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Nutritional Assessment Using the Prognostic Nutritional Index (PNI) and Controlling Nutritional Status (CONUT) Score Predicts Wound Healing In Patients with Diabetic Foot Ulcers

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Abstract

Aims

The aim was to examine whether the Prognostic Nutritional Index (PNI) and Controlling Nutritional Status (CONUT) score are predictors of wound healing in patients with diabetic foot ulcers (DFUs).

Materials and Methods

This was a hospital-based, single-center, observational, longitudinal cohort study of 349 Japanese patients (84 women, 265 men; mean (standard deviation) age 62.8 (12.8) years) with DFUs. The endpoint was complete wound healing. The classical Cox proportional model and competing-risks model were used to calculate the hazard ratios (HRs) and the 95% confidence interval (CI) for reaching the endpoint.

Results

During a median (range) follow-up of 2.3 (0.03-62.3) months, 220 patients (63.0%) reached the endpoint. In the multivariate Cox proportional hazards model, higher PNI was identified as an independent predictor for the endpoint (HRs 1.22, 95% CI 1.01-1.48, p=0.038). In the multivariate competing-risks model analysis, both higher PNI (HRs 1.26, 95% CI 1.03-1.53, p=0.024) and lower CONUT score (HRs 0.80, 95% CI 0.65-0.99, p=0.045) were identified as independent predictors for the endpoint. Similar results were obtained when the PNI and the CONUT score were treated as categorical variables (≥ median or less).

Conclusions

Nutritional status, as assessed using the PNI and CONUT score, is a novel clinical predictor for wound healing in patients with DFUs.

Keywords: Diabetic foot ulcer; Nutritional assessment; Prognostic nutritional index; Controlling Nutritional Status.

Introduction

Patients with diabetes have been shown to have a 15-25% chance of developing diabetic foot ulcers (DFUs) during their lifetime[1]. DFUs are associated with a higher risk of non-traumatic lower extremity amputation (LEA)[2]. Furthermore, mortality in patients with diabetes undergoing LEA remains extremely high[3]. Therefore, management of DFUs, including optimized vascular supply, appropriate plantar pressure redistribution, and infection control and treatment, is critical for patients with diabetes[4]. As nutrition plays a pivotal role in tissue regeneration and immune modulation [5-7], malnutrition is associated with delayed healing of DFUs [8,9], necessitating early nutritional assessment for the management of DFUs.

Several screening tools have been proposed to assess nutritional status in several conditions and diseases. Serum albumin levels have been the most commonly used marker for evaluating nutritional status in the clinical setting; however, this single indicator may be limited in its clinical application. The prognostic nutritional index (PNI) is an index based on serum albumin and the total lymphocyte count[10]. The controlling nutritional status (CONUT) score is calculated from serum albumin concentration, total peripheral lymphocyte count, and total cholesterol concentration, reflecting the nutritional status and immune function of the body[11]. Both indices are easily calculated from the data obtained from routine blood examinations, and they have been shown to predict adverse outcomes in various diseases[12-16]. However, to the best of our knowledge, there have been no studies examining the association of these indices with the prognosis of patients with DFUs. The aim of this study was to determine whether the PNI and CONUT score are reliable predictors of wound healing in patients with DFUs.

Methods

Study design and ethical issues

This was a hospital-based, single-center, observational, longitudinal cohort study that was approved by the Ethics Committee of Tokyo Women's Medical University (Approval No. 4975-R), in compliance with the Declaration of Helsinki, with utmost attention paid specifically to the protection of participant privacy.

Subjects

We recruited consecutive patients with type 1 and type 2 diabetes who presented with DFUs to the Foot Care Unit in the Diabetes Center of Tokyo Women's Medical University Hospital in Tokyo, Japan, between January 2015 and December 2019. Patients with missing values for baseline profiles were excluded.

