Fully Automated Artificial Intelligence Assessment of Aortic Stenosis by Echocardiography

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Background: Aortic stenosis (AS) is a common form of valvular heart disease, present in over 12% of the population age 75 years and above. Transthoracic echocardiography (TTE) is the first line of imaging in the adjudication of AS severity but is time-consuming and requires expert sonographic and interpretation capabilities to yield accurate results. Artificial intelligence (AI) technology has emerged as a useful tool to address these limitations but has not yet been applied in a fully hands-off manner to evaluate AS. Here, we correlate artificial neural network measurements of key hemodynamic AS parameters to experienced human reader assessment.

Methods: Two-dimensional and Doppler echocardiographic images from patients with normal aortic valves and all degrees of AS were analyzed by an artificial neural network (Us2.ai) with no human input to measure key variables in AS assessment. Trained echocardiographers blinded to AI data performed manual measurements of these variables, and correlation analyses were performed.

Results: Our cohort included 256 patients with an average age of 67.6 ± 9.5 years. Across all AS severities, AI closely matched human measurement of aortic valve peak velocity ($r = 0.97$, $P < .001$), mean pressure gradient ($r = 0.94$, $P < .001$), aortic valve area by continuity equation ($r = 0.88$, $P < .001$), stroke volume index ($r = 0.79$, $P < .001$), left ventricular outflow tract velocity-time integral ($r = 0.89$, $P < .001$), aortic valve velocity-time integral ($r = 0.96$, $P < .001$), and left ventricular outflow tract diameter ($r = 0.76$, $P < .001$).

Conclusions: Artificial neural networks have the capacity to closely mimic human measurement of all relevant parameters in the adjudication of AS severity. Application of this AI technology may minimize interscan variability, improve interpretation and diagnosis of AS, and allow for precise and reproducible identification and management of patients with AS. (J Am Soc Echocardiogr 2023;36:769-77.)

Keywords: Aortic stenosis, Echocardiography, Doppler, Artificial intelligence, Machine learning

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Abbreviations

2D = Two-dimensional

AI = Artificial intelligence

AS = Aortic stenosis

AV = Aortic valve

AVA = Aortic valve area

AVR = Aortic valve replacement

FDA = Food and Drug Administration

HEART = Heart Failure Etiology and Analysis Research Team

IEC = Individual equivalence coefficient

LVEF = Left ventricular ejection fraction

LVOT = Left ventricular outflow tract

LVOTd = Left ventricular outflow tract diameter

MPG = Mean pressure gradient

POCUS = Point-of-care ultrasound

SVi = Stroke volume index

TTE = Transthoracic echocardiography

Vmax = Peak velocity

VTI = Velocity-time integral

Aortic stenosis (AS) is the most common valvular heart disease in Western countries, present in over 12% of the population age 75 years and older,[1] and is uniformly progressive. Patients with a severe degree of AS experience a 25.6% 2-year all-cause mortality rate.[2] Even before symptom development or progression to severe obstruction, irreversible myocardial damage in the form of left ventricular hypertrophy, fibrosis, and impairment can occur, resulting in increased morbidity and mortality unmitigated by aortic valve replacement (AVR).[3-5] Thus, timely identification and appropriate risk stratification of these patients are critical.

Due to widespread availability and low testing risk, transthoracic echocardiography (TTE) is the first line of imaging in the diagnosis of AS. Current TTE techniques have several limitations, however. Accurate determination of AS severity by TTE requires advanced scanning and interpretation expertise, which may be lacking in general community settings. Moreover, in emergency room or acute inpatient settings, around-the-clock access to sonographers and cardiologists is unavailable and providers' time to scan is limited. Prompt identification of severe AS in acutely ill patients can have substantial implications for clinical management. The identification of automated TTE measurements to aid in classifying AS severity would improve accuracy and consistency while providing rapid diagnostic information to guide life-saving therapy.

Advances in artificial intelligence (AI), machine learning, and deep learning have demonstrated much promise in transforming the landscape of echocardiography. Some recent examples of the application of innovative AI technology to echocardiography include fully automated echocardiographic interpretation,[6] assessment of systolic and diastolic function,[7] and measurement of global longitudinal strain.[8] Although machine learning frameworks have been employed to risk stratify AS using manually derived TTE measurements,[9-11] a fully hands-off methodology has not been investigated.

The objective of this study was to test the ability of an artificial neural network to accurately measure aortic valve (AV) peak velocity (Vmax), AV velocity-time integral (VTI), AV mean pressure gradient (MPG), left ventricular outflow tract (LVOT) diameter (LVOTd), LVOT VTI, stroke volume index (SVi), and AV area (AVA) derived through the continuity equation from two-dimensional (2D) echocardiographic and Doppler images as compared against gold standard, trained human measurements.

METHODS

Study Population and Design

Clinically indicated echocardiographic images of adult patients ages ≥18 years with at least 1 TTE performed between September 1, 2008, and February 28, 2022, at the University of Illinois at Chicago were included to create this cohort. Two hundred fifty-six patients were randomly selected with no AS ($n = 94$) or mild ($n = 53$), moderate ($n = 63$), or severe ($n = 46$) AS. Exclusion criteria included the presence of a bicuspid AV or AV prosthesis. The study was approved by the University of Illinois at Chicago Institutional Review Board with waiver of consent.

