Cardiovascular Diabetology

RESEARCH

Open Access

Cardiovascular abnormalities already occurred in newly-diagnosed patients with early-onset type 2 diabetes

Hong Lian[1†], Qian Ren[1†], Wei Liu[1], Rui Zhang[1], Xiantong Zou[1], Simin Zhang[1], Yingying Luo[1], Wei Deng[2], Qiuping Wang[3], Lin Qi[4], Yufeng Li[5], Wenbo Wang[6], Liyong Zhong[7], Pengkai Zhang[1], Chengcheng Guo[1], Li Li[1], Yating Li[1], Tianhao Ba[1], Chaochao Yang[1], Lili Huo[2], Yan'ai Wang[2], Chunxia Li[3], Dejun Hao[4], Yajing Zhang[5], Yan Xu[6], Fang Wang[7], Xiangqing Wang[1], Fang Zhang[1], Siqian Gong[1], Wenjia Yang[1], Xueyao Han[1,9*] and Linong Ji[1,8,9*]

Abstract

Background The prevalence of early-onset type 2 diabetes (EOD) is rapidly increasing. This study intends to screen for early cardiovascular abnormalities in patients newly diagnosed with EOD and evaluate the cardiovascular risk across cluster phenotypes.

Method A total of 400 patients ≤ 40 years old with newly diagnosed type 2 diabetes were enrolled from the START cohort (the Study of The newly diAgnosed eaRly onset diabeTes). Cluster classification was performed using the K-means method based on age, BMI, HbA1c, HOMA2-β, HOMA2-IR, and GAD antibodies. Echocardiography and carotid ultrasound were performed within 3 months of diabetes diagnosis. Carotid ultrasound abnormalities included intimal thickening and plaque formation, while echocardiography assessed changes in cardiac structure and systolic/diastolic function. Cluster-specific partitioned polygenic scores (pPS) were used to validate our findings from a genetic perspective.

Result Carotid artery abnormalities were detected in 26.3% of patients, and echocardiography abnormalities were observed in 20.0%. Patients with severe insulin resistant diabetes (SIRD) had the highest incidence of carotid artery abnormality (40.0%). After adjusting for relevant risk factors, fasting C-peptide levels were significantly associated with a 1.247-fold increase in the risk of carotid artery abnormalities. Left atrial enlargement was more prevalent in the SIRD (16.7%) and mild obesity-related diabetes (MOD) (18.5%) classifications. A high proportion of patients with SIRD had abnormal left ventricular geometry (36.1%). Increases in BMI, fasting C-peptide level and HOMA2IR were accompanied by a further increase in left atrial enlargement risk by 1.136-, 1.781- and 1.687-fold respectively. The pPS

[†]Hong Lian and Qian Ren have contributed equally to this work.

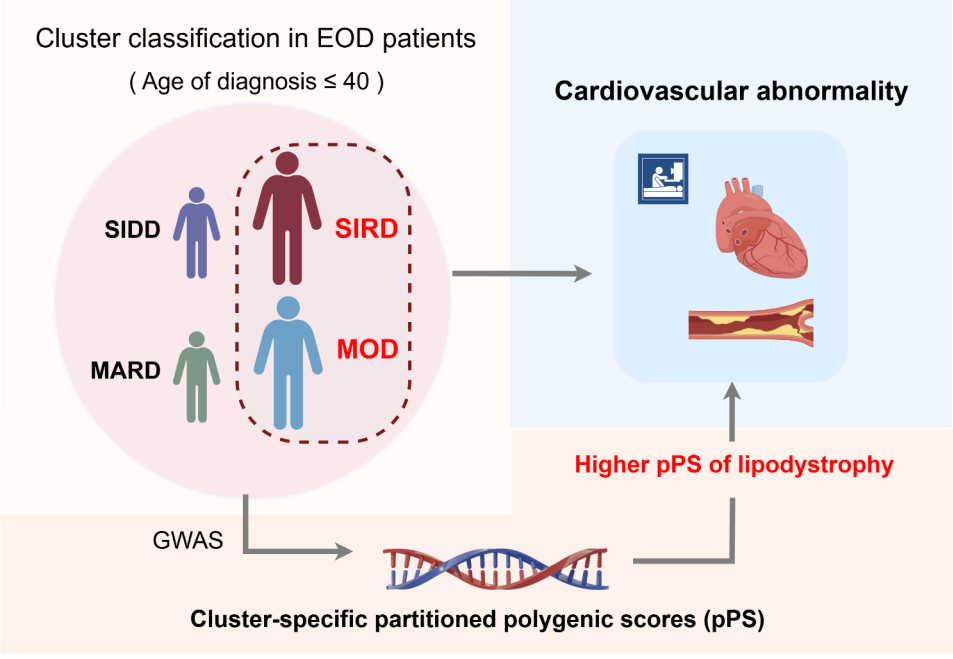
*Correspondence:
Xueyao Han
xueyaohan@sina.com
Linong Ji
jiln@bjmu.edu.cn

Full list of author information is available at the end of the article

for lipodystrophy was higher in the EOD group with plaque formation, and showed a significant linear correlation with the ratio of the left atrial anteroposterior diameter to body surface area (LAAP/BSA) ($R = 0.344$, $p < 0.001$).

Conclusion Heart and carotid artery abnormalities are common in patients with early-onset T2DM at the time of diagnosis. Patients with obesity and insulin resistance are at higher risk for cardiovascular abnormalities. Cluster classification based on clinical characteristics enables more accurate identification of patients at increased risk of cardiovascular complications at an early stage.

Graphical abstract



Keywords Cardiovascular abnormality, Cluster classification, Early-onset type 2 diabetes, SIRD, MOD, Partitioned polygenic scores

Introduction

Early-onset type 2 diabetes is defined as diabetes diagnosed before the age of 40 years. It has recently been recognized as one of the most serious health challenges of the 21st century, with the greatest relative increase in the incidence and prevalence of type 2 diabetes among younger population [1]. According to the China Chronic Disease and Risk Factors Surveillance, individuals aged 18–40 accounted for 11.5% of all patients with diabetes [2].

Growing evidence suggests that early-onset type 2 diabetes is the more aggressive form of the disease. Early-onset type 2 diabetes is associated with increased cardiovascular and coronary mortality [3, 4]. Patients with early-onset type 2 diabetes have twice the risk of developing macrovascular complications than those with late-onset type 2 diabetes (HR 7.9 vs. 3.8, respectively) [5]. A cross-sectional study conducted by the Chinese National Glycosylated Haemoglobin Surveillance System (CNHSS) reported that patients with early-onset type 2 diabetes have a higher risk of non-fatal cardiovascular disease than those with late-onset type 2 diabetes (OR 1.91, 95% CI 1.81 to 2.02) [6]. These findings highlight the need to evaluate the cardiovascular risk in individuals with early-onset diabetes mellitus.

To date, two large cohort studies have investigated cardiovascular risk assessment in young individuals with diabetes. In the TODAY study, adolescents and young adults with type 2 diabetes experienced worsening left ventricular diastolic function within 5–10 years of diagnosis, and 15.8% of patients exhibited cardiac structural abnormalities [7]. Similarly, in the SEARCH study, 25.5% of young patients with a median diabetes duration of 11.3 years showed structural abnormalities in the hearts, including left ventricular hypertrophy or concentric geometry, along with reduced left ventricular diastolic function [8]. However, these studies primarily focused on early-onset diabetes with an average duration of 10 years. It remains unclear whether cardiovascular abnormalities are present at the time of early-onset diabetes diagnosis.

A nationwide registry study showed that patients with type 2 diabetes mellitus (T2DM) experience twice the rate of cardiovascular events 30 years prior to diagnosis compared to controls [9]. Nevertheless, relevant research evidence in patients with early onset diabetes is still lacking.

Diabetic cardiomyopathy (DCM) is a diabetic pathophysiological condition characterized by structural, functional and metabolic changes in the heart [10]. Early manifestations of DCM include left atrial enlargement, left ventricular hypertrophy and diastolic dysfunction, while the late manifestations include cardiac fibrosis, left ventricular dilation, systolic dysfunction and heart failure symptoms. These changes are driven by insulin resistance, compensatory hyperinsulinemia, and hyperglycemia in the heart tissue, which occurs independently of other cardiac risk factors such as coronary artery disease (CAD) and hypertension [11]. Currently, diagnostic techniques and treatment of diabetic cardiomyopathy are still relatively nonspecific [12, 13]. Research on this area is essential, as early diagnosis and intervention may delay the progression of heart failure in patients with early-onset diabetes.

Furthermore, it is critical to identify patients with early-onset diabetes who are more vulnerable to cardiovascular disease. Recently, data-driven clustering has been proposed to refine diabetes classification and identify individuals more likely to experience complications. Clinical characteristics and outcomes vary across cluster types. For example, patients with severe insulin resistance subtypes have an increased risk of developing diabetic kidney disease [14]. We hypothesized that cluster classification could also identify subtypes of individuals with early-onset diabetes who are at higher cardiovascular risk.

Therefore, the START cohort (the Study of The newly diAgnosed eaRly onset diabeTes) was stablished in 2021 at the Diabetes Centre of Peking University People's Hospital to recruit newly diagnosed patients with early-onset diabetes and assess the presence of cardiovascular abnormalities at diagnosis. We used cluster classification at diagnosis to identify those with EOD who are more vulnerable to cardiovascular disease, and the cluster-specific partitioned polygenic scores (pPS) were used to verify our findings from a genetic perspective.

Methods

The research methods and relevant statistical methods were described in detail in the Supplementary method.

