Clinical Features and Outcomes of Acute Myocarditis in Patients with Swab-Confirmed Respiratory Viral Pathogens

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ABSTRACT **Background:** Acute myocarditis (AM) is an inflammatory cardiac condition with heterogeneous clinical manifestations that often overlap with other acute cardiac syndromes, making diagnosis challenging.

Objectives: To characterize the prevalence, clinical profile, and outcomes of AM patients with respiratory viral pathogen detection on nasopharyngeal swabs at admission.

Methods: We retrospectively analyzed all patients admitted to the Sheba Medical Center with confirmed AM between January 2005 and December 2020. Diagnosis was based on compatible presentation, elevated cardiac biomarkers, and supportive imaging findings. Nasopharyngeal swab results, when performed, were reviewed for respiratory viral detection.

Results: Among 425 identified AM cases, 146 (34%) underwent swab testing; 11 (8%) tested positive for respiratory viral pathogens, most commonly influenza A (n=5) and adenovirus (n=3). With one exception, all positive cases occurred during winter or early spring (10/77, 13%). Compared with swab-negative patients, swab-positive individuals were older (47 ± 22 vs. 35 ± 14 years, $P = 0.03$), more frequently female (45% vs. 14%, $P = 0.007$), and more often presented with dyspnea (55% vs. 25%, $P = 0.036$) but less commonly with ST-segment elevation (27% vs. 70%, $P = 0.003$). No differences were observed in inflammatory markers, imaging findings, or hospital stay.

Conclusions: Respiratory viral detection in AM is uncommon and predominantly seasonal. Nasopharyngeal swabbing is a simple, non-invasive tool that may help identify treatable viral pathogens and guide patient management. These data provide a pre-COVID-19 reference for future studies investigating the impact of viral infection on myocardial injury.

IMAJ 2026; 28: 156–161

KEY WORDS: acute myocarditis, clinical outcomes, nasopharyngeal swab, respiratory viruses, seasonal variation

Acute myocarditis (AM) is an inflammatory disease of the myocardium with diverse clinical manifestations, ranging from chest pain and arrhythmias to acute heart failure and sudden cardiac death [1]. Despite advances in noninvasive imaging, AM continues to pose diagnostic challenges because of its overlap with acute coronary syndrome [2,3]. The recently published 2025 European Society of Cardiology (ESC) guidelines for the management of myocarditis and pericarditis introduced the broader concept of inflammatory myopericardial syndrome and provide updated diagnostic algorithms [4]. Importantly, the guidelines acknowledge persistent uncertainty regarding the role of viral pathogen detection in routine evaluation, highlighting the need for robust clinical data to inform practice [4,5].

Viral infections remain a predominant trigger for AM worldwide, often preceded by flu-like prodromes [1,6]. Endomyocardial biopsy studies have identified viral genomes including adenovirus, enterovirus, human herpesvirus-6 (HHV-6), and parvovirus B19 within myocardial tissue of AM patients [7,8]. More recently, polymerase chain reaction (PCR) based testing of respiratory samples has broadened the implicated spectrum to community-acquired respiratory viruses such as influenza and adenovirus [9]. However, the diagnostic yield, seasonal distribution, and clinical implications of nasopharyngeal swab testing at presentation remain poorly characterized in large AM cohorts. A recent single-center study suggested that only a minority of AM patients test positive on respiratory viral swabs, with limited prognostic impact [10], underscoring the need for larger longitudinal datasets to clarify epidemiological features and clinical profiles.

Table 1. Baseline characteristics and clinical characteristics of patients with and without positive nasopharyngeal swab for viruses

