THE LANCET
Digital Health

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Tromp J, Seekings PJ, Hung C-L, et al. Automated interpretation of systolic and diastolic function on the echocardiogram: a multicohort study. *Lancet Digit Health* 2021; published online Dec 1. https://doi.org/10.1016/S2589-7500(21)00235-1.

Supplemental material

Supplementary table 1: Baseline characteristics of the Alberta HEART study.

Alberta HEART cohort	n=621
Age (years), mean (SD)	66 (12)
Men, n (%)	352 (57%)
Ethnicity	
Aboriginal	11 (2%)
African American	8 (1%)
Caucasian	564 (91%)
Asian	29 (5%)
Other	9 (1%)
BMI (Kg/m^2), median (IQR)	29.4 (25.7, 33.5)
Medical history, n (%)	
HF	360 (57%)
Diabetes	196 (32%)
CAD	211 (34%)
Atrial fibrillation	192 (31%)
COPD	89 (14%)
eGFR, median (IQR)	73 (56, 88)

Abbreviations: BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HF, heart failure; IQR, interquartile range; SD, standard deviation.

Supplementary table 2: Baseline characteristics of the participants included from MacKay Memorial Hospital, Taiwan.

MacKay Memorial Hospital Cohort	n=9,289
Age (years), mean (SD	66 (15)
Men, n (%)	4830 (52%)
Ethnicity	
Asian	9,289 (100%)
BMI (Kg/m^2), median (IQR)	24.6 (22.1, 27.4)
Medical history, %	
HF status (yes/no)	3987 (43%)
Diabetes	2751 (30%)
CAD	2783 (30%)
Atrial fibrillation	1447 (16%)
COPD	728 (8%)
eGFR Median (IQR)	71 (51, 87)

Abbreviations: BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HF, heart failure; IQR, interquartile range; SD, standard deviation.

Supplementary table 3A: Total number of videos and frames used for training and testing of 2D videos.

View	***Training***		***Testing***	
	Total Videos	Total Frames	Total Videos	Total Frames
A2C	552	9708	56	1223
A4C	740	9615	64	1218

PLAX	1015	9452	89	1208
2d more	2000	9042	200	1152

Abbreviations: A2C, Apical 2 Chamber; A4C, Apical 4 Chamber; PLAX, Parasternal Long Axis.

Supplementary table 3B: Total number images used for training and testing of Doppler modalities.

View	***Training***	***Testing***
PWTDI Lateral	1038	565
PWTDI Septal	1082	529
PW MV	1560	710
PW LVOT	1301	500
PW Others	2493	1466
CW TrV	1930	709
CW AoV	1536	549
CW Others	1853	1106
Mmode TrV	582	158
Mmode Others	4295	3183

Abbreviations: AoV, aortic outflow tract; CW, continuous wave Doppler; LVOT, left ventricular outflow tract; PW, pulsed wave Doppler; PWTDI, pulsed wave tissue Doppler imaging; TrV, tricuspid regurgitant velocity.

Supplementary table 4: Ground truths for training annotations in the Asia (ATTRACT) data.

View	Number of annotations
A2C	1429 (LV), 1371 (LA)
A4C	2710 (LV), 2552 (LA)
PLAX	1927 (LVID) 5814 (LV)
PW (MV)	2948
PWTDI	2077

Abbreviations: A2C, apical 2 chamber; A4C, apical 4 chamber; LVID, left ventricular internal diameters; PLAX, parasternal long axis; PW, pulsed wave Doppler; PWTDI, pulsed wave tissue Doppler imaging;

Supplementary table 5: Annotation performance with minimum, maximum and mean Dice coefficients for annotations of volumes of the left ventricle and left atrium on A2C and A4C in the Asia test set (ATTRaCT study).

	A2C		A4C	
	LV	LA	LV	LA
Min Dice	75.7%	76.0%	73.3%	81.4%
Max Dice	98.1%	98.3%	98.7%	98.3%
Mean Dice	93.0%	93.0%	93.8%	94.3%
1 SD	3.7%	3.1%	3.5%	2.6%
Sample size	688	263	747	340

Abbreviations: A2C, apical 2 chamber; A4C, apical 4 chamber; LA, left atrium; LV, left ventricle.

Supplementary table 6: Proportion of videos and images deemed of sufficient quality in the Canadian cohort (Alberta HEART Study).

