SUPPLEMENTAL APPENDIX

Results

Hereditary ATTR-CA

Among the 57 ATTRv patients, TTR variants diagnosed were Glu89Gln (n=15), Ile68Leu (n=13), Phe64Leu (n=5), Val122Ile (n=4), Val142Ile (n=4), Val30Met (n=4), Tyr78Phe (n=3), Ile88Leu (n=2), and Phe84Ile, Thr49Ala, Val112Ile, Gly77Arg, Gly67Glu, Ala109Ser, Ala120Ser.

Comparison between ATTRv- and ATTRwt-CA

During a median follow-up of 33 months (interquartile range 21-46), 22 (9%) of 234 ATTRwt-CA group died for CV causes and 5 (9%) among the 57 with ATTRv-CA group. No significant differences in mortality rate were found between ATTRv and ATTRwt patients (logRank p=0.728) (**Supplementary Figure 2**). In patients with ATTRv-CA, Cox univariable regression analysis showed that NYHA class and NAC score were significantly associated with CV mortality; however, only NAC score remained in a subsequent multivariable model (HR 7.93; 95% CI 1.05-36.71, p= 0.008) (**Supplementary Table 3**). In patients with ATTRwt-CA, Cox univariable regression analysis showed that LQRSV were significantly associated with CV mortality (HR 2.77; 95% CI 1.18-6.49, p= 0.019) and remained so (HR 2.84, 95% CI 1.01-1.16, p=0.048), also after adjusting for other covariates (**Supplementary Table 3**).

Supplemental Table 1. Baseline characteristics of the study population, based on CA subtype and presence of LQRSV.

	Study population n=411	**AL n=120**	**ATTR n=291**	**p value**	**No LRSV n=242**	**LQRSV n=169**	**p value**
Sex, %	M 341 (83) F 70 (17)	M 78 (65) F 42 (35)	M 263 (90) F 28 (10)	<0.001	M 205 (85) F 37 (15)	M 136 (81) F 33 (20)	0.26
Age, yrs	74 ± 11	66 ± 10	77 ± 9	<0.001	75 ± 10	72 ± 11	<0.001
BMI	25 ± 4	24 ± 4	26 ± 3	0.001	25 ± 4	25 ± 4	0.30
PM/ICD	25 (6)	6 (5)	19 (57)	0.56	15 (6)	10 (6)	0.91
NYHA class#							
I	67 (17)	21 (18)	46 (16)	0.66	44 (19)	23 (14)	0.25
II	231 (58)	55 (47)	176 (62)	0.006	144 (61)	87 (53)	0.16
III	96 (24)	36 (31)	60 (21)	0.040	48 (20)	48 (29)	0.032
IV	7 (2)	5 (4)	2 (1)	0.013	2 (1)	5 (3)	0.13
GFR, ml/min	65 ± 23	62 ± 30	65 ± 20	0.24	65 ± 23	64 ± 24	0.28
NT-proBNP ng/L	2904 (1094 – 5500)	2630 (990 – 7350)	2976 (1156 – 5009)	0.80	1957 (713 – 4448)	4189 (2137 – 7866)	<0.001
BNP ng/L	331 (154 – 782)	582 (187 – 1011)	251 (150 – 600)	0.021	233 (127 – 767)	550 (251 – 1140)	<0.001
Electrocardiography							
Atrial fibrillation	109 (27)	17 (14)	92 (32)	<0.001	58 (24)	51 (30)	0.160
1-degree AV block	117 (39)	23 (22)	94 (48)	<0.001	76 (42)	41 (35)	0.26
LBBB	41 (10)	3 (3)	38 (13)	0.001	35 (15)	6 (4)	<0.001
LAH	150 (49)	49 (41)	101 (35)	0.28	112 (47)	38 (23)	<0.001
RBBB	75 (18)	16 (13)	59 (20)	0.095	58 (24)	17 (10)	<0.001
TWI	82 (20)	39 (33)	43 (15)	<0.001	44 (18)	38 (23)	0.27
TWI lat/inflat	67 (16)	35 (29)	32 (11)	<0.001	34 (14)	33 (20)	0.13
Ant pseudoinfarction	122 (30)	47 (39)	75 (26)	0.007	51 (21)	71 (42)	<0.001
Inf pseudoinfarction	49 (12)	13 (11)	36 (13)	0.66	28 (12)	21 (13)	0.75
Peripheral QRS score	35 ± 16	33 ± 17	36 ± 15	0.13	45 ± 14	22 ± 5	<0.001
Precordial QRS score	78 ± 25	75 ± 25	79 ± 24	0.15	84 ± 25	69 ± 21	<0.001
Total QRS score	111 ± 35	106± 40	113 ± 33	0.085	127± 33	89 ± 25	<0.001
Ecocardiography							
LA diameter, mm	45 ± 8	44 ± 8	46 ± 7	0.083	46 ± 8	45 ± 7	0.55
IVSd, mm	17 ± 3	16 ± 3	18 ± 3	<0.001	17 ± 4	17 ± 3	0.36
PWTd, mm	15 ± 3	14 ± 3	15 ± 3	0.086	15 ± 3	15 ± 3	0.22
LVEDD, mm	45 ± 6	44 ± 6	46 ± 6	0.12	46 ± 6	44 ± 6	0.007
RWT	0.65 (0.55-0.79)	0.60 (0.50-0.74)	0.68 (0.57-0.80)	0.001	0.64 (0.53-0.80)	0.67 (0.57-0.76)	0.43
LVMi gr/m2	161 (131- 198)	142 (118- 167)	169 (141- 208)	<0.001	162 (134- 207)	155 (127- 187)	0.009

