Dialysis and Transplantation Open Access
ISSN: 2689-6028

Conceptual Paper

Volume 3 Issue 1

Neutrophil Gelatinase-Associated Lipocalin Level as a Marker of Malnutrition in Egyptian Hemodialysis: A Single Centre Study

Rasha Mahmoud[1], Alaa Sabry[1]*, Shimaa Alsaody[2], Heba Mossad[3] and Noha Abde Elsalam[1]

[1]Nephrology and Dialysis Unit, Mansoura University, Egypt

[2]Ministry of health, Mansoura University, Egypt

[3]Department of Clinical Pathology, Mansoura University, Egypt

***Corresponding author:** Alaa Sabry, Internal Medicine Department, Mansoura University, Tel: 0020502300543; Email: asabry2040@yahoo.com

Received Date: March 31, 2020; **Published Date:** May 16, 2020

Abstract

Background & aim of the study: Malnutrition is a common health problem and a marker of poor prognosis among hemodialysis patients Assessment of nutritional status of these patients is necessary to prevent this problem. NGAL is an iron transporting factor which increases in the serum in acute and chronic kidney disease. The aim of our study is to assess the use of NGAL as a marker of malnutrition in patients with stage 5 CKD treated by hemodialysis.

Subjects & methods: A cross-sectional study including 80 regular hemodialysis (HD) patients (51 males and 29 females), subjected to anthropometric measurements (Dry body weight, height, body mass index (BMI), Triceps skin fold thickness (TSF), Mid-upper arm circumference (MAC), Mid- arm muscle circumference (MAMC), Mid- arm muscle area (MAMA). Serum Neutrophil Gelatinase-associated Lipocalin level , Serum albumin, Blood urea, Complete blood count, Serum electrolytes were measured.

Results: In our study 100% of CKD having mild degree of malnutrition according to subjective global assessment SGA, MIS. Twenty-four hours dietary recall confirmed that most of patients were with low protein (96.2%) and calorie (68.8%) contents. NGAL serum levels were significantly (P=0.018) reduced in hemodialysis patients compared to control group and the level correlated with the severity of malnutrition. NGAL serum levels were significantly correlated with SGA (r =o, 247 P =0.027) and albumin serum levels (r =0.402, P<0.001). NGAL serum levels had a good ability (AUC=0.845) to predict severe malnutrition with good sensitivity (83.3%) and specificity (78.4%).

Conclusion: NGAL is well correlated with other standard markers used routinely in assessment of nutritional status of hemodialysis patients. Its serum levels had a good diagnostic power for malnutrition in haemodialysis patients.

Keywords: Hemodialysis; Malnutrition; Neutrophil gelatinase associated lipocalin

Abbreviations: HD: Hemodialysis; BMI: Body Mass Index; TSF: Triceps skin fold thickness; MAC: Mid-upper arm circumference; MAMC: Mid- arm muscle circumference; MAMA: Mid- arm muscle area; ESRD: End-stage renal disease; CKD: chronic kidney disease; NGAL: Neutrophil gelatinise-associated lipocalin; FFQ: Food frequency questionnaire; SPSS: Statistical Package of Social Science; MIS: Malnutrition-inflammation score.

Introduction

CKD is a major public health problem due to its high global prevalence (13.4%) [1]. Of whom 78% reside in low-income to middle-income countries (LMICs) [2]. This disease is a component of a new epidemic of chronic conditions that replaced malnutrition and infection as leading causes of mortality during the 20th century [3]. End-stage renal disease (ESRD) is one of the main health problems in Egypt. Currently, hemodialysis represents the main mode for treatment of chronic kidney disease stage 5 (CKD5) [4].

Malnutrition is considered a marker of poor prognosis in CKD. It is common among patients on maintenance hemodialysis. A 40% prevalence of malnutrition was found in patients with advanced renal failure at the beginning of dialysis treatment and is associated with higher rates of morbidity and mortality [5]. The patients' nutritional status is inversely associated with increased risk of hospitalization and mortality; thus constituting an important risk factor for the outcome of these patients .Therefore, assessing the nutritional status of patients is essential both to prevent malnutrition and to indicate appropriate intervention in malnourished patients, as well as success of dialysis is dependent on adequate nutrition [6]. Because malnutrition is the major co-morbid condition of patients on dialysis, regular monitoring of nutritional status, delivering adequate food intake, maintenance of adequate dialysis dose and therapeutic intervention are necessary. Dietary counselling should be a part of treatment to provide adequate calorie and protein intake [7].

