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Relationship between serial serum neutrophil-lymphocyte ratio, cardiovascular mortality, and all-cause mortality in Chinese peritoneal dialysis patients

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Abstract

Introduction

It is believed that the excessive cardiovascular (CV) burden of patients on peritoneal dialysis (PD) is closely associated with chronic inflammation. Neutrophil-lymphocyte ratio (NLR) is an inflammatory marker that was shown to correlate with CV outcomes. However, little is known about the significance of serial monitoring of serum NLR. We aimed to determine the prognostic value of serial NLR on all-cause mortality and CV mortality in PD patients.

Methods

Serial measurement of NLR was obtained from 225 incident PD patients in a single center, with each measurement one year apart. Patients were divided into two groups ('high' versus 'low') by the median value of NLR. The primary and secondary outcome measure was all-cause and CV mortality respectively.

Results

After a median of follow up for 43.9 months, patients with lower baseline NLR demonstrated a higher survival rate (p=0.01). Patients with persistently high NLR values on serial measurement had the lowest survival rate (p=0.03). Multivariate Cox regression showed that this group of patients had significantly higher all-cause mortality (HR 1.74, 95%CI 1.09 to 2.79, p=0.02). However, the NLR failed to demonstrate a statistically significant relationship with CV mortality.

Conclusions

While baseline NLR was an independent predictor of all-cause mortality in PD patients, persistent elevation in NLR appeared to further amplify the risk. Regular monitoring of serial serum NLR may enable early identification of patients who are at risk of adverse outcome.

Keywords: inflammation, mortality, neutrophil-lymphocyte ratio, peritoneal dialysis

Introduction

Patients suffering from end stage renal disease (ESRD) are known to have increased CV risk and mortality compared to the general population. According to the United States Renal Data System (USRDS) 2019 annual data report [1], the adjusted mortality rate for ESRD on dialysis was 165 per 1,000 patient-years in 2017 in the United State, while the mortality rate was 156 per 1,000 patient-years for peritoneal dialysis (PD) patients. Although the mortality rate dropped by 37% from 2001 to 2010 and by 7% from 2011 to 2017, cardiovascular disease (CVD) remained the leading cause of death in ESRD patients. Inflammation is common in PD patients, which has complex interaction with malnutrition and CVD [2]. The inflammatory burden and clinical outcomes in PD patients were commonly measured by markers like serum C-reactive protein and interleukin-6 levels. In addition to these two markers, neutrophil-to-lymphocyte ratio (NLR) was also extensively studied and applied in representing the inflammatory burden in PD patients.

Neutrophils play an important role in the innate immune system while lymphocytes are the key component in regulation of inflammation in the adaptive immune system. Inflammation leads to increased neutrophil production and decreased lymphocyte due to apoptosis, further resulting in perpetuation of inflammation. The serum NLR may therefore be an important prognostic marker. NLR was previously extensively studied and found to be correlated with various outcomes in patients with ischemic stroke [3], cardiovascular disease [4], malignancy [5] and COVID-19 [6]. Moreover, NLR was shown to predict CV outcome in patients with stage 4 chronic kidney disease [7], ESRD on haemodialysis [8] and PD [9,10]. Nonetheless, the significance of serial monitoring of NLR in clinical outcome in PD patients had never been studied. Therefore, we aimed to determine the prognostic value of serial NLR on CV mortality and all-cause mortality in PD patients in this study.

Methods

Study population

Patients on PD who attended regular follow up in the renal unit of Prince of Wales Hospital were retrospectively reviewed from January 1, 2010 to December 31, 2012. A repeated assessment was performed 1 year after the first evaluation. Patients with active infection one month before assessment were excluded. This study was approved by the Joint Chinese University Hong Kong-New Territories East Cluster Clinical Research Ethics Committee.

Data collection

Clinical data including age, gender, primary diagnosis of renal disease, comorbidities (diabetes, coronary artery disease, cerebrovascular accident, malignancy, peripheral vascular disease, chronic lung disease), anthropometric measurements and dialysis regimen were collected by reviewing patients' medical record. Biochemical data including hemoglobin level, white blood cell count, absolute neutrophil and lymphocyte level, C-reactive protein, albumin, residual glomerular filtration rate (rGFR), Kt/V, pulse wave velocity (PWV) were measured per protocol of our center. These data were collected at two different time-points. The first time-point was the time of enrollment into the study (which was 2 months after initiation of dialysis). The second time-point was 1 year after enrollment.

Baseline and serial measurement of NLR

NLR was obtained by dividing the absolute neutrophil count ($x10^9$/L) by the absolute lymphocyte count ($x10^9$/L). The patients were divided into two groups ('high' versus 'low') by the median value of NLR at baseline and follow-up, respectively. Therefore, after repeated measurement of the NLR, patients were further classified into 'persistently high NLR', 'persistently low NLR' and 'evolving NLR'.

