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Global Longitudinal Strain and Cardiac Events in Patients With Immune Checkpoint Inhibitor-Related Myocarditis

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ABSTRACT

BACKGROUND There is a need for improved methods for detection and risk stratification of myocarditis associated with immune checkpoint inhibitors (ICIs). Global longitudinal strain (GLS) is a sensitive marker of cardiac toxicity among patients receiving standard chemotherapy. There are no data on the use of GLS in ICI myocarditis.

OBJECTIVES This study sought to evaluate the role of GLS and assess its association with cardiac events among patients with ICI myocarditis.

METHODS This study retrospectively compared echocardiographic GLS by speckle tracking at presentation with ICI myocarditis (cases, n = 101) to that from patients receiving an ICI who did not develop myocarditis (control subjects, n = 92). Where available, GLS was also measured pre-ICI in both groups. Major adverse cardiac events (MACE) were defined as a composite of cardiogenic shock, arrest, complete heart block, and cardiac death.

RESULTS Cases and control subjects were similar in age, sex, and cancer type. At presentation with myocarditis, 61 cases (60%) had a normal ejection fraction (EF). Pre-ICI, GLS was similar between cases and control subjects (20.3 ± 2.6% vs. 20.6 ± 2.0%; p = 0.60). There was no change in GLS among control subjects on an ICI without myocarditis (pre-ICI vs. on ICI, 20.6 ± 2.0% vs. 20.5 ± 1.9%; p = 0.41); in contrast, among cases, GLS decreased to 14.1 ± 2.8% (p < 0.001). The GLS at presentation with myocarditis was lower among cases presenting with either a reduced (12.3 ± 2.7%) or preserved EF (15.3 ± 2.0%; p < 0.001). Over a median follow-up of 162 days, 51 (51%) experienced MACE. The risk of MACE was higher with a lower GLS among patients with either a reduced or preserved EF. After adjustment for EF, each percent reduction in GLS was associated with a 1.5-fold increase in MACE among patients with a reduced EF (hazard ratio: 1.5; 95% confidence interval: 1.2 to 1.8) and a 4.4-fold increase with a preserved EF (hazard ratio: 4.4; 95% confidence interval: 2.4 to 7.8).

CONCLUSIONS GLS decreases with ICI myocarditis and, compared with control subjects, was lower among cases presenting with either a preserved or reduced EF. Lower GLS was strongly associated with MACE in ICI myocarditis presenting with either a preserved or reduced EF. (J Am Coll Cardiol 2020;75:467–78) Crown Copyright © 2020 Published by Elsevier on behalf of the American College of Cardiology Foundation. All rights reserved.

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ABBREVIATIONS AND ACRONYMS

EF = ejection fraction

GLS = global longitudinal strain

ICI = immune checkpoint inhibitor

irAE = immune-related adverse effect

LVEF = left ventricular ejection fraction

MACE = major adverse cardiac event(s)

NT-proBNP = N-terminal pro-hormone B-type natriuretic peptide

TTE = transthoracic echocardiogram

Immune checkpoint inhibitors (ICIs) represent a significant advance in the treatment of patients with cancer (1). They work by promoting T-cell mediated anti-tumor activity (2). These therapies are approved for a multitude of cancers in metastatic and late-stage disease, and more recently in the adjuvant setting (3). During approval, it was anticipated that the activation of the immune system would result in immune-related adverse effects (irAEs) (4,5). Myocarditis is likely an uncommon irAE, but the reporting of ICI myocarditis has increased (6), and consistent data have shown that the case fatality rate with myocarditis related to an ICI is very high, ranging from 35% to 50% (2,3,6,7). However, our understanding of ICI myocarditis is limited, and this needs to improve as ICIs are being tested broadly in additional adjuvant settings and in combination with targeted and traditional cytotoxic therapies (1).

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A key limitation is the lack of robust techniques for the detection of ICI myocarditis and the lack of methods for risk stratification among patients who develop myocarditis (4). The measurement of left ventricular global longitudinal strain (GLS) has been extensively applied in the detection of cardiac injury with traditional cytotoxic chemotherapies and for the prediction of subsequent cardiac events after chemotherapy (8,9). Specifically, GLS decreases acutely among patients with chemotherapy-induced cardiotoxicity (10,11), and this reduction of GLS early after chemotherapy is predictive of the subsequent decline in ejection fraction (EF) (8,11,12). These findings have led to the recommendations for the use of GLS among patients at risk of chemotherapy-induced cardiotoxicity (13). There are no data on the use of GLS in ICI-related myocarditis. In addition, testing the role of GLS in this population may be of additional importance, as most cases present with a preserved EF among whom detection and risk stratification may be additionally challenging (3). Therefore, the aim of this study was to characterize the role of GLS among patients with ICI

