SUPPLEMENTARY FILES

Table S1. Cardiac biomarkers .

	TTS patients (*n* = 314)	STEMI patients (*n* = 452)	NSTEMI patients (*n* = 334)	*p* value	*p* value STEMI vs TTS	*p* value NSTEM I vs TTS	*p* value STEMI vs NSTEMI
Biology at admission							
Tn I, ng/L	1 [2.7]	1.3 [12]	0.4 [1.5]	<0.001	<0.001	1	<0.001
BNP, ng/mL	427.5 [967.2]	70 [183.2]	99.5 [199.5]	<0.001	<0.001	<0.001	0.445
BNP/Tn	468.2 [1435.5]	26.5 [145.8]	144 [811.0]	<0.001	<0.001	<0.001	0.082
Biology at peak							
Tn I, ng/L	2.2 [4.9]	64.3 [138.6]	3.3 [12.1]	<0.001	<0.001	1	<0.001
Day of peak Tn	0 [1]	1 [1]	1 [1]	<0.001	0.484	0.004	<0.001
BNP, ng/mL	666.0 [1203.2]	91 [257]	111 [216.2]	<0.001	<0.001	<0.001	1
Day of peak BNP	0 [2]	0 [0]	0 [0]	0.014	0.100	0.012	0.543
Peak BNP/peak Tn	228.3 [700.1]	1.2 [4.8]	21.4 [107.4]	<0.001	<0.001	<0.001	0.669
Biology at discharge							
Troponin I, ng/L	0.4 [1.2]	14.3 [30.8]	1.8 [5.1]	<0.001	<0.001	0.302	<0.001
BNP, ng/mL	323 [501.0]	89 [233]	102 [187]	<0.001	<0.001	<0.001	1

Data presented were number (percentage); quantitative variables as median [interquartile interval] or mean ± 95% confidence interval. BNP, brain natriuretic peptide; NSTEMI, non ST segment elevation myocardial infarction; STEMI, ST segment elevation myocardial infarction; TTS, Takotsubo syndrome; Tn I, Troponin I.

Table S2. Baseline characteristics of Takotsubo and ACS patients after propensity score.

	TTS patients (*n* = 152)	STEMI patients (*n* = 385)	NSTEMI patients (*n* = 245)	*p* value
Demographics				
Age	68.8 ± 13.6	62.8 ± 13.8	67 ± 13.7	<0.001
Female gender, *n* (%)	123 (80.9)	89 (23.1)	58 (23.7)	<0.001
Weight	66.4 ± 15.1	78.7 ± 16.3	81.2 ± 15.8	<0.001
CVD risk factors				
Hypertension, *n* (%)	83 (54.6)	197 (51.2)	170 (69.4)	<0.001
Diabetes mellitus, *n* (%)	25 (16.4)	77 (20)	72 (29.4)	0.0035
Dyslipidemia, *n* (%)	53 (34.9)	156 (40.5)	140 (57.1)	<0.001
Current tobacco use, *n* (%)	33 (21.7)	176 (45.7)	76 (31.0)	<0.001
Past tobacco use, *n* (%)	32 (21.1)	101 (26.2)	76 (31.0)	0.088
Backgroung				
History of malignancy, *n* (%)	38 (25)	24 (6.2)	15 (6.1)	<0.001
History of psychiatric disease, *n* (%)	44 (29.1)	9 (2.3)	2 (0.8)	<0.001
History of AF, *n* (%)	15 (9.9)	19 (5.0)	25 (10.2)	0.025
History of stroke, *n* (%)	10 (6.6)	23 (6.0)	30 (12.2)	0.014
History of PAD or ischemic heart disease, *n* (%)	29 (19.2)	66 (17.1)	75 (30.6)	<0.001
Chronic kidney disease, *n* (%)				
moderate (DFG 30–60)	30 (19.7)	40 (10.4)	29 (11.8)	
severe (15–30)	3 (2.0)	10 (2.6)	6 (2.4)	-
terminal (<15)	1 (0.7)	2 (0.5)	1 (0.4)	
Electrocardiogram at admission				
Q wave, *n* (%)	83 (55.3)	85 (47.5)	4 (1.7)	<0.001
Echocardiography				
LVEF at admission, %	39.2 ± 11.9	50.5 ± 11.2	54.5 ± 10.7	<0.001
RV involvement, *n* (%)	4 (2.9)	38 (9.9)	7 (2.9)	<0.001
Biology at admission				
CRP, mg/L	7.1 [33.1]	3.0 [8.6]	3.0 [6.9]	<0.001
Leukocytes, G/L	12.6 ± 5.9	11.9 ± 3.9	10.0 ± 5.1	<0.001
Hemoglobin, g/dL	13.3 ± 2.0	14.2 ± 1.7	13.9 ± 1.8	<0.001
Creatinine serum μmol/L	66.0 [30.4]	74.0 [25.6]	75.0 [26.2]	0.0417
GFR, mL/min/m^2	77.7 ± 29.6	81.1 ± 17.2	79.3 ±17.6	0.175
Plasma sodium level, mmol/L	137.7 ± 4.8	137.5 ± 3.1	138.3 ± 2.9	0.00657
Plasma potassium level, mmol/L	4.0 ± 0.5	4.0 ± 0.5	4.0 ± 0.5	0.354

