

This item is the archived peer-reviewed author-version of:

Malnutrition according to the 2018 GLIM criteria is highly prevalent in people with a diabetic foot ulcer but does not affect outcome

Reference:

Lauwers Patrick, Hendriks Jeroen, Van Bouwel Saskia, Verrijken An, Van Dessel Kristof, Van Gils Carolien, Peiffer Frida, Yogeswaran Suresh Krishnan, de Block Christophe, Dirinck Eveline.- Malnutrition according to the 2018 GLIM criteria is highly prevalent in people with a diabetic foot ulcer but does not affect outcome

Clinical nutrition ESPEN - ISSN 2405-4577 - 43(2021), p. 335-341

Full text (Publisher's DOI): <https://doi.org/10.1016/J.CLNESP.2021.03.029>

To cite this reference: <https://hdl.handle.net/10067/1791180151162165141>

Malnutrition according to the 2018 GLIM criteria is highly prevalent in people with a diabetic foot ulcer but does not affect outcome.

Running title: "Malnutrition and diabetic foot ulcer"

Patrick Lauwers, MD¹, Jeroen M.H. Hendriks, MD, PhD^{1,2}, Saskia Van Bouwel, MD³, An Verrijken, RDN, PhD^{4,5}, Kristof Van Dessel, RDN^{4,5}, Carolien Van Gils, RDN⁵, Frida Peiffer, MD⁵, Krishan Yogeswaran, MD¹, Christophe De Block, MD, PhD^{4,5}, Eveline Dirinck, MD, PhD^{4,5}

1 Department of Thoracic and Vascular Surgery, Antwerp University Hospital (UZA), Belgium

2 ASTARC, Division of Thoracic and Vascular Surgery, University of Antwerp, Belgium

3 Department of Orthopedic Surgery, Antwerp University Hospital (UZA), Belgium

4 Laboratory of Experimental Medicine and Pediatrics, Division of Endocrinology, University of Antwerp, Belgium

5 Department of Endocrinology, Diabetology and Metabolism, Antwerp University Hospital (UZA), Belgium

Corresponding author:

Patrick Lauwers, Antwerp University Hospital (UZA), Department of Thoracic and Vascular Surgery, Wilrijkstraat 10, B 2650 Edegem, Belgium.

Phone + 32 3 821 37 85; fax + 32 3 829 05 20; email patrick.lauwers@uza.be

Conflicts of interest: none.

Abstract

Objective. To estimate the prevalence of protein-energy malnutrition in people admitted for a diabetic foot ulcer (DFU) and to assess the relationship between malnutrition and DFU severity and outcome.

Methods. This prospective, observational cohort study included individuals consecutively admitted for a DFU between July 2016 and September 2019. The Global Leadership Initiative on Malnutrition (GLIM) criteria determined the prevalence of malnutrition. The SINBAD score reflected DFU severity. Outcome was evaluated at discharge and at 6 months. The independent contribution of nutritional status on DFU severity and outcome was investigated using logistic regression analysis.

Results. A total of 110 patients were included. Malnutrition, as defined by the GLIM criteria, was diagnosed in 26 cases; malnutrition was moderate in 9 and severe in 17. DFU severity differed significantly between subjects with malnutrition versus without malnutrition (SINBAD: 3.85 vs. 3.81, $p = 0.012$). Logistic regression analysis showed that severe malnutrition ($p = 0.015$) and hemoglobin level ($p = 0.003$) were independently linked to DFU severity. At 6-month follow-up, 39 DFU were healed, 36 patients had undergone an amputation (32 minor, 4 major) and 8 had died. No differences were noted in outcome at discharge or at 6 months according to nutritional status.

Conclusions. In 24% of patients, malnutrition was diagnosed. Severely malnourished individuals presented with more severe ulcers. However, malnutrition had no impact on the short-term outcome of a DFU.

Key words: malnutrition; GLIM-criteria; diabetic foot ulcer; diabetic foot; diabetes; SINBAD classification

Introduction

The lifetime risk for people with diabetes of developing a diabetic foot ulcer (DFU) is 25% (1). The pathophysiology of a DFU is complex, with neuropathy, angiopathy, and infection as provocative factors. DFU is the most important cause of non-traumatic lower extremity amputation (LEA) in Western countries (2), and one of the most frequent reasons for hospital admission in people with diabetes (1). Wound healing is hampered by local factors such as infection at the ulcer site and systemic factors such as poor glycemic control, vasculopathy, and nephropathy (3–4).

Wound healing is also dependent on the patient's nutritional status (5). The negative influence of malnutrition on wound healing and patient outcome has been demonstrated for pressure ulcers (6), venous ulcers (7), and burns (8). Nevertheless, although protein-energy malnutrition is common, with a reported prevalence of 20–40% for hospitalized patients, it remains frequently unrecognized (9–11).

