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COVID-19 Severity Potentially Modulated by Cardiovascular-Disease-Associated Immune Dysregulation

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Abstract: Patients with underlying cardiovascular conditions are particularly vulnerable to severe COVID-19. In this project, we aimed to characterize similarities in dysregulated immune pathways between COVID-19 patients and patients with cardiomyopathy, venous thromboembolism (VTE), or coronary artery disease (CAD). We hypothesized that these similarly dysregulated pathways may be critical to how cardiovascular diseases (CVDs) exacerbate COVID-19. To evaluate immune dysregulation in different diseases, we used four separate datasets, including RNA-sequencing data from human left ventricular cardiac muscle samples of patients with dilated or ischemic cardiomyopathy and healthy controls; RNA-sequencing data of whole blood samples from patients with single or recurrent event VTE and healthy controls; RNA-sequencing data of human peripheral blood mononuclear cells (PBMCs) from patients with and without obstructive CAD; and RNA-sequencing data of platelets from COVID-19 subjects and healthy controls. We found similar immune dysregulation profiles between patients with CVDs and COVID-19 patients. Interestingly, cardiomyopathy patients display the most similar immune landscape to COVID-19 patients. Additionally, COVID-19 patients experience greater upregulation of cytokine- and inflammasome-related genes than patients with CVDs. In all, patients with CVDs have a significant overlap of cytokine- and inflammasome-related gene expression profiles with that of COVID-19 patients, possibly explaining their greater vulnerability to severe COVID-19.

Keywords: COVID-19; coronary artery disease; cardiomyopathy; venous thromboembolism event; inflammation

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1. Introduction

In December 2019, widespread infection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was reported in Wuhan, China [1]. Since then, SARS-CoV-2, which causes COVID-19, has spread rapidly, and COVID-19 was declared a pandemic by the World Health Organization (WHO) on 11 March 2020 [2] Current research suggests that patients with existing comorbidities, including hypertension, cardiovascular disease, diabetes, and obesity are more likely to develop severe COVID-19 [3–5]. COVID-19 has also been known to induce myocardial injury, arrhythmia, acute coronary syndrome, and venous thromboembolism (VTE) [6–8]. Such cardiovascular damage has been attributed to cytokine storms triggered by the SARS-CoV-2 infection that can cause multi-organ damage [9,10]. Additionally, COVID-19 patients experience coagulation abnormalities, possibly leading to an increased risk of thromboembolic events [11]. In multiple autopsy studies,

thromboembolic events were identified in patients who had COVID-19 [12,13]. Specifically, in Schurink et al., it was found in multiple organs, including but not limited to the brain, lungs, heart, and kidneys [13]. Undeniably, research suggests links between cardiovascular disease (CVD) and COVID-19. However, the mechanisms by which CVD results in poorer COVID-19 prognosis remains unclear. As CVD encompasses a wide range of specific disorders, it would be impractical to obtain a dataset for all these disorders. In this study, we focused on three of the most common cardiovascular conditions: cardiomyopathy, VTE, and CAD.

Cardiomyopathy refers to diseases of the myocardium associated with mechanical and/or electricdysfunction [14]. In nonischemic dilated cardiomyopathy (NIDCM), the heart's ventricles are enlarged [15]. Cytokines and inflammasomes are known to play significant roles in cardiomyopathy pathogenesis, which suggests a commonality between cardiomyopathy and COVID-19, where excess inflammation is often induced [16–18].

VTE includes deep vein thrombosis, where a blood clot forms in a deep vein, typically in the lower extremities or pelvis, which may dislodge and result in pulmonary embolism (PE). Similar to VTE, COVID-19 patients have increased oxidative stress, which is one of the hallmarks for endothelial damage [19–21]. Additionally, COVID-19 patients have been shown to be at risk of thrombotic events [22–24]. Interestingly, in COVID-19 patients with thrombotic events, their D-dimer levels were found to be increased [23,24]. It is well established that the immune system functions in deep vein thrombosis pathogenesis, and the restriction of venous blood flow leads to the recruitment of neutrophils, monocytes, and platelets [25–27]. Since higher levels of monocytes and neutrophils have been observed in COVID-19 patients requiring ICU hospitalization, it is possible that such pre-existing immune dysregulation in COVID-19 VTE patients increases their risk of progressing to severe disease [28–30].

Lastly, coronary artery disease (CAD) pathogenesis also has an established immunological component [31]. Higher levels of C-reactive protein (CRP) [32], leukocytes [33], and cytokines [34] are associated with both CAD and severe COVID-19 patients [35–37]. Moreover, excessive pro-inflammatory cytokine production is associated with vascular damage that induces uncontrolled blood clotting [38]. This not only suggests that CAD patients are more vulnerable to severe COVID-19 [39], but also suggests that COVID-19 may exacerbate CAD.

In this project, we aimed to characterize and compare the dysregulation of the immune landscape in patients with cardiomyopathy, VTE, CAD, and COVID-19. We analyzed the expression of cytokine genes and inflammasome-related genes, the extent of immune infiltration, and the enrichment of immunological pathways and signatures. By comparing these features of the immune system, we hoped to gain a more comprehensive understanding of the cardiovascular-disease-mediated immune dysregulation that leaves patients more vulnerable to severe COVID-19.

2. Materials and Methods

2.1. Downloading Data

RNA-sequencing data were obtained from the following datasets: GSE116250 [40], GSE19151 [41], GSE90074 [42], and SRP262885 [43]. GSE116250, provided by Sweet et al., consists of the RNA sequencing of human left ventricular samples from 14 patients with no major cardiac history (nonfailing), 37 patients with NIDCM, and 13 patients with ICM. GSE19151, provided by Lewis et al., consists of the high-throughput sequencing of whole blood samples from 63 healthy controls, 23 patients with single VTE, and 17 patients with recurrent VTE on warfarin. GSE90074 consists of the RNA-sequencing data of PBMCs from 93 patients with and 50 patients without CAD. Lastly, SRP262885 consists of the RNA-sequencing data of platelets from 10 COVID-19 subjects and 5 healthy controls.

2.2. Differential Expression

For the cardiomyopathy and VTE cohorts, the Kruskal–Wallis test ($p < 0.05$) was used to determine differentially expressed genes. CAD cohorts were analyzed using the GEO2R software, which employs the limma (linear models for microarray analysis) R package ($p < 0.05$). Differential expression was applied to the COVID-19 platelet data to determine the genes that were differentially expressed ($p < 0.05$).

2.3. GSEA

To correlate gene expression to immune-associated signatures, gene set enrichment analysis (GSEA) was utilized. Pathways were chosen from the C2: CP set of signatures from the Molecular Signatures Database [44]. Signatures that were significantly enriched were those with a nominal p-value < 0.05.

2.4. CIBERSORTx

The CIBERSORTx algorithm was used to deconvolute the RNA-sequencing data to estimate the infiltration levels of 22 immune cell types [45].

3. Results

3.1. Comparing Immune Profiles of COVID-19 and Cardiomyopathy Patients

3.1.1. Similarities in Immune-Associated Gene Dysregulation in COVID-19 and Cardiomyopathy

Gene dysregulation was determined by comparing COVID-19 and cardiomyopathy samples to healthy controls for each study. Cardiomyopathy samples were separated into patients with ischemic cardiomyopathy (ICM) or nonischemic dilated cardiomyopathy (NIDCM). The two groups were individually compared against samples from patients with no major cardiovascular disease (healthy controls).

We found a significant overlap between COVID-19 patients and ICM and NIDCM patients' immune-associated (IA) gene expression. About half of the IA genes dysregulated in COVID-19 are dysregulated in either or both types of cardiomyopathy (Figure 1A). A complete list of dysregulated IA genes are found in Appendix A, Table A1. Cytokine-related genes that are dysregulated in both cardiomyopathy patients and COVID-19 patients include chemokines (CCL3, CCL4, CXCL4, etc.), interleukins or interleukin receptors (IL15, IL20RA, etc.), and genes in the transforming growth factor beta (TGFB) family. The inflammasome-related genes include genes in the caspase family (CASP2, CASP9, etc.), mitogen-activated protein kinase (MAPK)-related genes, and nuclear factor-kB (NF-kB) regulators (IKBKG, NFKBIA, etc.). IA gene dysregulation was very similar between dilated and ischemic cardiomyopathies. We observed that a significant number of IA genes were dysregulated in either of the cardiomyopathies but not in COVID-19 (Figure 1A).

Interestingly, we found that most of the genes dysregulated in both COVID-19 and cardiomyopathy were dysregulated to a greater degree in COVID-19 than in cardiomyopathy samples. This was observed for TGFB3, CCL4, IL15, and IL20RA in both ICM samples vs. COVID-19 samples and NIDCM samples vs. COVID-19 samples (Figure 1B). Furthermore, these dysregulated genes appeared to be similarly dysregulated in COVID-19 and corresponding healthy samples (Figure 1C). In contrast, these genes' expression in cardiomyopathy samples and corresponding healthy samples were only sometimes similar, without overwhelming differences in expression levels between the two cohorts (Figure 1C). Therefore, we believe that these dysregulated genes are dysregulated to a greater degree in COVID-19 than in cardiomyopathy.

The inflammasome-associated genes dysregulated in both COVID-19 and cardiomyopathy were upregulated in both conditions (Figure 1C), suggesting that they may upregulate inflammation through similar pathways.

