	116.63	2262.39
8	IL-18 signaling pathway WP4754	0.0001669	0.003108	17.31	150.53	8	Spinal cord injury WP2431	7.14E-08	1.563E-06	62.79	1033.23
9	Complement activation WP545	0.0002395	0.003255	105.05	875.77	9	MAPK signaling pathway WP382	7.73E-08	1.563E-06	37.96	621.67
10	PI3K/AKT/mTOR - VitD3 signaling WP4141	0.0002395	0.003255	105.05	875.77	10	T-Cell antigen receptor (TCR) pathway during Staphyloc	3.13E-07	5.432E-06	91.6	1371.81

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Up-regulated genes						Down-regulated genes					
Index	Name	*P*	Adjusted *P*	OR	Combined score	Index	Name	*P*	Adjusted *P*	OR	Combined score
					KEGG 2021 Human						
1	Viral protein interaction with cytokine and cytokine receptor	5.39E-08	0.000005448	65.41	1094.63	1	Rheumatoid arthritis	8.73E-22	1.04E-19	333.67	16179.87
2	*S. aureus* infection	0.000002687	0.0001202	51.42	659.61	2	Cytokine-cytokine receptor interaction	3.44E-14	2.05E-12	76.79	2380.51
3	Chagas disease	0.00000357	0.0001202	47.73	598.72	3	Leishmaniasis	4.60E-13	1.83E-11	165.93	4713.46
4	MAPK signaling pathway	0.00001113	0.0002285	21.29	242.84	4	Toll-like receptor signaling pathway	4.01E-12	1.17E-10	119.58	3138.04
5	Cytokine-cytokine receptor interaction	0.00001131	0.0002285	21.22	241.65	5	Th17 cell differentiation	4.91E-12	1.17E-10	115.97	3019.85
6	Influenza A	0.0000282	0.0004747	27.75	290.68	6	TNF signalling pathway	6.81E-12	1.35E-10	110.42	2839.31
7	NOD-like receptor signalling pathway	0.00003443	0.0004865	26.32	270.52	7	Inflammatory bowel disease	2.44E-11	4.15E-10	155.84	3808.22
8	Transcriptional misregulation in cancer	0.00004335	0.0004865	24.77	248.84	8	Pertussis	6.42E-11	9.55E-10	131.28	3081.03
9	Chemokine signaling pathway	0.00004335	0.0004865	24.77	248.84	9	IL-17 signaling pathway	2.37E-10	3.13E-09	104.33	2312.47
10	Pertussis	0.00006676	0.0006182	45.45	436.95	10	Viral protein interaction with cytokine and cytokine rece	3.45E-10	4.11E-09	97.64	2127.31
					Reactome 2016						
1	Chemokine receptors bind chemokines homo sapiens R-HSA-	3.18E-07	0.00005412	90.17	1348.92	1	Class A/1 (Rhodopsin-like receptors) homo sapiens R-HS	2.75E-10	3.13E-08	45.4	999.59
2	Interferon alpha/beta signaling homo sapiens R-HSA-909733	7.00E-07	0.00005951	73.22	1037.63	2	Immune system homo sapiens R-HSA-168256	1.33E-09	6.15E-08	20.6	421.06
3	Peptide ligand-binding receptors homo sapiens R-HSA-37527	0.00004424	0.001997	24.64	247.01	3	Chemokine receptors bind chemokines homo sapiens R	1.62E-09	6.15E-08	139.57	2825.17
4	Interferon signaling homo sapiens R-HSA-913531	0.00004698	0.001997	24.25	241.66	4	GPCR ligand binding homo sapiens R-HSA-500792	3.56E-09	1.02E-07	32.37	629.77

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Up-regulated genes						Down-regulated genes					
Index	Name	*P*	Adjusted *P*	OR	Combined score	Index	Name	*P*	Adjusted *P*	OR	Combined score
Reactome 2016											
5	Immune system homo sapiens R-HSA-168256	0.0001026	0.003487	7.37	67.72	5	MAPK targets/Nuclear events mediated by MAP kinase	1.57E-08	3.47E-07	204.67	3677.93
6	ATF4 activates genes homo sapiens R-HSA-380994	0.0003105	0.007375	91.33	737.73	6	Peptide ligand-binding receptors homo sapiens R-HSA-3	1.83E-08	3.47E-07	48.85	870.52
7	Class A/1 (Rhodopsin-like receptors) homo sapiens R-HSA-373	0.0003216	0.007375	14.5	116.62	7	Signal transduction homo sapiens R-HSA-162582	2.61E-07	3.91E-06	12.25	185.68
8	Cytokine signaling in immune system homo sapiens R-HSA-12	0.0003794	0.007375	9.84	77.5	8	MAP kinase activation in TLR cascade homo sapiens R-H	2.74E-07	3.907E-06	94.88	1433.6
9	PERK regulates gene expression homo sapiens R-HSA-381042	0.0003904	0.007375	80.78	633.99	9	TRAF6 mediated induction of proinflammatory cytokine	5.74E-07	7.275E-06	78.09	1122.16
10	GPCR ligand binding homo sapiens R-HSA-500792	0.001089	0.01852	10.38	70.79	10	Translocation of ZAP-70 to immunological synapse hom	9.56E-07	7.521E-06	207.95	2882.21
DisGeNET											
1	Influenza	3.56E-12	6.37E-09	36.92	973.35	1	Pneumonia	2.79E-17	6.62E-14	87.28	3326.82
2	Infection	2.05E-11	1.84E-08	36.77	905	2	Pneumonitis	1.89E-15	2.24E-12	82.39	2793.11
3	Diabetes	6.90E-10	4.12E-07	19.88	419.27	3	Eczema	4.69E-14	3.71E-11	60.64	1861.14
4	Asthma	1.03E-09	4.61E-07	19.14	396.13	4	Dermatitis, atopic	9.45E-14	4.73E-11	56.71	1700.71
5	Systemic scleroderma	2.23E-09	7.92E-07	26.35	524.86	5	Glomerulonephritis	1.10E-13	4.73E-11	88.57	2642.59
6	Lupus erythematosus, systemic	3.18E-09	7.92E-07	18.84	368.69	6	Allergic reaction	1.20E-13	4.73E-11	203.9	6066.84
7	Lung diseases	3.37E-09	7.92E-07	31.32	611	7	Asthma	2.20E-13	7.45E-11	40.27	1173.64
8	Stomach neoplasms	3.54E-09	7.92E-07	21.11	410.71	8	Rheumatoid arthritis	6.96E-13	2.06E-10	37.46	1048.76
9	Diabetes mellitus	4.97E-09	9.11E-07	16.49	315.19	9	Influenza	8.04E-13	2.12E-10	46.16	1285.45
10	Virus diseases	5.55E-09	9.11E-07	20.09	381.87	10	Tuberculosis	1.02E-12	2.42E-10	45.11	1245.62

