**Supplementary Online Content**

Huajie Zou, Yongping Xu, et al. Predictive Values of ANGPTL8 on Risk of All-cause Mortality in Diabetic patients: results from the REACTION Study

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Appendix 1: Predictor variables for QFrailty score

• Age (continuous variable)

• Geographical region in the United Kingdom (10 regions)

• Townsend deprivation score. This score is an area-level continuous score based on the patients’ postcode.11 Originally developed by Townsend,11 the score includes unemployment (as a percentage of those aged 16 years old or older who are economically active), non-car ownership (as a percentage of all households), non-home ownership (as a percentage of all households), and household overcrowding. These variables are measured for a given area of approximately 120 households using the 2011 census, and they are combined to yield a Townsend score for the area. A higher Townsend score implies a greater level of deprivation

• Ethnic group (nine categories)

• Alcohol intake (<1 unit/day, 1-2 units/day, 3-6 units/ day, 7-9 units/day, ≥9 units/day)

• Smoking status (non-smoker; former smoker; light, moderate, or heavy smoker)

• Body mass index (continuous variable)

• Unplanned admissions in past 12 months (0, 1, 2, or ≥3) as recorded in the linked hospital data

• Poor mobility (poor mobility, housebound, confined to chair, bedridden, requires home visits, receives mobility allowance)

• Lives in a care home (nursing home or residential care)

• Lives alone

• Atrial fibrillation

• Congestive heart failure

• Cardiovascular disease (myocardial infarction, angina, stroke, or transient ischaemic attack)

• Valvular heart disease

• Peripheral vascular disease

• Treated hypertension (hypertension and current antihypertensive treatment)

• Chronic kidney disease (stages 4 or 5)

• Diabetes (none, type 1, type 2)

• Hypothyroidism

• Hyperthyroidism

• Cancer

• Chronic liver disease or pancreatitis

• Malabsorption (including Crohn’s disease, ulcerative colitis, coeliac disease, steatorrhoea, blind loop syndrome)

• Peptic ulcer (gastric or duodenal ulcer, simple or complicated ulcer)

• Asthma or chronic obstructive airways disease

• Epilepsy

• Dementia

• Learning disability

• Osteoporosis

• Fragility fracture (hip, spine, shoulder, or wrist fracture)

• Parkinson’s disease or syndrome

• Rheumatoid arthritis

• Falls

• Bipolar disorder or schizophrenia

• Depression in past 12 months

• Venous thromboembolism

• Anaemia (haemoglobin <110 g/L)

• Abnormal liver function test result (bilirubin, alanine aminotransferase, or γ glutamyl transferase more than three times the upper limit of normal)

• High platelet count (>480×109/L)

• Leg ulcer (leg, shin, ankle or foot ulcer, ischaemic neuropathic, arterial, or venous ulcer)

• Blindness (registered blind or partially sighted or visual impairment)

• Appetite loss in past 12 months

• Weight loss in past 12 months (unexplained or abnormal weight loss)

• Urinary incontinence in past 12 months

• Nocturia in past 12 months

• Urinary retention in past 12 months (acute or chronic retention)

• Syncope (vasovagal symptom, faint, collapse, “funny turn,” drop attack) in past 12 months

• Dizziness in past 12 months

• Insomnia in past 12 months

• Dyspnoea in past 12 months (breathless at rest or on exertion, paroxysmal nocturnal dyspnoea)

• Hearing impairment or deafness in past 12 months

• Loneliness in past 12 months

• Use of anticoagulants (≥2 prescriptions in past six months)

• Use of antidepressants (≥2 prescriptions in past six months)

• Use of antipsychotics (≥2 prescriptions in past six months)

• Use of corticosteroids (≥2 prescriptions in past six months)

• Non-steroidal anti-inflammatory drugs (≥2 prescriptions in past six months)

**Table S1.** **Characteristics of patients with diabetes.**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Pre-existing diabetes | Newly diagnosed diabetes | p2 value |
|  | With treatment | Without treatment | p1 value | All |
| N (%) | 150 (19.5) | 153 (19.9) | - | 303 (39.4) | 466 (60.6) | - |
| ANGPTL8 (pg/mL) | 648.38$\pm $27.75 | 592.01$\pm $30.20 | 0.09 | 619.92$\pm $20.56 | 618.11$\pm $18.34 | 0.42 |
| **Primary outcome** |
|  Death | 8 (5.3) | 9 (5.9) | 1.00 | 17 (5.6) | 39 (8.4) | 0.16 |
| **Secondary outcomes** | 15 (10.0) | 22 (14.4) | 0.29 | 37 (12.2) | 54 (11.6) | 0.82 |
| MACE | 10 (6.7) | 15 (9.8) | 0.41 | 25 (8.3) | 37 (7.9) | 0.89 |
| HF | 3 (2.0) | 7 (4.6) | 0.34 | 10 (3.3) | 15 (3.2) | 0.95 |
| Renal dysfunction | 4 (2.7) | 4 (2.6) | 1.00 | 8 (2.6) | 15 (3.2) | 0.83 |

Abbreviation: MACE, new-onset major adverse cardiovascular events; HF, hospitalization of heart failure.

p1for significance of comparison between diabetic patients with or without treatment.
p2for significance of comparison between patients with newly diagnosed diabetes and patients with pre-existing diabetes.

