

## Original Article

# The correlation of death with malnutrition and micro-inflammation in maintenance hemodialysis patients

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**Abstract:** Objective: To investigate the correlation of death with malnutrition and micro-inflammatory responses in maintenance hemodialysis (MHD) patients. Methods: A total of 216 MHD outpatients were enrolled as research objects whose data were retrospectively studied. Their modified quantitative subjective global assessment (MQSGA) scores and their Malnutrition-Inflammation scores (MIS) were calculated. Their anthropometric indices were recorded. Their biochemical and micro-inflammatory indicators [tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), hypersensitive C-reactive protein (hs-CRP), and interleukin-6 (IL-6)] were also detected. The patients with micro-inflammation and malnutrition of different degrees were followed up for 1 year to observe their mortality. The nutritional indices and micro-inflammatory indicators were compared between the survival group and the death group. A COX regression analysis was performed on the independent predictors of death, and a Spearman correlation analysis was carried out. The area under the receiver operating characteristic (ROC) curve (AUC) was analyzed to evaluate the predictive efficiency of the relevant indices on death. Results: According to inclusion and exclusion criteria, 203 patients were ultimately included in this study, and 24 of them (11.82%) died one year later. There were statistically significant differences in the mortality between the patients with mild, moderate, and severe malnutrition in their MQSGA scores, MIS scores, and between the patients with and without micro-inflammatory responses ( $P < 0.05$ ). There were statistically significant differences between the survival and death groups in terms of their MQSGA scores, MIS scores, and their levels of albumin, serum creatinine (Scr), TNF- $\alpha$ , and hs-CRP ( $P < 0.05$ ). According to the COX regression analysis, the MIS and TNF- $\alpha$  levels are independent predictors of death in MHD patients ( $P < 0.05$ ). According to the Spearman correlation analysis, MIS is positively correlated with serum TNF- $\alpha$  levels in dead MHD patients ( $R^2 = 0.520$ ,  $P = 0.001$ ). The AUC of MIS combined with the TNF- $\alpha$  level for predicting the risk of death was 0.850, significantly higher than the 0.655 of MIS and the 0.630 of the TNF- $\alpha$  levels ( $P < 0.05$ ). Conclusion: The deaths of MHD patients are correlated with malnutrition and micro-inflammation, so MIS combined with the TNF- $\alpha$  level can synergistically improve the predictive efficiency of the patients' risk of death.

**Keywords:** Maintenance hemodialysis, malnutrition, micro-inflammation, death

## Introduction

According to an epidemiological investigation, the incidence of chronic kidney disease in China is about 8%-9%, and 1% of patients with the disease will progress to uremia. With the popularization and development of hemodialysis technology in recent years, the number of patients receiving clinical maintenance hemodialysis (MHD) has increased annually by 7%, which is significantly higher than the growth rate of the world population [1]. Although MHD significantly prolongs the patients' survival time, their mortality remains high for a variety

of reasons. MHD patients generally develop malnutrition of different degrees with an incidence rate as high as 60%-80%. Mainly characterized by the consumption of the muscle groups and clinically manifested as the loss of lean body mass and the decline of body mass, malnutrition is recognized as a main reason for MHD patients' high mortality [2].

Recent studies at home and abroad suggest that a micro-inflammatory response may be a major factor that causes malnutrition in MHD patients. The studies indicate that patients have a continuously low inflammatory state

