Reply to Suri *et al.*

From the Authors:

We really want to thank Suri and colleagues for their interest in our study (1) and for indicating that similar observations were made by other studies (2). However, as pointed out by them regarding erroneously citing the paper in which transmission occurred after symptom resolution, we want to clarify. In the cited study, the authors indicated that the transmission between index patients and other patients happened before symptom onset and not after the resolution of the symptoms, which is indeed correct (3). However, in the same study, the transmission was also reported between patient 1 and other patients (3, 4) who had no contact with the index patient. Patient 1 returned to work after the resolution of symptoms but was unaware of his infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). After confirmation of infection in the index patient upon return to China, patient 1 presented to the Division of Infectious Diseases and Tropical Medicine in Munich for further assessment. Patient 1 was found to be well with no signs of fever but had a very elevated viral load ($>10^8$ copies). Our citation referred to the transmission from patient 1 to patients 3 and 4 rather than from the index patient as was suggested by authors.

Another major point raised by the authors is the comparison between coronavirus and influenza infections. In the ferret model, the infective viral shedding time is limited to 5 days, whereas quantitative PCR (qPCR) positivity remains until Days 11–13. However, there are stark differences between influenza infection and coronavirus disease (COVID-19). Patients succumbing to COVID-19 remain positive for the virus until their death, even if it occurs 30–40 days after symptom onset, suggesting the ability of SARS-CoV-2 to persist in the body for prolonged times (4).

However, we agree with the need to find a better way to ascertain the shedding time in infected patients, as resources have been scarce to test all patients, especially multiple times, before being discharged from hospitals. In these conditions, patients are suggested to remain in isolation to avoid any spread of infection. However, we agree with the authors that it is possible that many of these patients do not shed the active virus despite being positive on qPCR. These findings need to be confirmed by large-scale studies in which throat swabs are indeed tested in a sufficient number of patients to determine if viral positivity on qPCR represents infective virus or just viral remnants that are unable to transmit along with the time kinetics. ■

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De Chang, M.D., Ph.D.*
Guoxin Mo, M.D.*
Xin Yuan, M.D.*
Yi Tao, M.D.
Chinese PLA General Hospital
Beijing, China

Xiaohua Peng, M.D.
Yale University School of Medicine
New Haven, Connecticut

Fusheng Wang, M.D.
Lixin Xie, M.D.‡
Chinese PLA General Hospital
Beijing, China

Lokesh Sharma, Ph.D.§
Charles S. Dela Cruz, M.D., Ph.D.§
Yale University School of Medicine
New Haven, Connecticut

Enqiang Qin, M.D.§
Chinese PLA General Hospital
Beijing, China

*These authors contributed equally to this work.
‡Corresponding author (e-mail: 2464277169@qq.com).
§These authors contributed equally to this work.

References

1. Chang D, Mo G, Yuan X, Tao Y, Peng X, Wang FS, *et al*. Time kinetics of viral clearance and resolution of symptoms in novel coronavirus infection [letter]. *Am J Respir Crit Care Med* 2020;201: 1150–1152.
2. Young BE, Ong SWX, Kalimuddin S, Low JG, Tan SY, Loh J, *et al*.; Singapore 2019 Novel Coronavirus Outbreak Research Team. Epidemiologic features and clinical course of patients infected with SARS-CoV-2 in Singapore. *JAMA* 2020;323: 1488–1494.
3. Rothe C, Schunk M, Sothmann P, Bretzel G, Froeschl G, Wallrauch C, *et al*. Transmission of 2019-nCoV infection from an asymptomatic contact in Germany. *N Engl J Med* 2020;382:970–971.
4. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, *et al*. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020;395: 1054–1062.

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Aortic Pulse Wave Velocity Predicts All-Cause Mortality in Chronic Obstructive Pulmonary Disease

To the Editor:

We read with keen interest the results of the SUMMIT (Study to Understand Mortality and Morbidity in COPD) randomized controlled trial of fluticasone furoate/vilanterol in patients with moderate chronic obstructive pulmonary disease (COPD) with a history of cardiovascular disease or at increased cardiovascular risk (1). The trial evaluated both the value of aortic pulse wave velocity (aPWV) to predict all-cause mortality (ACM) in this population and

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the effect of inhaled therapy on aPWV. A secondary endpoint was the cardiovascular composite of myocardial infarction, unstable angina, stroke, transient ischemic attack, and cardiovascular death.

We congratulate the authors on conducting this large population-based trial to evaluate an important clinical question. Although inhaled therapy had no effect on aPWV, the finding that aPWV may be useful to predict ACM in patients with COPD merits further consideration. First, we are interested to know what specific adjustments were included in the analysis of aPWV predicting ACM. "Various ischemic and vascular indicators" are mentioned (1). In particular, were adjustments for blood pressure and heart rate included? aPWV is influenced by these factors, and published data from the SUMMIT trial already showed a U-shaped curve of blood pressure to predict both ACM and cardiovascular events, whereas there was a linear relationship with increased heart rate (2–4). Another important question is whether the analysis included adjustment for other established Framingham cardiovascular risk factors, such as diabetes, hypertension, cholesterol level, and diabetes (5).