Despite the high burden of DFU worldwide and despite the fact that DFU patients, often elderly with multiple comorbidities, are theoretically at high risk of malnutrition, evidence on the potential influence of malnutrition on DFU severity and outcome is scarce. So far, only five studies have examined the prevalence of malnutrition in DFU (12–17). Although these studies had large differences in patient population and methodology, all of them invariably found an alarmingly high prevalence of patients at risk of malnutrition (49–70%) or being malnourished (15–62%). However, none of them used the recently introduced Global Leadership Initiative on Malnutrition (GLIM) consensus criteria to diagnose malnutrition (18).

The aim of present study was to estimate the prevalence of malnutrition as defined by the GLIM criteria in subjects admitted for a DFU at Antwerp University Hospital and to assess the relationship between malnutrition and DFU severity and outcome.

Research Design and Methods

Research Design

This is an observational prospective cohort study, conducted at the Antwerp University Hospital from July 1, 2016, to September 30, 2019. Individuals were screened and recruited consecutively. This study was approved by the local Ethics Committee (Registration n° 16/24/252; B300201628994).

Study population

All subjects admitted for a DFU were eligible for inclusion. Participation was on a voluntary basis, after written informed consent was obtained. Exclusion criteria were Charcot foot without ulcer; inability to provide informed consent due to language barrier, cognitive dysfunction, psychiatric disorders, or urgent surgery; admission for any reason other than an existing DFU; hospitalization in the preceding 3 months; prior bariatric surgery; current oncological treatment; pregnancy; age under 18 years; and presenting with a multiresistant infection. Follow-up ended on March 31, 2020.

Patient and DFU data

Demographic and socio-economic data, medical and surgical antecedents, medication, and diabetes-related parameters were recorded. Prior DFU, lower extremity amputation (LEA) and Charcot foot, and presence or absence of neuropathy, infection, and peripheral arterial disease (PAD) were specifically recorded (Supplementary file). All patients underwent a duplex ultrasound to screen for PAD. Transcutaneous oxygen measurement assessed the potential of wound healing, while revascularization options were evaluated after angiography in patients with an estimated Glomerular Filtration Rate (eGFR) of 30 ml/min or more. Parameters of interest with regard to the actual DFU were duration, localization, and treatment of DFU. DFU severity was reported according to the SINBAD classification (see further: classifications for DFU severity). Osteomyelitis was diagnosed with magnetic

resonance imaging (MRI), or, if MRI was not possible, based on clinical judgment (exposed bone, positive probe-to-bone test, and sausage toe) and X-ray findings. A blood analysis including hemoglobin, HbA1c, serum creatinine, and CRP levels was conducted upon admission.

Patients were treated by a multidisciplinary team according to the guidelines established by the International Working Group on the Diabetic Foot (19).

Nutritional evaluation

All patients underwent an extensive nutritional evaluation within 48 hours of admission. In order to screen for malnutrition, patients answered the questions of the NRS-2002; in addition, all patients were assessed by using the Mini Nutritional Assessment tool. Data necessary to apply the definition of malnutrition as presented by the Global Leadership Initiative on Malnutrition (GLIM) were present (18). This definition is based on a combination of three phenotypic and two etiologic criteria. The three phenotypic criteria are non-intentional weight loss, low body mass index (BMI), and reduced muscle mass. The two etiologic criteria are reduced food intake and inflammation. To diagnose malnutrition, at least one phenotypic criterion and one etiologic criterion should be present (18). In addition, the GLIM criteria offer a classification for the degree of malnutrition (moderate vs. severe malnutrition) (18). All individuals were grouped according to the GLIM criteria, based on nutritional status: group A (those without malnutrition), group B (individuals that were moderately malnourished), and group C (individuals that were severely malnourished).

Weight loss and reduced food intake were questioned during history taking. Each patient's body weight and height were recorded in order to calculate BMI. This was done in the morning, in the fasting state, and with an empty bladder. Body composition was determined by bioelectrical impedance analysis (BIA) as described by Lukaski (20). The BIA 101 device with Bodygram software (both by Akern Srl, Firenze, Italy) provided information on body

composition (ratio of body fat, muscle mass, and fluid accumulation). The muscle mass of the patient was assessed taking into account the appendicular skeletal muscle mass (ASMM). Due to the chronic inflammatory nature of DFU, all patients were considered to meet the inflammation criterion.Nutritional counseling

Since 2015, Antwerp University Hospital has implemented a hospital-wide nutritional screening protocol based on the Nutritional Risk Score-2002 (NRS-2002) (11). Attention is given to low BMI ($\text{BMI} < 20.5 \text{ kg/m}^2$), unintentional weight loss, reduced food intake, and critical illness. All patients are screened for malnutrition at admission by the hospital nurses, independent of the current nutritional study protocol. When patients are in good nutritional health, dietary intake and weight are monitored on a weekly basis; patients at risk for malnutrition receive a consult from a dietician with the aim of optimizing the patient's dietary intake.