**Table S2. Metabolic parameters and outcomes for control subjects and diabetic patients.**

|  |  |  |  |
| --- | --- | --- | --- |
| Characteristics | Control | Diabetes | p |
| N  | 769 | 769 | - |
| Male (%) | 266 (34.6) | 266 (34.6) | - |
| BMI  | 23.38$\pm $3.09 | 24.22$\pm $3.48 | <0.001 |
| ANGPTL8 (pg/mL) | 581.20$\pm $299.54 | 618.82$\pm $381.08 | 0.03 |
| HbA1c (%) | 5.56$\pm $0.34 | 7.17$\pm $1.97 | <0.001 |
| FPG (mmol/L) | 5.05$\pm $0.47 | 7.92$\pm $2.74 | <0.001 |
| 2h PG (mmol/L) | 5.72$\pm $1.10 | 12.17$\pm $4.84 | <0.001 |
| Fasting insulin (pmol/mL) | 6.09$ \pm $ 5.21 | 10.13$\pm $11.10 | <0.001 |
| HOMA-IR | 1.39$\pm $1.27 | 3.65$\pm $4.30 | <0.001 |
| HOMA-$β $(%) | 76.94$\pm $142.63 | 56.08$\pm $79.83 | <0.001 |
| Fasting HDL (mmol/L) | 1.40$\pm $0.35 | 1.43$\pm $0.38 | 0.07 |
| Fasting LDL (mmol/L) | 2.62$\pm $0.74 | 3.00$\pm $0.86 | <0.001 |
| Fasting TG (mmol/L) | 1.58$\pm $1.45 | 1.87$\pm $1.49 | <0.001 |
| Cholesterol (mmol/L) | 4.75$\pm $0.95 | 5.22$\pm $1.06 | <0.001 |
| eGFR (mL/min/1.73 m2) | 115.46$\pm $21.97 | 108.35$\pm $20.72 | <0.001 |
| Creatinine (μmol/L) | 63$\pm 12$ | 66$\pm $21 | <0.001 |
| Hypertension | 478 (62.2) | 583 (75.8) | <0.001 |
| Hyperlipidaemia | 287 (37.3) | 435 (56.6) | <0.001 |
| Outcomes  |
| Primary outcome |
|  Death | 19 (2.5) | 56 (7.3) | <0.001 |
|  Secondary outcomes | 44 (5.7) | 91 (11.8) | <0.001 |
|  MACE | 34 (4.4) | 62 (8.1) |  0.004 |
|  HF |  3 (0.4) | 12 (1.6) |  0.03 |
|  Renal dysfunction |  7 (0.9) | 23 (3.0) |  0.005 |

Abbreviation: BMI, body-mass index; HbA1c, glycated haemoglobin A1c; FPG, fasting plasma glucose; 2h PG, 2 h plasma glucose concentration; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β , homeostasis model assessment of β cell function; HDL, high density lipoprotein; LDL, low density lipoprotein; TG, triglycerides; ALT, alanine transaminase; AST aspartate aminotransferase; eGFR, glomerular filtration rate; MACE, new-onset major adverse cardiovascular events; HF, hospitalization for heart failure.

