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Authors
Quinaglia, Thiago
Gongora, Carlos
Awadalla, Magid
et al.

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ORIGINAL RESEARCH

Global Circumferential and Radial Strain Among Patients With Immune Checkpoint Inhibitor Myocarditis

Thiago Quinaglia, MD, PhD,[a] Carlos Gongora, MD,[a] Magid Awadalla, MD,[a] Malek Z.O. Hassan, MD,[a] Amna Zafar, MD,[a] Zsofia D. Drobni, MD,[a,b] Syed S. Mahmood, MD, MPH,[d] Lili Zhang, MD, ScM,[e] Otavio R. Coelho-Filho, MD, MPH,[f] Giselle A. Suero-Abreu, MD, PhD,[c] Muhammad A. Rizvi, MD,[g] Gagan Sahni, MD,[h] Anant Mandawat, MD,[i] Eduardo Zatarain-Nicolás, MD, PhD,[j] Michael Mahmoudi, MD, PhD,[k] Ryan Sullivan, MD,[l] Sarju Ganatra, MD,[m] Lucie M. Heinzerling, MD, PhD,[n] Franck Thuny, MD, PhD,[o] Stephane Ederhy, MD,[p] Hannah K. Gilman, BS,[a] Supraja Sama, BA,[a] Sofia Nikolaidou, BA,[a] Ana González Mansilla, MD, PhD,[j] Antonio Calles, MD, MSc,[j] Marcella Cabral, MD,[r] Francisco Fernández-Avilés, MD, PhD,[j] Juan José Gavira, MD, PhD,[s] Nahikari Salterain González, MD,[s] Manuel García de Yébenes Castro, MD, PhD,[s] Ana Barac, MD, PhD,[t] Jonathan Afilalo, MD,[r] Daniel A. Zlotoff, MD, PhD,[u] Leyre Zubiri, MD, PhD,[l] Kerry L. Reynolds, MD,[l] Richard Devereux, MD,[v] Judy Hung, MD,[q] Michael H. Picard, MD,[q] Eric H. Yang, MD,[w] Dipti Gupta, MD, MPH,[d] Caroline Michel, MD,[r] Alexander R. Lyon, MD, PhD,[x] Carol L. Chen, MD,[d] Anju Nohria, MD,[y] Michael G. Fradley, MD,[z] Paaladinesh Thavendiranathan, MD,[aa] Tomas G. Neilan, MD, PhD[a,u]

ABSTRACT

BACKGROUND Global circumferential strain (GCS) and global radial strain (GRS) are reduced with cytotoxic chemotherapy. There are limited data on the effect of immune checkpoint inhibitor (ICI) myocarditis on GCS and GRS.

OBJECTIVES This study aimed to detail the role of GCS and GRS in ICI myocarditis.

METHODS In this retrospective study, GCS and GRS from 75 cases of patients with ICI myocarditis and 50 ICI-treated patients without myocarditis (controls) were compared. Pre-ICI GCS and GRS were available for 12 cases and 50 controls. Measurements were performed in a core laboratory blinded to group and time. Major adverse cardiovascular events (MACEs) were defined as a composite of cardiogenic shock, cardiac arrest, complete heart block, and cardiac death.

RESULTS Cases and controls were similar in age (66 ± 15 years vs 63 ± 12 years; $P = 0.20$), sex (male: 73% vs 61%; $P = 0.20$) and cancer type ($P = 0.08$). Pre-ICI GCS and GRS were also similar (GCS: 22.6% ± 3.4% vs 23.5% ± 3.8%; $P = 0.14$; GRS: 45.5% ± 6.2% vs 43.6% ± 8.8%; $P = 0.24$). Overall, 56% (n = 42) of patients with myocarditis presented with preserved left ventricular ejection fraction (LVEF). GCS and GRS were lower in myocarditis compared with on-ICI controls (GCS: 17.5% ± 4.2% vs 23.6% ± 3.0%; $P < 0.001$; GRS: 28.6% ± 6.7% vs 47.0% ± 7.4%; $P < 0.001$). Over a median follow-up of 30 days, 28 cardiovascular events occurred. A GCS (HR: 4.9 [95% CI: 1.6-15.0]; $P = 0.005$) and GRS (HR: 3.9 [95% CI: 1.4-10.8]; $P = 0.008$) below the median was associated with an increased event rate. In receiver-operating characteristic (ROC) curves, GCS (AUC: 0.80 [95% CI: 0.70-0.91]) and GRS (AUC: 0.76 [95% CI: 0.64-0.88]) showed better performance than cardiac troponin T (cTnT) (AUC: 0.70 [95% CI: 0.58-0.82]), LVEF (AUC: 0.69 [95% CI: 0.56-0.81]), and age (AUC: 0.54 [95% CI: 0.40-0.68]). Net reclassification index and integrated discrimination improvement demonstrated incremental prognostic utility of GRS over LVEF ($P = 0.04$) and GCS over cTnT ($P = 0.002$).

CONCLUSIONS GCS and GRS are lower in ICI myocarditis, and the magnitude of reduction has prognostic significance. (J Am Coll Cardiol Img 2022;15:1883–1896) © 2022 the American College of Cardiology Foundation. Published by Elsevier. All rights reserved.

ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance

cTnT = cardiac troponin T

GCS = global circumferential strain

GLS = global longitudinal strain

GRS = global radial strain

ICI = immune checkpoint inhibitor

IDI = integrated discrimination improvement

IRAE = immune-related adverse effects

MACE = major adverse cardiovascular event

NRI = net reclassification index

ROC = receiver-operating characteristic

TTE = transthoracic echocardiogram

For more than a decade, immune checkpoint inhibitors (ICIs) have changed the paradigm of cancer treatment.[1] At present, ICIs are indicated for more than 70 types of cancer, and there are more than 5,000 ongoing clinical trials assessing these T-cell-targeting monoclonal antibodies.[2] ICIs unleash the immune system against malignancies by targeting the host's immune negative regulators. This action, however, results in a predictable series of immune-related adverse effects (IRAEs).[3,4] Myocarditis is an uncommon IRAE with ICIs but is associated with the highest fatality rate of all IRAEs.[5] Thus, improved methods for detection and risk stratification of ICI myocarditis are needed.

Lower left ventricular global longitudinal strain (GLS) by echocardiography has been shown to predict major adverse cardiovascular events (MACEs), a composite of cardiovascular death, cardiac arrest, cardiogenic shock, and complete heart block (CHB) among patients with ICI myocardit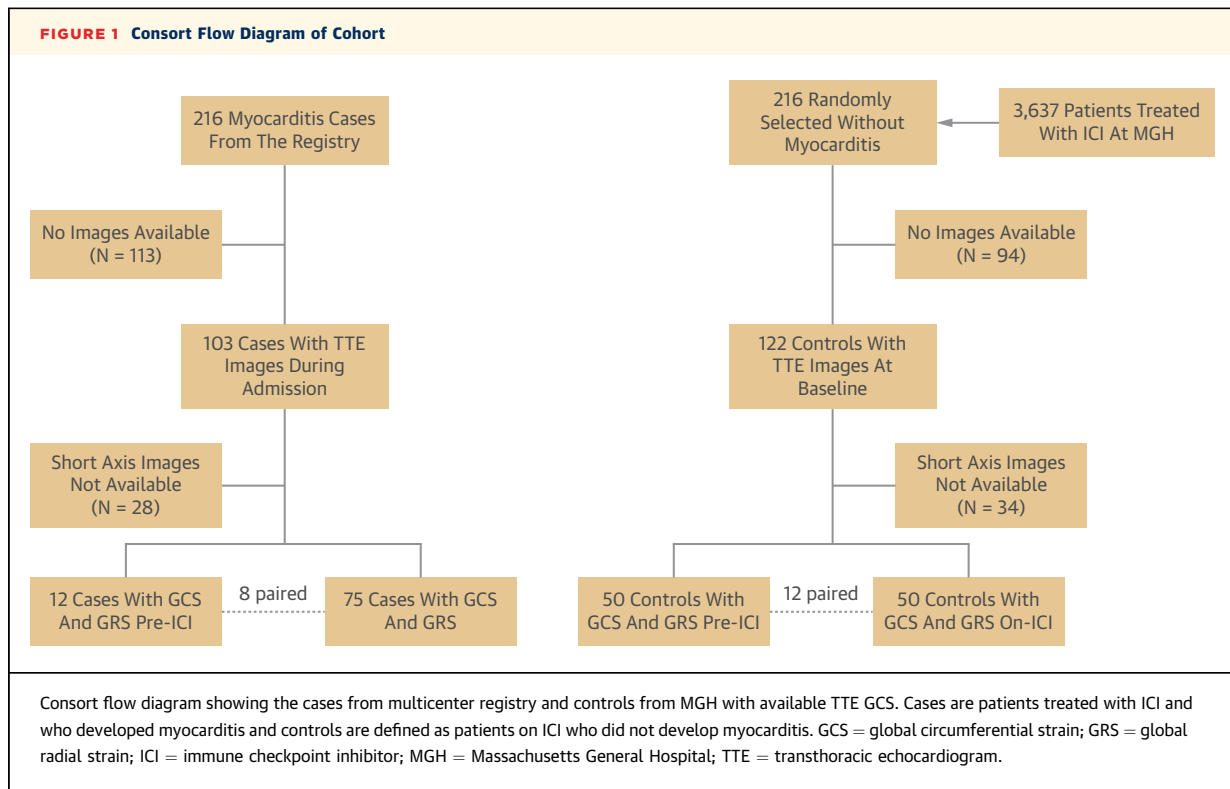is.[6] However, there are limited data measuring global circumferential strain (GCS) or global radial strain (GRS) in ICI myocarditis. Among patients treated with traditional cytotoxic chemotherapy, both GCS and GRS are reduced.[7,8] Furthermore, there are no data on the prognostic value of GCS and GRS among patients with ICI myocarditis. These parameters could provide additive information considering their complementary role in maintaining left ventricular systolic function.[9] Therefore, the aim of this study was to test the utility of the measurement of GCS and GRS in patients with ICI myocarditis.

