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Original article

Inflammation and nutritional status assessment by malnutrition inflammation score and its outcome in pre-dialysis chronic kidney disease patients

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SUMMARY

Background: Malnutrition-inflammation complex syndrome (MICS), hyperhomocysteinemia, calcium and phosphate levels derangement have been predicted as important contributing factors for the progression of cardiovascular burden. Among patients with earlier stage of CKD, hypoalbuminaemia and inflammation deliberated as non-traditional cardiovascular risk factors, which add more burden to circulatory disease, mortality and rapid advancement to CKD stage 5.

Aim: The aim of the study is to evaluate inflammation and nutritional status of CKD patients not on dialysis using Malnutrition inflammation score (MIS) and to verify the association with mortality in the follow-up period.

Methods and material: In this prospective cohort study 129 (66 males, 63 females) pre-dialysis CKD patients enrolled between June 2013 to August 2014 and censored until March 2017. Malnutrition and Inflammation assessed using Malnutrition inflammation score. Blood urea nitrogen, serum creatinine, albumin, Interleukin − 6, highly sensitive C reactive protein (hsCRP), total cholesterol and anthropometric data were analyzed.

Results: The Malnutrition inflammation score in pre-dialysis CKD patients ranged from 0 to 18 with the median score of two. During 36 or more months of follow-up, there were 30 (23.2%) deaths, 35 (27%) patients initiated on hemodialysis, one (0.7%) patient was initiated on peritoneal dialysis, two (1.4%) patients underwent renal transplantation and two (1.4%) patients were lost for follow-up. In this study, 33% had varying degree of malnutrition and inflammation. Patients who had MIS $\geq$7 had significant increase in IL-6 ($p = 0.003$) and HsCRP levels ($p < 0.001$) when compared with other tertiles of MIS. ROC curve analysis of MIS showed 56.5% sensitivity and 81% specificity in predicting death rate (AUC 0.709; 95% CI 0.604–0.815, $p < 0.001$). Kaplan–Meier survival analysis showed MIS $\geq$7 had a strong association (log rank test, $p < 0.001$) with mortality during 36 and more months of follow-up time. In unadjusted analyses, MIS (HR 1.140; 95% CI 1.054–1.233; $p < 0.05$) and HsCRP (HR 2.369; 95% CI 1.779–3.154; $p < 0.001$) found to be predictors of mortality. MIS and HsCRP remained predictors of mortality even after adjustments.

Conclusions: This study shows MIS is an important factor that determines mortality in pre-dialysis CKD patients during 36 and more months of follow-up time. Patients with MIS $\geq$7 have high risk for mortality and needs close monitoring. In clinical setting application of MIS has a greater utilization in pre-dialysis CKD patients. Further research with longitudinal assessment of MIS and its association with outcomes are warranted. Pre-dialysis CKD patients should be assessed for their nutritional status and inflammation using MIS regularly to prevent malnutrition and its associated complications through appropriate medical and nutritional intervention.

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1. Introduction

Cardiovascular related complications are the most important reason for poor survival in chronic kidney Disease (CKD) patients [1]. Malnutrition-inflammation complex syndrome (MICS), hyperhomocysteinemia, calcium and phosphate levels derangement have been determined as important contributing factors for the progression of cardiovascular burden [2]. There is an association between inflammation, atherosclerosis and malnutrition in CKD, hence the term malnutrition–inflammation complex syndrome. Among patients with CKD, hypoalbuminemia and inflammation contemplated as non-traditional cardiovascular risk factors, which add more burden to circulatory disease, mortality and rapid advancement to CKD stage 5 requiring renal replacement therapy [2,3].

The prevalence of malnutrition reported between 28 and 65% on various studies depending on criteria used in diagnosis [4–7]. Malnutrition Inflammation Score (MIS) could be a valid tool in evaluating the nutritional status of pre-dialysis CKD patients [8]. Most of the previous studies on malnutrition and inflammation were carried out in ESRD patients on dialysis with only a few studies available in CKD patients not on dialysis [4–6,9].

The aim of the study is to evaluate inflammation and nutritional status of CKD patients' not on dialysis using MIS and to study the outcome of the patients with different tertiles of MIS. This study also aims to find the association between MIS with different patient related parameters such as age, gender, estimated Glomerular filtration rate (e-GFR), BMI, anthropometry such as MAMC, MAC and TSF in our study population. The other objectives of the study is to find the correlation between MIS with inflammatory mediators such as Interleukin-6 and HsCRP in pre-dialysis CKD patients and comparison of demographic, nutrition, inflammation related factors between survivors and non-survivors.

2. Methods

2.1. Study design and study participants

In this prospective, single center, study on pre-dialysis CKD patients, which included 129 pre-dialysis CKD patients in the period between June 2013 to August 2014. The patients who visited the nephrology out patient's clinic were enrolled into the study after meeting the inclusion criteria of the study. The study participants were CKD patients who met the following inclusion criteria: (i) age greater than 18 years and $\leq$65 years old (ii) no past history of malignancy (iii) CKD stages 3–5. The study procedure was explained and for patients, who were keen, informed consent was collected to participate in this study and institutional ethical committee approval was obtained for the study.

