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RESEARCH ARTICLE

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Association between inflammatory indices reflecting the three axes of the malnutrition–inflammation–atherosclerosis (MIA) syndrome and anemia status in maintenance hemodialysis patients

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ABSTRACT

Anemia is a frequent complication of maintenance hemodialysis, and chronic inflammation is one of its central drivers. The malnutrition-inflammation-atherosclerosis (MIA) syndrome comprises three interacting axes that can be reflected by routine surrogate indices: the lymphocyte-to-hs-CRP ratio (LCR), the prognostic nutritional index (PNI), and the neutrophil-to-HDL-cholesterol ratio (NHR). This study examined how these three indices relate to anemia in patients on maintenance hemodialysis. We conducted a cross-sectional study of 116 patients, defining moderate anemia as a hemoglobin (Hb) concentration below 11 g/dL. Groups were compared using the t-test or Mann-Whitney test and the chi-square test, and independent associations were assessed with multivariable linear and logistic regression; the discriminatory ability of the combined model was evaluated by the area under the receiver operating characteristic curve (AUC). Anemia was present in 61 patients (52.6%). Compared with non-anemic patients, anemic patients had lower LCR and lower PNI (both $p < 0.05$), whereas NHR did not differ significantly. In the multivariable models, both LCR and NHR were independently associated with Hb concentration and with anemia status (all $p < 0.05$), while PNI lost significance after adjustment. The combined three-index model discriminated anemia with an AUC of 0.717 (95% CI, 0.63–0.81). In conclusion, LCR and NHR were relevant and consistent correlates of anemia, whereas PNI added little independent information. The combined model achieved acceptable discrimination, supporting a multi-index rather than a single-index approach when the inflammatory background of anemia is assessed in hemodialysis patients.

Key words: MIA syndrome; anemia; maintenance hemodialysis; lymphocyte-to-hs-CRP ratio; neutrophil-to-HDL ratio.

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1. Introduction

Anemia is among the most common complications in patients with end-stage renal disease receiving maintenance hemodialysis, contributing to cardiovascular events, hospitalization, impaired quality of life, and mortality [1]. Its pathogenesis is multifactorial, involving relative deficiency of endogenous erythropoietin, disordered iron metabolism, shortened erythrocyte survival, blood loss during dialysis, and—prominently—chronic inflammation [1, 2].

In dialysis patients, inflammation rarely occurs in isolation; it typically coexists with malnutrition and atherosclerosis, together forming the malnutrition–inflammation–atherosclerosis (MIA) syndrome, a complex closely tied to poor prognosis [3]. Each of its three axes can be reflected indirectly by simple indices derived from the routine complete blood count and biochemistry panel. The lymphocyte-to-hs-CRP ratio (LCR) integrates the lymphocyte count and high-sensitivity C-reactive protein (hs-CRP), capturing both inflammatory intensity and immune competence, and has been shown to be an independent predictor of outcomes in hemodialysis patients [4]. The prognostic nutritional index (PNI), calculated from albumin and the lymphocyte count, represents the inflammation–nutrition axis and predicts mortality in dialysis populations [5]. The neutrophil-to-HDL-cholesterol ratio (NHR) combines the neutrophil count with HDL-cholesterol, simultaneously reflecting inflammation and the lipid dysregulation of the atherosclerotic axis [6].

Importantly, these indices are derived entirely from routine blood tests and serve as accessible surrogates of the three MIA axes rather than as a diagnostic label of the syndrome; accordingly, the present study enrolled unselected maintenance hemodialysis patients and examined the three axes through these surrogate indices, without requiring a formal diagnosis of MIA syndrome. Although each index has been studied in different settings, data directly comparing the three indices that represent the three MIA axes, in relation to anemia in maintenance hemodialysis patients, remain limited. We therefore conducted this study to examine and compare the associations of LCR, PNI, and NHR with anemia, and to evaluate the ability of a combined model to discriminate anemia status.

2. Subjects and Methods

2.1. Study subjects

This was a cross-sectional study of 116 patients receiving maintenance hemodialysis at the Department of Nephrology, Ho Chi Minh City Hospital for Rehabilitation–Professional Diseases.

Inclusion criteria: age ≥ 18 years and clinically stable maintenance hemodialysis for ≥ 3 months.

