Role of malnutrition inflammation score and interleukin-6 on quality of life of regular hemodialysis patients

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ABSTRACT

Background: Malnutrition, systemic inflammation, and atherosclerosis known as MIA syndrome occurs in patients who have undergone regular hemodialysis (HD) and can lower their quality of life (QoL). Current study aimed to determine the interrelation of malnutrition and inflammation to QoL.

Methods: A cross-sectional analytic study was conducted in our hemodialysis installation. We performed Malnutrition Inflammation Score (MIS) and measure serum IL-6 to determine malnutrition and inflammation conditions in regular HD patients and utilized Kidney Disease Quality of Life-Short Form (KDQOL-SF) to assess QoL. MIS. IL-6 cut-off point were determined by the Receiver Operating Curves (ROC) then we performed linear regression to analyze the relationship level of MIS and IL-6 with level of QoL. We also used path analysis to prove the mechanism model of MIS and IL-6 to QoL on regular HD patients.

Results: This study consisted of 60 regular HD patients, 40 (66.7%) of men with mean age of 51.8 years and 78 months average of dialysis vintage. Good QoL was obtained ≥60 overall health (above the median value) and high level of MIS was obtained ≥5 with 75% sensitivity and 21.8% specificity, while high IL-6 level were ≥47.21 pg/mL, with 62.2% sensitivity and specificity of 78.3%. This study found the prevalence of protein-energy wasting (PEW) in regular HD patients was 81.7% by using high level of MIS. MIS were significantly correlated to IL-6 (r = 0.376, p = 0.003) however high level of MIS were uncorrelated to poor QoL. The mechanism of the interrelation of MIS, IL-6, and QoL showed on path analysis that MIS was 15% directly correlated to QoL, however, IL-6 indirectly correlated to QoL on regular hemodialysis patients.

Conclusion: MIS and IL-6 were correlated to QoL and MIS also correlated to IL-6. Malnutrition inflammatory score directly affected QoL but IL-6 indirectly affected QoL in regular HD patients.

Keywords: MIS, IL-6, quality of life, regular hemodialysis.


INTRODUCTION

There is an increasing number of regular hemodialysis (HD) patients worldwide. In 2010, it was recorded 2.6 million people in the world and 968,000 people in Asia needed dialysis. It is estimated that it will increase to 2.16 million people in Asia who need dialysis by 2030.1 Data from the Indonesian Renal Registry (IRR) 2017 reported that 77,892 patients were actively undergoing hemodialysis.3

Patients who underwent regular hemodialysis had a high prevalence of protein-energy wasting (PEW) (18-70%).3,4 There was low-grade systemic inflammation caused by increased cytokine production through the interaction of dialysis factors with nondialysis and genetic factors. Interleukin-6 as the main cytokine were obtained in regular HD patients had the effects in suppressing appetite, hypercatabolism, hypercoagulability, hypoalbumin, and atherosclerosis. Interleukin-6 is also associated with a poor prognosis of CKD patients.5 Decreased IL-6 excretion plays a major role in proinflammatory conditions due to reduced IL-6 receptors in the kidney and decrease in glomerular filtration rate (GFR) causes decreased in IL-6 clearance. This condition enhanced proinflammatory cytokine activity and increased malnutrition and inflammation known as MIA syndrome in regular hemodialysis patients.6

Kalantar-Zadeh et al have developed MIS to assess malnutrition in regular HD patients.7 Malnutrition-inflammation score is an easy and inexpensive instrument that consisting of 7 components of subjective global assessment (SGA) and 3 additional components of non-SGA namely total iron-binding capacity (TIBC), serum albumin, and body mass index (BMI). Several studies have been conducted to assess the relationship of QoL and MIS on patients who undergone regular HD, however, there were not many studies discussed the interrelation between QoL, MIS, and IL-6 in the case of regular HD patients.
METHODS

Study design
This study was a cross-sectional study to identify PEW on chronic hemodialysis patients in hemodialysis installation, Sanglah General Hospital Denpasar Bali, in June 2020.

Eligibility criteria
The study consisted of 60 regular HD subjects, above 18 years, who underwent hemodialysis for at least 3 months. The subjects have signed the informed consent. We excluded HD patients who had acute infection, malignancy, hepatitis B or C infection, HIV infection, and hospitalization. The research ethical commission of Sanglah General Hospital has approved this study protocol.

Baseline characteristics
Demographic data, history of disease, and anthropometry were obtained by interviewing and performed physical examination of hemodialysis patients and then recorded to the questionnaire.

