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Original Article

Frailty Status and Mortality Risk in Older Adults With Diabetes Mellitus

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Abstract

Background: Frailty, characterized by decreased physiological reserves and an increased risk of adverse health outcomes, is prevalent among older adults with diabetes mellitus (DM). This study aimed to investigate how frailty status affects mortality in older individuals with diabetes.

Methods: Patients previously diagnosed with DM who presented to a tertiary referral center between March 2020 and March 2022 were selected and followed up for at least two years. The frailty assessment used the Fried frailty phenotype criteria, and patients were categorized as frail, pre-frail, or robust. Multivariate regression models were utilized to identify mortality risk factors.

Results: The study cohort comprised 424 patients with a median age of 75 years, of which 65.8% were female. Among the patients, 28.3% were classified as frail and 66.0% as pre-frail. During the observation period, the overall mortality rate was 6.8%, with a significantly higher mortality rate in frail patients (15%) compared to pre-frail patients (3.9%) ($p<0.001$). Multivariate analysis identified frailty as a significant predictor of increased mortality risk in the overall population (HR=2.84, 95% CI: 1.20–6.69, p=0.017) and in men (HR=7.35, 95% CI: 1.17–48.35, p=0.033), but not in women (HR=2.70, 95% CI: 0.99–7.30, p=0.051).

Conclusion: Frailty markedly elevates the risk of mortality in older adults with DM, with this effect being particularly pronounced in males. These findings emphasize the significance of early identification and management of frailty in enhancing survival outcomes in this population.

Keywords: Frailty Syndrome, Risk Factors , Diabetes Mellitus, Mortality

INTRODUCTION

Diabetes mellitus (DM), a chronic metabolic disorder that causes elevated blood sugar levels, has become a global health challenge affecting 300 million individuals globally by 2025 and is a significant burden on healthcare systems (1,2).The main goal of diabetes treatment is to prevent vascular complications and improve prognosis (3). A complementary approach would be to achieve strict glycemic targets in patients with diabetes, as well as to consider factors that may have an impact on their prognosis.

Frailty refers to vulnerability to stressors and is characterized by a decrease in physiological reserves and an increased risk of adverse health outcomes, such as impaired functionality, long-term care placement, and death (4). Frailty classification categorizes individuals into three groups: frail, pre-frail, and robust, each exhibiting varying levels of susceptibility to functional decline (4). Knowing the differences between these subgroups allows for early and more precise diagnosis while also determining the types of approaches available for each. Integrating frailty assessments into regular clinical evaluations is essential for providing comprehensive and patient-centered healthcare.

In the medical community, there is growing interest in the connection between frailty and diabetes. Chronic

inflammation, increased oxidative stress, and insulin resistance can cause loss of musculoskeletal mass and muscle weakness in patients with DM ,leading to frailty (5,6). Moreover, frailty is believed to lead to chronic inflammation and oxidative stress, which are thought to be strongly associated with vascular complications and death. Previous studies showed that pre-frail and frail people were at increased risk of both hospitalization and death compared to robust, however, there is no comparison between pre-frail and frail patients (7,8). Besides, early detection and intervention are important because frailty can improve with proper intervention, which shows the importance of detecting frailty in each individual (9,10).

Demonstrating the relationship between DM and frailty is important for both health economics and patient benefits. This study aims to more comprehensively address the effect of frailty on mortality.

METHODS

Study cohort

This study was conducted on individuals aged 65 and over who applied to the geriatric outpatient clinic of a tertiary health centre between March 2020 and March 2022. Individuals with diabetes were evaluated and followed up for at least two years after inclusion in the study. Death data were obtained from the Ministry of Health Death Registry File and corroborated with the information from families and relatives. The study group was categorised as 'dead' or 'alive' depending on their death status at the end of the two-year follow-up. Patients with severe systemic or infectious diseases, terminal illnesses, metabolic disorders, visual or sensory impairments, communication difficulties, receiving home care services, and those lacking mortality data were excluded from the study (**Figure 1**). This study was conducted by the Declaration of Helsinki. All patients provided informed consent and the ethics committee approved the study.

