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Clinical frailty scale as a tool to predict outcomes after lower extremity amputation among patients with diabetes: A retrospective cohort study

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ABSTRACT

Aims: The primary aim of this study was to investigate how the Clinical Frailty Scale (CFS) associates with survival of patients with diabetes after lower extremity amputation (LEA).

Methods: This retrospective cohort study included patients with diabetes undergoing nontraumatic LEA at Tampere University Hospital during 2007–2020. Kaplan-Meier and Cox regression analyses were performed to evaluate the effect of CFS on overall survival (OS), amputation-free survival (AFS) and leg salvage (LS).

Results: A total of 1043 patients with mean age 71.0 years were included. Compared to patients with low CFS (1, 2), scores 3–4 and 5–9 were associated with reduced OS (HR 1.821, $p < 0.001$; HR 4.585, $p < 0.001$), AFS (HR 1.575, $p < 0.001$; HR 4.031, $p < 0.001$) and LS (HR 1.435, $p = 0.049$; HR 2.478, $p < 0.001$). The multivariable Cox regression analysis showed that CFS remained a significant predictor of OS, AFS and LS.

Conclusions: This study demonstrates a high prevalence of frailty among patients with diabetes undergoing LEA, suggesting that frailty assessment should be integrated into clinical decision-making for this patient population. The CFS score appears to be a promising tool for evaluating patients facing amputation to enhance survival rates.

1. Introduction

Diabetes affects approximately 537 million people worldwide, and this number is projected to increase to 643 million by 2030 and 783 million by 2045.¹ Patients with diabetes are at a risk of developing systemic complications, such as angiopathy and neuropathy, which can predispose them to serious foot problems that may progress to the point where limb amputation becomes necessary. Amputations are typically classified to major or minor. A major amputation is defined as an amputation above ankle joint, while a minor amputation refers to an amputation below the ankle joint, preserving the heel and often enabling the patient to ambulate without a prosthesis. The amputation level of a patient with diabetes is associated with their survival and quality of life.^{2,3}

Frailty syndrome is defined as a patient's vulnerability, consisting of physical, psychological, social and environmental factors.⁴ Key features of frailty syndrome include unintentional weight loss, exhaustion, weakness, slow walking speed, and low physical activity.⁵ Two or more

chronic diseases, female gender, and lower socioeconomic status are risk factors for frailty syndrome.⁵ Patients with frailty syndrome are at a higher risk for health deterioration and death compared to others of the same age.⁶ Various indexes are used to estimate frailty. Clinical Frailty Scale (CFS) assesses a patient's ability to move and live independently, rating frailty across nine levels.⁷ Charlson Comorbidity Index (CCI) considers both the number and severity of comorbid diseases.⁸ The 11-factor modified frailty index (mFI-11) is based in the number of selected comorbid diseases.⁹

Frailty and diabetic foot ulcers appear to be interrelated, as frailty can contribute to non-healing diabetic foot ulcer and lead to poor outcomes such as amputation.¹⁰ Both frailty and diabetes are systemic conditions associated with multiple comorbidities, suggesting that diabetes may accelerate the development of frailty. The term “senescent diabetic foot disease” refers to the condition where frailty and comorbid diseases intersect.¹¹ This condition has been illustrated by the triad of diabetes-related foot complications that lead to reduced overall survival (OS).¹¹ However, the prevalence of frailty among amputation patients

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with diabetes has not been previously reported. Additionally, the impact of frailty on the prognostic of patients with diabetes undergoing amputation has not been investigated in earlier studies.

The primary aim of this study was to investigate how CFS predicts the survival of patients with diabetes after lower extremity amputation (LEA). The secondary aims were to determine the prevalence of frailty among patients with diabetes undergoing LEA and test the practicality of CFS in estimating frailty in these patients.

2. Materials and methods

2.1. Patients

This retrospective cohort study was approved by the Institutional Research Board (ETL: 14545S). The study population included patients diagnosed with diabetes who underwent LEA at Tampere University Hospital between 2007 and 2020. Out of a total of 2022 LEA patients, 1081 had a diagnosis of either type 1 or type 2 diabetes. A total of 38 patients were excluded from the analysis because the amputation was canceled ($n = 15$) or performed in a district hospital ($n = 10$), the indication for amputation was trauma or malignancy ($n = 11$), or for other reasons ($n = 2$). Ultimately, 1043 patients who underwent non-traumatic amputation were included in the study. The flow chart of the patients selected for the study is presented in Fig. 1.

