Table S1. Overview of the publicly available summary-level data of genetic associations used for the analysis.

Phenotype	Description	Sample Size	Cases	Controls	Population	PMID
AMD	AMD cases vs controls	33,976	16,144	17,832	EUR	26691988
COVID-19	Critical Covid vs population	1,388,342	5,101	1,383,241	EUR	34237774
	Hospitalized Covid vs population	1,887,658	9,986	1,877,672		
	Covid infection vs population	1,683,768	38,984	1,644,784		

PMID: PubMed accession ID.

Table S2. Sample demography of gene expression dataset derived from 96 peripheral blood samples obtained from 32 COVID-19 patients and 8 controls at multiple time points, corresponding to different disease stages, measured from symptom onset (early: 19 samples within 10 days; middle: 36 samples between 11 and 20 days; late: 22 samples >21 days or later). This COVID-19 expression data was obtained from Gene Expression Omnibus (GEO; accession ID: GSE161731).

Age group	Control	Early	Middle	Late
N (Females)	19 (8)	19 (6)	36 (15)	22 (11)
Age Mean (SD)	18.37 (0.6)	46.44 (19.7)	41.06 (16.4)	41.82 (13.4)
10-20	19	2	1	1
20-30	0	4	13	7
30-40	0	5	8	2
40-50	0	0	3	5
50-80	0	8	11	7

Table S3. Sample demography of AMD gene expression dataset derived from human retinal pigment epithelium (RPE)/choroid tissues obtained from 9 AMD cases and 6 age-matched healthy controls, that were downloaded from the Gene Expression Omnibus (GEO; accession ID: GSE50195).

	Total	**AMD**	**Controls**
N (Females)	16 (8)	9 (5)	6 (3)
Age Mean (SD)	83.69 (6.01)	84.22 (6.55)	83.00 (5.66)

Table S4. Overview of the genetic variants used as instrumental variables for testing causal inference between AMD and COVID-19 traits (critical illness, hospitalization, and infection). We selected 23 uncorrelated (clumped at correlation threshold $r^2 < 0.01$) and common (MAF > 5%) genetic variants as instrumental variables that were associated with AMD at a p-value level of 5×10^{-8} or smaller. The table additionally includes summary-level data (beta coefficients of genetic association, their standard error and corresponding p-value) for AMD as exposure and three COVID-19 phenotypes, including critical illness, hospitalization, and infections, as outcomes. CH: chromosome; EA: effect allele; EAF: effect allele frequency; β: effect estimate; SE: standard error.

				AMD			COVID-19 Critical Illness			COVID-19 Hospitalization			COVID-19 Infection		
SNP	**CH**	**EA**	**EAF**	**β**	**SE**	**P**	**β**	**SE**	**P**	**β**	**SE**	**P**	**β**	**SE**	**P**
rs10801558	1	G	0.33	-0.96	0.02	2.5×10^{-308}	-0.01	0.03	0.58	-0.02	0.02	0.4	-0.02	0.01	0.09
rs62247658	3	T	0.45	-0.13	0.02	1.8×10^{-14}	-0.01	0.03	0.72	0.02	0.02	0.38	0.00	0.01	0.99
rs56339461	3	G	0.16	-0.13	0.02	2.6×10^{-9}	0.01	0.05	0.86	0.01	0.03	0.68	0.01	0.01	0.36
rs10033900	4	C	0.49	-0.14	0.02	5.4×10^{-17}	0.00	0.03	0.86	-0.02	0.02	0.27	-0.02	0.01	0.08
rs429608	6	A	0.12	-0.56	0.03	1.2×10^{-103}	-0.01	0.04	0.73	0.00	0.03	0.94	0.00	0.01	0.75
rs7803454	7	T	0.2	0.12	0.02	4.8×10^{-9}	0.00	0.03	0.90	0.01	0.02	0.57	0.02	0.01	0.21
rs1142	7	T	0.36	0.10	0.02	1.4×10^{-9}	0.04	0.03	0.14	-0.02	0.02	0.28	-0.01	0.01	0.58
rs10781182	9	G	0.32	-0.11	0.02	2.6×10^{-9}	-0.01	0.04	0.77	0.02	0.02	0.32	0.00	0.01	0.67
rs401186	9	T	0.2	-0.13	0.02	4.1×10^{-10}	0.07	0.04	0.08	0.05	0.03	0.07	0.01	0.01	0.37
rs11200633	10	T	0.32	1.04	0.02	2.5×10^{-308}	-0.03	0.03	0.43	-0.02	0.02	0.28	0.00	0.01	0.96
rs11624933	14	G	0.14	0.16	0.03	2.5×10^{-10}	-0.01	0.06	0.9	0.01	0.03	0.70	0.01	0.01	0.30
rs61985136	14	T	0.37	0.11	0.02	1.6×10^{-10}	0.05	0.03	0.12	0.01	0.02	0.57	0.02	0.01	0.08
rs2414577	15	C	0.37	-0.13	0.02	4.3×10^{-15}	-0.02	0.03	0.54	-0.01	0.02	0.79	-0.01	0.01	0.46
rs1864163	16	A	0.25	-0.17	0.02	6.3×10^{-19}	-0.04	0.03	0.21	-0.01	0.02	0.63	0.00	0.01	0.82
rs72802342	16	A	0.07	-0.23	0.03	5.0×10^{-12}	0.01	0.07	0.84	0.04	0.04	0.25	0.01	0.02	0.45
rs11080055	17	C	0.48	0.09	0.02	1.0×10^{-8}	-0.01	0.03	0.85	0.01	0.02	0.63	0.02	0.01	0.11
rs6565597	17	T	0.39	0.12	0.02	1.5×10^{-11}	-0.05	0.04	0.20	0.00	0.02	0.97	0.00	0.01	0.99
rs9973159	18	T	0.13	-0.13	0.02	9.4×10^{-8}	0.00	0.05	0.98	-0.02	0.03	0.52	0.00	0.01	0.81
rs11569415	19	A	0.24	0.34	0.02	5.4×10^{-67}	0.01	0.05	0.86	0.00	0.03	0.87	0.00	0.01	0.77
rs6073984	20	G	0.13	-0.15	0.02	3.4×10^{-10}	0.03	0.04	0.45	0.02	0.03	0.37	0.01	0.01	0.45
rs117739907	20	T	0.06	-0.28	0.03	3.2×10^{-16}	0.05	0.05	0.33	0.03	0.04	0.35	0.02	0.02	0.35
rs5754227	22	C	0.12	-0.26	0.03	1.1×10^{-24}	-0.01	0.04	0.79	0.00	0.03	0.97	0.00	0.01	0.93
rs8135665	22	T	0.21	0.13	0.02	5.6×10^{-11}	0.04	0.03	0.20	0.04	0.02	0.10	0.00	0.01	0.87

Table S5. Overview of the genetic variants used as instrumental variables for testing causal inference between the human cytokine Pdgfbb level and COVID-19 outcomes. We selected 4 uncorrelated (clumped at correlation threshold $r^2 < 0.01$) and common (MAF > 5%) genetic variants as instrumental variables that were associated with the Pdgfbb levels at a p-value level of 9×10^{-8} or smaller. The table additionally includes summary-level data (beta coefficients of genetic association, their standard error and corresponding p-value) for Pdgfbb as exposure and three COVID-19 phenotypes, including critical illness, hospitalization, and infections, as outcomes. CH: chromosome; EA: effect allele; EAF: effect allele frequency; β: effect estimate; SE: standard error.