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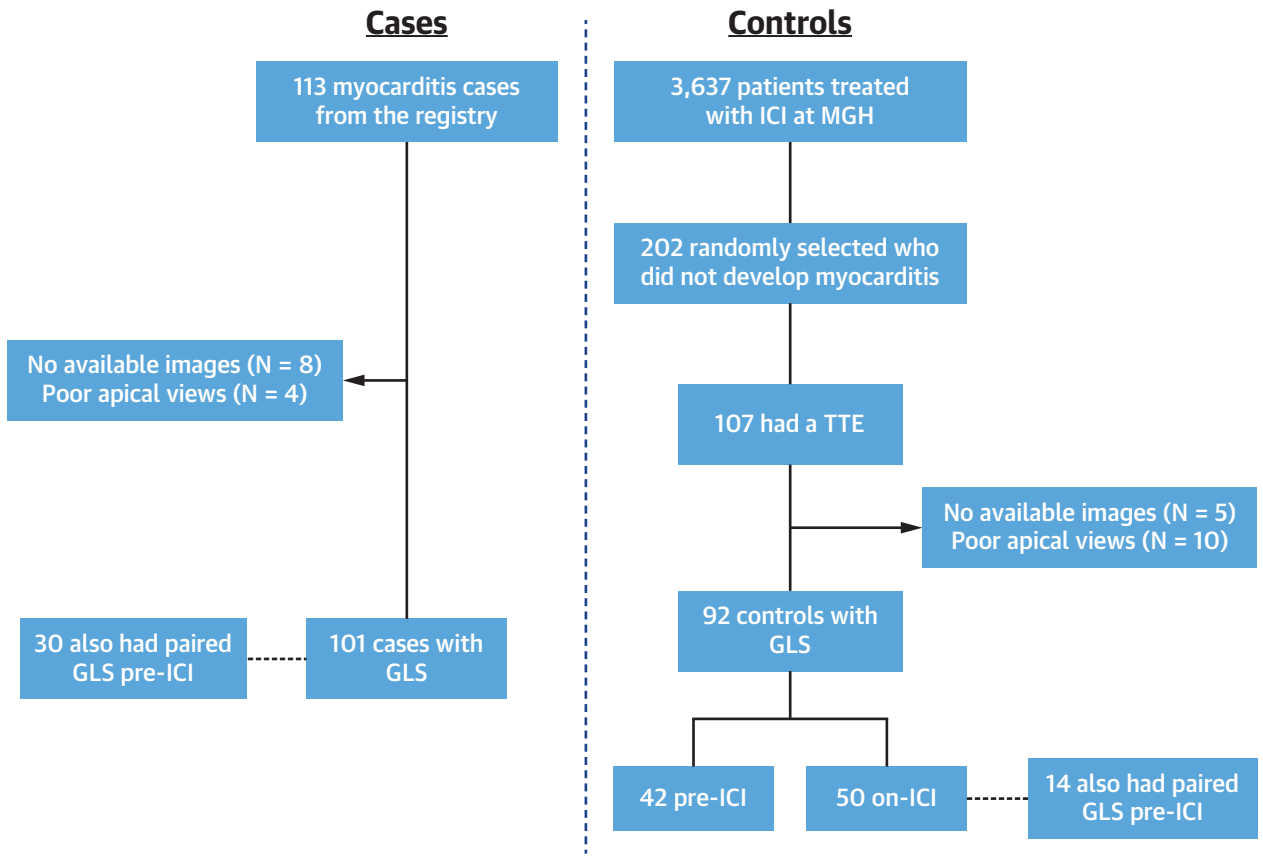
FIGURE 1 A Consort Flow Diagram of Cohort



A consort flow diagram showing the cases from multicenter registry and control subjects from MGH with available TTE GLS. GLS = global longitudinal strain; ICI = immune checkpoint inhibitor; MGH = Massachusetts General Hospital; TTE = transthoracic echocardiogram.

myocarditis. We hypothesized that GLS would be reduced, and this reduction in GLS with ICI myocarditis would predict adverse cardiac events. To evaluate these hypotheses, we leveraged a unique multicenter multinational registry of patients with ICI myocarditis.

METHODS

PATIENTS. The GLS was measured from 101 cases from a 19-center international registry designed for collating suspected cases of ICI-related myocarditis. This report presents data from cases presenting from November 2013 until January 2019. In an earlier report, we presented the baseline demographics and outcomes from the first 35 patients in the cohort (3). Control subjects were randomly derived from a registry of all patients started on ICI therapy during the same time interval in a single center (Massachusetts General Hospital, Boston, Massachusetts) who did not develop myocarditis. Control subjects were not matched to cases on any variables. Each center's institutional review board approved the study, and the requirement for written informed consent was waived as part of each center's institutional review board's approval.

COVARIATES. Demographics, cardiovascular risk factors, medications, and cardiac biomarker levels were retrospectively extracted from electronic medical records. Additionally, cancer-specific covariates including type, treatments, prior cardiotoxic chemotherapy, and radiation therapy were also recorded. Myocarditis admission-specific covariates included clinical presentation, physical examination, and cardiac biomarkers.

GLOBAL LONGITUDINAL STRAIN. Echocardiographic DICOM images from all centers were uploaded to a core laboratory, and GLS by speckle tracking was measured centrally using the vendor neutral TomTec-

TABLE 1 Description of Cases and Control Subjects

	Cases (n = 101)	Control Subjects (n = 92)	p Value
Age at start of ICI, yrs	66 ± 14	64 ± 14	0.42
Male	74 (73)	59 (64)	0.21
CV risk factors*			
Current or prior smoking	41 (49)	56 (61)	0.11
Hypertension	56 (57)	62 (67)	0.12
Diabetes mellitus	23 (24)	15 (16)	0.18
No CV risk factors	26 (26)	10 (11)	0.01
Coronary artery disease*	12 (13)	14 (15)	0.67
Stroke*	6 (7)	12 (11)	0.20
Atrial fibrillation	7 (7)	18 (20)	0.01
Heart failure	5 (5)	10 (11)	0.18
COPD*	12 (15)	18 (20)	0.39
Obstructive sleep apnea*	4 (5)	9 (10)	0.23
Chronic kidney disease*†	9 (11)	18 (20)	0.14
Body mass index, kg/m^2	28 ± 7	27 ± 7	0.32
Primary cancer type			
Head and neck	6 (6)	10 (11)	0.30
Breast	5 (5)	0 (0)	0.06
Hodgkin's lymphoma	2 (2)	2 (2)	1.00
Melanoma	41 (41)	39 (42)	0.88
Lung cancer	16 (16)	17 (18)	0.70
Pancreatic	2 (2)	0 (0)	0.50
Renal cell carcinoma	8 (8)	1 (1)	0.04
Glioblastoma	1 (1)	0 (0)	1.00
Other	18 (18)	13 (14)	0.56
Prior chemotherapy or radiation			
Radiation	29 (29)	52 (57)	<0.001
Anthracyclines	7 (7)	1 (1)	0.07
VEGF inhibitors	1 (1)	6 (7)	0.06

Values are mean ± SD or n (%). *Numbers given for values available. †Chronic kidney disease = glomerular filtration rate <60 ml/min/1.73 m^2.