Results

Clinical characteristics of patients with early-onset newly diagnosed type 2 diabetes in cluster classification

A total of 400 patients were recruited for this study. After excluding severe autoimmune diabetes (SAID) subtypes with positive GAD antibodies, 388 patients were classified into four subtypes using clustering analysis (Figure S1). The median age was 34 (30,38) years old and 72.94% (283/388) of the participants were men. A family history of diabetes was reported in 65.21% (253/388) of patients. The mean BMI was 29.56 ± 5.01 kg/m^2 in males, while 28.38 ± 5.27 kg/m^2 in female subjects. The median HbA1c level was 10.0 (7.9,11.4) % (Table 1). The distribution of subtypes among patients newly diagnosed with EOD was as follows: mild obesity-related diabetes (MOD), 45.1% (175/388); severe insulin-deficient diabetes (SIDD), 36.1% (140/388); severe insulin-resistant diabetes (SIRD), 11.6% (45/388); mild age-related diabetes (MARD), 7.2% (28/388) (Fig. 1). Notably, MOD accounted for the largest proportion of patients with EOD. The clinical characteristics of each subtype are presented in Table 1. Among these subtypes, patients with SIDD exhibited lower levels of fasting insulin (9.05 uU/ml [5.47–13.65]) and C-peptide (2.36 ng/ml [1.72–2.86]), while their fasting blood glucose levels were higher (238.14 mg/dL [189.59–291.60]) compared to the other three subtypes. Higher BMI values (32.11 ± 4.90 kg/m^2 and 32.10 ± 4.25 kg/m^2, respectively) and waist-to-hip ratios (0.96 ± 0.07 and 0.96 ± 0.06, respectively) were observed in patients with SIRD and MOD subtypes. However, patients with SIRD had lower HbA1c values (7.10 [6.55–8.30] vs. 9.60 [8.00-10.80] %) and higher fasting insulin levels (36.07 [26.48–45.03] vs. 18.13 [12.68–27.58] uU/ml) than patients with the MOD subtype.

Carotid artery abnormality in patients with newly diagnosed EOD in cluster classification

Carotid ultrasound was performed within 3 months of diagnosis in newly diagnosed patients to screen for early vascular abnormalities. Among the 293 patients who underwent carotid artery ultrasonography, the overall abnormality detection rate was 26.3% (77/293) (Table 2; Fig. 1). No significant differences in the clinical features were observed between patients who underwent carotid ultrasound and those who did not. (Table S2) The SIRD subtype exhibited a notably greater abnormal detection rate of 40.0% (14/35) than the other subtypes, which included the intima-media thickening in 37.1% (13/35) and plaque formation in 20.0% (7/35). This was followed by MOD with 26.0% (34/131) and SIDD with 25.7% (27/105). The MARD subtype had the lowest detection rate (9.1% [2/22]). Compared to EOD patients with normal carotid ultrasound findings, those with carotid artery abnormalities were older and had higher diastolic blood

Table 1 Clinical characteristics of patients with early-onset newly diagnosed type 2 diabetes in cluster classification

	Total	SIDD	SIRD	MOD	MARD	*p* value
Sample n%	388	36.1% (140/388)	11.6% (45/388)	45.1% (175/388)	7.2% (28/388)	
Male n%	72.94% (283/388)	73.6% (103/140)	53.3% (24/45)	82.9% (145/175)	39.3% (11/28)	<0.001
Age	34 (30,38)	34 (30,38)	36 (31,38)	35 (30,37)	34 (31,36)	0.551
Family history of diabetes, n%	65.21% (253/388)	61.4% (86/140)	68.9% (31/45)	65.7% (115/175)	75.0% (21/28)	0.502
SBP (mmHg)	131.03 ± 15.91	126.74 ± 14.18	129.97 ± 17.39	136.16 ± 15.14	121.37 ± 16.17	<0.001
DBP (mmHg)	81.62 ± 12.49	79.20 ± 11.86	82.29 ± 13.27	84.07 ± 12.33	77.11 ± 12.57	0.002
BMI (kg/m2)	male 29.56 ± 5.01 female 28.38 ± 5.27	25.71 ± 3.30	32.11 ± 4.90	32.10 ± 4.25	24.41 ± 2.53	<0.001
WHR	male 0.96 ± 0.06 female 0.89 ± 0.07	0.92 ± 0.06	0.96 ± 0.07	0.96 ± 0.06	0.87 ± 0.07	<0.001
Current smoking, n%	male 49.6% (134/270) female 2.9% (3/104)	33.6% (45/134)	27.9% (12/43)	44.1% (75/170)	18.5% (5/27)	0.02
Current drinking, n%	male 24.9% (67/269) female 1.0% (1/103)	18.9% (25/132)	18.6% (8/43)	18.8% (32/170)	11.1% (3/27)	0.771
F-INS (uU/ml)	14.32 (8.69,23.63)	9.05 (5.47,13.65)	36.07 (26.48,45.03)	18.13 (12.68,27.58)	10.53 (6.91,15.84)	<0.001
F-CP (ng/ml)	3.08 (2.32,4.16)	2.36 (1.72,2.86)	5.17 (4.65,6.24)	3.57 (2.97,4.37)	2.50 (1.75,3.14)	<0.001
FPG (mg/dL)	196.20 (139.05,257.72)	238.14 (189.59,291.60)	133.92 (113.58,148.95)	196.20 (147.60,242.82)	138.69 (125.60,170.37)	<0.001
HBA1c (%)	10.0 (7.9,11.4)	11.40 (10.35,12.73)	7.10 (6.55,8.30)	9.60 (8.00,10.80)	7.10 (6.50,7.90)	<0.001
ALT (U/L)	42.0 (22.0,76.0)	27.0 (16.3,46.0)	58.5 (28.8,97.3)	55.0 (30.0,88.0)	24.0 (12.0,59.5)	<0.001
AST (U/L)	26.0 (17.0,44.0)	19.5 (14.0,28.0)	38.0 (24.8,60.5)	34.0 (21.0,51.0)	20.0 (14.0,35.5)	<0.001
UA (umol/L)	male 412 (345,478) female 351 (295,417)	358 (298,420)	435 (388,500)	416 (341,483)	363 (298,447)	<0.001
CRE (umol/L)	64.58 ± 15.62	59.40 ± 13.24	70.61 ± 16.56	67.42 ± 15.67	62.01 ± 17.28	<0.001
TCHOL (mg/dL)	207.46 (179.91,238.01)	207.66 (177.50,241.69)	210.36 (186.49,244.10)	207.46 (180.69,236.85)	199.15 (170.15,238.01)	0.81
TG (mg/dL)	200.24 (137.55,324.94)	188.72 (106.76,302.13)	229.47 (180.08,390.28)	220.17 (147.08,364.81)	156.82 (82.84,209.98)	<0.001
HDL (mg/dL)	40.80 (35.58,47.47)	42.15 (35.58,49.88)	39.06 (35.48,44.86)	39.44 (34.80,45.15)	47.56 (38.48,54.33)	0.066
LDL (mg/dL)	129.35 (107.31,153.91)	128.77 (104.99,156.61)	132.25 (106.92,159.32)	129.74 (107.31,150.23)	124.13 (112.14,158.35)	0.95
TBIL (umol/L)	14.50 (11.00,18.80)	15.6 (11.5,19.0)	11.6 (9.2,14.1)	15.0 (11.1,19.0)	16.4 (11.5,21.3)	0.005
DBIL (umol/L)	4.30 (3.30,5.55)	4.2 (3.4,5.7)	3.8 (2.8,4.8)	4.6 (3.4,5.7)	4.3 (3.1,6.2)	0.035
eGFR (ml/min*1.73m2)	119.29 (111.23,126.00)	120.78 (115.29,128.24)	111.02 (98.28,116.67)	119.66 (110.34,125.79)	116.37 (104.51,121.99)	<0.001
UACR (mg/g)	14.87 (7.88,41.75)	16.73 (8.09,42.88)	14.38 (6.67,38.18)	17.05 (8.62,51.48)	8.78 (5.28,13.72)	0.011
UACR>30, n%	32.4% (116/358)	34.1% (45/132)	27.9% (12/43)	35.8% (57/159)	8.3% (2/24)	0.051
Hypertension, n%	60.4% (218/361)	48.0% (61/127)	65.9% (27/41)	72.3% (120/166)	37.0% (10/27)	<0.001
Hypertriglyceridemia, n%	49.4% (160/324)	46.9% (53/113)	60.5% (23/38)	52.0% (77/148)	28.0% (7/25)	0.067
Low high-density lipoproteinemia, n%	40.1% (130/324)	33.6% (38/113)	47.4% (18/38)	45.9% (68/148)	24.0% (6/25)	0.055
Hyperuricemia, n%	37.8% (122/323)	23.9% (27/113)	57.9% (22/38)	44.6% (66/148)	29.2% (7/24)	<0.001
Metabolic syndrome, n%	87.7% (313/357)	86.2% (106/123)	86.0% (37/43)	90.8% (148/163)	78.6% (22/28)	0.289
HOMA2-IR	3.35 ± 1.54	2.70 ± 1.25	4.73 ± 1.78	3.71 ± 1.40	2.15 ± 0.89	<0.001
HOMA2-β	48.7 (27.9,75.8)	25.3 (18.5,41.4)	134.9 (103.2,161.1)	54.4 (33.8,75.8)	60.1 (49.0,73.9)	<0.001
TyG index	9.96 ± 0.92	10.02 ± 0.95	9.86 ± 0.89	10.08 ± 0.86	9.11 ± 0.63	<0.001

1. Data were means ± SD or medians (interquartile ranges) for skewed variables and proportions (numbers) for categorical variables

