

# **SUPPLEMENTAL MATERIAL**

## **Supplemental Methods**

### **Data S1**

#### ***Study Participants Selection and Exclusion Criteria:***

The medical history includes hypertension, diabetes, hyperlipidemia treatment, atrial fibrillation, stroke, known coronary artery disease, end-stage renal disease [ESRD] or those underwent hemodialysis) and hospitalization from patients reimbursed by the National Health Insurance Bureau of Taiwan were extracted via electronic medical records review. Discharged HF diagnosis was defined as patients with acute decompensated heart failure receiving intravenous diuretics with evidence of pulmonary congestion/edema requiring hospitalization.

**Table S1. Baseline characteristics of study subjects categorized by QRS duration  $\leq 110$ ms or  $> 110$ ms**

<b>QRS duration</b>	<b>QRS duration <math>\leq 110</math> ms Number =826</b>	<b>QRS duration <math>&gt; 110</math> ms Number =117</b>	<b><i>p</i> value</b>
Demographics			
Age, years	76.4 $\pm$ 12.7	75.78 $\pm$ 13.1	0.622
Male, number (%)	286 (34.62%)	64 (54.7%)	<0.001
Height, m	1.56 $\pm$ 0.08	1.59 $\pm$ 0.1	0.023
Weight, kg	60.04 $\pm$ 14.23	63.84 $\pm$ 15.87	0.009
Body mass index, kg/m <sup>2</sup>	24.68 $\pm$ 6.31	25.31 $\pm$ 5.95	0.327
Systolic blood pressure, mmHg	141.67 $\pm$ 33.04	136.98 $\pm$ 30.35	0.148
Diastolic blood pressure, mmHg	73.73 $\pm$ 17.92	69.2 $\pm$ 18.34	0.011
Heart rate, bpm	90.36 $\pm$ 21.75	90.71 $\pm$ 23.24	0.872
History, number (%)			
Prior heart failure, number (%)	449 (54.36%)	67 (57.26%)	0.555
Hypertension, number (%)	607 (73.49%)	85 (72.65%)	0.848
Diabetes mellitus, number (%)	413 (50%)	63 (53.85%)	0.437
Coronary artery disease, number (%)	151 (18.28%)	29 (24.79%)	0.094
End stage renal disease/ hemodialysis, number (%)	95 (11.5%)	17 (14.53%)	0.344
Hyperlipidemia, number (%)	152 (18.4%)	20 (17.09%)	0.732
Stroke, number (%)	145 (17.55%)	19 (16.24%)	0.726
Atrial fibrillation, number (%)	160 (19.37%)	24 (20.51%)	0.771
Peripheral artery disease, number (%)	57 (6.9%)	8 (6.84%)	0.980

Laboratory			
White blood cells, $\times 10^3/\mu\text{L}$	10.04 $\pm$ 5.19	10.85 $\pm$ 6.30	0.129
Lymphocyte, $\times 10^3/\mu\text{L}$	15.15 $\pm$ 10.56	13.71 $\pm$ 11.01	0.174
Hemoglobin, g/dl	10.45 $\pm$ 2.44	10.35 $\pm$ 2.55	0.679
Fasting glucose, mg/dl	176.57 $\pm$ 113.09	168.74 $\pm$ 109.35	0.485
eGFR, ml/min/1.73m <sup>2</sup>	41.5 $\pm$ 33.08	37.59 $\pm$ 32.28	0.231
Albumin, g/dl	3.32 $\pm$ 0.59	3.36 $\pm$ 0.63	0.521
ALT, u/l	61.20 $\pm$ 157.44	65.94 $\pm$ 116.61	0.775
Serum sodium, mmol/L	130.71 $\pm$ 8.51	129.3 $\pm$ 7.24	0.089
Serum potassium, mmol/L	5.21 $\pm$ 1.26	5.48 $\pm$ 1.28	0.031
BNP, pg/mL	991.36 $\pm$ 1115.25	1001.95 $\pm$ 1193.00	0.926
Measurement			
LVEF, %	64.72 $\pm$ 6.48	64.13 $\pm$ 6.70	0.358
Prognostic nutritional score	41.09 $\pm$ 8.99	41.19 $\pm$ 9.23	0.913
Medications, number (%)			
ACEI/ARB	295 (35.71%)	31 (26.5%)	0.050
Beta-blocker	169 (20.46%)	23 (19.66%)	0.840
Aldosterone antagonists	138 (16.71%)	17 (14.53%)	0.553
Digoxin	48 (5.81%)	5 (4.27%)	0.500
Diuretics	370 (44.79%)	54 (46.15%)	0.782