Exclusion criteria: acute infection or an acute exacerbation within the preceding 4 weeks, malignancy, decompensated chronic liver disease, primary hematologic disease, and acute blood loss.

2.2. Variables and definitions

The three inflammatory-nutritional indices were calculated as follows:

LCR = lymphocyte count (10^9/L) / hs-CRP (mg/L);

PNI = albumin (g/L) + 5 × lymphocyte count (10^9/L);

NHR = neutrophil count (10^9/L) / HDL-cholesterol (mmol/L).

Each index was selected as a routinely available surrogate of one axis of the MIA syndrome and was interpreted accordingly. The LCR reflects the inflammatory axis: hs-CRP is an interleukin-6–driven acute-phase reactant that rises with inflammatory intensity, whereas the lymphocyte count falls with uraemia-related immune dysregulation, so a lower LCR denotes a heavier inflammatory burden [4, 7]. The PNI, originally derived by Onodera and computed here in SI units as albumin (g/L) + 5 × lymphocyte count (10^9/L), summarises the combined nutrition–inflammation axis, with lower values indicating a poorer nutritional–inflammatory state [5]. The NHR represents the atherosclerotic–metabolic axis, combining the pro-inflammatory neutrophil count with anti-inflammatory, anti-atherogenic HDL-cholesterol, so that a higher value conventionally denotes a greater inflammatory–atherogenic load [6]. Higher LCR and PNI therefore indicate a more favourable inflammatory–nutritional state, whereas a higher NHR conventionally indicates a less favourable one.

Moderate anemia was defined as a hemoglobin (Hb) concentration below 11 g/dL. Baseline variables collected included age, sex, body mass index (BMI), diabetes status, and the lipid profile.

2.3. Statistical analysis

Data were analyzed with Stata. Continuous variables are presented as mean ± standard deviation or as median (interquartile range) according to their distribution; categorical variables are presented as frequencies and proportions. Two-group comparisons used the t-test or Mann–Whitney test for continuous variables and the chi-square test for categorical variables. The independent associations of the three indices with Hb concentration and with anemia status (a binary outcome) were assessed using multivariable linear regression and multivariable logistic regression, respectively; the variance inflation factor (VIF) was examined to exclude multicollinearity. The ability of the combined model to discriminate anemia was evaluated by the area under the receiver operating characteristic curve (AUC). A two-sided $p < 0.05$ was considered statistically significant.

2.4. Research Ethics

The study was approved by the Ethics Committee of Ho Chi Minh City Hospital for Rehabilitation–Professional Diseases (approval No. 09.1/HĐĐĐ-BVPHCN-ĐTBNN, dated 24 April 2024).

3. Results

Among the 116 patients, the mean age was 54.1 ± 15.1 years and 57.8% were male. Anemia, defined by an Hb concentration below 11 g/dL, was present in 61 patients (52.6%). Compared with non-anemic patients, anemic patients had a lower prevalence of diabetes (26.2% versus 49.1%; p = 0.011) and a lower triglyceride concentration (p = 0.036). Among the inflammatory indices, both LCR and PNI were significantly lower in the anemic group, whereas NHR did not differ significantly between groups (Table 1).