COPD = chronic obstructive pulmonary disease; CV = cardiovascular; ICI = immune checkpoint inhibitors; VEGF = vascular endothelial growth factor.

Arena TTA2 (TomTec Imaging Systems GMBH, Unterschleissheim, Germany) by a cardiologist (M.A.) blinded to all other study, group, and time variables using the standard echocardiographic 3 apical views (4, 2, and 3 Ch). As GLS is a negative value, we took the absolute value |x| for a simpler interpretation. The primary comparison of interest was the GLS derived from echocardiograms performed at the time of presentation with myocarditis among 101 cases as compared with the GLS from 50 control subjects who were on an ICI and did not have myocarditis. The 101 cases were also compared to control subjects after separation by strata of left ventricular ejection fraction (LVEF). Several additional comparisons were included where data were available. To evaluate whether the pre-ICI GLS was similar between cases and control subjects, the GLS from 30 cases and 42 control subjects prior to ICI start were compared. To determine whether the GLS decreased from baseline among cases, the GLS values from 30 myocarditis cases pre-ICI and with myocarditis were measured and compared. To determine whether the GLS decreased from baseline among control subjects after starting an ICI, the GLS from 14 control subjects with paired samples, pre-ICI and on ICI were measured and compared (Figure 1).

DEFINITIONS AND OUTCOME OF INTEREST. The diagnosis of myocarditis was made using 2 methods: the presence of standard histological features on endomyocardial biopsy or autopsy (lymphocytic infiltration), or a standardized guideline-recommended scoring system for clinically suspected myocarditis among patients without a biopsy (3). This incorporates selected variables including the clinical, biomarker, and imaging features (13). Patients were followed for the development of major adverse cardiac events (MACE), defined, as previously (3), as a composite of cardiovascular death, cardiac arrest, cardiogenic shock, and hemodynamically significant complete heart block. In cases where cardiac arrest, cardiogenic shock, or complete heart block led to death, that case was counted as a cardiac death.

STATISTICAL ANALYSIS. Continuous variables were summarized as either mean ± SD or as the median and interquartile range (IQR), as appropriate, and categorical variables were presented as percentages. Comparisons by case status (case vs. control) and by MACE status were compared using the Student's *t*-test for continuous variables or either the chi-square or Fisher exact test for categorical variables. Kaplan-Meier curves and the log-rank test were generated to quantify the relationship between GLS (separated by tertiles among the whole cohort of cases, and by median GLS among the 2 groups: 1] cases with preserved EF; and 2] cases with reduced EF) and MACE-free survival. Cox proportional hazard models were constructed to quantify the association between GLS and follow-up time while controlling for LVEF. The proportional hazards assumption was evaluated by testing and graphically assessing the scaled Schoenfeld residuals. Linearity of model covariates was assessed using likelihood ratio tests (by comparing nested models with and without flexible parameterizations of covariates) as well as graphically via marginal effects plots. Hazard ratios (HRs) were estimated with and without the addition of potential confounders as covariates, and 95% confidence intervals (CIs) were estimated for each percent decrease in GLS. A total of 3 multivariable models were performed, all adjusting for LVEF, and

TABLE 2 Baseline Cancer Demographics

	Cases (n = 101)	Control Subjects (n = 92)	p Value
Single agent vs. combined			
Combination	27 (27)	7 (6)	<0.001
Monotherapy	74 (73)	86 (93)	<0.001
Overall types of ICI*			
Any anti-PD1	78 (77)	73 (79)	0.73
Any anti-CTLA4	11 (11)	16 (17)	0.22
Any anti-PDL1	12 (12)	4 (4)	0.07
Follow-up, days	175 [95, 352]	283 [101, 514]	0.02
Other immune side effects during treatment			
No other immune side effects	55 (54)	35 (38)	0.03
Hypophysitis/pituitary/adrenal	5 (5)	4 (4)	1.00
Pneumonitis	29 (29)	14 (15)	0.03
Hepatitis	7 (7)	5 (5)	0.77
Colitis	10 (10)	11 (12)	0.65
Dermatitis	6 (6)	1 (1)	0.12
Neurological	10 (10)	2 (2)	0.04
Gastritis	3 (3)	4 (4)	0.71

Values are n (%) or median [interquartile range]. All cases with ICI-associated myocarditis had ICI permanently discontinued. *Within monotherapy group.

CTLA4 = cytotoxic T-lymphocyte-associated protein 4; ICI = immune checkpoint inhibitors; PD1 = programmed cell death protein 1; PDL1 = programmed death-ligand 1.

TABLE 3 Description of Cases and Control Subjects With Pre-ICI TTEs

	Cases (n = 30)	Control Subjects (n = 42)	p Value
Pre-ICI treatment echocardiogram			
LVEF, %	61 ± 7	65 ± 9	0.03
LVIDd, mm	48 ± 5	45 ± 6	0.08
LVEDV, ml	97 ± 50	113 ± 44	0.23
LVESV, ml	50 ± 11	56 ± 26	0.34
SV, ml	47 ± 24	57 ± 25	0.33
CO, l/min	4.0 ± 2.5	4.7 ± 2.0	0.51
Max LA volumes, ml*	64 ± 34	59 ± 32	0.65
GLS, %	20.3 ± 2.6	20.6 ± 2.0	0.60
Pre-ICI treatment ECG*			
Sinus rhythm	19 (86)	37 (88)	1.00
Heart rate, beats/min	79 ± 15	83 ± 20	0.39
Pre-ICI home CV medications*			
Statin	5 (33)	11 (26)	0.74
Aspirin	5 (33)	11 (26)	0.74
Beta-blockers	4 (27)	14 (33)	0.75
ACE inhibitors or ARBs	4 (27)	10 (24)	1.00
Calcium-channel blocker	2 (13)	6 (14)	1.00

Values are mean ± SD or n (%). *Values given for those available.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CO = cardiac output; CV = cardiovascular; ECG = electrocardiogram; GLS = global longitudinal strain; ICI = immune checkpoint inhibitors; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; LVIDD = left ventricular internal dimension diameter; SV = stroke volume.

with additional adjustments for left ventricular internal diastolic dimension, age, and diabetes mellitus. All statistical tests were 2-sided, and 5% was set as the level of significance. Statistical analysis was performed using R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

PATIENT CHARACTERISTICS. The mean age of cases (n = 101) was 66 ± 14 years, with 73% men (Table 1). The median time to onset of myocarditis from starting ICI was 57 days (IQR: 27 to 122 days), and the most common presentations were chest pain and shortness of breath. At presentation, 40% had a reduced ejection fraction (EF) (<50%) and 60% had a preserved EF. In comparison with control subjects, myocarditis cases were evenly matched in age, sex, and cardiovascular risk factors (Table 1).

