Original Research

Relationship between Modified Body Mass Index and Prognosis of Renal Amyloid a Amyloidosis

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Abstract

Objectives: Overhydration occurs in nephrotic syndrome related to kidney involvement of amyloid A (AA) amyloidosis, which can cause an overestimation of body mass index (BMI). Modified BMI (mBMI, albumin×BMI) may be a better marker of nutritional status; therefore, we investigated the relationship between mBMI and the prognosis of patients with renal AA amyloidosis.

Methods: We retrospectively reviewed the data of patients with biopsy-proven renal AA amyloidosis who were followed up between January 2001 and May 2013. Data regarding baseline characteristics, etiology of amyloidosis, dialysis, and mortality were recorded. Patients were divided into two groups according to median mBMI (group 1, n=60 and group 2, n=61).

Results: The median age and follow-up period of the cohort (M/F 37/84) were 43 (19) years and 26 (56) months, respectively. Familial Mediterranean fever (37.2%) and tuberculosis (24.8%) were the most common etiologies. The baseline serum creatinine and albumin and proteinuria levels were 1.3 (2.2) mg/dL, 2.6 (1.5) g/dL, and 5.3 (7) g/day, respectively. The mBMIs of groups 1 and 2 were significantly different [41.5 (15.6) vs. 74.2 (21.8) g.kg/m², p =< 0.001]. Group 1 patients had shorter time to dialysis (13.9±20.8 vs. 25.7±28.1 months, p=0.040) and higher mortality (50% vs. 32.7%, p=0.041), whereas the rates of dialysis inception were similar. The area under the curve for mBMI as a predictor of mortality was larger than that for serum albumin and BMI in ROC analysis.

Conclusion: Lower mBMI has been associated with worse prognosis in renal AA amyloidosis. As an anthropometric measure of nutritional status, mBMI may be a better marker in patients with hypoalbuminemia.

Keywords: Amyloidosis; chronic renal failure; mortality.

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Amyloidosis is a group of diseases characterized by the accumulation of amorphous proteins called as amyloids in the extracellular space as insoluble beta layers and the resultant development of organ dysfunction.[1] Dependent on the type of the amyloid material, and thus on the etiology of the disease, currently, many types of amyloidosis have been defined; the most prevalent ones encountered among them are primary amyloidosis and amyloid A (AA) amyloidosis.[2] AA amyloidosis is assumed to develop due to continuous hepatic secretion of an acute phase re-

actant, serum amyloid A protein. Kidneys and the reticuloendothelial system are the most frequently involved organs. Renal involvement is mostly seen as the first finding for the diagnosis of AA amyloidosis, and it is also a worse prognostic factor as for the patient's survival.[3]

Apart from various metabolic problems arising from renal dysfunction, chronic renal failure (CRF) impairs the quality of life and induces critically important increases in mortality rates due to cardiovascular causes and infection.[4] Nutritional status is thought to play an important role in CRF-re-

lated morbidity and mortality.[5] Although body mass index (BMI) is not an ideal marker of nutritional status, it has been widely used as a parameter over the years.[6] In hypoalbuminemia-related diseases developed in association with chronic inflammation, proteinuria, and gastrointestinal involvement, body weight, which is a component of BMI, may be detected at unrealistically higher levels due to decreased oncotic pressure. Accordingly, when body weight is used as a marker of nutrition, it may yield inconsistent results in the prediction of a relationship between BMI and the prognosis of renal amyloidosis. Modified BMI (mBMI), which is calculated by multiplying the serum albumin levels by BMI, has been suggested as a potential compensation for erroneous estimates due to fluid retention. In this study, we aimed to investigate the correlation between the prognosis of the patients who developed CRF due to AA amyloidosis and mBMI.