Diagnosis of PEW
Malnutrition was determined as PEW by MIS. Malnutrition inflammation score is a quantitative nutritional screening tool that consists of medical history (5 questions), 2 questions of physical examination, one question of BMI, and 2 laboratory values (albumin and total iron binding capacity). Every question consists of score 0 indicate patients in normal nutrition while score 3 indicates severe nutrition deficit. All parts of the score were summed in ranges 0 to 30, which is score 0 indicates normal nutrition and score 30 indicates severe malnutrition and inflammations.

Quality of life Assessment
This study utilized KDQOL-SF, a specific tool in making assessment of QoL on patients who have undergone regular hemodialysis. It is a multidimensional, valid and reliable tool that consists of general scale (physical condition and emotional condition subscale) and nine areas of specific scale of QoL in HD patients. The physical subscale contains four areas (general health, physical function, playing physical role, and physical pain) and the emotional scale contains three areas (playing emotional role, social function, and mental health). Each area has 100 points.

Laboratory measurements
Interleukin-6 was obtained by measuring IL-6 serum with Enzyme link immune assay (ELISA) method. Routine laboratory measurements were obtained from patient's medical record at Sanglah General Hospital. All of the laboratory measurements were performed at Sanglah General Hospital laboratory.

Statistical analysis
Sample characteristics were analysed descriptively, presented in mean value (standard deviation) if the data were normally distributed, but in median value (interquartile range) if not normally distributed. Quality of life is classified as good and poor based on the median value. Good QoL is equal to or more than the median value and poor QoL is less than the median value. Malnutrition inflammation score was classified into high and low and cut-off values of MIS which was determined by the ROC curve. Interleukin-6 levels were classified into high and low and the cut-off value of high and low IL-6 levels was determined by the ROC curve. The relationship between high MIS and poor QoL was analysed with a 2 x 2 table (Chi-Square test) and determined the prevalence ratio (PR) with 95% confidence interval. The relationship between high IL-6 and poor QoL was analysed using Pearson’s correlation on normally distributed data. Path analysis was performed to analyse the relationship of MIS direct or indirectly with QoL of regular hemodialysis patients through IL-6 (PR) and 95% confidence interval. The relationship between high IL-6 levels was determined by the ROC curve.

RESULTS

Characteristics of Subjects
This study has included 60 regular HD patients, consisting of 40 (66.7%) male and 20 (33.3%) female with 51.8 years mean of age, and average length of time underwent HD was 78 months, as described in Table 1. Etiology of CKD were 14 (23.3%) diabetes and 46 (76.7%) non-diabetes, mean of blood sugar, BMI, MIS, and IL-6 were 102.68 ± 39.64 mg/dl; 22.35 ± 3.4; 7.32 ± 3.14; and 40.79 ± 23.7 pg/mL, respectively.

The median overall QoL score was 60, as the cut of point of good QoL. Then we classified into good QoL if score ≥60. We obtained 37 (61.7%) samples that had a good QoL and the remaining 23 (38.3%) had a poor QoL. We also described characteristics of the QoL aspects of regular HD patients as in Table 2. The three lowest scores were sexual function, emotion, and mental composite SF-12 as described below.

Relationship of MIS and Quality of Life
The MIS variable in this study was classified into high and low MIS. The cut-off point of MIS was determined by analysing the ROC curve. We obtained the cut-off point of MIS was ≥5 with sensitivity of 75% and specificity of 21.8% with AUC 40.5%, p = 0.205 (see Figure 1). This study obtained high MIS was 81.7%, and low MIS was 28.3% in regular HD patients.

There was no significant relationship between MIS (scores ≥ 5 and <5) and QoL (scores ≥ 60 and <60) (PR 1.01; 95% CI 0, 28.3–4.30; p = 0.882).

Relationship of IL-6 and Quality of Life
Interleukin-6 was also classified into high and low IL-6. The IL-6 cut off point was determined by the ROC curve, and we obtained IL-6 cut-off value for predicting poor QoL was 47.21 pg/mL, with sensitivity of 62.2% and specificity of 78.3%; AUC 67% (p = 0.027), see Figure 2.

Based on Chi-Square analysis, we obtained PR 2.56 (95% CI 1.00-6.54, p = 0.024). This study indicated that subjects with IL-6 more than equal to 47.21 pg/mL had a poor quality of life as indicated by QoL score <60 compared to patients with IL-6 less than 47.21 pg/mL, p <0.05.

