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RESEARCH ARTICLE

Age-related gene expression alterations by SARS-CoV-2 infection contribute to poor prognosis in elderly

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Abstract. The ongoing pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has affected millions of people worldwide and with notable heterogeneity in its clinical presentation. Probability of contracting this highly contagious infection is similar across age groups but disease severity and fatality among aged patients with or without comorbidities are reportedly higher. Previous studies suggest that age associated transcriptional changes in lung and immune system results in a proinflammatory state and increased susceptibility to infectious lung diseases. Similarly, SARS-CoV-2 infection could augment ageing-related gene expression alterations resulting in severe outcomes in elderly patients. To identify genes that can potentially increase covid-19 disease severity in ageing people, we compared age associated gene expression changes with disease-associated expression changes in lung/BALF and whole blood obtained from publicly available data. We observed (i) a significant overlap of gene expression profiles of patients' BALF and blood with lung and blood of the healthy group, respectively; (ii) a more pronounced overlap in blood compared to lung; and (iii) a similar overlap between host genes interacting with SARS-CoV-2 and ageing blood transcriptome. Pathway enrichment analysis of overlapping gene sets suggest that infection alters expression of genes already dysregulated in the elderly, which together may lead to poor prognosis. eQTLs in these genes may also confer poor outcome in young patients worsening with age and comorbidities. Further, the pronounced overlap observed in blood may explain clinical symptoms including blood clots, strokes, heart attack, multi-organ failure etc. in severe cases. This model based on a limited patient dataset seems robust and holds promise for testing larger tissue specific datasets from patients with varied severity and across populations.

Keywords. covid-19; SARS-CoV-2; biomarker; transcriptional changes; eQTL variants; SARS-CoV-2 poor prognosis; ageing.

Introduction

Since December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), that causes COVID-19 in humans (Siordia 2020) has spread rapidly across the world and is classified as a global pandemic by the World Health Organization (coronavirus (COVID-19) events as they happen; https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen). As of 2 July 2020, there have been 10.6 million confirmed COVID-19 cases with 519,766 deaths reported worldwide (https://ourworldindata.org), with continuing trend of sharp rise in both these categories in many countries/regions. The disease is highly heterogenous in its clinical presentation with most common symptoms being fever, cough, shortness of breath and fatigue. In addition, myalgia, neurological symptoms, ischaemic and haemorrhagic strokes, muscle injury and gastrointestinal symptoms are also reported in a subset of patients (Harapan *et al.* 2020). Several clinical trials are ongoing but as of date, no drugs or other therapeutics have been approved by the U.S. Food and Drug Administration (FDA) to prevent or treat COVID-19 (Sanders *et al.* 2020) and thus clinical management includes infection prevention and supportive care (Sanders *et al.* 2020). Efforts to combat COVID-19 are severely hampered by grossly inadequate knowledge of several important aspects of the illness ranging

from pathogen biology to host response, disease biology, target tissues and consequently treatment options. Therefore, there is an urgent need for a deeper understanding of the host–pathogen interaction biology of SARS-CoV-2, which in turn may offer important insights into general/personalized treatment strategies and management of the disease as well as development of new therapies.

Probability of contracting this highly contagious infection has been reported to be similar across age groups but severe clinical manifestations and increased mortality has been reported in elderly patients (Cohen *et al.* 2020; Hauser *et al.* 2020; Meyerowitz-Katz and Merone 2020; Wu *et al.* 2020). These observations suggest that there may be a comparatively stronger association between age and poor prognosis of COVID-19, but this may well be multifactorial. Therefore, the uncovering mechanism(s) underlying poor prognosis to SARS-CoV-2 infection among the affected elderly might be insightful for effective patient management and treatment. Several reports suggest that with the ageing, elderly population becomes more susceptible to various infectious disorders (Meyer 2001; Gavazzi and Krause 2002; López-Otín *et al.* 2003; Meiners *et al.* 2015). With ageing, transcriptional dysregulation occurs in genes involved in cellular oxidant/antioxidant systems, proinflammatory mediators (C-reactive protein, tumour necrosis factor α (TNF-α), interleukins (IL) 6, 1β), and cell regenerations that might overlap with viral mediated dysregulation (Franceschi and Campisi 2014; Meiners *et al.* 2015; de Almeida *et al.* 2020; Fulop *et al.* 2018). Similarly in severe COVID-19 patients, a 'cytokine storm' comprised of TNF-α, IL 6, 1β, 8, 12, interferon-gamma inducible protein (IP10), macrophage inflammatory protein 1A (MIP1A), and monocyte chemoattractant protein 1 (MCP1) (Cascella *et al.* 2020) and hypercoagulable state with increased risk of venous thromboembolism (Cevik *et al.* 2020) has been observed.

