THE VALUE OF MALNUTRITION – INFLAMMATION – ATHEROSCLEROSIS (MIA) SYNDROME FOR PREDICTION OF CARDIOVASCULAR EVENTS IN PATIENTS WITH END-STAGE RENAL DISEASE

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Abstract

Background: Mortality resulting from cardiovascular disease in patients with end-stage renal disease (ESRD) is high. In this study we studied characteristics of the malnutrition, inflammation, atherosclerosis (MIA) syndrome; clinical value syndrome for prediction of cardiovascular events in patients with ESRD. ***Subjects and methods:*** A total of 174 patients without infection (include: 57 predialysis patients, 56 continuous ambulatory peritoneal dialysis patients, 61 hemodialysis patients) were enrolled. Inflammatory markers (hs-CRP) and nutritional parameter (SGA) were determined. Carotid atherosclerosis was investigated by ultrasonographically evaluated carotid intima-media thickness (cIMT). CVD events (heart failure, cerebrovascular disease, coronary heart disease, hypertensive crisis) were evaluated during 12 months of follow-up. ***Results:*** (1) The characteristics of the malnutrition, inflammation, atherosclerosis (MIA) syndrome in patients with ESRD*:* (i) MIA2-3 group had an average systolic blood pressure higher than MIA0 and MIA1 group; (ii) MIA2-3 group had higher hs-CRP, IL-6 levels and lower serum albumin levels; (iii) MIA2-3 group had the prevalence of malnutrition and atherosclerosis higher than MIA1 group; 5.7% of the patients had all three risk factors. No signs of either malnutrition, inflammation or atherosclerosis were seen in 17.2% of patients. (2) Value of MIA syndrome for prediction of *cardiovascular events* in patients with ESRD during 12 months of follow-up: The HR for patients with M (malnutrition) and A (Atherosclerosis) was 2.47 (95% CI: 1.52 – 4.03; p = 0.001) and 1.77 (95% CI: 1.10 – 2.83; p = 0.02). The HR for patients with 2 or more elements in MIA syndrome was 1.54 (95% CI: 1.06-2.26; p = 0.03). ***Conclusion****:* Malnutrition, inflammation and atherosclerosis appear to be interrelated. The concurrent presence of malnutrition, inflammation and atherosclerosis increased the risk of *cardiovascular events in* patients with ESRD.

Keywords: Malnutrition-inflammation-atherosclerosis syndrome, MIA syndrome, end-stage renal disease

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1. BACKGROUND

Cardiovascular disease (CVD) remains the main cause of morbidity and mortality in all stages of chronic kidney disease (CKD). CVD often begins before end-stage renal disease (ESRD), and patients with reduced kidney function are more likely to die of CVD than to develop ESRD. The annual mortality rate due to CVD is about 9%, which is 10- to 20-fold higher than in the general population, even when adjusted for age, gender, race and diabetes mellitus [9]. Classic risk factors such as dyslipidaemia, hypertension and smoking are prevalent in many patients with ESRD, but studies have shown that excess CVD is not explained adequately by traditional risk factors. The inflammation plays a key role in the relationship between malnutrition, inflammation and atherosclerosis in ESRD. A strong association between malnutrition, inflammation and atherosclerosis in these patients suggests a syndrome called syndrome of malnutrition - inflammation - atherosclerosis (MIA syndrome) which related to rate high mortality [10]. In the study presented here, we studied characteristics of MIA syndrome and clinical value of MIA syndrome for prediction of cardiovascular events in patients with ESRD over a period of 12 months.

2. SUBJECTS AND METHODS

2.1. Subjects

A total of 174 patients without infection included: 57 predialysis patients, 56 continuous ambulatory peritoneal dialysis patients, 61 hemodialysis patients. These patients were treated at the department of nephrology and rheumatology and the department of dialysis, Hue central hospital, between 12/2013 and 10/2015.

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2.1.1. Patient selection criteria

2.1.1.1. Predialysis patients:

- Patients with ESRD due to chronic glomerulonephritis and chronic pyelonephritis.

- Patients ever receiving renal replacement therapy.

- Patients who not use the infusion of albumin, amino acids at least 1 month before selecting patients for testing; No signs of inflammation, infection; WBC count <10 K/uL.