2. *P* values were for the one-way ANOVA, Kruskal Wallis or χ2 analyses across the groups. A two-sided test with $p < 0.05$ was considered statistically significant

3. SIDD, severe insulin-deficient diabetes; SIRD, severe insulin resistant diabetes; MOD, mild obesity-related diabetes; MARD, mild age-related diabetes; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; WHR, Waist-to-Hip Ratio; FINS, fasting serum insulin; FCP, fasting c-peptide; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; ALT, alanine aminotransferase; AST, aspartate aminotransferase; UA, uric acid; CRE, creatinine; TCHOL, total cholesterol; TG, triglycerides; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; TBIL, total bilirubin; DBIL, Direct Bilirubin; eGFR, estimated glomerular filtration rate; UACR, urinary albumin/creatinine ratio; HOMA2-IR, Homeostatic Model Assessment of Insulin Resistance; HOMA2-β, Homeostatic Model Assessment of β-cell function; TyG index, triglyceride-glucose index

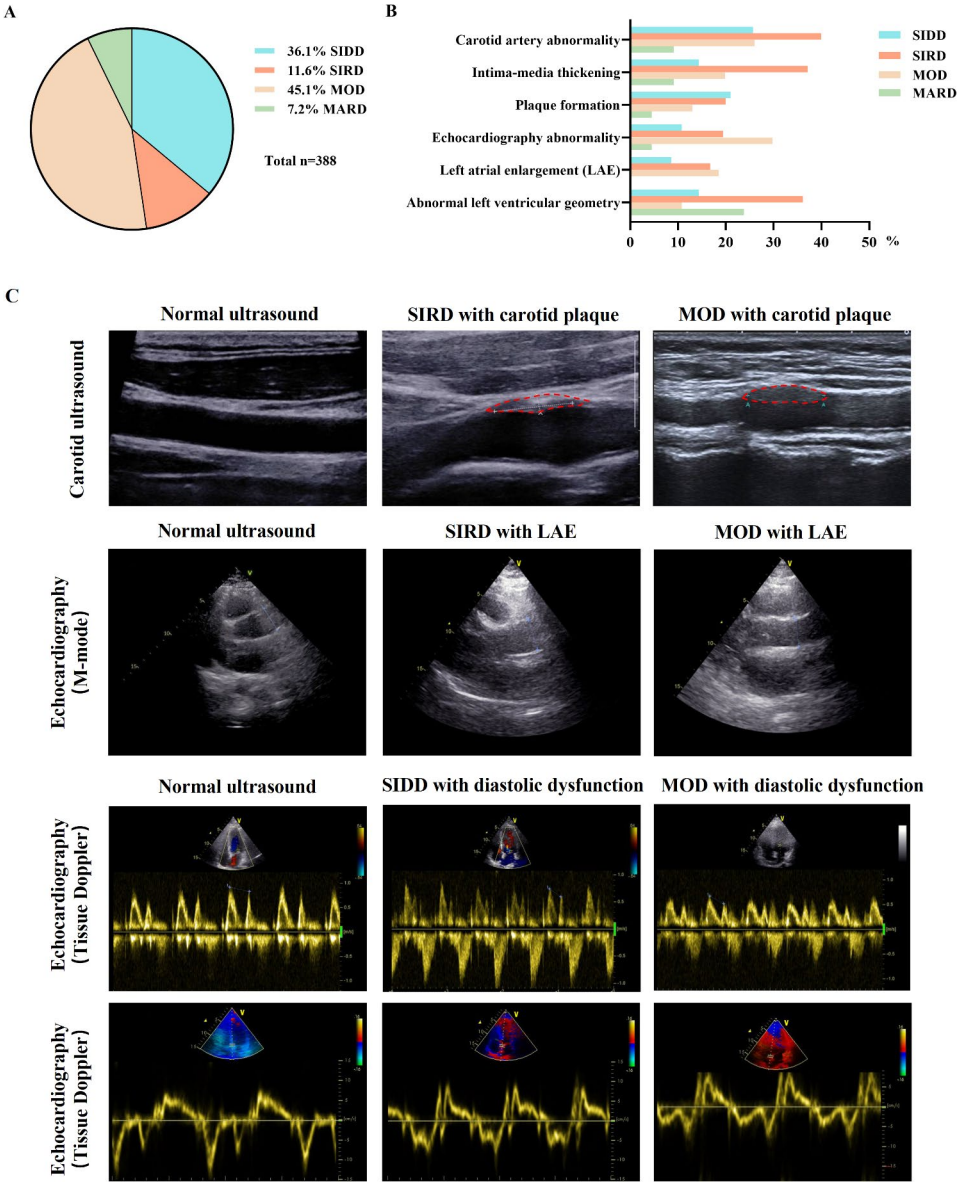


Fig. 1 Cardiovascular abnormality in patients with newly diagnosed EOD in cluster classification. **A** Cluster classification results of EOD patients in START cohort **B** Detection rate of ultrasound abnormalities in EOD patients by cluster classification **C** Representative images of carotid artery ultrasound and echocardiography in normal ultrasound group, SIDD, SIRD and MOD subtypes with abnormal echocardiography group. *SIDD* Severe insulin-deficient diabetes, *SIRD* Severe insulin resistant diabetes, *MOD* Mild obesity-related diabetes, *MARD* Mild age-related diabetes, *LAE* Left atrial enlargement

pressure, higher C-peptide levels, and poorer lipid control (Table S3).

Echocardiographic characteristics of patients with newly diagnosed EOD in cluster classification

Echocardiography was performed to assess structural and functional cardiac abnormalities in 275 patients with EOD, with an overall abnormality detection rate of 20.0% (55/275) (Table 2; Fig. 1). Major abnormalities included left atrial enlargement (LAE) in 13.5% (37/275), and abnormal left ventricular geometry in 16.5% (43/261) of the patients, which is one of the manifestations of left ventricular remodeling. The SIRD and MOD subtypes had significantly higher rates of left atrial enlargement than the other two groups: SIRD, 16.7% (6/36) and MOD, 18.5% (23/124). Table 3 presents the echocardiographic characteristics of the patients with EOD based on cluster analysis. No significant differences were found in systolic and diastolic function among the four subtypes. However, patients with SIRD and MOD exhibited larger cardiac and vascular lumen size and left ventricular volumes compared to the other two groups; left ventricular volumes differences disappeared after adjusting for body surface area (BSA) levels. It is worth noting that in

Table 2 The detection rate of early cardiovascular abnormalities in newly diagnosed EOD patients by cluster classification

	SIDD	SIRD	MOD	MARD	Overall	*p* value
n	140	45	175	28	388	
Carotid ultrasound	105	35	131	22	293	
Carotid artery abnormality	25.7% (27/105)	40.0% (14/35)	26.0% (34/131)	9.1% (2/22)	26.3% (77/293)	0.079
Intima-media thickening	14.3% (15/105)	**37.1% (13/35)**	19.8% (26/131)	9.1% (2/22)	19.1% (56/293)	**0.022**
Plaque formation	21.0% (22/105)	20.0% (7/35)	13.0% (17/131)	4.5% (1/22)	16.0% (47/293)	0.113
Echocardiography	93	36	124	22	275	
Echocardiography abnormality	10.8% (10/93)	19.4% (7/36)	29.8% (37/124)	4.5% (1/22)	20.0% (55/275)	0.001
Left atrial enlargement (LAE)	8.6% (8/93)	**16.7% (6/36)**	**18.5% (23/124)**	0.0% (0/22)	13.5% (37/275)	**0.031**
Left ventricular enlargement (LVE)	0.0% (0/93)	2.8% (1/36)	4.0% (5/124)	0.0% (0/22)	2.2% (6/275)	0.223
Abnormal left ventricular geometry	14.3% (12/84)	**36.1% (13/36)**	10.8% (13/120)	23.8% (5/21)	16.5% (43/261)	**0.008**
Interventricular septum thickening	0.0% (0/93)	0.0% (0/36)	5.6% (7/124)	0.0% (0/22)	2.5% (7/275)	0.046
Left ventricular diastolic dysfunction	4.3% (4/93)	0.0% (0/36)	8.9% (11/124)	4.5% (1/22)	5.8% (16/275)	0.201

1. Data were presented as proportions (numbers) for categorical variables

2. *P* values were for the χ 2 analyses or Fisher's Exact test across the groups. A two-sided test with $p < 0.05$ was considered statistically significant and presented in bold.

3. SIDD, severe insulin-deficient diabetes; SIRD, severe insulin resistant diabetes; MOD, mild obesity-related diabetes; MARD, mild age-related diabetes

terms of left ventricular remodeling, patients with SIRD showed a high proportion of abnormal left ventricular geometry (36.1% [13/36]), including concentric remodeling 27.8% (10/36), concentric hypertrophy 5.6% (2/36) and eccentric hypertrophy 2.8% (1/36) (Tables 2 and 3).

The clinical risk factors for carotid artery and echocardiography abnormalities in newly diagnosed EOD patients

Subsequently, the clinical features of the abnormal-detection group, identified through carotid artery ultrasound and echocardiography, were compared with those of the normal ultrasound group (Table S2-S9). The HOMA-IR and TyG index, which indicate insulin resistance, were significantly higher in patients with cardiovascular abnormalities compared to those with normal findings (Table S9). To further investigate the primary clinical factors contributing to these abnormalities, a logistic regression analysis was performed (Table 4). Poor lipid control was associated with a higher risk of carotid artery abnormalities. After adjusting for relevant risk factors, fasting C-peptide levels were significantly associated with a 1.247-fold increase in the risk (95%CI 1.017–1.530) of carotid artery abnormalities. Obesity and insulin resistance were identified as major risk factors for left atrial enlargement. Increases in BMI, fasting C-peptide levels, and HOMA2IR were associated with an adjusted increased risk of left atrial enlargement by factors of 1.136 (95%CI 1.050–1.228), 1.781 (95%CI 1.300-2.438) and 1.687-fold (95%CI 1.274–2.233) respectively. And increases in HOMA2IR was associated with an increased risk of cardiovascular abnormalities, with an odds ratio of 1.412 (95%CI 1.162–1.717).

