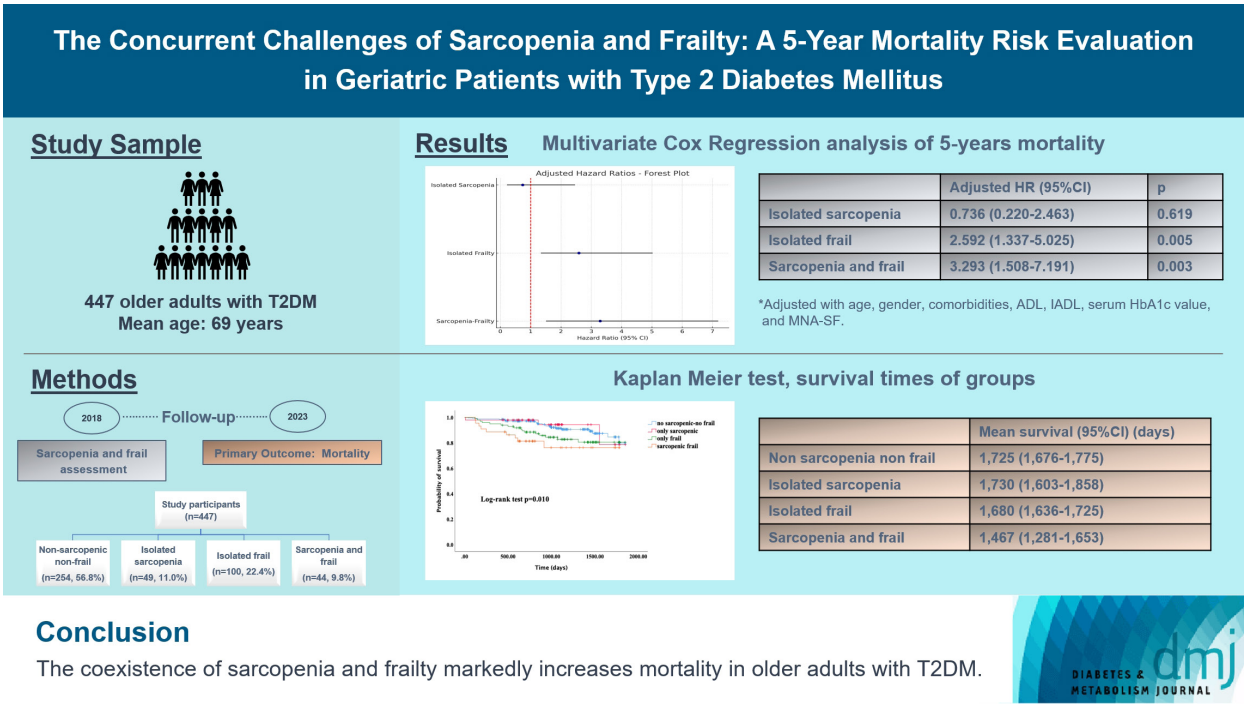
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Highlights

- **The median age was 75 years in the sarcopenia-frailty group and 68–71 years in other groups.**
- **ADL dependency was 20.5% in the sarcopenia-frailty group, but 0.8% in the robust group.**
- **Coexisting sarcopenia and frailty increased the risk of 5-year mortality by 3.29-fold.**

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The Concurrent Challenges of Sarcopenia and Frailty: A 5-Year Mortality Risk Evaluation in Geriatric Patients with Type 2 Diabetes Mellitus

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Background: Type 2 diabetes mellitus (T2DM) is common among older adults and may increase the risk of sarcopenia and frailty. This study evaluated the impact of sarcopenia and frailty on 5-year mortality in older adults with T2DM.
Methods: We assessed a cohort study of 447 adults with T2DM who were more than 60 years old. Following the guidelines set by the European Working Group on Sarcopenia in Older People 2 (EWGSOP2), we used bioelectrical impedance analysis to measure muscle mass and a handgrip dynamometer to measure muscle strength. We assessed frailty using the Fatigue, Resistance, Ambulation, Illnesses, and Loss of Weight (FRAIL) Scale. We categorised the patients into four groups: isolated sarcopenia, isolated frailty, both conditions (sarcopenia and frailty), or neither.
Results: The median age of the patients was 69 years, and 71.6% were female. Isolated sarcopenia was present in 11.0% of patients, isolated frailty in 22.4%, and both sarcopenia and frailty in 9.8%. After adjustment for age, sex, comorbidities, activities of daily living, glycemic control, and nutritional status, sarcopenia and frailty were significantly associated with an increased risk of 5-year mortality. Isolated frailty also significantly predicted mortality (hazard ratio, 2.59; 95% confidence interval, 1.34 to 5.03; $P=0.005$).
Conclusion: Sarcopenia and frailty were significant predictors of increased mortality risk in older adults with T2DM. Coexisting sarcopenia and frailty posed the highest risk. Early identification and targeted interventions for these conditions in older patients with T2DM are crucial to improving outcomes.