Neutrophil gelatinase-associated lipocalin (NGAL or LCN2) is an iron-transporting factor, Its circulating concentrations are elevated in acute and chronic kidney diseases and show a positive correlation with poor renal outcome and mortality, Low serum NGAL levels appear to be associated with current malnutrition and also its progressive worsening in maintenance HD patients [8]. To the best of our knowledge only one study sassed NGAL levels in maintenance HD patients and its association with nutritional status and markers of malnutrition.

Patients and Methods

Study Population

In this cross sectional study 80 regular HD patients (51 male and 29 females) were selected from two dialysis units of Dakahlia Governorate hospitals, Egypt over a period of one year. The dialysis ventage ranged was from 3 to 4 hour, three times weekly as dialysis schedule, with a blood flow rate range from 250 to 400 ml/min, the dialysate flow rate ranged from 500 to 800 ml/min and bicarbonate dialysis prescription was performed for all patients. All patients were dry-weight stable for at least 2 months before the start of the study.

Patients with acute kidney injury, Patients with obvious cause of malnutrition, Age below 18yeras or above70years ,Patients with acute illness or hospitalization within the last 3months, Patients with decompensated liver cirrhosis, Patients with decompensated heart failure, Patients with respiratory insufficiency, Patients with dementia, psychosis, depression or neurological diseases, History of therapy with corticosteroids or immunosuppressive drugs within the last 6 months were excluded from the study .

All cases of this study were interviewed face-to-face where detailed medical history were taken including: Socioeconomic data (education, income, family size), History fulfilled the SGA and malnutrition inflammation score (MIF), Dietary record: The patient were asked to record: Twenty-four hours dietary recall for 3 days. Food frequency questionnaire (FFQ) for commonly consumed food per week was taken.

Anthropometric measurement:

Dry body weight, height, body mass index (BMI) = weight (kg) / height ($\boldsymbol{m^2}$), Triceps skin fold thickness (TSF) was taken on the non-fistula arm, using Harpenden skin fold callibar. Mid _upper arm circumference (MAC), Mid_ arm muscle circumference (MAMC), MAMC (cm) (= MAC (cm) - [$\boldsymbol{TSF}$ ($\boldsymbol{cm}$) × $\mathbf{0.314}$], and mid- arm muscle area (MAMA) were measured.

Biochemical Measurements

Neutrophil Gelatinase-associated Lipocalin Level in blood using commercially available ELIZA kits. Peripheral venous samples were taken under fasting conditions and were obtained from all patients in pre dialysis session. The mid-week session was selected for sampling and samples were analysed according to standard methods used in the routine clinical laboratory. NGAL was measured in the serum using the ELISA commercially available kit (NOVA) bioneovan company, China. According to the manufacture`s instruments and its level was expressed as ng/ml. Serum albumin, Blood urea, Complete blood count. Serum electrolytes.

Routine clinical laboratory parameters were collected from patient's sheets such as:-serum urea, serum albumin, serum electrolytes and complete blood picture (CBC). Dialysis adequacy was assessed by monthly calculation of Single pool Kt/v (spKt/V), using the Daugirdas second-generation formula.

Statistical Analysis

The collected questionnaires were subjected to revision, and the collected data were coded, processed and analyzed using the Statistical Package of Social Science (SPSS) program for Windows (Standard version 22).The available information was assessed with one-sample Kolmogorov-Smirnov test. Qualitative data were defined by utilizing number and percentages. Continuous variables were evaluated as mean ± standard deviation for parametric information and median for non-parametric information. The two paired groups were compared with paired t test for parametric data and Wilcoxon signed rank test for non-parametric data. ANOVA test was utilized to evaluate more than 2 means while kruskilwallis test was used to compare more than 2 medians. Pearson correlation was utilized to correlate continuous parametric information while Spearman correlation was used to correlate continuous non parametric data. Sensitivity and specificity at various cut off points were evaluated by ROC curve.

Level of Significance

For all above statistical tests performed, the threshold of significance is stationary. Non-significant when the possibility of mistake is above 5% ($p > 0.05$). Significant when the possibility of mistake is below 5% ($p < 0.05$). The lesser the p-value acquired, the higher significant are the result.

Results

Epidemiological Data

The present study included 80 CKD patients stage V treated by chronic dialysis therapy with dialysis duration of 4-h sessions three times per week .As regard gender distribution, males were 51 cases (63.8%) of all studied cases, while females were 29 cases (36.2%). Demographic and laboratory data among the studied group are given in table 1.