	LAESV			*LVEDV*			*LVESV*			*LVEF*		
	N	Δ	Δ%	N	Δ	Δ%	N	Δ	Δ%	N	Δ	Δ%
2D videos												
A2C found	881			401			406			870		
Non-color-flow	871	10	1.1	395	6	1.5	400	6	1.5	859	11	1.3
Non focused	871	0	0.0	395	0	0.0	400	0	0.0	859	0	0.0
High quality view	855	16	1.8	395	0	0.0	393	7	1.8	859	0	0.0
High confidence measurement	763	91	10.8	360	35	8.9	358	35	8.9	848	11	1.3
Matching A4C found	752	11		352	8		353	5		832		
Non-color-flow	745	7	0.9	347	5	1.4	348	5	1.4	821	11	1.3
Non focused	745	0	0.0	347	0	0.0	348	0	0.0	821	0	0.0
High quality view	736	9	1.2	340	7	2.0	342	6	1.7	808	13	1.6
High confidence measurement	714	22	3.0	334	6	1.8	336	6	1.8	748	60	7.4
Total high confidence measurement	714	0	0.0	334	0	0.0	336	0	0.0	748	0	0.0
Doppler measurements												
	E-wave			*E' lateral*			*E' medial*					
	N	Δ	Δ%	N	Δ	Δ%	N	Δ	Δ%			
Doppler modality found	469			435			433					
High quality view	469	0	0.0	435	0	0.0	433	0	0.0			
High confidence measurement	420	49	10.4	400	35	8.0	386	47	10.9			

Abbreviations: A2C, apical 2 chamber; A4C, apical 4 chamber; LAESV, left atrial end systolic volume; LVEDV, left ventricular end diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end systolic volume; N, number of studies. Δ = difference, Δ% = difference as a percent of eligible echocardiograms evaluated.

Supplementary table 7: Automated versus human measurements in the Canadian cohort (Alberta HEART study), stratified to those with versus without atrial fibrillation.

Canada (Alberta HEART study)							
No atrial fibrillation							
	N	**R**	**MAE**	**RMSE**	**Absolute deviation vs. manual measurement (% of Manual)**		
					50	**75**	**95**
LVESV (mL)	218	0.89	15.4	19.3	13.4 (29%)	21.2 (68%)	34.9 (144%)
LVEDV (mL)	218	0.84	23.7	30.8	19.7 (21%)	31.5 (37%)	57.9 (82%)
LVEF (%)	513	0.72	8.3	10.5	6.7 (12%)	11.6 (21%)	21.3 (39%)
LAESV (mL)	483	0.83	10.1	14	7.6 (11%)	13.3 (18%)	27.8 (36%)
E wave (cm/s)	283	0.88	9.0	12.7	6.4 (10%)	12.0 (16%)	23.0 (32%)
e' lat (cm/s)	273	0.8	1.1	1.7	0.7 (9%)	1.4 (18%)	3.6 (51%)
e' med (cm/s)	260	0.74	0.88	1.4	0.5 (9%)	1.2 (19%)	2.8 (45%)
E/e’	427	0.78	1.9	3.2	1.3 (14%)	2.5 (22%)	5.3 (43%)
Atrial fibrillation							
	N	**R**	**MAE**	**RMSE**	**Absolute deviation vs. manual measurement (% of Manual)**		
					50	**75**	**95**
LVESV (mL)	118	0.93	18.6	27.3	12.5 (24%)	22.9 (51%)	55.5 (125%)
LVEDV (mL)	116	0.88	26.3	34.1	22.0 (22%)	29.9 (35%)	64.3 (72%)
LVEF (%)	235	0.76	9.1	11.4	7.6 (16%)	13.0 (25%)	22.0 (42%)
LAESV (mL)	231	0.86	13.6	18.8	10.3 (12%)	17.2 (21%)	38.5 (37%)
E wave (cm/s)	137	0.73	13.9	23.8	8.4 (9%)	14.6 (15%)	48.4 (48%)
e' lat (cm/s)	127	0.74	1.5	2.2	1.0 (13%)	2.1 (24%)	4.6 (65%)
e' med (cm/s)	126	0.67	1.0	1.7	0.5 (8%)	1.1 (20%)	3.9 (71%)
E/e’	159	0.86	2.7	4.8	1.5 (14%)	3.1 (22%)	8.2 (58%)

Abbreviations: LAESV, left atrial end systolic volume; LVEDV, left ventricular end diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end systolic volume; N, number of studies; R, correlation coefficient.

Supplementary table 8: Proportion of videos and images deemed of sufficient quality in the Taiwan cohort (MacKay Memorial Hospital).

