**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/m²) | 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 %) |  | **0.024** |
| 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/1.73m²) | 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 %) |  | **0.022** |
| 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 |
| 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/m²) | 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/1.73m²) | 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 %) |  | **0.006** |
| 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) | **0.018** |
| 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 %) |  |  |
| >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\*** |
| --- | --- | --- | --- |
| **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) | **0.036** |
| Male | 380 | 352 (92.6 %) |  | 177 | 149 (84.2 %) |  | **0.004** |
| Body mass index (kg/m²) | 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) | **0.004** |
| 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) | **0.002** |
| eGFR CKD-EPI formula (mL/min/1.73m²) | 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) | **0.002** |
| 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) | **0.029** |
| 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 |
| <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) | **<0.0001** |
| 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** |
| --- | --- | --- | --- |
| **Overall** |  miR-133a-3p | 0.561 (0.527 - 0.594) | **0.0004** |
|  miR-501-3p | 0.515 (0.486 - 0.544) | 0.31 |
| Log(NT-proBNP) | 0.693 (0.664 - 0.722) | **<0.0001** |
| **Control** |  miR-133a-3p | 0.561 (0.510 - 0.613) | **0.020** |
|  miR-501-3p | 0.529 (0.485 - 0.574) | 0.19 |
| Log(NT-proBNP) | 0.713 (0.671 - 0.755) | **<0.0001** |
| **ASV** |  miR-133a-3p | 0.565 (0.521 - 0.610) | **0.004** |
|  miR-501-3p | 0.507 (0.468 - 0.547) | 0.72 |
| Log(NT-proBNP) | 0.674 (0.633 - 0.715) | **<0.0001** |
| 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** |
| **Node 6** | 1 | 69 | 10 | 45 | 12 | 18 |
| **Node 7** | 2 | 22 | 7 | 10 | 9 | 2 |
| **Node 8** | 9 | 64 | 21 | 34 | 25 | 14 |
| **Node 9** | 11 | 49 | 26 | 24 | 33 | 10 |
| **Node 10** | 24 | 81 | 47 | 43 | 54 | 13 |
| **Node 11** | 35 | 45 | 53 | 17 | 60 | 1 |
| **Node 12** | 24 | 42 | 42 | 16 | 45 | 4 |
| **Node 13** | 46 | 29 | 63 | 8 | 66 | 1 |
| **Total** | 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.**

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