**Association Between Global Longitudinal Strain and Cardiac Events Among Patients with Immune Checkpoint Inhibitor-Related Myocarditis**

Magid Awadalla, MD1,2, Syed S. Mahmood, MD3, MPH, John D. Groarke, MB, BCH, MPH4, Malek Z.O. Hassan, MD1, Anju Nohria, MD4, Adam Rokicki, BS1, Sean P. T. Murphy, MD1, Nathaniel D. Mercaldo, PhD1, Lili Zhang, MD, MS1,2, Daniel A. Zlotoff, MD, PhD1, Kerry L. Reynolds, MD5, Raza M. Alvi, MD1, Dahlia Banerji, MD1, Shiying Liu, MD6, Lucie M. Heinzerling, MD, MPH7, Maeve Jones-O’Connor, MD1, Rula B. Bakar, MD1, Justine V. Cohen, DO5, Michael C. Kirchberger, MD7, Ryan J. Sullivan, MD5, Dipti Gupta, MD, MPH8, Connor P. Mulligan, BA1, Sachin P. Shah, MD9, Sarju Ganatra, MD9, Muhammad A. Rizvi, MD10, Gagan Sahni, MD11, Carlo G. Tocchetti MD, PhD12, Donald P. Lawrence, MD5, Michael Mahmoudi, MD, PhD13, Richard B. Devereux, MD3, Brian J. Forrestal, MD14, Anant Mandawat, MD15, Alexander R. Lyon MD, PhD16, Carol L. Chen, MD8, Ana Barac, MD, PhD14, Judy Hung, MD6, Paaladinesh Thavendiranathan, MD17, Michael H. Picard, MD6, Franck Thuny, MD18, Stephane Ederhy, MD19, Michael G. Fradley, MD20, Tomas G Neilan, MD, MPH, FACC1,2.

1Cardiac MR PET CT Program, Department of Radiology, Massachusetts General Hospital, Boston, Massachusetts; 2Cardio-Oncology Program, Division of Cardiology, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts; 3Cardiology Division, New York-Presbyterian Hospital, Weill Cornell Medical Center, New York, New York; 4Cardio-Oncology Program, Division of Cardiology, Department of Medicine, Brigham and Women’s Hospital, Boston, Massachusetts; 5Division of Oncology and Hematology, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts; 6Division of Cardiology, Massachusetts General Hospital, Boston, Massachusetts; 7Department of Dermatology, University Hospital Erlangen, Friedrich-Alexander-University Erlangen-Nurnberg (FAU), Germany; 8Cardiology Division, Memorial Sloan Kettering Cancer Center, Weill Cornell Medical College, New York, New York; 9Cardiology Division, Lahey Hospital & Medical Center, Burlington, Massachusetts; 10Division of Oncology and Hematology, Department of Medicine, Lehigh Valley Hospital, Allentown, Pennsylvania; 11The Mount Sinai Hospital, New York, New York; 12Department of Translational Medical Sciences, Federico II University, Naples, Italy; 13Faculty of Medicine, University of Southampton, Southampton, United Kingdom; 14Cardio-Oncology program, Division of Cardiology, Department of Medicine, MedStar Heart and Vascular Institute, MedStar Washington Hospital Center, Washington, DC; 15Cardio-Oncology Program, Department of Hematology and Medical Oncology, Winship Cancer Institute of Emory University, Emory University School of Medicine, Atlanta, Georgia; 16Cardio-Oncology Program, Royal Brompton Hospital and Imperial College, London, United Kingdom; 17Ted Rogers Program in Cardiotoxicity Prevention, Peter Munk Cardiac Center, Division of Cardiology, Toronto General Hospital, University of Toronto, Toronto, Ontario, Canada; Cardiology Division,18Cardiovascular Division, Department of Medicine, Aix-Marseille Universite, Marseille, France; 19Cardio-Oncology Program, Division of Cardiology, Hopitaux Universitaires est Paris, Paris, France; and the 20Cardio-Oncology Program, H. Lee Moffitt Cancer Center & Research Institute and University of South Florida Division of Cardiovascular Medicine, Tampa, Florida.