Classifications for DFU severity

Multiple classification systems describe DFU severity (21). At the 8th International Symposium on the Diabetic Foot in 2019, new global guidelines on the management of the diabetic foot were implemented. The SINBAD classification was proposed as the preferred framework for communication among health care professionals to describe DFU severity (19). This classification gives a grade of 0 or 1 to site (localization), ischemia, neuropathy, bacterial infection, area and depth of the ulcer. As such, the maximum score is 6 (22).

DFU and patient outcome

Outcome of the DFU was registered at discharge and after 6 months, and scored as DFU healing, amputation (minor or major), death, and lost to follow-up. An amputation distal to the ankle joint was considered as minor, whereas in major amputations the ankle joint was not preserved.

Statistical data processing

Data were recorded in a coded database. When a patient presented twice or more, only the first hospitalization was included.

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS, version 21.0 for Windows). A p-value <0.05 was considered statistically significant.

Data for normally distributed continuous variables were expressed as mean \pm standard deviation (SD), while not normally distributed continuous variables were expressed as median (minimum–maximum). Normality was tested using the Kolmogorov-Smirnov test. Data for categorical variables were presented as a number and percentage.

The χ^2 test or Mann-Whitney U test were used to compare categorical variables; for continuous variables the student-t test (normally distributed variables) or the Mann-Whitney U test (not normally distributed variables) were used. Logistic regression analysis determined which factors were significant predictors of DFU severity, according to SINBAD, and DFU outcome.

Using a univariable logistic regression analysis, the following parameters were screened for inclusion in a multivariable logistic regression model to assess their role in predicting DFU severity: age, gender, educational level, employment, diabetes type and duration, HbA1c levels, insulin dependency, retinopathy, nephropathy (based on eGFR), coronary ischemic heart disease, arterial hypertension, prior DFU or amputation, duration of DFU, presence of multiple DFUs, presence of Charcot foot, BMI, serum albumin, hemoglobin levels, and nutritional status. PAD, neuropathy, and localization and presentation of the DFU were not entered in the model, because these are contributing components of the SINBAD classification. DFU were categorized as severe (SINBAD ≥ 4) or less severe (SINBAD ≤ 3).

The same parameters supplemented with the SINBAD classification were screened for inclusion in a multivariable logistic regression model to assess their role in predicting

outcome. The combined endpoint of DFU healing including minor amputation was put forward to define outcome.

Results

Study population – patient data (Table 1)

A total of 164 individuals were hospitalized for a DFU. Of these, 54 (33%) were excluded for the following reasons: no informed consent because of language barrier (17), a cognitive deficit (9), not willing to participate (5), required urgent surgery (2); transferred from another department or from another hospital (13); and presence of multiresistant infection (8). This brings the final study population to 110 (Table 1).

Eighty percent of patients were male, with a mean age of 68 ± 12 years. Type 2 diabetes mellitus was more common than type 1 diabetes (84%). Ischemic coronary artery disease (42%), peripheral arterial disease (40%), and cerebrovascular disease (17%) were highly prevalent. Arterial hypertension and dyslipidemia were present in 89% and 76% of participants, respectively; 53% of the subjects were active or former smokers. After 6 months, 2 patients were lost to follow-up.

Nutritional evaluation

Based on the GLIM criteria (18), 26 patients (24%) were malnourished. Nine (8%) were moderately and 17 (15%) severely malnourished.

The phenotypic criteria of weight loss, low BMI, and reduced muscle mass were fulfilled in 15 (14%), 3 (3%), and 12 (11%) cases, respectively; the etiologic criteria of reduced food intake/assimilation and inflammation were present in 35 (32%) and 110 (100%) patients, respectively.

Small differences in demographic data were observed according to nutritional status (Table 1). All malnourished patients suffered from arterial hypertension (no malnutrition vs. malnutrition, $p = 0.046$). Patients that were moderately malnourished had the highest prevalence of ischemic heart disease (no malnutrition vs. moderate malnutrition, 42% vs. 78%, $p = 0.04$; moderate vs. severe malnutrition, 78% vs. 24%, $p = 0.009$) and dialysis

(moderate malnutrition vs. no malnutrition, 22% vs. 12%, $p = 0.019$), but had a significantly lower prevalence of neuropathy compared to those in good nutritional condition (83% vs. 56%, $p = 0.046$).

BMI was significantly lower in malnourished patients (26.5, range 18.1–39.6) compared to those presenting with a normal nutritional status (29.1, range 21.8–48.3; $p = 0.033$), although still in the overweight range.