Nutritional assessment and PWV measurement

Nutritional status of patients was represented by the malnutrition-inflammation score (MIS) [11] and subjective global assessment (SGA) [12]. MIS comprises 10 items with a total score of 30, a high MIS suggested worse nutrition. The SGA score has a 7-point scale and a high score indicated a better nutritional status. PWV served as a surrogate marker of arterial stiffness. It is measured by an automatic computerized recorder, and the results were analyzed using the Complior SP program (Artech Medical, Pantin, France). Carotid-radial PWV(CR-PWV) and carotid-femoral PWV(CF-PWV) were calculated by dividing the distance by the corresponding time period. A high PWV value was associated with poor vascular compliance and thus suboptimal vascular condition [13].

Outcome measures

All patients were followed up until death, conversion to hemodialysis (HD) or renal transplant, transferal to other centers, or the end of study (February, 2020). The primary outcome measure was all-cause mortality. The secondary outcome measure was CV mortality. CV mortality was defined as death due to myocardial infarction or cerebrovascular accidents. Censored events included transferal to HD, renal transplantation, or transferal to other renal centers.

Statistical analysis

Descriptive data were presented as frequency (%) for categorical data, mean ± standard deviation for normally distributed continuous data, median with interquartile range for skewed data respectively. The patients were divided into 3 tertiles according to their NLR values. The difference among the 3 groups were tested using one-way analysis of variance (ANOVA). Pearson's correlation analysis was used to test the correlation of NLR and other variables. Paired-samples t-test was used to evaluate the change of NLR from baseline to 1 year. Survival was analyzed by Kaplan-Meier method and survival curve of each group was compared by log-rank test. Patients who switched to HD, renal transplant, or other renal centers were censored. Cox proportional hazard model was used to determine the independent predictors of all-cause mortality and CV mortality. Results were presented as HR with 95% confidence interval (CI). Parameters which achieved a P-value of <0.1 in univariate analysis were included in the final multivariate Cox regression. In addition, Kt/V and rGFR were included in the final model given their established impact on mortality. Backward stepwise elimination was applied to remove insignificant variables. All statistical analyses were performed using Statistical Product and Service Solutions (SPSS) for Windows version 27. A P value of less than 0.05 was considered statistically significant. All probabilities were two-tailed.

Results

A total of 245 patients were evaluated and 20 of them were excluded because of active infection. Among these 20 patients, 10 had PD peritonitis, 4 had lower limb cellulitis, 3 had community acquired pneumonia, 2 had dialysis exit site infection, 1 had bacteremia (Figure 1). The baseline demographic data were summarized in Table 1 according to their baseline NLR values. The mean age was 59 ± 12.3 years, and 129 (57.3%) patients were male. The primary causes of ESRD were diabetic nephropathy (42.7%), chronic glomerulonephritis (26.2%), hypertensive nephrosclerosis (9.3%), polycystic kidney disease (4.4%), obstructive uropathy (5.3%), and uncertain (12.1%). 115 (51.1%) patients had diabetes, while 55 (24.4%) and 52 (23.1%) had ischemic heart disease and stroke at baseline respectively.

The enrolled patients were divided into 3 groups according to baseline NLR values. NLR values of 3.05 or below, 3.06 to 4.62 and 4.63 or above belong to group 1, 2 and 3 respectively. There were 75, 76, 74 patients in group 1, 2 and 3 respectively. There were no statistically significant differences in terms of baseline demographics, primary diagnosis, or comorbidity load, nutritional status, dialysis adequacy between the 3 groups. Interestingly, surrogates for inflammation including MIS and CRP did not correlate with baseline NLR (Table 2). Also, nutrition markers such as albumin and body mass index did not have significant association with NLR (Table 2). On the other hand, there was no significant difference in NLR between patients treated with continuous ambulatory peritoneal dialysis and automated peritoneal dialysis (4.61±3.13 vs 4.36±2.44, p=0.70).

Measurement of clinical and biochemical parameters (except MIS and SGA) were repeated 1 year after the first data collection per protocol of our center. Baseline hemoglobin and follow-up hemoglobin did not correlate with their corresponding NLR ($p > 0.05$). Moreover, there was an significant increase in hemoglobin level after 1 year (8.9±1.3 vs 9.5±1.7 g/dL, mean difference 0.47g/dL, 95% CI 0.25 to 0.70, $p<0.001$).

Baseline and follow-up NLR

Among the 225 patients enrolled into the study, 10 patients passed away within 1 year. Therefore, the second set of clinical and biochemical data were collected for 215 patients only.

The median of NLR values from the two different time-points were both 3.89. There was no significant change in NLR value after 1 year (mean difference 0.46, 95% CI -0.17 – 1.09, p=0.16).

Prognostic value of baseline NLR on all-cause and CV mortality

The median duration of follow up was 43.9 (interquartile range 22.6-72.6) months. During this period, 123 (57.2%) patients died, with CV cause accounting for 51 (41.4%) death. 36 (16.7%) patients switched to HD, 25 (11.6%) patients received renal transplant, 5 (2.3%) patients were transferred to other renal centers.

As shown in Figure 2, patients with lower baseline NLR demonstrated a higher survival rate (p=0.01). The 5-year survival for group 1, 2 and 3 were 58.9%, 55.3% and 31.9% respectively. For the second measurement, the 5-year survival for group 1, 2 and 3 were 57.8%, 40.4% and 55.5%. However, the difference in survival rate did not reach statistical significance (p=0.08) (not shown).

