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The Accuracy of Monocyte Lymphocyte Ratio as a Predictor of Mortality in Patients Undergoing Regular Haemodialysis at H Adam Malik General Hospital Medan

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ABSTRACT

Background: Chronic Kidney Disease (CKD) has become a world health problem with high morbidity and mortality rate. In CKD, chronic inflammation occurs, one of the causes including factors related to dialysis. Monocyte Lymphocyte Ratio (MLR) is a new haematology marker associated with tumour, inflammatory disease, and cardiovascular disease. MLR is also a predictor of infection complication in haemodialysis patients. The aim of this study is to assess the accuracy of MLR as a predictor of mortality in regular haemodialysis patients at H. Adam Malik General Hospital Medan

Method: This study is an analytic retrospective cohort study of CKD patients who undergoes regular haemodialysis, conducted in July-December 2023 at H. Adam Malik General Hospital Medan. Data were analysed using the SPSS program. Bivariate analysis was conducted to assess the correlation between the two variables. Then, ROC analysis was performed to assess the MLR as a mortality predictor.

Result: Total subject in this study was 60 regular haemodialysis patients with the majority of the subjects being male (88,3%), the mean age was 49,77± 13,09 years old and the mortality in this study was 16,7%. The median MLR value in this study was 0,345 (0,11-1,65). This study showed a significant relationship between MLR and mortality (p=0,003). MLR showed moderate performance to predict 30-days mortality in regular haemodialysis patients (AUC=74,4%).

Conclusion: MLR has moderate accuracy in predicting 30-day mortality in regular haemodialysis CKD patients.

Keywords: *Monocyte Lymphocyte Ratio; MLR; Chronic Kidney Disease; CKD; Mortality.*

INTRODUCTION

Chronic Kidney Disease (CKD) is a clinical syndrome caused by changes in kidney function and structure and is described as irreversible, slow-evolving, and progressive. CKD presents significant pathological abnormalities indicating higher risks of complications and mortality.[1] It has emerged as a global public health issue with increasing incidence, high costs, and elevated morbidity and mortality rates. CKD ranks tenth globally as a cause of death, with a significant increase over the past two decades. Mortality and morbidity in CKD are mainly due to cardiovascular

complications (50%) and infections (20%), which are related to immune system disturbances influenced by various factors. It is well known that about 30-50% patients undergoing haemodialysis experience chronic systemic inflammation.[2]

Inflammation in CKD can be caused by multiple factors, including dialysis-related factors such as mismatch and endotoxin back filtration from the dialysate, as well as non-dialysis-related factors such as unrelated infections and comorbidities. Despite progressive advancements in dialysis techniques to reduce dialysis-related risk factors, including inflammation, infection rates have not decreased. Infection-related morbidity depends on individual patient conditions, including immune system disorders, PEW (protein-energy wasting), comorbidities, dental diseases, immunosuppressant drug use, and, importantly, the presence of vascular access devices. Many CKD patients experience increased levels of inflammatory serum mediators including CRP (C-reactive protein), TNF-α (tumour necrosis factor-alpha), IL-6 (interleukin-6), and pentraxin-3. Routine monitoring of CRP levels is still not common in many dialysis centres, as it is time-consuming and costly.[3]

Monocytes are innate immune cells with functions similar to neutrophils, but they demonstrate better capabilities in killing intracellular pathogens like mycobacteria and fungi. Activated monocytes can also kill many tumour cells. Monocyte levels have been linked to the risk of cardiovascular events and death in CKD patients.[4] Lymphocytes are white blood cells responsible for antibody production, destruction of virus-infected and tumour cells, and regulation of immune responses. Lymphopenia, a decrease in lymphocyte count, is found in various systemic diseases, particularly cancer. CKD's end-stage is also associated with lymphopenia.[5]

Monocyte Lymphocyte Ratio (MLR) is a new haematological parameter associated with tumour-related, inflammatory, and cardiovascular diseases. MLR can predict infection complications in haemodialysis patients vulnerable to both symptomatic and asymptomatic infections. Studies have shown that higher MLR values are associated with increased mortality risk in cancer patients and correlate positively with high mortality and cardiovascular risk.[5,6] MLR values determined upon hospital admission have strong predictive capacities for all causes of death within 30 days in CKD patients undergoing haemodialysis for at least six months.[7]

Given the high incidence of CKD patients undergoing haemodialysis and the low usage of MLR as a predictor in CKD patients in Indonesia, along with previous foreign studies, researchers are interested in further investigating the accuracy of MLR as a mortality predictor in regular haemodialysis patients at H. Adam Malik General Hospital, Medan.