DFU and DFU severity at admission

More than half of the patients had already experienced a DFU in the past (55%), were already admitted for a DFU or Charcot foot (45%), or had already undergone one or more amputations (29%). However, no statistically significant differences were noted in the diabetic foot antecedents of the different nutritional groups.

Patients presented with longstanding ulcers (median duration 111 days, range 2–912) and had a high prevalence of osteomyelitis (61%). Ulcer localization was equally distributed between all groups, 85% being forefoot ulcers. PAD was present in 67% of the patients.

Patients with malnutrition presented with more severe DFU on average according to the SINBAD classification (malnourished vs. not malnourished, 3.85 vs. 3.81, $p = 0.012$). This difference is attributable to the individuals with severe malnutrition; these patients presented with the most severe ulcers according to SINBAD (severe vs. moderate malnutrition $p = 0.001$; severe vs. no malnutrition $p < 0.0001$).

Based on univariable analysis, logistic regression analysis determined which of following variables were significant predictors of DFU severity according to SINBAD (Hb, albumin, eGFR, educational level, coronary artery disease, DFU duration, and nutritional status).

Logistic regression analysis identified Hb ($p = 0.003$) and severe malnutrition ($p = 0.015$) as being independently associated with ulcer severity.

DFU and patient outcome (Table 2)

Median hospital stay was 28 days (range 2–132) with no statistically significant difference between nutritional groups. During hospitalization, 17 (23%) of 74 patients with PAD were treated by open or endovascular surgery. Revascularization was not performed in 19 (26%) patients because of renal insufficiency and considered not feasible in 16 (22%) or not necessary in 22 (30%) patients.

At discharge, 33 people (30%) had undergone an amputation, of which 90% were minor amputations. Three patients died, all of them in the group with normal nutritional status. One patient succumbed from a critical aortic valve stenosis in the postoperative period after a below-the-knee amputation, one patient was given palliative care as she refused a major amputation for deep limb ischemia, and a third patient died suddenly but no autopsy was performed (Table 2).

At 6 months, 71 (65%) cases had complete wound healing or underwent a minor amputation. Four patients (4%) underwent a major amputation, and eight (7%) had died. No statistically significant differences were found between groups according to nutritional status (Table 2).

Based on univariable analysis, the following variables were tested in a logistic regression model assessing the combined endpoint wound healing AND minor amputation at 6 months: active smoking, metabolic control, DFU duration, employment, age, SINBAD classification, and nutritional status.

Of these, only active smoking ($p = 0.003$) was a significant (negative) predictor of the combined endpoint wound healing and minor amputation.

Discussion

Prevalence of malnutrition in the DFU population

Despite the high burden of DFU worldwide, data on the prevalence of malnutrition in the DFU population is scarce; only five manuscripts on this topic were identified (12–17). A high number of DFU patients seem to be in a compromised nutritional state, as 49–70% of them were shown to be at risk for malnutrition (14,16); malnutrition was diagnosed in 15% (14), 29% (15), 32% (13), and 62% of patients (17).

However, it is difficult to make reliable comparisons with these studies, as all authors used different definitions of malnutrition and applied these to different study populations. Recently, major nutritional societies have taken the Global Leadership Initiative on Malnutrition (GLIM) and proposed consensus criteria for the diagnosis on malnutrition. The purpose was to implement these criteria in order to compare malnutrition prevalence and the outcomes of nutritional interventions throughout the world (17).

In present study, the GLIM criteria were implemented for a group of 110 consecutively hospitalized DFU patients. We found 24% of individuals to be malnourished. To the best of our knowledge, this is the first time the GLIM criteria were applied to a very well characterized DFU population. The diagnosis of malnutrition according to the GLIM criteria is retained when at least one phenotypic and one etiologic criterion is fulfilled. The etiologic criteria of reduced food intake/assimilation and inflammation were present in 32% and 100% of all patients, respectively. However, the phenotypic criteria of weight loss, low BMI, and reduced muscle mass were less prevalent. BMI does not seem to correctly reflect nutritional status. Indeed, although mean BMI was significantly lower for malnourished subjects, BMI was still in the overweight range for the majority of malnourished patients. This paradox has been observed previously; Vischer found a high prevalence of malnutrition (14%) or risk of malnutrition (75%) in people admitted with type 2 diabetes while being overweight (23).

Malnutrition and DFU severity at admission

Since the 8th International Symposium on the Diabetic Foot, the SINBAD classification is preferred for describing DFU severity (19). Based on this classification, a significant difference in ulcer severity was observed between patients in good nutritional condition versus malnourished patients. This difference was solely attributable to the individuals with severe malnutrition, as they presented with the highest SINBAD scores. In contrast, patients with moderate malnutrition—the smallest group—tended to present with the least severe ulcers. However, due to the small number of patients in this particular subgroup, it is not possible to draw significant conclusions on this. In a multivariable regression analysis, severe malnutrition was found to be a significant predictor of DFU severity, expressed by the SINBAD classification. In the first large-scale study on malnutrition and DFU, Zhang found a negative correlation between DFU severity and grade of malnutrition, assessed using the Subjective Global Assessment (SGA), in an Asian population. All patients presenting with the worst DFUs were malnourished, compared to only 11.7% in the group of individuals without DFU (17). The influence of malnutrition on DFU severity was not reported by other authors (12–16).