despite no obvious signs of infection, with elevated levels of serum inflammatory cytokines (hypersensitive C-reactive protein (hs-CRP), interleukin-6 (IL-6), and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ )) as the main manifestations [3]. As a sensitive indicator of the inflammatory state in the body, hs-CRP is a glycoprotein synthesized by the epithelium and liver after stimulation by IL-6 and TNF- $\alpha$ . Its slight increase indicates that the patient is in a micro-inflammatory state. A study has reported that the three cytokines significantly increase in MHD patients before treatment, which suggests that patients have a widespread micro-inflammatory state [4]. The coexistence of malnutrition and micro-inflammatory responses significantly increases the MHD patients' risk of death [5, 6]. Therefore, we analyzed the correlation of death with malnutrition and micro-inflammation in the patients to further improve the predictive efficiency of the risk of death. The modified quantitative subjective global assessment (MQSGA) is a method for the quantitative assessment of nutritional status. Compared with the traditional subjective global nutrition assessment, MQSGA prolongs the dialysis time and increases the complication assessment, with stronger repeatability and operability. This method is simple, non-invasive, requires no blood sample, and is quantitative, so it can reflect the patients' inflammation to some extent [7]. The Malnutrition-Inflammation score (MIS) increases the assessment of body mass index (BMI), plasma albumin, and total iron binding capacity (TIBC) based on the MQSGA score, making the assessment more comprehensive and scientific [8]. The MQSGA and MIS scores are widely used for accurately assessing the nutritional status of MHD patients [9]. There are previous studies that only use the MQSGA score to assess the nutritional status, only considering the effect of malnutrition on patient mortality, and only considering the effect of the inflammatory state on patient quality of life [10]. However, the effects of malnutrition and inflammation on patient death are still unclear. Therefore, the MQSGA and MIS scores were used to assess malnutrition in this study, and hs-CRP, IL-6, and TNF- $\alpha$  were used as micro-inflammatory indicators to explore the correlation of death with malnutrition and micro-inflammation in MHD patients, so as to improve their predictive efficiency of the risk of death.

### Information and methods

#### *General information*

Altogether 216 initially diagnosed outpatients, who underwent MHD and who were admitted to Zhuji People's Hospital of Zhejiang Province from January 2017 to January 2018, were enrolled as the study cohort. This study was approved by the Hospital Ethics Committee. The inclusion criteria were as follows: (1) the patients had a serum creatinine (Scr) level  $>707 \mu\text{mol/L}$  or an estimated glomerular filtration rate (eGFR)  $<10 \text{ mL/min}$  before treatment. (2) the patients underwent MHD using a MESALABS 90XL hemodialysis machine (USA) for more than 3 months, 2-3 times a week and 4 hours each time. (3) the patients and their families were informed of the research and signed the informed consent form, those who cooperated in treatment and follow-up. The exclusion criteria were as follows: (1) patients with severe cardiovascular and cerebrovascular diseases, malignant tumors, active hepatitis, peptic ulcers, immune diseases, or pulmonary tuberculosis; (2) patients with clinical inflammatory responses within 1 month; (3) patients treated with glucocorticoids, immunosuppressive agents, or antibiotics for a long time. According to the inclusion and exclusion criteria, the data of the included MHD patients were collected and retrospectively analyzed.

#### *Research methods*

The anthropometric indices were recorded. The MQSGA and MIS scores were calculated to evaluate nutritional status. The MQSGA scores included body mass changes, dietary changes, gastrointestinal symptoms, physiological function changes, complications, and the consumption of subcutaneous fat and muscles. Each item had 1 (normal) to 5 (severe) points [11], and the total scores ranged from 7-35 points. A high MQSGA score indicated severe malnutrition. Seven points indicated normal nutrition; 8-14 points indicated mild malnutrition; 15-21 points indicated moderate malnutrition; 22-35 points indicated severe malnutrition [12]. The MIS scores included medical history (body mass changes, dietary intake, gastrointestinal symptoms, bodily function, years of dialysis, complications), physical examinations (decline in fat reserves, muscle consumption), BMI, and

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laboratory examinations (albumin, TIBC), with 10 items total. Each item was scored from 0 (normal) to 3 (severe) points [13], and the total scores ranged from 0-30 points. A high MIS score indicated severe malnutrition. 0 indicated normal nutrition; 1-8 points indicated mild malnutrition; 9-18 points indicated moderate malnutrition; 19-30 points indicated severe malnutrition [14].

### *Clinical examinations*

The anthropometric indices were recorded, including height, body weight, BMI, biceps circumference, arm muscle circumference, and triceps skinfold thickness (TSF). On the day of dialysis, fasting elbow venous blood (3 mL) was drawn to detect the biochemical indicators (albumin, Scr, transferrin, ferritin, TIBC, hemoglobin) using an AU5800 fully-automated biochemical analyzer (Beckman Coulter, USA). An enzyme-linked immunosorbent assay (ELISA) was used to detect the levels of serum hs-CRP, IL-6, and TNF- $\alpha$ , with the method for blood collection being the same as before. The kits were purchased from the Wuhan Easy Diagnosis Biomedicine Co., Ltd. (Batch No.: 1715857), the Shanghai Kang Lang Biological Technology Co., Ltd. (Batch No.: 3682472), and the Shanghai Jimian Industry Co., Ltd. (Batch No.: 4824519), with the steps carried out in strict accordance with the kits' instructions. The patients were in a state of micro-inflammatory response if their serum hs-CRP level was higher than the upper limit of its normal level before dialysis on the next day. The detected normal range of the hs-CRP kit was 0-5 mg/L in this study, so the serum hs-CRP level >5 mg/L was defined as a state of micro-inflammatory response.