Table 1. Characteristics of the study patients by anemia status

Characteristic	Total (N = 116)	Anemia (N = 61)	Non-anemia (N = 55)	p
Age (years)	54.1 ± 15.1	54.7 ± 14.7	53.6 ± 15.6	0.675
Male, n (%)	67 (57.8)	33 (54.1)	34 (61.8)	0.401
BMI (kg/m²)	21.8 ± 3.6	21.5 ± 3.3	22.2 ± 3.9	0.272
Diabetes, n (%)	43 (37.1)	16 (26.2)	27 (49.1)	0.011
Hb (g/dL)	10.9 ± 1.6	9.7 ± 0.9	12.2 ± 1.0	<0.001
Albumin (g/L)	37.0 ± 3.6	36.8 ± 3.7	37.2 ± 3.5	0.609
Triglyceride (mmol/L)	1.6 (1.0–2.2)	1.4 (1.0–1.9)	1.7 (1.1–2.7)	0.036
Cholesterol (mmol/L)	3.7 ± 0.9	3.6 ± 0.7	3.8 ± 1.1	0.250
HDL-c (mmol/L)	1.0 ± 0.3	1.0 ± 0.2	1.0 ± 0.3	0.780
LDL-c (mmol/L)	1.9 ± 0.7	2.0 ± 0.7	1.9 ± 0.8	0.566
hs-CRP (mg/L)	2.1 (0.9–4.4)	2.2 (0.8–5.4)	1.8 (1.0–4.0)	0.274
Lymphocyte count (10^9/L)	1.5 ± 0.5	1.6 ± 0.6	1.5 ± 0.5	0.620
Neutrophil count (10^9/L)	4.3 ± 1.8	4.4 ± 2.0	4.0 ± 1.6	0.280
LCR (lymphocyte/hs-CRP)	0.7 (0.4–1.9)	0.5 (0.2–1.2)	0.8 (0.4–2.9)	0.009
PNI	44.7 ± 4.3	43.9 ± 4.6	45.6 ± 3.8	0.027
NHR (neutrophil/HDL-c)	4.1 (2.9–5.7)	3.8 (2.8–5.3)	4.2 (2.9–6.1)	0.212

Values are mean ± SD, median (interquartile range), or n (%). hs-CRP: high-sensitivity C-reactive protein; BMI: body mass index; Hb: hemoglobin; HDL-c: high-density lipoprotein cholesterol; LDL-c: low-density lipoprotein cholesterol; LCR: lymphocyte-to-hs-CRP ratio; PNI: prognostic nutritional index; NHR: neutrophil-to-HDL-cholesterol ratio.

In the multivariable linear regression model with Hb concentration as the dependent variable, LCR showed the strongest positive and independent association with Hb, NHR showed a weaker positive association, and PNI was not significant. All VIF values were close to 1 (≤ 1.11), indicating no meaningful multicollinearity (Table 2).

Table 2. Multivariable linear regression with hemoglobin concentration as the dependent variable

Variable	β	SE	VIF	p	95% CI
LCR	0.29	0.08	1.11	<0.001	0.13 to 0.44
PNI	0.02	0.03	1.08	0.504	−0.04 to 0.09
NHR	0.10	0.05	1.03	0.040	0.01 to 0.19

Model: R^2 = 0.130; adjusted R^2 = 0.107; F(3, 112) = 5.59; p = 0.0013. β: unstandardized regression coefficient; SE: standard error; VIF: variance inflation factor; CI: confidence interval.

Similarly, in the multivariable logistic regression model with anemia status as the dependent variable, LCR was the strongest independent correlate, followed by NHR, whereas PNI showed only a non-significant trend. Higher LCR and higher NHR were each associated with lower odds of anemia (Table 3). The combined three-index model discriminated anemia with acceptable ability, achieving an AUC of 0.717 (95% CI, 0.63–0.81; Figure 1).

Table 3. Multivariable logistic regression with anemia status as the dependent variable

Variable	OR	SE	VIF	p	95% CI
LCR	0.66	0.09	1.11	0.003	0.49 to 0.87
PNI	0.92	0.05	1.08	0.091	0.83 to 1.01
NHR	0.80	0.07	1.03	0.016	0.67 to 0.96

Model: likelihood-ratio $\chi^2(3)$ = 20.59; p < 0.001; pseudo-R^2 = 0.128; AUC = 0.717 (95% CI, 0.63–0.81). OR: odds ratio; SE: standard error; VIF: variance inflation factor; CI: confidence interval.