On univariate Cox regression, high baseline NLR value, old age, history of diabetes mellitus, ischemic heart disease, use of non-biocompatible solution, low albumin and high carotid-femoral pulse wave velocity were associated with

higher risk of all-cause mortality. Multivariate Cox regression showed that baseline NLR remained an independent predictor for all-cause mortality (HR 1.08, 95%CI 1.02 to 1.15, p=0.01), after adjusting for age, diabetes mellitus, use of non-biocompatible solution, and nutrition (Table 3). Specifically, every unit increase in baseline NLR was associated with 8% increase in all-cause mortality. Kt/V and GFR were not shown to have a significant relationship with all-cause mortality in univariate analysis (HR 0.85, 95% CI 0.62 to 1.18, p=0.34 and HR 0.99, 95% CI 0.93 to 1.05, p=0.68 respectively) or multivariate analysis.

Kaplan-Meier curves showed no significant difference in CV mortality between tertiles of baseline NLR (log-rank test, p=0.1) (not shown).

Prognostic value of serial NLR on all-cause and CV mortality

Patients were again categorized evenly into three tertiles according to their NLR measured after one year. The group with highest mean NLR value demonstrated a lowest survival rate (p=0.04) (not shown).

The patients were then classified into 3 groups, namely 'persistently high NLR', 'persistently low NLR' and 'evolving NLR'. The Kaplan-Meier curve (Figure 3) showed that patients who had persistently high NLR value after 1 year demonstrated worse survival rate, while those with persistently low NLR value after 1 year had better survival (p=0.03).

Kaplan-Meier curves were plotted similarly for the effects of follow-up NLR and change in NLR after 1 year (not shown) on CV mortality with the difference between various groups evaluated using the Log rank test. Nonetheless, they failed to demonstrate any statistically significant results in terms of patient's CV mortality.

On univariate Cox regression, persistently high NLR value were associated with higher risk of all-cause mortality. However, neither follow-up NLR value, nor change in NLR, was associated with all-cause mortality. Multivariate Cox regression, which included potential confounders as in the baseline model, was constructed to examine the prognostic role of serial NLR. Specifically, after adjusting for age, diabetes mellitus, use of non-biocompatible solution and nutrition, persistently high NLR value on serial measurement was an independent predictor for all-cause mortality (HR 1.74, 95%CI 1.09 to 2.79, p=0.02) (Table 4).

Baseline NLR, follow-up NLR, and the change in NLR value failed to demonstrate a statistically significant relationship with CV mortality in univariate analysis (p=0.99, 0.35 and 0.43 respectively).

Discussion

This study demonstrated that high baseline NLR is associated with increased all-cause mortality in incident PD patients. However, it was not associated with CV mortality.

Previous studies had demonstrated that the presence of peripheral neutrophilia was associated with adverse outcome in general patients with coronary artery disease [14], and that elevated total white blood cell counts strongly predicted all-cause and CV mortality upon initiation of PD [15]. Besides, lymphopenia was also studied to be a potential prognostic tool in coronary artery disease [16]. Therefore, elevated NLR may be an even more ideal and predictive prognostic tool. There were several proposed mechanisms for the association of NLR with CV diseases: neutrophils act as proinflammatory cells, initiate atherosclerosis, aggravate endothelial dysfunction, activate macrophages and promote foam cell formation [17]. On the other hand, immune activation and release of cytokine, e.g. tumor necrosis factor, may reduce lymphocytes by apoptosis [18].

There were previous studies which focused on the prognostic value of NLR in patients with stage 4 chronic kidney disease [7] and HD patients [8]. High NLR was found to be an independent predictor of all-cause mortality in both populations. Cai et al [19] also reported the independent association between NLR and arterial stiffness in PD patients. Our study results were consistent with previous studies which focused on mortality in PD patients. High NLR was reported to be independently associated with all-cause mortality in PD patients [9,10]. In the 5-year cohort study, Zhang et al reported that higher NLR value was an independent predictor for increased all-cause mortality (HR 2.60, 95%CI 1.04-6.54, p=0.042) and CV mortality (HR 2.89, 95%CI 1.01-8.28, p=0.04) in PD patients [10]. However, the HR of baseline NLR in all-cause mortality in our study was 1.08 only and the baseline NLR value was not associated with CV mortality. There are several reasons to account for the discrepancy. First, their study excluded patients who had chronic infection (including hepatitis B virus, hepatitis C virus, and human immunodeficiency virus), history of renal transplant, and use of immunosuppressive drugs within 3 months. These conditions were not excluded in our study but they possibly affect the baseline NLR value. Second, the median age of patients in their study was 54.7 years while that of ours was 59 years. The older age in our study might also increase the baseline NLR value and thus underestimate the corresponding HR. Third, it was of note that typical major CV risk factors, including age, prevalence of diabetes, history of CVD, and PWV, were comparable between the three groups at baseline, which may lead to similar CV outcomes. Despite being the major cause of mortality, CV death only accounted for 41.4%, which was significantly lower than two other published studies (61.2-64.9%) [9,10]. This may render our study underpowered to detect any potential predictive value of NLR. However, our study did show that, in spite of similar demographics, background comorbidity and nutrition status, NLR remained an independent predictor of all-cause mortality. This suggested NLR may play a pathophysiological role in addition to it well recognized association with inflammation and malnutrition. Importantly, our study is the first one to look into and provide insight on the significance and additional value of serial monitoring of NLR level. Our selection of incident patients, compared with prevalent patients in published literature [8-10], had the theoretical advantage of reducing Neyman bias.

