nature immunology

MATTERS ARISING

https://doi.org/10.1038/s41590-022-01227-w

Check for updates

Genetic determinants of mannose-binding lectin activity predispose to thromboembolic complications in critical COVID-19

Michael Hultström[1,2,3,4,13], Robert Frithiof[1,13], Jonathan Grip[5,6,13], Linnea Lindelöf[7,13], Olav Rooijackers[5,6], Sara Pigazzini[8], Mari Niemi[8], Mattia Cordioli[8], Lindo Nkambule[8], Tomislav Maricic[9], Kristina Nilsson Ekdahl[7,10], Bo Nilsson[7], Miklós Lipcsey[1,11], Hugo Zeberg[9,12,13] ✉ and Oskar Eriksson[7,13] ✉

ARISING FROM Stravalaci et al. *Nature Immunology* https://doi.org/10.1038/s41590-021-01114-w (2022)

A recent study demonstrated that the complement recognition protein mannose-binding lectin (MBL) can bind to glycosylated SARS-CoV-2 spike protein. Binding activated complement in a spike-dependent manner and inhibited severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in in vitro models[1]. Furthermore, genetic variants near or in the *MBL2* gene that encodes MBL in humans were suggested as being associated with COVID-19 requiring hospitalization.

In the present study, we carried out genetic and biochemical analyses of MBL activity in plasma in a multicenter cohort of critically ill COVID-19 patients and interrogated the publicly available summary statistics from the COVID-19 Human Genetics Initiative (COVID-19 HGI)[2]. We found no evidence that genetic variants that determine activity of the MBL pathway are associated with hospitalization or intensive care admission due to SARS-CoV-2 infection. Instead, we demonstrated that *MBL2* haplotypes determine risk for thrombotic complications in critically ill COVID-19 patients. Specifically, genetically determined MBL activity confers risk for pulmonary embolism in a U-shaped manner, where haplotypes associated with intermediate MBL activity are protective. Our results demonstrate a complement-dependent mechanism for COVID-19-associated thrombosis and provide an example of how genetic variation in the innate immune system modulates thrombosis risk.

Patients, 426, admitted to the intensive care units at 2 tertiary hospitals in Uppsala and Stockholm, Sweden, were prospectively included in the SweCovid initiative[3] between March 2020 and September 2021. Demographics and comorbidities of the cohort are shown in Supplementary Table 1. We analyzed MBL activity in plasma and used whole-genome genotyping data to impute genetic variants and construct haplotypes encompassing the *MBL2* gene.

MBL activity in plasma displays extensive interindividual variability, which is largely determined by genetic variants located in exon 1 of the *MBL2* gene or upstream of the transcription start site[4]. We imputed the genotypes of five genetic variants that, due to linkage disequilibrium, form six common *MBL2* haplotypes (Table 1, rows 1–5). These include two high-expressing haplotypes (legacy names HYA and LYA) and one low-expressing haplotype (legacy name LXA), where 'A' indicates that these haplotypes express wild-type MBL protein. In addition, three commonly occurring missense variants in the collagen-like domain of MBL (legacy names D, B and C; haplotypes HYD, LYB and LYC) lead to amino-acid substitutions that impair MBL multimerization in a dominant-negative manner, resulting in monomeric or oligomeric MBL with little or no lectin activity. These variants result in complete MBL deficiency in the homozygous state or in combination with the LXA haplotype, but show moderate MBL activity in combination with the high-expressing HYA and LYA haplotypes[5]. In agreement with previous studies, these *MBL2* haplotypes showed a strong genotype–phenotype correlation and predicted MBL activity in plasma (Fig. 1a). Allele frequencies of the individual genetic variants did not differ from the general European population in our cohort, which has predominantly European ancestry (Table 1, rows 1–5). In contrast, Stravalaci et al.[1] demonstrated a moderate association between the D allele (rs5030737-A), or a combination of missense variants, and risk of COVID-19 requiring hospitalization in an Italian cohort of 332 cases and 1,668 controls. As the D allele is a loss-of-function variant, it was suggested that MBL has a protective effect against severe COVID-19. However, the B and C variants (rs1800450-T and rs1800451-T) share a common biological effect with the D variant, and would therefore be expected to give rise to similar signals in association studies if MBL loss of function were associated with COVID-19 risk.