Subjective Global Assessment (SGA)
A: mild malnutrition
B: moderate malnutrition
C: severe malnutrition

Demographic and Laboratory data	Study group (n=80)	
	Mean ± SD	Min-Max
Age / years	55.82±7.07	45-70
Weight(kg)	71.50±11.13	42.5-98
Height(cm)	166.19±4.67	158-178
BMI kg\m^2	42.99±6.43	25.44-57.98
Gender Male Female	51 (63.8%) 29 (36.2%)	
T.S.F	Median=10	2-42
M.A.C	29.75±5.31	20-43
M.A.M.C(cm)	25.36±5.48	13.09-43.42
M.A.M.A(cm^2)	2.04±0.45	1.04-3.45
N.G.A.L mg\L	Median=51.89	11.42-267.04
Alb(gm\dl)	3.92±0.62	2.70-5.10
Na (meq\L)	146.89±10.96	125-171
Ca(meq\L)	8.76±1.24	6-12.6
Kt_V	1.36±0.35	0.32-2.18
K(meq\L)	4.60±0.91	2.70-6.80
URR	66.68±10.96	21-85

(T.S.F) Triceps skin fold.
(M.A.C) mid arm circumference.
(M.A.M.C) mid arm muscle circumference.
(M.A.M.A) mid arm muscle circumference area.
(U R R) urea rate reduction

Table 1: Demographic data among the studied group.

Prevalence of Malnutrition

According to Subjective Global Assessment (SGA) out of 80 CKD patients, 67.5% were mild malnourished (SGA 6-7), 25% were moderately malnourished (SGA 3-5) and 7.5% were severely malnourished (SGA 1-2). In this study, we use Twenty-four hours dietary recall and we found most of patients were with low protein (96.2%) and calorie (68.8%) contents. Similar to SGA, MIS revealed that 66.2% of patients were mild-, 26.2% were moderate- and 7.5 were sever-malnourished. Subjective global assessment, Protein content, Calories content and Malnutrition inflammation score among the studied group are given in Table 2.

Variables	Study group (n=80)	
	No	%
Subjective global assessment		
A	54	67.5
B	20	25.0
C	6	7.5
Protein content		
Normal	2	2.5
Low	77	96.2
High	1	1.2
Calories content		
Normal	15	18.8
Low	55	68.8
High	10	12.5
Malnutrition inflammation score		
Mild	53	66.2
Moderate	21	26.2
Sever	6	7.5
Malnutrition inflammation score Median (Min-Max)	6.5 (3-24)	

Table 2: Subjective global assessment, Protein content, Calories content and Malnutrition inflammation score among the studied group.

Correlation Between Serum NGAL and Demographic and laboratory Criteria

We did not find any correlation between plasma NGAL levels and any of the demographic or laboratory variables however there were a direct correlation between albumin (p=<0.001&,r=0.402) and SGA(p=0.402&r=-0.247) (data are given in table 3 and figures 1 and 2).

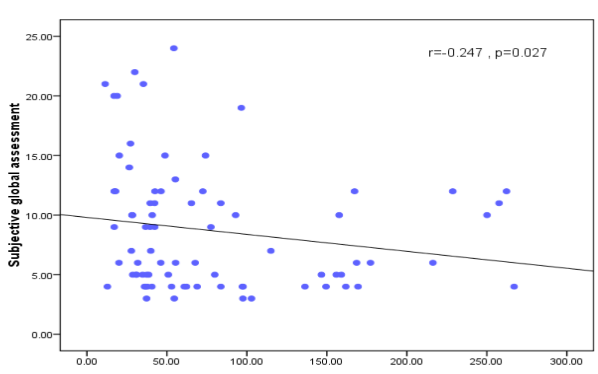

Figure 1: Scatter diagram for negative correlation between NGAL and Subjective global assessment.

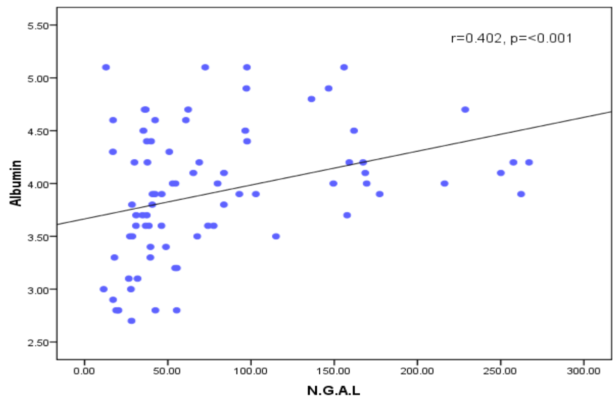

Figure 2: Scatter diagram positive correlation between NGAL and Subjective global assessment.