CANCER AND TREATMENT CHARACTERISTICS. The most common indications for an ICI were melanoma and lung cancer (Table 1). Patients with myocarditis were more likely to have received combination ICI therapy (Table 2); however, the majority were on single ICI therapy (73%). The median follow-up time was 283 days (IQR: 101 to 514 days) for control subjects, and 175 days (IQR: 95 to 352 days) for cases (Table 2). Among cases, 46% had experienced another ICI-related side effect (Table 2).

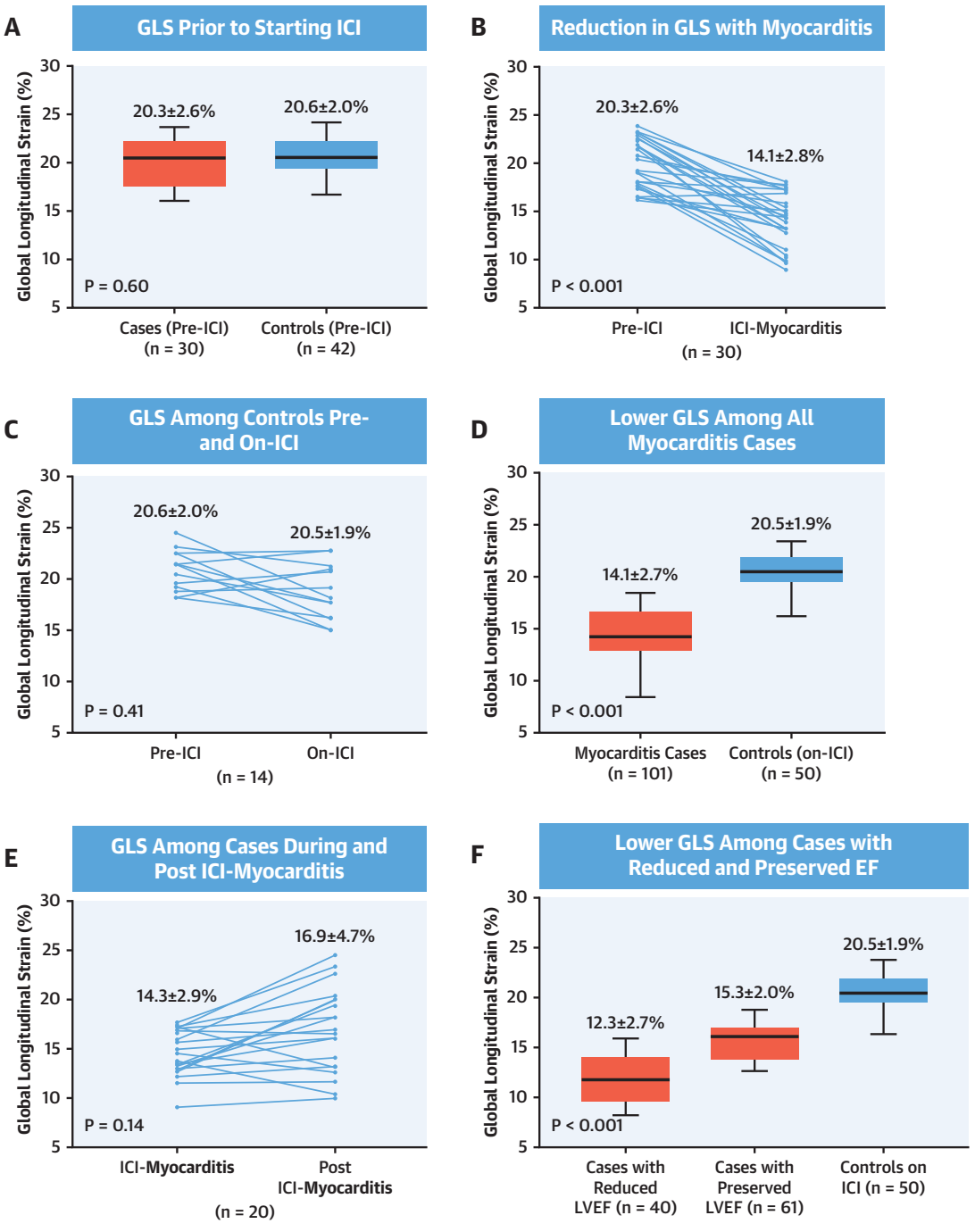
GLOBAL LONGITUDINAL STRAIN. Pre-ICI GLS in cases and control subjects. Among the 101 cases, 30 had an additional GLS measure from pre-ICI therapy. The pre-ICI GLS of cases was similar when compared with that of the 42 control subjects (cases vs. control subjects pre-ICI: 20.3 ± 2.6% vs. 20.6 ± 2.0%; p = 0.60) (Table 3, Figure 2A).

Serial GLS during ICI myocarditis among cases. Within the 30 myocarditis cases with paired GLS values (pre-ICI compared with the development of myocarditis), GLS decreased with the development of myocarditis (pre-ICI vs. during myocarditis 20.3 ± 2.6% vs. 14.1 ± 2.8%; p < 0.001) (Figure 2B).