Correlations between MIS and IL-6
MIS and IL-6 were normally distributed. MIS was significantly positively correlated with IL-6 (r = 0.376; p = 0.003) as showed in Figure 3.
Path analysis of MIS and QoL via IL-6
Path analysis showed that MIS directly affected QoL (B = -2.45, R2 = 15%, p = 0.003). Although MIS affected IL-6 (B = -2.75, R2 = 14%, p = 0.003), IL-6 did not affect QoL (B = 0.09, R2 = 1%, p = 0.44). Thus, MIS only has a direct effect on QoL by 15%, and indirectly through IL-6. Therefore, the effect of MIS on quality of life is non-mediated, see the Figure 4.

**DISCUSSIONS**
This study investigated the association of MIS as an assessment of nutritional status and inflammation with QoL through the inflammatory marker IL-6 in regular hemodialysis patients. The QoL assessment using KDQOL-SF questionnaire, showed that our regular HD patients had median overall health equal to 60. This data is better than data obtained in Iran about the mean of overall QoL on regular HD patients with KDQOL-SF was 50.37. This is understandable because most of the subjects in Iran had comorbid heart disease, diabetes mellitus, and malignancy, which resulted in lower overall QoL. Giashi reported the lowest aspects of QoL on emotion (34.30%), physical activity (39.48%), and vitality (44.51%). A few aspects of QoL in our study were also significantly low in sexual aspects (26.25%), emotions (33.73%), composite mental SF 12 (34.01%), composite physical SF 12 (40.50%), work status (41.67%), and fatigue (46.92%).

**Table 1.** Characteristics of Subjects (n=60 patients).

<table>
<thead>
<tr>
<th>Variable</th>
<th>n (%)</th>
<th>Mean ± SD</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>51.8 ± 11.30</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>40 (66.7)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>20 (33.3)</td>
<td></td>
</tr>
<tr>
<td>Length of HD (month)</td>
<td>78 ± 37</td>
<td></td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>136 ± 18</td>
<td></td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>80.60 ± 9.68</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.35 ± 3.40</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>10.92 ± 1.68</td>
<td></td>
</tr>
<tr>
<td>BS (mg/dL)</td>
<td>102.68 ± 39.64</td>
<td></td>
</tr>
<tr>
<td>Kalsium (mg/dL)</td>
<td>8.9 ± 0.96</td>
<td></td>
</tr>
<tr>
<td>Phosfat (mg/dL)</td>
<td>6.56 ± 1.90</td>
<td></td>
</tr>
<tr>
<td>URR (%)</td>
<td>72.70 ± 9.45</td>
<td></td>
</tr>
<tr>
<td>Kt/V</td>
<td>1.62 ± 0.39</td>
<td></td>
</tr>
<tr>
<td>Etiology of CKD</td>
<td></td>
<td></td>
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<tr>
<td>DM</td>
<td>14 (23.3)</td>
<td></td>
</tr>
<tr>
<td>Non-DM</td>
<td>46 (76.7)</td>
<td></td>
</tr>
<tr>
<td>MIS</td>
<td>7.32 ± 3.14</td>
<td></td>
</tr>
<tr>
<td>IL-6</td>
<td>40.79 ± 23.07</td>
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</table>


**Table 2.** Characteristics of Quality of Life Aspects (n = 60 HD patients).

<table>
<thead>
<tr>
<th>Aspects of QoL</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall health</td>
<td>62.17 ± 20.17</td>
</tr>
<tr>
<td>Work status</td>
<td>41.67 ± 33.40</td>
</tr>
<tr>
<td>Cognitive function</td>
<td>73.89 ± 18.40</td>
</tr>
<tr>
<td>Social interaction quality</td>
<td>75.44 ± 15.50</td>
</tr>
<tr>
<td>Sexual function</td>
<td>26.25 ± 39.64</td>
</tr>
<tr>
<td>Sleep</td>
<td>60.54 ± 14.41</td>
</tr>
<tr>
<td>Physical function</td>
<td>55.08 ± 23.80</td>
</tr>
<tr>
<td>Pain</td>
<td>67.62 ± 21.52</td>
</tr>
<tr>
<td>Emotion</td>
<td>33.73 ± 14.32</td>
</tr>
<tr>
<td>Social Function</td>
<td>62.71 ± 21.03</td>
</tr>
<tr>
<td>Fatigue</td>
<td>46.92 ± 15.79</td>
</tr>
<tr>
<td>Composite of physic SF 12</td>
<td>40.50 ± 8.91</td>
</tr>
<tr>
<td>Composite of mental SF 12</td>
<td>34.01 ± 6.27</td>
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QoL: quality of life; SD: standard deviation.
result in malnutrition, inflammation and decreased QoL on regular HD patients. Pro-inflammatory cytokines, especially IL-6, also have a direct effect on anorexia, depression causing anorexia and decreased food intake as well as increased total energy expenditure in regular HD patients. Interleukin-6 also induces leptin and increased anorexia effect. This condition affects fatigue, depression, and finally, decrease of the overall QoL.