### *Follow-up observation*

The patients were followed up for 1 year by telephone, medical record review, back-to-hospital treatment, and outpatient reexaminations, to record their survival. Patient death or withdrawal from the experiment was considered as the deadline. The mortality of the patients with malnutrition and micro-inflammation of different degrees was observed. Nutritional indices and micro-inflammatory indicators were compared between the survival and death groups.

### *Data processing*

SPSS 23.0 (IBM, USA) was used to process the experimental data. The measurement data

conforming to a normal distribution and homogeneity of variance were expressed using ( $\bar{X} \pm sd$ ), and the comparisons between groups were conducted using t tests. The measurement data conforming to skewed distributions were expressed using a median (quartile interval) (M (Q1-Q3)), and the comparisons between the groups were conducted using Mann-Whitney tests. The count data were expressed by rate and analyzed using  $\chi^2$  tests. A COX regression analysis was performed on the independent predictors of death, and a Spearman correlation analysis was carried out. The area under the receiver operating characteristic (ROC) curve (AUC) was analyzed to evaluate the predictive efficiency of the relevant indices on death. MedCalc17.0 (Broekstraat 52, 9030, Mariakerke, Belgium) was used to compare the AUC between the two groups through a DeLong test. The test level was  $\alpha=0.05$ , and the difference was statistically significant when  $P<0.05$ .

## Results

### *Basic data of the patients included*

According to the inclusion and exclusion criteria, the 203 patients' data were finally collected. The patients consisted of 115 males and 88 females, aged 36-78 years with an average age of (63.8 $\pm$ 4.3) years. The dialysis durations were 4-38 months, with an average dialysis duration of (17.5 $\pm$ 5.8) months. The average Scr level of the initial dialysis was 876.15 $\pm$ 218.38  $\mu$ mol/L. With respect to primary diseases, there were 79 cases of glomerulonephritis, 64 cases of diabetic nephropathy, 45 cases of hypertensive nephropathy, 8 cases of obstructive nephropathy, 3 cases of polycystic kidney, 2 cases of lupus nephritis, and 2 cases of unknown causes. See **Table 1**.

### *Comparison of the mortality between patients with malnutrition of different degrees*

Altogether 203 MHD patients were enrolled, and 24 of them (11.82%) died after one-year of follow-up. Their basic data are shown in **Table 2**. According to the MQSGA scores, there were 142 cases of mild malnutrition (69.95%), 43 cases of moderate malnutrition (21.18%), and 18 cases of severe malnutrition (8.87%), with the mortality being 2.11% (3/142), 13.95% (6/43), and 83.33% (15/18), respectively. The difference in the mortality was statistically significant between the patients with malnutrition of different degrees in their MQSGA scores

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**Table 1.** The demographic characteristics of the maintenance dialysis patients

Project	Number of cases/minimum and maximum	$\bar{x} \pm sd$
Age (years)	36-78	63.8±4.3
Gender (male/female)	115/88	
Dialysis duration (months)	4-38	17.5±5.8
Creatinine (μmol/L)	378.65-1497.24	876.15±218.38
Glomerulonephritis	79 (38.92%)	
Diabetic nephropathy	64 (31.53%)	
Hypertensive nephropathy	45 (22.17%)	
Obstructive nephropathy	8 (3.94%)	
Polycystic kidney	3 (1.48%)	
Lupus nephritis	2 (0.99%)	
Unknown causes	2 (0.99%)	