Kidney disease improving global outcomes (KDIGO) clinical practice guideline was used for diagnosis and classification of CKD [11]. Estimated Glomerular Filtration Rate (e-GFR) was assessed using CKD EPI 2009 equation to evaluate kidney function: e-GFR (mL/min/1.73 m^2) = 141 $\times$ min (Serum creatinine/κ, 1)α X max (Serum creatinine/κ,1)$-$1.209 $\times$ 0.993 Age $\times$ 1.018 [if female] $\times$ 1.159 [if black]. The baseline data such as demographic details, cause of CKD, history of cardiovascular disease, cerebrovascular disease, peripheral vascular disease, anthropometric parameters such as height, body weight, body mass index (BMI), mid arm circumference (MAC), Triceps skin fold thickness (TSF) and Mid arm muscle circumference (MAMC) were collected.

2.2. Clinical characteristics and lab data

Serum albumin, blood urea nitrogen, serum creatinine, phosphorus, calcium, Highly sensitive C reactive protein (hsCRP), total cholesterol, low density lipo protein (LDL), high – density lipo protein (HDL) were analyzed. Blood sample from CKD patients drawn after visiting nephrology clinic. Biochemical variables analyzed using the Biosystem A15 Automated biochemical analyzer. Serum albumin was analyzed using ADVIA 1800 fully automated analyzer (Siemens), HsCRP and TIBC levels was estimated by Dade Behring Dimension fully automated analyzer (Siemens) and Human Interleukin – 6 (IL-6) levels were assessed using Diaclone IL-6 ELISA kit (Diaclone SAS, France).

2.3. Malnutrition inflammation score

MIS was used for the evaluation of nutritional status and inflammation status [9]. MIS contains ten elements resulting from past medical history, physical examination of study participants, BMI and clinical laboratory parameters. There are totally ten elements and each element is characterized with the scores ranging from zero to three based on the level of severity. The summation of all components ranges from score of Zero (No malnutrition) to score of thirty (high degree of malnutrition and inflammation status). In this study, the subjects included were not on dialysis hence dialysis vintage was excluded from the final score. The final MIS was divided into four tertiles such as Tertile 1 (MIS = 0), second tertile (MIS = 1 to 3), third tertile (MIS = 4 to 6) and fourth tertile (MIS $\geq$ 7).

2.4. Follow-up and censored

In our study, follow-up of the study participants was continued until March 2017. The follow-up was censored in the event of death, renal transplantation, initiation of dialysis (Hemodialysis and Peritoneal Dialysis) and lost for follow-up.

2.5. Statistical analysis

Data are expressed in mean $\pm$ standard deviation, count and percentage. Student *t*-test used in the evaluation of differences between two groups for parametric data and Mann–Whitney *U*-test used for non-parametric data. One way Analysis of variance (ANOVA) was performed for comparison of 3 or more groups for parametric data and Kruskal–Wallis test used for non-parametric data. A tukey post hoc test was done to confirm the differences between groups for parametric data and Kruskal Wallis post hoc paired comparisons test was done for non-parametric data. Spearman rank correlation (rho) was performed to analyze the correlation between variables for non-parametric data and Pearson correlation was performed for parametric data. The validation of area under the curve (AUC) was done using Receiver operating characteristic (ROC) curve analysis, to determine the significance of MIS in predicting mortality. Sensitivity and specificity analysis was done to assess the best cut-off MIS to predict death rate. The predictors of mortality during the follow-up period were assessed using COX multivariate proportional hazards analysis and adjusted for variables based on significant difference between survivors and non-survivors after excluding serum albumin, TIBC and BMI those are already a part of Malnutrition Inflammation score. Survival analysis done using Kaplan–Meier survival to compare the groups and difference between the curves was confirmed using log rank test. Statistical significant was considered when $p < 0.05$. Statistical analysis was executed using IBM SPSS for Windows, version 20 (IBM Corporation., New York, USA).

3. Results

In this study 129 (66 males, 63 females) subjects were included. The study participants had a mean age of 50.6 $\pm$ 11.4 years. The

Table 1
Baseline demographic details and laboratory variables of pre-dialysis CKD subjects (n = 129).