Patients with ESRD on PD sustained a chronic inflammatory state and would undoubtedly influence the level of NLR with time. In our study, the baseline NLR, but not the follow-up NLR, was found to be an independent predictor for all-cause mortality. During the second measurement of NLR value when the patients had received 1 year of PD, there may be progression of inflammation burden due to ESRD per se, and variation of different clinical conditions after 1 year. This would probably explain the insignificant results for the follow-up NLR value in our study. However, as shown in Table 3, after adjusting for age, DM, use of non-biocompatible solution and nutrition, a persistently high NLR value on serial measurement had a stronger association with mortality compared with the baseline NLR alone (adjusted HR 1.74 vs 1.08). Therefore, serial measurement of NLR, compared with one-time measurement, is essential to improve its predictive ability on all-cause mortality. It is thus important to incorporate serial measurement of NLR in assessing a patient's prognosis, with a focus on identifying patients with persistently high NLR value on follow up. Nevertheless, it should be noted that there are indeed different interactions of NLR with various genetic, demographic and environmental factors [20,21]. Some of the factors exhibited time-dependent variation and thus, apart from the chronic inflammation from chronic kidney disease per se, would affect the level of NLR measured

in different time points. This may potentially explain the discrepancy of results using NLR value from two different time points in our study.

CRP is an acute phase reactant synthesized in the liver and is a commonly used marker of inflammation in chronic kidney disease. However, we observed that surrogates for inflammation including MIS and CRP did not correlate with the baseline NLR. There are two possible reasons. First, CRP level may demonstrate time-dependent within-person variation. Bower et al [22] evaluated the short-term, within-person variability in CRP measurement by recruiting 541 participants aged 16 to 69 years and performing repeated measurement of CRP, with each measurement 2.5 weeks apart. A significant within-person variability in CRP was observed after 2.5 weeks, the within-person coefficient of variation was 46.2% (95%CI, 42.9%-49.3%). Bogaty et al [23] made two to eight CRP measurements for 159 patients with stable ischemic heart disease at intervals varying from 15 days to 6 years and found within-patient variance of CRP to be 1.79mg/L (95%CI, 1.6-2.0). Hence, the study population in our study, who had a chronic inflammatory state, would likely have a similar within-person variability in CRP. Second, CRP was shown to have a more delayed response towards inflammation compared to white blood cells. Lee et al [24] studied the prognostic value of serial NLR in community acquired pneumonia. They reported that NLR value on day 4 of admission and the incremental change of NLR value from day 1 to day 4 were significant predictors of 30-day mortality, but CRP value on day 4 of admission and incremental change of CRP were not. In our study, it is possible that given the background of ESRD, a recent Tenckhoff catheter insertion followed by initiation of peritoneal dialysis will induce a certain degree of inflammation leading to time-dependent variation of CRP and NLR values. On the other hand, NLR did not correlate with nutrition markers such as serum albumin, body mass index, SGA or MIS. This suggested that its predictive value on all-cause mortality was independent from malnutrition.

However, several limitations existed in this study. First, the mean hemoglobin (8.9±1.3g/dL) in our study population was low compared to the usual target for cardiovascular disease prevention. However, it showed significant improvement after the first year; and the impact of hemoglobin variability (if any) in our cohort on CV mortality was not predictable. One possible reason for the relatively low baseline hemoglobin in our study was that erythropoiesis stimulating agents were not fully subsidized by the government in the early 2010s. Furthermore, a recent Korean study revealed that the adverse effect of anemia (defined as hemoglobin <10g/dL) on CV mortality became insignificant in younger patients compared with elderly (age >60) [25]. This may potentially explain the absence of association between anemia and CV mortality in the whole cohort as nearly half of them were younger than 60 years. Second, there was selection bias since the study was a single-center study involving a small number of patients, which limited the generalizability of our findings to others. Third, the causal relationship between NLR value and clinical outcome could not be established owing to the inherent deficit of a retrospective study. Lastly, the first measurement of clinical and biochemical data including NLR value was performed around 2 months after initiation of PD due to logistic reasons. Therefore, they may not represent the true baseline status of the patients. Moreover, it is still uncertain whether NLR value is a surrogate marker of inflammation, or it represents an increased risk per se, and given the poor correlation of NLR with CRP in our study, the physiological implication of NLR is yet to be determined.

Conclusion

This study suggested that NLR was an independent predictor of all-cause mortality in patients with ESRD on PD, while persistent elevation in NLR appeared to further amplify the risk. NLR is readily available and inexpensive. Routine monitoring of serial serum NLR may enable early identification of patients who are at risk of adverse outcome. Further large-scale prospective study would be required to study the NLR value above which the patients would have worse outcomes, and to explore the effective intervention to change NLR.

Acknowledgments

Nil

Statement of Ethics

This study was approved by the Joint Chinese University Hong Kong-New Territories East Cluster Clinical Research Ethics Committee (CREC Ref. 2008.276 and 2015.250). All studies procedures were conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent

Conflict of Interest Statement

The authors declare no conflicts of interest in relation to this work.