**Short title:** GLS and MACE in ICI-myocarditis

**Correspondence to:** Tomas G Neilan, MD, MPH, FACC, Cardio-Oncology Program and Cardiovascular Imaging Research Center (CIRC), Massachusetts General Hospital, 165 Cambridge Street, Suite 400, Boston, Massachusetts 02114, USA

(617)-724-5351
(617)-724-4152 (fax)

Email: tneilan@mgh.harvard.edu

**Disclosures:** Dr. Mahmood has received consultancy fees from OMR Globus, Alpha Detail, and Opinion Research Team. Dr. Nohria has received research support from Amgen; and has been a consultant for Takeda Oncology. Dr. Heinzerling has received consultancy, advisory board, and speaker fees from MSD, BMS, Roche, Novartis, Amgen, and Curevac. Dr. Sullivan has been a consultant to Merck and Novartis. Dr. Groarke has received research support from Amgen. Dr. Neilan has received advisory fees from Parexel, Aprea Therapeutics, BMS, and Intrinsic Imaging. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

**Abstract**

**Background:** There is a need for improved methods for detection and risk stratification of myocarditis associated with immune checkpoint inhibitors (ICI’s). 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.

**Methods:** We retrospectively compared echocardiographic GLS by speckle tracking at presentation with ICI-myocarditis (cases, n=101) and patients receiving ICI without myocarditis (controls, n=92). Where available, GLS was also measured pre-ICI in both groups. Major adverse cardiac events (MACE) was defined as a composite of cardiogenic shock, arrest, complete heart block, and cardiac death.

**Results:** Cases and controls were similar in age, sex, and cancer type. At presentation with myocarditis, 61 cases (60%) had a normal EF. Pre-ICI, GLS was similar between cases and controls (20.3±2.6 vs. 20.6±2.0 %, p=0.60). There was no change in GLS among controls 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 (HR 1.5, CI 1.2-1.8) and a 4.4-fold increase with a preserved EF (HR 4.4, CI 2.4-7.8).

**Conclusion:** GLS decreases with ICI-myocarditis and, compared to controls, 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.

**Condensed Abstract**

ICI-myocarditis is poorly characterized and improved methods for detection and risk stratification are required. GLS is a sensitive marker of cardiotoxicity. We compared GLS at presentation with ICI-myocarditis among 101 cases to 92 controls on ICIs without myocarditis, and assessed its association with MACE. GLS decreased with ICI-myocarditis and this decline, as compared to controls, was present in cases with both a reduced and preserved EF (12.3±2.7% vs. 15.3±2.0% vs. 20.5±1.9%, p<0.001). Over half the cases had a MACE, and lower GLS was strongly associated with MACE in cases presenting with either a preserved or reduced EF.

**Keywords:** Global longitudinal strain, Immune checkpoint inhibitors, myocarditis, major adverse cardiac events

**Abbreviations:**

CV= cardiovascular

EF= ejection fraction

GLS= global longitudinal strain

ICI= Immune checkpoint inhibitors

IrAE= Immune related adverse effect

LV= left ventricle

MACE= major adverse cardiac event

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

TTE= transthoracic echocardiogram

VEGF= vascular endothelial growth factor

**Introduction**

Immune checkpoint inhibitors (ICIs) represent a significant advance in the treatment of patients with cancer (1). They work by promoting T-cell mediated antitumor 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 the case fatality rate with myocarditis related to an ICI is very high, ranging from 35-50% (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).

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 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 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 101cases 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). Controls 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) and did not develop myocarditis. Controls 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 lab, and GLS by speckle tracking was measured centrally using the vendor neutral TomTec-Arena TTA2 (TomTec Imaging Systems GMBH, Germany) by a cardiologist blinded to all other study, group and time variables using the standard echocardiographic 3 apical views (4 Ch, 2 Ch 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 to the GLS from 50 controls who were on an ICI and did not have myocarditis. The 101 cases were also compared to controls after separation by strata of LVEF. Several additional comparisons were included where data were available. To evaluate whether the pre-ICI GLS was similar between cases and controls, the GLS from 30 cases and 42 controls 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 controls after starting an ICI, the GLS from 14 controls with paired samples, pre-ICI and on ICI were measured and compared (Figure 1).