Based on this limited understanding, we hypothesize that SARS-CoV-2 mediated transcriptional alterations may overlap with age mediated expression changes. Thus, expression of genes that changes during ageing, might get further augmented on SARS-CoV-2 infection, leading to severe outcome in elderly patients. We attempted to explore this possibility by performing comparative transcriptomics using available data from two target tissues, namely lung and blood in healthy ageing group and COVID-19 patients. We also compared transcriptomic profile of ageing lung and blood with host genes interacting with SARS-CoV-2 protein. We observed a significant overlap between gene expression profile in both lung and blood of healthy ageing group and COVID-19 patients; which was much more pronounced in blood. Further, there was a significant overlap between host genes interacting SARS-CoV-2 proteins in ageing blood but not in lungs. These observations support previous reports that SARS-COV-2, primarily affects the respiratory system but its effects may manifest in blood leading to multiorgan failure in severe cases of COVID-19 (Cascella *et al.* 2020; Varga *et al.* 2020).

Materials and methods

Study design

Identification of candidate genes: To identify the genes that determine poor prognosis in the elderly COVID-19 patients, we performed a comparative analysis of gene expression data as collected from bronchoalveolar-lavage fluid (BALF)/lung/blood from COVID-19 patients and healthy ageing group; and data of host genes interacting with SARS-CoV-2 proteins with transcription profile of ageing lung and blood (resources are mentioned below). This methodology was adopted from previous studies (Dugo *et al.* 2016; Elko *et al.* 2019). Overlaps between the following groups were documented: (i) patients' BALF with healthy ageing lung; (ii) patients' PBMCs with healthy ageing blood; (iii) host genes interacting with viral proteins with healthy ageing lung and blood.

Statistical analysis

Statistical significance of these overlaps, if any, were tested using hypergeometric test (http://nemates.org/MA/progs/overlap_stats_prog.html). Basic equation to find the probability of finding an overlap of genes using the above-mentioned program is provided in supplementary text.

Pathway analysis

Pathway enrichment of the significantly overlapping genes identified above was done using EnrichR (Chen *et al.* 2013; Kuleshov *et al.* 2016) which is an integrative web-based and mobile software application that currently includes 180,184 annotated gene sets from 102 gene set libraries and various interactive visualization approaches to display enrichment results using the JavaScrit library, Data Driven Documents.

eQTL analysis

eQTL variants of genes from significantly overlapping gene-sets for respective tissues (lung and blood) were obtained from GTEx v. 8 (https://gtexportal.org). With a view to obtain a universally applicable biomarker, a comparable minor allele frequency of the markers would be ideal and such a suitability was tested using F_{ST} or fixation index. This was done using 1000 genome phase 1 data with the help of an online tool SPSmart (http://spsmart.cesga.es) with F_{ST} (i) 0 to 0.05 representing low; (ii) 0.05 to 0.15, moderate; (iii) 0.15 to 0.25, high; and (iv) > 0.25, very high, genetic differentiation.

Identification of druggable targets

Finally, these genes identified above were screened for their druggability with FDA approved drugs using DGIdb website (http://dgidb.org).

Resources

Age associated genes: (i) Differentially expressed genes (DEGs) in lung and blood tissue identified in a recently published study using RNA-Seq based transcriptome profiles from human donors of various ages from GTEx (Yang *et al.* 2015) were enlisted. (ii) DEGs from two stage transcriptomic study performed in blood, based on meta-analysis data from six different studies (*n* = 7074 samples) in the discovery phase and 7909 additional whole-blood samples in the replication phase (Peters *et al.* 2015) were obtained.