MATERIALS & METHODS

The research conducted is an analytical retrospective cohort study. It was carried out using secondary data from patient medical records of those undergoing regular haemodialysis. The study was conducted at Haji Adam Malik General Hospital, Medan, from July 2023 to December 2023.

The research population consisted of chronic kidney disease patients undergoing regular haemodialysis, with the sample being those meeting inclusion and exclusion criteria. Sampling technique employed was consecutive sampling, with considerations for inclusion and exclusion criteria. Inclusion criteria included patients aged above 18 years, undergoing regular haemodialysis for more than 31 months, and having complete medical records. Exclusion criteria included patients diagnosed with CKD stages 1 to 4, those undergoing peritoneal dialysis, immunocompromised patients, patients with sepsis or autoimmune diseases, those with oncological or haematological disorders, and patients with major surgeries within the last 6 months.

Data collection involved retrieving patient demographics and haemodialysis duration

from medical records. Monocyte and lymphocyte values were obtained from laboratory examination sheets. Data collected were processed and analysed after recording.

STATISTICAL ANALYSIS

Normality tests such as Kolmogorov-Smirnov and Shapiro-Wilk were conducted, and appropriate statistical tests were applied for categorical and numerical variables. Univariate analysis involved analysing each research variable separately, presenting numerical variables with mean±SD for normal distribution and median (min-max) for non-normal distribution, while categorical variables were presented with frequency (n) and percentage (%). Bivariate analysis was performed using Chi-square or Fisher's exact test for categorical data, and independent T-test or Mann-Whitney U-test for numerical data. The accuracy of predictor variables in predicting outcomes was analysed using Receiver Operating Characteristic (ROC) curve analysis to determine sensitivity, specificity, and cut-off points. Significance was considered at $p<0.05$.

RESULT

A total of 60 samples meeting inclusion and exclusion criteria were collected from patients' medical records. The sample consisted of 40 males (66.7%) and 20 females (33.3%) with an average age of 49.77±13.09 years. Hypertension was the most prevalent risk factor among the subjects, found in 36 subjects (60%), followed by heart failure in 23 subjects (38.3%), diabetes mellitus in 6 subjects (10%), coronary artery disease in 5 subjects (8.3%), urinary tract stones in 2 subjects (3.3%), and peripheral artery disease in 1 subject (1.7%).

Laboratory parameters revealed the mean absolute monocyte count was $0.6\pm0.26x10^9$/L, while the mean absolute lymphocyte count was $1.48\pm0.72x10^9$/L. The median absolute neutrophil count was 4.72. The median MLR calculated in the study was 0.345. Overall, 10 subjects (16.7%) experienced mortality within 30 days. Data are shown in Table 1.

Table 1. Subject Characteristics

Variables	N (%)
Age	49.77 ± 13.09
Gender	
Male	40 (66.7)
Female	20 (33.3)
Risk Factors	
Hypertension	36 (60)
Diabetes Mellitus	6 (10)
Heart Failure	23 (38.3)
Coronary Heart Disease	5 (8.3)
Kidney Stones	2 (3.3)
Peripheral Artery Disease	1 (1.7)
Hemoglobin (g/dL)	8.17 ± 1.5
Hepatocyte (%)	24.89 ± 4.55
Absolute Monocyte ($x10^3$/uL)	0.6 ± 0.26
Absolute Lymphocyte ($x10^3$/uL)	1.48 ± 0.72
Absolute Neutrophil ($x10^3$/uL)	4.72 (1.72 – 13.63)
BUN (mg/dL)	69.57 ± 25.22
Creatinine (mg/dL)	13.2 (4.6 – 23.5)
MLR	0.345 (0.11 – 1.65)
Mortality	10 (16.7)

