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ORIGINAL RESEARCH

Longitudinal Validation of a Deep Learning Index for Aortic Stenosis Progression

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BACKGROUND: Aortic stenosis (AS) is a progressive disease requiring timely monitoring and intervention. While transthoracic echocardiography remains the diagnostic standard, deep learning–based approaches offer the potential for improved disease tracking. This study examined the longitudinal changes in a previously developed deep learning–derived index for AS continuum (DLi-ASc) and assessed its prognostic association with progression to severe AS.

METHODS: We retrospectively analyzed 2373 patients (7371 transthoracic echocardiographies) from 2 tertiary hospitals. DLi-ASc (scaled 0–100), derived from parasternal long-axis and short-axis views, was tracked longitudinally. The median follow-up duration was 42.8 (interquartile range, 22.2–75.7) months.

RESULTS: DLi-ASc increased in parallel with worsening AS stages (P for trend<0.001) and showed strong correlations with aortic valve maximal velocity (Pearson correlation coefficient, 0.69; P<0.001) and mean pressure gradient (Pearson correlation coefficient, 0.66; P<0.001). Higher baseline DLi-ASc was associated with a faster AS progression rate (P for trend<0.001). Additionally, the annualized change in DLi-ASc, estimated using linear mixed-effect models, correlated strongly with the annualized progression of aortic valve maximal velocity (Pearson correlation coefficient, 0.71, P<0.001) and mean pressure gradient (Pearson correlation coefficient, =0.68; P<0.001). In Fine–Gray competing risk models, baseline DLi-ASc was independently associated with progression to severe AS, even after adjustment for aortic valve maximal velocity or mean pressure gradient (hazard ratios per 10-point increase, 2.38 and 2.80, respectively).

CONCLUSIONS: DLi-ASc increased in parallel with AS progression and was independently associated with severe AS progression. These findings support its role as a noninvasive imaging-based digital marker for longitudinal AS monitoring and risk stratification.

Key Words: aortic stenosis ■ artificial intelligence ■ echocardiography ■ progression

Aortic stenosis (AS) is a progressive disease that worsens over time and is increasingly prevalent in aging populations.[1,2] Effective management requires timely monitoring and intervention. Transthoracic echocardiography (TTE) remains the gold standard for AS evaluation,[3,4] but its reliance on multiple Doppler-derived parameters introduces variability and requires operator expertise for accurate image acquisition and interpretation. To enhance objectivity and scalability, artificial intelligence (AI) has been explored for AS assessment, primarily in 2 directions: (1) automating conventional AS evaluation and (2) predicting significant or severe AS using limited imaging data.[5–8]

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CLINICAL PERSPECTIVE

What Is New?

- In this longitudinal validation study, the deep learning–derived index for aortic stenosis (AS) continuum increases consistently over time in parallel with worsening AS stages and conventional AS hemodynamic parameters.
- Both baseline deep learning–derived index for AS continuum and its annualized rate of increase are independently associated with future progression to severe AS, even after adjustment for conventional hemodynamic parameters.

What Are the Clinical Implications?

- The deep learning–derived index for AS continuum provides a quantitative, noninvasive digital biomarker that enables objective monitoring of AS progression, supports individualized risk-based follow-up, and may serve as a surrogate marker for evaluating therapies aimed at slowing disease progression.

Nonstandard Abbreviations and Acronyms

AS	aortic stenosis
AV	aortic valve
DL	deep learning
DLi-ASc	deep learning–derived index for aortic stenosis continuum
LMM	linear mixed model
mPG	mean pressure gradient
PCC	Pearson correlation coefficient
PLAX	parasternal long-axis
PSAX	parasternal short-axis
TTE	transthoracic echocardiography
V_{max}	maximal velocity

A number of deep learning (DL)-based indices for AS severity have recently been developed,[5–7] each differing in input views, labeling strategies, and modeling approaches. Among these, we developed a novel DL-derived index for the AS continuum (DLi-ASc) that can quantify AS severity using limited TTE views, either parasternal long-axis (PLAX) or parasternal short-axis (PSAX) view, within a multitask learning framework, where an ordinal AS severity grade prediction was combined with conventional echocardiographic parameter prediction to produce a continuous AS severity index, thereby enhancing robustness and interpretability.[5] Rigorous validation demonstrated its diagnostic accuracy and prognostic value, comparable to conventional AS parameters.

Some of these indices have also been evaluated for prognostic value in longitudinal follow-up.[9,10] However, prior longitudinal studies have predominantly relied on baseline DL scores to examine associations with progression or outcomes, without systemically characterizing temporal score trajectories or establishing their relationship to conventional hemodynamic progression or clinical outcomes.

In the present study, we extended the application of DLi-ASc to longitudinal AS assessment, aiming to (1) characterize temporal changes in DLi-ASc and express them as annualized rates, (2) examine whether these changes align with the progression of conventional echocardiographic parameters, and (3) evaluate the prognostic association of both baseline DLi-ASc and its annualized rate of change with severe AS progression. By addressing these gaps, this study aims to provide 1 of the first demonstrations that a DL-derived AS index can capture disease trajectory over time, offering a standardized and interpretable marker with potential value for risk stratification and long-term monitoring.

METHODS

The data that support the findings of this study are available upon reasonable request. Please contact the corresponding author (yeonyeeyoon@gmail.com) to request the minimal anonymized data set. Researchers with additional inquiries about the DL model developed in this study are also encouraged to reach out to the corresponding author.

Study Population

The study population was collected from 2 tertiary institutions in South Korea: Seoul National University Bundang Hospital (March 2006 to October 2024) and Chungnam National University Hospital (February 2010 to October 2024). Patients who underwent at least 2 serial TTE examinations and were diagnosed with AS, either at the time of the initial TTE or during follow-up, were included. A total of 2806 patients with 8663 TTE examinations were initially identified (South Korea: Seoul National University Bundang Hospital: 1639 patients, 5049 TTEs; Chungnam National University Hospital: 1167 patients, 3614 TTEs). To ensure the methodological consistency and reliability of AS severity assessment, the following exclusion criteria were applied on the basis of baseline TTE findings: (1) severe AS; (2) moderate or greater aortic regurgitation; (3) moderate or greater mitral stenosis or regurgitation; (4) discordant AS classification, defined as cases in which aortic

valve (AV) maximal velocity (V_{max}), mean pressure gradient (mPG), and AV area fell into different severity categories (Figure 1). After applying these exclusion criteria, 2373 patients with 7371 TTE examinations remained for analysis. This study was approved by the institutional review boards of the participating hospitals, with a waiver for informed consent due to its retrospective, observational design (South Korea: Seoul National University Bundang Hospital B-2302-808-101; Chungnam National University Hospital 2024-11-019). The study adhered to the revision of the Declaration of Helsinki (2013).

Clinical and Echocardiographic Data Acquisition

All TTE examinations were performed by trained echocardiographers or cardiologists following contemporary guidelines[3,4] and interpreted by board-certified cardiologists who specialized in echocardiography. AV sclerosis was defined as focal or diffuse thickening and calcification with V_{max} <2.0 m/s and preserved leaflet motion. For follow-up TTEs, when parameter discordance between V_{max}, mPG, and AV area was observed, AS severity was determined on the basis of the final interpretation documented by the attending cardiologist. In cases with indeterminate severity or potential low-flow states, if additional studies, such as dobutamine stress TTE or computed tomography–based AV calcium scoring, had been performed, the results were reviewed and incorporated into the final clinical interpretation. All available TTE examinations for each patient were collected; for those who underwent AV replacement during the follow-up period, only TTE data obtained before the procedure were included. AS severity metrics from each TTE were extracted from clinical reports used for the treatment decision-making.[3]

DL-Based AS Assessment Algorithm

The DL model used in this study has been previously described and is integrated into an AI-enhanced AS evaluation system (USfeat_valve.ai; Ontact Health, Seoul, Korea).[5] Briefly, the model uses a 3-dimensional convolutional neural network (r2plus1d18) to analyze TTE videos, generating a continuous severity score, the DLi-ASc (range, 0–100). This index quantifies AS severity on the basis of limited TTE views, specifically the PLAX and PSAX views at the AV level. To enhance the reliability of AS severity evaluation, the model incorporates ordered label mapping and multitask learning, leveraging auxiliary tasks to predict key TTE parameters such as AV V_{max}, mPG, and AV area. For each patient, if multiple PLAX or PSAX views were available, DLi-ASc was first averaged within each view type (PLAX and PSAX separately) and then averaged across both views. If only 1 view type was available, its score was used. The DLi-ASc was generated for all baseline and follow-up TTE examinations included in this study. The DL model successfully generated DLi-ASc for all cases, ensuring full data availability for longitudinal analysis with no exclusions due to model-processing failure.

