Artificial Intelligence-enabled Electrocardiogram Screens Low Left Ventricular Ejection Fraction with Degree of Confidence

Supplementary Materials

1. Supplementary Results

2. Supplementary Tables

3. Supplementary Figures

Result S1 | Performance of DLMs with root mean square error loss and probability density function of normal distribution loss.

The scatter plot of DLM predictions based on Method 1 (M1, the DLM trained by root mean square error) and Method 2 (M2, the DLM trained by probability density function of normal distribution) is described in **Figure S2**. Regarding the point estimation predicted by M1, the mean differences (SD), Pearson correlation coefficients, and MAEs were 1.49 (10.72)/1.57 (10.64), 0.59/0.56, and 8.11/8.11 in the internal/external validation sets, respectively. Regarding the point estimation predicted by M2, the mean differences (SD), Pearson correlation coefficients, and MAEs were 1.65 (9.81)/1.54 (9.75), 0.61/0.58, and 7.56/7.51 in the internal/external validation sets, respectively. Both predictions produced similar results compared to the actual EF. Therefore, the DLM trained by the probability density function of normal distribution loss was feasible in actual EF prediction.

Result S2 | Diagnostic performance of M1 to M3.

We used ROC curves to assess the DLM performance for detecting LVD based on M1-M3, which is shown in **Figure S3**. For detecting severe LVD, the cutoff points of the DLMs based on M1, M2, and M3 were 47.6, 49.1, and 0.212, and the AUC values, sensitivities, and specificities were as follows in the internal/external validation sets: AUC values of 0.9520/0.9395, 0.9578/0.9409, and 0.9549/0.9364, respectively; sensitivities of 85.4%/79.3%, 85.4%/77.3%, and 84.5%/76.2%, respectively; and specificities of 92.5%/92.4%, 92.6%/93.0%, and 92.5%/92.9%, respectively. The positive predictive value (PPV) and negative predictive value (NPV) were also mentioned. The performance of each method was similar, but the interpretabilities were significantly different in clinical practice. Physicians may not accept the use and predicted EF values of 47.6 and 49.1 as the cutoff points for diagnosing patients with an actual EF of ≤40%. In summary, we considered using the cumulative distribution function of the normal distribution to calculate the probability (M3) as the most feasible method in clinical practice, and further analyses were based on it.

Result S3 | Interpretation of different means and standard deviations in patients with and without each rhythm.

We used Student's t test and the F test to describe the mean and variance difference of EF in patients with and without each ECG rhythm among the internal and external validation sets, respectively. The standardized mean difference (SMD) was used to compare the outcomes between the above patients. As shown in Table S2, ECG rhythms, such as atrial fibrillation, complete left bundle branch block, incomplete left bundle branch block, ischemia/infraction, left atrial enlargement, left ventricular hypertrophy, pacemaker rhythm, prolonged QT interval, sinus rhythm, sinus tachycardia, supraventricular tachycardia, and ventricular premature complex, presented significant differences in EF in the mean and variance differences in both the internal and external validation sets. These phenomena could be explained by the wide range decrease in EF in patients with irregular rhythms. In addition, the EF in patients with sinus rhythm was significantly higher than that in patients without sinus rhythm, and the variability presented a relatively concentrated distribution. Therefore, the EF showed a slight change in ECG rhythm. Importantly, the first-degree AC block and junctional rhythm showed a significant mean reduction, but the variance was maintained in the internal valuation set.

Table S1 | Baseline characteristics in subset 1 and subset 2.

	Subset 1		Subset 2	
	Internal validation	External validation	Internal validation	External validation
Demography				
Sex (male)	164(52.6%)	261(55.2%)	3858(50.6%)	5845(49.7%)
Age (years)	76.2±12.1	79.0±12.1	63.4±16.6	65.8±18.1
BMI (kg/m^2)	24.9±4.4	24.6±4.2	24.5±4.3	24.4±4.3
Disease history				
DM	139(44.6%)	213(45.0%)	2267(29.8%)	3654(31.0%)
HTN	236(75.6%)	356(75.3%)	3970(52.1%)	6507(55.3%)
HLP	161(51.6%)	221(46.7%)	3140(41.2%)	5207(44.2%)
CKD	193(61.9%)	271(57.3%)	1857(24.4%)	2908(24.7%)
AMI	18(5.8%)	22(4.7%)	245(3.2%)	283(2.4%)
STK	104(33.3%)	148(31.3%)	1286(16.9%)	2198(18.7%)
CAD	142(45.5%)	227(48.0%)	2363(31.0%)	3658(31.1%)
HF	142(45.5%)	205(43.3%)	948(12.4%)	1492(12.7%)
Afib	182(58.3%)	284(60.0%)	495(6.5%)	752(6.4%)
COPD	108(34.6%)	174(36.8%)	1509(19.8%)	2783(23.6%)
Echocardiography data				
EF (%)	57.3±12.2	57.3±13.3	65.2±11.4	65.4±10.8
LV-D (mm)	49.5±7.7	48.6±7.8	47.3±7.1	47.1±6.8
LV-S (mm)	33.9±7.5	33.1±8.1	29.8±6.7	29.6±6.3
IVS (mm)	11.0±2.3	11.1±2.4	11.2±2.6	11.1±2.6
LVPW (mm)	9.6±1.7	9.6±1.6	9.3±1.7	9.1±1.7
LA (mm)	47.6±8.4	47.5±9.0	38.5±7.6	38.7±7.3
AO (mm)	33.8±4.2	33.7±4.6	32.8±4.5	32.8±4.3
RV (mm)	27.4±5.2	27.4±5.6	24.1±5.1	24.0±5.0
PASP (mmHg)	42.1±13.3	41.4±12.7	32.1±10.4	33.0±10.7
Arrhythmia				
Abnormal T wave	12(3.8%)	10(2.1%)	185(2.4%)	262(2.2%)
Atrial fibrillation	205(65.7%)	326(68.9%)	601(7.9%)	932(7.9%)
Atrial flutter	7(2.2%)	22(4.7%)	53(0.7%)	122(1.0%)
Atrial premature complex	13(4.2%)	7(1.5%)	216(2.8%)	410(3.5%)
Complete AV block	1(0.3%)	0(0.0%)	9(0.1%)	3(0.0%)
Complete left bundle branch block	8(2.6%)	9(1.9%)	70(0.9%)	141(1.2%)
Complete right bundle branch block	30(9.6%)	75(15.9%)	592(7.8%)	1117(9.5%)
First degree AV block	15(4.8%)	21(4.4%)	518(6.8%)	818(6.9%)
Incomplete left bundle branch block	2(0.6%)	6(1.3%)	47(0.6%)	86(0.7%)
Incomplete right bundle branch block	6(1.9%)	10(2.1%)	62(0.8%)	95(0.8%)
Ischemia/infarction	99(31.7%)	169(35.7%)	2610(34.3%)	4375(37.2%)
Junctional rhythm	3(1.0%)	2(0.4%)	19(0.2%)	41(0.3%)