**Table 2.** Basic information on the death or survival of the maintenance hemodialysis patients

Project	Death group	Survival group	$\chi^2/t$	P
Number of cases	24	179		
Age (years)	36-78	63.8±3.7	0.623	0.534
Gender (male/female)	64.3±5.2	100/79	0.379	0.538
Dialysis age (months)	15/9	17.4±4.7	1.192	0.235
Creatinine (μmol/L)	18.7±7.9	720.11±276.61	3.933	<0.001
Glomerulonephritis	945.23±117.54	71 (39.66%)	0.357	0.550
Diabetic nephropathy	8 (33.33%)	58 (32.40)	0.537	0.464
Hypertensive nephropathy	6 (25.0%)	40 (22.35%)	0.028	0.867
Obstructive nephropathy	5 (20.83%)	6 (3.35%)	1.387	0.239
Polycystic kidney	2 (8.33%)	2 (1.12%)	1.352	0.245
Lupus nephritis	1 (4.17%)	1 (0.56%)	2.824	0.093
Unknown causes	1 (4.17%)	1 (0.56%)	2.824	0.093

( $\chi^2=101.30$ ,  $P<0.001$ ). According to the MIS scores, there were 135 cases of mild malnutrition (66.50%), 46 cases of moderate malnutrition (22.66%), and 22 cases of severe malnutrition (10.84%), with the mortality being 2.22% (3/135), 13.04% (6/46), and 68.18% (15/22), respectively. The difference was statistically significant between the patients with malnutrition of different degrees in MIS ( $\chi^2=70.03$ ,  $P<0.001$ ). See **Figure 1**.

### *Comparison of the mortality between patients with and without micro-inflammatory responses*

A total of 107 cases had micro-inflammatory responses, with a mortality rate of 16.82% (18/107), while 96 cases had no micro-inflammatory responses, with a mortality of 6.25% (6/96). The difference in the mortality was sta-

tistically significant between the patients with and without micro-inflammatory responses ( $\chi^2=5.425$ ,  $P=0.020$ ). See **Figure 2**.

### *Comparison of the nutritional indices and the micro-inflammatory indicators between the survival and death groups*

There were statistically significant differences between the survival and death groups in their MQ-SGA scores, MIS scores, and their levels of albumin, Scr, TNF- $\alpha$ , and hs-CRP ( $P<0.05$ ). See **Table 3**.

### *Independent predictors of death*

The COX regression analysis showed that the MIS scores and the TNF- $\alpha$  level were independent predictors of death in the MHD patients ( $P<0.05$ ). See **Table 4**.

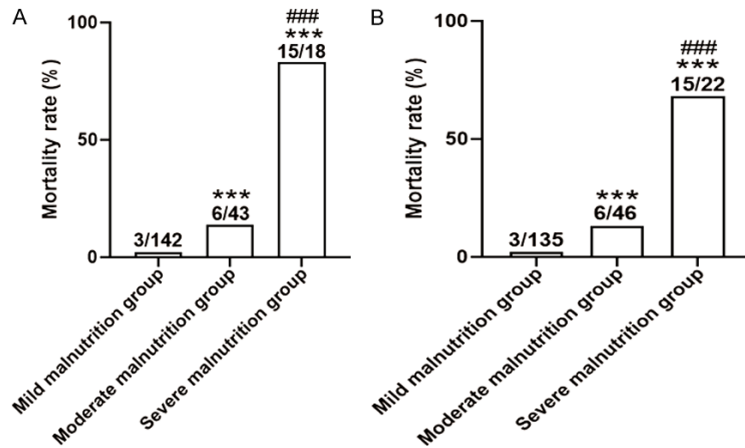
### *Spearman correlation analysis*

The Spearman correlation analysis showed that MIS (20.43±3.92) was positively correlated with serum TNF- $\alpha$  level (198.0-320.0) in the death of MHD patients, and the linear correlation coefficient  $R^2$  between the two was 0.520 ( $P=0.001$ ). See **Figure 3**.

