PREDICTIVE FACTORS FOR HEALTH-RELATED QUALITY OF LIFE IN TYPE 2 DIABETES PATIENTS

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PREDICTIVE FACTORS FOR HEALTH-RELATED QUALITY OF LIFE IN TYPE 2 DIABETES PATIENTS (Abstract) **Aims:** Diabetes-related characteristics and associated chronic conditions are said to influence the health-related quality of life (QoL) of patients with type 2 diabetes mellitus (T2DM). This study assessed the relationships between QoL, demographic, and disease-related variables in T2DM patients without established atherosclerotic disease. **Materials and methods**: This post hoc analysis included outpatient data from a cross-sectional study. Descriptive and inferential statistics were used to examine patient characteristics in relation to QoL scores and identify predictive factors for physical and mental health perceptions. QoL was evaluated with the 36-item Short Form Health Survey (SF-36) questionnaire. **Results**: The 138 T2DM patients enrolled were 49.3% men, 57.86 ± 8.82 years old, with T2DM for 1 to 21 years, without optimal glycemic control under oral glucose-lowering drugs (median HbA_{1c}7.8%). Mean physical and mental component summary scores (PCS, MCS) were 50.44 ± 16.22 and 47.78 ± 12.10, respectively. The lowest SF-36 scores were reported for physical functioning and vitality, and the highest for bodily pain. Women had significantly lower PCS scores compared to men (46.85 *vs.* 54.03, $p = 0.01$). The diastolic index E/e', CHA_2DS_2-VASc score and diabetes duration predicted lower PCS ($p \leq 0.01$), while the impact of age, glycemic control, neuropathy, diastolic dysfunction, and comorbidities on QoL was non-significant. The diastolic index E/e', CHA_2DS_2-VASc score and diabetes duration predicted lower PCS ($p \leq 0.01$). **Conclusions:** These results provide a nuanced view of what is clearly a complex set of relationships. Further longitudinal studies are necessary to ascertain the effects of these variables on the quality of life of T2DM patients. **Keywords:** QUALITY OF LIFE, SF-36V2, TYPE 2 DIABETES.

Health-related quality of life (HRQoL) is a multidimensional concept first introduced half a century ago that provides an accurate, comprehensive, and concise view of patients' perceived impact of chronic disease (with or without comorbidities) on their

lives. It considers physical, mental, cognitive, and psychosocial aspects. Diabetes mellitus has been independently associated with lower HRQoL scores, similar to pulmonary, cardiovascular, and oncologic conditions. The quality of life of patients with diabetes is a psychosocial concern with implications for their long-term adherence to treatment (1, 2, 3). Current recommendations highlight diabetes-related psychosocial screening and care protocols as an important component that should be integrated into annual routine diabetes management practices to prevent or delay complications and optimize quality of life (4, 5).

Self-reported data on general health, physical status, social functionality, emotional well-being, and self-care capacity provide a meaningful context for achieving the clinical and biological goals of medical, nutritional and pharmacologic interventions. HRQoL has been studied as a primary or secondary outcome in both observational and interventional studies, often using the Short Form 36 (SF-36), a standardized, freely available, easy-to-administer questionnaire (6, 7). SF-36 assesses perceived health status across multiple scales - general, physical, mental, and social functioning. Although SF-36 was not developed specifically for people with diabetes, it helps explore relevant issues in the lives of these patients (8).

This study aimed to analyze the relationships between QoL data surveyed with SF-36v2 and clinical-biological parameters in type 2 diabetes (T2DM) patients with incidental echocardiographic findings of diastolic dysfunction (DD), but without established atherosclerotic disease.

MATERIALS AND METHODS

This is a post hoc analysis of outpatient data collected from T2DM patients presenting at the Clinical Centre of Diabetes, Nutrition, and Metabolic Diseases Iasi between June 2016 and February 2018. It is part of a larger prospective observational study approved by the Ethics Committees of "Grigore T. Popa" University of Medicine and Pharmacy Iași and of "Sf. Spiridon" Emergency Clinical Hospital Iași.

The study enrolled 138 consenting T2DM patients treated with metformin and/or sulfonylurea or acarbose, and who were eligible for additional incretin-based medication due to inadequate glycemic control (HbA_{1c} > 7%). The exclusion criteria were: HbA_{1c} < 7%, type 1 or secondary pancreatic diabetes, elevated triglycerides >400 mg/dL, uncontrolled blood pressure (>140/90 mmHg), cardiovascular disease (atherosclerotic manifestations, valvular heart disease, moderate/severe mitral annular calcification, dysrhythmias, cardiac pacemakers), history of inflammatory acute/chronic conditions (pancreatitis, liver failure, gastrointestinal and kidney diseases, malignancies), psychiatric disorders, pregnancy or intention to become pregnant, and smoking or recent history of smoking (< 1-year withdrawal). The enrollment process was described in more detail in Grigorescu *et al*, 2021, 2023 (9, 10).