	Subset 1		Subset 2	
	Internal validation	External validation	Internal validation	External validation
Left anterior fascicular block	11(3.5%)	12(2.5%)	201(2.6%)	357(3.0%)
Left atrial enlargement	16(5.1%)	26(5.5%)	896(11.8%)	1577(13.4%)
Left axis deviation	10(3.2%)	17(3.6%)	210(2.8%)	286(2.4%)
Left posterior fascicular block	2(0.6%)	11(2.3%)	94(1.2%)	127(1.1%)
Left ventricular hypertrophy	66(21.2%)	112(23.7%)	1279(16.8%)	2263(19.2%)
Low QRS voltage	39(12.5%)	56(11.8%)	366(4.8%)	684(5.8%)
Pacemaker rhythm	9(2.9%)	5(1.1%)	96(1.3%)	100(0.8%)
Prolonged QT interval	29(9.3%)	55(11.6%)	370(4.9%)	589(5.0%)
Right atrial enlargement	3(1.0%)	3(0.6%)	214(2.8%)	333(2.8%)
Right ventricular hypertrophy	7(2.2%)	15(3.2%)	121(1.6%)	198(1.7%)
Second degree AV block	0(0.0%)	0(0.0%)	2(0.0%)	6(0.1%)
Sinus bradycardia	1(0.3%)	1(0.2%)	71(0.9%)	127(1.1%)
Sinus pause	1(0.3%)	2(0.4%)	11(0.1%)	25(0.2%)
Sinus rhythm	41(13.1%)	67(14.2%)	5752(75.5%)	8806(74.8%)
Sinus tachycardia	28(9.0%)	32(6.8%)	825(10.8%)	1246(10.6%)
Supraventricular tachycardia	14(4.5%)	9(1.9%)	101(1.3%)	159(1.4%)
Ventricular premature complex	63(20.2%)	79(16.7%)	529(6.9%)	854(7.3%)
Ventricular tachycardia	2(0.6%)	4(0.8%)	22(0.3%)	40(0.3%)
Wolff-Parkinson-White syndrome	312(100.0%)	473(100.0%)	2(0.0%)	9(0.1%)

*The subset1 excluded the patients with atrial fibrillation during echocardiography examination.

*The subset2 only included patients with sinus rhythm.

* Abbreviations: BMI, body mass index; DM, diabetes mellitus; HTN, hypertension; HLP, hyperlipidemia; CKD, chronic kidney disease; AMI, acute myocardial infarction; STK, stroke; CAD, coronary artery disease; HF, heart failure; Afib, atrial fibrillation; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; LV-D, left ventricle (end-diastole); LV-S, left ventricle (end-systole); IVS, interventricular septum; LVPW, left ventricular posterior wall; LA, left atrium; AO, aortic root; RV, right ventricle; PASP, pulmonary artery systolic pressure; PE, pericardial effusion.

Table S2 | Distribution of actual EF in patients with and without each ECG rhythm among internal and external validation set.