Variables	Positive swab (n=11)	Negative swab (n=135)	*P*-value
Age in years	47 ± 22	35 ± 14	0.03
Male	6 (55%)	116 (86%)	0.007
Prior coronary artery disease	2 (18%)	6 (4%)	0.06
Diabetes mellitus	2 (18%)	9 (8%)	0.122
Hypertension	2 (18%)	10 (14%)	0.43
Dyslipidemia	2 (18%)	21 (15%)	0.88
Smoking	4 (36%)	38 (28%)	0.56
Onset of symptoms prior to hospitalization (days)	10 ± 9	5 ± 6	0.192
Duration of hospitalization (days)	6 ± 6	6 ± 6	0.48
Pericardial chest pain	3 (27%)	55 (41%)	0.007
Non-pericardial chest pain	8 (73%)	80 (59%)	0.12
Dyspnea	6 (55%)	34 (25%)	0.036
Cough	5 (46%)	32 (24%)	0.11
Fever	7 (64%)	102 (76%)	0.38
Chills	2 (18%)	21 (16%)	0.82
Abdominal pain	2 (18%)	12 (9%)	0.31
Diarrhea	2 (18%)	10 (14%)	0.43
Computed tomography coronary	1 (9%)	26 (19%)	0.40
Conventional coronary angiography	4 (36%)	31 (23%)	0.32
Evidence of coronary artery disease	2 (18%)	21 (15%)	0.89
Significant coronary artery disease	0 (0%)	0 (0%)	1.00
Normal electrocardiogram	1 (9%)	13 (10%)	0.95
ST elevation	3 (27%)	95 (70%)	0.003
ST depression/T wave inversion	5 (46%)	36 (27%)	0.18
PR segment depression	2 (18%)	55 (41%)	0.14
Admission troponin (µg/l)	12 ± 31	7 ± 11	0.38
Peak troponin (µg/l)	10 ± 12	55 ± 156	0.33
C-reactive protein admission (mg/l)	61 ± 75	102 ± 94	0.07
Echocardiographic parameters			
Left ventricular ejection fraction %	51 ± 16	53 ± 11	0.59
Systolic pulmonary artery pressure (mmHg)	37 ± 16	26 ± 10	0.14
Reduced right ventricle function	1 (9%)	7 (5%)	0.58
Cardiac magnetic resonance parameters			
Magnetic resonance imaging (Yes/No)	7 (64%)	101 (74%)	0.45
Left ventricular ejection fraction %	57 ± 15	58 ± 9	0.85
Left ventricular end diastolic volume index (ml/m^2)	74 ± 15	82 ± 77	0.78
Left ventricular end systolic volume index (ml/m^2)	33 ± 21	34 ± 31	0.93
Sub-epicardial late gadolinium enhancement	7 (63%)	86 (64%)	1.00
Mid-wall lesions	2 (18%)	25 (19%)	0.9
Transmural lesions	0 (0%)	10 (7%)	0.4
Linear late gadolinium enhancement	3 (27%)	31 (23%)	0.68
Patchy late gadolinium enhancement	2 (18%)	37 (27%)	0.70
Diffuse late gadolinium enhancement	1 (9%)	24 (18%)	0.50
Anterior late gadolinium enhancement	0 (0%)	21 (16%)	0.163
Septal late gadolinium enhancement	7 (63%)	84 (62%)	1.00
Lateral late gadolinium enhancement	0 (0%)	22 (35%)	0.34
Inferior late gadolinium enhancement	5 (46%)	70 (52%)	0.89

Table 2. Comparison of admission and discharge medications among patients with and without positive nasopharyngeal swab for viruses

	Admission			Discharge		
Variable	Positive swab (n=11)	Negative swab (n=135)	*P*-value	Positive swab (n=11)	Negative swab (n=135)	*P*-value
Aspirin	7 (63%)	53 (39%)	0.11	3 (27%)	21 (16%)	0.32
Nonsteroidal anti-inflammatory drugs	4 (36%)	62 (46%)	0.54	3 (27%)	43 (32%)	0.74
Steroids	0 (0%)	9 (6%)	0.38	6 (5%)	0 (0%)	0.47
Colchicine	1 (9%)	70 (52%)	0.006	1 (9%)	65 (49%)	0.012
Beta blockers	5 (46%)	69 (51%)	0.72	5 (46%)	44 (33%)	0.40
Angiotensin converting enzyme inhibitor/angiotensin II receptor blockers	3 (27%)	45 (33%)	0.68	3 (27%)	40 (30%)	0.86
Loop diuretics	4 (36%)	10 (7%)	0.02	3 (27%)	5 (4%)	0.001

Table 3. Outcomes of patients with and without positive nasopharyngeal swab for viruses

Variable	Positive swab (n=11)	Negative swab (n=135)	*P*-value
Congestive heart failure	0 (0%)	11 (8%)	0.33
Ventricular arrhythmias	1 (9%)	2 (1%)	0.21
In hospital death	0 (0%)	0 (0%)	NA
Extracorporeal oxygenation membrane	0 (0%)	2 (1%)	1.00
Left ventricular assisted device	0 (0%)	0(0%)	NA
Intra-aortic balloon bump	0 (0%)	0 (0%)	NA
Vasopressors/inotropes	0 (0%)	3 (2%)	1.00
Mortality (30 days)	0 (0%)	0 (0%)	NA
Mortality (6 months)	0 (0%)	0 (0%)	NA
Mortality (1 year)	0 (0%)	0 (0%)	NA