**Definitions and outcome of interest:** The diagnosis ofmyocarditis was made using two 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 MACE, defined as prior, (3) as a composite of cardiovascular death, cardiac arrest, cardiogenic shock, and hemodynamically significant complete heart block (CHB). In cases where cardiac arrest, cardiogenic shock, or CHB lead to death, that case was counted as a cardiac death.

**Statistical analysis:** Continuous variables were summarized as either the mean ± standard deviation (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’s 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, 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 testing and graphically assess 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 (HR) 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. Three multivariable models were performed, all adjusting for LVEF, and 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% being male (Table 1A). The median time to onset of myocarditis from starting ICI was 57 days (IQR 27-122 days), and 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 controls, myocarditis cases were evenly matched in age, sex, and cardiovascular risk factors (Table 1A).

**Cancer and treatment characteristics:** The most commonindications for an ICI were melanoma and lung cancer (Table 1A). Patients with myocarditis were more likely to have received combination ICI therapy (Table 1B); however, the majority were on single ICI therapy (73%). The median follow-up time was 283 [IQR 101,514] days for controls, and 175 [IQR 95,352] days for cases (Table 1B). Among cases, 46% had experienced another ICI-related side effect (Table 1B).

**Global Longitudinal Strain:**

Pre-ICI GLS in cases and controls:Among the 101 cases, 30 had an additional GLS measure from pre-ICI therapy. The pre-ICI GLS of cases was similar when compared to that of the 42 controls (cases vs. controls pre-ICI: 20.3±2.6% vs. 20.6±2.0 %, p=0.60) (Table 2A) (Fig 2A).

Serial GLS during ICI-myocarditis among cases: Within the 30 myocarditis cases with paired GLS values (pre-ICI compared to 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) (Table 2A & 2B) (Fig 2B).

Serial GLS among ICI patients who did not develop myocarditis: The GLS of 14 controls 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) (Table 2A & 2B) (Fig 2C).

GLS at presentation with myocarditis compared to controls on ICI: The GLS among cases at admission for myocarditis (n=101) was lower than controls on ICI therapy without myocarditis (n=50) (myocarditis cases vs. controls on ICI, 14.1±2.7% vs. 20.5±1.9 %, p<0.001) (Table 2B) (Fig 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 TTEs, and 20 had a follow-up TTE at median time between imaging of 102 [IQR 36, 152] days. In follow-up, GLS increased from 14.3±2.9% to 16.9±4.7% (p=0.14, Fig. 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 to controls during ICI therapy (n=50) (cases with reduced EF vs. cases with preserved EF, controls on ICI: 12.3±2.7% vs. 15.3±2.0% vs. 20.5±1.9%, p<0.001 between the groups) (Fig 2F). There were no differences in GLS between biopsy-proven myocarditis cases when compared to non-biopsy proven cases (Supplementary Table 1).

**Cardiac Biomarkers:**

Among cases, troponin levels at admission (n=101) were elevated in 98/101 (97%), with a median value of 0.85 [IQR 0.17, 2.3] ng/dl. Among controls 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, NT-proBNP levels at admission were elevated in 73/83 (88%). The median NT-proBNP value among cases was 589 [IQR 208, 2413] pg/ml. Among controls on an ICI, a measure of NT-proBNP was available in 41 subjects. The median NT-proBNP value among controls on an ICI was 560 [IQR 243, 2093] 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).

**MACE:** Over a median follow-up of 162 [IQR 58, 334] days, 51 (51%) had a MACE. These included complete heart block (n=19), cardiogenic shock (n=14), cardiac arrest (n=12), and 6 CV 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 to controls (cases vs. controls, 46±19 vs. 61±19 mls, p<0.001, Table 2b). However, the SV among myocarditis cases with a MACE (55.7±26.6 mls) was similar to cases without MACE (43.5±11.1 mls, p=0.47). The components of MACE stratified by preserved and reduced LVEF as well as normal/abnormal GLS are summarized in Supplementary Table 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 to 15.9%, and lowest among cases with GLS ≥ 16% (p<0.001) (Fig 3A). Among patients with myocarditis presenting with a reduced EF, a GLS lower than 13% was associated with higher MACE (p<0.001) (Fig 3B). Similarly, among ICI myocarditis cases presenting with a preserved EF, a GLS lower than 16% was associated with higher MACE (p< 0.001) (Fig 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, 2.39), p<0.001), among cases with a reduced EF (HR 1.49, 95% CI (1.2, 1.84), p<0.001) and among cases with a preserved EF (HR 4.36, 95% CI (2.44, 7.79), p<0.001) (Table 3). An additional multivariable model adjusting for EF, left ventricular internal diastolic diameter (LVIDD), age and history of diabetes is available in Supplementary Table 3.