Data presented were number (percentage); quantitative variables as median [interquartile interval] or mean ± 95% confidence interval. AF, atrial fibrillation; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CRP, C-reactive protein; CVD, cardiovascular disease; DBP, diastolic blood pressure; GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction; NSTEMI, non ST segment elevation myocardial infarction; PAD, peripheral artery disease; RV, right ventricle; SBP, systolic blood pressure; STEMI, ST segment elevation myocardial infarction; TTS, Takotsubo syndrome.

Table S3. In hospital outcome and follow up after propensity score.

	TTS patients (*n* = 152)	STEMI patients (*n* = 385)	NSTEMI patients (*n* = 245)	*p* value
In-hospital events				
Cardiogenic shock, *n* (%)	24 (15.8)	11 (2.9)	0 (0)	<0.001
SVT, *n* (%)	34 (22.4)	11 (2.9)	7 (2.9)	<0.001
Sustained VT, *n* (%)	2 (1.3)	1 (0.3)	1 (0.4)	0.2918
3-degree AV block, *n* (%)	1 (0.7)	7 (1.8)	0 (0)	0.07667
In hospital mortality, *n* (%)	12 (7.9)	9 (2.3)	5 (2.0)	0.002173
Hospital length of stay, *n* (days)	7.0 [6.0]	5.0 [5.0]	4.0 [4.0]	0.607
Follow up events				
Hospitalization for acute HF, *n* (%)	10 (6.8)	22 (6.0)	6 (2.6)	0.1036
30-day mortality, *n* (%)	10 (6.9)	12 (3.1)	7 (2.9)	0.08561
1-year mortality, *n* (%)	20 (15.5)	19 (5.0)	16 (6.6)	<0.001
1-year CV mortality, *n* (%)	7 (4.9)	11 (2.9)	7 (2.9)	0.4627

Data presented were number (percentage); quantitative variables as median [interquartile interval] or mean ± 95% confidence interval; AV, atrio-ventricular; CV, Cardiovascular; HF, heart failure; NSTEMI, non ST segment elevation myocardial infarction; STEMI, ST segment elevation myocardial infarction; SVT, supraventricular tachycardia; TTS, Takotsubo syndrome; VF, ventricular fibrillation; VT, ventricular tachycardia.

Table S4. Cardiac biomarkers after propensity score.

	TTS patients (*n* = 152)	STEMI patients (*n* = 385)	NSTEMI patients (*n* = 245)	*p* value
Biology at admission				
TnI. ng/L	1.7 [3.8]	1.3 [9.9]	0.5 [1.8]	<0.001
BNP, ng/mL	188.0 [432.2]	74.0 [183]	88.0 [152.0]	<0.001
BNP/TnI	136.9 [421.2]	30.0 [144.0]	106.0 [298.0]	0.0398
Biology at peak				
TnI, ng/L	4.4 [7.7]	64.2 [129.2]	5.1 [15.4]	<0.001
Day of peak TnI	0 [1.0]	1.0 [1.0]	1.0 [1.0]	<0.001
BNP, ng/mL	411.5 [785.8]	91.0 [236.0]	90.0 [180.0]	<0.001
Day of peak BNP	1.0 [2.0]	0.0 [0.0]	0.0 [0.0]	0.00516
Peak BNP/peak TnI	101.0 [152.3]	1.6 [5.4]	18.1 [59.9]	<0.001
Biology at discharge				
TnI, ng/L	0.6 [1.8]	14.3 [30.5]	2.8 [6.7]	<0.001
BNP, ng/mL	252.0 [476.5]	90.0 [224.2]	88.0 [162,0]	<0.001

Data presented were number (percentage); quantitative variables as median [interquartile interval] or mean ± 95% confidence interval. BNP, brain natriuretic peptide; STEMI, ST segment elevation myocardial infarction; TTS, Takotsubo syndrome; Tn I, Troponin I.