				Pdgfbb			**Critical Illness**			**Hospitalization**			**Infection**		
SNP	**CH**	**EA**	**EAF**	**β**	**SE**	**P**	**β**	**SE**	**P**	**β**	**SE**	**P**	**β**	**SE**	**P**
rs72777070	2	G	0.11	0.11	0.02	$9.0\text{x}10^{-8}$	-0.03	0.04	0.48	-0.01	0.03	0.65	0.02	0.01	0.02
rs13412535	2	G	0.22	-0.34	0.02	$2.5\text{x}10^{-55}$	-0.02	0.03	0.44	0.00	0.02	0.83	-0.01	0.01	0.42
rs2324229	6	C	0.36	-0.09	0.02	$3.5\text{x}10^{-8}$	-0.03	0.03	0.20	-0.03	0.02	0.15	0.00	0.01	0.94
rs4965869	15	C	0.26	-0.18	0.02	$5.7\text{x}10^{-24}$	-0.02	0.04	0.62	-0.01	0.02	0.54	0.00	0.01	0.98

Table S6. Summary statistics of genome-wide significant ($P < 5.0x10^{-8}$) associations in the MTAG results of AMD and the three COVID-19 outcomes (critical illness, hospitalization, and infections).

Enclosed electronic excel file

Table S7. eQTL association summaries of rs130651 and rs482037 with *CACNA1I* in the whole bloods of the GTEx portal database.

Gene	SNP	Effect Allele	T-statistics	P-Value
CACNA1I	rs130651	A	3.8	$1.4x10^{-4}$
	rs4820371	T	2.3	0.02

Table S8. Summary statistics of *cis*-mQTL associations between the two SNPs (rs130651 and rs4820371) and CpGs located upstream of *PDGFB* (chr22:39619364-39640987) in the GoDMC database (http://www.godmc.org.uk).

SNP	EA	CpG ID	CpG BP*	Distance from PDGFB	Effect	SE	N	P
rs130651	A	cg01416388	chr22:39784597	143610	-0.12	0.01	19065	$5.18x10^{-28}$
		cg05872129	chr22:39784768	143781	-0.15	0.01	19065	$9.23x10^{-43}$
		cg24399712	chr22:39784795	143808	-0.15	0.01	19065	$2.73x10^{-43}$
		cg11247378	chr22:39784981	143994	-0.18	0.01	19065	$9.74x10^{-64}$
rs4820371	T	cg01093212	chr22:39715155	74168	-0.11	0.01	17974	$1.54x10^{-19}$
		cg17798944	chr22:39715224	74237	-0.18	0.01	16372	$1.55x10^{-45}$
		cg02038168	chr22:39784480	143493	-0.12	0.01	17974	$2.10x10^{-21}$
		cg01416388	chr22:39784597	143610	-0.14	0.01	17974	$1.91x10^{-29}$
		cg05872129	chr22:39784768	143781	-0.16	0.01	17974	$3.92x10^{-41}$
		cg24399712	chr22:39784795	143808	-0.16	0.01	17974	$5.17x10^{-41}$
		cg11247378	chr22:39784981	143994	-0.20	0.01	17974	$5.99x10^{-60}$

EA: effect allele. CHR: chromosome. BP: base pair position. SE: standard error. N: sample size. *The gene and CpG sites are mapped to the human genome reference build 37.

Table S9. Association summaries for differential gene expression analysis of *PDGFB* in the RNS-Seq data of bloods from COVID-19 patients in three different stages measured from the symptom onset (early ≤10 days, middle 11-20 days, late ≥ 21 days). This COVID-19 RNA-Seq data was obtained from Gene Expression Omnibus (GEO; accession ID: GSE161731).

	Middle vs. Early			Middle/Late vs. Early		
Age group	**FC**	**t**	**P**	**FC**	**t**	**P**
All	0.99	0.52	0.61	0.93	0.24	0.81
> 30	1.02	1.02	0.31	0.92	0.49	0.62
> 40	2.17	2.34	0.03	2.04	1.67	0.10
> 50	2.15	2.19	0.04	1.94	1.36	0.19

FC: fold change of *PDGFB* expression level between the two groups

Table S10. The gene ontology (GO) analysis of the MTAG Result from AMD and the COVID-19 infection. This GO Analysis was conducted using the MAGMA software. The gene-set association significance threshold is set to 8.45×10^{-6}.

		Infection		
Gene Set	**N Genes**	**Beta**	**SE**	**P**
High density lipoprotein particle remodeling	16	1.38	0.25	1.71×10^{-8}
Reverse cholesterol transport	16	1.23	0.26	1.53×10^{-6}
Humoral immune response mediated by circulating immunoglobulin	44	0.71	0.16	4.31×10^{-6}
Extracellular structure organization	396	0.20	0.05	3.53×10^{-6}

Table S11. Mendelian randomization associations between AMD and Pdgf-bb as exposures and the COVID-19 (critical illness, hospitalization, and infection) as outcomes using pleiotropy-robust Mendelian randomization approaches including weighted median (WM) and MR-Egger. The intercept of the MR-Egger method was used to test for directional pleiotropy. The estimates are odd ratios for AMD and AMD (complement) and beta for Pdgf-bb.

Exposure	Outcome	MR Method	Estimates	95% CI	P-value
AMD	Critical Illness	WM	1.00	(0.95 - 1.05)	0.97
		MR-Egger (intercept)	0.98	(0.93 - 1.03)	0.40 (0.35)
	Hospitalization	WM	1.00	(0.97 - 1.03)	0.98
		MR-Egger (intercept)	1.00	(0.95 - 1.05)	0.90 (0.88)
	Infection	WM	1.00	(0.98 - 1.02)	1.00
		MR-Egger (intercept)	1.00	(0.99 - 1.02)	0.65 (0.70)
AMD (Complement)	Critical Illness	WM	1.01	(0.96 - 1.07)	0.69
		MR-Egger (intercept)	1.02	(0.97 - 1.07)	0.44 (0.76)
	Hospitalization	WM	1.02	(0.98 - 1.06)	0.38
		MR-Egger (intercept)	1.01	(0.98 - 1.03)	0.64 (0.14)
	Infection	WM	1.01	(0.99 - 1.03)	0.16
		MR-Egger (intercept)	1.00	(0.97 - 1.02)	0.84 (0.052)
Pdgf-bb	Critical Illness	WM	0.07	(-0.10 - 0.23)	0.42
		MR-Egger (intercept)	0.03	(-0.14 - 0.20)	0.72 (0.76)
	Hospitalization	WM	0.01	(-0.09 - 0.12)	0.80
		MR-Egger (intercept)	-0.08	(-0.17 - 0.01)	0.08 (0.16)
	Infection	WM	0.02	(-0.03 - 0.08)	0.37
		MR-Egger (intercept)	0.01	(-0.06 - 0.07)	0.85 (0.54)

CI: Confidence interval. WM: Weighted median.

Table S12. Association summaries of the human cytokine Pdgfbb levels between COVID-19 cases and controls. The positive effect direction means that the mean levels of the cytokine Pdgfbb were higher in the cases compared to the controls.