2.2. Clinical variables and frailty evaluation

Data were collected through manual reviews of patient records, including the following variables: length of hospital stay, discharge details (another hospital, home, death), indication for amputation (infection, ischemia, trauma, malignancy), smoking status (current, former, non-smoker), excessive alcohol use, number of comorbid diseases, and number of medications listed at admission. This study utilized CFS, CCI and mFI-11 to evaluate frailty. Patient records were reviewed, and CFS was calculated using the CFS application by NHS Elect. Patients were categorized into three groups based on their frailty. The first group included fit patients (CFS 1–2), the second group included vulnerable patients (CFS 3–4) and the third group included mildly to severely frail patients (CFS 5–9). This categorization was found optimal in an earlier study.¹² Fig. 2 demonstrates CFS classification, and the grouping used in this study.⁷ Registered diagnoses in hospital records were used to calculate CCI and mFI-11 as described in previous studies.^{13,14}

2.3. Statistical analyses

The mean and standard deviation (SD) were calculated for normally distributed continuous variables (age), while the median and interquartile range (IQR) were calculated for skewed continuous variables

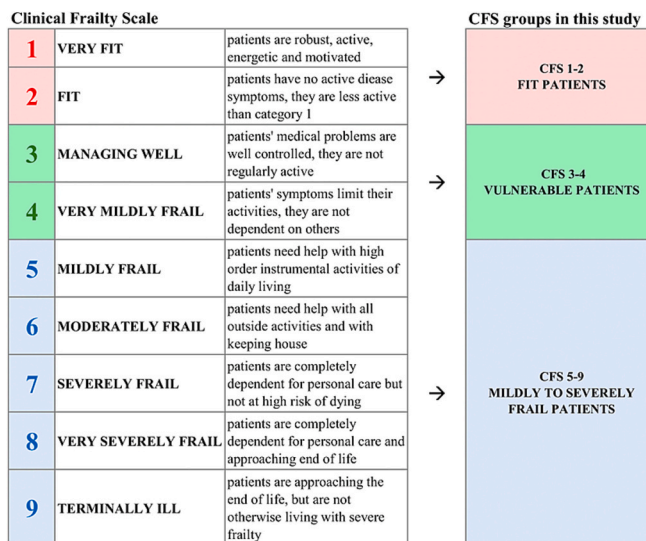


Fig. 2. Clinical Frailty Scale (CFS) classification and the grouping used in this study.

(number of comorbid diseases, number of medications, length of hospital stay, mFI-11, and CCI). Kaplan-Meier analyses and 10-year survival tables were used to evaluate OS, amputation-free survival (AFS) and leg salvage (LS). In OS, the endpoint was death; in AFS, the endpoint was death or a major amputation; and in LS, the endpoint was major amputation (censoring occurred in cases of death). AFS and LS analyses included only patients with minor amputation, whereas OS analyses included patients with both minor and major amputation.

The Cox regression multivariable model was used to evaluate the independent significance of CFS after adjusting for covariates. The covariates included in the multivariable model were CCI, gender, and amputation level. These were selected because CFS groups had different gender ratios, and CCI includes both age and comorbidities, which differed significantly between the CFS groups. Amputation level was included in the OS multivariable model since major amputation is a known risk factor for increased mortality.¹⁵ A p value <0.05 was considered statistically significant. Results are presented as hazard ratios (HR) with 95 % confidence intervals (CI).