Table S5. Univariate and multivariate analyses to identify independent predictors of 30-day- mortality.
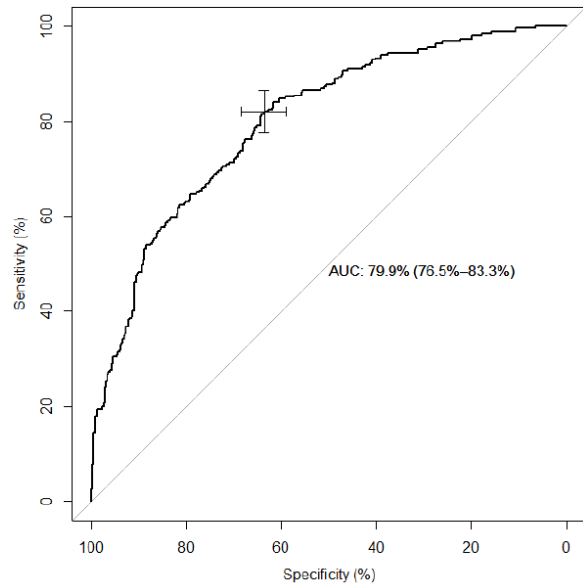
	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Patient characteristics				
Age, years	1.03 (1.00–1.07)	0.10		
Female gender	0.64 (0.22–1.85)	0.41		
Hypertension	0.75 (0.30–1.86)	0.53		
Diabetes mellitus	1.32 (0.46–3.79)	0.60		
Dyslipidemia	0.25 (0.07–0.86)	0.03	0.10 (0.01–0.84)	0.03
Current tobacco use	1.45 (0.50–4.17)	0.49		
Past tobacco use	0.63 (0.18–2.21)	0.47		
History of malignancy	2.43 (0.97–6.11)	0.06		
History of psychiatric disease	0.54 (0.17–1.65)	0.28		
History of AF	0.99 (0.28–3.53)	0.99		
History of PAD or ischemic heart disease	2.37 (0.93–6.06)	0.07		
Heart rate, bpm	1.02 (1.00–1.04)	0.06		
SBP, mmHg	0.92 (0.88–0.97)	<0.001	0.92 (0.88–0.96)	<0.001
LVEF on admission, %	0.98 (0.95–1.02)	0.43		
RV involvement	1.18 (0.15–9.59)	0.88		
Biology on admission				
Troponin I, ng/L	0.99 (0.91–1.08)	0.88		
BNP, ng/L	1.00 (1.00–1.00)	0.19		
CRP, mg/L	1.01 (1.00–1.01)	0.03	-*	-*
Leukocytes, G/L	1.05 (0.98–1.12)	0.16		
Hemoglobin, g/dl	0.79 (0.63–0.99)	0.04	-*	-*
Creatinine serum, μmol/L	1.00 (1.00–1.00)	0.43		
eGFR, mL/min/1.73 m²	1.00 (0.98–1.02)	0.86		
Plasma sodium level, mmol/L	0.92 (0.84–1.01)	0.07		

* excluded according to removal criteria. AF, atrial fibrillation; BNP, Brain Natriuretic Peptide; CRP, C-reactive protein; GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction; PAD, peripheral artery disease; RV, right ventricle; SBP, systolic blood pressure.