Study	PMID	COVID-19 Cases (#)	COVID-19 free Controls	Effect direction	P-value
Huang et al. 2020	31986264	ICU-Care COVID-19 cases (13)	28	+	0.013
Huang et al. 2020	31986264	No ICU COVID-19 cases (28)	28	+	0.009
Petrey et al. 2021*	32930456	COVID-19 cases (22)	22	+	<0.001

**Petrey et al.* analyzed the cytokine Pdgf-bb together with Pdgf-ab. PMID: PubMed accession ID.

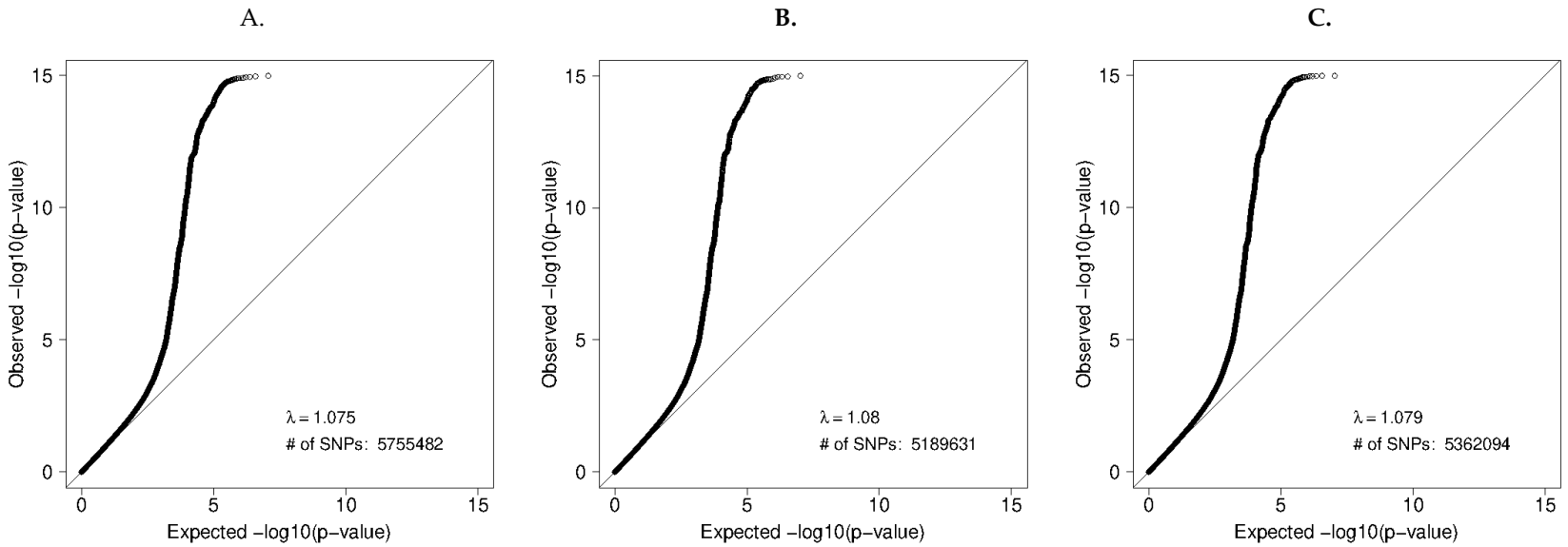
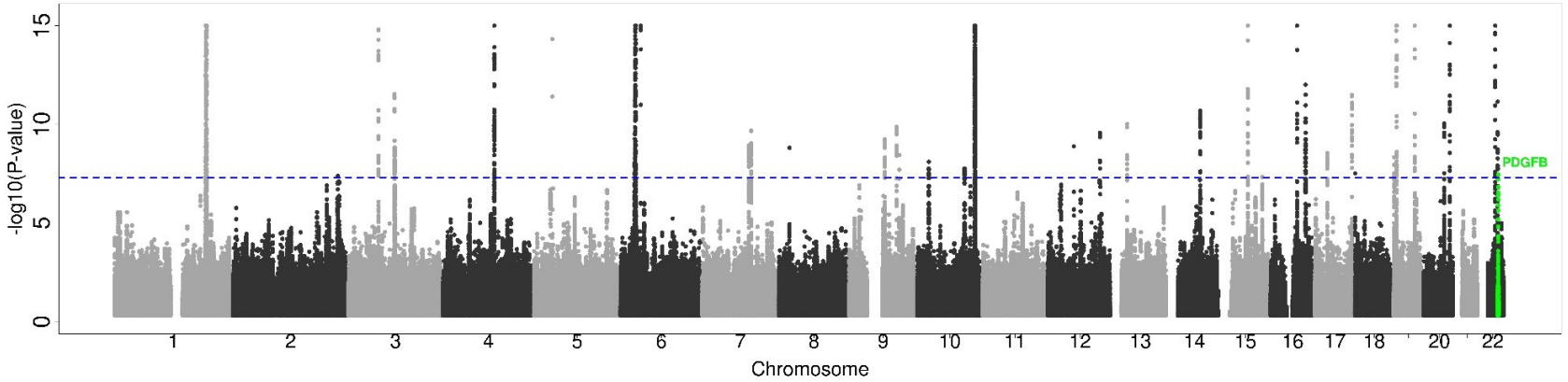
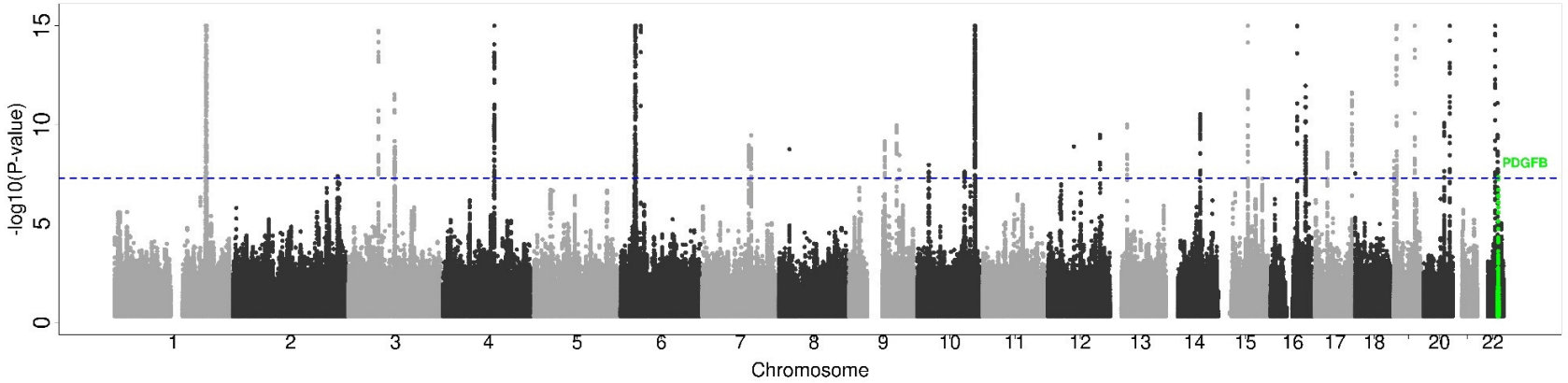


Figure S1. QQ plots of the MTAG results for AMD with the three COVID-19 outcomes: **A.** critical illness, **B.** hospitalization, and **C.** infections.

A.