All statistical analyses were planned and reviewed in collaboration with a professional statistician. A post hoc power analysis ($\alpha = 0.05$, power = 0.80, HR = 1.4) indicated that a sample size of 269 patients per group would be sufficient to detect statistically significant differences; the available sample size ($n = 1043$ across three groups) well exceeded this threshold. Kaplan-Meier analyses were performed using R software (R Core Team, 2023, Version 4.3.2), and all other analyses were

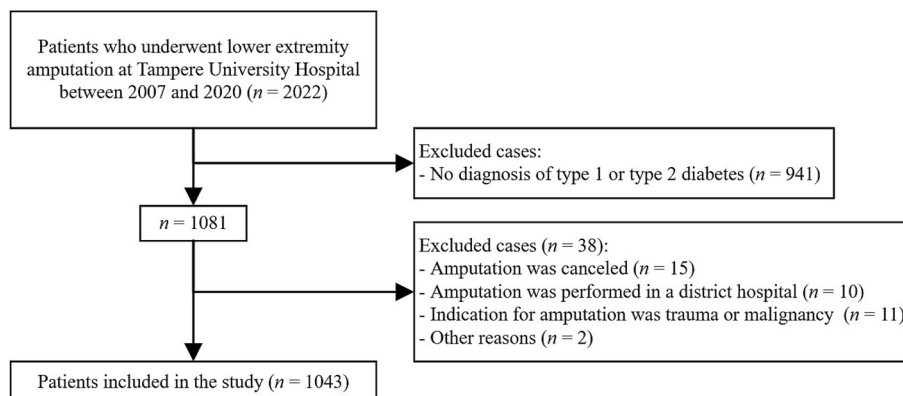


Fig. 1. Flow chart of study population.

performed using SPSS software (IBM SPSS Statistics, Version 29.0.1.0).

2.4. Reporting

This study was reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement to ensure comprehensive and transparent reporting of observational research.

3. Results

We included 1043 patients (718 male, 325 female) in the analyses. The mean age was 71.0 years (SD 12.5). Among the cohort, 847 patients (81.2 %) had peripheral arterial disease, 220 patients (21.1 %) had dyslipidemia, 668 patients (64.0 %) had hypertension, 387 patients (37.1 %) had coronary artery disease, 404 patients (38.7 %) had heart failure, and 111 patients (10.6 %) had chronic obstructive pulmonary disease.

Female patients were more often rated as CFS 5 or higher (44.3 % vs. 30.1 %) and discharged to another hospital (83.1 % vs. 72.1 %, $p < 0.001$). They also had a greater median number of medications compared to male patients (11.5 (IQR 8) vs. 10 (IQR 7), $p = 0.007$).

The characteristics and comorbidities stratified by CFS are presented in Table 1. As the CFS class increased, the mean age of patients was higher ($p < 0.001$), ischemia as an indication for amputation instead of infection was more common ($p < 0.001$), major amputation was more common ($p < 0.001$), and discharge to another hospital instead of home was more common ($p < 0.001$). A higher CFS class correlated with higher mFI-11 ($p < 0.001$) and CCI ($p < 0.001$) scores. Both the number of diseases ($p < 0.001$) and the number of medications ($p < 0.001$) were higher in patients with a higher CFS score.

A Kaplan-Meier analysis was performed to estimate the impact of CFS on survival outcomes. OS, AFS, and LS were compared across the CFS groups (Fig. 3). In univariate Cox regression analysis, patients with CFS scores of 3–4 and 5–9 had reduced OS (HR 1.821, $p < 0.001$; HR 4.585, $p < 0.001$), AFS (HR 1.575, $p < 0.001$; HR 4.031, $p < 0.001$), and LS (HR 1.435, $p = 0.049$; HR 2.478, $p < 0.001$) compared to those with CFS 1–2 (Table 2). The multivariable model showed that CFS, CCI, and amputation level remained significant predictors of OS, while CFS and CCI remained significant predictors of AFS and LS (Table 3). Gender did not have significant effect on OS ($p = 0.181$), AFS ($p = 0.983$) or LS ($p = 0.354$).

4. Discussion

This large retrospective cohort study found a high prevalence of clinical frailty among patients with diabetes undergoing LEA. A higher CFS score was associated with reduced OS, AFS, and LS. The CFS score remained a significant independent predictor for both OS and AFS in a multivariable model.