Keywords: Aged; Diabetes mellitus, type 2; Frailty; Mortality; Sarcopenia

INTRODUCTION

The global ageing population presents significant challenges in the management of chronic conditions. Over 500 million patients worldwide have been diagnosed with type 2 diabetes mellitus (T2DM), nearly half of whom are over the age of 65 [1]. Patients with T2DM frequently experience comorbidities such as neuropathy, nephropathy, and retinopathy, which are directly associated with the progression of the disease. Additionally, conditions such as sarcopenia and frailty, though not necessarily part of the direct pathophysiological course of T2DM, may further exacerbate its clinical impact [2].

Sarcopenia is notably more prevalent among patients with T2DM, with reported rates ranging from 5% to 50%, compared to those without the condition [3]. The underlying mechanisms of T2DM—including mitochondrial dysfunction, elevated pro-inflammatory cytokines (tumor necrosis factor-α, interleukin 1 [IL-1], IL-5, and IL-6), and hormonal imbalances (e.g., reduced testosterone and insulin like growth factor 1, as well as alterations in leptin and ghrelin)—contribute to insulin

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resistance and muscle protein degradation [4-6]. These processes increase the risk of sarcopenia, which is often considered a secondary consequence of T2DM [7,8].

Frailty, which is influenced by a complex interplay of genetic, epigenetic, and environmental factors, is another common condition coexisting with T2DM. T2DM accelerates the development of frailty through mechanisms such as arteriosclerosis, chronic inflammation, insulin resistance, oxidative stress, and mitochondrial dysfunction [4]. Both sarcopenia and frailty are associated with adverse clinical outcomes, including increased risks of falls, hospitalizations, and mortality [6,9].

Improving the quality of life for older adults remains a central goal in healthcare. Early identification and effective management of conditions such as frailty and sarcopenia are critical, especially in older adults with T2DM [10]. Moreover, these comorbidities often influence treatment strategies more significantly in older patients than in younger patients. Therefore, timely detection of sarcopenia and frailty is essential for optimizing treatment outcomes in this group [11].

This study investigated the impact of sarcopenia and frailty on 5-year mortality in older adults with T2DM receiving outpatient care. By emphasizing the importance of early detection of these comorbidities, this research underscores the need for individualized treatment strategies in clinical practice for older adults with T2DM.

METHODS

Study participants

This comparative study included outpatients aged 60 years and older who were diagnosed with T2DM and attended a tertiary healthcare facility between November 2018 and November 2023. The exclusion criteria included patients with diseases that could affect handgrip strength (HGS) measurements, such as malignancy, immobility, peripheral neuropathy, hand osteoarthritis, or dementia. Furthermore, patients were excluded from the bioelectrical impedance analysis (BIA) if they had cardiovascular stents, pacemakers, joint prostheses, or observable edema.

Ethical considerations

The Clinical Research Ethics Committee of Erciyes University approved the study (approval number: 2024/243). Written consent was obtained from all patients.

Demographic and clinical evaluation

Demographic information, encompassing age, gender, body mass index (BMI), and comorbidities, was documented for all patients. The use of antidiabetic medications, including metformin and insulin, was recorded. Serum glycosylated hemoglobin (HbA1c) levels were assessed following an 8-hour overnight fast, conducted in the morning.

Comprehensive geriatric assessment

A geriatrician performed all geriatric assessments and anthropometric measurements at baseline. Physical performance was evaluated using the activities of daily living (ADL) and instrumental activities of daily living (IADL) measures. ADL encompasses six elements: eating, bowel and bladder management, toileting, transfers, dressing, and bathing. IADL comprises eight elements: telephone usage, meal preparation, shopping, financial management, household tasks, laundry, travel beyond walking distance, and medication administration. All activities were categorised as either dependent or independent. Impairment was defined as the need for assistance with at least one item on the corresponding scale [12,13].