Bivariate analysis was conducted to determine whether there was a significant relationship or difference between the characteristics of study subjects based on mortality. These analyses were done using Independent T-Test for variables such as age, haemoglobin, absolute monocyte, absolute lymphocyte, and BUN, meanwhile, analysis of MLR, absolute neutrophil and creatinine was done using the Mann-Whitney U-Test, and Chi-Square test was used for analysis of gender, hypertension,

diabetes mellitus, heart failure, coronary heart disease, kidney stones, and peripheral heart disease. The bivariate analysis, as seen in Table 2, revealed statistically significant differences ($p < 0.05$) in several parameters, including the history of hypertension, heart failure, coronary artery disease, absolute monocyte count, absolute lymphocyte count, absolute neutrophil count, and MLR.

Table 2. Bivariate Analysis of Subject Characteristics with Mortality

Variables	Mortality		p Value
	Yes N=10 (16.7)	No N=50 (83.3)	
Age	54.5 ± 12.44	48.82 ± 13.13	0.214
Male	8 (13.3)	32 (53.3)	0.471
Female	2 (3.3)	18 (30)	
Hypertension	9 (15)	27 (45)	0.040
Diabetes Mellitus	2 (3.3)	4 (6.7)	0.259
Heart Failure	7 (11.7)	16 (26.7)	0.035
Coronary Heart Disease	3 (5)	2 (3.3)	0.029
Kidney Stones	1 (1.7)	1 (1.7)	0.308
Peripheral Artery Disease	1 (1.7)	0 (0)	0.167
Hemoglobin (g/dL)	8.22 ± 1.31	8.16 ± 1.55	0.907
Hepatocyte (%)	24.51 ± 3.9	24.96 ± 4.7	0.750
Absolute Monocyte ($x10^3$/uL)	0.76 ± 0.37	0.57 ± 0.23	0.045
Absolute Lymphocyte ($x10^3$/uL)	0.83 ± 0.54	1.61 ± 0.69	0.001
Absolute Neutrophil ($x10^3$/uL)	7.8 (2.79 - 13.63)	4.56 (1.72 - 10)	0.009
BUN (mg/dL)	61.7 ± 46.72	71.2 ± 18.69	0.277
Creatinine (mg/dL)	7 (5 - 21.3)	13.8 (4.6 - 23.5)	0.023
MLR	0.84 (0.18 – 1.65)	0.33 (0.11 – 0.90)	0.015

ROC analysis was conducted to assess the accuracy of the MLR in predicting 30-day mortality in CKD patients undergoing regular haemodialysis. The result yielded an area under the curve (AUC) of 74.4%. This indicates that MLR can be utilized to predict 30-day mortality in CKD patients undergoing regular haemodialysis with moderate ability (AUC > 70%) (Figure 1).

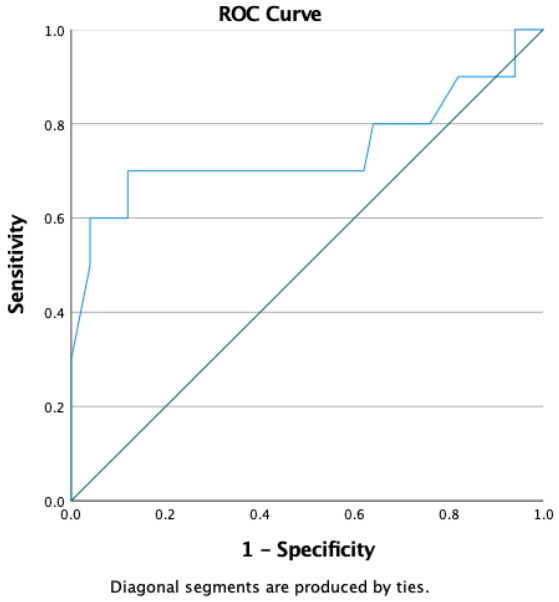

Figure 1. MLR ROC Curve on Mortality

Based on the line graph in Figure 2, the obtained cut-off value of the MLR for predicting 30-day mortality in patients with chronic kidney disease undergoing regular haemodialysis is 0.40. This cut-off value comes with a sensitivity of 70% and a specificity of 68%.