Only 16.4 % of the patients were rated as clinically fit (CFS 1–2), while 39.1 % were rated as vulnerable (CFS 3–4). The remainder of the patients were classified as mildly to severely frail (CFS 5–9). As far as we know, clinical frailty has not been studied earlier among patients with diabetes undergoing LEA. However, among patients with diabetes, the prevalence of frailty has been reported to range between 32 % and 48 %, compared to a community prevalence of 5–10 %.¹⁶ Furthermore, among patients with critical limb threatening ischemia the prevalence of frailty has been reported to range between 27 % and 88 % with an average prevalence of 60 %, and among patients with diabetic foot ulcers the prevalence of frailty has been reported to be 71 %.¹⁷ An earlier meta-analysis estimated that among patients undergoing LEA, the prevalence of frailty is 42–80 %.¹⁸ Two of these studies used CFS to evaluate frailty and reported CFS 4 or higher in 63.6 % of patients and CFS 5 or higher in 52 % of patients.^{19,20} In our study 34.5 % of patients were rated as CFS 5 or higher. The proportion might be expected to be higher

Table 1

Patient characteristics and comorbidities stratified by Clinical Frailty Scale. CFS = Clinical Frailty Scale.

Characteristics	CFS 1–2	CFS 3–4	CFS 5–9	<i>p</i> value
Number of patients (%)	275 (26.4)	408 (39.1)	360 (34.5)	
Mean age in years ± SD	64.6 ± 12.6	70.0 ± 11.2	77.0 ± 11.0	< 0.001 ^a
Male (vs. female), number (%)	206 (74.9)	296 (72.5)	216 (60.0)	< 0.001 ^b
Smoking status, number (%)				0.202 ^b
Current	54 (21.0)	93 (25.1)	54 (19.2)	
Former	81 (31.5)	125 (33.8)	107 (38.1)	
Non-smoker	122 (47.5)	152 (41.1)	120 (42.7)	
Excessive use of alcohol, number (%)	40 (14.5)	76 (18.6)	39 (10.8)	0.010 ^b
Number of diseases, median (IQR)	4 (3)	4 (3)	5 (2)	< 0.001 ^a
Number of medications, median (IQR)	8 (5.5)	10 (6.25)	14 (7)	< 0.001 ^a
Indication for amputation, number (%)				< 0.001 ^b
Infection	203 (73.8)	238 (58.3)	184 (51.1)	
Ischemia	55 (20.0)	142 (34.8)	132 (36.7)	
Both	17 (6.2)	28 (6.9)	44 (12.2)	
Amputation level, number (%)				< 0.001 ^b
Minor	229 (83.3)	287 (70.3)	166 (46.1)	
Major	46 (16.7)	121 (29.7)	194 (53.9)	
Length of stay, median (IQR)	6 (7)	6 (6)	5 (4)	0.013 ^a
Discharge, number (%)				< 0.001 ^c
Another hospital	160 (58.2)	311 (76.4)	316 (87.8)	
Home	115 (41.8)	92 (22.6)	42 (11.7)	
Death	0 (0)	4 (1.0)	2 (0.6)	
11-factor modified frailty index, median (IQR)	2 (3)	4 (3)	5 (3)	< 0.001 ^a
Charlson comorbidity index, median (IQR)	5 (3)	6 (3)	8 (2)	< 0.001 ^a
Comorbidities, number (%)				
Peripheral arterial disease	180 (65.5)	335 (82.1)	332 (92.2)	< 0.001 ^c
Dyslipidemia	60 (21.8)	104 (25.5)	56 (15.6)	0.003 ^c
Hypertension	170 (61.8)	270 (66.2)	228 (63.3)	0.476 ^c
Coronary artery disease	87 (31.6)	166 (40.7)	134 (37.2)	0.055 ^c
Heart failure	75 (27.3)	167 (40.9)	162 (45.0)	< 0.001 ^c
Chronic obstructive pulmonary disease	26 (9.5)	41 (10.0)	44 (12.2)	0.475 ^c

Boldface type indicates statistical significance.

^a Kruskal Wallis Test.

^b Chi-Square Test.

^c Fisher-Freeman-Halton Exact Test.

than in the aforementioned studies, as patients requiring amputation are likely to be more severely ill than non-amputated diabetics.