	Internal validation set						External validation set					
	with	without	SMD[a]	*p value*[b]	F value	*p value*[c]	with	without	SMD[a]	*p value*[b]	F value	*p value*[c]
Abnormal T wave	62.94±12.25	65.22±11.34	0.20	0.01	0.86	0.13	62.00±13.86	65.43±10.75	0.32	<0.01	0.60	<0.01
Atrial fibrillation	57.95±14.39	65.78±10.86	0.70	<0.01	0.57	<0.01	59.44±13.46	65.86±10.43	0.60	<0.01	0.60	<0.01
Atrial flutter	58.90±12.94	65.20±11.35	0.56	<0.01	0.77	0.14	60.35±12.94	65.40±10.80	0.47	<0.01	0.70	<0.01
Atrial premature complex	63.58±12.18	65.21±11.34	0.14	0.04	0.87	0.13	63.99±12.07	65.40±10.79	0.13	0.01	0.80	<0.01
Complete AV block	62.94±10.06	65.16±11.37	0.20	0.56	1.28	0.76	49.50±28.65	65.35±10.83	1.46	0.01	0.14	<0.01
Complete left bundle branch block	47.24±18.68	65.33±11.15	1.61	<0.01	0.36	<0.01	54.38±17.21	65.48±10.67	1.03	<0.01	0.38	<0.01
Complete right bundle branch block	65.19±10.98	65.16±11.41	<0.01	0.95	1.08	0.22	65.17±11.03	65.37±10.82	0.02	0.57	0.96	0.36
First degree AV block	63.69±11.57	65.27±11.35	0.14	<0.01	0.96	0.53	64.20±11.91	65.44±10.75	0.11	<0.01	0.81	<0.01
Incomplete left bundle branch block	54.93±18.18	65.22±11.29	0.91	<0.01	0.39	<0.01	54.46±15.94	65.43±10.75	1.02	<0.01	0.46	<0.01
Incomplete right bundle branch block	61.10±14.68	65.19±11.34	0.36	<0.01	0.60	<0.01	66.05±10.39	65.34±10.84	0.06	0.53	1.09	0.60
Ischemia/infraction	63.52±12.61	66.01±10.57	0.22	<0.01	0.70	<0.01	64.20±11.74	66.03±10.21	0.17	<0.01	0.76	<0.01
Junctional rhythm	56.18±13.64	65.18±11.36	0.79	<0.01	0.69	0.20	58.66±14.65	65.37±10.81	0.62	<0.01	0.54	<0.01
Left anterior fascicular block	64.74±11.88	65.17±11.36	0.04	0.59	0.91	0.36	63.94±12.03	65.39±10.79	0.13	0.01	0.80	<0.01
Left atrial enlargement	61.68±14.94	65.62±10.72	0.35	<0.01	0.52	<0.01	63.67±13.19	65.61±10.40	0.18	<0.01	0.62	<0.01
Left axis deviation	65.36±11.09	65.16±11.38	0.02	0.80	1.05	0.62	65.49±11.02	65.35±10.83	0.01	0.83	0.97	0.67
Left posterior fascicular block	65.28±10.64	65.16±11.38	0.01	0.92	1.15	0.39	64.06±12.31	65.36±10.82	0.12	0.18	0.77	0.03
Left ventricular hypertrophy	61.44±13.85	65.91±10.65	0.40	<0.01	0.59	<0.01	62.88±13.04	65.94±10.16	0.28	<0.01	0.61	<0.01
Low QRS voltage	62.98±12.56	65.27±11.30	0.20	<0.01	0.81	<0.01	64.79±10.69	65.38±10.85	0.05	0.16	1.03	0.61
Pacemaker rhythm	61.45±13.35	65.21±11.34	0.33	<0.01	0.72	0.02	58.23±14.94	65.41±10.78	0.66	<0.01	0.52	<0.01
Prolonged QT interval	60.57±13.74	65.40±11.19	0.43	<0.01	0.66	<0.01	60.76±14.45	65.59±10.56	0.45	<0.01	0.53	<0.01
Right atrial enlargement	65.34±11.59	65.16±11.37	0.02	0.82	0.96	0.67	64.89±11.93	65.36±10.80	0.04	0.44	0.82	0.01
Right ventricular hypertrophy	65.85±10.61	65.15±11.38	0.06	0.50	1.15	0.31	66.25±9.29	65.33±10.86	0.08	0.24	1.37	<0.01
Second degree AV block	57.25±13.79	65.16±11.37	0.70	0.33	0.68	0.45	66.17±9.28	65.35±10.84	0.08	0.85	1.36	0.80
Sinus bradycardia	68.71±7.68	65.13±11.40	0.32	0.01	2.20	<0.01	65.41±10.21	65.35±10.84	0.01	0.95	1.13	0.37
Sinus pause	66.09±4.89	65.16±11.38	0.08	0.79	5.42	0.01	61.44±12.78	65.36±10.83	0.36	0.07	0.72	0.19

Sinus rhythm	66.76±9.66	60.22±14.43	0.59	<0.01	2.23	<0.01	66.77±9.42	61.12±13.36	0.54	<0.01	2.01	<0.01
Sinus tachycardia	61.00±14.55	65.67±10.82	0.41	<0.01	0.55	<0.01	62.04±13.38	65.74±10.43	0.34	<0.01	0.61	<0.01
Supraventricular tachycardia	59.05±14.78	65.24±11.30	0.55	<0.01	0.58	<0.01	58.74±15.20	65.44±10.74	0.62	<0.01	0.50	<0.01
Ventricular premature complex	60.15±14.38	65.54±11.02	0.48	<0.01	0.59	<0.01	61.02±13.76	65.69±10.50	0.43	<0.01	0.58	<0.01
Ventricular tachycardia	63.14±15.66	65.17±11.36	0.18	0.40	0.53	0.02	59.95±14.65	65.37±10.82	0.50	<0.01	0.55	<0.01
Wolff–Parkinson–White syndrome	61.50±16.26	65.16±11.37	0.32	0.65	0.49	0.31	66.22±9.30	65.35±10.84	0.08	0.81	1.36	0.68

[a]SMD: Standardized mean difference.

[b]Represents a significant level of mean EF in patients with or without ECG rhythm.

[c]Represents a significant level of the variance of EF in patients with or without ECG rhythm based on the F value.

*Significance level is defined as 0.05.