Variables	Pre-dialysis CKD patients
Male:female	66(51%):63(49%)
Hypertension	91 (71%)
Diabetes mellitus	58 (45%)
History of cardiovascular disease	19 (15%)
Smoking	14 (11%)
Mean age (years)	50.6 ± 11.4
Body mass index (Kg/m^2)	24.8 ± 5.5
Systolic blood pressure (mm Hg)	122 ± 24
Diastolic blood pressure (mm Hg)	77 ± 14
Mid arm circumference (cm)	27 ± 4.4
Triceps skinfold Thickness (mm)	12 ± 7
Mid arm muscle circumference (cm)	23 ± 3.6
e-GFR (mL/min/1.73 m^2)	30.4 ± 14
Serum BUN (mg/dL)	29.5 ± 19.3
Serum creatinine (mg/dL)	2.8 ± 1.4
Serum albumin (g/dl)	4 ± 0.5
Total protein (g/dl)	7.5 ± 0.8
Total iron binding capacity (μg/dL)	280 ± 73
Total cholesterol (mg/dL)	207 ± 57
HDL cholesterol (mg/dL)	34 ± 10
LDL cholesterol (mg/dL)	111 ± 21
Triglycerides (mg/dL)	153 ± 66
Highly sensitive CRP (mg/dL)[a]	0.6 (0.3–1.7)
Interleukin 6 (pg/ml)[a]	5.82 (1.8–10.8)
Malnutrition inflammation score[a]	2 (1–5)

[a] Median with interquartile range.

clinical characteristics and demography of patients presented in Table 1.

The primary kidney disease was hypertensive nephrosclerosis (38%), diabetic nephropathy (34%) and other causes (28%). Fifteen percent of subjects had previous history of cardio vascular disease. Fifty (38.8%) subjects had stage 3 CKD (GFR range, 30–59 ml/min), 48 (37.2%) had stage 4 CKD (GFR range, 15–29 ml/min) and 31 (24%) had stage 5 CKD (GFR, <15 ml/min). The clinical characteristics of patients stratified based on stage of CKD described in Table 2.

A tukey post hoc test revealed that blood urea nitrogen and creatinine were significantly higher in CKD stage 5 than other stages of CKD ($p < 0.001$). The mean systolic blood pressure was found to be significantly high in CKD 5 (129 ± 23 mm of Hg) patients than stage 3 CKD (115 ± 22 mm of Hg) patients ($p = 0.044$). The Kruskal Wallis post hoc paired comparisons test showed median MIS was significantly higher in patient with CKD stage 5 than patients with CKD stage 3 ($p = 0.004$). Median IL-6 levels increased with the increase in the stage of CKD however, it was not statistically significant.

3.1. Prevalence of malnutrition and inflammation

The Malnutrition inflammation score in pre-dialysis CKD patients ranged from 0 to 18 with the median score of two. Thirty three percent (42) of our study population had MIS of zero, 34% (45) had scores ranging from 1 to 3, 18% (23) had scores between 4 and 6 and 15% (19) had scores above 7. The Clinical details and laboratory variables of patients stratified based on tertiles of MIS were presented in Table 3.

Eighteen percent of our study population had MIS between 4 and 6 and 15% had MIS ≥7, which denotes the poor nutritional status of these groups of patients. Among patients who had MIS ≥7 had significant increase in IL-6 and HsCRP levels when compared with other two tertiles of MIS (Fig. 1). Serum albumin and serum TIBC levels were also lower among patients with MIS ≥7 and it was found to be statistically significant. Patients with MIS ≥7 had significantly lower levels of MAC, MAMC and TSF than other tertiles of MIS.

In our study, MIS had a significant positive correlation with HsCRP, IL-6 levels, blood urea nitrogen, creatinine, phosphorus and calcium phosphorus product denoting elevated levels of above variables is associated with malnutrition and inflammation. Serum albumin, TIBC, anthropometric measurements such as MAC, TSF, MAMC and BMI had a significant negative correlation with MIS indicating that patients with malnutrition and inflammation have lower levels of Serum albumin, MAMC and MAC (Table 4).

During 36 or more months of follow-up, there were 30 (23.2%) deaths, 35 (27%) patients were initiated on hemodialysis, one (0.7%) patient was initiated on peritoneal dialysis, two (1.4%) patients underwent renal transplantation and two (1.4%) patients were lost for follow-up. The baseline characteristics of non-survival and survival group was compared and presented in Table 5. Comparison

Table 2
Demographic details and laboratory variables of study participants stratified based on CKD stage (n = 129).

