



Deposited via The University of Sheffield.

White Rose Research Online URL for this paper:

<https://eprints.whiterose.ac.uk/id/eprint/240163/>

Version: Accepted Version

Article:

Leng, S., Guo, J., Alabed, S. et al. (2026) Digital twin model predicts prognosis in pulmonary arterial hypertension. JACC: Cardiovascular Imaging, 19 (4). pp. 565-567. ISSN: 1936-878X

<https://doi.org/10.1016/j.jcmg.2025.11.006>

© 2026 The Authors. Except as otherwise noted, this author-accepted version of a journal article published in JACC: Cardiovascular Imaging is made available via the University of Sheffield Research Publications and Copyright Policy under the terms of the Creative Commons Attribution 4.0 International License (CC-BY 4.0), which permits unrestricted use, distribution and reproduction in any medium, provided the original work is properly cited. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>

Reuse

This article is distributed under the terms of the Creative Commons Attribution (CC BY) licence. This licence allows you to distribute, remix, tweak, and build upon the work, even commercially, as long as you credit the authors for the original work. More information and the full terms of the licence here: <https://creativecommons.org/licenses/>

Takedown

If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.

Digital Twin Model Predicts Prognosis in Pulmonary Arterial Hypertension

Shuang Leng, PhD,^{a,b+} Jiajun Guo, MD,^{c+} Samer Alabed, MD, FRCR, PhD,^{d,e} Ru San Tan, MBBS, MRCP,^{a,b} Ping Chai, MBBS, MMed,^{f,g} Lynette Teo, MBChB, FRCR, MMed,^{g,h} Xiaodan Zhao, PhD,^a Alistair Young, PhD,ⁱ James M Wild, PhD,^{d,j,k} John C Allen, PhD,^b Dexiang Zong, M.Eng,^a Ju Le Tan, MBBS, MRCP,^{a,b} James Wei-Luen Yip, MD,^{f,g} Andrew J Swift, PhD,^{d,e,j,k} Yucheng Chen, MD, PhD,^{c*} David G Kiely, MD,^{d,k,l} Liang Zhong, PhD,^{a,b,m*}

^aNational Heart Centre Singapore, Singapore

^bDuke-NUS Medical School, Singapore

^cCardiology Division/Cardiovascular Imaging and Target Therapy Lab, West China Hospital, Sichuan University, China

^dDepartment of Infection, Immunity and Cardiovascular Disease, University of Sheffield, Sheffield, United Kingdom

^eDepartment of Clinical Radiology, Sheffield Teaching Hospitals, Sheffield, United Kingdom

^fDepartment of Cardiology, National University Heart Centre, Singapore

^gYong Loo Lin School of Medicine, National University of Singapore, Singapore

^hDepartment of Diagnostic Imaging, National University Hospital, Singapore

ⁱKing's College London, United Kingdom

^jNational Institute for Health and Care Research Sheffield Biomedical Research Centre, Sheffield, United Kingdom

^kINSIGNEO, Institute for In Silico Medicine, University of Sheffield, Sheffield, United Kingdom

^lSheffield Pulmonary Vascular Disease Unit, Royal Hallamshire Hospital, Sheffield, United Kingdom

^mDepartment of Biomedical Engineering, National University of Singapore, Singapore

Running title: Digital Twin Predicts PAH Outcomes

⁺Drs Leng and Guo contributed equally to this paper.

^{*}Co-corresponding authors: **Yucheng Chen**, Cardiology Division/Cardiovascular Imaging and Target Therapy Lab, West China Hospital, Sichuan University, Guo Xue Xiang No 37, Chengdu, Sichuan, 610041, China; chenycheng2003@126.com; **Liang Zhong**, National Heart Research Institute Singapore, National Heart Centre Singapore, 5 Hospital Drive, 169609, Singapore; gmszl@nus.edu.sg.

