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Quantifying the individual disease duration-adjusted burden of complications in persons with type 2 diabetes

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ABSTRACT

Background and aims: The burden of type 2 diabetes (T2D)-related complications (DRCs) shows marked inter-individual variability. We aimed to develop a method to estimate the burden and rate of accumulation of complications in relation to disease duration using standard clinical assessments.
Methods and results: We analyzed the clinical records of 1302 subjects from four diabetes clinics who underwent comprehensive screening for macrovascular and microvascular complications. Overt and subclinical complications were defined using standardized criteria and assigned 3 and 1 point, respectively. Microvascular and macrovascular complications tended to cluster (chi2 $p < 0.0001$). The global DRC score increased with diabetes duration ($r = 0.34$, $p = 1*10\text{-}21$), and regression analysis indicated a theoretical score of zero approximately 13 years before diagnosis. Assuming −13 years as intercept, we calculated the individual rate of complication accrual and classified patients into tertiles corresponding to low (LB), moderate (MB), and high burden (HB) groups. The mean accrual rates were 0.14 [95%CI:0.13-0.16], 0.88 [95%CI:0.85-0.91], and 2.31 [95%CI: 2.24-2.39] points per 10 years, respectively. According to these models, the first subclinical complication was expected to occur approximately 65 years after diagnosis in the lowest tertile and 2 and 9 years before diagnosis in the moderate and highest tertiles, respectively. The three groups showed only marginal differences in age, diabetes duration, and HbA1c.
Conclusion: Using real-world data, we identified thresholds that allow classification of patients with T2D according to the rate of accrual of complications relative to disease duration. This framework may facilitate research aimed at identifying biological determinants of variability in complication development.
Trial registration: NCT07250607, registered on 23/11/2025.

1. Introduction

The chronic clinical complications of type 2 diabetes (T2D) damage multiple systems, tissues and organs, representing a serious threat for the quality of life [1] and a major burden for the health care system [2]. Their prevention is, in fact, at the center of the guidelines for the treatment of T2D [3], which emphasize the importance of an aggressive control of all the known risk factors for micro- (μVC) and macrovascular (MaVC) complications, as well as the use of drugs with proven benefit.

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List of abbreviations

ACR – Albumin-to-Creatinine Ratio
ADA – American Diabetes Association
ASCVD – Atherosclerotic Cardiovascular Disease
CAC – Coronary Artery Calcium
CHD – Coronary Heart Disease
CKD – Chronic Kidney Disease
CVD – Cerebrovascular Disease
DNI – Diabetic Neuropathy Index
DKD – Diabetic Kidney Disease
DPN – Diabetic Peripheral Neuropathy
DR – Diabetic Retinopathy
DRC – Diabetes-Related Complication(s)
EGFR – Estimated Glomerular Filtration Rate
HbA1c – Glycated Hemoglobin
HB-DRC – High Burden of Diabetes-Related Complications
IQR – Interquartile Range
LB-DRC – Low Burden of Diabetes-Related Complications
MaVC – Macrovascular Complication(s)
MAlbU – Macroalbuminuria
MNSI – Michigan Neuropathy Screening Instrument
MM-DRC – Moderate Burden of Diabetes-Related Complications
μAlbU – Microalbuminuria
μVC – Microvascular Complication(s)
NSTEMI – Non–ST-Elevation Myocardial Infarction
O – Overt complication
PAD – Peripheral Arterial Disease
p-eGFR – Predicted Estimated Glomerular Filtration Rate (adjusted for age)
RIACE – Renal Insufficiency And Cardiovascular Events (study)
SC – Subclinical complication
SPECT – Single-Photon Emission Computed Tomography
STEMI – ST-Elevation Myocardial Infarction

Despite this and the recent availability of very effective therapeutic strategies, the incidence of diabetes-related complications (DRC) is only modestly declining with time [4]. The incidence of both MaVC and μVC is hardly predictable and major risk factors (smoking, disease duration, HbA1c, blood pressure and lipids) only explain 50-60% of the interindividual variability [5]. Also, the relationship between DRC and exposure to the disease is complex. Indeed, μVC are already present in 40-50% of patients with T2D at diagnosis [6], whilst a substantial fraction (50%) of subjects does not develop any μVC even after 50 years of type 1 diabetes (T1D) [7]. Clearly, we still do not fully understand what predisposes to the development of DRC above and beyond exposure to hyperglycemia.

Progress in this field has been limited because most epidemiological studies have focused on specific cohorts (new-onset T2D [8], ADVANCE study [9] or on a limited set of either μVC [10,11] or MaVC [12], with a poor distinction between overt and subclinical manifestations [13]. A previous attempt to study the susceptibility to DRC focused on long-term survivors and non survivors [14], not providing a strategy for capturing the individual predisposition in quantitative terms at any disease duration and in a real-world clinical care setting.