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Up-regulated genes						Down-regulated genes				
Index	Name	*P*	Adjusted *P*	OR	Combined score	Index	Name	*P*	Adjusted *P*	OR	Combined score
Drug perturbations from GEO up						Drug perturbations from GEO down					
1	Lipopolysaccharide 11970143 human GSE3140 sample 3595	6.36E-15	3.73E-12	67.79	2216.05	Etanercept DB00005 human GSE11903 sample 2608	2.84E-09	1.10E-06	44.77	881.07	
2	Lipopolysaccharide 11970143 human GSE3140 sample 3594	4.55E-13	1.33E-10	54.98	1562.29	IFN beta-1b DB00068 human GSE26104 sample 3	7.20E-09	1.39E-06	38.93	729.84	
3	Lipopolysaccharide 11970143 human GSE5504 sample 3486	1.44E-12	2.81E-10	48.72	1328.43	Etanercept DB00005 human GSE11903 sample 2610	1.88E-08	2.42E-06	33.7	599.53	
4	Formaldehyde 712 rat GSE7002 sample 3552	3.73E-12	5.47E-10	44.05	1159.1	Formaldehyde 712 rat GSE7002 sample 3539	3.26E-08	3.15E-06	31	534.51	
5	Lipopolysaccharide 11970143 human GSE5504 sample 3485	5.19E-12	6.08E-10	42.54	1105.47	Quercetin 5280343 human GSE13899 sample 3182	2.17E-07	0.0000168	31.67	485.93	
6	Bleomycin DB00290 mouse GSE43695 sample 3104	1.18E-11	1.15E-09	48.87	1229.57	Ubiquinol 9962735 human GSE21351 sample 3448	3.58E-07	0.00002308	29	430.48	
7	Soman 7305 rat GSE13428 sample 2633	2.40E-11	2.01E-09	36.16	884.12	Formaldehyde 712 rat GSE7002 sample 3548	6.47E-07	0.00003579	26.11	372.14	
8	Bleomycin DB00290 mouse GSE43695 sample 3106	5.18E-11	3.79E-09	41.11	973.55	Formaldehyde 712 rat GSE7002 sample 3540	7.50E-07	0.00003628	25.44	358.83	
9	IFN beta-1a DB00060 human GSE26104 sample 3186	1.68E-10	1.09E-08	35.8	805.71	Etanercept DB00005 human GSE7524 sample 3295	9.80E-07	0.00004215	24.26	335.68	
10	IFN-alphacon1 DB05258 human GSE5542 sample 2473	1.55E-09	9.08E-08	34.71	704.2	IFN-Î²-1b (Betaferon) DB00068 human GSE26104	0.000001963	0.00007598	31.36	412.08	

GEO, Gene Expression Omnibus; OR, odds ratio; TLR, toll like receptor; *S. aureus, Staphylococcus aureus* GEO, Gene Expression Omnibus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TNF, tumor necrosis factor; IL, interleukin; COPD, chronic obstructive pulmonary disease; IFN, Interferon

Supplementary Table IIH. Gene set enrichment analysis of severe all western (combined) samples

Upregulated genes						Downregulated genes					
Index	Name	*P*	Adjusted *P*	OR	Combined score	Index	Name	*P*	Adjusted *P*	OR	Combined score
COVID-19 related gene sets 2021											
1	500 genes up-regulated by SARS-CoV-2 in human lung cells f	9.52E-57	4.47E-54	5.86	755.92	1	Top 500 up genes for SARS-CoV-2 infection in Rhesus m	2.32E-37	1.10E-34	4	337.37
2	Top 500 up genes for SARS-CoV-2 infection in Rhesus macaq	3.01E-56	7.08E-54	5.97	762.66	2	Top 500 up genes for SARS-CoV-2 late-stage infection i	1.21E-25	2.87E-23	3.13	179.75
3	Top 500 up genes for SARS-CoV-2 infection in Rhesus macaq	4.24E-55	6.64E-53	5.81	727.77	3	Top 500 down genes for SARS-CoV-2 early infection in	5.97E-25	9.41E-23	3.08	172
4	500 genes upregulated by SARS-CoV-2 in human lung tissue f	7.98E-54	7.50E-52	5.86	716.22	4	SARS perturbation; 220 down genes from GEN3VA; Hu	1.34E-24	1.58E-22	4.86	267.31
5	Healthy human lung biopsy versus COVID-19 infected human lun	7.98E-54	7.50E-52	5.86	716.22	5	500 genes downregulated by MHV-A59 in murine spleen	5.03E-24	4.76E-22	3.21	172.25
6	Top 500 up genes for SARS-CoV-2 infection in Rhesus macaq	3.05E-49	2.39E-47	5.38	600.51	6	Top 500 down genes for SARS-CoV-2 infection in Rhesu	5.03E-23	3.96E-21	3.09	158.72
7	COVID-19 patients PBMC up	1.47E-47	9.87E-46	5.03	541.92	7	Top 500 up genes for SARS-CoV-2 infection in Rhesus m	5.17E-21	3.50E-19	2.93	137.03
8	Top 500 up genes for SARS-CoV-2 infection in Rhesus macaq	7.41E-47	4.35E-45	5.22	554.64	8	500 genes downregulated by MHV-A59 in murine sple	1.64E-20	9.67E-19	2.93	133.34
9	Top 500 up genes for SARS-CoV-2 infection 48 hpi in human	1.74E-46	9.06E-45	5.29	557.29	9	Top 500 up genes for SARS-CoV-2 infection in Rhesus m	2.03E-18	1.07E-16	2.77	112.78
10	500 genes up-regulated by SARS-CoV-2 in human Calu3 cells	5.53E-42	2.60E-40	4.72	448.55	10	COVID-19 patients PBMC down	4.11E-18	1.95E-16	4.21	168.68
HMDB metabolites											
1	Hexadecanoyl-CoA (HMDB01338)	0.0008561	0.08978	5	35.34	1	UTP (HMDB00285)	3.18E-03	0.7378	2.93	16.88

