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COVID-19 susceptibility and severity for dyslipidemia: A mendelian randomization investigation

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ABSTRACT

Background: The severe acute respiratory syndrome coronavirus in 2019 (COVID-19) is still spreading and causing deaths worldwide, which further increased the burden of chronic diseases. Dyslipidemia is a common metabolic syndrome, which is a major risk factor for cardiovascular disease. However, studies on whether there is a direct causal relationship between COVID-19 and the exacerbation of hyperlipidemia are still scarce.
Methods: Two-sample Mendelian randomization was conducted using publicly available summary statistics from independent cohorts of European ancestry. For COVID-19 and hyperlipidemia, we used data from the ieu open GWAS project database. Inverse variance-weighted, mendelian randomization Egger, weighted median, simple mode, and weighted mode mendelian randomization analyses were performed, together with a range of sensitivity analyses.
Results: There is no direct causal relationship between COVID-19 and dyslipidemia, regardless of COVID-19 severity or either dyslipidemic outcome. In combination with previous studies, the reason for the clinical outcome that COVID-19 increased the burden of dyslipidemia may be due to the exacerbation of pre-existing disease caused by COVID-19.
Conclusions: COVID-19 has no direct causal relationship with dyslipidemia.

1. Introduction

The severe acute respiratory syndrome Coronavirus in 2019 (COVID-19) is still spreading and causing deaths worldwide. According to data submitted to WHO, 756,581,850 cases of COVID-19 have been diagnosed and 6,844,267 patients have died due to COVID-19 worldwide since its discovery as of February 17, 2023. Although the incidence has been significantly reduced due to advances in prevention and management measures and empirical targeted treatment, the morbidity and mortality of COVID-19 remain very high, as evidenced by the latest data of more than 6.7 million new cases and 64,000 deaths during the last month (January 16 to February 12, 2023) [1].

Since all organs in the body are affected by COVID-19, previous studies have shown that COVID-19 is often closely related to the prognosis of pulmonary function [2], coagulation [3], cardiovascular and cerebrovascular diseases [4–8]. Recently, studies related to COVID-19 have focused on the association between COVID-19 and dyslipidemia. Dyslipidemia is a common metabolic disorder, and

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the most common clinical subtype is hyperlipidemia, which is characterized by elevated levels of total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and reduced high-density lipoprotein cholesterol (HDL-C) [9]. In addition, hyperlipidemia is a major risk factor for atherosclerotic cardiovascular disease, hypertension, and cerebrovascular disease [9–12].

The previous study revealed that hyperlipidemia, especially higher total cholesterol and ApoB levels, increases the susceptibility and severity of COVID-19 [13], and an increase in dyslipidemia and hypolipidemic agents use after COVID-19 was observed [14]. However, studies on whether there is a direct causal relationship between COVID-19 and the exacerbation of hyperlipidemia are still scarce.

Mendelian randomization (MR) is a complementary approach to epidemiologic observations that uses genetic variation as an instrumental variable (IV) and assesses its association with clinical outcomes. The characteristics of MR allow for reliable randomization groupings and reduce the influence of confounding factors, making the results dependable, especially in exploring the causal association between exposure and outcomes. Therefore, we conducted an MR study to investigate the relationship between COVID-19 and dyslipidemia further (Fig. 1).

2. Materials and methods

2.1. Study design

A two-sample MR approach was used to assess the causal effect between COVID-19 and dyslipidemia, according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines. Single nucleotide polymorphisms (SNPs) were chosen as IVs to investigate the association between COVID-19 and dyslipidemia. All selected SNPs met the following hypotheses: (1) The selected SNPs were significantly associated with COVID-19, (2) The selected SNPs were not associated with any other known confounders, (3) The SNPs have an effect on dyslipidemia only through COVID-19.

