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Association between COVID-19 and telomere length: A bidirectional Mendelian randomization study

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Abstract

Several traditional observational studies suggested an association between COVID-19 and leukocyte telomere length (LTL), a biomarker for biological age. However, whether there was a causal association between them remained unclear. We aimed to investigate whether genetically predicted COVID-19 is related to the risk of LTL, and vice versa. We performed bidirectional Mendelian randomization (MR) study using summary statistics from the genome-wide association studies of critically ill COVID-19 ($n = 1\,388\,342$) and LTL ($n = 472\,174$) of European ancestry. The random-effects inverse-variance weighted estimation method was applied as the primary method with several other estimators as complementary methods. Using six single-nucleotide polymorphisms (SNPs) of genome-wide significance as instrumental variables for critically ill COVID-19, we did not find a significant association of COVID-19 on LTL ($\beta = 0.0075$, 95% confidence interval [CI]: -0.018 to 0.021, $p = 0.733$). Likewise, using 97 SNPs of genome-wide significance as instrumental variables for LTL, we did not find a significant association of LTL on COVID-19 (odds ratio = 1.00, 95% CI: 0.79–1.28, $p = 0.973$). Comparable results were obtained using MR-Egger regression, weighted median, and weighted mode approaches. We did not find evidence to support a causal association between COVID-19 and LTL in either direction.

KEYWORDS
bidirectional two-sample Mendelian randomization, COVID-19, telomere length.

1 | INTRODUCTION

The current COVID-19 pandemic, because of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, has led to enormous health and economic consequences worldwide. The majority of individuals who died from COVID-19 are the aged, those with cardiovascular disease (CVD), diabetes, chronic obstructive pulmonary disease (COPD), and cancer alike.[1–3] In contrast, young adults, infants, and children typically had milder clinical symptoms.[4–6] Respiratory failure and multiorgan dysfunction resulting from impaired immune response and uncontrolled inflammatory process are the leading causes of death in COVID-19 patients.[7–9] The severe infection, occasionally along with a "cytokine-storm" symptom in which the level of oxidative stress increase significantly,[10,11] may alter host cell physiology and cellular functions.[12–14]

At the population level, SARS-CoV-2 and COVID-19 may lead to aging-related diseases or accelerate the aging process.

As specialized structures at the ends of chromosomes, telomeres maintain genome stability.[15] As cells divide and DNA replicates, telomeres become progressively shorter because of the "end replication problem."[16,17] Telomeres have been proposed as one of the biomarkers of aging for a long.[18] In addition to aging, environmental factors, such as exposure to pollutants, smoking, and oxidative stress, may shorten telomeres, and lead to an increased risk of aging-related diseases.[19–22] Several studies reported that COVID-19 was associated with shorter leukocyte telomere length (LTL). Mongelli et al.,[23] Sanchez-Vazquez et al.,[24] Benetos et al.,[25] Dos Santos et al.,[26] and Froidure et al.[27] conducted case-control studies and discovered that severe post-COVID-19 survivors had shorter

telomeres compared with milder post-COVID-19 survivors or COVID-19-free people, which suggested significant correlations of LTL with COVID-19 severity. However, the observed association between COVID-19 and LTL in observational studies might be biased because of confounding factors.[28,29] Thus, it is not clear whether COVID-19 infection is the cause or consequence of LTL shortening.