Provided that experimental studies show that all DRC share a common background in terms of pathophysiology [15], and on the basis of solid evidence supporting the notion that μVC and MaVC tend to cluster in the same subjects [16–18], we first tested if this also occurs in our population by evaluating the involvement of three μVC (retina, kidney, peripheral nervous system) and three MaVC (coronary, cerebrovascular, peripheral arteries) districts in terms of overt or subclinical conditions. The second objective was to develop a structured clinical score and an algorithm to quantify the individual predisposition to accumulate the most common DRC, accounting for their relationship with disease duration. Algorithms to predict the development of Ma and μVC in patients with T2D have been proposed and validated but they are based only on classical risk factors, which explain only part of the large interindividual variability [5]. Our aim was to provide a tool that facilitates the studies focusing on the biologic bases of vulnerability to DRC.

2. Methods

2.1. Study protocol

The *"EXTREME phenotypes to identify the patients with Type 2 Diabetes who are susceptible or resistant to complications and to reveal the mechanisms"* (EXTREME-T2D) study consists of two parts. The first is a cross-sectional survey describing the clustering of μVC and MaVC in a large cohort of T2D patients (n = 1302), to establish solid criteria to define the phenotypes with low, moderate, and high burden of DRCs (LB, MB, HB-DRC, respectively). In the second part of the project, 250 subjects from each group will be recruited and compared in terms of phenotype, endotype and lifestyle to reveal the factors underlying the heterogeneity in the susceptibility to DRC.

The present study presents the data of the first cross-sectional part. The survey was conducted in four different Diabetology Units in Pisa, Bari, Catania (Italy) and Athens (Greece). All Units run outpatient clinics and are referral centers for the local population. Data were retrieved from electronic clinical records at each center and collected during extra visits when missing.

2.2. Inclusion criteria

The main inclusion criteria were: *1)* age 40-85 years old, *2)* all ethnicities, *3)* either sex, *4)* diagnosis of T2D before turning 75 years old, *5)* BMI <40 kg/m^2, *6)* HbA1c <8.5% (69 mmol/mol). Exclusion criteria included: patients with diagnosis of T1D, MODY, LADA, or other documented secondary forms of diabetes, patients affected by any chronic inflammatory diseases, active cancer, significant liver dysfunction, uncontrolled thyroid disorders, or any other significant life expectancy-changing systemic disease. Patients with these characteristics regularly attending the clinic (at least 4 visits in the previous 5 years) were included in the study. Patients must have undergone an extensive DRCs screening within 24 months from the data collection visit, allowing for only one missing test to identify subclinical complications. Considering the uncertainty of the diagnosis of T2D, and the presence of μVC and MVC also in subjects with dysglycemia [19,20], any complication diagnosed 5 years before the diagnosis of diabetes was considered related to diabetes.

2.3. Assessment of DRCs

DRCs were assessed by the presence of clinical events/conditions or subclinical disease as routinely done through history and laboratory/imaging tests and were divided into μVC and MaVC. MaVC included coronary heart disease (CHD), cerebrovascular (CVD) or peripheral atherosclerotic arterial disease (PAD) while the μVC domain included chronic kidney disease (CKD), diabetic retinopathy (DR) and diabetic polyneuropathy (DPN), according to ADA/EASD definitions [21,22]. Any single DRC was classified as overt or subclinical according to its severity or clinical significance.

Overt CHD (O-CHD) was considered as any evidence of acute coronary syndrome (STEMI, NSTEMI, unstable angina), history of coronary

revascularization or evidence of silent myocardial infarction at EKG (pathological Q waves) or at echocardiography, myocardial scintigraphy/SPECT or cardiac MRI. Subclinical CHD (SC-CHD) was defined by the presence of at least one plaque ≥40% and <75% at coronary angio-CT, a CAC score >100 Agatston, or a positive stress test (ultrasound, ECG, or nuclear imaging stress test) deemed not to be further investigated with angiography by the cardiologist. SC-CHD was investigated in symptomatic patients, or asymptomatic patients at very high CV risk (SCORE2-D >20%) and otherwise defined as absent. Overt CVD (O-CVD) was defined as a history of ischemic stroke or carotid revascularization. SC-CVD was defined as the presence of any carotid atherosclerotic plaque at ultrasound examination. According to the JASE recommendations [23], plaque was defined by the presence of any focal thickening thought to be atherosclerotic in origin and encroaching into the lumen of any segment of the carotid artery (protuberant-type plaque) ≥2 mm or causing a percent narrowing of the diameter ≥30%. Overt PAD (O-PAD) was considered as any amputation due to atherosclerotic-related ischemia or any peripheral revascularization, either previously performed or planned. SC-PAD was defined by the presence of left or right leg Ankle-Brachial Index (ABI) < 0.9.