	LAESV			*LVEDV*			*LVESV*			*LVEF*		
	N	Δ	Δ%	N	Δ	Δ%	N	Δ	Δ%	N	Δ	Δ%
2D videos												
A2C found	2764			19350			19354			9199		
Non-color-flow	2202	562	20.3	18898	452	2.3	18902	452	2.3	9047	152	1.7
Non focused	2202	0	0.0	18898	0	0.0	18902	0	0.0	9047	0	0.0
High quality view	2202	0	0.0	18898	0	0.0	18351	551	2.9	8831	216	2.4
High confidence measurement	2174	28	1.3	18480	418	2.2	18263	88	0.5	8765	66	0.7
Matching A4C found	1985			17857			17723			8474		
Non-color-flow	1941	44	2.2	17473	384	2.2	17368	355	2.0	8305	169	2.0
Non focused	1941	0	0.0	17473	0	0.0	17368	0	0.0	8305	0	0.0
High quality view	1921	20	1.0	17125	348	2.0	17047	321	1.8	8152	153	1.8
High confidence measurement	1892	29	1.5	17057	68	0.4	16989	58	0.3	8109	43	0.5
Total high confidence measurement	1892	0	0.0	16939	118	0.7	16989	0	0.0	7724	385	4.7
Doppler measurements												
	E-wave			*E' lateral*			*E' medial*					
	N	Δ	Δ%	N	Δ	Δ%	N	Δ	Δ%			
Doppler modality found	22115			8844			6268					
High quality view	22062	53	0.2	8829	15	0.2	6254	14	0.2			
High confidence measurement	18659	3403	15.4	6348	2481	28.1	4654	1600	25.6			

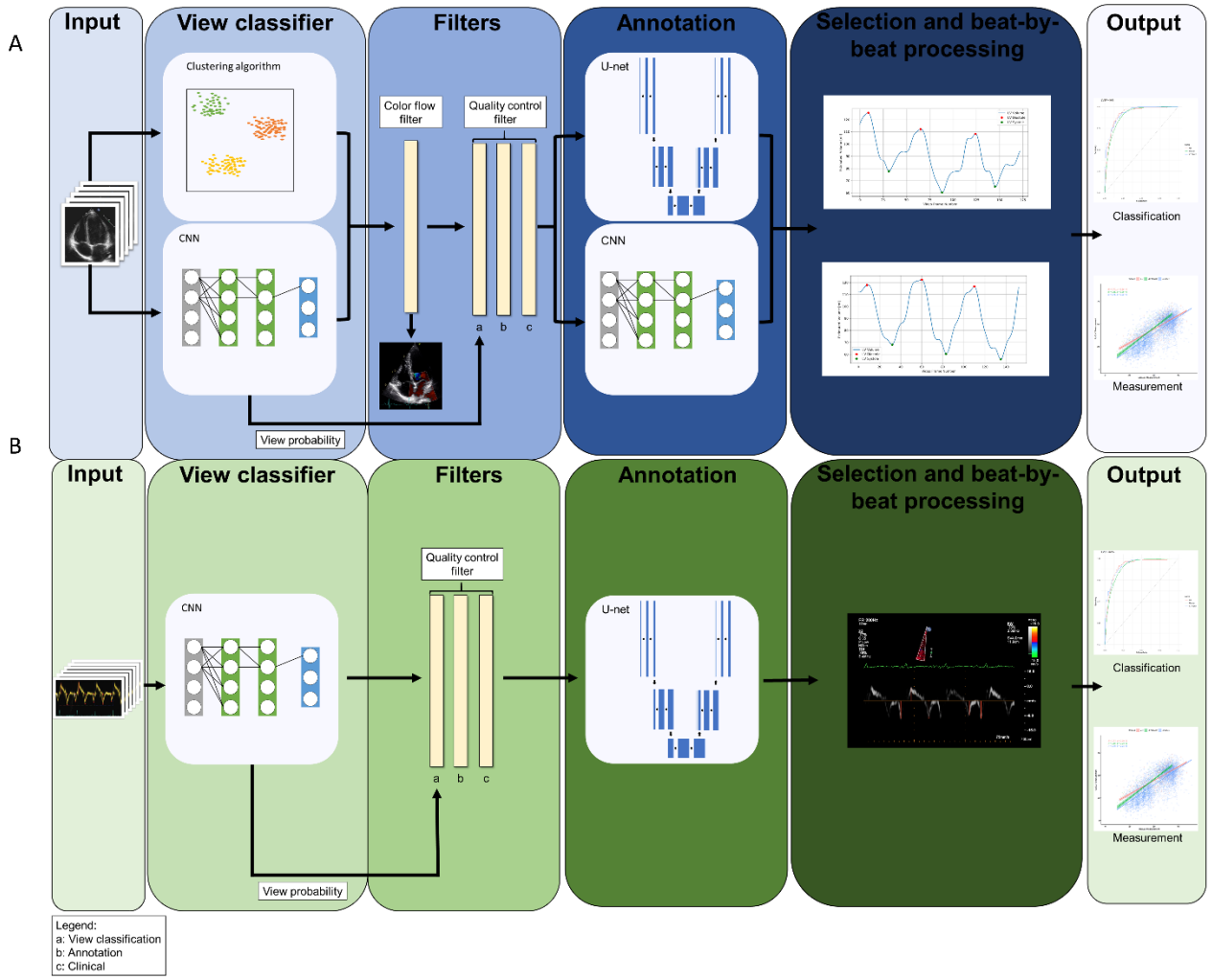
Abbreviations: A2C, apical 2 chamber; A4C, apical 4 chamber; LAESV, left atrial end systolic volume; LVEDV, left ventricular end diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end systolic volume; N, number of studies. Δ = difference, Δ% = difference as a percent of eligible echocardiograms evaluated.