A clinical dietitian assessed the nutritional status using the Mini Nutritional Assessment-Short Form (MNA-SF). The Timed Up and Go (TUG) test assessed the time, in seconds, needed for a patient to stand from a conventional chair (seat height approximately 46 cm), traverse a distance of 3 m, pivot, return to the chair, and sit down once again [14].

Evaluation of frailty

Frailty was evaluated utilising the FRAIL scale, including five domains: fatigue, resistance, ambulation, illnesses, and weight loss. Patients were categorised as non-frail with a total score of 0, pre-frail with a total score of 1–2, and frail with a total score of 3–5 [15].

Assessment of sarcopenia

We used the SARC-F questionnaire to assess limitations in strength (S), assistance walking (A), rising from a chair (R), climbing stairs (C), and falls (F). A score of 4 or above signifies an elevated risk of sarcopenia [16].

Muscle strength was assessed via a handgrip dynamometer (Takei TKK5401 Digital Handgrip Dynamometer, Niigata City, Japan), with patients in a seated position and their elbows extended. Three measurements were obtained from the dominant hand, with a 1-minute interval between each measurement.

The average of these measurements was documented. The European Working Group on Sarcopenia in Older People 2 (EWGSOP2) standards stipulate that HGS levels below 27 kg for men and below 16 kg for females signify low muscle strength [17].

Skeletal muscle mass (SMM; kg) was measured using BIA (Bodystat Quad Scan 1500, Bodystat, Isle of Man, UK) [18]. In older adults who are overweight or obese, muscle mass was adjusted based on BMI for better accuracy. SMM was adjusted by BMI and defined as the skeletal muscle mass index (SMMI) (kg/BMI). According to the EWGSOP2 guidelines, low muscle mass is characterised as an SMMI of less than 1.049 kg/BMI for men and less than 0.823 kg/BMI for females [17,18].

According to the EWGSOP2 recommendations, probable sarcopenia is defined only by low muscle strength. The diagnosis of sarcopenia requires the presence of both low muscle mass and low muscle strength. Severe sarcopenia is characterised by a combination of slow walking speed, low muscle mass, and low muscle strength [7].

Walking speed served as an additional indicator of physical performance. A walking speed below 0.8 m/sec was deemed indicative of compromised physical performance [7].

Outcomes and follow-up

The primary outcome of the study was all-cause mortality. Mortality data were acquired from the patients' medical records. The follow-up duration was determined from the date of the initial examination to either the date of death or the final follow-up, spanning from November 2018 to November 2023.

Statistical examination

Descriptive statistics for continuous variables are shown as mean±standard deviation for data that follow a normal distribution, or as median (interquartile range [IQR]) for data that do not follow a normal distribution, based on the Shapiro-Wilk test. Categorical variables are represented as frequencies (percentages). The chi-square test was employed to evaluate the differences in categorical variables among the four groups.

The association between isolated frailty, isolated sarcopenia, coexisting sarcopenia and frailty, and 5-year mortality was examined with multivariable Cox regression analysis after adjusting for the following confounding variables: age, sex, comorbidities, ADL, IADL, serum HbA1c levels, and MNA-SF score. Survival probabilities for patients grouped by their sarcopenia and frailty status (isolated frailty, isolated sarcopenia, and coexisting sarcopenia and frailty, and the non-sarcopenic/non-frail group as the reference) were calculated using Kaplan-Meier analysis. All statistical analyses were performed using SPSS software version 26.0 (IBM Co., Armonk, NY, USA). Statistical significance was set at $P<0.05$.

RESULTS

A total of 551 patients were initially enrolled in the study; however, 104 were excluded based on predefined exclusion criteria, resulting in a final sample of 447 patients. The median age of the patients was 69 years (IQR, 65 to 75), and 71.6% were female. Among the patients, 11.0% (49/447) had isolated sarcopenia, 22.4% (100/447) had isolated frailty, and 9.8% (44/447) had both sarcopenia and frailty. The remaining 56.8% (254/447) were classified as neither sarcopenic nor frail (Fig. 1).