Data collection and blood sample measurements

General information, including diabetic micro- and macrovascular complications were collected from the medical records. Cardiovascular diseases (CVD) included myocardial infarction, coronary revascularization, and stroke.Peripheral artery disease (PAD) was defined asan ankle-brachial index (ABI) < 0.9 or a history of peripheral revascularization.

Data on the laboratory examinations, including hemoglobin A1c (HbA1c), serum albumin, lipid profiles, creatinine, complete blood cell count including total lymphocyte count, and C-reactive protein (CRP) were obtained at the first visit. The estimated glomerular filtration rate (eGFR) was calculated based on serum creatinine levels, age, and sex [17]. In this study, chronic kidney disease (CKD) was defined as having an eGFR< 60 mL/min/1.73 m^2 or being on renal replacement therapy (RRT).

Definitions of the PNI and the CONUT score

The PNI was calculated as 10 × serum albumin (g/dL) + 0.005 × lymphocyte count (/μL)[10]. Higher PNI indicates better nutritional status. The CONUT score was calculated as the sum of the scores of the three parameters classified by their respective cut-off values, ranging from 0 to 12[11]. Lower CONUT scores have been shown to indicate better nutritional status.

Treatment of DFUs

A DFUs was defined as full-thickness skin loss. All patients were treated at the Foot Care Unit during the study period. Diagnosis of osteomyelitis was based on the probe-to-bone test[18] and magnetic resonance imaging. The treatment of DFUs was standardized according to the International Consensus on the Diabetic Foot[19]. Revascularization and LEA were performed according to the multidisciplinary team consensus.

Study endpoint

The endpoint of this study was complete wound healing. LEA was defined as a complete loss in the transverse plane of any part of the lower limb. Wound-related death was defined as death with an unhealed ulcer with or without any amputation. The follow-up period was the time from enrollment to wound healing, LEA, wound-related death, or last clinical follow-up, whichever occurred first. The last follow-up date was February 2020.

Statistical Analysis

Continuous variables were expressed as arithmetic means with standard deviation (SD) or geometric means with 95% confidence interval (CI), as appropriate according to data distribution. Categorical data were expressed as numbers (%).

The association of serum albumin levels, PNI, and CONUT score with the endpoint was examined by the time-to-event analysis, treating these markers categorically and numerically. In the categorical analysis, patients were dichotomized into 2 groups with lower and higher levels of the markers based on their respective median values. The cumulative incidence of wound healing was estimated using the Kaplan-Meier method, and the differences between the groups were examined by the log-rank test. Hazard ratios (HRs) between the dichotomized groups, as well as per 1-SD increment for wound healing were estimated using the classical Cox proportional hazards model analysis. In addition, the Fine and Gray sub distribution hazard model was constructed, wherein wound-related death and LEA were defined as competing risks. In these models, the following variables were incorporated as independent variables: age, sex, BMI, HbA1c, logarithmically transformed CRP, low-density lipoprotein (LDL) cholesterol, history of PAD, CVD, and LEA, presence of CKD and osteomyelitis, use of antihypertensive agents, and current smoking. P values < 0.05 were considered statistically significant. All statistical analyses were performed using the SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Clinical characteristics of the study subjects

During the period described above, 421 consecutive patients presented with DFUs to the Foot Care Unit in the Diabetes Center of Tokyo Women's Medical University Hospital in Tokyo, Japan. After excluding those with missing values for baseline profiles (n=72), a total of 349 patients were studied.

Baseline clinical characteristics and laboratory data foroverall participants are presented in Table 1. There were 84 women and 265 men, with the mean (SD) age of 62.8 (12.8) years. A total of 309 patients (88.3%) had type 2 diabetes, 162 (46.4%) had a history of CVD, 161 (46.1%) had a history of PAD, and 266 patients had CKD, of whom 149 patients (56.1%) had advanced CKD requiring RRT. The median (range) total lymphocyte count (/μL) was 1,323 (78-5,295). The most frequent ulcer site was toe (62.8%), among which 96 (27.5%) ulcers were accompanied by osteomyelitis.