- Age ≥ 18 years; agreed to participate in the study.

- No exclusion criteria.

2.1.1.2. Continuous ambulatory peritoneal dialysis patients

- Patients with ESRD who had been receiving CAPD for at least 2 months and all subjects were stable.

- Patients with ESRD due to chronic glomerulonephritis and chronic pyelonephritis.

- Do not use the infusion of albumin, amino acids at least 1 month before selecting patients for testing; No signs of inflammation, infection; WBC count <10 K/uL; Not being in a state of peritonitis, an infection of tube feet; Had not been transplanted.

- Age ≥ 18 years; agreed to participate in the study.

2.1.1.3. Hemodialysis patients

- Patients with ESRD who had been receiving hemodialysis for at least 2 months and all subjects were stable.

- Patients with ESRD due to chronic glomerulonephritis and chronic pyelonephritis.

- Do not use the infusion of albumin, amino acids at least 1 month before selecting patients for testing; No signs of inflammation, infection; WBC count <10 K/uL; None of these patients developed vein-graft occlusion. Had not been transplanted.

- Age ≥ 18 years; agreed to participate in the study.

2.1.2. Exclusion criteria

- Patients with edema; ascites detected by clinical examination; Accompanied by one of the following diseases: malignant disease, chronic lung disease, cirrhosis; Patients with autoimmune diseases who had been receiving immunosuppressant drugs; Acute exacerbation of chronic kidney failure; Surgical intervention within 1 month before selecting patients for testing.

2.2. Methods

This is a prospective observational cohort study, cardiovascular events was evaluated at a 12-months follow-up.

Diagnostic criteria MIA syndrome: M (Malnutrition) was measured with the 7-point SGA (malnutrition: the majority of the items SGA≤5) [8]. I (Inflammation) was measured with hs-CRP (>5mg/l) [5]. A (Atherosclerosis): was investigated by carotid intima-media thickness (cIMT≥ 0.9 mm and/or presence of plaque) [4].

The patients were classified into 4 groups: MIA0, MIA1, MIA2, MIA3. CVD events were evaluated include: heart failure, cerebrovascular disease, coronary heart disease, hypertensive crisis.

Dyslipidemia: was measured with AACE guidelines 2012 [1].

The others parameters: age, sex, blood pressure, albumin, prealbumin, interleukin 6 (IL-6), hemoglobin (Hb).

Venous blood samples were taken in the morning after an overnight fast, before dialysis.

Data processing with SPSS 22.0.

3. RESULTS

Table 1. The characteristics of MIA syndrome in patients with ESRD

MIA syndrome Characteristics		MIA0 (N=30) (a)	MIA1 (N=73) (b)	MIA2-3 (N=71) (c) (a)&(b)	p		
					(b)&(c)	(a)&(c)	
Age (years)	X±SD	46.73±14.73	47.44±14.93	49.38±15.55	>0.05	>0.05	>0.05
Sex (male)	n (%)	16 (53.3)	30 (41.1)	37 (52.1)	>0.05	>0.05	>0.05
Systolic blood pressure (mmHg)	X±SD	137.67±15.47	141.92±16.13	148.31±19.27	>0.05	**<0.05**	**<0.05**
Diastolic blood pressure (mmHg)	X±SD	82.33±7.74	83.84±9.07	85.78±10.37	>0.05	>0.05	>0.05
SGA≤ 5	n (%)	-	28 (32,6)	58 (67,4)	-	**<0,001**	-
Albumin (g/l)	X±SD	38.19±4.60	37.15±4.41	35.77±4.92	>0.05	>0.05	**<0.05**
Prealbumin (g/l)	X±SD	0.32±0.10	0.33±0.10	0.30±0.09	>0.05	>0.05	>0.05