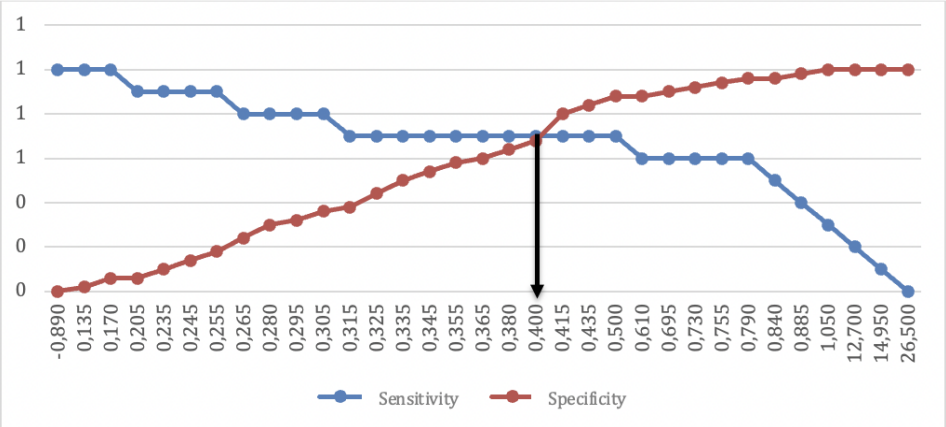

Figure 2. Cut-off, sensitivity and specificity of MLR with mortality line graphic

Table 3 and 4 presents the AUC value and significance level of MLR in predicting mortality in patients with regular haemodialysis in CKD and bivariate analysis data of MLR with 30-day mortality that is grouped based on the cut-off value obtained from the ROC analysis, respectively. Furthermore, MLR in patients was found to be statistically significant as a predictor of mortality with a p-value of 0.016. MLR values ≥0.4 are considered as high MLR, while MLR values <0.4 are considered as low MLR. The analysis revealed a significant relationship between MLR and 30-day mortality with a p-value of 0.035.

Table 3. AUC value and significance level of MLR in predicting mortality in patients with regular haemodialysis in CKD

Variable	AUC	95% CI	p value	Cut-off	Sensitivity	Specificity
MLR	74.4%	52 – 96%	0.016	0.40	70%	68%

Table 4. bivariate analysis data of MLR with 30-day mortality

Variable	Mortality		p value
	Yes N=10 (16.7)	No N=50 (83.3)	
MLR			0.035
High	7 (11.7)	16 (26.7)	
Low	5 (3)	34 (56.6)	

DISCUSSION

Chronic systemic inflammation is a common occurrence in haemodialysis patients, and it represents a significant risk factor for cardiovascular morbidity and mortality in these individuals. This study investigates the relationship between MLR as a predictor of mortality in patients with regular haemodialysis in CKD.[8] The study found an average age of 49.77±13.09 years, with the majority of subjects being male (66.7%). These findings are consistent with data from the IRR in 2017, where the majority of HD patients were aged between 45-64 years. The most common risk factor found in this study was hypertension, with 53 subjects (88.3%) affected, which aligns with previous studies indicating that hypertension is the leading cause of CKD in Indonesia.[9]

The study revealed an average absolute monocyte count of 0.6±0.26, with a higher average absolute monocyte count in the CKD group that experienced mortality within 30 days (0.76±0.37 vs 0.57±0.23, p=0.045). This finding is consistent with previous studies by Kato et al., which found a higher average monocyte count in subjects who died. The study also found a significant relationship between absolute lymphocyte count and mortality, with a lower average absolute lymphocyte count in subjects who died (0.83±0.54 vs 1.61±0.69, p=0.001).[10] Furthermore, supported by Bowe et al., which found higher mortality rates in groups with higher monocyte counts.[11]