Statistical Analysis

All statistical analyses were conducted in both the full cohort and the training-excluded cohort, which excluded all patients whose TTE examinations were used

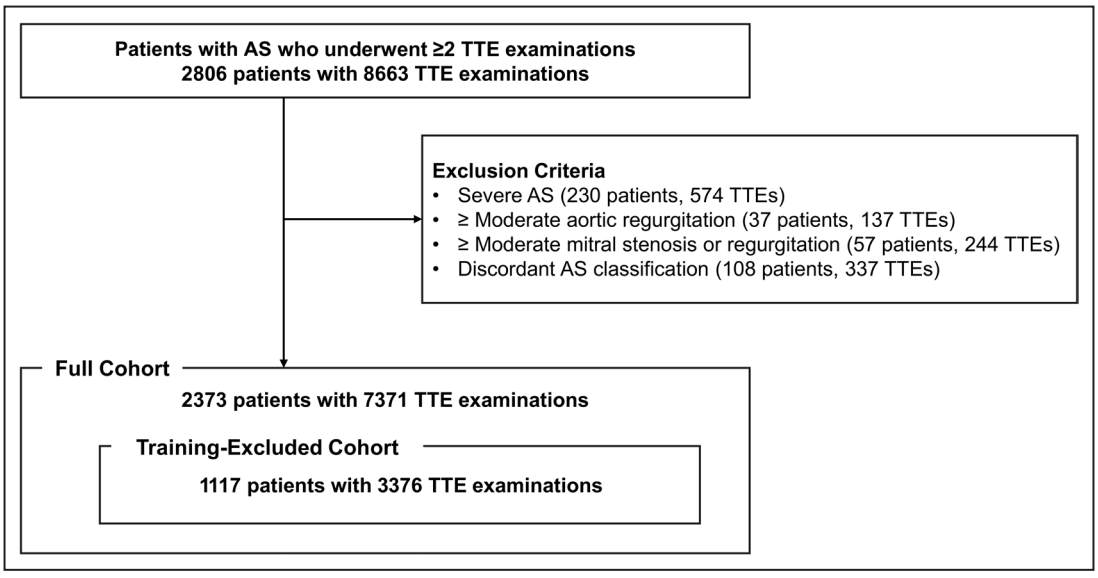

Figure 1. Study population.
AS indicates aortic stenosis; and TTE, transthoracic echocardiography.

in the training phase of the DLi-ASc model (Figure 1).[5] This parallel analytical approach was implemented to ensure the robustness and generalizability of our findings, while addressing concerns about potential data leakage and overfitting.[11]

Clinical data are described in the study as the median with interquartile range (IQR) or mean with 95% CI for continuous variables and as number and percentage for factorial variables. Baseline characteristics were compared between the cohorts, with significant differences determined using the Kruskal–Wallis test and χ^2 test, as appropriate.

The temporal progression of AS severity was illustrated using a proportional stacked bar plot, showing the relative distribution of AS stage (normal AV, AV sclerosis, mild AS, moderate AS, and severe AS) over the follow-up period. This trend was further stratified according to baseline AS severity categories. To assess the significance of ordinal changes in AS stage over time, we used a cumulative link mixed model, which accounts for repeated measurements and varying intervals between TTEs.[12] The temporal changes of DLi-ASc were visualized using ridge density plots and analyzed using a linear mixed model (LMM), adjusting for repeated TTE measurements and irregular follow-up intervals.[13] The same modeling approach was applied to AV V_{max} and AV mPG, enabling estimation of annual progression rates based on all available serial measurements.

The relationships between DLi-ASc and conventional AS parameters (AV V_{max} and mPG) were evaluated using scatterplots with Pearson correlation coefficients (PCCs). To examine the association between baseline DLi-ASc and the rate of AS progression, we stratified patients by baseline DLi-ASc categories (<25, 25 to <50, 50 to <75, and ≥75) and compared the annualized progression rate of V_{max} and mPG across groups. These trends were visualized using violin plots and tested for significance using linear trend analysis. In addition, the associations between the estimated annualized progression rate of DLi-ASc, V_{max}, and mPG, each estimated using LMMs, were also evaluated using scatterplots with PCCs.

We evaluate the prognostic association of both baseline DLi-ASc and its annualized rate of change with progression to severe AS. The earliest TTE demonstrating severe AS was designated as the event date, while patients who did not progress to severe AS were censored at their last available TTE. A competing risk analysis was performed using a Fine–Gray subdistribution hazard model.[14] Two types of competing events were considered: (1) death occurring before the patient fulfilled echocardiographic criteria for severe AS and (2) AV replacement performed for other indications before meeting those criteria. The proportional hazards assumption was tested, and no statistically significant violation was found.

The discriminative ability for baseline DLi-ASc for progression to severe AS was evaluated using time-dependent receiver operating characteristic curves, with the area under the curve quantifying discriminative performance over time. Spline curve analyses were performed to visualize the continuous association between each index (baseline value or annualized rate) and the subdistribution hazard of severe AS progression at 3 and 5 years, thereby identifying empirical inflection points. Based on these findings, baseline DLi-ASc was then evaluated both as a continuous variable (per 10-point increase) and as a categorical variable (<50, 50 to <60, 60 to <70, and ≥70). The annualized rate of change in DLi-ASc was assessed as a continuous variable (per 1-point/y increase) and in predefined categories (<1.0, 1.0 to <1.2, 1.2 to <1.4, and ≥1.4 points/y).

For both indices, we constructed Fine–Gray models under 3 adjustment strategies: (1) clinical factors only (age, sex, and estimated glomerular filtration rate); (2) clinical factors plus AV V_{max}; and (3) clinical factors plus AV mPG. For models evaluating the annualized rate of change in DLi-ASc, baseline DLi-ASc was additionally included as a covariate. Variance inflation factors were calculated for all models to assess collinearity. Subdistribution hazard ratios (HRs) with 95% CIs were reported for both continuous and categorical analyses. In addition, to exclude prediagnostic variability and evaluate the prognostic association of DLi-ASc and its annualized rate of change in a clinically confirmed AS population, we conducted a sensitivity analysis restricted to patients whose baseline TTE corresponded to the first examination at which AS was clinically diagnosed. The Fine–Gray competing risk model was reapplied in this subset using the same adjustment strategies to ensure consistency with the primary analysis. Furthermore, to account for potential interval censoring due to irregular echocardiographic follow-up intervals, we performed a sensitivity analysis using parametric survival models for interval-censored data.[15] A proportional hazards model with a Weibull baseline distribution was applied, following the same adjustment strategies as in the Fine–Gray models.

All statistical analyses were performed using R software version 4.5.0 (R Development Core Team, Vienna, Austria). Two-sided *P* values <0.05 were considered statistically significant.