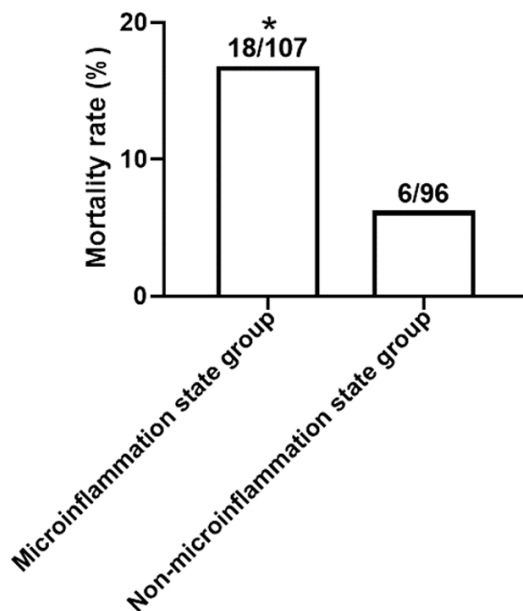
### *Analysis of the ROC curves for predicting death*

The ROC curves of detection alone and joint detection for predicting death are shown in **Figure 4**. The AUC of MIS combined with the TNF- $\alpha$  level for predicting death was 0.850 (the standard error was 0.100), significantly larger than the 0.655 of the MIS score (the standard error was 0.133) and the 0.630 of TNF- $\alpha$  level (the standard error was 0.128). The Delong test showed that the differences were statistically

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**Figure 1.** Comparison of the mortality between patients with different degrees of malnutrition. A: The comparison of mortality between the mild, moderate, and severe malnutrition groups according to the MQSGA score. B: The comparison of mortality between the mild, moderate, and severe malnutrition groups according to the MIS score. \*\*\* $P < 0.001$ , compared with that in the mild malnutrition group. ### $P < 0.001$ , compared with that in the moderate malnutrition group.



**Figure 2.** The effects of the micro-inflammatory response on mortality in patients with maintenance hemodialysis. \* $P < 0.05$ , compared with the patients without micro-inflammatory responses.

significant ( $Z=2.053$  and  $2.657$ ,  $P=0.008$  and  $0.040$ , respectively).

### Discussion

Malnutrition, the most common and intractable complication of MHD, is recognized as an inde-

pendent risk factor affecting MHD patients' prognosis. However, whether this complication can be used as a predictor of death risk remains to be discussed because of its unclear influencing mechanisms [15]. Schoming first proposed a chronic micro-inflammatory state in uremic patients in 2000 [16]. Recent studies have confirmed that a micro-inflammatory response is a hidden pathological state in MHD patients, so it may be an important reason for causing and exacerbating malnutrition [17-19].

A study has shown that the one-year mortality of MHD patients with malnutrition significantly increases by 2-5 times [20]. In our study, there was a

statistically significant difference in the mortality between the patients with mild, moderate, and severe malnutrition in their MQSGA and MIS scores; the mortality increased with the increasing severity of malnutrition; the mortality of the patients with micro-inflammatory responses was significantly higher than the mortality of those without micro-inflammatory responses. These findings are similar to those of Choi SR and others [21], which may be related to malnutrition and micro-inflammation that form a vicious circle and aggravate organ function damage.

In order to further analyze the influence of nutritional status and micro-inflammatory responses on the death risk of MHD patients, the patients were followed up for 12 months, and their MQSGA and MIS scores were compared between the survival and death groups. The results showed that the two scores in the death group were significantly higher than those in the survival group, indicating that the severity of malnutrition may be positively correlated with the risk of death. This is consistent with the findings of Yamada and others that the risk of death increases by 3 times with the increase of every 10 units in the MIS score [22]. In our study, the Scr level in the death group was significantly higher than it was in the survival group, but the albumin level was significantly lower than it was in the survival group. This sug-

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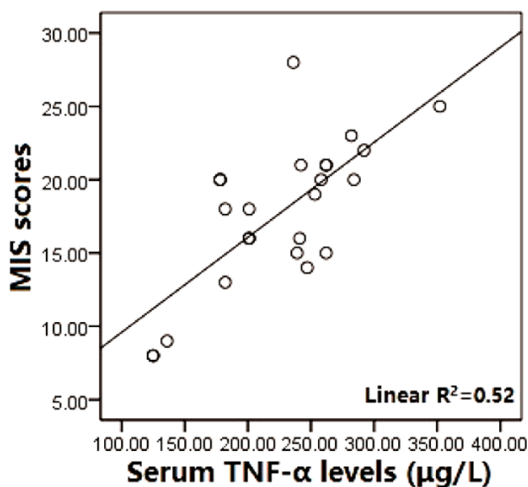
**Table 3.** Comparison of the nutritional indices and micro-inflammatory indicators between the survival and death groups