Keywords: pulmonary arterial hypertension, cardiovascular magnetic resonance, digital twin, biventricular modeling, prognosis

Sources of Funding

This study has received funding support from the National Medical Research Council of Singapore (NMRC/OFIRG/0018/2016, NHIC-I2D-2502365, MOH-001903-01). The funder had no role in the design and conduct of the study; collection; management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

Disclosures

Dr Kiely has received personal fees for consultancy work, educational talks and participation in steering committees from Acceleron, Ferrer, GSK, MSD, and Janssen; and has received funding from the National Institute for Health and Care Research, Sheffield Biomedical Research Centre.

Right ventricular (RV) size and function are established predictors of mortality in pulmonary arterial hypertension (PAH). The left and right ventricles (LV and RV) interact closely through shared septal and pericardial mechanics, and LV functional impairment, including strain reduction, has been linked to worse outcomes.¹ Traditional volumetric indices, however, incompletely characterize complex geometric remodeling. Shape alterations—subtle and regionally heterogeneous—may provide additional prognostic information. We integrated patient-specific digital twin models derived from cardiovascular magnetic resonance (CMR) with atlas-based analysis to investigate 3D biventricular shape features in relation to remodeling, PAH subtypes, and adverse events in PAH.

We studied 322 patients with PAH from three registries (ASPIRE,² INITIATE,³ West China Hospital⁴). Patients were classified as compensated (mean right atrial pressure [RAP] <10 mmHg) or decompensated (RAP ≥10 mmHg). Risk was stratified using the REVEAL score. The primary endpoint was all-cause mortality. The North Sheffield Research Ethics Committee, the SingHealth Centralised Institutional Review Board, and the Ethics Committee of West China Hospital approved the study protocol. Informed consent was obtained from participants enrolled in the INITIATE registry and West China Hospital, while consent was waived for anonymized retrospective data from the ASPIRE registry. CMR was performed on 1.5T or 3T scanners from multiple vendors according to a standardized protocol.

AI-based segmentation of the LV and RV endocardial and epicardial borders was performed at end-diastole and end-systole using MASS software. Valve and apical landmarks were derived from standard long-axis views, and the RV free wall and septum were separated at insertion points. Contours were converted to 3D coordinates using DICOM information. A biventricular surface mesh was customized for each patient by correcting breath-hold

misregistration using least-squares optimization and deforming the mesh with a diffeomorphic registration algorithm. The resulting meshes represented LV, RV, and all four cardiac valves. Rigid alignment and Procrustes analysis enabled construction of a statistical atlas, and principal component analysis (PCA) of concatenated end-diastolic and end-systolic meshes captured both geometry and motion.⁵ Fourteen PCA modes explained 82% of population-level shape variation. Preservation of mesh topology ensured point-wise correspondence between end-diastolic and end-systolic meshes, allowing calculation of myocardial surface area strain (AS) globally and regionally for LV and RV segments. Associations of PCA modes and surface AS with survival were tested using univariate and multivariable Cox regression, with Kaplan-Meier and receiver operating characteristic (ROC) analyses assessing prognostic and clinical utility. The incremental values of PCA modes to established risk scores (REVEAL) for predicting mortality were assessed using C-statistic.

The PAH cohort included 134 idiopathic (IPAH), 129 associated with connective tissue disease (PAH-CTD), and 47 associated with congenital heart disease (PAH-CHD). Median REVEAL score was 8, 46% were in WHO functional class III-IV, and 32% exhibited RV decompensation. Analysis of 3D biventricular shape features showed that PCA modes 1 and 2 were associated with RV decompensation, with area under the curve (AUC) values of 0.636 (95% confidence interval [CI], 0.580-0.691) and 0.650 (95% CI, 0.593-0.703), respectively. One-way ANOVA demonstrated significant differences in PCA modes 1 and 2 across PAH subtypes ($F=10.288$ and 9.819 ; both $P<0.0001$), indicating that RV shape variation differs by etiology. Post-hoc analysis confirmed significant differences between IPAH and PAH-CTD for PCA mode 1 ($P<0.0001$), between IPAH and PAH-CHD for PCA mode 2 ($P<0.0001$), and between PAH-CTD

and PAH-CHD for both PCA modes ($P<0.0001$). These findings suggest that PAH-CTD exhibits the most pronounced RV morphological deviation among the PAH subtypes.

