Accepted Article

Journal of Frailty, Sarcopenia and Falls

Original Article

Assessment of Frailty Status and Its Association with Heart Rate Variability and Body Composition Among Patients with Type 2 Diabetes Mellitus: A Cross-Sectional Study

Pranav Venkatachaliah Kanamanapalli[1], Saranya Kuppusamy[2], Dukhabandhu Naik[3], Kavitha Natarajan[2], Senthil Kumar Subramanian[4]

[1]Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry, India;
[2]Department of Physiology, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry, India;
[3]Department of Endocrinology, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry, India;
[4]Department of Physiology, All India Institute of Medical Sciences (AIIMS), Madurai, Tamil Nadu, India

Abstract

Objective: To evaluate frailty status and its association with heart rate variability (HRV), body composition, and metabolic profile in patients with Type 2 Diabetes Mellitus (T2DM). **Methods**: In this cross-sectional study, 139 T2DM patients (age 50-65 years) were recruited. Frailty status was classified as non-frail, pre-frail, or frail using the Physical Frailty Phenotype (PFP) criteria. Outcome measures included HRV from a 5-minute ECG, body composition via bioelectrical impedance analysis, and a full metabolic profile. **Results**: The prevalence of pre-frailty or frailty was 95%. Increasing frailty status was significantly associated with autonomic dysfunction, characterized by reduced parasympathetic and increased sympathetic HRV indices (e.g., higher LF:HF ratio, p=0.003). Frail patients had a significantly higher fat percentage (p=0.015) and lower lean percentage (p=0.015) compared to non-frail participants. Poorer glycemic control (HbA1c: p=0.003) and a more adverse lipid profile were also significantly associated with worsening frailty. **Conclusion**: Frailty is highly prevalent in this T2DM cohort and is associated with significant adverse changes in autonomic function, body composition, and cardiometabolic health, highlighting the need for a multifaceted management approach.

Keywords: Cardiovascular Risk, Diabetes Mellitus, Frailty, Heart Rate Variability, Sarcopenia

Introduction

Globally, the prevalence of diabetes mellitus has been increasing, among aged people, due to a rise in average life expectancy[1]. In 2019, the prevalence in India has reached 8.9% from 7.1% in 2009[2]. Diabetes mellitus (DM) is a chronic metabolic disorder characterized by hyperglycemia that results from profound dysregulation in carbohydrate, protein, and fat metabolism. The resultant insulin deficiency and insulin resistance (IR) are known to contribute to muscle protein loss, leading to a higher prevalence of sarcopenia in this population. For instance, a meta-analysis of Asian populations reported the prevalence of sarcopenia at 15.9% in individuals with diabetes, compared to 10.8% in those without[3].

Sarcopenia is the main attribute to physical frailty. Clinically, frailty represents a loss of physiological reserve

The authors have no conflict of interest.

Corresponding author: *Dr. Saranya Kuppusamy Additional Professor, Department of Physiology, JIPMER, Puducherry, India*

E-mail: *ktsaran28@gmail.com*

Edited by: *Jagadish K. Chhetri*

Accepted *29 September 2025*

that makes an individual highly susceptible to adverse outcomes following a stressor event. It's the resultant of gradual deterioration in physiological systems with advancing age, which accentuates the risk of complications. Studies have shown decreased lean mass to be linked with metabolic disorders, IR, and frailty. DM with sarcopenia could provide an early pathophysiologic environment for frailty onset. The frailty could be attributed to varied microvascular-macrovascular complications of DM, increasing mortality and morbidity. Hence, DM, sarcopenia, and frailty are intricately interrelated. Bioelectrical impedance analysis (BIA) is a recognized non-invasive technique for assessing muscle mass[5].

Frailty is assessed by Fried frailty phenotype also known as physical frailty phenotype (PFP)[6]. It has five criteria namely, weakness, exhaustion, low physical activity, slowness & unintentional loss of weight. Individuals fulfilling 1 to 2 of these criteria are considered prefrail, while those fulfilling 3 or more are considered as frail[6].

Frailty could lead to increased cardiovascular disease (CVD) risk[9]. In diabetes, Cardiac Autonomic Neuropathy (CAN) is an early and serious complication, resulting in increased CVD risk. Heart rate variability (HRV) is an objective, non-invasive and an early predictor of CAN and CVD risk. Impaired heart rate variability (HRV) has long been reported in patients with diabetes mellitus (DM)[10], and more recently, it has also been evidenced among older adults with frailty[11]. However, there is a paucity of research specifically exploring the association between HRV and frailty within the diabetic population itself, representing a critical knowledge gap.

A growing body of research from India has begun to elucidate the relationship between diabetes, muscle health, and frailty. Large-scale analyses of the Longitudinal Ageing Study in India (LASI) have confirmed that diabetes is associated with higher odds of sarcopenia and related phenotypes like sarcopenic obesity in older adults[12]. This is complemented by findings from numerous hospital-based studies, which document a substantial prevalence of sarcopenia and identify age and physical inactivity as key determinants in patients with type 2 diabetes[13-15]. Furthermore, research has explicitly linked diabetes to frailty, highlighting sarcopenic obesity as a critical phenotype that amplifies the risk for falls and functional decline[16,17]. While this work establishes the structural and functional decline, the role of cardiac autonomic dysfunction—a key complication of diabetes—in this triad is less understood. For instance, one Indian study connected decreased muscle performance with impaired heart rate variability (HRV)[18], but a comprehensive investigation integrating a formal frailty assessment with HRV analysis remains a specific knowledge gap. Therefore, our study was designed to fill this gap by integrating HRV analysis with a comprehensive frailty and body composition assessment in an Indian T2DM population.

