## Title
Long-Term Implications of Abnormal Left Ventricular Strain During Sepsis.



## Journal
Critical Care Medicine, 49(4)

## ISSN
0090-3493

## Authors
Beesley, Sarah J
Sorensen, Jeff
Walkey, Allan J
et al.

## Publication Date
2021-04-01

## DOI
10.1097/ccm.0000000000004886

Peer reviewed

HHS Public Access

Author manuscript

*Crit Care Med*. Author manuscript; available in PMC 2022 April 01.

Published in final edited form as:

*Crit Care Med*. 2021 April 01; 49(4): e444–e453. doi:10.1097/CCM.0000000000004886.

# Long-term Implications of Abnormal Left Ventricular Strain during Sepsis

**Sarah J. Beesley, MD MS**[1,2], **Jeff Sorensen, MStat**[1], **Allan J. Walkey, MD**[3], **Joseph E. Tonna, MD,MS**[4,5], **Michael J. Lanspa, MD MS**[1], **Ellie Hirshberg, MD**[1,2,6], **Colin K. Grissom, MD**[1,2], **Benjamin D. Horne, PhD MStat MPH**[7,8], **Rebecca Burk, MD**[1,2], **Theodore P. Abraham, MD**[9], **Robert Paine, MD**[2], **Samuel M. Brown, MD MS FCCM FASE**[1,2]

[1]Pulmonary Division, Intermountain Medical Center, Salt Lake City, UT

[2]Pulmonary Division, University of Utah School of Medicine, Salt Lake City, UT

[3]Pulmonary Division, Boston University, Boston, MA

[4]Division of Cardiothoracic Surgery, University of Utah School of Medicine, Salt Lake City, UT

[5]Division of Emergency Medicine, University of Utah School of Medicine, Salt Lake City, UT

[6]Department of Pediatrics, University of Utah School of Medicine, Salt Lake City, UT

[7]Intermountain Medical Center Heart Institute, Intermountain Healthcare, Salt Lake City, UT

[8]Division of Cardiovascular Medicine, Department of Medicine, Stanford University, Stanford, CA

[9]Division of Cardiology, University of California San Francisco, San Francisco, CA

## Abstract

**Objectives—**Septic cardiomyopathy (SCM) develops frequently in patients with sepsis and likely increases short-term mortality. However, whether SCM is associated with long-term outcomes after sepsis is unknown. We investigated whether septic patients with SCM have worse long-term outcomes than septic patients without SCM.

**Design—**Retrospective cohort study

**Patient and Setting—**We studied a cohort of adult patients with sepsis admitted to an intensive care unit (ICU).

Corresponding author: Sarah J Beesley, MD MS, Shock Trauma Intensive Care Unit, 5121 South Cottonwood Street, Murray, UT 84107, Telephone: 801-507-6556, Fax: 801-507-5578, Sarah.beesley@imail.org.

CONTRIBUTORS

SJB, RP, JET, CG, SMB designed the study. SJB, SMB, JET, RP and JS analyzed and interpreted the data. SJB drafted the report, and all other authors revised it. All authors gave final approval of the report to be published.

Conflicts of Interest: None.

The Intermountain Institutional Review Board approved this study with waiver of informed consent.

**Copyright Form Disclosure:** Dr. Walkey received funding from UptoDate. Dr. Tonna's institution received funding from National Heart, Lung, and Blood Institute (NHLBI), NCATS, and LivaNova; he received funding from Philips Healthcare; and he received support for article research from National Institutes of Health (NIH). Dr. Burk received funding from Intermountain Research and Medical Foundation. Dr. Paine's institution received funding from NHLBI and the Department of Veterans Affairs. The remaining authors have disclosed that they do not have any potential conflicts of interest.

**Measurements—**Left ventricular global longitudinal systolic strain (LV GLS) was our primary measure of SCM. We employed a suite of multivariable survival analyses to explore linear and non-linear associations between LV GLS and major adverse cardiovascular events (MACE), which included death, stroke and myocardial infarction. Our primary outcome was MACE through 24 months after ICU discharge.

**Main Results—**Among 290 study patients, median LV GLS was −16.8% (IQI −20.4% to −12.6%), and 38.3% (n=111) of patients experienced a MACE within 24 months after discharge. On our primary, linear analysis, there was a trend (p=0.08) toward association between LV GLS and MACE (OR 1.03, CI <1 to 1.07). On our non-linear analysis, the association was highly significant (p<0.001) with both high and low LV GLS associated with MACE among patients with preexisting cardiac disease. This association was pronounced among patients who were younger (age < 65 years) and had Charlson comorbidity index > 5.

**Conclusions—**Among patients with sepsis and preexisting cardiac disease who survived to ICU discharge, LV GLS demonstrated a U-shaped association with cardiovascular outcomes through 24 months. The relationship was especially strong among younger patients with more comorbidities. These observations are likely of use to design of future trials.

### Keywords

sepsis; cardiomyopathy; septic cardiomyopathy; cardiovascular event

## Introduction

Sepsis is a serious condition in which infection leads to a host response that is sufficiently dysregulated as to cause organ dysfunction. This dysfunction may lead to disability and death.[1–3] Cardiac dysfunction develops in 40–70% of adult patients with sepsis or septic shock.[4–6] While cardiac dysfunction in sepsis can take many forms—including systolic and diastolic dysfunction of all cardiac chambers—we focus here on intrinsic systolic dysfunction of the left ventricle, what we and others term septic cardiomyopathy (SCM).[7–9] Early evidence suggests an association between SCM and early mortality in sepsis.[10] The relationship between SCM in the ICU and long-term major adverse cardiovascular events (MACE), such as stroke or myocardial infarction, is unknown.