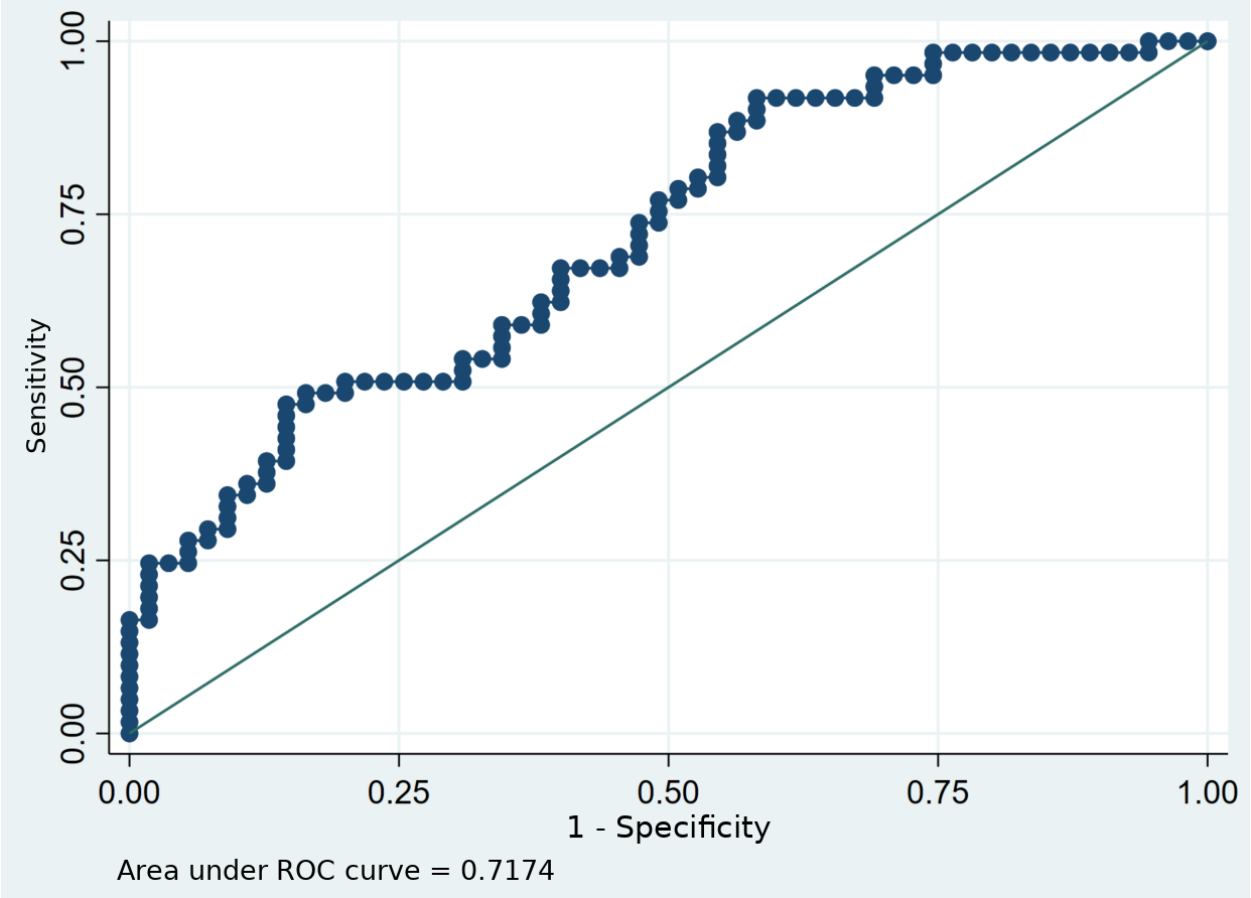

Figure 1. Receiver operating characteristic (ROC) curve of the combined three-index model for discriminating anemia status.

4. Discussion

This study simultaneously examined three indices representing the three axes of the MIA syndrome in relation to anemia in maintenance hemodialysis patients. LCR and NHR were associated with anemia status, whereas PNI showed no statistically significant independent association. The combined three-index model achieved acceptable discrimination of anemia (AUC 0.717). The differences among the three indices reflect the distinct biology of their individual components.

LCR was the most prominent index: it was lower in the anemic group and was independently associated with both Hb concentration and the risk of anemia. This result is concordant with the international literature. In hemodialysis patients, Chen et al. (2023) reported that a low LCR was an independent predictor of mortality [4], and a low LCR has likewise been linked to poor prognosis across inflammatory and oncological diseases [7]. LCR integrates two signals that reflect inflammatory burden in the same direction: hs-CRP is an acute-phase reactant regulated by IL-6 and represents the intensity of inflammation, which directly drives hepcidin-mediated functional iron deficiency and erythropoietin resistance, whereas a falling lymphocyte count reflects immune dysregulation and exhaustion induced by uremia and sustained chronic inflammation [2, 4]. As inflammation intensifies, the lymphocyte count declines and hs-CRP rises, so LCR falls steeply in parallel with suppressed erythropoiesis. LCR therefore captures the inflammatory axis, the core determinant of the anemia of inflammation.