Comparison of the cluster-specific partitioned polygenic scores between normal and abnormal echocardiography findings in newly diagnosed patients with EOD

A total of 662 SNVs were included in the cluster-specific partitioned polygenic scores (pPS) calculations (Table S10 and S11). The relevant pPS of eight mechanistic clusters of each individual were calculated and analyzed in combination with carotid artery and echocardiographic abnormalities. The results showed that the pPS of the lipodystrophy cluster was higher in the early-onset diabetes group with carotid artery abnormalities than that in the group with normal carotid ultrasound findings, although the difference was not statistically significant (pPS: 0.02250 ± 0.0025 for abnormalities vs. 0.02195 ± 0.0021 for controls, $p = 0.062$). (Table 5) However, the pPS for lipodystrophy was significantly higher in patients with plaque formation compared to those without carotid artery abnormality (pPS: 0.02263 ± 0.0021 for abnormalities vs. 0.02195 ± 0.0021 for controls, $p = 0.048$). The pPS for lipodystrophy showed a trend toward linear correlation with TG and TCHOL levels ($R = 0.098$, $p = 0.086$ and $R = 0.101$, $p = 0.075$, respectively). Although no significant differences in pPS were observed between the normal and abnormal echocardiogram groups (Table S12), a significant linear correlation was found between the left anterior and posterior atrium diameter (LAAP/BSA) and the pPS for lipodystrophy after adjusting for age and gender ($R = 0.344$, $p < 0.001$).

Discussion

This study revealed that carotid artery abnormalities were present in 26.3% of patients, while echocardiographic abnormalities were observed in 20.0% of patients at the time of diagnosis with type 2 diabetes before the age of 40 years. The SIRD subtype exhibited a notably higher incidence rate of carotid artery abnormalities

Table 3 Echocardiographic characteristics of patients with early-onset newly diagnosed type 2 diabetes in cluster classification

	Total	SIDD	SIRD	MOD	MARD	*p* value
Sample n%	275	93	36	124	22	
BSA (m2)	2.03 ± 0.25	1.90 ± 0.19	2.08 ± 0.24	2.17 ± 0.21	1.79 ± 0.18	<0.001
Heart cavity dimensions						
IVSTd (cm)	0.89 (0.80,0.98)	0.83 (0.76,0.94)	0.90 (0.80,0.98)	0.92 (0.85,1.00)	0.80 (0.75,0.89)	<0.001
IVSTd/BSA (cm/m2)	0.43 (0.39,0.48)	0.44 (0.39,0.50)	0.44 (0.39,0.48)	0.42 (0.38,0.46)	0.46 (0.41,0.51)	0.119
LAAP (cm)	3.40 (3.10,3.64)	3.30 (3.02,3.50)	3.49 (3.27,3.76)	3.43 (3.21,3.71)	3.06 (2.95,3.33)	<0.001
LAAP/BSA (cm/m2)	1.67 ± 0.22	1.73 ± 0.21	1.70 ± 0.26	1.62 ± 0.21	1.75 ± 0.22	0.001
LVEDd (cm)	4.76 ± 0.45	4.62 ± 0.41	4.82 ± 0.45	4.88 ± 0.43	4.56 ± 0.45	<0.001
LVEDd/BSA (cm/m2)	2.35 ± 0.29	2.43 ± 0.29	2.34 ± 0.32	2.26 ± 0.23	2.58 ± 0.31	<0.001
LVEDs (cm)	2.99 (2.73,3.23)	2.88 (2.61,3.10)	3.03 (2.74,3.28)	3.10 (2.83,3.33)	2.80 (2.64,3.18)	<0.001
LVEDs/BSA (cm/m2)	1.48 ± 0.18	1.52 ± 0.17	1.48 ± 0.16	1.43 ± 0.17	1.64 ± 0.20	<0.001
LVPWTd (cm)	0.86 (0.78,0.94)	0.80 (0.75,0.90)	0.91 (0.79,0.98)	0.89 (0.80,0.95)	0.83 (0.71,0.95)	<0.001
LVPWTd/BSA (cm/m2)	0.42 (0.38,0.46)	0.42 (0.38,0.47)	0.43 (0.38,0.49)	0.41 (0.37,0.45)	0.49 (0.42,0.52)	<0.001
Vascular diameter						
Ao Diam (cm)	2.97 ± 0.36	2.95 ± 0.31	2.93 ± 0.33	3.06 ± 0.38	2.63 ± 0.26	<0.001
Ao Asc (cm)	2.91 ± 0.31	2.82 ± 0.24	2.92 ± 0.30	3.00 ± 0.33	2.80 ± 0.37	<0.001
MPAD (cm)	2.22 ± 0.23	2.17 ± 0.23	2.27 ± 0.14	2.26 ± 0.23	2.10 ± 0.24	0.003
LV volumes						
EDV (ml)	110.01 ± 23.39	100.43 ± 20.61	113.29 ± 21.99	118.08 ± 23.12	95.37 ± 17.79	<0.001
EDV/BSA (ml/m2)	53.98 ± 9.97	52.84 ± 10.53	55.45 ± 10.90	54.34 ± 9.33	54.04 ± 9.78	0.617
ESV (ml)	35.75 (27.84,44.04)	32.10 (25.42,40.60)	35.40 (28.16,43.69)	39.42 (31.60,45.90)	27.57 (23.98,39.07)	0.001
ESV/BSA (ml/m2)	17.63 (14.53,21.02)	17.22 (14.13,20.25)	17.23 (13.90,20.69)	17.99 (15.38,21.44)	16.24 (13.47,22.10)	0.861
LV geometry						
LVM (g)	142.44 ± 35.35	126.94 ± 33.01	150.71 ± 33.81	154.25 ± 33.02	122.73 ± 29.22	<0.001
LVMI (g/m2)	69.75 ± 15.23	66.63 ± 16.21	72.64 ± 16.17	71.24 ± 14.07	68.73 ± 14.76	0.107
LVHL	0.87 (0.80,0.95)	0.80 (0.76,0.91)	0.91 (0.80,0.96)	0.91 (0.85,0.97)	0.81 (0.74,0.91)	<0.001
RWT	0.35 (0.33,0.39)	0.35 (0.32,0.38)	0.38 (0.32,0.43)	0.36 (0.33,0.38)	0.36 (0.33,0.42)	0.237
Normal geometry, NG	83.5% (218/261)	85.7% (72/84)	63.9% (23/36)	89.2% (107/120)	76.2% (16/21)	0.005
Concentric remodeling, CR	14.9% (39/261)	13.1% (11/84)	27.8% (10/36)	10.8% (13/120)	23.8% (5/21)	
Concentric hypertrophy, CH	0.8% (2/261)	0.0% (0/84)	5.6%(2/36)	0.0% (0/120)	0.0% (0/21)	
Eccentric hypertrophy, EH	0.8% (2/261)	1.2% (1/84)	2.8% (1/36)	0.0% (0/120)	0.0% (0/21)	
Systolic function						
LVEF (%)	66.95 ± 5.05	66.93 ± 5.43	67.37 ± 5.34	66.72 ± 4.85	67.58 ± 4.22	0.841
Diastolic function						
MV Avel, A (cm/s)	64.68 (55.78,74.80)	61.60 (54.25,77.09)	65.35 (56.57,73.84)	65.98 (56.22,76.41)	61.28 (57.35,69.93)	0.464
MV Evel, E (cm/s)	77.40 (68.00,90.96)	78.89 (69.76,96.88)	76.66 (64.97,85.30)	77.00 (67.16,90.00)	79.35 (66.25,91.42)	0.224
E/A	1.26 ± 0.35	1.32 ± 0.33	1.19 ± 0.31	1.23 ± 0.37	1.27 ± 0.40	0.152
e'-s (cm/s)	8.60 (7.50,10.30)	9.50 (7.90,10.80)	8.30 (6.65,9.35)	8.30 (7.35,10.20)	8.30 (7.65,10.60)	0.058
E/e'	9.26 ± 2.25	9.01 ± 2.36	9.65 ± 2.15	9.37 ± 2.28	8.84 ± 1.69	0.545

1. Data were presented as means ± SD or medians (interquartile ranges) for skewed variables and proportions (numbers) for categorical variables

2. *P* values were for the one-way ANOVA, Kruskal Wallis or χ 2 analyses across the groups. A two-sided test with $p < 0.05$ was considered statistically significant

3. SIDD, severe insulin-deficient diabetes; SIRD, severe insulin resistant diabetes; MOD, mild obesity-related diabetes; MARD, mild age-related diabetes; BSA, Body surface area; LV, Left ventricular; IVSTd, Interventricular septum end diastolic thickness; LAAP, Left atrial anteroposterior diameter; LVEDd, Left ventricular end diastolic diameter; LVEDs, Left ventricular end systolic diameter; LVPWTd, Left ventricular posterior wall thickness in diastole; Ao Diam, Aortic root diameter; Ao Asc, Ascending aorta diameter; MPAD, Main pulmonary artery diameter; EDV, End diastolic volume; ESV, End systolic volume; LVM, Left ventricular mass; LVMI, Left ventricular mass index; LVHL, Left ventricular myocardial hypertrophy level; RWT, Relative wall thickness; LVEF, Left ventricular ejection fraction; MV Avel, A, Mitral valve peak A velocity; MV Evel, E, Mitral valve peak E velocity; E/A, Mitral valve E/A value; e'-s, Early diastolic mitral annular velocity at the interventricular septal annulus; E/e', Mitral septum E/e' value

(40.0%) and abnormal left ventricular geometry (36.1%). Both the SIRD and MOD subtype displayed a greater prevalence of LAE. The findings indicate that abnormalities in the carotid artery and heart structure are common in patients newly diagnosed with EOD and are primarily associated with obesity and insulin resistance.