Mendelian randomization (MR) is an instrumental variable method that uses the single-nucleotide polymorphism (SNP) as an instrument variable (IV) to infer the causal relationship between two traits and has the advantage of minimizing bias due to confounding factors and reverse causality.[30–34] In this study, we employed a bidirectional two-sample MR design to examine the potential bidirectional relationship between COVID-19 and LTL.
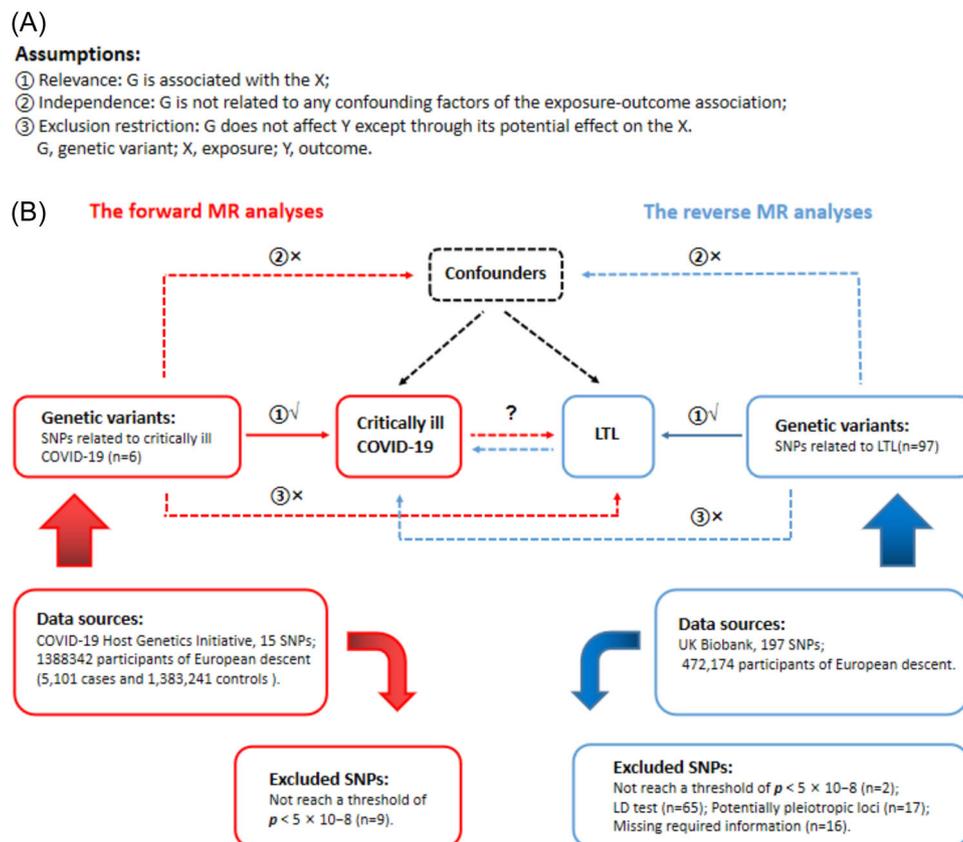
2 | MATERIALS AND METHODS

2.1 | Study design description

Figure 1 shows a brief description of this bidirectional MR design between COVID-19 and LTL. We performed a total of two MR analyses using summary statistics from a genome-wide association study (GWAS) to investigate the bidirectional association between critically ill COVID-19 and LTL. The forward MR analyses considered critically ill COVID-19 as the exposure and LTL as the outcome, while the reverse MR analyses LTL as the exposure and critically ill COVID-19 as the outcome. The core MR assumptions are shown in Figure 1. This study is based on publicly available summary statistics, therefore no ethical approval is required.

2.2 | Selection of instrumental variables for MR analyses

Appropriate instrumental variables for MR analyses were selected from two different GWAS summary results. First, SNPs were selected at a threshold of genome-wide significance ($p < 5 \times 10^{-8}$). Second, appropriate SNPs were kept based on linkage disequilibrium as measured by $r^2 > 0.01$ in the European 1000 Genome reference panel. Then, those associating with the outcome with $p < 5 \times 10^{-8}$ were excluded. When harmonizing exposure and outcome data, palindromic SNPs with intermediate allele frequencies were removed. We estimated the F-statistics to evaluate the instrument strength. $F < 10$ indicates weak instrument strength.[35,36]

(A)

Assumptions:
① Relevance: G is associated with the X;
② Independence: G is not related to any confounding factors of the exposure-outcome association;
③ Exclusion restriction: G does not affect Y except through its potential effect on the X.
   G, genetic variant; X, exposure; Y, outcome.

(B)

FIGURE 1 Description of the study design in this bidirectional MR study. (A) MR analyses depend on three core assumptions. (B) Sketch of the study design. The red represented the forward MR analyses, with critically ill COVID-19 as exposure and LTL as the outcome. The blue represented the reverse MR analyses, with LTL as exposure and critically ill COVID-19 as the outcome. LD, linkage disequilibrium; LTL, leukocyte telomere length; MR, Mendelian randomization; SNPs, single-nucleotide polymorphisms.