Limb voltage-to-mass ratio	0.20 (0.14 – 0.28)	0.21 (0.15 – 0.31)	0.19 (0.14 – 0.27)	0.24	0.25 (0.19 – 0.34)	0.14 (0.10 – 0.18)	<0.001
Total voltage-to-mass ratio	0.65 (0.53 – 0.86)	0.70 (0.53 – 0.99)	0.64 (0.52 – 0.83)	0.058	0.74 (0.57 – 0.95)	0.58 (0.45 – 0.71)	<0.001
Myocardial volume	155 (128-198)	135 (112-159)	160 (134-198)	<0.001	155 (128-198)	148 (121-178)	0.009
Pericardial effusion	73 (18)	31 (27)	57 (21)	0.19	29 (12)	44 (26)	<0.001
Max size, mm	6 ± 3	6 ± 2	6 ± 4	0.44	6 ± 3	6 ± 3	0.95
LVEF, %	54 ± 10	56 ± 10	54 ± 10	0.055	54 ± 11	55 ± 9	0.80
E/e’	17 ± 8	18 ± 9	17 ± 8	0.25	17 ± 8	18 ± 8	0.44
TAPSE, mm	19 ± 5	19 ± 5	18 ± 5	0.79	19 ± 5	18 ± 4	0.001
sPAP, mmHg	36 ± 12	34 ± 1	37± 12	0.020	36 ± 12	38 ± 12	0.11

Categorical values are reported as n (%), continuous values are reported in mean ± SD if normally distributed, median (Q1-Q3) if not normally distributed. #Missing data in AL=3, in ATTR=7. Abbreviations: M= male; F=female; AL=light-chain amyloidosis; ATTR= transthyretin amyloidosis ; CA= cardiac amyloidosis; BMI= body mass index; PM=pacemaker; ICD= implantable cardioverter-defibrillator; NYHA=New York Heart Association; GFR= glomerular filtration rate; AV= atrio-ventricular; TWI=T-wave inversion; LBBB=left bundle branch block; RBBB=right bundle branch block; LAH=left anterior hemiblock; LA= left atrium; IVSd= interventricular septum in diastole; LVEDD= left ventricular end diastolic diameter; PWTd= posterior wall thickness in diastole; RWT= relative wall thickness; LVMi= left ventricular mass index; LVEF= left ventricular ejection fraction; TAPSE=tricuspid annular peak systolic excursion; sPAP= systolic pulmonary artery pressure.