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Upregulated genes						Downregulated genes					
Index	Name	*P*	Adjusted *P*	OR	Combined score	Index	Name	*P*	Adjusted *P*	OR	Combined score
HMDB metabolites											
2	Carbon dioxide (HMDB01967)	0.001614	0.08978	2.48	15.96	2	N1-Acetylspermine (HMDB01186)	0.007051	0.7378	5.9	29.23
3	Iron (HMDB00692)	0.004501	0.08978	1.81	9.79	3	CTP (HMDB00082)	0.01801	0.7378	2.44	9.81
4	Palmitic acid (HMDB00220)	0.004897	0.08978	5.9	31.38	4	D-Ribose 5-phosphate (HMDB01548)	0.03787	0.7378	4.04	13.24
5	1-(1Z-hexadecenyl)-sn-glycero-3-phosphoethanolamine (HM)	0.01007	0.08978	3.38	15.54	5	D-ribulose 5-phosphate (HMDB00618)	0.06715	0.7378	3.14	8.49
6	1-hexadecyl-2-(9Z-octadecenoyl)-sn-glycero-3-phosphoethan	0.01007	0.08978	3.38	15.54	6	Guanosine triphosphate (HMDB01273)	0.1137	0.7378	1.19	2.59
7	PE (P-16:0/14:0) (HMDB11335)	0.01007	0.08978	3.38	15.54	7	Acetic acid (HMDB00042)	0.1417	0.7378	1.85	3.61
8	PE (P-16:0/14:1 (9Z)) (HMDB11336)	0.01007	0.08978	3.38	15.54	8	Glutathione (HMDB00125)	0.1417	0.7378	1.67	3.25
9	PE (P-16:0/15:0) (HMDB11337)	0.01007	0.08978	3.38	15.54	9	C33H56N7O17P3S (HMDB03712)	0.1469	0.7378	2.65	5.09
10	PE (P-16:0/16:1 (9Z)) (HMDB11339)	0.01007	0.08978	3.38	15.54	10	Guanosine diphosphate (HMDB01201)	0.1512	0.7378	1.5	2.83
Disease perturbations from GEO up						Disease perturbations from GEO down					
1	Septic shock C0036983 human GSE9692 sample 307	3.84E-104	3.22E-101	9.6	2286.83	1	H1N1 DOID-0050211 human GSE27131 sample 514	3.71E-60	3.12E-57	13.9	1901.98
2	H1N1 DOID-0050211 human GSE27131 sample 514	1.32E-87	5.53E-85	9.23	1846.55	2	Huntington's disease DOID-12858 human GSE24250 sa	1.11E-39	4.65E-37	5.56	499.14
3	Dengue disease DOID-12205 human GSE51808 sample 556	1.56E-65	4.36E-63	7.91	1181.06	3	Autism spectrum disorder DOID-0060041 human GSE2	3.31E-38	9.25E-36	5.51	475.7
4	Dengue hemorrhagic fever DOID-12206 human GSE51808 sa	2.79E-61	5.85E-59	7.5	1045.05	4	Huntington's disease DOID-12858 human GSE24250 sa	1.33E-29	2.80E-27	3.89	258.36
5	Swine influenza DOID-0050211 human GSE48466 sample 49	1.05E-48	1.76E-46	7.61	840.42	5	PD DOID-14330 human GSE6613 samp	1.32E-27	2.22E-25	4.05	250.45
6	Dengue fever DOID-12206 human GSE51808 sample 447	8.59E-48	1.20E-45	6.66	722.06	6	Rotavirus infection of children C1442797 human GSE27	3.81E-27	5.33E-25	4.14	252.05

Contd...

Upregulated genes						Downregulated genes					
Index	Name	*P*	Adjusted *P*	OR	Combined score	Index	Name	*P*	Adjusted *P*	OR	Combined score
Disease perturbations from GEO up						Disease perturbations from GEO down					
7	sJIA DOID-848 human	3.12E-41	3.74E-39	5.6	522.38	7	Overexertion C0161750 human GSE3606 sample 286	8.53E-27	1.02E-24	4.06	243.52
8	Autism spectrum disorder DOID-0060041 human GSE25507 s	4.19E-41	4.40E-39	6.18	574.71	8	SLE DOID-9074 human GSE1	1.65E-26	1.73E-24	4.26	252.95
9	SLE DOID-9074 human GSE3	1.03E-34	9.64E-33	5.57	435.66	9	Pulmonary hypertension C0020542 human GSE703 sa	6.99E-26	6.51E-24	5.82	337.03
10	West Nile fever DOID-2366 human GSE30719 sample 874	2.97E-33	2.49E-31	3.95	295.57	10	Acute myeloid leukemia DOID-9119 human GSE9476 sa	1.42E-25	1.19E-23	3.32	190
WikiPathway 2021 Human											
1	Immune response to tuberculosis WP4197	4.64E-10	2.61E-07	16.61	356.88	1	Cytoplasmic Ribosomal Proteins WP477	4.62E-28	2.61E-25	11.67	734.52
2	Retinoblastoma gene in cancer WP2446	2.13E-09	4.17E-07	4.83	96.4	2	TCR and Co-stimulatory Signaling WP2583	4.08E-08	1.15E-05	8.75	148.85
3	Type II IFN signaling (IFNG) WP619	2.23E-09	4.17E-07	9.08	180.97	3	IL-18 signaling pathway WP4754	2.41E-07	4.55E-05	2.21	33.61
4	Hepatitis B infection WP4666	5.81E-08	0.000008147	3.21	53.55	4	Modulators of TCR signaling and T cell activation WP50	4.17E-07	5.89E-05	4.31	63.29
5	Host-pathogen interaction of human coronaviruses - interfer	2.03E-07	0.0000228	7.86	121.14	5	Cancer immunotherapy by PD-1 blockade WP4585	5.39E-07	0.00006094	9.23	133.24
6	Integrated breast cancer pathway WP1984	5.86E-07	0.00005244	2.98	42.7	6	TCR signaling pathway WP69	0.000002305	0.0001973	3.22	41.76
7	Type I IFN induction and signaling during SARS-CoV-2	6.54E-07	0.00005244	7.7	109.67	7	T-cell antigen receptor (TCR) pathway during Staphylo	0.000002444	0.0001973	3.91	50.56
8	VEGFA-VEGFR2 signaling pathway WP3888	0.000001743	0.000102	1.98	26.29	8	Pathogenesis of SARS-CoV-2 mediated by nsp9-nsp10	0.0000111	0.0007838	7.8	89.04
9	Novel intracellular components of RLR p	0.000001748	0.000102	4.58	60.69	9	Allograft rejection WP2328	0.00001844	0.001158	2.94	32.02