-log10(P-value)
0
5
10
15
PDGFB
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
20
22
Chromosome

B.


-log10(P-value)
0
5
10
15
PDGFB
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
20
22
Chromosome

C.

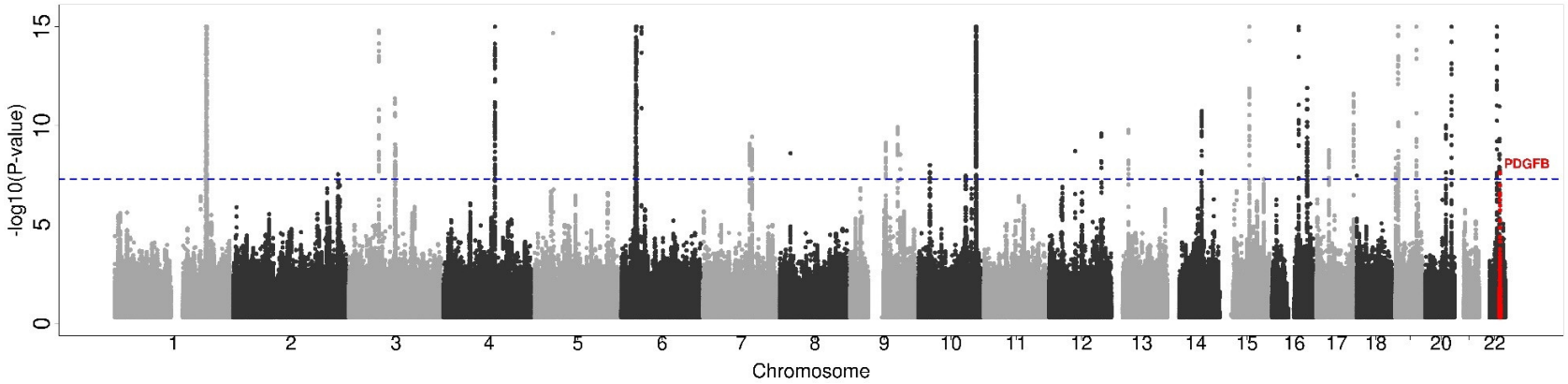


Figure S2. Manhattan plots of the MTAG results for AMD with the three COVID-19 outcomes: **A.** critical illness, **B.** hospitalization, and **C.** infections.

A. critical illness, **B.** hospitalization, and **C.** infections

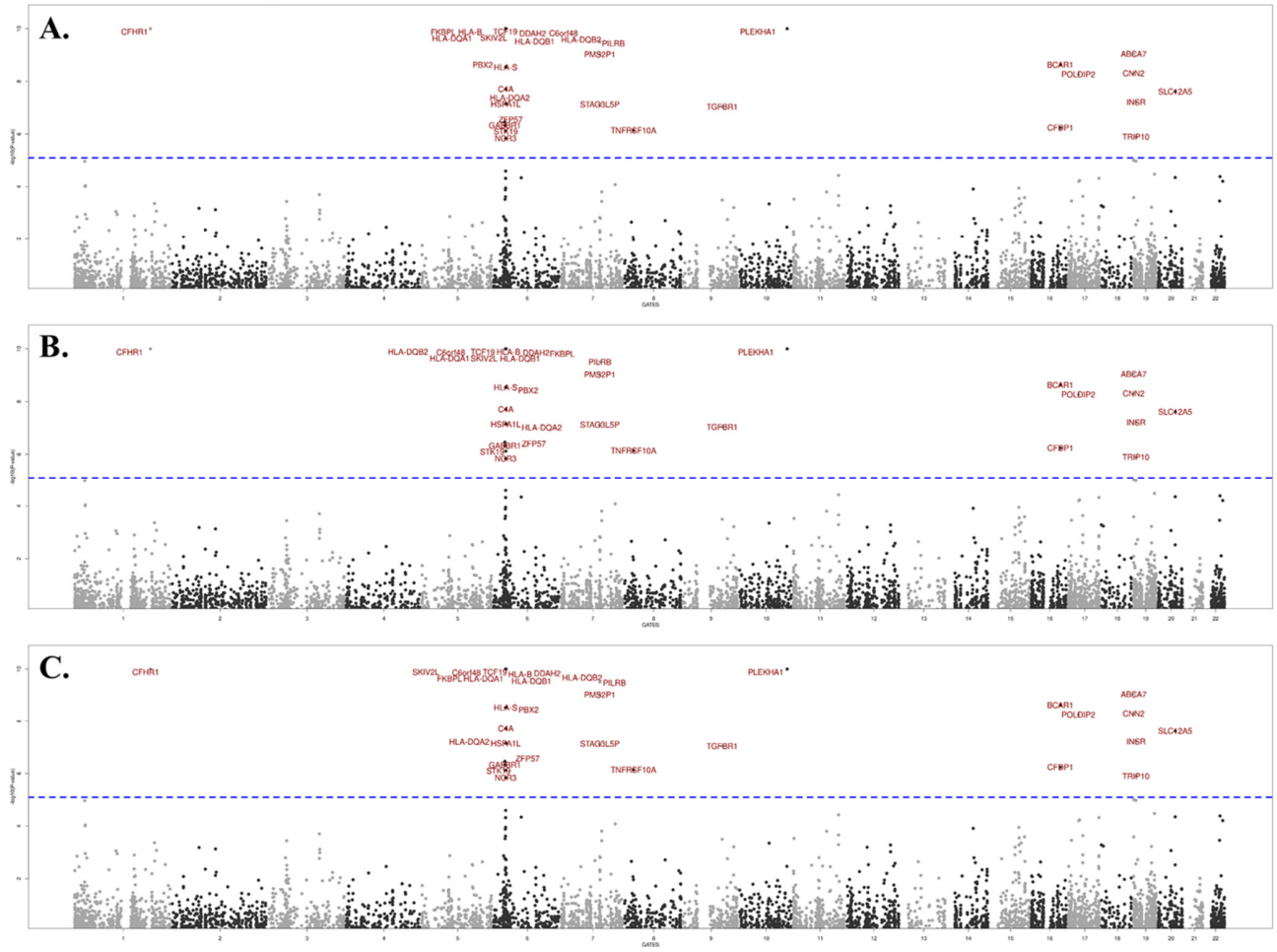


Figure S3. Manhattan plots of S-Predixcan results in the blood tissue using the MTAG results for AMD with the three COVID-19 outcomes including.