Follow-up results

During a median (range) follow-up of 2.3 (0.03-62.3) months, a total of 220 patients (63.0%) achieved complete wound healing. Median time to the endpoint was 2.2 (0.1-44.4) months. LEA was performed in 81 patients (23.2%), the level of which was above the ankle in 20 patients and below the ankle in the remaining 61 patients. Wound-related death occurred in 8 patients (2.3%).

Survival analysis according to the serum albumin, PNI, and CONUT score

The median (range) serum albumin, PNI, and CONUT score of overall subjects were 3.6 g/dL (1.1-4.7 g/dL), 42.5 (16.3-62.6), and 3 (0-12), respectively. As shown in Figure 1, cumulative incidence of wound healing was significantly higher in patients with higher serum albumin, higher PNI, and lower CONUT scores than their respective counterparts ($p<0.001$).

Association between nutritional status and wound healing

The associations of serum albumin, PNI, and CONUT score with wound healing are shown in Table 2. In the univariate Cox proportional hazards model, each 1-SD increase in serum albumin and PNI, and 1-SD decrease in CONUT score significantly increased the HRs of wound healing by 7% ($p=0.002$), 31% ($p=0.001$), and 24% ($p=0.001$), respectively, indicating that higher serum albumin and PNI, and lower CONUT score were significantly associated with beneficial effects of wound healing. Even after adjustment for covariates mentioned above, higher PNI remained significantly associated with higher incidence of wound healing. On the other hand, the associations of serum albumin or CONUT score with wound healing were no more significant statistically.

In the Fine and Gary subdistribution hazard model, considering wound-related death and LEA as competing risks, the univariate analysis also found significant association of these 3 indices with incidence of wound healing. In the multivariate analysis, levels of the PNI as well as CONUT score, but not serum albumin, remained as predictors of wound healing.

Finally, serum albumin, PNI, and CONUT score were treated as categorical variables by dichotomizing these values at the median. Both the Cox proportional hazard model and Fine and Gray subdistribution model, yielded almost the identical results, except for significant association between lower CONUT score and higher incidence of wound healing in the multivariate Cox

Table 1: Baseline demographic and laboratory data of the 349 participants

Status	
Age (years)	62.8 ± 12.8
Men (%)	265 (75.9)
Type 2 diabetes (%)	308 (88.3)
Duration of diabetes (years)	23.8 ± 11.7
BMI (kg/m^2)	25.2 ± 4.9
Former smoker (%)	203 (58.2)
Current smoker (%)	70 (20.1)
MedicationInsulin treatment (%)	234 (67.0)
Antihypertensive agents (%)	250 (71.6)
Antilipemic agents (%)	166 (47.6)
Antithrombotic agents (%)	222 (63.6)
Medical history	
Diabetic retinopathy (%)	301 (86.2)
Proliferative diabetic retinopathy (%)	196 (56.2)
Dialysis (%)	109 (31.2)
Post kidney transplantation (%)	40 (11.5)
History of cardiovascular diseases (%)	162 (46.4)
History of peripheral artery diseases (%)	161 (46.1)
History of amputation (%)	69 (19.8)
Laboratory data	
Albumin (g/dL)	3.5 ± 0.7
HbA1c (%)	7.9 ± 1.9
HbA1c (mmol/mol)	62.9 ± 20.3
Total cholesterol (mg/dL)	168 ± 45
Total cholesterol (mmol/L)	4.3 ± 1.2
Triglycerides (mmol/L)	1.5 ± 0.9
HDL cholesterol (mmol/L)	1.3 ± 0.4
LDL cholesterol (mmol/L)	2.4 ± 0.9
Creatinine (non-dialysis patients) (mg/dL)	1.4 ± 1.2
eGFR (non-dialysis patients) (mL/min/1.73 m^2)	45.3 (41.9-49.0)
WBC count (/μL)	7779 (7467-8103)
Total lymphocyte count (/μL)	1261 (1200-1325)
C-reactive protein (mg/dL)	1.0 (0.8-1.2)
PNI	41.7 ± 8.0
CONUT	4 ± 3
Ulcer characteristics	
Location (%)	
Toe	219 (62.8)
Plantar	81 (23.2)
Heel	18 (5.2)
Other than above	31 (8.9)
Ulcer size >4 cm^2 (%)	108 (30.9)
Presence of osteomyelitis (%)	96 (27.5)