Supplementary table 9: Performance of automated measurements in studies from Taiwan (MacKay Memorial Hospital), stratified to those with versus without atrial fibrillation.

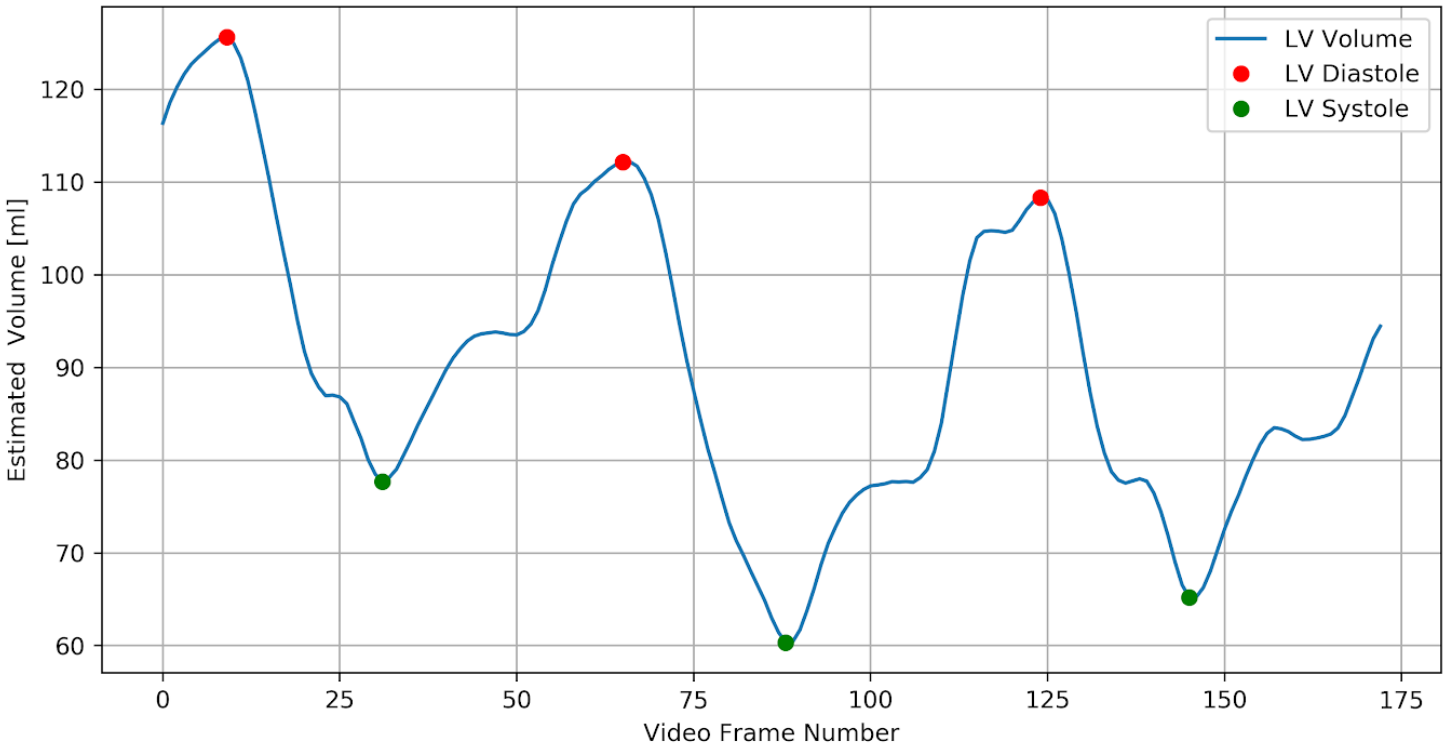
No atrial fibrillation							
	N	**R**	**MAE**	**RMSE**	**Absolute deviation vs. manual measurement (% of Manual)**		
					50	**75**	**95**
LVESV (mL)	13168	0.82	12.5	20.3	7.3 (20%)	14.3 (34%)	45.9 (68%)
LVEDV (mL)	13146	0.74	24	30.7	19.8 (20%)	33.9 (31%)	60 (55%)
LVEF (%)	4347	0.79	9.9	12.2	8.6 (18%)	14.2 (29%)	23.5 (50%)
LAESV (mL)	NA	NA	NA	NA	NA	NA	NA
E wave (cm/s)	15222	0.69	10.9	17.5	6.5 (10%)	13.7 (20%)	36.8 (45%)
e' lat (cm/s)	6165	0.88	1.6	2.0	1.4 (16%)	2.1 (26%)	3.8 (51%)
e' med (cm/s)	NA	NA	NA	NA	NA	NA	NA
E/e’	NA	NA	NA	NA	NA	NA	NA
Atrial fibrillation							
	N	**R**	**MAE**	**RMSE**	**Absolute deviation vs. manual measurement (% of Manual)**		
					50	**75**	**95**
LVESV (mL)	1700	0.83	15.7	23.0	10.6 (21%)	20.2 (36%)	46.8 (62%)
LVEDV (mL)	1683	0.74	32	39.9	28.0 (25.3)	43.8 (37%)	74.6 (54%)
LVEF (%)	1274	0.67	11.3	14.2	9.6 (21%)	16.1 (32%)	29 (53%)
LAESV (mL)	NA	NA	NA	NA	NA	NA	NA
E wave (cm/s)	1448	0.65	16.3	26.2	9.4 (11%)	20.4 (24%)	55.9 (54%)
e' lat (cm/s)	182	0.79	1.8	2.6	1.3 (19%)	2.3 (32%)	4.6 (62%)
e' med (cm/s)	NA	NA	NA	NA	NA	NA	NA
E/e’	NA	NA	NA	NA	NA	NA	NA