Variables	N.G.A.L	
	R	P
Age	0.026	0.821
Weight	0.009	0.935
Height	-0.129	0.255
B.M.I	0.034	0.766
T.S.F	-0.006	0.960
M.A.C	0.065	0.570
M.A.M.C	0.056	0.624
M.A.M.A	-0.010	0.926
Alb	0.402	<0.001*
Na	0.027	0.812
Ca	0.052	0.647
Kt_V	0.023	0.840
K	0.127	0.263
Hb	0.013	0.910
R.B.C.s	-0.010	0.929
W.B.C.s	0.144	0.202
Plat	0.169	0.134
B.I_before	-0.101	0.375
B.I_After	-0.105	0.353
Cr_before	0.040	0.725
Cr_After	-0.047	0.682
Subjective global assessment	-0.247	0.027*

R: Spearman correlation
*: significant P value
Table 3: Correlation between N.G.A.L and demographic and laboratory parameters.

Correlation Between NGAL Levels and other Markers of Maluntrion

Spearman correlation analysis revealed that NGAL serum levels were significantly correlated with SGA (*r* =o, 247 *P* =0.027) and albumin serum levels (*r* =0.402, *P*<0.001) (Figures 1& 2).

Correlation Between KT/v and Clinical Markers of Nutrition

This table show significant positive correlation between Kt\V and B.M.I, T.S.F, M.A.C, Alb, Na, Blood urea before dialysis and subjective global assessment. Also interpret nonsignificant positive correlation between Kt / V and Age, Weight, Height, M.A.M.C , M.A.M.A , Ca , K, Hb and Platelets.

On the other hand it shows significant negative correlation with Blood urea after dialysis and Creatinine after dialysis. Also non-significant negative correlation with R.B.C.s × 10^3, W.B.C.s, and Creatinine before dialysis, with their corresponding p value (Table 4).

Variables	Kt_V	
	r	P
Age	0.035	0.755
Weight	0.149	0.186
Height	0.121	0.284
B.M.I	0.223	0.047*
T.S.F	0.354	0.001*
M.A.C	0.248	0.026*
M.A.M.C	0.054	0.632
M.A.M.A	0.087	0.443
Alb	0.275	0.014*
Na	0.429	<0.001*
Ca	0.011	0.921
K	0.182	0.107
Hb	0.204	0.070
R.B.C.s	-0.128	0.258
W.B.C.s	-0.104	0.358
Plat	0.172	0.126
B.I_before	0.352	0.001*
B.I_After	-0.724	<0.001*
Cr_befor	-0.112	0.324
Cr_After	-0.256	0.022*
Subjective global assessment	0.468	<0.001*

R: Pearson correlation

Table 4: Correlation between KT V and other parameters.

Receiver Operating Characteristic Analysis (ROC curve)

In this study NGAL serum levels were significantly (*P*=0.018) reduced with the severity of malnutrition. Using ROC curve analysis, NGAL serum levels had a good ability area under the curve(AUC=0.845) to predict severe malnutrition with good sensitivity (83.3%) and specificity (78.4%).95%confidence interval (CI)(0.70-0.98).The best NGAL cut-off value able to identify sever subjective global assessment was found to be<35.68 (Table 5 and figure 3).

AUC	95% CI		Cut off	Sensitivity	Specificity	PPV	NPV	Accuracy
	Lower	Upper						
0.845	0.70	0.98	<35.68	83.3%	78.4%	23.8%	98.3%	78.7%

AUC: area under the curve, CI: confidence Interval, PPV: positive predictive value, NPV: negative predictive value.
Table 5: Roc curve for prediction of Sever Subjective global assessment by Serum NGAL.