In our data, a higher CFS score was associated with reduced OS, AFS, and LS. The association between clinical frailty and survival has not been studied earlier among patients with diabetes undergoing LEA. Previous studies have identified frailty as a significant predictor of postoperative complications and poor outcomes following LEA and revascularization.^{19,21} Takeji et al. showed that higher CFS was associated with reduced OS rates (80.5 % for CFS 1–3, 63.1 % for CFS 4–6, and 49.3 % for CFS 7–9, $p < 0.001$) and AFS rates (77.9 % for CFS 1–3, 60.5

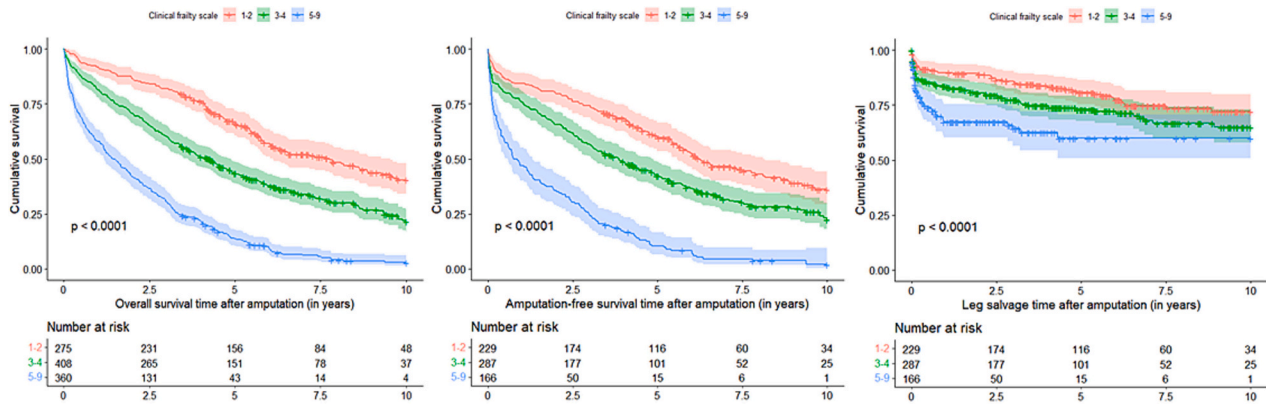


Fig. 3. Kaplan-Meier curves compare overall survival time, amputation-free survival time and leg salvage time after amputation between subgroups stratified by clinical frailty scale.

Table 2

Univariate Cox regression analysis of overall survival, amputation-free survival and leg salvage. CFS = Clinical Frailty Scale, OS = overall survival, AFS = amputation-free survival, LS = leg salvage.

Clinical frailty	OS (n = 1043)		AFS (n = 682)		LS (n = 681 ^a)	
	HR	95 % CI	HR	95 % CI	HR	95 % CI
CFS 1-2	1		1		1	
CFS 3-4	1.821	1.485-2.233	1.575	1.260-1.970	1.435	1.001-2.056
CFS 5-9	4.585	3.740-5.621	4.031	3.165-5.135	2.478	1.666-3.687

Boldface type indicates statistical significance.

^a Cox regression excludes one case that is censored before the earliest event in a stratum.

Table 3

Multivariable Cox regression analysis of overall survival, amputation-free survival and leg salvage. CFS = Clinical Frailty Scale, OS = overall survival, AFS = amputation-free survival, LS = leg salvage.

Influencing factor	OS (n = 1043)		AFS (n = 682)		LS (n = 681 ^a)	
	HR	95 % CI	HR	95 % CI	HR	95 % CI
Clinical frailty						
CFS 1-2	1		1		1	
CFS 3-4	1.390	1.130-1.709	1.258	1.001-1.579	1.270	0.878-1.835
CFS 5-9	2.347	1.879-2.932	2.403	1.845-3.129	1.839	1.189-2.844
Charlson comorbidity index	1.279	1.235-1.326	1.254	1.203-1.307	1.119	1.044-1.201
Gender	0.901	0.774-1.050	1.002	0.819-1.227	0.858	0.621-1.186
Amputation level	1.379	1.181-1.610				

Boldface type indicates statistical significance.