PNI was lower in the anemic group in the univariate analysis, consistent with its established role as an index of malnutrition and inflammation and as a predictor of mortality in dialysis patients [5]. A notable difference, however, was that PNI lost all significance once it was entered into the multivariable model alongside LCR and NHR. PNI and LCR share the lymphocyte component, so much of the immune-inflammatory signal that PNI carries is expressed more directly and more strongly by LCR; meanwhile, the other component of PNI-albumin-did not differ between the two groups in our sample. In other words, for a cross-sectional anemia outcome, the inflammatory axis expressed through the lymphocyte-to-hs-CRP ratio outweighs the nutritional axis represented by albumin. This does not contradict earlier studies, because the prominent prognostic value of PNI has been demonstrated mainly for time-to-mortality outcomes, in which nutritional status-particularly albumin-plays a greater role, rather than for anemia status at a single time point.

In most previous studies, a higher NHR reflects more severe inflammation and lipid dysregulation and is therefore linked to worse outcomes, such as increased cardiovascular risk and mortality [6] or greater albuminuria. In our study, by contrast, a higher NHR was associated with a lower risk of anemia-a direction of association that is opposite to what would be expected of an inflammatory marker. In this sample, HDL-cholesterol was almost uniform between the two groups and very low, a feature characteristic of the uremic milieu, in which HDL-cholesterol is not only reduced in quantity but also loses its anti-inflammatory and antioxidant functions and may become frankly dysfunctional [8, 9]. When HDL-cholesterol barely varies, NHR is in practice driven almost entirely by the neutrophil count, and the metabolic–atherosclerotic signal that underlies the prognostic value of NHR in cardiovascular disease is largely absent in this population. In hemodialysis patients, a higher neutrophil count may reflect better-preserved bone marrow proliferative capacity, which parallels better erythropoiesis and hence a higher hemoglobin concentration; conversely, severe anemia often accompanies diffuse marrow suppression with simultaneous reduction of multiple cell lines. In this specific context, therefore, NHR reflects the hematopoietic activity of the marrow more than a harmful inflammatory burden.

Overall, although the three indices are viewed through the three facets of the MIA syndrome, they contribute very differently to the anemia outcome: the chronic inflammatory axis (LCR) is the strongest determinant, the nutritional axis (PNI) may have been masked by an excessively high background level of chronic inflammation, and the metabolic axis (NHR) manifests in a way that reflects hematopoiesis rather than inflammation alone. These differences indicate that composite indices derived from the complete blood count should not be regarded as interchangeable, and still less should a single index be used to infer anemia status. The fact that the combined model reached an AUC of 0.717-higher than the discrimination usually reported for any single index in the literature-supports the value of a multi-index approach. In practice, these indices should be used as adjunctive tools, in combination with direct assessment of anemia.

This study has several limitations. Its cross-sectional design does not permit causal inference, whereas the relationship between inflammation and anemia is inherently bidirectional. The regression models were mutually

adjusted among the three indices but were not adjusted for clinical factors that may act as confounders, such as the dose of erythropoiesis-stimulating agents (ESAs), iron stores, dialysis vintage, and comorbidities; notably, the prevalence of diabetes differed between the two groups, and the ESA dose-a strong determinant of hemoglobin concentration-was not included in the models. Finally, this was a single-center study with a small sample size; the associations of these inflammatory indices should be confirmed in prospective studies with full multivariable adjustment and larger samples.

It is worth considering the likely direction of the bias introduced by these unmeasured confounders. The most influential is the ESA dose. In routine care, more inflamed patients-those with a lower LCR-are more ESA-hyporesponsive and are therefore given higher ESA doses to reach hemoglobin targets; in a recent pooled analysis, patients with higher baseline hs-CRP required substantially greater ESA doses to achieve comparable hemoglobin [10, 11]. Because this compensatory up-titration selectively raises hemoglobin in precisely the most inflamed (low-LCR) patients, it flattens the observed LCR–hemoglobin gradient. The associations we report are therefore more likely to be attenuated (shrunk toward the null) than exaggerated, and the true, ESA-independent relationship between inflammation and anemia may be stronger than the coefficients in Table 2 suggest. Iron status behaves differently: functional iron deficiency is largely a downstream mediator of the inflammation → hepcidin → restricted-erythropoiesis pathway rather than an independent confounder, so its omission means our estimates capture the total effect of inflammation on anemia-including its iron-restricted component-rather than being biased in a fixed direction; had iron indices been forced into the model, part of the genuine inflammatory effect would have been over-adjusted away. By contrast, the between-group imbalance in diabetes prevalence (lower among anemic patients) is a classical confounder whose net effect on the index-haemoglobin associations is less predictable and could act in either direction. Taken together, the unmeasured ESA dose most plausibly biases our key associations toward the null, whereas residual confounding by comorbidity adds uncertainty of indeterminate direction-both of which reinforce the need for the prospective, fully adjusted study proposed above.