The demographic and clinical characteristics of the four groups (i.e., isolated sarcopenia, isolated frailty, sarcopenia and frailty, and non-sarcopenic/non-frail groups) are presented in Table 1. The median age of the sarcopenia and frailty group was 75 years (IQR, 68 to 82), which was significantly higher than that of the other groups ($P<0.001$).

The HGS of female patients in the sarcopenia and frailty group was 12 kg (IQR, 10 to 15), and the HGS of male patients in this group was 20 kg (IQR, 17 to 24); these values were significantly lower than those in the other three groups in both male and female patients ($P<0.001$).

Among the cohort, 11.0% (49/447) had isolated sarcopenia, 22.4% (100/447) had isolated frailty, 9.8% (44/447) had both

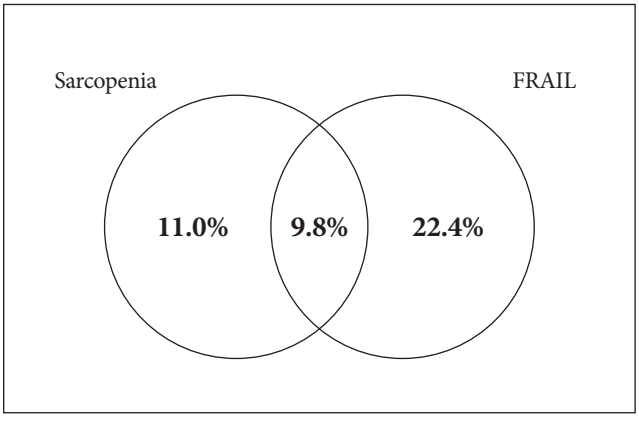


Fig. 1. The prevalence of sarcopenia, frail and sarcopenic frail group. FRAIL, Fatigue, Resistance, Ambulation, Illnesses, and Loss of Weight.

sarcopenia and frailty, and 56.8% (254/447) were non-sarcopenic and non-frail. The sarcopenia and frailty group had the highest median age (75 years [IQR, 68 to 82], $P<0.001$). HGS was significantly reduced in this group, at 12 kg (IQR, 10 to 15) in female patients and 20 kg (IQR, 17 to 24) in male patients ($P<0.001$). They also had significantly lower SMMI ($P<0.001$), greater dependence in ADL and IADL ($P<0.001$ for both), and impaired physical performance, including slower gait speed and prolonged TUG test times ($P<0.001$). Median HbA1c was higher in the sarcopenia and frailty group (8.0 [IQR, 7.0 to 9.2], $P=0.035$), and the median MNA-SF score indicated higher malnutrition risk (8.0 [IQR, 7.0 to 10.0], $P<0.001$). Patients with sarcopenia and frailty had a significantly lower SMMI adjusted for BMI than the other groups ($P<0.001$) (Table 1).

In our study sample, 50.8% of patients were using metformin. The majority of patients on metformin (61.2% [139/227]) were non-sarcopenic and non-frail ($P<0.001$) (Table 1). The median SARC-F score for the sarcopenia and frailty group was 6.0 (IQR, 4.0 to 7.0), significantly exceeding those of the other groups ($P<0.001$) (Table 1).

Multivariable Cox regression analysis revealed that older adults with T2DM who had both sarcopenia and frailty had a significantly increased risk of 5-year mortality (adjusted hazard ratio [HR], 3.29; 95% confidence interval [CI], 1.51 to 7.19;