Traditionally, SCM has been understood as an acute, transient cardiac dysfunction (affecting both ventricles in their systolic and diastolic phases[7]) that resolves within days to a week.[11] Left ventricular (LV) global longitudinal systolic strain (GLS), a measure of the deformation of the myocardium, has been introduced and validated as a replacement for LV ejection fraction (LVEF) for assessment of LV function because it is substantially less dependent on loading conditions.[12, 13] In sepsis specifically, LV GLS has been demonstrated to be a more sensitive parameter than LVEF for diagnosing LV dysfunction.[8, 13–16] In parallel, increased risk for cardiovascular complications and/or death has been identified for septic patients in the months and years after hospital discharge.[17–20] Whether the degree of LV dysfunction itself is associated these long-term cardiovascular and vital status outcomes is not known.

To address this gap, we studied a retrospective cohort of adult patients with sepsis and an echocardiogram performed within the first 72 hours of ICU admission to determine whether SCM, as measured using LV GLS, was associated with long-term major cardiovascular events, including death.

## Methods

Participants included patients at least 18 years old with severe sepsis or septic shock (using the then-current SEPSIS-2 definition[21]) admitted to a study ICU between October 2012 and November 2015. Patients had clinically suspected infection, two or more systemic inflammatory response syndrome criteria and had either shock (systolic blood pressure <90 mmHg despite intravenous fluid challenge of ≥ 20 ml/kg or infusion of vasopressors) or severe sepsis (lactate > 4 mmol/L).[21, 22] Exclusion criteria included known pregnancy, primary diagnosis of acute coronary syndrome or major cardiac dysrhythmia, or alternative diagnosis for systemic inflammatory response syndrome (e.g., trauma, anaphylaxis, hemorrhage). Comorbidities and risk factors for cardiac disease were extracted from the electronic medical record,[23] as were demographic and clinical data, including APACHE II[24], Elixhauser score[25], Charlson comorbidity index[26], source of infection, vasopressor administration, and need for mechanical ventilation or renal replacement therapy.

The relationship between abnormal cardiac contractility and short-term mortality has already been established,[10, 27] which allows us to pose a related but distinct question. Specifically, we are interested in long-term outcomes among patients discharged from the ICU, after presumed resolution of the acute critical illness. These patients, if they suffer long-term cardiovascular complications, may be candidates for, e.g., trials of cardioprotective medications initiated at ICU discharge. Given prior work on short-term outcomes and our interest in the fate of ICU survivors, we excluded patients who died at or before ICU discharge.

The majority (>75%) of patients with severe sepsis or septic shock admitted to the study ICU undergo clinical echocardiography within 24 hours of ICU admission per a standard sepsis protocol; all study patients had an echocardiogram within 24 hours of ICU admission. From clinical echocardiograms, we measured LVEF, LV GLS, and regional wall motion abnormalities (RWA). Based on established precedent in septic patients, abnormal strain was defined as LV GLS >−17% for purposes of illustration in survival curves.[27, 28] Left ventricular GLS was measured using semi-automated speckle tracking on the Image-Arena platform (Tomtec Imaging Systems, Unterschleissheim, Germany). Strain measurements were performed by experienced sonographers or Level-II echocardiographer physicians using apical two- and four- chamber views and values were averaged among views. Patients whose echocardiographic images had poor image quality were excluded. Unrelated results from this study cohort related to short-term outcomes have been published elsewhere.[13, 27, 29]

Time from ICU discharge to MACE was collected until 24 months after hospital discharge. Our definition of MACE included death, stroke, or myocardial infarction,[30, 31] based on

established algorithms for International Classification of Disease coding (see appendix 1) and prior studies.[32, 33] Mortality was determined from the Intermountain death record, which incorporates vital status from hospital and Utah state records, and from the US Social Security death master file.

Our primary interest was the relationship between LV GLS and MACE at 24 months. To improve the accuracy of this analysis, we controlled for key covariates. Starting with 61 candidate covariates (see eTable 1), we used machine learning (a technique called XGboost; details in online supplement) to define the most important covariates. In our primary prespecified analysis, we used Cox proportional hazards regression to measure the association between GLS and MACE, adjusting for the covariates identified by machine learning.

Prior work has assumed a linear relationship between LV GLS and adverse cardiovascular outcomes, which motivated our use of linear models.[34] Given the possibility that the relationship between LV GLS and MACE is non-linear among septic patients, however, and to explore the possibility that the association between LV GLS and MACE varies based on the value of other variables, we performed a prespecified sensitivity analysis using nonlinear models in the generalized additive model (GAM) framework (details in the online supplement). Finally, we repeated the same modeling steps for time to death separately.

In exploratory analyses intended to assess whether preexisting cardiac morbidity affected any observed associations, we included baseline chronic heart failure and/or myocardial infarction (as defined by the Elixhauser and Charlson sub-scores[25]). Statistical analyses were performed in R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).[35]

The Intermountain Institutional Review Board approved this study with waiver of informed consent.

## Results

The parent cohort included 393 sepsis patients; 59 of them died at or before ICU discharge and were thus excluded from analysis. Poor image quality prevented LV GLS measurement in 44 patients. We thus included 290 patients in our analytic dataset. We report demographic and clinical information in Table 1 (see also eTable 2 in the online data supplement). On average, LV GLS was abnormal: median LV GLS was −16.8% (IQI −20.4% to −12.6%). Median LVEF was 61.4% (IQI 53.8% to 68%). Regional wall motion abnormalities were noted in only 26 (9%) patients, although approximately half (n=148) had a history of myocardial infarction or chronic heart failure. Septic shock was defined by receipt of vasopressors: 113 patients (39%) had septic shock; median LV GLS for patients with severe sepsis vs. septic shock was similar (−16.6 vs. −17.0, p=0.70). The primary outcome (MACE after ICU discharge) occurred in 111 (38.3%) patients by 24 months (96 deaths, 7 myocardial infarctions, and 8 strokes). Median time to MACE was 112 (IQI 19.5 to 354) days; 3 patients experienced MACE prior to hospital discharge (all deaths).