Materials and Methods

Study design and population

This is a cross-sectional study, conducted in Department of Physiology, JIPMER, Puducherry. Participants were recruited from patients attending the Endocrinology outpatient department at the Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry, India. A convenience sampling strategy was employed.

The inclusion and exclusion criteria were as follows:

Inclusion criteria:

- Age between 50 and 65 years.
- A confirmed diagnosis of Type 2 Diabetes Mellitus as per American Diabetic Association (ADA) criteria (i.e., FBG ≥126 mg/dl, 2hr BG ≥200 mg/dl, or HbA1c ≥6.5%)4.
- Currently receiving treatment for T2DM.

Exclusion criteria:

- Previously diagnosed endocrine disorders, cardiovascular disease, renal disorder, pulmonary disorder, psychiatric disorders, or malignancy.

Procedure

To minimize potential measurement bias, all data collection procedures were standardized and conducted by trained research personnel according to a strict protocol. The participants were instructed to report at the Autonomic function testing lab in the Physiology Department of our Institute, in loose fitting clothing and two hours after food. Participant confidentiality was maintained throughout the study.

Personal details

A brief history was taken regarding name, age, occupation, smoking, alcohol, dietary pattern (Veg/Non-Veg), disease duration, and drug history. Physical activity was assessed using the International Physical Activity Questionnaire–short form (IPAQ-short). Based on the official scoring protocol, which calculates total MET-minutes/week from the frequency, duration, and intensity of activities, participants were categorized into low, moderate, or high physical activity levels. The detailed scoring criteria are provided in Supplementary File 1.

Anthropometric assessment

Anthropometric parameters, viz. height, weight, waist circumference (WC) & hip circumference (HC) were measured. Height was measured using a wall-mounted stadiometer, to the nearest 1mm. Weight was measured with electronic weighing scale to the nearest 0.5 kg, avoiding zero & parallax errors. WC was measured at the narrowest circumference between the lower costal border of 10th rib and top of the iliac crest. HC was taken at the level of greatest posterior protuberance of the gluteal region. The Quetelet's index {Weight(kg)/[Height(m)]^2} was used to calculate Body Mass Index (BMI). Waist-hip ratio (WHR) was derived as WC/HC.

Body composition analysis

Body composition was analyzed using a Bodystat Quad scan 4000 bioelectrical impedance device. After 10 minutes of supine rest, signal-inducing electrodes were attached to the dorsal surfaces of the right metacarpophalangeal and metatarsophalangeal joints. Voltage-sensing electrodes were positioned 5 cm proximal to the signal-inducing electrodes at the pisiform prominence (wrist) and between the malleoli (ankle). After participant details were entered, a 500–800 μA current at a 50 kHz frequency was applied. The device's software derived fat mass (kg), lean mass (kg), fat percentage (%), and lean percentage (%) from the measured impedance.

Assessment of Frailty

Frailty status was evaluated using the criteria of the "Physical Frailty Phenotype (PFP)"[6,7]. This assessment was based on participant responses to a questionnaire and direct performance measurements for the following five criteria. A score of '1' was given if a criterion was met, and '0' if it was not.

- **Slowness**: Defined as a walking time for 15 feet (4.57m) that was greater than or equal to the sex- and height-specific cut-off (Men: ≥7 sec for height ≤173 cm, ≥6 sec for >173 cm; Women: ≥7 sec for height ≤159 cm, ≥6 sec for >159 cm). The best value of two trials was used.
- **Weakness**: Defined as a handgrip strength lower than the sex- and BMI-specific cut-off (e.g., Men with BMI ≤24: <29 kg; Women with BMI ≤23: <17 kg). The average of three trials was used.
- **Low Physical Activity**: Defined as a "Low" activity level as categorized by the IPAQ-short questionnaire.
- **Fatigue**: Considered present if the participant answered "a moderate amount of the time" or "most of the time" to either of two questions from the CES-D scale ("I felt that everything I did was an effort" or "I could not get going").
- **Weight loss**: Considered present if the participant reported an unintentional loss of >10 lbs (≥4.5 kg) or ≥5% of body mass in the past year.

Frailty was categorized based on the total score: **Non-frail** (0 criteria), **Pre-frail** (1-2 criteria), and **Frail** (≥3 criteria).

Basal cardiovascular parameters

After 10 minutes of supine rest, Systolic & Diastolic Blood pressure (SBP & DBP) & heart rate (HR), were measured using an automated BP apparatus (Omron HEM-8712). Rate pressure product (RPP), mean arterial pressure (MAP) and Pulse Pressure (PP) were derived.

Short term HRV Analysis

Short-term analysis of HRV was done as per European Task Force 1996 guidelines. It was analyzed with resting 5-minute lead II ECG recording acquired with BIOPAC MP 150 (BIOPAC Inc.,USA). Kubios software version 2.0 was used for HRV analysis after artifact correction. Time domain indices (TDI) [SDNN, RMSSD, NN50, pNN50] & Frequency domain indices (FDI) [LF (ms^2), HF (ms^2), Total Power (ms^2), LF (n.u.), HF (n.u.), LF/HF ratio] were derived.

Blood parameters

Fasting blood glucose (FBG), glycated hemoglobin (HbA1c), and a full lipid profile—including total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL), and low-density lipoprotein (LDL)—were obtained from the patients' electronic medical records. All biochemical assays were performed at the institute's central accredited laboratory using standardized, automated methods. Very low-density lipoprotein (VLDL) and lipid risk ratios (TC/HDL, LDL/HDL, TG/HDL, and atherogenic index) were subsequently calculated.

Sample size calculation

The required sample size was estimated to be 135, based on an expected frailty prevalence of 9.3%[8], a desired precision of 5%, and a 95% confidence interval. To allow for potential dropouts or exclusions, we enrolled a total of 139 participants. A convenience sampling strategy was employed for participant recruitment.