RESULTS

Baseline Characteristics

A total of 2373 patients with 7371 TTE examinations were included in the full analysis cohort. The training-excluded cohort, consisting of patients with no overlap with the DLi-ASc training data set, comprised 1117 patients and 3376 TTEs (Figure 1). The median age was 76 years (IQR, 69–82)

Table 1. Baseline Characteristics of the Full Cohort and the Training-Excluded Cohort

	Full cohort (n=2373)	Training-excluded cohort (n=1117)
Age, y	76 (69–82)	75 (68–81)
Men	1093 (46.1)	523 (46.8)
Women	1280 (53.9)	594 (53.2)
Body surface area	1.7 (1.5–1.8)	1.6 (1.5–1.8)
Baseline AS severity		
Normal	200 (8.4)	197 (17.6)
AV sclerosis	449 (18.9)	301 (26.9)
Mild AS	1263 (53.2)	386 (34.6)
Moderate AS	461 (19.4)	233 (20.9)
Baseline DLi-ASc	49 (46–52)	49 (45–52)
Follow-up, mo	42.8 (22.2–75.7)	47.8 (21.0–87.8)
No. of TTEs	7371	3376
No. of TTE follow-ups	3 (2–4)	3 (2–3)
At least 3 examinations	1259 (53.1)	569 (50.9)
At least 4 examinations	639 (26.9)	276 (24.7)

Values are given as number (percentage) or median (interquartile range). AS indicates aortic valve stenosis; AV, aortic valve; DLi-ASc, deep learning–derived index for the aortic stenosis continuum; and TTE, transthoracic echocardiography.

in the full cohort and 75 years (IQR, 68–81) in the training-excluded cohort, with a similar sex distribution (Table 1). Baseline AS severity in the full cohort included normal AV (8.4%), AV sclerosis (18.9%), mild AS (53.2%), and moderate AS (19.4%). In the training-excluded cohort, the distribution shifted toward earlier disease stages, with a higher proportion of normal AV (17.6%) and AV sclerosis (26.9%) and a lower proportion of mild AS (34.6%). Median baseline DLi-ASc values were similar between the 2 groups: 49 (IQR, 46–52) in the full cohort and 49 (IQR, 45–52) in the training-excluded cohort. Median follow-up duration was slightly longer in the training-excluded cohort (47.8 versus 42.8 months), though the median number of follow-up TTEs was comparable (3 [IQR, 2–4] versus 3 [IQR, 2–3]). Comparative baseline characteristics stratified by institution (South Korea: Seoul National University Bundang Hospital versus Chungnam National University Hospital) are presented in Table S1.

Temporal Changes in AS Severity and Corresponding DLi-ASc Distributions

The median follow-up duration from baseline TTE was 42.8 (IQR, 22.2–75.7) months in the full cohort and 47.8 (IQR, 21.0–87.8) months in the training-excluded cohort. As shown in Figure 2, the distribution of AS stages demonstrated a progressive shift toward more advanced stages over time in both cohorts, with increasing proportions of moderate and severe AS as the follow-up period extended (*P* for trend<0.001, based on the cumulative link mixed model). This trend was consistently observed across all baseline AS severity categories (all *P* for trend<0.001; Figure S1). Longitudinal trends of conventional AS parameters were examined using LMM. Annualized progression rates were 0.06 m/s per year (95% CI, 0.05–0.10) for V_{max} and 0.67 mm Hg/y (95% CI, 0.34–1.34) for mPG in the full cohort, and 0.07 m/s per year (95% CI, 0.05–0.10) and

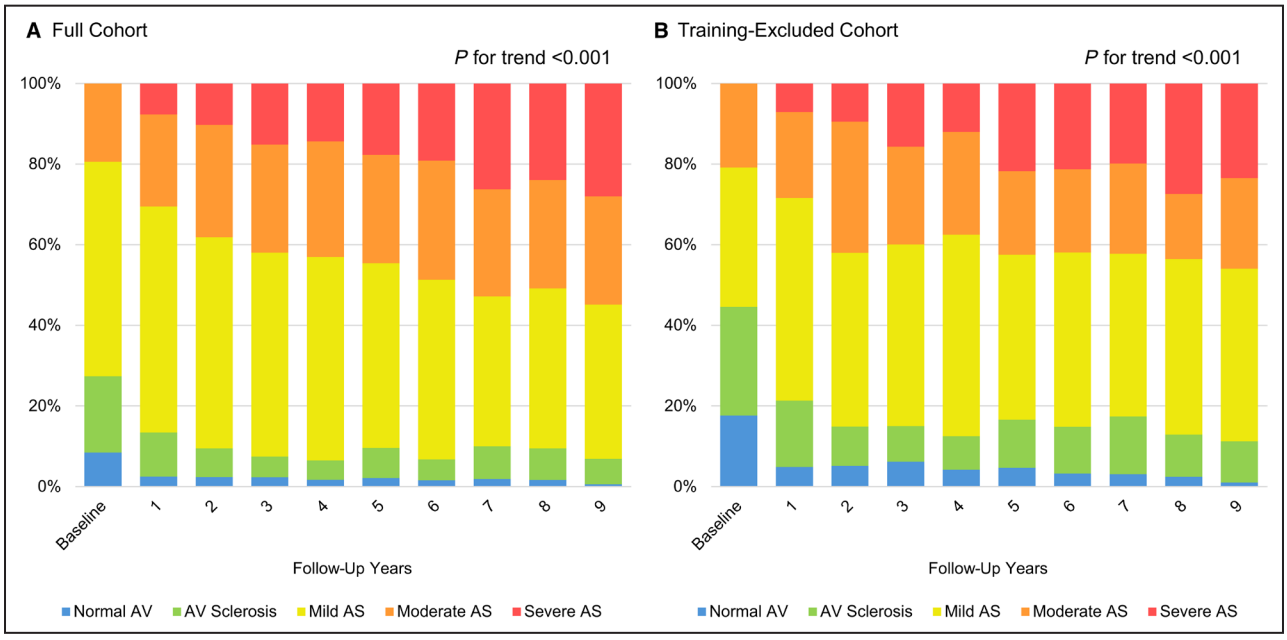

Figure 2. Temporal progression of AS severity over follow-up years.
A, Full cohort. **B**, Training-excluded cohort. AS indicates aortic stenosis; and AV, aortic valve.