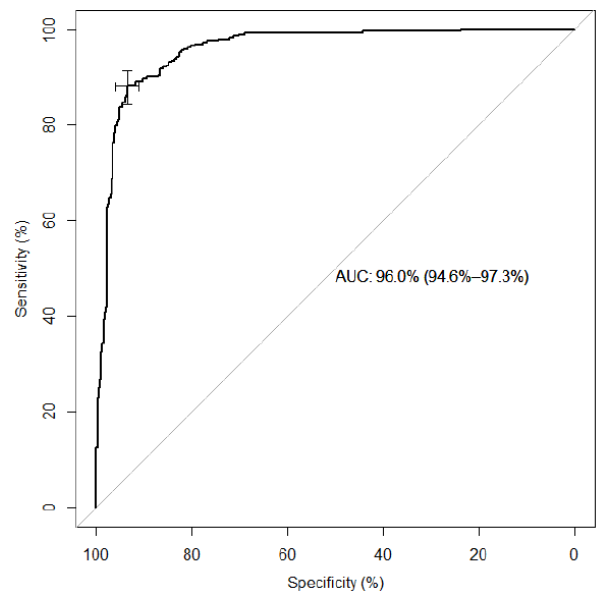**Table S6.** Univariate and multivariate analyses to identify independent predictors of 1-year – mortality.

	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Patient characteristics				
Age, years	1.01 (0.99–1.04)	0.21		
Female gender	0.64 (0.30–1.38)	0.25		
Hypertension	0.85 (0.44–1.65)	0.64		
Diabetes mellitus	1.61 (0.76–3.39)	0.22		
Dyslipidemia	0.27 (0.12–0.62)	0.002	0.18 (0.07–0.47)	<0.001
Current tobacco use	1.01 (0.43–2.34)	0.99		
Past tobacco use	1.30 (0.61–2.79)	0.49		
History of malignancy	3.66 (1.85–7.22)	<0.001	-*	-*
History of psychiatric disease	0.83 (0.40–1.71)	0.61		
History of AF	0.68 (0.25–1.87)	0.46		
History of PAD or ischemic heart disease	1.55 (0.76–3.17)	0.22		
Heart rate, bpm	1.02 (1.01–1.04)	0.002	1.02 (1.00–1.03)	0.04
SBP, mmHg	0.95 (0.92–0.98)	0.003	-*	-*
LVEF on admission, %	0.95 (0.93–0.98)	0.004	0.95 (0.92–0.98)	0.004
RV involvement	6.50 (1.97–21.48)	0.002	-*	-*
Biology on admission				
Troponin I, ng/L	1.01 (0.97–1.06)	0.56		
BNP, ng/L	1.00 (1.00–1.00)	0.008	-*	-*
CRP, mg/L	1.01 (1.00–1.01)	<0.001	-*	-*
Leukocytes, G/L	1.06 (1.01–1.11)	0.02	-*	-*
Hemoglobin, g/dl	0.73 (0.62–0.87)	<0.001	0.76 (0.63–0.93)	0.006
Creatinine serum, μmol/L	1.00 (1.00–1.01)	0.25		
eGFR, mL/min/1.73 m^2	0.99 (0.97–1.00)	0.047	-*	-*
Plasma sodium level, mmol/L	0.90 (0.84–0.97)	0.004	-*	-*

* excluded according to removal criteria. AF, atrial fibrillation; BNP, Brain Natriuretic Peptide; CRP, C-reactive protein; GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction; PAD, peripheral artery disease; RV, right ventricle; SBP, systolic blood pressure.
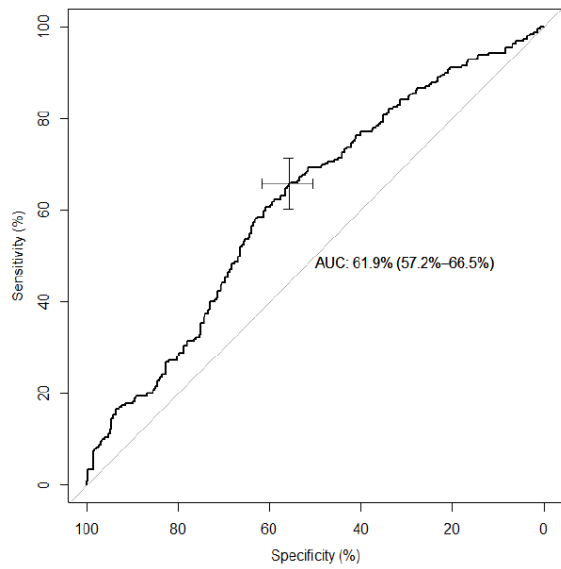
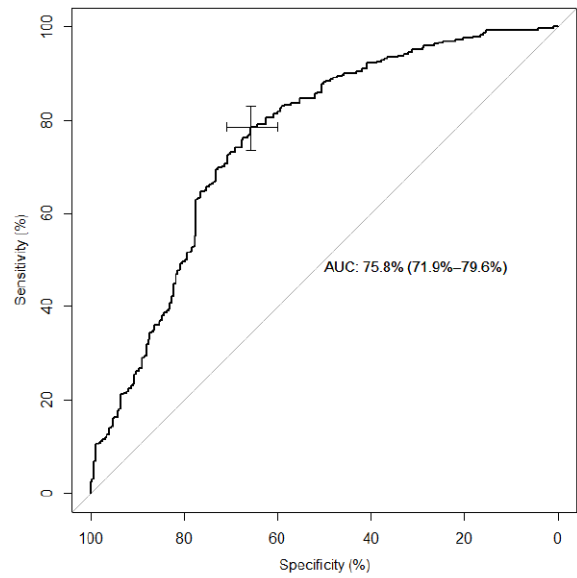**Figure a.** TTS *vs* STEMI, ROC curve for BNP/TnI at admission (supplementary files)