Statistical Analysis

All data were analyzed using IBM SPSS Statistics for Windows, Version 25.0. The normality of continuous data was assessed using the Shapiro-Wilk test. Normally distributed data were presented as mean ± standard deviation (SD), while non-normally distributed data were expressed as median and interquartile range (IQR). Categorical variables were presented as frequencies and percentages (%). To compare variables across the three frailty groups (non-frail, pre-frail, frail), the chi-square test was used for categorical data. For continuous data, a one-way ANOVA (for normal distribution) or the Kruskal-Wallis H test (for skewed distribution) was employed. Post-hoc analysis was conducted using the Bonferroni correction for multiple comparisons. The relationship between frailty score and other continuous variables was assessed using Spearman's rank correlation coefficient. An analysis stratified by duration of diabetes was also performed to explore its role as a potential confounder. All analyses were conducted assuming complete case data. A p-value of < 0.05 was considered statistically significant.

Results

Among 139 diabetes mellitus patients, 55.39% (n=77) of patients were frail, 39.56% (n=55) were prefrail

Variable	Non-frail	Pre-frail	Frail	Total
Prevalence	7 (5%)	56 (40%)	76 (55%)	139
Sex				
Male	5 (71%)	40 (71%)	60 (79%)	105
Female	2 (29%)	16 (29%)	16 (21%)	34
Drug History				
OHA	5 (71%)	31 (55%)	46 (60%)	82
OHA+Insulin	2 (29%)	25 (45%)	30 (40%)	57
OHA: Oral hypoglycemic drugs.				

Table 1. Baseline Characteristics of the Study Population by Frailty Status (n=139).

Characteristics	No Frail (n = 7)	Pre-frail (n = 55)	Frail (n = 77)	P value
	n (%)	n (%)	n (%)	
Dietary Pattern				
Non - Veg	5 (71.4%)	51 (92.7%)	65 (84.4%)	0.168
Veg	2(28.6%)	4 (7.3%)	12 (15.6%)	
Physical activity				
Low	0	24 (43.6%)	65 (84.4%)	<0.001***
Moderate	7 (100%)	31 (56.4 %)	12 (15.6%)	
High	0	0	0	
Smoking				
Yes	1 (14.3%)	7 (12.7%)	13 (16.9%)	0.804
No	6 (85.7%)	48 (87.3%)	64 (83.1%)	
Alcohol				
Yes	2 (28.6%)	17 (30.9 %)	25 (32.5%)	0.966
No	5 (71.4%)	38 (69.1%)	52 (67.5%)	
Duration of DM				
≤ 5 years	4 (57.1%)	14 (25.5 %)	1 (1.3 %)	<0.001***
6-9 years	2 (28.6%)	14 (25.5 %)	17 (22.1%)	
≥ 10 years	1 (14.3 %)	27 (49.1 %)	59 (76.6%)	

*The values are expressed as frequency with percentage. Comparison of frequency distribution of categorical variables between the groups was assessed by chi-square test. *p<0.05 is considered as statistically significant. ***: p-value <0.001;**: p-value <0.01;*: p-value < 0.05.*

Table 2. Frequency distribution of lifestyle factors, physical activity and duration of DM across the frailty status among the study participants.

and 5.03% (n=7) had no frailty. Regarding drug history, both the pre-frail and frail groups had a higher proportion of patients on Oral Hypoglycemic Agents (OHA) alone compared to those on a combination of OHA and insulin. In both the prefrail and frail groups, the proportion of males was higher than females (Table 1).

Physical activity showed a significant difference across the frailty groups (p<0.001). The frail group had predominantly more participants with low physical activity than moderate physical activity (84.4 % vs 15.6%). In

Parameters	No Frail (n=7)	Pre frail (n=55)	Frail (n=77)	P value
Age	58.00 (11)	59.00 (18)	59.00 (13)	0.871
Duration of DM $^{\#}$	5.00 (16)	9.00 (26)	13.00 (27) †††,‡‡	<0.001 ***
Height (cm) $^{\#}$	161.00 (30)	164.00 (37)	165.00 (33)	0.520
Weight (Kg) $^{\#}$	65.00 (27.1)	68.00 (55.4)	69.5 (46.0)	0.151
WC (cm) $^{\#}$	94.00(12)	95.00 (38)	102.00 (47) †††,‡	<0.001 ***
HC (cm) $^{\#}$	96.00(13)	96.00 (35)	98.00(33)	0.254
BMI $^{\#}$	23.94 (12.28)	25.12(14.20)	25.72(14.34)	0.266
Waist Hip Ratio $^{\#}$	0.94 (0.139)	0.98 (0.344)	1.04 (0.402) †††	<0.001 ***
Fat (Kg) $^{\#}$	18.5 (30.7)	26.50 (34.8)	33.4 (43.3) ††,‡	<0.001 ***
Lean (Kg) $^{\$}$	38.86 ± 7.30	40.43 ± 11.32	38.89 ± 10.80	0.715
Fat % $^{\#}$	33.97 (33.47)	39.848 (46.802)	46.71(64.81) †	0.015 *
Lean % $^{\#}$	66.03 (33.47)	60.15(46.80)	53.28(64.81) †	0.015 *
BFMI $^{\#}$	7.6 (6.8)	8.7 (13.4)	11.4 (15.2) ††,‡	0.001 **
FFMI $^{\#}$	16.8 (7.2)	14.5 (11.3)	12.9 (12.0) †	0.009 **