Among μVC, overt diabetic kidney disease (O-DKD) was defined as the presence of a ≥50% reduction with respect to the predicted-for-age eGFR (*p*-eGFR = *100-(age-50)*0.94*) [24] and/or macroalbuminuria (MAlbU), defined as urinary albumin to creatinine ratio (ACR) ≥300 mg/g. Subclinical DKD (SC-DKD) was considered as a 25-49% reduction with respect to the *p*-eGFR and/or microalbuminuria (μAlbU), defined as ACR 30-299 mg/g. The use of the normalization for the *p*-eGFR was motivated by the fact that we wanted to focus on the kidney damage that is produced by diabetes and not by ageing. Overt diabetic retinopathy (O-DR) was defined as the presence of any type of proliferative retinopathy/high-risk non-proliferative retinopathy, or any previous treatment (anti-VEGF/laser treatment) in either eye. The presence of low/middle-risk non-proliferative retinopathy or background retinopathy was considered subclinical DR (SC-DR). Polyneuropathy (DPN) was assessed by the Diabetic Neuropathy Index (DNI) or Michigan Neuropathy Screening Instrument exam (MNSI exam) in subsets of the whole cohort (n = 960 and n = 749, respectively) and by either method in 1211 patients. In the 498 subjects who had both, the two scores were strongly correlated ($r^2 = 0.79$, $\rho = 0.86$) and showed an intercept close to zero (0.2 ± 0.01), therefore for these patients we calculated the mean of the two scores. Overt DPN (O-DPN) was defined by the presence of a score >4, while a subclinical disease (SC-DPN) was defined by the presence of a score >2.5 and ≤4. These cut-off values were chosen on the basis of the studies on the relationship between scores and the probability of confirmed DPN [25], which is 50% for our subclinical and >70% for our overt definition criteria.

From the clinical records, the value of HbA1c of the last 3 consecutive visits in the previous 2-3 years was collected and averaged to estimate the degree of metabolic control.

2.4. DRC score

Each complication, defined as already described, contributed to generate a score. The scoring was discussed by a consensus of 6 clinical experts (A.N., L.L., L.F., A.S., N.T., E.R.) who agreed on considering all overt complications equal in terms of relevance and establishing a gradient of 3:1 to reflect the clinical gradient between overt and subclinical complications. With the only exception of DPN, overt and subclinical complications in the same district can coexist, so the highest score for all the other domains is 4 points. The μVC and the MaVC scores were calculated as the sum of all overt and subclinical scores of the respective 3 main districts ranging from 0 to 11 and from 0 to 12, respectively; and the sum of the two scores is the global DRC score (range 0-23). When data on one subclinical complication was missing, it was assumed as absent.

2.5. Statistical analysis

Continuous variables were summarized as mean ± standard deviation (SD), and prevalence data as median and interquartile range (IQR). Differences among groups of continuous variables were tested through ANOVA and, if statistically significant, the student t-test was used for comparisons between two groups. Differences in prevalence data were tested through Chi-^{2} test. Simple and multivariate least squares linear regression analyses and logistic regression analyses were performed through standard methods (JMP Student Edition).

3. Results

3.1. Study population

A total of 2452 subjects were screened in the 4 units by retrieving data from the electronic clinical records. Among them, 1302 subjects had the required minimal set of information and were used for the final analysis (Suppl. Fig. 1), 281 from Pisa, 492 from Catania, 300 from Bari and 229 from Athens. Median [IQR] age was 69 [65-72] years, the proportion of females was 38%, the median duration of diabetes was 15 [7–23] years. Only 20% of patients showed neither overt nor subclinical μVC or MaVC. Overt and subclinical MaVC complications were present in 30.0% and 45.5% of patients, respectively, while overt and subclinical μVC complications were observed in 36.3% and 60.6% of patients, respectively.

The prevalence of each overt and subclinical complication is shown in Fig. 1. The most common O-MaVC was CHD (22%), followed by PAD (8%) and CVD (7%), and in 19% of the affected subjects 2 or 3 districts were involved. The most common subclinical MaVC was CVD (37%), followed by PAD (19%) and CHD (4%), and in 31% of these patients 2 or 3 districts were involved. The most common overt μVC were DR (16%) and DPN (15%) followed by CKD (10%), and in 36% of these patients it involved more than 1 district. The most common subclinical μVC was CKD (33%), followed by DPN (19%) and DR (16%); more than one district was involved in 27% of these cases. The coexistence of subclinical and overt DRC was relevant for CHD and DR, was minor for CVD, PAD and CKD, and absent for DPN (due to the adopted classification criteria).

3.2. Overlap among macro- and microvascular complications

Subclinical and overt μVC and MaVC tended to cluster, and large fractions of patients presented the two conditions simultaneously

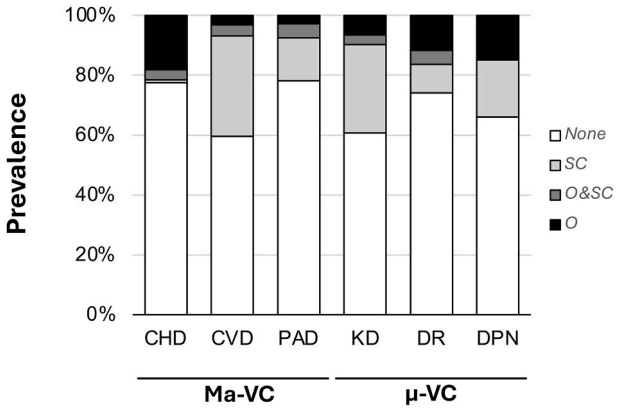

Fig. 1. Prevalence of overt and subclinical (and their combination) micro and macrovascular complications in each district.
O: overt, SC: subclinical, μVC: microvascular complications, MaVC: macrovascular complications, CHD: coronary artery disease, CVD: cerebrovascular disease, PVD: peripheral vascular disease, KD: kidney disease, DR: diabetic retinopathy, DPN: diabetic peripheral neuropathy.