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Upregulated genes						Downregulated genes					
Index	Name	*P*	Adjusted *P*	OR	Combined score	Index	Name	*P*	Adjusted *P*	OR	Combined score
WikiPathway 2021 Human											
10	SARS-CoV-2 innate immunity evasion and cell-specific immu	0.000001819	0.000102	4.32	57.09	10	TGF-beta signalling pathway WP366	0.00002109	0.001192	2.47	26.62
KEGG 2021 Human											
1	Epstein-Barr virus infection	1.81E-17	5.65E-15	4.49	173.12	1	Ribosome	1.51E-14	4.69E-12	4.06	129.18
2	NOD-like receptor signaling pathway	9.64E-13	1.51E-10	3.9	108.02	2	Coronavirus disease	4.41E-12	6.85E-10	2.98	78.05
3	Hepatitis B	2.09E-10	2.18E-08	3.65	81.42	3	Herpes simplex virus 1 infection	2.34E-08	2.42E-06	1.93	33.87
4	Toxoplasmosis	1.33E-08	0.000001037	3.93	71.23	4	Th17 cell differentiation	3.23E-08	2.51E-06	3.47	59.87
5	Measles	1.81E-08	0.000001134	3.48	62.03	5	T cell receptor signaling pathway	1.78E-07	0.00001107	3.32	51.53
6	TNF signalling pathway	5.22E-08	0.00000272	3.75	62.85	6	Hematopoietic cell lineage	1.88E-06	0.00009752	3.1	40.85
7	Cellular senescence	1.15E-07	0.000005158	3.11	49.64	7	Th1 and Th2 cell differentiation	3.73E-06	0.0001657	3.12	38.95
8	Influenza A	1.59E-07	0.000006235	2.95	46.1	8	NF-kappa B signalling pathway	1.68E-05	0.0006515	2.75	30.28
9	Hepatitis C	4.23E-07	0.00001472	2.97	43.54	9	Primary immunodeficiency	0.00002252	0.0007782	4.63	49.56
10	Human T-cell leukaemia virus 1 infection	6.73E-07	0.00002106	2.55	36.26	10	Human T-cell leukaemia virus 1 infection	0.00005237	0.001629	2	19.75
Reactome 2016											
1	Immune system homo sapiens R-HSA-168256	9.35E-20	1.20E-16	2.07	90.9	1	L13a-mediated translational silencing of ceruloplasmin	1.06E-33	7.04E-31	11.95	907.58
2	IFN signaling homo sapiens R-HSA-913531	2.67E-14	1.71E-11	4.02	125.62	2	3’ -UTR-mediated translational regulation homo sapien	1.06E-33	7.04E-31	11.95	907.58
3	IFN alpha/beta signaling homo sapiens R-HSA-909733	5.40E-14	2.30E-11	8	244.26	3	GTP hydrolysis and joining of the 60S ribosomal subuni	2.44E-33	1.08E-30	11.66	875.68
4	Cytokine signalling in immune system homo sapiens R-HSA-1	1.18E-11	3.77E-09	2.24	56.25	4	Formation of a pool of free 40S subunits homo sapiens	4.36E-33	1.44E-30	13.19	983.08

Contd...

Upregulated genes						Downregulated genes					
Index	Name	*P*	Adjusted *P*	OR	Combined score	Index	Name	*P*	Adjusted *P*	OR	Combined score
Reactome 2016											
5	IFN gamma signaling homo sapiens R-HSA-877300	1.76E-11	4.50E-09	5.38	133.12	5	Gene expression homo sapiens R-HSA-74160	3.87E-32	1.03E-29	2.22	160.35
6	Hemostasis homo sapiens R-HSA-109582	2.42E-08	0.000005155	2.03	35.68	6	Cap-dependent translation initiation homo sapiens R-	5.52E-32	1.05E-29	10.33	743.31
7	Cell cycle, mitotic homo sapiens R-HSA-69278	6.58E-08	0.00001203	2.1	34.74	7	Eukaryotic translation initiation homo sapiens R-HSA-7	5.52E-32	1.05E-29	10.33	743.31
8	Innate immune system homo sapiens R-HSA-168249	2.83E-07	0.00004517	1.76	26.49	8	Peptide chain elongation homo sapiens R-HSA-156902	4.18E-31	6.93E-29	14.44	1010.02
9	Cell cycle homo sapiens R-HSA-1640170	0.000001127	0.0001517	1.86	25.5	9	Eukaryotic translation elongation homo sapiens R-HSA	3.09E-30	4.10E-28	12.86	873.97
10	TLR4 cascade homo sapiens R-HSA-16	0.000001279	0.0001517	3.19	43.3	10	NMD independent of the	3.09E-30	4.10E-28	12.86	873.97
DisGeNET											
1	Influenza	7.90E-20	6.35E-16	2.87	126.25	1	Chronic lymphocytic leukaemia	5.02E-09	4.01E-05	1.63	31.06
2	Lupus erythematosus, systemic	3.24E-18	1.30E-14	2.21	89.13	2	Lymphoma	1.02E-07	2.78E-04	1.52	24.42
3	Breast Carcinoma	2.15E-17	5.76E-14	1.59	61.08	3	T-Cell Lymphoma	1.04E-07	2.78E-04	2.13	34.17
4	Malignant neoplasm of breast	2.90E-17	5.82E-14	1.59	60.37	4	HIV coinfection	4.65E-07	9.29E-04	3.21	46.87
5	Neoplasm metastasis	1.84E-16	2.94E-13	1.62	58.69	5	Leukemia	9.12E-07	0.001458	1.39	19.28
6	Leukemia	2.20E-16	2.94E-13	1.84	66.48	6	Pallor	2.05E-06	0.002729	4.15	54.35
7	Leukemia, myelocytic, acute	9.01E-16	9.60E-13	1.88	65.06	7	Lymphoma, T-cell, cutaneous	2.46E-06	0.002807	2.1	27.14
8	Rheumatoid arthritis	9.56E-16	9.60E-13	1.85	63.81	8	Peripheral T-cell lymphoma	4.04E-06	0.003967	2.72	33.83
9	Liver cirrhosis, experimental	1.40E-15	1.25E-12	2.31	79	9	Reticulocyte count (procedure)	5.53E-06	0.003967	2.23	26.96
10	Malignant neoplasm of prostate	1.92E-15	1.55E-12	1.64	55.62	10	Leukaemia, T-cell	5.55E-06	0.003967	1.86	22.51
Drug perturbations from GEO up						Drug perturbations from GEO down					
1	IFN beta-1a DB00060 human GSE26104 sample 3187	2.56E-60	2.32E-57	7.12	976.82	1	Mycophenolic acid DB01024 human GSE14630 sample	1.25E-20	1.13E-17	3.82	175.18

Contd...

Upregulated genes						Downregulated genes					
Index	Name	*P*	Adjusted *P*	OR	Combined score	Index	Name	*P*	Adjusted *P*	OR	Combined score
Drug perturbations from GEO up						Drug perturbations from GEO down					
2	IFN beta-1a DB00060 human GSE26104 sample 3186	2.25E-55	1.02E-52	6.37	802.17	2	Etanercept DB00005 human GSE7524 sample 3295	8.24E-20	3.72E-17	3.1	136.14
3	IFN beta-1a DB00060 human GSE26104 sample 3188	2.30E-48	6.95E-46	6.31	692.02	3	Motexafin gadolinium (4 h) DB05428 human GSE2189 s	4.70E-18	1.41E-15	3.28	130.89
4	IFN-Î²-1b (Betaferon) DB00068 human GSE26104 sam	5.91E-47	1.34E-44	6.12	651.95	4	Resveratrol DB02709 human GSE36930 sample 3497	3.21E-17	7.24E-15	3.13	119.02
5	IFN beta-1b DB00068 human GSE26104 sample 3185	4.25E-43	7.69E-41	6.17	601.78	5	Zinc acetate 11192 human GSE2964 sample 3589	5.19E-17	9.36E-15	4.06	152.08
6	Lipopolysaccharide 11970143 human GSE40885 sample 2475	6.01E-42	9.07E-40	6.14	583.21	6	Tibolone 444008 human GSE12446 sample 3204	1.99E-16	3.00E-14	3.07	110.81
7	Quercetin 5280343 human GSE13899 sample 3182	4.45E-36	5.75E-34	5.71	464.93	7	Estradiol 5757 human GSE4668 sample 3063	4.25E-16	5.48E-14	3.5	123.81
8	Lipopolysaccharide 11970143 human GSE3140 sample 3594	9.01E-34	1.02E-31	5.16	392.58	8	Atorvastatin DB01076 human GSE11393 sample 3196	6.24E-16	7.04E-14	3.06	107.17
9	Lipopolysaccharide 11970143 human GSE5504 sample 3486	1.27E-33	1.27E-31	4.8	363.67	9	Estradiol DB00783 human GSE4668 sample 2727	2.82E-15	2.83E-13	3.28	109.78
10	Lipopolysaccharide 11970143 human GSE5504 sample 3485	4.31E-33	3.90E-31	4.42	329.03	10	Promyelocytic leukaemia DB00755 human GSE5007 sam	3.85E-15	3.47E-13	3.04	100.76

