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Original Article

A New Index on Malnutrition: The Advanced Lung Cancer Inflammation Index and Its Relation to Mortality in Chronic Kidney Disease

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ABSTRACT

Objective: Malnutrition is a complication of chronic kidney disease (CKD) that contributes to poor survival. The Advanced Lung Cancer Inflammation Index (ALI) was designed to assess systemic inflammation in patients with metastatic cell lung cancer. The Geriatric Nutritional Risk Index (GNRI) was shown to predict mortality in patients undergoing dialysis. Considering the role of inflammation and malnutrition in mortality, this study aimed to investigate the relationship between a new index, ALI, in concordance with GNRI, and mortality in HD and PD patients.

Methods: Patients undergoing maintenance hemodialysis (HD) and peritoneal dialysis (PD) at our institution between February 2012 and October 2022 were studied retrospectively. Advanced Lung Cancer Inflammation Index and GNRI were calculated by recommended formulas. The primary outcome was all-cause mortality.

Results: A total of 176 patients (88 with HD and 88 with PD) were included in the study. The mean age was 50 ± 16 years. In receiver operating characteristic analysis for ALI, the best cutoff value was 36.9 to predict mortality with a sensitivity of 88% and specificity of 72.8%, and the area under the curve was 0.850 (95% CI, 0.763-0.937; $P < .005$) in HD patients and 37.2 to predict mortality with a sensitivity of 88% and specificity of 67.1 %, and the area under the curve was 0.832 (95% CI: 0.729-0.934; $P < .005$) in PD patients. In the Cox regression analysis, the major factors affecting mortality were age, C-reactive protein level, ALI, and GNRI.

Conclusion: The nutritional risk assessment measures, GNRI and ALI, predict mortality in CKD patients.

Keywords: Hemodialysis, peritoneal dialysis, Advanced Lung Cancer Inflammation Index, mortality

INTRODUCTION

Chronic kidney disease (CKD) is an important global health problem that is characterized by a high incidence of morbidity and mortality.[1] Malnutrition, an important complication of CKD, substantially contributes to low survival rates.[2,3] To mitigate mortality, nutritional status should be evaluated every 1-3 months.[4] The Geriatric Nutritional Risk Index (GNRI) has been validated as a mortality risk predictor in dialysis patients using nutritional assessment data.[5,6]

Numerous factors contribute to the development of chronic inflammatory condition in patients with CKD. The activation of macrophages and monocytes results in oxidative stress and an increase in pro-inflammatory cytokine production,[7] both of which initiate the inflammatory cascade. Severe cardiovascular events and malnutrition-inflammation-atherosclerosis syndrome are associated with inflammation,[8-10] both of which are associated with elevated mortality risk.

Initially, the purpose of developing the Advanced Lung Cancer Inflammation Index (ALI) was to evaluate the extent of systemic inflammation among individuals with metastatic non-small cell lung cancer. Body mass index (BMI), serum albumin (Alb) level, and neutrophil -to-lymphocyte ratio (NLR) were utilized in the computation of ALI. Its reliability as an indicator of unfavorable

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outcomes in various types of malignancies, Crohn's disease, and acute decompensated heart failure has been previously demonstrated.[11-14]

Taking into account the role of malnutrition and inflammation in CKD mortality, the purpose of this study was to investigate the correlation between hemodialysis (HD) and peritoneal dialysis (PD) patient mortality and GNRI and ALI.

METHODS

Ethics committee approval was obtained from Prof. Dr. Cemil Taşçıoglu City Hospital. All procedures were conducted in accordance with ethical rules and the principles of the Declaration of Helsinki. Due to the retrospective nature of the study, informed consent forms were omitted.

Patients on regular maintenance HD and PD at our institution between February 2012 and October 2022 were studied retrospectively. Patients under 18 and those with insufficient information, diagnosed with cancer, connective tissue disease, or an acute infection at the time of dialysis initiation, were excluded from the research.

The data of the patients were scanned retrospectively from the patient files. Risk factors such as age, gender, diabetes mellitus, hypertension, and drugs were scanned from patient files. Daugirdas[15] formula was used to compute Kt/V for urea.

Geriatric Nutritional Risk Index was calculated using serum Alb level and body size as follows: [14.89 × serum Alb (g/dL)] + {41.7 × [current body weight (kg)/standard body weight (kg)]}.[5] Standard body weight was calculated as height (m^2) × 22. Suppose the current weight was greater than the standard weight, the ratio of current to standard weight = 1. According to the standard classification method of the GNRI, patients were divided into 4 grades (high risk: GNRI < 82; moderate: 82 ≤ GNRI < 92; low: 92 ≤ GNRI ≤ 98; no risk: GNRI > 98).