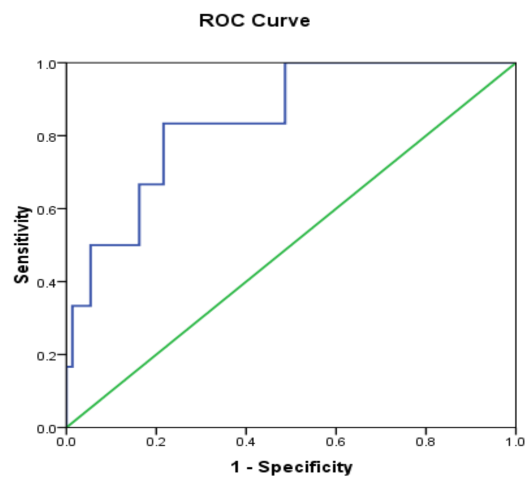

Figure 3: Roc curve for prediction of Sever Subjective global assessment by Serum NGAL.

Discussion

Chronic kidney disease (CKD) is an enormous public health problem that is inexorably characterized by very high health care costs and poor health outcomes [9]. Complications of CKD represent significant burden on global healthcare resources and only few countries have sufficiently robust economies to meet the challenge posed by this disease [5]. Malnutrition was defined according to the American Society for Parenteral and Enteral Nutrition as "an imbalance between nutrient intake and requirement causing cumulative deficits of protein, energy or micronutrients that may negatively affect development, growth and other relevant outcomes [10]. CKD patients are at substantial malnutrition risk and many studies reported high malnutrition prevalence rate in both children and adults with CKD. Malnutrition pathogenic mechanisms in CKD are complex and involve multiple pathophysiologic alterations including hormonal derangements, decreased appetite and nutrient intake, metabolic imbalances, increased catabolism, inflammation, and dialysis related abnormalities [10].

Several studies reported that between 28% and 65% of CKD patients are having malnutrition based on different criteria used for diagnosis, including patients undergoing maintenance Haemodialysis [11]. In our study 100% of CKD having some degree malnutrition according to SGA, MIS, however most of our patients have mild malnutrition. This could be attributed to poor education about nutrition and good dietation among patients and absence of routine renal dietician in most of dialysis units in Egypt.

Most of patients included in this study were obese with mean BMI±SD of 42.99±6.43. Recent studies provided direct evidence that being obese or overweight increases risk of advanced CKD, and that this remains true regardless CKD different etiologies [12,13]. Strategies to reduce weight among those who are obese or overweight may reduce CKD risk, with each unit reduction in BMI yielding similar relative reductions in risk [12].

In this study, ESRD were more common in males (63.8%) than females (36.2%) patients. The prevalence of CKD is higher in women compared with men, and this difference has been consistent over time (from13.7percentage versus 9.8% in 1988–1994 to 15.4% versus 12.8% in 2011–2012). In contrast, the lifetime risk of ESRD has been found to be up to 50% higher in men compared with women. These findings suggest that women may have slower kidney function decline compared with men or that they are more likely to die before progressing to ESRD [14]. However, sex differences in CKD progression are affected by several other factors like hypertension [15]. Albuminuria, hyperglycaemia body mass index, dyslipidaemia, lifestyle factors sex, hormones and renal structure [16-21].

In this study, we evaluated through anthropometry the presence of malnutrition and nutritional risk in CKD patients. According to other studies [22,23] the variables evaluated were triceps skin fold (TSF), mid arm circumference (MAC), mid arm muscle circumference (MAMC) and mid arm muscle circumference area (MAMA). Findings revealed a significant decrease in these anthropometric parameters. Similar to our results [24], suggested a significant decrease in some anthropometric parameters including BMI, fat mass, TSF, MAC, MAMC and MAMA with advanced malnutrition in haemodialysis patients. Also, similar values of TSF, MAC and MAMC reported by in similar group of patients [25].

In our study the prevalence of malnutrition was high as majority of our patients showed some degree of malnutrition. According to Subjective Global Assessment (SGA) out of 80 CKD patients, 67.5% were mild malnourished (SGA 6-7), 25% were moderately malnourished (SGA 3-5) and 7.5% were severely malnourished (SGA 1-2). Nutritional assessment of CKD patients is vital function of health care providers [26]. SGA tool, originally created by, it uses patient history as well as physical examination to rate malnutrition severity in CKD [27].

Malnutrition is common in CKD patients. Several studies have shown prevalence between 23-76% of patients on haemodialysis [11]. Similar to our results in older adults with advanced CKD, winhalk et al. [28], reported similar percentages in a multicentre prospective observational cohort study included six European countries. In another study by Ebrahimzadeh Koor B et al. across section study based on the SGA score, They found that 6.3% were well nourished, 50% had mild malnutrition and 43.8% suffered from moderate malnutrition; and no case of severe malnutrition [29] . In contrast to our results Gupta A, et al. [26] had a cross section study on 100 patients stage 5 CKD on haemodialysis using malnutrition score reported that 29% were mildly malnourished, 64% were moderately malnourished and 7% were severely malnourished. Such variations in malnutrition prevalence may be associated with other factors such as age, dialysis therapy quality and comorbid conditions [30].