**Discussion**

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

Global longitudinal strain is a sensitive measure of cardiac function and cardiac injury (14,15). As compared to 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, reproducible within an acceptable range (14,19,20), 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, with a similar diagnostic performance as compared to other conventional assessments such as the Lake-Louise criteria on magnetic resonance (26). The study finding of a decrease in GLS with myocarditis may be of additional importance among cancer patients where due to overlapping symptoms of chest pain and shortness of breath the diagnosis may be challenging. The finding is also of key additional importance to the majority of patients who present with a preserved EF, when, 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 35-50% (3,30,31); in contrast, the case fatality rate for myocarditis unrelated to an ICI is markedly lower, ranging from 9-16% (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 (37,38). 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 anti-cancer efficacy (39); however, recent data suggest caution where very high-dose immunosuppression may be associated with worse cancer outcomes (40). 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.

**Limitations**

This study needs to be interpreted within the context of the study design. Myocarditis with ICI’s is uncommon and with an uncommon adverse event, a multicenter international registry, as compared to 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 controls 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 and thus it was not possible determine if the GLS decrease occurred prior to the development of myocarditis. Whilst 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, while 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 irAE’s and the use of combination ICI therapy.

**Conclusion**

Among patients with ICI myocarditis, GLS is reduced and the GLS with myocarditis is lower (among patients 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 anti-tumor efficacy.

**Perspectives**

**Competency in Medical Knowledge:** ICI-related myocarditis runs a fulminant course, with over half experiencing a MACE. Speckle tracking GLS is a proven and reproducible marker of standard chemotherapy-induced cardiotoxicity. This sensitive marker may have an advantage in detecting earlier myocardial deformation compared to LVEF, and levels were associated with MACE.

**Translational Outlook 1:** LVEF provides an overall assessment of cardiac function, however a decline normally occurs at a late stage of cardiotoxicity. Earlier detection of cardiotoxicity may allow identification of patients at high-risk of future MACE and potential for prevention.

**Translational Outlook 2:** Additional research is required at a larger scale, where serial GLS measurements are performed prospectively in all patients commencing treatment on ICIs and assessing how GLS may predict MACE in those who develop ICI-myocarditis.

**References:**

1. Sondak VK, McArthur GA. Adjuvant immunotherapy for cancer: the next step. Lancet Oncol. 2015 May;16(5):478–80.

2. Johnson DB, Balko JM, Compton ML, Chalkias S, Gorham J, Xu Y, et al. Fulminant Myocarditis with Combination Immune Checkpoint Blockade. N Engl J Med. 2016 Nov 3;375(18):1749–55.

3. Mahmood SS, Fradley MG, Cohen JV, Nohria A, Reynolds KL, Heinzerling LM, et al. Myocarditis in Patients Treated With Immune Checkpoint Inhibitors. J Am Coll Cardiol. 2018 Apr 24;71(16):1755–64.

4. Ganatra S, Neilan TG. Immune Checkpoint Inhibitor-Associated Myocarditis. The Oncologist. 2018 Aug;23(8):879–86.

5. Zhang L, Jones-O’Connor M, Awadalla M, Zlotoff DA, Thavendiranathan P, Groarke JD, et al. Cardiotoxicity of Immune Checkpoint Inhibitors. Curr Treat Options Cardiovasc Med. 2019 Jun 8;21(7):32.

6. Neilan TG, Rothenberg ML, Amiri-Kordestani L, Sullivan RJ, Steingart RM, Gregory W, et al. Myocarditis Associated with Immune Checkpoint Inhibitors: An Expert Consensus on Data Gaps and a Call to Action. The Oncologist. 2018 Aug;23(8):874–8.