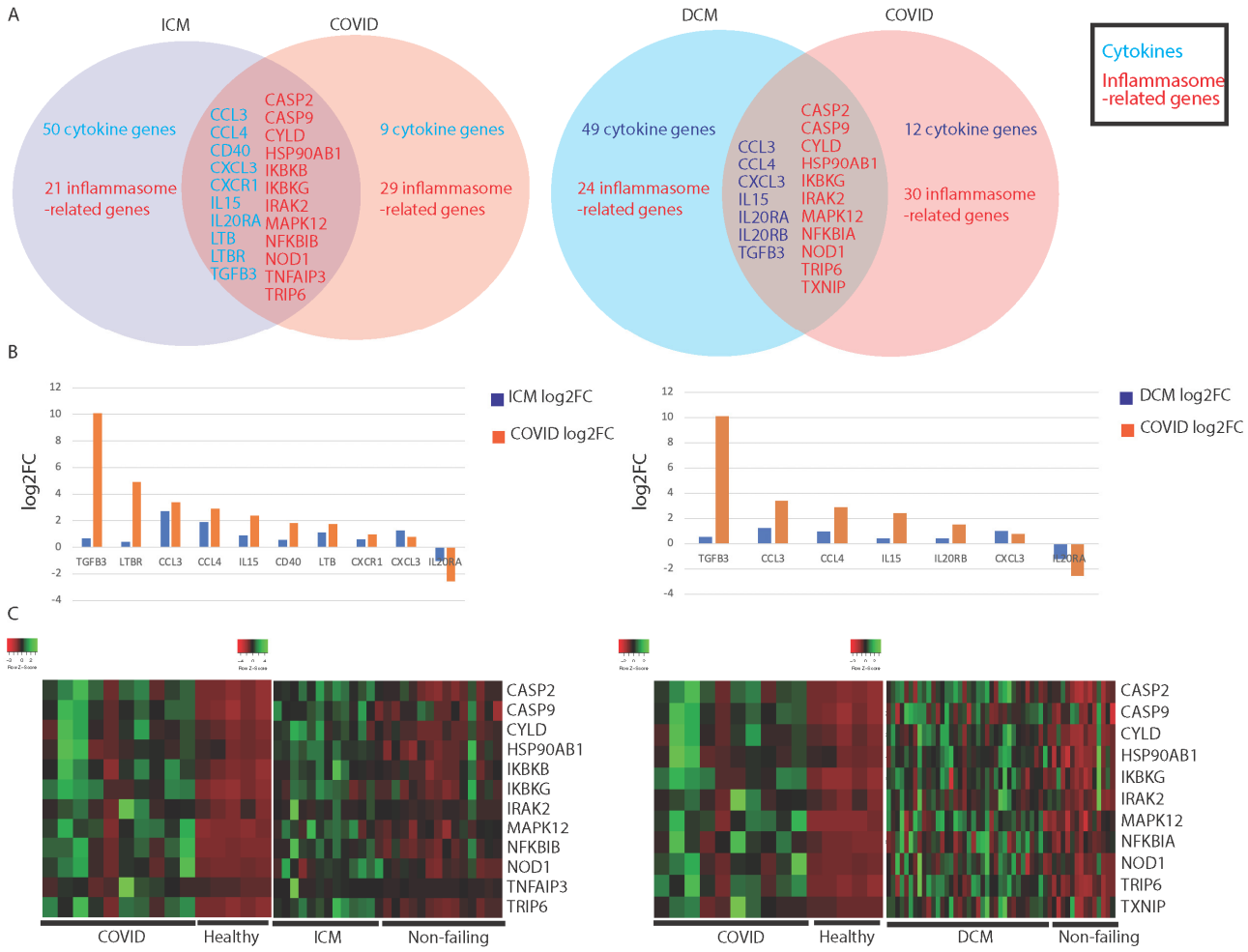

Figure 1. Comparing ischemic cardiomyopathy (ICM), nonischemic dilated cardiomyopathy (NIDCM), and COVID-19 patients. (**A**) Summary of commonly dysregulated cytokine- and inflammasome-related genes in COVID-19 and ICM/NIDCM patients. Cytokines are represented in blue and inflammasome-related genes are in red. (**B**) Bar plots of the log2 fold change of significantly dysregulated cytokine genes in COVID-19 and ICM/NIDCM patients. (**C**) Heatmaps illustrating similar patterns of dysregulation of inflammasome-related genes in COVID-19 and ICM/NIDCM patients compared to their respective controls.

3.1.2. Comparison of Immune Cell Population Abundance in COVID-19 vs. Cardiomyopathy

We discovered that the levels of T and B cells were unchanged in healthy vs. COVID-19 patients (See Appendix A, Figure A1A). The most noticeable change in immune cell abundance occurred in macrophages for COVID-19 patients, where M0 macrophage levels were dramatically reduced and M1 and M2 macrophage levels were slightly increased (See Appendix A, Figure A1A). Both cardiomyopathies elicited greater immune cell abundance changes than COVID-19, with the changes being more pronounced for ICM. The levels of M1 and M2 macrophages increased in ICM, similar to what was observed for COVID-19 (See Appendix A, Figure A1B). The levels of T- and B-cell subtypes changed more dramatically in ICM and NIDCM than in COVID-19. In summary, the levels of inflammatory macrophages increased for both cardiomyopathy and COVID-19 patients, while the levels of other immune cell types did not correlate between the two conditions.

3.1.3. Evaluation of Canonical Pathways Correlated with Genes Dysregulated in Both COVID-19 and Cardiomyopathy

We analyzed genes that are dysregulated in both COVID-19 and cardiomyopathy to assess if they dysregulate common pathways in the two conditions. Interleukin 1 receptor-associated kinase 2 (IRAK2), upregulated in both COVID-19 and ICM, was associated with the upregulation of the FCER1 and TP63 pathways, both of which are associated with inflammation and immune activation (See Appendix A, Figure A2A) [46,47]. IRAK2 is a promoter of NF-kB signaling [48]. Caspase 2 (CASP2), also upregulated in COVID-19 and cardiomyopathy, is associated with the downregulation of IFIH, which is capable of recognizing viruses and inducing inflammation [49,50]. Finally, CYLD lysine 63 deubiquitinase (CYLD) was correlated with multiple identical pathways for both COVID-19 samples and ICM samples. CYLD is upregulated in both COVID-19 and cardiomyopathy and was found to correlate with the activation of FGFR2, an important promoter of inflammation [51], and TXA2, a gene that is upregulated in platelets (See Appendix A, Figure A2A) [52]. CYLD is an inhibitor of inflammation [53]. Since the majority of correlations were between IA genes and pro-inflammatory pathways and signatures, the dysregulation of CYLD represents an exception, and we hypothesize that CYLD may be expressed as a response to attenuate excessive inflammation. We found that the overwhelming majority of pathways that correlated with dysregulated genes in both COVID-19 and NIDCM are associated with CYLD, and these pathways are primarily pro-plotting, pro-cell aggregation, and pro-inflammation (See Appendix A, Figure A2A), supporting the possibility that CYLD is released in response to inflammation.

3.2. Comparing Immune Profiles of COVID-19 and VTE Patients

3.2.1. Similarities in Immune-Associated Gene Dysregulation in COVID-19 and VTE

We compared the immune landscape between COVID-19 samples and blood samples from VTE patients to find similarities in IA gene and pathway expression. VTE patients were classified into single occurrence VTE (single VTE) and recurrent VTE. Compared to the similarities in IA genes dysregulated between COVID-19 and cardiomyopathy, the similarities between COVID-19 and VTE are less pronounced.

Two cytokine-associated genes (CCL4 and CD40) were dysregulated in COVID-19 and single VTE, and one cytokine-associated gene (CCL4) was dysregulated in COVID-19 and recurrent VTE (Figure 2A). A complete list of dysregulated cytokine- and inflammasome-associated genes are found in Appendix A, Table A2. CCL4 recruits immune cells, including macrophages, monocytes, and T cells [54], suggesting that COVID-19 and VTE may both exhibit the increased recruitment of inflammatory immune cells. The upregulation of CCL4 was much greater in COVID-19 than in VTE, however (Figure 2B). Two inflammasome-related genes were found to be dysregulated in VTE and COVID-19. BCL2L1 is known to be highly upregulated in inflamed tissue [55], and it was found to be upregulated in COVID-19 and both single and recurrent VTE (Figure 2C), while CASP4 directs the noncanonical upregulation of inflammasomes [56]. Interestingly, CASP4 was found to be upregulated in both COVID-19 and recurrent VTE but downregulated in single VTE (Figure 2C), which suggests that the gene could contribute to the development of recurrent VTE.