Data are expressed as numbers (%), means ± SD, or geometric means (95% confidence interval). Abbreviations: BMI: body mass index, HbA1c: hemoglobin A1C, HDL: high-density lipoprotein, LDL: low-density lipoprotein, eGFR: estimated glomerular filtration rate, WBC: white blood cell, PNI: prognostic nutritional index, CONUT: controlling nutritional status, SD: standard deviation

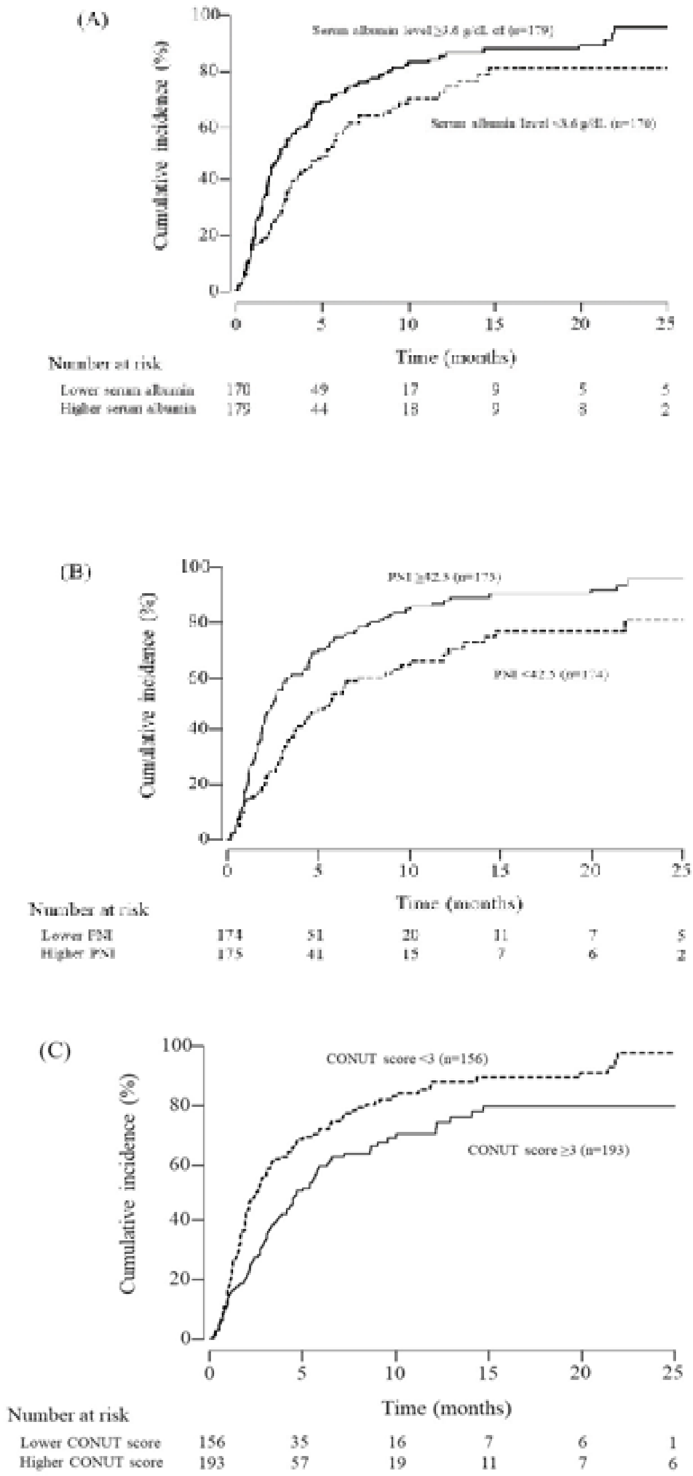

Figure 1: Cumulative incidence of wound healing in two groups dichotomized by (A) serum albumin levels of 3.6 g/dL, (B) the PNI of 42.5, and (C) the CONUT score of 3.
Abbreviations: PNI: prognostic nutritional index, CONUT: Controlling Nutritional Status.

Table 2: Multivariate Cox proportional hazards model and competing-risks regression model to examine the association of nutritional indices with wound healing

	Cox proportional hazards model		Competing-risks regression model	
	HRs (95% CI)	p value	HRs (95% CI)	p value
<analysis as a continuous variable>				
Serum albumin	1.16 (0.96-1.40)	0.120	1.17 (0.96-1.42)	0.131
PNI	1.22 (1.01-1.48)	0.038	1.26 (1.03-1.53)	0.024
CONUT score	0.84 (0.68-1.03)	0.095	0.80 (0.65-0.99)	0.045
<analysis as a categorical variable>				
Higher serum albumin	1.33 (0.96-1.86)	0.092	1.30 (0.91-1.84)	0.149
Higher PNI	1.78 (1.27-2.49)	0.001	1.78 (1.24-2.57)	0.002
Higher CONUT score	0.67 (0.48-0.93)	0.018	0.69 (0.49-0.97)	0.033

Patients were dichotomized by serum albumin levels of 3.6 g/dL, the PNI of 42.5, and the CONUT score of 3. Hazard ratios of complete wound healing were estimated using a Cox proportional hazards model and a competing-risks regression model adjusting for age, sex, body mass index, haemoglobin A1C, logarithmically transformed C-reactive protein, low-density lipoprotein cholesterol, history of peripheral artery diseases, cardiovascular diseases, and lower extremity amputations, presence of chronic kidney disease and osteomyelitis, use of antihypertensive agents, and current smoking.
Hazard ratios per 1-SD increment of complete wound healing as a continuous variable were estimated.