METHODS

INDIVIDUALS. Patient data were obtained from a multicenter international registry involving 29 sites. The registry involves sites in North America (United States and Canada), Europe (France, Spain, Italy, Germany) and South America (Brazil). The database was housed in a platform called REDCap (Research Electronic Data Capture), a web-based application developed to capture data for clinical research. The instrument was designed to compile cases of ICI-related myocarditis. The data presented were collected from November 2013 until February 2021.

From the [a]Cardiovascular Imaging Research Center (CIRC), Division of Cardiology and Department of Radiology, Massachusetts General Hospital, Boston, Massachusetts, USA; [b]Heart and Vascular Center, Semmelweis University, Budapest, Hungary; [c]Department of Medicine, Rutgers New Jersey Medical School, Newark, New Jersey, USA; [d]Cardiology Service, Memorial Sloan Kettering Cancer Center, Weill Cornell Medicine, New York, New York, USA; [e]Cardio-Oncology Program, Division of Cardiology, Department of Medicine, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, New York, USA; [f]Discipline of Cardiology, Department of Medicine, Faculty of Medical Science, State University of Campinas, Campinas, Brazil; [g]Division of Oncology and Hematology, Department of Medicine, Lehigh Valley Hospital, Allentown, Pennsylvania, USA; [h]Cardiology-Oncology Program, Mount Sinai Hospital, New York, New York, USA; [i]Cardio-Oncology Program, Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University School of Medicine, Atlanta, Georgia, USA; [j]Cardiology Department, Hospital General Universitario Gregorio Marañón, Centro de Investigación Biomédica en Red CardioVascular (CIBER-CV), Madrid, Spain; [k]Faculty of Medicine, University of Southampton, Southampton, United Kingdom; [l]Massachusetts General Hospital Cancer Center, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts, USA; [m]Cardio-Oncology Program, Division of Cardiovascular Medicine, Lahey Hospital and Medical Center, Burlington, Massachusetts, USA; [n]Department of Dermatology and Allergy, LMU Klinikum, Munich, Germany and Department of Dermatology, University Hospital Erlangen, Germany; [o]Mediterranean University Center of Cardio-Oncology, Aix-Marseille University, North Hospital, Marseille, France; [p]Cardio-Oncology Program, Division of Cardiology, Hopitaux Universitaires Est Parisien, Paris, France; [q]Division of Cardiology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA; [r]Department of Cardiology or Diagnostic Radiology, Jewish General Hospital, McGill University, Montréal, Québec, Canada; [s]Cardio-Oncology Program, Department of Cardiology, Clínica Universidad de Navarra, Pamplona and Madrid, Spain; [t]Cardio-Oncology Program, MedStar Heart and Vascular Institute, MedStar Washington Hospital Center, Washington, DC, USA; [u]Cardio-Oncology Program, Division of Cardiology, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts, USA; [v]Cardiology Division, New York-Presbyterian Hospital, Weill Cornell Medical Center, New York, New York, USA; [w]UCLA Cardio-Oncology Program, Division of Cardiology, Department of Medicine, University of California at Los Angeles, Los Angeles, California, USA; [x]Cardio-Oncology Service, Royal Brompton Hospital and Imperial College London, London, UK; [y]Cardio-Oncology Program, Division of Cardiology, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA; [z]Cardio-Oncology Center of Excellence, Division of Cardiovascular Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania, USA; and the [aa]Ted Rogers Program in Cardiotoxicity Prevention, Peter Munk Cardiac Center, Division of Cardiology, Toronto General Hospital, University of Toronto, Toronto, Ontario, Canada.

FIGURE 1 Consort Flow Diagram of Cohort

Consort flow diagram showing the cases from multicenter registry and controls from MGH with available TTE GCS. Cases are patients treated with ICI and who developed myocarditis and controls are defined as patients on ICI who did not develop myocarditis. GCS = global circumferential strain; GRS = global radial strain; ICI = immune checkpoint inhibitor; MGH = Massachusetts General Hospital; TTE = transthoracic echocardiogram.

Echocardiographic images of 75 patients were available from a total of 216 myocarditis cases (on February 23, 2021). For comparison, a control group of 216 patients was selected to match the cases group in a 1:1 ratio to cases. These were randomly selected from a cohort of 3,637 patients treated with ICI at a single academic institution (Massachusetts General Hospital). We performed an individual chart review to ensure no clinical diagnosis of myocarditis was made and to select those with available echocardiogram images while being treated with an ICI (Figure 1). Controls were not matched to cases on any characteristics. Each center's institutional review board approved the study including the waiver for the requirement of the written informed consent. Previous cardiac disease or the administration of a potentially cardiotoxic cancer therapy was not an exclusion criterion in the case or control group. Myocarditis in the control group after starting an ICI was excluded through review of each of the electronic health records using search terms such as "myocarditis."

Demographics, cardiovascular risk factors, medications, and cardiac biomarker data, as well as cancer types, specific oncologic treatments, previous cardiotoxic chemotherapy, and radiation therapy data were extracted from electronic medical records.

Myocarditis admission- specific covariates included clinical presentation, physical examination, and cardiac biomarkers.