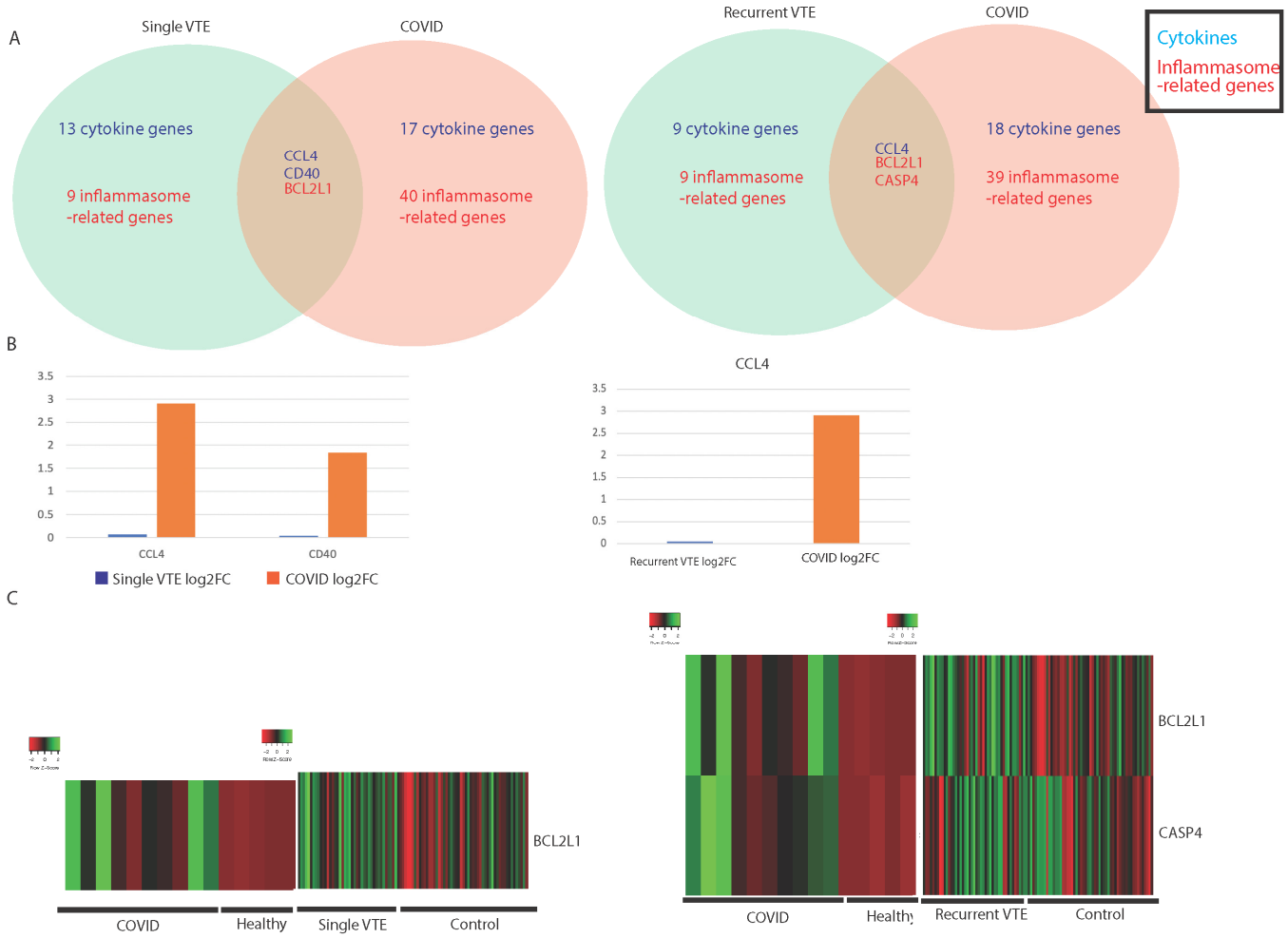

Figure 2. Comparing single venous thromboembolism (VTE), recurrent VTE, and COVID-19 patients. (**A**) Summary of commonly dysregulated cytokine- and inflammasome-related genes in COVID-19 and single/recurrent VTE patients. Cytokines are denoted in blue and inflammasome-related genes are in red. (**B**) Bar plots of the log2 (fold change) of significantly dysregulated cytokine genes in COVID-19 and single/recurrent VTE patients. (**C**) Heatmaps of inflammasome-related genes in COVID-19 and single/recurrent VTE patients.

3.2.2. Comparison of Immune Cell Population Abundance in COVID-19 vs. VTE

We found that naive B cells were dramatically reduced in abundance in VTE patients, which may indicate adaptive immune activation (See Appendix A, Figure A1C). This was the only significant immune cell population change in VTE patients that was observed and does not correlate to changes in COVID-19.

3.2.3. Evaluation of Canonical Pathways Correlated with Genes Dysregulated in COVID-19 and VTE

BCL2L1 and CASP4 were the only genes found to be dysregulated in both COVID-19 and VTE and also correlated with similar pathways in both patient cohorts (Figure 3A,B). BCL2L1 was found to be upregulated in COVID-19 and both VTE cohorts (Figure 3C). However, the direction of correlation to pathways was the complete opposite between COVID-19 and recurrent VTE (See Appendix A, Figure A2C). The high correlation strength for each cohort suggests BCL2L1 is involved in both COVID-19 and recurrent VTE but functions in opposite ways. On the other hand, CASP4 expression was correlated with over 10 pathways in the same direction for both COVID-19 and recurrent VTE (See Appendix A, Figure A2C). It was also found to be upregulated in both COVID-19 and recurrent VTE (Figure 3C). The pathways correlated with CASP4 were immune related (antigen process-

ing and cross presentation) and general metabolism related (ABC transporter, oxidative phosphorylation). Therefore, while CASP4 likely functions similarly in COVID-19 and recurrent VTE, its precise role requires further investigation.

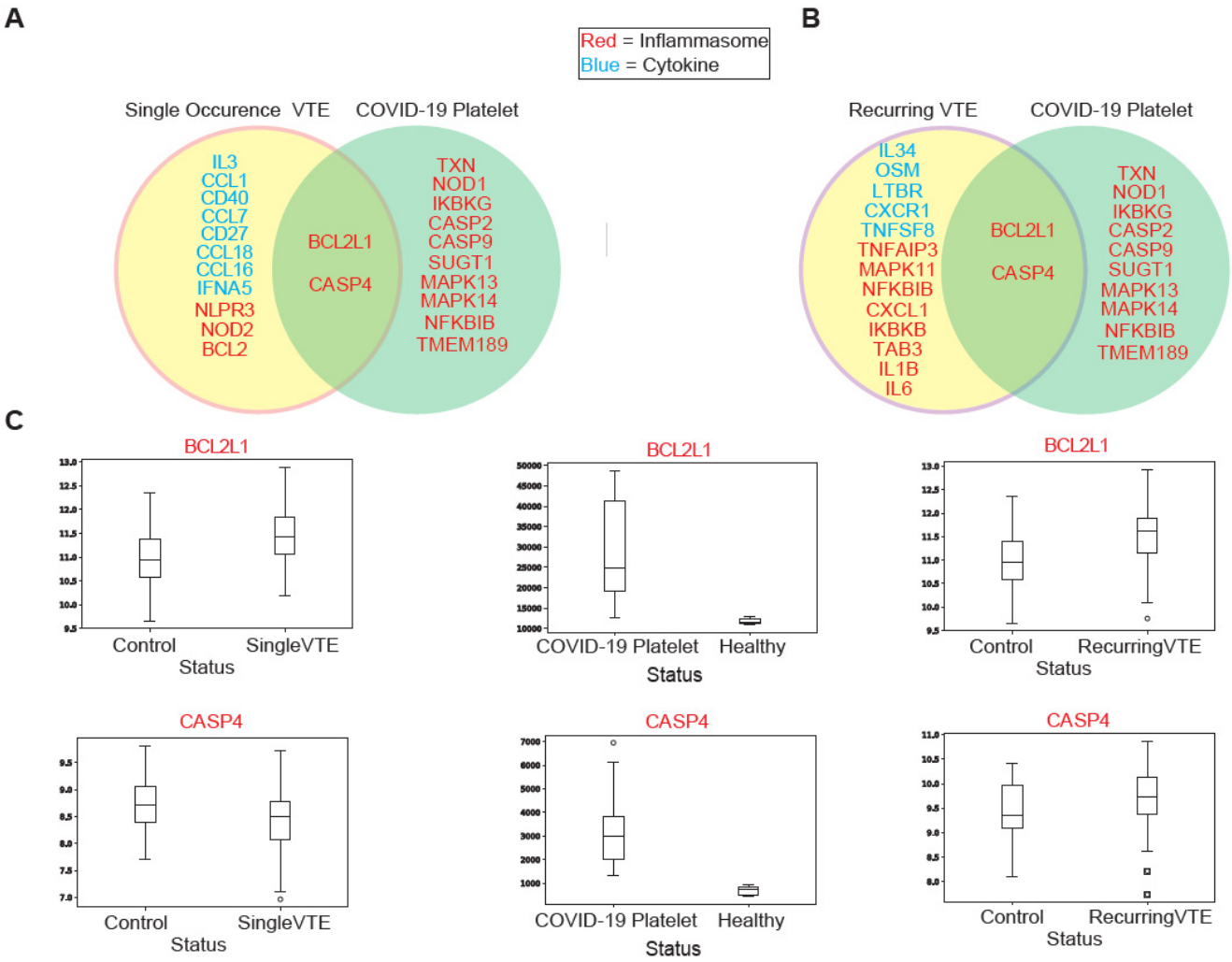

Figure 3. (**A**) Summary of common dysregulated genes correlated with pathways in single venous thromboembolism (VTE) and COVID-19. (**B**) Summary of common dysregulated genes correlated with pathways in recurring VTE and COVID-19. (**C**) Boxplots of CASP4 and BCL2L1 expression in COVID-19 and VTE cohorts.

3.3. Comparing Immune Profiles of COVID-19 and CAD Patients

3.3.1. Similarities in Immune-Associated Gene Dysregulation in COVID-19 and CAD

We found a significant overlap in IA gene expression in COVID-19 and CAD. About a third of the IA genes dysregulated in CAD were also found to be dysregulated in COVID-19 (Figure 4A). The complete list of dysregulated cytokine and inflammasome-associated genes are found in Appendix A, Table A3.

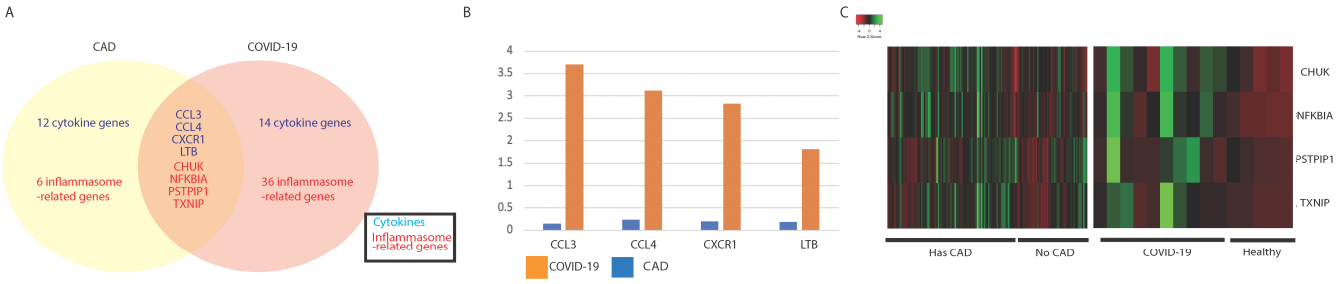

Figure 4. Comparing coronary artery disease (CAD) and COVID-19 patients. (**A**) Summary of commonly dysregulated cytokine- and inflammasome-related genes in COVID-19 and CAD patients. Cytokines are in blue and inflammasome-related genes are in red. (**B**) Bar plots of the log2 fold change of significantly dysregulated cytokine genes in COVID-19 and CAD patients. (**C**) Heatmaps of inflammasome-related genes in COVID-19 and CAD patients.

