

## **Additional file Information**

**Additional file 1: Table S1: Baseline characteristics in patients included and not included in the current investigation**

Variable	Patients included in the SERVE-HF biomarker substudy (n=809)			Patients not included in the current investigation (n=222)			Patients included in current investigation (n=587)			p-value*
	N	Mean ± SD/n (%)	Median (Q1 - Q3)	N	Mean ± SD/n (%)	Median (Q1 - Q3)	N	Mean ± SD/n (%)	Median (Q1 - Q3)	
Study intervention group	809			222			587			0.94
Control		397 (49.1 %)			108 (48.6 %)			289 (49.2 %)		
ASV		412 (50.9 %)			114 (51.4 %)			298 (50.8 %)		
Country	809			222			587			0.80
Austria		29 (3.6 %)			7 (3.2 %)			22 (3.7 %)		
Switzerland		3 (0.4 %)			0 (0.0 %)			3 (0.5 %)		
Germany		776 (95.9 %)			215 (96.8 %)			561 (95.6 %)		
Netherlands		1 (0.1 %)			0 (0.0 %)			1 (0.2 %)		
Age (years)	809	69.3 ± 9.7	71 (63 - 76)	222	68.8 ± 9.6	71 (62 - 76)	587	69.5 ± 9.8	71 (63 - 77)	0.25
Male	809	734 (90.7 %)		222	207 (93.2 %)		587	527 (89.8 %)		0.14
Body mass index (kg/m <sup>2</sup> )	801	28.7 ± 4.9	28.3 (25.4 - 31.1)	219	28.8 ± 4.6	28.4 (25.5 - 31.2)	582	28.7 ± 5.0	28.1 (25.2 - 31.1)	0.42
NYHA class III/IV	805	589 (73.2 %)		222	168 (75.7 %)		583	421 (72.2 %)		0.37
LVEF (%)	581	33.2 ± 7.7	35 (29 - 40)	137	32.3 ± 8.0	34 (27 - 38)	444	33.5 ± 7.7	35 (29 - 40)	0.13
Diabetes	805	316 (39.3 %)		222	73 (32.9 %)		583	243 (41.7 %)		<b>0.024</b>
Ischemic HF	791	441 (55.8 %)		219	115 (52.5 %)		572	326 (57.0 %)		0.26
Systolic blood pressure (mmHg)	798	123.7 ± 19.6	120 (110 - 136)	221	122.2 ± 18.6	120 (110 - 130)	577	124.3 ± 19.9	120 (110 - 140)	0.30
Left bundle-branch-block	794	206 (25.9 %)		221	56 (25.3 %)		573	150 (26.2 %)		0.86
Atrial fibrillation	795	232 (29.2 %)		221	56 (25.3 %)		574	176 (30.7 %)		0.16
Cardiac device	809	437 (54.0 %)		222	124 (55.9 %)		587	313 (53.3 %)		0.53
Haemoglobin (g/dL)	797	14.0 ± 1.6	14.1 (13.0 - 15.1)	220	14.2 ± 1.5	14.2 (13.1 - 15.3)	577	13.9 ± 1.6	14.1 (12.9 - 15.0)	0.078
eGFR CKD-EPI formula (mL/min/1.73m <sup>2</sup> )	790	57.9 ± 21.0	56.9 (41.9 - 73.6)	220	60.0 ± 20.8	58.7 (45.6 - 74.5)	570	57.1 ± 21.0	55.8 (40.6 - 72.8)	0.097
6-min walk distance (m)	771	330.9 ± 124.8	343 (253 - 420)	213	336.0 ± 124.6	350 (260 - 420)	558	329.0 ± 125.0	340 (250 - 423)	0.53
ACEI or ARB	809	749 (92.6 %)		222	209 (94.1 %)		587	540 (92.0 %)		0.37
Beta-blocker	809	748 (92.5 %)		222	211 (95.0 %)		587	537 (91.5 %)		0.10
Aldosterone antagonist	809	424 (52.4 %)		222	131 (59.0 %)		587	293 (49.9 %)		<b>0.022</b>
Diuretic	809	698 (86.3 %)		222	189 (85.1 %)		587	509 (86.7 %)		0.57
Cardiac glycoside	809	201 (24.8 %)		222	51 (23.0 %)		587	150 (25.6 %)		0.47
Antiarrhythmic drug	809	143 (17.7 %)		222	42 (18.9 %)		587	101 (17.2 %)		0.61
Epworth Sleep Scale score	804	7.0 ± 4.5	6 (4 - 9)	218	7.2 ± 4.7	6 (4 - 10)	586	6.9 ± 4.4	6 (4 - 9)	0.51
AHI (n events/hr)	808	30.2 ± 12.5	28 (20 - 38)	222	30.2 ± 12.1	28 (20 - 37)	586	30.3 ± 12.7	27 (20 - 38)	0.88
Central apnea index/total AHI (%)	808	48.1 ± 29.3	50 (22 - 73)	222	49.8 ± 29.2	51 (24 - 74)	586	47.4 ± 29.4	48 (22 - 73)	0.28
Central AHI/total AHI (%)	808	81.0 ± 15.1	84 (70 - 94)	222	81.8 ± 15.4	85 (70 - 95)	586	80.7 ± 15.0	84 (69 - 93)	0.21
Oxygen Desaturation index	805	33.5 ± 18.0	32 (20 - 44)	220	34.2 ± 19.4	33 (20 - 46)	585	33.2 ± 17.4	31 (21 - 44)	0.54