*$^{\$}$ - The parametric data are presented as mean ± SD, and its statistical analysis was performed using one way ANOVA test with post hoc Bonferroni test done for intragroup analysis. $^{\#}$ - The non – parametric data are presented as median (IQR), and its statistical analysis was performed using the Kruskal Wallis test with post hoc Bonferroni test done for intragroup analysis. The p- value <0.05 was statistically considered significant across the groups; ***: p-value <0.001;**: p-value <0.01;*: p-value < 0.05; within the prefrail & frail groups ; ††† : p-value <0.001; ††: p-value <0.01; †: p-value < 0.05; within no frail & frail groups ‡‡‡ : p-value <0.001; ‡‡: p-value <0.01; ‡: p-value < 0.05; DM: Diabetes Mellitus, WC: Waist Circumference, HC: Hip Circumference, BMI: Body Mass Index, BFMI: Body Fat Mass Index, FFMI: Free Fat Mass Index.*

Table 3. Comparison of sociodemographic profile, anthropometric and body composition indices across the frailty status among the study participants.

the prefrail group 43.6% had low physical activity and 56.4% had moderate physical activity. All the participants with no frailty had moderate physical activity. None of the participants had high physical activity. Dietary pattern and frequency distribution of smoking and alcohol intake did not vary significantly among the frailty groups (Table 2).

The participants were of a comparable age among the frailty groups. There was a significant increase (p<0.001) in the median duration of Diabetes Mellitus of the study participants from 5 years, 9 years to 13 years among no frail, prefrail and frail group respectively. When the duration of DM was categorized, a clear trend emerged. The majority of non-frail participants (57.1%) had DM for ≤5 years. Conversely, the frail group was predominantly composed of patients with long-standing disease; a substantial 76.6% of frail participants had a DM duration of ≥10 years, compared to just 14.3% of the non-frail group in that same category.

The comparison of anthropometric measurements across frailty status among the study participants showed no significant change in the hip circumference and BMI, and a significant increase in WC and WHR (p<0.001). Also, on comparison of body composition parameters it showed significant increase (p=0.015) in fat % with significant decrease (p=0.015) in lean % across the frailty status in the study participants (Table 3).

A significant increase in heart rate (p<0.001), SBP (p=0.006), DBP (p=0.038) and RPP (p<0.001) was observed. The PP and MAP were found to be increased though not significant across the frailty status among the study participants (Table 4).

A significant decrease in TDI i.e., SDNN (p<0.001), RMSSD (p=0.001), NN50 (p=0.005) and pNN50 (p<0.001) was observed. Also, among the FDI there was a significant decrease in Total power (p=0.006), HF power (p<0.001), HF nu (p=0.002) with a significant increase in LF (n.u.) (p=0.003) and LF: HF ratio (p=0.003) among the study participants across the frailty status (Table 5).

A significant increase in FBG (p=0.009), HbA1c (p=0.003), TC (p<0.001), TG (p=0.006), LDL (p=0.010), VLDL (p=0.002) with a significant decrease in HDL levels with a significant decrease (p<0.001), across the frailty status was seen. The lipid risk ratios were significantly increased (p<0.001), among the study participants across

Parameters	No Frail (n=7)	Pre frail (n=55)	Frail (n=77)	P value
HR (beats/min) $^{\#}$	78.00(20)	82.00(34)	86.00(37) †††,‡	<0.001***
SBP (mmHg) $^{\$}$	133.14 ±13.64	137.62±8.330	142.36±10.79 †	0.006 **
DBP (mmHg) $^{\#}$	82.00(15)	88.00(28)	92.00(36)	0.038 *
PP (mmHg) $^{\#}$	48.00(37)	49.00(32.00)	50.00(40)	0.205
MAP (mmHg) $^{\$}$	102.00±8.03	104.83±6.22	108.15±8.31	0.332
RPP $^{\$}$	103.12±11.63	111.53±14.04	123.03±14.54 †††,‡‡	<0.001***

*$^{\$}$ - The parametric data are presented as mean ± SD, and its statistical analysis was performed using one way ANOVA test with post hoc bonferroni test done for intragroup analysis. $^{\#}$ - The non – parametric data are presented as median (IQR), and its statistical analysis was performed using the Kruskal Wallis test with post hoc bonferroni test done for intragroup analysis. The p- value <0.05 was statistically considered significant acorss the groups; ***: p-value <0.001; **: p-value <0.01;*: p-value < 0.05; within the prefrail & frail groups; ††† : p-value <0.001; ††: p-value <0.01; †: p-value < 0.05; within no frail & frail groups ‡‡‡ : p-value <0.001; ‡‡: p-value <0.01; ‡: p-value < 0.05. HR: Heart Rate, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, PP: Pulse Pressure, MAP: Mean Arterial Pressure, RPP: Rate Pressure Product*

Table 4. Comparison of cardiovascular parameters across the frailty status among the study participants.

Parameters	No Frail (n=7)	Pre frail (n=55)	Frail (n=77)	P value
Time domain Indices				
SDNN (ms) $^{\$}$	25.043±5.6589	23.767±11.19	16.744±5.900 ††,‡	<0.001***
RMSSD (ms) $^{\#}$	16.00(9.2)	14.1(44.7)	9.9(29.5) ††,‡	0.001 **
NN50 $^{\#}$	12.00(61)	6.00(38)	3.00(23) ‡	0.005 **
pNN50 $^{\#}$	3.6(7.38)	1.60(19.20)	0.500(8.30) †,‡‡	<0.001***
Frequency domain indices				
LF (ms^2) $^{\#}$	522.0(455)	430.00(859)	326.00(1011)	0.132
HF (ms^2) $^{\#}$	316.00(243)	219.00(605)	124(511) †††,‡‡	<0.001***
TP (ms^2) $^{\#}$	1211.00(971)	1018.00(1705)	713(1979) ‡	0.006 **
LF (nu) $^{\#}$	62.29(18.43)	68.11(38.27)	75.773(48.53) ‡‡	0.003 **
HF (nu) $^{\#}$	37.71(18.43)	32.48(38.36)	24.22(48.53) †,‡	0.002 **
LF:HF $^{\#}$	1.65(1.29)	2.136(6.58)	3.127(6.415) ‡‡	0.003 **