The patients underwent physical examination, blood and urine sample tests (lipids, glycated hemoglobin HbA_{1c}, glycemia, insulin, C-peptide, high sensitivity C-reactive protein, interleukin (IL)-6, Tumour Necrosis Factor (TNF)-alpha, uric acid, etc.), and resting electrocardiography (11). Values of the ratio between mitral E wave velocity and mitral A wave velocity (E/A), mitral annular velocity with tissue Doppler imaging (e'), left ventricular ejection fraction (LVEF), fractional shortening (FS), E-

wave deceleration time (EDT), isovolumic relaxation time (IVRT), interventricular septum (IVS), left ventricular posterior wall (LVPW), left atrium volume (LAV) were measured by transthoracic echocardiography. The estimated glomerular filtration rate (eGFR) was computed using the CKD-EPI creatinine equation. The methods used for measuring HbA_{1c} and immunological parameters were DCCT-aligned ion-exchange high-performance liquid chromatography (Bio-Rad D-10™) and chemiluminescence (IMMULITE 1000). The thromboembolic risk score CHA_2DS_2-VASc was calculated based on age > 75 years, female sex, the presence of diabetes, congestive heart failure, hypertension, vascular disease, and past stroke events (12).

The patients were also asked to complete the Romanian version of the SF-36v2 questionnaire, consisting of 36 items grouped into 8 domains: Physical Functioning Scale (10 items), Physical Impairment Problems Scale (4 items), Social Functioning Scale (2 items), Physical Pain Scale (2 items), Mental Health Scale (5 items), Problems Caused by Emotional States Scale (3 items), Vitality Scale (4 items). All responses were re-coded to a linear 0-100 scale, with higher scores indicating better HRQoL. The two summary scores - the *physical component summary* (PCS) and the *mental component summary* (MCS) - were calculated according to the user's manual: the PCS was comprised of the scales PF, RP, BP, and GH, while MCS was computed from the remaining RE, SF, MH, and VT scales (6).

The statistical analysis was performed using IBM SPSS Statistics for Windows (version 20, SPSS Inc, Chicago, IL, USA). P-values < 0.05 were considered statistically significant. Continuous variables were assessed for conformity to normal distribution using the Kolmogorov-Smirnov test. Parametric and non-parametric tests (ANOVA, Kruskal-Wallis, Mann-Whitney U) were applied to compare mean/median questionnaire scores or mean ranks between specific groups (i.e., stratified by gender, presence of neuropathy). Receiver-operating characteristic (ROC) curves and areas under the curves (AUCs) were also considered (13).

RESULTS

Data collected from 138 patients aged 57.86±8.82, of whom 49.3% were men, are summarized in tables I and II. The patients had a diabetes history of 1 to 21 years (median value 5) and HbA_{1c} levels >7% on enrollment. The SF-36 scores averaged 50.44 ± 16.22 for self-reported physical health (PCS) and 47.78 ± 12.10 for the mental component (MCS). More details are shown in tables II and IV.

PCS had a weak association with eGFR ($r = 0.217$, $p = 0.011$), CHA_2DS_2-VASc ($r = -0.219$, $p = 0.01$), and E/e' ($r = -0.213$, $p = 0.013$), while MCS was associated with E/e' ($r = -0.202$, $p = 0.019$) and TNF-alpha ($r = -0.169$, $p = 0.048$) values. The following significant correlations were also noted between SF-36 components and patient characteristics:

- General health (GH) correlated with weight ($r = -0.169$, $p = 0.048$), abdominal circumference (WC, $r = -0.186$, $p = 0.029$), and LDL-cholesterol ($r = 0.194$, $p = 0.023$);
- Vitality (VT) correlated with left atrium length ($r = -0.185$, $p = 0.043$);
- Bodily pain (BP) correlated with CHA_2DS_2-VASc ($r = -0.250$, $p = 0.003$), HOMA-IR ($r = -0.190$, $p = 0.025$), index C-peptide ($r = 0.169$, $p = 0.047$), E/e' ($r = -$

0.173, p = 0.044), E/A (r = 0.170, p = 0.047), and EDT (r = 0.204, p = 0.017);

- Physical functioning (PF) correlated with CHA_2DS_2-VASc (r = -0.194, p = 0.022), C peptide (r = 0.184, p = 0.031), and HOMA-IR (r = 0.169, p = 0.048);

- Role physical (RP) correlated with age (r = -0.174, p = 0.041), CHA_2DS_2-VASc (r = -0.201, p = 0.018), and TNF-alpha (r = -0.208, p = 0.014).

Subgroup analyses based on age, sex, DD, degree of inadequate glycemic control, neuropathy, and other comorbidities (hypertension, dyslipidemia, obesity, metabolic dysfunction-associated fatty liver disease) revealed significant SF-36 score differences only for self-assessed physical health between men and women (54.03 vs. 46.85, p = 0.01) (table III). The presence of comorbidities did not seem to affect the PCS and MCS scores (16.7% of patients had three comorbidities, 42% had two, and 32.6% had just one). Patients with mitral annular calcifications and/or aortic atheromatosis had higher MCS scores (50.43 ± 12.06 vs 45.49 ± 11.74, p = 0.016), similar to patients with dyslipidemia.

Further analyses based on the qualitative variables revealed significant differences for the following scales:

- patients with obesity had significantly lower scores (51.63 ± 17.89 vs 44.90 ± 16.88, p = 0.032) for **general health** compared to those with BMI < 30 kg/m^2;

- men reported higher scores for **bodily pain** compared to women (mean ranks 82.49 vs 56.89, p<0.01), and patients with neuropathy had lower scores for this scale (62.30 vs 75.30, p = 0.05);

- **social functioning** scores were lower in patients with ≥ 3 comorbidities (p = 0.041);

- **emotional role** scores were lower in patients with ≥ 4 criteria for metabolic syndrome (41.38 *vs.* 78.82, p = 0.05), which described almost all patients.

TABLE I.