Indicators	Survival group	Death group	t/ $\chi^2$	P
Number of cases	41.47±7.95	35.54±6.84	5.524	0.016
Albumin (g/L)	98.14±6.32	94.52±5.87	0.362	0.637
Hemoglobin (g/L)	720.11 (223.0-1247.0)	945.23 (446.01-1453.0)	15.713	0.000
Scr ( $\mu\text{mol/L}$ )	2059.0 (1064.0-3067.0)	1982.0 (894.0-3125.0)	0.828	0.171
Ferroprotein ( $\mu\text{g/L}$ )	2.41±0.48	2.23±0.59	0.471	0.528
Transferrin (mmol/L)	2457.0 (1449.0, 3461.0)	2435.0 (1428.0, 3691.0)	0.626	0.373
Total iron binding capacity (mg/L)	21.59±2.33	20.28±3.11	0.617	0.382
BMI ( $\text{kg/m}^2$ )	27.52±4.38	26.47±4.81	0.725	0.274
Biceps circumference (cm)	23.08±3.53	22.36±3.47	0.235	0.764
Upper arm muscle circumference (cm)	11.82±4.85	10.58±4.79	0.158	0.841
TSF (mm)	12.28±4.38	24.24±5.39	6.477	0.013
MQSGA score (score)	7.19±3.13	20.43±3.92	5.391	0.019
MIS score (score)	42.0 (26.0, 58.0)	259.0 (198.0, 320.0)	19.428	0.000
TNF- $\alpha$ ( $\mu\text{g/L}$ )	5.0 (1.0, 9.0)	13.0 (3.0, 26.0)	8.625	0.000
hs-CRP (mg/L)	1.5 (0.6, 4.0)	3.0 (0.8, 8.0)	0.647	0.352
IL-6 (ng/L)	41.47±7.95	35.54±6.84	5.524	0.016

Note: Scr: Serum creatinine; BMI: Body Mass Index; TSF: Triceps Skin Fold; MQSGA: Modified Quantitative Subjective Global Assessment; MIS: Malnutrition inflammation score; TNF- $\alpha$ : Tumor Necrosis Factor  $\alpha$ ; hs-CRP: High-sensitivity C-reactive protein; IL-6: Interleukin-6.

**Table 4.** Independent predictors of the death of maintenance hemodialysis patients

Variate	B	SE	Wald	P	Exp (B)	95% CI
MIS score	0.360	0.100	12.823	0.000	1.433	1.177-1.745
TNF- $\alpha$	0.028	0.010	7.710	0.005	1.029	1.008-1.049

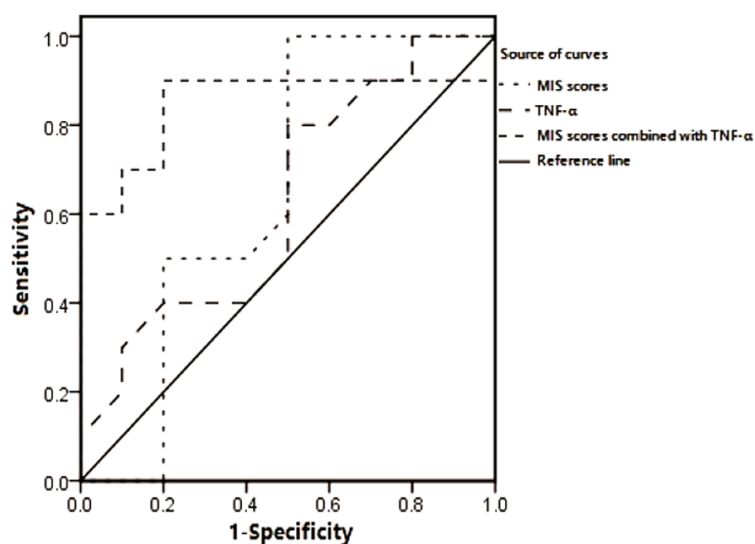


**Figure 3.** Correlation between the MIS score and the serum TNF- $\alpha$  level.

gests that Scr can reflect protein intake to some extent in MHD patients with poor prognoses before dialysis, and albumin has a half-life

of about 21 days, both of which can be used to evaluate the nutritional status. According to Vaziri et al., the combined quantification of the levels of hemoglobin, ferritin, and transferrin is helpful in assessing the nutritional status of MHD patients [23]. In our study, the levels of hemoglobin, ferritin, TIBC, and BMI, the biceps circumference, the arm muscle circumference, and the TSF in the death group were slightly lower than they were in the survival group, without any statistically significant differences. The results may be associated with the effects of protein loss, abnormal iron reserves, dyslipidemia, and dialysis levels, so they are different from those of MacDougall and others. This is possibly because of different primary diseases, disease severity, and the dialysis age between the two studies. In their study, the primary disease in the survival group was mainly diabetic nephropathy (71.23%), while the primary disease in the death group was mainly glomerulonephritis (67.53%); the severity in the survival group was significantly