ALT: alanine transaminase; LVEF: left ventricular ejection fraction; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II-receptor blocker; BNP, B-type natriuretic peptide; BMI, body mass index; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HR, heart rate; LVEF, left ventricular ejection fraction;

**Table S2. The LV/RV structure and function in study subjects categorized by QRS duration  $\leq 110$  ms or  $> 110$  ms**

<b>Fragmented QRS</b>	<b>QRS <math>\leq 110</math>ms Number =828</b>	<b>QRS <math>&gt; 110</math>ms Number =132</b>	<b><i>p</i> value</b>
<b>LV structure</b>			
Septal wall thickness, mm	9.97 $\pm$ 1.96	10.33 $\pm$ 2.00	0.052
Posterior wall thickness, mm	10.02 $\pm$ 1.88	10.48 $\pm$ 2.13	0.012
LV internal dimension, mm	46.35 $\pm$ 6.12	47.90 $\pm$ 6.31	0.008
LV EDV index, ml	44.8 $\pm$ 14.7	45.42 $\pm$ 13.98	0.650
LV ESV index, ml	15.2 $\pm$ 9.4	15.6 $\pm$ 8.8	0.660
LVEF, %	68.3 $\pm$ 14.1	67.5 $\pm$ 13.1	0.580
LV mass, gm	164.65 $\pm$ 58.58	182.05 $\pm$ 72.33	0.009
LV mass index, gm/m <sup>2</sup>	95.37 $\pm$ 30.86	102.78 $\pm$ 39.24	0.046
LV M/V ratio	2.20 $\pm$ 0.89	2.30 $\pm$ 0.76	0.313
<b>LV function</b>			
Mitral E/A ratio	16.57 $\pm$ 7.45	16.11 $\pm$ 6.55	0.587
DT, ms	212.21 $\pm$ 76.28	200.01 $\pm$ 80.26	0.090
IVRT, ms	86.38 $\pm$ 33.07	89.05 $\pm$ 31.59	0.386
TDI-e', cm/s	5.56 $\pm$ 1.78	5.69 $\pm$ 2.07	0.528
TDI-s', cm/s	5.63 $\pm$ 1.36	5.69 $\pm$ 1.60	0.731
Mitral E/TDI-e'	16.57 $\pm$ 7.45	16.11 $\pm$ 6.55	0.587
TR Velocity, m/sec	3.02 $\pm$ 0.46	3.00 $\pm$ 0.44	0.676

RV structure and function			
RV EDA, cm <sup>2</sup>	30.82±12.87	35.23±17.35	0.007
RV ESA, cm <sup>2</sup>	16.32±8.63	19.27±11.87	0.009
RVFAC, %	48.22±7.89	46.54±9.12	0.031
Atrial structure			
LA Volume index, mL/m <sup>2</sup>	28.43±13.14	29.63±13.56	0.353
RA Volume index, mL/m <sup>2</sup>	22.41±12.71	28.46±30.82	0.035

LV, left ventricular; RV, right ventricular; EDV, end-diastolic volume; EDA, end-diastolic area; ESA, end-systolic area; FAC, fractional area change; ESV, end-systolic volume; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; LV M/V, left ventricular mass to volume ratio; DT, deceleration time; IVRT, interventricular relaxation time; LA, left atrial; RA, right atrial; TDI, tissue Doppler imaging; TR, tricuspid regurgitation.