ECHOCARDIOGRAPHIC DATA. Echocardiographic data were obtained according to the American Society of Echocardiography and European Association of Echocardiography guidelines.[10,11] The equipment used to obtain the images was determined by each of the participating sites, and this information was not available in the registry. Strain analyses were performed centrally in a core lab using TomTec software, Arena TTA2 (TomTec Imaging Systems). Available echocardiographic digital imaging and communications in medicine (DICOM) images were uploaded from each of the participating centers. A certified cardiologist blinded to the study groups, clinical information, and timing of examination analyzed basal, mid, and apical left ventricular short-axis views to obtain GCS and GRS. GLS was also assessed, as previously described, and published.[6] The analyses compared data obtained before ICI start from cases who subsequently developed myocarditis and controls who were treated with ICI and did not develop myocarditis and data obtained after ICI start from cases at the time of presentation of myocarditis and controls who were on ICIs and did not develop

TABLE 1 Baseline Characteristics of Patients Treated With Immune Checkpoint Inhibitor and Control Patients

	Cases (n = 75)	Controls (n = 50)	P Value
Male	55 (73.3)	30 (60)	0.20
Age, y	66 (15)	63 (12)	0.20
Ethnic group, race			
White	68 (91)	48 (96)	0.50
Asian	3 (4.0)	0 (0)	0.30
Black or African American	1 (1.3)	0 (0)	>0.90
Hispanic/Latino	1 (2.7)	0 (0)	0.50
Unknown	2 (4.0)	2 (4.1)	>0.90
Clinical variables			
Body mass index, kg/m^2	27 (6.6)	27.4 (7.2)	0.80
Systolic blood pressure, mm Hg	127 (21.9)	126 (0.7)	>0.90
Diastolic blood pressure, mm Hg	71 (11.1)	70 (0.7)	>0.90
Cardiovascular risk factors			
Hypertension	46 (61)	33 (66)	0.70
Diabetes mellitus	18 (24)	6 (12)	0.10
Smoking current or previous	39 (53)	28 (56)	0.50
Comorbidities			
Chronic obstructive pulmonary disease	15 (20)	8 (16)	0.60
Chronic kidney disease	7 (9.6)	7 (14)	0.40
Heart failure	7 (9.5)	4 (8.2)	>0.90
Coronary artery disease	13 (17)	7 (14)	0.90
Cardiovascular medications			
Beta-blockers	24 (32)	17 (35)	>0.90
Calcium-channel blockers	11 (15)	7 (14)	>0.90
Statins	33 (45)	13 (27)	0.04
Aspirin	23 (31)	13 (27)	0.60

Values are n (%) or mean (SD), unless otherwise indicated.

myocarditis. For the purposes of this study, the absolute GCS and GLS values are presented. Data from 26 participants were measured a second time in a blinded fashion and separated by at least a 2-month time window by the primary reader and a second reader to assess reproducibility. Intraobserver and interobserver intraclass correlation coefficients were calculated using 1-way random effects and 2-way mixed effects, respectively, and the results reported.

CARDIAC MAGNETIC RESONANCE IMAGING. Patients underwent cardiac magnetic resonance (CMR) imaging at the discretion of the attending physician, as previously described.[12,13] In brief, images were electrocardiogram (ECG)-gated and acquired during breath-holds with patients in supine position, using either 1.5- or 3.0-T scanners. The CMR protocols included cine steady-state free-precession images to assess cardiac function and mass with a slice thickness of 8 mm and no gap. Black-blood T2-weighted short tau inversion recovery sequences were used to assess myocardial edema. Late gadolinium enhancement (LGE) was evaluated 10 to 15 minutes after administration of contrast material in both

magnitude and phase-sensitive inversion recovery images with 8-mm thickness slices and 2-mm gaps. Images were interpreted locally by experienced readers, and results were added to REDCap.

ENDOMYOCARDIAL BIOPSY. When clinically indicated, endomyocardial biopsy was performed. At least 5 myocardial samples (1-2 mm in size) from the right ventricle were obtained. The diagnosis required evidence of lymphocytic infiltration with myocyte degeneration-necrosis based on the Dallas histopathologic criteria.[14,15] When deemed necessary by the investigator, the tissue was analyzed through additional immunohistochemistry, as recommended by international guidelines.[16]

DEFINITIONS AND OUTCOMES OF INTEREST. The diagnosis of myocarditis was made either by the presence of standard histologic features (see the Endomyocardial Biopsy section) on endomyocardial biopsy or autopsy or by a standardized guideline-recommended scoring system for clinically suspected myocarditis among patients without biopsy.[17] The diagnosis of ICI myocarditis was made as follows: standard features on histopathology[15] (see Endomyocardial Biopsy); diagnostic criteria for clinically suspected myocarditis as recommended by the European Society of Cardiology guidelines: in brief, ≥1 suggestive clinical symptom, plus ≥1 supporting laboratory-imaging study in the absence of obstructive coronary stenosis. Patients in the myocarditis group were followed for the development of MACEs, which was defined as a composite of cardiovascular death, cardiac arrest, cardiogenic shock, and CHB. With cases in which cardiac arrest, cardiogenic shock, or CHB led to death, the event was counted as a cardiovascular death.

STATISTICAL ANALYSIS. Continuous variables are presented as mean ± SD and categorical variables as absolute numbers (percentages). Comparisons between cases and controls were done with Student's *t*-test for continuous variables or either chi-square or Fisher's exact test for categorical variables. Values of GCS and GRS at the time of presentation with myocarditis for cases were compared with the values among controls (those treated with ICI who did not develop myocarditis). Additional analyses included the comparison of GCS and GRS before starting ICI. For this analysis of paired data, a Wilcoxon signed-rank test was used because the assumption of normal distribution was not met in these smaller sample sizes. For the survival analysis in those with myocarditis, the median absolute values of GCS and GRS were selected. Kaplan-Meier curves were created to depict the difference in MACE rate between groups. Cox regression models were built to quantify

the differences between myocarditis groups stratified by GCS and GRS medians and adjust the results for the covariates age and LVEF. The proportional hazards assumption was evaluated testing and graphically assessing the scaled Schoenfeld residuals. Linearity of model covariates was assessed graphically via marginal effects plots.

The general performance of GCS, GRS, GLS, troponin, age, and left ventricular ejection fraction (LVEF) for the prediction of MACEs during ICI myocarditis was evaluated by receiver-operating characteristic (ROC) areas. We then tested for the equality of the ROC area of each of these parameters against a "gold standard," defined as the predictor with the largest area among them. This procedure was done to determine whether there were significant differences in the predictive performances (ie, ROC areas) of each of these parameters. Furthermore, to ascertain the capacity of the strain variables to discriminate the subjects who experience MACEs as classified by the other variables (troponin, LVEF, and age), we applied the net reclassification index (NRI) and integrated discrimination improvement (IDI) tests as proposed previously.[18] For that purpose, we stratified the cases cohort by risk of MACE (above and below 50% risk) and calculated whether GCS, GRS, or GLS correctly reclassified patients to a greater or lower risk to what was defined by the other variables. We also established cutoff values using the Youden index to calculate sensitivity, specificity, and negative and positive predictive values for each of the predictors. All statistical tests were 2-sided, and the level of significance was set in 5%. Statistical analysis was performed using R Version 4.0.5 (R Foundation for Statistical Computing) and Stata Version 16.1 (StataCorp).
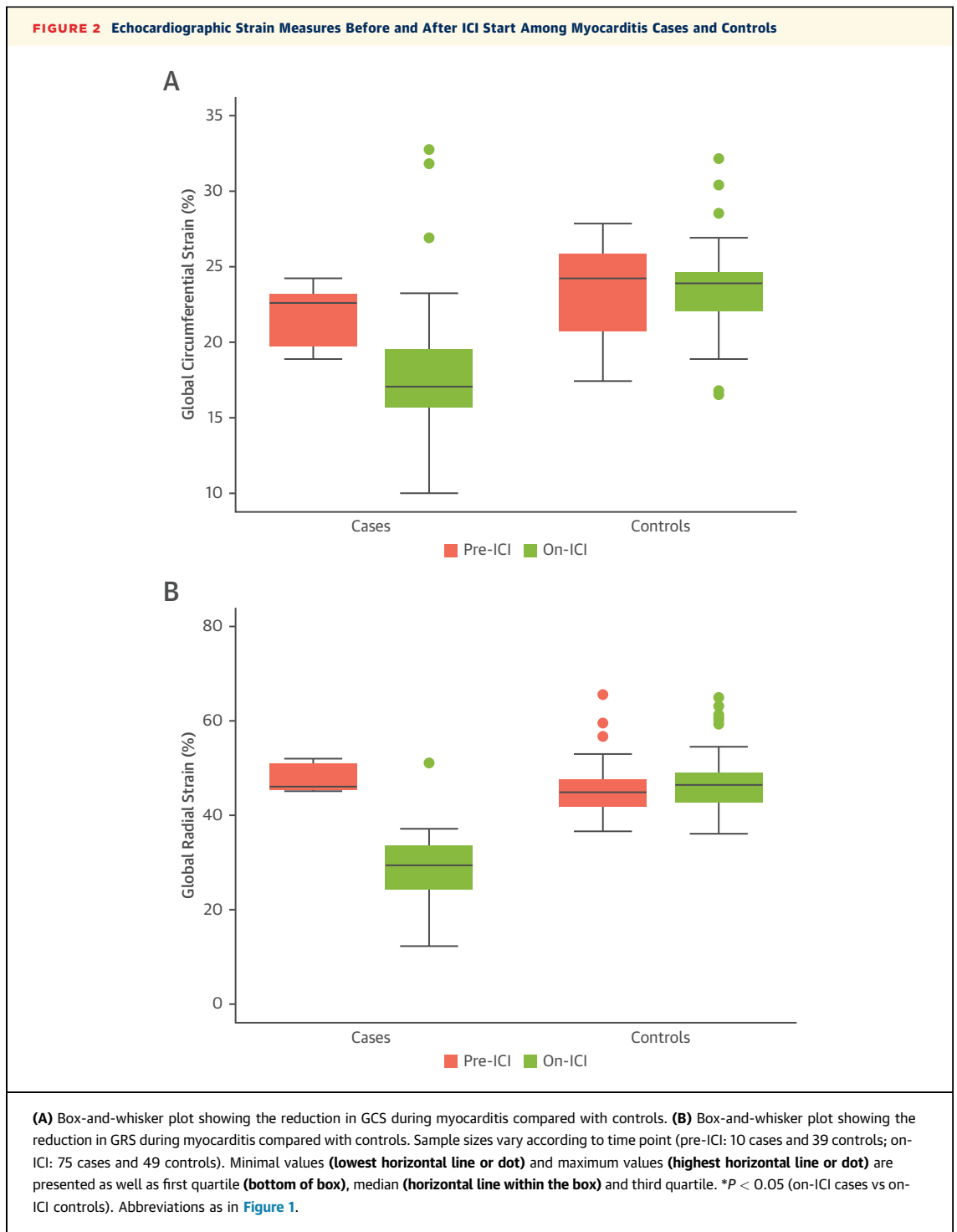
RESULTS