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Authors' Contributions

L.F.S.L and C.C.S conceived the idea of this study. L.F.S.L. and J.K.C.N. devised the method of analysis. W.W.S.F., G.C.K.C., P.M.S.C., K.M.C. collected data. L.F.S.L and J.K.C.N carried out the statistical analyses. L.F.S.L. prepared the manuscript. C.B.L., P.L. and C.C.S. supervised the whole project and provided mentorship. All authors provided intellectual input and endorsed to the final manuscript.

Data Availability Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Reference

1. Saran R, Robinson B, Abbott KC, Bragg-Gresham J, Chen X, Gipson D, et al. US renal data system 2019 annual data report: Epidemiology of kidney disease in the United States. Am J Kidney Dis. 2020;75.1: A6–7
2. Li PK-T, Ng JK-C, Mcintyre CW. Inflammation and peritoneal dialysis. Semin Nephrol. 2017;37(1):54–65
3. Zhang J, Ren Q, Song Y, He M, Zeng Y, Liu Z, et al. Prognostic role of neutrophil–lymphocyte ratio in patients with acute ischemic stroke. Medicine (Baltimore). 2017;96(45): e8624
4. Wang X, Zhang G, Jiang X, Zhu H, Lu Z, Xu L. Neutrophil to lymphocyte ratio in relation to risk of all-cause mortality and cardiovascular events among patients undergoing angiography or cardiac revascularization: a meta-analysis of observational studies. Atherosclerosis. 2014;234(1):206–13
5. Templeton AJ, McNamara MG, Šeruga B, Vera-Badillo FE, Aneja P, Ocaña A, et al. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. J Natl Cancer Inst. 2014;106(6): dju124
6. Eslamijouybari M, Heydari K, Maleki I, Moosazadeh M, Hedayatizadeh-Omran A, Vahedi L, et al. Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios in COVID-19 patients and control group and relationship with disease prognosis. Caspian J Intern Med. 2020 Autumn;11(Suppl 1):531–5
7. Yuan Q, Wang J, Peng Z, Zhou Q, Xiao X, Xie Y, et al. Neutrophil-to-lymphocyte ratio and incident end-stage renal disease in Chinese patients with chronic kidney disease: results from the Chinese Cohort Study of Chronic Kidney Disease (C-STRIDE). J Transl Med. 2019;17(1):86
8. Li H, Lu X, Xiong R, Wang S. High neutrophil-to-lymphocyte ratio predicts cardiovascular mortality in chronic hemodialysis patients. Mediators Inflamm. 2017; 2017:9327136.

9. Lu X, Wang S, Zhang G, Xiong R, Li H. High neutrophil-to-lymphocyte ratio is a significant predictor of cardiovascular and all-cause mortality in patients undergoing peritoneal dialysis. Kidney Blood Press Res. 2018;43(2):490–9

10. Zhang L, Nie Y, Guo M, Wang L, Shi Y, Jiang X, et al. Neutrophil to lymphocyte ratio as a predictor of long-term outcome in peritoneal dialysis patients: A 5-year cohort study. Blood Purif. 2021;50(6):772–8

11. He T, An X, Mao HP et al. A malnutrition-inflammation score is correlated with morbidity and mortality in maintenance hemodialysis patients. Am J Kidney Dis. 2001; 38.6: 1251-1263.

12. Enia G, Sicuso C, Alati G, Zoccali C. Subjective global assessment of nutrition in dialysis patients. Nephrol Dial Transplant. 1993;8(10):1094–8.

13. Szeto C-C, Kwan BC-H, Chow K-M, Leung C-B, Law M-C, Li PK-T. Prognostic value of arterial pulse wave velocity in peritoneal dialysis patients. Am J Nephrol 2012;35(2):127–33

14. Kirtane AJ, Bui A, Murphy SA, Barron HV, Gibson CM. Association of peripheral neutrophilia with adverse angiographic outcomes in ST-elevation myocardial infarction. Am J Cardiol. 2004;93(5):532–6.

15. Johnson DW, Wiggins KJ, Armstrong KA, Campbell SB, Isbel NM, Hawley CM. Elevated white cell count at commencement of peritoneal dialysis predicts overall and cardiac mortality. Kidney Int. 2005;67(2):738–43.

16. Ommen SR, Gibbons RJ, Hodge DO, Thomson SP. Usefulness of the lymphocyte concentration as a prognostic marker in coronary artery disease. Am J Cardiol. 1997;79(6):812–4.

17. Soehnlein O. Multiple roles for neutrophils in atherosclerosis. Circ Res. 2012 ;110(6):875–88.

18. Castro A, Bemer V, Nóbrega A, Coutinho A, Truffa-Bachi P. Administration to mouse of endotoxin from gram-negative bacteria leads to activation and apoptosis of T lymphocytes. Eur J Immunol. 1998;28(2):488–95.

19. Cai K, Luo Q, Zhu B, Han L, Wu D, Dai Z, et al. Neutrophil-lymphocyte ratio is associated with arterial stiffness in patients with peritoneal dialysis. BMC Nephrol. 2016 ;17(1).