Abbreviations: PNI: prognostic nutritional index, CONUT: controlling nutritional status, HRs: hazard ratios, CI: confidence interval.

Discussion

In this single-center, observational, longitudinal study using a historical cohort, a lower PNI was significantly associated with higher incidence of wound healing in patients with DFUs. The association was independent of other risk factors, and it was confirmed by both classical survival analysis and a competing risks model. Results of CONUT score were almost identical, except for non-significant impact in the multivariate Cox proportional hazard model. In contrast, there were no associations between serum albumin levels, whether treated as categorical or continuous variable, and wound healing in either the multivariate Cox or Fine and Gray model. To the best of our knowledge, this is the first report showing that the PNI and the CONUT score may be independent predictors of wound healing in patients with DFUs.

Because of nutrient loss and poor food intake due to diabetes-related complications and comorbidities [20], malnutrition is commonly observed in patients with DFUs. Since nutrition has a pivotal role in immune modulation, poor nutritional status may facilitate the development of severe foot infections [21], leading to increased metabolism and further additional nutrient losses [22]. Therefore, during the wound healing process,rapid and precise assessment of nutritional status, adequate energy intake, and nutrition management are important.

Serum albumin level has been traditionally used as a useful index for evaluating nutritional status in the clinical setting. In this study of patients with diabetes, we were unable to find significant association between serum albumin levels and the outcome of DFUs in either the classical survival analysis or competing risks model. Other pathophysiological processes such as hepatocellular function, renal function, and inflammation may induce hypoalbuminemia[23], limiting its applicability.