Serial GLS among ICI patients who did not develop myocarditis. The GLS of 14 control subjects with paired measurements pre-ICI and on ICI therapy were compared, and similar values were noted (pre-ICI vs. on ICI: 20.6 ± 2.0% vs. 20.5 ± 1.9%; p = 0.41) (Figure 2C).

GLS at presentation with myocarditis compared to control subjects on ICI. The GLS among cases at admission for myocarditis (n = 101) was lower than control subjects on ICI therapy without myocarditis (n = 50) (myocarditis cases vs. control subjects on ICI,

FIGURE 2 GLS Among Cases and Control Subjects



(A) Box plot graph of GLS among cases and control subjects pre-ICI showing lower values among cases compared with control subjects. **(B)** Spaghetti plot graph of GLS among cases showing the reduction in GLS with the development of myocarditis. **(C)** Spaghetti plot graph of GLS among control subjects showing no change in GLS among control subjects on ICI who did not develop myocarditis. **(D)** Box plot graph of GLS among cases during presentation with myocarditis and control subjects on ICI who did not develop myocarditis, showing lower GLS values among the cases compared with control subjects. **(E)** Spaghetti plot graph of GLS among cases with follow-up values post-discontinuation of ICI therapy compared with during ICI myocarditis admission, showing improved GLS post-discontinuation of therapy. **(F)** Box plot graph of GLS among cases presenting with both a reduced and preserved EF compared with control subjects, showing lower GLS among cases compared with control subjects irrelevant of EF. Box plots summarizing data from minimal values **(lowest horizontal line),** first quartile **(bottom of box),** median **(horizontal line within the box),** third quartile **(top of box),** and maximum values **(highest horizontal line).** GLS = global longitudinal strain; ICI = immune checkpoint inhibitor; LVEF = left ventricular ejection fraction.

14.1 ± 2.7% vs. 20.5 ± 1.9%; p < 0.001) (Table 4, Figure 2D).

GLS among ICI myocarditis cases post-discontinuation of ICI-therapy and starting steroids. Among the 101 cases with ICI myocarditis, 42 were treated at Massachusetts General Hospital or the Brigham and Women's Hospital in Boston. Of these 42, 9 died prior to any follow-up transthoracic echocardiograms (TTEs), and 20 had a follow-up TTE at median time between imaging of 102 days (IQR: 36 to 152 days). In follow-up, GLS increased from 14.3 ± 2.9% to 16.9 ± 4.7% (p = 0.14) (Figure 2E). This was an absolute increase of 2.6% and a relative increase of 18% in the GLS with cessation of ICI and treatment with immunosuppression.

GLS among ICI myocarditis cases stratified by LVEF. Among the 101 ICI myocarditis cases, 61 presented with a preserved EF (60%) with a mean of 62 ± 7% and 40 with reduced EF (40%) with a mean of 33 ± 8%. Of all 101 cases, 31 had a GLS ≥16%, 16 had a GLS ≥17%, and 2 had a GLS ≥18%. The GLS was lower in patients with myocarditis presenting with both a reduced and preserved EF compared with control subjects during ICI therapy (n = 50) (cases with reduced EF vs. cases with preserved EF, control subjects on ICI: 12.3 ± 2.7% vs. 15.3 ± 2.0% vs. 20.5 ± 1.9%; p < 0.001 between the groups) (Figure 2F). There were no differences in GLS between biopsy-proven myocarditis cases when compared with nonbiopsy-proven cases (Online Table 1).

CARDIAC BIOMARKERS. Among cases, troponin levels at admission (n = 101) were elevated in 98 of 101 (97%), with a median value of 0.85 ng/dl (IQR: 0.17 to 2.3 ng/dl). Among control subjects on an ICI, a measure of troponin was available in 59 subjects, all of which were <0.01 ng/dl. This difference was statistically significant (p < 0.001). Among cases, higher admission troponin correlated with lower GLS (r = −0.26; p = 0.008). There was no association between admission troponin and lower EF (r = −0.1; p = 0.29). Among cases, N-terminal pro hormone B-type natriuretic peptide (NT-proBNP) levels at admission were elevated in 73 of 83 (88%). The median NT-proBNP value among cases was 589 pg/ml (IQR: 208 to 2,413 pg/ml). Among control subjects on an ICI, a measure of NT-proBNP was available in 41 subjects. The median NT-proBNP value among control subjects on an ICI was 560 pg/ml (IQR: 243 to 2,093 pg/ml). There was a trend toward a higher NT-proBNP level in cases (p = 0.07). Among cases, higher admission NT-proBNP trended toward correlation with a lower GLS (r = −0.21; p = 0.06). There was an association between higher admission NT-proBNP and lower EF (r = −0.32; p = 0.003).

TABLE 4 TTE Variables Among Cases During ICI Myocarditis and Control Subjects During ICI Therapy

	Cases (n = 101)	Control Subjects (n = 50)	p Value
LVEF, %	61 ± 6	64 ± 8	0.02
Preserved LVEF (≥50%)	61 (60)	48 (96)	<0.001
LVIDd, mm	48 ± 6	45 ± 5	0.002
LVIDs, mm	35 ± 9	30 ± 5	0.002
LVEDV, ml	112 ± 43	115 ± 34	0.67
LVESV, ml	65 ± 36	55 ± 21	0.07
SV, ml	47 ± 19	60 ± 19	<0.001
CO, l/min	3.9 ± 1.8	5.2 ± 2.7	0.01
GLS, %	14.1 ± 2.7	20.5 ± 1.9	<0.001
Absolute Change in GLS from pre-ICI, %	7.2 [3.0, 8.9]*	0.1 [−2.5, 1.2]*	<0.001
Percentage change in GLS from pre-ICI, %	−34.3 [−42.5, −14.4]*	0.4 [4.4, 11.9]*	<0.001
Change in GLS from pre-ICI >15%	21 (71)*	3 (21)*	0.004