Individuals with early-onset diabetes have a higher risk of cardiovascular mortality compared to those with late-onset diabetes [15]. This increased risk is attributed to prolonged exposure to the disease and the poorer metabolic phenotype observed in individuals with early-onset diabetes. The detrimental impact of these risk factors

Table 4 Regression model of carotid ultrasound and echocardiogram abnormalities

Abnormality	**Carotid artery abnormality**	
Multivariable model 1	Odds ratio (95%CI)	*p* value
Age	1.099 (1.026–1.178)	0.008
TCHOL	1.403 (1.136–1.731)	0.002
FCP	1.255 (1.023–1.540)	0.029
Multivariable model 2		
Age	1.104 (1.030–1.183)	0.005
LDL	1.419 (1.053–1.913)	0.021
FCP	1.247 (1.017–1.530)	0.034
Abnormality	**Left atrial enlargement**	
Multivariable model 3	Odds ratio (95%CI)	*p* value
BMI	1.136 (1.050–1.228)	0.002
Multivariable model 4		
FCP	1.781 (1.300-2.438)	<0.001
Multivariable model 5		
HOMA2IR	1.687 (1.274–2.233)	<0.001
Abnormality	**Cardiovascular abnormality**	
Multivariable model 6	Odds ratio (95%CI)	*p* value
HOMA2IR	1.412 (1.162–1.717)	0.002

1. Multivariable model 1 and 2 was adjusted for gender, SBP, DBP, smoking

2. Multivariable model 3, 4, 5 and 6 was adjusted for age, gender, SBP, DBP, smoking, TG, LDL, and HbA1c

3. Cardiovascular abnormality: patients with at least one carotid ultrasound or echocardiogram abnormality

4. SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; FINS, fasting serum insulin; FCP, fasting c-peptide; HbA1c, hemoglobin A1c; TCHOL, total cholesterol; LDL, low-density lipoprotein cholesterol; TG, triglycerides; HOMA2IR, Homeostatic Model Assessment of Insulin Resistance

extends beyond disease duration [16]. The TODAY and SEARCH studies, which are pivotal in early-onset diabetes research, found that young patients with an average disease duration of 10 years already exhibited structural abnormalities in the heart and reduced left ventricular diastolic function [7, 8]. However, the presence of cardiovascular changes at the time of diagnosis has not been previously explored. A key contribution of this study is the use of ultrasound screening to assess cardiovascular abnormalities in a newly diagnosed EOD cohort. The results showed that a significant proportion of patients had cardiac and carotid artery abnormalities. Pathological changes in the carotid vessels are closely linked to structural and functional alterations in the heart, with insulin resistance and obesity serving as primary risk factors. These findings underscore the importance of early screening for cardiovascular abnormalities in patients with EOD.

Atherosclerosis is the primary pathological process underlying cardiovascular disease. It can begin in early life, remaining latent for extended periods without obvious clinical symptoms, and is predominantly concentrated in the peripheral arteries and carotid arteries [17]. The most commonly detected change in atherosclerosis is the thickening of the carotid intima. In this study, the detection rate of carotid intima-media thickening was 19.1% (56/293) in patients newly-diagnosed with early-onset type 2 diabetes. Carotid intima-media thickness (cIMT), measured using carotid ultrasound, serves as a non-invasive evaluation index. The Mannheim carotid intima-media thickness consensus indicates that, in clinical trials, intima-media thickness can be used as a surrogate endpoint to evaluate the efficacy of cardiovascular risk factor modification [18]. Other studies have reported similar findings in patients with early-onset type 2 diabetes. For example, a study comparing cIMT between 14 and 30 years old normal controls and newly diagnosed EOD patients found significantly increased cIMT in the latter group, with an odds ratio of 3.93 (95% CI 1.90–6.07, $P = 0.001$) [19]. Another study also found that patients with T2DM had a higher mean cIMT value than the control group, but there was no difference in cIMT

Table 5 Comparison of cluster-specific pPS between normal and carotid artery abnormality in newly diagnosed EOD patients

Cluster	**Normal**	**Carotid artery abnormality**	***p* value**	**Normal**	**Plaque formation**	***p* value**
n	206	75	281	206	47	253
Lipodystrophy	0.02195 ± 0.0021	0.02250 ± 0.0025	**0.062**	0.02195 ± 0.0021	0.02263 ± 0.0021	**0.048**
Obesity	0.01317 ± 0.0006	0.01314 ± 0.0005	0.669	0.01317 ± 0.0006	0.01323 ± 0.0006	0.56
Metabolic_syndrome	0.01883 ± 0.0011	0.01859 ± 0.0009	0.084	0.01883 ± 0.0011	0.01875 ± 0.0009	0.641
Body_fat.	0.01490 ± 0.0008	0.01490 ± 0.0008	0.968	0.01490 ± 0.0008	0.01479 ± 0.0007	0.395
Liver_lipid_metabolism	0.02309 ± 0.0070	0.02399 ± 0.0059	0.318	0.02309 ± 0.0070	0.02377 ± 0.0058	0.537
Beta_cell_+PI	0.02535 ± 0.0033	0.02555 ± 0.0032	0.655	0.02535 ± 0.0033	0.02512 ± 0.0034	0.666
Beta_cell_-PI	0.02660 ± 0.0019	0.02642 ± 0.0016	0.494	0.02660 ± 0.0019	0.02663 ± 0.0014	0.907
Residual_glycaemic	0.01518 ± 0.0007	0.01521 ± 0.0007	0.774	0.01518 ± 0.0007	0.01537 ± 0.0006	0.104
Total_pPS	0.01699 ± 0.0004	0.01698 ± 0.0004	0.850	0.01699 ± 0.0004	0.01704 ± 0.0004	0.519

1. Data were presented as means ± SD for continuous variables

2. P values were for the t-test analyses across the groups. A two-sided test with $p < 0.05$ was considered statistically significant. The p value of pPS for lipodystrophy between normal and carotid artery abnormality was presented in bold

3. Total_pPS means weighted pPS for 662 type 2 diabetes-associated loci

4. Abbreviation: pPS, the cluster-specific partitioned polygenic scores; PI, proinsulin

between the early-onset and late-onset diabetes groups ($p = 0.464$) [20].

Carotid plaque formation, a manifestation of intimal thickening, further increases the cardiovascular risk [21]. In this study, the detection rate of carotid plaques in patients with early onset diabetes was 16.0% (47/293). Another study found that atherosclerotic plaque detection rates were nearly twice as high in patients with early-onset T2DM compared to those with late-onset T2DM (10.4% vs. 6.1%, respectively) [20]. These results highlight the prevalence of carotid intimal thickening and abnormal plaque formation in patients with early onset diabetes, emphasizing the importance of early screening for carotid artery abnormalities.

Cluster classification revealed that patients with SIRD subtype had a higher incidence of carotid artery abnormalities, including intima-media thickening and plaque formation. After adjusting for relevant risk factors, fasting C-peptide levels were significantly associated with a 1.247-fold increase in the risk of carotid artery abnormalities. These findings suggest that insulin resistance is an important risk factor for atherosclerosis. Consistent with this, the insulin Resistance Atherosclerosis Study (IRAS), which used cIMT as an indicator of atherosclerosis, found a significant negative association between insulin sensitivity and cIMT in a study cohort of 457 Hispanics and 542 non-Hispanic whites [22]. Given the challenges of clinically evaluating insulin resistance, our clustering classification method can identify patients with a greater risk of carotid abnormalities and perform early screening of SIRD subtypes by ultrasound.

Echocardiographic abnormalities were detected in 20% of the patients with early-onset diabetes, including LAE in 13.5% and abnormal left ventricular geometry in 16.5%. Left atrial enlargement is a morphological variation of the left atrium and a pathophysiological response to volume and pressure overload, resulting in impaired systolic and diastolic function of the left ventricle [23]. The PAMELA Study monitored 1,045 individuals aged 25–74 years from the general population over 10 years, and identified 123 new cases of LAE (11.8% prevalence) among them [24]. In this study, the prevalence of LAE in patients with early-onset type 2 diabetes was 13.5%. LAE is considered a sensitive indicator of left ventricular preload, which is primarily caused by hypertension-induced pressure overload, obesity-related volume overload, or a combination of both [25]. Studies have demonstrated that LAE can independently predict the development of clinically significant cardiovascular disease and heart failure [26–28]. The presence of LAE in patients with early-onset diabetes may be an early phenomenon, highlighting the need for early management of relevant cardiovascular risk factors.

Cluster classification findings demonstrated that the SIRD subtype exhibited a high detection rate of LAE (16.7%), with elevated fasting C-peptide levels and HOMA-IR identified as primary risk factors. These results indicate that insulin resistance is a major risk factor for LAE. During the progression of insulin resistance, certain metabolic changes may contribute to the development of cardiovascular disease [29, 30]. The Framingham Heart Study found that the covariate-adjusted LA size increased across HOMA-IR quartiles in both men and women [31]. LAE has also been observed in children and adolescents and is associated with insulin resistance and abdominal obesity [32].