Variable	Patients included in the SERVE-HF biomarker substudy (n=809)			Patients not included in the current investigation (n=222)			Patients included in current investigation (n=587)			p-value*
	N	Mean ± SD/n (%)	Median (Q1 - Q3)	N	Mean ± SD/n (%)	Median (Q1 - Q3)	N	Mean ± SD/n (%)	Median (Q1 - Q3)	
Average oxygen saturation (%)	809	92.7 ± 2.4	93 (92 - 94)	222	92.5 ± 2.6	93 (91 - 94)	587	92.8 ± 2.4	93 (92 - 94)	0.48
Minimum oxygen saturation (%)	808	80.6 ± 6.8	82 (77 - 85)	222	80.0 ± 7.2	81 (76 - 85)	586	80.9 ± 6.6	82 (78 - 85)	0.064
Time with oxygen saturation <90% (min)	803	51.4 ± 66.6	24 (5 - 70)	219	59.4 ± 73.5	28 (6 - 90)	584	48.4 ± 63.6	22 (5 - 65)	0.13
Cheyne-Stokes respiration	702			196			506			0.25
<20%		145 (20.7 %)			39 (19.9 %)			106 (20.9 %)		
20-50%		278 (39.6 %)			87 (44.4 %)			191 (37.7 %)		
>50%		279 (39.7 %)			70 (35.7 %)			209 (41.3 %)		
NT-proBNP (pg/mL)	794	2646 ± 4330	1396 (605 - 3066)	211	2451 ± 3127	1356 (612 - 3197)	583	2717 ± 4691	1400 (605 - 3036)	0.89
Primary outcome	809	430 (53.2 %)		222	119 (53.6 %)		587	311 (53.0 %)		0.94
Time to primary outcome (years)	809	2.4 ± 1.9	2.1 (0.6 - 3.7)	222	2.4 ± 2.0	2.1 (0.6 - 4.3)	587	2.3 ± 1.8	2.1 (0.7 - 3.6)	0.78
Time to follow-up (years)	809	3.1 ± 1.8	3.0 (1.9 - 4.6)	222	3.2 ± 2.0	3.1 (1.5 - 4.9)	587	3.1 ± 1.8	3.0 (1.9 - 4.4)	0.51

N: number of available values; SD: standard deviation; Q1: first quartile; Q3: third quartile.

\* p-value from Wilcoxon test for continuous variables, Fisher's exact test for categorical variables.

ACEI: angiotensin-converting enzyme inhibitors; AHI: apnea hypoapnea index; ARB: angiotensin II receptor blockers; ASV: Adaptive-Servo Ventilation; CV: cardiovascular; HF: heart failure; LVEF: left ventricular ejection fraction; NYHA class: New York Heart Association