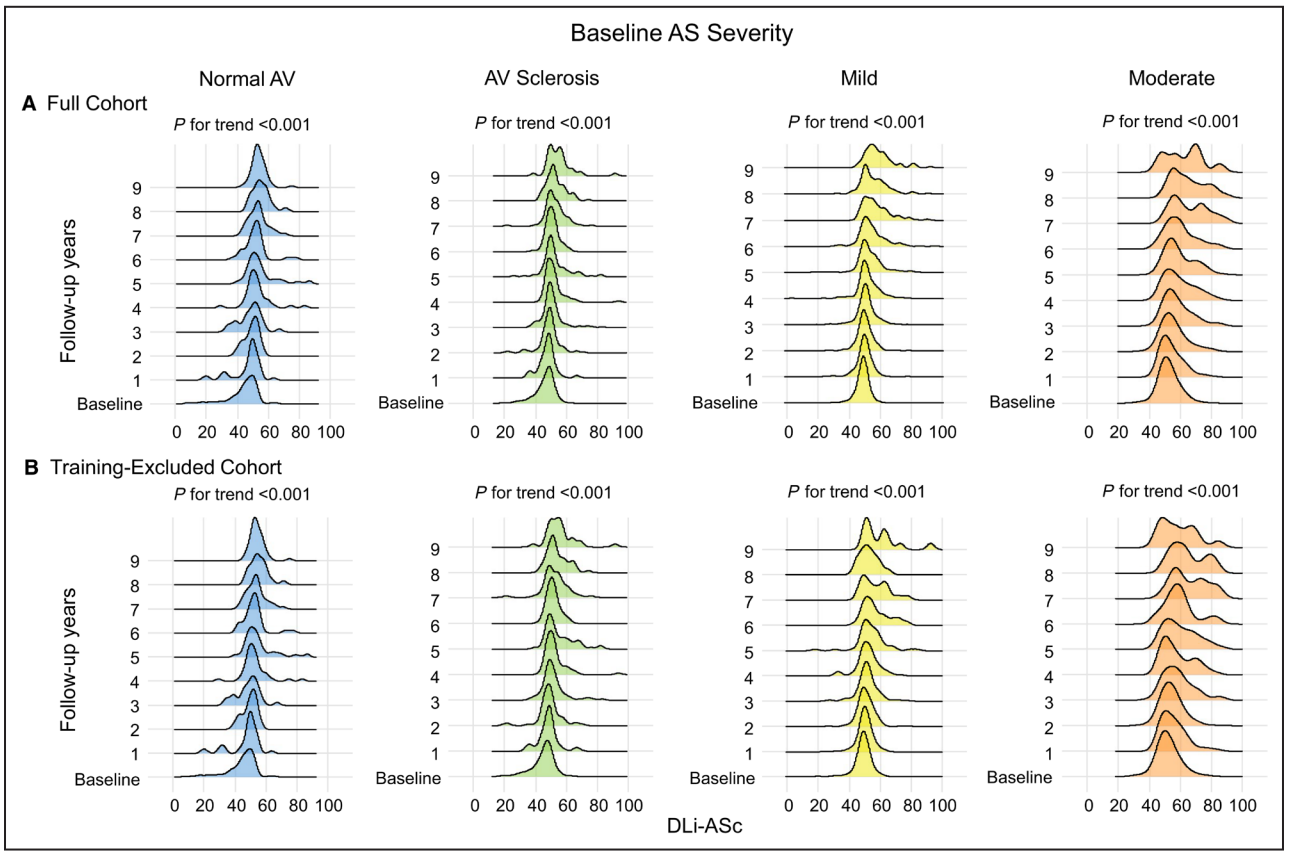

Figure 3. Temporal trends in DLi-ASc across baseline AS severity categories.
A, Full cohort. **B**, Training-excluded cohort. AS indicates aortic stenosis; AV, aortic valve; and DLi-ASc, deep learning–derived index for the aortic stenosis continuum.

0.83 mm Hg/y (95% CI, 0.50–1.44), respectively, in the training-excluded cohort (Table S2).

In parallel, DLi-ASc also increased longitudinally across all baseline AS severity categories. As illustrated in Figure 3, the density distributions of DLi-ASc shifted progressively toward higher values over follow-up years, with all trends statistically significant (*P* for trend<0.001). Corresponding median DLi-ASc values at baseline and follow-up are summarized in Table S3. For example, in the full cohort, DLi-ASc increased from 44 to 49 in normal AV, from 48 to 50 in AV sclerosis, from 49 to 53 in mild AS, and from 56 to 63 in moderate AS over 6 years. These patterns were also observed in the training-excluded cohort. The annualized rate of DLi-ASc progression was 1.11 (95% CI, 1.03–1.55) in the full cohort and 1.11 (95% CI, 1.02–1.23) in the training-excluded cohort, with progressively higher rates observed across worsening baseline severity categories (all *P* for trend<0.001; Table S2).

For complementary visualization of individual-level DLi-ASc trajectories, subject-level connected line plots are also provided (Figure S2). These findings align with Figure 3, reinforcing DLi-ASc's potential as a surrogate marker for monitoring long-term AS progression. While DLi-ASc generally increased over time, transient decreases were observed in 33.9% of consecutive TTE pairs, mostly when the follow-up interval was short (median, 13 months). When comparing only the first and last TTEs (median, 43 months), the proportion showing a net decrease dropped to 23.2%, again predominantly in cases with shorter follow-up. Notably, the absolute magnitude of DLi-ASc change increased with longer interscan intervals (Figure S3), suggesting that short-term decreases are more likely due to technical or image-related variability than true biological improvement.

Association of DLi-ASc With AS Severity and Progression

Analysis of all TTE examinations during follow-up revealed a significant positive correlation between DLi-ASc and conventional AS parameters in both the full and training-excluded cohorts, indicating that higher DLi-ASc values reflect greater hemodynamic severity. In the full cohort, PCC was 0.69 (95% CI, 0.67–0.70; *P*<0.001) for AV V_{max} and 0.66 (95% CI, 0.65–0.68; *P*<0.001) for AV mPG; in the training-excluded cohort, the corresponding values were 0.67 (95% CI, 0.65–0.69; *P*<0.001) and 0.61 (95% CI, 0.59–0.63; *P*<0.001), respectively (Figure 4). In addition, DLi-ASc also demonstrated significant correlation with AV area, although to a lesser degree than with

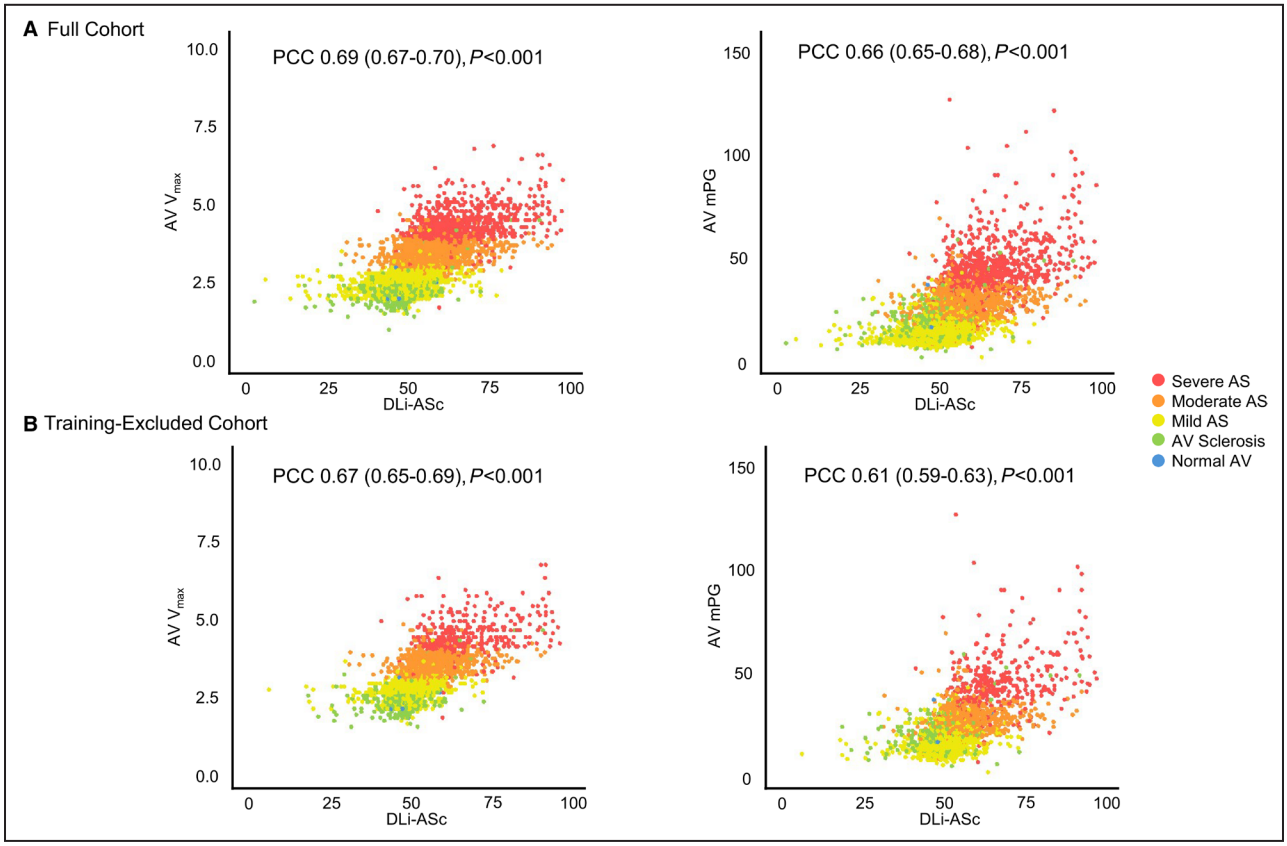

Figure 4. Association of DLi-ASc with conventional hemodynamic parameters of AS.
A, Full cohort. **B**, Training-excluded cohort. AS indicates aortic stenosis; AV, aortic valve; DLi-ASc, deep learning–derived index for the aortic stenosis continuum; PCC, Pearson correlation coefficient; and V_{max}, maximal velocity.

V_{max} or mPG (Figure S4). PCC values were 0.59 (95% CI, 0.57–0.62; *P*<0.001) in the full cohort and 0.54 (95% CI, 0.47–0.60; *P*<0.001) in the training-excluded cohort.