We further interrogated these variants in COVID-19 HGI release 6, the largest meta-analysis of genetic association studies on

[1]Anesthesiology and Intensive Care Medicine, Department of Surgical Sciences, Uppsala University, Uppsala, Sweden. [2]Integrative Physiology, Department of Medical Cell Biology, Uppsala University, Uppsala, Sweden. [3]Department of Epidemiology, McGill University, Montréal, Quebec, Canada. [4]Lady Davis Institute of Medical Research, Jewish General Hospital, Montréal, Quebec, Canada. [5]Department of Perioperative Medicine and Intensive Care, Karolinska University Hospital, Stockholm, Sweden. [6]Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Stockholm, Sweden. [7]Department of Immunology, Genetics and Pathology, Uppsala University, Uppsala, Sweden. [8]Institute for Molecular Medicine Finland, University of Helsinki, Helsinki, Finland. [9]Department of Evolutionary Genetics, Max Planck Institute for Evolutionary Anthropology, Leipzig, Germany. [10]Linnaeus Center for Biomaterials Chemistry, Linnaeus University, Kalmar, Sweden. [11]Hedenstierna Laboratory, Department of Surgical Sciences, Uppsala University, Uppsala, Sweden. [12]Department of Neuroscience, Karolinska Institutet, Stockholm, Sweden. [13]These authors contributed equally: Michael Hultström, Robert Frithiof, Jonathan Grip, Linnea Lindelöf, Hugo Zeberg, Oskar Eriksson. ✉e-mail: hugo.zeberg@ki.se; oskar.eriksson@igp.uu.se

Table 1 | Candidate genetic variants in *MBL2* locus and their association with COVID-19 outcome in the COVID-19 HGI (release 6)

rs ID	Coordinates and alleles (GRCh38/hg38)	Legacy name	AF SweCovid	AF gnomAD (European non-Finnish)	ORs for hospitalization in COVID-19 HGI (95% CI)	*P* value for hospitalization in COVID-19 HGI	Odds ratios for advanced respiratory support in COVID-19 HGI (95% CI)	*P* value for advanced respiratory support in COVID-19 HGI
rs1800451	chr10:52771466:C:T	C	0.02	0.02	1.01 (0.96–1.07)	0.64	1.12 (1.01–1.26)	0.04
rs1800450	chr10:52771475:C:T	B	0.15	0.14	1.02 (0.99–1.05)	0.25	1.02 (0.97–1.08)	0.39
rs5030737	chr10:52771482:G:A	D	0.07	0.07	0.99 (0.95–1.04)	0.75	1.00 (0.93–1.08)	0.99
rs7096206	chr10:52771925:G:C	X/Y	0.78	0.77	0.99 (0.96–1.01)	0.34	0.96 (0.90–0.99)	0.02
rs11003125	chr10:52772254:G:C	L/H	0.34	0.38	0.99 (0.97–1.01)	0.41	0.96 (0.92–1.00)	0.04
rs150342746	chr10:53229424:C:T	N/A	0.01	8.6×10^{-3}	1.11 (0.96–1.28)	0.17	1.22 (0.96–1.56)	0.10
rs10824845	chr10:52963964:G:A	N/A	0.09	0.08	1.02 (0.98–1.07)	0.28	1.01 (0.94–1.09)	0.72
rs11816263	chr10:53083059:C:A	N/A	0.36	0.32	1.00 (0.98–1.03)	0.80	N/A	N/A
rs74974397	chr10:53104393:A:G	N/A	0.03	0.03	1.05 (0.98–1.13)	0.16	1.12 (1.00–1.25)	0.04
rs71032688	chr10:53082503:A:AT	N/A	0.73	0.75	0.99 (0.96–1.02)	0.45	N/A	N/A
rs117108247	chr10:53155596:C:T	N/A	0.03	0.03	1.05 (0.98–1.13)	0.15	1.10 (0.99–1.23)	0.08