**Additional file: 1: Table S2: Baseline characteristics and miRNA levels according to study groups**

Variable	Overall (n=587)			Control (n=289)			ASV (n=298)			p-value
	N	Mean ± SD/ n (%)	Median (Q1 - Q3)	N	Mean ± SD/ n (%)	Median (Q1 - Q3)	N	Mean ± SD/ n (%)	Median (Q1 - Q3)	
Age (years)	587	69.5 ± 9.8	71 (63 - 77)	289	69.5 ± 10.2	71 (63 - 77)	298	69.5 ± 9.4	71 (64 - 77)	0.74
Male	587	527 (89.8 %)		289	260 (90.0 %)		298	267 (89.6 %)		0.89
Body mass index (kg/m <sup>2</sup> )	582	28.7 ± 5.0	28.1 (25.2 - 31.1)	287	28.9 ± 5.5	28.0 (25.2 - 31.2)	295	28.5 ± 4.5	28.3 (25.2 - 31.0)	0.83
NYHA class III/IV	583	421 (72.2 %)		287	211 (73.5 %)		296	210 (70.9 %)		0.52
LVEF (%)	444	33.5 ± 7.7	35 (29 - 40)	219	33.7 ± 7.4	35 (30 - 40)	225	33.4 ± 7.9	35 (29 - 40)	0.71
Diabetes	583	243 (41.7 %)		287	124 (43.2 %)		296	119 (40.2 %)		0.50
Ischemic HF	572	326 (57.0 %)		278	155 (55.8 %)		294	171 (58.2 %)		0.61
Systolic blood pressure (mmHg)	577	124.3 ± 19.9	120 (110 - 140)	283	123.9 ± 19.8	120 (110 - 138)	294	124.6 ± 20.1	121 (110 - 140)	0.70
Left bundle-branch-block	573	150 (26.2 %)		283	74 (26.1 %)		290	76 (26.2 %)		1.00
Atrial fibrillation	574	176 (30.7 %)		284	77 (27.1 %)		290	99 (34.1 %)		0.071
Cardiac device	587	313 (53.3 %)		289	152 (52.6 %)		298	161 (54.0 %)		0.74
Haemoglobin (g/dL)	577	13.9 ± 1.6	14.1 (12.9 - 15.0)	284	14.0 ± 1.6	14.1 (13.0 - 15.1)	293	13.9 ± 1.6	14.1 (12.9 - 15.0)	0.63
eGFR CKD-EPI formula (mL/min/1.73m <sup>2</sup> )	570	57.1 ± 21.0	55.8 (40.6 - 72.8)	280	58.0 ± 21.4	56.8 (42.7 - 74.2)	290	56.3 ± 20.7	55.2 (39.5 - 71.1)	0.29
6-min walk distance (m)	558	329.0 ± 125.0	340 (250 - 423)	271	331.6 ± 130.7	341 (250 - 435)	287	326.5 ± 119.5	330 (250 - 419)	0.32
ACEI or ARB	587	540 (92.0 %)		289	269 (93.1 %)		298	271 (90.9 %)		0.36
Beta-blocker	587	537 (91.5 %)		289	269 (93.1 %)		298	268 (89.9 %)		0.19
Aldosterone antagonist	587	293 (49.9 %)		289	155 (53.6 %)		298	138 (46.3 %)		0.083
Diuretic	587	509 (86.7 %)		289	257 (88.9 %)		298	252 (84.6 %)		0.14
Cardiac glycoside	587	150 (25.6 %)		289	64 (22.1 %)		298	86 (28.9 %)		0.072
Antiarrhythmic drug	587	101 (17.2 %)		289	37 (12.8 %)		298	64 (21.5 %)		<b>0.006</b>
Epworth Sleep Scale score	586	6.9 ± 4.4	6 (4 - 9)	289	6.9 ± 4.6	6 (4 - 9)	297	6.8 ± 4.2	6 (4 - 9)	0.84
AHI (n events/hr)	586	30.3 ± 12.7	27 (20 - 38)	289	31.1 ± 13.6	29 (21 - 38)	297	29.5 ± 11.8	27 (19 - 38)	0.25
Central apnea index/total AHI (%)	586	47.4 ± 29.4	48 (22 - 73)	289	50.3 ± 29.9	53 (24 - 76)	297	44.6 ± 28.6	45 (19 - 67)	<b>0.018</b>
Central AHI/total AHI (%)	586	80.7 ± 15.0	84 (69 - 93)	289	81.1 ± 15.2	85 (70 - 93)	297	80.3 ± 14.8	82 (68 - 93)	0.48
Oxygen Desaturation index	585	33.2 ± 17.4	31 (21 - 44)	287	33.8 ± 18.3	32 (20 - 44)	298	32.6 ± 16.6	30 (21 - 42)	0.43
Average oxygen saturation (%)	587	92.8 ± 2.4	93 (92 - 94)	289	92.8 ± 2.5	93 (91 - 95)	298	92.7 ± 2.2	93 (92 - 94)	0.33
Minimum oxygen saturation (%)	586	80.9 ± 6.6	82 (78 - 85)	289	80.5 ± 7.1	82 (77 - 86)	297	81.3 ± 6.2	82 (78 - 85)	0.45
Time with oxygen saturation <90% (min)	584	48.4 ± 63.6	22 (5 - 65)	289	50.2 ± 65.9	20 (4 - 71)	295	46.7 ± 61.3	23 (7 - 61)	0.62
Cheyne-Stokes respiration	506			252			254			0.17
<20%		106 (20.9 %)			55 (21.8 %)			51 (20.1 %)		
20-50%		191 (37.7 %)			85 (33.7 %)			106 (41.7 %)		