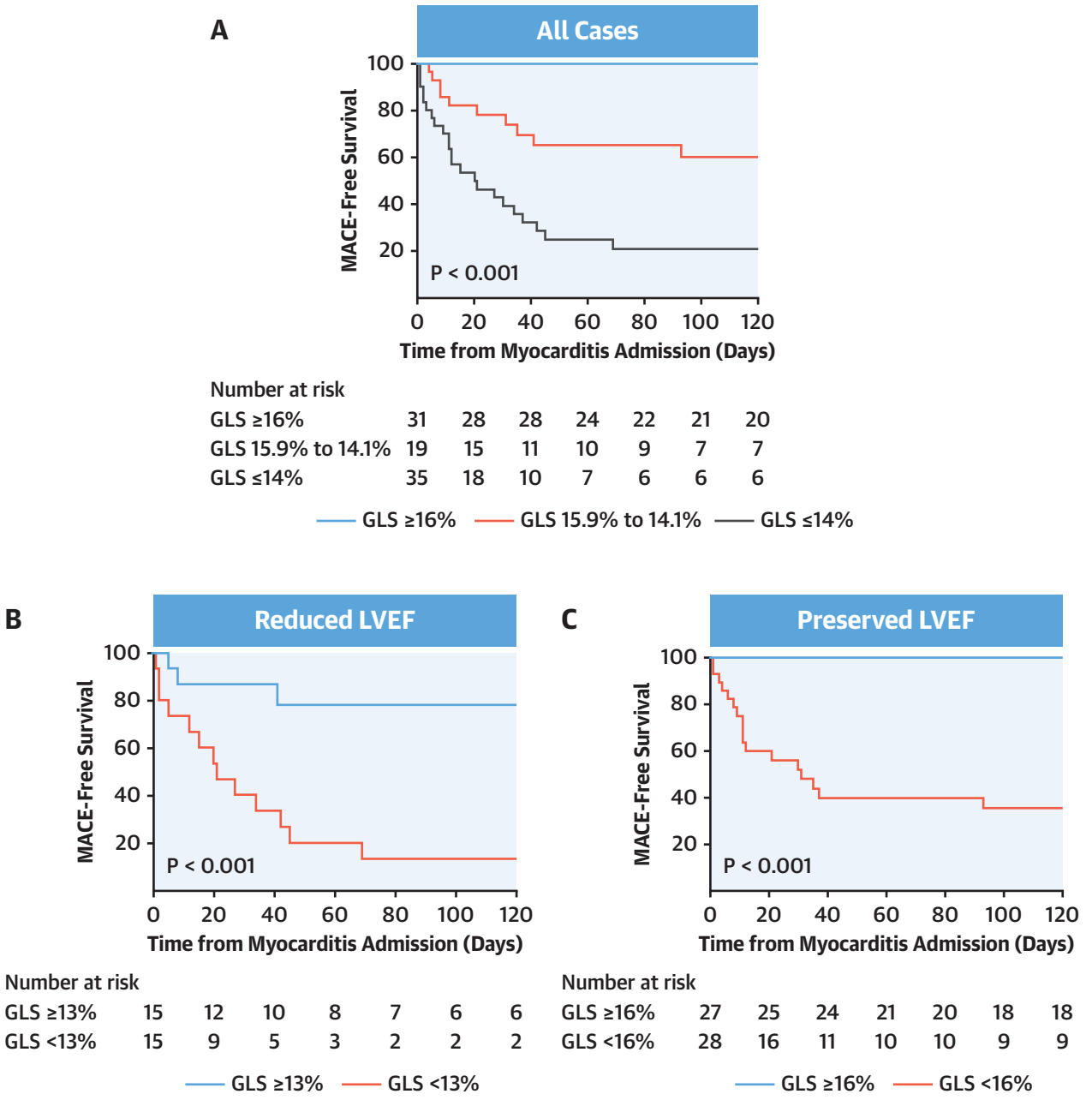
Values are mean ± SD, n (%), or median [IQR]. Thirty of the 101 cases, and 14 of the 50 control subjects with a TTE during ICI had a TTE prior to commencing ICI therapy. *Values given for those available.

CO = cardiac output; GLS = global longitudinal strain; IQR = interquartile range; LVIDd = left ventricular internal diameter in diastole; LVIDs = left ventricular internal dimension in systole; SV = stroke volume; other abbreviations as in Table 3.

MAJOR ADVERSE CARDIAC EVENTS. Over a median follow-up of 162 days (IQR: 58 to 334 days), 51 (51%) had a MACE. These included complete heart block (n = 19), cardiogenic shock (n = 14), cardiac arrest (n = 12), and 6 cardiovascular deaths. The LVEF among myocarditis cases with MACE (n = 51) was 45 ± 16%, and among cases without MACE (n = 50) was 55 ± 15% (p = 0.002). The stroke volume (SV) was lower among cases compared with control subjects (cases vs. control subjects, 47 ± 19 ml vs. 60 ± 19 ml; p < 0.001) (Table 4). However, the SV among myocarditis cases with a MACE (55.7 ± 26.6 ml) was similar to cases without MACE (43.5 ± 11.1 ml; p = 0.47). The components of MACE stratified by preserved and reduced LVEF as well as normal/abnormal GLS are summarized in Online Tables 2A and 2B.

In follow-up, among the entire group, when separated by tertiles, MACE was highest among cases with a GLS ≤14%, followed by GLS in the range between 14.1% and 15.9%, and lowest among cases with GLS ≥16% (p < 0.001) (Figure 3A). Among patients with myocarditis presenting with a reduced EF, a GLS lower than 13% was associated with higher MACE (p < 0.001) (Figure 3B). Similarly, among ICI myocarditis cases presenting with a preserved EF, a GLS lower than 16% was associated with higher MACE

FIGURE 3 Kaplan-Meier Survival Curves Showing the Association of MACE and GLS Among Cases



(A) Kaplan-Meier curve of MACE-free survival among all cases stratified by tertiles of GLS values showing highest MACE-free survival among cases with a GLS ≥16% and lowest among cases with a GLS ≤14% ($p < 0.001$). **(B)** Kaplan-Meier curve of MACE-free survival among cases with reduced LVEF stratified by GLS values above and below the median value of 13%, showing increased MACE-free survival among cases with GLS ≥13% compared with GLS <13% ($p < 0.001$). **(C)** Kaplan-Meier curve of MACE-free survival among cases with preserved LVEF stratified by GLS values above and below the median value of 16%, showing increased MACE-free survival among cases with GLS ≥16% compared with GLS <16% ($p < 0.001$). GLS= global longitudinal strain; LVEF= left ventricular ejection fraction; MACE= major adverse cardiac event.