Both PCA modes correlated with the REVEAL score (mode 1, $r=-0.17$; mode 2, $r=-0.33$; $P<0.05$). RV basal and middle surface AS exhibited stronger negative correlations ($r=-0.34$ and -0.46 ; $P<0.0001$). Stratification by REVEAL risk categories revealed significant differences in PCA modes and RV AS across low-, intermediate-, and high-risk groups (all $P<0.0001$), with greater RV shape deviations and impaired strain observed in higher-risk patients. ROC analysis confirmed predictive ability for distinguishing intermediate/high from low-risk patients (RV middle AS, AUC 0.752; RV basal AS, AUC 0.743; PCA mode 2, AUC 0.691).

During a median follow-up of 30 months (range 1-102), 70 deaths occurred. In univariate Cox regression, PCA modes 1 and 2 (hazard ratio [HR], 0.75 and 0.70; $P=0.014$ and 0.005) and RV basal and middle AS (HR, 0.96 and 0.97; $P=0.0001$) were associated with mortality. In multivariable Cox regression, age ($P=0.007$), REVEAL score ($P=0.014$), pulmonary vascular resistance (PVR, $P=0.015$), RV mass index ($P=0.002$), and combined PCA modes 1 and 2 ($P=0.040$) were identified as independent predictors of mortality, after adjustment of confounders including myocardial tissue properties (RV mass index and RV global longitudinal strain), RV remodeling (RV volumes, RV ejection fraction, RV/LV volume ratio), and pulmonary hypertension severity (RAP, mean pulmonary artery pressure [mPAP], PVR). In sequential nested Cox models, the REVEAL-based model was significantly improved by the addition of combined PCA modes 1 and 2, increasing the C-statistic from 0.74 to 0.77 ($P=0.038$). Kaplan-Meier curves further demonstrated lower survival among patients with lower combined PCA mode scores.

Interpretation of PCA modes indicated complementary remodeling patterns. Mode 1 reflected RV maladaptation, with lower values associated with RV dilation, higher RV/LV volume ratio, and reduced contractility—features consistent with advanced RV dysfunction. Mode 2 captured LV-centric remodeling, with higher values correlating with preserved LV volumes, elongated LV shape, and better RV contractility, suggesting a more adaptive phenotype. These patterns help explain the differential remodeling observed across PAH subtypes: PAH-CTD patients demonstrated the most severe RV morphological deviations and adverse clinical outcomes, while IPAH and PAH-CHD showed less pronounced RV remodeling. Regional RV AS at basal and mid-ventricular levels further identified early mechanical dysfunction preceding overt volumetric changes, providing additional prognostic information. Collectively, these findings indicate that 3D biventricular shape features and surface strain provide complementary insights into PAH pathophysiology.

In conclusion, 3D biventricular shape analysis identifies PAH subtype-specific remodeling and predicts RV decompensation, risk stratification, and adverse outcomes, highlighting its potential to improve patient-specific prognostication.

References

1. Alabed S, Shahin Y, Garg P, et al. Cardiac-MRI predicts clinical worsening and mortality in pulmonary arterial hypertension: A systematic review and meta-analysis. *J Am Coll Cardiol Img.* 2021;14:931-942.
2. Hurdman J, Condliffe R, Elliot CA, et al. ASPIRE registry: assessing the Spectrum of Pulmonary hypertension Identified at a REferral centre. *Eur Respir J.* 2012;39:945-955.
3. Leng S, Tan RS, Guo J, et al. Cardiovascular magnetic resonance-assessed fast global longitudinal strain parameters add diagnostic and prognostic insights in right ventricular volume and pressure loading disease conditions. *J Cardiovasc Magn Reson.* 2021;23:38.
4. Guo J, Wang J, Wang L, et al. Left ventricular underfilling in PAH: A potential indicator for adaptive-to-maladaptive transition. *Pulm Circ.* 2023;13:e12309.
5. Mauger C, Gilbert K, Lee AM, et al. Right ventricular shape and function: cardiovascular magnetic resonance reference morphology and biventricular risk factor morphometrics in UK Biobank. *J Cardiovasc Magn Reson.* 2019;21:41.