Variable	Overall (n=587)			Control (n=289)			ASV (n=298)			p-value*
	N	Mean ± SD/ n (%)	Median (Q1 - Q3)	N	Mean ± SD/ n (%)	Median (Q1 - Q3)	N	Mean ± SD/ n (%)	Median (Q1 - Q3)	
>50%		209 (41.3 %)			112 (44.4 %)			97 (38.2 %)		
NT-proBNP (pg/mL)	583	2717 ± 4691	1400 (605 - 3036)	287	2649 ± 4557	1395 (571 - 3092)	296	2783 ± 4823	1415 (649 - 2990)	0.55
miR-133a-3p	584	4.14 ± 3.04	4.61 (0.21 - 6.67)	286	4.10 ± 3.00	4.65 (0.21 - 6.59)	298	4.17 ± 3.07	4.58 (0.21 - 6.75)	0.71
miR-501-3p	557	12.51 ± 1.55	11.54 (11.54 - 13.56)	269	12.42 ± 1.47	11.54 (11.54 - 13.14)	288	12.58 ± 1.61	11.54 (11.54 - 13.78)	0.32
Primary outcome	587	311 (53.0 %)		289	142 (49.1 %)		298	169 (56.7 %)		0.069
Time to primary outcome (years)	587	2.3 ± 1.8	2.1 (0.7 - 3.6)	289	2.5 ± 1.9	2.2 (0.7 - 3.9)	298	2.2 ± 1.7	2.0 (0.7 - 3.3)	0.054
Time to follow-up (years)	587	3.1 ± 1.8	3.0 (1.9 - 4.4)	289	3.2 ± 1.8	3.0 (2.0 - 4.5)	298	3.0 ± 1.8	2.9 (1.8 - 4.2)	0.36

N: number of available values; SD: standard deviation; Q1: first quartile; Q3: third quartile.

\*p-value from Wilcoxon test for continuous variables, Fisher's exact test for categorical variables.

ACEI: angiotensin-converting enzyme inhibitors; AHI: apnea hypoapnea index; ARB: angiotensin II receptor blockers; ASV: Adaptive-Servo Ventilation; CV: cardiovascular; HF: heart failure; LVEF: left ventricular ejection fraction; NYHA class: New York Heart Association

### Additional file 1: Table S3: Baseline characteristics according to the primary outcome (Screening)

Variable	Patients in the screening phase (n=20)			Patients without primary outcome (n=10)			Patients with primary outcome (n=10)			p-value*
	N	Mean ± SD/n (%)	Median (Q1 - Q3)	N	Mean ± SD/n (%)	Median (Q1 - Q3)	N	Mean ± SD/n (%)	Median (Q1 - Q3)	
Study intervention group	20			10			10			1.00
Control		12 (60.0 %)			6 (60.0 %)			6 (60.0 %)		
ASV		8 (40.0 %)			4 (40.0 %)			4 (40.0 %)		
Age (years)	20	66.1 ± 10.5	69 (58 - 73)	10	65.4 ± 11.5	69 (64 - 73)	10	66.9 ± 10.1	67 (58 - 74)	0.97
Male	20	18 (90.0 %)		10	9 (90.0 %)		10	9 (90.0 %)		1.00
Diabetes	20	20 (100.0 %)		10	10 (100.0 %)		10	10 (100.0 %)		NA
Systolic blood pressure (mmHg)	20	119.5 ± 15.2	118 (110 - 130)	10	117.7 ± 8.8	118 (115 - 120)	10	121.4 ± 20.1	118 (110 - 130)	1.00
Atrial fibrillation	20	2 (10.0 %)		10	1 (10.0 %)		10	1 (10.0 %)		1.00
Cardiac device	20	10 (50.0 %)		10	5 (50.0 %)		10	5 (50.0 %)		1.00
6-min walk distance (m)	18	368.8 ± 108.2	398 (306 - 420)	10	365.5 ± 123.4	378 (306 - 420)	8	373.0 ± 94.0	410 (320 - 432)	0.79
Diuretic	20	16 (80.0 %)		10	8 (80.0 %)		10	8 (80.0 %)		1.00
NT-proBNP (pg/mL)	20	2007 ± 2356	1156 (485 - 1989)	10	1442 ± 1494	680 (359 - 2032)	10	2571 ± 2962	1553 (719 - 1946)	0.25