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TGF, tumor growth factor; IL, interleukin; TCR, T-cell receptor; TNF, tumor necrosis factor; RLR, RIG-I-like receptor; sJIA, systemic juvenile idiopathic arthritis; SLE, systemic lupus erythematosus; GEO, Gene Expression Omnibus; IFN, interferon; PD, parkinson’s disease; NMD, nonsense mediated decay; OR, odds ratio; TLR4, toll like receptor 4

Supplementary Table IIIA. HMDB-based enriched genes for CO_2, hexadecanoyl-CoA and palmitic acid responses from combined all severe Western samples

CO_2		Hexadecanoyl-CoA		Palmitic acid	
Gene	FC	Gene	FC	Gene	FC
CA12	1.23598	SPTLC1		ACOT7	
ALAS2	1.03539	ACOT7		ACSL1	
ALAS1	1.02261	SPTLC2		PPT1	
IDH1	1.73029	ACSL1		ACSL4	
PLOD3	1.5762	PPT1		ACSL3	
CSAD	1.32374	ACSL4			
PGD	1.21	ACADM			
UPB1	1.51613	ACSL3			
PISD	1.30123				
SPTLC1	1.03358				
SPTLC2	1.06864				
ASPH	1.77				
CA2	2.9536				
CA5A	2.39933				
CA4	1.41429				
HPD	1.98665				
DLD	1.19746				

Supplementary Table IIIB. Gene set enrichment of CO2 responsive genes from severe western samples (HMDB-based enriched) by Enrichr

Upregulated genes					
Index	Name	*P*	Adjusted *P*	OR	Combined score
	COVID-19 related gene sets 2021				
1	Top 500 up genes for SARS-CoV-2 infection in Rhesus macaqu	5.10E-04	3.62E-02	13.24	100.35
2	Top 500 upregulated genes for SARS-CoV-2 infection in huma	5.85E-04	3.62E-02	12.75	94.89
3	Top 500 upregulated genes for SARS-CoV-2 infection in huma	5.89E-04	3.62E-02	12.72	94.58
4	500 genes down-regulated by MHV-A59 in murine liver cells f	4.66E-03	1.21E-01	10.33	55.46
5	500 genes down-regulated by SARS-CoV-2 in human Organoid	5.43E-03	1.21E-01	9.77	50.94
6	447 genes down-regulated by SARS-CoV-2 infection in Vero E	5.86E-03	1.21E-01	9.5	48.8
7	Top 500 down genes for SARS-CoV-2 infection in Rhesus maca	6.24E-03	1.21E-01	9.28	47.12
8	Top 500 up genes for SARS-CoV-2 infection in Rhesus macaqu	6.82E-03	1.21E-01	8.97	44.76
9	Top 500 up genes for SARS-CoV-2 infection in Rhesus macaqu	7.19E-03	1.21E-01	8.8	43.43
10	500 genes up-regulated by SARS-CoV-2 in human Caco2 cells a	7.48E-03	1.21E-01	8.67	42.44
	HMDB metabolites				
1	Carbon dioxide (HMDB01967)	2.54E-41	3.80E-38	338470	31637759.6
2	Pyridoxal 5’-phosphate (HMDB01491)	1.23E-11	9.18E-09	181.12	4549.91
3	CO3 (HMDB03538)	2.54E-10	1.26E-07	682.87	15086.94
4	Coenzyme A (HMDB01423)	1.36E-08	0.00000506	91.08	1650.05
5	Oxoglutaric acid (HMDB00208)	2.59E-08	0.000007732	180.53	3153.79
6	Succinyl coenzyme A (HMDB01022)	1.85E-07	0.00004593	389.06	6032.53
7	Zinc (HMDB01303)	6.00E-07	0.0001279	78.52	1124.96
8	ACO (HMDB01206)	0.00001451	0.002707	79.08	881.06
9	Iron (HMDB00692)	0.00001813	0.003008	32.22	351.82
10	Formyl-CoA (HMDB03419)	0.00005275	0.007875	242.08	2384.53
	Disease perturbations from GEO up				
1	COPD - C0024117 hum	3.05E-04	7.32E-02	15.22	123.2
2	Huntington’s disease DOID-12858 human GSE24250 sample 4	8.07E-04	7.32E-02	19.43	138.37
3	Macular degeneration C0024437 human GSE1719 sample 46	1.33E-03	7.32E-02	16.26	107.61
4	Rheumatoid arthritis DOID-7148 human GSE15573 sample 904	1.58E-03	7.32E-02	15.3	98.69
5	Adenocarcinoma of lung C0152013 human GSE1987 sample 4	1.61E-03	7.32E-02	15.19	97.66
6	Cardiomyopathy DOID-0050700 human GSE9128 sample 781	1.77E-03	7.32E-02	14.71	93.23

Contd...