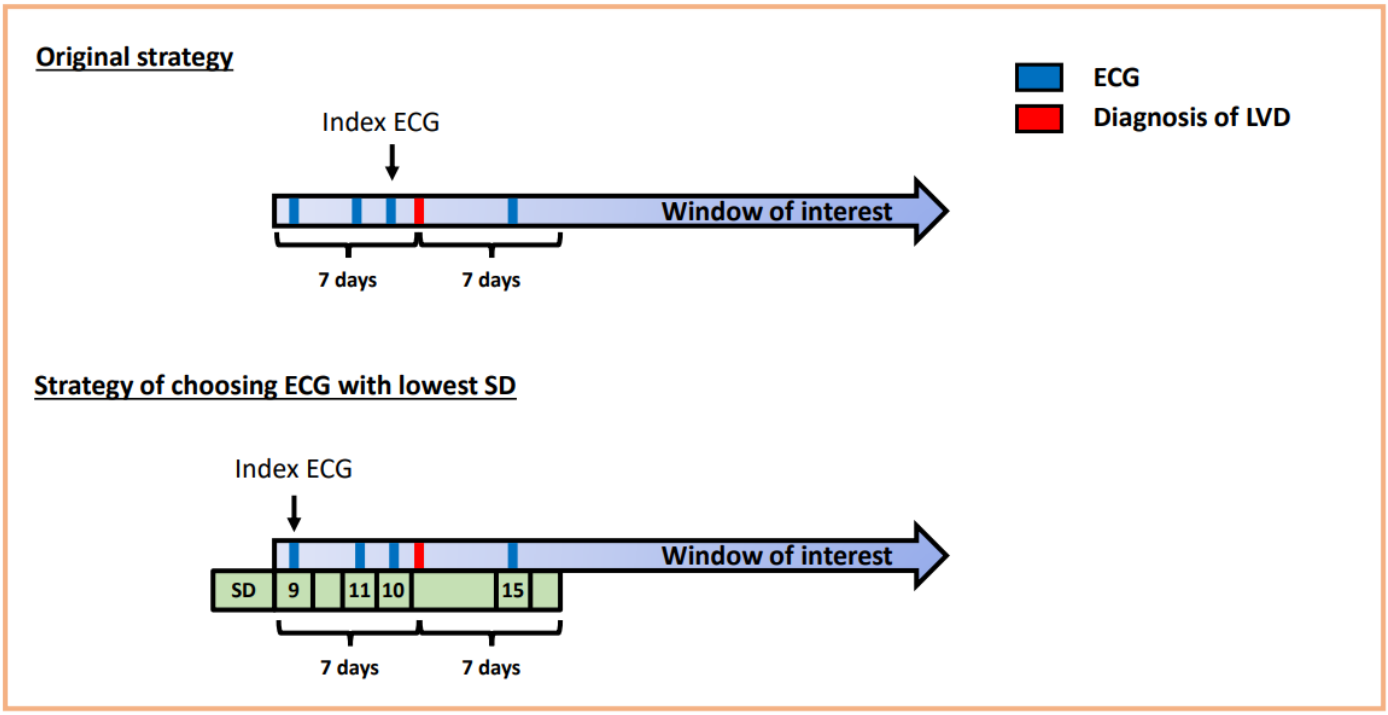

Figure S1| ECG selection and windows of interest for patients with lowest-SD ECGs. We selected the relatively short time interval of ECGs among patients with multiple records during the window of interest as our original strategy. We then attempted to select the ECG with the lowest estimated SD, which was used to compare whether to enhance the performance based on better image quality.