Furthermore, stratification by baseline DLi-ASc categories revealed significant positive trends, with higher baseline DLi-ASc associated with faster progression of both AV V_{max} and mPG (all *P* for trend<0.001; Figure 5). In addition, annualized progression parameters derived from LMMs (Figure 6) showed strong positive correlations between changes in DLi-ASc and corresponding changes in AV V_{max} (PCC, 0.71 [95% CI, 0.69–0.73]; *P*<0.001) and mPG (PCC, 0.68 [95% CI, 0.66–0.70]; *P*<0.001). The training-excluded cohort demonstrated consistent results, with PCCs of 0.72 (95% CI, 0.69–0.74; *P*<0.001) for V_{max} and 0.66 (95% CI, 0.63–0.69; *P*<0.001) for mPG. These findings suggest that both the baseline level and longitudinal increase in DLi-ASc are closely aligned with the hemodynamic progression of AS.

Prognostic Association of DLi-ASc With Severe AS Progression

Fine–Gray competing risk models demonstrated that baseline DLi-ASc exhibited good discriminative ability for severe AS progression, with time-dependent areas under the curve ranging from 0.89 to 0.92 (Figure S5). Spline curve analyses using Fine–Gray competing risk models demonstrated that the subdistribution hazard of severe AS progression at 3 and 5 years rose sharply once baseline DLi-ASc exceeded ≈50, providing an empirical inflection point (Figure S6). Based on this observation, patients were stratified into predefined categories (<50, 50 to <60, 50 to <60, and ≥70).

To further evaluate the independent prognostic association of DLi-ASc, we fitted a competing risk model using 3 adjustment strategies: (1) clinical factors only (age, sex, and estimated glomerular filtration rate), (2) clinical factors plus AV V_{max}, and (3) clinical factors plus AV mPG. In the full cohort, baseline DLi-ASc remained significantly associated with severe AS progression under all models (Table 2). The adjusted HR per 10-point increase was 4.03 (95% CI, 3.40–4.78) with clinical factors only, 2.41 (95% CI, 2.09–2.78) after additional adjustment for AV V_{max}, and 2.81 (95% CI, 2.41–3.29) after adjustment for mPG. Categorical DLi-ASc groups were also significantly associated with increased risk compared with the <50 reference

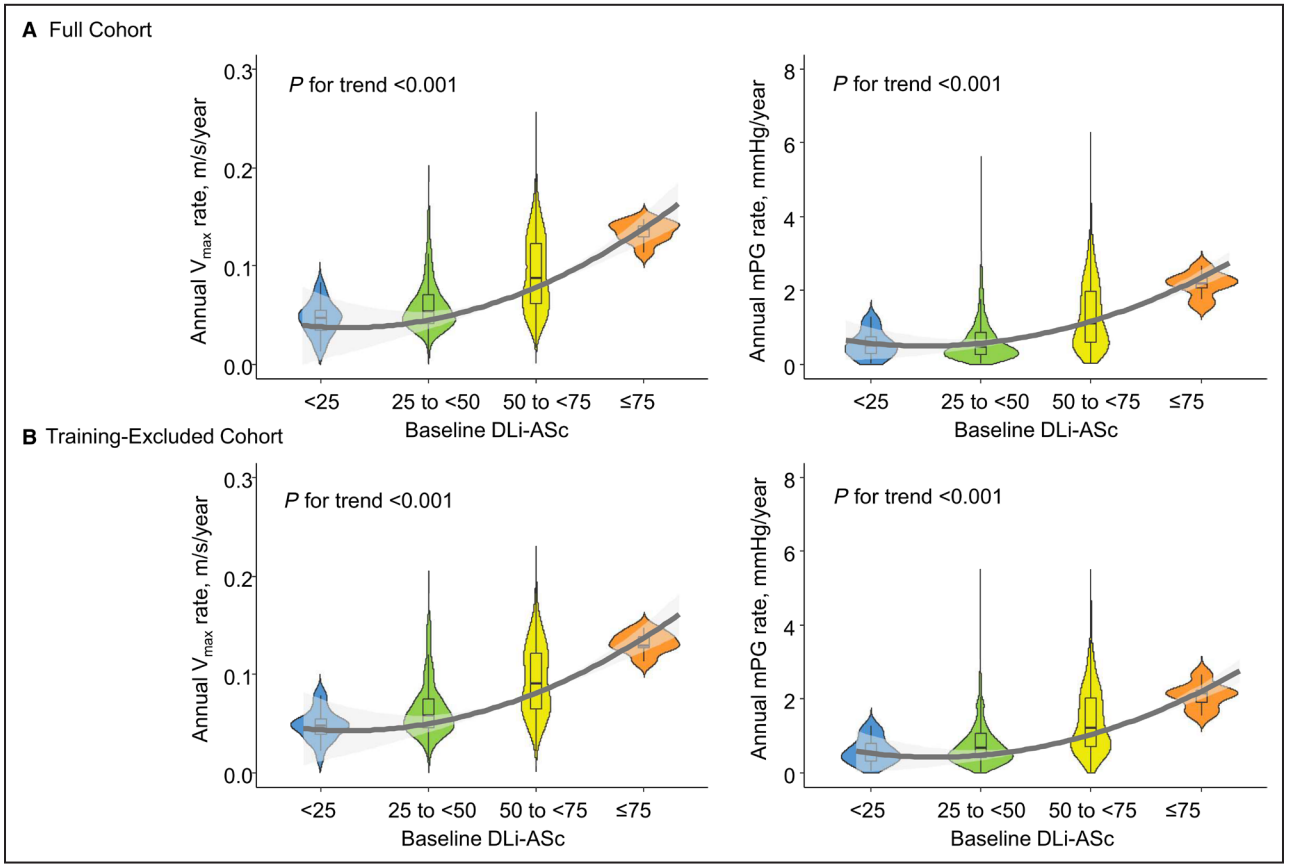

Figure 5. Baseline DLi-ASc and its association with annualized changes in AV V_{max} and mPG.
A, Full cohort. **B**, Training-excluded cohort. AV indicates aortic valve; DLi-ASc, deep learning–derived index for the aortic stenosis continuum; mPG, mean pressure gradient; and V_{max}, AV maximal velocity.

group. For example, in the V_{max}-adjusted model, DLi-ASc of 60 to 70 and ≥70 were associated with HRs of 4.59 (95% CI, 2.37–8.89) and 10.80 (95% CI, 5.60–20.81), respectively. In the training-excluded cohort, the adjusted HR per 10-point increase in DLi-ASc was 3.21 (95% CI, 2.65–3.89) with clinical factors only, 2.19 (95% CI, 1.82–2.62) with V_{max} adjustment, and 2.53 (95% CI, 2.08–3.07) with mPG adjustment. Consistent findings were observed for categorical DLi-ASc groups. Variance inflation factors for DLi-ASc and Doppler covariates were all <2.0 across models, indicating that multicollinearity was not a material concern.

Cumulative incidence curves accounting for death and AV replacement as a competing risk demonstrated a gradual increase in the risk of severe AS progression across higher baseline DLi-ASc categories in both full and training-excluded cohorts (Figure 7). Notably, patients with baseline DLi-ASc ≥60 consistently showed greater cumulative incidence than those with lower DLi-ASc; the curves for the 60 to 70 and ≥70 groups appeared largely comparable over time.

To evaluate the robustness of the prognostic association of DLi-ASc in a clinically confirmed AS population, we performed a sensitivity analysis excluding prediagnosis TTEs, defining baseline as the first examination at which AS was diagnosed (Figure S7). In this subset, DLi-ASc remained independently associated with severe AS progression across all adjustment models. For example, in the full cohort, the adjusted HR per 10-point increase was 1.86 (95% CI, 1.59–2.17) after AV V_{max} adjustment and 2.11 (95% CI, 1.79–2.49) after AV mPG adjustment. Similar associations were observed in the training-excluded cohort. These findings confirm the robustness of DLi-ASc as a prognostic marker even when restricted to postdiagnosis follow-up.