MAIN POINTS

- Malnutrition is a common consequence of chronic kidney disease (CKD) and is associated with a poor prognosis.
- Due to metabolic acidosis, chronic inflammation, endocrine and metabolic abnormalities, and an increase in protein catabolism that results in a negative nitrogen balance, CKD patients are more susceptible to malnutrition.
- Subjective methods like GNRI and ALI are predictors of malnutrition. GNRI and ALI determined at the beginning of the dialysis period is associated with mortality.
- The patients who had worse scores may have benefit from intentional care about malnutrition.

Advanced Lung Cancer Inflammation Index was calculated as; BMI × serum Alb/NLR.

Statistical Package for the Social Sciences (IBM Corp.; Armonk, NY, USA) for Windows 25.0 was used for statistical analysis. Data about continuous variables were expressed as mean ± standard deviation if otherwise is not indicated. Intergroup comparisons were made with Student's *t*-test (in data with a normal distribution) or with Mann-Whitney *U*-test (in data without normal distribution). Categorical variables were compared with the Chi-square test. The unadjusted univariate Cox proportional hazard regression analyses were applied to roughly show the impact of each variable on all-cause mortality; then, the multivariate Cox proportional hazards analyses were performed to qualify the independent predictors for mortality. The variables included in the multivariate analyses were those considered clinically relevant (diabetes mellitus, age, dialysis vintage) or with *P*-values less than 0.15 in univariate analyses, while BMI, Alb, and NLR were excluded due to their direct correlation with ALI and GNRI. Time-dependent receiver operating characteristic (ROC) curves were used to calculate the cutoff value of ALI and GNRI, and the area under the curve (AUC) was measured. A *P*-value less than .05 was considered statistically significant.

RESULTS

A total of 110 HD and 95 PD patients were analyzed retrospectively, and 176 patients were included in the study. Eighty-eight were on HD treatment and 88 were on PD treatment. The mean age was 50 ± 16 years, and the mean dialysis vintage was 5.4 ± 2.1 years. Eighty (50.6%) of the patients were male. Forty-two of the patients (23.9%) died during follow-up. In GNRI groups, 45 patients (25.6%) had a high and moderate risk of malnutrition. Significant demographic and laboratory findings of the patients can be seen in Table 1.

The patient population is grouped into 2 groups: patients died (group 1) and alive (group 2). The patients in group 1 were older (56.1 ± 14.2 vs. 48.3 ± 17.1; *P* = .006). C-reactive protein (CRP) [4 (0.6-24.8) vs. 1.4 (0.1-17.7); *P* = .00], dialysis vintage (5.9 ± 4.3 vs. 3.7 ± 2.1; *P* = .00), NLR (2.58 ± 0.8 vs. 2.01 ± 0.6; *P* = .00) were significantly increased in group 1. Albumin level and KT/V were decreased in group 1 (Table 2). Measures ALI and GNRI were significantly increased in the patients who survived [(52.1 ± 18.7 vs. 32.9 ± 14.6; *P* = .00) and (98.3 ± 7.46 vs. 88.02 ± 9.4; *P* = .00); respectively].

Patients are grouped in terms of dialysis type, and receiver operating characteristic curve (ROC) analysis was made to determine the cutoff values of ALI and

Table 1. Baseline Characteristics

	N = 176
Males, *n* (%) Females,*n*(%)	89(50.6%) 87(49.4%)
Age, years	50 ± 16
Hemodialysis, n(%)	88(50%)
Peritoneal dialysis, n(%)	88(50%)
Dialysis vintage, years	5.4±2.1
Presence of diabetes, *n* (%)	44(25%)
History of cardiovascular events, *n* (%)	29(16.5%)
Diabetic nephropathy, *n* (%)	44(25%)
Chronic glomerulonephritis, *n* (%)	20(11.4%)
Hypertension, *n* (%)	69(39.2%)
Polycystic disease, *n* (%)	6(3.4%)
Hemoglobin, g/dL	10.8±2.3
Serum albumin, g/dL	3.7±0.6
Serum creatinine, mg/dL	8.4±2.4
Serum uric acid, mg/dL	5.7±1.1
Serum C-reactive protein, mg/dL	2(0.1-24.8)
Serum total cholesterol, mg/dL	176±49
Serum triglycerides, mg/dL	175±99
Intact parathormone, pg/mL	478.1(5.7-2978)
Kt/V ratio for urea	1.79±0.35
GNRI Index	95.88±9.08
GNRI group *Major*	17(9.7%)
Moderate	28(15.9%)
Mild	45(25.6%)
Absent	86(48.9%)
ALI	47.5±19.5
Died, n(%)	42(23.9%)