N: number of available values; SD: standard deviation; Q1: first quartile; Q3: third quartile.

\*p-value from Wilcoxon test for continuous variables, Fisher's exact test for categorical variables.

ASV: Adaptive-Servo Ventilation

## Additional file 1: Table S4: Baseline characteristics according to the primary outcome (technical validation)

Variable	Patients in the technical validation phase (n=60)			Patients without primary outcome (n=30)			Patients with primary outcome (n=30)			p-value*
	N	Mean ± SD/n (%)	Median (Q1 - Q3)	N	Mean ± SD/n (%)	Median (Q1 - Q3)	N	Mean ± SD/n (%)	Median (Q1 - Q3)	
Study intervention group	60			30			30			1.00
Control		32 (53.3 %)			16 (53.3 %)			16 (53.3 %)		
ASV		28 (46.7 %)			14 (46.7 %)			14 (46.7 %)		
Age (years)	60	68.4 ± 9.8	71 (61 - 76)	30	68.2 ± 11.2	71 (64 - 77)	30	68.6 ± 8.3	70 (60 - 75)	0.76
Male	60	58 (96.7 %)		30	29 (96.7 %)		30	29 (96.7 %)		1.00
Diabetes	60	10 (16.7 %)		30	5 (16.7 %)		30	5 (16.7 %)		1.00
Atrial fibrillation	60	10 (16.7 %)		30	5 (16.7 %)		30	5 (16.7 %)		1.00
Cardiac device	60	32 (53.3 %)		30	16 (53.3 %)		30	16 (53.3 %)		1.00
6-min walk distance (m)	56	324.2 ± 125.1	350 (258 - 420)	29	307.2 ± 128.4	320 (240 - 396)	27	342.6 ± 121.2	380 (267 - 429)	0.19
Diuretic	60	55 (91.7 %)		30	28 (93.3 %)		30	27 (90.0 %)		1.00
NT-proBNP (pg/mL)	60	2251 ± 2417	1304 (575 - 3448)	30	1714 ± 1574	1041 (482 - 3232)	30	2789 ± 2968	1351 (719 - 3687)	0.19

N: number of available values; SD: standard deviation; Q1: first quartile; Q3: third quartile.

\*p-value from Wilcoxon test for continuous variables, Fisher's exact test for categorical variables.