Patient characteristics overall and based on QoL scores

Studied Variable	Overall (N = 138)	PCS		*p-value*	MCS		*p-value*
		< median (N = 69)	> median (N = 69)		< median N = 68	> median N = 70	
Age (years)	57.86±8.82	58.87 ± 8.43	56.84 ± 9.14	0.178	58.21 ± 8.99	57.51 ± 8.69	0.647
Sex male (n)	68 (49.30%)	26 (18.84%)	42 (30.43%)	**0.006**	31 (22.47%)	37 (26.81%)	0.39
Sex female (n)	70 (51.70%)	43 (31.16%)	27 (19.57%)		37 (26.81%)	33 (23.91%)	
Weight (kg)	91.11 ± 14.71	91.72 ± 13.52	90.51±15.84	0.631	91.95 ± 15.31	90.30±14.17	0.513
BMI (kg/m^2)	32.65 ± 5.50	33.43 ± 5.10	31.86 ± 5.81	0.095	33.21 ± 5.89	32.10 ± 5.08	0.241
WC (cm)	109.13±10.74	110.46±11.01	108.08±10.43	0.194	110.04±11.40	108.52±10.11	0.408
DM duration * (y)	5 (8)	7 (8)	4 (8)	**0.046**	6 (9)	5.5 (7)	0.904
Neuropathy + (n)	61 (44.2%)	34 (24.64%)	27 (19.57%)	0.23	32 (23.19%)	29 (21.01%)	0.31
Neuropathy - (n)	77 (55.8%)	35 (25.36%)	42 (30.43%)		36 (26.09%)	41 (29.71%)	
HbA_{1c} * (%)	7.8 (1.11)	7.85 (1.08)	7.88 (1.4)	0.443	7.85 (1.33)	7.8 (1.2)	0.917
Fasting glycemia * (mg/dL)	162 (46)	158.5 (58)	166.5 (45)	0.592	160.5 (56)	162 (49)	0.371
Insulin * (µIU/mL)	11.2 (9.39)	12 (9.51)	12.3 (9.44)	0.676	13.3 (12.29)	10.25 (7.98)	0.274
C-peptide * (ng/mL)	3.26 (2.22)	3.35 (2.09)	2.89 (1.53)	0.371	3.38 (2)	2.83 (1.49)	0.273
HOMA-IR	5.74 ± 3.87	5.79 ± 3.75	5.68 ± 4.02	0.874	6.07 ± 3.70	5.41 ± 4.03	0.322

Studied Variable	Overall (N = 138)	PCS		*p*-value	MCS		*p*-value
		< median (N = 69)	> median (N = 69)		< median N = 68	> median N = 70	
HOMA C-peptide	4.02 ± 2.10	4.16 ± 2.07	3.89 ± 2.14	0.447	4.30 ± 2.07	3.76 ± 2.13	0.138
Index C-peptide *	0.24 (0.19)	0.22 (0.28)	0.27 (0.18)	0.371	0.21 (0.17)	0.27 (0.21)	0.085
Total cholesterol (mg/dL)	195.33 ± 46.11	189.90 ± 46.25	201.77 ± 45.14	0.101	195.07 ± 46.77	195.59 ± 45.80	0.948
LDL-cholesterol (mg/dL)	103.12 ± 38.96	97.63 ± 36.78	108.62 ± 40.54	0.098	103.34 ± 40.43	102.92 ± 37.76	0.949
HDL-cholesterol (mg/dL)	56.79 ± 15.27	56.62 ± 16.13	56.97 ± 14.65	0.894	56.61 ± 16.39	56.97 ± 14.20	0.892
Triglycerides (mg/dL)	202.57 ± 90.46	197.62 ± 90.12	207.51 ± 91.19	0.523	208.87 ± 88.57	196.44 ± 92.49	0.422
eGFR (mL/min/1.73 m^2)	82 ± 16.37	79.07 ± 17.77	87.12 ± 17.43	**0.008**	84.09 ± 18.49	82.13 ± 17.58	0.525
ACR (mg/g)	27.14 ± 48.64	28.19 ± 50.80	26.02 ± 46.15	0.826	28.37 ± 49.78	26.02 ± 48.04	0.811
Uric acid (mg/dL)	5.48 ± 1.43	5.53 ± 1.37	5.53 ± 1.37	0.694	5.37 ± 1.41	5.59 ± 1.45	0.380
hsCRP * (mg/L)	5.35 (9.18)	5.87 (9.17)	5.33 (8.6)	0.332	5.38 (9.51)	4.91 (9.15)	0.914
IL-6 * (pg/mL)	3.52 (4.66)	2.48 (1.86)	2.05 (0.95)	0.123	2.39 (1.64)	2.00 (1.12)	0.099
TNF-α * (pg/mL)	8.73 (7.66)	7.94 (3.65)	7.35 (3.91)	0.079	7.89 (3.26)	6.72 (3.95)	**0.025**

*Data are expressed as medians and IQR (non-normal distribution); PCS: physical component summary; MCS: mental component summary; BMI: body mass index; WC: waist circumference; DM: diabetes mellitus; HbA_{1c}: glycated hemoglobin; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; HOMA C-peptide: Homeostatic Assessment Model of C-peptide; eGFR: estimated glomerular filtration rate; UACR: albumin-to-creatinine ratio in urine; hsCRP: high-sensitive C-reactive protein; IL-6: interleukin 6; TNF-α: tumor necrosis factor-alpha.

TABLE II.