20. Lin BD, Hottenga J-J, Abdellaoui A, Dolan CV, de Geus EJC, Kluft C, et al. Causes of variation in the neutrophil-lymphocyte and platelet-lymphocyte ratios: a twin-family study. Biomark Med. 2016;10(10):1061–72.

21. Howard R, Scheiner A, Kanetsky PA, Egan KM. Sociodemographic and lifestyle factors associated with the neutrophil-to-lymphocyte ratio. Ann Epidemiol. 2019; 38:11-21. e6.

22. Bower JK, Lazo M, Juraschek SP, Selvin E. Within-person variability in high-sensitivity C-reactive protein. Arch Intern Med. 2012;172(19):1519–21.

23. Bogaty P, Brophy JM, Boyer L, Simard S, Joseph L, Bertrand F, et al. Fluctuating inflammatory markers in patients with stable ischemic heart disease. Arch Intern Med. 2005;165(2):221–6.

24. Lee H, Kim I, Kang BH, Um S-J. Prognostic value of serial neutrophil-to-lymphocyte ratio measurements in hospitalized community-acquired pneumonia. PLoS One. 2021;16(4): e0250067.

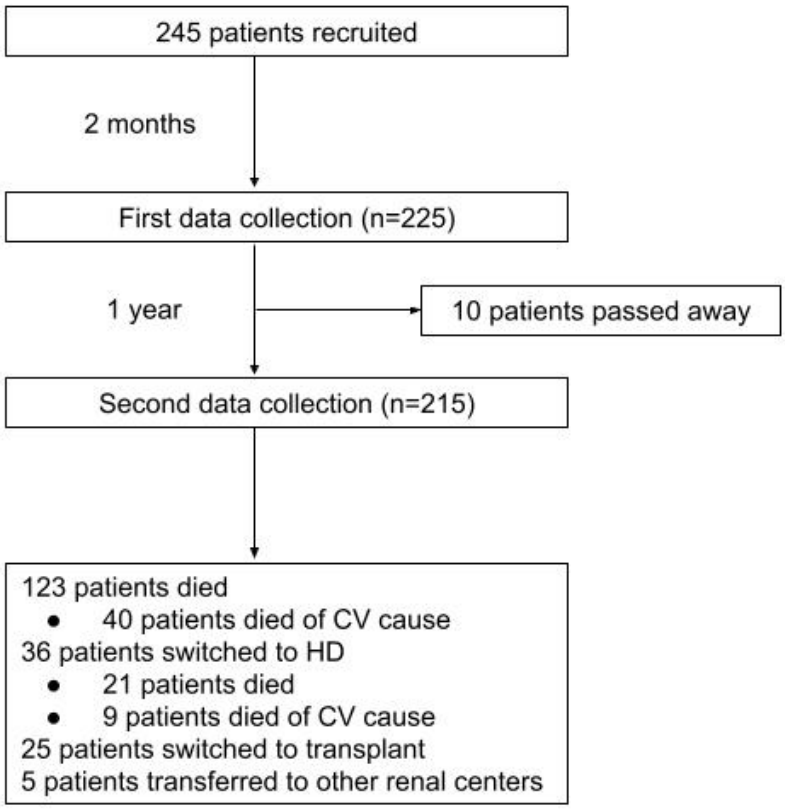
25. Ko EJ, Kim YK, Cho JH, Kim YS, Kang SW, Kim NH, et al. The differential effects of anemia on mortality in young and elderly end-stage renal disease patients. Kidney Res Clin Pract. 2020 Jun 30;39(2):192-201.