2.3 | Data sources and instrumental variables selection for critically ill COVID-19

We used a centralized meta-analysis data comprised of 15 European cohorts for critically ill COVID-19,[37] which was obtained from the COVID-19 Host Genetics Initiative (https://www.covid19hg.org/results/r5/), consisting of 5101 cases and 1 383 241 controls (Supporting Information: Table 1). The critically ill COVID-19 cases included patients who were hospitalized because of symptoms associated with laboratory-confirmed SARS-CoV-2 infection and required respiratory support or whose primary cause of death was COVID-19.[37] The control groups were selected as genetically ancestry-matched samples without known SARS-CoV-2 infection if that information was available.[37] Fifteen SNPs associated with critically ill COVID-19 were identified in this GWAS and were selected as instrumental variables. Among the 15 SNPs, 9 SNPs with $p > 5 \times 10^{-8}$ were excluded. Thus, we finally included 6 variants as genetic instruments in the MR analyses (Figure 1, Supporting Information: Table 2).

2.4 | Data sources and instrumental variables selection for LTL

Data sources for LTL were taken from the UK Biobank (https://figshare.com/s/caa99dc0f76d62990195), including 472 174 UKB participants[38] (Supporting Information: Table 1). For reverse MR analyses, we selected the appropriate instrumental variables among 197 independent loci associated with LTL. Two SNPs with $p > 5 \times 10^{-8}$ were excluded, 65 SNPs were removed by using PLINK clumping with $r^2 > 0.01$, and 17 SNPs were removed because of its potentially pleiotropic loci, and 16 SNPs were excluded as the required information for MR analyses was missing. Finally, 97

instrumental variables were selected for MR analyses (Figure 1, Supporting Information: Table 3).

2.5 | Statistical analysis

The random-effects inverse-variance weighted (IVW) method was used as the main statistical method to estimate the potential bidirectional causal associations between critically ill COVID-19 and LTL. The IVW method is based on a hypothesis that all core assumptions of MR are valid. However, IVs influence the outcome through other pathways indicating that there exist potential horizontal pleiotropic effects, and the causal estimate from IVW could be biased. Therefore, we performed the sensitivity analyses by using the MR-Egger[39] and weighted median[40] methods, from which we can estimate the causal relationship accurately even though the existence of invalid SNPs.

As MR depends on three core IV assumptions for the main analyses (Figure 1), we reported the methods applied to assess the assumptions or justify their validity. For the relevance assumption, R^2 was calculated to represent the proportion of variance in the exposure variable explained by the genetic variants. We estimated the F-statistics to evaluate the instrument strength of the association between IVs and risk of exposure of interest. $F < 10$ indicates weak instrument strength.[35,36] For the exclusion restriction assumption, the MR-Egger regression intercept, and its 95% confidence intervals (CIs) were used to investigate the degree of bias in casual estimates due to directional pleiotropy.[39,41] Besides this, the horizontal pleiotropy was assessed by employing the Mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO) global test and the outlying SNPs were excluded through the MR-PRESSO outlier test.[42] As well, after removing outlying IVs, we also investigated whether there was a statistically significant difference compared with the former one. We also tested heterogeneity for IVW and MR-Egger

TABLE 1 Telomere length and its association with critically ill COVID-19 in the MR analyses

Exposure	Outcome	No. of SNPs	Methods	OR (95% CI)	β (SE)	p
The forward MR analyses						
Critically ill COVID-19	LTL	6	IVW		0.0075 (0.0220)	0.734
			MR-Egger		−0.0006 (0.0571)	0.992
			Weighted median		−0.0095 (0.0141)	0.497
			Weighted mode		−0.0199 (0.0142)	0.220
The reverse MR analyses						
LTL	Critically ill COVID-19	97	IVW	1.00 (0.79–1.28)	0.004 (0.125)	0.973
			MR-Egger	1.19 (0.78–1.81)	0.174 (0.213)	0.415
			Weighted median	1.28 (0.86–1.90)	0.249 (0.202)	0.217
			Weighted mode	1.29 (0.87–1.94)	0.258 (0.205)	0.211