In the present study, we address this knowledge gap by evaluating the prevalence, seasonal patterns, and clinical features of patients with swab-confirmed viral respiratory infections at admission for AM. We used data from a large tertiary referral center over a 15-year period preceding the coronavirus disease 2019 (COVID-19) era. We compared the clinical profile and outcomes of AM patients with and without positive nasopharyngeal swabs for respiratory viruses in the pre-COVID era, thereby establishing a baseline framework for interpreting the evolving impact of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and other emerging respiratory viruses on myocarditis.

PATIENTS AND METHODS

We retrospectively evaluated the records of all patients admitted to Sheba Medical Center with a diagnosis of AM between January 2005 and December 2020. Patients were initially identified using International Classification of Diseases, Ninth Revision (ICD-9) codes 422.0, 422.91, 422.92, 422.93, 422.99, and 429.89 recorded in hospital discharge forms, and diagnoses were confirmed through review of clinical records. Patients with a current diagnosis of acute coronary syndrome were excluded. Only patients with symptom onset ≤ 30 days prior to admission were included. A detailed description of the study population has been reported previously [11-14]. Patients presenting with fever or respiratory symptoms underwent nasopharyngeal swabbing for respiratory viruses upon hospital admission at the discretion of the treating physician, as part of the routine in our center. Specimens were tested for the following: influenza A/B, human metapneumovirus (hMPV), parainfluenza virus, rhinovirus, respiratory syncytial virus, and adenovirus. We used Allplex™ RV multiplex real-time RT-PCR kit (Seegene Inc., South Korea). Accordingly, patients were classified as swab positive or swab negative.

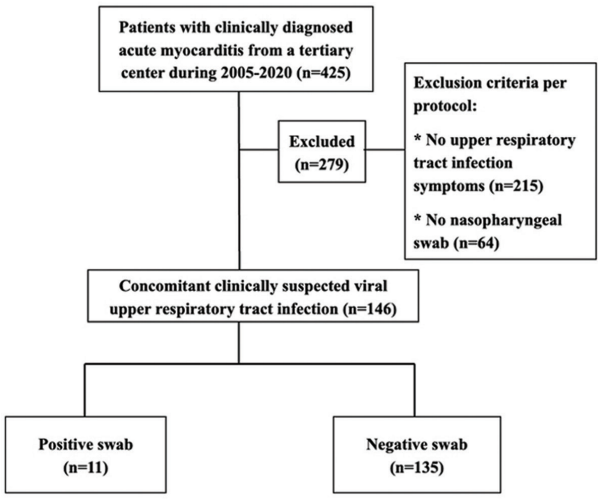
Clinical profiles and laboratory results were extracted from medical records. Imaging data, including echocardiography, coronary computed tomography angiography, and cardiac magnetic resonance imaging (CMR), were also collected. Patients who underwent CMR were scanned 3–5 days after admission. Myocarditis was confirmed using updated ESC Lake Louise criteria [2]. The diagnosis of myocarditis was considered in each patient based on a combination of medical history, clinical presentation, physical findings, ECG changes, echocardiographic assessment, and markers of myocardial injury.

The primary endpoint was in-hospital major adverse cardiac events, defined as a composite of acute heart failure, ventricular arrhythmias, and/or in-hospital mortality. Secondary endpoints included all-cause mortality at 30 days, 6 months, and 1 year, as well as any of the following: use of an intra-aortic balloon pump, implantation of a left ventricular assist device, initiation of

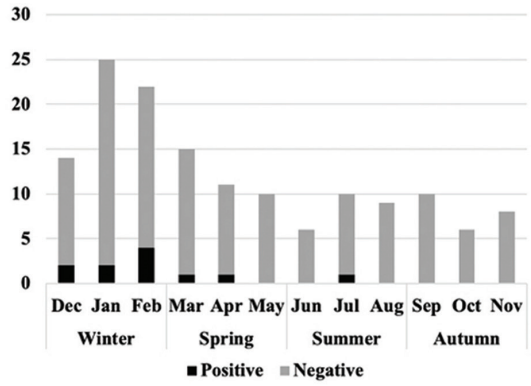
inotropic or vasopressor therapy, or use of extracorporeal membrane oxygenation. Mortality outcomes were determined by cross-referencing patient records with the National Population Registry of Israel. The study protocol was approved by the Sheba Medical Center institutional review board (SMC-4593-17).