The five genetic variants that form the major *MBL2* haplotypes are indicated by their legacy names: rs1800451 (p.Gly57Glu), rs1800450 (p.Gly54Asp) and rs5030737 (p.Arg52Cys) are missense variants, whereas rs7096206 and rs11003125 are promoter variants; rs150342746, rs10824845, rs11816263, rs74974397, rs71032688 and rs117108247 were identified as candidate variants associated with COVID-19 risk in the study by Stravalaci et al.[1]. Allele frequencies (AFs) give the frequency of the alternative (nonreference) allele. AFs for individuals of European non-Finnish ancestry are shown as a reference and were obtained from gnomAD (gnomad.broadinstitute.org). Outcomes in COVID-19 HGI were either hospitalization or requirement for respiratory support more than supplemental oxygen. The hospitalization analysis is based on 24,274 hospitalized cases and 2,061,529 controls whereas the respiratory support analysis is based on 8,779 cases and 1,001,875 controls. N/A, not available.

COVID-19 to date[2]. We found no effect of the D allele on either hospitalization or care requiring more respiratory support than supplemental oxygen (Table 1). Similar results were obtained for the B allele, whereas the C allele was nominally significant for the latter outcome, but with a modest odds ratio (OR) that did not pass multiple testing correction. These results show that genetic variants that impair MBL function do not substantially increase the risk of COVID-19 requiring hospitalization or advanced respiratory support.

Stravalaci et al.[1] also conducted an extended analysis of a 1-MB region encompassing the *MBL2* locus and found several candidate genetic variants for COVID-19 risk. Interrogation of COVID-19 HGI revealed that none of these variants was associated with COVID-19 requiring hospitalization (Table 1, rows 6–11). The G allele at rs74974397 was nominally significant for COVID-19 requiring advanced respiratory support, but did not pass multiple testing correction. We also analyzed these variants in the SweCovid cohort. Allele frequencies did not differ from the general population (Table 1, rows 6–11) and we did not observe a significant effect on MBL activity in plasma for any of these variants ($P > 0.05$).

Even though MBL does not affect the risk of hospitalization or severity on SARS-CoV-2 infection, it could still modulate the clinical phenotype. We categorized the individual *MBL2* haplotypes according to MBL activity into three groups (high activity, intermediate activity and deficient; Fig. 1b) and analyzed their association with outcome in the SweCovid cohort. *MBL2* haplotype groups were not associated with either the need for invasive ventilation or renal replacement therapy or 90-day survival (Supplementary Table 2). Instead, we observed a strong association with thrombotic complications and pulmonary embolism. Unexpectedly, the association was U shaped, with intermediate *MBL2* activity haplotypes being protective (Fig. 1c and Supplementary Table 2). Pulmonary embolism is a major complication among hospitalized COVID-19 patients[6] and may be the result of a primary pulmonary thrombosis without a coexisting distal venous thrombosis[7]. The protective effect of intermediate *MBL2* haplotypes was even more pronounced in this group, suggesting that MBL primarily influences thrombotic reactions in the lung.

The hypercoagulable state in severe COVID-19 is well recognized and characterized by widespread fibrin deposition in lung capillaries and elevated plasma D-dimer levels[8–10]. Biomarker analysis showed a nonsignificant trend toward lower D-dimer levels in the intermediate *MBL2* haplotype group, as well as significantly higher levels of the coagulation inhibitor antithrombin, which together indicate a lower degree of coagulation activation (Supplementary Table 3). Despite conferring protection from thrombosis, intermediate *MBL2* haplotypes were not associated with increased survival, in line with observations that pulmonary embolisms do not contribute significantly to COVID-19 mortality if managed appropriately[6,11].