The machine learning variable selection (see eFigure 1a and Supplemental Results) identified LV GLS, Charlson score, organ failure days at 28 days, ventilator free days in ICU, hemoglobin on ICU admit, Elixhauser score, and age as the most important variables. The proportional hazards regression suggested a possible association between GLS and MACE (*HR* 1.03 for each 1-point increase in LV GLS, CI <1.00 to 1.07, $p$=0.08). A Kaplan Meier plot (Figure 1) of time to MACE, based on whether patients were above or below the LV GLS threshold of −17%, suggested consistent separation between the two groups. When restricted to death as the outcome, the association was not significant (*HR* 1.02, *CI* 0.99 to 1.06, $p$=0.22).

In the secondary analysis exploring non-linear associations, LV GLS was significantly associated with MACE ($p$<0.001) and death ($p$<0.001). The marginal effect plots (Figure 2) demonstrated a U-shaped association between LV GLS and MACE: both high and low values of LV GLS were associated with greater risk of MACE. The association between LV GLS and MACE was especially pronounced among younger (age <65 years) patients with more comorbidities (Charlson Comorbidity Index >5).

In the sensitivity analysis exploring the role of preexisting cardiac disease, the U-shaped relationship between LV GLS and MACE was clearly present among patients with either chronic heart failure or myocardial infarction. The relationship was absent among patients with neither chronic heart failure nor myocardial infarction (Figure 3).

## Discussion

In a large single-center cohort of septic patients with early formal echocardiograms performed, we identified a substantial, non-linear association between a non-invasive marker of septic cardiomyopathy (LV GLS) and long-term cardiovascular outcomes. Multiple studies summarized in a meta-analysis demonstrate that abnormalities in LV GLS are associated with hospital mortality.[10] We asked an important, complementary question: among ICU survivors, does evidence of SCM during the ICU stay predict subsequent cardiovascular complications? We identified an association between LV GLS and long-term cardiovascular outcomes among ICU survivors. Ours is the first observation to our knowledge suggesting that the relationship between LV GLS and clinical outcomes is U-shaped rather than linear and to suggest that the effects may be largely if not wholly restricted to patients with preexisting cardiac disease. These findings appear to represent important new insights into long-term outcomes after sepsis and may identify a group of patients suitable for targeted clinical trials of cardioprotective agents (e.g., anti-platelet agents or beta-adrenergic antagonists).

Our observations contribute to evolving literature regarding the heightened risk of cardiovascular complications among sepsis survivors.[18, 31, 36] The mechanisms for this period of elevated risk are not yet clear, but may relate to age and antecedent cardiac disease in combination with an inflammatory-infectious insult.[17, 37] Our observations suggest the possibility that there may be cardiac-specific abnormalities that play a role in this heightened vulnerability to cardiovascular complications. The observed effect is most prominent in younger patients with a greater number of comorbidities. We hypothesize that the U-shaped

relationship may reflect two distinct processes. First, patients with higher than normal contractility may be experiencing a more severe acute illness associated with high catecholamine levels and severe afterload reduction, both of which may induce artificially high contractility. Second, patients with lower than normal contractility may be suffering more directly from cardiac toxicity or exacerbation of preexisting cardiac disease. The U-shaped relationship may thus identify two groups of patients who may benefit from targeted efforts to prevent cardiovascular complications among ICU survivors.

We acknowledge the possibility that our findings reflect the implications of baseline cardiac dysfunction rather than a specific effect of septic cardiomyopathy. Although neither history of chronic heart failure nor myocardial infarction was identified as an important predictor of MACE, our regression models suggested that the observed relationship was restricted to those with a history of cardiac dysfunction. Whether acute or chronic abnormalities in LV GLS underlie the long-term effects we observed is not clear. A two-hit mechanism is possible, whereby preexisting cardiac dysfunction makes a patient more susceptible to sepsis-associated LV dysfunction. It may also be that the higher risk-adjusted hazard of MACE among patients with more negative LV GLS represents greater acute severity of illness though the association between hyperkinesis and MACE persisted even after control for severity of illness measures like APACHE II and persistence of organ dysfunction. Future prospective studies should dissect the contributions of both acute and chronic cardiac dysfunction, including the possible relevance of physiological stress associated with hyperkinesis, to clinical outcomes. Our observations also contribute to knowledge in this area, emphasizing the importance of measuring and controlling for baseline cardiac function, as well as age and baseline comorbidities, in studies of cardiac dysfunction in sepsis. Similarly, other studies evaluating mortality after sepsis and ICU admission have also identified this group of patients as bearing increased risk for mortality.[38, 39]

Although our cohort size is large compared to many other studies in critical care echocardiography, sample size nevertheless limits both the precision of our estimates and our power to explore heterogeneity in the association between LV GLS and MACE.[40] We note that non-mortality constituents of MACE were relatively uncommon in our cohort; much of the effect was driven by post-discharge death. We are limited by the lack of specific information on cause of death. An extended definition of MACE to include acute coronary syndrome and heart failure exacerbations could be included in future work. Although the study ICUs routinely perform clinical echocardiograms on septic patients admitted to the ICU, selection bias may still distort our findings. The nature of such selection bias would likely be toward more severely ill patients who are thus likely enriched somewhat for septic cardiomyopathy. We did not include a non-septic cohort which limits our ability to compare septic to non-septic patients; however, our core observation relates to LV GLS during sepsis to longer term outcomes for this population. Additionally, we did not include serial echocardiogram measurements that might further add to the understanding of the heart in sepsis and reduce bias from missingness of echo data in the few cases where the LV GLS was not able to be determined from the images. Our approach to missingness in these cases was case wise deletion. We also acknowledge that we did not record information on mean airway pressure or positive end expiratory pressure among patients undergoing mechanical

ventilation, which may have influenced our estimates. However, LV GLS is relatively insensitive to changes in ventilator settings.