These two datasets were merged for blood transcriptomics and all the protein coding genes (and not any small RNAs such as miRNA, lncRNA etc.) that were reported in either study were considered. All genes showing a different direction of expression change were removed from the analysis. A total of 2877 and 2283 protein coding genes were found to be upregulated and downregulated, respectively in blood of healthy ageing group. Similarly, a total of 363 and 592 protein coding genes were found to be upregulated and downregulated, respectively in ageing lung. These genes have been subsequently referred to as 'age-associated DEGs'.

SARS-CoV-2 associated genes: Henceforth the DEGs in COVID-19 positive patients are referred to as 'SARS-CoV-2-associated DEGs' and were obtained from two recent studies: (i) DEGs in BALFs identified comparing laboratory-confirmed COVID-19 patients (SARS2) (*n* = 8, median age 50.5 years) with healthy controls without known respiratory diseases (healthy) (*n* = 20) (Zhou *et al.* 2020). (ii) DEGs in PBMCs and BALF identified by comparing three COVID-19 patients (median age 37 years) and three healthy donors (Xiong *et al.* 2020).

BALF transcriptomics from these two datasets were merged and all the protein coding genes (and not any small RNAs such miRNA, lncRNA etc.) that are reported in either study were considered. All genes showing a different direction of expression change were removed from the analysis.

Host genes interacting with SARS-CoV-2 proteins: Host genes that were found to be interacting with SARS-COV-2 viral proteins henceforth referred as 'SARS-CoV2-interacting genes' and were collected from recent studies mentioned below. (i) Three hundred and thirty-two high-confidence SARS-CoV-2-human protein–protein interactions (PPIs) were obtained by analysing the data generated by expressing 26 of the 29 SARS-CoV-2 proteins in HEK293 cells in a recent study (Gordon *et al.* 2020). (ii) Computation and literature based interactome data that were generated using available sequences for viral protein candidates (such as wS, wORF3a, wE, wM, wORF6, wORF7a, wORF7b, wORF8, wN and wORF10) in a recent study (Srinivasan *et al.* 2020).

Results

Test of hypothesis (figure 1) by a comparative analysis of DEGs in the different sample sets described under study design (figure 2) revealed significant overlaps between them (table 1; table 1 in electronic supplementary material at http://www.ac.in/jgenet/), which are briefly presented below (table 1; table 1 in electronic supplementary material), are briefly presented below. The most notable findings include (i) significant overlap ($P < 1.4E-04$) between the upregulated SARS-CoV-2 associated DEGs in patients' BALF and upregulated age associated DEGs in healthy ageing. (ii) Significant overlap ($P < 6.53E-07$) between the upregulated SARS-CoV-2 associated DEGs in patients' PBMCs and upregulated age associated DEGs in healthy ageing blood. (iii) Nominally significant overlap ($P < 0.03$) between the downregulated SARS-CoV-2 associated DEGs in patients' PBMCs and downregulated age associated DEGs in healthy ageing blood. (iv) Significant overlap between the SARS-CoV-2 interacting genes and up ($P < 0.002$) / down ($P < 1.04E-06$) regulated age associated DEGs in healthy ageing blood (table 1; table 1 in electronic supplementary material).
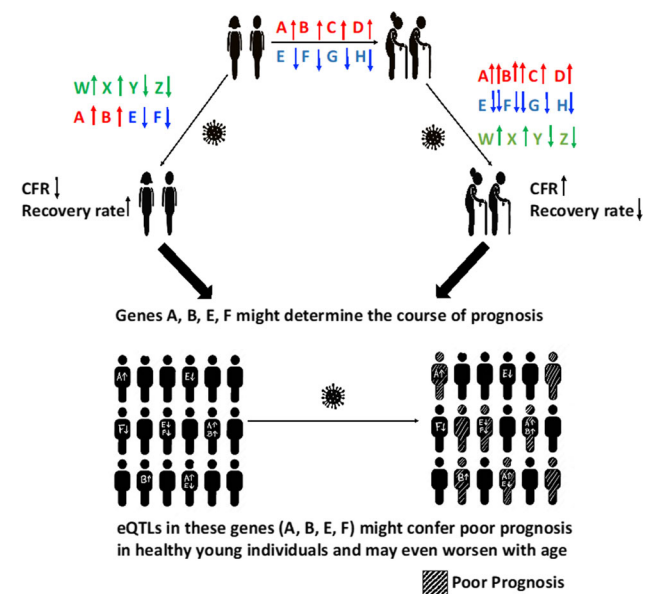