**Table S3. The clinical outcome for HHF, CV mortality, all-cause mortality, and composite end-points in non-fQRS, inferior fQRS, anterior/lateral fQRS**

		Hospitalization for Heart failure (HHF)			CV Mortality		
Fragmented QRS		Non-fQRS	Inferior fQRS	Anterior/Lateral fQRS	Non-fQRS	Inferior fQRS	Anterior/Lateral fQRS
events, n (%)	N	459 (69.9%)	143 (65%)	44 (53%)	551 (83.9%)	172 (78.2%)	59 (71.1%)
	Y	198 (30.1%)	77 (35%)	39 (47%)	106 (16.1%)	48 (21.8%)	24 (28.9%)
Event Rate (per 100 person-years)		11.4	14.2	23.4	5.9	8.5	12.9
Crude Model		(Reference)	1.20 [0.92, 1.57] <i>p</i> =0.17	1.90 [1.35, 2.68]* <i>p</i> <0.001	(Reference)	1.40 [1.00, 1.97] <i>p</i> =0.052	1.98 [1.27, 3.08]* <i>p</i> =0.003
Model 1 (HR) (95% CI)		(Reference)	1.20 [0.92, 1.56] <i>p</i> =0.17	1.89 [1.34, 2.66]* <i>p</i> <0.001	(Reference)	1.44 [1.02, 2.03]* <i>p</i> =0.036	2.16 [1.38, 3.37]* <i>p</i> =0.001
Model 2 (HR) (95% CI)		(Reference)	1.20 [0.92, 1.56] <i>p</i> =0.17	1.89 [1.34, 2.67]* <i>p</i> <0.001	(Reference)	1.44 [1.02, 2.03]* <i>p</i> =0.038	2.16 [1.38, 3.37]* <i>p</i> =0.001
Model 3 (HR) (95% CI)		(Reference)	1.09 [0.83, 1.42] <i>p</i> =0.53	1.90 [1.34, 2.69]* <i>p</i> <0.001	(Reference)	1.44 [1.02, 2.05]* <i>p</i> =0.039	2.00 [1.26, 3.16]* <i>p</i> =0.003
		All-cause Mortality			Composite Endpoints		
Fragmented QRS		Non-fQRS	Inferior fQRS	Anterior/Lateral fQRS	Non-fQRS	Inferior fQRS	Anterior/Lateral fQRS



events, n (%)	N	450 (68.5%)	133 (60.5%)	40 (48.2%)	283 (43.1%)	69 (31.4%)	23 (27.7%)
	Y	207 (31.5%)	87 (39.6%)	43 (51.8%)	374 (56.9%)	151 (68.6%)	60 (72.3%)
Event Rate (100 person-years)		11.5	15.5	23.2	48.7	54.2	65.1
Crude Model		(Reference)	1.31 [1.02, 1.68]* <i>p</i> =0.037	1.81 [1.31, 2.52]* <i>p</i> <0.001	(Reference)	1.27 [1.05, 1.53]* <i>p</i> =0.015	1.49 [1.13, 1.95]* <i>p</i> =0.004
Model 1 (HR) (95% CI)		(Reference)	1.35 [1.05, 1.74]* <i>p</i> =0.019	2.00 [1.43, 2.77]* <i>p</i> <0.001	(Reference)	1.28 [1.05, 1.54]* <i>p</i> =0.012	1.54 [1.17, 2.02]* <i>p</i> =0.002
Model 2 (HR) (95% CI)		(Reference)	1.34 [1.05, 1.73]* <i>p</i> =0.021	2.00 [1.44, 2.78]* <i>p</i> <0.001	(Reference)	1.27 [1.05, 1.54]* <i>p</i> =0.013	1.54 [1.17, 2.03]* <i>p</i> =0.002
Model 3 (HR) (95% CI)		(Reference)	1.35 [1.04, 1.74]* <i>p</i> =0.024	1.84 [1.32, 2.56]* <i>p</i> <0.001	(Reference)	1.21 [1.00, 1.47] <i>p</i> =0.055	1.53 [1.16, 2.02]* <i>p</i> =0.003