Table 1. Demographic and clinical characteristics of patients

Variable	Total ($n=447$)	Isolated sarcopenic ($n=49$)	Isolated frail ($n=100$)	Sarcopenia and frail ($n=44$)	Non-sarcopenic/ non-frail ($n=254$)	*P* value
Age, yr	69 (65–75)	71 (67–74)	70 (66–76)	75 (68–82)	68 (65–73)	<0.001
Sex						0.038
Male	127 (28.4)	16 (32.7)	17 (17)	15 (34.1)	79 (31.1)	
Female	320 (71.6)	33 (67.3)	83 (83)	29 (65.9)	175 (68.9)	
BMI, kg/m²	31.2 (27.7–36.5)	31.7 (29.0–36.4)	31.8 (27.3–37.5)	32.0 (27.6–37.2)	31.0 (27.7–35.0)	0.645
Hand grip strength, kg						
Male	28 (23–36)	23 (21–25)	28 (21–34)	20 (17–24)	30 (28–40)	<0.001
Female	20 (16–23)	13 (11–14)	20 (17–23)	12 (10–15)	21 (19–25)	<0.001
SMMI adjusted for BMI, m²						
Male	1.06 (0.96–1.18)	0.88 (0.79–0.97)	1.15 (1.05–1.19)	0.94 (0.88–0.98)	1.10 (1.04–1.21)	<0.001
Female	0.70 (0.62–0.79)	0.65 (0.60–0.74)	0.72 (0.62–0.80)	0.64 (0.59–0.70)	0.72 (0.65–0.82)	<0.001
Dependent on ADL	30 (6.7)	2 (4.1)	17 (17.0)	9 (20.5)	2 (0.8)	<0.001
Dependent on IADL	121 (27.1)	14 (28.6)	47 (47.0)	30 (68.2)	30 (11.8)	<0.001
SARC-F	3.0 (1.0–5.0)	2.0 (1.0–4.0)	4.5 (3.0–7.0)	6.0 (4.0–7.0)	1.0 (1.0–3.0)	<0.001
4mWT, m/sec	1.00 (0.78–1.25)	1.23 (1.0–1.48)	1.03 (0.83–1.25)	1.50 (1.13–1.75)	0.87 (0.73–1.11)	<0.001
TUG, sec	11.7 (9.5–14.5)	13.0 (10.0–15.0)	13.0 (10.0–17.0)	17.0 (14.0–21.0)	10.9 (8.8–12.9)	<0.001
No. of comorbidities	3 (2–4)	3 (2–4)	3 (3–5)	4 (3–5)	3 (2–3)	<0.001
MNA-SF score	11.0 (9.0–13.0)	10.0 (9.0–12.0)	10.0 (8.0–12.0)	8.0 (7.0–10.0)	12.0 (10.0–14.0)	<0.001
Use of metformin	227 (50.8)	32 (65.3)	40 (40.0)	16 (36.4)	139 (54.7)	0.003
Use of insulin	133 (31.5)	12 (24.4)	31 (31.0)	20 (45.5)	70 (27.6)	0.090
HbA1c, %	7.3 (6.5–8.6)	7.2 (6.4–8.3)	7.1 (6.3–8.4)	8.0 (7.0–9.2)	7.3 (6.5–8.7)	0.035
Mortality	50 (11.2)	3 (6.1)	16 (16.0)	9 (20.5)	22 (8.7)	0.029

Values are presented as median (interquartile range) or number (%). Cox regression model showed that both only frailty and sarcopenia frailty after adjusting for age, gender, comorbidities, ADL, IADL, serum HbA1c value, MNA-SF score was significantly associated with 5-year mortality (hazard ratio [HR], 2.59; 95% confidence interval [CI], 1.34 to 5.03; $P=0.005$; and HR, 3.29; 95% CI, 1.51 to 7.19; $P=0.003$, respectively) (Table 2).

BMI, body mass index; SMMI, skeletal muscle mass ındex; ADL, activities of daily living; IADL, instrumental activities of daily living; SARC-F, Strength, Assistance with walking, Rise from a chair, Climb stairs, and Falls; 4mWT, 4 m Walking Test; TUG, Timed Up and Go; MNA-SF, Mini Nutritional Assessment-Short Form; HbA1c, glycosylated hemoglobin.

Table 2. Univariate and multivariate Cox regression analysis of 5-year mortality

	Unadjusted multivariate HR (95% CI)	*P* value	Adjusted multivariate HR (95% CI)	*P* value
Isolated sarcopenia	0.815 (0.244–2.726)	0.740	0.736 (0.220–2.463)	0.619
Isolated frailty	1.914 (1.005–3.647)	0.048	2.592 (1.337–5.025)	0.005
Sarcopenia-frailty	3.140 (1.441–6.843)	0.004	3.293 (1.508–7.191)	0.003

Adjusted for age, sex, comorbidities, activities of daily living, instrumental activities of daily living, serum glycosylated hemoglobin value, and Mini Nutritional Assessment-Short Form. The reference group comprised individuals without sarcopenia and frailty.
HR, hazard ratio; CI, confidence interval.