In this study we used Twenty-four hours dietary recall and we found most of patients were with low protein (96.2%) and calorie (68.8%) contents. While this method is known to provide an accurate estimate of mean dietary intake, it may exaggerate the variability of intake in the study population biasing measured associations toward the null [31]. Low calorie intake and protein content due to decreased appetite is an important malnutrition cause in CKD. Anorexia considered as early index of uremia that occurs when GFR be <60 mL/min/1.73 m^2. As limitation of dietary protein intake decreases accumulation of protein metabolism derived toxic substances, reduced protein intake due to anorexia may be regarded as adaptive process to relieve uremic symptoms in patients with renal failure. Also, anorexia is caused by inflammation, changes in plasma adiponectin and leptin concentrations, depression, comorbidity and side effects of medications [32].

To confirm what we have reached, also in this study the overall nutritional assessment was achieved using the malnutrition-inflammation score (MIS). Similar to SGA, MIS revealed that 66.2% of patients were mild-, 26.2% were moderate- and 7.5 were sever-malnourished. Many studies reported comparable results between MIS and SGA as nutritional assessment tools for CKD patients treated not only by hemodialysis but also those treated with peritoneal dialysis [33].

In clinical practice, evaluating hemodialysis adequacy is of critical importance. Measures like blood urea nitrogen are not suitable for hemodialysis adequacy assessment as its values are largely affected by diet [34]. The urea kinetic modelling of the dialysis dose (Kt/V) proposed by Daugirdas [35] is hemodialysis competence measure that can be individualized for each patient. Dialysis adequacy (Kt/V) can affect the nutritional status of patients [34]. Kt/V was adequate in all malnutrition groups. These findings are consistent with an earlier report in which HD patients with Kt/V>1.4 had a significantly higher rate of malnutrition than patients with Kt/V ≤1.4 [36].

In contrast to Kt/V, in this study NGAL serum levels were significantly (P=0.018) reduced with the severity of malnutrition. Using ROC curve analysis, NGAL serum levels had a good ability (AUC=0.845) to predict severe malnutrition with good sensitivity (83.3%) and specificity (78.4%). Previous studies reported that NGAL serum levels were associated with nutritional status of CKD patients. Bolignano D, et al. reported that NGAL is involved in iron equilibrium maintenance and demonstrated that hemodialysis patients have altered NGAL values. Thus, NGAL might be an assessment tool of iron deficiency and may be used in iron therapy management for hemodialysis patients [37].

In this study, Spearman correlation analysis revealed that NGAL serum levels were significantly correlated with SGA (r =o,247 P =0.027) and albumin serum levels (r =0.402, P<0.001). Similar to our results Imamaki H et al. showed that maintenance hemodialysis patients with decreased NGAL serum levels were associated with reduced in albumin, as representative nutritional status indicator, serum levels. These findings can be caused by neutropenia and malnutrition . They found that high NGAL levels in these patients were closely related to good nutritional status at present and preserved serum albumin levels after a year, and thus potentially with reduced mortality and morbidity [8] .

Findings reported by this study concerning the association between NGAL serum levels and malnutrition in CKD were comparable with other established diagnostic methods. SGA is a useful and reproducible method for nutritional status assessment in dialysis patients. However, SGA technique, according to the National Kidney Foundation, needs greater validation regarding specificity, sensitivity, inter- and intra-observer variability, accuracy, and correlation with other nutritional markers [25].

Limitation of the Study

Limitation of our study was short (one year for collecting data) and small scale study involving only two dialysis centres. In addition, limitation was cross sectional method that only assessed nutritional status, lab and serum NGAL levels at one time. We recommended the use of NGAL serum levels to follow-up hemodialysis patient's nutritional status.

Another limitation was low numbers of samples in our study. Othermulticenter studies using large number of patients are recommended to evaluate the value of serum NGAL in predication of severe malnutrition and compare it with other established nutritional markers.

Conclusion

NGAL is well correlated with other standard markers used routinely in assessment of nutritional status of hemodialysis patients. Patients with high NGAL levels were closely related to good nutritional status. Its serum levels had a good diagnostic power for severe-malnourished patients, as it help us for early prediction to malnutrition.

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