ASV: Adaptive-Servo Ventilation

**Additional file 1: Table S5: Comparison of baseline characteristics according to median value of miR-501-3p**

Variable	miR-501-3p ≤ median (n=380)			miR-501-3p > median (n=177)			p-value <sup>*</sup>
	N	Mean ± SD/n (%)	Median (Q1 - Q3)	N	Mean ± SD/n (%)	Median (Q1 - Q3)	
Study intervention group	380			177			0.58
Control		187 (49.2 %)			82 (46.3 %)		
ASV		193 (50.8 %)			95 (53.7 %)		
Age (years)	380	70.0 ± 9.6	71 (64 - 77)	177	67.9 ± 10.4	70 (62 - 76)	<b>0.036</b>
Male	380	352 (92.6 %)		177	149 (84.2 %)		<b>0.004</b>
Body mass index (kg/m <sup>2</sup> )	376	28.3 ± 4.6	27.9 (25.1 - 30.6)	176	29.5 ± 5.5	28.7 (26.0 - 32.0)	0.020
NYHA class III/IV	377	275 (72.9 %)		176	120 (68.2 %)		0.27
LVEF (%)	296	34.2 ± 7.7	35 (30 - 40)	126	31.9 ± 7.3	32 (27 - 38)	<b>0.004</b>
Diabetes	377	145 (38.5 %)		176	82 (46.6 %)		0.078
Ischemic HF	368	216 (58.7 %)		175	88 (50.3 %)		0.079
Systolic blood pressure (mmHg)	373	124.4 ± 20.9	120 (110 - 140)	174	124.3 ± 18.0	120 (110 - 140)	0.91
Left bundle-branch-block	372	100 (26.9 %)		171	45 (26.3 %)		0.92
Atrial fibrillation	372	108 (29.0 %)		172	55 (32.0 %)		0.48
Cardiac device	380	207 (54.5 %)		177	94 (53.1 %)		0.78
Haemoglobin (g/dL)	373	13.8 ± 1.6	13.9 (12.8 - 15.0)	174	14.2 ± 1.4	14.4 (13.4 - 15.1)	<b>0.002</b>
eGFR CKD-EPI formula (mL/min/1.73m <sup>2</sup> )	368	56.2 ± 20.8	56.0 (39.8 - 71.2)	172	59.7 ± 21.3	56.1 (44.5 - 77.6)	0.13
6-min walk distance (m)	359	341.9 ± 122.9	355 (270 - 430)	169	304.4 ± 127.6	312 (200 - 405)	<b>0.002</b>
ACEI or ARB	380	352 (92.6 %)		177	162 (91.5 %)		0.73
Beta-blocker	380	343 (90.3 %)		177	164 (92.7 %)		0.43
Aldosterone antagonist	380	196 (51.6 %)		177	83 (46.9 %)		0.32
Diuretic	380	325 (85.5 %)		177	159 (89.8 %)		0.18
Cardiac glycoside	380	84 (22.1 %)		177	51 (28.8 %)		0.090
Antiarrhythmic drug	380	62 (16.3 %)		177	37 (20.9 %)		0.19
Epworth Sleep Scale score	380	6.6 ± 4.3	6 (4 - 9)	176	7.2 ± 4.4	6 (4 - 10)	0.11
AHI (n events/hr)	380	30.6 ± 12.7	28 (20 - 38)	176	29.8 ± 12.9	26 (20 - 37)	0.39
Central apnea index/total AHI (%)	380	46.7 ± 29.5	46 (21 - 73)	176	48.9 ± 28.9	52 (24 - 74)	0.39
Central AHI/total AHI (%)	380	80.0 ± 14.8	82 (67 - 93)	176	82.5 ± 15.4	86 (72 - 96)	<b>0.029</b>
Oxygen Desaturation index	378	33.9 ± 18.0	32 (21 - 44)	177	32.1 ± 16.6	30 (20 - 43)	0.40
Average oxygen saturation (%)	380	92.8 ± 2.3	93 (92 - 94)	177	92.7 ± 2.5	93 (91 - 94)	0.71
Minimum oxygen saturation (%)	379	81.0 ± 6.9	82 (78 - 86)	177	80.3 ± 6.3	82 (77 - 85)	0.080
Time with oxygen saturation <90% (min)	377	46.4 ± 62.4	21 (4 - 62)	177	54.3 ± 68.3	26 (7 - 79)	0.11
Cheyne-Stokes respiration	333			147			0.39



Variable	miR-501-3p ≤ median (n=380)			miR-501-3p > median (n=177)			p-value*
	N	Mean ± SD/n (%)	Median (Q1 - Q3)	N	Mean ± SD/n (%)	Median (Q1 - Q3)	
<20%		72 (21.6 %)			30 (20.4 %)		
20-50%		129 (38.7 %)			49 (33.3 %)		
>50%		132 (39.6 %)			68 (46.3 %)		
NT-proBNP (pg/mL)	377	2835 ± 4504	1439 (607 - 3226)	176	2483 ± 5059	1328 (566 - 2446)	0.13
Primary outcome	380	200 (52.6 %)		177	95 (53.7 %)		0.86
Time to primary endpoint (years)	380	2.2 ± 1.8	2.1 (0.5 - 3.4)	177	2.6 ± 2.0	2.2 (0.9 - 4.0)	0.055
Time to follow-up (years)	380	2.9 ± 1.7	2.8 (1.7 - 4.0)	177	3.6 ± 1.8	3.9 (2.1 - 5.0)	<b>&lt;0.0001</b>

N: number of available values; SD: standard deviation; Q1: first quartile; Q3: third quartile.