2.2. Data sources

All data included in this MR analysis were obtained from ieu open gwas project database, a database that summarized various published public GAWS data. The exposure datasets for this MR study were defined by COVID-19 (ebi-a-GCST011073, n = 1683768), severe COVID-19 (ebi-a-GCST011075, n = 1388342), and COVID-19 hospitalization (ebi-a-GCST011081, n = 1887658), the outcome GWAS datasets for assessing dyslipidemia were dyslipidemia (finn-b-E4 HYPERLIPNAS), LDL-C (ieu-b-5089) VLDL cholesterol (met-*d*-VLDL C), HDL-C (ieu b-109), TC (met-*d*-Total C), TG (ieu-b-111), apolipoprotein A (ieu-b-107), apolipoprotein B (ieu-b-108), ratio of apolipoprotein B to apolipoprotein A1 (met-*d*-ApoB byApoA1), and lipoprotein A (ukb-*d*-30790), all exposure and outcome cases were European descent. Detailed characteristics of the exposures and outcomes of GAWS were shown in Table 1.

2.3. Selection of genetic instruments variables

SNPs meeting the following two criteria: (1) GWAS-associated *P* value $< 1*10^{-6}$ [15]. (2) linkage disequilibrium $R^2 < 0.001$, and clumping distance equal to 10,000 kb [16], were considered can minimize the risk of bias from high linkage disequilibrium values. Besides, the F statistics were calculated to evaluate the strength of the associations, and SNPs with F statistic values > 10 were considered to be independently associated with COVID-19 [17].

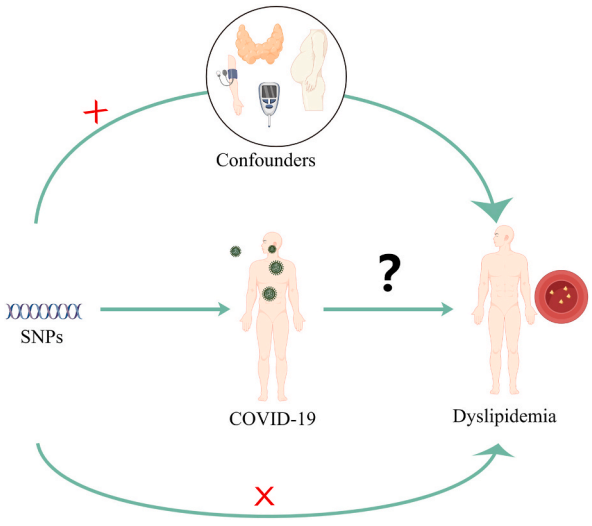

Fig. 1. Graphical abstract.

Table 1
Characteristics of GWAS.

GWAS ID	Year	Trait	Ethnicity	Sample size	Num of SNPs
ebi-a-GCST011073	2020	COVID-19	European	1,683,768	8,660,177
ebi-a-GCST011081	2020	COVID-19 hospitalized	European	1,887,658	8,107,040
ebi-a-GCST011075	2020	COVID-19 severe	European	1,388,342	9,739,225
finn-b-E4_HYPERLIPNAS	2021	Hyperlipidaemi	European	201,794	16,380,389
ieu-b-5089	2022	LDL cholesterol	European	201,678	12,321,875
met-*d*-VLDL_C	2020	VLDL cholesterol	European	115,078	12,321,875
ieu-b-109	2020	HDL cholesterol	European	403,943	12,321,875
met-*d*-Total_C	2020	Total cholesterol	European	115,078	12,321,875
ieu-b-111	2020	triglycerides	European	441,016	12,321,875
ieu-b-107	2020	apolipoprotein A-I	European	393,193	12,321,875
met-*d*-ApoB_by_ApoA1	2020	Ratio of apolipoprotein B to apolipoprotein A1	European	115,078	12,321,875
ieu-b-108	2020	apolipoprotein B	European	439,214	12,321,875
ukb-*d*-30790 raw	2018	Lipoprotein A	European	377,572	13,583,854

$$R^2 = 2 * (1 - \mathrm{MAF}) * \mathrm{MAF} * \beta^2 \quad (1)$$

Note: MAF is the minor effect of allele frequency. B is the strength of SNP efficacy on the outcome.

$$F = \frac{R^2(N-2)}{1-R^2} \quad (2)$$

Note: R^2 is linkage disequilibrium. N is the sample size.