Table 3. Kaplan–Meier analysis of survival by sarcopenia and frailty status

	Mean survival (95% CI), day
Non-sarcopenic non-frail	1,725 (1,676–1,775)
Only sarcopenic	1,730 (1,603–1,858)
Only frail	1,680 (1,636–1,725)
Sarcopenic frail	1,467 (1,281–1,653)

CI, confidence interval.

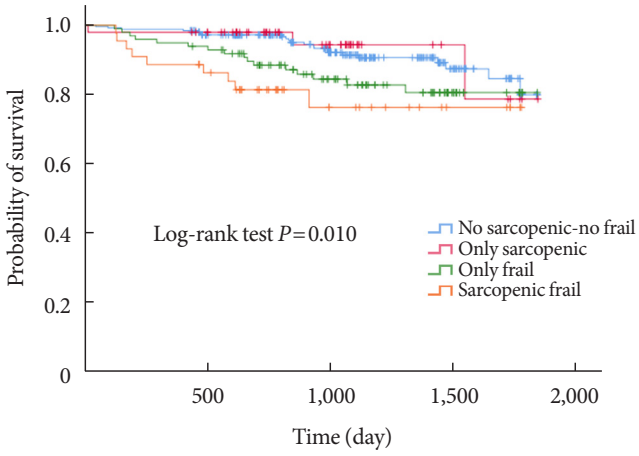


Fig. 2. Kaplan-Meier test, survival times of groups.

P=0.003) compared to those without these conditions. Additionally, patients with isolated frailty also demonstrated a significantly elevated mortality risk (adjusted HR, 2.59; 95% CI, 1.34 to 5.03; *P*=0.005). In contrast, isolated sarcopenia was not independently associated with increased mortality risk (adjusted HR, 0.74; 95% CI, 0.22 to 2.46; *P*=0.619) (Table 2).

Kaplan-Meier survival analysis demonstrated significantly reduced survival in the sarcopenia and frailty group (mean survival, 1,467 days [95% CI 1,281 to 1,653], *P*=0.010) compared to other groups (Table 3, Fig. 2).

DISCUSSION

This study is the first to examine the impact of sarcopenia and frailty on mortality among older patients with T2DM undergoing outpatient treatment in Türkiye. Our findings indicate that older adults with T2DM with both sarcopenia and frailty face a 3.29-fold increased risk of mortality compared to those who are non-sarcopenic and non-frail. Additionally, isolated frailty was associated with a 2.59-fold increased mortality risk and reduced survival. These findings highlight the substantial prognostic significance of coexisting sarcopenia and frailty on survival outcomes in older adults with T2DM.

T2DM is one of the leading causes of death worldwide. The mortality risk in patients with T2DM is approximately twice as high as that of age-matched patients without T2DM [19]. A study by Li et al. [20] found that the mortality rate in the pre-frail group was 3.6%, while it was 22.7% in the frail group. Takahashi et al. [21] reported a significant association between sarcopenia and all-cause mortality in elderly patients with T2DM undergoing outpatient care. In our survival analysis, patients with sarcopenia and frailty had significantly shorter survival than the other groups, with a mean survival of 1,467 days (95% CI 1,281 to 1,653; *P*=0.010) (Table 3). To our knowledge, this is the first study to specifically assess the prognostic implications of sarcopenia and frailty on survival in older patients with T2DM, offering novel contributions to the existing literature.

The relationship between sarcopenia and T2DM creates a detrimental cycle, with each condition exacerbating the other. T2DM accelerates the processes leading to muscle mass loss, which is associated with elevated blood sugar levels and interactions between Krüppel-like factor 15 (KLF15) and WW domain–containing E3 ubiquitin protein ligase 1 (WWP1) [22,23]. Furthermore, T2DM can exacerbate frailty by contributing to

insulin resistance and chronic inflammation, which increase the care needs of affected patients.

Numerous studies have demonstrated the association between T2DM and frailty. A study of patients aged 60 years and older found that T2DM was associated with a two-fold increased likelihood of developing frailty (odds ratio, 2.18) [24]. Long-term studies also indicate that being frail might increase the risk of developing T2DM, creating a harmful cycle between the two conditions [25].