Abbreviations: LAESV, left atrial end systolic volume; LVEDV, left ventricular end diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end systolic volume; N, number of studies; NA, not available; R, correlation coefficient.

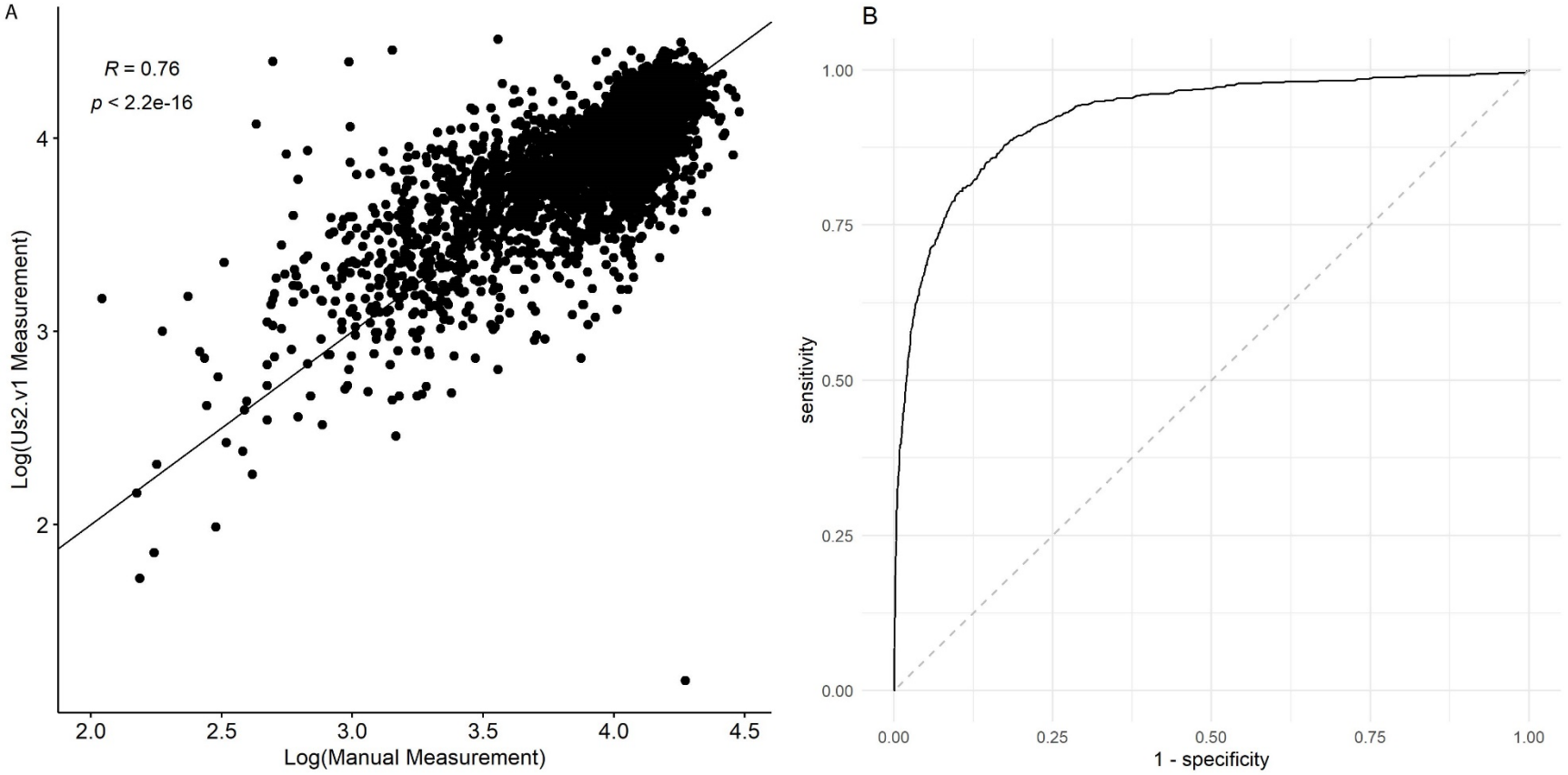
Supplementary figure 1: Schematic overview of the *Us2.v1* workflow for 2D videos (A) and Doppler modalities (B).