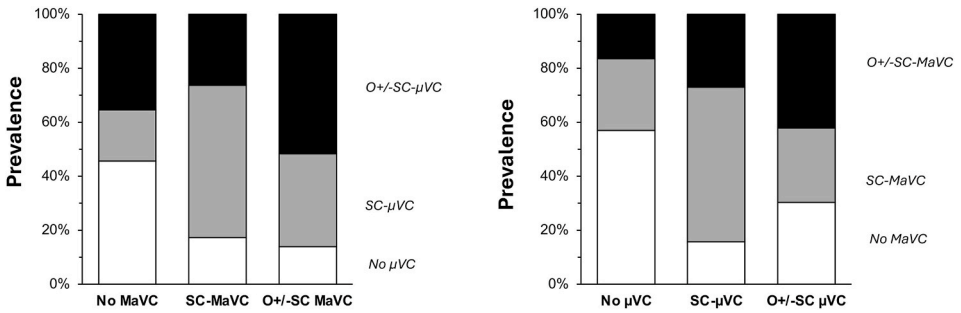

Fig. 2. Prevalence of absent, subclinical (SC) only and overt with or without SC (O ± SC) microvascular complications (μVC) according to the presence of absent, subclinical SC only and overt with or without SC (O ± SC) macrovascular complications (MaVC) and vice versa.

(Fig. 2, χ^2 74.4, p = $3*10^{-15}$). After adjusting for sex, center, age and diabetes duration, the presence of any overt μVC increased the risk of having an overt MaVC by approximately 2-fold (OR [95% CI]: 1.72 [1.30-2.80]), likewise the presence of any subclinical μVC (OR [95% CI]: 1.93 [1.48-2.51]), and vice versa. Among the different subtypes of overt μVC the association of each with any overt MaVC was strongest for DPN (OR [95% CI]: 1.75 [1.24-2.47]), followed by DR (OR [95% CI]: 1.56 [1.11-2.18]), and DKD (OR [95% CI]: 1.52 [1.02-2.26]). Among the different subclinical μVC the association was strongest for DKD (OR [95% CI]: 1.81 [1.39-2.35]), followed by DPN (OR [95% CI]: 1.68 [1.23-2.30]), and DR (OR [95% CI]: 1.36 [0.96-1.91]). After adjusting for center, sex, age and diabetes duration, the presence of any subclinical μVC was associated with a 30% increase in the presence of subclinical MaVC (OR [95% CI]: 1.30 [1.02-1.66]).

3.3. Diabetes duration and macro- and micro vascular complications

The burden of both subclinical and overt μVC and MaVC increased across diabetes duration classes (Fig. 3), and the strength of the association was strongest for overt μVC (Chi^2 127.1, p = $1.9*10^{-18}$), followed by subclinical μVC (Chi^2 82.6, p = $3.0*10^{-10}$), overt MaVC (Chi^2 56.2, p = $8.4*10^{-6}$), and subclinical MaVC (Chi^2 53.7, p = $2.0*10^{-5}$). After adjustment for center and sex, each 5-year increase in diabetes duration was associated with a significantly higher likelihood of having any overt μVC (OR [95% CI]: 1.31 [1.22-1.40]) or any overt MaVC (OR [95% CI]: 1.18 [1.11-1.26]), and of having any subclinical μVC (OR [95% CI]: 1.18 [1.11-1.25]) or any subclinical MaVC (OR [95% CI]: 1.13 [1.07-1.20]). After adding age to the multivariable adjustment, the association between diabetes duration and subclinical MaVC lost statistical significance (OR [95% CI]: 1.02 [0.96-1.09]), while the other