*$^{\$}$ - The parametric data are presented as mean ± SD, and its statistical analysis was performed using one way ANOVA test with post hoc bonferroni test done for intragroup analysis. $^{\#}$ - The non – parametric data are presented as median (IQR), and its statistical analysis was performed using the Kruskal Wallis test with post hoc bonferroni test done for intragroup analysis. The p- value <0.05 was statistically considered significant acorss the groups; ***: p-value <0.001;**: p-value <0.01;*: p-value < 0.05; within the prefrail & frail groups ; ††† : p-value <0.001; ††: p-value <0.01; †: p-value < 0.05; within no frail & frail groups ‡‡‡ : p-value <0.001; ‡‡: p-value <0.01; ‡: p-value < 0.05. SDNN: Standard deviation of NN intervals; RMSSD: Root mean square of standard deviation; NN50: consecutive NN intervals with difference >50ms; pNN50: percentage of NN50 intervals; TP: Total power; LF: Low frequency; HF: High frequency; LF: HF ratio: Low frequency: High-frequency ratio.*

Table 5. Comparison of heart rate variability parameters across the frailty status among the study participants.

Parameters	No Frail (n=7)	Pre frail (n=55)	Frail (n=77)	P-value
FBG (mg/dl) #	152.0(42)	158.00(90)	165.0 (206) ††	0.009 **
HbA1c (%) #	8.3 (3.9)	9.3 (5.9)	11.2 (8.4) ††, ‡	0.003 **
TC (mg/dl) #	346.00 (210)	367.00 (481)	404.0 (539) ††	<0.001***
TG (mg/dl) #	158.00 (91)	173.00 (389)	198.0 (422) ††	0.006 **
HDL (mg/dl) $	37.86±5.699	35.09±7.006	29.56±6.534 †††, ‡‡	<0.001***
LDL (mg/dl) #	122.00 (103)	131.00 (139)	142.00 (101) †	0.010 *
VLDL (mg/dl) #	25.00 (29)	29.00 (52)	35.00 (55) ††	0.002 **
TC/HDL #	8.65 (7.75)	10.91 (16.34)	13.7 (32.90) †††, ‡‡	<0.001***
LDL/HDL #	3.00 (3.65)	3.81 (6.34)	4.88 (7.87) †††, ‡‡	<0.001***
TG/HDL #	4.325 (4.011)	5.03 (12.42)	6.95 (22.61) †††, ‡	<0.001***
Atherogenic Index#	1.396 (0.276)	1.46 (0.674)	1.564 (0.995) †††, ‡	<0.001***

*$ - The parametric data are presented as mean ± SD, and its statistical analysis was performed using one way ANOVA test with post hoc bonferroni test done for intragroup analysis. # - The non – parametric data are presented as median (IQR), and its statistical analysis was performed using the Kruskal Wallis test with post hoc bonferroni test done for intragroup analysis. The p-value <0.05 was statistically considered significant acorss the groups; ***: p-value <0.001;**: p-value <0.01;*: p-value < 0.05; within the prefrail & frail groups ; ††† : p-value <0.001; ††: p-value <0.01; †: p-value < 0.05; within no frail & frail groups ‡‡‡ : p-value <0.001; ‡‡: p-value <0.01; ‡: p-value < 0.05. FBG: Fasting Blood Glucose, HbA1c: Glycated Hemoglobin, TC: Total Cholesterol, TG: Triglycerides, HDL: High Density Lipoprotein, LDL: Low Density Lipoprotein, VLDL: Very Low density lipoprotein.*

Table 6. Comparison of metabolic profile across the frailty status among the study participants.

the frailty status (Table 6).

The relationship between the frailty score and other key variables is detailed. The frailty score showed a significant positive correlation with duration of DM (r=0.447, p<0.001), Waist Circumference (r=0.347, p<0.001), Waist-Hip Ratio (r=0.317, p<0.001), and fat percentage (r=0.200, p=0.018). Conversely, it had a significant negative correlation with lean percentage (r=-0.200, p=0.018). Regarding autonomic function, the score was negatively correlated with Total Power (r=-0.178, p=0.036) and positively correlated with the LF:HF ratio (r=0.355, p<0.001). All assessed metabolic parameters showed a strong and significant correlation with a higher frailty score, including FBG (r=0.390, p<0.001), HbA1c (r=0.472, p<0.001), and all adverse lipid measures (e.g., TC, TG, LDL), while HDL showed a significant negative correlation (r=-0.463, p<0.001) (Table 7).

There was a significant positive correlation of LF:HF ratio with waist circumference (p=0.003) and waist hip ratio (p=0.01). Frailty score had a significant positive correlation with LF-HF ratio (p<0.001). A significant positive correlation of LF-HF ratio was observed with fasting blood glucose, HbA1c and several lipid profile parameters. LF-HF had a significant negative correlation with HDL (Table 8).

Physical activity had a significant correlation with frailty status when the duration of DM was ≥10 years (p<0.001) (Table 9).

Discussion

The principal finding of this study is the remarkably high prevalence of frailty among Indian patients with Type 2 Diabetes Mellitus, with 95% of the cohort classified as either pre-frail or frail. Our results demonstrate that this frailty status is not an isolated condition but is significantly associated with a cluster of risk factors, including longer diabetes duration, physical inactivity, adverse body composition, autonomic dysfunction, and a worsening cardiometabolic profile.