7. Awadalla M, Golden DLA, Mahmood SS, Alvi RM, Mercaldo ND, Hassan MZO, et al. Influenza vaccination and myocarditis among patients receiving immune checkpoint inhibitors. J Immunother Cancer. 2019 Feb 22;7(1):53.

8. Sawaya H, Sebag IA, Plana JC, Januzzi JL, Ky B, Tan TC, et al. Assessment of Echocardiography and Biomarkers for the Extended Prediction of Cardiotoxicity in Patients Treated With Anthracyclines, Taxanes, and Trastuzumab. Circ Cardiovasc Imaging. 2012 Sep 1;5(5):596–603.

9. Negishi K, Negishi T, Hare JL, Haluska BA, Plana JC, Marwick TH. Independent and incremental value of deformation indices for prediction of trastuzumab-induced cardiotoxicity. J Am Soc Echocardiogr. 2013 May;26(5):493–8.

10. Plana JC, Galderisi M, Barac A, Ewer MS, Ky B, Scherrer-Crosbie M, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2014 Sep;27(9):911–39.

11. Plana JC, Galderisi M, Barac A, Ewer MS, Ky B, Scherrer-Crosbie M, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2014 Oct;15(10):1063–93.

12. Negishi K, Negishi T, Hare JL, Haluska BA, Plana JC, Marwick TH. Independent and incremental value of deformation indices for prediction of trastuzumab-induced cardiotoxicity. J Am Soc Echocardiogr. 2013 May;26(5):493–8.

13. Caforio ALP, Pankuweit S, Arbustini E, Basso C, Gimeno-Blanes J, Felix SB, et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J. 2013 Sep;34(33):2636–48, 2648a–2648d.

14. Thavendiranathan P, Poulin F, Lim K-D, Plana JC, Woo A, Marwick TH. Use of myocardial strain imaging by echocardiography for the early detection of cardiotoxicity in patients during and after cancer chemotherapy: a systematic review. J Am Coll Cardiol. 2014 Jul 1;63(25 Pt A):2751–68.

15. Smiseth OA, Torp H, Opdahl A, Haugaa KH, Urheim S. Myocardial strain imaging: how useful is it in clinical decision making? Eur Heart J. 2016 Apr 14;37(15):1196–207.

16. Ersbøll M, Valeur N, Mogensen UM, Andersen MJ, Møller JE, Velazquez EJ, et al. Prediction of all-cause mortality and heart failure admissions from global left ventricular longitudinal strain in patients with acute myocardial infarction and preserved left ventricular ejection fraction. J Am Coll Cardiol. 2013 Jun 11;61(23):2365–73.

17. Haugaa KH, Grenne BL, Eek CH, Ersbøll M, Valeur N, Svendsen JH, et al. Strain echocardiography improves risk prediction of ventricular arrhythmias after myocardial infarction. JACC Cardiovasc Imaging. 2013 Aug;6(8):841–50.

18. Haugaa KH, Edvardsen T. Global longitudinal strain: the best biomarker for predicting prognosis in heart failure? Eur J Heart Fail. 2016;18(11):1340–1.

19. Negishi T, Negishi K, Thavendiranathan P, Cho G-Y, Popescu BA, Vinereanu D, et al. Effect of Experience and Training on the Concordance and Precision of Strain Measurements. JACC Cardiovasc Imaging. 2017;10(5):518–22.

20. Thavendiranathan P, Grant AD, Negishi T, Plana JC, Popović ZB, Marwick TH. Reproducibility of echocardiographic techniques for sequential assessment of left ventricular ejection fraction and volumes: application to patients undergoing cancer chemotherapy. J Am Coll Cardiol. 2013 Jan 8;61(1):77–84.

21. Stokke TM, Hasselberg NE, Smedsrud MK, Sarvari SI, Haugaa KH, Smiseth OA, et al. Geometry as a Confounder When Assessing Ventricular Systolic Function: Comparison Between Ejection Fraction and Strain. J Am Coll Cardiol. 2017 Aug 22;70(8):942–54.