Methods

We retrospectively reviewed the data of patients with biopsy-proven renal AA amyloidosis who were followed up at the nephrology clinic between January 2001 and May 2013. All patients included in the analysis underwent renal biopsies, and histopathological analyses established the diagnosis of AA amyloidosis. Cases of other types of amyloidosis were excluded. From the patients' follow-up files and hospital records, demographic data including clinical, laboratory, and follow-up data were retrieved. The patients who came for the control visit at least once after the establishment of the diagnosis of amyloidosis were included.

When investigated for the etiology of AA amyloidosis, the criteria published by Livneh et al.[7] for the diagnosis of Familial Mediterranean fever (FMF) were considered. Other etiological factors were determined after re-examination of the patient files. MDRD -4 formula was used to calculate creatinine clearance, and the stages of renal failure were determined according to the K/DOQI-NKF guidelines.[8, 9]

During the first admission of the patients, BMI was calculated as the body weight in kilograms divided by the square of the height in meters and mBMI was calculated by multiplying the serum albumin level (gr/dl) with BMI. The patients were divided into the following two groups: group 1 (n=60), mBMI <57.3 kg/m^2 and group 2, mBMI ≥57.3 kg/m^2.

Since it is a retrospective analysis and the personal ID of the patients was kept secret, the approval of an Ethics Committee was not obtained. The study was performed in compliance with the principles of Declaration of Helsinki.

Statistical Analysis

Data with normal distribution were expressed as mean± standard deviation and those without normal distribution were given as median±interquartile range (IQR). For the comparison of parametric variables and nonparametric variables, Student t test and Mann–Whitney U test were used, respectively. For the comparison of categorical variables, the chi-square test was used. For the predictors of survival, Cox proportional hazards model and linear analysis (Enter model) were used. For renal and patient survival analysis, Kaplan–Meier curves and log rank (Mantel–Cox) tests were used. The ROC curve was used to calculate the predictive values of mBMI for mortality. P<0.05 was considered as statistically significant. For analyses, SPSS 20.0 software (SPSS Inc., Chicago, USA) was used.

Results

The median age and follow-up period of 121 patients (F/M: 37/84) were 43 (19) years and 26 (56) months, respectively (Table 1). As etiological factors for AA amyloidosis, FMF (n=45) and tuberculosis (n=30) were most frequently detected. The median creatinine, eGFR, serum albumin, and urine protein levels were detected as 1.3 (2.2) mg/dl, 60.3 (79.7) ml/min/1.73m^2, 2.6 (1.5) gr/dl, and 5.3 (7) gr/d, respectively. Any intergroup difference was not observed with respect to the distribution of age, sex, body weight, BMI, etiological factors, and serum urea and creatinine levels. However, the follow-up period, mBMI, and serum albumin levels were significantly higher in group 2.

Survival Analysis

The frequency of development of renal failure requiring dialysis till the end of follow-up period was not different between the groups. However, the time elapsed till dialysis and renal and patient survival times were shorter and the mortality rate was higher in group 1 than in group 2 (Table 2). Kaplan–Meier survival graphics outlined the renal and patient survival rates between the groups (Figs. 1, 2). In multivariate survival and linear regression analysis, we observed that mBMI could significantly predict mortality; however, except for the time to dialysis, other factors could not significantly predict mortality (Tables 3, 4).

In the analysis of correlation between mortality and mBMI using ROC analysis, when the area under curve (AUC) was 0.667 (p=0.002) and the threshold value for mBMI was accepted as 45.7, then the negative and positive predictive values for mortality were determined as 0.607 and 0.689, respectively (Fig. 3). When BMI, serum albumin, and mBMI were compared with respect to their correlations with mortality using ROC analysis, the AUC of mBMI was larger than that of the other two parameters (Fig. 4).

