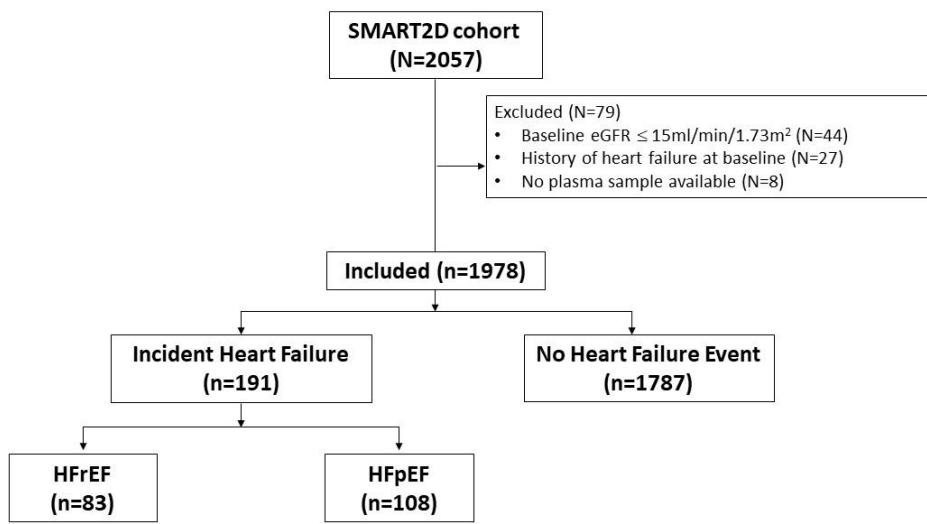
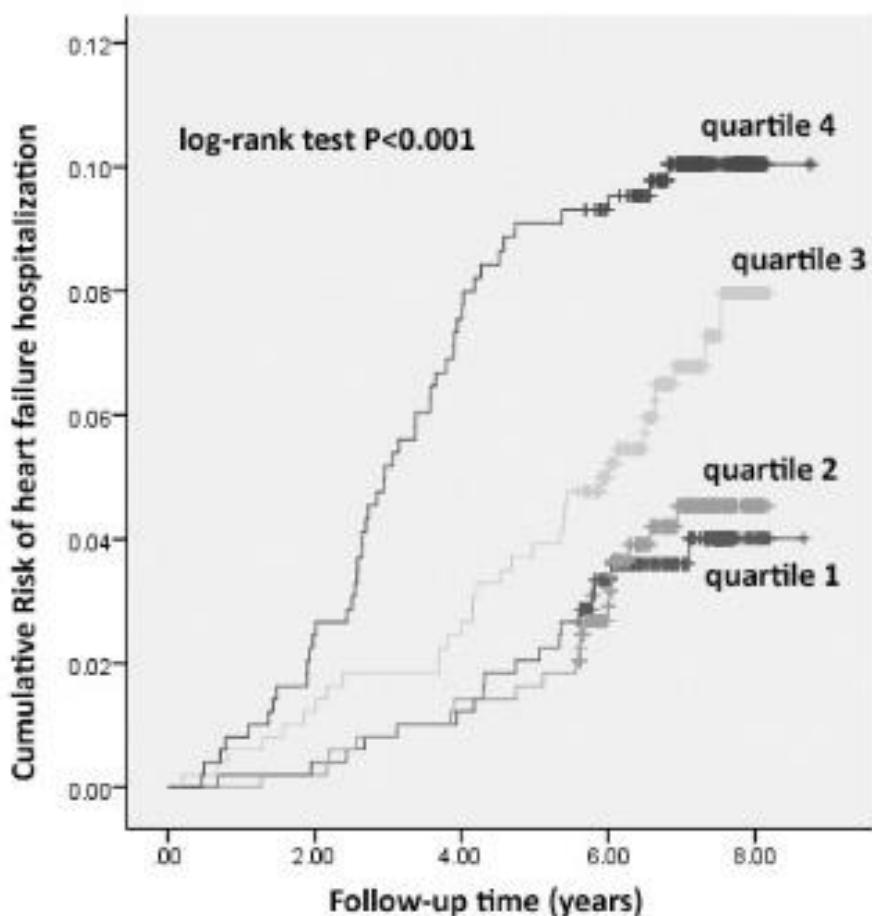