hs-CRP (mg/l)	median (25^{th};75^{th})	1.88 (1.23-3.24)	1,56 (0.61-4.18)	4.80 (1.04-11.40)	>0.05	**<0.01**	**<0.01**
IL-6 (pg/ml)	median (25^{th};75^{th})	4.85 (3.15-22.75)	7.60 (4.76-37.25)	17.10 (6.50-111.00)	>0.05	**<0.05**	**<0.01**
Presence of atherosclerosis	n (%)	-	29 (33)	59 (67)		**<0,001**	-
CT (mmol/l)	X±SD	5.07±1.28	5.04±1.27	5.11±1.55	>0.05	>0.05	>0.05
TG (mmol/l)	X±SD	2.20±1.25	2.07±1.14	2.06±1.43	>0.05	>0.05	>0.05
HDL-C (mmol/l)	X±SD	1.10±0.37	1.12±0.40	1.19±0.38	>0.05	>0.05	>0.05
LDL-C (mmol/l)	X±SD	3.02±1.15	2.99±1.08	3.03±1.15	>0.05	>0.05	>0.05
Hb (g/dl)	X±SD	10.32±1.91	10.02±1.77	9.70±1.91	>0.05	>0.05	>0.05

- MIA2-3 group had an average systolic blood pressure higher than MIA0 and MIA1 group.
- MIA2-3 group had higher hs-CRP, IL-6 levels and lower serum albumin levels.
- MIA2-3 group had the prevalence of malnutrition and atherosclerosis higher than MIA1 group (p<0,05).

Table 2. MIA syndrome is associated with cardiovascular events

MIA group	MIA0(N=30) (a)		MIA1 (N=73) (b)		MIA2-3(N=71) (c)		p		
Cardiovascular events	n	%	n	%	n	%	(a)&(b)	(b)&(c)	(c)&(a)
No	22	73.7	47	64.4	31	43.7	>0.05	>0.05	**<0.05**
Yes	8	26.7	26	35.6	40	56.3			

- MIA2-3 group had the prevalence of cardiovascular events higher than MIA0 group (56.3% vs. 26.7%, p<0.05).

Table 3. The relationship between components of MIA syndrome and other factors with cardiovascular events.

Parameters \ Cardiovascular events		No (N = 100)	Yes (N = 74)
SGA≤5	n (%)	36 (36.0)	50 (67.6)
	p	**<0,001**	
hs-CRP > 5,0 (mg/l)	n (%)	34 (34.0)	17 (23.0)
	p	>0.05	
Presence of atherosclerosis	n (%)	42 (42.0)	46 (62.2)
	p	**<0,01**	
Age (years)	X±SD	47.98±15.12	48.28±15.18
	p	>0.05	
Sex (male)	n (%)	51(51.0)	32 (43.2)
	p	>0.05	
Presence of anemia	n (%)	89 (89.0)	69 (93.2)
	p	>0.05	
Presence of hypertension	n (%)	72 (72.0)	59 (79.7)
	p	>0.05	

CT ≥ 5,2 (mmol/l)	n (%)	47 (47.0)	31 (41.9)
	p	>0,05	
TG ≥ 1,7 (mmol/l)	n (%)	55 (55,0)	36 (48,6)
	p	>0.05	
LDL-C ≥ 3,4 (mmol/l)	n (%)	37 (37.0)	22 (29.7)
	p	>0.05	
HDL-C (mmol/l) Male: ≤1,01; Female: ≤1,3	n (%)	56 (56.0)	42 (56.8)
	p	>0.05	
Albumin (g/l)	X±SD	37.04±4.86	36.40±4.53
	p	>0.05	
Prealbumin (g/l)	X±SD	0.32±0.92	0.31±0.11
	p	>0.05	
IL-6 (pg/ml)	median (25^{th};75^{th})	10.40 (4.31-52.48)	10.85 (5.35-38.03)
	p	>0.05	

- There is a relationship between malnutrition and atherosclerosis with cardiovascular events.

Table 4. Relative risks of cardiovascular events [hazard ratio (HR) with 95% confidence interval] associated with the presence of factors in MIA syndrome during 12 months of follow-up

Factors	HR	KTC 95%	p
M M0 M1	 1 2.47	 1.52 – 4.03	 **0.001**
A A0 A1	 1 1.77	 1.10 – 2.83	 **0.02**

The HR for patients with M (malnutrition) and A (Atherosclerosis) was 2.47 (95% CI: 1.52 – 4.03; p = 0.001) and 1.77 (95% CI: 1.10 – 2.83; p = 0.02).