The PNI was designed to evaluate nutritional status using the serum albumin level and the total lymphocyte count[10]. Various studies have shown that a PNI is an independent prognostic factor in patients with cancer, liver cirrhosis, cardiovascular diseases, and chronic renal failure[14,15,26, 27]. However, no previous studies have investigated the association between the PNI and DFUs. The present study found the combination of serum albumin and the total lymphocyte count suitable for use as a tool that allows rapid evaluation of the nutritional status of patients with DFUs. The mechanism underlying the association of a lower total lymphocyte count with wound healing were unable to elucidate in the present observational cohort study. One explanation for this could be related to the severity of inflammation. Lymphocytes have a modulatory effect on controlling inflammation, such as sepsis, caused by DFUs[28]. Therefore, lymphocyte counts are affected by accelerated apoptosis due to a systemic inflammatory process[29-30]. Meanwhile, lymphocyte counts might simply be a marker of nutritional status, which is intimately associated with the immune system. Advanced malnutrition causesdeficiencies of essential vitamins and essential amino acids, leading to the depression of cell-mediated or humoral immunity[12]. Taken together, a lower total lymphocyte count resulting from DFUs might contribute to further progression of DFUs in a vicious cycle.

The CONUT score is a screening tool also for evaluating nutritional status calculated from serum albumin and the total lymphocyte count, in addition to the total cholesterol level[11].As with the

PNI, the CONUT score has been proven useful for the prediction of the prognosis of various diseases[12,13, 16]. A low cholesterol level is associated with a low lipoprotein levels, which reflect malnutrition. Studies have shown that total cholesterol levels could be associated with prognosis in patients with sepsis[31]. In the present study, many patients were treated with antilipemic agents, affecting serum cholesterol levels. A Japanese report showed that statin use did not affect the CONUT score in patients with type 2 diabetes, because the CONUT score was more affected by the serum albumin level[32]. Therefore, the present study's findings may have been unaffected by the antilipemic agents. Further studies on the association between the CONUT score and antilipemic agents are needed.

The present study has several limitations. First, the present findings were based on analyses using a historical cohort. Second, this study was carried out in a single urban university hospital, limiting the generalizability of the results. Third, this study was performed using a small cohort. Finally, time-dependent changes in the parameters during the follow-up period were not evaluated.

Conclusion

The present study showed that both the PNI and the CONUT score were novel clinical predictors forwound healing in patients with DFUs. Since serum albumin level alone had little impact on the outcome, immune function, rather than nutritional status, may be more crucial in the process of wound healing. The management of DFUs, emphasizing an approach that includes improving nutritional status as well as and assessing immune function is considered important.

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Conflict of interest

No potential conflicts of interest relevant to this article were reported.

Author Contributions

Y.O. conceived of the study, designed the protocol, contributed to data collection and preparation, analyzed all data, wrote the manuscript, contributed to the interpretation of the results, and approved the final version. K.I. designed the protocol, contributed to data collection and preparation, analyzed all data, wrote the manuscript, contributed to the interpretation of the results, and approved the final version.T.B. designed the protocol, analyzed all data, wrote the manuscript, contributed to the interpretation of the results, and approved the final version. T.B. is the guarantor of this work.