The evaluation of chronic conditions overall and based on QoL scores

Studied Variable	Overall (N = 138)	PCS		*p*-value	MCS		*p*-value
		< median (N = 69)	> median (N = 69)		< median N = 68	> median N = 70	
Comorbidities							
Dyslipidemia + (%)	99 (71.7%)	43 (31.16%)	56 (40.58%)	0.128	43 (31.16%)	56 (40.58%)	**0.023**
Dyslipidemia - (%)	39 (29.3%)	23 (16.66%)	16 (11.60%)		25 (18.12%)	14 (10.14%)	
Hypertension + (%)	93 (67.4%)	48 (34.78%)	45 (32.60%)	0.358	47 (34.06%)	46 (33.33%)	0.404
Hypertension - (%)	45 (32.6%)	21 (15.22%)	24 (17.40%)		21 (15.21%)	24 (17.40%)	
MAFLD+ (%)	106 (76.81%)	55 (39.86%)	51 (36.96%)	0.420	55 (39.86%)	51 (36.96%)	0.180
MAFLD - (%)	32 (23.19%)	14 (10.14%)	18 (13.04%)		13 (9.42%)	19 (13.76%)	
Obesity + (%)	92 (66.67%)	51 (36.96%)	41 (29.71%)	**0.052**	48 (34.78%)	44 (31.88%)	0.217
Obesity - (%)	46 (33.33%)	18 (13.04%)	28 (73.68%)		20 (14.50%)	26 (18.84%)	
Cardiac status							
With DD (%)	98 (71%)	49 (35.50%)	49 (35.50%)	0.574	50 (36.23%)	48 (34.78%)	0.325
Without DD (%)	40 (29%)	20 (14.50%)	20 (14.50%)		18 (13.04%)	22 (15.94%)	
LVEF (%)	67.14 ± 9.35	67.68 ± 9.78	66.59 ± 8.93	0.497	67.09 ± 9.55	67.19 ± 9.26	0.951
FS (%)	38.16 ± 7.89	38.27 ± 8.20	38.05 ± 7.59	0.875	37.95 ± 8.16	38.37 ± 7.64	0.766
E/A *	0.93 (0.68)	1.06 (0.83)	0.89 (0.63)	0.818	0.87 (0.72)	0.95 (0.63)	0.620
E/e'	6.54 ± 1.84	6.97 ± 1.96	6.10 ± 1.10	**0.006**	6.89 ± 1.93	6.21 ± 1.69	**0.031**
EDT *	190 (58)	177.5 (44)	203 (65)	**0.010**	185 (48)	195 (65)	0.545
IVRT *	104 (25)	100 (20)	100 (30)	0.509	100 (70)	100 (20)	0.752

Studied Variable	Overall (N = 138)	PCS		*p*-value	MCS		*p*-value
		< median (N = 69)	> median (N = 69)		< median N = 68	> median N = 70	
IVS *	11 (2)	12 (2.8)	11 (2)	0.505	12 (3)	11 (2)	0.178
LVPW *	11 (2)	11 (2)	11 (2)	0.260	11 (2)	11 (2)	0.446
LAVi *	42 (18)	42 (20)	39 (18)	0.725	39 (14)	43 (19)	0.280
CHA_2DS_2-VASc *	3 (1)	3 (2)	2 (1)	**0.009**	3 (1)	3 (4)	0.542
NT-proBNP * (pg/mL)	63 (77.1)	65 (88.6)	59 (71.24)	0.615	74 (90.24)	54.5 (66.14)	0.276

* Data are expressed as medians and IQR; PCS: physical component summary; MCS: mental component summary; MAFLD: Metabolic dysfunction-associated fatty liver disease; DD: diastolic dysfunction; LVEF: left ventricular ejection fraction; FS: fractional shortening; E: mitral E wave velocity (rapid filling) with pulsed Doppler; A: mitral A wave velocity (atrial contraction) with pulsed Doppler; e': mitral annular velocity with tissue Doppler imaging; EDT: E-wave deceleration time; IVRT: isovolumic relaxation time; IVS: interventricular septum; LVPW: left ventricular posterior wall; LAVi: indexed left atrium volume; CHA_2DS_2VASc: thromboembolic risk score; NT-proBNP: N-terminal pro-brain natriuretic peptide.

TABLE III.

Associations between QoL components and diabetes-related factors

Studied Variable		PCS	*p*-value	MCS	*p*-value
Age (years)	< 50	51.50 ± 13.72	0.713	47.45 ± 13.45	0.934
	50 - 64	50.86 ± 16.82		48.12 ± 12.00	
	> 64	48.37 ± 17.25		47.27 ± 11.34	
Sex	Male	54.03 ± 16.59	**0.010**	48.63 ± 12.39	0.418
	Female	46.95 ± 15.18		46.96 ± 11.74	
Diabetes duration (years)	< 5	52.17 ± 14.92	0.331	46.19 ± 12.05	**0.031**
	5 - 10	50.70 ± 17.30		52.09 ± 12.01	
	> 10	47.12 ± 17.15		45.90 ± 11.43	
BMI (kg/m^2)	< 25	52.22 ± 16.31	0.870	51.27 ± 11.94	0.754
	25 - 29.9	51.32 ± 16.95		47.98 ± 9.97	
	> 30	49.93 ± 16.04		47.46 ± 13.04	
HbA_{1c} (%)	< 7.5	49.22 ± 17.18	0.824	46.49 ± 12.72	0.658
	7.5 - 8	50.91 ± 16.64		48.77 ± 12.28	
	> 8	51.16 ± 15.20		48.14 ± 11.49	
Neuropathy	with	49.46 ± 15.67	0.531	47.17 ± 11.30	0.597
	without	51.21 ± 16.44		48.27 ± 12.75	
Hypertension	with	50.09 ± 16.45	0.721	47.80 ± 12.26	0.983
	without	51.15 ± 15.91		47.75 ± 11.90	
Dyslipidemia	with	51.76 ± 16.00	0.128	49.00 ± 12.14	**0.023**
	without	47.09 ± 16.52		44.68 ± 11.58	
MAFLD	with	49.13 ± 15.79	0.567	47.44 ± 12.03	0.841
	without	50.92 ± 16.43		47.91 ± 12.19	
Obesity	with	49.69 ± 16.13	0.441	47.35 ± 13.01	0.518
	without	51.95 ± 16.49		48.65 ± 10.12	
Met. syndrome criteria	≤ 3	51.16 ± 16.33	0.678	47.82 ± 10.92	0.979
	≥ 4	49.98 ± 16.24		47.76 ± 12.87	

