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Prevalence and clinical outcomes of myocarditis and pericarditis in 718,365 COVID-19 patients

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Abstract

Background: COVID-19 has a wide spectrum of cardiovascular sequelae including myocarditis and pericarditis; however, the prevalence and clinical impact are unclear. We investigated the prevalence of new-onset myocarditis/pericarditis and associated adverse cardiovascular events in patients with COVID-19.

Methods and results: A retrospective cohort study was conducted using electronic medical records from a global federated health research network. Patients were included based on a diagnosis of COVID-19 and new-onset myocarditis or pericarditis. Patients with COVID-19 and myocarditis/pericarditis were 1:1 propensity score matched for age, sex, race and comorbidities to patients with COVID-19 but without myocarditis/pericarditis. The outcomes of interest were 6-month all-cause mortality, hospitalisation, cardiac arrest, incident heart failure, incident atrial fibrillation and acute myocardial infarction, comparing patients with and without myocarditis/pericarditis.

Of 718,365 patients with COVID-19, 35,820 (5.0%) developed new-onset myocarditis and 10,706 (1.5%) developed new-onset pericarditis. Six-month all-cause mortality was 3.9% (n = 702) in patients with myocarditis and 2.9% (n = 523) in matched controls ($p < .0001$), odds ratio 1.36 (95% confidence interval (CI): 1.21–1.53). Six-month all-cause mortality was 15.5% (n = 816) for pericarditis and 6.7% (n = 356) in matched controls ($p < .0001$), odds ratio 2.55 (95% CI: 2.24–2.91). Receiving critical care was associated with significantly higher odds of mortality for patients with myocarditis and pericarditis. Patients with pericarditis seemed to associate with more new-onset cardiovascular sequelae than those with myocarditis. This finding was consistent when looking at pre-COVID-19 data with pneumonia patients.

Conclusions: Patients with COVID-19 who present with myocarditis/pericarditis associate with increased odds of major adverse events and new-onset cardiovascular sequelae.

KEYWORDS
cardiovascular sequelae, COVID-19, MACE, myocarditis, pericarditis

1 | INTRODUCTION

Myocarditis and pericarditis are non-ischaemic inflammatory diseases of the myocardium and pericardium, respectively.[1,2] The clinical presentation of these two conditions is highly variable and may be proceeded by coryzal symptoms or non-specific features of general malaise, fatigue or diarrhoea. At the other extreme, cardiac inflammation may stimulate myocardial infarction, symptomatic arrhythmias, heart failure, cardiogenic shock or sudden cardiac death.[3] Although the aetiology of myocarditis and pericarditis is heterogeneous, infection is the most common cause,[1] with viral pathogens the most commonly implicated in the developed world.[4]

The hallmark of COVID-19 is respiratory involvement, ranging from mild upper respiratory symptoms to acute respiratory distress syndrome.[5] However, severe COVID-19 has been implicated in multi-organ involvement, with several observational case series showing a significant proportion of cardiac involvement among hospitalised patients.[6–8] Moreover, cardiac injury seems to be significantly correlated with increased in-hospital mortality in COVID-19 patients.[7] COVID-19 has a wide spectrum of cardiovascular sequelae, including acute-onset heart failure, arrhythmias, acute coronary syndrome, myocarditis and cardiac arrest. A growing body of evidence has described cardiac involvement in COVID-19, including myocarditis,,[9,10] pericarditis,[11] or more generally, increased biomarkers of cardiac injury,[12] all of which may associate with poor prognosis.[13,14]

Despite recent case reports, the prevalence and clinical impact of new-onset presentation of myocarditis and pericarditis in adults with COVID-19 are unclear. Therefore, using a global federated health research network, the aim of the present study was to investigate the prevalence and associated adverse events and cardiovascular sequelae in patients with COVID-19 who also present with new-onset myocarditis/pericarditis.