Echocardiography and Experienced Reader Evaluation

Transthoracic echocardiogram studies were performed by trained sonographers using commercially available ultrasound systems (Philips, GE, Siemens). A standardized imaging protocol was utilized that included assessments of valvular function based on the American Society of Echocardiography guidelines.[12,13] Relevant measured echocardiographic variables included AV Vmax (m/sec), MPG (mm Hg), AV VTI by continuous-wave Doppler (cm), LVOT VTI by pulse wave Doppler (cm), and LVOTd (cm). When Vmax was > 2 m/sec, additional interrogation of apical, suprasternal notch, and right parasternal windows was performed with a nonimaging Pedoff probe. These measurements were used to calculate AVA by the continuity equation, where $\text{AVA} = \frac{\left[\pi\left(\frac{\text{LVOTd}}{2}\right)^2 \times \text{LVOT VTI}\right]}{\text{AV VTI}}$. The SVi was also calculated, where $\text{SVi} = \pi\left(\frac{\text{LVOTd}}{2}\right)^2 \times \text{LVOT VTI}$.

Patients were initially selected for the study based on the aortic severity classification listed on the final sonography report read by an experienced, National Board of Echocardiography–certified cardiologist. Manual measurements of AV VTI and LVOT VTI were then performed by 3 trained physicians (K.D., B.S., A.T.). Due to the potential for error in calculation of the AVA as a squared value, the LVOTd was measured by 2 level III echocardiographers (H.K., M.K.). The LVOTd was measured by both human reader and AI in midsystole, at the level of leaflet insertion. Typically, these values are all single representative measurements. In cases of atrial fibrillation or significant beat-to-beat variability, however, the readers averaged 5 representative beats to come to the final AV VTI and LVOT VTI values; post-extrasystolic beats were excluded.[13] The final AS classification was made based on the European Association of Echocardiography/American Society of Echocardiography recommendations for the assessment of valvular stenosis.[13,14] In cases of concordance between Vmax, MPG, and AVA, AS classification was assigned automatically. In cases of discordance, the level III echocardiographers (H.K., M.K.) rendered final expert adjudication utilizing the entirety of the echocardiogram. All readers were blinded to AI data.

Us2.ai

Us2.ai has developed a Food and Drug Administration– (FDA-) approved AI-driven solution that automates the interpretation of the echocardiogram, thus providing clinical decision support to expert and nonexpert medical practitioners. The Us2.ai algorithms have been cleared by the US FDA following validation at the Harvard/Brigham and Women's Hospital Echo Core Lab, where the deep-learning interpretations of 23 echocardiographic

HIGHLIGHTS

- AI was applied to echocardiograms with normal AVs and AS.
- AI and human measurements of AV Doppler and area measurements were closely matched.
- Artificial neural networks have the capacity to mimic human measurements in AS.

parameters—including cardiac volumes, ejection fraction, and Doppler measurements—were compared with 3 repeated measurements by core lab human experts. The primary outcome metric was the individual equivalence coefficient (IEC), which compares the disagreement between deep learning and human readers relative to the disagreement among human readers. The predetermined noninferiority criterion was 0.25 for the upper bound of the 95% CI. Secondary outcomes included measures of agreement, including the mean absolute deviation. Among 602 studies from 600 participants (421 with heart failure, 179 controls, 69% women) with a mean age of 57 ± 16 years, the point estimates of IEC were all <0, indicating that the disagreement between the deep-learning and human measures were lower than the disagreement among 3 core lab readers, and the upper bound of the 95% CI of IECs fell below the prespecified success criterion of 0.25. Secondary end points showed good agreement of automated with human expert measurements, with comparable or lower mean absolute deviations between automated and human experts relative to the mean absolute deviation among human experts. This prior prospective validation study demonstrated excellent agreement between deep learning and expert human interpretation for a wide range of echocardiographic measurements.

Furthermore, the Us2.ai algorithms have been externally validated in diverse real-world cohorts:[7] in a curated data set from Canada (Alberta Heart Failure Etiology and Analysis Research Team; HEART; n = 1,029 echocardiograms), a real-world data set from Taiwan (n = 31,241), the US-based EchoNet-Dynamic data set (n = 10,030), and an independent prospective assessment of the Asian (ATTRaCT) and Canadian (Alberta HEART) data sets (n = 142) with repeated independent measurements by 2 expert sonographers. In the ATTRaCT test set, the automated workflow classified 2D videos and Doppler modalities with accuracies (number of correct predictions divided by the total number of predictions) ranging from 0.91 to 0.99. The deep-learning algorithms were demonstrated to automatically annotate 2D videos and Doppler modalities with similar accuracy to manual measurements by expert sonographers.

Building upon this work, Us2.ai has created deep-learning algorithms to automate measurements necessary to AS severity adjudication. To the authors' knowledge, no prior data exist examining the accuracy of fully automated AS assessment as compared against expert human reader measurements.