Variables	CKD Stage 3 (n = 50)	CKD Stage 4 (n = 48)	CKD Stage 5 (n = 31)	p value
Male gender[a]	25 (50%)	25 (52%)	16 (52%)	0.977
Hypertension[a]	35 (70%)	31 (65%)	25 (81%)	0.309
Diabetes mellitus	24 (48%)	20 (42%)	14 (45%)	0.820
History of cardiovascular disease[a]	8 (16%)	3 (6%)	8 (26%)	0.049
Smoking[a]	3 (6%)	5 (10%)	6 (19%)	0.170
Age (years)[b]	49 ± 12	53 ± 11	50 ± 9	0.313
Body mass index (Kg/m^2)[b]	24.7 ± 4.8	25.3 ± 5.7	24.2 ± 6.3	0.671
e-GFR (mL/min/1.73 m^2)[b]	46 ± 7	25 ± 3	13 ± 3	<0.001
Serum BUN (mg/dL)[b]	18 ± 8	30 ± 14	47 ± 18	<0.001
Serum creatinine (mg/dL)[b]	1.7 ± 0.3	2.6 ± 0.6	4.8 ± 1.3	<0.001
Serum albumin (g/dl)[b]	4.1 ± 0.4	3.9 ± 0.6	3.6 ± 0.5	0.179
Total protein (g/dl)[b]	7.6 ± 0.9	7.6 ± 0.7	7.5 ± 0.6	0.906
Total iron binding capacity (μg/dL)[b]	294 ± 73	280 ± 78	259 ± 62	0.120
Systolic blood pressure (mm Hg)[b]	115 ± 22	125 ± 27	129 ± 23	0.042
Diastolic blood pressure (mm Hg)[b]	73 ± 15	78 ± 13	79 ± 16	0.152
Total cholesterol (mg/dL)[b]	203 ± 60	212 ± 58	207 ± 51	0.744
HDL cholesterol (mg/dL)[b]	45 ± 8	40 ± 7	38 ± 8	0.338
LDL cholesterol (mg/dL)[b]	135 ± 64	140 ± 58	151 ± 65	0.265
Triglycerides (mg/dL)[b]	161 ± 60	153 ± 73	144 ± 67	0.513
Highly sensitive CRP (mg/dL)[c]	0.51 (0.2–1.7)	0.66 (0.3–1.6)	1.1 (1.1–1.9)	0.468
Interleukin 6 (pg/ml)[c]	2.14 (0.9–5.9)	5.6 (1.8–9.3)	9.3 (5.9–12.3)	0.088
Malnutrition inflammation score[c]	1 (1–3)	2 (1–5)	4 (2–6)	0.021

[a] Number and percentage between groups using Chi-square test.
[b] Mean and Standard deviation between groups using Analysis of variance (ANOVA).
[c] Median with interquartile range using Kruskal–Wallis analysis.

Table 3
Clinical details and laboratory variables of patients stratified based on MIS (n = 129).

Variables	MIS = 0 (n = 42)	MIS (1–3) (n = 45)	MIS (4–6) (n = 23)	MIS (≥7) (n = 19)	p
Male gender	23 (55%)	18 (40%)	14 (61%)	11 (58%)	0.299
Age (years)	51 ± 11	52 ± 10	53 ± 11	43 ± 15	0.020
Body mass index (Kg/m^2)	26 ± 3.7	26 ± 6	21 ± 3.9	19 ± 3.3	<0.001
Mid arm circumference (cm)	28.2 ± 3.6	28.7 ± 4.4	25.3 ± 3.6	22.5 ± 3	<0.001
Triceps skinfold thickness (mm)	13 ± 7	14 ± 7	10 ± 4	7 ± 5	<0.001
Mid arm muscle circumference (cm)	24.1 ± 3.5	24.1 ± 3.4	22.2 ± 3.4	20.4 ± 2.9	<0.001
e-GFR (mL/min/1.73 m^2)	36 ± 12	30 ± 14	24 ± 14	26 ± 14	0.004
Serum BUN (mg/dL)	21 ± 10	32 ± 19	35 ± 19	36 ± 17	<0.001
Serum creatinine (mg/dL)	2.2 ± 0.8	2.8 ± 1.4	3.5 ± 1.8	3.3 ± 1.4	0.002
Serum albumin (g/dl)	4.2 ± 0.3	4.1 ± 0.5	3.9 ± 0.5	3.5 ± 0.5	<0.001
Total protein (g/dl)	7.8 ± 0.6	7.7 ± 0.6	7.2 ± 0.9	7 ± 0.8	<0.001
Total iron binding capacity (μg/dL)	324 ± 61	272 ± 61	268 ± 72	219 ± 74	<0.001
Total cholesterol (mg/dL)	200 ± 58	216 ± 56	210 ± 55	201 ± 60	0.560
HDL cholesterol (mg/dL)	40 ± 6	41 ± 7	43 ± 9	31 ± 12	0.522
LDL cholesterol (mg/dL)	106 ± 28	123 ± 18	95 ± 24	87 ± 28	0.369
Triglycerides (mg/dL)	147 ± 70	163 ± 62	160 ± 70	143 ± 65	0.599
Highly sensitive CRP (mg/dL)[a]	0.35 (0.1–0.5)	0.86 (0.4–1.7)	1.13 (0.7–1.6)	2.85 (0.8–3.4)	<0.001
Interleukin 6 (pg/ml)[a]	2.02 (0.9–5.5)	5.99 (2.1–9.3)	6.92 (2.7–24.9)	15.2 (9.42–25.2)	0.003

[a] Median with interquartile range.

of blood urea nitrogen, creatinine, e-GFR, inflammatory markers HsCRP, IL-6 and MIS between survivors and non-survivors revealed a difference between the groups during the follow-up period and it was found to be statistically significant.

3.1.1. Sensitivity and specificity analysis using ROC curve

ROC curve analysis of MIS showed 56.5% sensitivity and 81% specificity in predicting mortality (AUC 0.709; 95% CI 0.604–0.815, p = 0.001) (Fig. 2).