\*p-value from Wilcoxon test for continuous variables, Fisher's exact test for categorical variables.

### Additional file 1: Table S6: C-index for miRNAs and NT-proBNP

Subgroup	miRNA	C-index (95% CI)	p-value
<b>Overall</b>	miR-133a-3p	0.561 (0.527 - 0.594)	<b>0.0004</b>
	miR-501-3p	0.515 (0.486 - 0.544)	0.31
	Log(NT-proBNP)	0.693 (0.664 - 0.722)	<b>&lt;0.0001</b>
<b>Control</b>	miR-133a-3p	0.561 (0.510 - 0.613)	<b>0.020</b>
	miR-501-3p	0.529 (0.485 - 0.574)	0.19
	Log(NT-proBNP)	0.713 (0.671 - 0.755)	<b>&lt;0.0001</b>
<b>ASV</b>	miR-133a-3p	0.565 (0.521 - 0.610)	<b>0.004</b>
	miR-501-3p	0.507 (0.468 - 0.547)	0.72
	Log(NT-proBNP)	0.674 (0.633 - 0.715)	<b>&lt;0.0001</b>

ASV : Adaptive-Servo Ventilation; CI: confidence interval.

Additional file 1: **Table S7. Number of participants with event (Positive) within time points (1, 3 and 5 years), and those without event.**

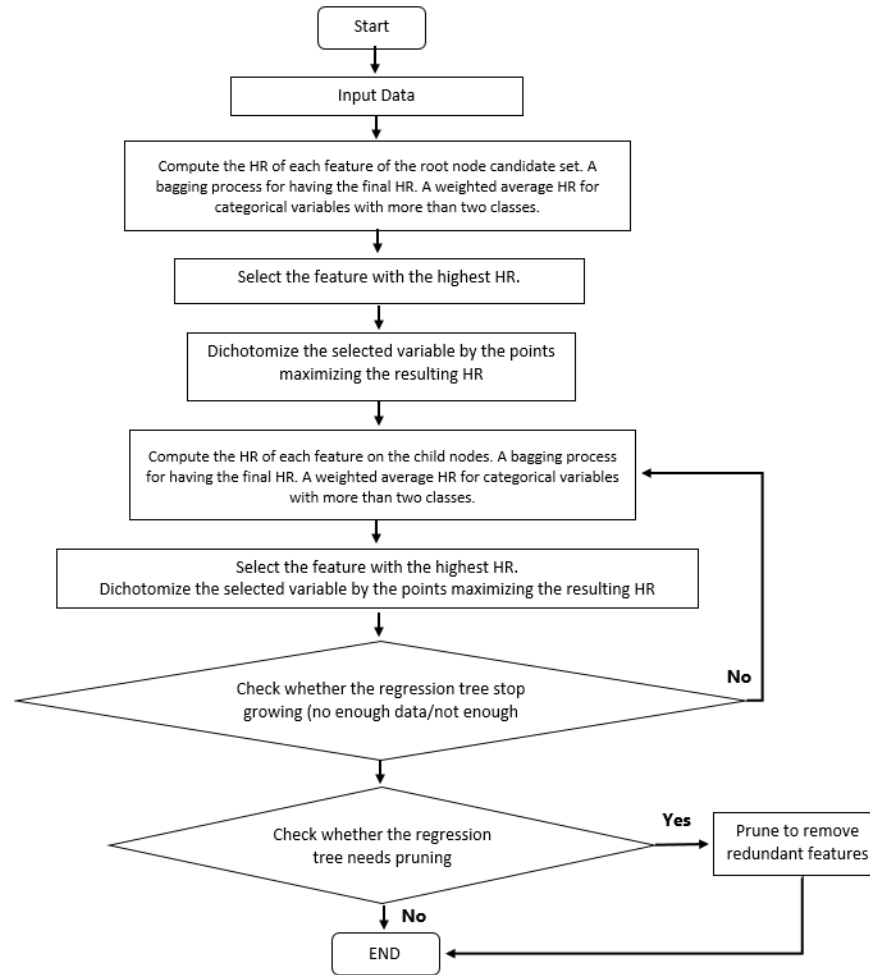
	1 Year		3 Year		5 Year	
	Positive	Negative	Positive	Negative	Positive	Negative
<b>Node 6</b>	1	69	10	45	12	18
<b>Node 7</b>	2	22	7	10	9	2
<b>Node 8</b>	9	64	21	34	25	14
<b>Node 9</b>	11	49	26	24	33	10
<b>Node 10</b>	24	81	47	43	54	13
<b>Node 11</b>	35	45	53	17	60	1
<b>Node 12</b>	24	42	42	16	45	4
<b>Node 13</b>	46	29	63	8	66	1
<b>Total</b>	155	401	269	197	304	63