INDIVIDUALS. Cases and controls were similar in age (66 ± 15 vs 63 ± 12 years; $P = 0.20$), sex (male: 73.3% vs 61.2%; $P = 0.22$), and race (White: 91% vs 96%; $P = 0.50$). There were no differences noted in the occurrence of cardiovascular risk factors or the presence of established cardiovascular disease between the groups at baseline (Table 1). Melanoma and lung cancer were the most common cancer types (Table 2). Cases had a higher prevalence of renal cell carcinoma (9.7% vs 0; $P = 0.04$). Other cancer types were similar in proportions among groups. Approximately one-half of cases and controls developed other IRAEs after start of ICI. the most common IRAE was pneumonitis in both cases and controls (27% vs 16%;

TABLE 2 Baseline Cancer Demographics			
	Cases (n = 75)	Controls (n = 50)	P Value
Cancer types			
Melanoma	28 (37)	26 (53)	0.08
Lung	14 (19)	16 (32)	0.12
Breast	3 (4.0)	0 (0)	0.30
Renal cell carcinoma	7 (9.3)	0 (0)	0.04
Head and neck	3 (4.0)	1 (2.0)	>0.90
Hodgkin lymphoma	1 (1.3)	1 (2.0)	>0.90
Glioblastoma	1 (1.3)	0 (0)	>0.90
Pancreatic	1 (1.3)	0 (0)	>0.90
Other	17 (23)	6 (12)	0.14
Most recent ICI type			
Monotherapy			
Pembrolizumab	36 (48)	14 (29)	0.03
Nivolumab	17 (23)	21 (42)	0.03
Ipilimumab	3 (4.0)	9 (18)	0.01
Atezolizumab	2 (2.7)	2 (4.1)	0.60
Durvalumab	0 (0)	0 (0)	>0.90
Tremelimumab	0 (0)	1 (2.0)	0.40
Avelumab	1 (1.3)	0 (0)	>0.90
Combination therapy			
Ipilimumab + nivolumab	15 (20)	6 (12)	0.30
Ipilimumab + pembrolizumab	4 (5.3)	0 (0)	0.20
Tremelimumab + avelumab	1 (1.3)	0 (0)	>0.90
Tremelimumab + durvalumab	2 (2.7)	0 (0)	0.50
Summary of all ICI given			
Pembrolizumab	41 (55)	24 (49)	0.50
Nivolumab	31 (41)	28 (56)	0.13
Ipilimumab	23 (31)	20 (41)	0.20
Atezolizumab	2 (2.7)	4 (8.2)	0.20
Durvalumab	2 (2.7)	0 (0)	0.50
Tremelimumab	3 (4.0)	1 (2.0)	>0.90
Avelumab	2 (2.7)	0 (0)	0.50
Other immune-related adverse events			
Pneumonitis	20 (27)	8 (16)	0.20
Hepatitis	11 (15)	5 (10)	0.50
Neurologic	10 (13)	1 (2.0)	0.05
Colitis	8 (11)	8 (16)	0.40
Dermatitis	6 (8.0)	1 (2.0)	0.20
Hypophysitis/pituitary/adrenal axis disorder	5 (6.7)	5 (10)	0.50
Myositis	3 (4.0)	0 (0)	0.30
Nephritis	1 (1.3)	0 (0)	>0.90
Vasculitis	1 (1.3)	0 (0)	>0.90
No other immune side effects	35 (47)	25 (51)	0.60

Values are n (%).
ICI = immune checkpoint inhibitor.

$P = 0.20$) and a marginal increase in neurologic IRAEs was observed in cases compared with controls (13% vs 2%; $P = 0.05$) (Table 2). Overall, 56% (n = 42) of cases had a preserved LVEF ($\geq$50%) at presentation with myocarditis. Overall, 53 of the 75 patients underwent CMR studies. Of the CMR studies performed, 44 were

FIGURE 2 Echocardiographic Strain Measures Before and After ICI Start Among Myocarditis Cases and Controls

(A) Box-and-whisker plot showing the reduction in GCS during myocarditis compared with controls. (B) Box-and-whisker plot showing the reduction in GRS during myocarditis compared with controls. Sample sizes vary according to time point (pre-ICI: 10 cases and 39 controls; on-ICI: 75 cases and 49 controls). Minimal values **(lowest horizontal line or dot)** and maximum values **(highest horizontal line or dot)** are presented as well as first quartile **(bottom of box)**, median **(horizontal line within the box)** and third quartile. *$P < 0.05$ (on-ICI cases vs on-ICI controls). Abbreviations as in **Figure 1**.

performed with a 1.5-T magnet, and 9 were performed with 3.0-T.

The median time from the first dose of ICI to myocarditis admission to a hospital was 68 (IQR: 31-158) days. From admission to event censoring, 28 events occurred over a median follow-up of 30 (IQR: 2-97) days. The median time from baseline (pre-ICI) transthoracic echocardiogram (TTE) to ICI start was 54 (IQR: 16-159) days for cases and 100 (IQR: 60-241) days for controls. The median time from ICI start to

on-ICI echocardiogram was 71 (IQR: 33-159) days for cases and 280 (IQR: 190-502) days for controls.

ECHOCARDIOGRAPHIC DATA. Correlation analyses between the different strain modalities are presented in the supplemental data (Supplemental Figure 1). Twelve cases and 50 controls had echocardiograms performed before ICI start enabling GCS and GRS measurements (Figure 2).

Pre-ICI GCS and GRS in cases and controls. Baseline echocardiogram features are presented in Table 3. No baseline pre-ICI differences were noted regarding the echocardiographic and electrocardiographic (ECG) parameters evaluated. Pre-ICI GRS values were reduced for 6 patients (1 from cases and 5 from controls).[19] Nineteen patients (4 from cases and 15 from controls) had reduced pre-ICI GCS values.[19] This difference was not significant between groups. the lower limits of normal range were defined as 35.1% for GRS and 20.9% for GCS, based on a large meta-analysis.[19] in this study, interobserver intraclass correlations (ICCs) were of 97% for GLS, 95% for GCS, and 91% for GRS, and intraobserver ICCs of 94% for GLS, 96% for GCS, and 97% for GRS. Eight of the cases had paired measures available—before ICI and during admission for myocarditis—and 12 of the controls (Supplemental Figure 2).