Date Availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. American Diabetes Association. Consensus Development Conference on Diabetic Foot Wound Care, 7-8 April 1999, Boston, Massachusetts. Diabetes Care.1999;22(8):1354-1360.doi:10.2337/diacare.22.8.1354.
2. Jeffcoate WJ and Harding KG. Diabetic foot ulcers. Lancet. 2003;361(9368):1545-1551.doi:10.1016/S0140-6736(03)13169-8.
3. Icks A, Scheer M, Morbach S, Genz J, Haastert B, Giani G, et al. Time-dependent impact of diabetes on mortality in patients after major lower extremity amputation: survival in a population-based 5-year cohort in Germany. Diabetes Care. 2011;34(6):1350-3154. doi:10.2337/dc10-2341.
4. Alavi A, Sibbald RG, Mayer D, Goodman L, Botros M, Armstrong DG, et al. Diabetic foot ulcers: Part II. Management. J Am Acad Dermatol. 2014;70(1):21.e1-e24;doi:10.1016/j.jaad.2013.07.048.
5. ArnoldM and Barbul A.Nutrition and wound healing. Plast ReconstrSurg.2006;117(7Suppl):42S-58S.doi:10.1097/01.prs.0000225432.17501.6c.
6. Stechmiller J. Understanding the Role of Nutrition and Wound Healing. Nutr Clin Pract. 2010;25(1):61-68.doi:10.1177/0884533609358997.
7. Demling RH, Nutrition, anabolism, and the wound healing process: an overview.Eplasty.2009;9: e9.
8. Gau BR, Chen HY, Hung SY, Yang HM, Yeh JT, Huang CH, et al. Erratum to "The impact of nutritional status on treatment outcomes of patients with limb-threatening diabetic foot ulcers". J Diabetes Complications. 2016;30(5):971.doi: 10.1016/j.jdiacomp.2016.04.009.
9. Shan-Shan Zhang, Zheng-Yi Tang, Ping Fang, Hong-Jie Qian, Lei Xu, Guang Ning. 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.
10. Onodera T, Goseki N, Kosaki G. Prognostic nutritional index in gastrointestinal surgery of malnourished cancer patients. Nihon Geka Gakkai Zasshi.1984;85(9):1001-1005.
11. Ignacio de Ulíbarri J, González-Madroño A, de Villar NGP, P González, B González, A Mancha, et al. CONUT: a tool for controlling nutritional status. First validation in a hospital population.Nutr Hosp.2005;20(1):38-45.
12. Shirakabe A, Hata N, Kibayashi N, Okazaki H, Matsushita M, Shibata Y, et al. The prognostic impact of malnutrition in patients with severely decompensated acute heart failure, as assessed using the Prognostic Nutritional Index (PNI) and Controlling Nutritional Status (CONUT) score. Heart Vessels.2018;33(2):134-144.doi: 10.1007/s00380-017-1034-z.
13. Sun X, Luo L, Zhao X, Ye P. Controlling Nutritional Status (CONUT) score as a predictor of all-cause mortality in elderly hypertensive patients: a prospective follow-up study. BMJ Open 2017;7:e015649.doi:10.1136/bmjopen-2016-015649.
14. Dolapoglu A, Avci E, Kiris T, Bugra O. The predictive value of the prognostic nutritional index for postoperative acute kidney injury in patients undergoing on-pump coronary bypass surgery. J Cardiothorac

Surg.2019;14:74.doi:10.1186/s13019-019-0898-7.