Table 2. Comparision of the patients died and alive

	Died (n=42)	Alive (n= 134)	*p*
Males, *n* (%)	21(50%)	68(50.7%)	0.933
Females, n(%)	21(50%)	66(49.3%)	
Age, years	56.1±14.2	48.3±17.1	***0.006***
Hemodialysis, n(%)	17(40.5%)	71(53%)	0.157
Peritoneal dialysis, n(%)	25(59.5%)	63(47)	0.157
Dialysis vintage, years	5.9±4.3	3.7±2.2	***0.001***
Presence of diabetes, *n* (%)	19(45.2%)	31(23.1%)	0.006
History of cardiovascular events, *n* (%)	9(21.4%)	20(14.9%)	0.322
Hemoglobin, g/dL	10.7±1.6	10.8±1.6	0.401
Neutrophil lymphocyte ratio	2.58±0.8	2.01±0.6	***0.00***
Serum albumin, g/dL	3.5±0.7	3.8±0.5	***0.00***
Serum creatinine, mg/dL	8±2.1	8.6±2.5	0.767
Serum uric acid, mg/dL	5.7±1.3	5.8±1.1	0.176
Serum C-reactive protein, mg/dL	4(0.6—24.8)	1.4(0.1-17.7)	***0.00***
Serum total cholesterol, mg/dL	184±5.6	173±46	0.983
Serum triglycerides, mg/dL	159±82	180±103	0.320
Intact parathormone, pg/mL	388 (5.7-2398)	506 (18.8-2978)	0.812
Kt/V ratio for urea	1.69±0.26	1.83±0.37	***0.024***
GNRI	88.02±9.4	98.3±7.46	***0.00***
ALI	32.9±14.6	52.1±18.7	***0.00***

GNRI to predict mortality. For HD patients, ROC analysis demonstrated that the best cutoff value of GNRI to predict mortality was 97.5 with 94% sensitivity and 73% specificity (area under ROC curve 0.873 [95% CI, 0.799-0.948], $P < .005$) and 98.36 for PD with 88% sensitivity and 66.6% specificity (area under ROC curve 0.774 [95% CI, 0.659-0.889], $P < .005$). For ALI, the best cutoff value was 36.9 to predict mortality with a sensitivity of 88% and specificity of 72.8%, and the AUC was 0.850 (95% CI, 0.763-0.937; $P < .005$) in HD patients and 37.2 to predict mortality with a sensitivity of 88% and specificity of 67.1%, and the AUC was 0.832 (95% CI, 0.729-0.934; $P < .005$) in PD patients (Figure 1 and 2).

To determine the major factors affecting mortality, Cox regression analysis was conducted, and age, CRP, ALI, and GNRI were identified as significant determinants of mortality (Table 3).

DISCUSSION

In HD and PD patients, ALI and GNRI values at admission were independent predictors of long-term all-cause mortality according to this retrospective, observational, single-center study. Comparable AUCs were observed between the ALI and GNRI for predicting long-term mortality in both population categories.

Malnutrition, an important complication of CKD, is associated with an unfavorable prognosis. The prevalence of malnutrition in patients with CKD ranges from 36% to 42%.[2] Patients with CKD are at a heightened risk of malnutrition owing to metabolic acidosis, chronic inflammation,