2 | METHODS

2.1 | Study design and participants

A retrospective observational study was conducted within TriNetX, a global federated health research network with access to electronic medical records (EMRs) from participating healthcare organisations including academic medical centres, specialty physician practices and community hospitals, predominantly in the United States. The TriNetX network was searched on 19 August 2021 for patients with COVID-19 aged 18–90 years identified in EMRs between 20 January 2020 and 1 June 2020. In addition, a pre-COVID-19 cohort was included (between 20 January 2019 and 1 June 2019) presenting patients with an EMR of pneumonia to validate the prevalence and associated outcomes of myocarditis/pericarditis observed in the COVID-19 cohorts. Reporting of this study conforms to broad EQUATOR guidelines[15] and the more specific Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[16]

Patients with COVID-19 were identified following criteria provided by TriNetX based on Centers for Disease Control and Prevention (CDC) coding guidelines.[17] Patients were included if they had one or more of the following International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes in patient EMRs: U07.1 COVID-19; B97.29 other coronaviruses as the cause of diseases classified elsewhere; B34.2 coronavirus infection, unspecified; or a positive test result identified with COVID-19 specific laboratory Logical Observation Identifiers Names and Codes (LOINCs). Myocarditis was identified with the following ICD-10-CM codes in patient EMRs: I40, acute myocarditis; I41, myocarditis in diseases classified elsewhere; I51.4 myocarditis, unspecified; B97.8 other viral agents as the cause of diseases classified elsewhere; or B89, unspecified parasitic disease. Pericarditis was identified with the following ICD-10-CM codes in patient EMRs: I30, acute pericarditis; I31, other diseases of the pericardium; I32, pericarditis in disease classified elsewhere. Pneumonia (used to validate the COVID-19 analyses) was identified by ICD-10-CM code, J18.

The TriNetX platform only uses aggregated counts and statistical summaries of de-identified information. No protected health information or personal data are made available to users of the platform. Thus, research studies using the TriNetX research network do not require ethical approval as no identifiable patient data are received. TriNetX database performs extensive internal data quality assessments with every refresh based on conformance, completeness and plausibility.[18] This includes the evaluation of clinical correctness and agreements of network insights with external information.

2.2 | Data collection

The TriNetX network was searched on 19 August 2020, and an anonymised data set of patients was analysed within the online database. The COVID-19 cohort, both with and without myocarditis/pericarditis, were aged ≥18 years with a diagnosis between 20 January 2020 (date COVID-19 first confirmed in the United States)[19] and 1 June 2020 (allowing for 6-month follow-up). At the time

of the search, 53 participating healthcare organisations had data available for patients who met the study inclusion criteria.

2.3 | Statistical analysis

All statistical analyses were completed within the TriNetX online platform. Baseline characteristics were compared using chi-squared tests for categorical variables and independent-sample t tests for continuous variables. Propensity score matching (PSM) was used to control for differences in the cohorts and/or known risk factors for cardiovascular disease and all-cause mortality. PSM was therefore used to match patients with COVID-19 and myocarditis/pericarditis to patients with COVID-19 without myocarditis/pericarditis. PSM was also conducted for the pneumonia cohort analyses with and without myocarditis/pericarditis. Patients were 1:1 PSM using logistic regression for age, sex, race, hypertensive diseases, ischaemic heart diseases, heart failure, cerebrovascular diseases, diabetes mellitus, chronic kidney disease, diseases of the respiratory system, diseases of the digestive system and diseases of the nervous system. These variables were chosen because they are established risk factors for cardiovascular disease and/or mortality or were significantly different between the two cohorts. The TriNetX platform uses 'greedy nearest neighbour matching' with a calliper of 0.1 pooled standard deviations. Following PSM, logistic regressions produced odds ratios with 95% confidence intervals (CIs) for 6-month incidence of all-cause mortality, hospitalisation, cardiac arrest, incident heart failure, incident atrial fibrillation (AF) and acute myocardial infarction, comparing patients with/without myocarditis and pericarditis. Statistical significance was set at $p < 0.05$.

3 | RESULTS

3.1 | Patient characteristics

The COVID-19 cohort used in this study was distributed between the four large Census Bureau designated regions of the United States as follows: 17% in the Northeast, 19% in the Midwest, 45% in the South and 19% in the West. Of 718,365 patients with COVID-19, 35,820 (5.0%) developed new-onset myocarditis and 10,706 (1.5%) developed new-onset pericarditis. Compared to propensity-matched controls, patients who developed myocarditis/pericarditis had higher proportions of comorbidities. Although not all variables were statistically non-significant, following PSM, the myocarditis (Table S1) and pericarditis (Table S2) cohorts were deemed well-matched.