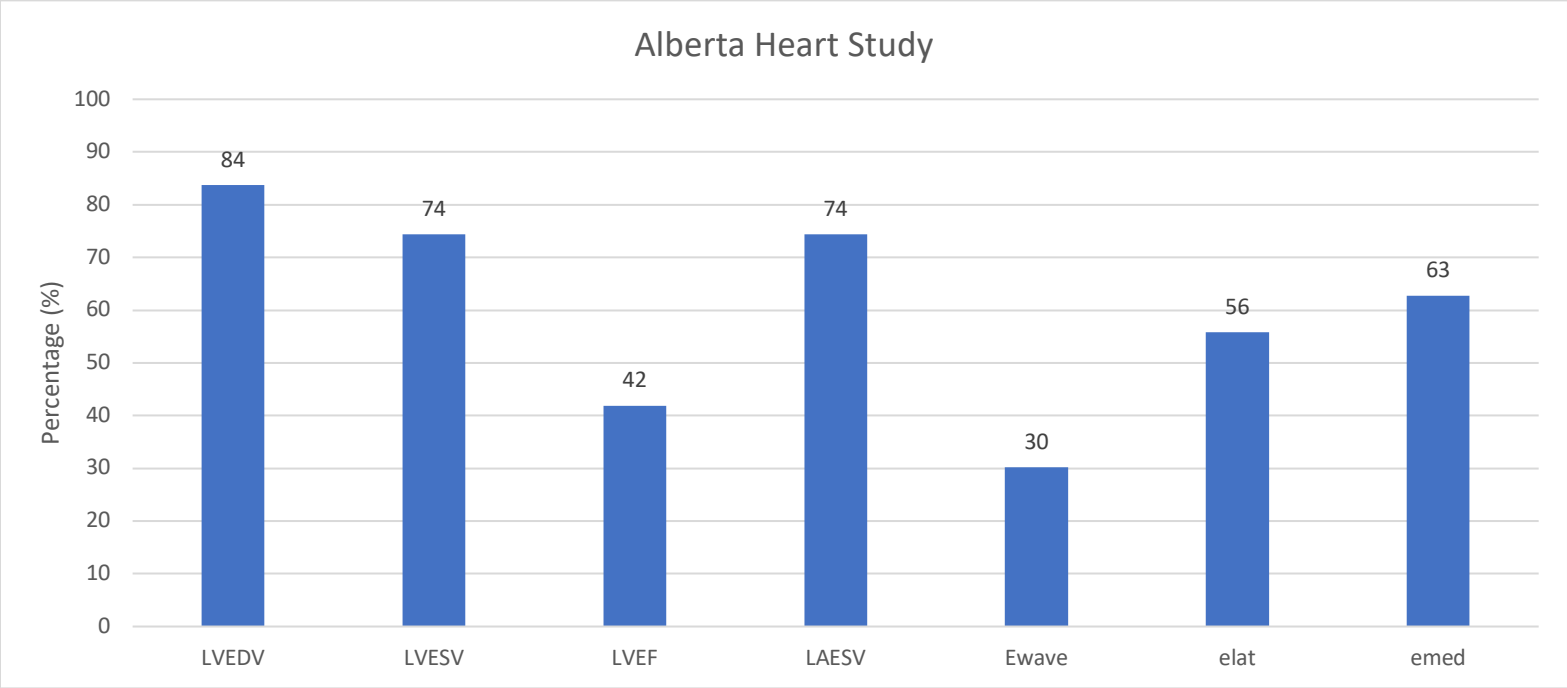
Supplementary figure 2: Example of volume curve to determine peak systole and diastole.