Table 1. Basic characteristics of the patients

	All patients (n=121)	Group 1 (n=60)	Group 2 (n=61)	P
Demographic characteristics				
Age (years)	43 (19)	42 (18)	44 (22)	0.654
Sex (F/M)	37/84	15/45	22/39	0.187
Follow-up (months)	26 (56)	15 (33)	35 (59)	0.001
Body weight (kg)	62 (15)	60.4 (16)	62 (14)	0.323
Body mass index (kg/m^2)	21.9 (3.2)	21.4 (3.9)	22.2 (2.5)	0.065
mBMI	57.3 (32.9)	41.5 (15.6)	74.2 (21.8)	<0.001
Etiologic factors of amyloidosis (n)				
AAA	45	19	26	0.402
Tuberculosis	30	19	11	
Bronchiectasis	8	3	5	
Inflammatory bowel disease	4	1	3	
Romatologic	10	6	4	
Unknown	24	12	12	
Laboratory				
BUN (mg/dL)	44 (60)	40.5 (46)	55 (72)	0.420
Creatinine (mg/dL)	1.3 (2.2)	1.28 (2.7)	1.56 (2)	0.699
eGFR (ml/min)	60.3 (79.7)	66.7 (87.9)	57.9 (77.3)	0.701
Hemoglobin (g/dl)	12 (3)	12.2 (3)	12 (3)	0.215
Uric acid (mmol/L)	5.9 (2.2)	5.5 (2.3)	6.2 (2.3)	<0.001
Sodium (mmol/l)	139 (4)	139 (3.9)	139 (4)	0.416
Potassium (meq/L)	4.5 (1)	4.4 (1)	4.5 (1)	0.099
Albumin (g/dl)	2.6 (1.5)	1.9 (0.7)	3.4 (1.1)	<0.001
Calcium (mg/dL)	8.5 (1.3)	8.2 (1.3)	8.8 (1.1)	<0.001
Phosphorus (mg/dL)	4.5 (1.5)	4.6 (1.4)	4.4 (1.7)	0.324
Intact PTH (pg/ml)	75 (101)	73.5 (81)	78 (141)	0.866
Total cholesterol (mmol/L)	233 (146)	295.5 (162)	200 (100)	<0.001
LDL (mmol/L)	145 (117)	179 (150)	124 (76)	<0.001
Triglyceride (mmol/L)	180 (170)	250 (216)	136 (105)	<0.001
Ferritin (ng/ml)	105 (180)	151 (234)	63 (130)	0.003
Proteinuria (gr/24 h)	5.3 (7)	7.1 (8)	3.7 (6)	<0.001

Table 2. Comparison between patient and renal survivals according to mBMI groups

	Group 1 (n=60)	Group 2 (n=61)	P
Requirement for dialysis (n, %)	35 (58%)	33 (54%)	0.639
Time to dialysis (months)	13.9±20.8	25.7±28.1	0.040
Renal survival (months)	49.2±7.4	75.1±8.9	0.027
Mortality (n, %)	30 (50%)	20 (32.7%)	0.041
Patient survival (months)	58.9±9.1	106.9±10.4	0.003

Data were presented as mean±SD. mBMI, modified body mass index.

Discussion

The correlation between survival and nutritional status in patients with CRF demonstrates marked differences when compared with the general population. In a population generally accepted as healthy, a J-shaped relationship was observed between BMI and mortality (in other words, the risk of mortality increases below and above the range of 22.5–24.9). Besides, it has been demonstrated that protein-energy loss and inflammation are important predictors of mortality; in cases with CRF, heart failure, cirrhosis, chronic pulmonary disease, and cancer, survival times prolong in line with increase in BMI.[10, 11] This relationship between obesity and survival has been called as "obesity paradox." Although obesity is known as an important risk factor for

Table 3. Multivariate survival analysis of the predictors of mortality (Cox proportional hazards model)

Predictors of mortality	Beta	Odds ratio	95 % Confidence Interval		P
			Lower	Upper	
Age (years)	0.004	1.004	0.980	1.028	0.757
Time to dialysis (months)	-0.027	0.974	0.958	0.990	0.002
Serum albumin (g/dl)	0.324	1.382	0.458	4.171	0.566
eGFR (ml/min)	-0.009	0.991	0.973	1.009	0.308
Serum creatinine (mg/dl)	-0.098	0.907	0.775	1.060	0.220
Proteinuria (g/24 h)	-0.027	0.974	0.918	1.033	0.381
mBMI	-0.018	0.983	0.966	0.999	0.040

mBMI, Modified body mass index.