Artificial Intelligence Analysis

All studies retrospectively had the AI algorithms applied to their images. Transthoracic echocardiograms were deidentified and manually uploaded to the Us2.ai platform. Us2.ai's platform automates the entire workflow of echocardiographic analysis and interpretation, including (1) identifying the correct 2D, color flow, or Doppler view; (2) determining cardiac structures by segmentation and annotation; and (3) generating decision support outcomes about cardiac structure and function, namely, Vmax, MPG, and AVA (Figure 1).

A rigorous confidence check process is utilized to ensure accuracy in the measurements. The view classifier convoluted neural network assesses the shape and placement of the annotation trace, evaluates systolic and diastolic phase congruency with the electrocardiogram, and checks that the automated measurement falls within a physiologic range. The highest-quality data are obtained across all image files and all frames within each file. The convoluted neural network follows decision rules and will exclude images from further analysis if they fail the prespecified checks and no measurement will be generated.

Aortic valve area is calculated by the AI system using the same LVOT-based continuity equation utilized by the human readers, described above. The AI averages all quality-checked LVOT and AV VTI measurements in the echocardiogram to arrive at the final value used in the continuity calculation. No member of the Us2.ai team was involved in manual echocardiographic data acquisition, and all AI measurements were performed in an automated manner with no human manipulation.

Statistical Analysis

All numerical data are presented with mean ± SD or median with interquartile range according to their distributions. Proportions of patients were reported by the number of patients out of the total studied patients. Patient characteristics and echocardiographic measures were summarized using descriptive statistics. Correlation coefficients between human and AI algorithms measurements were tested using Pearson's correlation. Significance is tested by Pearson's product moment correlation coefficient. All statistical analyses were performed using R version 3.4.1 (Foundation for Statistical Computing). A 2-tailed P value of <.05 was considered statistically significant.

RESULTS

Artificial Intelligence

All 256 patient echocardiograms were submitted through the Us2.ai platform, which performed a series of quality checks before yielding automated measurements (Figure 2). A total of 37 studies (14%) had at least 1 uninterpretable parameter (LVOTd, AV VTI, or LVOT VTI) due to various 2D image or Doppler data quality issues, which ultimately resulted in an inability to calculate AVA in these studies. The most common cause for exclusion was an inability to confidently measure LVOTd in 16 (6%) studies. In all 256 echocardiograms, the AI was able to make at least 1 AS measurement: Vmax, MPG, and/or AVA.

Baseline Characteristics

Baseline characteristics are shown in Table 1. Of the initial 256 patient cohort, further demographic and comorbidity data were unavailable for 3 individuals; 138 (53.9%) were male, 120 (46.8%) were Black, and the mean age was 67.6 ± 9.5 years. Ninety-four patients had no AS, 53 had mild AS, 63 had moderate AS, and 46 had severe AS, as adjudicated by human readers. Relevant comorbidities in the