22. Ewer MS, Ali MK, Mackay B, Wallace S, Valdivieso M, Legha SS, et al. A comparison of cardiac biopsy grades and ejection fraction estimations in patients receiving Adriamycin. J Clin Oncol. 1984 Feb;2(2):112–7.

23. Ewer MS, Lenihan DJ. Left ventricular ejection fraction and cardiotoxicity: is our ear really to the ground? J Clin Oncol. 2008 Mar 10;26(8):1201–3.

24. Cardinale D, Sandri MT, Colombo A, Colombo N, Boeri M, Lamantia G, et al. Prognostic value of troponin I in cardiac risk stratification of cancer patients undergoing high-dose chemotherapy. Circulation. 2004 Jun 8;109(22):2749–54.

25. Voigt J-U, Pedrizzetti G, Lysyansky P, Marwick TH, Houle H, Baumann R, et al. Definitions for a common standard for 2D speckle tracking echocardiography: consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. J Am Soc Echocardiogr. 2015 Feb;28(2):183–93.

26. Kasner M, Aleksandrov A, Escher F, Al-Saadi N, Makowski M, Spillmann F, et al. Multimodality imaging approach in the diagnosis of chronic myocarditis with preserved left ventricular ejection fraction (MCpEF): The role of 2D speckle-tracking echocardiography. Int J Cardiol. 2017 Sep 15;243:374–8.

27. Cardinale D, Colombo A, Lamantia G, Colombo N, Civelli M, De Giacomi G, et al. Anthracycline-induced cardiomyopathy: clinical relevance and response to pharmacologic therapy. J Am Coll Cardiol. 2010 Jan 19;55(3):213–20.

28. Fallah-Rad N, Lytwyn M, Fang T, Kirkpatrick I, Jassal DS. Delayed contrast enhancement cardiac magnetic resonance imaging in trastuzumab induced cardiomyopathy. J Cardiovasc Magn Reson. 2008 Jan 22;10:5.

29. Ammirati E, Cipriani M, Moro C, Raineri C, Pini D, Sormani P, et al. Clinical Presentation and Outcome in a Contemporary Cohort of Patients With Acute Myocarditis. Circulation. 2018 Sep 11;138(11):1088–99.

30. Lyon AR, Yousaf N, Battisti NML, Moslehi J, Larkin J. Immune checkpoint inhibitors and cardiovascular toxicity. Lancet Oncol. 2018 Sep;19(9):e447–58.

31. Mir H, Alhussein M, Alrashidi S, Alzayer H, Alshatti A, Valettas N, et al. Cardiac Complications Associated With Checkpoint Inhibition: A Systematic Review of the Literature in an Important Emerging Area. Can J Cardiol. 2018 Aug;34(8):1059–68.

32. D’Ambrosio A, Patti G, Manzoli A, Sinagra G, Di L, Silvestri F, et al. The fate of acute myocarditis between spontaneous improvement and evolution to dilated cardiomyopathy: a review. Heart. 2001 May;85(5):499–504.

33. Magnani JW, Dec GW. Myocarditis: current trends in diagnosis and treatment. Circulation. 2006 Feb 14;113(6):876–90.

34. Haugaa KH, Smedsrud MK, Steen T, Kongsgaard E, Loennechen JP, Skjaerpe T, et al. Mechanical dispersion assessed by myocardial strain in patients after myocardial infarction for risk prediction of ventricular arrhythmia. JACC Cardiovasc Imaging. 2010 Mar;3(3):247–56.

35. Kearney LG, Lu K, Ord M, Patel SK, Profitis K, Matalanis G, et al. Global longitudinal strain is a strong independent predictor of all-cause mortality in patients with aortic stenosis. Eur Heart J Cardiovasc Imaging. 2012 Oct;13(10):827–33.

36. Park JJ, Park J-B, Park J-H, Cho G-Y. Global Longitudinal Strain to Predict Mortality in Patients With Acute Heart Failure. J Am Coll Cardiol. 2018 May 8;71(18):1947–57.

37. Caspar T, Fichot M, Ohana M, El Ghannudi S, Morel O, Ohlmann P. Late Detection of Left Ventricular Dysfunction Using Two-Dimensional and Three-Dimensional Speckle-Tracking Echocardiography in Patients with History of Nonsevere Acute Myocarditis. J Am Soc Echocardiogr. 2017 Aug;30(8):756–62.