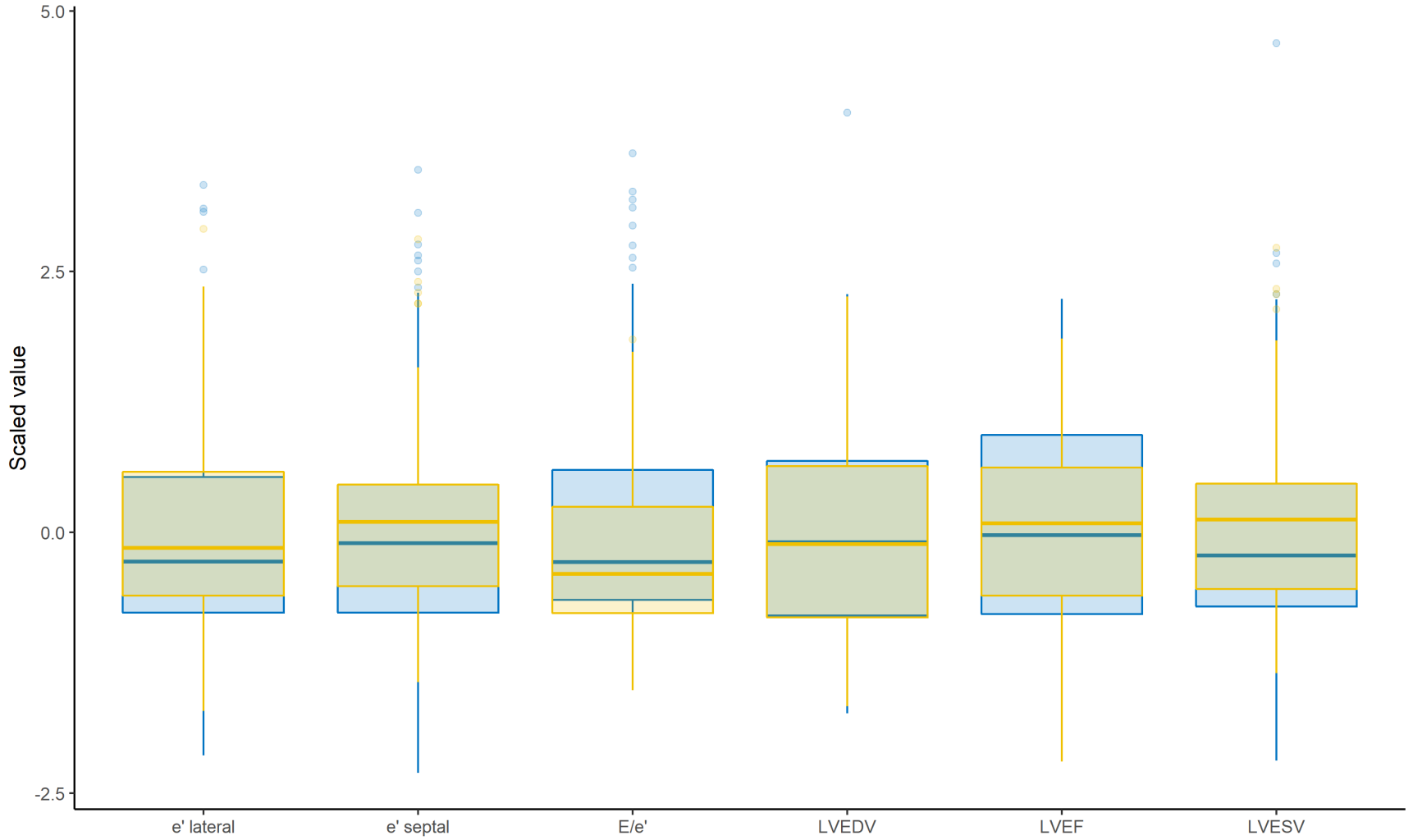
Supplementary figure 3: (A): Scatterplot for association between *Echonet-dynamic* ground truth and automated LVEF values; (B): AUC for detecting systolic dysfunction (LVEF<40% versus above) in *Echonet-dynamic* dataset.



Supplementary figure 4: Proportion of cases where the automated measurement was preferred over the human measurement. Abbreviations: Elat, e' lateral; emed, e' medial; LAESV, left atrial end systolic volume; LVEDV, left ventricular end diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end systolic volume.



Supplementary figure 5: Scaled values of human measurements (blue) versus automated measurements (yellow). Abbreviations: LAESV, left atrial end systolic volume; LVEDV, left ventricular end diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end systolic volume.



Supplemental methods

Cohort descriptions

Training and test cohort: Asia (ATTRaCT platform).