Supplemental Table 2. Comparison between the different quantitative QRS Voltage measures in predicting CV mortality in the study population, and divided into AL- and ATTR-CA.

		AUC	SE	95%CI	p	Best cut-off	Sensitivity (%)	Specificity (%)
ALL	Limb QRS score	0.698	0.039	0.58-0.74	<0.001	30 mm	60	75
	Precordial QRS score	0.546	0.042	0.46-0.63	0.29	86 mm	35	79
	Total QRS score	0.595	0.041	0.51-0.68	0.030	120 mm	39	81
	Limb Voltage-to-mass ratio	0.636	0.041	0.56-0.72	0.002	0.18	63	61
	Total Voltage-to-mass ratio	0.604	0.043	0.52-0.69	0.017	0.65	54	65
AL-CA	Limb QRS score	0.643	0.058	0.50-0.74	0.048	31 mm	52	82
	Precordial QRS score	0.494	0.061	0.38-0.61	0.93	85 mm	33	78
	Total QRS score	0.555	0.061	0.43-0.68	0.390	116 mm	38	81
	Limb Voltage-to-mass ratio	0.618	0.059	0.54-0.76	0.058	0.24	50	69
	Total Voltage-to-mass ratio	0.625	0.052	0.50-0.75	0.052	0.68	57	63
ATTR-CA	Limb QRS score	0.654	0.057	0.54-0.77	0.013	32 mm	59	71
	Precordial QRS score	0.571	0.061	0.45-0.69	0.25	75 mm	48	72
	Total QRS score	0.595	0.058	0.48-0.71	0.13	118 mm	41	80
	Limb Voltage-to-mass ratio	0.652	0.063	0.53-0.78	0.014	0.16	66	67
	Total Voltage-to-mass ratio	0.628	0.058	0.51-0.74	0.038	0.63	54	70

Abbreviations: AUC= area under the curve; SE= standard error.

Supplemental Table 3. Predictors of CV Mortality in ATTRv- and ATTR-wt -CA.