Our observations are hypothesis-generating and point to several lines of future research rather than immediate clinical application. First, follow-up cardiovascular evaluations should be considered among sepsis survivors, especially those who experienced extremes of LV GLS during the ICU admission. Second, prospective clinical trials of cardioprotection based on abnormal LV GLS during sepsis—especially among younger patients with prior cardiac comorbidity—may be indicated. Such therapies might include beta blockers, ACE inhibitors, or anti-platelet agents. Third, mechanistic biomarkers both during and at the conclusion of an ICU admission for sepsis may be fruitful topics for research. Fourth, additional echocardiographic measures beyond LV GLS may also be associated with long-term complications. In this current analysis, we did not repeat prior studies evaluating the associations between LVEF and LV GLS and, while considered as a candidate variable, LVEF was not significantly associated with MACE at 24 months.

## Conclusion

Among survivors of an ICU admission for sepsis, LV GLS appears to be associated with long-term adverse outcomes, with both high and low values associated with worse outcomes. The association is most prominent among younger patients with comorbidities.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgements:

We acknowledge the time and support of our patients, the study participants, and their family members. We also appreciate the work of our Intermountain Research team which includes our excellent sonographer Troy Olsen and our dedicated research coordinators Katie Brown and Naresh Kumar.

Funding and support

The research reported in this publication was supported (in part or in full) by the National Center for Advancing Translational Sciences of the National Institutes of Health under Award Number UL1TR001067. Intermountain Research and Medical Foundation providing funding for the assembly of the study cohort. JET was supported by a career development award (K23HL141596) from the National Heart, Lung, And Blood Institute (NHLBI) of the National Institutes of Health (NIH). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. None of the funding sources were involved in the design or conduct of the study, collection, management, analysis or interpretation of the data, or preparation, review or approval of the manuscript.

## References

1. Angus DC, van der Poll T: Severe sepsis and septic shock. N Engl J Med 2013, 369(9):840–851. [PubMed: 23984731]
2. Liu V, Escobar GJ, Greene JD, Soule J, Whippy A, Angus DC, Iwashyna TJ: Hospital deaths in patients with sepsis from 2 independent cohorts. JAMA 2014, 312(1):90–92. [PubMed: 24838355]
3. Gaieski DF, Edwards JM, Kallan MJ, Carr BG: Benchmarking the incidence and mortality of severe sepsis in the United States. Crit Care Med 2013, 41(5):1167–1174. [PubMed: 23442987]

4. Romero-Bermejo FJ, Ruiz-Bailen M, Gil-Cebrian J, Huertos-Ranchal MJ: Sepsis-induced cardiomyopathy. Current cardiology reviews 2011, 7(3):163–183. [PubMed: 22758615]
5. Sato R, Nasu M: A review of sepsis-induced cardiomyopathy. Journal of intensive care 2015, 3:48. [PubMed: 26566443]
6. Pulido JN, Afessa B, Masaki M, Yuasa T, Gillespie S, Herasevich V, Brown DR, Oh JK: Clinical spectrum, frequency, and significance of myocardial dysfunction in severe sepsis and septic shock. Mayo Clinic proceedings 2012, 87(7):620–628. [PubMed: 22683055]
7. Beesley SJ, Weber G, Sarge T, Nikravan S, Grissom CK, Lanspa MJ, Shahul S, Brown SM: Septic Cardiomyopathy. Crit Care Med 2018, 46(4):625–634. [PubMed: 29227368]
8. Palmieri V, Innocenti F, Guzzo A, Guerrini E, Vignaroli D, Pini R: Left Ventricular Systolic Longitudinal Function as Predictor of Outcome in Patients With Sepsis. Circulation Cardiovascular imaging 2015, 8(11):e003865; discussion e003865.
9. Martin L, Derwall M, Al Zoubi S, Zechendorf E, Reuter DA, Thiemermann C, Schuerholz T: The Septic Heart: Current Understanding of Molecular Mechanisms and Clinical Implications. Chest 2018.
10. Sanfilippo F, Corredor C, Fletcher N, Tritapepe L, Lorini FL, Arcadipane A, Vieillard-Baron A, Cecconi M: Left ventricular systolic function evaluated by strain echocardiography and relationship with mortality in patients with severe sepsis or septic shock: a systematic review and meta-analysis. Crit Care 2018, 22(1):183. [PubMed: 30075792]
11. Parker MM, Shelhamer JH, Bacharach SL, Green MV, Natanson C, Frederick TM, Damske BA, Parrillo JE: Profound but reversible myocardial depression in patients with septic shock. Ann Intern Med 1984, 100(4):483–490. [PubMed: 6703540]
12. Stanton T, Leano R, Marwick TH: Prediction of all-cause mortality from global longitudinal speckle strain: comparison with ejection fraction and wall motion scoring. Circulation Cardiovascular imaging 2009, 2(5):356–364. [PubMed: 19808623]
13. Lanspa MJ, Pittman JE, Hirshberg EL, Wilson EL, Olsen T, Brown SM, Grissom CK: Association of left ventricular longitudinal strain with central venous oxygen saturation and serum lactate in patients with early severe sepsis and septic shock. Crit Care 2015, 19:304. [PubMed: 26321626]
14. Dalla K, Hallman C, Bech-Hanssen O, Haney M, Ricksten SE: Strain echocardiography identifies impaired longitudinal systolic function in patients with septic shock and preserved ejection fraction. Cardiovasc Ultrasound 2015, 13:30. [PubMed: 26134971]
15. Ng PY, Sin WC, Ng AK, Chan WM: Speckle tracking echocardiography in patients with septic shock: a case control study (SPECKSS). Critical care (London, England) 2016, 20(1):145.
16. Shahul S, Gulati G, Hacker MR, Mahmood F, Canelli R, Nizamuddin J, Mahmood B, Mueller A, Simon BA, Novack V et al.: Detection of Myocardial Dysfunction in Septic Shock: A Speckle-Tracking Echocardiography Study. Anesth Analg 2015, 121(6):1547–1554. [PubMed: 26397444]
17. Ou SM, Chu H, Chao PW, Lee YJ, Kuo SC, Chen TJ, Tseng CM, Shih CJ, Chen YT: Long-Term Mortality and Major Adverse Cardiovascular Events in Sepsis Survivors. A Nationwide Population-based Study. Am J Respir Crit Care Med 2016, 194(2):209–217. [PubMed: 26808711]
18. Yende S, Linde-Zwirble W, Mayr F, Weissfeld LA, Reis S, Angus DC: Risk of cardiovascular events in survivors of severe sepsis. Am J Respir Crit Care Med 2014, 189(9):1065–1074. [PubMed: 24456535]
19. Shankar-Hari M, Rubenfeld GD: Understanding Long-Term Outcomes Following Sepsis: Implications and Challenges. Curr Infect Dis Rep 2016, 18(11):37. [PubMed: 27709504]
20. Prescott HC, Langa KM, Liu V, Escobar GJ, Iwashyna TJ: Increased 1-year healthcare use in survivors of severe sepsis. Am J Respir Crit Care Med 2014, 190(1):62–69. [PubMed: 24872085]
21. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, Cohen J, Opal SM, Vincent JL, Ramsay G: 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med 2003, 31(4):1250–1256. [PubMed: 12682500]
22. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM et al.: The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016, 315(8):801–810. [PubMed: 26903338]