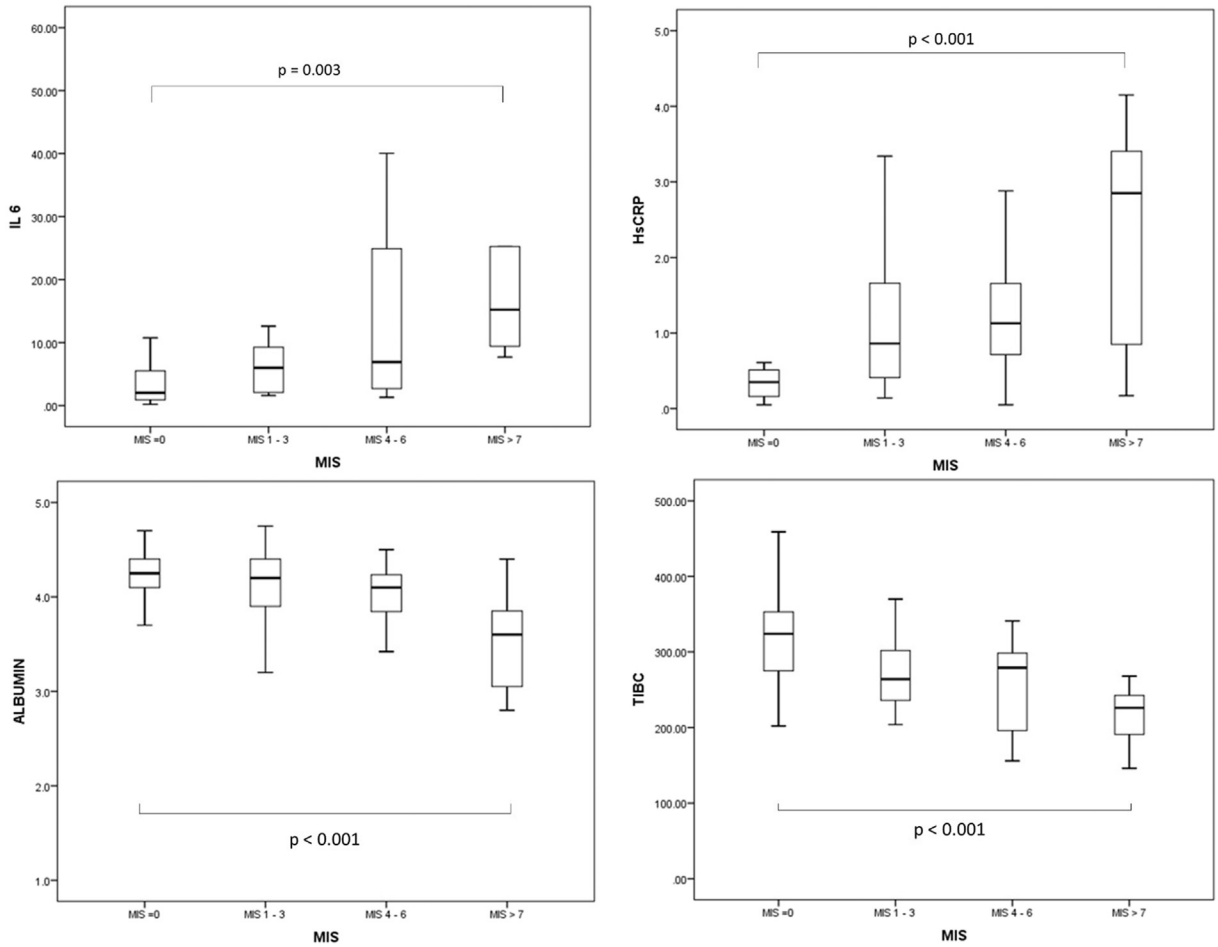

Fig. 1. Box plot graphs depicting various tertiles of MIS with IL-6, HsCRP, Serum albumin and TIBC.

Table 4
Correlation of various variables with malnutrition inflammation score in pre-dialysis CKD patients.

Variables	Correlation coefficient	p value
Age (years)	−0.206	0.019
Body mass index (Kg/m^2)	−0.490	<0.001
Mid arm circumference (cm)	−0.470	<0.001
Triceps skinfold thickness (mm)	−0.333	<0.001
Mid arm muscle circumference (cm)	−0.380	<0.001
e-GFR (mL/min/1.73 m^2)	−0.246	0.005
Serum BUN (mg/dL)	0.283	0.001
Serum creatinine (mg/dL)	0.264	0.003
Serum albumin (g/dl)	−0.464	<0.001
Total protein (g/dl)	−0.351	<0.001
Total iron binding capacity (μg/dL)	−0.444	<0.001
Total cholesterol (mg/dL)	−0.051	0.566
HDL cholesterol (mg/dL)	−0.400	0.432
LDL cholesterol (mg/dL)	−0.453	0.308
Triglycerides (mg/dL)	0.102	0.891
Corrected calcium (mg/dL)	0.145	0.100
Serum phosphorus (mg/dL)	0.349	<0.001
Calcium × phosphorus product (mg^2/dL^2)	0.290	0.001
Highly sensitive CRP (mg/dL)	0.564	<0.001
Interleukin 6 (pg/ml)	0.352	0.030

3.1.2. Kaplan–Meier survival analysis

Kaplan–Meier curves for Gender, MIS, IL-6 and HsCRP were analyzed (Fig. 3). MIS, IL-6, HsCRP had a strong association (log rank test, $p < 0.001$) with mortality during 36 and more months of follow-up time.