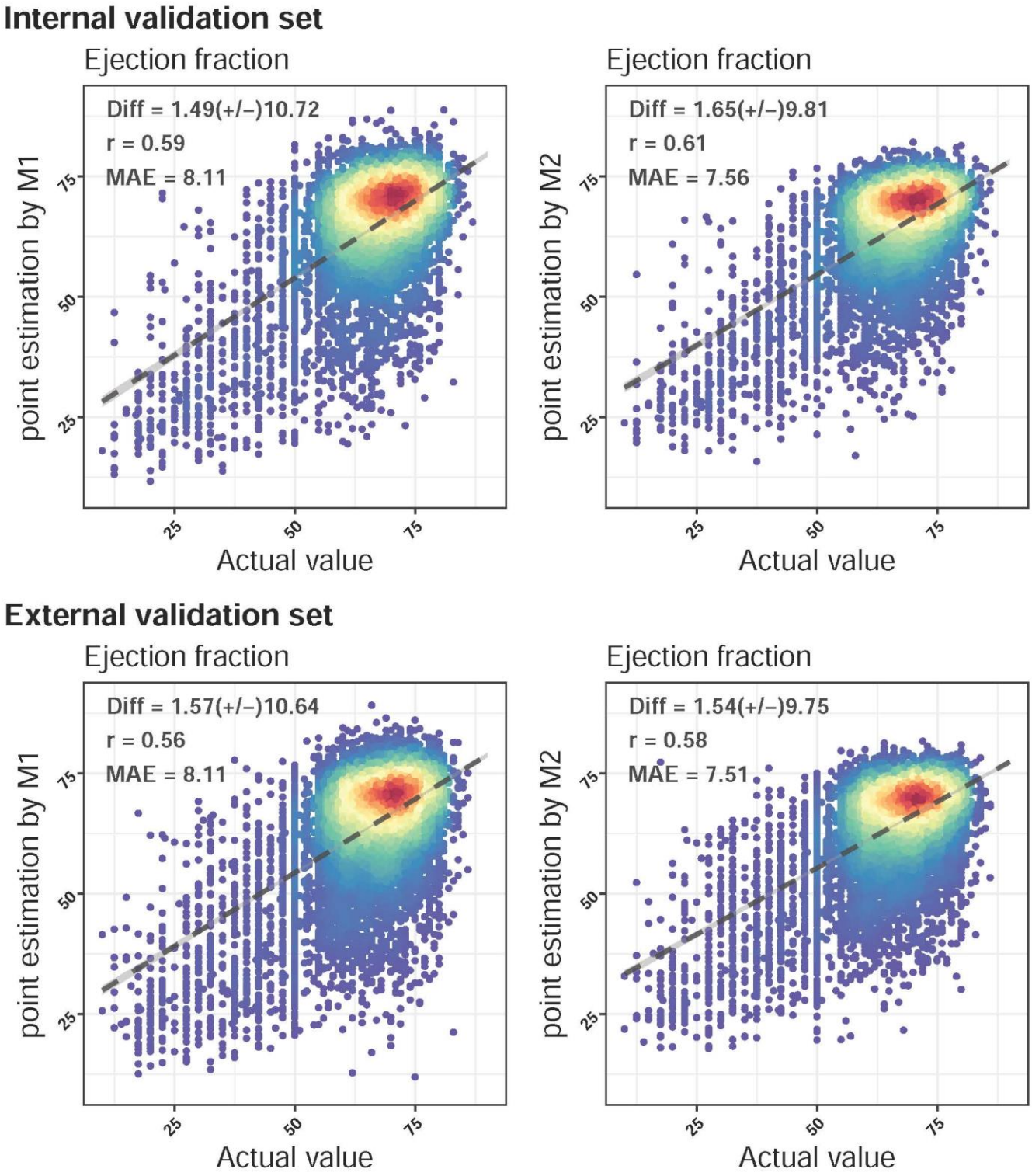

Figure S2 | Scatter plots of DLM predictions based on two methods (M1 and M2). M1 is the DLM predicting the EF trained by the classical loss function of root mean square error. M2 is the DLM predicting the EF trained by the proposed loss function. We presented the mean difference (Diff) with standard deviation, Pearson correlation coefficients (r), and mean absolute error (MAE) to demonstrate the accuracy of the DLM. In summary, the accuracies of M1 and M2 are similar.

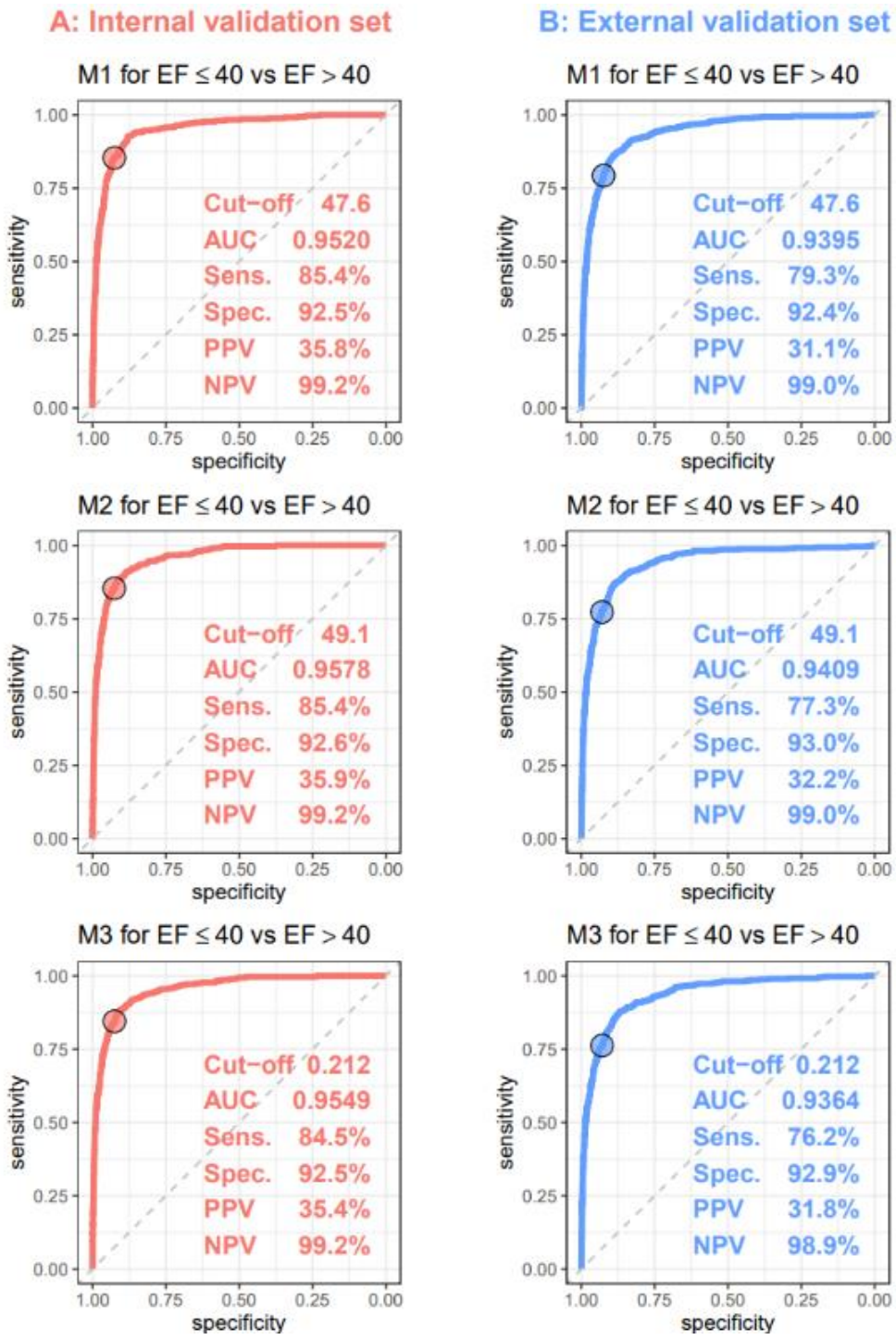

Figure S3 | ROC curve of DLM predictions based on three methods (M1-M3). Left ventricular dysfunction was defined as an actual EF ≤40. M1 is the DLM predicting the EF trained by the classical loss function of root mean square error, and the ROC curve was generated by point estimation by the DLM. M2 is the DLM predicting the EF trained by the proposed loss function, and the ROC curve was generated by the point estimation by this DLM. M3 uses the same DLM as M2, but we calculated based on clinical point, estimated EF, and estimated SD by the cumulative distribution function of normal distribution. The cutoff point was selected based on the maximum Youden's index in the tuning set and presented using a circle mark, and the area under the ROC curve (AUC), sensitivity (Sens.), specificity (Spec.), positive predictive value (PPV), and negative predictive value (NPV) were calculated based on the cutoff point. In summary, M3 is easier to explain than M1 and M2, and their accuracies were similar.