5. Conclusion

In maintenance hemodialysis patients, the three indices representing the three axes of the MIA syndrome are associated with anemia in different ways. LCR was the strongest and most consistent correlate, directly reflecting the inflammatory axis that is central to the anemia of inflammation. PNI had little independent value, owing to its overlap with LCR and to the absence of a between-group difference in albumin. NHR showed an unexpected inverse association, most likely reflecting the neutrophil count and the hematopoietic activity of the marrow rather than inflammatory burden. The combined three-index model achieved acceptable discrimination, supporting a multi-index approach combined with direct assessment of anemia rather than reliance on any single index.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Declaration of Generative AI and AI-Assisted Technologies

The authors declare that no artificial intelligence (AI) was used during the research process or in the writing of this manuscript

The authors used [name of AI, Ex: ChatGPT-4 / Claude 3.5] to [doing something] during the research process and the writing of this manuscript

Author Contributions

Identify authors who participated in the research in the following roles: Conceptualization and study design, performing experiments, data analysis, interpretation of results, preparing figures, drafting the manuscript, editing and critical review of the manuscript, and final approval of the manuscript.

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Mối liên quan giữa các chỉ số viêm phản ánh ba trục của hội chứng suy dinh dưỡng – viêm – xơ vữa (MIA) và tình trạng thiếu máu ở bệnh nhân lọc máu chu kỳ

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TÓM TẮT

Thiếu máu là biến chứng phổ biến ở bệnh nhân lọc máu chu kỳ, trong đó viêm mạn tính giữ vai trò quan trọng. Hội chứng suy dinh dưỡng – viêm – xơ vữa (MIA) gồm ba trục có thể được phản ánh bằng các chỉ số thay thế từ xét nghiệm thường quy: tỉ số bạch cầu lympho/hs-CRP (LCR), chỉ số dinh dưỡng tiên lượng (PNI) và tỉ số bạch cầu trung tính/HDL-c (NHR). Nghiên cứu nhằm khảo sát mối liên quan giữa ba chỉ số trên với thiếu máu ở bệnh nhân lọc máu chu kỳ. Nghiên cứu cắt ngang trên 116 bệnh nhân lọc máu chu kỳ; thiếu máu mức độ trung bình được định nghĩa khi Hb < 11 g/dL. So sánh hai nhóm, hồi quy tuyến tính và logistic đa biến và phân tích ROC của mô hình phối hợp được thực hiện. Có 61 bệnh nhân (52,6%) thiếu máu. LCR và PNI ở nhóm thiếu máu thấp hơn nhóm không thiếu máu ($p < 0,05$); khác biệt NHR không có ý nghĩa. Trong hồi quy đa biến, LCR và NHR liên quan độc lập với Hb ($p < 0,05$) và với tình trạng thiếu máu ($p < 0,05$), trong khi PNI mất ý nghĩa sau hiệu chỉnh. Mô hình phối hợp ba chỉ số đạt AUC 0,717 (KTC 95%: 0,63–0,81). LCR và NHR là những chỉ số liên quan và nhất quán với tình trạng thiếu máu; PNI ít giá trị độc lập. Mô hình phối hợp đạt khả năng phân biệt chấp nhận được, ủng hộ tiếp cận đa chỉ số khi đánh giá nền viêm của thiếu máu ở bệnh nhân lọc máu.

Từ khóa: hội chứng MIA; thiếu máu; lọc máu chu kỳ; tỉ số lympho/hs-CRP; tỉ số neutrophil/HDL-c.