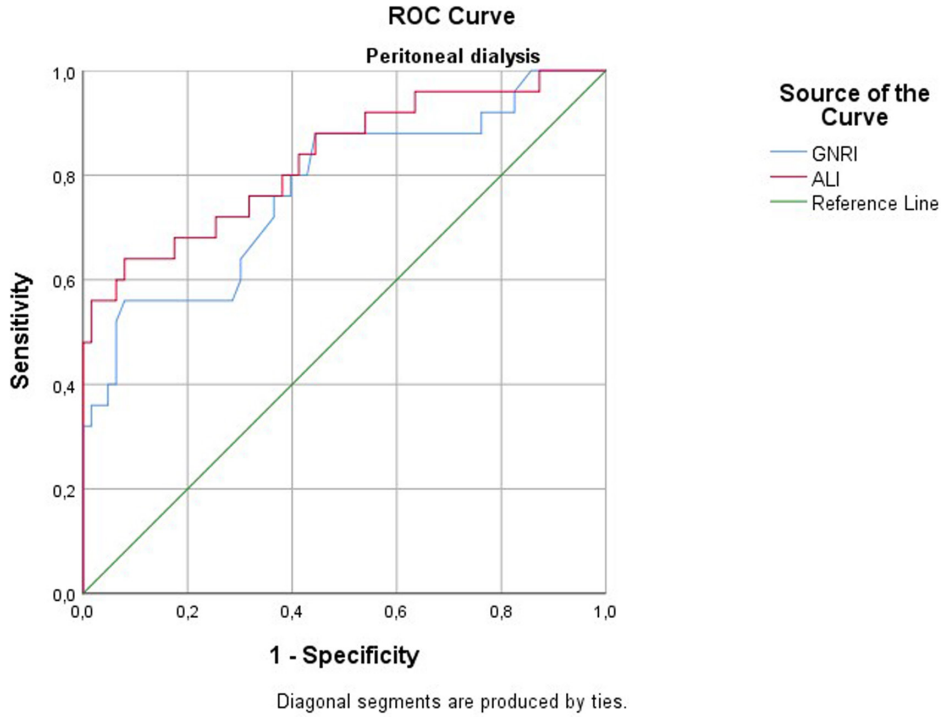

Figure 1. ROC curve of ALI in HD patients.

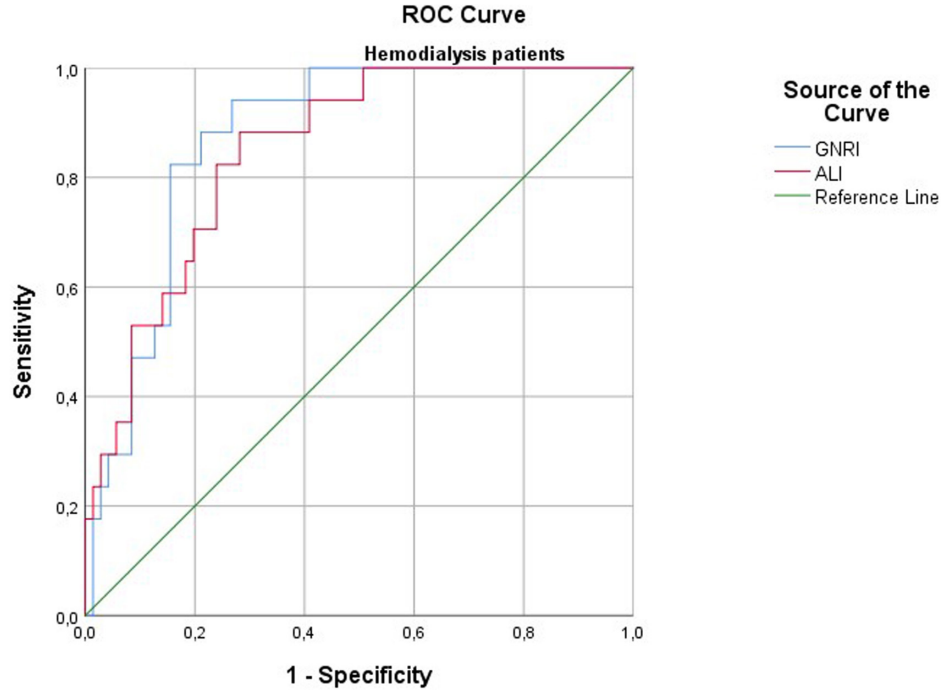

Figure 2. ROC curve of ALI in PD patients.

endocrine and metabolic abnormalities, and an increase in protein catabolism, which leads to a negative nitrogen balance.[3-5] Thus, early detection of malnutrition could potentially contribute to a more favorable prognosis.

In the present study, the GNRI was identified as a significant determinant of mortality in HD and PD patients. Receiver operating curve analysis determined the GNRI mortality prediction cutoff value for HD patients to be

Table 3. Cox- regression odds ratios of outcome

	Univariate Cox regression		Multivariate Cox regression	
	OR (95% CI)	*P*	OR (95% CI)	*P*
GNRI	0.89 (0.810- 0.941)	**.001**	0.869 (0.805-939)	**.001**
ALI	0.921 (0.860-0.960)	**.001**	0.910 (0.866- 0.956)	**.001**
CRP	1.18 (1.1-1.3)	**.002**	1.172 (1.06-1.129)	**.002**
3-mon mortality[II]	1.05 (1.01-1.1)	**.009**	1.49 (1.012-1.087)	**.009**

ALI, Advanced Lung Cancer Inflammation Index; CRP, C-reactive protein, GNRI, Geriatric Nutritional Risk Index.