We performed an additional sensitivity analysis accounting for potential interval censoring due to irregular echocardiographic follow-up intervals (Table S4). Using parametric survival models for interval-censored data with a Weibull baseline distribution, the results were consistent with the primary Fine–Gray analyses. In the full cohort, the adjusted HR per 10-score increase in baseline DLi-ASc was 2.73 (95% CI, 2.37–3.16) after adjustment for AV V_{max}

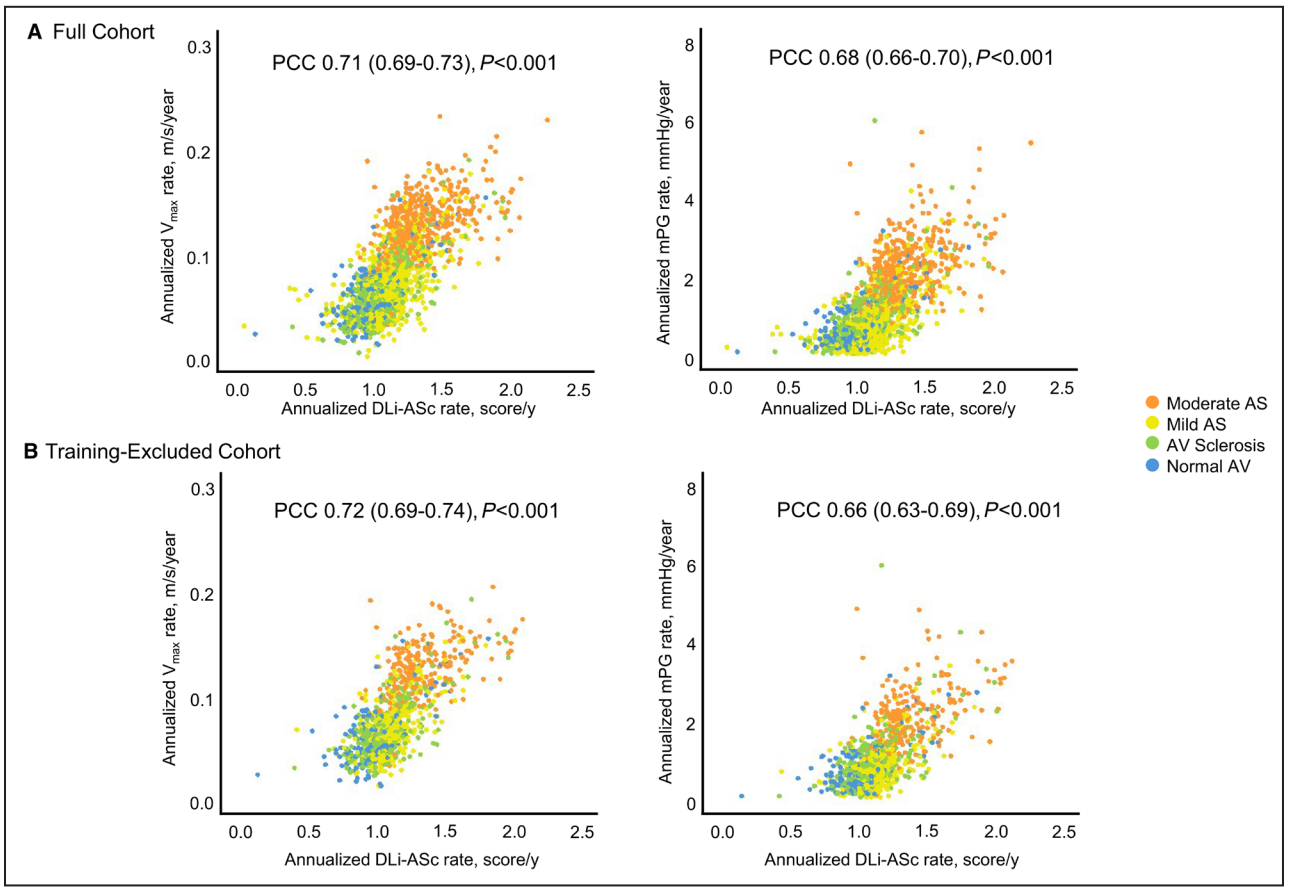

Figure 6. Association between annual rates of DLi-ASc and conventional AS parameters.
A, Full cohort. **B**, Training-excluded cohort. AS indicates aortic stenosis; DLi-ASc, deep learning-derived index for the aortic stenosis continuum; and PCC, Pearson correlation coefficient.

and 3.45 (95% CI, 3.02–3.95) after adjustment for AV mPG. Similar results were found in the training-excluded cohort. These results further confirmed the robustness of the prognostic association of DLi-ASc with severe AS progression, even when potential interval censoring was accounted for.

Table 2. Prognostic Value of Baseline DLi-ASc for Severe AS Progression Under Different Adjustment Strategies

	Unadjusted HR (95% CI)	Adjusted HR (95% CI) (clinical factors)	Adjusted HR (95% CI) (clinical factors+AV V_{max})	Adjusted HR (95% CI) (clinical factors+AV mPG)
Full cohort				
DLi-ASc, per 10-score increase	3.88 (3.18–4.74)	4.01 (3.38–4.75)	2.38 (2.07–2.76)	2.80 (2.39–3.27)
DLi-ASc <50	Reference	Reference	Reference	Reference
DLi-ASc 50 to <60	4.68 (3.81–5.74)	4.86 (3.94–6.00)	3.11 (2.55–3.80)	3.66 (2.98–4.51)
DLi-ASc 60 to <70	24.23 (17.28–33.97)	25.28 (17.96–35.59)	4.53 (2.34–8.77)	7.01 (3.84–12.78)
DLi-ASc 70≤	31.82 (15.12–66.93)	33.18 (16.31–67.51)	10.63 (5.51–20.50)	16.13 (8.36–31.12)
Training-excluded cohort				
DLi-ASc, per 10-score increase	3.02 (2.40–3.80)	3.16 (2.61–3.83)	2.15 (1.80–2.58)	2.49 (2.05–3.03)
DLi-ASc <50	Reference	Reference	Reference	Reference
DLi-ASc 50 to <60	4.73 (3.56–6.29)	4.85 (3.62–6.52)	3.03 (2.30–3.99)	3.54 (2.66–4.73)
DLi-ASc 60 to <70	15.53 (9.79–24.64)	16.06 (10.08–25.57)	3.50 (1.32–9.28)	6.04 (2.52–14.47)
DLi-ASc 70≤	19.38 (5.89–63.77)	20.13 (6.41–63.20)	9.38 (3.47–25.36)	13.82 (4.90–38.99)

Clinical factors include age, sex, and estimated glomerular filtration rate. Subdistribution HRs were estimated using Fine–Gray competing risk models for severe AS progression. AS indicates aortic valve stenosis; AV, aortic valve; DLi-ASc, deep learning–derived index for the aortic stenosis continuum; HR, hazard ratio; mPG, mean pressure gradient; and V_{max}, maximal velocity.