15. Yost G, Tatooles A, Bhat G. Preoperative Nutritional Assessment with the Prognostic Nutrition Index in Patients Undergoing Left Ventricular Assist Device Implantation. ASAIO J.2018;64(1):52-55.doi: 10.1097/MAT.0000000000000625.
16. Kuroda D, Sawayama H, Kurashige J, Iwatsuki M, Eto T, Tokunaga R, et al. Controlling Nutritional Status (CONUT) score is a prognostic marker for gastric cancer patients after curative resection. Gastric Cancer.2018;21(2):204-212.doi:10.1007/s10120-017-0744-3.
17. Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, et al. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis. 2009;53(6):982-992.doi: 10.1053/j.ajkd.2008.12.034.
18. Grayson ML, Gibbons GW, Balogh K, E Levin, A W Karchmer. Probing to Bone in Infected Pedal Ulcers A Clinical Sign of Underlying Osteomyelitis in Diabetic Patients. JAMA 1995;273(9):721-723.
19. Schaper NC, Netten JJ, Apelqvist J, B A Lipsky , K Bakker. Prevention and management of foot problems in diabetes: a Summary Guidance for Daily Practice 2015, based on the IWGDF Guidance Documents. Diabetes Metab Res Rev. 2016;32 Suppl 1:7-15.doi: 10.1002/dmrr.2695.
20. Prompers L, Huijberts M, Apelqvist J, E Jude, A Piaggesi, K Bakker, et al. High prevalence of ischaemia, infection and serious comorbidity in patients with diabetic foot disease in Europe. Baseline results from the Eurodiale study. Diabetologia.2007;50(1):18-25.doi:10.1007/s00125-006-0491-1.
21. Keusch GT. The History of Nutrition: Malnutrition, Infection and Immunity. J Nutr. 2003;133(1):336S-340S.doi: 10.1093/jn/133.1.336S.
22. Legendre C, Debure C, Meaume S, Lok C, Golmard JL, Senet P. Impact of protein deficiency on venous ulcer healing. J Vasc Surg. 2008;48(3):688-93.doi: 10.1016/j.jvs.2008.04.012.
23. Bonilla-Palomas JL, Gámez-López AL, Moreno-Conde M, María Cristina López-Ibáñez, Manuel Anguita-Sánchez, Angel Gallego de la Sacristana, et al. Hypoalbuminemia in acute heart failure patients: causes and its impact on hospital and long-term mortality. J Card Fail. 2014;20(5):350-358.doi: 10.1016/j.cardfail.2014.01.016.
24. Cereda E, Mini Nutritional Assessment. Curr Opin Clin Nutr Metab Care. 2012;15(1):29-41.doi: 10.1097/MCO.0b013e32834d7647.
25. Dunning T, Sinclair A, Colaguiuri S. New IDF Guideline for managing type 2 diabetes in older people. Diabetes Res Clin Pract. 2014;103(3):538-540.doi: 10.1016/j.diabres.2014.03.005.
26. Alvares-da-Silva MR and Reverbel da Silveira T. Comparison between handgrip strength, subjective global assessment, and prognostic nutritional index in assessing malnutrition and predicting clinical outcome in cirrhotic outpatients. Nutrition.2005;21(2):113-117.doi: 10.1016/j.nut.2004.02.002.
27. M. Kanda, T. Fujii, Y. Kodera, S. Nagai, S. Takeda, A. Nakao. Nutritional predictors of postoperative outcome in pancreatic cancer. British Journal of Surgery. 2011;98(2): 268-274.doi:10.1002/bjs.7305.
28. Liu WY, Lin SG, Wang LR, FangCC, Lin YQ, Braddock M, et al. Platelet-to-Lymphocyte Ratio: A Novel Prognostic Factor for Prediction of 90-day Outcomes in Critically Ill Patients With Diabetic Ketoacidosis. Medicine (Baltimore).2016;95(4):e2596.doi:10.1097/MD.0000000000002596.
29. De Jager CP, Van Wijk PT, Mathoera RB, Jacqueline de Jongh-Leuvenink, Tom van der Poll, Peter C Wever. Lymphocytopenia and neutrophil-lymphocyte count ratio predict bacteremia better than conventional infection markers in an emergency care unit. Crit Care. 2010;14(5):R192.doi: 10.1186/cc9309.
30. Medzhitov R. Origin and physiological roles of inflammation. Nature. 2008;454(7203):428-435.doi: 10.1038/nature07201.
31. Yamano S, Shimizu K, Ogura H, Hirose T, Hamasaki T, Shimazu T, et al. Low total cholesterol and high total bilirubin are associated with prognosis in patients with prolonged sepsis. J Crit Care. 2016;31(1):36-40.doi: 10.1016/j.jcrc.2015.09.033.
32. Mineoka Y, Ishii M, Hashimoto Y, Nakamura N, Fukui M. Malnutrition assessed by controlling nutritional status is correlated to carotid atherosclerosis in patients with type 2 diabetes. Endocr J. 2019;66(12):1073-1082.doi: 10.1507/endocrj.EJ19-0107.