3.1.3. Cox proportional hazards analysis

Using univariate analysis the variables identified to have significant difference between survivors and non-survivors were considered for the adjustment of models after excluding serum albumin, TIBC and BMI, which were already part of Malnutrition Inflammation score. In unadjusted analyses, MIS (HR 1.140; 95% CI 1.054–1.233; $p < 0.05$) and HsCRP (HR 2.369; 95% CI 1.779–3.154; $p < 0.001$) were found to be predictors of mortality. MIS and HsCRP remained predictors of mortality even after adjustments in pre-dialysis CKD patients (Table 6).

Table 5
Comparison of baseline clinical, nutritional and demographic data between surviving and non-survival patients after follow-up of 36 months or more.

Variables	Survivals (n = 59)	Non survivals (n = 30)	p value
Male gender	33 (69%)	15 (31%)	0.656
Age (years)	51 ± 12	52 ± 10	0.727
Body mass index (Kg/m^2)	25.4 ± 5.2	24.9 ± 6.7	0.663
Mid arm circumference (cm)	27.6 ± 4	26.5 ± 4.5	0.303
Triceps skinfold thickness (mm)	12 ± 6	12 ± 8	0.745
Mid arm muscle circumference (cm)	24 ± 4	23 ± 3	0.109
e-GFR (mL/min/1.73 m^2)	34 ± 13	23 ± 14	0.001
Serum BUN (mg/dL)	24 ± 12	36 ± 19	0.003
Serum creatinine (mg/dL)	2.3 ± 0.9	3.5 ± 1.7	0.002
Serum albumin (g/dl)	4.0 ± 0.5	3.8 ± 0.4	0.101
Total protein (g/dl)	7.6 ± 0.8	7.3 ± 0.7	0.072
Total iron binding capacity (μg/dL)	276 ± 71	265 ± 65	0.481
Total cholesterol (mg/dL)	205 ± 56	216 ± 63	0.437
HDL cholesterol (mg/dL)	39 ± 9	25 ± 6	0.130
LDL cholesterol (mg/dL)	117 ± 21	104 ± 21	0.440
Triglycerides (mg/dL)	163 ± 68	147 ± 66	0.287
Malnutrition inflammation score[a]	2 (1–4)	3.5 (2–7)	0.001
Highly sensitive CRP (mg/dL)[a]	0.48 (0.2–1)	2.1 (1.2–3.2)	<0.001
Interleukin 6 (pg/ml)[a]	2.3 (1.6–6)	12.4 (8–30.4)	0.015

[a] Median with interquartile range.

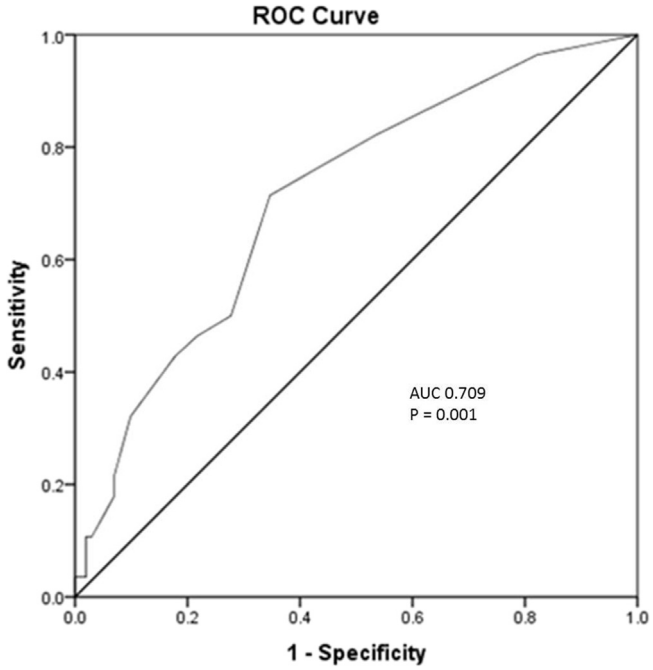

Fig. 2. Receiver operating characteristic (ROC) curve of MIS predicting mortality in pre-dialysis CKD patients at 36 months or more of follow-up.

4. Discussion

This study shows MIS is an important factor that determines mortality in pre-dialysis CKD patients during 36 and more months of follow-up time. The risk for mortality increases 13.7% with each point of MIS. MIS ≥7 is a high risk for mortality when compared with other groups of MIS. FC Amparo et al. [8] reported similar findings after comparing anthropometry and biomarkers of malnutrition with MIS which predicted the outcomes and concluded that higher MIS is related with increased risk for mortality in non-dialysis CKD patients.