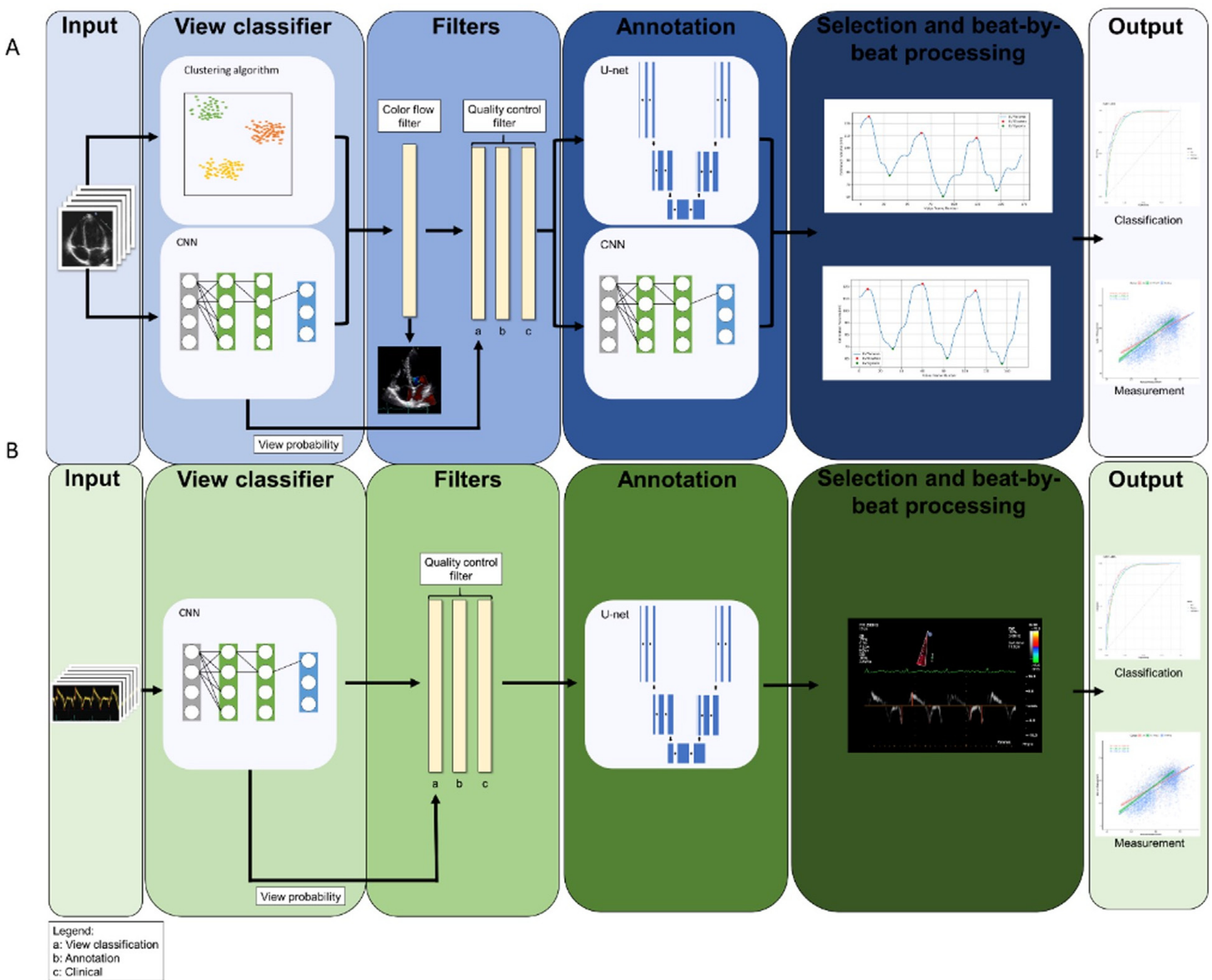

Figure 1 Schematic overview of Us2.ai workflow for 2D videos **(A)** and modalities **(B)**.

overall cohort included coronary artery disease in 109 (42.6%), type II diabetes in 105 (41.0%), hypertension in 166 (64.8%), and hyperlipidemia in 103 (40.2%). Left ventricular ejection fraction (LVEF) was < 30% in 15 (6.9%) and preserved, with LVEF ≥ 50%, in 169 (66.0%).

Correlation and Agreement

Correlation and agreement between AI-derived AS parameters and experienced human reader measured values are shown in Figures 3 to 5. Strong positive correlation and agreement were demonstrated between AI and manual measurements of the core variables used in the continuity-based calculation of AVA. These include LVOT VTI ($r = 0.89$, $P < .001$), AV VTI ($r = 0.96$, $P < .001$), and LVOTd ($r = 0.76$, $P < .001$). Utilizing these measurements, AVA showed an excellent correlation ($r = 0.88$, $P < .001$). Artificial intelligence–based SVi also demonstrated strong correlation ($r = 0.79$, $P < .001$), as did Vmax ($r = 0.97$, $P < .001$) and MPG ($r = 0.94$, $P < .001$). Table 2 shows similarity in the mean measurements of each of these parameters made by human readers compared with AI, across all degrees of AS severity. Finally, in Table 3, intraclass correlation coefficients are reported, showing high interobserver agreement between human readers across all AS measurements.

DISCUSSION

To the best of our knowledge, this is the first study demonstrating the capacity of an AI technology to accurately quantify AS severity with no human input beyond image acquisition. Our main findings are that the Us2.ai algorithm closely matches expert human measurement of AV Vmax ($r = 0.97$, $P < .001$), MPG ($r = 0.94$, $P < .001$), AVA ($r = 0.88$, $P < .001$), and SVi ($r = 0.79$, $P < .001$) across normal AVs and all grades of AS severity. Artificial intelligence technology has the capacity to closely mimic experienced human measurement of all relevant parameters in the adjudication of AS severity.

Artificial intelligence technology has previously been used on echocardiographic data sets, with measurements performed by expert human readers, to predict outcomes in AS. Machine learning, a subcategory of AI, leverages the use of complex computing and statistical algorithms to process vast quantities of information to identify the highest-yield relationships among the data.[15] Playford and colleagues[10] created an AI algorithm that used phenotypic characteristics such as LVEF, diastology, and AV Vmax abstracted from echocardiography reports to correctly grade 95.3% of severe AS patients against the gold standard AVA by continuity equation. The AI algorithm was also a significant predictor of 5-year mortality,