Malnutrition and DFU outcome

The population in the present study was representative of the Belgian DFU population, both in terms of patient and DFU characteristics (24). Ulcer healing at 6 months, including minor amputation, was reached in 65% of patients (compared to 49–54% in the Belgian population) with acceptable and comparable major amputation (4%) and death rates (7%). One quarter of patients had a persisting ulcer, which is lower than in the Belgian data (24).

However, despite the fact that malnourished patients presented with more severe DFU, no statistically significant differences in wound healing, amputation, or mortality rates were found between well-nourished and malnourished patients at discharge or after a 6-month

follow-up. Potential explanations for this might be the longstanding presence of the DFUs, the overall high prevalence of severe comorbidities (cardiovascular disease and renal insufficiency), the severity of DFU at presentation (61% had a DFU with underlying osteomyelitis), and/or the intensive treatment by a multidisciplinary team as reflected by a long hospitalization time (median 28 days).

In our cohort, 86% of DFU patients were visited by a dietician during their hospital stay. This high frequency of dietary counseling, due to the hospital-wide implemented nutritional protocol and due to the high interest of the team in nutritional condition, might have induced a discrete optimization of the nutritional status of individuals hospitalized for a DFU and thus might have positively biased the outcome of the presented DFU population.

Five authors reported on malnutrition and outcome in a DFU population previously (12–17).

In three Asian study populations, nutritional status was found to be an independent predictor of patient outcome at discharge and after a 6-month follow-up (14,16,17). Zhang found that malnourished patients had statistically significantly higher amputation (30%) and mortality (17%) rates, while the majority of DFUs in well-nourished patients healed (86%) (17). Gau reported that the major amputation rate was 6 to 11 times higher in malnourished people; malnutrition was independently associated with the outcomes of both major and minor amputations (14). Xie retrospectively examined mortality rates in a cohort of 271 adults undergoing a lower extremity amputation for their DFU; 72 persons (26.6%) died. Malnutrition was identified as an independent predictor of mortality, after both major and minor amputation (16).

In two European studies, Eneroth found lower percentages of wound healing for malnourished patients (24% vs. 50%), while Rouland observed better overall DFU healing rates after 6 months for well-nourished people. However, neither author could demonstrate significant differences in outcome between well-nourished and malnourished people (13,15).

All three Asian studies reported markedly higher major amputation and death rates compared to the present and the two other European studies. Many factors might contribute to these differences.

First, a selection bias might have occurred. Eneroth and Rouland only included people with non-infected ulcers (13,15), and Rouland excluded patients with severe comorbidities (15). In contrast, Xie retrospectively studied patients undergoing a LEA, in general patients with more comorbidities and more severe ulcers (16). In the present study, nine older patients with a major cognitive deficit, generally at high risk for malnutrition, were excluded, also potentially inducing a selection bias.

Second, the prevalence of malnutrition or risk of malnutrition was high in all three Asian studies. In particular, the high number of malnourished patients in the study by Zhang (62%) stands out. As most of the older definitions of malnutrition rely on weight and BMI, global differences in BMI should be taken into account. One should remember that these previous studies did not use the GLIM criteria to define malnutrition, in which a correction is made for the different posture of the Asian population.

Third, the effect of nutritional supplementation as executed by Eneroth and Rouland might have influenced DFU outcome at 6 months, although neither author was able to find a statistically significant benefit.

Finally, the complex pathophysiology and nature of the DFU, combined with differences in local resources and approach, might also explain differences in outcome on a global level.

Strengths and Limitations

The strength of this study is that this is the first time the GLIM criteria were applied to a DFU population. Due to strict selection criteria, this study included a homogenous patient cohort with severe foot ulcers. Patients were well characterized, and nutritional status was assessed

in great detail. Patient and DFU characteristics were comparable to those of the Belgian IQED-foot data (24).

This is a single-center study, with a modest number of patients. After screening, one third of patients (54 out of 164) were excluded. This high exclusion rate might potentially induce a selection bias. On the other hand, excluding these patients leaves a more homogenous study population, which can be regarded as a strength and not a limitation.

In addition, comparison with other papers is difficult because the guidelines on malnutrition screening (GLIM criteria) and staging of the diabetic foot (SINBAD) were only proposed in 2019 and are not yet widely implemented. Future studies should use these novel criteria to allow valid comparisons.