23. Taylor GS, Muhlestein JB, Wagner GS, Bair TL, Li P, Anderson JL: Implementation of a computerized cardiovascular information system in a private hospital setting. American heart journal 1998, 136(5):792–803. [PubMed: 9812073]
24. Knaus WA, Draper EA, Wagner DP, Zimmerman JE: APACHE II: a severity of disease classification system. Crit Care Med 1985, 13(10):818–829. [PubMed: 3928249]
25. Pine M, Jordan HS, Elixhauser A, Fry DE, Hoaglin DC, Jones B, Meimban R, Warner D, Gonzales J: Enhancement of claims data to improve risk adjustment of hospital mortality. JAMA 2007, 297(1):71–76. [PubMed: 17200477]
26. Charlson ME, Pompei P, Ales KL, MacKenzie CR: A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. Journal of chronic diseases 1987, 40(5):373–383. [PubMed: 3558716]
27. Lanspa MJ, Shahul S, Hersh A, Wilson EL, Olsen TD, Hirshberg EL, Grissom CK, Brown SM: Associations among left ventricular systolic function, tachycardia, and cardiac preload in septic patients. Annals of intensive care 2017, 7(1):17. [PubMed: 28213737]
28. Boissier F, Razazi K, Seemann A, Bedet A, Thille AW, de Prost N, Lim P, Brun-Buisson C, Mekontso Dessap A: Left ventricular systolic dysfunction during septic shock: the role of loading conditions. Intensive Care Med 2017, 43(5):633–642. [PubMed: 28204860]
29. Lanspa MJ, Gutsche AR, Wilson EL, Olsen TD, Hirshberg EL, Knox DB, Brown SM, Grissom CK: Application of a simplified definition of diastolic function in severe sepsis and septic shock. Crit Care 2016, 20(1):243. [PubMed: 27487776]
30. Smeeth L, Thomas SL, Hall AJ, Hubbard R, Farrington P, Vallance P: Risk of myocardial infarction and stroke after acute infection or vaccination. N Engl J Med 2004, 351(25):2611–2618. [PubMed: 15602021]
31. Corrales-Medina VF, Alvarez KN, Weissfeld LA, Angus DC, Chirinos JA, Chang CC, Newman A, Loehr L, Folsom AR, Elkind MS et al.: Association between hospitalization for pneumonia and subsequent risk of cardiovascular disease. JAMA 2015, 313(3):264–274. [PubMed: 25602997]
32. Muhlestein JB, Horne BD, Bair TL, Li Q, Madsen TE, Pearson RR, Anderson JL: Usefulness of in-hospital prescription of statin agents after angiographic diagnosis of coronary artery disease in improving continued compliance and reduced mortality. Am J Cardiol 2001, 87(3):257–261. [PubMed: 11165956]
33. Horne BD, Muhlestein JB, Bhandary D, Hoetzer GL, Khan ND, Bair TL, Lappe DL: Clinically feasible stratification of 1-year to 3-year post-myocardial infarction risk. Open heart 2018, 5(1):e000723.
34. Krishnasamy R, Isbel NM, Hawley CM, Pascoe EM, Burrage M, Leano R, Haluska BA, Marwick TH, Stanton T: Left Ventricular Global Longitudinal Strain (GLS) Is a Superior Predictor of All-Cause and Cardiovascular Mortality When Compared to Ejection Fraction in Advanced Chronic Kidney Disease. PLoS One 2015, 10(5):e0127044.
35. R Development Core Team: R: A Language and Environment for Statistical Computing. In. Vienna, Austria: R Foundation for Statistical Computing; 2014.
36. Vallabhajosyula S, Jentzer JC, Geske JB, Kumar M, Sakhuja A, Singhal A, Poterucha JT, Kashani K, Murphy JG, Gajic O et al.: New-Onset Heart Failure and Mortality in Hospital Survivors of Sepsis-Related Left Ventricular Dysfunction. Shock 2018, 49(2):144–149. [PubMed: 28727607]
37. Corrales-Medina VF, Musher DM, Wells GA, Chirinos JA, Chen L, Fine MJ: Cardiac complications in patients with community-acquired pneumonia: incidence, timing, risk factors, and association with short-term mortality. Circulation 2012, 125(6):773–781. [PubMed: 22219349]
38. Gayat E, Cariou A, Deye N, Vieillard-Baron A, Jaber S, Damoisel C, Lu Q, Monnet X, Rennuit I, Azoulay E et al.: Determinants of long-term outcome in ICU survivors: results from the FROG-ICU study. Crit Care 2018, 22(1):8. [PubMed: 29347987]
39. Prescott HC, Osterholzer JJ, Langa KM, Angus DC, Iwashyna TJ: Late mortality after sepsis: propensity matched cohort study. BMJ 2016, 353:i2375. [PubMed: 27189000]
40. Kent DM, Rothwell PM, Ioannidis JP, Altman DG, Hayward RA: Assessing and reporting heterogeneity in treatment effects in clinical trials: a proposal. Trials 2010, 11:85. [PubMed: 20704705]