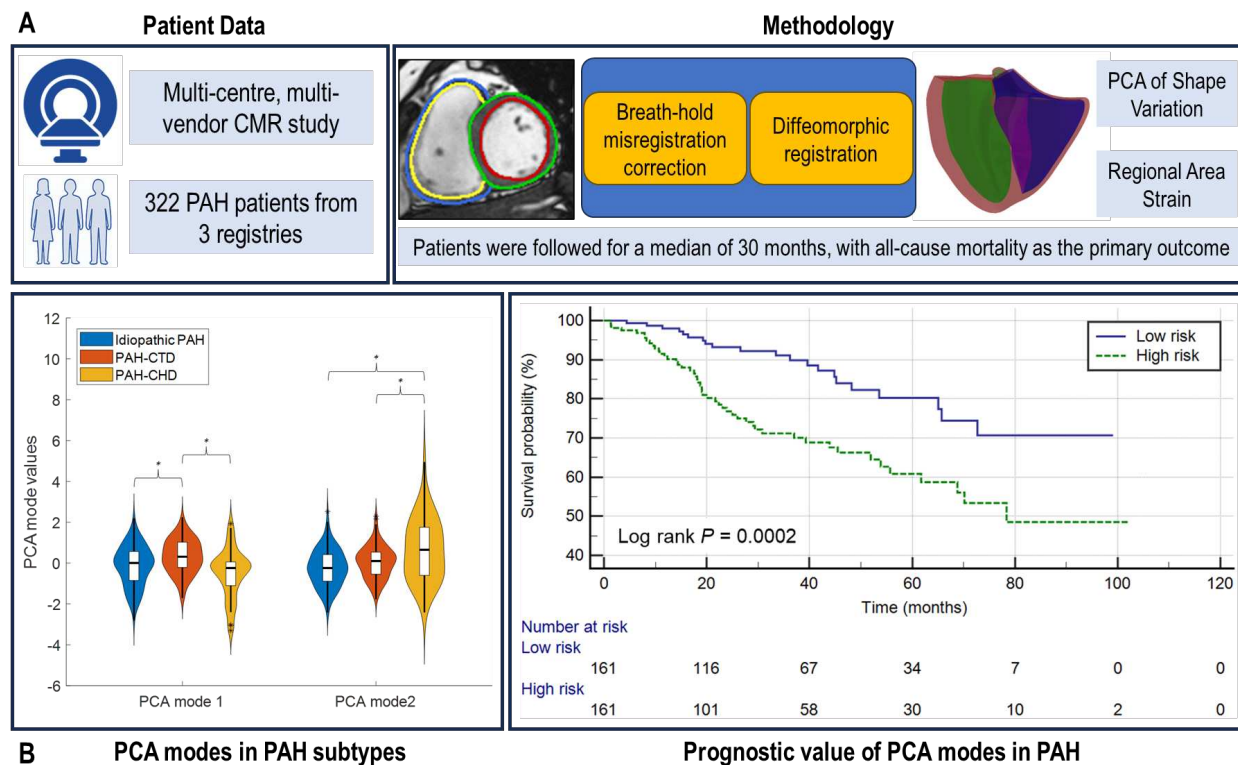


Figure titles and legends

Figure 1. Digital Twin Model Identifies PAH Subtype-Specific Remodeling and Predicts Prognosis. (A) Study population and methodology (full analysis pipeline). (B) Key findings: distribution of PCA modes 1 and 2 across PAH subtypes; Kaplan-Meier survival analysis of two risk subgroups derived from combined PCA modes 1 and 2. CMR, cardiovascular magnetic resonance; PAH, pulmonary arterial hypertension; PCA, principal component analysis; PAH-CTD, PAH associated with connective tissue disease; PAH-CHD, PAH associated with congenital heart disease.