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**Figure 4.** The ROC curve for predicting death in maintenance hemodialysis patients with MIS scores and TNF- $\alpha$  levels.

slighter than it was in the death group, and the dialysis age was significantly lower than it was in the death group ( $16.8 \pm 8.4$  months vs.  $29.2 \pm 9.1$  months); the difference in the Scr level between the two groups ( $617.31 \pm 168.71$   $\mu\text{mol/L}$  vs.  $857.05 \pm 228.24$   $\mu\text{mol/L}$ ) was statistically significant [24]. In addition, levels of TNF- $\alpha$  and hs-CRP in the death group were significantly higher than they were in the survival group. This supports the hypothesis that micro-inflammation affects the prognosis of MHD patients, during which the mechanism of action is that micro-inflammatory cytokines mediate proteolysis, lead to malnutrition, and then increase the patients' death risk.

Kalantar-zadeh first proposed that MIS included BMI, serum albumin, and TIBC on the basis of the dialysis malnutrition score [25], but some scholars still question the use of the score to evaluate the nutritional status of MHD patients. One study analyzed many indices (including the MIS and MQSGA scores, albumin, and prealbumin) commonly used to predict malnutrition in MHD patients. The results of its multiple regression analysis showed that MIS was most closely related to the nutritional indices, and the correlation coefficient was the largest ( $r=0.752$ ), with a statistically significant difference. The correlation coefficients of the MQSGA score, albumin, and prealbumin were 0.562, 0.412, and 0.397, respectively. These findings indicate that MIS can accurately evaluate the malnutrition status of MHD patients and better predict

their death risk, so it is significantly better than other indices [26]. The data of our study are also consistent with the above research results, supporting the idea that MIS can be used to predict the patients' death risk and guide the early detection and intervention in malnutrition. In our study, the independent predictors of patient death were analyzed using a COX regression model. The results showed that the nutritional status represented by the MIS score and the micro-inflammation represented by the TNF- $\alpha$  level could be used to predict the patients' death risk. Additionally, the AUC of the MIS score combined with

the TNF- $\alpha$  level for predicting death was 0.850, significantly larger than the 0.655 of the MIS score and the 0.630 of the TNF- $\alpha$  level. These findings demonstrate that the combination can improve the predictive efficiency of the risk of death synergistically. In this study, MIS was positively correlated with serum the TNF- $\alpha$  level in the death of MHD patients, which is basically consistent with the research results of Tayebi et al. [27]. This indicates that malnutrition is closely related to micro-inflammation in patient deaths, and that patients with high MIS scores have micro-inflammatory responses. The reasons for the above results are as follows: (1) Inflammatory cytokines inhibit the central nervous system and reduce appetite and nutrient intake. (2) Pro-inflammatory cytokines inhibit the synthetase activity of meat and plasma proteins, promote muscle protein decomposition, and increase capillary permeability and the loss of various proteins. (3) Long-term micro-inflammatory responses disturb the metabolism and hormone secretion of patients, inhibit erythropoiesis, and increase iron consumption in vivo.

However, this study still has certain limitations, such as the small size of the cohort, the lack of a long-term follow-up, and the lack of dynamic data to evaluate nutritional status. Therefore, a large-scale clinical research trial with multiple centers, large sample sizes, and a long-term follow-up should be conducted in the future to

provide an experimental and theoretical basis for accurately predicting the death risk of MHD patients and guiding clinical intervention in malnutrition and micro-inflammation.

In summary, the death of MHD patients is correlated with malnutrition and micro-inflammation, so the MIS score combined with the TNF- $\alpha$  level can synergistically improve the predictive efficiency of the patients' risk of death.

### Disclosure of conflict of interest

None.

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