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Reply:

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REPLY:



We thank Marquez et al for their interest in our study.¹ Their points are worthy of a discussion. Our article demonstrates a highly sensitive and specific biomarker, namely apical ground-glass opacification (GGO) seen on carotid CTA, in a cohort of patients with suspected stroke during the pandemic (sensitivity, 75% [95% CI, 56–87]; specificity, 81% [95% CI, 71–88]; OR = 11.65 [95% CI, 4.14–32.78]; $P = .001$). The sample was accrued continuously from March through April 2020 from a population scanned for the indication of suspected acute stroke, not for suspected coronavirus disease 2019 (COVID-19). This study simply highlights the importance of vigilance in assessment of the lung apices when reporting carotid CTAs in the population with suspected acute stroke. Most patients in our study were without typical symptoms of COVID-19. We used other information readily available at the time of the carotid CTA acquisition but were unable to find any other additional biomarkers. This included demographics, clinical history, symptoms and signs, as well as chest radiographs² (which are typically obtained shortly after the admission of patients with acute stroke). In summary, we recommend routinely analyzing lung apices in patients with stroke undergoing carotid CTA, because this rapid and easy assessment of apices is valuable, opportunistic, and “free” information in a routine and unmodified scan. The apical analysis simply identifies patients likely to have COVID-19 with early downstream benefits such as limiting disease transmission.

We reiterate that reverse transcriptase polymerase chain reaction (RT-PCR) should not be omitted or replaced. Such patients still require formal RT-PCR testing according to hospital policy. In some hospitals, RT-PCR testing may be required for all emergency admissions; in others, it may be just for those patients who have clinical features suggestive of COVID-19. Regardless of RT-PCR indication, we again point out that RT-PCR takes hours to process. In the interim, the opportunistic and free information we describe in analyzing the lung apices is of benefit. In our hospitals, apical analysis is now articulated in reports to good effect, for example, changing staff personal protective equipment requirements (eg, from a fluid-repellant surgical mask to an FFP3 or N95 mask), and directing a patient to a side room instead of an open ward, pending RT-PCR results.

We agree that chest CT findings of COVID-19 are useful when found; however, we highlight that guidance from both the Royal College of Radiologists (UK) and the American College of Radiology do not recommend routine chest CT scanning as a means of diagnosing Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2).^{3,4}

It remains challenging to draw definitive conclusions from any index test (apical GGO analysis) compared with a reference standard (RT-PCR), which itself is not of optimal sensitivity.⁵ However, our study showed that apical GGO alone is a prognostic biomarker of 30-day mortality. In other words, regardless of

whether RT-PCR had been performed, and regardless of the RT-PCR result if performed, the absence of apical GGO confers a survival advantage compared with those with the presence of apical GGO (5.7% versus 18.0% mortality, $P = .017$; hazard ratio = 3.51 [95% CI, 1.42–8.66]; $P = .006$). This would further support the use of an opportunistic and free biomarker in a routine scan as being valuable.

We concur and mention in our article that the inferior and posterior pulmonary segments are more often affected in SARS-CoV-2 infection; however, we do not recommend routinely scanning the entire lungs with chest CT, without clinical indication, in keeping with the published guidance mentioned above.

Regarding the suggestion to include comorbidities and risk factors for stroke, we refer the authors to Online Table 4. Here it shows that key stroke risk factors were included in our study (hypertension, diabetes mellitus, atrial fibrillation, hyperlipidemia, history of stroke/TIA, and smoking status) and were incorporated as covariates in the bivariate and multivariate analyses.

Our primary objective was to determine candidate diagnostic biomarkers for COVID-19, but we agree there were some interesting additional findings from our study regarding the association between SARS-CoV-2 infection and stroke. For example, a contributory mechanism to COVID-19-related excess mortality might be thromboembolic because increased carotid occlusion was associated with GGO (16.0% versus 3.4%, $P = .004$; OR = 6.82 [95% CI, 1.97–23.53]; $P = .002$), and our multivariate analysis suggested carotid occlusion was likely to be an independent predictor of death.

While this study was based in London, United Kingdom, and included 3 hospitals with a nonwhite population ranging from 10% to 40%, with patients from a variety of socioeconomic status in the catchment area, we believe the biomarker would benefit from further rigorous temporal and spatial validation. In other words, having developed the biomarker, we should now test it on a cohort of patients from hospitals throughout an entire nation with prospective data collection at a subsequent time point in the pandemic. Such a study to obtain highly representative samples of the populations with acute stroke during the COVID-19 pandemic is currently underway.⁶

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