Figure 1. A schematic view of the hypothesis of cumulative gene expression changes leading to poor prognosis among the elderly COVID-19 patients.
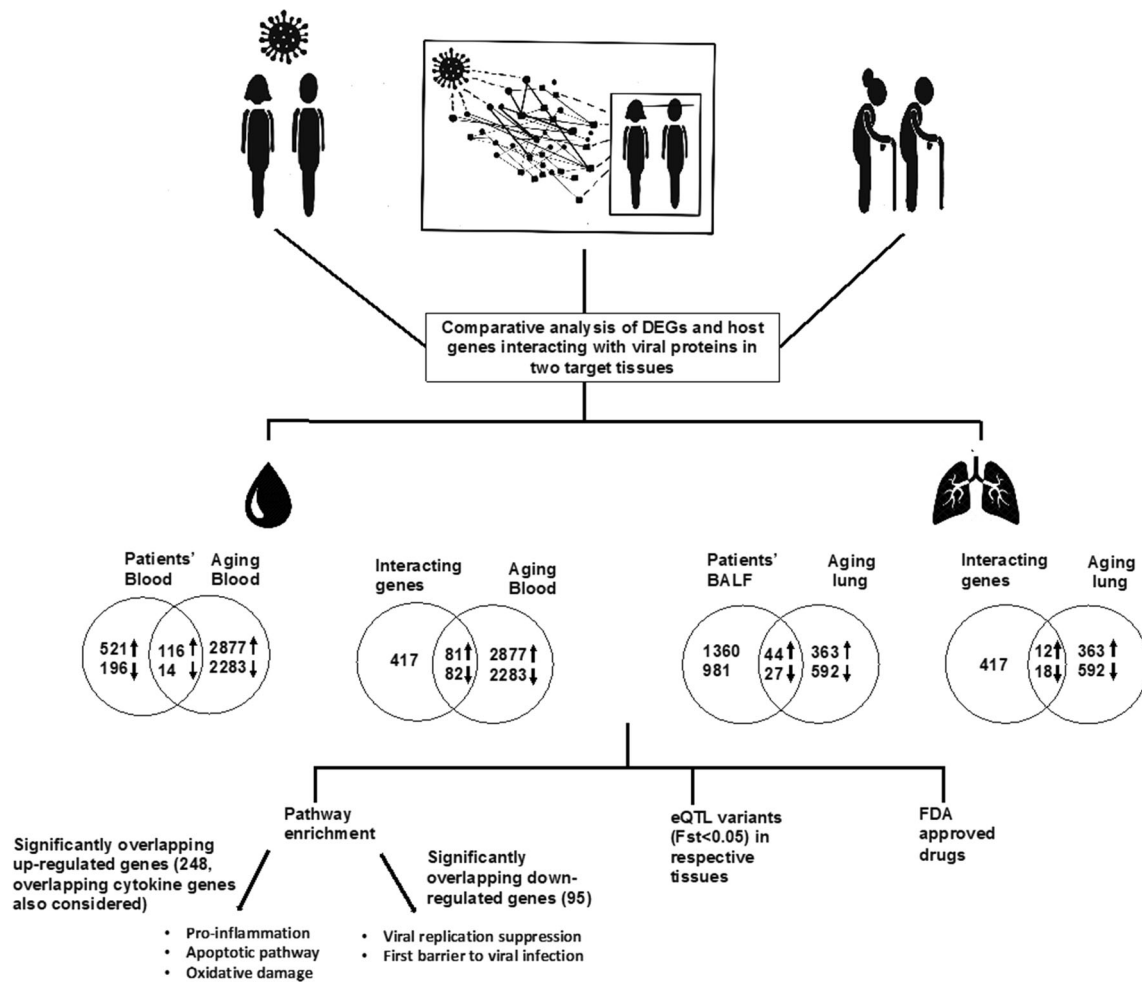
Figure 2. Workflow and results of the comparative transcriptomics across different study groups.