38. Goncalves A, Madureira A, Sousa C, Martins E, Macedo F, Melao F, et al. Global assessment of left ventricle longitudinal strain in patients after acute myocarditis: going further in left ventricular function. Eur Heart J [Internet]. 2013 Aug 1 [cited 2019 Mar 21];34(suppl\_1). Available from: https://dx.doi.org/10.1093/eurheartj/eht309.P3869

39. Haanen JB a. G, Carbonnel F, Robert C, Kerr KM, Peters S, Larkin J, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017 Jul 1;28(suppl\_4):iv119–42.

40. Liu D, Jenkins RW, Sullivan RJ. Mechanisms of Resistance to Immune Checkpoint Blockade. Am J Clin Dermatol. 2019 Feb;20(1):41–54.

**Figure Legends**

**Figure 1:**

**Title- Consort Flow Diagram of Cohort**

**Caption-** Consort flow diagram showing the cases from multicenter registry and controls from MGH with available TTE GLS. GLS= global longitudinal strain; ICI= immune checkpoint inhibitors; MGH= Massachusetts General Hospital; TTE= transthoracic echocardiogram.

**Figure 2:**

**Title- GLS among Cases and Controls**

**Caption- A-** Box plot graph of GLS among cases and controls pre-ICI showing lower values among cases compared to controls; **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 controls showing no change in GLS among controls on ICI who did not develop myocarditis; **D-** Box plot graph of GLS among cases during presentation with myocarditis and controls on ICI who did not develop myocarditis, showing lower GLS values among the cases compared to controls; **E-** Spaghetti plot graph of GLS among cases with follow-up values post discontinuation of ICI-therapy compared to 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 to controls, showing lower GLS among cases compared to controls 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 inhibitors; LVEF= left ventricular ejection fraction.

**Figure 3:**

**Title- Kaplan- Meier survival curves showing the association of MACE and GLS among Cases**

**Caption- 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 to 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 to GLS <16% (p<0.001). GLS= global longitudinal strain; LVEF= left ventricular ejection fraction; MACE= major adverse cardiac event.

**Figure 4:**

**Title- Central Illustration: GLS in ICI-myocarditis**

**Caption:** Central illustration showing the association of different GLS cut-offs and MACE among cases with reduced and preserved EF. NT-proBNP= N-terminal pro hormone B-type natriuretic peptide; ECG= electrocardiogram; EF= ejection fraction; GLS= global longitudinal strain; ICI= immune checkpoint inhibitors; MACE= major adverse cardiac event.

|  |  |  |  |
| --- | --- | --- | --- |
| **Table 1A: Description of cases and controls** | **Cases****(n=101)** | **Controls****(n=92)** | ***P Value*** |
|  |  |  |  |  |  |  |  |  |
| Age at start of ICI, years | 66±14 | 64±14 | 0.42 |
| Male | 74 (73) | 59 (64) | 0.17 |
| *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) | 0.19 |
| 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/m2 | 28±7 | 27±7 | 0.32 |
| *Primary cancer type* |  |  |  |
|  Head and neck | 6 (6) | 10 (11) | 0.22 |
|  Breast | 5 (5) | 0 | 0.06 |
|  Hodgkin’s lymphoma | 2 (2) | 2 (2) | 1.00 |
|  Melanoma | 41 (41) | 39 (42) | 0.80 |
|  Lung cancer | 16 (16) | 17 (19) | 0.70 |
|  Pancreatic | 2 (2) | 0 | 0.50 |
|  Renal cell carcinoma | 8 (8) | 1 (1) | 0.04 |
|  Glioblastoma | 1 (1) | 0 | 1.00 |
|  Other | 18 (18) | 13 (14) | 0.49 |
| *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 (%), unless otherwise indicated. \*Numbers given for values available. \*\*Chronic kidney disease = glomerular filtration rate <60 ml/min/1.73 m2. ICI = immune checkpoint inhibitors; CV = cardiovascular; COPD = chronic obstructive pulmonary disease; VEGF = vascular endothelial growth factor.  |