Cytokine-related genes that were found to be dysregulated in both CAD patients and COVID-19 patients include chemokines (CCL3 and CCL4), chemokine receptor CXCR1, and a TNFSF gene, LTB. The inflammasome-related genes that were found include NF-kB regulators (NFKBIA and CHUK), an alpha arrestin (TXNIP), and an F-BAR domain-containing protein (PSTPIP1). Similar to cardiomyopathy, we found that most genes dysregulated in both COVID-19 and CAD were dysregulated to a greater degree in COVID-19 samples than in CAD samples. This was observed for CCL3, CCL4, CXCR1, and LTB (Figure 4B).

3.3.2. Comparison of Immune Cell Population Abundance in COVID-19 vs. CAD

Similar to COVID-19 patients, the memory B cells in CAD patients were more abundant (See Appendix A, Figure A1D).

3.3.3. Evaluation of Pathways Correlated with Genes Dysregulated in COVID-19 and CAD

We analyzed genes that are dysregulated in both COVID-19 and CAD to assess if they are associated with similar pathways in the two conditions. Notably, we discovered that CHUK, PSTPIP1, and CCL3, upregulated in both COVID-19 and CAD, were associated with the upregulation of many inflammatory pathways in both conditions, including the IL12, IL10, IL23, and P53 regulation pathways (See Appendix A, Figure A2C).

4. Discussion

In this project, we characterized the immune landscape of cardiomyopathy, VTE, CAD, and COVID-19 patients, drawing important parallels between COVID-19 and cardiovascular-disease-mediated immune dysregulation. Of the four genes that were more severely dysregulated in COVID-19 compared to cardiomyopathy, two were reported to be dysregulated in COVID-19 patients: pro-inflammatory CCL4 was highly expressed in the bronchoalveolar lavage fluid of COVID-19 patients [57], and IL15 modulates inflammation and functions in viral clearance [58,59]. In fact, IL15 is part of an immune-based biomarker signature associated with mortality in COVID-19 patients, and CCL4 has been shown to be elevated in COVID-19 patients who eventually died due to the disease [60]. As we report that these cytokines are also upregulated in patients with cardiomyopathy, it is possible that such pre-existing immune dysregulation could explain the higher COVID-19 mortality rates of patients with cardiomyopathy and COVID-19. Our findings on immune cell abundance in COVID-19 and cardiomyopathy patients also point to a more robust innate immune response in COVID-19 patients, which is plausible as research has shown that a hyperinflammatory innate immune response coupled with an impaired adaptive immune response may lead to tissue damage in COVID-19 patients [59–61]. Conversely, the elevated levels of T and B cells in cardiomyopathy patients indicate a stronger adaptive immune response, which is now considered an increasingly important factor in cardiovascular disease pathogenesis [62–64]. Comparing COVID-19 and cardiomyopathy patients,

we found elevated levels of inflammatory macrophages in both groups of patients. This could suggest that cardiomyopathy patients are more susceptible to hyperinflammation in COVID-19 and are thus more likely to progress to severe COVID-19.

We then analyzed overlapping gene expression pathway dysregulation between cardiomyopathy and COVID-19 patients. Upregulated CASP2 and IRAK2 are of particular interest due to their inflammatory roles. CASP2 is a pro-inflammatory gene and IRAK2 promotes NF-kB, which is a central activator of inflammation. Overall, genes dysregulated in both cardiomyopathy and COVID-19 appear to promote inflammation, which may indicate why cardiovascular disease patients experience poorer clinical outcomes, as greater inflammation correlates with severity and death in COVID-19 [56].

Exploring immune-associated (IA) gene dysregulation in VTE and COVID-19 revealed several IA genes dysregulated in both conditions. Cytokine CCL4 has been shown to be upregulated in COVID-19 patients [65] and in patients who develop cardiovascular diseases [66]. Inflammasome-related genes BCL2L1 and CASP4 are tied to inflammatory caspases. CASP4 is an inflammatory caspase and promotes pro-inflammatory cytokine secretion [67]. Conversely, BCL2L1 inhibits caspase release. With both genes being upregulated in VTE and COVID-19, future analysis must be carried out to examine how these genes function differently in VTE and COVID-19. Interestingly, in both COVID-19 and single VTE, BCL2L1 expression is negatively correlated to canonical pathway expression, but in recurring VTE they are positively correlated. CASP4, on the other hand, only has overlapping significant canonical pathways with COVID-19 in recurrent VTE. From these pathways, we observe that CASP4 functions similarly in recurrent VTE and COVID-19. Together, these results show that VTE and COVID-19 patients share similar upregulation of inflammation-associated genes, which could explain why rates of venous thromboembolism events are higher in COVID-19 patients, as well as why venous thromboembolism events are associated with higher risk of death in COVID-19 patients [68,69].

Lastly, we compared the immune landscape and canonical pathways of CAD and COVID-19 patients. Of the significantly dysregulated cytokines in both COVID-19 and CAD, pro-inflammatory cytokines CCL3 and CCL4 have been associated with COVID-19 severity [59]. Of the inflammasome-related genes, CHUK is of particular interest. CHUK forms part of the IκB kinase (IKK) complex that is involved in the phosphorylation and degradation of IκBα, allowing for the transcription of NF-kB-dependent genes. Following coronavirus infection, the NF-kB pathway is activated via the MyD88 pathway [70], and increased transcription of NF-kB-dependent genes has implications for cardiomyopathy, atherosclerosis, and COVID-19 severity. Specifically, NF-kB activation in endothelial cells triggers the expression of adhesion molecules that are responsible for the invasion and homing of macrophages [71–76], contributing to atherosclerosis pathogenesis [77]. In addition, TNFa and IL6 expressions have been shown to be triggered by SARS via the NF-kB pathway [78]. These cytokines have been implicated in macrophage activation syndrome and cytokine storms and are associated with COVID-19 severity [79–81]. Interestingly, IRAK2, another NF-kB pathway regulator, is upregulated in cardiomyopathy patients. IRAK2, when phosphorylated with IRAK1 and IRAK4, recruits Ub ligase and activates TRAF6. TRAF6 activates the NF-kB pathway via the IKK complex. In summary, COVID-19 upregulates both IRAK2 and CHUK, while atherosclerosis only upregulates CHUK, and cardiomyopathy upregulates IRAK2, suggesting that NF-kB activation may be critical in all three conditions. Given that hyperactivation of the NF-kB pathway in B cells has been implicated in cytokine storms and the pathogenesis of severe and critical COVID-19 [82], our results suggest that the upregulation of this pathway in patients with pre-existing cardiovascular disease could be key to explaining their poorer COVID-19 prognoses.

5. Conclusions

In conclusion, we found that cardiomyopathy, VTE, and CAD patients display significant similarities in inflammation-related gene expression to COVID-19 patients. Therefore, when a patient with the above cardiovascular conditions contracts COVID-19, COVID-19

could further dysregulate the expression of inflammatory genes already dysregulated, leading to more severe inflammation. This may explain why patients with cardiovascular disease are more likely to develop severe COVID-19 and tend to have poorer clinical outcomes [83,84]. Furthermore, we found that patients with CAD display a similar dysregulated immune landscape to COVID-19 patients, possibly indicating why CAD patients are at higher risk of severe COVID-19. Interestingly, cardiomyopathy patients display more similar immune dysregulation to COVID-19 patients than VTE or CAD patients vs. COVID-19 patients. This observation could explain the fact that COVID-19 mortality is increased in congestive heart failure patients, as demonstrated in a study of 31,461 adults [85]. Our findings suggest that investigating the relationships between specific cardiovascular diseases and COVID-19 severity and mortality is meaningful and offers insight into COVID-19 immune dysregulation. However, our study has several limitations. We had limited COVID-19 platelet data, specifically normal patients. This may have impacted our differential expression analysis and thus reduced the statistical power of our analysis. However, the direction of dysregulation of many of the genes identified was consistent with existing literature. Additionally, we used platelet data instead of blood samples. To validate our results, in vitro and in vivo experiments can be done. Despite these limitations, we believe our study advances our understanding of the relationship between cardiovascular disease and COVID-19. Our study also encourages the examination of potential treatment strategies such as anti-inflammatory steroids and ACE2 inhibitors to downregulate inflammation in COVID-19 patients with CVDs.

Author Contributions: Conceptualization, W.M.O.; methodology, W.M.O.; software, N/A; validation, A.C.L., G.C., C.C. and N.S.; formal analysis, A.C.L., G.C., C.C. and N.S.; investigation, A.C.L., G.C., C.C. and N.S.; resources, W.M.O.; data curation, N/A; writing—original draft preparation, A.C.L., G.C. and W.T.L.; writing—review and editing, A.C.L., G.C., W.T.L., J.C., P.R.T. and E.Y.C.; visualization, A.C.L. and G.C.; supervision, W.M.O.; project administration, W.M.O.; funding acquisition, W.M.O. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