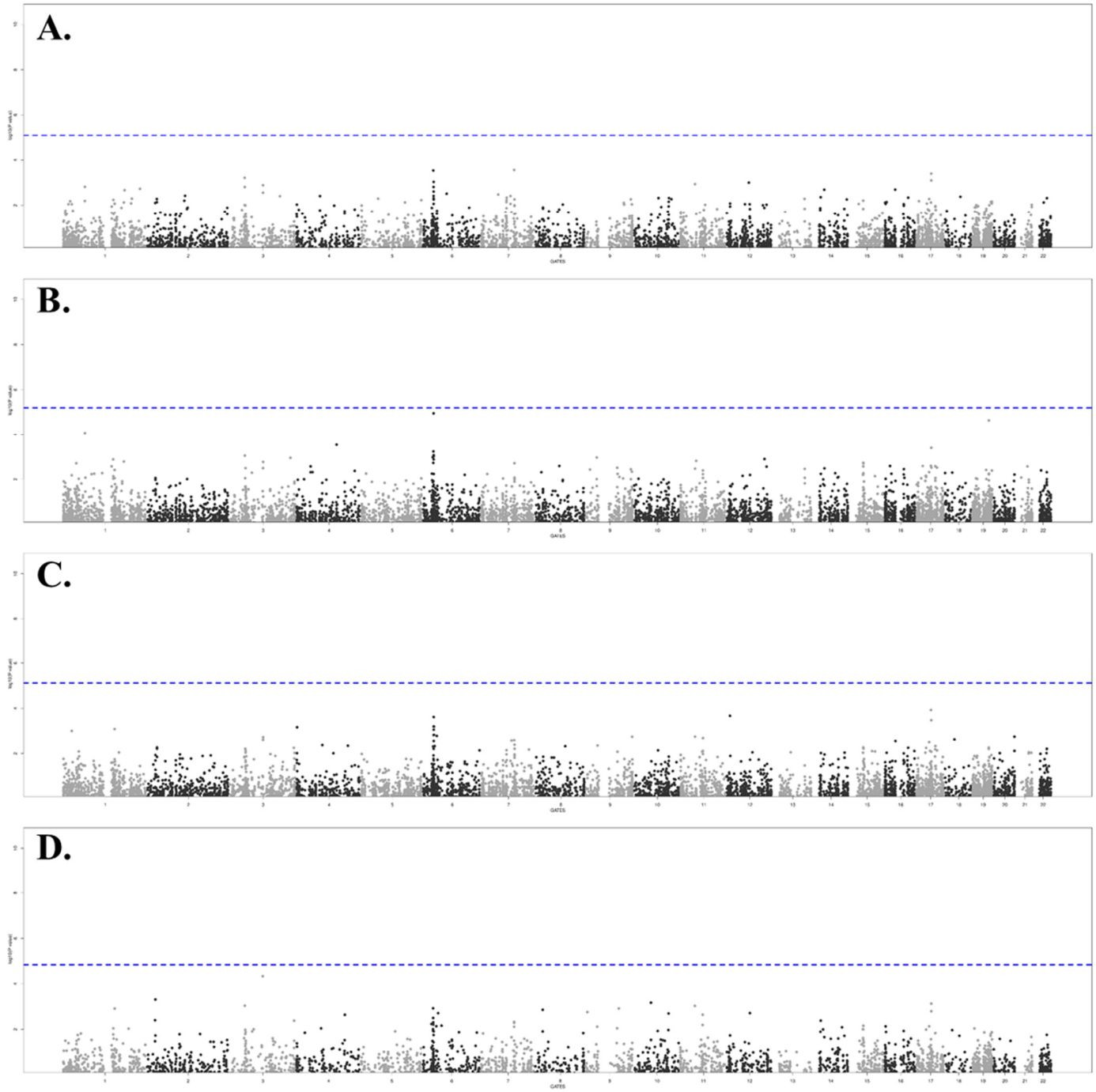


Figure S4. Manhattan plots of S-Predixcan results in **A.** bloods, **B.** lung, **C.** aorta (artery) and **D.** coronary (artery) using the MTAG results for AMD with the COVID-19 critical illness.

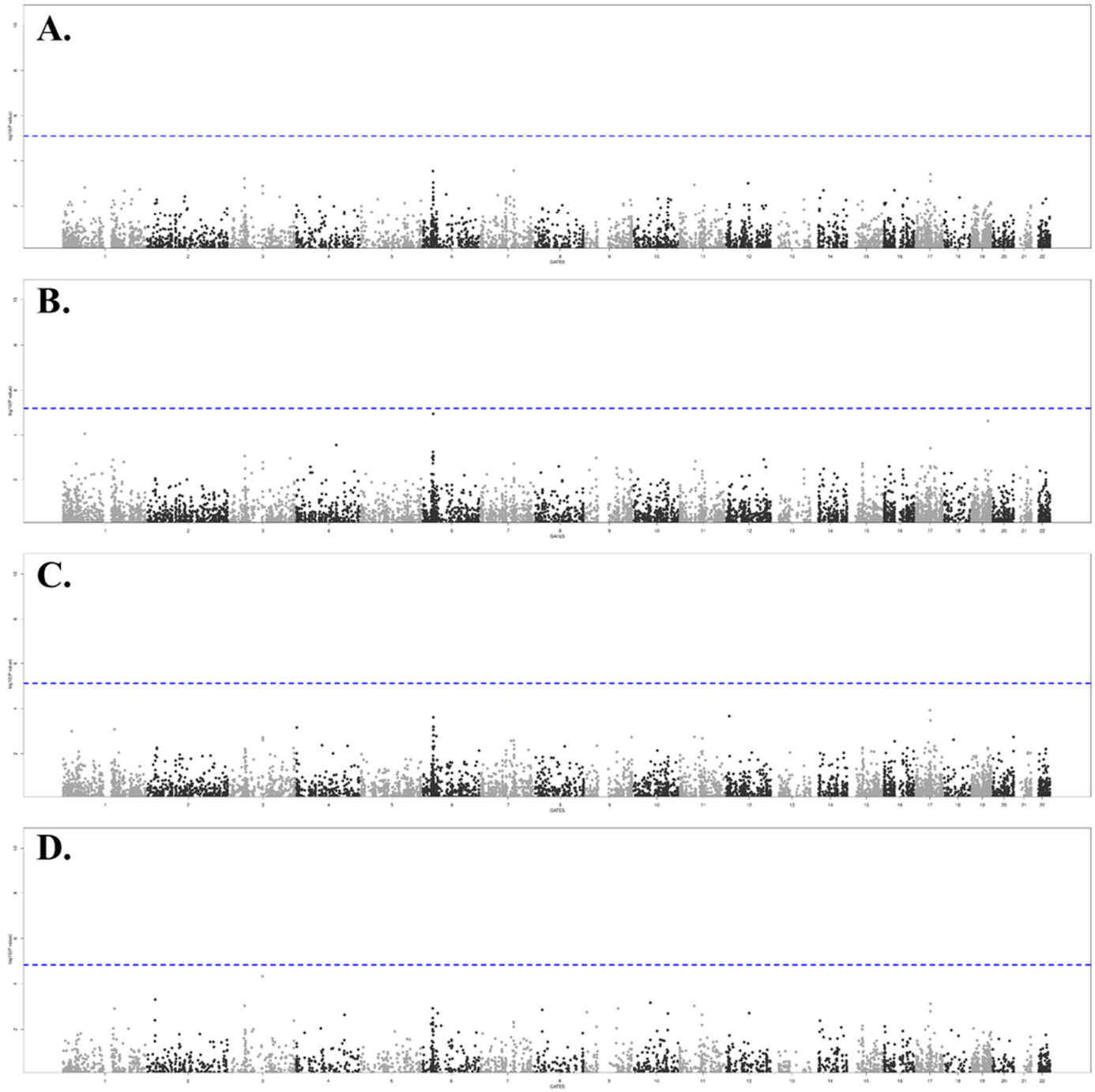


Figure S5. Manhattan plots of S-Predixcan results in **A.** bloods, **B.** lung, **C.** aorta (artery) and **D.** coronary (artery) using the MTAG results for AMD with the COVID-19 hospitalization.