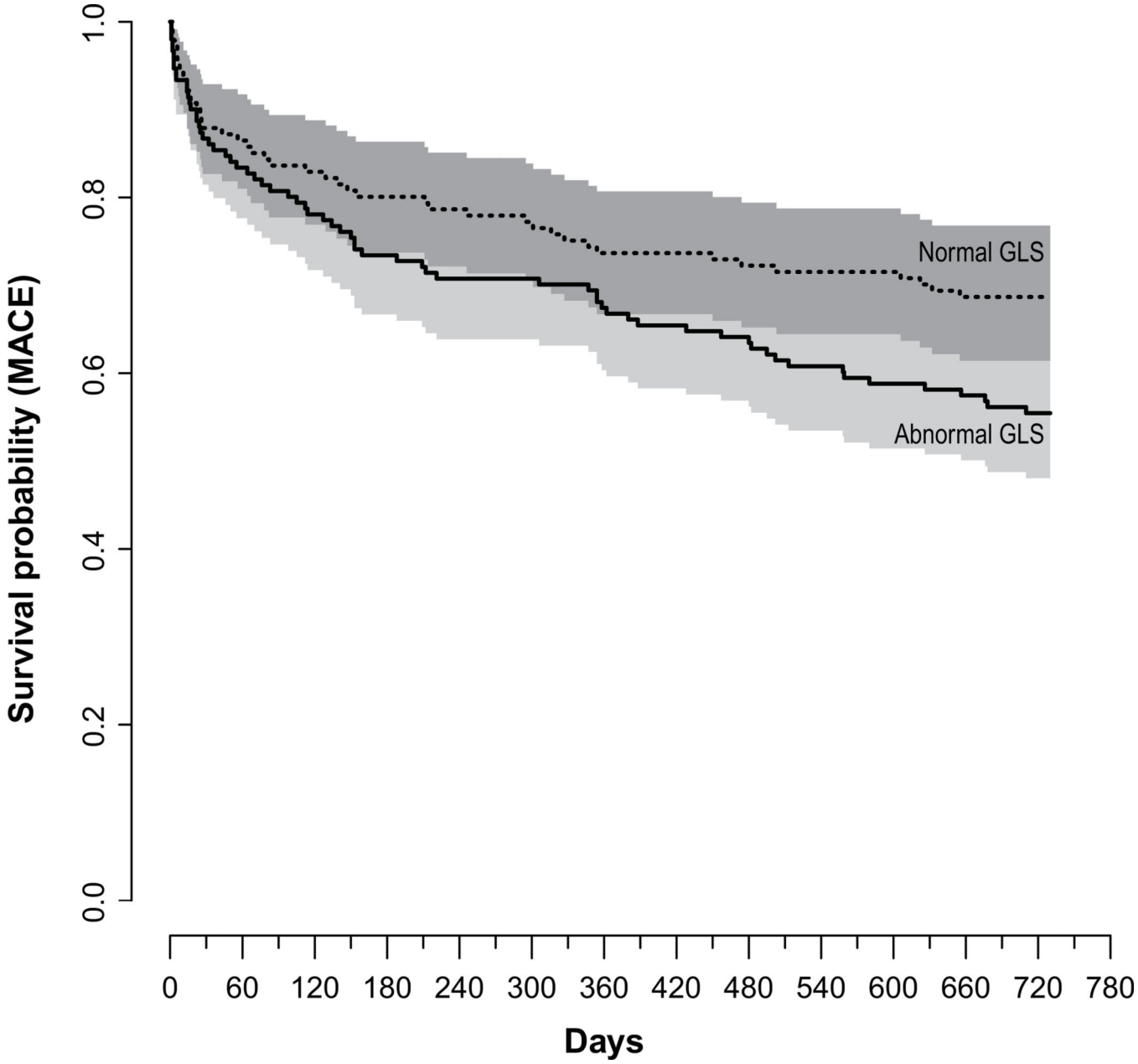


**Figure 1. Kaplan Meier plot of time to MACE based on normal vs abnormal GLS (abnormal GLS >−17)**

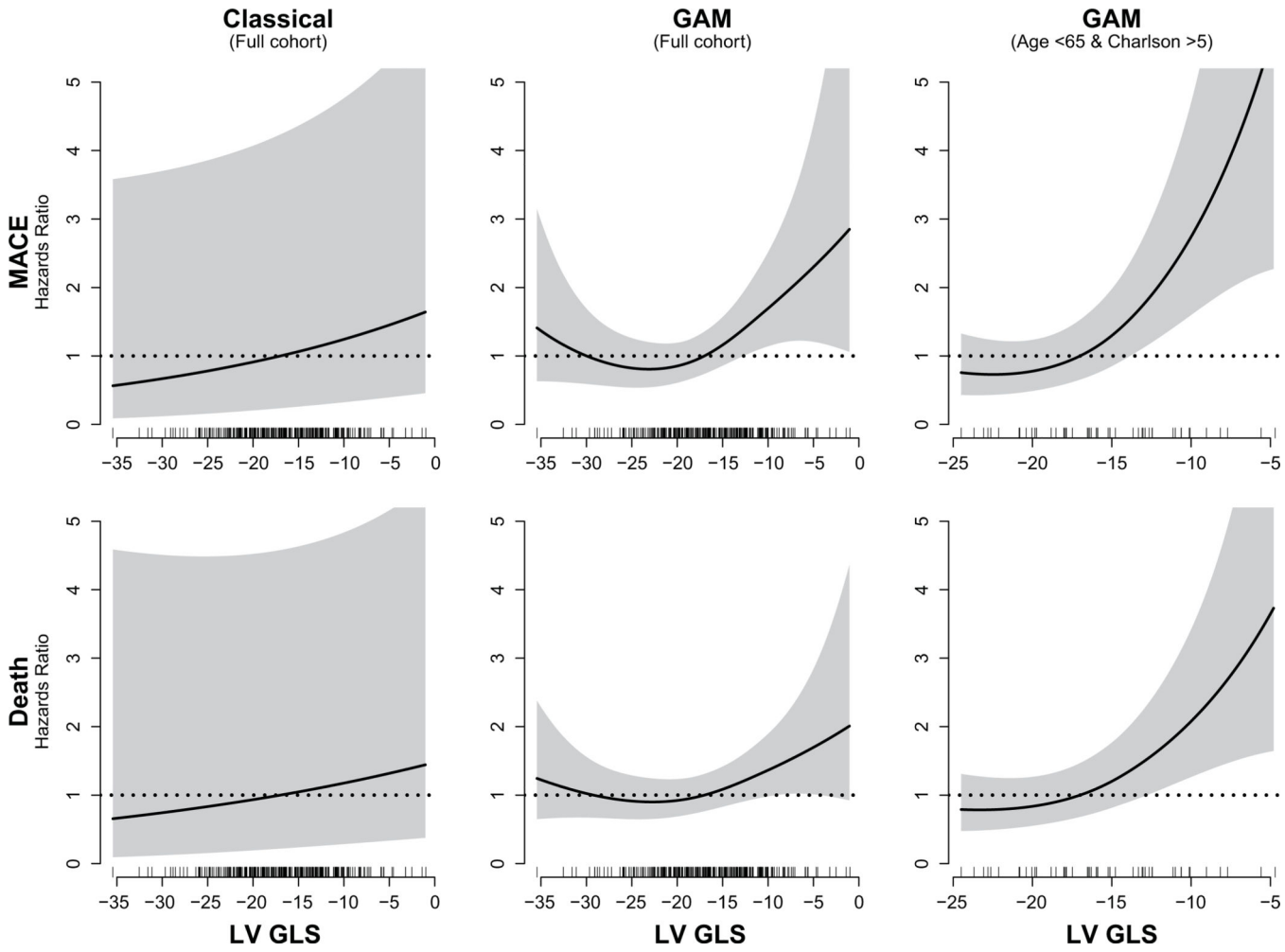


**Figure 2. Marginal Effect plot for MACE and Death of LVGLS**

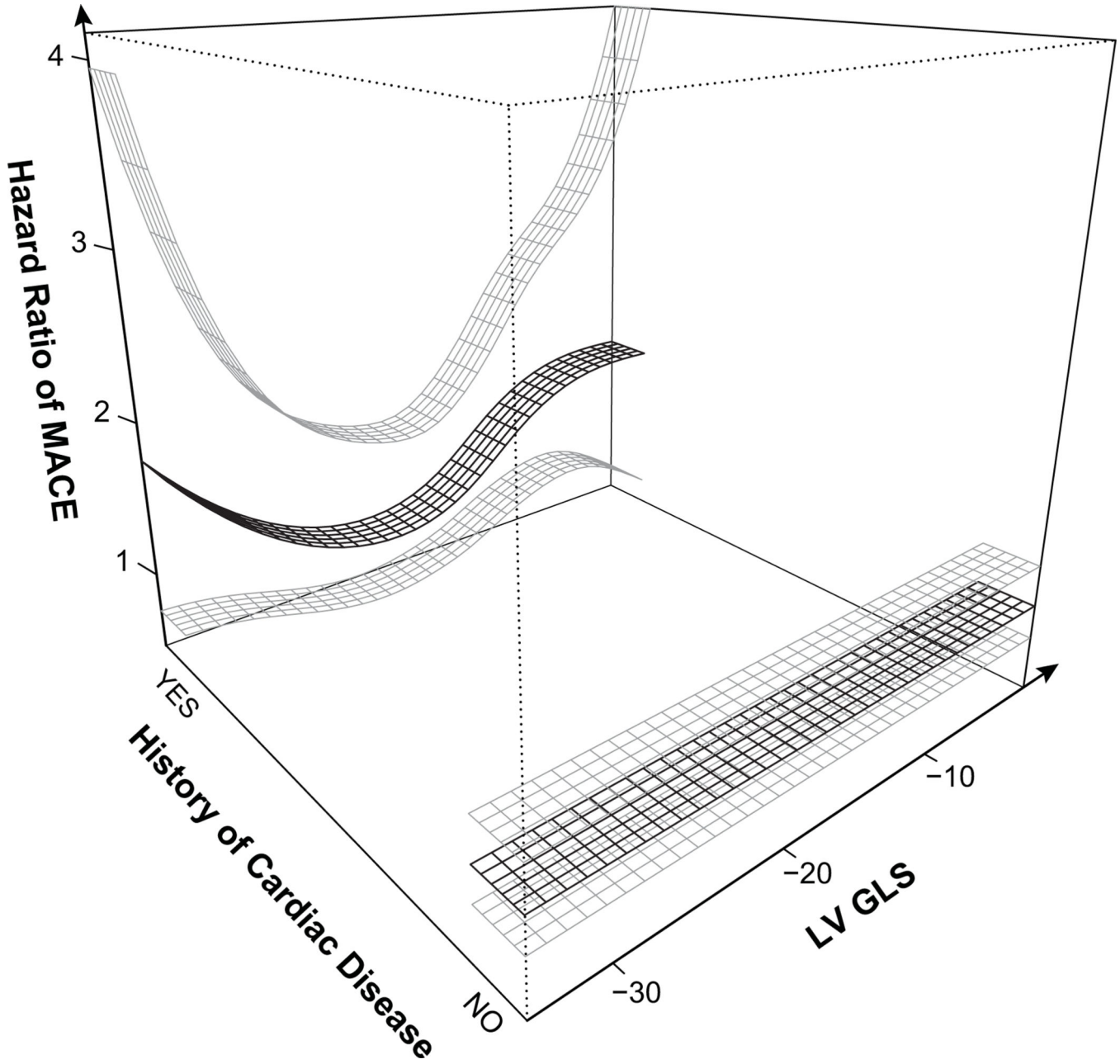


**Figure 3. Model of Strain and MACE by pre-existing cardiac disease**

**Table 1.**

Patient Information

| Variable | Full Cohort (N=290) | GLS ≤ −17% (N=140) | GLS > −17% (N=150) |
|---|---|---|---|
| Age (years) | 64 (IQI 51–74.8) | 63.5 (IQI 51–74) | 64 (IQI 51.2–75) |
| Female sex, % (N) | 53.8% (n=156) | 64.3% (n=90) | 44% (n=66) |
| Body mass index (kg/m$^2$) | 27.4 (IQI 23.6–32.8) | 26.9 (IQI 23–32.8) | 28.1 (IQI 25–32.8) |
| Charlson Comorbidity Index | 5 (IQI 2–7) | 4 (IQI 2–6) | 5 (IQI 3–8) |
| Elixhauser Score | 9 (IQI 6–12) | 9 (IQI 6–12) | 9 (IQI 7–12) |
| History of coronary artery disease | 17.6% (n=51) | 10% (n=14) | 24.7% (n=37) |
| History of cerebrovascular accident | 7.9% (n=23) | 6.4% (n=9) | 9.3% (n=14) |
| History of atrial fibrillation | 14.5% (n=42) | 8.6% (n=12) | 20% (n=30) |
| History of statin use on ICU admit | 32.4% (n=94) | 28.6% (n=40) | 36% (n=54) |
| Betablocker therapy on ICU admit | 25.2% (n=73) | 15.7% (n=22) | 34% (n=51) |