Then, the multi-effectivity of SNPs was further analyzed to investigate the correlation between SNPs and dyslipidemia, and the SNPs directly related to dyslipidemia were removed, and the remaining SNPs would be determined as potential IVs, and the corresponding SNPs will be extracted from the outcome GAWS. In addition, the effect of substitutions of missed SNPs on the analysis results was unknown, so only SNPs found in the GAWS results were included in the MR analysis, while the effect of SNPs not included in the outcome on the result was neglected [16].

2.4. MR analysis

After the identification of the IVs to be included in the MR analysis, we performed an MR analysis using the TwosampleMR package, in which five complementary analysis methods, inverse variance-weighted, MR Egger, weighted median, simple mode, and weighted mode, were used to make different assumptions about horizontal multi-effects, all using a random effects model. Inverse variance weighted (IVW) was the primary outcome and guided the results, in the IVW analysis, the slope of the weighted regression of the SNP-outcome effects on the SNP-exposure effects, where the intercept constrained to zero, represented the resulting estimate, $P < 0.05$ indicates a causal effect of exposure on outcome [18]. MR Egger, Weighted median, Simple mode, and Weighted mode were the complements to IVW. MR-Egger allows for pleiotropic effects for all genetic variants, but requires pleiotropic effects to be independent of the variance-exposure association, with an intercept of $P > 0.05$ for non-pleiotropy [19]. Weighted median allows the use of invalid instruments under the assumption that at least half of the instruments used in the MR analysis are valid. In addition, Cochran's Q statistic (MR-IVW) and Rucker's Q statistic (MR Egger) were used to detect the heterogeneity of our MR analysis, and $P > 0.05$ indicated no heterogeneity [20], and the leave one out method was used to analyze the sensitivity of each SNP to the outcome. Besides, we used the TwosampleMR and MR-PRESSO package to detect multi-effectivity for the SNPs [21].

2.5. Accounting for pleiotropy

To minimize the effect of pleiotropy on the outcome, we also reviewed whether the included SNPs were associated with potential risk factors from the PhenoScanner database [22,23], a platform providing comprehensive information on genotypic and phenotypic associations. Diabetes [24], hypertension [25], hypothyroidism, and obesity [26] were defined as dyslipidemia-related confounders in this study, and SNPs associated with these potential confounders were excluded.

3. Results

3.1. Selection of IVs for COVID-19 susceptibility and severity

After p-value screening and LD removal, a total of 46 SNPs were eligible, of which 13 SNPs were identified for COVID-19, 20 SNPs for severe COVID-19, and 13 SNPs for COVID-19 hospitalization, respectively, and no SNPs were excluded for multiple effects (Table S1). After harmonization and radial MR, a total of 46 SNPs was identified as IVs, of which 13 SNPs overlapped between COVID-19 and hyperlipidemia, with no missing SNPs in outcomes and no SNPs associated with dyslipidemia or confounders. 20 SNPs overlapped between severe COVID-19 and hyperlipidemia without any SNP associated with dyslipidemia or confounders, while SNP rs237698 could not be found in UKB (ukb-d-30790) GAWS, SNP rs957775 could not be found in IEU(ieu-b-5089, ieu-b-109, ieu-b-111,

ieu-b-107, and ieu-b-108) GWAS, and SNP rs163485 could not be found in Finn (finn-b-E4_HYPERLIPNAS) and IEU (ieu-b-5089, ieu-b-109, ieu-b-111, ieu-b-107, and ieu-b-108) GAWS. 13 SNPs overlapped between COVID-19 hospitalization and hyperlipidemia, with no missing SNPs in outcomes and no SNPs associated with dyslipidemia or confounders (Table S2). The expected total number of results is 460, and 12 items are missing, which is less than 5% and does not affect the results, so the loss is partially ignored [16].