Table 1. The results of the comparative analysis of DEGs across different sample sets.

| | SARS-Cov-2 associated genes | | SARS-Cov-2 interacting genes | Age associated DEGs | | Number of common genes between study groups; *P* value | | | |
| | | | | | | | | | |
Direction of DEG	Patients' BALF	Patients' PBMCs		Ageing lung	Ageing blood	Patients' BALF and ageing lung	Patients' PBMCs and ageing blood	SARS-Cov2 interacting genes and ageing lung	SARS-Cov2_interacting genes with ageing blood
Up	1360	521	417	363	2877	44; 1.4E-04	116; 6.53E-07	12; 0.07	82; 0.002
Down	981	196		592	2283	27; 0.39	14; 0.03	18; 0.07	81; 1.04E-06

Pathway enrichment

As the number of genes in each gene-set was very small to identify the enriched pathways, if any, all the genes from significant gene-sets and showing change in same direction were considered together for pathway enrichment analysis. Cytokine genes that are frequently found to be upregulated in patients and which overlapped with healthy ageing expression profiles were also included. Six of the 21 upregulated cytokine genes in patients, overlapped with ageing related genes in the blood but none with ageing lung. Upregulated genes in the healthy ageing group that overlap with SARS-CoV-2 associated genes and SARS-CoV-2 interacting genes were seen to be enriched in a range
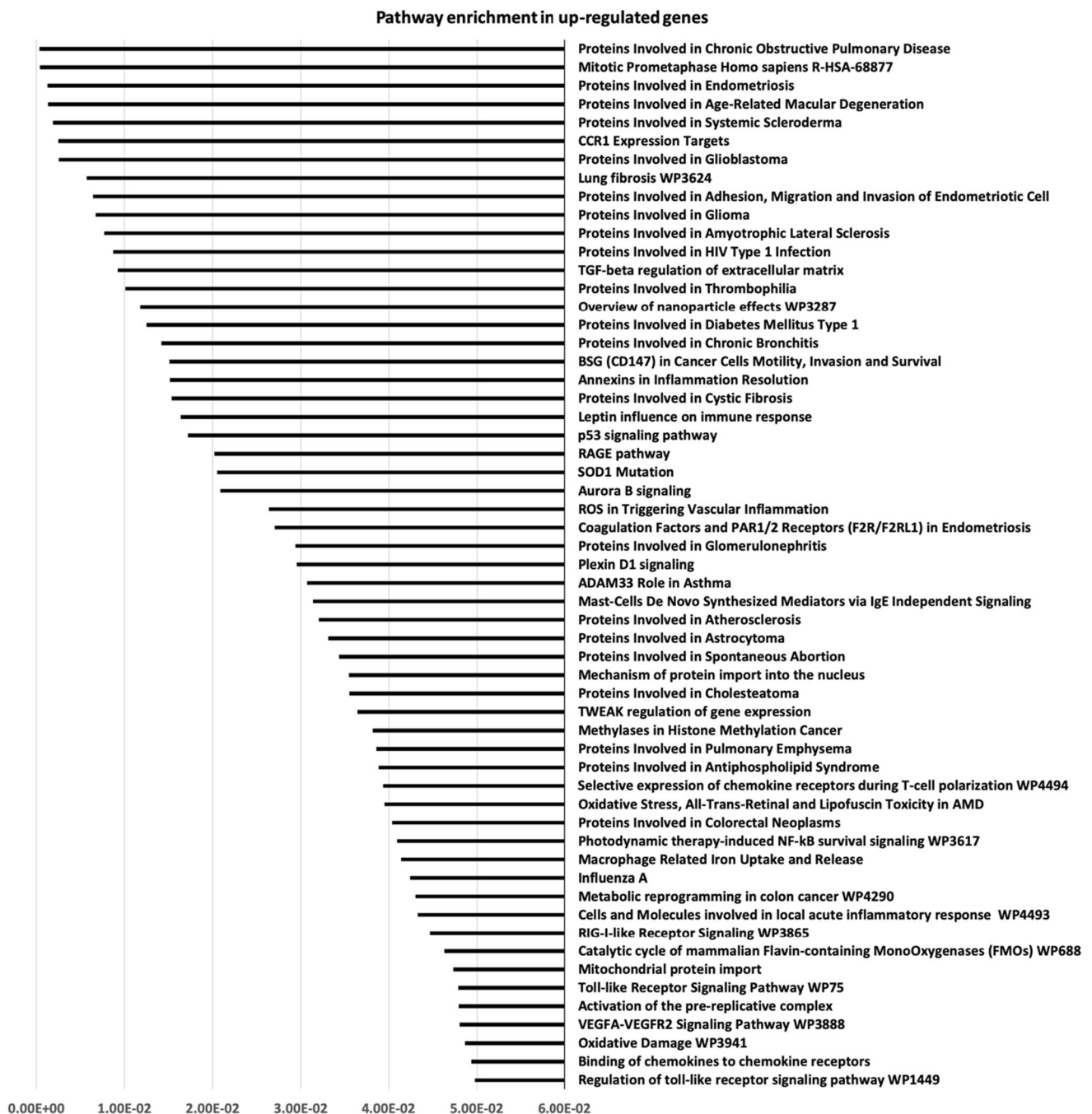
Pathway enrichment in up-regulated genes