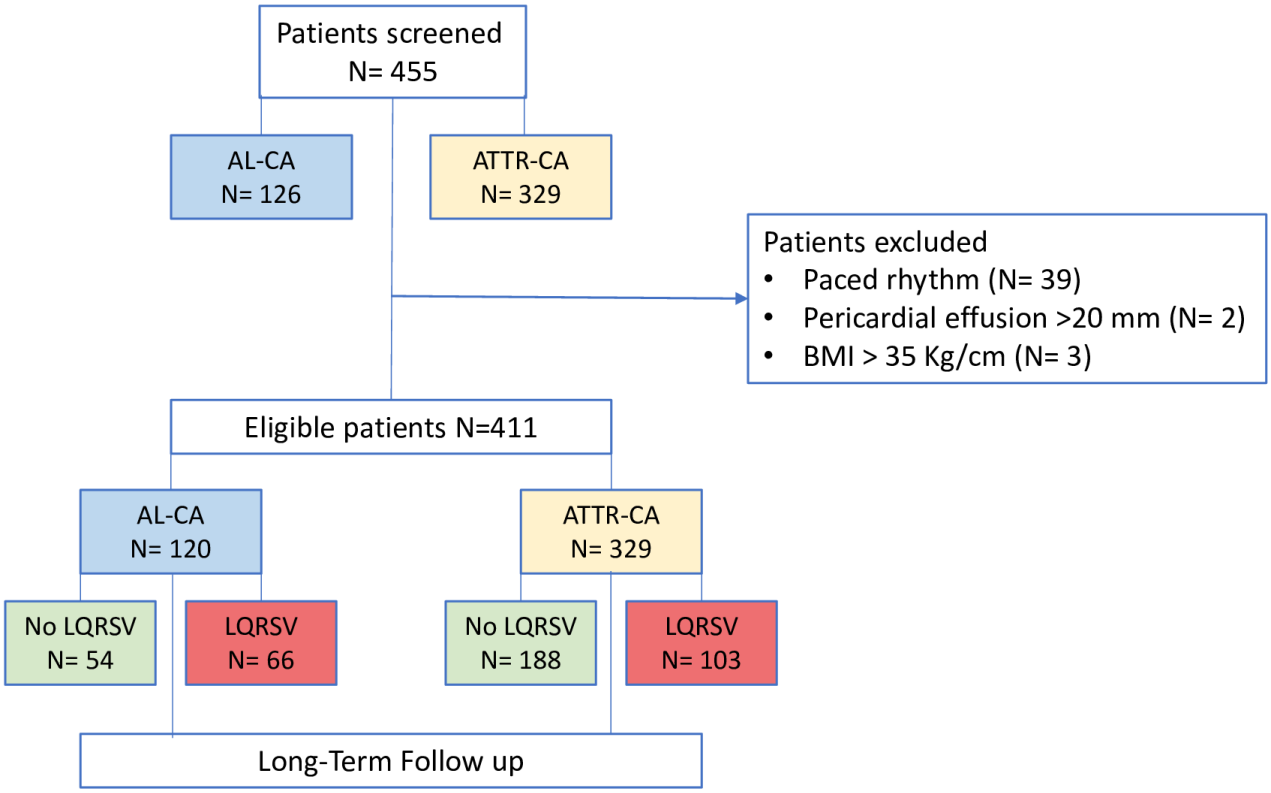
		Univariable analysis			Multivariable analysis		
		HR	**CI**	**p**	**HR**	**CI**	**p**
ATTR v - CA	Age (years)	1.028	0.949-1.114	0.45			
	NYHA class	5.135	1.053-25.050	0.043	1.680	0.253-11.182	0.59
	GFR, ml/min	0.995	0.946-1.045	0.83			
	NAC ATTR staging	10.23	2.730-38.311	0.001	7.928	1.053-36.713	0.008
	Peripheral low QRS voltages	2.981	0.495-17.942	0.23			
	LA diameter, mm	1.007	0.967-1.047	0.75			
	IVSd, mm	1.029	0.822-1.289	0.80			
	PWTd, mm	1.066	0.867-1.310	0.55			
	LVEDD, mm	0.989	0.858-1.139	0.87			
	RWT	2.274	0.052-10.081	0.67			
	LVMi gr/m2	1.002	0.993-1.012	0.67			
	Total voltage-to-mass ratio	0.808	0.036-18.281	0.89			
	Pericardial effusion	0.880	0.098-7.879	0.91			
	LVEF, %	1.008	0.910-1.116	0.88			
	E/e’	1.050	0.913-1.207	0.50			
	TAPSE, mm	1.022	0.819-1.275	0.85			
	sPAP, mmHg	0.969	0.880-1.068	0.53			
ATTR wt - CA	Age (years)	0.973	0.911-1.039	0.42			
	NYHA class	3.493	1.691-7.214	0.001	1.127	0.474-2.682	0.78
	GFR, ml/min	0.995	0.946-1.045	0.83			
	NAC ATTR staging	3.577	1.964-6.513	<0.001	4.498	1.936-10.449	0.029
	Peripheral low QRS voltages	2.773	1.184-6.496	0.019	2.838	1.005-1.160	0.048
	LA diameter, mm	1.065	1.003-1.031	0.040	1.077	0.953-8.452	0.071
	IVSd, mm	0.977	0.857-1.113	0.72			
	PWTd, mm	0.990	0.846-1.158	0.89			
	LVEDD, mm	1.018	0.948-1.094	0.62			
	RWT	0.878	0.077-10.039	0.67			
	LVMi gr/m2	1.000	0.992-1.009	0.95			
	Total voltage-to-mass ratio	0.137	0.016-1.183	0.071			
	Pericardial effusion	1.191	0.351-4.044	0.78			
	LVEF, %	0.957	0.923-0.992	0.018	0.947	0.903-0.993	0.023
	E/e’	1.030	0.981-1.081	0.24			
	TAPSE, mm	0.876	0.784-0.979	0.020	1.014	0.876-1.173	0.85
	sPAP, mmHg	1.023	0.989-1.057	0.19			

Models performed with Cox Proportional Hazards Regression Analysis. Abbreviations as in Supplementary Table 1.