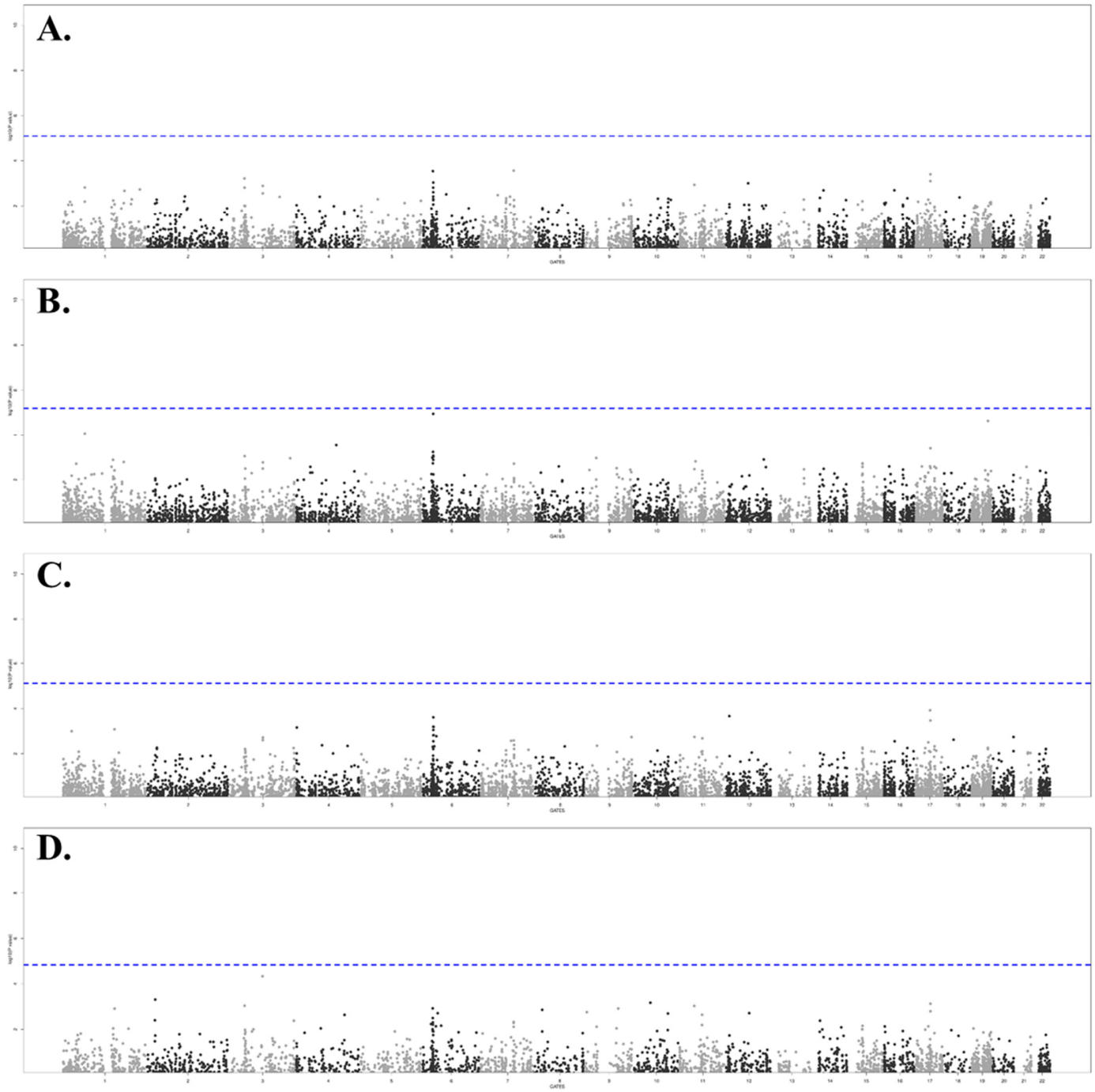
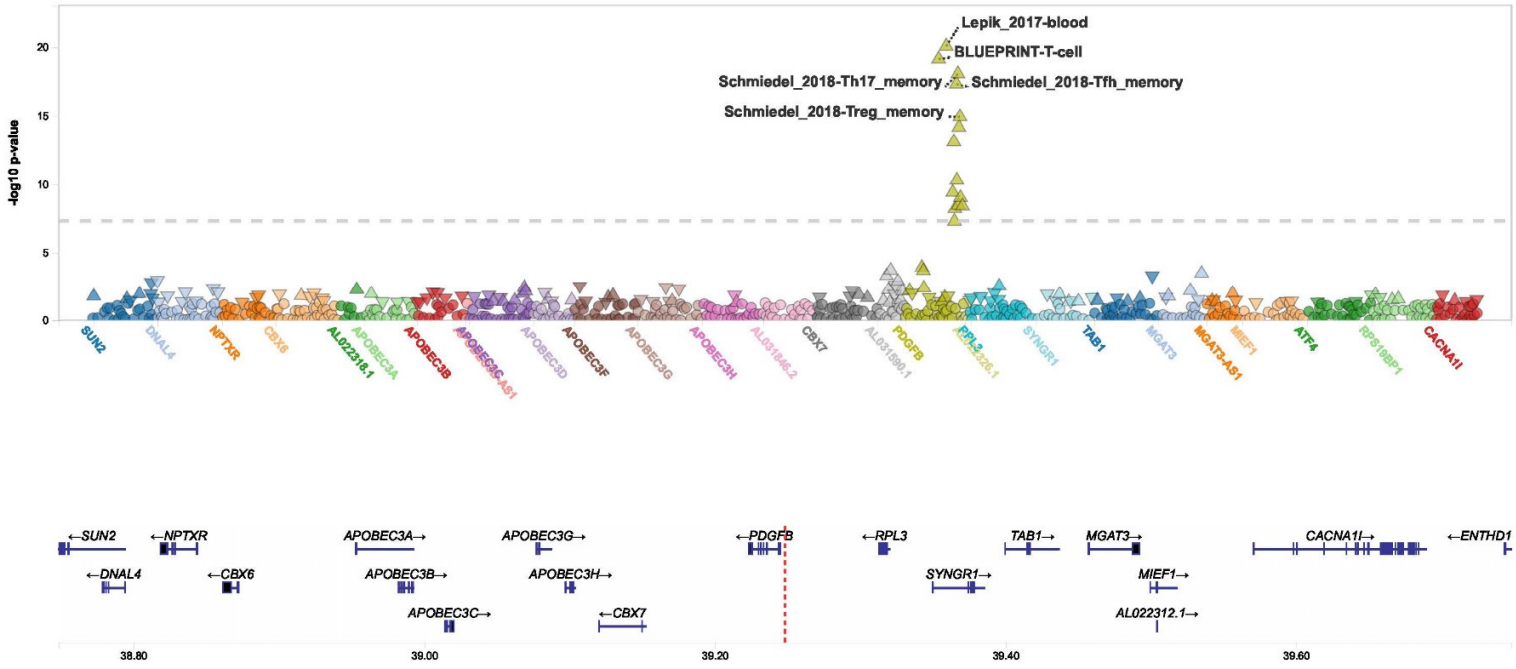


Figure S6. Manhattan plots of S-Predixcan results in **A.** bloods, **B.** lung, **C.** aorta (artery) and **D.** coronary (artery) using the MTAG results for AMD with the COVID-19 infection.