Figure b. TTS *vs* STEMI, ROC curve for BNP/TnI at peak (supplementary files)

Figure S1. TTS *vs* STEMI: ROC curves for BNP/TnI at admission (Figure a) and at peak (Figure b); BNP, B-natriuretic peptide; STEMI, ST segment elevation myocardial infarction; Tn, Troponin; TTS, Takotsubo syndrome
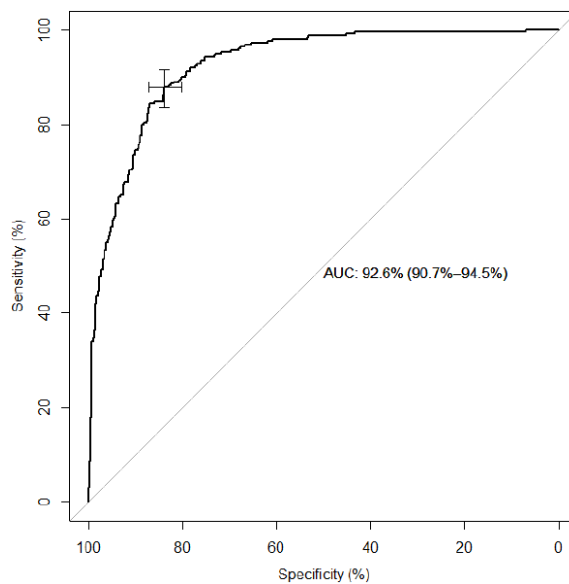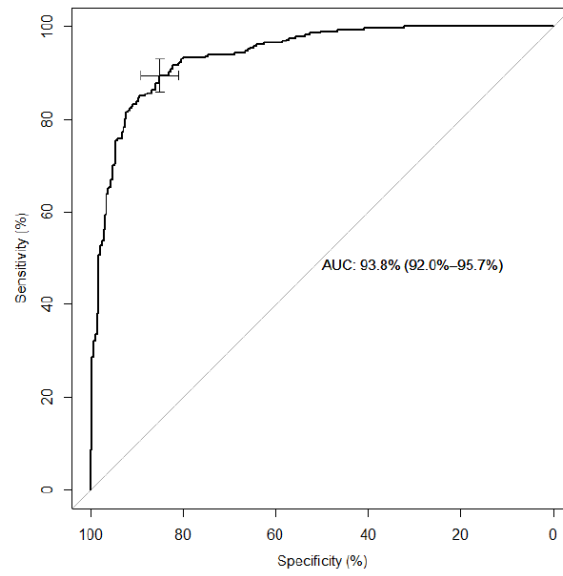
NSTEMI	196.25	TAKO TSUBO

Figure a. TTS *vs* NSTEMI, ROC curve for BNP/TnI at admission (supplementary files)

NSTEMI	76.50	TAKO TSUBO

Figure b. TTS *vs* NSTEMI, ROC curve for BNP/TnI at peak (supplementary files)