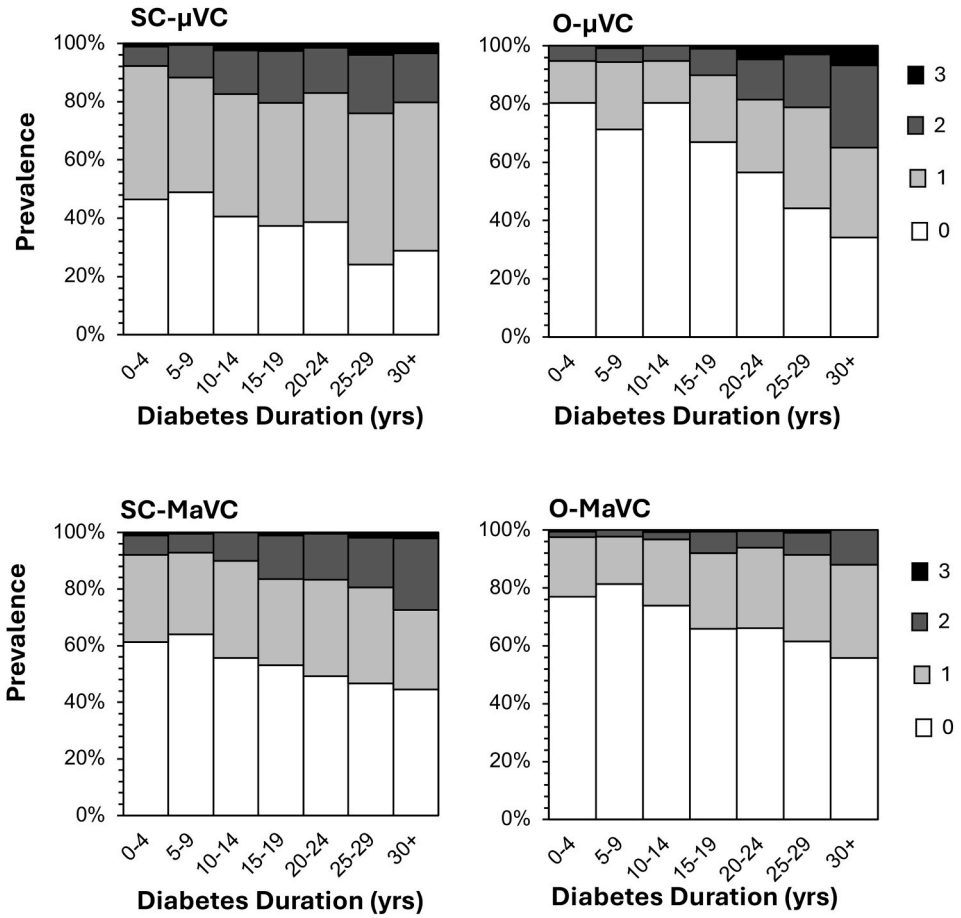

Fig. 3. Prevalence of the number (0,1, 2 or 3) of subclinical (SC) and overt (O) micro (μ) and macro (Ma) vascular complications across classes of diabetes duration.

complications were only marginally affected, and age emerged as an independent risk factor solely for MaVC.

3.4. DRC score

We first calculated the global μVC and MaVC scores as the sum of all subclinical (1 point) and overt (3 points) manifestation for each type of vascular complications and found a significant correlation between the two scores ($\rho = 0.26$, $p = 1*10^{-21}$). Both were correlated with disease duration and HbA1c, respectively, and the strength of these associations was greater for μVC ($\rho = 0.33$, $p = 1.0*10^{-21}$ and $\rho = 0.21$, $p = 2.1*10^{-13}$) than MaVC ($\rho = 0.20$, $p = 1.9*10^{-12}$ and $\rho = 0.12$, $p = 5.0*10^{-5}$). The sum of μVC and MaVC scores generates the global DRC score, whose distribution was skewed to the right (Suppl. Fig. 2); the median score was 2.0 [IQR: 5.0], and the range was 0-18 and was higher in men compared to women (4.0 *vs* 2.8, $p < 0.001$). The DRC score correlated both with age (+0.10 points/year [95%CI: 0.07-0.12], ρ=0.26, $p = 9.1*10^{-22}$) and diabetes duration (+0.12 points/year [95%CI: 0.10-0.14], $\rho = 0.34$, $p = 2.2*10^{-36}$). A stepwise regression model including center, diabetes duration, HbA1c, age and sex indicated that diabetes duration ranked first as predictor of DRC ($r^2 = 0.13$). However, the model showed a global r^2 of 0.23, suggesting the presence of other major determinants of the individual accrual of DRC.

3.5. Defining different phenotypes of complications burden

The calculation of the individual accrual rate of DRC requires an estimate of the time point at which the DRC score is = 0, which on the basis of the linear regression between diabetes duration and DRC score in the whole population was −13 years (13 years before the diagnosis). We therefore calculated the DRC accrual speed [DRC score/(diabetes duration+13.0)] of each participant and grouped participants in tertiles. Based on the linear regression equations of each tertile, the mean accrual rate (∂DRC score/10yrs) were: 0.14 [95%CI: 0.13-0.16], 0.88 [95%CI: 0.85-0.91], and 2.31 [95%CI 2.24-2.39] points/10 yrs (Fig. 4). According to these models, the predicted time to the first subclinical complication (DRC score = 1), relative to the duration of diabetes, was 65 years after diagnosis in the lowest tertile and 2 and 9 years before diagnosis in the moderate and highest tertiles, respectively. The three groups were defined, respectively, as with low (LB), moderate (MB), and high (HB) burden of DRC. The clinical characteristics of the three phenotypes are shown in Table 1. Patients with HB-DRC were more often male, slightly older and had minor differences in disease duration and HbA1c compared to LB-DRC. LB-DRC patients had no overt complications, neither μVC or MaVC, while overt MaVC was present in approximately 1/5 of MB-DRC and 3/4 of HB-DRC patients, and overt μVC was present in 23% of MB-DRC and 64% of HB-DRC patients, in whom more than one MaVC and more than one μVC district were frequently involved (16 and 27% of the cases, respectively). Subclinical μVC and MaVC were present in a small fraction of the LB-DRC patients, while the prevalence of subclinical MaVC was seven-fold higher in MB-DRC and ten-fold higher in HB-DRC; the prevalence of subclinical μVC was three-fold higher in both MB-DRC and HB-DRC patients (the lack of a gradient being justified by the high prevalence of overt μVC in the latter). Involvement of more than one macrovascular district was observed exclusively in HB-DRC patients (32%), whereas multiple microvascular districts were affected in 16% of MB-DRC and 24% of HB-DRC patients.