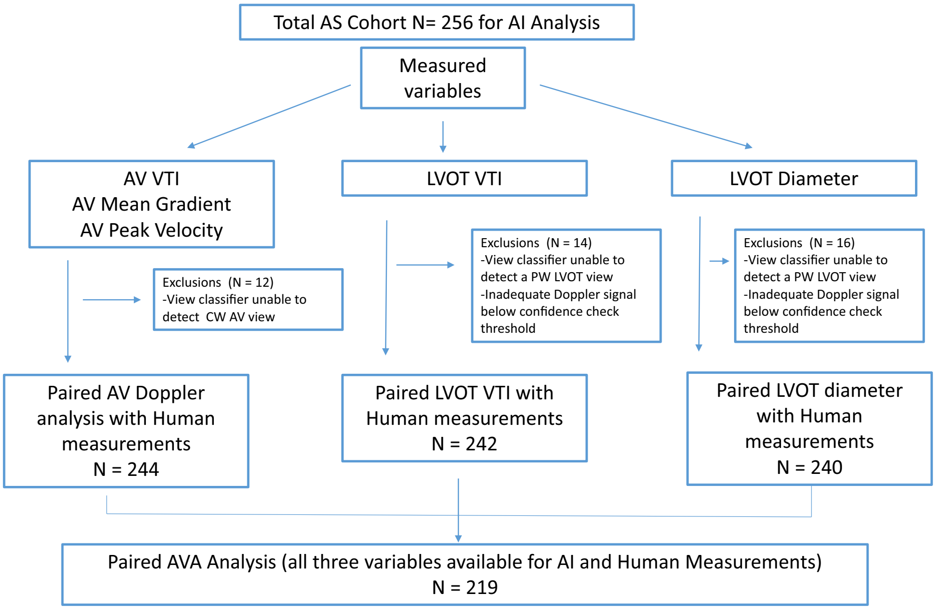

Figure 2 Flow chart demonstrating the yield of successful AI analysis of Doppler and LVOTd measurements. Artificial intelligence analysis was performed on the entire cohort (N = 256), with exclusions applied by the software for the variables depending on the ability to detect the appropriate view and application of confidence checks. Paired comparison with manually obtained measurements was performed. For AVA analysis, paired comparison was performed only if all 3 necessary variables by continuity (AVA VTI, LVOT VTI, and LVOTd) were obtainable. See text for further details and abbreviations.

Table 1 Baseline demographic and echocardiographic characteristics

	AS severity				
Variable	Normal (n = 94)	Mild (n = 53)	Moderate (n = 63)	Severe (n = 46)	P value
Age, years, mean ± SD	65.5 ± 8.2	64.9 ± 9.0	68.8 ± 9.3	73.2 ± 10.2	<.001
Gender, male	56 (59.6)	27 (50.9)	31 (49.2)	24 (52.2)	.57
Race					.012
Caucasian	16 (17)	10 (19.2)	13 (21.3)	9 (19.6)	
African American	56 (59.6)	17 (32.7)	28 (45.9)	19 (41.3)	
Other	10 (10.6)	3 (5.8)	4 (6.6)	2 (4.3)	
Ethnicity					
Hispanic	12 (12.8)	22 (42.3)	16 (26.2)	16 (34.8)	
Hypertension	74 (78.7)	44 (84.6)	7 (11.3)	41 (89.1)	.327
Hyperlipidemia	31 (33)	23 (44.2)	23 (37.1)	26 (56.5)	.006
Diabetes mellitus	31 (33)	22 (42.3)	34 (54.8)	18 (39.1)	.483
Coronary artery disease	30 (31.9)	15 (28.8)	40 (64.5)	24 (52.2)	.113
Ejection fraction:					.863
<30	5 (5.7)	2 (4.1)	3 (5)	5 (11.6)	
30-39	7 (8)	5 (10.2)	4 (6.7)	4 (9.3)	
40-49	11 (12.5)	7 (14.3)	10 (16.7)	8 (18.6)	
50-70	65 (73.9)	35 (71.4)	43 (71.7)	26 (60.5)	

Data are expressed as n (%) unless otherwise specified.