According to Koraishy et al., a monocyte count >0.56 k/cmm is associated with a risk of death (HR: 1.40, 95% CI 1.38-1.41), and a strong negative correlation was found between high monocyte counts and low eGFR (15-30 mL/min/1.73m^2) with

p<0.001.[12] Jeng et al. stated that patients with CD16+ monocytes in the fourth quartile (<21.5, ≤29.2) have a significantly higher risk of death, with HR ranging from 2.83-30.85 for cardiovascular mortality and 1.21-5.84 for all-cause mortality after adjusting for supporting variables.[13]

These findings may be due to uremic conditions in patients with CKD leading to inflammation and calcification through increased monocyte adhesion and extravasation, as well as increased inflammatory potential of monocytes and macrophages. Accumulation of CD14+/CD16+ monocytes can lead to endothelial dysfunction, vascular inflammation, and arteriosclerosis.[14]

This study found a significant relationship between absolute lymphocyte count and mortality, with a lower average absolute lymphocyte count in subjects who died (0.83±0.54 vs 1.61±0.69, p=0.001). This result is supported by previous research showing lower lymphocyte counts in CKD patients undergoing haemodialysis compared to control groups, particularly in CD4+ and B cell subpopulations.[15] Another study by Xiang et al. showed that decreased absolute T cell count, naive T cell count, and naive CD8+ cell count are significant predictors of mortality. After further testing, adjusting for conventional and non-conventional mortality-related risk factors, decreased absolute T cell count, decreased absolute naive T cell count, and decreased naive CD8+ cell count was independently associated with all-cause mortality in regular haemodialysis CKD patients.[16]

A cohort study by Kuwae et al. found that the lowest quartile of lymphocyte percentage (≤15.5%) had the highest mortality rate at 22.9%, and compared to the highest quartile, a lymphocyte percentage ≤15.5% was associated with an 11% increase in mortality and a 68% increase in hospitalization duration.[17] In CKD patients, there are immune system changes resembling aging or chronic inflammation. Furthermore, uraemia will increase the regulation of immune cells. Decreased counts of naive lymphocytes, T cells, and dendritic cells are major characteristics. This effect is more pronounced in haemodialysis patients compared to peritoneal dialysis patients. Recent studies show that patients with end-stage CKD show a decrease in T cell receptors with clonal expansion, which may increase the risk of infection, malignancy, and cardiovascular disease.[18]

In this study, the median MLR was found to be 0.345 (range 0.11-1.65), with a higher median MLR in CKD subjects who experienced mortality (0.83 vs 0.33). Based on ROC analysis, the AUC of MLR in this study was 74.7%, indicating that MLR can predict mortality within 30 days with moderate accuracy. Meanwhile, the MLR cut-off value in this study was 0.40, with a sensitivity of 70% and specificity of 68% for predicting mortality within 30 days. These findings are supported by Muresen et al., where MLR showed moderate ability to predict mortality within 30 days with an AUC of 79.2%. In that study, the optimal MLR cut-off value for predicting mortality was 0.63, with a sensitivity of 79.7% and specificity of 71.4% (p<0.001).[19] These results align closely with the findings of Liao et al., where MLR had a cut-off value of 0.38, with a sensitivity of 78% and specificity of 63.4% in predicting all-cause mortality based on ROC analysis.[20] Additionally, another study by Zhang et al. stated that an MLR ≥ 0.43 is an important prognostic factor in determining mortality in regular haemodialysis patients.[21]