On-ICI GCS and GRS in cases and controls. In total, 75 cases and 50 controls were compared in this analysis (Table 4). The GCS was lower in cases (absolute values) compared with controls (ICI-treated patients without myocarditis) (17.5% ± 4.2% vs 23.6% ± 3.0%; *P* < 0.001) (Figure 2) and among subgroups presenting with both a preserved (19.7% ± 3.8% vs 23.6% ± 3.0%; *P* < 0.001) and a reduced LVEF (14.6% ± 2.7% vs 20.9% ± 2.3%; *P* < 0.001). Similarly for GRS, values were lower in cases compared with controls (28.6 %± 6.7% vs 47.0% ± 7.4%; *P* < 0.01). a lower GRS was also observed in those patients with myocarditis presenting with both preserved LVEF (31.7% ± 5.5% vs 47.0% ± 7.6%; *P* < 0.001) and reduced LVEF (24.7% ± 6.1% vs 49.2% ± 4.7%; *P* < 0.005). Correlation coefficients above 0.67 were obtained for all of them.

MACE PREDICTION WITH GCS AND GRS. A survival analysis was performed to assess the association between GCS and GRS and MACE in the myocarditis group. An absolute GCS value below the median (17.1%) was associated with an increased rate of events (HR: 4.9 [95% CI: 1.6-15.0]; *P* = 0.005) (Figure 3), after adjustment for age and LVEF. The association was also noted when GCS was treated as a continuous variable, adjusted for the same covariates (HR: 1.18 [95% CI: 1.03-1.35]; *P* = 0.02). In the preserved LVEF subgroup, the association remained

TABLE 3 Description of Baseline TTE and ECG Data Before ICI Start From Patients Who Subsequently Developed Myocarditis and Controls Who Were Treated With ICI and Did Not Develop Myocarditis

	Cases (n = 12)	Controls (n = 50)	*P* Value
TTE			
LVEF, %	62 ± 9	65 ± 9	0.30
LVIDD, mm	49 ± 6.6	44 ± 5.7	0.10
LVIDS, mm	34 ± 9	29 ± 4.7	0.07
LA maximum volume, mL	58 ± 20	61 ± 25	0.80
GLS, %	20.4 ± 2.7	20.3 ± 2.0	0.67
GCS, %	22.6 ± 3.4	23.5 ± 3.8	0.14
GRS, %	45.5 ± 6.2	43.6 ± 8.8	0.24
Electrocardiogram			
Sinus rhythm, %	8 (80)	37 (94)	0.40
Heart rate, beats/min	93 (18)	89 (20)	0.70

Values are mean ± SD or n (%). Absolute values are presented for GLS and GCS. The controls with TTE performed before ICI start (n = 50) are not necessarily the same as those controls who had a TTE performed after ICI start (n = 50). From the control cohort, an overlap of 12 patients had paired TTE data performed before and after ICI start.

ECG = electrocardiogram; GCS = global circumferential strain; GLS = global longitudinal strain; GRS = global radial strain; LA = left atrial; LVEF = left ventricular ejection fraction; LVIDD = end-diastolic left ventricular internal dimension; LVIDS = end-systolic left ventricular internal diameter; TTE = transthoracic echocardiogram; other abbreviation as in Table 2.

(unadjusted) (HR: 4.2 [95% CI: 1.2-14.9]; *P* = 0.02) but not in the reduced LVEF (unadjusted) (HR: 5.6 [95% CI: 0.74-42.1]; *P* = 0.09) (Table 5).

A GRS below the median (29.4%) was also associated with an increased rate of events (HR: 3.92 [95% CI: 1.42-10.78]; *P* = 0.008) (Figure 4) after adjustment for age and LVEF. The association between GRS and events was also noted when the variable was treated as continuous and controlled for the same covariates (HR: 1.07 [95% CI: 1.001-1.15]; *P* = 0.04). In the preserved LVEF subgroup, the association remained (unadjusted) (HR: 3.9 [95% CI: 1.08-13.8]; *P* = 0.04) but not in the reduced LVEF (unadjusted) (HR: 3.9 [95% CI: 0.9-16.9]; *P* = 0.07) (Table 5).

PERFORMANCE OF STRAIN MODALITIES AND TRADITIONAL BIOMARKERS IN THE PREDICTION OF MACEs. In multiple ROC curves, GLS had the largest AUC (Figure 5) and thus was considered the "gold standard" for the purpose of multiple ROC curves comparison. The multiple ROC curves comparison was performed to rank the MACE predictors and to assess whether there was a significant difference between them. All ROC areas from the different predictors were different from GLS (*P* < 0.05) in the unadjusted analysis, and in the adjusted analysis, GCS prediction performance was the only one not different from GLS (Table 6). An attempt for creating new continuous variables yielding larger areas under the ROC curves was performed aggregating different

TABLE 4 Description of TTE and ECG Data After ICI Start From Cases at the Time of Presentation of Myocarditis and Controls Who Were on ICIs and Did Not Develop Myocarditis

	Cases (n = 75)	Controls (n = 50)	P Value
TTE			
LVEF, %	50 ± 18	64 ± 8	<0.001
LVIDD, mm	48 ± 7	45 ± 5	0.03
LVIDS, mm	34 ± 9	30 ± 5	0.01
LA maximum volume, mL	65 ± 41	80 ± 41	0.30
GLS, %	14.3 ± 3.2	20.5 ± 1.9	<0.001
GCS, %	17.5 ± 4.2	23.6 ± 3.0	<0.001
GRS, %	28.6 ± 6.7	47.0 ± 7.4	<0.001
Electrocardiogram			
Sinus rhythm, %	62 (83)	42 (86)	0.60
Heart rate, beats/min	82 (22)	92 (30)	0.04

Values are mean ± SD or n (%). Absolute values are presented for GLS and GCS. The controls with TTE performed before ICI start (n = 50) are not necessarily the same as those controls who had a TTE performed after ICI start (n = 50). From the control cohort, an overlap of 12 patients had paired TTE data performed before and after ICI start.

Abbreviations as in **Tables 2 and 3**.

tests (indices). However, GLS remained the test with the highest accuracy in predicting MACEs (sensitivity: 71%; specificity: 89%; positive predictive value; 80%, negative predictive value: 84%) (Supplemental Table 1). GCS had the highest sensitivity and negative predictive value. Troponin T also had a high sensitivity and negative predictive value (Supplemental Table 1).

Both GLS and GRS improved the classification of risk by the lowest LVEF obtained during myocarditis admission. Fifteen percent (7 of 47) of the cases of patients who did not have events were reclassified to a lower (<50%) risk group, and 36% (10 of 28) of the cases who experienced events were reclassified to a higher (≥50%) risk group by GLS (P = 0.001) (Supplemental Table 2). Eleven percent (5 of 47) of the cases with patients who did not have events were reclassified to a lower (<50%) risk group, and 11% (3 of 28) of the cases with patients who experienced events were reclassified to a higher (≥50%) risk group by GRS (P = 0.04) (Supplemental Table 3). The integrated discrimination improvement analyses were significant for GLS (estimate: 0.17; P ≤ 0.01), GCS (estimate: 0.08; P ≤ 0.01), and GRS (estimate: 0.06; P = 0.01) (Supplemental Table 4).