\* denotes  $p < 0.05$  by the Cox linear regression model. HR: hazard ratio; CI: confidence interval

**Model 1:** age; **Model 2:** age, sex; **Model 3:** age, sex, BMI, hypertension, diabetes, prior hHF, coronary artery disease, CVA, eGFR, and LVEF.

hHF, hospitalization for heart failure; CV, cardiovascular; HR, hazard ratio; BMI, body mass index; CVA, cerebrovascular accident; DM,

diabetes mellitus; eGFR, estimated glomerular filtration rate; HTN, hypertension; LVEF, left ventricular ejection fraction

**Table S4. QRS duration as a continuous variable after excluding those presenting RBBB, LBBB, and PPM, and was categorized as  $\leq 110$ ms (reference) or  $>110$ ms.**

		<b>Hospitalization for Heart failure (HHF)</b>		<b>All-cause Mortality</b>	
QRS Duration		QRS duration $\leq 110$ ms	QRS Duration $>110$ ms	QRS duration $\leq 110$ ms	QRS Duration $>110$ ms
Events, n	N	550	276	542	83
	Y	60	57	284	34
Model 1 (HR) (95% CI)		(Reference)	1.733[1.298, 2.312]* $p < 0.001$	(Reference)	0.987[0.684, 1.422] $p = 0.943$
Model 2 (HR) (95% CI)		(Reference)	1.710[1.276, 2.289]* $p < 0.001$	(Reference)	0.980[0.676, 1.419] $p = 0.914$
Model 3 (HR) (95% CI)		(Reference)	1.654[1.215, 2.51]* $p = 0.001$	(Reference)	0.958[0.645, 1.423] $p = 0.832$
		<b>CV Mortality</b>		<b>Composite Endpoints</b>	
QRS Duration		QRS duration $\leq 110$ ms	QRS Duration $>110$ ms	QRS duration $\leq 110$ ms	QRS Duration $>110$ ms
Events, n	N	550	276	542	83
	Y	60	57	284	34
Model 1 (HR) (95% CI)		(Reference)	1.733[1.298, 2.312]* $p < 0.001$	(Reference)	0.987[0.684, 1.422] $p = 0.943$
Model 2 (HR) (95% CI)		(Reference)	1.710[1.276, 2.289]* $p < 0.001$	(Reference)	0.980[0.676, 1.419] $p = 0.914$
Model 3		(Reference)	1.654[1.215, 2.51]*	(Reference)	0.958[0.645, 1.423]

(HR) (95% CI)			$p = 0.001$		$p = 0.832$
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\* refers to  $p < 0.05$ .

**Model 1:** Age

**Model 2:** Age + Sex;

**Model 3:** Age + Sex + BMI, + HTN + DM + CHF + Hyperlipidemia + CVD + eGFR + LVEF;

HR, hazard ratio; CI, confidence interval; BMI, body mass index; HTN, hypertension; DM, diabetes mellitus; CHF, congestive heart failure; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; AF, atrial fibrillation

**Table S5. Biomarker, left ventricular structure and function in the patients with known coronary artery disease across non-fQRS, inferior fQRS, and anterior/lateral fQRS groups**