Abbreviations: CI, confidence interval; IVW, inverse variance weighted; LTL, leukocyte telomere length; MR, Mendelian randomization; OR, odds ratio; SNPs, single-nucleotide polymorphisms.
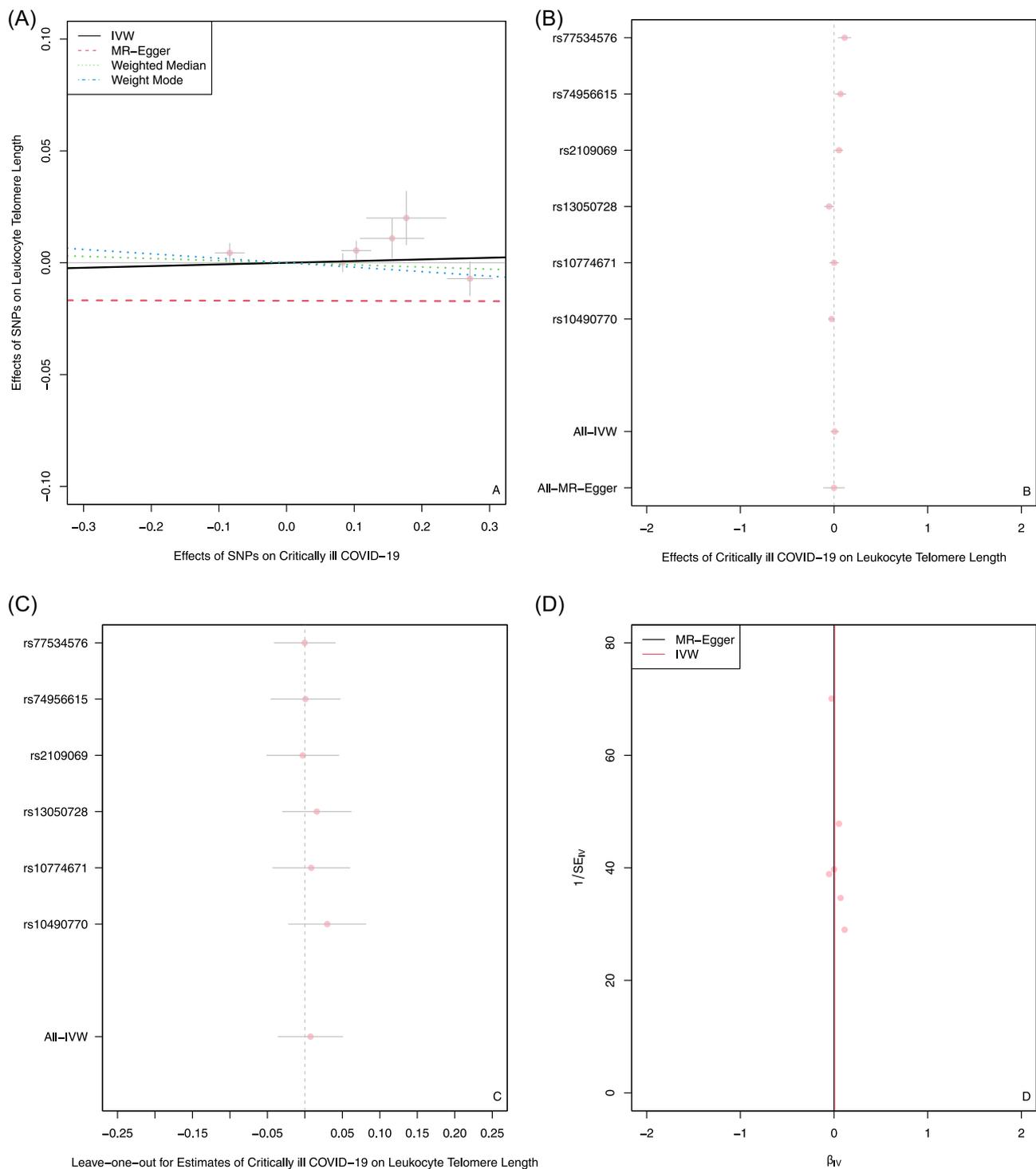
FIGURE 2 The forward MR analyses: Casual effect of critically ill COVID-19 on LTL. (A) Scatter plot of the association between critically ill COVID-19 and LTL. The four methods applied in the current manuscript were all depicted. Lines in black, red, green, and blue represent IVW, MR-Egger, weighted median, and weight mode methods. (B) A forest plot was used to show the MR estimate and 95% CI values (gray line segment) for each SNP, which also shows the IVW and MR-Egger results at the bottom. (C) Leave-one-out analyses to evaluate whether any single instrumental variable was driving the causal effect. (D) A funnel plot was applied to detect whether the observed association was along with obvious heterogeneity. CI, confidence interval; IVW, inverse variance weighted; LTL, leukocyte telomere length; MR, Mendelian randomization; SNPs, single-nucleotide polymorphisms.