Patient and disease characteristics

Data related to subjects' sociodemographic characteristics including age, gender, marital status, education status, body mass index (BMI), smoking and alcohol status, and comorbidities [hypertension, coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), cerebrovascular disease (CVD), and Parkinson's disease (PD)] were gathered from patient self-reports and medical records. Having ≤5 years of education was noted as a lower educational level. Drug history was evaluated, and polypharmacy was defined as ≥ 5 drugs (11).

Frailty was assessed using the Fried frailty phenotype criteria, which includes five parameters: weakness, slowness, exhaustion, low physical activity, and unintentional weight loss. The patients were classified as frail (3-5), pre-frail (1-2), or robust (0) based on these criteria (12). The cognitive evaluation was performed using the Mini-Mental State Examination (MMSE), with patients scoring ≤26 considered to have cognitive impairment (13, 14). Barthel index was used to determine functional status, and the functional impairment was defined as < 90 points (range 0-100) (15). Nutritional status was assessed using the Mini-Nutritional Assessment-Short Form (MNA-SF) (range 0-14) and a score ≤11 was denoted as undernutrition (16). Complete blood count, liver and kidney function tests, fasting plasma glucose, HbA1c, HDL, LDL, cholesterol, triglycerides, and vitamin D levels were noted in the laboratory tests.

STATISTICAL ANALYSIS

The Statistical Package for Social Sciences (SPSS) (IBM SPSS Inc., IL, Chicago, U.S.) was used for statistical analysis. Numerical variables were presented in the form of absolute numbers and percentages, average standard deviation, and median (minimum-maximum), if applicable. When comparing continuous data, the student t-test or the Mann-Whitney U-test was used. Data distribution was analyzed using the Kolmogorov-Smirnov test. Categorical analysis. The chi-square test was used for the comparison of categorical variables. In univariate analysis, variables with statistical significance (p≤0.10) were selected to construct a multivariate regression model to test the association between mortality and frailty status. The Hosmer-Lemeshow (H-L) test was used for the fitness of the model. Hazard ratios (HR) and their 95% confidence intervals (CI) were reported from the models. A p-value of less than 0.05 was accepted as statistically significant.

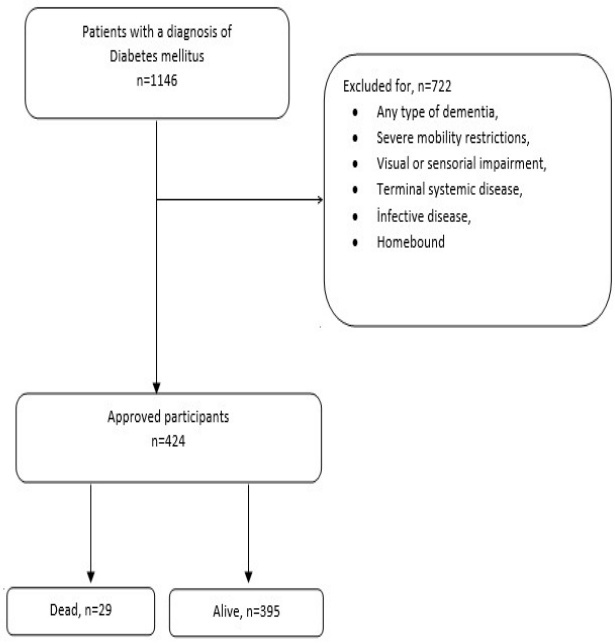

Figure 1. Flow chart of patient selection process.

RESULTS

Baseline Characteristics

A total of 424 patients diagnosed with diabetes were included in the study. The median age was 75 (65-98) years, more than half (65.8%) were female, and the median BMI was 28.7 (14.4-51.5). The most common comorbidities were hypertension (85.1%), CAD (34.2%), and depression (34.0%). The geriatric assessment showed that 28.3% of the patients with DM were frail and 66.0% had pre-frail. Polypharmacy was the most prevalent geriatric syndrome (65.1%), followed by cognitive impairment (35.6%), and undernutrition (21.0%). The median HbA1c level was 7.1% (5.0%-15.1%). The remaining data, including the laboratory parameters, are listed in **Table 1**.

Comparison of Groups' Characteristics

During the study period, 6.8% (n=29) of the patients died. Among them, 18 (3.9%) were pre-frail and 11 (15%) were frail. There were no statistically significant difference between the two groups in terms of gender and age. CVD was more common, and hemoglobin levels were lower in the mortality group. No significant difference was observed between the HbA1c values. Frailty, cognitive impairment, and undernutrition were also more prominent in these subjects. None of the robust patients died during the follow-up period (**Table 1**).