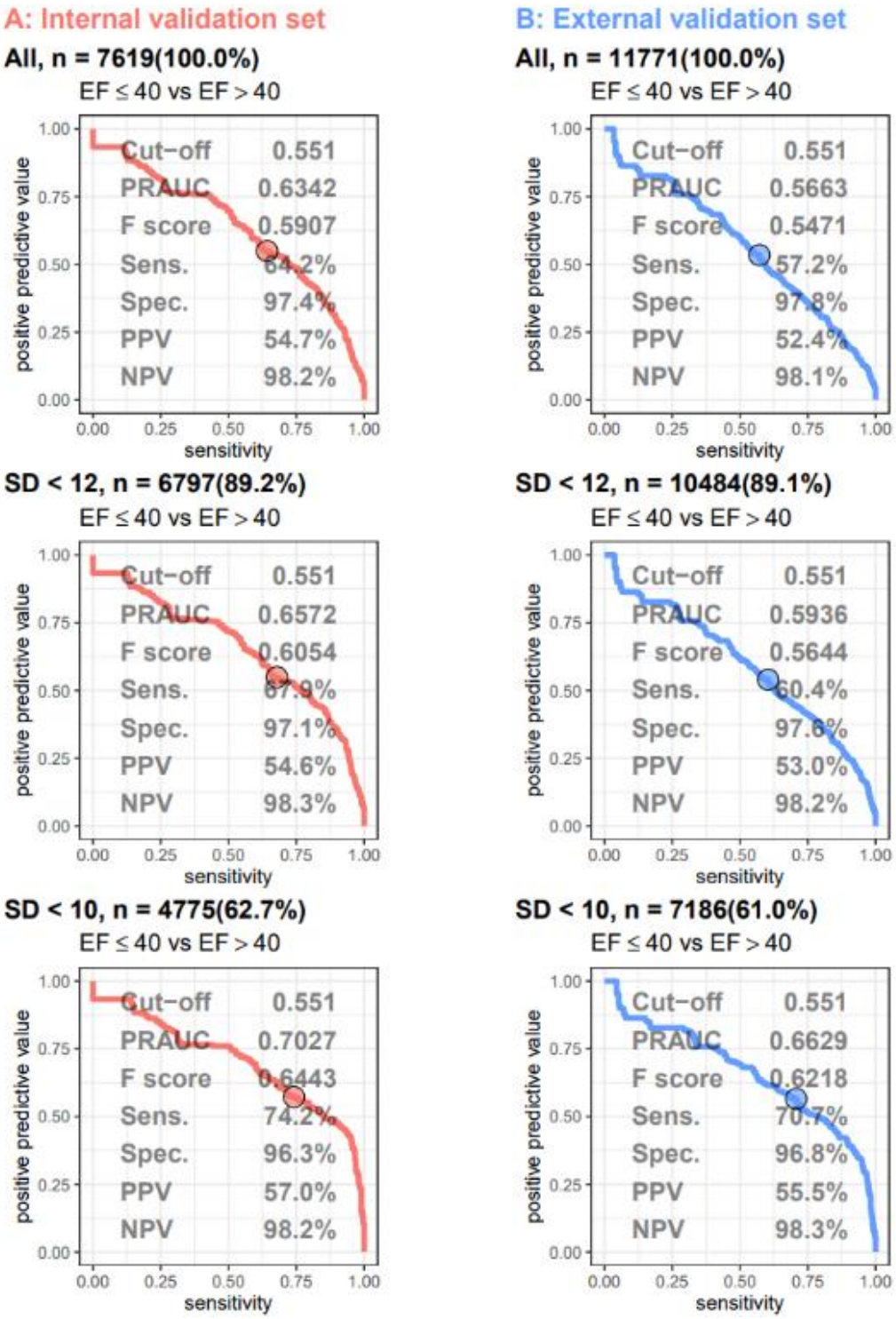

Figure S4 | PRROC curve of DLM predictions based on ECG to detect left ventricular dysfunction. Left ventricular dysfunction was defined as an actual EF of ≤40. The risk probability was calculated based on the clinical point, estimated EF, and estimated SD by the cumulative distribution function of the normal distribution. The cutoff point was selected based on the maximum F-score in the tuning set and presented using a circle mark, and the area under the PRROC curve (PRAUC), sensitivity (Sens.), specificity (Spec.), positive predictive value (PPV), and negative predictive value (NPV) were calculated based on the cutoff point.