Additionally, patients with the MOD subtype exhibited a higher proportion of LAE (18.5%, 23/124), with BMI identified as a risk factors. Few mechanistic studies have explored the relationship between obesity and left atrial size or evaluated whether this enlargement should be considered pathological. The left atrial volume of healthy obese subjects (mean BMI of 37.2 kg/m2) was approximately 50% larger than that of non-obese controls of the same age and sex (mean BMI of 26.2 kg/m2) 33. The PAMELA Study found that BMI was an independent predictor of LAE during a 10-year follow-up period [24]. These findings suggest that obesity is a risk factor for LAE in both patients with and without diabetes.

In addition to LAE, this study found a high proportion of abnormal left ventricular geometry (16.5%) in patients with early-onset diabetes. Ventricular remodelling, which results in abnormal left ventricular geometry, is a progressive pathological change in the structure and shape of the ventricle caused by various injuries [34]. Abnormal ventricular remodelling is a key pathological basis of heart failure, involving changes in ventricular mass, volume, and geometry. This represents an adaptive response of the heart to injury. Multiple studies have demonstrated that diabetes mellitus and impaired fasting glucose (IFG) are associated with early changes in left ventricular geometry and function in adolescents and young adults, which are generally linked to future cardiovascular disease risk [7, 8, 35, 36]. In this study, patients with the SIRD subtype had the highest proportion of abnormal left ventricular geometry, with left ventricular remodelling of up to 36.1%. The Coronary Artery Risk Development in Young Adults (CARDIA) cross-sectional study explored how long-term exposure to abnormal blood glucose and insulin resistance in young adults leads to cardiac dysfunction and remodelling in middle-aged adults. Over 25 years of follow-up, high insulin resistance in early adulthood was found to adversely affect left ventricular remodelling and function in middle age [37]. These results indicate that abnormal glucose metabolism can have adverse effects on target organs early in life, with insulin resistance playing a key role in its pathogenesis.

An analysis from the Framingham Heart Study unequivocally demonstrated the prognostic value of echocardiography in detecting left ventricular remodelling or left ventricular hypertrophy [38]. Significant differences in cardiac function, haemodynamics, and clinical outcomes exist between different ventricular remodelling modes [39]. In this study, concentric remodelling was observed in 27.8% of patients with the SIRD subtype, while 5.6% exhibited concentric hypertrophy and 2.8% had eccentric hypertrophy. The earliest change in left ventricular pressure overload is an increase in relative wall thickness (RWT). When left ventricular mass (LVM) is normal, this manifests as concentric remodelling; when LVM is increased, it manifests as concentric hypertrophy to maintain normal left ventricular systolic stress. Eccentric left ventricular remodelling is commonly observed in patients with volume overload or systolic heart failure [40]. Thus, the left ventricular remodelling observed in patients with early-onset diabetes primarily represents early changes, with left ventricular systolic function remaining compensatory at this stage. These results highlight the importance of early screening for cardiovascular abnormalities and suggest that early intervention should be implemented in patients with early-onset diabetes associated with insulin resistance.

Genome-wide association analysis related to clustering can provide insights into the etiological heterogeneity of T2D across different populations and help analyse the pathophysiological trajectory of disease occurrence and development from a genetic perspective. This approach indicates that disease progression and genetic burden are linked to specific biological pathways. Studies have confirmed clusters of lipodystrophy in which T2D risk alleles are associated with elevated fasting insulin, WHR, blood pressure, and triglycerides and are associated with lower body fat percentage and HDL cholesterol [41, 42]. Genetic mutation-associated lipodystrophy mediates severe insulin resistance owing to lipid dysfunction or abnormal fat distribution [43]. This study found that the pPS for the lipodystrophy cluster was higher in patients with early-onset diabetes and existing carotid artery abnormalities, particularly in those with carotid plaques. Fat-related insulin resistance may play a potential role in disease development. Although the effect sizes of the cluster-specific components of pPS segmented by genome-wide association studies (GWAS) were small, they may stimulate subsequent pathophysiological processes. These findings are consistent with the results of our regression analysis and further demonstrates that insulin resistance is a key risk factor for diabetes-related cardiovascular abnormalities.

The pathophysiological mechanisms linking insulin resistance to cardiovascular abnormalities include hypertension, endothelial dysfunction, dyslipidaemia, inflammation, and other factors [44, 45]. Insulin resistance promotes platelet aggregation by reducing nitric oxide production within endothelial cells while increasing the release of pro-coagulant factors, thereby contributing to endothelial cell dysfunction [46]. Furthermore, insulin resistance induces changes in myocardial metabolic substrates. The metabolic flexibility of the myocardium, which is essential for meeting high metabolic demands, is compromised under conditions of insulin resistance, resulting in elevated lipid oxidation and diminished glucose oxidation [47]. Additionally, insulin resistance adversely affects diastolic function by impairing the calcium handling capabilities of the myocardium [48].

In terms of treatment, more rigorous lifestyle interventions are recommended for patients with early-onset diabetes, combined with weight management, control of blood glucose and lipid homeostasis, and strict blood pressure control. Lifestyle and behavioural interventions are the cornerstones of primary prevention of T2DM and CVD. The 5-year results from the Diabetes Remission Clinical Trial (DiRECT) suggest that rigorous weight management may help delay or avoid the clinical complications of diabetes [49]. Medications with proven cardiovascular protective effect, such as sodium-dependent glucose transporter 2 inhibitors (SGLT2i) or glucagon-like peptide-1 receptor agonist (GLP-1RA) should be prioritised [50, 51]. At the same time, owing to the heterogeneity of type 2 diabetes, early combination therapy should be considered to better address the diverse pathogenic mechanisms of the disease [52]. For personalised diabetes management, individualised diagnosis and treatment of early-onset diabetes are being explored worldwide, as seen in the ongoing PRISM study [53].

This study has some limitations. First, as a cross-sectional study with a limited sample size, it lacks longitudinal data to characterise the progression of early-stage diabetes and only reflects the characteristics at the time of diagnosis. The validation and generalisability of the findings require confirmation through larger, multiregional cohort studies. Second, the study lacks data from "normal healthy control with age and gender matching" and "newly-onset DM patients with age > 40 years old". Consequently, cardiovascular abnormalities in patients with early-onset newly diagnosed diabetes cannot be directly compared with those in healthy controls or individuals with late-onset diabetes. Third, we assessed left atrial enlargement solely by measuring the left anteroposterior and posterior diameters (LAAP), without considering left atrial volume index. This approach may have led to an underestimation of the actual LA size of the left atrium. However, LAAP has demonstrated a strong positive linear correlation with left atrial volume index and remains widely used as a reliable measurement in clinical

practice and research settings owing to its repeatability [54, 55]. Fourth, although the study adjusted for well-known cardiovascular risk factors, residual confounders, such as underlying inflammatory factors (e.g. highly sensitive C-reactive protein), adiponectin levels, and leptin levels, may still affect the results. Finally, because the discovery dataset comprised a multi-ethnic sample, some SNVs were absent from the loci information detected by the ASAMD chip used in this study; consequently, these loci were not incorporated into the pPS calculation.

Conclusion

The findings of this study demonstrated that cardiovascular abnormalities are prevalent in patients with early-onset type 2 diabetes at the time of diagnosis. Patients with obesity (MOD) and insulin resistance (SIRD) should be closely monitored for the potential development of cardiac and carotid vascular abnormalities. Cluster classification based on clinical characteristics can improve the identification of individuals at higher risk of cardiovascular complications, facilitating early intervention and targeted management strategies.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-025-02665-0 .

Supplementary Material 1

Supplementary Material 2

Acknowledgements

We would like to extend our sincere thanks to the participants of this study who volunteered their time to participate in the research. We would also like to thank the clinicians and researchers of our partner hospitals for their assistance in patient enrollment and clinical sample collection.

Author contributions

H.L. and Q.R. participated in patient enrollment, analyzed clinical data and composed scholarly article. W.L., R.Z., XT.Z., SM.Z. and YY.L. were responsible for patient enrollment. W.D., QP.W., L.Q., YF.L., WB.W., LY.Z. participated in multi-center patient inclusion and project coordination. PK.Z., CC.G., L.L., YT.L., TH.B., CC.Y. were responsible for receiving and storing clinical samples, recording and organizing relevant data. LL.H., YA.W., CX.L., DJ.H., YJ.Z., Y.X., F.W. were responsible for receiving multi-center patient' clinical samples, recording relevant data. XQ.W., F.Z., SQ.G., WJ.Y. provided assistance for outpatient enrollment. LN.J. and XY.H. were tasked with the application for research projects and the strategic planning of overall research progress. All authors have given their consent for the submitted manuscript.

Funding

This study was supported by the Beijing Municipal Science and Technology committee Fund (Z201100005520012).

Availability of data and materials

Data supporting the results of this study are available on request from the corresponding authors. The data cannot be made public because of privacy or ethical restrictions.