The study also identified a concerning trend towards a worsening metabolic profile with increasing frailty. Glycated hemoglobin (HbA1c) and FBG level were significantly increased in frail patients than non-frail counterparts. This indicates poorer long-term glycemic control, potentially due to challenges with diabetes management in the setting of frailty. Furthermore, the lipid profile exhibited a concerning pattern. TC, TG, VLDL, LDL, were all significantly elevated in frail patients, while HDL, the "good" cholesterol, was significantly lower. These observations indicate a heightened risk of CVD in frail individuals with T2DM, as supported by the findings of Casals et al[19]. The observed correlations between frailty and a worsening metabolic profile underscore the need for comprehensive care that addresses not only diabetes management but also cardiovascular risk factors in frail patients.

This aligns with previous research by Kulkarni et al[12].

Parameters	Frailty score	
	r- value	p-value
Duration of DM	0.447	<0.001 ***
Waist Circumference (cm)	0.347	<0.001 ***
Waist Hip Ratio	0.317	<0.001 ***
Fat %	0.200	0.018 *
Lean %	-0.200	0.018 *
TP (ms^2)	-0.178	0.036 *
LF:HF	0.355	<0.001 ***
FBG (mg/dl)	0.390	<0.001 ***
HbA1c (%)	0.472	<0.001 ***
TC (mg/dl)	0.392	<0.001 ***
TG (mg/dl)	0.356	<0.001 ***
HDL (mg/dl)	-0.463	<0.001 ***
LDL (mg/dl)	0.358	<0.001 ***
VLDL (mg/dl)	0.440	<0.001 ***
TC/HDL	0.553	<0.001 ***
LDL/HDL	0.505	<0.001 ***
TG/HDL	0.481	<0.001 ***
Atherogenic Index	0.494	<0.001 ***

*The data were analysed using Spearman's correlation. p: Spearman's coefficient; p <0.05 was considered statistically significant; ***: p-value <0.001;**: p-value <0.01;*: p-value < 0.05; DM: diabetes Mellitus; TP: Total power; LF: HF ratio: Low frequency: High-frequency ratio; FBG: Fasting Blood Glucose, HbA1c: Glycated Hemoglobin, TC: Total Cholesterol, TG: Triglycerides, HDL: High Density Lipoprotein, LDL: Low Density Lipoprotein, VLDL: Very Low density lipoprotein.*

Table 7. Correlation of frailty score with body composition and metabolic profile among the study participants.

Parameters	LF:HF	
	r-value	p-value
Duration of DM	0.106	0.216
Frailty score	0.355	<0.001 ***
Waist Circumference (cm)	0.250	0.003 **
Waist Hip Ratio	0.217	0.010 *
Fat %	0.125	0.143
Lean %	-0.125	0.143
FBG (mg/dl)	0.245	0.004 **
HbA1c (%)	0.246	0.003 **
TC (mg/dl)	0.171	0.044 *
TG (mg/dl)	0.198	0.02 *
HDL (mg/dl)	-0.193	0.023 *
LDL (mg/dl)	0.119	0.161
VLDL (mg/dl)	0.216	0.011 *
TC/HDL	0.241	0.004 **
LDL/HDL	0.204	0.016 *
TG/HDL	0.255	0.002 **
Atherogenic Index	0.254	0.003 **

*The data were analysed using Spearman's correlation. p: Spearman's coefficient; p <0.05 was considered statistically significant; ***: p-value <0.001;**: p-value <0.01;*: p-value < 0.05; DM: diabetes Mellitus; TP: Total power; LF: HF ratio: Low frequency: High-frequency ratio; FBG: Fasting Blood Glucose, HbA1c: Glycated Hemoglobin, TC: Total Cholesterol, TG: Triglycerides, HDL: High Density Lipoprotein, LDL: Low Density Lipoprotein, VLDL: Very Low-density lipoprotein.*

Table 8. Correlation of heart rate variability with frailty score, body composition and metabolic profile among the study participants.

Normally, as people age, the natural decline in physical function, muscle mass, and resilience, increases frailty risk[13]. Furthermore, diabetes itself can exacerbate these declines by impacting cardiovascular health, the nervous system and through development of complications. Additionally, lifestyle factors like physical inactivity, poor diet and smoking can contribute to both diabetes progression and frailty as noted by Chen et al[13,14]. But in our study, the participants were of a comparable age across the frailty groups. Also, they had a similar pattern of dietary intake and smoking/alcohol behavior across the frailty groups.

Notably, the duration of diabetes and physical activity emerged as significant factors associated with frailty. The observed increase in frailty score with longer diabetes duration suggests a cumulative effect of the disease on frailty development[15]. Decrease in physical activity can result in the early onset of frailty[16]. These findings underscore the importance of early intervention in diabetes management and promoting healthy aging practices to potentially mitigate frailty risk.

Interestingly, the study did not reveal significant differences in body mass index (BMI) across frailty categories. However, we observed a striking trend towards central obesity, as evidenced by higher WC and WHR in frail patients. This suggests a shift towards fat accumulation around the abdomen, which is linked to poorer health outcomes. Furthermore, a significant decrease in lean mass

Characteristics	No Frail (n = 7)	Pre-frail (n = 55)	Frail (n = 77)	P value
	n (%)	n (%)	n (%)	
Duration ≤ 5 years				
PA Low	0	5 (35.7%)	0	0.298
PA Moderate	4 (100%)	9 (64.3%)	1 (100%)	
Duration 6-9 years				
PA Low	0	7 (50%)	13 (76.5%)	0.063
PA Moderate	2 (100%)	7 (50%)	4 (23.5%)	
Duration ≥10 years				
PA Low	0	12 (44.4%)	52 (88.1%)	<0.001***
PA Moderate	1 (100%)	15 (55.6%)	7 (11.9%)	

*The values are expressed as frequency with percentage. Comparison of frequency distribution of categorical variables between the groups was assessed by chi-square test. *p<0.05 is considered as statistically significant. ***: p-value <0.001; **: p-value <0.01; *:p-value < 0.05. DM: Diabetes mellitus, PA: Physical activity.*

Table 9. Association of physical activity with frailty considering the duration of DM.