Upregulated genes					
Index	Name	*P*	Adjusted *P*	OR	Combined score
Disease perturbations from GEO up					
7	Essential Hypertension C0085580 rat GSE1675 sample 412	1.93E-03	7.32E-02	14.25	89.11
8	Hepatitis C DOID-1883 human GSE20948 sample 597	1.96E-03	7.32E-02	14.16	88.24
9	Adenocarcinoma of esophagus C0279628 human GSE1420 sa	2.30E-03	7.32E-02	13.38	81.31
10	Esophagus adenocarcinoma DOID-4914 human GSE1420 samp	2.38E-03	7.32E-02	13.21	79.8
WikiPathway 2021 Human					
1	Heme Biosynthesis WP561	2.44E-05	0.0007562	380.5	4041.3
2	TCA Cycle and Deficiency of Pyruvate Dehydrogenase complex	0.00008103	0.001256	190.18	1791.63
3	Sphingolipid Metabolism (general overview) WP4725	0.0001856	0.001563	120.98	1039.39
4	Sphingolipid Metabolism (integrated pathway) WP4726	0.0002017	0.001563	115.71	984.56
5	Sphingolipid pathway WP1422	0.0002917	0.001808	95.02	773.48
6	Proximal tubule transport WP4917	0.001056	0.005455	48.31	331.09
7	Amino Acid metabolism WP3925	0.002664	0.0118	29.8	176.68
8	Pentose Phosphate Metabolism WP134	0.005936	0.023	208.09	1066.85
9	Cytosine methylation WP3585	0.007625	0.02624	156.05	760.96
10	Trans-sulfuration pathway WP2333	0.008469	0.02624	138.71	661.82
KEGG 2021 Human					
1	Nitrogen metabolism	8.44E-10	2.87E-08	472.66	9875.27
2	Glycine, serine, and threonine metabolism	0.000004942	0.00008402	115.52	1411.36
3	Proximal tubule bicarbonate reclamation	0.0001702	0.001929	126.74	1099.91
4	Citrate cycle (TCA cycle)	0.0002917	0.002479	95.02	773.48
5	Porphyrin and chlorophyll metabolism	0.0006016	0.004091	64.85	480.94
6	Sphingolipid metabolism	0.0007811	0.004426	56.56	404.65
7	Glutathione metabolism	0.001056	0.005129	48.31	331.09
8	Lysine degradation	0.001288	0.005475	43.55	289.77
9	Sphingolipid signaling pathway	0.004503	0.01701	22.64	122.32
10	Taurine and hypotaurine metabolism	0.009313	0.02878	124.83	583.76
Reactome 2016					
1	Metabolism Homo sapiens R-HSA-1430728	5.30E-14	2.70E-12	71.67	2190.93
2	Reversible hydration of carbon dioxide Homo sapiens R-HSA-1	1.76E-10	4.49E-09	768.27	17255.78
3	Erythrocytes take up oxygen and release carbon dioxide Hom	0.00001898	0.0003227	443.93	4826.43
4	Heme biosynthesis Homo sapiens R-HSA-189451	0.00003723	0.0003796	295.91	3017.8
5	Erythrocytes take up carbon dioxide and release oxygen Hom	0.00004466	0.0003796	266.31	2667.47
6	O_2/CO_2 exchange in erythrocytes Homo sapiens R-HSA-14809	0.00004466	0.0003796	266.31	2667.47
7	Metabolism of porphyrins Homo sapiens R-HSA-189445	0.00009179	0.0006688	177.49	1649.98

Contd...

Upregulated genes					
Index	Name	*P*	Adjusted *P*	OR	Combined score
Disease perturbations from GEO up					
8	Metabolism of lipids and lipoproteins Homo sapiens R-HSA-55	0.0001702	0.001085	12.31	106.87
9	Sphingolipid de novo biosynthesis Homo sapiens R-HSA-1660	0.0003535	0.002003	85.82	682.02
10	Histidine, lysine, phenylalanine, tyrosine, proline, and tryptoph	0.0005468	0.002789	68.18	512.16
DisGeNET					
1	Acute intermittent porphyria	6.16E-06	0.002821	106.84	1281.71
2	Intellectual disability	7.79E-06	0.002821	10.02	117.89
3	Distal sensory impairment of all modalities	0.00002439	0.004493	380.5	4041.3
4	Metabolic acidosis	0.00002695	0.004493	63.7	670.18
5	Erythropoietic Protoporphyria	0.00003723	0.004493	295.91	3017.8
6	Sensory Neuropathy, Hereditary	0.00003723	0.004493	295.91	3017.8
7	Hereditary Sensory and Autonomic Neuropathies	0.00008103	0.007384	190.18	1791.63
8	Neuropathy	0.00008188	0.007384	21.65	203.75
9	Hereditary Sensory Autonomic Neuropathy, Type 1	0.00009179	0.007384	177.49	1649.98
10	Glaucoma	0.0002535	0.0167	16	132.5
Drug perturbations from GEO up					
1	Haloperidol 3559 mouse GSE6511 sample 2471	2.56E-04	3.77E-02	15.96	131.98
2	Ubiquinol 9962735 mouse GSE15129 sample 3465	2.69E-04	3.77E-02	15.75	129.44
3	Fenretinide 5288209 rat GSE3952 sample 3559	3.15E-04	3.77E-02	27.06	218.21
4	Quercetin DB04216 mouse GSE38136 sample 3437	5.71E-04	4.70E-02	12.83	95.82
5	Curcumin 969516 human GSE16160 sample 3425	1.01E-03	4.70E-02	17.93	123.64
6	Troglitazone DB00197 rat GSE21329 sample 2832	1.09E-03	4.70E-02	17.48	119.28
7	Quercetin DB04216 mouse GSE38136 sample 3438	1.21E-03	4.70E-02	16.85	113.2
8	Rosiglitazone DB00412 human GSE5679 sample 2809	1.36E-03	4.70E-02	16.13	106.42
9	Rosiglitazone 77999 rat GSE5509 sample 3567	1.58E-03	4.70E-02	15.3	98.69
10	Methylprednisolone 6741 rat GSE490 sample 3673	1.58E-03	4.70E-02	15.3	98.69

OR, odds ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; GEO, Gene Expression Omnibus; COPD, chronic obstructive pulmonary disease

Supplementary Table IIIC. Nutrigenomics (blood transcriptome) analysis of CO_2 responsive genes from severe western samples (HMDB-based enriched) using NutriGenomeDB

Experiment info	Genes	Nes	Molecular function enrichment
GSE20940 MACROPHAGES LACTOBACILLUSRHAMNOSUS (LC705) 6H Details	3	0.8101309	Analysis
GSE20940 MACROPHAGES LACTOBACILLUSRHAMNOSUS (LGG) 24H Details	3	−0.5839413	Analysis
GSE20940 MACROPHAGES LACTOBACILLUSRHAMNOSUS (LC705) 24H Details	3	-0.5604759	Analysis
GSE20940 MACROPHAGES LACTOBACILLUSRHAMNOSUS (LGG) 6H Details	1	0.7909029	Analysis
GSE10896 U937MONOCYTES CURCUMIN 18H Details	5	0.7564358	Analysis
GSE10896 U937MONOCYTES CURCUMIN 4H Details	4	−0.80686986	Analysis
GSE20114 PATIENTS ERYTHROCYTES DHA Details	2	−0.90099186	Analysis

Supplementary Table IIID. Gene set enrichment of palmitic acid responsive genes from severe western samples (HMDB-based enriched) by Enrichr