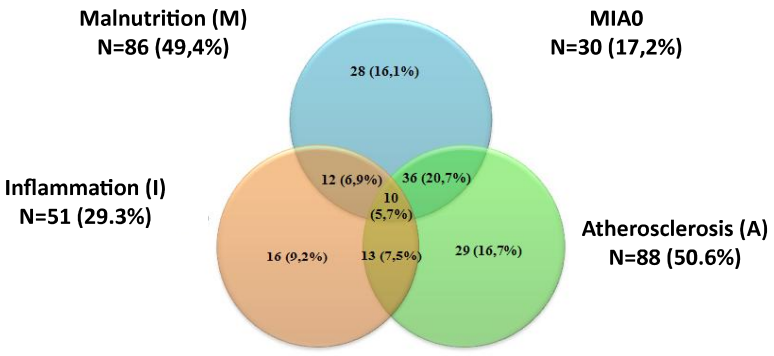

Figure 1. The presence of malnutrition, inflammation and atherosclerosis, as well as all possible combinations

The overlap of the presence of the three factors in MIA syndrome is shown in Figure 1. Of all patients at baseline: 17.2% had no risk factor; 16,1% suffered from malnutrition only; 9.2% suffered from inflammation only; 16.7% had only atherosclerosis and 35.1% of the patients had any combination of two risk factors; 5.7% of the patients had all three risk factors.

Table 5. Relative risks of cardiovascular events [hazard ratio (HR) with 95% confidence interval] associated with the presence of MIA syndrome during 12 months of follow-up

MIA syndrome	HR	KTC 95%	p
MIA0	1		
MIA1	1.39	0.63-3.07	0.41
MIA2-3	1.54	1.06-2.26	**0.03**

The HR for patients with 2 or more elements in MIA syndrome was 1.54 (95% CI: 1.06-2.26; p = 0.03).

Table 6. Binary logistic regression analysis with calculated cardiovascular events as dependent variable

Factors	B	p	OR (95%CI)
M	1.294	**< 0.001**	3.647 (1.901 – 6.995)
I	-0.433	> 0.05	0.649 (0.314 – 1.341)
A	0.806	**< 0.05**	2.238 (1.168 – 4.290)
Constant	-1.270		

The risk of cardiovascular events = 1,294 x M + 0,806 x A - 1,270

4. DISCUSSION

4.1. The characteristics of MIA syndrome in patients with ESRD

In this study, the patients with 2 or more elements in MIA syndrome had many unfavorable factors such as: (1) higher prevalence of malnutrition; (2) higher values of systolic blood pressure; (3) higher hs-CRP, IL-6 levels and lower serum albumin levels; (4) higher prevalence of atherosclerosis. These factors will contribute to an increased risk of morbidity and mortality resulting from cardiovascular disease by the following reasons:

- Malnutrition and hypoalbuminemia have been shown to be important predictors of mortality and hospitalization in patients with CRF (chronic renal failure). In a prospective, longitudinal, observational, multicenter study of incident dialysis patients (Netherlands Cooperative Study on the Adequacy of Dialysis-2 (NECOSAD-II) Study), the 7-point SGA was assessed 3 and 6 months after the start of dialysis and subsequently every 6 months during 7 years of follow-up. Results of study showed that: malnutrition at baseline assessed with SGA was associated with a 2-fold increased mortality risk in 7 years of follow-up. Time-dependently, this association was even stronger, which indicated that malnutrition was associated with a remarkably high risk of short-term mortality [8]. In the study of Stenvinkel P et al. (1999), malnourished CRF patients presented several clinical and biochemical features that could be speculated to increase the risk of accelerated atherosclerosis: higher age, increased prevalence of cigarette smoking, elevated plasma Lp(a) levels, and lower levels of the antioxidant vitamin E [10].

- Uncontrolled high blood pressure is a risk factor of developing ESRD, contribute to an increased risk of morbidity and mortality resulting from cardiovascular disease in this patient group.