In several prospective studies among CKD patients the clinical utility of MIS was evaluated and has been observed to have strong association with death rate, morbidity, poor quality of life, disturbed sleep patterns and resistance to erythropoietin [9,21,22]. This study also evaluated the inflammation and status of nutrition in non – dialysis patients with CKD. Malnutrition prevalence is high among pre-dialysis CKD patients, affects the quality of life poorly and it is linked with higher death rate and hospitalization rate [5]. The causes of poor status of nutrition in pre-dialysis CKD and in patients undergoing maintenance hemodialysis are several and multifactorial [16]. The poor nutritional status is typically termed as “protein energy malnutrition” is due to reduced intake of nutrients, which are the essential substrate necessary for growth of tissue and for maintenance of normal homeostasis. Intake of very low-protein diet is associated with low nitrogen balance in pre-dialysis CKD patients [17]. In this study, 33% of CKD patients had varying degree of malnutrition and inflammation. The patients were considered to be malnourished if they had two or more following criteria such as serum albumin <3.5 g/dl, MIS >3, BMI <20 kg/m^2, MAMC less than 23 cm in females and 25 cm in males and patients were considered to have inflammation if their HsCRP levels were above 0.6 mg/dl. Several studies report between 28% and 65% of CKD patients having malnutrition based on different criteria used for diagnosis, including patients undergoing maintenance Hemodialysis [4–7, 10, 11].

In this study, MIS had a significant positive correlation with HsCRP and IL-6. Patients with high tertiles of MIS had significantly