Figure 1. Cohort derivation and nasopharyngeal swab viral pathogen results

[A] Flow diagram illustrating selection of patients included in the analysis



[B] Descriptive analysis of nasopharyngeal swab results for viral pathogens



Virus name	Positive swab
Influenza A	5
Adenovirus	3
Human parainfluenza	1
Rhinovirus	1
Human metapneumovirus	1

Continuous variables are expressed as mean ± standard deviation (SD), and categorical variables as counts and percentages. Group comparisons for continuous variables were performed using the Student's *t*-test. Categorical variables were compared using the chi-square or Fisher's exact test, as appropriate. For all analyses, *P*-value < 0.05 was considered statistically significant.

RESULTS

Overall, between the years 2005 and 2020 a total of 425 patients were hospitalized with a diagnosis of AM. Of these, 146 patients underwent nasopharyngeal swab testing for respiratory viruses at admission, 11 (8%) tested positive, most commonly influenza (n=5) and adenovirus (n=3). Apart from a single case of hMPV identified in July, all positive cases occurred during the winter and early spring months (10/77, 13%) [Figure 1].

Baseline characteristics of swab-positive and swab-negative patients are summarized in Table 1. Compared with swab-negative patients, swab-positive patients were older (47 ± 22 vs. 35 ± 14 years, $P = 0.03$) and less frequently male (55% vs. 86%, $P = 0.007$). The prevalence of cardiovascular risk factors including diabetes, hypertension, dyslipidemia, and smoking was similar between the groups, although a prior history of coronary artery disease tended to be more common in swab-positive patients (18% vs. 4%, $P = 0.06$). Swab-positive patients were more likely to present with dyspnea (55% vs. 25%, $P = 0.036$) and less likely to report pericardial chest pain (27% vs. 41%, $P = 0.007$). Other systemic symptoms, such as fever, cough, or gastrointestinal complaints, did not differ significantly. The onset of symptoms prior to hospitalization tended to be longer in swab-positive patients, although this difference was not statistically significant (10 ± 9 vs. 5 ± 6 days, $P = 0.192$). Hospital length of stay was similar between groups (6 ± 6 vs. 6 ± 6 days, $P = 0.48$). Electrocardiographic findings demonstrated less frequent ST-segment elevation in swab-positive patients (27% vs. 70%, $P = 0.003$), while the prevalence of T-wave inversion, PR-segment depression, and normal tracings was similar. Laboratory values, including peak troponin (10 ± 12 vs. 55 ± 156 µg/L, $P = 0.33$) and C-reactive protein (61 ± 75 vs. 102 ± 94 mg/L, $P = 0.07$), did not differ significantly. Cardiac imaging revealed no group differences in ventricular function, chamber dimensions, or the presence and distribution of late gadolinium enhancement on cardiac magnetic resonance.

Medications used for myocarditis management in both groups are provided in Table 2. Swab-positive patients were less frequently treated with colchicine (admission 9% vs. 52%, $P = 0.006$; discharge 9% vs. 49%, $P = 0.012$) but more often received loop diuretics (admission 36% vs. 7%, $P = 0.02$; discharge 27% vs. 4%, $P = 0.001$). Prescription rates of aspirin, corticosteroids, beta-blockers, and renin–angiotensin system inhibitors were similar.

Clinical outcomes are detailed in Table 3. Overall, there were no significant adverse events recorded during hospitalization and/or during follow-up, including all-cause mortality.

DISCUSSION

In this large single-center cohort spanning over 15 years, we found that only a small minority of patients admitted with AM tested positive (8%) for respiratory viral pathogens on nasopharyngeal swabs. Nonetheless, several consistent patterns emerged: positive cases clustered in the winter–spring months and patients were older and more frequently female. They presented with a more distinct clinical presentation, including more frequent dyspnea and less common ST-segment elevation. Importantly, outcomes were uniformly favorable, with no mortality or recurrent events at one year, irrespective of viral swab status.