Is a U-shaped association between MBL activity and thrombosis biologically plausible? Deficiency in early complement components is associated with defective clearance of cellular debris and apoptotic cells[12,13]. Given the data presented by Stravalaci et al.[1], MBL recognition of spike protein expressed on SARS-CoV-2-infected cells could assist in their clearance, thus removing an important source of potentially thrombogenic material from the intravascular space. In contrast, in the context of haplotypes associated with high MBL activity, SARS-CoV-2-infected cells could instead provide an abundant substrate for MBL-dependent complement activation. The prothrombotic effects of excessive complement activation are well recognized and stem from complement-mediated endothelial damage and induction of tissue factor expression on monocytes[14]. In this scenario, intermediate MBL levels may provide sufficient clearance of thrombogenic material, and yet will not lead to bystander cell damage and cell activation due to unconstrained complement activation. In support of this concept, a U-shaped association between MBL and thrombosis risk has been observed in the case of cardiovascular disease and diabetes, where intermediate MBL levels were protective[15].

A challenge in host genetic studies is the plethora of factors that can modulate genetic risk. As the COVID-19 pandemic has unfolded, changes in treatment strategies and virus variants have followed that may contribute to differences in effect size of genetic associations. In this context it should be noted that the SweCovid cohort covers the first three major pandemic waves corresponding