Lepik_2017-blood
BLUEPRINT-T-cell
Schmiedel_2018-Th17_memory
Schmiedel_2018-Tfh_memory
Schmiedel_2018-Treg_memory
-log10 p-value
20
15
10
5
0
SUN2
DNAL4
NPTXR
CBX6
AL022318.1
APOBEC3A
APOBEC3B
APOBEC3C-AS1
APOBEC3D
APOBEC3F
APOBEC3G
APOBEC3H
AL031846.2
CBX7
AL031590.1
PDGFB
RPL3-226.1
SYNGR1
TAB1
MGAT3
MGAT3-AS1
MIEF1
ATF4
RPS19BP1
CACNA1I
←SUN2
←NPTXR
APOBEC3A→
APOBEC3G→
←PDGFB
←RPL3
TAB1→
MGAT3→
CACNA1I→
←ENTHD1
←DNAL4
←CBX6
APOBEC3B→
APOBEC3H→
SYNGR1→
MIEF1→
APOBEC3C→
←CBX7
AL022312.1→
38.80
39.00
39.20
39.40
39.60

A.

B.

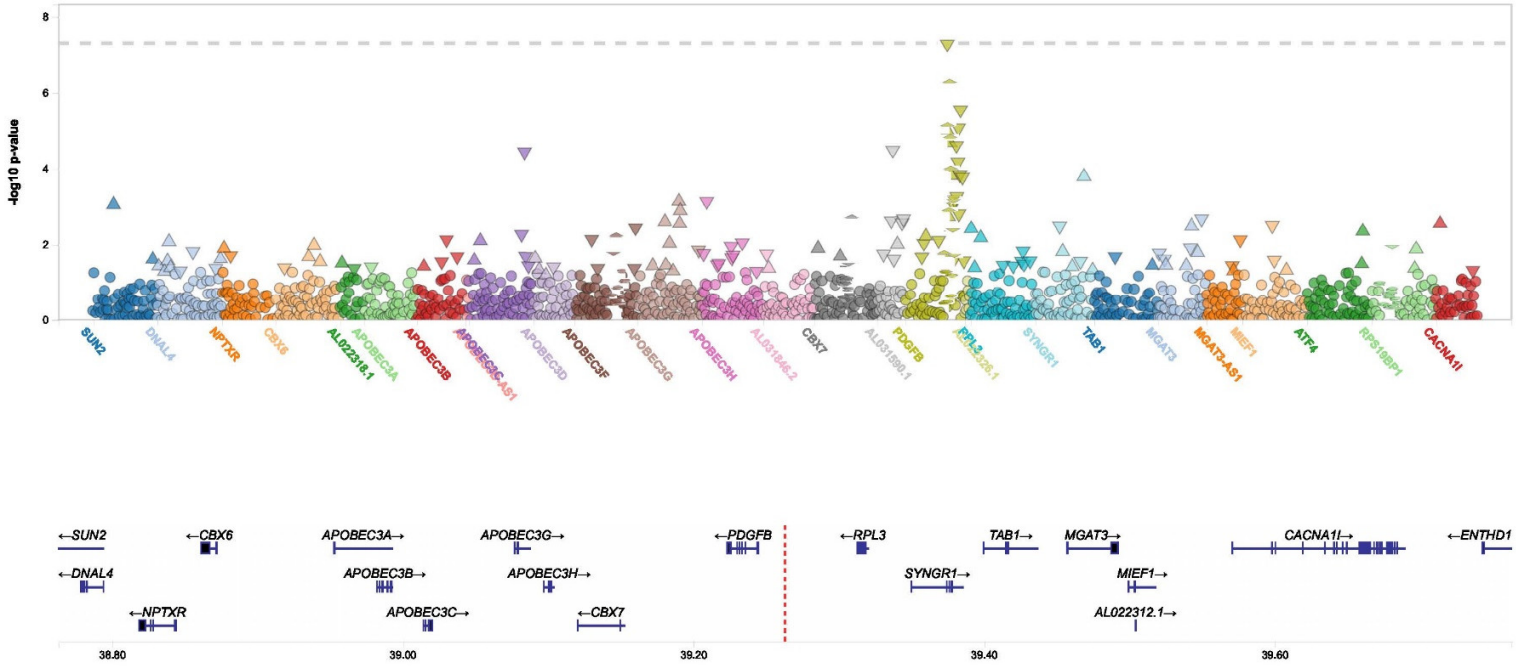


Figure S7. The eQTL P-values from the FIVEx database (https://fivex.sph.umich.edu) of **A.** rs130651 and **B.** rs4820371 with the genes located 500 kilobase pairs from the SNPs. These SNPs are significant cis-eQTLs for regulating *PDGFB* only. We exclude the non-coding genes. The red vertical dot lines indicate the locations of the SNPs. The top eQTL summary statistics are presented in **Table 2**.