Conclusion

Based on the GLIM criteria, the prevalence of malnutrition in the present DFU population reached 24%, with 15% being severely malnourished. Based on the SINBAD classification, severely malnourished patients presented with the most severe ulcers. However, no relation was found between nutritional status at admission and outcome of the DFU at 6 months.

Acknowledgments and conflict of interest statement

The authors' responsibilities were as follows: Patrick Lauwers, Eveline Dirinck, and Jeroen Hendriks conceptualized the study; Patrick Lauwers, Saskia Van Bouwel, Frida Peiffer, Krishan Yogeswaran, and Eveline Dirinck recruited patients and collected patient data; An Verrijken, Kristof Van Dessel, and Carolien Van Gils were responsible for nutritional evaluation of the patients; Patrick Lauwers, Eveline Dirinck, Jeroen Hendriks, and Christophe De Block contributed to data interpretation; Patrick Lauwers wrote the manuscript; all authors critically reviewed and approved the manuscript.

The authors wish to thank dr Kristien Wouters for statistical support.

This study was not granted with financial support.

The authors do not have any conflict of interest.

Table 1. Patient characteristics.

	No malnutrition (group A; n = 84)	Malnutrition (group B + C; n = 26)			* **
		All patients with malnutrition (group B + C; n = 26)	Moderate malnutrition (group B; n = 9)	Severe malnutrition (group C, n = 17)	
Male gender (%)	67 (80)	21 (81)	6 (67)	15 (88)	ns
age (years)	68 (31–89)	70 (49–82)	72 (53–85)	68 (49–92)	ns
Abuses/ cardiovascular risk factors					
smoking (%)	42 (50)	16 (62)	4 (44)	12 (71)	ns
arterial hypertension (%)	72 (86)	26 (100)	9 (100)	17 (100)	Group A vs. B + C: p = 0.042
dyslipidemia (%)	63 (75)	20 (77)	8 (89)	12 (71)	ns
Diabetes					
Diabetes type 2 (%)	68 (81)	24 (92)	9 (100)	15 (88)	ns
HbA1c (%)	7.4 (3.2–15)	7.2 (4.5–13.3)	6.7 (5.7–9.6)	7.4 (4.5–13.3)	ns
HbA1c (mmol/mol)	57 (11–140)	55 (25–121)	49 (38–81)	57 (25–121)	
neuropathy (%)	70 (83)	19 (73)	5 (56)	14 (82)	Group A vs. B: p = 0.046
nephropathy (%)	66 (79)	21 (81)	7 (78)	14 (82)	ns
dialysis (%)	3 (4)	3 (12)	2 (22)	1 (6)	Group A vs. B: p = 0.019
insulin treatment (%)	44 (52)	14 (54)	4 (44)	10 (59)	ns
Medical history					
coronary heart disease (%)	35 (42)	11 (42)	7 (78)	4 (24)	Group A vs. B: p = 0.04; Group B vs. C: p = 0.009
peripheral arterial disease (%)	33 (39)	11 (42)	5 (56)	6 (35)	ns
cerebrovascular accident (%)	12 (14)	7 (27)	2 (22)	5 (29)	ns
Physical examination					
BMI (kg/m ²)	29.1 (21.8–48.3)	26.5 (18.1–39.6)	26.0 (20.4–36.9)	26.7 (18.1–39.6)	Group A vs. B + C: p = 0.033
Lab results					
Hemoglobin (g/dl)	12.1 (7.4–15.1)	11.9 (8.9–15.3)	11.5 (9.4–14.4)	12.2 (8.9–15.3)	ns
eGFR (ml/min)	60.4 (5–113.9)	64.8 (5.4–111)	44.9 (5.4–97.8)	75.4 (21.7–111.0)	Group B vs. C: p = 0.025
c reactive protein (mg/dl)	25 (0–290)	34.2 (0–156)	36.7 (0–141)	32.4 (0–156)	Group A vs. B + C:

					<p>p = 0.037; Group A vs. C: p = 0.025</p>
--	--	--	--	--	--

Normally distributed continuous variables were expressed as mean \pm standard deviation (SD), not normally distributed continuous variables as median (minimum–maximum); data for categorical variables as a number and percentage.

*ns, not statistically different. This implies group A vs. group B + C; and group A vs. group B, B vs. C, and A vs. C.

**A Mann-Whitney U test was performed for comparison of categorical variables between groups A and B (no versus moderate malnutrition), groups A and C (no versus severe malnutrition), and groups B and C (moderate versus severe malnutrition).

**A Mann-Whitney U test was performed for comparison of categorical variables between groups A versus (B + C) (no malnutrition versus all groups with malnutrition), except for gender, dyslipidemia, retinopathy, neuropathy, nephropathy, coronary ischemic heart disease, peripheral arterial disease, and insulin-use, where a X^2 -test was used.