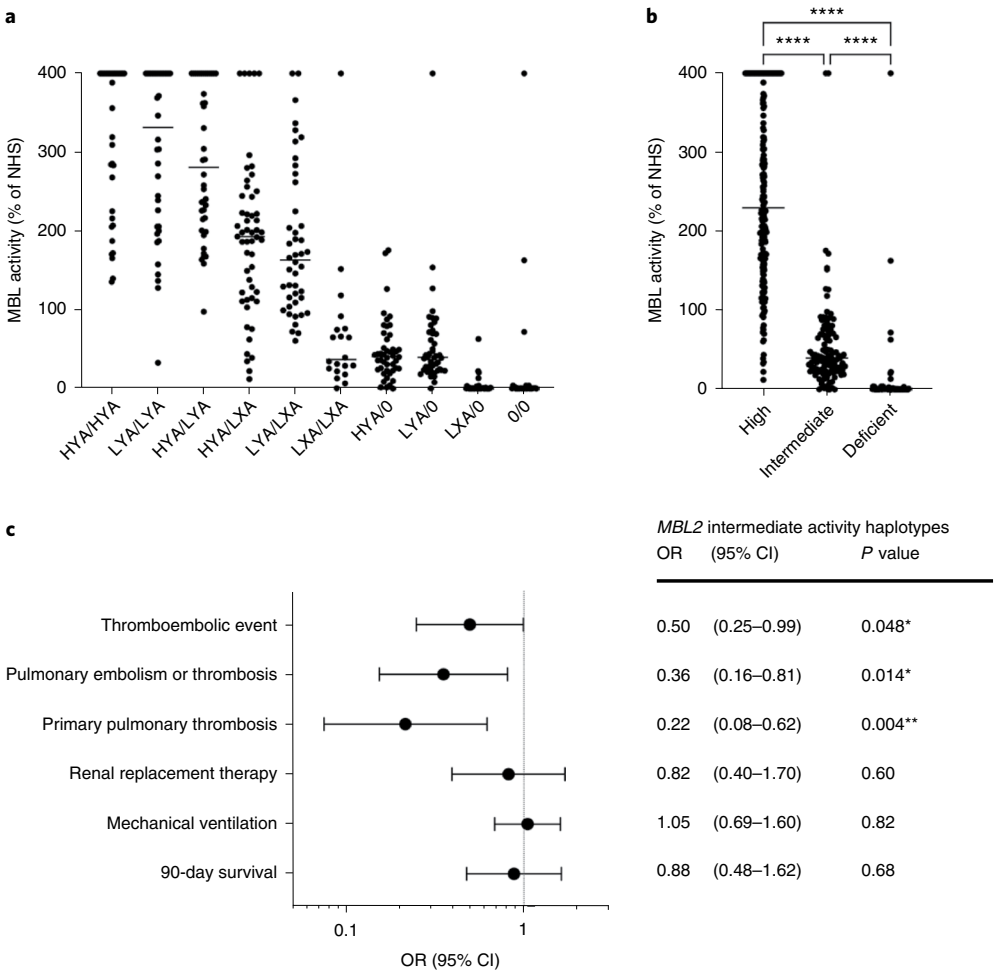

Fig. 1 | *MBL2* haplotypes predict MBL activity in plasma and thromboembolic complications during intensive care. a, MBL activity across individual haplotype combinations. MBL activity in plasma at day 1 of intensive care was measured by a functional ELISA using a mannan matrix for MBL capture. Activity is expressed as a percentage of pooled normal human serum (NHS). The genetic variants shown in Table 1, rows 1–5 give rise to six major *MBL2* haplotypes, which are denoted by their legacy names: HYA, LYA, LXA, HYD, LYB and LYC. The HYA, LYA and LXA haplotypes encode wild-type MBL protein and are referred to as 'A' haplotypes. The HYD, LYB and LYC haplotypes contain the missense variants referred to as the D, B or C alleles, respectively, and are shown together as '0' haplotypes because they share a common deleterious effect on MBL activity. **b**, Haplotypes categorized according to MBL activity into high (HYA/HYA, LYA/LYA, HYA/LYA, HYA/LXA, LYA/LXA), intermediate (LXA/LXA, HYA/0, LYA/0) and deficient (LXA/0, 0/0). MBL activity differed significantly between the groups (230% (168–400, median and interquartile range) for the high group, 40% (24–70) for the intermediate group and 0.56% (0.00–1.25) for the deficient group; $P < 0.0001$). The horizontal bars indicate the median. **c**, Forest plot displaying ORs with 95% confidence intervals (CIs) for thromboembolic events, renal replacement therapy, need for mechanical ventilation and 90-day survival. Primary pulmonary thrombosis comprises events without a known concurrent distal venous thrombosis. A logistic regression model with *MBL2* intermediate activity haplotypes, sex and age as covariates was used. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{****}P < 0.0001$.

to the original SARS-CoV-2 variant as well as the alpha and delta variants of concern. Likewise, COVID-19 HGI, release 6 represents a world-wide meta-analysis of COVID-19 studies from the start of the pandemic until 30 April 2021, thus taking into account differences in hospital systems and geographical locations.

The unique polymorphic nature of the *MBL2* locus, with a high frequency of naturally occurring knockouts devoid of functional MBL, allows for an assessment of the role of MBL activity in observational studies. We show that genetically determined MBL deficiency does not influence the risk of COVID-19 requiring hospitalization or admission to intensive care. Instead, our results demonstrate that the interaction between genetic variation in the *MBL2* gene and SARS-CoV-2 infection determines thrombosis risk in critically ill patients, a finding with important clinical implications given the high rate of thrombotic complications in COVID-19 patients.

Online content

Any methods, additional references, Nature Research reporting summaries, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41590-022-01227-w.

Received: 19 February 2022; Accepted: 26 April 2022;
Published online: 27 May 2022

References

1. Stravalaci, M. et al. Recognition and inhibition of SARS-CoV-2 by humoral innate immunity pattern recognition molecules. *Nat. Immunol.* **23**, 275–286 (2022).
2. Niemi, M. E. K. et al. Mapping the human genetic architecture of COVID-19. *Nature* **600**, 472–477 (2021).