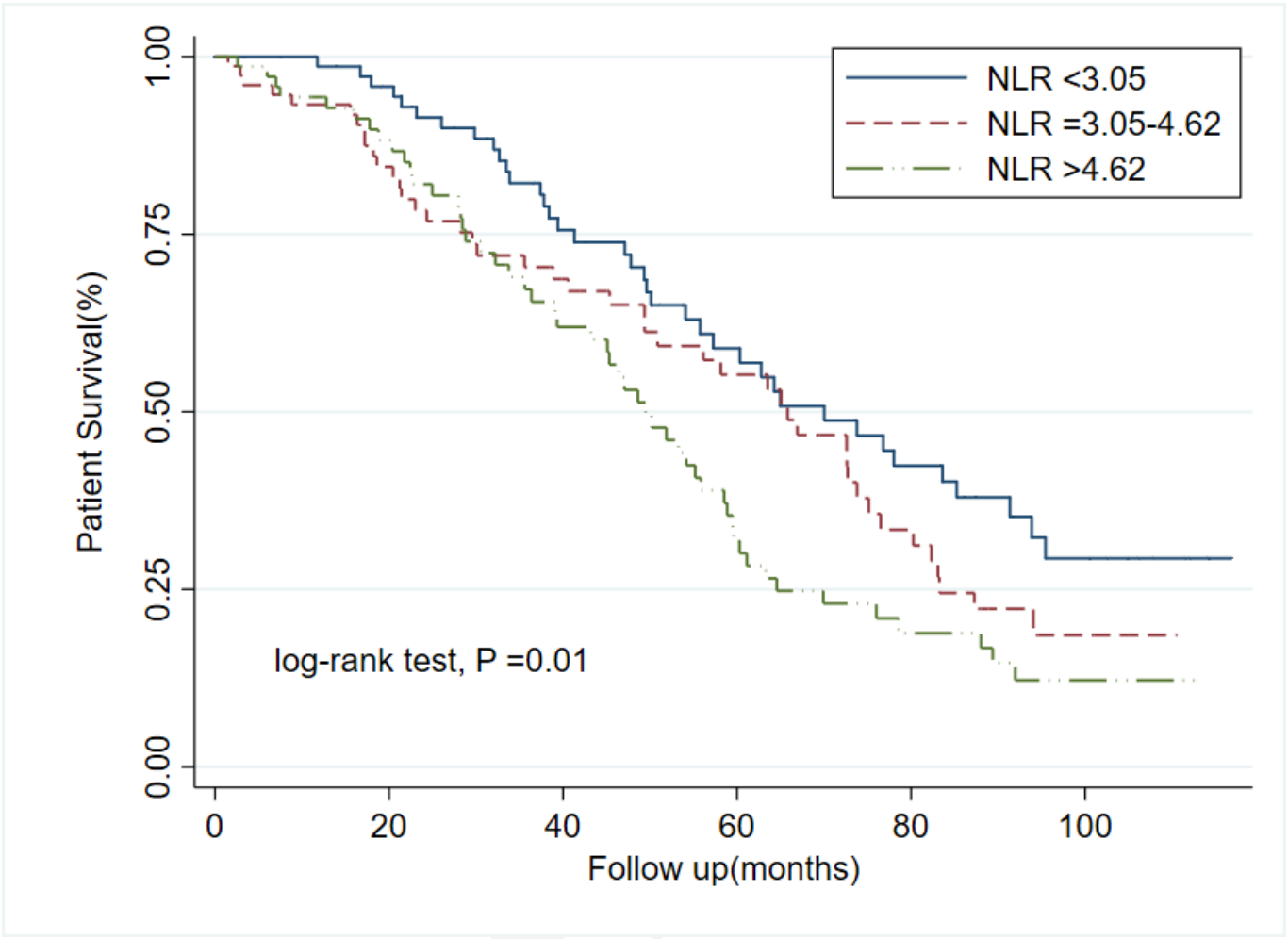
Figure legend

Figure 1. Flow diagram of patient's enrollment and their outcomes.

Figure 2. Kaplan-Meier survival curves for three different NLR groups according to their baseline NLR value. NLR, neutrophil to lymphocyte ratio

Figure 3. Kaplan-Meier survival curve for patients with persistently high NLR, persistently low NLR, and evolving NLR. NLR, neutrophil to lymphocyte ratio