Mortality-related Factors

No deaths were observed in the robust group. Therefore, all-cause mortality-related factors were analyzed exclusively among pre-frail and frail individuals using the Cox regression model. On the univariate analysis, CVD (HR=3.01, 95% CI: 1.06-8.60, p=0.039), frailty (HR=4.32, 95% CI: 1.97-9.45, p<0.001), cognitive impairment (HR=2.37, 95% CI: 1.10-5.07, p=0.027), and undernutrition (HR=2.69, 95% CI: 1.23 -5.88, p=0.013) were associated with the risk of two-year all-cause mortality. After adjusting for these confounding factors as well as age and gender, only frailty status remained statistically significant in multivariate analysis. Being frail (HR=2.84, 95% CI (1.20–6.69), p=0.017)

Table 1. Baseline characteristics of the participants in terms of mortality status

Variables	**Overall (n= 424)**	**Dead (n= 29)**	**Alive (n= 395)**	**p-value**
Age (years), median (range)	75 (65-98)	76 (65-91)	75 (65-98)	0.453
Gender (female), n (%)	279 (65.8)	21 (72.4)	258 (65.3)	0.545
BMI, median (range)	28.7 (14.4-51.5)	28.3 (21.0-38.1)	28.8 (14.4-51.5)	0.816
Marital status (married), n (%)	253 (60.1)	13 (44.8)	240 (61.2)	0.115
Education time (≤ 5 years), n (%)	283 (66.7)	18 (62.1)	265 (67.1)	0.683
Current smokers, n (%)	21 (5.0)	2 (6.9)	19 (4.8)	0.647
Current alcohol users, n (%)	7 (1.7)	-	7 (1.8)	1.000
Comorbidities, n (%)				
Hypertension	361 (85.1)	28 (96.6)	333 (84.3)	0.11
Coronary artery disease	145 (34.2)	14 (51.7)	131 (33.2)	0.107
Chronic obstructive lung disease	47 (11.1)	4 (13.8)	43 (10.9)	0.548
Cerebrovascular disease	29 (6.8)	5 (17.2)	24 (6.1)	0.039
Depression	144 (34.0)	14 (48.3)	130 (32.9)	0.105
Parkinson's disease	12 (2.8)	2 (6.9)	10 (2.5)	0.195
Frailty status,n (%)				
Frail	120 (28.3)	18 (62.1)	102 (25.8)	<0.001
Pre-frail	280 (66.0)	11 (37.9)	269 (68.1)	
Robust	24 (5.7)	-	24 (6.1)	
Polypharmacy (≥5 drugs), n (%)	276 (65.1)	23 (79.3)	253 (64.1)	0.109
Cognitive impairment, n (%)	151 (35.6)	16 (55.2)	135 (34.2)	0.027
Functional impairment, n (%)	60 (14.2)	7 (24.1)	53 (13.4)	0.161
Undernutrition, n (%)	89 (21.0)	12 (41.4)	77 (19.5)	0.009
Laboratory parameters, serum, median (range)				
Hemoglobin (g/dl)	13.1 (6.4-16.8)	12. 1 (11.1-15.6)	13.2 (6.4-16.8)	0.002
Creatinine (mg/dl)	0.9 (0.5-3.3)	0.9(0.5–3.3)	0.9 (0.5-2.5)	0.761
HbA1c (%)	7.1 (5.0-15.1)	6.9 (5.3-11.3)	7.2 (5.0-15.1)	0.522
Vitamin D (ng/ml)	25 .0 (4.2-139.0)	14.0 (5.0-66.0)	25.8 (4.2-139.0)	0.355
LDL cholesterol (mg/dl)	113 (27-215)	101 (47-206)	113 (27-215)	0.530
HDL cholesterol (mg/dl)	49 (19-93)	43 (29-66)	49 (19-93)	0.235
Triglyceride (mg/dl)	135 (47-579)	122 (80-311)	137 (47-579)	0.732

BMI; body mass index; HbA1c; hemoglobin a1c; LDL; low-density lipoprotein; HDL; high-density lipoprotein; Triglyceride; triglyceride; Vitamin D; vitamin d; Creatinine; creatinine; Polypharmacy; polypharmacy; Cognitive impairment; cognitive impairment; Functional impairment; functional impairment; Undernutrition; undernutrition; Hemoglobin (Hb); hemoglobin.