3.2. MR effect of COVID-19 susceptibility and severity on dyslipidemia

The results of IVW suggest that COVID-19, severe COVID-19, and COVID-19 hospitalization had no causal effect on dyslipidemia, LDL-C, VLDL cholesterol, HDL-C, TC, TG, apolipoprotein A, ratio of apolipoprotein B to apolipoprotein A1, apolipoprotein B, and lipoprotein A (Tables 2–4). Consistently, results of MR Egger, weighted median, simple mode, and weighted mode also suggest that no causal relationship between COVID-19, severe COVID-19, and COVID-19 hospitalization and dyslipidemia (Table S3).

The results of MR-IVW and MR Egger analysis demonstrated no heterogeneity in MR analysis of COVID-19, severe COVID-19, and COVID-19 hospitalization and dyslipidemia (Table S4).

The intercept test of MR Egger analysis demonstrates no horizontal pleiotropy in that the MR analyses COVID-19, severe COVID-19, and COVID-19 hospitalization and dyslipidemia ($P > 0.05$). Besides, the leave-one-out analysis showed that although several SNPs had a strong effect on the results, overall our MR analysis was not driven by a single SNP (Figure S1～S3).

4. Discussion

To our knowledge, this is the initial large-scale MR analysis aimed at investigating the genetic causal relationship between COVID-19 and dyslipidemia. In this study, the MR approach performed a causal analysis of COVID-19, severe COVID-19, and COVID-19 hospitalization and dyslipidemia at the genetic level, effectively avoiding the shortcomings of traditional observational studies, such as small sample size, the complexity of implementing randomized cohorts, and ethical review. Although previous research has suggested that hyperlipidemia increases the risk of COVID-19 [13], in our study, we found that COVID-19 does not elevate the risk of hyperlipidemia when exposure and outcomes are considered.

Depending on individual immunity, the person usually develops clinical symptoms within the first 3–14 days of COVID-19, mainly including cough, fever, sore throat, myalgia, diarrhea, vomiting, and abdominal pain, but without image-omics evidence of pneumonia [27,28]. If the disease continues to worsen, about 1 week after the initial onset, there are imaging signs of pneumonia, along with shortness of breath, progressive exertional dyspnea, acute cardiac injury, sepsis, and even incidence of grand-glass opacities that led to death [29,30]. Despite the passage of 3 years, COVID-19 and SARS-CoV-2 variants, such as the Delta and Omicron variants, are still rampant. Which causes neurological sequelae such as loss of taste and smell, headaches, encephalopathy, and even strokes [31]. Meanwhile, many clinical reports indicate that COVID-19 and SARS-CoV-2 variants further increase the burden of chronic diseases, such as increasing the dosage of antihypertensive drugs in hypertensive patients [32,33], reducing the stabilization of glucose in diabetic patients [34,35], causing the worsening of chronic inflammation, and causing coagulation [36]. In addition, an increasing number of studies have noticed the effects of COVID-19 on lipids. Based on the national health care databases of the US Department of Veterans Affairs, colleagues conducted a cohort study that included 51,919 COVID-infected patients compared to non-COVID-19-infected patients and concluded that COVID-19 increases the risk of dyslipidemia and increases the use of anti-lipid agents [14]. Similarly, Paul et al. conducted an analysis of the potential mechanisms of increased lipid burden in COVID-19 and concluded that patients with hyperlipidemia diagnosed with COVID-19 should be intensified with anti-lipid agents as soon as possible to reduce the risk of acute cardiovascular disease [37]. Since hyperlipidemia is a major risk factor for atherosclerotic cardiovascular disease, hypertension, and cerebrovascular disease, it is necessary to perform this MR analysis to investigate the causal association between COVID-19 and dyslipidemia.