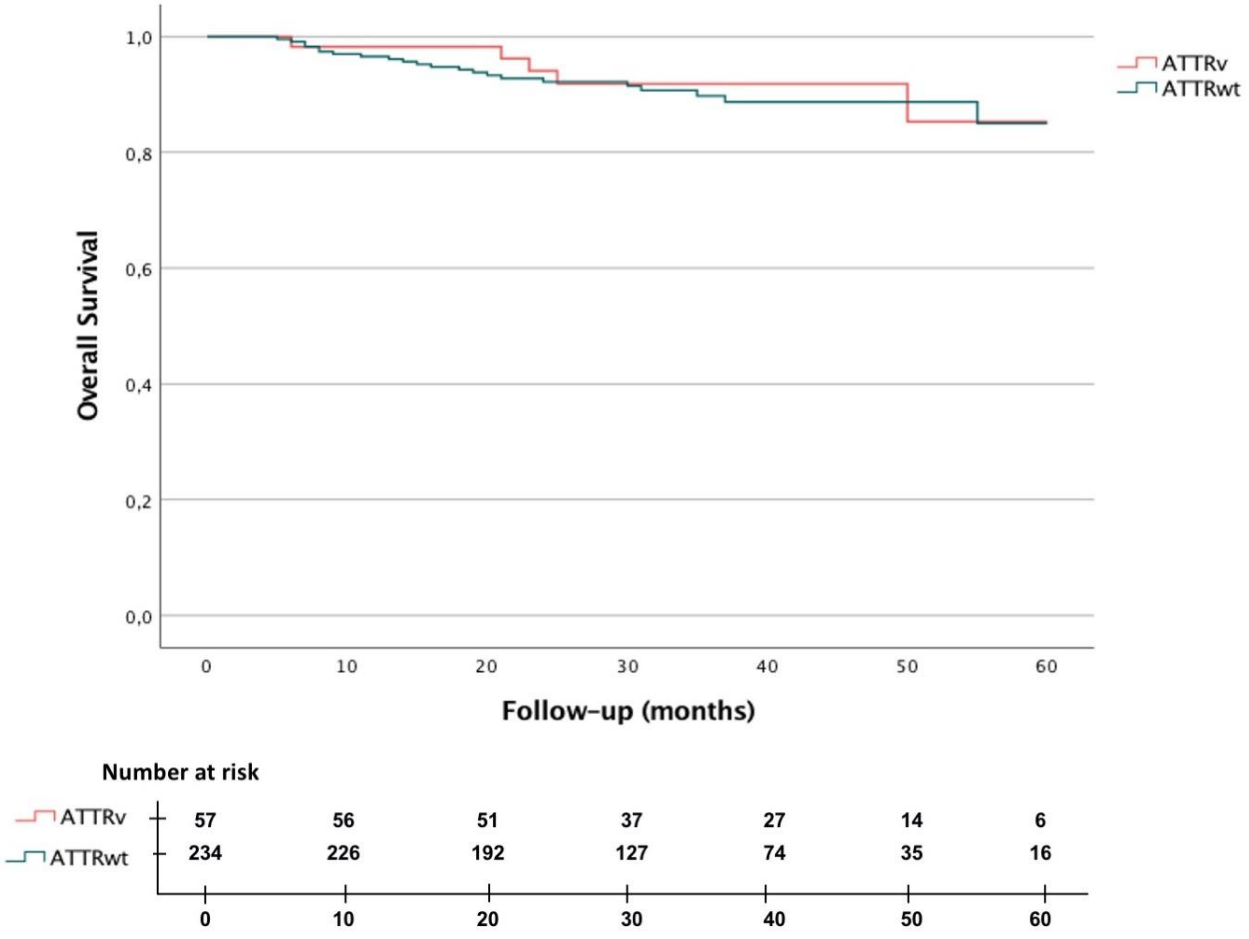
Supplemental Table 4. Fine & Gray estimates of cumulative incidence plot for the competing risk model (Supplemental Figure 6, panel B).