Simple diagnostic thresholds can be derived from the two boundary lines separating MB-DRC from the other two groups (Fig. 4), whose slopes were 1.43 and 0.46 per 10 years of diabetes duration, respectively. For any given patient, a DRC score exceeding (diabetes duration + 13 years, expressed in decades) × 1.43 identifies HB-DRC, whereas a score below (diabetes duration + 13 years, in decades) × 0.46 indicates LB-DRC; intermediate values define MB-DRC. For example, at a diabetes duration of 20 years, these thresholds correspond to DRC scores above 4.7 and below 1.5 points.

4. Discussion

In this large, real-world cohort of persons with T2D, we provide a simple, clinically grounded method to quantify the individual burden of DRCs that takes into account the exposure to the disease. The large sample size and heterogeneity of the cases together with the adoption of a data-based modeling of the natural history of complications accrual (linear and starting 13 years before the diagnosis) allowed us to find reliable diagnostic thresholds to identify three distinct phenotypes of DRC accrual speed (low, moderate, and high), that are characterized by strikingly different rates of complications despite comparable age, HbA1c, and disease duration.

The prevalence of overt macrovascular complications in our cohort (30%) was consistent with estimates from Italian (39%) and European (35%) populations with T2D [26]. The prevalence of CHD (19%) exceeded that reported in the DAI study (10%) [27] likely reflecting the older age (69 vs 66 yrs), longer duration of diabetes (16 vs 8 yrs) and higher prevalence of male subjects (62 vs 50%) in our cohort. The disproportion observed between subclinical CHD (4%) and CVD (38%)

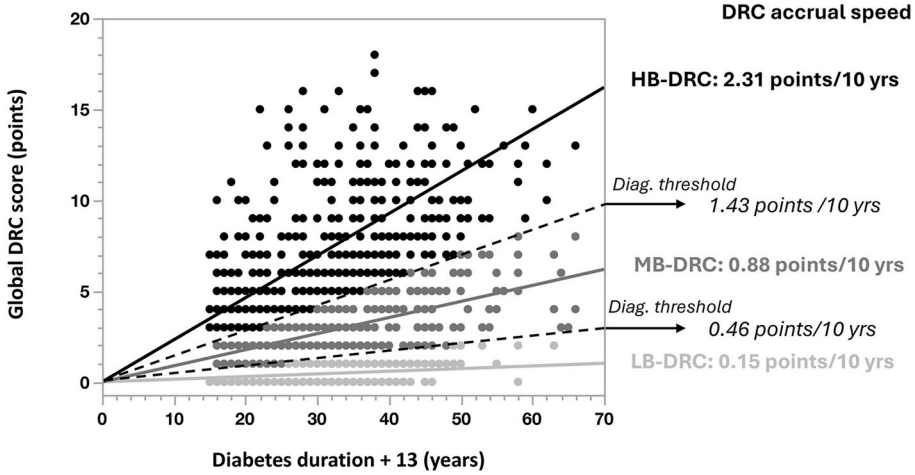

Fig. 4. Scatterplot showing the relationship between the DRC score and diabetes duration (+13 years). Subjects were divided into tertiles of presumed complication-development speed, assuming a zero value at −13 years for all, as estimated by the unconstrained regression in the whole cohort. Continuous lines show the fitted regressions for each tertile (fixed intercept at −13 years), and dotted lines indicate the thresholds defining the three burden categories: low (LB-DRC), moderate (MB-DRC), and high (HB-DRC). Mean slopes values (complication speeds) of each tertile and the diagnostic cut-off values are shown.

Table 1
Characteristics of the patients according to the susceptibility to develop diabetes-related complications (DRCs).