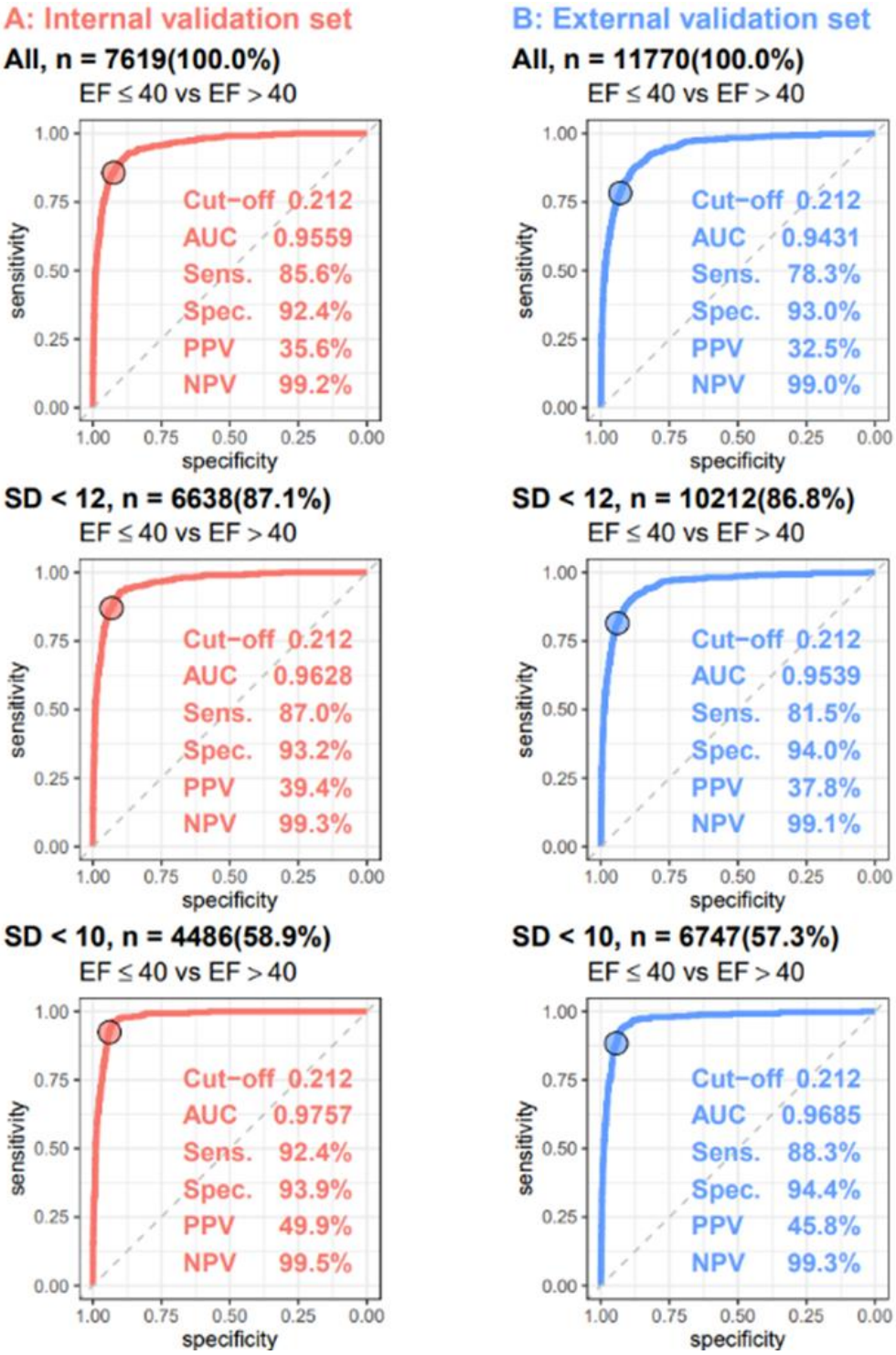

Figure S5 | ROC curve of DLM predictions based on the strategy of selecting the ECG with the lowest SD to detect left ventricular dysfunction. Left ventricular dysfunction was defined as an actual EF ≤40. The risk probability was calculated based on the clinical point, estimated EF, and estimated SD by the cumulative distribution function of the normal distribution. We replaced the original ECG based on the strategy described in Figure S1. The cutoff point was selected based on the maximum Youden's index in the tuning set and presented using a circle mark, and the area under the ROC curve (AUC), sensitivity (Sens.), specificity (Spec.), positive predictive value (PPV), and negative predictive value (NPV) were calculated based on the cutoff point.