3. SweCovid. The genetic predisposition to severe COVID-19. Genomic analysis of critically ill COVI-19 patients in Sweden. https://swecovid.org
4. Garred, P. et al. A journey through the lectin pathway of complement—MBL and beyond. *Immunol. Rev.* **274**, 74–97 (2016).
5. Madsen, H. O. et al. Interplay between promoter and structural gene variants control basal serum level of mannan-binding protein. *J. Immunol.* **155**, 3013–3020 (1995).
6. Miró, Ò. et al. Pulmonary embolism in patients with COVID-19: incidence, risk factors, clinical characteristics, and outcome. *Eur. Heart J.* **42**, 3127–3142 (2021).
7. Ackermann, M. et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. *N. Engl. J. Med.* **383**, 120–128 (2020).
8. Leentjens, J., Haaps, T. F., van, Wessels, P. F., Schutgens, R. E. G. & Middeldorp, S. COVID-19-associated coagulopathy and antithrombotic agents—lessons after 1 year. *Lancet Haematol.* **8**, e524–e533 (2021).
9. Eriksson, O. et al. Mannose-binding lectin is associated with thrombosis and coagulopathy in critically ill COVID-19 patients. *Thromb. Haemost.* **120**, 1720–1724 (2020).
10. Lipcsey, M. et al. The outcome of critically ill COVID-19 patients is linked to thromboinflammation dominated by the kallikrein/kinin system. *Front. Immunol.* **12**, 627579 (2021).
11. Gómez, C. A. et al. Mortality and risk factors associated with pulmonary embolism in coronavirus disease 2019 patients: a systematic review and meta-analysis. *Sci. Rep.* **11**, 16025 (2021).
12. Leffler, J., Bengtsson, A. A. & Blom, A. M. The complement system in systemic lupus erythematosus: an update. *Ann. Rheum. Dis.* **73**, 1601–1606 (2014).
13. Stuart, L. M., Takahashi, K., Shi, L., Savill, J. & Ezekowitz, R. A. B. Mannose-binding lectin-deficient mice display defective apoptotic cell clearance but no autoimmune phenotype. *J. Immunol.* **174**, 3220–3226 (2005).
14. Eriksson, O., Mohlin, C., Nilsson, B. & Ekdahl, K. N. The human platelet as an innate immune cell: interactions between activated platelets and the complement system. *Front. Immunol.* **10**, 1590 (2019).
15. Gedebjerg, A. et al. Mannose-binding lectin and risk of cardiovascular events and mortality in type 2 diabetes: a Danish cohort study. *Diabetes Care* **43**, 2190–2198 (2020).

Reporting summary

Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

Data have been deposited at the European Genome–Phenome Archive (available at ega-archive.org) under the accession number EGAS00001006266. The COVID-19 HGI summary statistics are available at https://www.covid19hg.org/results/r5 and on the GWAS (Genome Wide Association Studies) Catalog (study code GCST011074).

Acknowledgements

We thank research nurses J. Wessbergh and E. Söderman for their expertize in compiling patient data, and Biobank assistants P. Karlsson, E. Danielsson, L. Spång, A. Svensson and K. Kilsand for sample collection and patient inclusion. Genotyping was performed by the Genotyping Laboratory of the Institute for Molecular Medicine Finland (FIMM) Technology Centre, University of Helsinki, and by the National Genomics Infrastructure at SciLifeLab, Uppsala University. We thank the Science for Life Laboratory, the National Genomics Infrastructure (NGI) and Uppmax for providing assistance in genotyping and computational infrastructure. The study was funded by the SciLifeLab/Knut and Alice Wallenberg national COVID-19 research program (grant nos. KAW 2020.0182 and KAW 2020.0241 to M.H.) the Swedish Heart–Lung Foundation (grant nos. 20210089, 20190639 and 20190637 to M.H. and 20200822 to B.N.), Swedish Research Council (grant nos. 2014-02569 and 2014-07606 to R.F., 2021-03050 to H.Z. and 2021-02252 to B.N.), the Swedish Kidney Foundation (grant no. F2020-0054 to R.F.), the Swedish Society of Medicine (grant nos. SLS-943007 to O.E. and SLS-938101 to M.H.), the Jeansson foundation (grant no. J2021-0062 to O.E.) and the Göran Gustafsson Foundation (to O.E.). Funding bodies had no role in the design of the study, data collection, interpretation or writing of the manuscript.

Author contributions

All the authors contributed to project design and planning, data analysis and interpretation. M.H., R.F., J.G., O.R. and M.L. collected patient data and materials. L.L. performed MBL activity assays. T.M. performed DNA extraction. S.P., M.N., M.C. and L.N. performed genotyping and quality control. K.N.E. and B.N. provided vital reagents and tools. H.Z. led the genotyping effort, and performed genotype imputations and COVID-19 HGI analyses. O.E. conceived the study, devised the methodology and wrote the first draft. J.G. and L.L. shared authorship as second authors. All authors revised the paper and approved the final version for publication.