The relatively low yield of respiratory viral swabs (8% in this cohort, 13% during winter and early spring) mirrors findings from a smaller study, which reported a positivity rate of 18.0% [10]. While myocardial biopsy studies frequently identify viral genomes such as parvovirus B19 or enteroviruses [7,8], the disconnect between respiratory tract findings and myocardial tissue highlights the complexity of AM pathogenesis. Positive swabs may reflect systemic viral dissemination, a bystander infection, or a true etiological trigger. Given this ambiguity, routine use of respiratory swab testing in suspected AM remains debated in clinical practice, as also acknowledged in the recent ESC guidelines [4]. Our findings reinforce the notion that swab positivity provides epidemiological and contextual insight rather than direct diagnostic certainty.

Nearly all positive cases in our cohort were identified during the winter and early spring, consistent with the established epidemiology of influenza and adenovirus circulation [15,16]. This seasonal pattern not only strengthens the plausibility of respiratory viruses as triggers for AM but also provides a framework for anticipating case surges during periods of high community viral activity. Such epidemiological awareness may help clinicians contextualize presenting symptoms during seasonal influenza epidemics and, in the post-2020 era, during SARS-CoV-2 waves.

Despite swab-positive patients in our cohort being older, more often female, and experiencing longer-lasting symptoms, particularly dyspnea, they had an excellent prognosis, with no cases of acute heart failure, mechanical circulatory support, or mortality during hospitalization or at 1-year follow-up. Similarly, the cohort reported by Ammirati et al. [10] demonstrated a female predominance among viral-positive patients. However, in contrast to our findings, viral positivity in their study was associated with a higher risk of adverse short-term outcomes, particularly among patients presenting with cardiogenic shock or low ejection fraction. Causative viruses in the latter study differed from ours, with four of the nine positive patients presenting with rhinovirus and three with seasonal coronavirus. These differences may also reflect variations in baseline severity and patient selection, suggesting that viral detection alone does not universally predict poor outcomes in AM. Together, these observations underscore the importance of integrating viral testing with clinical severity and hemodynamic status when assessing prognosis [11,12,17]. In addition, respiratory viral detection may have implications for therapy. Although there is no consensus regarding antiviral therapy for influenza associated AM, successful cases have been reported, and early treatment may have theoretical potential to prevent development of myocarditis [4]. It is noteworthy that in our cohort, none of the patients received oseltamivir, presumably due to late presentation.

Several limitations merit consideration. First, viral swab testing was performed at the discretion of treating physicians, potentially introducing selection bias. Second, testing methods and panels evolved over the 15-year study period, which may have influenced detection rates. Third, the sample of swab-positive patients was small, limiting statistical power to detect outcome differences. In addition, our cohort focuses on the pre-COVID period. With the emergence of SARS-CoV-2 and subsequent widespread use of multiplex PCR respiratory panels, the landscape of viral-associated myocarditis has shifted dramatically [18]. Last, viral detection in the nasopharynx does not prove causality for myocarditis and may represent coincidental infection.

Nevertheless, this study provides a valuable baseline reference for interpreting myocarditis epidemiology

in the pre–COVID-19 era. Considering the therapeutic potential of respiratory viruses, and the simplicity of non-invasive nasopharyngeal swab testing, universal testing of patients with AM presenting with fever and/or any respiratory symptoms should be considered. Future multicenter studies with systematic testing are needed to clarify the prognostic role and implications of viral swab positivity, delineate pathogen-specific AM phenotypes, and determine whether integrating viral diagnostics meaningfully guides clinical management.

CONCLUSIONS

Respiratory viral detection on nasopharyngeal swabs in AM is uncommon but offers valuable epidemiological and clinical context. The consistent winter–spring clustering, female predominance, and benign course observed in our cohort suggest that viral positivity more often characterizes a mild, self-limited phenotype rather than increased disease severity. This finding underscores the importance of interpreting viral results within their clinical and hemodynamic context. As nasopharyngeal swabbing is a simple, non-invasive test with potential therapeutic implications particularly when identifying treatable pathogens such as influenza, its use may help guide treatment in appropriate clinical settings. Overall, our data provide a pre-pandemic benchmark for future studies exploring the interaction between viral infection, immune response, and myocardial injury in the post–COVID-19 era.

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Never, never be afraid to do what's right, especially if the well-being of a person or animal is at stake.
Society's punishments are small compared to the wounds we inflict on our soul when we look the other way.
Martin Luther King, Jr. (1929–1968), African-American civil rights leader
best known for advancing civil rights through nonviolence and civil disobedience