| Antiplatelet therapy on ICU admit | 27.2% (n=79) | 24.3% (n=34) | 30% (n=45) |
| Anticoagulation on ICU admit | 16.9% (n=49) | 14.3% (n=20) | 19.3% (n=29) |
| Tobacco use, ever | 38.6% (n=112) | 43.6% (n=61) | 34% (n=51) |
| SOFA on ICU day 1 | 9 (IQI 6–12) | 8 (IQI 6–12) | 9 (IQI 7–12) |
| APACHE II at ICU admission | 23 (IQI 16.5–30) | 23 (IQI 16–30) | 23 (IQI 18–31) |
| New atrial fibrillation in ICU | 10% (n=29) | 5.7% (n=8) | 14% (n=21) |
| New dialysis in ICU | 6.9% (n=20) | 5% (n=7) | 8.7% (n=13) |
| Cerebrovascular accident in ICU | 1.4% (n=4) | 0.7% (n=1) | 2% (n=3) |
| Myocardial infarction in ICU | 4.8% (n=14) | 2.1% (n=3) | 7.3% (n=11) |
| Sepsis source | | | |
| *Pulmonary* | 40% (n=116) | 37.9% (n=53) | 42% (n=63) |
| *Urinary* | 20.7% (n=60) | 17.9% (n=25) | 23.3% (n=35) |
| *Intraabdominal* | 15.9% (n=46) | 18.6% (n=26) | 13.3% (n=20) |
| *Skin or soft tissue* | 12.4% (n=36) | 11.4% (n=16) | 13.3% (n=20) |
| *Other* | 11% (n=32) | 14.3% (n=20) | 8% (n=12) |
| Lactate, Initial in ICU (mmol/L) | 3.2 (IQI 1.9–5.4) | 2.9 (IQI 1.8–4.6) | 3.5 (IQI 2–6) |
| Lactate, Peak in ICU (mmol/L) | 3.6 (IQI 2.2–6) | 3.3 (IQI 2.1–4.9) | 4.2 (IQI 2.4–7) |
| Troponin, Initial in ICU (ng/ml) | 0 (IQI 0–0.2) | 0 (IQI 0–0.1) | 0 (IQI 0–0.3) |