Competing interests

The authors declare no competing interests.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41590-022-01227-w.

Correspondence and requests for materials should be addressed to Hugo Zeberg or Oskar Eriksson.

Peer review information *Nature Immunology* thanks the anonymous reviewers for their contribution to the peer review of this work.

nature portfolio

Corresponding author(s): Oskar Eriksson

Last updated by author(s): Apr 24, 2022

Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒ The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒ A description of all covariates tested
☐	☒ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	The summary statistics of each cohort was provided as described in the Methods section.
Data analysis	Genetic data in PLINK-format was converted to VCF using PLINK (version 1.9) for subsequent phasing and imputation using the TopMED imputation server. Genetic variants were queried in the imputed VCF using tabix (version 1.14).

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

Data will be available from the European Genome-Phenome Archive (available at ega-archive.org) pending completion of data submission and data access agreements.
The COVID-19 Host Genetics Initiative summary statistics are available at https://www.covid19hg.org/results/r5/ and are available on GWAS Catalog (study code GCST011074).

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	All patients that fulfilled the criteria for study inclusion and provided informed consent were included.
Data exclusions	A PCR confirmed SARS-Cov-2 infection was required for study inclusion, hence patients that had suspected COVID-19 that was not possible to confirm were excluded from the study.
Replication	For the SweCovid cohort, patients were recruited from two independent and geographically separated hospitals. Selected results were replicated in the COVID-19 Human Genetics Initiative, the largest meta-analysis of COVID-19 genetic association studies to date. The MBL activity assay has been validated previously. Antibodies used in the assay were confirmed to be specific for MBL, and do not bind other related complement proteins.
Randomization	Not relevant to the present study, as it would be unrealistic and unethical to randomize individuals to SARS-CoV-2 infection.
Blinding	There were no treatment or interventions that were part of the study. Clinicians treating COVID-19 patients could not be blinded for practical reasons. The genotype status did not influence the choice to hospitalize COIVD-19 patients. Researchers were blinded to genotype data when performing clinical data adjudication.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☐	☒ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Human research participants
☐	☒ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used	The antibody against human MBL was from R&D Systems, Cat. No. AF2307, lot UIG0119031.
Validation	The anti-MBL antibody was extensively validated for the MBL activity assay. No signal was obtained when tested in other assays. Samples from individuals with loss-of-function mutations in MBL were used as negative controls; the assay gave no signal for these samples.

Human research participants

Policy information about studies involving human research participants

Population characteristics	Please refer to Supplemental table 1 in the manuscript for details on the study population such as demographic data and co-morbidities of the SweCovid cohort. Population characteristics for the contributing studies to the COVID19 Host Genetics Intitative are given in Supplementary Table 1 of the flagship paper available at: doi: https://doi.org/10.1038/s41586-021-03767-x.
Recruitment	Participants were continuously recruited as they were admitted to the intensive care unit with confirmed COVID-19. Given these criteria, self-selection bias is deemed unlikely.

Ethics oversight	SweCovid was approved by the Swedish Ethical Review Authority. The COVID19 Host Genetics Initiative complies with all relevant ethical regulations and the contributing genetic association studies were approved by the VA Central Institutional Review Board (VA Million Veteran Program), the Jewish General Hospital research ethics board (Biobanque Québécoise de la COVID-19), the Institutional Review Board of Perelman School of Medicine at University of Pennsylvania (Penn Medicine Biobank), the Institutional Review Board of Columbia University (Columbia University Biobank), the research ethics committees of Scotland 15/SS/0110; England, Wales and Northern Ireland 19/WM/0247 (GenOMICC), and the North West Multi-centre Research Ethics Committee (UK Biobank).

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	NCT04316884 (SweCovid)
Study protocol	www.clinicaltrials.gov
Data collection	SweCovid participants were recruited between March 13, 2020 and September 3, 2021. Data was collected continuously at the study centers.
Outcomes	Outcomes were mortality, kidney and respiratory failure, and thromboembolic events. Details on the outcomes were extracted form the participants' medical records.