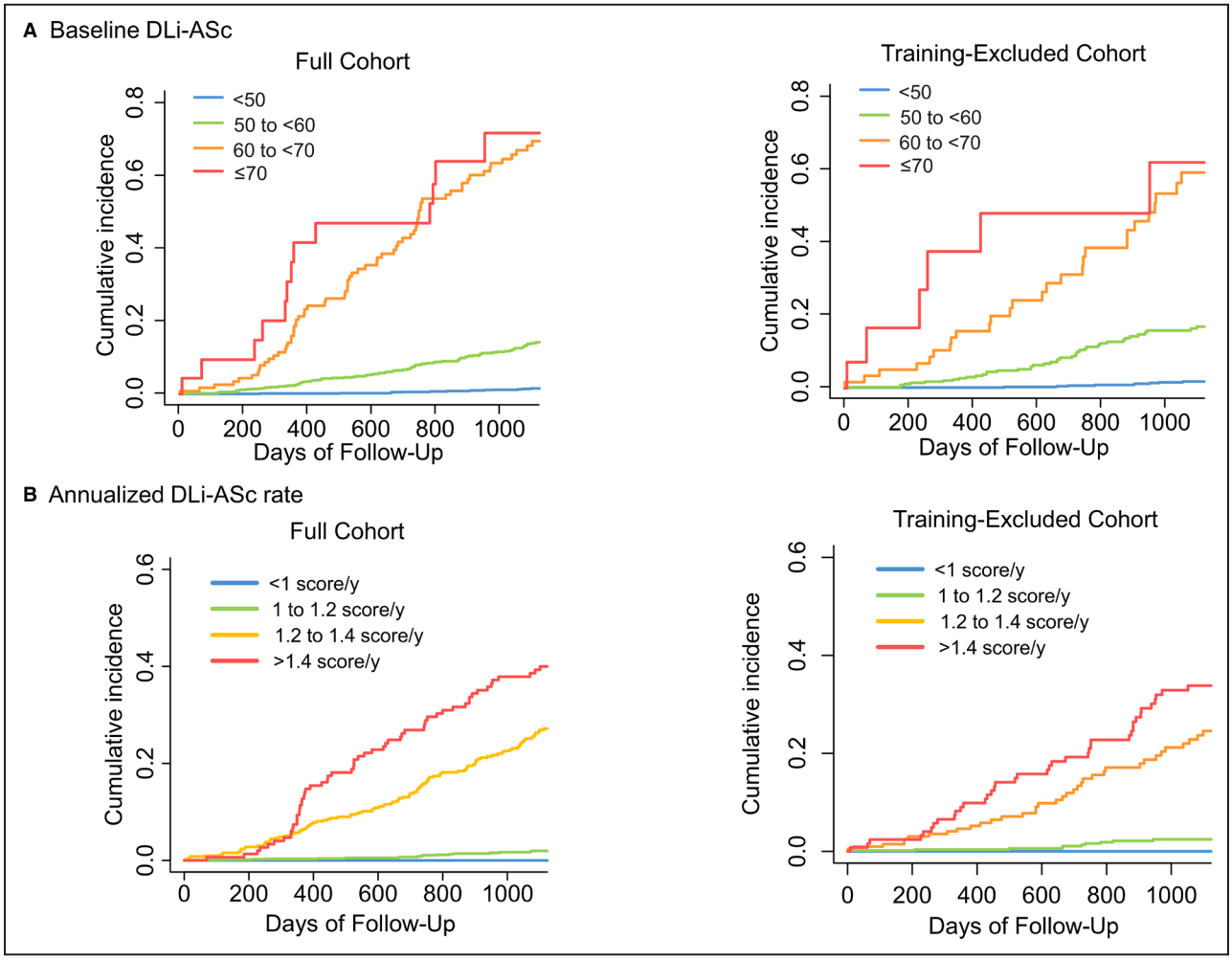

Figure 7. Cumulative incidence of severe AS progression stratified by baseline DLi-ASc and its annualized change.
A, Baseline DLi-ASc. **B**, Annualized DLi-ASc rate. AS indicates aortic stenosis; and DLi-ASc, deep learning–derived index for the aortic stenosis continuum.

Prognostic Association of the Annualized Rate of Change in DLi-ASc

Spline curve analyses demonstrated a generally linear increase in the subdistribution hazard of severe AS progression at 3 and 5 years with higher annualized rates of change in DLi-ASc, indicating a graded relationship between the trajectory of DLi-ASc and progression risk (Figure S8). To complement continuous analysis, we also evaluated the categorical annualized rate group (<1.0, 1.0 to <1.2, 1.2 to <1.4, and ≥1.4 points/y).

We evaluated prognostic association using 3 adjustment strategies, each including baseline DLi-ASc: (1) DLi-ASc plus clinical factors only (age, sex, and estimated glomerular filtration rate), (2) DLi-ASc plus clinical factors and baseline AV V_{max}, and (3) DLi-ASc plus clinical factors and baseline AV mPG. The annualized rate remained significantly associated with severe AS progression across all models (Table 3). When analyzed as a categorical variable, compared with <1.0 score/y, an increase ≥1.4 scores/y was associated with adjusted HRs of 12.30 (95% CI, 5.83–25.96) in the V_{max}-adjusted model and 20.02 (95% CI, 9.17–43.71) in the mPG-adjusted model. Variance inflation factors for baseline DLi-ASc, its annualized rate, and Doppler covariates were all <2.5 across models, indicating no evidence of problematic multicollinearity.

Cumulative incidence analyses further demonstrated that patients with a rapid annualized increase (≥1.2 points/y) had a substantially higher risk of progression to severe AS compared with those with slower progression (Figure 7). These findings highlight that both baseline DLi-ASc and its trajectory provide complementary prognostic information, supporting a more dynamic approach to patient surveillance.

All analyses were repeated in the training-excluded cohort (Table 3, Figure 7) and in a subset excluding prediagnosis TTEs (Figure S9), and results were

Table 3. Prognostic Value of Annualized Rate of Change in DLi-ASc for Severe AS Progression Under Different Adjustment Strategies

	Adjusted HR (95% CI) (baseline DLi-ASc)	Adjusted HR (95% CI) (clinical factors+baseline DLi-ASc)	Adjusted HR (95% CI) (clinical factors+AV V_{max}+baseline DLi-ASc)	Adjusted HR (95% CI) (clinical factors+AV mPG+Baseline DLi-ASc)
Full cohort				
Annualized DLi-ASc increasing rate, per score/y	13.25 (8.87–19.79)	13.07 (8.84–19.32)	2.39 (1.19–4.80)	3.88 (2.03–7.42)
<1 score/y	Reference	Reference	Reference	Reference
1–1.2 score/y	3.26 (3.08–12.7)	6.54 (3.21–13.33)	5.58 (2.76–11.25)	6.38 (3.13–12.99)
1.2–1.4 score/y	32.15 (15.90–65.00)	33.03 (16.32–66.86)	17.20 (8.12–36.45)	23.32 (11.15–48.78)
>1.4 score/y	42.51 (20.94–86.30)	43.65 (21.51–88.57)	13.60 (6.20–29.84)	20.02 (9.17–43.71)
Training-excluded cohort				
Annualized DLi-ASc increasing rate, per score/y	15.52 (10.03–24.00)	15.25 (9.92–23.44)	2.22 (1.29–3.83)	3.63 (2.14–6.14)
<1 score/y	Reference	Reference	Reference	Reference
1–1.2 score/y	5.38 (2.49–11.58)	5.48 (2.54–11.84)	4.72 (2.24–9.94)	5.32 (2.51–11.28)
1.2–1.4 score/y	25.50 (11.82–55.02)	25.30 (11.72–54.60)	13.25 (5.95–29.50)	17.40 (8.08–37.46)
>1.4 score/y	36.56 (17.14–78.02)	36.54 (17.11–78.06)	11.08 (4.75–25.86)	15.33 (6.93–33.94)

Clinical factors include age, sex, and estimated glomerular filtration rate. Subdistribution HRs were estimated using Fine–Gray competing risk models for severe AS progression. AS indicates aortic stenosis; AV, aortic valve; DLi-ASc, deep learning–derived index for the aortic stenosis continuum; HR, hazard ratio; mPG, mean pressure gradient; and V_{max}, maximal transvalvular velocity.

consistent across both sensitivity analyses, confirming the robustness of these findings.

DISCUSSION

In this longitudinal study, we applied previously validated DLi-ASc to serial TTE examination. Both baseline score and annualized rate of change were strongly associated with progression of conventional echocardiographic parameters (AV V_{max} and mPG) and were independently associated with severe AS progression in competing risk-adjusted models. By quantifying temporal score change as annualized rates, we demonstrated that DLi-ASc not only mirrors the natural trajectory of AS but also provides prognostic information beyond baseline risk stratification. Taken together, these findings highlight the complementary value of baseline DLi-ASc and its trajectory: The baseline score identifies patients predisposed to faster progression, while the rate of change refines risk estimation during follow-up and enables more dynamic disease monitoring.