TABLE 2 Pleiotropy and heterogeneity analyses

| Exposure | Outcome | No. of SNPs | MR-Egger regression | | MR PRESSO | | Heterogeneity analyses | | |
			Intercept	p_intercept	Global test p	Correct p*	Method	Q	Q_pval
Critically ill COVID-19	LTL	6	0.001	0.885	0.004	0.174	IVW	29.853	<0.001
							MR-Egger	29.677	<0.001
The reverse MR analyses									
LTL	Critically ill COVID-19	97	−0.006	0.352	0.485	NA	IVW	90.434	0.497
							MR-Egger	89.465	0.496

Abbreviations: IVW, inverse variance weighted; LTL, leukocyte telomere length; MR PRESSO, Mendelian randomization pleiotropy residual sum and outlier; SNPs, single-nucleotide polymorphisms.

*If MR PRESSO global test detects the horizontal pleiotropy and there is a significant difference before and after removing the outlier, correct p is calculated by removing instruments variants that have horizontal pleiotropy.

TABLE 3 Genetically predicted telomere length and its association with critically ill COVID-19 using 15 instrumental variables

Exposure	Outcome	No. of SNPs	Methods	β (SE)	p
Critically ill COVID-19	LTL	15	IVW	0.0010 (0.0050)	0.841
			MR-Egger	−0.0035 (0.0140)	0.806
			Weighted median	−0.0093 (0.0047)	0.045
			Weighted mode	−0.0106 (0.0060)	0.102

Abbreviations: IVW, inverse variance weighted; LTL, leukocyte telomere length; MR, Mendelian randomization; SNPs, single-nucleotide polymorphisms.

methods via Cochran's Q statistics and funnel plots.[43] Finally, several sensitivity analyses, such as leave-one-out analysis and single SNP analysis, were applied to identify whether a single SNP influenced the main causal relationship.[41] Power calculation for this MR study was obtained via an online web tool (https://sb452.shinyapps.io/power/).

For binary outcome, an odds ratio (OR) and 95% CI were applied to estimate the degree of a causal relationship. The causal estimate for both the binary and continuous outcomes, p-value, β, and its standard error were also presented. All p-values are two-tailed. All analyses were performed by applying the *TwoSampleMR* and *MendelianRandomization* packages in R (version 4.2.0, www.r-project.org/).