The prevalence of sarcopenia varies among people with T2DM, with Takahashi et al. [21] finding it in 14.6% of 396 patients and Oguz et al. [26] finding it in 25.6% of a group in Türkiye. Our study found a sarcopenia prevalence of 11%, with 9.8% of patients classified as having both sarcopenia and frailty. These differences may be attributed to variations in the diagnostic criteria used for sarcopenia across studies.

Frailty is common among older patients with T2DM. Hubbard et al. [27] observed that 42.2% of patients with T2DM were frail, while Oguz et al. [26] found a frailty prevalence of 44% among older patients with T2DM in Türkiye. In our study, 22.4% of patients had isolated frailty, 9.8% had both sarcopenia and frailty, and a total of 32.2% were classified as frail, which aligns with previous research findings.

Studies have indicated that T2DM increases limitations in ADL and IADL [28]. Our study confirmed these findings, with 6.7% of patients dependent in ADL and 27.1% dependent on IADL. The sarcopenia and frailty group showed much higher rates of needing help with basic daily activities (20.5%) and more complex tasks (68.2%) than the other groups. These findings suggest that sarcopenia and frailty contribute to a substantial decline in functional independence in older patients with T2DM. Previous studies have shown that older adults with T2DM who have sarcopenia often have higher HbA1c levels, and a larger proportion exceed the target HbA1c level (≥7%) compared to those without sarcopenia [26]. In our study, the median HbA1c was significantly higher in the sarcopenia and frailty group (P=0.035). These data indicate that poor glycemic control may worsen both sarcopenia and frailty, emphasizing the need for customised glycemic management strategies that account for the patient's functional level and comorbidities in older adults. Furthermore, sarcopenia and frailty may adversely affect blood glucose management, establishing a detrimental cycle that necessitates meticulous and personalised therapeutic strategies.

Metformin is commonly used in the management of T2DM, and some studies have suggested its potential effects on muscle strength and sarcopenia [29]. In our cohort, 50.8% of patients were using metformin, with a significantly higher proportion (65.3%) of patients with isolated sarcopenia using metformin (P=0.03). The sarcopenia and frailty group had a lower metformin usage rate (36.4%) than the isolated sarcopenia group but a similar rate to the isolated frailty group (40.0%). This finding may suggest that metformin was discontinued in frail patients due to increased comorbidity burden or potential concerns regarding its tolerability and safety in this population.

This study's strengths include its long follow-up duration of 5 years and its substantial sample size, providing robust data on the impact of sarcopenia and frailty on mortality in older patients with T2DM. However, a limitation is that the cohort consisted solely of patients with T2DM, preventing comparisons with non-T2DM patients. Future research with control groups of non-T2DM patients is essential to confirm these findings and explore their broader applicability.

Our research indicates that geriatric syndromes, including sarcopenia, and frailty are significantly correlated with unfavorable outcomes in older adults with T2DM. Our data indicate that patients with T2DM and both sarcopenia and frailty exhibit elevated mortality rates and reduced survival duration. In clinical practice, this underscores the essential importance of early detection of comorbidities such as sarcopenia and frailty in formulating treatment programs for older patients with T2DM. Addressing disability is a core concern in geriatrics, with significant emphasis on maintaining quality of life, retaining patient functionality, and particularly preventing conditions that could lead to disability. This evaluation facilitates the formulation of treatment regimens in a more efficient and personalised way.

In conclusion, this study demonstrates that geriatric syndromes specifically sarcopenia and frailty are significantly associated with adverse outcomes in older adults with T2DM. Our findings show that patients with both sarcopenia and frailty experience significantly higher mortality rates and shorter survival times compared to their non-sarcopenic or non-frail counterparts. These results highlight the critical importance of early identification and management of these comorbidities in the clinical care of older adults with T2DM. Preventing disability remains a central goal in geriatric medicine, with an emphasis on maintaining functional independence and quality of life. Integrating the assessment of sarcopenia and frailty into routine clinical evaluations should enable

the development of more effective and individualized treatment strategies for this vulnerable population.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Conception or design: B.E.C., S.A.
Acquisition, analysis, or interpretation of data: B.E.C., N.T.O., S.A.
Drafting the work or revising: B.E.C., C.B.C., Y.S.S.A., S.A.
Final approval of the manuscript: all authors.

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