GLS also improved the classification of risk by troponin T at admission. Eleven percent (5 of 47) of the patients who did not have events were reclassified to a lower (<50%) risk group, and 43% (12 of 28) of the patients who experienced events were reclassified to a higher (≥50%) risk group by GLS (P = 0.001) (Supplemental Table 5). The integrated
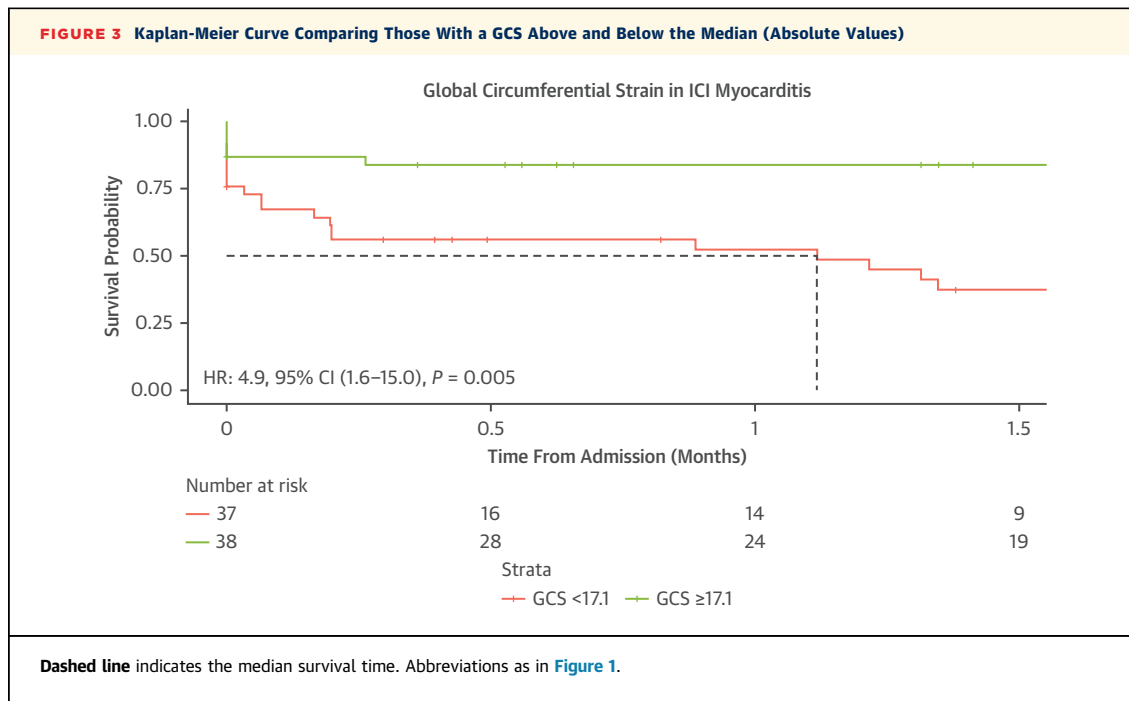
discrimination improvement analyses were significant for GLS (estimate: 0.28; P ≤ 0.001), GCS (estimate: 0.15; P ≤ 0.001) and GRS (estimate: 0.11; P ≤ 0.01) (Supplemental Table 6). The results of the study are summarized, highlighting the additive value of GLS and GCS over troponin T (**Central Illustration**). An alternative approach is also presented based on the incremental value of GLS and GCS over LVEF (Supplemental Figure 3).

DISCUSSION

The main finding of this study is that GCS and GRS are lower in ICI myocarditis patients compared with those values among patients on ICIs who did not develop myocarditis. The lower GCS and GRS values were observed in patients presenting with both preserved and reduced LVEF. Also, in follow-up, a lower GCS and GRS predicted subsequent MACEs after the diagnosis of ICI myocarditis. Finally, all strain modalities—GLS included—provided greater prognostic information compared with other traditional biomarkers used for risk stratification in ICI myocarditis.

ECHOCARDIOGRAPHIC DATA. A reduction in both GCS and GRS has been noted in patients receiving traditional cytotoxic chemotherapy. According to a previous systematic review containing data from 1,504 patients, a reduction in GCS of 11% to 16.7%—and in GRS, of 6% to 17%—can be associated with early myocardial changes of cardiotoxicity.[8] Reductions in GCS and GRS have also been demonstrated in late cancer survivors who underwent cytotoxic chemotherapy.[20-22] However, there are limited data on echocardiographic GCS or GRS during ICI use. In a clinical study (n = 69) baseline and 1-month echocardiograms after initiation of ICI revealed a reduction in GLS, but similar GRS and GCS in patients without myocarditis.[23] A CMR prospective study showed that GLS, unlike GRS and GCS, are reduced after start of ICI also in patients without myocarditis.[24] This study also shows an increase in myocardial edema (increased T1 and T2 relaxation times). In this paper, the paired data indicated a reduction in all strain parameters for patients with myocarditis but not for controls on ICI.

In this study, there was a modest reduction of all strain parameters in cases of ICI myocarditis without an average reduction in LVEF. This may reflect a diffuse lymphocyte infiltration compared with conditions such as hypertrophic cardiomyopathy—in which a patchy distribution of myocyte fibrosis and disarray are seen—that leads to loss of the base-to-apex strain increase gradient to compensate for reductions in GLS. This finding has been described

FIGURE 3 Kaplan-Meier Curve Comparing Those With a GCS Above and Below the Median (Absolute Values)

Dashed line indicates the median survival time. Abbreviations as in **Figure 1**.

since early stages of cardiac involvement of Fabry disease when LVEF is still preserved.[25] As demonstrated in a previous CMR imaging study[12] in ICI myocarditis, the myocardium can be affected in different layers and segments. Patterns described may vary from no LGE to diffuse LGE, and range from subendocardial, subepicardial, transmural, and mixed patterns, which may reflect this diffuse infiltration of the myocardium.

Our findings are complementary to a recent CMR paper among a cohort of 20 patients with ICI myocarditis. In that study, strain parameters were assessed by feature tracking.[26] The authors showed that GLS, GCS, and GRS were reduced (compared with reference values[27,28]) and all correlated with cardiac index. The mechanism for the reduction in GCS and GRS in that study, like ours, was not clear, but most patients presented with increased cardiac inflammation (T2-weighed abnormal images) and fibrosis (presence of LGE images). Other mechanisms are possible, including the occurrence of in situ inflammation combined with preserved myocyte integrity. For example, in an animal model in which mice were treated with ICI, there was a reduction in GRS associated with myocardial inflammation (increased T-cell infiltration) and down-regulation of proteins

TABLE 5 Univariate and Multivariate Analysis (Cox Regression Models)
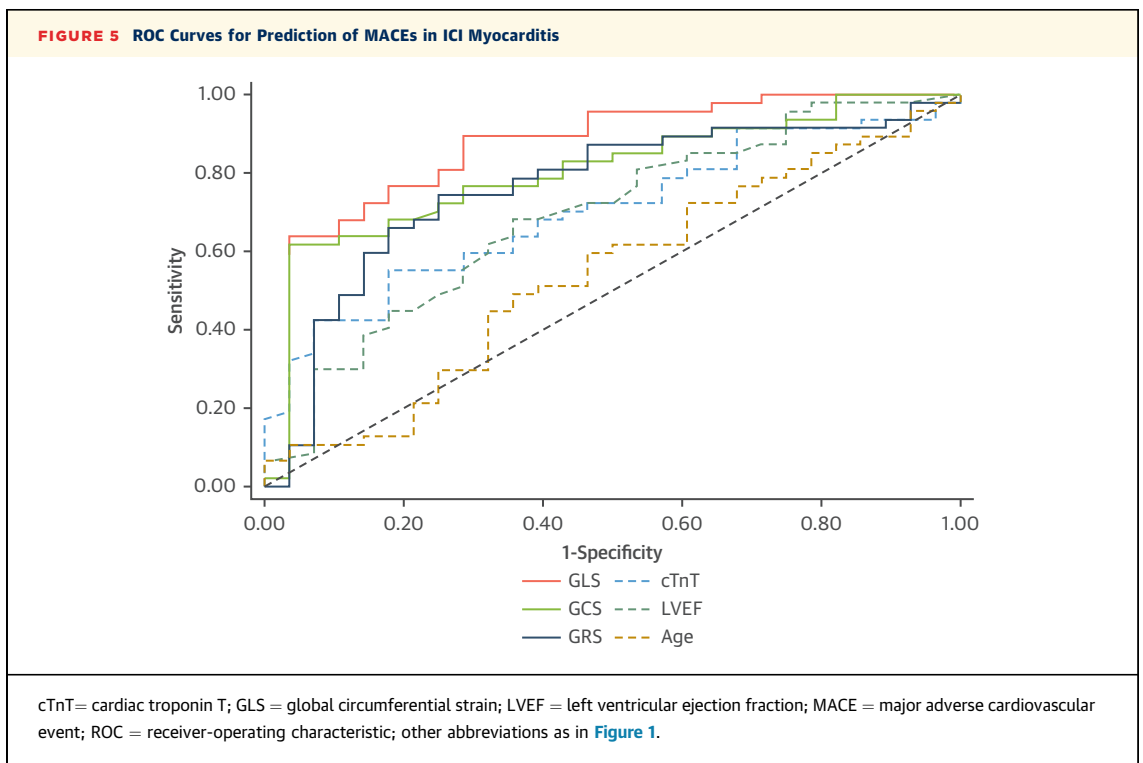
	Univariate Analysis				Multivariable Analysis	
	Preserved LVEF		Reduced LVEF		Entire Cohort of Cases	
	Coefficient	*P* Value	Coefficient	*P* Value	Coefficient	*P* Value
GCS	4.2 (1.2-14.9)	0.02	5.6 (0.74-42.1)	0.09	4.9 (1.6-15.0)	0.005
LVEF	—	—	—	—	1.0 (0.97-1.02)	0.88
Age at ICI start	—	—	—	—	1.0 (0.96-1.01)	0.33
GRS	3.9 (1.08-13.8)	0.04	3.9 (0.9-16.9)	0.07	3.9 (1.4-10.8)	0.008
LVEF	—	—	—	—	1.0 (0.97-1.01)	0.37
Age at ICI start	—	—	—	—	1.0 (0.97-1.02)	0.50