	HR	**95% CI**	**p-value**
NAC I – No LQRSV	-	-	-
NAC I – LQRSV	2.32	0.48 - 11.2	0.32
NAC II – No LQRSV	4.41	1.17 - 16.7	0.029
NAC II – LQRSV	12.9	4.03 - 41.6	<0.001
NAC III – No LQRSV	17.4	3.69 - 81.7	<0.001
NAC III - LQRSV	13.4	2.62 - 68.7	0.002

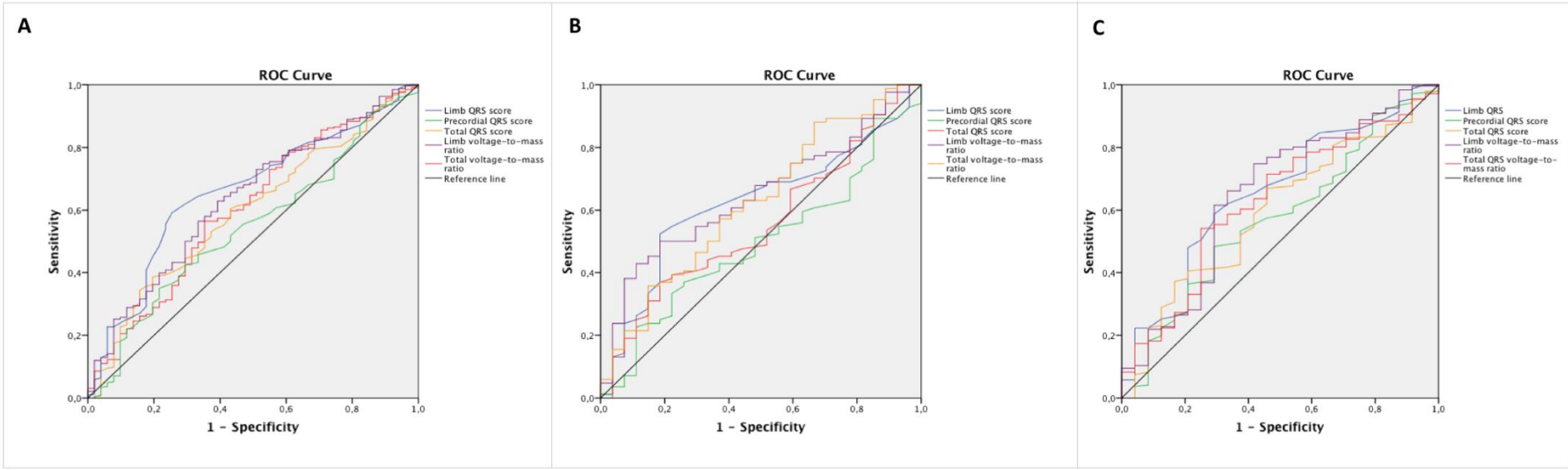
Supplemental Figure 1. Study flowchart.