^a Cox regression excludes one case that is censored before the earliest event in a stratum.

% for CFS 4-6, and 46.2 % for CFS 7-9, $p < 0.001$) after revascularization in patients with critical limb ischemia.¹⁹ Sareh et al. demonstrated that frailty was associated with higher in-hospital mortality (4 % vs. 2 %, $p < 0.001$), as well as higher readmission rates and increased healthcare costs after minor LEA.²¹

In our study, the association between CFS and LS suggests that patients with more severe frailty have a higher risk of amputation. This finding indicates that frailty not only increases mortality but also impacts AFS. The CFS score remained significant for both OS and AFS in the multivariable model, indicating that it is an independent factor depicting the risk of death and major amputation.

In our study, retrospectively determined CFS correlated with other frailty indexes that consider the number of diseases and functional capabilities (CCI and mFI-11). CCI has been shown to predict mortality in patients with diabetic foot disease.²² In contrast, while mFI-11 does not predict mortality, it has been associated with other postoperative complications such as severe sepsis and readmission.^{9,23} The correlation between these indexes is likely due to the simultaneity and synergy between the phenomena these tools evaluate (comorbidities, aging, and

functional daily living performance). Since CFS retained significant in multivariable model, it appears to provide relevant information beyond what is explained by age and comorbidities alone.

Therefore, it may be beneficial to assess frailty using CFS among patients undergoing amputation. As an earlier study shows, mortality rates are higher after major amputations in patients with diabetic foot infections, highlighting the importance of considering amputation level in clinical decision-making.¹⁵ Overall, patients with CFS 5-9 are frail, and their prognosis is impaired even without amputation.²⁴ In contrast, patients with CFS 3-4 manage well or are only mildly frail, but their prognosis after amputation is worse compared to clinically very fit or fit patients with CFS 1-2, which may be relevant in clinical decision-making.

The strengths of this study include a comprehensive dataset encompassing all amputations performed on patients with diabetes at a tertiary hospital. Additionally, the study features a long follow-up period, with valid mortality data obtained from the national registry. Only one patient lacked sufficient data to determine the CFS score from medical records, and only one patient had missing diagnosis codes

entirely. Thus, the study benefits from highly complete and detailed information about the overall patient population, which enables the generalizability of the study findings within this patient population.

The limitations of this study include a manually collected data, which increases the potential for errors. To enhance the consistency of the manually collected data, a single researcher gathered information from all patients, ensuring reliable comparisons within this dataset. However, relying on a single researcher may limit the comparability of the CFS classification to those conducted by others. Another limitation of this study is the retrospective nature, which poses inherent challenges including the possibility for insufficient data. Nonetheless, we successfully determined the CFS for all but one patient. Additionally, the retrospective nature of the study allows only for the demonstration of an association between variables and does not establish a direct cause-and-effect relationship.

In conclusion, this study demonstrates a high prevalence of frailty among patients with diabetes undergoing LEA, with over 73 % of patients rated as CFS 3 or higher. Our findings indicate that higher CFS scores are associated with decreased OS, AFS, and LS. Moreover, the CFS score was an independent predictor of both mortality and the necessity for major amputation, suggesting that frailty assessment should be integrated into clinical decision-making for patients with diabetes facing amputation to enhance survival rates and improve the quality of life in the post-amputation period.

Abbreviations

AFS	Amputation-free survival
CCI	Charlson Comorbidity Index
CFS	Clinical Frailty Scale
CI	Confidence interval
HR	Hazard ratio
IQR	Interquartile range
LEA	Lower extremity amputation
LS	Leg salvage
mFI-11	11-Factor Modified Frailty Index
OS	Overall survival
SD	Standard deviation
SPSS	Statistical Package for the Social Sciences

CRediT authorship contribution statement

Hilma Tillqvist: Writing – original draft, Visualization, Formal analysis, Data curation. **Miska Vuorlaakso:** Writing – review & editing, Methodology, Conceptualization. **Mika Helminen:** Writing – review & editing, Visualization, Formal analysis. **Juha Kiiski:** Writing – review & editing, Conceptualization. **Ilkka Kaartinen:** Writing – review & editing, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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