Supplementary Figure 1: Participant selection flow chart



Supplementary Figure 2: Cumulative Risk of Heart Failure Hospitalization Stratified by plasma LRG1 quartiles



Supplementary Table 1: Baseline clinical and biochemical characteristics in participant with and without incident heart failure (HF)

	With incident HF (N=191)	Without incident HF (N=1787)	P value
Plasma LRG1 (IQR, µg/ml)	20.4 (15.1-29.0)	15.4 (11.3-21.6)	<0.001
Index age (years)	61.6 ± 10.0	56.8 ± 10.8	<0.001
Male sex (%)	52.4	50.6	0.64
Ethnicity (%)			<0.001
Chinese	38.2	52.7	
Malay	36.1	20.4	
Asian Indian	25.7	26.9	
Diabetes duration (years)	14.9 ± 10.4	10.7 ± 8.7	<0.001
Active smoker (%)	8.5	8.6	0.94
ASCVD history (%)	12.0	7.2	0.02
Body mass index (kg/m²)	29.4 ± 5.8	27.5 ± 5.2	<0.001
HbA1c (%)	8.4 ± 1.5	7.7 ± 1.3	<0.001
Heart rate (bpm)	72.2 ± 11.9	70.8 ± 10.8	0.08
Blood pressure (mmHg)			
Systolic pressure	151 ± 21	139 ± 18	<0.001
Diastolic pressure	80 ± 9	79 ± 9	0.32
Mean arterial pressure	104 ± 11	99 ± 10	<0.001
Lipids profile (mM)			
HDL Cholesterol	1.2 ± 0.3	1.3 ± 0.4	0.004
LDL Cholesterol	2.8 ± 0.9	2.8 ± 0.8	0.72
Triacylglycerol (IQR)	1.7 (1.2-2.3)	1.4 (1.0-1.9)	<0.001
Baseline renal function			
eGFR (ml/min/1.73m²)	66 ± 27	89 ± 24	<0.001
urine ACR (µg/mg) IQR	196 (31-1103)	19 (6-68)	<0.001
C-reactive protein (µg/ml)	3.0 (1.1-7.1)	1.9 (0.6-4.5)	<0.001
Medications usage (%)			
Statin	88.4	79.9	0.005
Insulin	54.5	25.3	<0.001
RAS blocker	79.5	58.1	<0.001
Calcium channel blocker	44.5	18.4	<0.001
Beta blocker	35.1	14.0	<0.001
Diuretics	39.8	11.0	<0.001

Data were presented as mean ± SD, median (interquartile range) or percentages. ASCVD, atherosclerotic cardiovascular disease; eGFR, estimated glomerular filtration function; ACR, albumin-to-creatinine ratio; RAS, renin-angiotensin system. Between-group differences were compared by Student t test, Mann-Whitney U test or X² test where appropriate. Variables with significant between- group differences have been highlighted in bold font.

Supplementary Table 2: Association of baseline plasma LRG1 with risk of incident heart failure (HF) in cause-specific Cox regression model

	Model without LRG1		Model with LRG1	
	OR (95% CI)	P value	OR (95% CI)	P value
1-SD natural log- LRG1	----	----	1.78 (1.33- 2.38)	<0.001
LRG1-time coefficient (year)	--		0.93 (0.87-1.00)	0.04
Age (years)	1.05 (1.03- 1.07)	<0.001	1.06 (1.04- 1.08)	<0.001
Male sex †	1.02 (0.74- 1.42)	0.89	1.23 (0.87- 1.72)	0.25
Malay ethnicity †	1.83 (1.28- 2.63)	0.001	1.72 (1.20- 2.46)	0.003
Asian Indian ethnicity †	1.54 (1.04- 2.27)	0.03	1.33 (0.90- 1.98)	0.16
Active smoker †	1.06 (0.60- 1.86)	0.85	1.00 (0.57- 1.77)	0.99
Diabetes duration (years)	1.01 (0.99- 1.02)	0.51	1.01 (0.99- 1.02)	0.48
ASCVD history †	1.38 (0.87- 2.18)	0.17	1.47 (0.93- 2.33)	0.10
Body Mass Index (kg/m ²)	1.06 (1.03- 1.09)	<0.001	1.06 (1.03- 1.10)	<0.001
HbA1c (%)	1.37 (1.23- 1.52)	<0.001	1.39 (1.25- 1.55)	<0.001
Mean arterial pressure (mmHg)	1.01 (0.99- 1.02)	0.35	1.01 (0.99- 1.02)	0.39
Heart rate (beat/min)	1.01 (1.00-1.02)	0.13	1.01 (0.99- 1.02)	0.30
HDL cholesterol (mM)	0.67 (0.38- 1.15)	0.15	0.76 (0.44- 1.31)	0.32
LDL cholesterol (mM)	0.93 (0.78- 1.12)	0.44	0.93 (0.78- 1.12)	0.46
Ln Triacylglycerol	0.88 (0.61- 1.25)	0.47	0.98 (0.69- 1.39)	0.90
Ln ACR	1.41 (1.29- 1.54)	<0.001	1.39 (1.27- 1.52)	<0.001
eGFR (ml/min/1.73m ²)	0.99 (0.98- 1.00)	<0.001	0.99 (0.99- 1.00)	0.02