| Troponin, Peak in ICU (ng/ml) | 0.1 (IQI 0–0.7) | 0.1 (IQI 0–0.3) | 0.1 (IQI 0–0.8) |
| Glasgow coma scale on ICU admit | 13 (IQI 8–15) | 14 (IQI 8.8–15) | 13 (IQI 8–14) |
| Vasopressors at time of echo | 39% (n=113) | 40.7% (n=57) | 37.3% (n=56) |
| Vasopressors anytime in ICU | 71.4% (n=207) | 73.6% (n=103) | 69.3% (n=104) |
| Norepinephrine equivalent, max dose in ICU (mcg/kg/min) | 0.1 (IQI 0–0.2) | 0.1 (IQI 0–0.2) | 0.1 (IQI 0–0.2) |
| Mechanical ventilation while in ICU | 32.8% (n=95) | 30% (n=42) | 35.3% (n=53) |
| Ventilator free days in ICU | 28 (IQI 22–28) | 28 (IQI 20.8–28) | 28 (IQI 24–28) |
| P/F Ratio at time of echo | 248.2 (IQI 151–335.6) | 262.6 (IQI 189.2–350.2) | 230 (IQI 138.1–318.2) |

| Variable | Full Cohort (N=290) | GLS ≤ −17% (N=140) | GLS > −17% (N=150) |
|---|---|---|---|
| Total intravenous fluid given within 12 hours of echo (ml) | 1812.5 (IQI 7–3007.9) | 1385 (IQI 5.9–3550) | 1999 (IQI 13.2–3000) |
| Organ failure free days at 28 days | −16.8 (IQI −20.4−−12.6) | −20.7 (IQI −23−−18.8) | −12.7 (IQI −15.1−−10.6) |
| ICU Length of stay (days) | 2.7 (IQI 1.9–4.5) | 2.6 (IQI 1.9–4.6) | 2.7 (IQI 1.9–4.4) |

SOFA: Sequential Organ Failure Assessment; APACHE: Acute Physiology and Chronic Health Evaluation