Malnutrition inflammation score has been developed to assess PEW as well as inflammation in this study. By analysing with the ROC curve, we obtained the MIS cut off point was 5 with sensitivity of MIS is moderate (75%) to predict the QoL of regular HD patients, although the specificity is 21.8%. This study obtained high MIS (≥5) in most of the sample were 49 people (81.7%). This suggests that the majority of regular HD patients were malnourished and MIS is moderately sensitive but unspecific to predict poor QoL in regular HD patients. A study by Harvinder et al. in Malaysia on 155 regular HD patients, which examined MIS against International Society of Renal Nutrition and Malnutrition (ISRN) criteria determined MIS cut off point by ROC curve and obtained MIS ≥5 as malnourished. Therefore, the prevalence of high MIS was 88% of regular HD patients. The prevalent of malnutrition were similar to those obtained in this study. After performing correlative analysis between categorical of MIS and overall QoL, the study obtained that high MIS was not correlated with poor QoL. A study in Los Angeles on 809 regular HD patients showed that only MIS in the 4th quartile (MIS > 8) correlated with poor QoL, but the other MIS quartiles were not significant. The difference between these results and ours may be explained that the study by Rambod divided MIS into 4 quartiles and only the 4th quartile was associated with poor QoL. Sohrabi et al. in Iran which were examined 87 HD patients that obtained MIS was not related to overall health status but had a negative relationship with several aspects of QoL, namely total physical aspects and total mental aspects. Sohrabi found mean of MIS 9.6 as mild to moderate malnutrition and the mean of MIS in severe malnutrition was 14.7. Severe malnutrition was correlated to total QoL as well as those found in other studies, this is because several aspects are covered in aspect QoL and only higher scores of MIS are correlated to aspects of QoL.

Interleukin-6 is secreted by immune cells as well as fat cells and plays a role in inflammation. In apparently healthy individuals, IL-6 levels were found in men of 6.4 pg/mL and in women 5.8 pg/mL. In CKD patients, IL-6 also produced by resident kidney cells, namely endothelial, mesangial and tubular epithelial cells and also podocytes secreted IL-6 at certain levels (10). We obtained IL-6 cut-off point by ROC curve analysis 47.21 pg/mL that predicted the overall QoL with sensitivity 62.2% and specificity 78.3% and AUC of 67%. High interleukin-6 level (≥ 47.21

Figure 1. ROC Curve of MIS to QoL in Regular HD Patients.

Figure 2. ROC curve of IL-6 to Predicts poor QoL on Regular HD Patients.
are several nutritional assessments for detecting PEW. Malnutrition inflammation score is a reliable and simple nutritional assessments tool to determine nutritional status of regular HD patients.

In regular HD patients, inflammation is due to increased production of inflammatory factors, especially IL-6 due to interactions between dialysis factors, comorbidities and genetic factors, and also decreased IL-6 excretion due to decreased kidney function and decreased IL-6 excretion receptors, thereby increasing the occurrence of inflammation. There

pg / mL) was strongly and significantly associated (RR 2.56; p < 0.05) with a poor overall QoL score. Our study was similar to study conducted by Bacci et al. in Brazil, recruited 31 regular HD patients, obtained that IL-6 was significantly negative correlated with activity limitation one aspect of QoL. Bossola et al in Rome Italy examined 100 regular HD patients that obtained that fatigue, was significantly correlated with IL-6. This is due to the effect of IL-6 in inflammation which affects to anorexia, depression, fatigue, PEW, and then decrease the aspects of the QoL of regular HD patients.

In regular HD patients, inflammation is due to increased production of inflammatory factors, especially IL-6 due to interactions between dialysis factors, comorbidities and genetic factors, and also decreased IL-6 excretion due to decreased kidney function and decreased IL-6 excretion receptors, thereby increasing the occurrence of inflammation. There

Figure 3. Correlation and regression between MIS and IL-6.

Figure 4. Non-mediated mechanism of MIS to QoL via IL-6.

CONCLUSION

High IL-6 level was associated with poor QoL in regular HD patients and MIS was correlated with serum Interleukin-6 levels in regular HD patients. Malnutrition inflammation score directly affected QoL and indirectly via Interleukin-6 in regular HD patients.

DISCLOSURES

Conflict of interest

The authors declare no conflict of interest.
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Ethical clearance
This research has been approved by the Research Ethics Committee of the Faculty of Medicine, Udayana University/Sanglah Central General Hospital Denpasar.

Author contributions
All authors contributed equally throughout research, drafting, reviewing, and finalizing the manuscript.

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