High MLR (≥0.4) also had a significant association with mortality with a p-value of 0.035. This finding is consistent with a previous study involving 398 regular haemodialysis patients, where a higher median MLR was found in the group experiencing cardiovascular events or death compared to the group without cardiovascular events during a 5-year follow-up period (0.37 vs 0.33). A significant association was found between MLR and cardiovascular events or mortality with a p-value of 0.001.[21] Similarly, the

results of this study are supported by previous research involving 461 end-stage CKD subjects undergoing regular haemodialysis, where a higher median MLR was found in the group experiencing mortality within 30 days (1 vs 0.45, p<0.001). In the high MLR group (>0.63), mortality was significantly higher compared to the low MLR group (32.35% vs 4.81%, p<0.001). Multivariate analysis revealed that high MLR was associated with a 9.46 times higher risk of mortality within 30 days (95% CI 5.06-17.69, p<0.001).[19]

Another study by Qiu et al. mentioned that hospitalization duration, 30-day mortality, and 90-day mortality were significantly higher in the MLR > 0.71 group compared to the MLR < 0.28 group and the group with 0.28 ≤ MLR ≤ 0.71 with a p-value of <0.05.[22] Similar findings were also observed in a study by Xiang et al., where the mortality rates for the lowest, middle, and highest MLR tertials were 3.65, 7.02, and 11.5 per 100 patients per year, respectively. Significant differences in survival rates were observed among these three MLR groups (p<0.001). MLR was independently associated with all-cause mortality (HR 4.842; 95% CI 2.091-11.214, p<0.001) and cardiovascular mortality (HR 6.985, 95% CI 1.943-25.115, p=0.003).[23]

A study by Muto et al. reported that the high MLR group (>0.35) had a shorter period without cardiovascular events compared to the low MLR group (log-rank test=5.50, p=0.018). The risk ratio for cardiovascular events after adjusting for age, gender, and diabetes was 2.43 (95% CI 1.22-4.84) in the high MLR group compared to the low MLR group.[24] In 396 patients undergoing peritoneal dialysis, a high MLR (>0.2168) was associated with lower survival rates compared to the low MLR group (p=0.008). After adjusting for traditional risk factors such as age, diabetes mellitus, history of CVD, smoking, and hyperlipidaemia, MLR remained an independent predictor of mortality (HR=2.519, 95% CI=1.020-6.214, p=0.045).[25] Another study combining monocyte-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio values in regular haemodialysis patients showed that the combination of these ratios was a predictor of mortality with HR=4.562 (95% CI 1.342-15.504, p=0.015).[26]

High mortality in dialysis patients is not only caused by cardiovascular disease but also by other causes, particularly infection complications. Currently, MLR is an inflammatory biomarker widely used in infectious, autoimmune, cancer, and cardiovascular diseases.[22] A study indicated that MLR is a more sensitive predictor of cardiovascular events compared to NLR.[23] This is because monocytes directly reflect systemic oxidative stress, inflammation, tissue damage, and contribute to the process of arteriosclerosis. Meanwhile, lymphocytes reflect immune function.[27] MLR is an inflammation marker and can be a better predictor of morbidity and mortality than absolute monocyte count because absolute monocyte count is easily influenced by infection, stress, or medications. Additionally, monocytes are immune cells derived from the innate immune system, so MLR can predict infection complications in dialysis patients prone to symptomatic or asymptomatic infections.[28] Based on the above description, MLR is one of the modalities that can be used to predict mortality in regular haemodialysis CKD patients. Moreover, MLR is a marker that can easily be performed based on routine laboratory tests in haemodialysis patients without needing to consider increased costs.[21]

CONCLUSION

This study investigated the predictive value of MLR for mortality in patients undergoing regular haemodialysis due to chronic kidney disease at H. Adam Malik General Hospital Medan. The study found that MLR could effectively predict mortality, with a determined cut-off value of 0.4, sensitivity of 70%, and specificity of 68%, yielding an accuracy of 74.4%. The study also revealed

a 30-day mortality rate of 16.7% among these patients.

Further research on the accuracy of MLR should be conducted in a multi-centre setting to obtain data representative of patients undergoing regular haemodialysis in Indonesia. Subsequent researchers could continue the study by observing clinical outcomes such as mortality, success rates, and survival of patients undergoing regular haemodialysis to assess the ability of MLR in predicting clinical outcomes in these patients.

Declaration by Authors

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