In our study, we analyzed COVID-19 with 10 dyslipidemia-related outcomes separately, and the results differed from the logical expectation that there was no causal association between each severity of COVID and dyslipidemia. This MR analysis was conducted based on three MR criteria: (a) IVs were closely related to COVID-19; (b) IVs were independent of confounders. and (c) IVs influenced outcomes only through their effects on exposure and not through alternative factors. In addition, we searched the Phenoscancer to

Table 2
MR effect of COVID-19 on dyslipidemia.

Exposure	Outcome	Beta	*P*
COVID-19	Hyperlipidaemia	−0.063	0.691
COVID-19	apolipoprotein A	0.022	0.313
COVID-19	apolipoprotein B	0.018	0.599
COVID-19	HDL cholesterol	0.008	0.672
COVID-19	triglycerides	−0.033	0.075
COVID-19	LDL cholesterol	0.029	0.48
COVID-19	Ratio of apolipoprotein B to apolipoprotein A1	0.03	0.378
COVID-19	Total cholesterol	0.034	0.409
COVID-19	VLDL cholesterol	0.042	0.329
COVID-19	Lipoprotein A	−0.626	0.294

Note: Beta is the influence that exposure inflicts on the outcome, the higher the value the stronger the influence.

Table 3
MR effect of severe COVID-19 on dyslipidemia.

Exposure	Outcome	Beta	*P*
severe COVID-19	Hyperlipidaemia	−0.042	0.299
severe COVID-19	apolipoprotein A	0.005	0.436
severe COVID-19	apolipoprotein B	0.011	0.298
severe COVID-19	HDL cholesterol	0.001	0.789
severe COVID-19	triglycerides	−0.003	0.659
severe COVID-19	LDL cholesterol	0.009	0.494
severe COVID-19	Ratio of apolipoprotein B to apolipoprotein A1	0.018	0.126
severe COVID-19	Total cholesterol	0.012	0.346
severe COVID-19	VLDL cholesterol	0.017	0.184
severe COVID-19	Lipoprotein A	−0.127	0.481

Note: Beta is the influence that exposure inflicts on the outcome, the higher the value the stronger the influence.

Table 4
MR effect of COVID-19 hospitalization on dyslipidemia.

Exposure	Outcome	Beta	*P*
COVID-19 hospitalization	Hyperlipidaemia	−0.069	0.299
COVID-19 hospitalization	apolipoprotein A	0.013	0.301
COVID-19 hospitalization	apolipoprotein B	0.008	0.621
COVID-19 hospitalization	HDL cholesterol	0.005	0.609
COVID-19 hospitalization	triglycerides	−0.004	0.716
COVID-19 hospitalization	LDL cholesterol	0.012	0.564
COVID-19 hospitalization	Ratio of apolipoprotein B to apolipoprotein A1	0.015	0.502
COVID-19 hospitalization	Total cholesterol	0.014	0.52
COVID-19 hospitalization	VLDL cholesterol	0.018	0.454
COVID-19 hospitalization	Lipoprotein A	−0.492	0.096

Note: Beta is the influence that exposure inflicts on the outcome, the higher the value the stronger the influence.

ensure that our finding was not influenced by potential risk confounders. The selection of IVs fully considered the severity of COVID-19, increasing the accuracy of our MR analysis. The present MR analysis was based on a rigorous screening of exposures and IVs. Therefore, the conclusion that there is no causal association between COVID and dyslipidemia is reliable.

In order to determine the underlying cause for the disparate outcomes observed in this study, we conducted an extensive review of relevant literature and concluded that while COVID-19 does not directly increase the burden of dyslipidemia, it increases the risk of confounders that may increase the burden of dyslipidemia, such as inflammatory response, diabetes, hypertension, hypothyroidism, obesity, among others. While further studies are needed to validate this assumption, it serves as a cautionary signal for clinicians. Patients infected with COVID-19 should be actively managed for pre-existing chronic diseases and monitored for lipid levels to reduce the risk of associated acute and fatal outcomes.