Multivariable cause-specific Cox regression outcome: time to incident heart failure or death whichever occurred first. All variables in the table were included in the model as covariates.

† Female sex, Chinese ethnicity, non-active smokers and those with no ASCVD history were taken as references, respectively; Ln, natural logarithmically transformed; ASCVD, atherosclerotic cardiovascular disease; ACR, albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate. Variables which were significantly associated with risk of incident HF have been highlighted in bold font.

Supplementary Table 3: Participant clinical, biochemical characteristics and transthoracic echocardiographic parameters stratified by heart failure subtypes

	HFrEF (LVEF < 50%, N=83)	HFpEF (LVEF ≥ 50%, N=108)	P value
LVEF (%)	35.1 ± 8.0	58.5 ± 3.3	By design
Plasma LRG1 (IQR, µg/ml)	19.1 (13.5-26.7)	20.8 (15.8-31.6)	0.21
Index age (years)	60.0 ± 9.7	62.7 ± 10.2	0.07
Male sex (%)	67.5	40.7	<0.001
Ethnicity (%)			0.33
Chinese	37.3	38.9	
Malay	34.9	37.0	
Asian Indian	27.7	24.1	
Diabetes duration (years)	15.1 ± 10.6	14.7 ± 10.3	0.80
Active smoker (%)	13.4	4.7	0.03
ASCVD history (%)	12.0	12.0	0.90
Body mass index (kg/m ²)	28.8 ± 5.6	30.0 ± 6.0	0.16
HbA1c (%)	8.5 ± 1.7	8.4 ± 1.4	0.60
Resting heart rate (beat/min)	73 ± 12	72 ± 12	0.66
Blood pressure (mmHg)			
Systolic pressure	151 ± 21	152 ± 20	0.76
Diastolic pressure	82 ± 9	78 ± 9	0.02
Mean arterial pressure	105 ± 11	103 ± 11	0.27
Lipids profile (mM)			
HDL Cholesterol	1.17 ± 0.34	1.26 ± 0.30	0.05
LDL Cholesterol	2.79 ± 0.84	2.76 ± 0.90	0.85
Triacylglycerol (IQR)	1.63 (1.11-2.02)	1.74 (1.24-2.40)	0.31
Baseline renal function			
eGFR (ml/min/1.73m ²)	68 ± 27	65 ± 28	0.45
uACR (µg/mg) IQR	315 (36-955)	168 (27-1278)	0.72
C-reactive protein (µg/ml)	2.62 (0.81-5.72)	3.44 (1.29-7.79)	0.11
NT-proBNP (IQR, pg/ml)	6833 (2616-15727)	1616 (462-6252)	<0.001
Transthoracic Echocardiography			
Right Atrial Pressure (mmHg)	3 (3-3)	3 (3-3)	
TAPSV (cm/s)	11 (8-13)	13 (10-15)	--
PASP (mmHg)	35 (30-41)	35 (26-47)	--
LAVI (ml/m ²)	39 (32-49)	40 (28-51)	--
LVMI (male, g/m ²)	117 (95-145)	106 (87-125)	--
Male LVMI ≥ 115 g/m ² (%)	54.5	36.4	--
LVMI (female, g/m ²)	114 (92-154)	102 (85-124)	--
Female LVMI ≥ 95 g/m ² (%)	74.1%	57.1%	--
Mitral E/A-wave ratio	1.0 (0.8-1.9)	0.8 (0.7-1.2)	--
E/A-wave ratio ≤ 0.8 (%)	33.3	48.0	--
E/A-wave ratio ≥ 2.0 (%)	22.0	2.0	--
Average E/e' ratio	16 (12-21)	13 (10-17)	--
E/e' ratio ≥ 13 (%)	70.1	55.8	--
E/e' ratio 8-13 (%)	27.3	38.5	--

Data were presented as mean ± SD, median (interquartile range) or percentages. Between-group differences were compared by Student t test, Mann-Whitney U test or X² test where appropriate.