**Table S3. Partial correlations between ANGPTL8 levels and clinical variables in control subjects and diabetic patients.**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Control |  | Diabetes |
| Model 1 | Model 2 | Model 3 | Model 1 | Model 2 | Model 3 |
| r | p value | Partial r | p value | Partial r | p value | r | p value | Partial r | p value | Partial r | p value |
| Age | 0.423 | 0.000 | 0.418 | 0.000 | 0.421 | 0.000 | 0.204 | 0.000 | 0.165 | 0.000 | 0.177 | 0.000 |
| BMI | 0.061 | 0.090 | 0.131 | 0.000 | 0.101 | 0.005 |  | -0.112 | 0.002 | -0.044 | 0.219 | -0.074 | 0.041 |
| WHR | 0.055 | 0.127 | 0.017 | 0.646 | 0.013 | 0.730 |  | -0.062 | 0.086 | -0.056 | 0.119 | -0.065 | 0.072 |
| SBP | 0.168 | 0.000 | 0.029 | 0.429 | 0.015 | 0.676 |  | 0.031 | 0.389 | -0.022 | 0.536 | -0.014 | 0.693 |
| Duration of diabetes | - | - | - | - | - | - |  | 0.063 | 0.081 | 0.083 | 0.021 | 0.078 | 0.031 |
| HbA1c | 0.095 | 0.008 | -0.009 | 0.794 | -0.021 | 0.568 |  | -0.032 | 0.379 | 0.035 | 0.332 | 0.029 | 0.418 |
| FPG | 0.006 | 0.860 | -0.018 | 0.625 | -0.026 | 0.477 |  | 0.013 | 0.709 | 0.067 | 0.064 | 0.0762 | 0.089 |
| 2h PG | 0.046 | 0.204 | 0.011 | 0.770 | 0.003 | 0.943 |  | 0.051 | 0.161 | 0.081 | 0.024 | 0.078 | 0.032 |
| Fasting insulin | -0.002 | 0.951 | 0.038 | 0.294 | 0.021 | 0.559 |  | -0.018 | 0.625 | 0.020 | 0.583 | -0.002 | 0.967 |
| HOMA-IR | -0.004 | 0.922 | 0.032 | 0.379 | 0.015 | 0.688 |  | -0.003 | 0.926 | 0.038 | 0.298 | 0.013 | 0.716 |
| HOMA-$β$ | 0.004 | 0.907 | 0.001 | 0.988 | -0.006 | 0.877 |  | -0.064 | 0.077 | -0.038 | 0.288 | -0.047 | 0.195 |
| HDL  | 0.008 | 0.817 | -0.039 | 0.278 | 0.005 | 0.900 |  | -0.091 | 0.012 | -0.150 | 0.000 | -0.086 | 0.017 |
| LDL  | 0.055 | 0.126 | 0.028 | 0.442 | 0.035 | 0.330 |  | -0.090 | 0.013 | -0.070 | 0.051 | -0.036 | 0.319 |
| TG  | 0.058 | 0.110 | 0.091 | 0.012 | 0.069 | 0.057 |  | 0.068 | 0.059 | 0.123 | 0.001 | 0.030 | 0.407 |
| Cholesterol | 0.074 | 0.039 | 0.038 | 0.293 | -0.024 | 0.501 |  | -0.065 | 0.072 | -0.044 | 0.219 | 0.019 | 0.598 |
| ALT | 0.007 | 0.849 | 0.041 | 0.258 | 0.030 | 0.405 |  | 0.066 | 0.068 | 0.079 | 0.029 | 0.072 | 0.046 |
| AST | 0.056 | 0.124 | 0.016 | 0.663 | 0.016 | 0.662 |  | 0.150 | 0.000 | 0.126 | 0.000 | 0.134 | 0.000 |
| eGFR | -0.225 | 0.000 | -0.135 | 0.000 | -0.123 | 0.000 |  | -0.126 | 0.000 | -0.137 | 0.000 | -0.130 | 0.000 |
| Creatinine | 0.215 | 0.000 | 0.118 | 0.001 | 0.108 | 0.003 |  | 0.154 | 0.000 | 0.107 | 0.003 | 0.096 | 0.008 |

\* when a variable was calculated in the partial correlation, it would not be included in adjustment model.

Model 1 was unadjusted.

Model 2 was adjusted by age, sex and BMI.

Model 3 was adjusted by all variables in model 2 plus HDL, LDL, TG, cholesterol.

Abbreviation: BMI, body-mass index; WHR, waist hip rate; SBP, systolic blood pressure; HbA1c, glycated haemoglobin A1c; FPG, fasting plasma glucose; 2h PG, 2 h plasma glucose concentration; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment of β cell function; HDL, high density lipoprotein; LDL, low density lipoprotein; TG, triglycerides; ALT, alanine transaminase; AST aspartate aminotransferase; eGFR, glomerular filtration rate.

**Table S4. Predictive** **values** **for all-cause mortality in combination with ANGPTL8 in QFrailty score.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Variables | AUC | SE | p for individual | 95% CI | p for comparison |
| Lower bound  | Upper bound  |
| All participants  |  |
| QFrailty score | 0.59 | 0.038 | 0.013 | 0.51 | 0.66 | 0.000 |
| QFrailty score + ANGPTL8 | 0.71 | 0.031 | 0.000 | 0.65 | 0.77 |
| Diabetic patients |  |
| QFrailty score | 0.59 | 0.044 | 0.032 | 0.50 | 0.67 | 0.000 |
| QFrailty score + ANGPTL8 | 0.70 | 0.037 | 0.000 | 0.63 | 0.78 |
| Control subjects |  |
| QFrailty score | 0.57 | 0.073 | 0.304 | 0.43 | 0.71 | 0.01 |
| QFrailty score + ANGPTL8 | 0.71 | 0.058 | 0.002 | 0.59 | 0.82 |

Abbreviation: AUC, area under the curve; CI, confidential interval; SE, standard error

**Figure S1. Flow diagram for the study population selection.**