Table 4. Linear regression analysis of mBMI as a predictor of mortality (Enter method)

Predictor	Beta	p	95% Confidence interval	
			Lower	Upper
Constant	0.788	<0.001	0.564	1.012
mBMI	-0.006	<0.001	-0.010	-0.003

CRF and end-stage renal failure, it has not been fully understood how higher BMI values demonstrate protective effect in patients who developed CRF during and before dialysis.[12-14] However, the possible roles played by obesity-related hemodynamic stability, defense against endotoxins in circulation provided by lipoproteins, protective cytokine profile, retention of toxins by fat mass, and antioxidation provided by muscle mass have been suggested within this context.[11]

In the MEDLINE database, a study investigating the correlation between the nutritional status of patients with AA amyloidosis and prognosis could not be found. Since AA amyloidosis is a systemic and progressive disease and different from CRF cases related to other etiologies, it may induce more severe malnutrition because of the development of malabsorption syndrome due to involvement of gastrointestinal system or occurrence of restrictive cardiomyopathy secondary to cardiac involvement. Besides, since AA amyloidosis develops secondary to uncontrolled systemic inflammation and malnutrition-inflammation complex is a robust predictor of mortality, there might be a
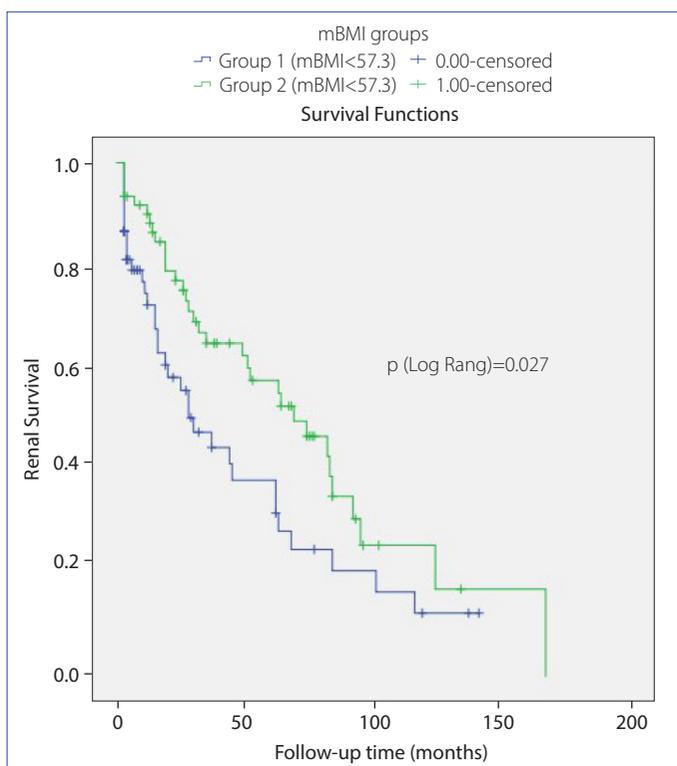