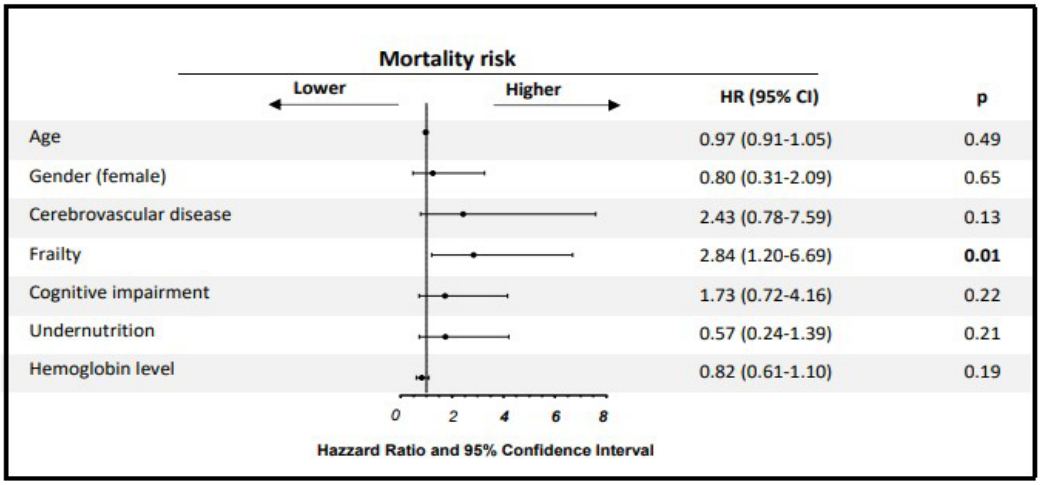

Figure 2. Forest plot of multivariate regression analysis on the causal association between frailty status and other factors and mortality risk in older adults with diabetes mellitus.

was related to an increased risk of two-year mortality compared to being pre-frail (**Figure 2**). The Hosmer–Lemeshow (H–L) test, an inferential goodness-of-fit test, yielded a Chi-Square of 7.573 and was insignificant (p= 0.476), suggesting that the model was a high fit of the data. Analysis by gender subgroup revealed that frailty was associated with mortality in men (HR= 7.35, 95% CI: 1.17–48.35, p=0.033), but not in women (HR= 2.70, 95% CI: 0.99–7.30, p=0.051), which was statistically marginally significant.

DISCUSSION

Our study of older adults with DM revealed that frail individuals had a 2.84 times higher risk of two-year mortality than pre-frail, with no deaths recorded in the robust group. The two-year mortality rate was 6.8% and was significantly higher in frail patients. The association between frailty and mortality was statistically significant in men but was marginally insignificant in women.

Previous studies have shown that frailty increases the mortality of patients with DM. A limited number of studies have compared robust groups with frailty states, but none have directly focused on pre-frail and frail groups. A cohort study involving 560,795 patients with a mean age of 56 years found the mortality risk to be 1.13 times higher in the pre-frail group and 1.25 times higher in the frail group than in the robust group (17). Given that this study focused on a much younger population and did not conduct a direct comparison of the two frailty conditions head-to-head, its findings should not be directly contrasted with our definitive results Additionally, according to a recently published meta-analysis, mortality risks in non-frail and frail patients were 1.23 and 1.84 times higher, respectively, than in healthy individuals (18). In accordance with previous research suggesting distinct outcomes for pre-frail and frail individuals, our study found a 2.84-fold increase in the risk of death between these two groups. It is also known that frailty is a bidirectional dynamic process and there may be transitions between frailty states. In a study conducted by Kojime et al, 25% of pre-frail patients and 3% of frail patients returned to a robust state (19). In light of these findings, detecting and addressing diabetes in its early stages will contribute to improved survival of these patients.