Appendix A

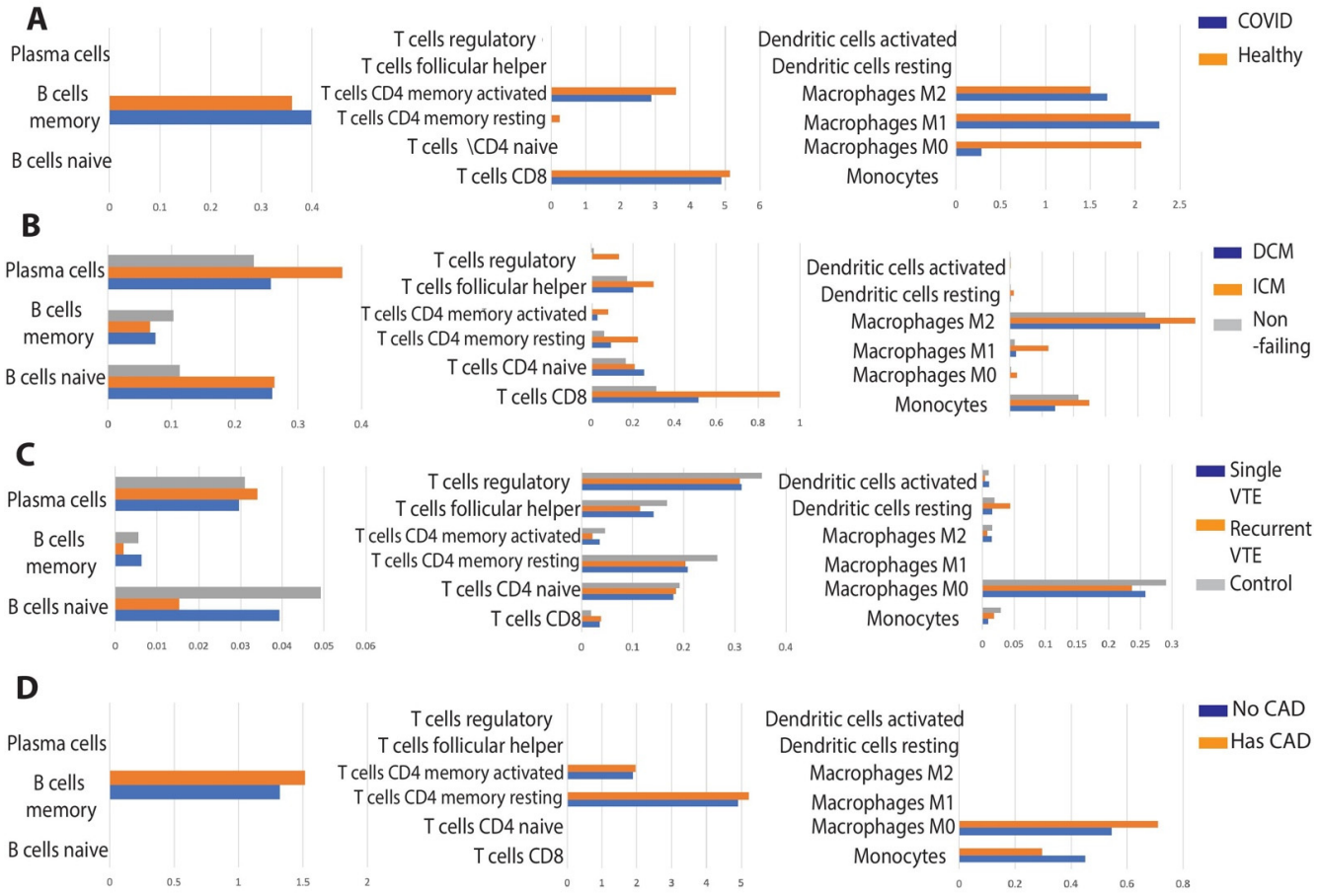

Figure A1. Bar charts comparing immune cell infiltration between (**A**) COVID-19, (**B**) ischemic cardiomyopathy/ non-ischemic dilated cardiomyopathy, (**C**) single venous thromboembolism (VTE)/recurrent VTE, and (**D**) coronary artery disease patients.

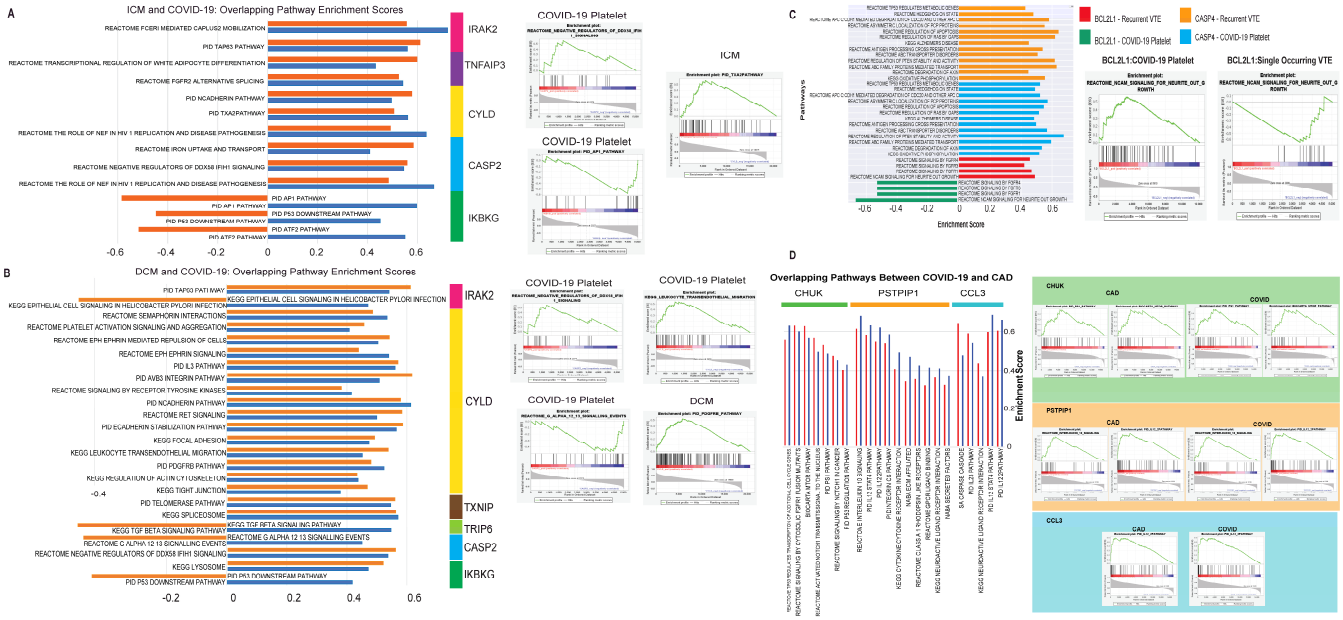

Figure A2. (**A**) Bar plots showing direction of correlation between genes and canonical pathways for genes dysregulated in both ischemic cardiomyopathy (ICM) and COVID-19 patients. (**B**) Bar plots showing direction of correlation between genes

and canonical pathways for genes dysregulated in both nonischemic dilated cardiomyopathy (NIDCM) and COVID-19 patients. (**C**) Bar plots showing direction of correlation between CASP4/BCL2L1 and canonical pathways and enrichment plots showing BCL2L1's correlation to pathways is opposite in COVID-19 and recurrent venous thromboembolism (VTE) patients. (**D**) Bar plots showing the direction of correlation between CHUK, PSTPIP1, and CCL3 and canonical pathways and enrichment plots of CHUK, PSTPIP1, and CCL3 showing correlation to pathways are similar in COVID-19 and coronary artery disease patients.

Table A1. Complete list of dysregulated cytokine and inflammasome-related genes.

ICM Only			ICM and COVID-19	COVID-19 Only		DCM Only			DCM and COVID-19	COVID-19 Only	
CCL17	CXCR4	TNF	CCL3	CCL2	MAPK3	CCL11	CXCR4	TNF	CCL3	CD40	MAPK8
CCL21	IFNA14	TNFSF12	CCL4	CKLF	MAPK8	CCL17	EPO	TNFSF11	CCL4	CXCL5	NAIP
CCL22	IL11	TNFSF13	CD40	CXCL5	MAPK9	CCL2	IFNA14	TNFSF12	CXCL3	CXCR1	NFKBIB
CCL24	IL11RA	TNFSF13B	CXCL3	EPOR	NAIP	CCL22	IL10	TNFSF13B	IL15	EPOR	POLR2J4
CCL5	IL12A	TNFSF8	CXCR1	IL15RA	NFKBIA	CCL24	IL11	TNFSF14	IL20RA	IL1RN	RELA
CCL8	IL16	TNFSF9	IL15	IL1RN	POLR2J4	CCL5	IL11RA	BIRC2	IL20RB	LTB	SUGT1
CCR10	IL17B	APP	IL20RA	IL20RB	PSTPIP1	CCL8	IL12A	BIRC3	TGFB3	LTBR	TAB1
CCR3	IL17C	BIRC2	LTB	TGFB1	RELA	CCR1	IL13	CARD8	CASP2	TGFB1	TAB3
CCR4	IL17D	CARD8	LTBR	TGFBR2	SUGT1	CCR10	IL15RA	CCL11	CASP9	CCL2	TNFAIP3
CCR7	IL1A	CCL5	TGFB3	BCL2L1	TAB1	CCR3	IL16	CCL2	CYLD	CKLF	TRAF6
CD27	IL1B	CCL8	CASP2	BIRC3	TAB3	CCR4	IL17B	CCL5	HSP90AB1	IL15RA	UBE2N
CD4	IL2	CXCL1	CASP9	CARD6	TMEM189	CCR7	IL17D	CCL8	IKBKG	TGFBR2	BIRC3
CKLF	IL23A	CXCL2	CYLD	CASP4	TRAF6	CD27	IL18	CXCL2	IRAK2	BCL2L1	HSP90AA1
CX3CL1	IL25	HSP90AA1	HSP90AB1	CASP8	TXN	CD4	IL20	HSP90AA1	MAPK12	CARD6	IRAK1
CXCL1	IL27	IL1B	IKBKB	CHUK	TXNIP	CKLF	IL23A	IL18	NFKBIA	CASP4	MAPK1
CXCL10	IL33	IL6	IKBKG	HSP90AA1	UBE2N	CX3CL1	IL25	IRAK1	NOD1	CASP8	MAPK10
CXCL14	IL34	MAPK1	IRAK2	HSP90B1		CXCL14	IL33	MAP3K7	TRIP6	CHUK	MAPK9
CXCL16	IL6	MAPK11	MAPK12	IRAK1		CXCL16	OSMR	MAPK1	TXNIP	HSP90B1	PSTPIP1
CXCL2	IL9R	MAPK9	NFKBIB	MAPK1		CXCL2	TGFB2	MAPK10		IKBKB	TMEM189
CXCL9	OSM	NFKB1	NOD1	MAPK10		CXCL9	TGFBR1	MAPK9		MAPK13	TXN
CXCR2	TGFB2	NLRC4	TNFAIP3	MAPK13		CXCR2	TGFBR2	NLRC4		MAPK14	
CXCR3	TGFBR1	NLRP3	TRIP6	MAPK14		CXCR3	TGFBR3	NLRP1		MAPK3	
		TAB2						NLRP3			
		TAB3						PSTPIP1			
		TNF						PYCARD			
		TRAF6						TAB2			
		XIAP						TMEM189			
-	-	-	-	-	-	-	-	TNF	-	-	-
								TXN			

Table A2. Complete list of dysregulated cytokine and inflammasome-related genes.