Fragmented QRS group	Non-fQRS (n= 215)	Inferior fQRS (n= 76)	Anterior/lateral fQRS (n= 34)	<i>p</i> value
<b>Biomarker</b>				
BNP, pg/mL (n=314) <sup>a</sup>	558[241, 1300]	695[268.5, 1480]	920.5[516, 3300]*†	<0.001
Troponin-I (n=309) <sup>a</sup>	0.04[0.02, 0.18]	0.06[0.02, 0.13]	0.14 [0.04, 0.62]*†	0.008
<b>LV structure</b>				
LV mass index, gm/m <sup>2</sup>	101.5 ± 29.5	104.5 ± 34.3	115.1 ± 32.8	0.069
LVEDV index, mL	46.1 ± 14.5	46.4 ± 18.8	54.2 ± 17.3*	0.038
LVEF, %	63.5 ± 6.4	63.2 ± 7.6	61.6 ± 6.7	0.307
<b>LV systolic and diastolic function</b>				
DT, ms	213.4 ± 78.6	213.0 ± 78.4	185.0 ± 78.4	0.140
IVRT, ms	88.1 ± 32.2	89.5 ± 35.2	95.3 ± 40.2	0.521
TDI-e', cm/s	5.4 ± 1.6	5.0 ± 1.5	4.5 ± 1.3	0.018
TDI-s', cm/s	5.4 ± 1.3	5.4 ± 1.6	4.8 ± 1.3	0.199
Mitral E / TDI-e'	16.8 ± 7.7	18.0 ± 7.4	22.7 ± 13.3*	0.012
TR Velocity, cm/s	2.98 ± 0.44	2.98 ± 0.43	3.17 ± 0.56	0.086
LA volume index, mL/m <sup>2</sup>	28.4 ± 12.7	27.9 ± 10.6	34.8 ± 13.9*†	0.027

Data are expressed as mean ± SD or percentage.

\* *p*<0.05 vs Non-fQRS; † *p*<0.05 vs Inferior fQRS. <sup>a</sup> Troponin-I and BNP are expressed as median [25<sup>th</sup> percentile, 75<sup>th</sup> percentile].

LV, left ventricular; EDV, end-diastolic volume; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; LV, left ventricular mass to volume ratio; DT, deceleration time; IVRT, interventricular relaxation time; LA, left atrial; TDI, tissue Doppler imaging; TR, tricuspid regurgitation. Other abbreviations as Table 1 and Table 2.

**Table S6. Hazard ratio of hospitalization for heart failure, cardiovascular death, all-cause death, and composite endpoint in the patients with known coronary artery disease and presence of inferior fQRS and anterior/lateral fQRS**

Fragmented QRS group	Non-fQRS (n= 215)		Inferior fQRS (n= 76)		Anterior/lateral fQRS (n= 34)	
	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Hospitalization for heart failure	- (reference)	- (reference)	1.14 (0.76-1.73) <i>p</i> = 0.523	0.98 (0.64-1.49) <i>p</i> = 0.908	1.26 (0.71-2.22) <i>p</i> = 0.425	1.23 (0.69-2.17) <i>p</i> = 0.484
Cardiovascular death	- (reference)	- (reference)	1.26 (0.71-2.23) <i>p</i> = 0.430	1.25 (0.70-2.23) <i>p</i> = 0.460	2.46 (1.27-3.08) <i>p</i> = 0.007	2.60 (1.29-5.11) <i>p</i> = 0.007
All-cause death	- (reference)	- (reference)	1.12 (0.72-1.75) <i>p</i> = 0.613	1.10 (0.69-1.74) <i>p</i> = 0.692	2.29 (1.39-3.78) <i>p</i> = 0.001	2.27 (1.35-3.82) <i>p</i> = 0.002
Composite endpoint	- (reference)	- (reference)	1.10 (0.80-1.52) <i>p</i> = 0.552	1.00 (0.72-1.39) <i>p</i> = 0.994	1.52 (1.00-2.32) <i>p</i> = 0.051	1.43 (0.93-2.20) <i>p</i> = 0.104

Adjusted for age, sex, body mass index, estimated glomerular infiltration rate, diabetes mellitus, hypertension  
fQRS, fragmented QRS; HR, hazard ratio; CI, confidence interval

**Figure S1.** Study flowchart showing the enrollment criteria for patients discharged with HFpEF. The patients with overt or incomplete bundle branch block or a permanent pacemaker were excluded. All study participants were divided into non-fQRS, inferior and anterior/lateral fQRS groups.