	LS-DRC	MS-DRC	HS-DRC	ANOVA	LS-DRC vs HS-DRC
N	415	426	434		
Center 1/2/3/4, %	24/32/30/14	21/36/26/17	22/47/9/22	<0.0001	-
Age, yrs	66.2 ± 9.4	68.5 ± 9.1	69.6 ± 8.5	<0.0001	<0.0001
Women, %	40.0	35.1	25.0	<0.0001	<0.0001
Diabetes Duration, yrs	14.8 ± 9.0	16.1 ± 11.5	16.4 ± 10.5	<0.040	0.0699
eGFR (ml/min/1.76m^2)	91 ± 23	83 ± 12	68 ± 27	<0.0001	<0.0001
eGFR (%)	108 ± 26	100 ± 31	81 ± 34	<0.0001	<0.0001
HbA1c (%) (n=1079)	6.8 ± 1.0	6.9 ± 1.1	7.2 ± 1.3	<0.0001	<0.0001
MaVC score, median [IQR]	0 [0-0]	1 [0-2]	4 [1-5]	<0.0001	<0.0001
μVC score, median [IQR]	0 [0-0]	1 [0-2]	4 [2-6]	<0.0001	<0.0001
DRC score, median [IQR]	0 [0-1]	2 [1-4]	7 [5-9]	<0.0001	<0.0001
O-CHD, %	0.0	12.4	50.5	<0.0001	-
O-CVD, %	0.0	4.2	16.3	<0.0001	-
O-PAD, %	0.0	1.6	20.3	<0.0001	-
Any O-MVC, %	0.0	18.4	73.2	<0.0001	-
N° of O-MaVC 1/2/3, %	0/0/0	18/0/0	53/15/1	<0.0001	
SC-CHD, %	0.5	2.1	10.1	<0.0001	-
SC-CVD, %	14.2	43.4	53.0	<0.0001	-
SC-PAD, %	1.9	16.0	38.2	<0.0001	-
Any SC-MaVC, %	16.4	52.1	67.1	<0.0001	-
N° of SC-MaVC 1/2/3, %	16/0/0	42/9/0	35/30/2	<0.0001	
O-DR, %	0.0	12.4	36.2	<0.0001	-
O-KD, %	0.0	4.5	24.4	<0.0001	-
O-DPN, %	0.0	7.3	36.4	<0.0001	-
Any O-μVC, %	0.0	22.5	64.1	<0.0001	-
N° of O-μVC 1/2/3, %	0/0/0	21/2/0	36/22/5	<0.0001	
SC-DR, %	3.4	15.0	23.7	<0.0001	-
SC-KD, %	12.5	39.0	45.6	<0.0001	-
SC-DPN, %	6.8	24.9	25.8	<0.0001	-
Any SC-μVC, %	21.7	63.2	68.9	<0.0001	-
N° of SC-μVC 1/2/3, %	21/1/0	47/16/0	45/21/3	<0.0001	

SC: subclinical, O: overt, CHD: coronary heart disease, CVD: cerebro-vascular disease, PAD: peripheral artery disease, DR: diabetic retinopathy, KD: kidney disease, DPN: diabetic peripheral neuropathy.

in our database is attributable to differences in the diagnostic accessibility: coronary atherosclerosis typically requires more complex tests and specific clinical indication (symptoms or very high cardiovascular risk), whereas carotid ultrasonography is often performed as a routine assessment and we also adopted a low threshold for subclinical CVD (stenosis ≥30% and plaque ≥2.0 mm). This approach was intended to partially offset the expected under-detection of coronary atherosclerosis, which often coexists with carotid disease. Our prevalence of subclinical PAD (19%) is consistent with previous studies (12-22%) [28], after accounting for differences in diagnostic definitions and population characteristics. Comparisons for microvascular complications are less straightforward, given the variability in classification criteria across studies. Less variability is expected from DR which is more standardized, and our prevalence (26%) is close to the data from the RIACE cohort [29] and from a European survey [30] which reported prevalences of 22 and 25%, respectively. Similarly, the prevalence of CKD, defined by reduced eGFR and/or microalbuminuria (39%), closely matched that of the RIACE cohort (37.5%) [31] reinforcing the representativeness of our population. We have used age-adjusted criteria for establishing the degree of eGFR reduction given that in an older population the usual criteria might produce overestimates. We expressed eGFR as a percentage of the predicted value for age (*p*-eGFR%), to detect kidney dysfunction beyond the physiologic age-related decline. As expected, eGFR was more closely related to age ($r^2 = 0.15$; stβ = 0.38, $p < 0.0001$) than *p*-eGFR% ($r^2 = 0.01$; stβ = −0.09, $p = 0.002$), supporting the validity of this approach. The prevalence of DPN (15% overt and 19% subclinical) was consistent with previous studies reporting values between 15 and 30% depending on the adopted criteria [32]. Altogether these data indicate that the quality of our screening of both overt and subclinical μVC and MaVC DRCs was robust and accurate, and that our population adequately represents real-world patients with T2D attending specialty clinics.

The clustering of μVC and MaVC observed in our cohort agrees with recent data from the UK Biobank [17] where individuals with MaVC exhibited a 1.5- to 1.6-fold higher risk of developing μVC, values that are quantitatively similar to our cross-sectional estimates. Similarly, other studies have consistently shown that the presence of μVC (especially microalbuminuria and DR) represents a risk factor for MaVC [33–36]. This reciprocal link between the two conditions, presumably based on common metabolic stressors (hyperglycemia, dyslipidemia, insulin resistance) acting upon shared pathogenetic mechanisms (oxidative stress, inflammation, endothelial dysfunction, DNA methylation) [37], represents a solid support for the adoption of a global μVC and MaVC score to assess the individual susceptibility of developing DRCs.

As expected, the association between DRCs and disease duration in our study population was strong, yet in the context of a large interindividual variability, which justifies the need of a clinical tool to identify the individual with a high burden of DRC, that takes into consideration the duration of the disease. An interesting finding of our study is that, in T2D, the complications start to accumulate several years before the presumed diagnosis, the first subclinical one appearing 2 and 9 years before in the MB- and HB-DRC groups, respectively. This observation is in strong agreement with other studies [38,39], with the concept of the "common soil" [40] and with the fact that frequently the diagnosis is delayed.