97.5% and 98.36%, respectively. This finding aligns with those of previous studies.[5,6]

Albumin and BMI are indicators of malnutrition and are included in the GNRI[16] as constituent elements. Hypoalbuminemia is induced by inflammation and a low BMI is correlated with muscle and adipose tissue atrophy.[17,18,19] Both markers were correlated with mortality. Given that the GNRI concurrently comprises these 2 components, it is anticipated that it will exhibit superiority in detecting mortality.[20]

The study additionally identified an independent correlation between the ALI and mortality among HD and PD patients.

Advanced Lung Cancer Inflammation Index, which is computed by combining BMI, Alb, and NLR, potentially provides a more comprehensive assessment of nutritional status and systemic inflammation. Decreased BMI and serum Alb levels are indicative of a low ALI score, whereas an elevated NLR signifies inadequate nutritional status and heightened inflammation.

Inflammation is associated with atherosclerotic cardiovascular disease, diabetes mellitus, and CKD.[21] The independent predictive value of neutrophil and lymphocyte counts for mortality in 44 144 end stage renal disease (ESRD) patients was demonstrated in a recent study.[22] In activated neutrophils,[23,24] elevated concentrations of myeloperoxidase, matrix metalloproteinase-2, matrix metalloproteinase-9, and reactive oxygen metabolites have been identified. These mediators have the potential to induce plaque instability by promoting adhesion of the endothelium.[24] The release of extracellular traps by apoptotic neutrophils, which may contain cell-free deoksiribonükleik asit (DNA), exacerbates inflammation.[25,26]

Initial applications of the ALI evaluated systemic inflammation in patients with advanced cell lung cancer. Subsequently, it was demonstrated to be a reliable predictor of mortality.[11] As an improved index compared to BMI, albumin, and NLR,[14] ALI can predict the prognosis of numerous types of cancer, Crohn's disease, and heart failure, according to recent studies. Maeda et al.[15] assessed the prognostic significance of ALI in patients diagnosed with acute decompensated heart failure and discovered that individuals with low ALI had a greater risk of mortality. The association between reduced ALI and mortality in CKD patients may be attributable to malnutrition and inflammation.

Inflammation can manifest in dialysis patients owing to various factors, including endotoxin contamination in dialysis fluid, membrane incompatibility with HD, reduced cytokine clearance, elevated oxidative stress, and infection.[11,14,15] In spite of the considerable progress made in dialysis treatment, CRP, which serves as an indicator of inflammation, has remained elevated in 24% of patients in Japan and 30%-60% in Europe and North America.[16,27-30] Chronic inflammation is characterized by a reduction in hepatic protein synthesis and an increase in proteolysis via the activation of the ubiquitin–protease system. It induces malnutrition and increases energy expenditure by suppressing appetite and interfering with oral intake.[30-32] Inflammation further promotes insulin resistance and destruction of muscle cells.[33] Malnutrition and inflammation must be monitored concurrently in patients with ESRD; therefore, employing indices that represent both conditions will facilitate follow-up.

This study had a number of limitations. The indices were computed using parameters estimated at the onset of the trial because of the retrospective design of the study. However, the temporal evolution of these parameters remains unclear. Determination of daily dietary composition, which is crucial for nutritional assessment, is an ongoing process. Further investigation is required to ascertain the association between mortality, the GNRI, ALI, and food consumption. In addition, anthropometric and laboratory indicators that are strongly associated with nutritional status, such as triceps skinfold thickness, upper arm circumference, and mid-arm muscle circumference, can be employed to assess the utility of the GNRI and ALI in nutritional evaluation, along with prealbumin and transferrin levels.

In summary, the GNRI and ALI are straightforward nutritional risk assessment tools that are appropriate for the ongoing surveillance of patients with CKD to detect malnutrition. The current study examined the association between mortality and baseline GNRI and ALI in adult PD

and HD patients. While research has been conducted on GNRI in patients undergoing HD and PD, to our knowledge, this is the first study to investigate the association between ALI and mortality in patients with CKD. Potentially affecting the prognosis of patients with CKD, dynamic changes in nutritional status necessitate prospective research employing longitudinal analysis of ALI in conjunction with GNRI or other methodologies, such as Subjective Global Assesment (SGA).

Ethics Committee Approval: Ethics committee approval was received for this study from Prof. Dr. Cemil Taşçıoğlu City Hospital Ethics Committee (Date: June 20, 2022; Number: E-48670771-514.99).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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Author Contributions: Concept – T.D.; Design – T.D.; Supervision – S.A.; Resources – S.A.; Materials – S.A.; Data Collection – S.A.; Analysis and/or Interpretation – T.D.; Literature Search -T.D.; Writing Manuscript – T.D.; Critical Review – S.A.; Other – T.D.

Declaration of Interests: The authors declare that they have no competing interests.

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