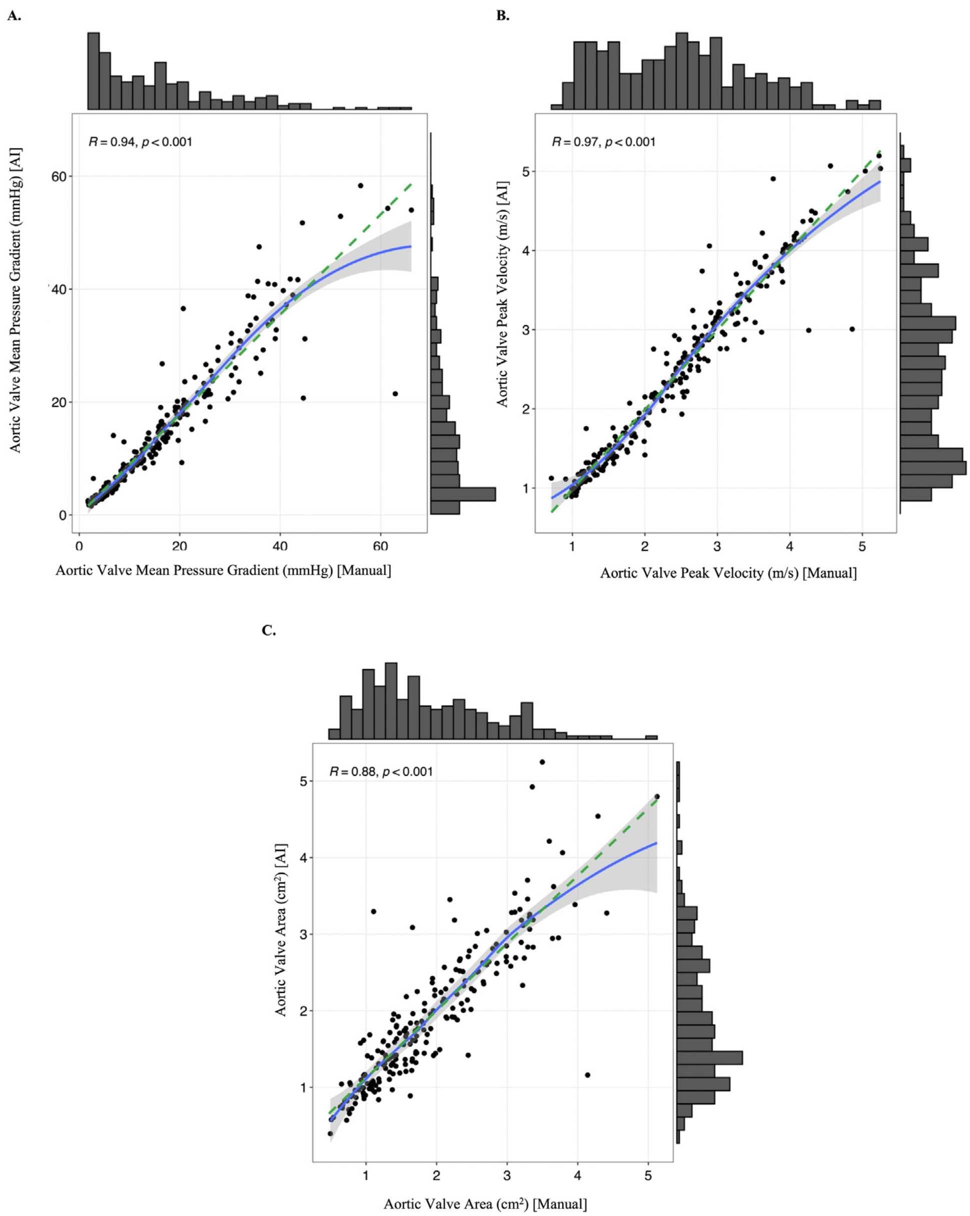

Figure 3 Artificial intelligence to experienced (manual) human reader correlations for AV Vmax, mean gradient, and AVA by continuity equation.

adjusted for age, sex, AV Vmax, and SVi, outperforming the continuity-based AVA alone. Indexed AVA, LVEF, Vmax, MPG, and SVi were utilized by Sengupta and colleagues[9] to generate a machine-learning framework that classified high- and low-risk AS. Progression to AVR or progression to death in those who did not receive AVR was better predicted by AI than by conventional classification of disease severity. However, all this prior work has relied on expert- or core lab human operator–adjudicated TTE data, which requires high-level imaging expertise and is susceptible to interobserver variability.

The technical skill requirements and time constraints in the echocardiographic assessment of AS are very real barriers in medical practice. Rural or community sites may not have access to formal cardiac imaging at all, and even in centers with echocardiography laboratories experienced in valvular heart disease, emergency rooms and inpatient wards frequently lack 24-hour per day, 7-day per week access to sonographers and echocardiographers. Point-of-care ultrasound (POCUS) technology has emerged as a tool to aid in bedside assessment of AS. Sachpekidis and colleagues[16] recently showed that point-of-care, handheld echocardiography with continuous-wave Doppler capability can provide AV Vmax similar to measurements obtained on cart-based echocardiography systems, allowing for the accurate diagnosis of clinically significant AS at the bedside. At this time, accurate POCUS AS assessment can only be performed by a limited group of providers with adequate training in echocardiography and valvular heart disease. Incorporation of cloud-based AI technology with POCUS would remove the need for such advanced training, offering high-quality, nearly instantaneous AS grading at the bedside to improve patient triage and management.