($p < 0.001$) (**Figure 3C**). Similarly, an absolute (9.5 ± 2.1%) and relative (47 ± 7%) drop in GLS in reduced EF was predictive of MACE, and an absolute (7.8 ± 2.8%) and relative (35 ± 10%) drop in GLS in preserved EF was predictive of MACE. In the multivariable model adjusted for EF, GLS was predictive of MACE among all patients (HR: 1.93; 95% CI: 1.56 to 2.39; $p < 0.001$), among cases with a reduced EF (HR: 1.49; 95% CI: 1.2 to 1.84; $p < 0.001$), and among cases with a preserved EF (HR: 4.36; 95% CI: 2.44 to 7.79; $p < 0.001$) (**Table 5**). An additional multivariable model adjusting for EF, left ventricular internal diastolic diameter, age, and history of diabetes is available in Online Table 3.

TABLE 5 Multivariable Model

Global Longitudinal Strain	Hazard Ratio	95% CI	p Value
All cases	1.93	1.56-2.39	<0.001
Cases with reduced EF	1.49	1.20-1.84	<0.001
Cases with preserved EF	4.36	2.44-7.79	<0.001

Regression analysis, adjusting for left ventricular ejection fraction (EF). Complete multivariable model results are listed in Online Table 1.

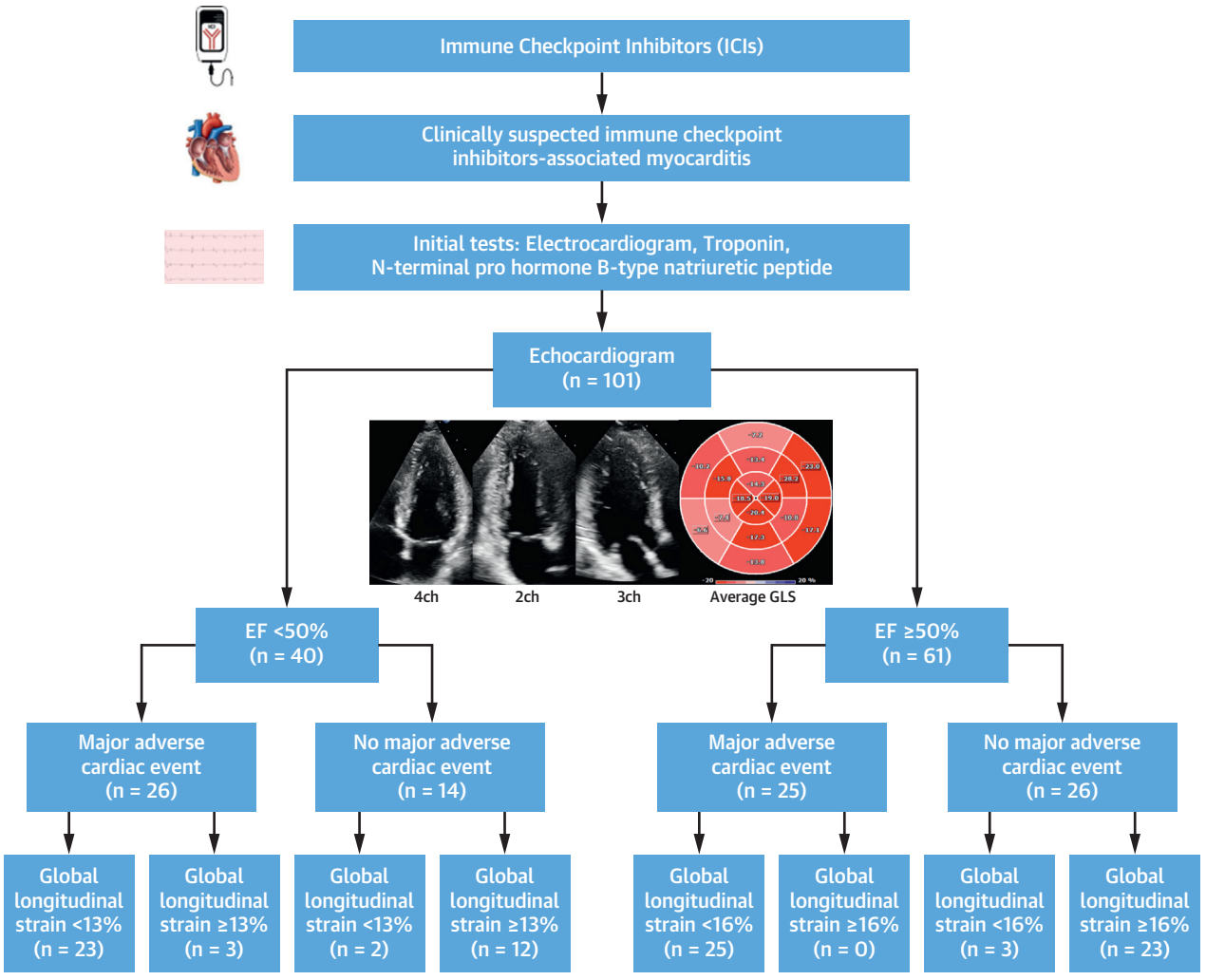
DISCUSSION

In this report, we leveraged a large international multicenter registry to present the first data characterizing the role of GLS among patients with ICI myocarditis. The study had the following novel findings: 1) GLS pre-ICI therapy was similar between cases and control subjects; 2) GLS decreased with the development of ICI-related myocarditis but did not change among control subjects who did not develop myocarditis; 3) GLS was reduced among ICI myocarditis cases presenting either with a reduced EF, or importantly, with a preserved EF; and 4) lower GLS was a strong predictor of MACE among myocarditis cases, presenting with either a preserved or reduced EF (**Central Illustration**).