3.2 | Myocarditis and COVID-19

Following PSM, six-month all-cause mortality was 3.9% ($n = 702$) in patients with COVID-19 who presented with myocarditis and 2.9% ($n = 523$) in the matched controls without myocarditis ($p < .0001$), odds ratio 1.36 (95% CI: 1.21–1.53). Associated odds of rehospitalisation (odds ratio 1.90 (95% CI 1.80–2.01) and acute myocardial infarction (odds ratio 1.37 (95% CI 1.17–1.61) were also higher in the myocarditis cohort compared with controls. Associated odds of cardiac arrest, incident heart failure and incident AF were not significantly different between the myocarditis cohort and controls. Among subgroups, mortality was higher in all except those aged < 45 years and those not hospitalised following COVID-19 (Table 1).

3.3 | Pericarditis and COVID-19

Following PSM, 6-month all-cause mortality was 15.5% ($n = 816$) in patients with COVID-19 who presented with new-onset pericarditis and 6.7% ($n = 356$) in the matched controls without pericarditis ($p < .0001$), odds ratio 2.55 (95% CI: 2.24–2.91). Associated odds of rehospitalisation, cardiac arrest, incident heart failure, incident AF and acute myocardial infarction were also significantly higher in the pericarditis cohort compared with controls. Mortality was higher among all subgroups (Table 2).

Pneumonia and myocarditis/pericarditis (pre-COVID-19 analyses).

Of the total pneumonia cases ($n = 128{,}939$), 3.1% ($n = 4012$) developed myocarditis and 1.9% (n = 2,497) developed pericarditis. Myocarditis was associated with significantly higher odds of rehospitalisation compared with controls. Pericarditis was associated with significantly higher odds for mortality, rehospitalisation, cardiac arrest, heart failure, AF and myocardial infarction. The complete prevalence and outcome data for the pneumonia cohort are presented in Table S3.

4 | DISCUSSION

Collectively, this retrospective analysis represents the largest follow-up data set of its kind for patients with COVID-19 and presentation of new-onset myocarditis or pericarditis. The findings of the present study suggest that myocarditis and pericarditis in patients with COVID-19 associate with significantly increased odds of all-cause mortality, rehospitalisation and acute myocardial infarction. Associated odds of cardiac arrest, incident heart failure and incident AF were higher in patients with pericarditis compared with matched controls. In contrast, associated

TABLE 1 Six-month odds ratios (95% CI) for adverse events and cardiovascular sequalae in patients with COVID-19–associated myocarditis, following propensity score matching

Cohort	Sample size	Mortality	Hospitalisation	Cardiac arrest	Heart failure	Atrial fibrillation	Acute myocardial infarction
Total	35,820	1.36 (1.21, 1.53)	1.90 (1.80, 2.01)	1.09 (0.82, 1.46)	0.96 (0.79, 1.18)	0.95 (0.74, 1.21)	1.37 (1.17, 1.61)
Female	20,194	1.41 (1.18, 1.69)	1.74 (1.61, 1.88)	1.13 (0.70, 1.83)	0.86 (0.62, 1.17)	0.83 (0.56, 1.22)	1.41 (1.11, 1.80)
Male	15,592	1.41 (1.21, 1.64)	2.12 (1.96, 2.29)	1.00 (0.70, 1.43)	1.03 (0.79, 1.35)	0.91 (0.66, 1.24)	1.36 (1.11, 1.67)
Age <45	20,774	1.19 (0.85, 1.68)	1.50 (1.36, 1.62)	1.72 (1.00, 2.94)	0.96 (0.62, 1.49)	0.77 (0.37, 1.58)	1.84 (1.32, 3.00)
Age 45–70	14,444	1.24 (1.03, 1.49)	2.12 (1.95, 2.30)	1.22 (0.79, 1.88)	0.80 (0.60, 1.08)	0.85 (0.59, 1.20)	1.33 (1.07, 1.64)
Age >70	5,556	1.49 (1.26, 1.75)	2.31 (2.06, 2.59)	0.64 (0.39, 1.06)	1.02 (0.74, 1.40)	1.02 (0.70, 1.48)	1.41 (1.86, 1.82)
Not hospitalised following COVID−19 diagnosis	27,438	0.94 (0.79, 1.11)	0.57 (0.53, 0.63)	0.94 (0.58, 1.53)	0.60 (0.45, 0.79)	0.57 (0.40, 0.80)	0.92 (0.73, 1.16)
Hospital inpatient following COVID−19 diagnosis	6,452	1.68 (1.40, 2.00)	6.64 (5.95, 7.41)	1.07 (0.71, 1.60)	1.36 (0.96, 1.94)	1.48 (0.94, 2.34)	1.48 (1.17, 1.88)
Received critical care following COVID−19 diagnosis	1,898	2.95 (2.19, 3.97)	6.68 (5.47, 8.17)	1.64 (0.95, 2.85)	1.55 (0.82, 2.91)	1.42 (0.62, 2.53)	1.38 (0.95, 2.01)