Single VTE Only	Single VTE and COVID-19	COVID-19 Only			Recurrent VTE Only	Recurrent VTE and COVID-19	COVID-19 Only		
CCL1	CCL4	CCL2	MAPK8	IKBKB	CD27	CCL4	CCL2	MAPK3	IKBKB
CCL16	CD40	CCL3	NAIP	IKBKG	CXCL10	BCL2L1	CCL3	MAPK8	IKBKG
CCL18	BCL2L1	CKLF	NFKBIA	IRAK1	CXCL8	CASP4	CD40	NAIP	IRAK1
CCL7		CXCL3	NFKBIB	IRAK2	IFNG		CKLF	NFKBIA	IRAK2
CD27		CXCL5	NOD1	TAB1	IL13		CXCL3	NFKBIB	TAB1
CXCL10		CXCR1	POLR2J4	TAB3	IL16		CXCL5	NOD1	TAB3
CXCL8		EPOR	PSTPIP1	TMEM189	IL1A		CXCR1	POLR2J4	TMEM189
IL13		IL15	SUGT1	TNFAIP3	IL3		EPOR	PSTPIP1	TNFAIP3
IL16		IL15RA	CASP4	TRAF6	TNFSF10		IL15	SUGT1	TRAF6
IL1A		IL1RN	MAPK1	TRIP6	MAPK1		IL15RA	MAPK1	TRIP6
IL3		IL20RA	MAPK9	TXN	MAPK9		IL1RN	MAPK9	TXN
TNFSF10		IL20RB	RELA	TXNIP	RELA		IL20RA	RELA	TXNIP
IFNA5		LTB	BIRC3	UBE2N	BIRC2		IL20RB	BIRC3	UBE2N
BCL2		LTBR	CARD6		CARD8		LTB	CARD6	
CASP5		TGFB1	CASP2		CASP5		LTBR	CASP2	
IL18		TGFB3	CASP8		IL18		TGFB1	CASP8	
NLRP3		TGFBR2	CASP9		IL1B		TGFB3	CASP9	
NOD2		MAPK10	CHUK		NLRP3		TGFBR2	CHUK	
CASP4		MAPK12	CYLD				MAPK10	CYLD	
MAPK1		MAPK13	HSP90AA1				MAPK12	HSP90AA1	
MAPK9		MAPK14	HSP90AB1				MAPK13	HSP90AB1	
RELA		MAPK3	HSP90B1				MAPK14	HSP90B1	

Table A3. Complete list of dysregulated cytokine and inflammasome-related genes.

CAD Only	CAD and COVID-19	COVID-19 Only		
CCR4	CCL3	CCL2	CASP4	MAPK9NAIP
CD27	CCL4	CKLF	CASP8	NFKBIB
CD40	CXCR1	CXCL3	CASP9	NOD1
CXCR3	LTB	CXCL5	CYLD	POLR2J4
CXCR4	CHUK	EPOR	HSP90AA1	RELA
IL17B	NFKBIA	IL15	HSP90AB1	SUGT1
IL21	PSTPIP1	IL15RA	HSP90B1	TAB1
IL6	TXNIP	IL1RN	IKBKB	TAB3
OSM		IL20RA	IKBKG	TMEM189
TNFSF10		IL20RB	IRAK1	TNFAIP3
TNFSF13B		LTBR	IRAK2	TRAF6
TNFSF14		TGFB1	MAPK1	TRIP6
CASP1		TGFB3	MAPK10	TXN
CASP5		TGFBR2	MAPK12	UBE2N
MAPK11		BCL2L1	MAPK13	
NLRP3		BIRC3	MAPK14	
PYCARD		CARD6	MAPK3	
TAB2		CASP2	MAPK8	

References

1. Zhu, N.; Zhang, D.; Wang, W.; Li, X.; Yang, B.; Song, J.; Zhao, X.; Huang, B.; Shi, W.; Lu, R.; et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N. Engl. J. Med.* **2020**, *382*, 727–733. [CrossRef] [PubMed]
2. Tsitsiou, E.; Lindsay, M.A. microRNAs and the immune response. *Curr. Opin. Pharmacol.* **2009**, *9*, 514–520. [CrossRef]
3. Yang, J.; Zheng, Y.; Gou, X.; Pu, K.; Chen, Z.; Guo, Q.; Ji, R.; Wang, H.; Wang, Y.; Zhou, Y. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: A systematic review and meta-analysis. *Int. J. Infect. Dis.* **2020**, *94*, 91–95. [CrossRef] [PubMed]
4. Pranata, R.; Huang, I.; Lim, M.A.; Wahjoepramono, E.J.; July, J. Impact of cerebrovascular and cardiovascular diseases on mortality and severity of COVID-19–systematic review, meta-analysis, and meta-regression. *J. Stroke Cerebrovasc. Dis.* **2020**, *29*, 104949. [CrossRef]
5. Tian, W.; Jiang, W.; Yao, J.; Nicholson, C.J.; Li, R.H.; Sigurslid, H.H.; Wooster, L.; Rotter, J.I.; Guo, X.; Malhotra, R. Predictors of mortality in hospitalized COVID-19 patients: A systematic review and meta-analysis. *J. Med. Virol.* **2020**, *92*, 1875–1883. [CrossRef]
6. Shi, S.; Qin, M.; Shen, B.; Cai, Y.; Liu, T.; Yang, F.; Gong, W.; Liu, X.; Liang, J.; Zhao, Q.; et al. Association of Cardiac Injury with Mortality in Hospitalized Patients with COVID-19 in Wuhan, China. *JAMA Cardiol.* **2020**, *5*, 802–810. [CrossRef] [PubMed]
7. Guo, T.; Fan, Y.; Chen, M.; Wu, X.; Zhang, L.; He, T.; Wang, H.; Wan, J.; Wang, X.; Lu, Z. Cardiovascular Implications of Fatal Outcomes of Patients With Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol.* **2020**, *5*, 811–818. [CrossRef] [PubMed]
8. Shi, S.; Qin, M.; Cai, Y.; Liu, T.; Shen, B.; Yang, F.; Cao, S.; Liu, X.; Xiang, Y.; Zhao, Q.; et al. Characteristics and clinical significance of myocardial injury in patients with severe coronavirus disease 2019. *Eur. Heart J.* **2020**, *41*, 2070–2079. [CrossRef]
9. Tay, M.Z.; Poh, C.M.; Rénia, L.; Macary, P.A.; Ng, L.F.P. The trinity of COVID-19: Immunity, inflammation and intervention. *Nat. Rev. Immunol.* **2020**, *20*, 363–374. [CrossRef] [PubMed]
10. Vaninov, N. In the eye of the COVID-19 cytokine storm. *Nat. Rev. Immunol.* **2020**, *20*, 277. [CrossRef] [PubMed]
11. Connors, J.M.; Levy, J.H. Thromboinflammation and the hypercoagulability of COVID-19. *J. Thromb. Haemost.* **2020**, *18*, 1559–1561. [CrossRef]
12. Wichmann, D.; Sperhake, J.P.; Lutgehetmann, M.; Steurer, S.; Edler, C.; Heinemann, A.; Heinrich, F.; Mushumba, H.; Kniep, I.; Schroder, A.S.; et al. Autopsy Findings and Venous Thromboembolism in Patients With COVID-19: A Prospective Cohort Study. *Ann. Intern. Med.* **2020**, *173*, 268–277. [CrossRef] [PubMed]
13. Schurink, B.; Roos, E.; Radonic, T.; Barbe, E.; Bouman, C.S.C.; de Boer, H.H.; de Bree, G.J.; Bulle, E.B.; Aronica, E.M.; Florquin, S.; et al. Viral presence and immunopathology in patients with lethal COVID-19: A prospective autopsy cohort study. *Lancet Microbe* **2020**, *1*, e290–e299. [CrossRef]
14. Braunwald, E. Cardiomyopathies. *Circ. Res.* **2017**, *121*, 711–721. [CrossRef] [PubMed]
15. CDC–NCHS–National Center for Health Statistics. Cdc. Gov. 2021. Available online: https://www.cdc.gov/nchs/index.htm (accessed on 26 May 2021).
16. Rose, N.R. Critical Cytokine Pathways to Cardiac Inflammation. *J. Interf. Cytokine Res.* **2011**, *31*, 705–710. [CrossRef]
17. An, N.; Gao, Y.; Si, Z.; Zhang, H.; Wang, L.; Tian, C.; Yuan, M.; Yang, X.; Li, X.; Shang, H.; et al. Regulatory Mechanisms of the NLRP3 Inflammasome, a Novel Immune-Inflammatory Marker in Cardiovascular Diseases. *Front. Immunol.* **2019**, *10*, 1592. [CrossRef] [PubMed]