This study also has several limitations. Firstly, the exposures and outcomes analyzed herein were exclusively based on the European populations, making the findings informative for these demographics only, and additional research is needed to assess their applicability to other ethnicities. Secondly, the magnitude of the MR analysis, with its inclusion of numerous outcomes, resulted in overall results that were not entirely consistent with previous studies. Therefore, further investigation is warranted to explore the impact of potential confounding factors on outcomes. Finally, multicenter, large-sample studies with long-term follow-up are inevitable.

5. Conclusion

Our findings strongly support the notion that COVID-19 is not directly causally related to dyslipidemia. This holds true regardless of the severity of COVID-19 or the specific dyslipidemic outcome considered. While certain studies have indicated an association between COVID-19 and a higher burden of dyslipidemia, it is possible that this association is primarily driven by the exacerbation of pre-existing dyslipidemic conditions due to COVID-19. Our study, at the very least, suggests that there is no direct causal relationship between COVID-19 and dyslipidemia.

Ethics approval and consent to participate

Review and/or approval by an ethics committee was not needed for this study because our research is based on public databases.

Author contribution statement

Yi Liang: Performed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.
Liang Liu; Bo Liang: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data;

Wrote the paper.

Data availability statement

Data included in article/supplementary material/referenced in article.

Consent for publication

Not applicable.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix ASupplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e20247.

References

[1] World, H.O, COVID-19 Weekly Epidemiological Update, 2023, 130 published. (Accessed 15 February 2023).
[2] M. Agrawal, et al., In-line treatments and clinical initiatives to fight against COVID-19 outbreak, Respir. Med. 191 (2022), 106192.
[3] N. Brito-Dellan, N. Tsoukalas, C. Font, Thrombosis, cancer, and COVID-19, Support. Care Cancer 30 (10) (2022) 8491–8500.
[4] T. Castiello, et al., COVID-19 and myocarditis: a systematic review and overview of current challenges, Heart Fail. Rev. 27 (1) (2022) 251–261.
[5] J. Liu, A. Deswal, U. Khalid, COVID-19 myocarditis and long-term heart failure sequelae, Curr. Opin. Cardiol. 36 (2) (2021) 234–240.
[6] K.S. Hingorani, S. Bhadola, A.M. Cervantes-Arslanian, COVID-19 and the brain, Trends Cardiovasc. Med. 32 (6) (2022) 323–330.
[7] S. Nannoni, et al., Stroke in COVID-19: a systematic review and meta-analysis, Int. J. Stroke 16 (2) (2021) 137–149.
[8] D. Roy, et al., Neurological and Neuropsychiatric impacts of COVID-19 pandemic, Can. J. Neurol. Sci. 48 (1) (2021) 9–24.
[9] A.J. Berberich, R.A. Hegele, A modern approach to dyslipidemia, Endocr. Rev. 43 (4) (2022) 611–653.
[10] H.C. Diener, G.J. Hankey, Primary and secondary prevention of ischemic stroke and cerebral hemorrhage: JACC focus seminar, J. Am. Coll. Cardiol. 75 (15) (2020) 1804–1818.
[11] L. Iuliano, et al., Radiolabeled native low-density lipoprotein injected into patients with carotid stenosis accumulates in macrophages of atherosclerotic plaque : effect of vitamin E supplementation, Circulation 101 (11) (2000) 1249–1254.
[12] A.J. Lusis, Atherosclerosis, Nature 407 (6801) (2000) 233–241.
[13] K. Zhang, et al., Causal associations between blood lipids and COVID-19 risk: a two-sample mendelian randomization study, Arterioscler. Thromb. Vasc. Biol. 41 (11) (2021) 2802–2810.
[14] E. Xu, Y. Xie, Z. Al-Aly, Risks and burdens of incident dyslipidaemia in long COVID: a cohort study, Lancet Diabetes Endocrinol. 11 (2) (2023) 120–128.
[15] R. Miao, et al., Diet-derived circulating antioxidants and risk of stroke: a mendelian randomization study, Oxid. Med. Cell. Longev. 2022 (2022), 6457318.
[16] X. Chen, et al., Kidney damage causally affects the brain cortical structure: a Mendelian randomization study, EBioMedicine 72 (2021), 103592.
[17] X. Wu, et al., Circulating white blood cells and lung function impairment: the observational studies and Mendelian randomization analysis, Ann. Med. 53 (1) (2021) 1118–1128.
[18] S. Burgess, A. Butterworth, S.G. Thompson, Mendelian randomization analysis with multiple genetic variants using summarized data, Genet. Epidemiol. 37 (7) (2013) 658–665.
[19] S. Burgess, S.G. Thompson, Interpreting findings from Mendelian randomization using the MR-Egger method, Eur. J. Epidemiol. 32 (5) (2017) 377–389.
[20] G. Hemani, et al., The MR-Base Platform Supports Systematic Causal Inference across the Human Phenome, vol. 7, Elife, 2018.
[21] M.J. Shu, et al., Migraine and ischemic stroke: a mendelian randomization study, Neurol Ther 11 (1) (2022) 237–246.
[22] M.A. Kamat, et al., PhenoScanner V2: an expanded tool for searching human genotype-phenotype associations, Bioinformatics 35 (22) (2019) 4851–4853.
[23] J.R. Staley, et al., PhenoScanner: a database of human genotype-phenotype associations, Bioinformatics 32 (20) (2016) 3207–3209.
[24] H. Cao, et al., Bidirectional causal associations between type 2 diabetes and COVID-19, J. Med. Virol. 95 (1) (2023), e28100.
[25] A. Baranova, H. Cao, F. Zhang, Causal associations and shared genetics between hypertension and COVID-19, J. Med. Virol. 95 (4) (2023), e28698.
[26] A. Baranova, et al., A phenome-wide investigation of risk factors for severe COVID-19, J. Med. Virol. 95 (1) (2023), e28264.
[27] H.A. Rothan, S.N. Byrareddy, The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak, J. Autoimmun. 109 (2020), 102433.
[28] W. Wang, J. Tang, F. Wei, Updated understanding of the outbreak of 2019 novel coronavirus (2019-nCoV) in Wuhan, China, J. Med. Virol. 92 (4) (2020) 441–447.
[29] A.L. García-Basteiro, et al., Monitoring the COVID-19 epidemic in the context of widespread local transmission, Lancet Respir. Med. 8 (5) (2020) 440–442.
[30] C. Huang, et al., Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, Lancet 395 (10223) (2020) 497–506.