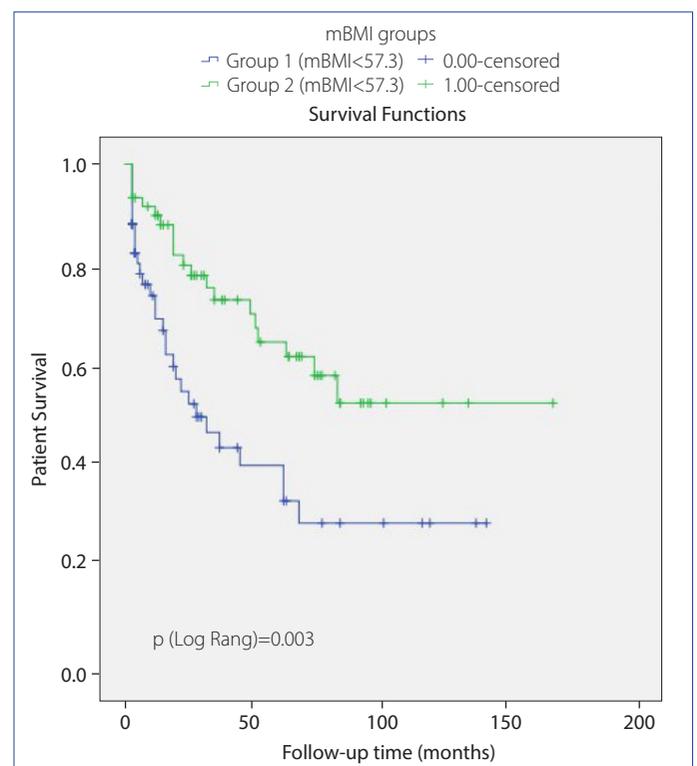**Figure 1.** Renal survival curve of mBMI according to groups.

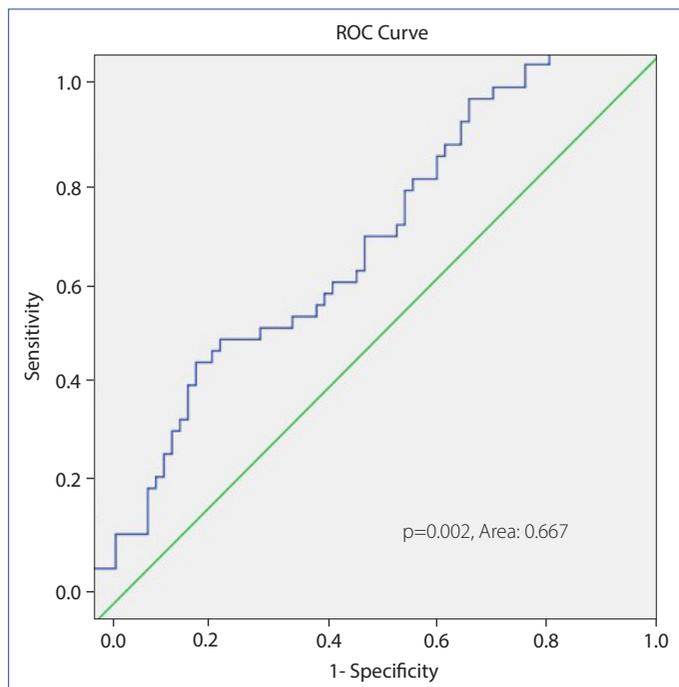**Figure 2.** Patient survival curve of mBMI according to groups.

Figure 3. ROC analysis of the correlation between mBMI and mortality.
For the cutoff value of 45.71, sensitivity, 50%; specificity, 77.5%; positive odds ratio, 2.222, negative odds ratio, 0.645; positive predictive value, 0.689; negative predictive value, 0.607.

Figure 4. ROC analysis comparing the correlation between BMI, albumin, and mBMI with mortality.
AUC (area under curve) values (95% Confidence Interval, p value) of BMI, albumin, and mBMI were 0.617 (0.512–0.722, p=0.029), 0.643 (0.545–0.742, p=0.007), and 0.667 (0.571–0.763, p=0.002,) respectively.

relationship between malnutrition and survival in patients with AA amyloidosis due to the severity of amyloidosis and additional risk rendered by malnutrition.[15, 16]