3 | RESULTS

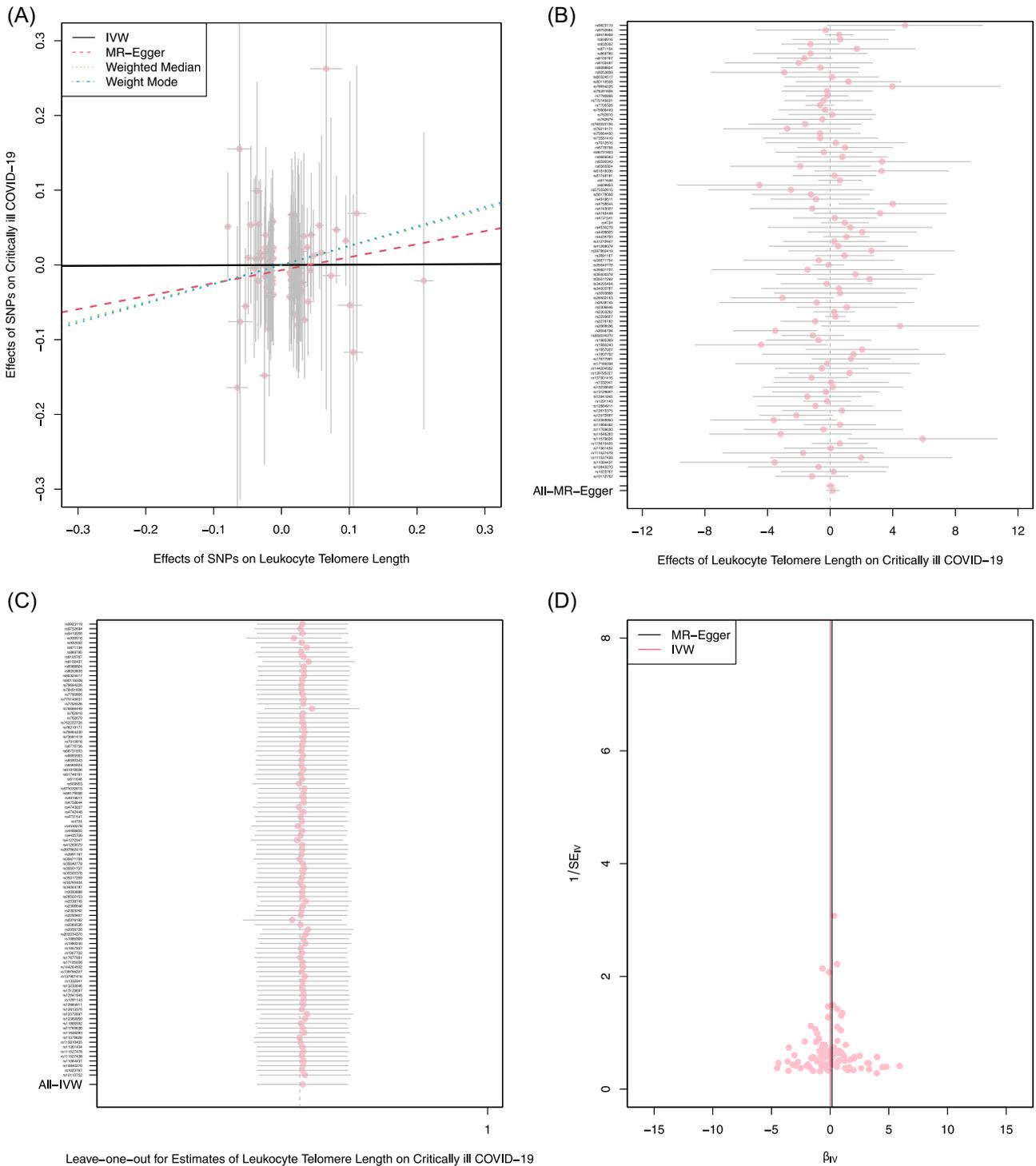### 3.1 | The casual effect of critically ill COVID-19 on LTL

As shown in Table 1 and the scatter plot (Figure 2A), the IVW result suggested that genetically predicted critically ill COVID-19 was not significantly associated with LTL (β and 95% CI: 0.0075, −0.018 to 0.021; p = 0.733). No significant association was identified in other models. Although MR-Egger regression analyses showed no incidence of potential directional pleiotropy, the MR PRESSO result indicated notable horizontal pleiotropy

across SNPs in the causal estimates (Table 2, global test p = 0.004). However, even after removing instrumental variables which had horizontal pleiotropy, the p-value was still not significant (Table 2, corrected p = 0.174). In addition, by combining Cochran's Q p-value in IVW and MR-Egger methods (Table 2, all p-value of Cochran's Q < 0.001) with the funnel plot (Figure 2D), it was suggested that the observed association was along with obvious heterogeneity. However, even using the weighted median method, no significant association was observed (Table 1, beta and 95% CI: −0.0095, −0.018 to 0.009; p = 0.490).

To increase statistical power, we additionally performed a secondary analysis by selecting SNPs that were of a significance level of $p < 5 \times 10^{-7}$ (Supporting Information: Table 4). The results showed that COVID-19 was not significantly associated with LTL (Table 3).

3.2 | The causal effect of LTL on critically ill COVID-19

As shown in Table 1, the scatter plot (Figure 3A) and forest plots (Figure 3B), the IVW result showed LTL was not causally related to critically ill COVID-19 (OR and 95% CI: 1.00, 0.79–1.28; p = 0.973). The other three results were in line with the IVW results. Both MR-Egger regression analyses (Table 2, intercept = −0.006, p = 0.352)

(A)

(B)

(C)

(D)

FIGURE 3 The reverse MR analyses: Casual effect of LTL on critically ill COVID-19. (A) Scatter plot of the association between critically ill COVID-19 and LTL. The four methods applied in the current manuscript were all depicted. Lines in black, red, green, and blue represent IVW, MR-Egger, weighted median, and weight mode methods. (B) A forest plot was used to show the MR estimate and 95% CI values (gray line segment) for each SNP, also show the IVW and MR-Egger MR results at the bottom. (C) Leave-one-out analyses to evaluate whether any single instrumental variable was driving the causal effect. (D) A funnel plot was applied to detect whether the observed association was along with obvious heterogeneity. CI, confidence interval; IVW, inverse variance weighted; LTL, leukocyte telomere length; MR, Mendelian randomization; SNPs, single-nucleotide polymorphisms.

and the MR PRESSO result (Table 2, global test $p = 0.485$) showed no incidence of potential pleiotropy. The Cochran's Q test in the IVW method (Table 2, $Q = 90.434$, $p = 0.497$) and MR-Egger method (Table 2, $Q = 89.465$, $p = 0.496$) suggested that there was an absence of heterogeneity in the IVs. Furthermore, even if removing any single SNP, the observed association didn't significantly change in leave-one-out analyses (Figure 3C), suggesting the stability of the results.

4 | DISCUSSION

In this bidirectional two-sample MR study, we did not find an association between critically ill COVID-19 and LTL from MR analyses.

As mentioned previously, several previous observational studies have suggested that shorter TL was likely to be independently associated with critically ill COVID-19, which might be biased by potential confounding factors and reverse causality, for example, they all had measured TL after SRAS-CoV-2 infection. Thus, we are unable to interpret whether shorter TL aggravated virus infection or telomere shortening (TS) was due to a "cytokine-storm" symptom in response to virus infection. However, in our study, neither the forward MR analyses nor the reverse direction suggested a significant association between critically ill COVID-19 and TL. In addition, our results of the reverse MR analyses were in line with a one-sample MR study which used a set of 130 genome-wide significant ($p < 5 \times 10^{-8}$) genetic variants measured several years before SARS-CoV-2 infection to reduce bias.[44]

We have not obtained significant results; however, several hypotheses have been put forward. According to an "Amplifier/Rheostat Hypothesis," shorter TL along with genomic instability as well as a decrease in cell proliferative capacity, might cause cell senescence, the decline in B and T lymphopoiesis, negative consequences on the immune competence and induce cytokine storm, driving to more severe SARS-CoV-2 infection as well as promoting telomeres shorten even more.[13,45,46] We can't dismiss these biological mechanisms. Of note, TL is influenced by genetic and environmental factors.[13,47] The majority of individuals who died from COVID-19 were adults with age-related dysfunction and chronic diseases, such as CVD, diabetes, COPD, and so on.[1-3] Those diseases are all risk factors for TS, which may play an important role in the biological mechanisms. For example, several studies demonstrated that smokers have shorter telomeres than nonsmokers.[48,49] Therefore, the results we obtained in this study drive us to make a hypothesis that shorter TL observed in severe post-COVID-19 survivors attributed to the interaction between SRAS-CoV-2 infection and initial physical condition. There is a complicated association between critically ill COVID-19 and TL, instead of pure causal relevance.

Compared with traditional observational studies, the greatest advantage in this study is that the causal estimate obtained by MR avoids reverse causality and confounding bias. As well, applying comprehensive GWASs data for MR analyses can improve the accuracy of the estimated effect. However, several limitations can't be avoided in our study. First, based on three core assumptions in the MR study, instrument strength of the association between IVs and risk of exposure of interest is expected to be high, while relatively low in our study. Secondly, through Cochran's Q value in the forward MR analyses, obvious heterogeneity can't be eliminated. Although the results were robust in all methods, a small number of genetic instruments, a small sample size, or potential sample overlap between exposure and outcome might lead to bias. In addition, the results can't be generalized to other ethnicities and races as the population we used was Europeans.

In conclusion, our bidirectional MR study indicated neither the forward nor the reverse direction showed a causal association between critically ill COVID-19 and LTL. Facing the fact that SARS-CoV-2 infection has caused high mortality in the elderly, further investigations are encouraged to explore the relevance between critically ill COVID-19 and TL.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in COVID-19 Host Genetics Initiative. These data were derived from the following resources available in the public domain: Telomere GWAS.

ETHICS STATEMENT

The present Mendelian randomization analysis was based on summary data from previous studies that had gained written informed consent and ethics approval. No ethical permit is required for the secondary analysis of summary data.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.