The workflow was prototyped using data from the ATTRaCT program, which contains data from the Asian Sudden Cardiac Death in Heart Failure (ASIAN-HF) registry and the ATTRaCT cohort, which have previously been described[1]. Briefly, the ASIAN-HF registry is a multinational registry of Asian patients with HF from 46 medical centers across 11 regions (Taiwan, Hong Kong, China, India, Malaysia, Thailand, Singapore, Indonesia, Philippines, Japan, and Korea). The study included 6,480 patients with HF prospectively enrolled. Patients were eligible if they were >18 years of age with symptomatic HF (at least 1 previous episode of decompensated HF in the previous 6 months resulting in a hospital admission or treatment in outpatient clinic). Patients with severe valvular heart disease as a cause of HF, with a life-threatening comorbidity with a life expectancy <1 year, or unable or unwilling to give consent were excluded. By design, all patients underwent a protocolized echocardiogram at inclusion.

In the ATTRaCT cohort, consecutive patients with HF from any of the six public health care institutions (together serving >80% of Singapore's population) in Singapore were included. Patients were >18 years, presenting to hospital with a primary diagnosis of HF; or attending a hospital clinical for management of HF within 6 months of an episode of decompensated HF, which either: resulted in a hospital admission (primary diagnosis); or was treated in the outpatient clinic. Exclusion criteria were severe valve disease as the primary cause of HF, a primary diagnosis of acute coronary syndrome causing transient pulmonary edema, end-stage renal failure (estimated glomerular filtration rate [eGFR] <15 mL/min/m^2) or being on dialysis, having isolated right-sided HF, life-threatening comorbidity with a life expectancy of <1 year,

unable or unwilling to give consent and lastly concurrent participation in a clinical trial of new pharmacotherapy. Controls included free-living adults without HF identified from the general community of Singapore via random sampling of all residents in continuous precincts within 5 districts of Singapore by door-to-door census. Controls underwent standardized clinical examination and echocardiography identical applied to patients with HF.

All participants in ASIAN-HF and ATTRaCT provided informed consent prior to enrolment, and the protocols were approved by the institutional review boards of all involved institutions.

External validation: Canada cohort (Alberta HEART Study).

The Alberta HEART Study is a prospective, observational cohort study of participants with, or at risk for, HF. Briefly, participants are adults (>18 years) recruited from Alberta, Canada, primarily from Edmonton and Calgary[2]. Enrolment was stratified according to participants at high risk for developing HF, prevalent HF, or healthy age- and sex-matched controls without evidence of diabetes, coronary artery disease, hypertension, or organ disease. All participants signed informed consent, and the study is approved by the Health Research Ethics Boards at the University of Alberta, Covenant Health and the University of Calgary. After consent, patients were enrolled and had a comprehensive clinical exam, and protocolized echocardiogram. 2D echocardiography in the Alberta HEART study was performed on IE33 (Philips) scanners and read by experienced sonographers according to American Society of Echocardiography (ASE) guidelines. Atrial fibrillation in the Alberta HEART Study was defined as a medical history of atrial fibrillation.

External validation: Taiwan cohort (MacKay Memorial Hospital)

This dataset included 31,241 studies of healthy participants, patients with chronic comorbidities without prevalent HF, and patients with HF. Studies were performed during an annual cardiovascular health check-up and at outpatient clinic. Participants were excluded if they had isolated right-sided HF, significant valvular heart disease, pulmonary hypertension, congenital heart disease, acute coronary syndrome, or end-stage renal disease (estimated glomerular filtration rate [eGFR] <15 mL/min/m^2). Diagnosis of HF was independently adjudicated by an experienced cardiologist with HF subspecialty. Echocardiograms were read by local sonographers or cardiologists with and without a HF subspeciality. Use of the data was approved by the ethnic board of MacKay memorial hospital.

Comparison with human experts.

To compare the variability of automated measurements versus expert human measurements, two expert sonographers performed a blinded annotation of a random sample of studies from the Alberta HEART cohort and ATTRaCT cohort which were not used for training of the algorithm. The view classifier identified the correct view per study, which was presented to the two expert sonographers for manual annotations. These studies were then automatically annotated, without any additional tuning of the algorithm.

Re-evaluation by expert clinicians

Three sonographers manually reviewed the top 15 studies with the highest absolute difference between the original human label and automated measurement. The sonographers were provided with two blinded measurements: the automated measurement and the original human measurement. The expert human sonographers were then asked to select which of the two

measurements belonged to the original study shown and to add any relevant comments on the quality of the video or acquisition, or the presence of arrhythmia.

References.

1. Lam, C. S. P. *et al.* Asian Sudden Cardiac Death in Heart Failure (ASIAN-HF) registry. *Eur. J. Heart Fail.* **15**, 928–936 (2013).

2. Ezekowitz, J. A. *et al.* The Alberta Heart Failure Etiology and Analysis Research Team (HEART) study. *BMC Cardiovasc. Disord.* **14**, 91 (2014).