18. Zeng, C.; Duan, F.; Hu, J.; Luo, B.; Huang, B.; Lou, X.; Sun, X.; Li, H.; Zhang, X.; Yin, S.; et al. NLRP3 inflammasome-mediated pyroptosis contributes to the pathogenesis of non-ischemic di-lated cardiomyopathy. *Redox Biol.* **2020**, *34*, 101523. [CrossRef]
19. Poredos, P.; Jezovnik, M.K. Endothelial Dysfunction and Venous Thrombosis. *Angiology* **2018**, *69*, 564–567. [CrossRef]
20. Cecchini, R.; Cecchini, A.L. SARS-CoV-2 infection pathogenesis is related to oxidative stress as a response to aggression. *Med. Hypotheses* **2020**, *143*, 110102. [CrossRef] [PubMed]
21. Gavriilaki, E.; Anyfanti, P.; Gavriilaki, M.; Lazaridis, A.; Douma, S.; Gkaliagkousi, E. Endothelial Dysfunction in COVID-19: Lessons Learned from Coronaviruses. *Curr. Hypertens. Rep.* **2020**, *22*, 63. [CrossRef]
22. Zhang, L.; Feng, X.; Zhang, D.; Jiang, C.; Mei, H.; Wang, J.; Zhang, C.; Li, H.; Xia, X.; Kong, S.; et al. Deep Vein Thrombosis in Hospitalized Patients With COVID-19 in Wuhan, China. *Circulation* **2020**, *142*, 114–128. [CrossRef]
23. Bilaloglu, S.; Aphinyanaphongs, Y.; Jones, S.; Iturrate, E.; Hochman, J.; Berger, J.S. Thrombosis in Hospitalized Patients With COVID-19 in a New York City Health System. *JAMA* **2020**, *324*, 799–801. [CrossRef]
24. Spyropoulos, A.C. The management of venous thromboembolism in hospitalized patients with COVID-19. *Blood Adv.* **2020**, *4*, 4028. [CrossRef] [PubMed]
25. Von Bruhl, M.L.; Stark, K.; Steinhart, A.; Chandraratne, S.; Konrad, I.; Lorenz, M.; Khandoga, A.; Tirniceriu, A.; Coletti, R.; Kollnberger, M.; et al. Monocytes, neutrophils, and platelets cooperate to initiate and propagate venous thrombosis in mice in vivo. *J. Exp. Med.* **2012**, *209*, 819–835. [CrossRef] [PubMed]
26. Brill, A.; Fuchs, T.A.; Savchenko, A.S.; Thomas, G.; Martinod, K.; De Meyer, S.F.; Bhandari, A.A.; Wagner, D.D. Neutrophil extracellular traps promote deep vein thrombosis in mice. *J. Thromb. Haemost.* **2012**, *10*, 136–144. [CrossRef]
27. Fuchs, T.A.; Brill, A.; Wagner, D.D. Neutrophil Extracellular Trap (NET) Impact on Deep Vein Thrombosis. *Arterioscler. Thromb. Vasc. Biol.* **2012**, *32*, 1777–1783. [CrossRef] [PubMed]
28. Zhou, Y.; Fu, B.; Zheng, X.; Wang, D.; Zhao, C.; Qi, Y.; Sun, R.; Tian, Z.; Xu, X.; Wei, H. Pathogenic T cells and inflammatory monocytes incite inflammatory storm in severe COVID-19 patients. *Natl. Sci. Rev.* **2020**, *7*, 998–1002. [CrossRef]
29. Zhang, D.; Guo, R.; Lei, L.; Liu, H.; Wang, Y.; Wang, Y.; Dai, T.; Zhang, T.; Lai, Y.; Wang, J.; et al. COVID-19 infection induces readily detectable morphological and inflammation-related phenotypic changes in peripheral blood monocytes, the severity of which correlate with patient outcome. *medRxiv* **2020**. [CrossRef]
30. Wang, D.; Hu, B.; Hu, C.; Zhu, F.; Liu, X.; Zhang, J.; Wang, B.; Xiang, H.; Cheng, Z.; Xiong, Y.; et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. *JAMA* **2020**, *323*, 1061–1069. [CrossRef]
31. Skaggs, B.J.; Hahn, B.H.; McMahon, M. Accelerated atherosclerosis in patients with SLE—mechanisms and management. *Nat. Rev. Rheumatol.* **2012**, *8*, 214–223. [CrossRef] [PubMed]
32. Pasceri, V.; Willerson, J.T.; Yeh, E.T.H. Direct Proinflammatory Effect of C-Reactive Protein on Human Endothelial Cells. *Circulation* **2000**, *102*, 2165–2168. [CrossRef]
33. Leibovitz, E.; Hertz, Y.; Liberman, E.; Sclarovsky, S.; Berliner, S. Increased adhesiveness of white blood cells in patients with unstable angina: Additional evidence for an involvement of the immune-inflammatory system. *Clin. Cardiol.* **1997**, *20*, 1017–1020. [CrossRef]
34. Min, X.; Lu, M.; Tu, S.; Wang, X.; Zhou, C.; Wang, S.; Pang, S.; Qian, J.; Ge, Y.; Guo, Y.; et al. Serum Cytokine Profile in Relation to the Severity of Coronary Artery Disease. *BioMed Res. Int.* **2017**, *2017*, 4013685. [CrossRef]
35. Ali, N. Elevated level of C-reactive protein may be an early marker to predict risk for severity of COVID-19. *J. Med Virol.* **2020**, *92*, 2409–2411. [CrossRef]
36. Zhao, K.; Li, R.; Wu, X.; Zhao, Y.; Wang, T.; Zheng, Z.; Zeng, S.; Ding, X.; Nie, H. Clinical features in 52 patients with COVID-19 who have increased leukocyte count: A retrospective analysis. *Eur. J. Clin. Microbiol. Infect. Dis.* **2020**, *39*, 2279–2287. [CrossRef] [PubMed]
37. Tang, Y.; Liu, J.; Zhang, D.; Xu, Z.; Ji, J.; Wen, C. Cytokine Storm in COVID-19: The Current Evidence and Treatment Strategies. *Front. Immunol.* **2020**, *11*, 1708. [CrossRef] [PubMed]
38. COVID-19 and vascular disease. *EBioMedicine* **2020**, *58*, 102966. [CrossRef] [PubMed]
39. Nishiga, M.; Wang, D.W.; Han, Y.; Lewis, D.B.; Wu, J.C. COVID-19 and cardiovascular disease: From basic mechanisms to clinical perspectives. *Nat. Rev. Cardiol.* **2020**, *17*, 543–558. [CrossRef] [PubMed]
40. Guan, W.J.; Liang, W.H.; Zhao, Y.; Liang, H.-R.; Chen, Z.-S.; Li, Y.-M.; Liu, X.-Q.; Chen, R.-C.; Tang, C.-L.; Wang, T.; et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: A nationwide analysis. *Eur. Respir. J.* **2020**, *55*, 2000547. [CrossRef]
41. Lewis, D.A.; Stashenko, G.J.; Akay, O.M.; Price, L.I.; Owzar, K.; Ginsburg, G.S.; Chi, J.T.; Ortel, T.L. Whole blood gene expression analyses in patients with single versus recurrent venous thromboembolism. *Thromb. Res.* **2011**, *128*, 536–540. [CrossRef] [PubMed]
42. Ravi, S.; Schuck, R.N.; Hilliard, E.; Lee, C.R.; Dai, X.; Lenhart, K.; Willis, S.; Jensen, B.C.; Stouffer, G.A.; Patterson, C.; et al. Clinical Evidence Supports a Protective Role for CXCL5 in Coronary Artery Disease. *Am. J. Pathol.* **2017**, *187*, 2895–2911. [CrossRef] [PubMed]
43. *RNA-seq of Platelets from SARS-CoV-2 Covid-19*; University of Utah: Salt Lake City, UT, USA, 2020.
44. Liberzon, A.; Subramanian, A.; Pinchback, R.; Thorvaldsdóttir, H.; Tamayo, P.; Mesirov, J.P. Molecular signatures database (MSigDB) 3.0. *Bioinformatics* **2011**, *27*, 1739–1740. [CrossRef] [PubMed]