In a post-transplantation survival analysis of 21 patients who had undergone orthotopic liver transplantation because of familial amyloidotic polyneuropathy secondary to transthyretin mutation, a significant correlation was not detected between pretransplant BMI and mortality, whereas statistically significantly lower rates of mortality were reported in patients with higher mBMI.[17] The authors indicated that instead of renal involvement, which is frequently seen in cases with AA amyloidosis, cardiac and gastrointestinal disorders and peripheral nerve damage had developed in this study population.[17] The predictive factors of survival were examined in patients in the waiting list of cardiac transplantation because of end-stage heart failure due to AL type amyloidosis; a correlation between only lower BMI values and lower survival rates was demonstrated.[18] In another study where 128 patients with AL amyloidosis were examined with respect to the relationship between malnutrition and survival, the investigators reported that independent from the stage of cardiac involvement and hematological response, patients with BMI <22 kg/m^2 had nearly two times increased rates of mortality.[19] Findings detected in these studies tend to support the argument that malnutrition developed in cases of chronic diseases may contribute to mortality or at least it may be an important
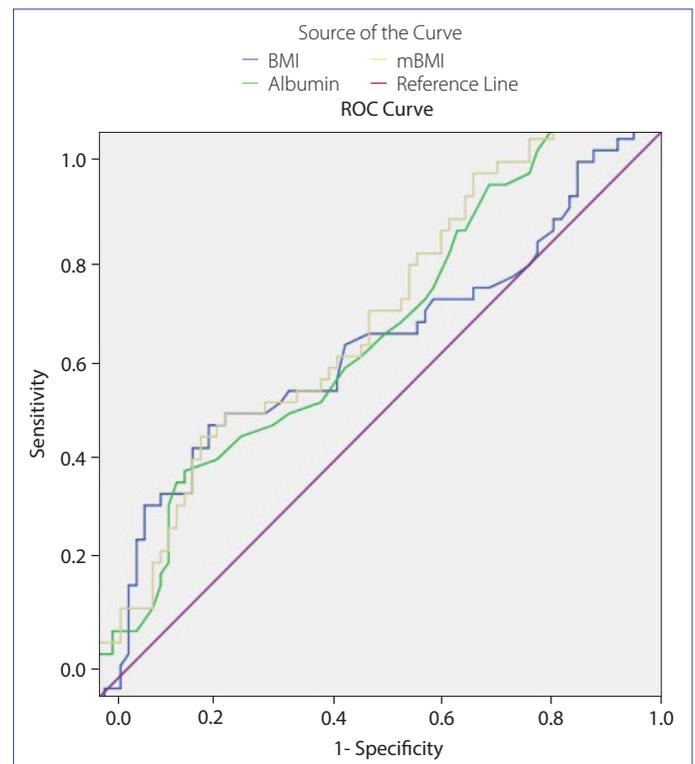
predictor of mortality. However, contrary to our study, amyloidotic involvement is related mostly to extrarenal organs.

In our study, a negative correlation was detected between mBMI, as a marker of malnutrition, and mortality; although a similar patient population has not been analyzed hitherto, comparable results have been obtained in studies performed in cases with amyloidosis with different etiologies. As a marker of nutritional status, mBKİ has been recognized as an important mortality predictor of malnutrition in patients with CRF associated with AA amyloidosis. Besides, contrary to solely serum albumin level or BMI, available evidence suggests that mBMI may reflect the nutritional status more accurately. Despite its retrospective design, first, in this study, the relationship between the group of patients with AA amyloidosis and survival was investigated.

The retrospective design of the study, limited number of study patients, and inability to investigate other parameters related to nutritional status are the limitations of our study.

Conclusion

AA amyloidosis with renal involvement has higher morbidity and mortality. The correlation between nutritional status and prognosis was also observed in patients with CRF

associated with AA amyloidosis, as in patients with CRF associated with other etiologies. However, mBMI, instead of BMI, has been considered to be a more helpful parameter as a marker of nutritional status in AA amyloidosis associated with proteinuric renal failure.

Disclosures

Ethics Committee Approval: The study was approved by the Local Ethics Committee.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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