Note: Myocarditis based on first instance recorded within EMRs within the 6-month period following a COVID-19 diagnosis. Sample size is number of patients in analysis with and without myocarditis/pericarditis, following propensity score matching. Propensity score matched for age, sex, race and comorbidities (hypertensive diseases, ischaemic heart diseases, heart failure, cerebrovascular diseases, diabetes mellitus, chronic kidney disease, diseases of the respiratory system, diseases of the digestive system and diseases of the nervous system).

TABLE 2 Six-month odds ratios (95% CI) for adverse events and cardiovascular sequalae in patients with COVID-19–associated pericarditis, following propensity score matching

Cohort	Sample size	Mortality	Hospitalisation	Cardiac arrest	Heart failure	Atrial fibrillation	Acute myocardial infarction
Total	10,706	2.55 (2.24, 2.91)	2.77 (2.55, 3.00)	2.94 (2.18, 3.97)	2.90 (2.26, 3.71)	2.50 (1.90, 3.20)	2.22 (1.89, 2.61)
Female	5,282	2.39 (1.97, 2.90)	2.75 (2.44, 3.09)	4.14 (2.43, 7.06)	2.85 (1.97, 4.11)	2.17, (1.50, 3.17)	2.38 (1.87, 3.04)
Male	5,268	2.90 (2.42, 3.47)	2.88 (2.57, 3.24)	2.53 (1.75, 3.67)	3.67 (2.55, 5.29)	2.02 (1.45, 2.82)	2.06 (1.66, 2.55)
Age <45	2,210	2.75 (1.82, 4.14)	3.81 (3.15, 4.61)	3.48 (1.71, 7.07)	6.04 (3.05, 11.99)	1.57 (0.70, 5.00)	3.29 (1.92, 5.62)
Age 45–70	5,432	3.28 (2.70, 3.98)	2.86 (2.55, 3.21)	3.35 (2.22, 5.06)	4.21 (2.81, 6.33)	2.78 (1.93, 3.99)	2.23 (1.81, 2.76)
Age >70	3,420	2.24 (1.83, 2.74)	2.06 (1.79, 2.38)	1.85 (1.11, 3.09)	1.72 (1.17, 2.53)	1.95 (1.33, 2.86)	1.91 (1.47, 2.49)
Not hospitalised following COVID−19 diagnosis	5,986	2.36 (1.94, 2.86)	0.89 (0.79, 1.01)	2.41 (1.56, 3.73)	3.34 (2.33, 4.79)	2.31 (1.58, 3.38)	1.96 (1.54, 2.50)
Hospital inpatient following COVID−19 diagnosis	4,180	3.05 (2.51, 3.70)	9.92 (8.60, 11.44)	2.38 (1.61, 5.18)	3.33 (2.23, 4.97)	2.07 (1.42, 3.01)	2.13 (1.71, 2.66)
Received critical care following COVID−19 diagnosis	1,746	3.25 (2.43, 4.36)	12.65 (10.03, 15.96)	3.01 (1.75, 5.19)	4.80 (2.44, 9.44)	2.16 (1.23, 3.79)	2.49 (1.78, 3.48)