The explanation for the relationship between frailty and increased mortality risk is unclear, but some hypotheses have been proposed. Frailty has been linked to an increase in inflammatory markers, with levels rising progressively as individuals transition from a robust to frailty state (20,21). Chronic hyperglycemia in diabetes also causes an increase in the production of inflammatory cytokines (22). Cardiovascular morbidities, impaired immune function, and muscle catabolism are just some of the complications that can be caused by chronic inflammation, which can lead to increased mortality (20,22). This may be one of the mechanisms explaining the difference in mortality between the frail and pre-frail groups in our study. Insulin resistance and metabolic dysfunction, which are also frequently seen in frailty due to deterioration of body composition, are the main features of diabetes (23,24). The combination of DM and frailty further leads to muscle weakness, diminished physiological reserve, increased risk of cardiovascular events and poor prognosis (25,26). In addition, individuals with diabetes and frailty have an increased risk of falling due to decreased muscle mass, and hypoglycemia which is a frequent complication of both conditions (27-30). This elevated fall risk may contribute to the higher mortality rates. The evaluation tool used in our study (12) includes parameters that are linked to mortality, so it's not surprising that having more of these parameters worsens prognosis. These mechanisms underline importance of integrated care approaches that address both diabetes management and early frailty awareness to improve outcomes and reduce mortality in this vulnerable population.

The overall mortality rate in this study was 6.8%, while it was 3.9% in pre-frail group and increased to 15% in frail group. Studies conducted with inpatients with DM reported mortality rates ranging from 3.6% to 20% in pre-frail individuals and from 22.7% to 32.5% in frail individuals (31). The mortality rates in these studies were significantly greater than those observed in our research, possibly due to their hospitalization. Given that these patients require inpatient care and treatment, it can be concluded that they have more severe comorbidities than those in our study population, leading to an increased risk of death (32). Additionally, frailty was linked to higher mortality in male patients, whereas this association showed limited insignificance in female patients in our study. Gender plays a significant role in DM mortality rates (33). Despite the differences in frailty definitions, epidemiological studies have shown that frailty is more prevalent among women, whereas frailty in men is more linked to mortality (34,35). In men, physiological mechanisms, such as lower physiological reserves and higher neuroendocrine and testosterone hormone levels, may have led to frailty being more associated with mortality compared to women (36,37). They are also less likely to express their health concerns or perceive themselves as ill, which often results in delayed healthcare seeking (38,39). Furthermore, men have less access to preventive and early treatment opportunities (38). Thus, males may be receiving interventions at a more advanced stage, post the onset of frailty. These social factors may also contribute to the higher mortality associated with frailty in men. It is noteworthy that the mortality rate is significantly higher in frail individuals, and it is crucial to recognize that men are particularly vulnerable to this condition.

Limitations

This study had several strengths and limitations. Our findings were supported by a significant number of patients and a detailed examination of potential confounding factors. Since no studies comparing mortality between frailty and pre-frailty in diabetic patients have been found, we consider our research crucial for filling this gap in knowledge. Furthermore, our study highlighted the prognostic role of the difference between pre-frail and frail states in diabetes management. The fact that the study was single-centre and cross-sectional limits the generalizability of the results. Large-scale studies are needed to assess effect size. Furthermore, it is important to acknowledge that the absence of data on diabetes duration and treatment in our study may affect the observed mortality outcomes.

CONCLUSION

This research shows a strong association between frailty and mortality in older adults with DM, emphasizing the need for early detection and treatment of this vulnerable status. This study highlights the importance of more personalized approaches to frailty management in patients with DM. Our findings reveal a significant difference in mortality rates between pre-frail and frail individuals, especially among men. Identifying individuals with DM at the pre-frail stage and implementing preventive strategies to halt the progression to frailty are crucial for reducing mortality rates in advanced ages. Future research should concentrate on the mechanisms responsible for the pre-frail to frail transition and examine the influence of gender on frailty outcomes.

DECLERATIONS

Ethical Issues: This study was conducted in accordance with the Declaration of Helsinki and was approved by the Health Sciences University Clinical Research Ethics Committee; year: 2020 IRB no: 58. Informed consent was obtained from all participants involved in this study.
Funding and Conflict of Interest: The authors declare that this research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. There are no conflicts of interest to disclose related to this study.
Referee Evaluation Process: Externally peer-reviewed.
Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version of the study.
Special Thanks: None
AI: We only used a grammar program to help review ing our writing for grammar at the final stage.

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