In this report we intentionally did not perform any analysis of plausible determinants of DRCs, like smoking, exposure to different degrees of metabolic control, body mass index, plasma lipids, blood pressure or ongoing therapies. Our aim, here, was exclusively to depict, in a real-life context, the prevalence of μVC and MaVC, building up a score relatively easy to adopt in a diabetes clinic, where international guidelines are constantly applied and diabetologists pay effort in performing a global screening of complications, but do not quantitatively interpret the acquired information. The extreme difference in the burden of DRCs among the three phenotypes (Table 1) despite marginally different age, disease duration and HbA1c, offers an estimate of how large the variability in susceptibility to DRC is. The LB subjects appear almost immune to DRCs, while the HB ones have accumulated DRC points at an average speed that is 3-fold higher than the MB-DRC. The definition of this speed in each patient could be used not only for research purposes, but also to synthesize the clinical workup and eventually modulate the intensity of care. To this end, we have prepared a clinical tool available online (https://drcscore.netlify.app/) where the diagnosis of DRC **burden** is easily obtained, as well as the individual estimate of the rate of developing complications. Interestingly, two experts clinicians (A.N. and A.S.) tried to guess the presumed class and had a success rate of 58%.

Some aspects of this study require a critical discussion. First, our conclusion applies to outpatients regularly attending a specialty clinic without important comorbidities, severe obesity and metabolic decompensation. This selection might have reduced the burden of complications which is known to be higher in the patients not regularly attending a specialty clinic and in those with poor compliance to the therapy. On the other hand, it is also true that the referral centers in public health care systems tend to attract the clinically more complex individuals and

this might compensate the selection bias. The risk of an underrepresentation of the less complex patients is attenuated by the fact that access to university-affiliated diabetes clinics in Italy and Greece is relatively open, and indeed a substantial fraction of patients had no MaVC (41%) or μVC (37%) and were free of any complication (20%). Clearly our data need to be replicated in different countries and settings.

Second, we have somewhat neglected the role of sex even though male subjects have a burden of MaVC (any subclinical and any overt) that is 2.1-fold higher than female. We did not generate separated criteria for the following reasons: the prevalence of overt and subclinical μVC was not different and, as a matter of fact, guidelines for cardiovascular prevention do not establish different thresholds for men and women to define the risk, and the intensity of the intervention, finally a two-fold larger sample size would have been necessary to establish sex specific robust criteria. When exploring the associations between variables we have systematically entered sex as a covariate in the multivariate models.

Third, we recognize that the assumption regarding the linearity of the model of accrual of DRC is arbitrary. Possibly, the development of complications follows a non-linear kinetics with respect to disease duration, but the exposure to a disease is usually measured as a linear function of time and the best fit of the data was linear. This assumption might have produced an error in the value of the intercept (-13 years) that was necessary to calculate the DRC accrual speed. To assess the relevance of this point estimate, we have performed also the regression analysis using -5 as intercept value, and this have yielded a change in the classification in only 5.8% of cases, exclusively between adjacent categories.

Finally, we acknowledge that the decision of adopting the same value for overt and subclinical complications of different nature and a 3:1 ratio between the two is arbitrary. The equivalence of the different complications, was generated by the expert consensus considering the difficulty of establishing a clear hierarchy, which ultimately depends on the severity of the damage, the treatment received, the patient's habits and personal values. It should be also noted that our score has no prognostic value, it only helps in evaluating the antecedent patient's predisposition to accumulate DRCs. The ratio 3:1 also was decided by expert consensus and its impact on the classification is mild; when we modified the weighting ratio from 3:1 to 4:1, the reclassification rate remained minimal (3.2%), confirming the consistency of our results.

5. Conclusions

In summary, we confirm that the variability in developing DRC after exposure to the disease is huge in patients with T2D, that Ma- and μ-VC tend to cluster and by using a simple algorithm it is possible to estimate the individual burden of DRCs in real-world patients. This tool could facilitate the research on the factors that confer a predisposition to develop DRC. External validation in independent cohorts and prospective studies is necessary before the score can be used to inform clinical decision-making in a personalized medicine context.

Ethics approval and consent to participate

Ethical considerations

The study protocol was first approved by the Tuscany Regional Ethical Committee, Section AREA VASTA NORD OVEST, N° 23585_NATALI and then the approval was extended at the Local Ethic Committee of each center. The study has been registered on Clinicaltrial.gov (NCT07250607). All participants provided written informed consent before enrolment.

Availability of data

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Authors contribution

A.N. conceived the study, developed the design, and supervised all phases of the project. L.S. coordinated data acquisition across centers and performed the primary analyses. L.S., S.G., M.C., D.T., N.C., I.C., S. M., I.A., N.T., E.R., D.F., G.S., F.D., F.G., L.L., L.F. and A.S. contributed to patient recruitment, clinical phenotyping, and verification of complication assessments. L.S., S.G., M.C. and A.N. drafted the manuscript. All authors critically revised the text, approved the final version, and agreed to be accountable for the integrity of the work.

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Declaration of competing interest

The authors declare that they have no competing interests that are relevant to the content of this article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2026.104716.

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