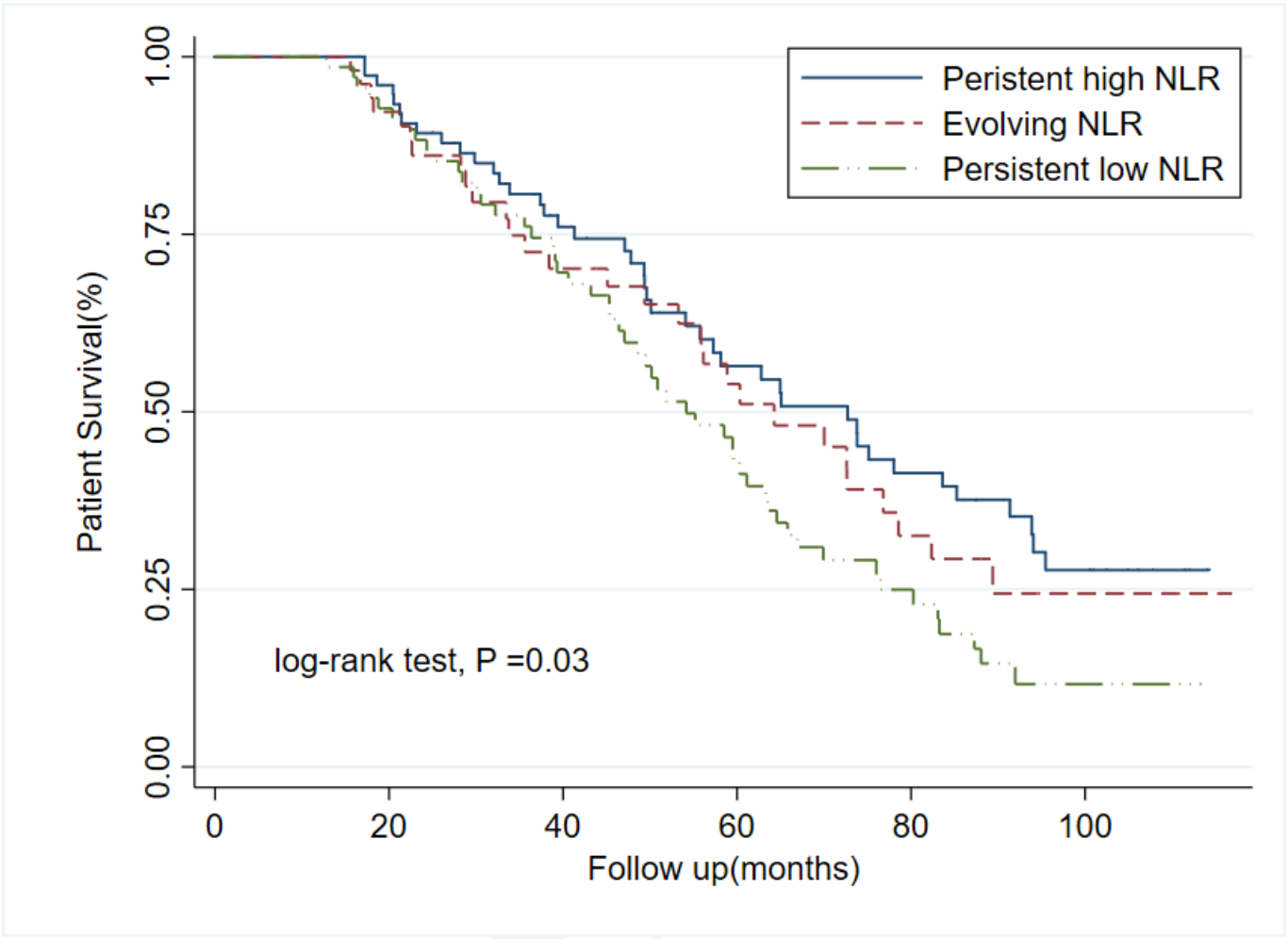


Table 1. Demographic and baseline characteristics of the study population.

Variables	Total (n = 225)	NLR ≤ 3.05 (n = 75)	3.05<NLR ≤ 4.62 (n = 76)	NLR >4.62 (n = 74)	p value
NLR	3.89 ± 3.06	2.54 ± 0.42	3.92 ± 0.45	6.04 ± 3.86	<0.01
Age (years)	59 ± 12.3	58 ± 13.9	58 ± 12.1	60 ± 10.6	0.53
Male	129 (57.3%)	42 (56%)	47 (61.8%)	40 (54.1%)	0.61
Primary diagnosis					0.36
DMN	96 (42.7%)	27 (28.1%)	31 (32.3%)	38 (39.6%)	-
GN	59 (26.2%)	26 (44.1%)	18 (30.5%)	15 (25.4%)	-
HTN	21 (9.3%)	6 (28.6%)	6 (28.6%)	9 (42.9%)	-
PKD	10 (4.4%)	4 (40%)	5 (50%)	1 (10%)	-
Urological disease	12 (5.3%)	5 (41.7%)	4 (33.3%)	3 (25%)	-
Other/unknown	27 (12%)	7 (25.9%)	12 (44.4%)	8 (29.6%)	-
DM	115 (51.1%)	34 (45.3%)	36 (47.4%)	45 (60.8%)	0.12
IHD	55 (24.4%)	25 (33.3%)	15 (19.7%)	15 (20.3%)	0.10
CVA	52 (23.1%)	15 (20%)	18 (23.7%)	19 (25.7%)	0.71
Malignancy	21 (9.3%)	7 (9.3%)	8 (10.5%)	6 (8.1%)	0.88
MIS	6.9 ± 3.6	7.1 ± 2.9	6.7 ± 3.7	7.0 ± 4.1	0.83
SGA	5.3 ± 0.9	5.3 ± 1.0	5.3 ± 0.9	5.3 ± 0.9	0.99
Biocompatible solution	32 (14.2%)	13 (40.6%)	8 (25%)	11 (34.4%)	0.48
Hb (g/dL)	8.9 ± 1.3	9.1 ± 1.2	9.0 ± 1.3	8.8 ± 1.2	0.42
WCC ($x10^9$/L)	6.6 ± 2.2	6.1 ± 1.6	6.8 ± 1.6	8.2 ± 2.5	<0.01
CRP (mg/l)	4.1 ± 3.0	4.2 ± 0.8	4.4 ± 1.6	5.0 ± 5.0	0.36
Neutrophil ($x10^9$/L)	4.6 ± 2.0	3.7 ± 1.0	4.6 ± 1.1	6.3 ± 2.4	<0.01
Lymphocyte ($x10^9$/L)	1.1 ± 0.4	1.5 ± 0.4	1.2 ± 0.3	0.9 ± 0.3	<0.01
Albumin (g/l)	35 ± 4.6	34 ± 4.2	35.2 ± 4.8	35.6 ± 4.5	0.15
GFR (ml/min/1.73m^2)	2.9 ± 2.7	3.6 ± 2.6	3.2 ± 2.8	3.1 ± 2.7	0.44
Total weekly Kt/V	2.1 ± 0.6	2.1 ± 0.6	2.1 ± 0.6	2.1 ± 0.5	0.67
CR-PWV	10.9 ± 1.6	11.1 ± 1.5	10.8 ± 1.5	10.8 ± 1.8	0.44
CF-PWV	11.7 ± 2.4	11.8 ± 2.6	11.2 ± 2.3	12 ± 2.4	0.10

NLR, neutrophil to lymphocyte ratio; DMN, diabetic nephropathy; GN, glomerulonephritis; HTN, hypertensive nephropathy; PKD, polycystic kidney disease; DM, diabetes mellitus; IHD, ischemic heart disease; CVA, cardiovascular disease; MIS, Malnutrition Inflammation Score; SGA, