DOI: 10.1002/jmv.28194

LETTER TO THE EDITOR

JOURNAL OF MEDICAL VIROLOGY WILEY

Associations between pulse rate and COVID-19

To the editor,

Risk factors associated with the severity and mortality of COVID-19 include obesity, cardiovascular diseases, diabetes, and smoking.[1-5] Meanwhile, COVID-19 can lead to a myriad of post-COVID consequences.[2,6,7] As one of the most fundamental signs of life, heart rate is a vital predictor of cardiovascular risk and mortality. In clinical practice, heart rate is assessed by pulse rate (PR). While cardiovascular conditions are among the most studied contributors to mortality due to COVID-19,[1] whether elevated PR could be associated with the susceptibility to or severity of the disease is not yet known. Exploring the link between PR and COVID-19 may help improve the management of coronavirus infection.

We sought to test the potential associations between PR and COVID-19 using the Mendelian randomization (MR) framework. The summary statistics for the outcomes of COVID-19 were obtained from the COVID-19 Host Genetics Initiative (HGI), including SARS-CoV-2 infection (COVID vs. population, including 122 616 cases and 2 475 240 controls), hospitalized COVID-19 (hospitalized COVID vs. population, including 32 519 cases and 2 062 805 controls), and critical COVID-19 (very severe respiratory confirmed COVID vs. population, including 13,769 cases and 1,072,442 controls).[8] Cases of critical illness of COVID-19 were individuals who required respiratory support in a hospital or who died due to the disease. The SARS-CoV-2 infection data set mainly reflects the overall susceptibility to the virus, whereas the hospitalized and critical COVID-19 datasets represent the severity of the disease. Therefore, we collectively called the latter two outcomes "severe COVID-19." The PR GWAS data set included 430 029 participants from The UK Biobank (UKB),[9] which was obtained from YangLab.[10] The PR was assessed in the UKB participants at rest. All the participants of the datasets were of European origin.

The main analyses were performed using the inverse-variance weighted (IVW) method and complemented with the weighted median and MR-Egger methods implemented in TwoSampleMR.[11] The intercept from the MR-Egger regression was utilized to evaluate the average horizontal pleiotropy. The significant associations between PR and COVID-19-related outcomes were determined by IVW-based FDR < 0.05. Single-nucleotide polymorphisms (SNPs) with genome-wide significance ($p < 5 \times 10^{-8}$) in the PR data set were selected as IVs and further pruned using a clumping r^2 cutoff of 0.001 within a 10 Mb window. For each MR analysis, we removed SNPs not present in the outcome data set.

In the MR analysis, a total of 1144–1147 IVs were derived from the PR GWAS data set. Our MR analysis showed that genetic liability to higher PR was associated with higher risks for SARS-CoV-2 infection (odds ratio [OR]: 1.05, 95% confidence interval (CI): 1.01–1.09, $p = 0.023$, false discovery rate [FDR] = 0.034), hospitalized COVID-19 (OR: 1.14, 95% CI: 1.03–1.26, $p = 0.011$, FDR = 0.032), and critical COVID-19 (OR: 1.16, 95% CI: 1.00–1.35, $p = 0.043$, FDR = 0.043; Table 1). The sensitivity analyses revealed that the directions of causal effect estimates across the methods were largely the same. The tests of MR-Egger regression did not support the directional pleiotropy of the IVs for the MR analysis (MR-Egger intercept < 0.01, $p > 0.05$).

Our study provides evidence for the associations between an increased PR and COVID-19 outcomes. Our results indicated that a 1 − SD increase in PR translates to a 5% increased risk for COVID-19 infection, a 14% increased risk for COVID-19 hospitalization, and a 16% increased risk for critical COVID-19. Thus, the associations of higher PR with COVID-19 are severity dependent, with the largest impact on more adverse outcomes of the illness.

A higher PR indicates the presence of either cardiovascular dysfunction or comorbidities, which may explain the associations between PR and COVID-19 outcomes. It is also important to note that immunity is coordinated by neural circuits which may explain the synergistic effects between immune-related and antiviral approaches previously noted in the treatment of COVID-19.[12] Our study suggests that PR-lowering medications may benefit patients with acute COVID-19, while PR-elevating drugs should be used with caution. In addition, these results justify the inclusion of the PR into the proposed formulas for the rapid assessment of COVID-19-related risks of inpatient mortality.

In summary, our study suggests that PR is a useful indicator for COVID-19 susceptibility and severity, which may facilitate the prediction of in-hospital mortality among COVID-19 patients.

TABLE 1 Associations between pulse rate and the COVID-19 outcomes

Outcome	Method	b (se)	OR [95% CI]	N_IV	Egger_intercept	Egger_se	P_pleiotropy	*p*	FDR
Critical COVID-19	IVW	0.152 (0.075)	1.16 [1.00–1.35]	312	−0.004	0.004	0.291	0.043	0.043
Critical COVID-19	WM	0.126 (0.102)	1.13 [0.93–1.38]	312	−0.004	0.004	0.291	0.213	
Critical COVID-19	MR Egger	0.404 (0.250)	1.50 [0.92–2.45]	312	−0.004	0.004	0.291	0.107	
Hospitalized COVID-19	IVW	0.133 (0.052)	1.14 [1.03–1.26]	312	−0.002	0.003	0.519	0.011	0.032
Hospitalized COVID-19	WM	0.108 (0.064)	1.11 [0.98–1.26]	312	−0.002	0.003	0.519	0.094	
Hospitalized COVID-19	MR Egger	0.238 (0.171)	1.27 [0.91–1.77]	312	−0.002	0.003	0.519	0.165	
SARS-CoV-2 infection	IVW	0.048 (0.021)	1.05 [1.01–1.09]	311	0	0.001	0.706	0.023	0.034
SARS-CoV-2 infection	WM	0.065 (0.030)	1.07 [1.01–1.13]	311	0	0.001	0.706	0.03	
SARS-CoV-2 infection	MR Egger	0.072 (0.068)	1.07 [0.94–1.23]	311	0	0.001	0.706	0.289	

Abbreviations: b (se), the standard error for the unstandardized beta; CI, confidence interval; FDR, false discovery rate; IVW, inverse variance weighted; N_IV, number of instrumental variables; OR, odds ratio; WM, weighted median.

AUTHOR CONTRIBUTIONS

Fuquan Zhang conceived the project, supervised the study, and analyzed the data. Ancha Baranova and Fuquan Zhang wrote the manuscript. Hongbao Cao and Yong Xu revised the manuscript for intellectual content. All authors critically reviewed and revised the manuscript, and agreed to the published version of the manuscript.

ACKNOWLEDGMENTS

The authors thank all investigators and participants from the COVID-19 Host Genetics Initiative and UKB for sharing these data.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in the Covid19 Host Genetics Initiative (https://www.covid19hg.org/results/r7/) and YangLab (https://yanglab.westlake.edu.cn/).

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