Studied Variable		PCS	*p*-value	MCS	*p*-value
Diastolic dysfunction	with	51.24 ± 15.72	0.336	47.98 ± 11.26	0.786
	without	48.47 ± 17.44		47.30 ± 14.64	
CHA_2DS_2-VASc	< 3	53.46 ± 16.21	**0.048**	47.84 ± 12.46	0.961
	≥ 3	47.97 ± 15.92		47.74 ± 11.89	

PCS: physical component summary; MCS: mental component summary; BMI: body mass index; MAFLD: Metabolic dysfunction-associated fatty liver disease; CHA_2DS_2VASc: thromboembolic risk score.

TABLE IV.

SF-36 scales - descriptive and associative statistics

SF-36	GH	BP*	MH	PF*	RE*	RP*	VT	SF*	PCS	MCS
Mean/median*	47.13	67.50	41.65	35	66.66	50	36.81	50	50.44	47.78
Std. Dev. / IQR	17.45	35	9.12	40	100	100	13.64	15.63	16.22	12.10
r - PCS	0.206	0.699	0.036	-0.23	0.433	0.841	0.036	0.103	1	0.448
p-value	0.016	<0.001	NS	0.007	<0.001	<0.001	NS	NS	-	<0.001
r - MCS	0.208	0.316	0.130	-0.378	0.866	0.547	0.211	0.382	0.448	1
p-value	0.014	<0.001	NS	<0.001	<0.001	<0.001	0.013	<0.001	<0.001	-

GH, general health; BP, bodily pain; MH, mental health; PF, physical functioning; RE, role emotional; RP, role-physical; VT, vitality; SF, social functioning; PCS, physical component summary; MCS, mental component summary; NS statistically non-significant: p > 0.05, r: coefficients of correlations with PCS and MCS.

ROC curves predictive of lower PCS were found for E/e' (AUC = 0.643, CI 0.549-0.736, p = 0.005), CHA_2DS_2-VASc (AUC = 0.623, CI 0.530-0.716, p = 0.013), and diabetes duration (AUC = 0.613, CI 0.549-0.736, p = 0.005), as illustrated in first figure.

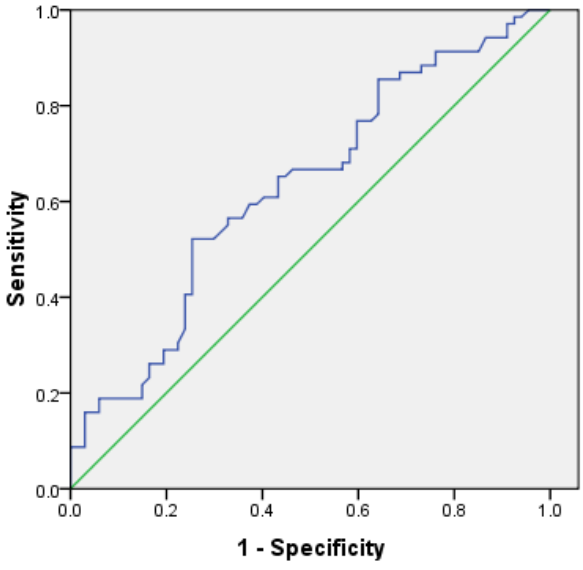

Fig. 1. Receiver-operating characteristics (ROC) curve for E/e'

DISCUSSION

There is growing interest in understanding and addressing the factors associated with a decline in health-related quality of life for people with type 2 diabetes as a way to improve healthcare services and patient adherence. This post hoc analysis of 138 T2DM Romanian patients without overt manifestations of atherosclerotic disease focused on the associations between patient-reported outcomes and characteristics with proported effects on QoL (metabolic profile, pre-existing chronic conditions).

QoL was assessed using the PCS and MCS scores of the SF-36v2 questionnaire, similar to other published and ongoing observational and interventional research from Europe and elsewhere (14, 15, 16). A minimum SF-36 score change of 3-5 points has been proposed as clinically relevant, with due caution when interpreting it as a significant improvement or decline. Furthermore, comparisons across studies should be made with circumspection, acknowledging the substantial heterogeneity of the studied populations in terms of their general, metabolic, and pathology-related characteristics (17, 18, 19).