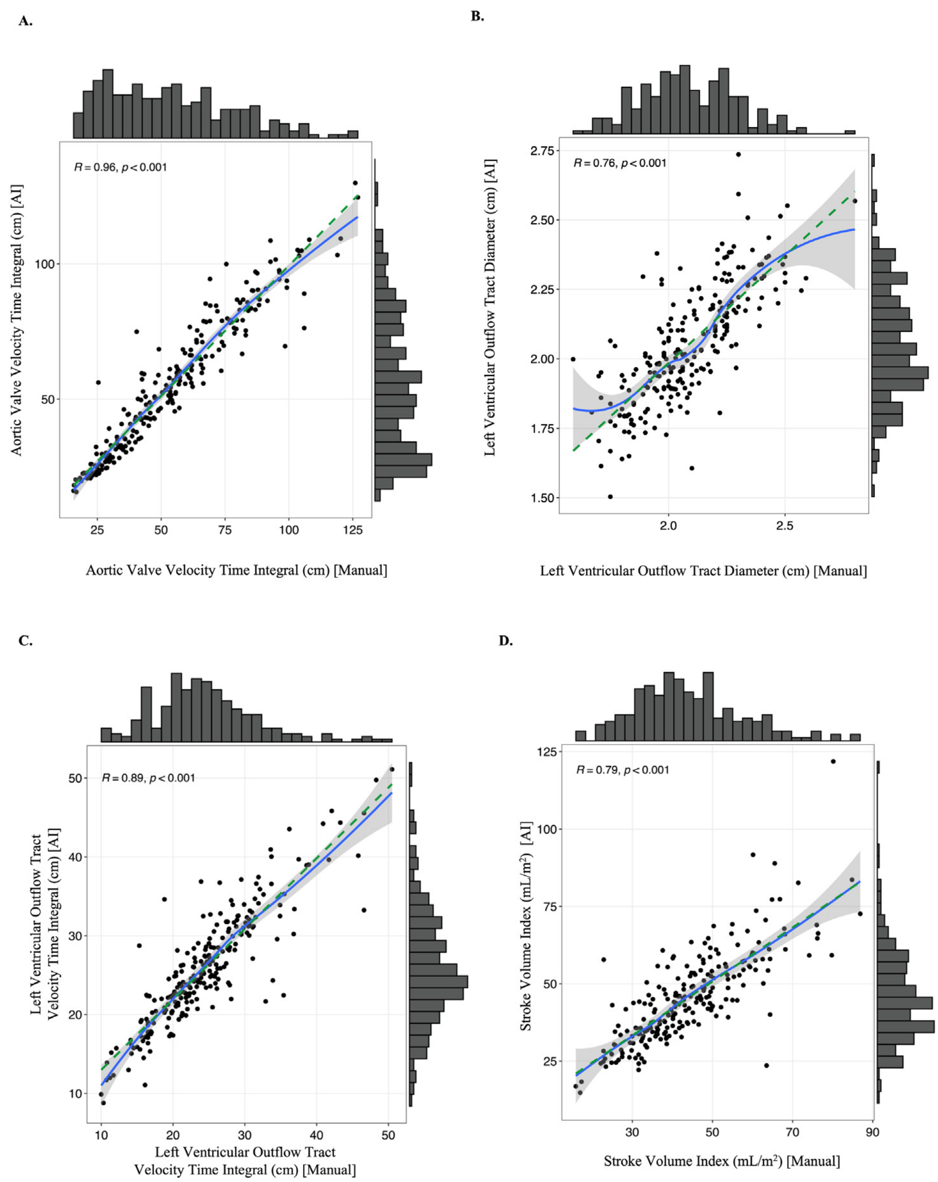

Figure 4 Artificial intelligence to experienced (manual) human reader correlations for AV and LVOT VTI, LVOTd, and SVi.

Beyond POCUS applications, AI-based AS assessment has tremendous implications in formal echocardiography laboratories. Maintaining high levels of accuracy in AS grading requires significant time commitments by reading physicians and sonographers with each study performed, to ensure 2D measurements and Doppler tracings are accurate. Small variations in LVOTd, for example, can result in complete reclassification of severity. Resource-intensive continuing education and quality control are necessary to maintain interreader and interscan consistency. Scanning and measuring extract a physical toll as well, with significantly higher rates of work-related musculoskeletal injuries reported in sonographers compared with peer employees.[17] Moreover, with the widespread use of transcatheter AV replacement, the field of valvular heart disease is moving toward increasingly nuanced AS evaluation, to separate out subpopulations who may benefit from earlier valve replacement therapy. As cardiologists collect and report more variables, the per scan time requirements and diagnostic complexity continue to increase. Deep-learning platforms that function effectively using only imaging data can be leveraged to create multivariate algorithms delivering precise, patient-specific risk-prognostic information to guide AVR therapy.

Limitations

This study is of a retrospective cohort design, with limitations intrinsic to such a study type. Additionally, 15% of the original cohort demonstrated inadequate image quality for at least 1 of the measurements by AI. A substantial portion of the excluded cases were related to LVOTd measurement, which is one of the most technically challenging aspects of AS assessment even for the expert echocardiographer. Related to this issue, the lowest agreement between AI and human