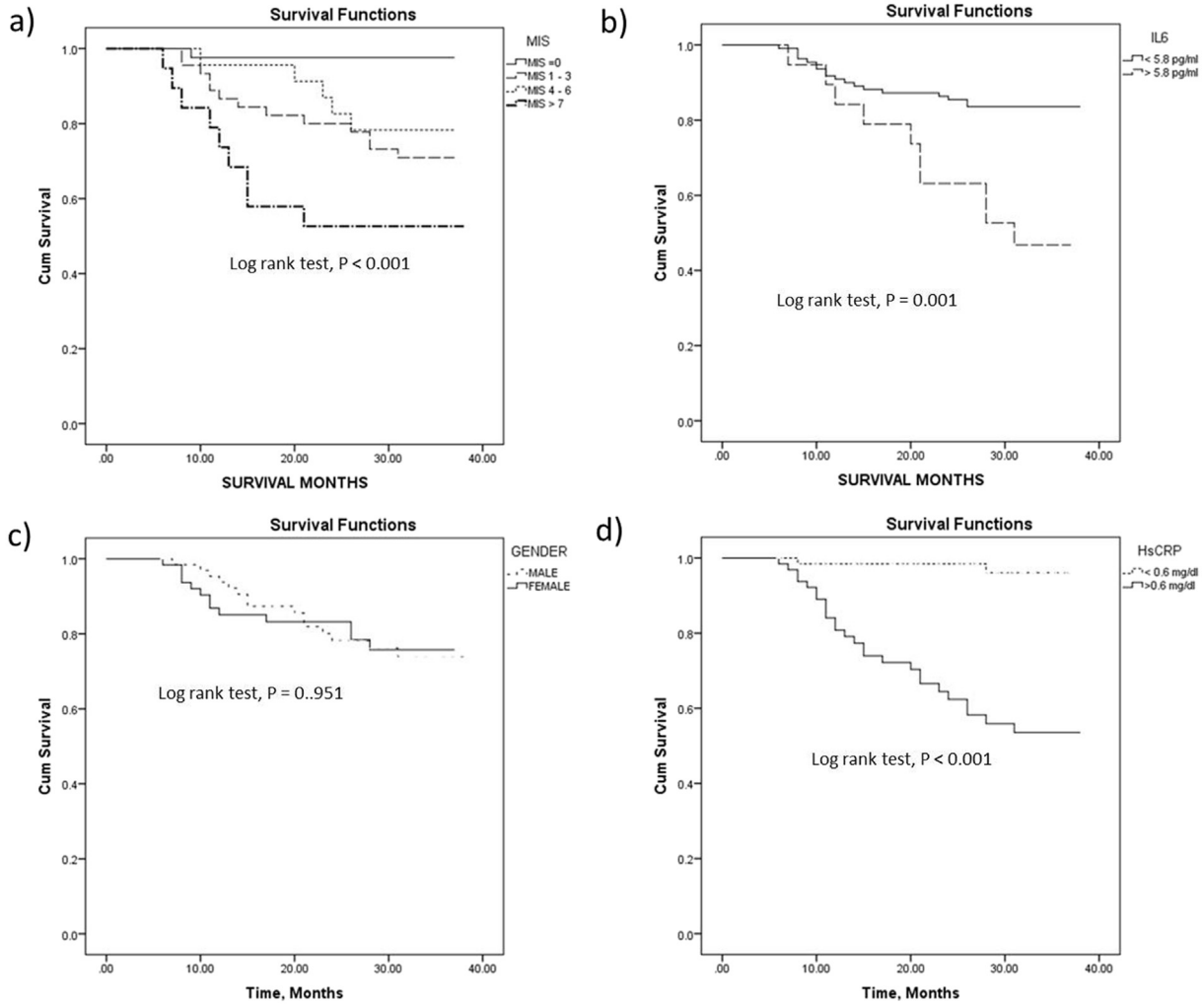

Fig. 3. Survival curves by follow-up period for MIS, IL-6, HsCRP and Gender in cumulative survival of 36 months or more. Fig. 3b and d Kaplan Meier estimates for mortality based on median IL-6 and median HsCRP levels.

elevated levels of HsCRP and IL-6. Interleukin – 6 increases with the decrease in Glomerular filtration rate. Kidney removes several pro-inflammatory cytokines and in renal failure, there is a decrease renal IL-6 clearance, which accounts for the increased IL-6 levels for pre-dialysis CKD and ESRD patients [12]. Seventy two percent of our study population had elevated HsCRP levels, which show high prevalence of inflammation. Inflammation per se is a predictor of morbidity, mortality and low quality of life [9]. IL-6 and HsCRP levels were incrementally increased across increasing MIS tertiles and significant positive correlation with MIS, HsCRP and IL-6 levels were observed. The correlation of MIS with HsCRP and IL-6 suggests the utilization of MIS as a marker of inflammatory condition in pre-dialysis CKD patients, alternative to HsCRP and IL-6, which are not analyzed regularly in the day-to-day clinical practice due to their increased cost. Rambod et al. [21] reported similar observation in hemodialysis patients in which MIS showed superiority in assessing mortality risk when compared to HsCRP and Interleukin 6.

Table 6
Hazard Ratio for mortality of pre-dialysis CKD patients according to multivariate Cox Proportional hazards model.

Variables	Model (Follow-up 36 months) HR (95% CI)	p
MIS	1.137 (1.025–1.262)	0.015
Blood Urea Nitrogen	0.969 (0.405–2.317)	0.944
Creatinine	1.476 (0.607–3.589)	0.390
IL-6	1.223 (0.827–1.805)	0.310
e-GFR	0.989 (0.940–941.041)	0.679
HsCRP	2.551 (1.791–793.631)	0.001

Numerous studies reported that serum albumin as a one of the trustworthy marker of nutritional status and the levels are modifiable based on nutritional management [18,19]. Chronic inflammatory state may influence serum albumin levels in CKD and ESRD patients [19]. Serum albumin found to have negative correlation with MIS in our study population. Patients with MIS at higher tertiles had significantly lower serum albumin levels. Serum albumin and HsCRP levels have significant negative correlation in our patients, which denotes patients with Inflammation will have lower serum albumin levels. Stenvinkel et al. [15] reported similar findings in their study population. Serum TIBC levels were higher among patients with better nutritional status. The most probable explanation would be iron deficiency, which in turn result in reduced iron deposit and lower levels of serum transferrin. MIS contains several important clinical markers of nutritional condition, in addition, it also contains routinely evaluated clinical laboratory markers such as serum albumin and TIBC when combined together demonstrates important relationship with nutritional status, hospitalization rates, and death rates in patients with CKD [20]. MIS is a

useful tool in detecting malnutrition and inflammation in our study population. In our study, there is a significant increase of MIS with increasing stage of CKD. These findings are in line with pervious observations on MIS among pre-dialysis CKD subjects [8].

The serum triglyceride levels were elevated among patients in our study however, it was not statistically significant. A higher level of serum triglyceride further intensifies the previously elevated cardiovascular risk in pre-dialysis CKD patients with malnutrition. Jai Prakash et al. observed significant high levels of serum triglyceride in malnourished CKD patients than non-malnourished patients [6].

The complications of poor nutrition and inflammation in chronic kidney disease includes poor life quality, depression, sleep disorder, erythropoietin resistance, increased susceptibility to infections and worsening of heart failure [13,14]. This provides a justification to include assessment of nutritional status and inflammation using MIS as part of CKD management as this study revealed the presence of malnutrition in early stages of CKD and worsens with the course of CKD. There were a few limitations in our study. The study was observational and there were smaller sample size across each group of CKD. The samples were from single centre and continuous measurements of variables were not performed during the follow-up period.

This study shows MIS is an important factor that determines mortality in pre-dialysis CKD patients during 36 and more months of follow-up time. Patients with MIS $\geq$7 have high risk of mortality and needs close monitoring. In clinical setting application of MIS has a greater utilization in pre-dialysis CKD patients. Further research with longitudinal assessment of MIS and its association with outcomes are warranted. Pre-dialysis CKD patients should be assessed for their nutritional status and inflammation using MIS regularly to prevent malnutrition and its associated complications through appropriate medical and nutritional intervention.

Conflicts of interest

The authors declare no conflict of interest.

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