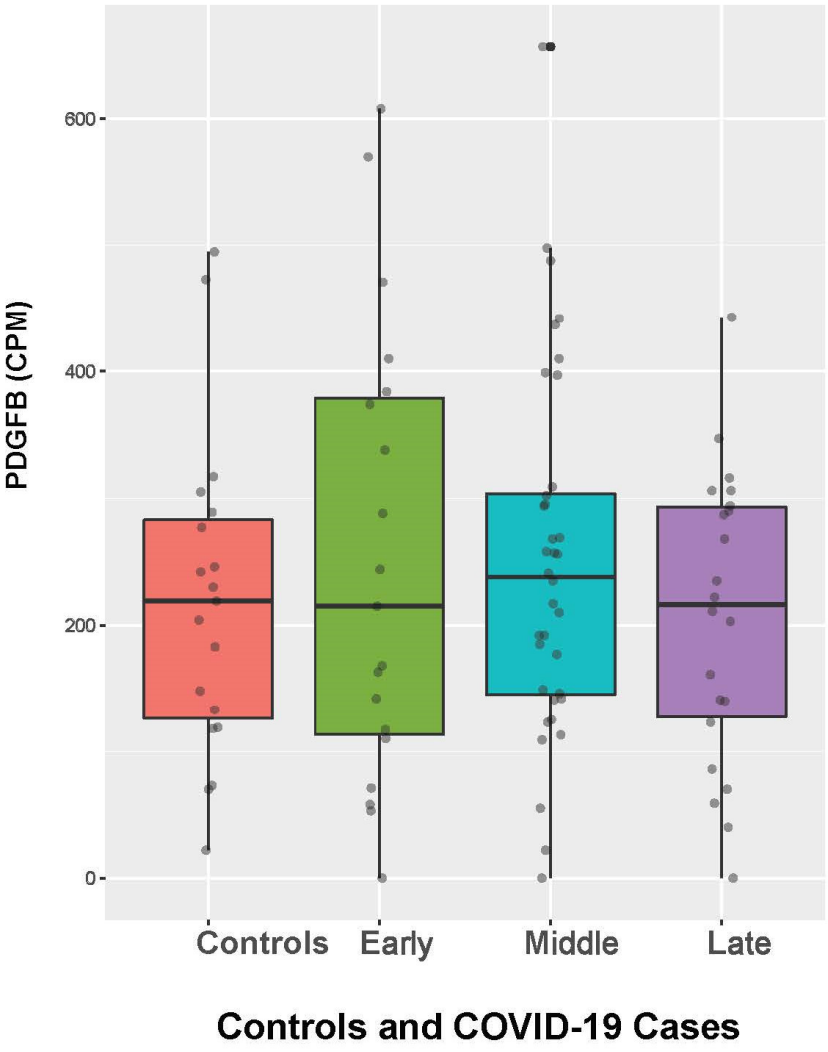
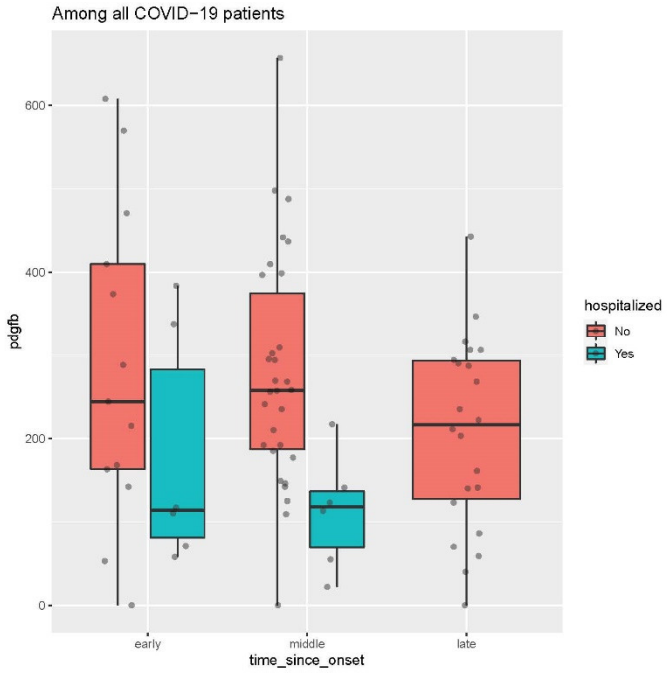
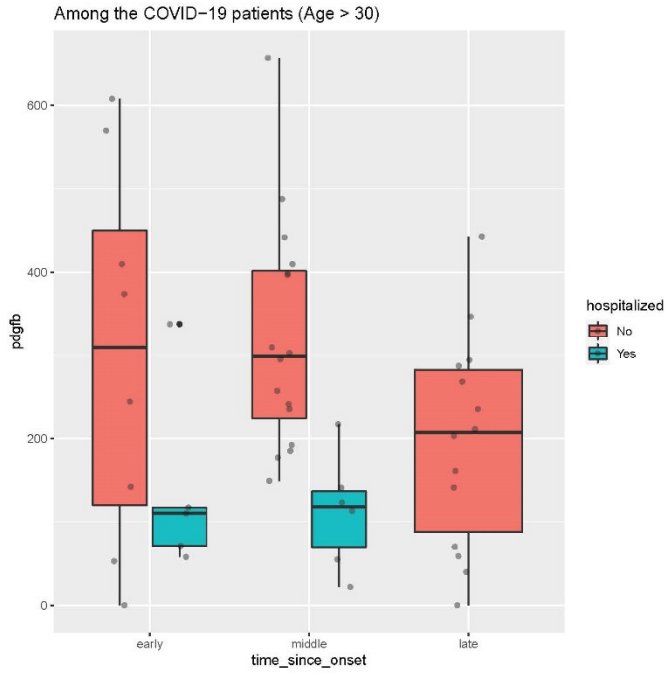


Figure S8. *PDGFB* gene expression levels across COVID-19-free controls and COVID-19 patients in the three different stages by the time after the symptom onset (early ≤10 days, middle 11-20 days, late ≥ 21 days). The Y-axis is the *PDGFB* gene expression level in the counts-per-million (CPM) unit.

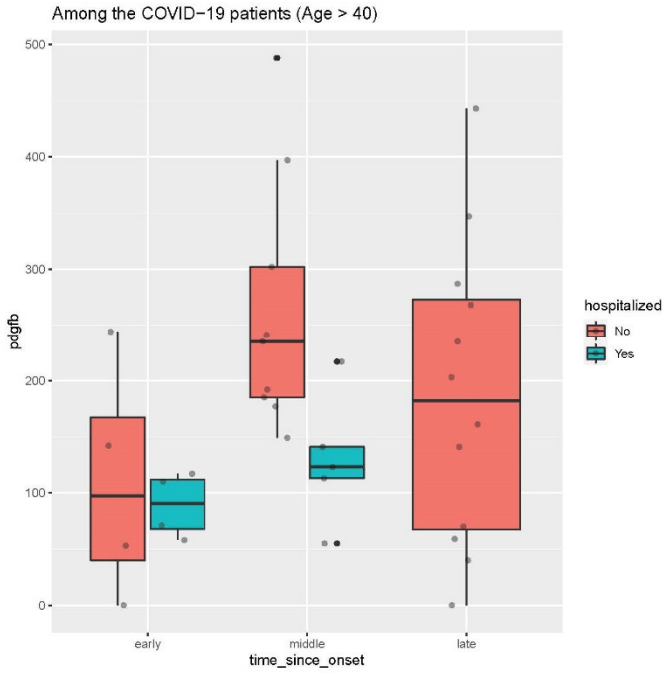
A.


Among all COVID−19 patients
600
400
200
0
plgfb
early
middle
late
time_since_onset
hospitalized
No
Yes

B.


Among the COVID−19 patients (Age > 30)
plgfb
600
400
200
0
early
middle
late
time_since_onset
hospitalized
No
Yes

C.


Among the COVID−19 patients (Age > 40)
plgfb
500
400
300
200
100
0
early
middle
late
time_since_onset
hospitalized
No
Yes

D.

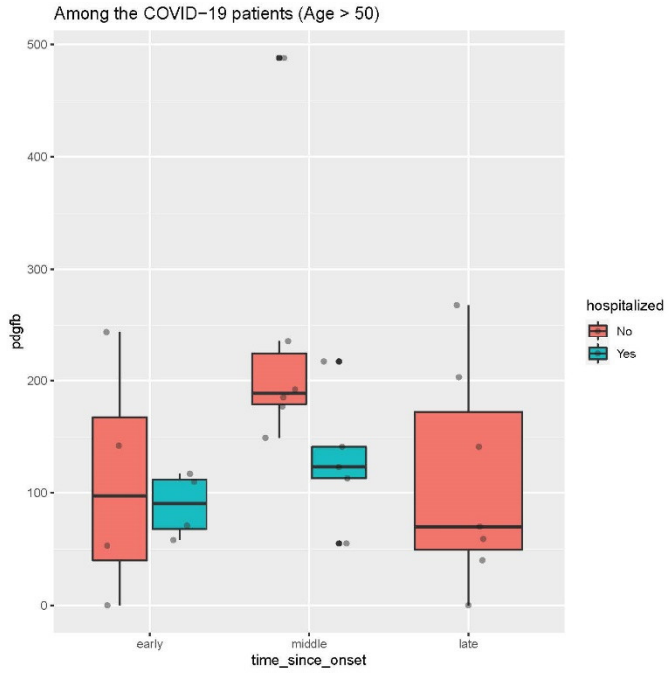


Figure S9. PDGFB gene expression levels at the three different stages of COVID-19 by the time after the symptom onset (early ≤10 days, middle 11-20 days, late ≥ 21 days) in different age groups: **A.** all sample, **B.** age > 30, **C.** age > 40, and **D.** age > 50.