Table 2. Patient and DFU outcomes.

	No malnutrition (group A, n = 84)	Malnutrition			* **
		All patients with malnutrition N = 26	Moderate malnutrition (Group B, n = 9)	Severe malnutrition (Group C, n = 17)	
outcome at discharge (n = 110)					
DFU healed (%)	5 (6)	1 (4)	0 (0)	1 (6)	ns
persistent DFU (%)	50 (60)	17 (65)	7 (78)	10 (59)	ns
amputation (%)*	25 (30)	8 (31)	2 (22)	6 (35)	ns
minor amputation (%)	24 (29)	6 (23)	1 (11)	5 (29)	ns
major amputation (%)	1 (1)	2 (8)	1 (11)	1 (6)	ns
died during hospitalization (%)	3 (4)	0 (0)	0 (0)	0	ns
duration of hospitalization (days)	28 (2–132)	28 (2–103)	24 (6–49)	31 (2–103)	ns
outcome at 6 months (n = 110)					
DFU healed (%)	29 (35)	10 (38)	5 (56)	5 (29)	ns
persistent DFU (%)	19 (23)	6 (23)	2 (22)	4 (24)	ns
amputation (%)	28 (33)	8 (31)	2 (22)	6 (35)	ns
minor amputation (%)	26 (31)	6 (23)	1 (11)	5 (29)	ns
major amputation (%)	2 (2)	2 (8)	1 (11)	1 (6)	ns
died (%)	6 (7)	2 (8)	0 (0)	2 (12)	ns
Lost to follow-up (%)	2 (2)	0 (0)	0 (0)	0 (0)	ns

Data are presented as a number (and percentage). Duration of hospitalization is presented as number of days.

*ns, not statistically different. This implies group A vs. group B + C; and group A vs. group B, B vs. C, and A vs. C.

**A Mann-Whitney U test was performed for comparison of categorical variables between groups A and B (no versus moderate malnutrition), groups A and C (no versus severe malnutrition), and groups B and C (moderate versus severe malnutrition).

**A Mann-Whitney U test was performed for comparison of the outcome parameters at discharge between groups A versus (B + C) (no malnutrition versus all groups with malnutrition), except for the parameters “healed DFU including cases healed after minor amputation (yes/no)” and “amputation (yes/no)”, where a X^2 -test was used.

**A Mann-Whitney U test was performed for comparison of the outcome parameters at 6 months between groups A versus (B + C) (no malnutrition versus all groups with malnutrition), except for the parameters “healed DFU (yes/no)”, “healed DFU including cases healed after minor amputation (yes/no)” and “amputation (yes/no)”, where a X^2 -test was used.

References

1. Boulton AJM, Vileikyte L, Ragnarson-Tennvall G, Apelqvist J. The global burden of diabetic foot disease. *Lancet* 2005;366:1719-1724. DOI: 10.1016/S0140-6736(05)67698-2
2. Claessen H, Avalosse H, Guillaume J, Narres M, Kvitkina T, Arend W, Morbach S, Lauwers P, Nobels F, Boly J, Van Hul C, Doggen K, Dumont I, Felix P, Van Acker K, Icks A. Decreasing rates of major lower-extremity amputation in people with diabetes but not in those without: a nationwide study in Belgium. *Diabetologia* 2018;61(9):1966-1977. doi: 10.1007/s00125-018-4655-6
3. Baltzis D, Eleftheriadou I, Veves A. Pathogenesis and treatment of impaired wound healing in diabetes mellitus: new insights. *Advances in Therapy* 2014;31(8):817-836. doi.org/10.1007/s12325-014-0140-x
4. Sharp A, Clark J. Diabetes and its effects on wound healing. *Nursing Standard* 2011;25(45):41-47. DOI: 10.7748/ns2011.07.25.45.41.c8626
5. Molnar JA, Vlad LG, Gumus T. Nutrition and chronic wounds: improving clinical outcome. *Plast Reconstr Surg* 2016;138(3S):71S-81S. doi: 10.1097/PRS.0000000000002676
6. Alhaug J, Gay CL, Henriksen C, Lerdal A. Pressure ulcer is associated with malnutrition as assessed by Nutritional Risk Screening (NRS 2002) in a mixed hospital population. *Food Nutr Res* 2017;61(1):1324230. DOI: 10.1080/16546628.2017.1324230
7. Barber GA, Weller CD, Gibson SJ. Effects and associations of nutrition in patients with venous leg ulcers: a systematic review. *J Adv Nurs* 2017;00:1-14. DOI: 10.1111/jan.13474
8. Demling RH. The incidence and impact of pre-existing protein energy malnutrition on outcome in elderly burn patient population. *J Burn Care Rehabil* 2005;26(1):94-100. DOI: 10.1097/01.BCR.0000150302.71007.80
9. Anderson K, Hamm RL. Factors that impair wound healing. *J Am Coll Clin Wound Spec* 2012;4(4):84-91. DOI: 10.1016/j.jccw.2014.03.001
10. Correia MITD, Waitzberg DL. The impact of malnutrition on morbidity, mortality, length of hospital stay and costs evaluated through a multivariate model analysis. *Clin Nutr* 2003;22(3):235-239. DOI: 10.1016/s0261-5614(02)00215-7
11. Kondrup J, Allison SP, Elia M, Vellas B, Plauth M. ESPEN Guidelines for nutrition screening. *Clin Nutr* 2003;22(4):415-421. DOI: 10.1016/s0261-5614(03)00098-0
12. Lauwers P, Dirinck E, Van Bouwel S, Verrijken A, Van Dessel K, Van Gils C, Sels M, Peiffer F, Van Schil P, De Block C, Hendriks J. Malnutrition and its relation with diabetic foot ulcer severity and outcome: a review. *Lauwers P, Acta Clin Belg* 2020;29:1-7. doi: 10.1080/17843286.2020.1800315
13. Eneroth M, Larsson J, Oscarsson C, Apelqvist J. Nutritional supplementation for diabetic foot ulcers: the first RCT. *J Wound Care* 2004;13(6):230-234. DOI: 10.12968/jowc.2004.13.6.26627
14. Gau BR, Chen HY, Hung SY, Yang HM, Yeh JT, Huang CH, Sun JH, Huang YY. The impact of nutritional status on treatment outcomes of patients with limb-threatening