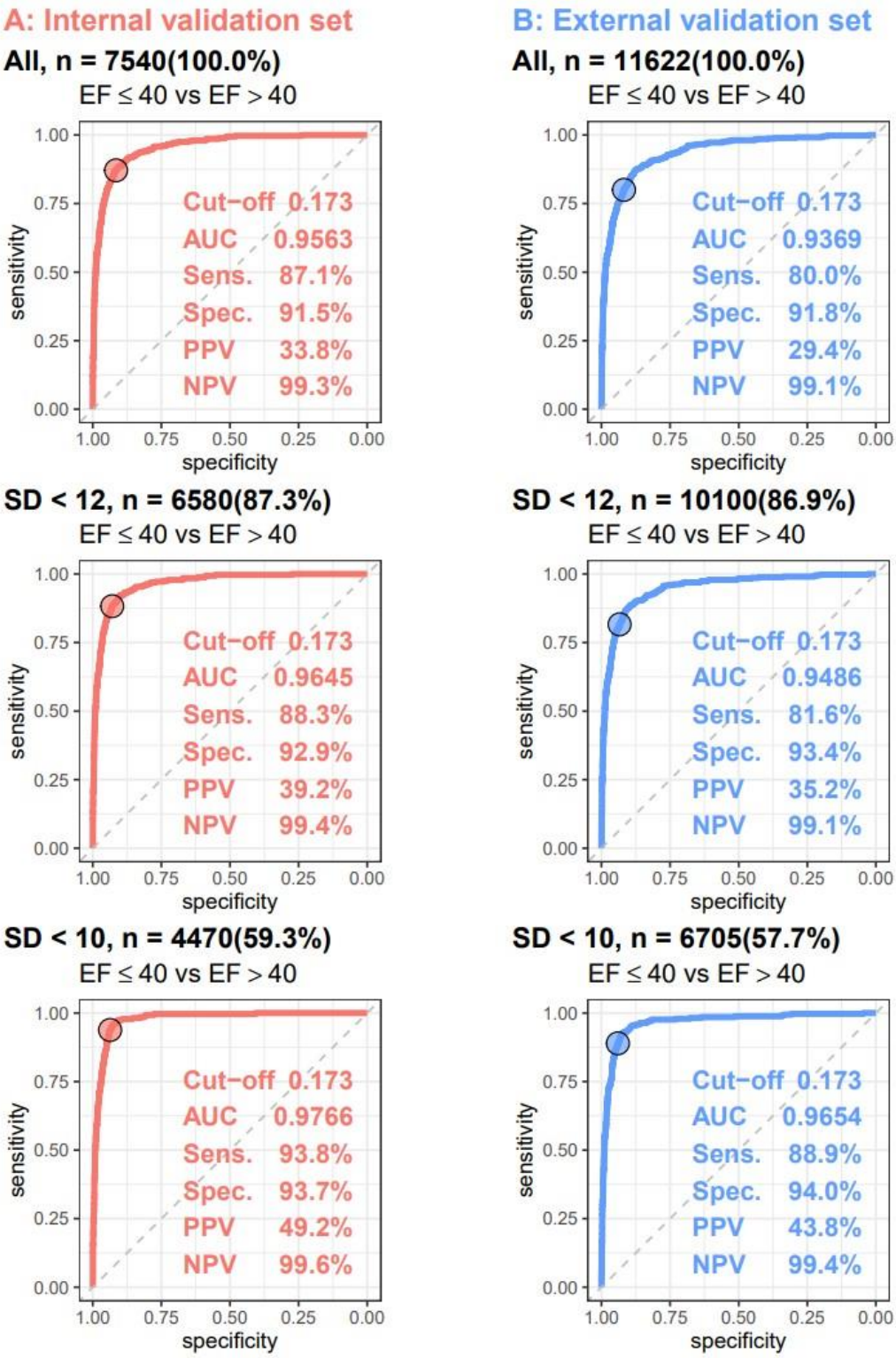

Figure S6 | ROC curve of DLM predictions in subset 1 to detect left ventricular dysfunction. The risk probability was calculated based on the clinical point, estimated EF. The cutoff point was selected based on the maximum Youden's index in the tuning set and presented using a circle mark, and the area under the ROC curve (AUC), sensitivity (Sens.), specificity (Spec.), positive predictive value (PPV), and negative predictive value (NPV) were calculated based on the cutoff point.

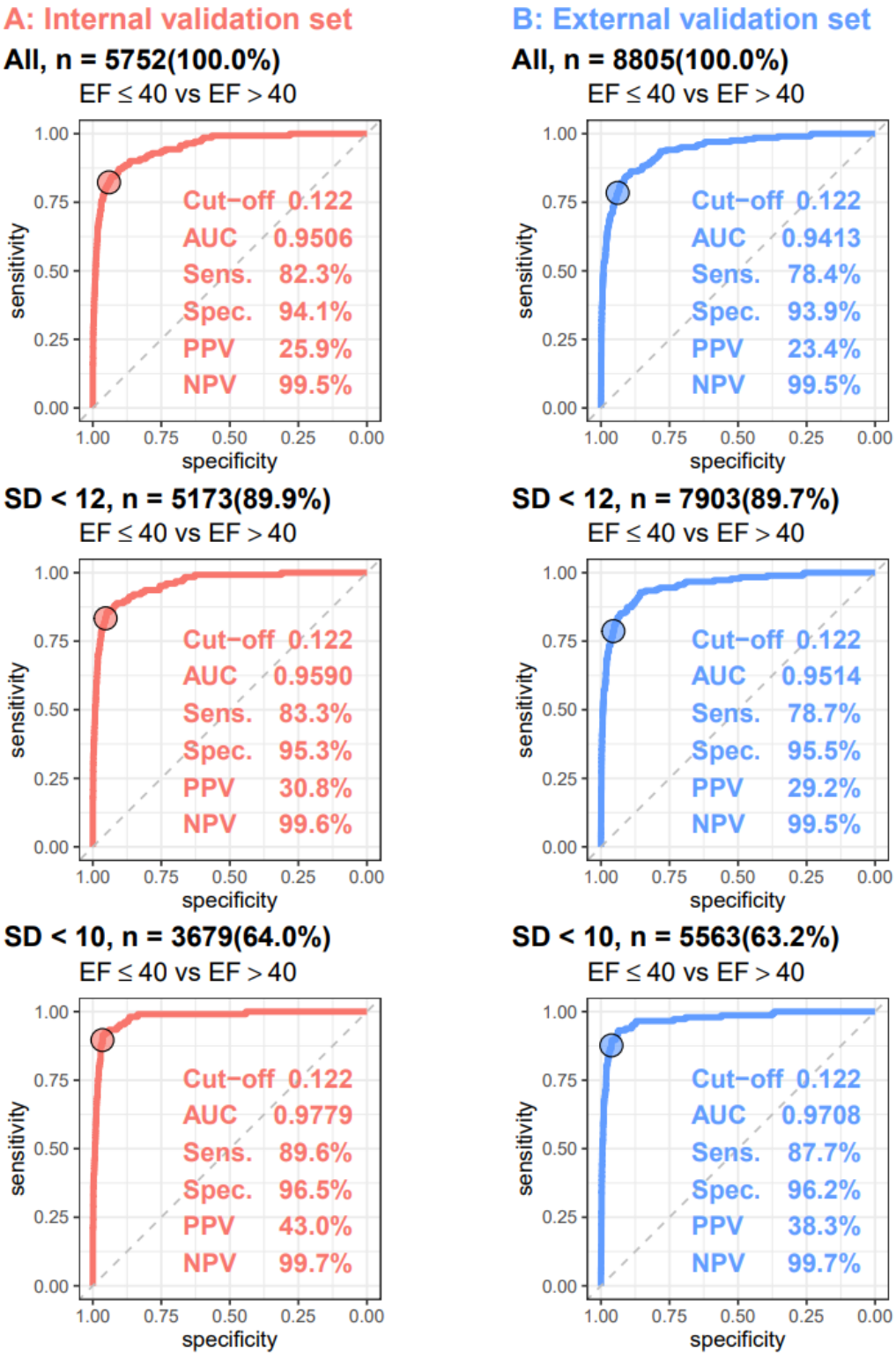

Figure S7 | ROC curve of DLM predictions in subset 2 to detect left ventricular dysfunction. The risk probability was calculated based on the clinical point, estimated EF. The cutoff point was selected based on the maximum Youden's index in the tuning set and presented using a circle mark, and the area under the ROC curve (AUC), sensitivity (Sens.), specificity (Spec.), positive predictive value (PPV), and negative predictive value (NPV) were calculated based on the cutoff point.