In our study, the lowest SF-36 scores were reported for physical functioning, followed by vitality, and the highest were for bodily pain. Compared to previous research on age-standardized Romanian general population, our patients' PCS and MCS scores were substantially lower: 74.52 ± 19.44 vs. 50.44 ± 16.22 and 71.70 ± 19.02 vs 47.78 ± 12.10, respectively (20). At the same time, the mean PCS and MCS values were within the range of scores reported for patients with diabetes from other geographical regions/countries: Greece (39.96 and 38.24), Spain (44.9 and 51.2), Netherlands (49.4 and 53.9), India (52 and 46), Ethiopia (40.15 and 48.11), and United States (52 and 46) (21, 22, 19, 23, 24, 25). Moreover, the mean values of our patients' PCS and MCS scores were comparable to those reported in other clinical research investigating the effects of new drugs or weight loss programs (26, 27, 28, 16). For example, in an interventional clinical trial on 563 uncontrolled T2DM patients of similar mean age (55 years), slightly higher HbA_{1c} (8.32%), and higher BMI (37.1 kg/m^2), an intensive weight loss program yielded no significant differences in SF-36 scores assessed after 12 months, compared to a control group: PCS 45.7 vs 45.2, and MCS 51.5 vs 51.6 (16).

While some researchers have demonstrated associations between glycemic control and HRQoL domains, in other studies and our analysis, HbA_{1c} was not associated with PCS and MCS (29). In a multivariate analysis of 5-year data from 1,876 patients with T2DM from Denmark, the Netherlands, and the UK, no significant associations were identified between HbA_{1c} and SF-36 scores after adjustment for age, sex, BMI, type of antihyperglycemic drugs, and education status. Even so, 60% of the patients with HbA_{1c} below 7% and who were treated with oral medication had higher SF-36 scores (PCS 46.2 and MCS 54.6) (30). In another study where 1,352 patients with T2DM filled out the SF-36 questionnaire, a multivariate analysis adjusting for disease duration and other risk factors found significantly higher PCS and MCS scores in patients with an HbA_{1c} below 6.9% versus above 8.6% (31). These differing results across studies suggest that we have yet to learn about the complexities of the proport-

ed relationships.

At the same time, systematic reviews and meta-analyses confirm that patients with a longer duration of diabetes, chronic complications and hypertension have lower QoL scores. In our data, patients' quality of life decreased as the duration of the disease increased, which is consistent with the results of other studies (14). However, the difference was significant only for MCS.

Comorbidities were highly prevalent in our study, especially hypertension (67.4%), dyslipidemia (71.74%), and MAFLD (75.46%) only twelve patients had none. Almost all patients had abdominal obesity and metabolic syndrome, of which 60.9% met at least 4 criteria. In addition, 83 patients had diastolic dysfunction diagnosed according to the 2016 guideline, of whom 71 with grade 1 severity (and all the patients had normal systolic function). By comparison, the prevalence of these common chronic conditions in other studies varied from 27.71% to 78.2% for hypertension, from 43.5% to 98.3% for dyslipidemia, and was only 32.8% for the metabolic syndrome (32, 24, 33, 34). Our data set was, therefore, suitable for exploring the relationship between comorbidities and QoL.

Available research into the impact of comorbidities on the quality of life in type 2 diabetes patients has been reviewed recently in a meta-analysis, with the key finding that each additional chronic condition decreased the PCS score by approximately 3% (36). Nonetheless, in our study, the number of comorbidities did not appear to undermine the health-related quality of life, nor did the presence of subclinical diastolic dysfunction, which is consistent with other studies that evaluated such relationships (19, 37). This raises interesting questions for further research, e.g. could a satisfying relationship with one's physician, good adherence to medical treatment, or some other aspects of healthcare give patients a certain level of psychological comfort and reassurance that counterbalances the otherwise negative impact of the disease severity and complexity?

In addition, DD did not correlate with QoL either, similar to the findings of Edelman *et al.*, 2011 (38*).* However, we noted that the diastolic index E/e' was a significant predictor for lower scores attributed to physical health. E/e' was also significantly higher in patients with PCS and MCS scores below median values. This could be investigated further, considering the well-known role of echocardiographic parameters in one's objective vitality, as well as recent research supporting the inclusion of the self-reported SF-36 vitality item in the cardiovascular risk stratification algorithms for T2DM patients (39).

In our previous research, DD was predicted by the CHA2DS2-VASc score (40). Typically, CHA2DS2-VASc serves as a decision-making tool when establishing the need for anticoagulant therapy in patients with atrial fibrillation. Recently, more potential applications have been explored, such as for the prediction of rehospitalization and all-cause mortality or in the risk assessment for cardiac and cerebrovascular events even in patients without atrial fibrillation (41, 42, 43). In this study, CHA2DS2-VASc was predictive of a poorer quality of life in terms of perceived physical health. From a practical perspective, this score is based on readily available data and is easy for diabetes specialists to calculate during routine check-ups, so it is worth knowing and exploiting its full predictive potential.

The relatively small number of participants is a limit of this study, and further multivariate analysis was not appropriate because of insufficient demographic data (marital, educational or employment status), psychological data (stress or anxiety levels), or health literacy levels. The nature of this post hoc analysis could not support assertions of causality explaining the observed associations. Moreover, all patients had HbA_{1c} levels above 7% and no severe complications, so comparisons with data from patients with adequate glycemic control were not possible in our study.

We recognize the complex relationship between HRQoL, diabetes-specific, and other factors. The use of a validated tool to assess patient-reported outcomes, the nuanced analysis, and the identification of predictors for a lower quality of life are the main strengths of this study. The results can contribute to international data collection efforts and allow the experiences of Romanian patients to be included in forthcoming meta-analyses.