|  |  |  |  |
| --- | --- | --- | --- |
| **Table 1B: Baseline Cancer Demographics** | **Cases****(n=101)** | **Controls****(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 |
| Days of follow-up [IQR] | 175 [95, 352] | 283 [101, 514] | 0.02 |
| Other immune side effects during treatment |  |  |  |
|  No other immune side effects | 55 (54) | 35 (38) | 0.02 |
|  Hypophysitis/pituitary/adrenal | 5 (5) | 4 (5) | 1.00 |
|  Pneumonitis | 29 (29) | 14 (15) | 0.02 |
|  Hepatitis | 7 (7) | 5 (5) | 0.67 |
|  Colitis | 10 (10) | 11 (12) | 0.65 |
|  Dermatitis | 6 (6) | 1 (1) | 0.12 |
|  Neurological | 10 (10) | 2 (2) | 0.03 |
|  Gastritis | 3 (3) | 4 (4) | 0.71 |
| Values are n (%) or mean ± SD. All cases with ICI-associated myocarditis had ICI permanently discontinued. †Within monotherapy group. anti-CTLA4 = anti-cytotoxic T-lymphocyte-associated protein 4; anti-PD1 = anti-programmed cell death protein 1; anti-PDL1 = anti-programmed death-ligand 1; ICI = immune checkpoint inhibitors. |

|  |  |  |  |
| --- | --- | --- | --- |
| **Table 2A: Description of cases and controls with pre-ICI TTEs** |  **Cases** **(n=30)** |  **Controls** **(n=42)** | ***P Value*** |
|  |  |  |  |
| Pre- ICI treatment echocardiogram |  |  |  |
|  LVEF, %  | 61±7 | 65±9 | 0.03 |
|  LVIDD, mm  | 48±5 | 45±6 | 0.08 |
|  LVEDV, mls | 97±50 | 113±44 | 0.23 |
|  LVESV, mls | 50±11 | 56±26 | 0.34 |
|  SV, mls | 47±24 | 58±25 | 0.33 |
|  CO, L/min | 4.0±2.5 | 4.7±2.0 | 0.51 |
|  Max LA volumes, mls\* | 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 ARB | 4 (27) | 10 (24) | 1.00 |
|  Calcium-channel blocker | 2 (13) | 6 (14) | 1.00 |
| Values are mean ± SD or n (%), unless otherwise indicated. \*Values given for those available. LVEF = left ventricular ejection fraction; LVIDD = left ventricular internal dimension diameter; LVEDV= left ventricular end diastolic volume; LVESV= left ventricular end systolic volume; SV=stroke volume; CO= cardiac output; CV = cardiovascular; ECG = electrocardiogram; ICI = immune checkpoint inhibitors; ACE = Angiotensin Converting Enzyme; ARB = Angiotensin Receptor Blockers  |

|  |  |  |  |
| --- | --- | --- | --- |
| **Table 2B: TTE variables among cases during ICI-myocarditis and controls during ICI therapy** |  **Cases** **(n=101)** |  **Controls** **(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, mls | 112±43 | 115±34 | 0.67 |
|  LVESV, mls | 65±36 | 55±21 | 0.07 |
|  SV, mls | 46±19 | 61±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 |
|  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%, n (%) | \*21 (71) | \*3 (21) | 0.004 |
| Values are mean ± SD or n (%), unless otherwise indicated. Thirty of the 101 cases, and fourteen of the 50 controls with a TTE during ICI, had a TTE prior to commencing ICI therapy. \*Values given for those available. LVEF = left ventricular ejection fraction; LVIDd = left ventricular internal diameter in diastole; LVIDs= left ventricular internal dimension in systole; LVEDV= left ventricular end diastolic volume; LVESV= left ventricular end systolic volume; SV=stroke volume; CO= cardiac output; GLS= global longitudinal strain. |

|  |  |  |  |
| --- | --- | --- | --- |
| **Table 3: Multivariable Model** | **Hazard Ratio** | **95% CI** | ***P Value*** |
| *Global Longitudinal Strain:* |  |  |  |  |
| 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 LVEF. Complete multivariable model results are listed in supplementary table 1. |