45. Chen, B.; Khodadoust, M.S.; Liu, C.L.; Newman, A.M.; Alizadeh, A.A. Profiling Tumor Infiltrating Immune Cells with CIBERSORT. *Methods Mol. Biol.* **2018**, *1711*, 243–259. [PubMed]
46. Shin, J.S.; Greer, A.M. The role of FcepsilonRI expressed in dendritic cells and monocytes. *Cell Mol. Life Sci.* **2015**, *72*, 2349–2360. [CrossRef]
47. Mehta, S.Y.; Morten, B.C.; Antony, J.; Henderson, L.; Lasham, A.; Campbell, H.; Cunliffe, H.; Horsfield, J.A.; Reddel, R.R.; Avery-Kiejda, K.A.; et al. Regulation of the interferon-gamma (IFN-gamma) pathway by p63 and Delta133p53 isoform in different breast cancer subtypes. *Oncotarget* **2018**, *9*, 29146–29161. [CrossRef]
48. Keating, S.E.; Maloney, G.M.; Moran, E.M.; Bowie, A.G. IRAK-2 participates in multiple toll-like receptor signaling pathways to NFkappaB via activation of TRAF6 ubiquitination. *J. Biol. Chem.* **2007**, *282*, 33435–33443. [CrossRef]
49. Weber, M.; Gawanbacht, A.; Habjan, M.; Rang, A.; Borner, C.; Schmidt, A.M.; Veitinger, S.; Jacob, R.; Devignot, S.; Kochs, G.; et al. Incoming RNA Virus Nucleocapsids Containing a 5′-Triphosphorylated Genome Activate RIG-I and Antiviral Signaling. *Cell Host Microbe* **2013**, *13*, 336–346. [CrossRef] [PubMed]
50. Wang, C.; Liu, Z.; Ke, Y.; Wang, F. Intrinsic FGFR2 and Ectopic FGFR1 Signaling in the Prostate and Prostate Cancer. *Front. Genet.* **2019**, *10*, 12. [CrossRef] [PubMed]
51. Hamanaka, N. Eicosanoids in Mammals. *Compr. Nat. Prod. Chem.* **1999**, *1*, 159–206.
52. Mukherjee, S.; Kumar, R.; Tsakem Lenou, E.; Basrur, V.; Kontoyiannis, D.L.; Ioakeimidis, F.; Mosialos, G.; Theiss, A.L.; Flavell, R.A.; Venuprasad, K. Deubiquitination of NLRP6 inflammasome by Cyld critically regulates intestinal inflammation. *Nat. Immunol.* **2020**, *21*, 626–635. [CrossRef]
53. Castellino, F.; Huang, A.Y.; Altan-Bonnet, G.; Stoll, S.; Scheinecker, C.; Germain, R.N. Chemokines enhance immunity by guiding naive CD8+ T cells to sites of CD4+ T cell–dendritic cell interaction. *Nature* **2006**, *440*, 890–895. [CrossRef] [PubMed]
54. Szauter, K.M.; Jansen, M.K.; Okimoto, G.; Loomis, M.; Kimura, J.H.; Heller, M.; Ku, T.; Tiirikainen, M.; Boyd, C.D.; Csiszar, K.; et al. Persistent Inflammatory Pathways Associated with Early Onset Myocardial Infarction in a Medicated Multiethnic Hawaiian Cohort. *Biochem. Insights* **2011**, *4*, BCI.S6976. [CrossRef]
55. Casson, C.; Yu, J.; Reyes, V.M.; Taschuk, F.O.; Yadav, A.; Copenhaver, A.M.; Nguyen, H.T.; Collman, R.G.; Shin, S. Human caspase-4 mediates noncanonical inflammasome activation against gram-negative bacterial pathogens. *Proc. Natl. Acad. Sci. USA* **2015**, *112*, 6688–6693. [CrossRef] [PubMed]
56. Xiong, Y.; Liu, Y.; Cao, L.; Wang, D.; Guo, M.; Jiang, A.; Guo, D.; Hu, W.; Yang, J.; Tang, Z.; et al. Transcriptomic characteristics of bronchoalveolar lavage fluid and peripheral blood mononucle-ar cells in COVID-19 patients. *Emerg. Microbes Infect.* **2020**, *9*, 761–770. [CrossRef]
57. Kandikattu, H.K.; Venkateshaiah, S.U.; Mishra, A. Synergy of Interleukin (IL)-5 and IL-18 in eosinophil mediated pathogenesis of allergic diseases. *Cytokine Growth Factor Rev.* **2019**, *47*, 83–98. [CrossRef] [PubMed]
58. Verbist, K.C.; Klonowski, K.D. Functions of IL-15 in anti-viral immunity: Multiplicity and variety. *Cytokine* **2012**, *59*, 467–478. [CrossRef]
59. Huang, C.; Wang, Y.; Li, X.; Ren, L.; Zhao, J.; Hu, Y.; Zhang, L.; Fan, G.; Xu, J.; Gu, X.; et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* **2020**, *395*, 497–506. [CrossRef]
60. Abers, M.S.; Delmonte, O.M.; Ricotta, E.E.; Fintzi, J.; Fink, D.L.; de Jesus, A.A.A.; Zarember, K.A.; Alehashemi, S.; Oikonomou, V.; Desai, J.V.; et al. An immune-based biomarker signature is associated with mortality in COVID-19 patients. *JCI Insight* **2021**, *6*. [CrossRef]
61. Xu, Z.; Shi, L.; Wang, Y.; Zhang, J.; Huang, L.; Zhang, C.; Liu, S.; Zhao, P.; Liu, H.; Zhu, L.; et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir. Med.* **2020**, *8*, 420–422. [CrossRef]
62. Bansal, S.S.; Ismahil, M.A.; Goel, M.; Zhou, G.; Rokosh, G.; Hamid, T.; Prabhu, S.D. Dysfunctional and Proinflammatory Regulatory T-Lymphocytes Are Essential for Ad-verse Cardiac Remodeling in Ischemic Cardiomyopathy. *Circulation* **2019**, *139*, 206–221. [CrossRef]
63. Bansal, S.S.; Ismahil, M.A.; Goel, M.; Patel, B.; Hamid, T.; Rokosh, G.; Prabhu, S.D. Activated T Lymphocytes are Essential Drivers of Pathological Remodeling in Ischemic Heart Failure. *Circ. Heart Fail.* **2017**, *10*, e003688. [CrossRef] [PubMed]
64. Blanton, R.M.; Carrillo-Salinas, F.J.; Alcaide, P. T-cell recruitment to the heart: Friendly guests or unwelcome visitors? *Am. J. Physiol. Heart Circ. Physiol.* **2019**, *317*, H124–H140. [CrossRef]
65. Merad, M.; Martin, J.C. Pathological inflammation in patients with COVID-19: A key role for monocytes and macrophages. *Nat. Rev. Immunol.* **2020**, *20*, 355–362. [CrossRef] [PubMed]
66. Chang, T.T.; Chen, J.W. Emerging role of chemokine CC motif ligand 4 related mechanisms in diabetes mellitus and cardiovas-cular disease: Friends or foes? *Cardiovasc. Diabetol.* **2016**, *15*, 117. [CrossRef]
67. Papoff, G.; Presutti, D.; Lalli, C.; Bolasco, G.; Santini, S.; Manelfi, C.; Fustaino, V.; Alemà, S.; Ruberti, G. CASP4 gene silencing in epithelial cancer cells leads to impairment of cell migration, cell-matrix adhesion and tissue invasion. *Sci. Rep.* **2018**, *8*, 17705. [CrossRef]
68. Malas, M.B.; Naazie, I.N.; Elsayed, N.; Mathlouthi, A.; Marmor, R.; Clary, B. Thromboembolism risk of COVID-19 is high and associated with a higher risk of mortality: A systematic review and meta-analysis. *EClinicalMedicine* **2020**, *29–30*, 100639. [CrossRef] [PubMed]
69. Tan, B.K.; Mainbourg, S.; Friggeri, A.; Bertoletti, L.; Douplat, M.; Dargaud, Y.; Grange, C.; Lobbes, H.; Provencher, S.; Lega, J.-C. Arterial and venous thromboembolism in COVID-19: A study-level meta-analysis. *Thorax* **2021**. [CrossRef]

70. Clerkin, K.J.; Fried, J.A.; Raikhelkar, J.; Sayer, G.; Griffin, J.M.; Masoumi, A.; Jain, S.S.; Burkhoff, D.; Kumaraiah, D.; Rabbani, L.; et al. COVID-19 and Cardiovascular Disease. *Circulation* **2020**, *141*, 1648–1655. [CrossRef] [PubMed]
71. De Wit, E.; van Doremalen, N.; Falzarano, D.; Munster, V.J. SARS and MERS: Recent insights into emerging coronaviruses. *Nat. Rev. Microbiol.* **2016**, *14*, 523–534. [CrossRef] [PubMed]
72. Collins, R.G.; Velji, R.; Guevara, N.V.; Hicks, M.J.; Chan, L.; Beaudet, A.L. P-Selectin or intercellular adhesion molecule (ICAM)-1 deficiency substantially protects against atherosclerosis in apolipoprotein E-deficient mice. *J. Exp. Med.* **2000**, *191*, 189–194. [CrossRef] [PubMed]
73. Brasier, A.R. The nuclear factor-kappaB-interleukin-6 signalling pathway mediating vascular inflammation. *Cardiovasc. Res.* **2010**, *86*, 211–218. [CrossRef] [PubMed]
74. Gareus, R.; Kotsaki, E.; Xanthoulea, S.; van der Made, I.; Gijbels, M.J.; Kardakaris, R.; Polykratis, A.; Kollias, G.; de Winther, M.P.; Pasparakis, M. Endothelial cell-specific NF-kappaB inhibition protects mice from atherosclerosis. *Cell Metab.* **2008**, *8*, 372–383. [CrossRef]
75. Merhi-Soussi, F.; Kwak, B.; Magne, D.; Chadjichristos, C.; Berti, M.; Pelli, G.; James, R.W.; Mach, F.; Gabay, C. Interleukin-1 plays a major role in vascular inflammation and atherosclerosis in male apolipoprotein E-knockout mice. *Cardiovasc. Res.* **2005**, *66*, 583–593. [CrossRef] [PubMed]
76. Nakashima, Y.; Raines, E.W.; Plump, A.S.; Breslow, J.L.; Ross, R. Upregulation of VCAM-1 and ICAM-1 at atherosclerosis-prone sites on the endothelium in the ApoE-deficient mouse. *Arterioscler. Thromb. Vasc. Biol.* **1998**, *18*, 842–851. [CrossRef] [PubMed]
77. Tikellis, C.; Jandeleit-Dahm, K.; Sheehy, K.; Murphy, A.; Chin-Dusting, J.; Kling, D.; Sebokova, E.; Cooper, M.; Mizrahi, J.; Woollard, K. Reduced plaque formation induced by rosiglitazone in an STZ-diabetes mouse model of atherosclerosis is associated with downregulation of adhesion molecules. *Atherosclerosis* **2008**, *199*, 55–64. [CrossRef]
78. Pamukcu, B.; Lip, G.Y.H.; Devitt, A.; Griffiths, H.R.; Shantsila, E. The role of monocytes in atherosclerotic coronary artery disease. *Ann. Med.* **2010**, *42*, 394–403. [CrossRef]
79. Wang, W.; Ye, L.; Ye, L.; Li, B.; Gao, B.; Zeng, Y.; Kong, L.; Fang, X.; Zeng, H.; Wu, Z.; et al. Up-regulation of IL-6 and TNF-alpha induced by SARS-coronavirus spike protein in murine macrophages via NF-kappaB pathway. *Virus Res.* **2007**, *128*, 1–8. [CrossRef]
80. McGonagle, D.; Sharif, K.; O'Regan, A.; Bridgewood, C. The Role of Cytokines including Interleukin-6 in COVID-19 induced Pneumonia and Macrophage Activation Syndrome-Like Disease. *Autoimmun. Rev.* **2020**, *19*, 102537. [CrossRef] [PubMed]
81. Zhou, F.; Yu, T.; Du, R.; Fan, G.; Liu, Y.; Liu, Z.; Xiang, J.; Wang, Y.; Song, B.; Gu, X.; et al. Articles Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. *Lancet* **2020**, *395*, 1054–1062. [CrossRef]
82. Hirano, T.; Murakami, M. COVID-19: A New Virus, but a Familiar Receptor and Cytokine Release Syndrome. *Immun.* **2020**, *52*, 731–733. [CrossRef]
83. Ye, Q.; Wang, B.; Mao, J. The pathogenesis and treatment of the 'Cytokine Storm' in COVID-19. *J. Infect.* **2020**, *80*, 607–613. [CrossRef] [PubMed]
84. Madjid, M.; Safavi-Naeini, P.; Solomon, S.D.; Vardeny, O. Potential Effects of Coronaviruses on the Cardiovascular System: A Review. *JAMA Cardiol* **2020**, *5*, 831–840. [CrossRef] [PubMed]
85. Sweet, M.E.; Cocciolo, A.; Slavov, D.; Jones, K.L.; Sweet, J.R.; Graw, S.L.; Reece, T.B.; Ambardekar, A.V.; Bristow, M.R.; Mestroni, L.; et al. Transcriptome analysis of human heart failure reveals dysregulated cell adhesion in dilated cardiomyopathy and activated immune pathways in ischemic heart failure. *BMC Genom.* **2018**, *19*, 1–14. [CrossRef] [PubMed]