Note: Pericarditis based on first instance recorded within EMRs within the 6-month period following a COVID-19 diagnosis. Sample size is number of patients in analysis with and without myocarditis/pericarditis, following propensity score matching. Propensity score matched for age, sex, race and comorbidities (hypertensive diseases, ischaemic heart diseases, heart failure, cerebrovascular diseases, diabetes mellitus, chronic kidney disease, diseases of the respiratory system, diseases of the digestive system and diseases of the nervous system).

odds of cardiac arrest, incident heart failure and incident AF were not higher in patients with myocarditis compared to matched controls. Therefore, although new-onset myocarditis was more prevalent (5.0%) than pericarditis (1.5%) in patients with COVID-19, the latter seems to be associated with more substantial adverse events and cardiovascular sequelae.

Previous work has demonstrated that in 222 non-COVID-19, biopsy-proven, viral myocarditis cases, the rate of mortality was 19.2% in 4.7 years of follow-up.[20] In a nationwide Danish registry of nearly 8,000 patients with pericarditis, the absolute 5-year mortality was 7.1% compared with 4.2% in matched controls without pericarditis.[21] In the present study, results demonstrate the associated odds of adverse events and cardiovascular sequelae between COVID-19 patients with myocarditis/pericarditis and patients with COVID-19 only. Odds of mortality were 1.90 (95% CI 1.80–2.01) and 2.55 (95% CI: 2.24–2.91) in patients with myocarditis and pericarditis, respectively. Although this has not been previously investigated, these findings are complimentary to that of Shi et al who demonstrated that cardiac injury was common (19.7%) among 416 hospitalised patients with COVID-19 in Wuhan, China.[7] Moreover, patients with cardiac injury had higher mortality (51.2%) than those without cardiac injury (4.5%; $p < .001$), and those who received intensive care were more likely to have cardiac injury.

Although we did not investigate cardiac injury per se, we also found an increasing magnitude of the odds of mortality associated with COVID-19 severity, measured by proxy from hospitalisation records. Indeed, data suggested a dose-response, with 68% (1.40–2.00) and 195% (2.19–3.97) higher odds of all-cause mortality in COVID-19 patients with myocarditis who were either hospitalised or received critical care, respectively. Moreover, there was no increase in the odds of mortality in COVID-19 patients with myocarditis who were not hospitalised with COVID-19 initially. Similarly, for COVID-19 patients with pericarditis, there were increasing odds of all-cause mortality in patients who were not hospitalised, hospitalised and received critical care following a COVID-19 diagnosis. Thus, the clinical importance of new-onset myocarditis/pericarditis in patients with COVID-19 seems to be dependent on the severity of initial viral infection.

In a cohort of German patients recently recovered from COVID-19, cardiac magnetic resonance revealed ongoing myocardial inflammation in 60 patients (60%), independent of pre-existing conditions, severity, overall course of the acute illness and time from the original diagnosis.[6] This aligns with previous non-COVID-19 research that demonstrated clinical presentation with congestive heart failure, ventricular tachycardia/ventricular fibrillation or AF/atrial flutter did not predict survival in patients with myocarditis.[22] In contrast and in the present study, patients who presented with new-onset myocarditis/pericarditis had higher proportions of comorbidities including cardiovascular, metabolic, nervous and digestive conditions. This is in keeping with a previous study whereby patients with pre-existing cardiovascular diseases seemed to be more susceptible to COVID-19–induced heart injury. Specifically, 30% and 60% of patients with cardiac injury had a history of coronary heart disease and hypertension, respectively, which were significantly more prevalent than in those without cardiac injury.[7]

In a single case of COVID-19 in a young child, it was proposed that there was a direct effect of the SARS-CoV-2 infection on cardiac tissue, which in this case was a major contributor to the presentation of new-onset myocarditis and heart failure.[23] This case, among others,[24,25] provides evidence that COVID-19 may be a multisystem inflammatory syndrome,[26] and as in the present study, its cardiovascular sequelae present a significant risk to health. It has been proposed that the pathophysiology of viral myocarditis is a combination of direct cell injury and T-lymphocyte–mediated cytotoxicity, which can be augmented by the cytokine storm syndrome.[27] Mechanisms for COVID-19–associated myocarditis/pericarditis may therefore be similar, given that myocardial localisation of COVID-19 has been reported in a case study of a 69 years old who received endomyocardial biopsy.[28]