CONCLUSIONS

In this study of T2DM patients without established atherosclerotic disease, self-reported quality of life was mostly independent of diabetes-related factors such as glycemic control, chronic complications, and comorbidities. Conversely, diabetes duration, the diastolic index E/e', and CHA_2DS_2-VASc score, were associated with lower physical health perception. This and other forthcoming studies can inform the design of prospective and interventional research, as well as educational programs targeting better quality of life for T2DM patients as a primary or secondary endpoint.

CONFLICT OF INTEREST AND FUNDING

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REFERENCES

1. Mohammed MA, Moles RJ, Harrison J, Chen TF. Health Outcomes and Quality of Life. *Encyclopedia of Pharmacy Practice and Clinical Pharmacy*; Baha, Z-U-D, Ed.; Elsevier: Amsterdam, The Netherlands, 2019; 3A: 59-72.
2. ICHOM Diabetes in Adults Working Group, Type 1 and Type 2 Diabetes in Adults, November 2018, Data Collection Reference Guide. Version 1.0.0 Revised February 28th, 2019. Available online: https://ichom.org/files/medical-conditions/diabetes-in-adults/dia-reference-guide.pdf (accessed on 13 June 2024).
3. Speight J, Holmes-Truscott E, Hendrieckx C, Skovlund S, Cooke D. Assessing the impact of diabetes on quality of life: What have the past 25 years taught us? *Diabet Med* 2020; 37: 483-492.
4. Young-Hyman D, de Groot M, Hill-Briggs F, Gonzalez JS, Hood K, Peyrot M. Psychosocial Care for People with Diabetes: A Position Statement of the American Diabetes Association. *Diabetes Care* 2016; 39: 2126-2140.
5. American Diabetes Association. 5. Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes: Standards of Care in Diabetes-2024. *Diabetes Care* 2024; 47(Suppl.1): S77-S110.
6. Ware J, Kosinski M, Bjorner J, Turner-Bowker D, Gandek B, Maruish M. *Development. User's Manual for the SF-36v2® Health Survey*. Quality Metric Incorporated: Lincoln, RI, USA, 2007.

7. Trikkalinou A, Papazafiropoulou AK, Melidonis A. Type 2 diabetes and quality of life. *World J Diabetes* 2017; 8(4):120.
8. Emad-Eldin M, Balata GF, Elshorbagy EA, Hamed MS, Attia MS. Insulin therapy in type 2 diabetes: Insights into clinical efficacy, patient-reported outcomes, and adherence challenges. *World J Diabetes* 2024; 15(5): 828-852.
9. Grigorescu E-D, *et al* Self-reported satisfaction to treatment, quality of life and general health of type 2 diabetes patients with inadequate glycemic control from north-eastern Romania. *Int J Environ Res Public Health* 2021; 18(6): 3249.
10. Grigorescu E-D, *et al* Effects of incretin-based treatment on the diastolic (dys)function in patients with uncontrolled type 2 diabetes mellitus: A prospective study with 1-year follow-up. *Diagnostics* 2023; 13(17): 2817.
11. Balta A, *et al* Broad electrocardiogram syndromes spectrum: From common emergencies to particular electrical heart disorders. *J Pers Med* 2022; 12(11): 1754.
12. Lip GYH, Nieuwlaat R, Pisters R, Lane DA, Crijns HJGM. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach. *Chest* 2010; 137(2): 263-272.
13. Lionte C, Sorodoc V, Tuchilus C, Cimpoiesu D, Jaba E. Biomarkers, lactate, and clinical scores as outcome predictors in systemic poisons exposures. *Hum Exp Toxicol* 2017; 36(7): 651-662.
14. Jafari A, Moshki M, Ghelichi-Ghojogh M, Nejatian M. Role of diabetes health literacy, psychological status, self-care behaviors, and life satisfaction in predicting quality of life in type 2 diabetes. *Scientific Reports* 2024; 14(1).
15. Pérez Hernández MF, *et al* Electroacupuncture efficacy in diabetic polyneuropathy: Study protocol for a double-blinded randomized controlled Multicenter Clinical Trial. *BMC Complement Med Ther* 2024; 24(1): 90.
16. Holland-Carter L, *et al* Impact on psychosocial outcomes of a nationally available weight management program tailored for individuals with type 2 diabetes: Results of a randomized controlled trial. *J Diabetes Complications* 2017; 31(5): 891-897.
17. Bjorner JB, Lyng Wolden M, Gundgaard J, Miller KA. Benchmarks for interpretation of score differences on the SF-36 health survey for patients with diabetes. *Value in Health* 2013; 16(6): 993-1000.
18. Grigorescu E-D, *et al* The inflammatory marker HSCRP as a predictor of increased insulin resistance in type 2 diabetics without atherosclerotic manifestations. *Rev Chim* 2019; 70(5): 1791-1794.
19. Werkman NC, *et al* Disease severity-based subgrouping of type 2 diabetes does not parallel differences in quality of life: The Maastricht Study. *Diabetologia* 2024; 67(4): 690-702.
20. Mardare I, Furtunescu FL, Bratu EC. Measuring health related quality of life - methods and tools. *Acta Medica Transilvanica* 2019; 24(2): 6-8.
21. Papadopoulos AA, Kontodimopoulos N, Frydas A, Ikonomakis E, Niakas D. Predictors of health-related quality of life in type II diabetic patients in Greece. *BMC Public Health*. 2007; 7: 186.
22. Marcos-Delgado A, *et al* Health-related quality of life in individuals with metabolic syndrome: A cross-sectional study. *Semergen* 2020; 46(8): 524-537.
23. Rani M, Kumar R, Krishan P. Metabolic correlates of health-related quality of life in patients with type 2 diabetes mellitus. *J Pharm Pract* 2019; 32(4): 422-427.
24. Esubalew H, Belachew A, Seid Y, Wondmagegn H, Temesgen K, Ayele T. Health-related quality of life among type 2 diabetes mellitus patients using the 36-Item Short form health survey (SF-36) in central Ethiopia: A multicenter study. *Diabetes Metab Syndr Obes* 2024; 17: 1039-1049.
25. Impact of intensive lifestyle intervention on depression and health-related quality of life in type 2 diabetes: The look ahead trial. *Diabetes Care* 2014; 37(6): 1544-1553.

