Cardiac Involvement After Recovering From COVID-19

To the Editor I read with interest the article by Puntmann et al.1 regarding the cardiac magnetic resonance (CMR) imaging findings in a group of 100 patients with asymptomatic to a severe course of coronavirus disease 2019 (COVID-19) after a median of 2 to 3 months from diagnosis. I was surprised by the high frequency of cardiac involvement still present in that group, including signs of fibrosis in 78% of patients and ongoing inflammation in 60% of them. The study drew large media attention around the world and brings serious clinical concerns regarding the potential need for in-depth cardiologic screening in all patients after recovering from COVID-19.

The recent study by my coauthors and me2 on persistent subclinical changes in CMR imaging after a median of 7 months from myocarditis in children revealed ongoing active inflammation in 28% of patients and healed myocarditis with persistent scars in 44% of patients. Therefore, a 2-fold lower frequency of persistent myocardial changes, detected later from the onset of the disease, was observed in our group of adolescents with confirmed myocarditis. We did not use T1 and T2 mapping techniques, which are able to detect a subtler myocardial injury or ongoing myocardial inflammation,3 but the difference was still remarkably large, especially considering asymptomatic or mildly affected patients composed a significant amount of the post-COVID-19 group.2

Therefore, I would like to raise some comments regarding the study by Puntmann et al.,1 which might explain the high frequency of cardiac involvement detected. First, the application of the modified Lake Louise criteria,4 requiring the presence of both T1 and T2 relaxation time elevation to diagnose an ongoing inflammation, was not reported in the article, and although T1 and T2 usually rise in parallel, on that occasion, the frequency of ongoing myocarditis, at least theoretically, could range from 38% to 60%. Second, Puntmann et al.1 used reference criteria for cutoff values of elevated T1 and T2 from studies performed on a 3-T Philips scanner, while their study was done on a 3-T Siemens scanner. In my opinion, these values are not interchangeable. The reference ranges reported for a 3-T Philips scanner are much lower than reference values for a 3-T Siemens scanner, which have been summarized in our report5 and are higher by approximately 100 milliseconds for T1 and 10 milliseconds for T2. Therefore, a cutoff point could have been set too low, leading to many false-positive findings. However, only 3 patients with the most severe course had a myocardial biopsy to verify that hypothesis.

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To the Editor We read with great interest the article by Puntmann et al.1 on a cohort of German patients affected by coronavirus disease 2019 (COVID-19) and investigated by cardiovascular magnetic resonance (CMR) imaging. The authors’ observations are very similar to our own findings from a region of eastern France that was also severely affected by COVID-19. However, the interpretation of the results by Puntmann et al.,1 particularly concerning the potential long-term persistence of myocardial inflammation, seems very alarmist, and in any case excessive, given the current state of understanding.

The most prevalent abnormality reported in the article by Puntmann et al.1 was myocardial inflammation, which was predominantly characterized by moderate increases in myocardial T1 and T2. However, criteria for true myocarditis were not met on the endomyocardial biopsies obtained in a few patients with severe cardiac involvement,1 a finding that is concordant with results from previous autopsy studies.2

Moreover, rises in myocardial T2 and T1 are not specific to inflammation and may relate to a noninflammatory edema, as already documented in patients with chronic kidney disease.3 In our university hospital, myocardial extracellular volume, computed with the additional recording of postcontrast T1 sequences,4 was found to be constantly increased on CMR imaging recorded in 4 patients with a recent history of COVID-19 and presenting significant increases in blood cardiac enzymes. This fluid overload could explain the concomitant observation of small increases in myocardial T2 and T1 as well as in myocardial mass, similar to that documented in the article by Puntmann et al.1 However, in our recent experience, all these increases are much more unusual when patients are investigated during the later course of COVID-19 (this part of our study is still ongoing).

The mechanism underpinning cardiac involvement in patients with COVID-19 is currently poorly understood and surely complex. In general terms, tissue damage related to COVID-19 is not only the result of local inflammatory mechanisms but also possibly the result of vascular-related damage, such as capillary leakage and vessel thrombosis.5

The CMR imaging study by Puntmann et al.1 makes a significant contribution to the description of myocardial damage associated with COVID-19, but it does so over a relatively
In Reply As the awareness about the numerous late effects of coronavirus disease 2019 (COVID-19) infection is taking hold, there is a growing understanding that cardiac involvement constitutes an important part of early and late stages of the COVID-19 illness. We recently demonstrated high prevalence of cardiac inflammation by cardiac magnetic resonance imaging in patients recovered from COVID-19 illness, with no trend of abating with the time passed from the acute COVID-19 illness. We emphasized the absence of longitudinal studies and hard outcome data, precluding any speculation on the long-term effects of these findings and indicated the need for more research. Yet in some parts of the press and by Filippetti et al, our findings have been described as “alarmist.” Filippetti et al suggest that the results of myocardial biopsies did not meet the criteria for true myocarditis, as used by Lindner et al.2 Notably, Lindner et al2 and our article1 both used the established pathological definitions by the World Health Organization and International Society and Federation of Cardiology.3 Whereas there was evidence of acute lymphocytic infiltration in myocardial biopsies months after the infection in our study,1 this was not the feature in patients who died during the acute illness.2 In our view, these findings are informative and complementary; cardiovascular damage and heart failure during the acute COVID-19 illness may result from exertion through febrile status, tachycardias, and general hypoxia, especially in those with preexisting cardiovascular conditions. However, later stages reveal intrinsic inflammatory myocardial involvement, accompanied by clinical manifestation of chronic fatigue and palpitations, thus explaining the different patterns in myocardial biopsies.