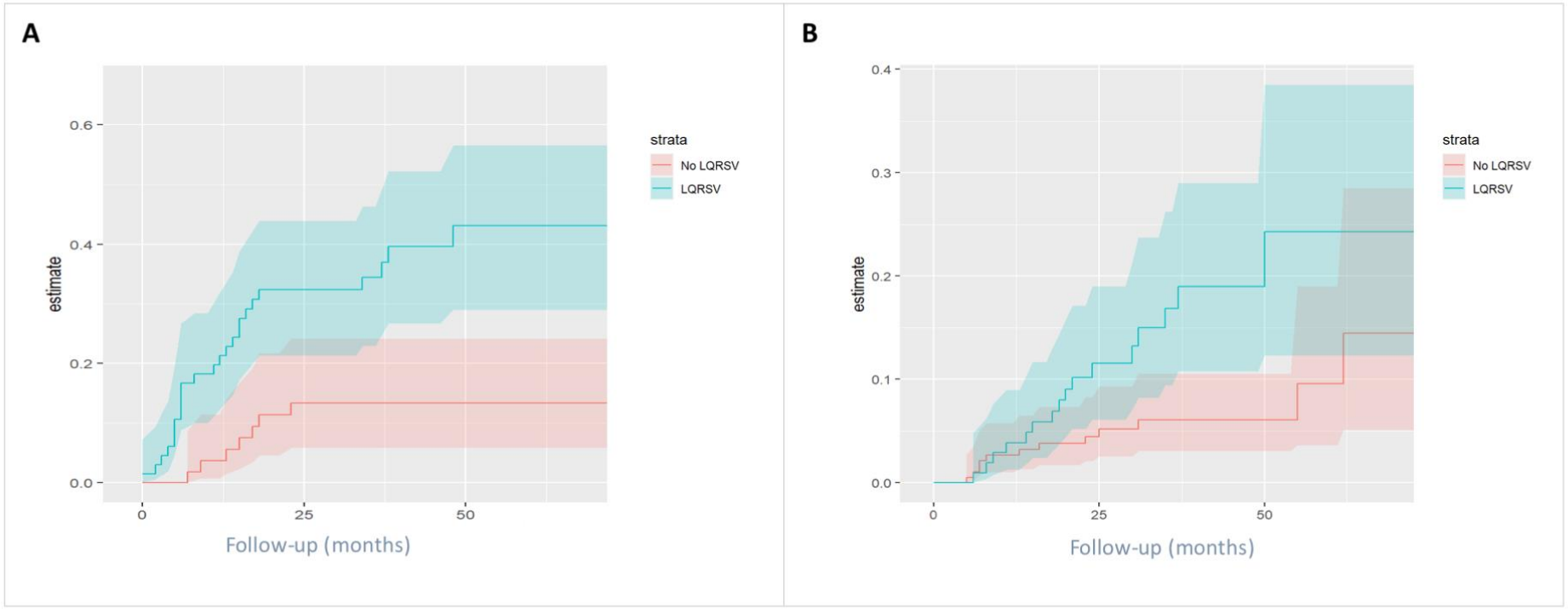
Supplemental Figure 2. Survival curves based on Kaplan-Meier survival analysis in patients with ATTRv- and ATTR-CA.



Supplemental Figure 3. ROC curve showing the different capability of limb, precordial and QRS score, limb and total voltage-to-mass ratios in predicting CV mortality, in all patients (panel A), AL-CA (panel B) and ATTR-CA (panel C).



Supplemental Figure 4. Cumulative incidence plot for the competing risk model (CV mortality shown in Panel A) in AL patients. Fine & Gray HR for LQRSV vs. No LQRSV 3.14 (CI 1.46 - 6.75, p-value 0.003). Cumulative incidence plot for the competing risk model (CV mortality shown in Panel B) in ATTR patients. Fine & Gray HR for LQRSV vs. No LQRSV 2.66 (CI 1.27 -5.56, p-value 0.010).



Supplemental Figure 5. Cumulative incidence plot for the competing risk model (CV mortality shown in Panel A). Fine & Gray HR for NAC grade II vs I 5.59 (CI 2.28 - 13.7, p-value <0.001) and for NAC grade III vs I 11.3 (CI 3.62 - 35.0, p-value <0.001). Cumulative incidence plot for the competing risk model (CV mortality shown in Panel B). Fine & Gray estimates in Supplemental table 4.