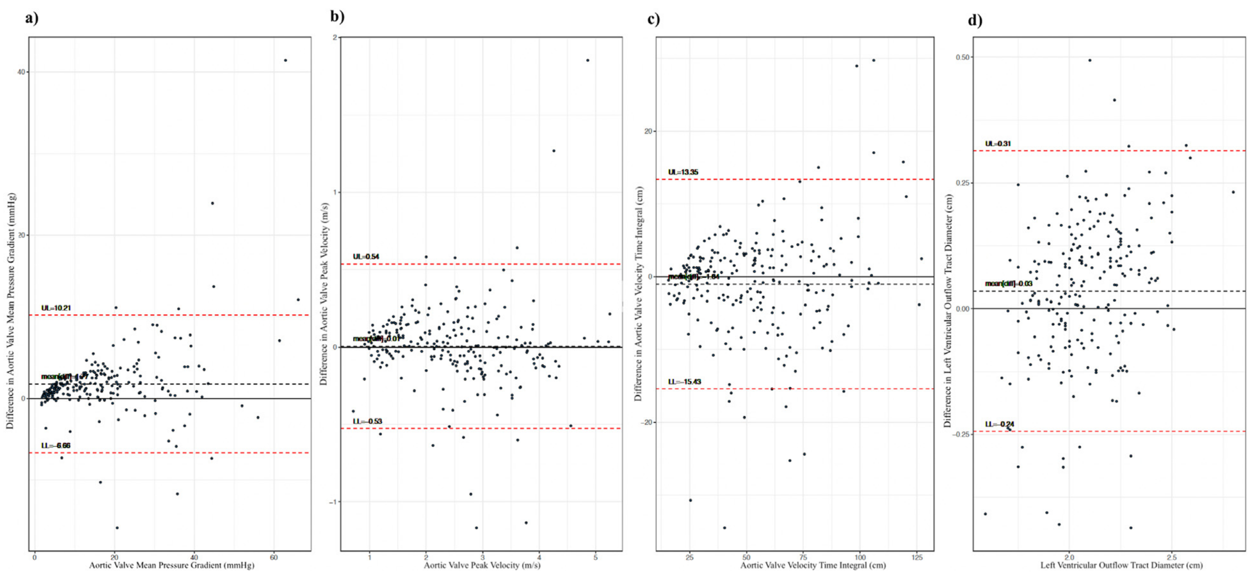

Figure 5 Bland-Altman plots of agreement between AI and human echocardiographic measurements.

measurement was seen with LVOTd. The AI algorithm utilizes all frames of all available video files to generate an LVOTd, whereas the human reader measured from a visually assessed most optimal frame. This may in part explain the discrepancy. Further training of the AI system will be required to reduce the exclusion rate and improve LVOTd measurement. The current technology allows the user to review the LVOTd measurement made by the AI as a secondary quality control; although no human manipulation of AI measurements was required in this cohort, this transparency serves as a further check against any image segmentation errors.

Both a limitation and a benefit, AI takes all available, quality-checked tracings for Doppler measurements and averages to create a final value. While human readers excluded post-extrasystolic beats, AI currently does not have that capacity. This may result in some disagreement between human and AI measurements in atrial fibrillation or cases with substantial beat-to-beat variability.

Future Directions

Future work will aim to utilize AI to categorize AS severity, incorporating multiple echocardiographic variables. There is often incongruency among Vmax, MPG, and AVA when classifying AS, and in those instances, expert readers report a holistic evaluation of the stenosis severity, incorporating an assessment of overall data quality, valve calcium burden, and valve motion together with hemodynamic measures. Utilizing clinical outcomes data to train artificial neural networks to categorize AS severity using complete echocardiograms may result in more nuanced classification of AS.

Table 2 Comparative AS measurements between human reader and AI

	Manual			
	No AS	Mild AS	Moderate AS	Severe AS
Human reader				
LVOTd, cm	2.18 ± 0.18	2.07 ± 0.21	2.05 ± 0.19	1.97 ± 0.18
LVOT VTI, cm	23.49 ± 6.56	28.26 ± 7.96	25.71 ± 7.10	20.57 ± 5.76
AV Vmax, m/sec	1.59 ± 0.54	2.59 ± 0.67	3.01 ± 0.75	3.51 ± 0.79
AV MPG, mm Hg	32.67 ± 12.55	54.86 ± 16.56	67.88 ± 19.71	79.48 ± 22.21
AV VTI, cm	32.67 ± 12.55	54.86 ± 16.56	67.88 ± 19.71	79.48 ± 22.21
AI				
LVOTd, cm	2.10 ± .0.20	2.03 ± 0.19	2.06 ± 0.23	1.96 ± 0.20
LVOT VTI, cm	24.58 ± 6.50	29.38 ± 8.04	27.27 ± 6.87	22.34 ± 6.00
AV Vmax, m/sec	1.52 ± 0.54	2.65 ± 0.77	2.96 ± 0.79	3.54 ± 0.78
AV MPG, mm Hg	32.80 ± 13.14	57.49 ± 17.86	68.79 ± 20.63	79.38 ± 19.68
AV VTI, cm	32.80 ± 13.14	57.49 ± 17.86	68.79 ± 20.63	79.39 ± 19.68
AVA, cm^2	2.78 ± 0.74	1.73 ± 0.39	1.38 ± 0.38	0.91 ± 0.25

Data are expressed as mean ± SD.

Table 3 Intraclass correlation coefficients for human reader parameters

	Intraclass correlation coefficient [95% CI] $P < .001$
LVOTd	0.860 [0.759, 0.918]
LVOT VTI	0.952 [0.928, 0.968]
AV VTI	0.924 [0.886, 0.950]
AV MPG	0.928 [0.892, 0.952]
AV Vmax	0.945 [0.918, 0.964]

CONCLUSION

Artificial neural networks have the capacity to closely mimic human measurement of all relevant parameters in the adjudication of AS severity. Application of this AI technology may minimize interscan variability, improve interpretation and diagnosis of AS, and allow for precise and reproducible identification and management of patients with AS.

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