The definition of myocarditis remains a subject of considerable discussion. Classically, it relies on the results of myocardial biopsies, which is rarely used prior to considerable structural heart impairment. The biopsy criteria have been changing over time and include “other immunohistochemical criteria.”4 Similarly, cardiac magnetic resonance–based criteria were expanded to accommodate for novel parameters by various combinations of techniques and findings to be regarded as positive, as suggested by Malek. We observe that none of these proposed criteria are underpinned by strong outcome studies to serve as a diagnostic criterion standard,4 necessitating imminent further research. The modern definitions must include the early changes, such as myocardial water and diffuse fibrosis, as demonstrated in patients with COVID-19 in our study1 and also in other autoimmune models of myocarditis, and which occur prior to development of structural heart disease.

Malek also further refers to the technical issues with T1 mapping and the difficulty in transferring between different vendors and techniques. Importantly, we did not use the vendor products. We established our own T1 mapping MOLLI variant forming the basis of the Goethe CVI Approaches, first on Philips (version 4) and later transferred onto Siemens by harmonizing all parameters (well beyond solely the inversion scheme). We undertook extensive validation work in phantom, histological correlations, disease models, and outcome data as well as intraindividual comparisons between the vendor platforms. We thank the authors of the letters for their interest and discussion.

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Organ Acceptance and Outcomes—
A Surgeon’s Perspective

To the Editor  We read with great interest the analysis of US National Transplant Registry data by Choi et al.1 This sophisticated analysis showed higher facility-level organ offer acceptance rates were associated with lower waitlist mortality, which is not surprising since the logical result of a high acceptance rate is fewer people waiting on the waitlist. Additionally, posttransplant mortality was equivalent among first-rank vs lower-rank offers, indicating, they concluded, that outcomes would be the same regardless of who accepted the organ. The findings are timely considering current revisions in United Network for Organ Sharing allocation and provide an avenue for further efforts to reduce waitlist mortality and improve overall transplant outcomes.

Nonetheless, there are issues that ought to be further explored as we interpret these findings. First, higher surgical volumes generally result in better outcomes.2 Importantly, hospital structural factors may influence this observed association more than simply individual surgeon volume. Logically, transplant programs with high organ acceptance rates would have more organs to transplant and therefore higher volumes compared with programs with similar number of offers but a lower acceptance rate. How does the volume-outcomes relationship contribute to the findings by Choi et al1; are lower acceptance rates perhaps a consequence of those same structural factors that foster the volume-outcome relationship (fewer available surgeons; limited availability of resources, such as dedicated beds and procuring teams; or risk-averse multidisciplinary teams)?

Second, since this retrospective analysis shows association but not necessarily causation, it is possible that centers with higher recent transplant mortality rates have become more selective to improve their publicly reported transplant outcomes. They may reject organs looking for the perfect donor to theoretically increase the odds of a better outcome in the immediate future.

Third, did the authors consider immortal time bias, accounting for time alive on the waitlist? Without a time-dependent analysis to account for this bias, Choi et al1 may have falsely overestimated the survival penalty of the varying acceptance rates. For instance, centers with lower offers could have sicker patients who ultimately do not undergo a transplant. Finally, considering new allocation systems as organs are offered from distant centers with higher travel time and changing recipient characteristics, a follow-up study to evaluate organ offer and acceptance would be timely.

Again, a well-done, important study that may result in policy and structural changes for organ offer evaluation, reimbursement for transplant centers, or potentially universal guidelines for organ acceptability in the current era of public scrutiny.

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In Reply Briefly, we examined variability in acceptance rates of heart offers made to the highest-priority candidates on the waitlist and its association with waitlist mortality. These rates varied considerably among centers, and every 10% increase in adjusted first-rank offer acceptance rate was associated with a 27% reduction in the rate of waitlist mortality, without detriment in 5-year adjusted posttransplant patient survival or graft failure.1

To address the first question from Engelhardt and colleagues, the association between higher surgical volumes and better posttransplant outcomes has been reported,2 but the focus of our study is on waitlist mortality. We considered center volume in the analysis of acceptance rates by a proxy of number of first-rank offers made to each center, and there was no obvious association. This suggests there are factors beyond center volume that influence organ acceptance patterns and waitlist mortality, including organ procurement organization risk aversion and incentives to optimize posttransplant outcomes that may be at odds with increasing acceptance rates and reducing waitlist mortality. Certainly, surgical volume is a result of many structural factors in the hospital system, some of which may influence both acceptance behavior and surgical volume. The national registry does not provide this information.

Whether centers with higher recent transplant mortality rates have become more selective to improve their publicly reported outcomes is an important question that warrants further investigation. The US Centers for Medicare & Medicaid Services evaluates these outcomes, including waitlist mortality and posttransplant survival, the latter of which is directly tied to funding. Information regarding centers’ evaluation status is not publicly known; however, further work would be possible by examining programs with large, recent changes in their acceptance rates and determining if high mortality in prior years was associated with lower acceptance rates.