(muscle) with concomitant increase in fat percentage were observed with increasing frailty. This aligns with the work of Dodds et al., who suggest that reduced muscle mass and increased body fat can impair physical function and strength, the key components of frailty[17]. These findings highlight altered body composition, particularly a decrease in lean % and an increase in fat %, as a potential target for interventions aimed at reducing frailty in T2DM patients.

The study also points towards heightened cardiovascular stress in frail individuals. Patients with greater frailty exhibited significantly higher HR, BP and RPP. These trends suggest a potential for increased cardiovascular workload and strain. This aligns with the understanding that frailty is often associated with reduced physiological resilience, making individuals more susceptible to cardiovascular stressors. In fact, a recent meta-analysis by Debain et al. found that frail older adults have a significantly higher likelihood of autonomic dysfunction, including impaired cardiovascular responses to stress, which is consistent with our findings of elevated cardiovascular parameters at rest[21]. These findings suggest that T2DM patients with frailty may benefit from regular monitoring of cardiovascular health and potential interventions to improve cardiovascular function.

Our study revealed significant alterations in HRV indices across frailty categories, suggesting a reduction in parasympathetic activity and a shift towards sympathetic dominance in frail individuals. This finding of globally reduced HRV and impaired cardiac autonomic control is well-supported by previous research in community-dwelling older adults, which has consistently demonstrated that frailty coincides with reduced cardiovascular dynamical complexity and lower overall HRV measures[22,23]. More specifically, our observation of sympathetic predominance is directly corroborated by a pilot study from Katayama et al., who also reported a significant autonomic imbalance characterized by a shift toward sympathetic predominance in frail elderly women[24]. A key contribution of our work is demonstrating this pattern specifically within a T2DM population, as the diabetic status of participants was not clearly reported in these foundational studies. This is a critical distinction, as patients with diabetes are already prone to autonomic dysfunction. Our findings suggest that frailty introduces an additional layer of sympathovagal imbalance, likely compounding the overall cardiovascular risk in this vulnerable group.

A key finding with significant clinical implications is the role of physical activity as a determinant of frailty, particularly in patients with long-standing diabetes (≥10 years). Our analysis consistently showed that even in the presence of a long disease duration, individuals undertaking moderate physical activity were less likely to be frail. This aligns with evidence highlighting physical activity as a vital factor in mitigating frailty and improving cardiovascular health[20]. As a readily modifiable lifestyle factor, promoting regular physical activity represents a promising and accessible primary intervention to delay the onset of frailty and reduce subsequent cardiovascular risk in this vulnerable population.

Limitations

This study has several limitations that should be acknowledged. First, its cross-sectional design precludes any inference of causality; we can identify significant associations, but not determine whether frailty leads to these outcomes or vice-versa. Second, participants were recruited from a single tertiary care center using a convenience sampling method, which may limit the generalizability of our findings to the broader diabetic population in other settings. Third, while we accounted for key variables like the duration of diabetes, the possibility of residual confounding from unmeasured factors (e.g., specific medications, nutritional details) cannot be entirely ruled out. Finally, our statistical approach was limited to univariate analysis; a multivariate analysis to identify the most significant independent predictors of frailty should be a goal for future research. Future longitudinal studies with multi-center recruitment would also be beneficial to confirm and expand upon our findings.

Conclusions

Our study demonstrates a high prevalence of frailty in patients with T2DM, where it presents as a multifaceted syndrome linked to adverse body composition, autonomic dysfunction, and poor cardiometabolic health. These findings underscore the necessity of a holistic management approach that moves beyond glycemic control to include strategies for improving cardiovascular resilience, with physical activity being a cornerstone intervention.

Ethics Approval

This cross-sectional analytical study received approval from the Institutional Ethics Committee (Human) of JIPMER, Puducherry, India (Approval No. JIP/IEC-OS/288/2023) and the Institute Undergraduate Research Monitoring committee. The study was conducted in accordance with the ethical guidelines set by the Indian Council of Medical Research (ICMR).

Consent to Participate

All participants provided written informed consent after a detailed explanation of the study protocol and prior to their inclusion in the study.

Authors' Contributions

Contribution of the concept and design of work: Saranya Kuppusamy, Dukhabandhu Naik, Senthil Kumar Subramanian. Data Acquisition: Pranav K V, Kavitha Natarajan, Saranya Kuppusamy. Data Analysis and interpretation: Saranya Kuppusamy, Senthil Kumar Subramanian, Kavitha Natarajan. Drafting of manuscript: Saranya Kuppusamy, Senthil Kumar Subramanian, Pranav K V. All authors read and approved the final manuscript and agree to be accountable for all aspects of the current work.

Funding

The research work was selected under the Short-Term Studentship (STS-2023) programme of the Indian Council of Medical Research (ICMR).

Acknowledgments

The authors would like to thank all participants in this study.