Figure 3. Result of pathway enrichment analysis of upregulated genes in the healthy ageing group overlapping with SARS-CoV-2 associated genes and SARS-CoV-2 interacting genes.

of signalling pathways, including p53, chemokine and cytokine mediated inflammation, EGF receptor, TGF-beta, AGE-RAGE, Toll-like receptor mediated, NF-kappa B, VEGFA-VEGFR2 and genes involved in ROS in triggering vascular inflammation, oxidoreductive damage, T cell polarization, lung fibrosis, chronic obstructive pulmonary disorder (COPD), and local acute inflammatory response (representative pictures at figure 3; table 2 in electronic supplementary material). Downregulated genes in the healthy ageing group that overlap SARS-CoV-2 associated and SARS-CoV-2 interacting genes were seen to be enriched in pathways such as PI3K-Akt-mTOR-signalling, membrane trafficking, HIV and influenza RNA transport, ISG15 antiviral mechanism, cellular export machinery that interacts with NEP/NS2 (representative pictures at figure 4; table 3 in electronic supplementary material).

Pathway enrichment in down-regulated genes

Figure 4. Result of pathways enrichment analysis of downregulated genes in the healthy ageing group overlapping with SARS-CoV-2 associated genes and SARS-CoV-2 interacting genes.

eQTL analysis

eQTL variants in genes from significantly overlapping gene-sets from the respective tissues namely lung and blood were identified (table 2; table 4 in electronic supplementary material). F_{ST} test was performed to identify the variants with low genetic differentiation among different population. A large number of eQTL variants with $F_{ST} < 0.05$ were found in each group (table 2; table 4 in electronic supplementary material). Further analysis of these may enable identification of variant(s) which could be used as a biomarker(s).

Table 2. Number of genes with significant eQTL variants in each group and number of variants with $F_{ST}<0.05$ among them.

Direction of expression change in patients and healthy ageing group	Upregulated				Downregulated	
Gene-set common between study groups (n)	Patients' BALF and ageing lung (44)	Patients' PBMCs and ageing blood (116)	SARS-CoV-2 interacting genes with ageing blood (82)	Cytokine and ageing blood (6)	Patients' PBMCs and ageing blood (14)	SARS-CoV-2 interacting with ageing blood (81)
Number of eGenes in GTEx dataset (n)	22	58	44	3	8	49
Total number of eQTL variants	1163	2717	2118	72	90	2269
Number of variants with $F_{ST} < 0.05$	395	1215	1611	40	34	1302

Identification of druggable gene targets

It may be mentioned that SARS-CoV-2 interacting genes were excluded from this analysis since they have already been reported previously (Gordon *et al.* 2020). Efforts to identify novel druggable targets for FDA approved drugs from among 259 genes from significantly overlapping gene sets between different groups shown above (table 1), yielded a total of 48 druggable genes mostly from the immune system related pathways. A total of 205 FDA approved drugs could potentially target them (table 5 in electronic supplementary material).