LVEF, left ventricular ejection fraction; TAPSV, tricuspid annular peak systolic velocity; PASP, pulmonary arterial systolic pressure; LAVI, left atrial volume index; LVMI, left ventricle mass index; NT-proBNP and transthoracic echocardiographic data were obtained at time of HF diagnosis. All other variables were collected at cohort enrolment (baseline).

Supplementary Table 4: Association of plasma LRG1 with HFrEF (LVEF <50%) and HFpEF (LVEF ≥50%) in unadjusted cause- specific Cox regression models

Plasma LRG1	HFrEF		HFpEF	
	HR (95% CI)	P value	HR (95% CI)	P value
Continuous				
1-SD increment	1.69 (0.98- 2.91)	0.06	1.34 (0.94- 1.91)	0.11
Categorical				
Quartile 1	Reference	-	Reference	-
Quartile 2	1.76 (0.66- 4.69)	0.26	1.07 (0.45- 2.53)	0.88
Quartile 3	1.52 (0.39- 5.89)	0.55	1.25 (0.48- 3.27)	0.65
Quartile 4	4.84 (0.95- 24.81)	0.06	2.36 (0.74- 7.54)	0.15

Cause- specific Cox regression model outcome: time-to- subtype incident heart failure or death whichever occurred first. Plasma LRG1 was modelled as continuous variable (1-SD of log-transformed LRG1) and categorical variable (quartiles), respectively.

Supplementary Table 5: Prediction of incident HF and HHF by plasma LRG1 and TRS-HF_{DM} risk score †

	Incident HF			Incident HHF		
	HR (95% CI)	P value	AUC	HR (95% CI)	P value	AUC
TRS- HF only			0.79 (0.75- 0.82)			0.81 (0.76- 0.85)
0 (N=951)	Reference	-		Reference	-	
1 (N=584)	3.94 (2.44- 6.37)	<0.001		4.26 (2.17- 8.29)		<0.001
2 (N=284)	9.41 (5.85- 15.15)	<0.001		13.38 (7.04 25.41)		<0.001
≥ 3 (N=159)	19.60(12.10-31.75)	<0.001		23.56(12.22-45.42)		<0.001
TRS- HF + LRG1			0.81 (0.77-0.85)			0.84 (0.80-0.88)
TRS- HF						
0 (N=951)	Reference	-		Reference	-	
1 (N=584)	3.80 (2.35- 6.14)	<0.001		4.12 (2.11- 8.06)		<0.001
2 (N=284)	8.76 (5.43- 14.12)	<0.001		12.63 (6.64- 24.04)		<0.001
≥ 3 (N=159)	16.17(9.91-26.37)	<0.001		19.96(10.26-38.84)		<0.001
Plasma LRG1						
1-SD	2.14 (1.60-2.86)	0.003		2.31 (1.52-3.50)		<0.001

Cause- specific Cox regression model outcome: time-to- incident heart failure (HF) or hospitalization HF (HHF).

AUC is calculated as Harrell C index for 5-year risk of incident HF and HHF, respectively, and 95% CI was estimated by 1000- time bootstrap resampling.

† TRS-HF_{DM} score was an integer- based scheme with 5 clinical variables included: eGFR below 60 ml/min/1.73m², urinary albuminuria-to-creatinine ratio (ACR) 30-300 µg/g, prevalent coronary artery disease and atrial fibrillation were assigned 1 point each, urinary ACR above 300 µg/g was assigned 2 points. The component of prior HF in the score scheme was omitted because the current study focuses on incident HF and HHF (Berg DD, et al. Circulation 2019;140:1569–1577. DOI: 10.1161/CIRCULATIONAHA.119.042685)