The role of AI in TTE is evolving. Early applications focused on automating manual measurements, enhancing accuracy, and reproducibility. With most TTE parameters now capable of automation, AI has expanded to disease severity assessment, as seen in diastolic dysfunction[16,17] and AS evaluation.[8] More recently, AI has progressed beyond parameter-based analysis to DL-based direct TTE video analysis, aiming to mimic expert visual assessment. Some efforts have targeted specific conditions with high clinical relevance, such as AS,[5–7] diastolic dysfunction,[16] hypertrophic cardiomyopathy, and pericardial disease,[18,19] developing task-oriented models that provide precise evaluation of a single disease. In parallel, similar research efforts have also pursued comprehensive multitask or foundation models, such as PanEcho,[20] EchoPrime,[21] EchoCLIP,[22] and EchoFM,[23] which aim to replicate the global synthesis performed by expert echocardiographers across multiple findings. In our previous study, we developed a DL model capable of accurately assessing AS severity using PLAX and PSAX views.[5] The strength of this DL-based index lies in its ability to mimic visual analysis while providing a quantitative digital marker. Our prior work validated this approach in a large cross-sectional cohort, confirming its diagnostic performance. However, while the model was designed to reflect the AS disease continuum, whether DLi-ASc would increase in parallel with AS progression over time remained unclear.

Several DL-based indices have been proposed for AS severity assessment[5–7] differing in input views, labeling strategies, and intended clinical applications. Holste et al introduced a PLAX view–based model trained to detect severe AS (digital AS severity index) and demonstrated high diagnostic performance in both internal and external test cohorts.[6] A subsequent follow-up study by Oikonomou et al extended the evaluation of this same model to baseline prognostic analyses and longitudinal follow-up, showing that baseline scores predicted subsequent severe AS and AV replacement.[9] While our study shares a

similar conceptual framework with this prior work,[9] it was designed to extend this line of research in 2 key directions. First, we demonstrated that a DLi-ASc not only reflects future progression but also increases longitudinally in parallel with the natural course of AS, establishing it as a dynamic biomarker that captures disease trajectory. Second, we showed that the annualized rate of DLi-ASc increase was independently associated with severe AS progression beyond baseline DLi-ASc, highlighting that both the static level and its temporal change convey complementary risk information. Together, these distinctions advance the role of DL-based indices from static cross-sectional predictors to dynamic longitudinal markers capable of capturing both disease severity and progression velocity.

Cumulative incidence analyses, together with categorical Fine–Gray models, consistently demonstrated that both higher baseline scores (particularly ≥60) and rapid annualized increases (≥1.2 points/y) were associated with a sharp rise in the risk of severe AS progression. This concordance across analytic approaches reinforces the robustness of these thresholds and underscores the complementary value of baseline level and longitudinal trajectory in identifying patients at higher risk. These findings support the potential role of DLi-ASc in guiding personalized surveillance strategies: Rather than applying uniform monitoring intervals to all patients with AS, integrating both baseline and longitudinal information may enable earlier detection of rapid progression and tailoring follow-up intensity. In addition, although current AS management primarily focuses on AV replacement after severe AS develops, the ability to quantify AS progression with DLi-ASc could become particularly valuable if medical treatment to slow AS progression becomes available in the future. In such contexts, both baseline and longitudinal DLi-ASc could serve as objective digital markers for monitoring treatment response and identifying patients who may benefit from earlier or more aggressive intervention. Despite its promise, clinical implementation of AI-based tools like DLi-ASc may be influenced by factors such as accessibility, cost, and integration into existing echocardiographic workflows. Further research should validate its clinical applicability across diverse settings and to develop strategies for seamless implementation in standardized clinical pathways.

This study has several limitations. First, the retrospective nature of data collection introduces inherent constraints. In particular, the data set was derived from electronic health records, where TTEs were performed on the basis of clinical indications rather than a standardized protocol. This indication-driven acquisition may introduce variability in follow-up timing and disease spectrum, which could affect the generalizability of our findings, especially when extending validation to community-based cohorts. Irregular TTE intervals, inherent to such indication-driven follow-up, limited the precision of annual progression estimates based on either conventional AS parameters or DLi-ASc. To address this, we used LMMs, which account for repeated measures and variable follow-up intervals, thereby reducing bias from irregular TTE schedules and improving the robustness of the estimated progression rate. While a prospective study with a standardized follow-up protocol would be the most rigorous design for validating DLi-ASc as a longitudinal monitoring tool, such studies require substantial time, resources, and patient enrollment. Large-scale retrospective analyses such as the present work are, therefore, a necessary first step to generate the preliminary evidence needed to justify and design such prospective investigations. Moreover, most real-world AS surveillance occurs in nonprotocolized environments; thus, our findings provide insight into the potential performance of DLi-ASc in the setting where it would most likely be applied.

In addition, although commonly used,[9,24] progression tracking relied primarily on flow-dependent metrics such as V_{max} and mPG, which are susceptible to variations in stroke volume and hemodynamic loading conditions. However, diagnosis of severe AS was not based solely on these parameters but rather on comprehensive clinical interpretation that incorporated flow status documented in TTE reports and, when available, results from additional diagnostic tests. For future validation, prospective studies with standardized follow-up protocols, incorporating both flow-dependent and flow-independent measures such as computed tomography–based AV calcium scoring, could further validate the value of DLi-ASc in assessing the temporal dynamics of AS progression in a more systematic manner and may also enable advanced modeling approaches, such as trajectory clustering or unsupervised pattern recognition, to explore distinct AS progression phenotypes.

Furthermore, although coronary artery disease is a major competing risk in patients with mild to moderate AS, coronary artery disease–specific diagnostic or outcome data were not uniformly available due to the retrospective design. To mitigate potential bias, we applied a Fine–Gray competing risk model, treating death as a competing event. Still, the lack of adjudicated coronary artery disease outcomes remains a limitation, and future studies should incorporate comprehensive ischemic event data to further evaluate the prognostic value of DLi-ASc.

The data set was derived from 2 tertiary hospitals in South Korea, where TTE examinations were performed by specialized cardiologists with expertise in echocardiography. While this ensures high-quality imaging and reliable data, it also raises concerns about generalizability to resource-limited settings, where nonexperts often perform TTE. Since DLi-ASc was

developed to enhance AS assessment across diverse clinical environments, further studies are needed to evaluate its performance in settings with limited echocardiographic expertise. In addition, the study cohort was restricted to patients who had AS diagnosed either at baseline or during follow-up, with exclusion of those with discordant AS classification or moderate to severe concomitant valvular disease. This strategy was intended to minimize confounding when tracking AS progression with flow-dependent parameters, but it inevitably narrows the study population and may limit broader applicability. Extending validation to a more inclusive population, particularly those without significant AS at baseline, remains an important direction for future research. Additionally, while DL analysis was successfully performed in all cases and DLi-ASc generally increased over time, transient decreases were occasionally observed, particularly with short follow-up intervals. These likely reflect technical or image-related variability, representing an inherent limitation of DL-based image analysis. Because discrimination metrics (area under the curve) for DLi-ASc were estimated within the same data set in which score thresholds were derived, these performance estimates should be interpreted with caution, as some degree of optimism bias may exist. Finally, to ensure broader generalizability, additional research in diverse racial and geographic populations is essential to establish the clinical applicability and real-world implications of DLi-ASc.

CONCLUSIONS

This study demonstrated the utility of DLi-ASc as a dynamic, longitudinal marker for monitoring and characterizing the progression of AS. Both baseline levels and the annualized rate of change were significantly associated with faster hemodynamic progression and were independently associated with future severe AS in competing risk–adjusted models. By showing that a DL-derived index not only mirrors the natural course of AS but also that its rate of increase carries independent prognostic value, this work advances AI-based echocardiographic biomarkers from static evaluation toward dynamic disease tracking and risk refinement. Together, the baseline level and longitudinal trajectory of DLi-ASc provide complementary information, supporting its potential as a noninvasive imaging biomarker to monitor disease course, identify high-risk patients, and guide personalized surveillance strategies.

ARTICLE INFORMATION

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Disclosures

Y.E.Y., J.J., J.K., and S.A.L. are currently affiliated with Ontact Health, Inc. J.J., J.K., and S.A.L are coinventors on a patent related to this work filed by Ontact Health (Method for Providing Information on Severity of Aortic Stenosis and Device Using the Same). H.J.C., and Y.E.Y. hold stock in Ontact Health, Inc. The other authors have no conflicts of interest to declare.

Supplemental Material

Tables S1–S4
Figures S1–S9

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