Declarations

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Endocrinology, Peking University People's Hospital, Beijing 100044, People's Republic of China
[2]Department of Endocrinology, Beijing Jishuitan Hospital, Beijing 100035, People's Republic of China
[3]Department of Endocrinology, Bejing Fangshan District Liangxiang Hospital, Beijing 102400, People's Republic of China
[4]Department of Endocrinology, Bejing Yanhua Hospital, Beijing 102500, People's Republic of China
[5]Department of Endocrinology, Beijing Pinggu Hospital, Beijing 101299, People's Republic of China
[6]Department of Endocrinology, Beijing Univesity Shougang Hospital, Beijing 100144, People's Republic of China
[7]Department of Endocrinology, Capital Medical University Beijing Tiantan Hospital, Beijing 100050, People's Republic of China
[8]Peking University Diabetes Centre, Beijing 100191, People's Republic of China
[9]Department of Endocrinology and Metabolism, Peking University People's Hospital, No. 11, Xizhimen South Street, Xicheng District, Beijing 100044, People's Republic of China

Received: 31 December 2024 / Accepted: 25 February 2025
Published online: 26 March 2025

References

1. Magliano DJ, Sacre JW, Harding JL, Gregg EW, Zimmet PZ, Shaw JE. Young-onset type 2 diabetes mellitus - implications for morbidity and mortality. Nat Rev Endocrinol. 2020;16:321–31. https://doi.org/10.1038/s41574-020-0334-z.
2. Wang L, Peng W, Zhao Z, Zhang M, Shi Z, Song Z, Zhang X, Li C, Huang Z, Sun X, et al. Prevalence and treatment of diabetes in China, 2013–2018. JAMA. 2021;326:2498–506. https://doi.org/10.1001/jama.2021.22208.
3. Chan JC, Lau ES, Luk AO, Cheung KK, Kong AP, Yu LW, Choi KC, Chow FC, Ozaki R, Brown N, et al. Premature mortality and comorbidities in young-onset diabetes: a 7-year prospective analysis. Am J Med. 2014;127:616–24. https://doi.org/10.1016/j.amjmed.2014.03.018.
4. Kim SM, Lee G, Choi S, Kim K, Jeong SM, Son JS, Yun JM, Kim SG, Hwang SS, Park SY, et al. Association of early-onset diabetes, prediabetes and early glycaemic recovery with the risk of all-cause and cardiovascular mortality. Diabetologia. 2020;63:2305–14. https://doi.org/10.1007/s00125-020-05252-y.
5. Hillier TA, Pedula KL. Complications in young adults with early-onset type 2 diabetes: losing the relative protection of youth. Diabetes Care. 2003;26:2999–3005. https://doi.org/10.2337/diacare.26.11.2999.
6. Huo X, Gao L, Guo L, Xu W, Wang W, Zhi X, Li L, Ren Y, Qi X, Sun Z, et al. Risk of non-fatal cardiovascular diseases in early-onset versus late-onset type 2 diabetes in China: a cross-sectional study. Lancet Diabetes Endocrinol. 2016;4:115–24. https://doi.org/10.1016/S2213-8587(15)00508-2.
7. Group TS. Longitudinal changes in cardiac structure and function from adolescence to young adulthood in participants with type 2 diabetes mellitus: the TODAY follow-up study. Circ Heart Fail. 2020;13:e006685. https://doi.org/10.1161/CIRCHEARTFAILURE.119.006685.
8. Shah AS, Isom S, Dabelea D, D'Agostino R Jr., Dolan LM, Wagenknecht L, Imperatore G, Saydah S, Liese AD, Lawrence JM, et al. A cross sectional study to compare cardiac structure and diastolic function in adolescents and young adults with youth-onset type 1 and type 2 diabetes: the SEARCH for diabetes in youth study. Cardiovasc Diabetol. 2021;20:136. https://doi.org/10.1186/s12933-021-01328-0.
9. Gyldenkerne C, Kahlert J, Thrane PG, Olesen KKW, Mortensen MB, Sorensen HT, Thomsen RW, Maeng M. 2-Fold more cardiovascular disease events decades before type 2 diabetes diagnosis A nationwide registry study. J Am Coll Cardiol. 2024;84. https://doi.org/10.1016/j.jacc.2024.06.050.
10. Tan Y, Zhang ZG, Zheng C, Wintergerst KA, Keller BB, Cai L. Mechanisms of diabetic cardiomyopathy and potential therapeutic strategies: preclinical and clinical evidence. Nat Rev Cardiol. 2020;17:585–607. https://doi.org/10.1038/s41569-020-0339-2.