- The increased levels of inflammatory markers in patients MIA2-3 partly reflect greater inflammation in these subjects. Meanwhile, inflammation may be associated closely with malnutrition, participate in the process of atherosclerosis and promote progression of atherosclerosis in patients with ESRD.

n this study, we also find the overlap of the presence of the three factors in MIA syndrome. Previously, Stenvinkel P et al. (1999) showed that: the prevalence of malnutrition (44%), inflammation (32%), and carotid plaques (72%) in their predialysis patient population. No signs of either malnutrition, inflammation, or carotid plaques were seen in 24 (22%) of the CRF patients. A considerable portion of CRF patients with carotid plaques had signs of either malnutrition (24%), inflammation (13%), or both (30%). Note that a vast majority of patients with inflammation and malnutrition (97% and 89%,

respectively) had carotid plaques [10]. In the study of Renee de Mutsert et al. (2008): of all patients at baseline, 38% had no risk factor, 10% suffered from malnutrition only, 11% suffered from inflammation only, 14% had only cardiovascular diseases and 22% of the patients had any combination of two risk factors. Only in 6% of the patients were all three risk factors concurrently present [7] .

4.2. Clinical value of MIA syndrome measured as cardiovascular events over a period of 12 months.

In this study, we demonstrate that malnutrition and atherosclerosis are independent predictors of cardiovascular events in patients with ESRD. But we can not demonstrate inflammation (hs-CRP>5mg/l) as an independent predictor factor of cardiovascular events. Elevated levels of CRP and other inflammatory markers have been linked to the increased cardiovascular risk, morbidity, and mortality in dialysis patients [2], [12]. CRP has been reported to be an important predictor of mortality in hemodialysis patients. One of the possible explanations for the discrepancy with these studies is the definition used for cardiovascular events (cases of hospitalisation resulting from cardiovascular diseases). In addition, hs-CRP levels were measured only once at baseline, so it can not represent chronic inflammation.

One of the major findings of this study is that if patients with 2 or more elements, the risk of cardiovascular events during follow-up period of 12 months will increase (HR: 1.54 (95% CI: 1.06 to 2.26; p = 0.03).

The study in the hemodialysis patients of Qureshi AR et al. (2002) showed that the mortality at 36 months was 0% when none of these complications was present, whereas the mortality was 75% in those patients with all three risk factors present at baseline [6].

Another study of Renee de Mutsert et al. (2008) in dialysis patients: patients with either malnutrition (HR: 1.6; 95% CI: 1.3–2.0), inflammation (HR: 1.6; 95% CI: 1.3–2.0) or cardiovascular diseases (CVD) (HR:1.7; 95% CI: 1.4–2.1) had an increased mortality risk. In patients with all three risk factors, the crude mortality rate of 45/100 person-years was 16 deaths/100 person-years higher than expected from the addition of the solo effects of malnutrition, inflammation and CVD. The relative excess risk due to interaction was 2.9 (95% CI: 0.3–5.4), implying additive interaction. After adjustment for age, sex, treatment modality, primary kidney diseases, diabetes and malignancy the HR for patients with all three risk factors was 4.8 (95% CI: 3.2–7.2).

Stenvinkel P et al. has found strong relationships between malnutrition, elevated CRP levels, and the prevalence of CVD in patients starting peritoneal dialysis. In addition, they also demonstrated that decreased survival time is associated with an increase of components of the MIA syndrome [11].

In determining an interaction effect, the present study aimed to translate epidemiological observations into evidence for the existence of a syndrome, where the whole is more than its parts. Several theories have been proposed to explain the supposed links between malnutrition, inflammation and CVD, but the pathophysiological mechanisms involved remain unclear. Inflammation, mediated by proinflammatory cytokines, may predispose to both malnutrition and CVD in ESRD. Cytokines have been shown to mediate proteolysis in muscle, to upregulate basal metabolic rate and to inhibit appetite and food intake [3]. Atherosclerosis has been recognized to be an inflammatory disease. Finally, malnutrition may aggravate existing inflammation and accelerate atherosclerosis. In summary, these epidemiological data support the presence of an interaction effect between malnutrition, inflammation and CVD, resulting in excess mortality in patients with ESRD.

5. CONCLUSION

Malnutrition, inflammation and atherosclerosis appear to be interrelated. The concurrent presence of malnutrition, inflammation and atherosclerosis increased the risk of cardiovascular events in patients with ESRD.

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