Values are HR (95% CI), unless otherwise indicated. Cox-regression analysis comparing GCS and GRS above and below the median (the absolute values were used). Data are regression coefficients and 95% CIs in parentheses. Major adverse cardiovascular events: cardiogenic shock, cardiac arrest, complete heart block, and cardiac death. *P* < 0.05 was used for statistical significance.

Abbreviations as in **Tables 2 and 3**.

FIGURE 4   Kaplan-Meier Curve Comparing Those With GRS Above and Below the Median

Global Radial Strain in ICI Myocarditis

HR: 3.9, 95% CI (1.4–10.8), $P = 0.008$

Number at risk

38	17	15	9
37	27	23	19

Strata
— GRS <29.4   — GRS ≥29.4

Dashed line indicates the median survival time. Abbreviations as in **Figure 1**.
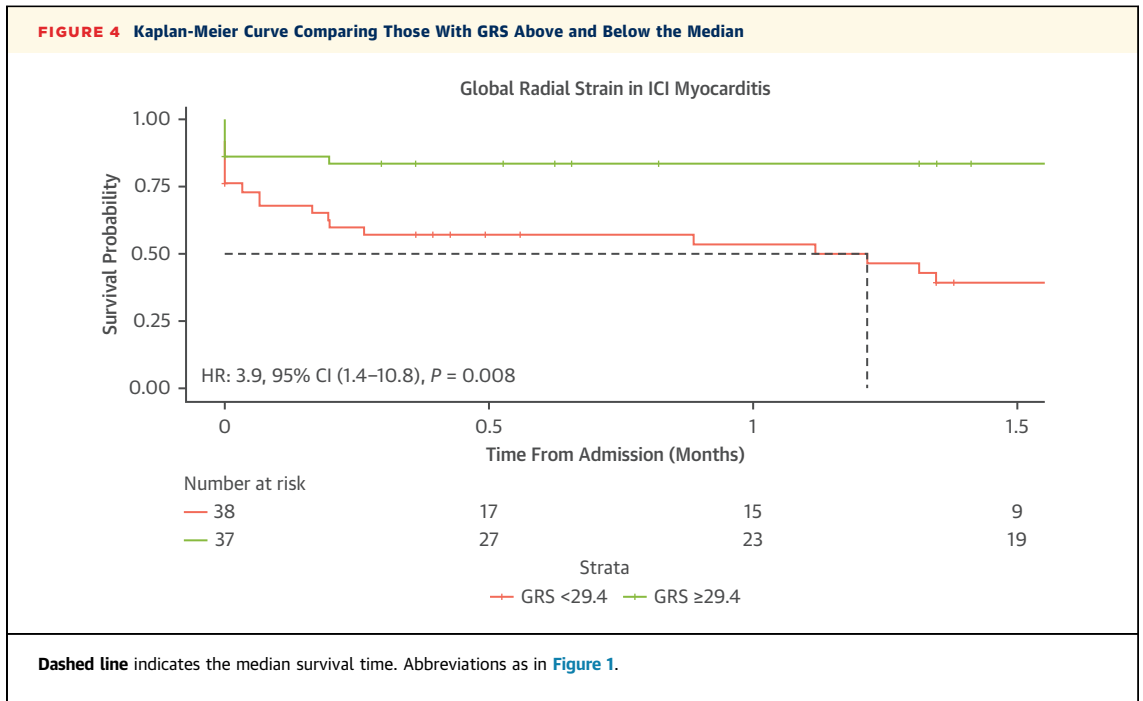
for cardiomyocyte contraction (L-type calcium channel beta-2, among others) without evidence of myocarditis.[29] In a parallel clinical study (n = 7), the same team performed serial measures of GLS in patients with melanoma receiving ICI and showed a reduction; again, none of the participants had clinical evidence of myocarditis. Mass spectrometry revealed disrupted energy metabolism and calcium

FIGURE 5   ROC Curves for Prediction of MACEs in ICI Myocarditis

— GLS   --- cTnT
— GCS   --- LVEF
— GRS   --- Age

cTnT = cardiac troponin T; GLS = global circumferential strain; LVEF = left ventricular ejection fraction; MACE = major adverse cardiovascular event; ROC = receiver-operating characteristic; other abbreviations as in **Figure 1**.

TABLE 6 Prediction Accuracy of MACE in ICI Myocarditis (C-Statistic)

	AUC (95% CI)	P Value	Cutoff	Sensitivity	Specificity	PPV	NPV
GLS	0.87 (0.78-0.96)	–	13.4	0.71	0.89	0.80	0.84
GCS	0.80 (0.70-0.91)	0.03	17.9	0.96	0.62	0.60	0.97
GRS	0.76 (0.64-0.88)	0.01	27.9	0.75	0.74	0.64	0.83
Troponin T, ng/L	0.70 (0.58-0.82)	<0.01	185	0.82	0.55	0.52	0.84
LVEF	0.69 (0.56-0.81)	<0.01	50	0.64	0.68	0.54	0.76
Age	0.54 (0.40-0.68)	<0.01	79	0.21	0.87	0.50	0.65

Values are n (%), unless otherwise indicated. Troponin T was defined as the first obtained at admission, LVEF as the lowest measured during admission and age was established at the time of ICI start. P values were calculated for the comparison with GLS, and cutoff values set using Youden index test.

MACE = major adverse cardiovascular event; NPV = negative predictive value; PPV = positive predictive value; other abbreviations as in Tables 2 and 3.

homeostasis as a putative underlying pathomechanism for impaired myocardial function, in accordance to what was demonstrated in the animal model.[29]

MACE PREDICTION WITH GCS AND GRS. In patients treated with traditional cytotoxic chemotherapy, reductions in GLS have been associated with a future decrease in LVEF or the development of heart failure, but a less consistent association has been reported for GCS and GRS.[8,30,31] To our knowledge, this is the first study to demonstrate the association of reduced values of GCS and GRS and clinical outcomes in patients who develop myocarditis while on ICI therapy. As shown for GLS,[6] the GCS and GRS variables predicted MACEs when treated either as a categorical or a continuous variable. An absolute GCS value below 17.1% was associated with a nearly 5-fold increase in events after adjustment for age and LVEF (Figure 3). Similarly, for a GRS value below 29.4%, there was an approximate 4-fold increase in events (Figure 4). Specifically, for each single point of GCS or GRS reduction, there is a respective increase in 18% or 7% in the rate of MACEs. Of importance, when the subgroup with preserved LVEF was analyzed separately, the association remained significant (unadjusted) for both GCS and GRS.