Figure S2. TTS *vs* NSTEMI: ROC curves for BNP/TnI at admission (Figure a) and at peak (Figure b); BNP, B-natriuretic peptide; NSTEMI, non ST segment elevation infarction; Tn, Troponin; TTS, Takotsubo syndrome.
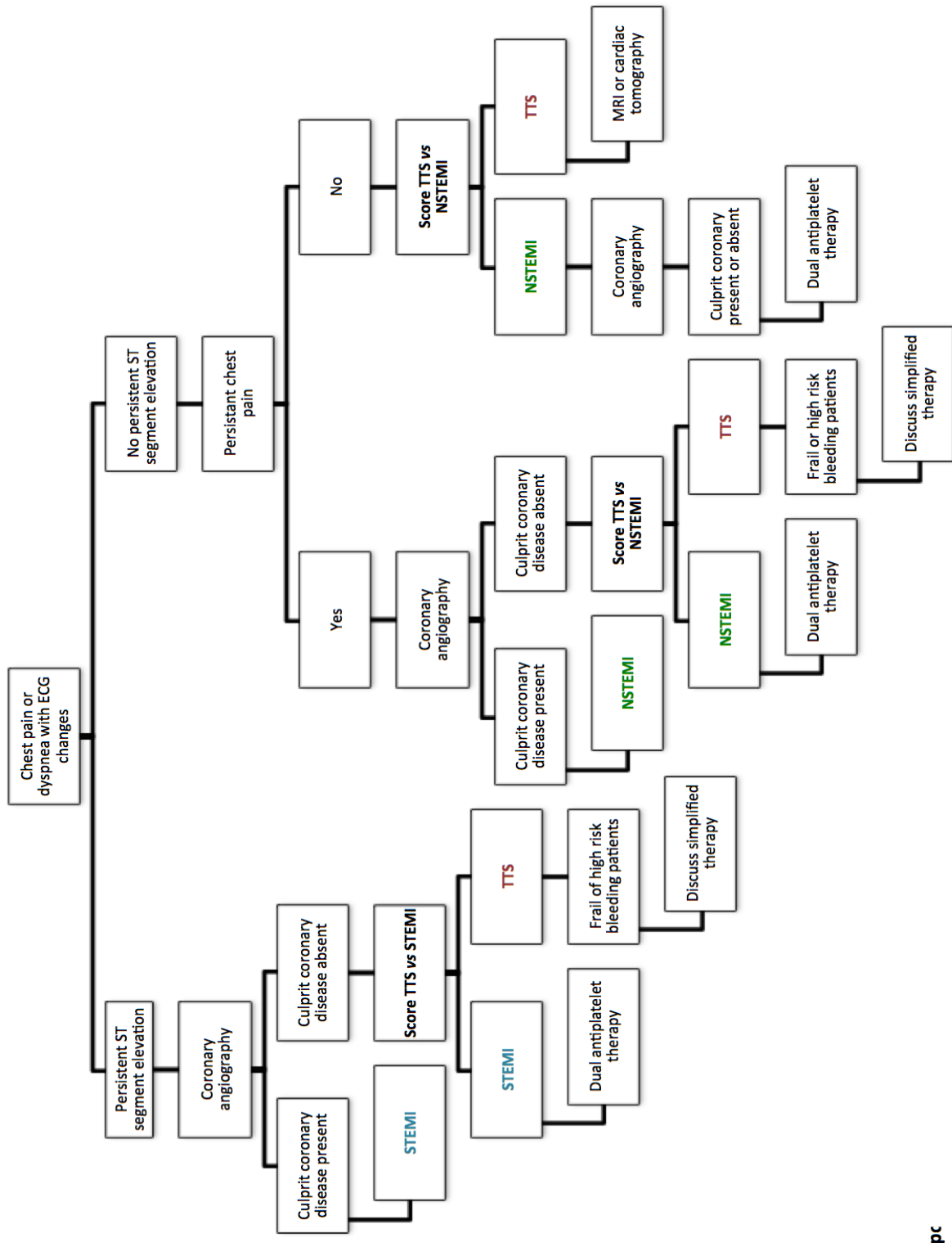

STEMI	0.3851	TAKO TSUBO

Figure S3. TTS *vs* STEMI, ROC curve for the complex score; STEMI, ST segment elevation myocardial infarction; TTS, Takotsubo syndrome

AUC: 93.8% (92.0%–95.7%)

NSTEMI   0.4406   TAKO TSUBO

Figure S4. TTS *vs* NSTEMI, ROC curve for the complex score; NSTEMI, non ST segment elevation infarction; TTS, Takotsubo syndrome.

Figure S5. Proposed new diagnostic algorithm to discriminate TTS from ACS; NSTEMI, non ST segment elevation infarction; STEMI, ST segment elevation myocardial infarction; TTS, Takotsubo syndrome.

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