A further point of interest is the lack of relationship between aPWV and the cardiovascular composite (which included cardiovascular death), despite elevated aPWV predicting ACM. This is striking and leads to the question, what did patients in the study die from? And was aPWV associated with any other cause of death? The authors point out previous studies' findings of elevated aPWV in patients with COPD and speculate on mechanisms linking aPWV to cardiovascular disease in patients with COPD. However, the results of this study do not support an association between aPWV and cardiovascular events in patients with COPD.

Importantly, many of these surrogate markers of cardiovascular risk only add moderately to standard risk factors (6). The importance of routinely assessing cardiovascular risk in patients with COPD using validated risk scores such as Framingham or QRISK and mitigating such risk in individual patients is likely to remain the optimal clinical and cost-effective approach to reduce cardiovascular risk in patients with COPD. ■

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Marie Fisk, M.R.C.P., Ph.D.*
Ian Wilkinson, F.R.C.P., D.M.
University of Cambridge and Cambridge University Hospitals NHS Foundation Trust
Cambridge, United Kingdom

ORCID ID: 0000-0002-1292-7642 (M.F.).

*Corresponding author (e-mail: mf503@medschl.cam.ac.uk).

References

1. Crim C, Anderson JA, Calverley PMA, Celli BR, Cowans NJ, Martinez FJ, *et al*. Pulse wave velocity in chronic obstructive pulmonary disease and the impact of inhaled therapy (SUMMIT): a randomized double-blind clinical trial. *Am J Respir Crit Care Med* [online ahead of print] 4 Feb 2020; DOI: 10.1164/rccm.201908-1639LE.
2. Byrd JB, Newby DE, Anderson JA, Calverley PMA, Celli BR, Cowans NJ, *et al*.; SUMMIT Investigators. Blood pressure, heart rate, and mortality in chronic obstructive pulmonary disease: the SUMMIT trial. *Eur Heart J* 2018;39:3128–3134.
3. Safar ME. Arterial stiffness as a risk factor for clinical hypertension. *Nat Rev Cardiol* 2018;15:97–105.
4. Papaioannou TG, Oikonomou E, Lazaros G, Christoforatou E, Vogiatzi G, Tsalamandris S, *et al*. The influence of resting heart rate on pulse wave velocity measurement is mediated by blood pressure and depends on aortic stiffness levels: insights from the Corinthia study. *Physiol Meas* 2019;40:055005.
5. Vallée A, Yannoutsos A, Temmar M, Dreyfuss Tubiana C, Spinu I, Zhang Y, *et al*. Determinants of the aortic pulse wave velocity index in hypertensive and diabetic patients: predictive and therapeutic implications. *J Hypertens* 2018;36:2324–2332.
6. Wang TJ, Gona P, Larson MG, Tofler GH, Levy D, Newton-Cheh C, *et al*. Multiple biomarkers for the prediction of first major cardiovascular events and death. *N Engl J Med* 2006;355:2631–2639.

Reply to Fisk and Wilkinson

From the Authors:

We thank Fisk and Wilkinson for their interest in our study showing that higher baseline pulse wave velocity (PWV) was predictive of increased all-cause mortality among patients with chronic obstructive pulmonary disease (COPD) in the SUMMIT (Study to Understand Mortality and Morbidity in COPD) trial (1). They raise several important points in their letter. First, the legend of Figure 1 in our article lists the numerous covariables included in the Cox model. Many of the factors, such as diabetes and cardiovascular disease (CVD) or other risk factors, were included in the model among the "cardiovascular entry criteria" (*see* main paper [2]). Cholesterol concentrations *per se* were not measured. However, blood pressure (in particular) and heart rate are independent predictors of PWV and were not included in the model (3). We acknowledge this as a limitation, but we note that there are numerous covariables already in the model with a wide nonsignificant confidence interval. It is unlikely that adjusting for more variables, including blood pressure, would further strengthen the association.

Fisk and Wilkinson correctly note that the study's primary endpoint was all-cause mortality, and as such, we chose to evaluate the association of PWV with this endpoint. In the entire patient population with moderate airflow limitation, we expected that most deaths would be cardiovascular in nature (4), and in fact, 43% of all deaths in SUMMIT were adjudicated as cardiovascular; of these deaths, 9% were caused by myocardial infarction, 9% were caused by cerebrovascular accidents, 70% were sudden deaths, 1% were cardiac surgery–related procedural deaths, and 10% were of other cardiovascular causes (2). As noted, we did not observe a significant association of PWV with the composite cardiovascular endpoint. Given the fewer number of cardiovascular composite events, our study likely lacked the power to detect this association or statistical

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