11. Jia GH, DeMarco VG, Sowers JR. Insulin resistance and hyperinsulinaemia in diabetic cardiomyopathy. Nat Reviews Endocrinol. 2016;12:144–53. https://doi.org/10.1038/nrendo.2015.216.
12. Aroda VR, Taub PR, Stanton AM. Diabetes with cardiomyopathy at the juncture of knowledge and prevention. J Am Coll Cardiol. 2021;78:1599–602. https://doi.org/10.1016/j.jacc.2021.08.026.
13. Heather LC, Gopal K, Srnic N, Ussher JR. Redefining diabetic cardiomyopathy: perturbations in substrate metabolism at the heart of its pathology. Diabetes. 2024;73:659–70. https://doi.org/10.2337/dbi23-0019.
14. Ahlqvist E, Storm P, Karajamaki A, Martinell M, Dorkhan M, Carlsson A, Vikman P, Prasad RB, Aly DM, Almgren P, et al. Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables. Lancet Diabetes Endocrinol. 2018;6:361–9. https://doi.org/10.1016/S2213-8587(18)30051-2.
15. Echouffo-Tcheugui JB, Niiranen TJ, McCabe EL, Henglin M, Jain M, Vasan RS, Larson MG, Cheng S. An Early-Onset subgroup of type 2 diabetes: a multigenerational, prospective analysis in the Framingham heart study. Diabetes Care. 2020;43:3086–93. https://doi.org/10.2337/dc19-1758.
16. Vijayakumar G, Sreehari GK, Vijayakumar A, Jaleel A. Distinct predictors and comorbidities in early onset type 2 diabetes mellitus among Asian Indians. Metab Syndr Relat Disord. 2017;15:458–64. https://doi.org/10.1089/met.2017.0047.
17. Weber C, Noels H. Atherosclerosis: current pathogenesis and therapeutic options. Nat Med. 2011;17:1410–22. https://doi.org/10.1038/nm.2538.
18. Touboul PJ, Hennerici MG, Meairs S, Adams H, Amarenco P, Bornstein N, Csiba L, Desvarieux M, Ebrahim S, Hernandez Hernandez R et al. Mannheim carotid intima-media thickness and plaque consensus (2004-2006-2011). An update on behalf of the advisory board of the 3rd, 4th and 5th watching the risk symposia, at the 13th, 15th and 20th European Stroke Conferences, Mannheim, Germany, 2004, Brussels, Belgium, 2006, and Hamburg, Germany, 2011. *Cerebrovasc Dis*. 2012;34:290–296. https://doi.org/10.1159/000343145
19. Gu W, Huang Y, Zhang Y, Hong J, Liu Y, Zhan W, Ning G, Wang W. Adolescents and young adults with newly diagnosed type 2 diabetes demonstrate greater carotid intima-media thickness than those with type 1 diabetes. Diabet Med. 2014;31:84–91. https://doi.org/10.1111/dme.12335.
20. Contreras-Rodriguez A, Gomez-Diaz RA, Tanus-Hajj J, Talavera JO, Mondragon-Gonzalez R, Wacher NH. Carotid intima-media thickness, ankle-arm index, and inflammation profile in Mexican patients with early and late onset type 2 diabetes. Rev Invest Clin. 2015;67:240–9.
21. Johri AM, Nambi V, Naqvi TZ, Feinstein SB, Kim ESH, Park MM, Becher H, Sillesen H. Recommendations for the assessment of carotid arterial plaque by ultrasound for the characterization of atherosclerosis and evaluation of cardiovascular risk: from the American society of echocardiography. J Am Soc Echocardiogr. 2020;33:917–33. https://doi.org/10.1016/j.echo.2020.04.021.
22. Howard G, O'Leary DH, Zaccaro D, Haffner S, Rewers M, Hamman R, Selby JV, Saad MF, Savage P, Bergman R. Insulin sensitivity and atherosclerosis. The insulin resistance atherosclerosis study (IRAS) investigators. Circulation. 1996;93:1809–17. https://doi.org/10.1161/01.cir.93.10.1809.
23. Benjamin EJ, D'Agostino RB, Belanger AJ, Wolf PA, Levy D. Left atrial size and the risk of stroke and death. The Framingham heart study. Circulation. 1995;92:835–41. https://doi.org/10.1161/01.cir.92.4.835.
24. Bombelli M, Cuspidi C, Facchetti R, Sala C, Tadic M, Brambilla G, Re A, Villa P, Grassi G, Mancia G. New-onset left atrial enlargement in a general population. J Hypertens. 2016;34:1838–45. https://doi.org/10.1097/HJH.0000000000001022.
25. Stritzke J, Markus MR, Duderstadt S, Lieb W, Luchner A, Doring A, Keil U, Hense HW, Schunkert H, Investigators MK. The aging process of the heart: obesity is the main risk factor for left atrial enlargement during aging the MONICA/KORA (monitoring of trends and determinations in cardiovascular disease/cooperative research in the region of Augsburg) study. J Am Coll Cardiol. 2009;54:1982–9. https://doi.org/10.1016/j.jacc.2009.07.034.
26. Appleton CP, Galloway JM, Gonzalez MS, Gaballa M, Basnight MA. Estimation of left ventricular filling pressures using two-dimensional and doppler echocardiography in adult patients with cardiac disease. Additional value of analyzing left atrial size, left atrial ejection fraction and the difference in duration of pulmonary venous and mitral flow velocity at atrial contraction. J Am Coll Cardiol. 1993;22:1972–82. https://doi.org/10.1016/0735-1097(93)90787-2.
27. Essayagh B, Antoine C, Benfari G, Messika-Zeitoun D, Michelena H, Le Tourneau T, Mankad S, Tribouilloy CM, Thapa P, Enriquez-Sarano M. Prognostic implications of left atrial enlargement in degenerative mitral regurgitation. J Am Coll Cardiol. 2019;74:858–70. https://doi.org/10.1016/j.jacc.2019.06.032.
28. Wozakowska-Kaplon B. Changes in left atrial size in patients with persistent atrial fibrillation: a prospective echocardiographic study with a 5-year follow-up period. Int J Cardiol. 2005;101:47–52. https://doi.org/10.1016/j.ijcard.2004.03.010.
29. Hill MA, Yang Y, Zhang L, Sun Z, Jia G, Parrish AR, Sowers JR. Insulin resistance, cardiovascular stiffening and cardiovascular disease. Metabolism. 2021;119:154766. https://doi.org/10.1016/j.metabol.2021.154766.
30. Ormazabal V, Nair S, Elfeky O, Aguayo C, Salomon C, Zuniga FA. Association between insulin resistance and the development of cardiovascular disease. Cardiovasc Diabetol. 2018;17:122. https://doi.org/10.1186/s12933-018-0762-4.
31. Rutter MK, Parise H, Benjamin EJ, Levy D, Larson MG, Meigs JB, Nesto RW, Wilson PW, Vasan RS. Impact of glucose intolerance and insulin resistance on cardiac structure and function: sex-related differences in the Framingham heart study. Circulation. 2003;107:448–54. https://doi.org/10.1161/01.cir.0000045671.62860.98.
32. Hirschler V, Acebo HL, Fernandez GB, de Lujan Calcagno M, Gonzalez C, Jadzinsky M. Influence of obesity and insulin resistance on left atrial size in children. Pediatr Diabetes. 2006;7:39–44. https://doi.org/10.1111/j.1399-543X.2006.00139.x.
33. Aiad NN, Hearon C Jr., Hieda M, Dias K, Levine BD, Sarma S. Mechanisms of left atrial enlargement in obesity. Am J Cardiol. 2019;124:442–7. https://doi.org/10.1016/j.amjcard.2019.04.043.
34. Meng T, Wang P, Ding J, Du R, Gao J, Li A, Yu S, Liu J, Lu X, He Q. Global research trends on ventricular remodeling: a bibliometric analysis from 2012 to 2022. Curr Probl Cardiol. 2022;47:101332. https://doi.org/10.1016/j.cpcardiol.2022.101332.
35. De Marco M, de Simone G, Roman MJ, Chinali M, Lee ET, Calhoun D, Howard BV, Devereux RB. Cardiac geometry and function in diabetic or prediabetic adolescents and young adults: the strong heart study. Diabetes Care. 2011;34:2300–5. https://doi.org/10.2337/dc11-0191.
36. Shah AS, Khoury PR, Dolan LM, Ippisch HM, Urbina EM, Daniels SR, Kimball TR. The effects of obesity and type 2 diabetes mellitus on cardiac structure and function in adolescents and young adults. Diabetologia. 2011;54:722–30. https://doi.org/10.1007/s00125-010-1974-7.
37. Kishi S, Gidding SS, Reis JP, Colangelo LA, Venkatesh BA, Armstrong AC, Isogawa A, Lewis CE, Wu C, Jacobs DR Jr., et al. Association of insulin resistance and glycemic metabolic abnormalities with LV structure and function in middle age: the CARDIA study. JACC Cardiovasc Imaging. 2017;10:105–14. https://doi.org/10.1016/j.jcmg.2016.02.033.
38. Levy D, Murabito JM, Anderson KM, Christiansen JC, Castelli WP. Echocardiographic left ventricular hypertrophy: clinical characteristics. The Framingham heart study. Clin Exp Hypertens A. 1992;14:85–97. https://doi.org/10.3109/10641969209036173.
39. Gaasch WH, Zile MR. Left ventricular structural remodeling in health and disease: with special emphasis on volume, mass, and geometry. J Am Coll Cardiol. 2011;58:1733–40. https://doi.org/10.1016/j.jacc.2011.07.022.
40. Triposkiadis F, Giamouzis G, Boudoulas KD, Karagiannis G, Skoularigis J, Boudoulas H, Parissis J. Left ventricular geometry as a major determinant of left ventricular ejection fraction: physiological considerations and clinical implications. Eur J Heart Fail. 2018;20:436–44. https://doi.org/10.1002/ejhf.1055.
41. Kim H, Westerman KE, Smith K, Chiou J, Cole JB, Majarian T, von Grotthuss M, Kwak SH, Kim J, Mercader JM, et al. High-throughput genetic clustering of type 2 diabetes loci reveals heterogeneous mechanistic pathways of metabolic disease. Diabetologia. 2023;66:495–507. https://doi.org/10.1007/s00125-022-05848-6.
42. Suzuki K, Hatzikotoulas K, Southam L, Taylor HJ, Yin X, Lorenz KM, Mandla R, Huerta-Chagoya A, Melloni GEM, Kanoni S, et al. Genetic drivers of heterogeneity in type 2 diabetes pathophysiology. Nature. 2024;627:347–57. https://doi.org/10.1038/s41586-024-07019-6.
43. Yaghootkar H, Scott RA, White CC, Zhang W, Speliotes E, Munroe PB, Ehret GB, Bis JC, Fox CS, Walker M, et al. Genetic evidence for a normal-weight metabolically obese phenotype linking insulin resistance, hypertension, coronary artery disease, and type 2 diabetes. Diabetes. 2014;63:4369–77. https://doi.org/10.2337/db14-0318.
44. Fan YJ, Yan ZP, Li TT, Li AL, Fan XB, Qi ZW, Zhang JP. Primordial drivers of diabetes heart disease: comprehensive insights into insulin resistance. Diabetes Metab J. 2024;48:19–36. https://doi.org/10.4093/dmj.2023.0110.
45. Zavaroni I, Bonora E, Pagliara M, Dallaglio E, Luchetti L, Buonanno G, Bonati PA, Bergonzani M, Gnudi L, Passeri M, et al. Risk-factors for coronary-artery disease in healthy-persons with hyperinsulinemia and normal

glucose-tolerance. New Engl J Med. 1989;320:702–6. https://doi.org/10.1056/Nejm198903163201105.
46. Wang CCL, Gurevich I, Draznin B. Insulin affects vascular smooth muscle cell phenotype and migration via distinct signaling pathways. Diabetes. 2003;52:2562–9. https://doi.org/10.2337/diabetes.52.10.2562.
47. Stanley WC, Recchia FA, Lopaschuk GD. Myocardial substrate metabolism in the normal and failing heart. Physiol Rev. 2005;85:1093–129. https://doi.org/10.1152/physrev.00006.2004.
48. Quan C, Du Q, Li M, Wang RZ, Ouyang Q, Su S, Zhu SS, Chen QL, Sheng Y, Chen L et al. A PKB-SPEG signaling nexus links insulin resistance with diabetic cardiomyopathy by regulating calcium homeostasis. *Nat Commun*. 2020;11. doi: ARTN 2186. 1038/s41467-020-16116-9.
49. Lean MEJ, Leslie WS, Barnes AC. 5-year follow-up of the randomised diabetes remission clinical trial (DiRECT) of continued support for weight loss maintenance in the UK: an extension study (12, Pg 233, 2024). Lancet Diabetes Endo. 2024;12:e17–17. https://doi.org/10.1016/S2213-8587(24)00128-1.
50. Kutz A, Kim DH, Wexler DJ, Liu J, Schneeweiss S, Glynn RJ, Patorno E. Comparative cardiovascular effectiveness and safety of SGLT-2 inhibitors, GLP-1 receptor agonists, and DPP-4 inhibitors according to frailty in type 2 diabetes. Diabetes Care. 2023;46:2004–14. https://doi.org/10.2337/dc23-0671.
51. Zelniker TA, Braunwald E. Mechanisms of cardiorenal effects of Sodium-Glucose cotransporter 2 inhibitors: JACC State-of-the-Art review. J Am Coll Cardiol. 2020;75:422–34. https://doi.org/10.1016/j.jacc.2019.11.031.
52. ElSayed NA, Aleppo G, Bannuru RR, Bruemmer D, Collins BS, Ekhlaspour L, Gaglia JL, Hilliard ME, Johnson EL, Khunti K, et al. 2. Diagnosis and classification of diabetes. Diabetes Care. 2024;47:S20–42. https://doi.org/10.2337/dc24-S002.
53. O CK, Fan YN, Fan BQ, Lim C, Lau ESH, Tsoi STF, Wan R, Lai WY, Poon EWM, Ho J et al. Precision medicine to redefine insulin secretion and Monogenic Diabetes-Randomized controlled trial (PRISM-RCT) in Chinese patients with young-onset diabetes: design, methods and baseline characteristics. Bmj Open Diab Res Ca. 2024;12. doi: ARTN e004120. 1136/bmjdrc-2024-004120.
54. Barbieri A, Bursi F, Zanasi V, Veronesi B, Cioni E, Modena MG. Left atrium reclassified: application of the American society of Echocardiography/European society of cardiology cutoffs to unselected outpatients referred to the echocardiography laboratory. J Am Soc Echocardiogr. 2008;21:433–8. https://doi.org/10.1016/j.echo.2007.08.025.
55. Rusinaru D, Tribouilloy C, Grigioni F, Avierinos JF, Suri RM, Barbieri A, Szymanski C, Ferlito M, Michelena H, Tafanelli L, et al. Left atrial size is a potent predictor of mortality in mitral regurgitation due to flail leaflets: results from a large international multicenter study. Circ Cardiovasc Imaging. 2011;4:473–81. https://doi.org/10.1161/CIRCIMAGING.110.961011.

Publisher's note