References

1. Sinclair A, Saeedi P, Kaundal A, et al. Diabetes and global ageing among 65-99-year-old adults: Findings from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Res Clin Pract. 2020;162:108078.
2. Pradeepa R, Mohan V. Epidemiology of type 2 diabetes in India. Indian J Ophthalmol. 2021;69:2932-8.
3. Chung SM, Moon JS, Chang MC. Prevalence of Sarcopenia and Its Association With Diabetes: A Meta-Analysis of Community-Dwelling Asian Population. Front Med (Lausanne). 2021;8:681232.
4. American Diabetes Association. Standards of Medical Care in Diabetes—2022 Abridged for Primary Care Providers. Clin Diabetes. 2022;40:10-38.
5. Gonzalez MC, Barbosa-Silva TG, Heymsfield SB. Bioelectrical impedance analysis in the assessment of sarcopenia. Curr Opin Clin Nutr Metab Care. 2018;21:366-74.
6. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56:M146-56.
7. Chang YW, Chen WL, Lin FG, et al. Frailty and its impact on health-related quality of life: a cross-sectional study on elder community- dwelling preventive health service users. PLoS One. 2012;7:e38079.
8. Prashantha B, Balgi V, Bharath MS, et al. Frailty and pre-frailty in elderly type 2 diabetes mellitus: Determinants and adverse outcomes. J Cardiovasc Dis Res. 2021:12:3146-52.
9. Ko D, Bostrom JA, Qazi S, et al. Frailty and Cardiovascular Mortality: A Narrative Review. Curr Cardiol Rep. 2023;25(4):249-59.
10. Coopmans C, Zhou TL, Henry RMA, et al. Both Prediabetes and Type 2 Diabetes Are Associated With Lower Heart Rate Variability: The Maastricht Study. Diabetes Care. 2020;43:1126-33.
11. Arantes FS, Rosa Oliveira V, Leão AKM, et al. Heart rate variability: A biomarker of frailty in older adults? Front Med (Lausanne). 2022;9:1008970.
12. Das S. The impact of diabetes on sarcopenia in community-dwelling older adults in India: key findings from the longitudinal ageing study in India (LASI). Diabetes Epidemiology and Management. 2023;12:100158.
13. Kaur I, Das S, Chandel S, Chandel S. Possible sarcopenia, sarcopenic obesity phenotypes and their association with diabetes: Evidence from LASI wave-1 (2017-18). Diabetes & Metabolic Syndrome. 2025;19(2):103185.
14. Tripathi D, Sethi P, et al. Prevalence of sarcopenia and its determinants in people with type 2 diabetes: Experience from a tertiary care hospital in north India. Diabetes & Metabolic Syndrome. 2023;17(12):102902.
15. Yogesh YM, Mody M, Makwana N, et al. The Hidden Battle Within: Shedding Light on the Coexistence of Sarcopenia and Sarcopenic Obesity among Participants with Type 2 Diabetes in a Tertiary Care Hospital. Gujarat Indian J Endocrinol Metab. 2024;28(1):80–85.
16. Basu S, Maheshwari V. Diabetes and frailty in community dwelling older adults in India: insights from the longitudinal aging study in India. International Journal of Diabetes in Developing Countries. 2024.
17. Maheshwari V, Basu S. Sarcopenic obesity burden, determinants, and association with risk of frailty, falls, and functional impairment

in older adults with diabetes: A propensity score matching analysis. Cureus. 2024.
18. Ansari MA, Zaidi AS, Akhter P, et al. Association of muscle performance and heart rate variability in middle-aged type 2 diabetes mellitus. J Family Med Prim Care. 2025;14(4):1502-1512.
19. Casals C, Casals Sánchez JL, Suárez Cadenas E, et al. Frailty in older adults with type 2 diabetes mellitus and its relation with glucemic control, lipid profile, blood pressure, balance, disability grade and nutritional status. Nutr Hosp. 2018;35(4):820-6.
20. Angulo J, El Assar M, Álvarez-Bustos A, et al. Physical activity and exercise: Strategies to manage frailty. Redox Biol. 2020;35:101513.
21. Debain A, Loosveldt FA, Knoop V, et al. Frail older adults are more likely to have autonomic dysfunction: A systematic review and meta-analysis. Ageing Res Rev. 2023;88:101925.
22. Chaves PH, Varadhan R, Lipsitz LA, et al. Physiological complexity underlying heart rate dynamics and frailty status in community-dwelling older women. J Am Geriatr Soc. 2008;56(9):1698-703.
23. Varadhan R, Chaves PH, Lipsitz LA, et al. Frailty and impaired cardiac autonomic control: new insights from principal components aggregation of traditional heart rate variability indices. J Gerontol A Biol Sci Med Sci. 2009;64(6):682-7.
24. Katayama PL, Dias DP, da Silva LE, et al. Cardiac autonomic modulation in non-frail, pre-frail and frail elderly women: a pilot study. Aging Clin Exp Res. 2015;27(5):621-9.

Supplementary File 1.

IPAQ-short Scoring Protocol.

Participants were classified into one of three physical activity levels based on their total activity over the last 7 days, according to the official guidelines for the International Physical Activity Questionnaire (IPAQ) short form.

Activity Categories

<u>Low</u>: This category includes participants who did not meet the criteria for either the moderate or high categories.

<u>Moderate</u>: This category includes participants who met any of the following criteria:
a. 3 or more days of vigorous-intensity activity of at least 20 minutes per day.
b. 5 or more days of moderate-intensity activity or walking of at least 30 minutes per day.
c. 5 or more days of any combination of walking, moderate-intensity, or vigorous-intensity activities achieving a minimum total of at least 600 MET-minutes/week.

<u>High</u>: This category includes participants who met either of the following criteria:
a. Vigorous-intensity activity on at least 3 days, accumulating a minimum of at least 1500 MET-minutes/week.
b. 7 or more days of any combination of walking, moderate-intensity, or vigorous-intensity activities accumulating a minimum of at least 3000 MET-minutes/week.