Upregulated genes					
Index	Name	*P*	Adjusted *P*	OR	Combined score
COVID-19 related gene sets 2021					
1	332 proteins enriched in AP-MS using various SARS-CoV-2 pro	2.37E-04	1.16E-02	35.97	300.34
2	COVID19-All 332 protein host PPI from Krogan	2.37E-04	1.16E-02	35.97	300.34
3	Top 500 up genes for SARS-CoV-2 infection in Rhesus macaqu	6.70E-04	2.19E-02	24.98	182.55
4	COVID19-Nsp10 protein host PPI from Krogan	5.59E-03	4.80E-02	219.55	1138.86
5	SARS-CoV perturbation; 338 up genes from GEN3VA; Human	6.46E-03	4.80E-02	21.03	106
6	Down regulated gene from COVID-19 infected bronchoalveola	8.88E-03	4.80E-02	17.78	83.97
7	Top 500 upregulated genes in mouse fat with SARS-CoV-2 infe	9.49E-03	4.80E-02	17.16	79.91
8	Top 500 up genes for SARS-CoV-2 infection Day 21 in ferret rig	1.02E-02	4.80E-02	16.49	75.61
9	500 genes down-regulated by MHV-A59 in murine liver cells f	1.08E-02	4.80E-02	16	72.43
10	COVID19-M protein host PPI from Krogan	1.19E-02	4.80E-02	98.34	435.44
HMDB metabolites					
1	Hexadecanoyl-CoA (HMDB01338)	1.70E-24	2.73E-23	159800	8745757.6
2	Coenzyme A (HMDB01423)	3.74E-16	2.99E-15	1565.4	55606.06
3	Palmitic acid (HMDB00220)	4.20E-15	2.24E-14	3700.56	122502.6
4	L-Serine (HMDB00187)	1.27E-05	0.00005084	555	6256.61
5	Adenosine monophosphate (HMDB00045)	8.59E-05	0.000271	51.1	478.47
6	Phosphoric acid (HMDB02142)	1.17E-04	0.000271	45.89	415.4
7	Pyrophosphate (HMDB00250)	1.19E-04	0.000271	45.71	413.26
8	Pyridoxal 5'-phosphate (HMDB01491)	0.0002965	0.000593	103.79	843.15
9	Carbon dioxide (HMDB01967)	0.0005509	0.0009794	75.39	565.75
10	Magnesium (HMDB00547)	0.000633	0.001013	25.48	187.64
Disease perturbations from GEO up					
1	Essential Hypertension C0085580 rat GSE1675 sample 412	1.75E-04	1.98E-02	39.92	345.32
2	Nicotine dependence DOID-0050742 human GSE6264 sample	3.28E-04	1.98E-02	32.08	257.37
3	Obesity C0028754 human GSE474 sample 236	3.31E-04	1.98E-02	32	256.41
4	Chronic myeloid leukemia DOID-8552 mouse GSE48438 sampl	3.55E-04	1.98E-02	31.22	247.98
5	Colitis DOID-0060180 human GSE6731 sample 761	3.86E-03	7.41E-02	27.55	153.1
6	Neurofibromatosis DOID-8712 mouse GSE1482 sample 665	4.65E-03	7.41E-02	25.01	134.32
7	Huntington's disease DOID-12858 human GSE1751 sample 79	4.92E-03	7.41E-02	24.26	128.9
8	Hyperlipidemia C0020473 rat GSE3512 sample 38	5.07E-03	7.41E-02	23.9	126.32

Contd...

Upregulated genes					
Index	Name	*P*	Adjusted *P*	OR	Combined score
Disease perturbations from GEO up					
9	Bacterial Infection C0004623 human GSE4748 sample 414	5.32E-03	7.41E-02	23.3	122.01
10	Hepatitis C DOID-1883 human GSE20948 sample 599	5.73E-03	7.41E-02	22.41	115.7
WikiPathway 2021 Human					
1	Mitochondrial LC-Fatty Acid Beta-Oxidation WP368	2.49E-11	5.24E-10	1536.85	37521.5
2	Fatty acid beta-oxidation WP143	4.85E-10	5.09E-09	665.4	14271.22
3	PPAR signaling pathway WP3942	7.97E-09	5.58E-08	316.33	5898.92
4	Omega-3/Omega-6 FA synthesis WP4723	1.53E-08	6.41E-08	1089.87	19615.82
5	Omega-9 FA synthesis WP4724	1.53E-08	6.41E-08	1089.87	19615.82
6	Fatty acid transporters WP5061	3.42E-08	1.20E-07	799.08	13737.58
7	Fatty Acid Biosynthesis WP357	6.45E-08	1.93E-07	630.73	10443.16
8	Ferroptosis WP4313	4.12E-07	0.000001082	323.59	4757.48
9	Cholesterol metabolism (includes both Bloch and Kandutsch-R	6.33E-07	0.000001476	278.36	3973.18
10	Thermogenesis WP4321	0.000008408	0.00001766	113.64	1328.04
KEGG 2021 Human					
1	Fatty acid degradation	1.29E-09	1.67E-08	511.62	10472.91
2	PPAR signalling pathway	1.20E-08	7.77E-08	284.6	5191.86
3	Fatty acid biosynthesis	3.42E-08	1.48E-07	799.08	13737.58
4	Ferroptosis	4.45E-07	0.000001445	315.06	4608.17
5	Adipocytokine signalling pathway	0.000002174	0.000005651	181.15	2361.98
6	Peroxisome	0.000003665	0.000007941	151.24	1893
7	Fatty acid elongation	0.00004889	0.0000908	266.23	2642.52
8	Thermogenesis	0.00008265	0.0001343	51.78	486.78
9	Sphingolipid metabolism	0.0001631	0.0002356	141.45	1233.64
10	Sphingolipid signaling pathway	0.0009602	0.001248	56.62	393.44
Reactome 2016					
1	Metabolism of lipids and lipoproteins Homo sapiens R-HSA-55	1.33E-12	1.60E-11	154728	4230838.99
2	Fatty Acyl-CoA Biosynthesis Homo sapiens R-HSA-75105	1.78E-12	1.60E-11	898.87	24319.3
3	Triglyceride Biosynthesis Homo sapiens R-HSA-75109	1.86E-11	1.12E-10	544.56	13454.14
4	Fatty acid, triacylglycerol, and ketone body metabolism Homo	4.19E-11	1.88E-10	281.25	6720.88
5	Synthesis of very long-chain fatty acyl-CoAs Homo sapiens R-H	6.27E-11	2.26E-10	1175	27604.36
6	Metabolism Homo sapiens R-HSA-1430728	6.77E-09	2.03E-08	144736	2722611.02
7	Sphingolipid de novo biosynthesis Homo sapiens R-HSA-1660	0.00007346	0.0001889	214.63	2043.05