PERFORMANCE OF STRAIN MODALITIES AND TRADITIONAL BIOMARKERS IN THE PREDICTION OF MACEs. In non-ICI myocarditis, LVEF and cardiac troponin have an established role in determining prognosis.[32-34] LGE by CMR has also been shown to predict further events in different LVEF strata.[35-37] With ICI-myocarditis, the prognostic impact of LVEF, troponin, and GLS has also been demonstrated.[6,17] In the current study, in addition to showing the prognostic role of GCS and GRS in ICI myocarditis, we compare the traditional biomarkers to the echocardiographic strain modalities. We show that the parameters with the greatest impact in predicting

events were the 3 echocardiographic strain modalities (GLS, GCS, and GRS, in that order) (Figure 5). In multiple ROC curves, GLS, GCS, and GRS showed better performance than cardiac troponin T (cTnT), LVEF, and age.

GLS, of the strain variables, was the most balanced as it was associated with the highest positive predictive value (0.80) combined with a good negative predictive value. Thus, when used in isolation, it is the best measure to predict events. GCS was the strain parameter with the highest negative predictive value (0.97). In this cohort, from all patients who had GCS above the cutoff only, 1 had an event out of 28 patients who presented with MACEs. Finally, GRS was the strain modality with the smallest area under the ROC curve. Nevertheless, GRS performed better than the usual parameters used, cTnT, LVEF, and age (by both net reclassification index and integrated discrimination improvement).

STUDY LIMITATIONS. This study needs to be interpreted within the context of the study design. First, myocarditis related to ICI use is uncommon, and a retrospective international multicenter registry was the most realistic design to provide initial data. Second, only limited paired data were available for this analysis. Eight cases and 12 controls had pre- and on-ICI (during myocarditis, for cases) GCS and GRS. All other echocardiographic measures correspond to a single time point. Third, cases and controls had on-ICI TTEs performed in different time points. If values return to baseline values after a transient ICI-induced decrease, controls may have had their on-ICI TTE at a time point that may have not detected a transient decrease in strain parameters. Finally, Although GCS and GRS may help predict events after ICI myocarditis, other covariates, such as previous cancer treatments or comorbidities, could not be added to the model because of limited sample size and number of events.

CENTRAL ILLUSTRATION Event Rate Stratification in Immune Checkpoint Inhibitor Myocarditis
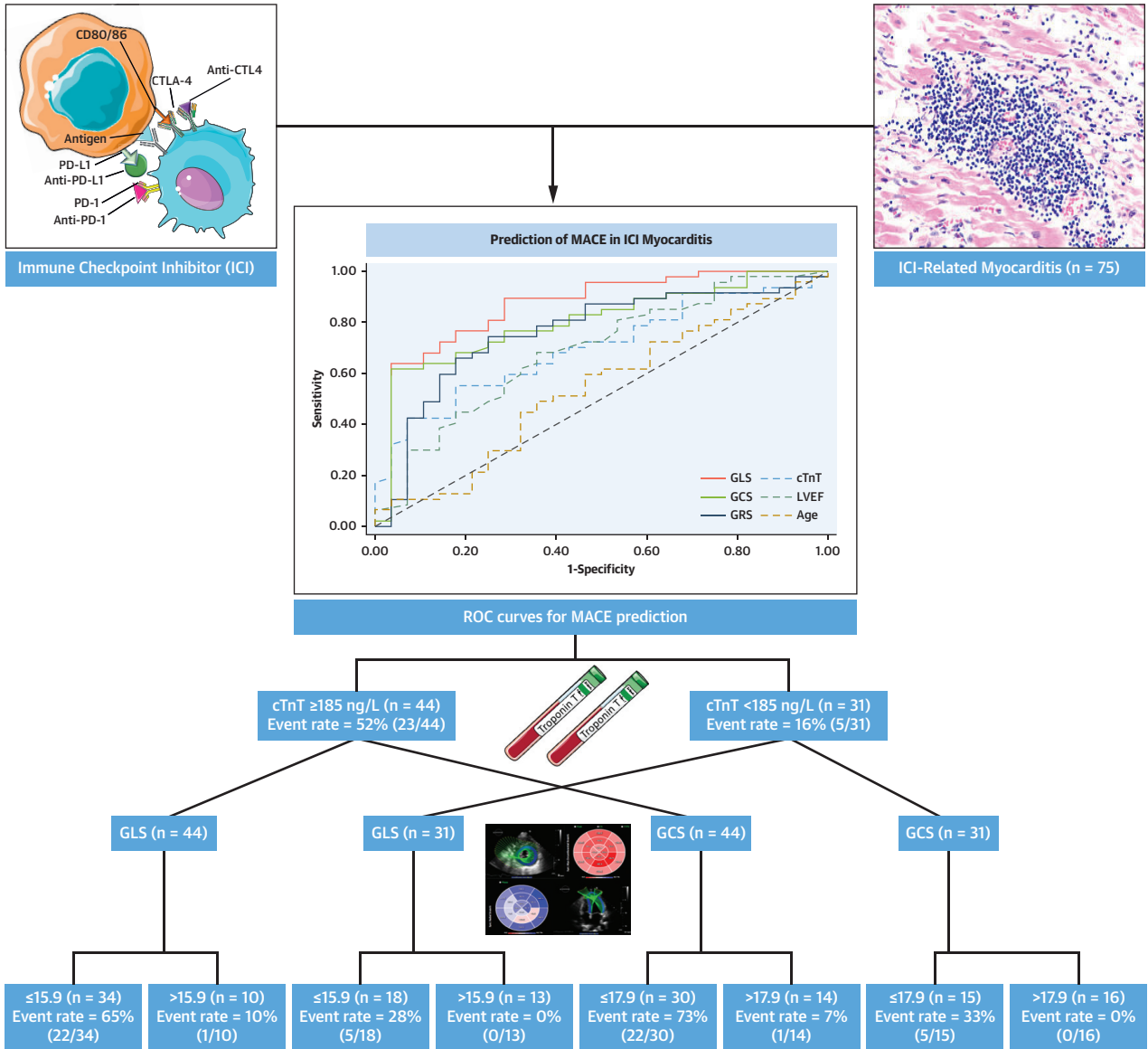
Quinaglia T, et al. J Am Coll Cardiol Img. 2022;15(11):1883–1896.

Event rate stratification using strain modalities from echocardiography and circulating troponin T in a retrospective immune checkpoint inhibitor (ICI) myocarditis cohort. cTnT = cardiac troponin T; GCS = global circumferential strain; GLS = global longitudinal strain; GRS = global radial strain; LVEF = left ventricular ejection fraction; MACE = major adverse cardiovascular event; ROC = receiver-operating characteristic.

CONCLUSIONS

GCS and GRS are lower in patients with ICI myocarditis, and the magnitude of their reduction has prognostic significance. GLS, GCS, and GRS predict MACEs with better accuracy than LVEF, cTnT, and age after diagnosis of ICI myocarditis. Thus, having a full assessment of myocardial deformation could yield a

more thorough assessment of subendocardial and subepicardial myocardial fiber damage. ICI myocarditis is a life-threatening condition in which correct immunosuppressant therapy could be lifesaving. Accurate biomarkers may allow precise risk stratification and treatment. Strain measures could fulfill this gap and perhaps be included in future guidelines. However, larger prospective studies are needed to confirm our findings. Also, further studies are needed to evaluate whether pre-ICI echocardiographic parameters can predict new onset myocarditis and allow for risk stratification even before initiation of ICI.

ADDRESS FOR CORRESPONDENCE: Dr Thiago Quinaglia A.C. Silva, Cardiovascular Imaging Research Center (CIRC), Massachusetts General Hospital, 165 Cambridge Street, Suite 400, Boston, Massachusetts 02114, USA. E-mail: tquinaglia@mgh.harvard.edu OR tquinaglia@gmail.com. Twitter: @quinagliathiag1.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Immune checkpoint inhibitors are a highly effective class of cancer drugs and are being prescribed increasingly. Myocarditis is an uncommon immune adverse event but has a mortality rate of up to 50%. The use of GCS and GRS, along with GLS, can predict cardiovascular events with a better performance than traditional biomarkers in the setting of this disease.

TRANSLATIONAL OUTLOOK: Large prospective cohorts are needed to validate the current findings and better outline the temporal relationship between immune checkpoint inhibitor start and the change in strain parameters as well as to understand if these early changes could predict later myocarditis.

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APPENDIX For supplemental figures, tables, and a reference, please see the online version of this paper.