GLS is a sensitive measure of cardiac function and cardiac injury (14,15). Compared with EF, measurement of GLS improves risk stratification, redefines criteria for disease classification, and may help determine treatment in asymptomatic left ventricular dysfunction resulting from a wide variety of etiologies (16–18). The measurement of GLS is validated, is reproducible within an acceptable range (14,19,20), is widely available, and does not require any additional imaging beyond standard TTE images. Consistent studies have demonstrated a reduction in GLS despite a preserved EF among patients at risk for cardiac injury and cardiac dysfunction (21). This is particularly relevant for monitoring of patients with cancer who are being treated with traditional cytotoxic chemotherapy drugs, where pathological cardiac injury occurs despite a preserved EF (22–24). As a result, GLS has been proposed for monitoring of cardiotoxicity related to traditional cytotoxic chemotherapies (10,25). There are no prior data on the measurement of GLS among patients with ICI myocarditis. In the general population, a reduction in GLS has been noted among patients with suspected myocarditis, even those with a preserved EF, and this decline in GLS had a similar diagnostic performance when compared with other conventional assessments such as the Lake-Louise criteria on magnetic resonance (26). The study finding of a decrease in GLS with myocarditis is of additional importance among cancer patients, as due to overlapping symptoms of chest pain and shortness of breath, the diagnosis may be challenging. The finding is also of particular relevance to the majority of patients who present with a preserved EF, as with aggressive immunosuppression, there is still potential for reversibility in myocyte damage (27,28).

Traditionally, myocarditis unrelated to an ICI, presenting with a preserved EF, is a comparatively benign entity (29); in contrast, data from this group and others have shown that myocarditis related to an ICI is not (2–4,6). Specifically, consistent data have shown that myocarditis with an ICI is associated with a case-fatality rate ranging from 35% to 50% (3,30,31); in contrast, the case fatality rate for myocarditis unrelated to an ICI is markedly lower, ranging from 9% to 16% (32,33). Previously, GLS has been shown to provide prognostic information beyond EF among a broad range of cardiovascular disease from post-myocardial infarction (34) to patients with aortic stenosis (35), and including patients with heart failure (36) and with myocarditis (26,37). For example, among patients with heart failure, each 1% increase in GLS is associated with a 5% decreased risk of mortality ($p < 0.001$) (36). In this report, GLS was found to be predictive of MACE among cases with either a preserved or a reduced EF. The magnitude of the decrease in GLS in our study also had prognostic significance, where each 1% reduction was associated with a 1.5-fold increase in MACE among cases with reduced EF and a 4.4-fold increase in MACE in those with a preserved EF. These findings may have treatment implications. The standard primary therapy for ICI myocarditis is high-dose immunosuppression with steroids. Initial data suggested the high-dose steroids may be safe and do not affect anticancer efficacy (38); however, recent data suggest caution where very high-dose immunosuppression may be

CENTRAL ILLUSTRATION **Global Longitudinal Strain in Immune Checkpoint Inhibitor-Myocarditis**



Awadalla, M. et al. J Am Coll Cardiol. 2020;75(5):467-78.

The association of different global longitudinal strain cut-offs and major adverse cardiac events among cases with reduced and preserved ejection fraction (EF).

associated with worse cancer outcomes (39). Therefore, the use of GLS may allow the identification of a group of patients at lower risk of subsequent adverse cardiac events and help avoid unnecessary immunosuppression.

STUDY LIMITATIONS. This study needs to be interpreted within the context of the study design. Myocarditis with ICIs is uncommon, and with an uncommon adverse event. Therefore, a multicenter international registry, as compared with a prospective study, represents the most practical method to provide initial insights. However, the use of echocardiography varies by center. For example, not all patients in this multicenter registry had a measure of GLS performed prior to starting ICI, and among control subjects, the reasons why some had a TTE and others did not were physician dependent. Also, patients who developed myocarditis did not routinely have serial echocardiograms performed; thus, it was not possible to determine if the GLS decrease occurred prior to the development of myocarditis. Although GLS may help identify those at higher or lower risk of ICI myocarditis, changes in GLS may occur due to cardiovascular disease that would not be treated with immunosuppression treatment of ICI

myocarditis, such as coronary artery disease, heart failure, or cardiotoxicity from radiation therapy or standard chemotherapeutic agents such as anthracyclines. Additionally, although GLS provided prognostic information beyond measurement of GLS in patients with a preserved and a reduced EF, the modest number of events in each stratum precluded the addition of other covariates such as the presence of diabetes, the occurrence of other irAEs, and the use of combination ICI therapy.

CONCLUSIONS

Among patients with ICI myocarditis, GLS is reduced among those presenting with both a preserved and reduced EF. In follow-up, the decrease in GLS is strongly associated with major adverse cardiac events in ICI myocarditis, and, importantly, among those with a preserved EF. Additional work is needed to test if the GLS decrease occurs prior to the development of clinical myocarditis, can provide an early method of detection, and whether tailoring immunosuppressive therapy based on the measurement of GLS at presentation with myocarditis may be of value in decreasing the marked morbidity and mortality associated with ICI myocarditis while not compromising the antitumor efficacy.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: ICI-related myocarditis runs a fulminant course, with MACE in more than one-half of the cases. Speckle-tracking GLS, a marker of traditional chemotherapy-induced cardiotoxicity, may detect myocardial deformation before changes in EF occur in ICI-related myocarditis.

TRANSLATIONAL OUTLOOK: Large-scale prospective studies are necessary to clarify the time course of changes in GLS during treatment with ICIs and identify patients susceptible to myocarditis and associated adverse outcomes.

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KEY WORDS global longitudinal strain, immune checkpoint inhibitors, major adverse cardiac events, myocarditis

APPENDIX For supplemental tables, please see the online version of this paper.