Those without event and without enough follow-up (censored with a follow-time below the considered point) are removed from both the Positive and the Negative groups.

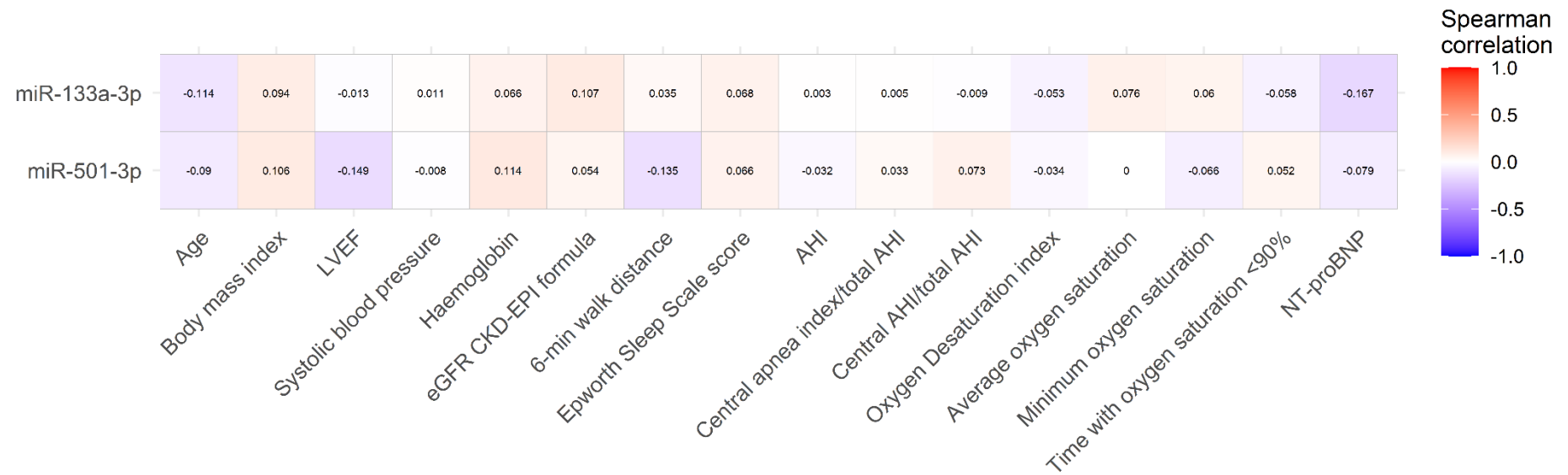
Additional file 1: **Table S8. Classification metrics at different time points.**

	<b>1 Year</b>	<b>3 Year</b>	<b>5 Year</b>
<b>Positivity criteria</b>	<b>Nodes 10, 11, 12,13</b>	<b>Nodes 9, 10, 11, 12, 13</b>	<b>Nodes 8, 9, 10, 11, 12, 13</b>
<b>Sensitivity (Recall)</b>	83.2%	85.9%	93.1%
<b>Specificity</b>	50.9%	45.2%	31.7%
<b>PPV (Precision)</b>	39.6%	68.1%	72.7%
<b>PNV</b>	89.9%	70.1%	48.8%
<b>F1-Score</b>	54.0%	76.0%	81.7%
<b>Accuracy</b>	59.9%	63.9%	82.6%

PPV: Predictive Positive Value. PNV: Predictive Negative Value  
 Positive criteria define the Nodes predicting patients as positive.  
 Numbers based on those reported in the previous table.



Additional file 1: **Figure S1. Flow-diagram for the customized-CART algorithm.**



Additional file 1: **Figure S2. Correlation coefficient maps between microRNA expression levels and baseline clinical characteristics.** Correlations between continuous variables were assessed with Spearman rank correlation coefficients, represented as rho values.