[31] E. Normandin, et al., Neuropathological features of SARS-CoV-2 delta and omicron variants, J. Neuropathol. Exp. Neurol. 82 (4) (2023) 283–295.
[32] R. Sommerstein, et al., Coronavirus disease 2019 (COVID-19): do angiotensin-converting enzyme inhibitors/angiotensin receptor blockers have a biphasic effect? J. Am. Heart Assoc. 9 (7) (2020), e016509.
[33] G. Yang, et al., Effects of angiotensin II receptor blockers and ace (Angiotensin-Converting enzyme) inhibitors on virus , inflammatory status, and clinical outcomes in patients with COVID-19 and hypertension: a single-center retrospective study, Hypertension 76 (1) (2020) 51–58.
[34] F. Alberici, et al., A report from the Brescia Renal COVID Task Force on the clinical characteristics and short-term outcome of hemodialysis patients with SARS-CoV-2, Kidney Int. 98 (1) (2020) 20–26.
[35] Y. Cheng, et al., Kidney disease is associated with in-hospital death of patients with COVID-19, Kidney Int. 97 (5) (2020) 829–838.
[36] N. Tang, et al., Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia, J. Thromb. Haemostasis 18 (4) (2020) 844–847.
[37] P. Durrington, Blood lipids after COVID-19, Lancet Diabetes Endocrinol. 11 (2) (2023) 68–69.