4.1 | Limitations

A number of limitations are noteworthy. First, the data were collected from healthcare organisation EMR databases and some health conditions may be underreported. Indeed, recording of ICD codes in administrative data sets may vary by factors such as age, number of comorbidities, severity of illness, length of hospitalisation and whether in-hospital death occurred.[29] Specifically, the method of diagnosis of myocarditis/pericarditis from EMRs is unknown. However, we have investigated the prevalence and clinical outcomes of myocarditis and pericarditis following a pneumonia diagnosis in January-June 2019 (i.e. pre-COVID-19), in order to verify associations with cardiovascular outcomes in the COVID-19 cohort. Findings revealed that of the total pneumonia cases ($n = 128{,}939$), 3.1% ($n = 4012$) developed myocarditis and 1.9% ($n = 2{,}497$) developed pericarditis (lower, albeit not dissimilar from prevalence in the COVID-19 cohort). In the pneumonia cohort, myocarditis was associated with significantly higher odds of rehospitalisation only, whereas pericarditis associated with significantly higher odds for all outcomes (mortality, hospitalisation, cardiac arrest, heart failure, atrial fibrillation and myocardial infarction; Table S3). This is largely

aligned with the higher odds of cardiovascular outcomes observed with pericarditis compared with myocarditis in the COVID-19 cohort, presented in this paper. We could also not determine the influence of attending different healthcare organisations due to data privacy restrictions. In addition, outcomes which occurred outside of the TriNetX network are not well captured. Second, the data were from multiple healthcare organisations in the United States but may not be representative of the wider population, thus the generalisability of the results beyond this cohort is unclear. Third, longer follow-up time periods (beyond 6 months) would be interesting, particularly for mortality and cardiovascular disease outcomes. Fourth, immortal time bias needs to be considered when interpreting rates of myocarditis and pericarditis in patients with COVID-19. It is possible that the rates reported in this study are an underrepresentation of the true prevalence. Further, our results should not be interpreted as causal; that is, it can only be interpreted that new-onset myocarditis/pericarditis was associated with higher mortality rates seen in the present study; we do not know if myocarditis/pericarditis are determinants, contributors or markers of effect. Indeed, residual confounding may have impacted our results, including lifestyle factors, socio-economic status and other health markers/conditions, which were not available from EMRs. Subsequent prospective work is needed to further investigate the cardiac involvement of COVID-19, especially in patients presenting with severe cases.

5 | CONCLUSION

Findings from the present study suggest that COVID-19 patients who present with new-onset myocarditis/pericarditis are associated with significantly higher odds of all-cause mortality, relative to patients with COVID-19 only. Further, the severity of COVID-19 seems to be associated with more severe outcomes among patients with myocarditis and pericarditis. Finally, although myocarditis was more prevalent, pericarditis seemed to be associated with higher odds of mortality and new-onset cardiovascular sequelae (a finding that we have confirmed in pre-COVID-19 pneumonia analyses). Therefore, the targeting of early intervention and monitoring for patients with new-onset myocarditis/pericarditis following a COVID-19 diagnosis should be considered for populations with pre-existing cardiovascular disease and risk factors.

CONFLICTS OF INTEREST

Benjamin JR Buckley has received funding from Bristol-Myers Squibb (BMS)/Pfizer. Stephanie L Harrison has received funding from BMS. Elnara Fazio-Eynullayeva and Paula Underhill are employees of TriNetX LLC. Deirdre A Lane has received investigator-initiated educational grants from BMS, has been a speaker for Boehringer Ingeheim and BMS/Pfizer and has consulted for BMS, Boehringer Ingelheim and Daiichi-Sankyo. Gregory YH Lip: consultant for Bayer/Janssen, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Novartis, Verseon and Daiichi-Sankyo and speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim and Daiichi-Sankyo. No fees are directly received personally.

CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

CODE AVAILABILITY

Not applicable.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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