26. Kolotkin RL, Jeppesen OK, Baker-Knight J, Lee SY, Tokita A, Kadowaki T. Effect of once-weekly subcutaneous semaglutide 2.4mg on weight- and health-related quality of life in an East Asian population: Patient-reported outcomes from the step 6 trial. *Clinical Obesity* 2023; 13(4): e12589.
27. Bjorner JB, Larsen S, Lübker C, Holst-Hansen T. The improved health utility of once-weekly subcutaneous semaglutide 2.4 mg compared with placebo in the step 1-4 obesity trials. *Diabetes Obes Metab* 2023; 25(8): 2142-2150.
28. Jódar E, Michelsen M, Polonsky W *et al* Semaglutide improves health-related quality of life versus placebo when added to standard of care in patients with type 2 diabetes at high cardiovascular risk (SUSTAIN 6). *Diabetes Obes Metab* 2020; 22: 1339-1347.
29. Volčanšek Š, Lunder M, Janež A. Health-related quality of life assessment in older patients with type 1 and type 2 diabetes. *Healthcare* 2023; 11(15): 2154.
30. Kuznetsov L, *et al* Diabetes-specific quality of life but not health status is independently associated with glycaemic control among patients with type 2 diabetes: A cross-sectional analysis of the ADDITION-Europe trial cohort. *Diabetes Res Clin Pract* 2014; 104: 281-287.
31. Engström MS, *et al* Health-related quality of life and glycaemic control among adults with type 1 and type 2 diabetes—a nationwide cross-sectional study. *Health Qual Life Outcomes* 2019; 17: 1-11.
32. Kintzoglanakis K, Pavlou-Skantzis L, Themeli T, Kyprianou M, Paschou SA. Determinants of health-related quality of life of patients with type 2 diabetes and multimorbidity: A cross-sectional study. *Hormones* 2024/ doi: 10.1007/s42000-024-00545-y.
33. Pati S, *et al* Impact of comorbidity on health-related quality of life among type 2 diabetic patients in primary care. *Prim Health Care Res Dev* 2021; 21(e9): 1-8.
34. Sajjadi SS, Bagherniya M, Soleimani D, *et al* Effect of propolis on mood, quality of life, and metabolic profiles in subjects with metabolic syndrome: a randomized clinical trial. *Sci Rep* 2023; 13: 4452.
35. Chen S, Chen S, Lai Y, *et al* Abdominal obesity and hypertension are correlated with health-related quality of life in Taiwanese adults with metabolic syndrome. *BMJ Open Diabetes Res Care* 2020; 8: e000947.
36. Makovski TT, Schmitz S, Zeegers MP, Stranges S, van den Akker M. Multimorbidity and quality of life: Systematic Literature Review and meta-analysis. *Ageing Res Rev* 2019; 53:100903.
37. Verhulst M, Teeuw W, Gerdes V, Loos B. Self-reported oral health and quality of life in patients with type 2 diabetes mellitus in primary care: A multi-center cross-sectional study. *Diabetes Metab Syndr Obes* 2019; 12: 883-899.
38. Edelmann F, *et al* Impaired physical quality of life in patients with diastolic dysfunction associates more strongly with neurohumoral activation than with echocardiographic parameters: Quality of life in diastolic dysfunction. *Am Heart J* 2011; 161(4): 797-804.
39. Vergara M, Östgren CJ, Nyström FH, Israelsson H. Sense of vitality is associated with cardiovascular events in type 2 diabetes independently of traditional risk factors and arterial stiffness. *Diabet Med* 2022; 40(2): e14938.
40. Grigorescu ED. *Implications of the incretin treatment on the subclinical inflammatory status and the cardiac function in patients diagnosed with type 2 diabetes* [dissertation]. "Grigore T. Popa" University of Medicine and Pharmacy, Iași, Romania; 2021.
41. Sonaglioni A, Lonati C, Rigamonti E, *et al* CHA_2DS_2-VASc score stratifies mortality risk in heart failure patients aged 75 years and older with and without atrial fibrillation. *Aging Clin Exp Res* 2022; 34: 1707-1720.
42. Harb SC, Wang TK, Nemer D, *et al*. CHA_2DS_2-VASc score stratifies mortality risk in patients with and without atrial fibrillation. *Open Heart* 2021; 8(2): e001794
43. Tahir H, *et al* Use of CHA2DS2-VASc Score in Patients without Atrial Fibrillation: Review of Literature. *J Card Cardi Sur* 2021; 1: 5.
44.