- diabetic foot ulcers. *J Diabetes Complications* 2016;30(1):138-142. doi: 10.1016/j.jdiacomp.2015.09.011
15. Rouland A, Fourmont C, Sberna AL, Aho Glele LS, Mouillot T, Simoneau I, Vergès B, Petit JM, Bouillet B. Malnutrition in type 2 diabetic patients does not affect healing of foot ulcers. *Acta Diabetologia* 2019;56(2):171-176. doi: 10.1007/s00592-018-1233-9
 16. Xie Y, Zhang H, Ye T, Ge S, Zhuo R, Zhu H. The geriatric nutritional risk index independently predicts mortality in diabetic foot ulcer patients undergoing amputations. *J Diabetes Res* 2017;e5797194. Retrieved from <https://www.hindawi.com/journals/jdr/2017/5797194> (accessed 1 June 2020). doi: 10.1155/2017/5797194
 17. Zhang SS, Tang ZY, Fang P, Qian HJ, Xu L, Ning G. Nutritional status deteriorates as the severity of diabetic foot ulcers increases and independently associates with prognosis. *Exp Ther Med* 2013;5(1):215-222. doi: 10.3892/etm.2012.780
 18. Cederholm T, Jensen GL, Correia I, Gonzalez MC, Fukushima R, Higashiguchi T, Baptista G, Garazzoni R, Blaauw R, Coats A, et al. GLIM criteria for the diagnosis of malnutrition – a consensus report from the global clinical nutrition community. *Clin Nutr* 2019;38(1):1-9. doi.org/10.1002/jpen.1440
 19. International Working Group on the Diabetic Foot. Retrieved from <https://iwgdfguidelines.org> (accessed 1 June 2020)
 20. Lukaski HC, Johnson PE, Bolonchuk WW, Lykken GI. Assessment of fat-free mass using bioelectrical impedance measurements of the human body. *Am J Clin Nutr* 1985, 41(4):810-817. DOI: 10.1093/ajcn/41.4.810
 21. Game F. Classification of diabetic foot ulcers. *Diabetes Metabolism Research and Reviews* 2016;32:186-194. doi.org/10.1002/dmrr.2746
 22. Ince P, Abbas ZG, Lutale JK, Basit A, Ali SM, Chohan F, Morbach S, Möllenberg J, Game FL, Jeffcoate WJ. Use of the SINBAD classification system and score in comparing outcome of foot ulcer management on three continents. *Diabetes Care* 2008;31(5):964-967. doi.org/10.2337/dc07-2367
 23. Vischer UM, Perrenoud L, Genet C, Ardigo S, Registe-Rameau Y, Herrmann FR. The high prevalence of malnutrition in elderly diabetic patients: implications for anti-diabetic drug treatments. *Diabet Med* 2010;27(8):918-24. doi.org/10.1111/j.1464-5491.2010.03047.x
 24. Doggen K, Van Acker K, Beele H, Dumont I, Felix P, Lauwers P, Lavens A, Matricali G, Randon C, Weber E, Van Casteren V, Nobels F. Implementation of a quality improvement initiative in Belgian diabetic foot clinics: feasibility and initial results. *Diabetes Metabolism Research and Reviews* 2014;30(5):435-443. doi: 10.1002/dmrr.2524