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Upregulated genes					
Index	Name	*P*	Adjusted *P*	OR	Combined score
Reactome 2016					
8	Sphingolipid metabolism Homo sapiens R-HSA-428157	0.0003727	0.0008387	92.22	728.06
9	PPARA activates gene expression Homo sapiens R-HSA-19897	0.0008665	0.001643	59.7	420.97
10	Regulation of lipid metabolism by Peroxisome proliferator-act	0.0009128	0.001643	58.12	406.8
DisGeNET					
1	Distal sensory impairment of all modalities	5.03E-06	0.001095	951.67	11609.88
2	Sensory neuropathy, Hereditary	7.69E-06	0.001095	740.11	8715.63
3	Hereditary sensory and autonomic neuropathies	0.00001675	0.001353	475.67	5230.88
4	Hereditary sensory autonomic neuropathy, Type 1	0.00001898	0.001353	443.93	4826.43
5	Pain Disorder	0.00006056	0.003452	237.67	2308.19
6	Sensorimotor neuropathy	0.00009771	0.004094	184.78	1706.14
7	Arthritis, adjuvant-induced	0.0001313	0.004094	158.33	1415.15
8	Arthritis, collagen-induced	0.0001313	0.004094	158.33	1415.15
9	Arthritis, experimental	0.0001313	0.004094	158.33	1415.15
10	Dysautonomia, familial	0.0001436	0.004094	151.12	1337.16
Drug perturbations from GEO up					
1	Rosiglitazone 77999 mouse GSE11343 sample 2672	1.34E-04	7.16E-03	43.83	390.87
2	Triiodothyronine-[13C6] hydrochloride (T3 thyronine) 534422	1.82E-04	7.16E-03	39.38	339.11
3	Perfluorooctanoic Acid 9554 mouse GSE13044 sample 3517	1.91E-04	7.16E-03	38.73	331.59
4	Lapatinib DB01259 human GSE38376 sample 2586	1.93E-04	7.16E-03	38.6	330.12
5	Triiodothyronine-[13C6] hydrochloride (T3 thyronine) 534422	1.97E-04	7.16E-03	38.35	327.21
6	Perfluorooctanoic acid 9554 mouse GSE13044 sample 3516	2.12E-04	7.16E-03	37.36	316
7	Triiodothyronine-[13C6] hydrochloride (T3 thyronine) 534422	2.14E-04	7.16E-03	37.24	314.64
8	Triiodothyronine-[13C6] hydrochloride (T3 thyronine) 534422	2.39E-04	7.16E-03	35.86	299.09
9	Pioglitazone DB01132 rat GSE21329 sample 2842	2.76E-04	7.16E-03	34.07	279.14
10	TRIIODOTHYRONINE-[13C6] hydrochloride (T3 thyronine) 534422	3.08E-04	7.16E-03	32.81	265.33

GEO, Gene Expression Omnibus; OR, odds ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; HMDB, human metabolome database; MHV, mouse hepatitis virus; PPI, propetin protein interaction; PPAR, peroxisome proliferator-activated receptor

Supplementary Table IIIE. Nutrigenomics (blood transcriptome) analysis of all Indian and western samples

GEO ID	Cell/cell line	Treatment/food/nutrient	Asymp_Ind (S)		Severe_Ind (S)		Severe_Ind (N)		Severe_Greece		Severe_USA		Severe_Spain	
			Genes	NES	Genes	NES			Genes	NES	Genes	NES	Genes	NES
GSE20940	Macrophages	Macrophages *L. rhamnosus* (LC705) -24H	130	4.1646204	190	3.1264043	104	0.91462755	458	3.1838264	306	0.788777	17	−0.995084
GSE20940	Macrophages	Macrophages *L. rhamnosus* (LGG)-24H	131	4.0703416	185	2.9378035	104	−0.45948756	402	2.345102	298	1.211781	17	−0.896059
GSE20940	Macrophages	Macrophages *L. rhamnosus* (LC705) -6H	113	3.0153298	163	2.2732701	92	−0.47376412	359	2.0160742	284	0.945468	20	1.375418
GSE20940	Macrophages	Macrophages *L. rhamnosus* (LGG) -6H	115	2.938601	177	1.8950764	94	0.65645915	382	1.9588804	287	0.774275	19	1.473976
GSE10896	Monocytes	Monocytes Curcumin - 18H	100	1.5762284	138	0.8184068	93	0.8737108	229	−1.129351	243	−0.816069	1	−0.911989
GSE10896	Monocytes	Monocytes Curcumin - 4H	76	1.296273	123	0.7495827	95	1.1188513	196	−1.4995713	211	−1.254086	3	−1.422674
GSE20114	Erythrocytes	Erythrocytes DHA	95	1.069365	98	−0.59336984	99	−0.44983175	227	−0.57671726	234	−1.493321	2	1.291555

NOG calculation

			Asymp Ind (S)	Severe Ind (S)	Severe Ind (N)	Severe Ind (Combined)	Severe Greece	Severe USA	Severe Spain	West (Combined)
GSE20940	Macrophages	Macrophages *L. rhamnosus* (LC705) -24H	130	190	104	243	458	306	17	682
GSE20940	Macrophages	Macrophages *L. rhamnosus* (LGG)-24H	131	185	104	243	402	298	17	635
GSE20940	Macrophages	Macrophages *L. rhamnosus* (LC705) -6H	113	163	92	229	359	284	20	568
GSE20940	Macrophages	Macrophages *L. rhamnosus* (LGG) -6H	115	177	94	214	382	287	19	595
GSE10896	Monocytes	Monocytes Curcumin - 18H	100	138	93	189	229	243	1	417
GSE10896	Monocytes	Monocytes Curcumin - 4H	76	123	95	163	196	211	3	363
GSE20114	Erythrocytes	Erythrocytes DHA	95	98	99	143	227	234	2	425
				NES-based analysis						
GSE20940	Macrophages	Macrophages *L. rhamnosus* (LC705) -24H	4.1646204	3.1264043	0.91462755	2.6152196	3.1838264	0.78877735	−0.9950839	1.5016583
GSE20940	Macrophages	Macrophages *L. rhamnosus* (LGG)-24H	4.0703416	2.9378035	−0.45948756	2.390768	2.345102	1.2117805	−0.8960592	1.4213064
GSE20940	Macrophages	Macrophages *L. rhamnosus* (LC705) -6H	3.0153298	2.2732701	−0.47376412	1.5741	2.0160742	0.94546837	1.375418	−0.80026525

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NES-based analysis										
			Asymp Ind (S)	Severe Ind (S)	Severe Ind (N)	Severe Ind (Combined)	Severe Greece	Severe USA	Severe Spain	West (Combined)
GSE20940	Macrophages	Macrophages *L. rhamnosus* (LGG) -6H	2.938601	1.8950764	0.65645915	1.9463556	1.9588804	0.7742753	1.4739759	1.0705541
GSE10896	Monocytes	Monocytes Curcumin - 18H	1.5762284	0.8184068	0.8737108	0.9986717	−1.129351	−0.8160694	−0.91198856	−1.0653994
GSE10896	Monocytes	Monocytes Curcumin - 4H	1.296273	0.7495827	1.1188513	0.8244213	−1.4995713	−1.2540859	−1.4226735	−3.610044
GSE20114	Erythrocytes	Erythrocytes DHA	1.069365	−0.59336984	−0.44983175	−0.7448559	−0.57671726	−1.4933206	1.291555	−1.0177021

GEO, Gene Expression Omnibus; NES, net enrichment score; NOG, number of overlapping genes; *L. rhamnosus, Lactobacillus rhamnosus*