Discussion

COVID-19, the recent pandemic has affected individuals of all age groups as well as all ethnicities. However, poor prognosis has been witnessed in the elderly effected group with or without comorbidities (Hauser *et al.* 2020; Cohen *et al.* 2020; Meyerowitz-Katz and Merone 2020; Wu *et al.* 2020). The overall case fatality rate (CFR) for cases with age 70 to 79 years is 8.0% and for cases with age 80 years and above it is 14.8%; which is strikingly higher compared to 0.4% in cases below 50 years of age, based on a study that included 72314 cases from China (Wu and McGoogan 2020). It is well known that with ageing there is a notable increase in circulating proinflammatory cytokines even in the absence of an immunological threat and also a reduction in proteins that maintain homeostasis of the immune system, thus entailing a greater risk for many diseases (cancer, cardiovascular and neurodegenerative disorders, COPD, lung cancer, interstitial lung disease etc.) (Panda *et al.* 2009; López-Otín *et al.* 2013; Meiners *et al.* 2015; Angelidis *et al.* 2019). Thus, we reasoned that comparing naturally occurring, age-dependent transcriptional changes with those observed in COVID19 patients and/or known SARS-COV-2 interacting proteins may provide insights into the age-associated poor prognosis in COVID-19.

Three noteworthy findings emerged from our study: (i) a significant overlap was witnessed between DEGs in patients' BALF/blood and in ageing lung and blood; (ii) this overlap was more pronounced in blood compared to lung; and (iii) a similar overlap between SARS-CoV-2 interacting proteins and DEGs in ageing blood but not in lung (table 1) and warrant discussion. Pathway enrichment analysis of the overlapped gene sets suggest that genes involved in pathways such as proinflammatory, apoptotic, T cell polarization, viral replication suppression (figures 3 & 4; tables 2 & 3 in electronic supplementary material) remain dysregulated in elderly patients. Upon SARS-CoV-2 infection, expression of these genes gets further dysregulated resulting in poor prognosis in case of elderly patients.

As for the second novel observation, the higher extent of overlap between SARS-CoV-2 associated / SARS-CoV-2 interacting genes and DEGs in blood among the heathy ageing group, may explain the range of clinical symptoms including high prevalence of blood clots, strokes and heart attack as well as multi-organ failure in a subset of severe patients reported in this disorder (Harapan *et al.* 2020; Cevik *et al.* 2020). Our observations are corroborated by a recent report of SARS-CoV-2 mediated damage to endothelial cells lining the blood vessels probably leading to blood clotting, strokes and heart attacks (Varga *et al.* 2020). We observed that proinflammatory genes such as *IFNG*, *CCL4*, *CCR9*, *BCL2*, *TIMP1*, *TNF*, *C2*, *CCR2*, *VEGFA* (table 1 in electronic supplementary material) remain upregulated in aged individuals which might cause the 'cytokine storm' observed in severe patients. Further, higher expression of these genes may lead to over activation of T cell polarization and TGF-beta pathways in affected elderly patients (figure 3), which can cause functional exhaustion of T cells (Swain *et al.* 2012; Kahan *et al.* 2015) that has been reported in elderly patients (Diao *et al.* 2020). Of note, one of these genes, namely *CCR9* was found to be significantly ($P = 1.15 \times 10^{-10}$) associated with COVID-19 in a recent genomewide association study that included 835 patients and 1255 control participants from Italy and 775 patients and 950 control

subjects from Spain (Ellinghaus *et al.* 2020), lending support to our findings.

Taken together these observations, eQTLs in the genes identified in our study (table 2; table 4 in electronic supplementary material) may also confer poor prognosis in young patients but this may worsen with age and comorbidities. However, their utility as prognostic biomarkers across different populations may be assessed only when more data of patients become available and these genes are characterized as COVID-19 patients. On the other hand, variants with $F_{ST} > 0.05$ may be tested for correlation with population specific severity. Additionally, identification of genes involved in influenza and HIV infection in our study (figures 3&4; tables 2&3 in electronic supplementary material) may be of considerable relevance for drug repurposing for treatment of COVID-19 patients.

In summary, our analysis (i) identified probable candidate genes for poor prognosis among the affected elderly group; (ii) identified potential druggable targets as well as FDA approved drugs opening the possibility of drug repurposing; and (iii) seems to provide early explanation for manifestation of blood related symptoms and probably multiorgan damage. Finally, although these leads are preliminary based on a very limited patient dataset, the model holds promise to be tested as and when more tissue specific patient derived data from different age groups and/or from different populations become available. Our study is limited by nonavailability of large tissue specific transcriptomic datasets of COVID-19 patients across age groups, and with varying severity and from different populations to validate the hypothesis.

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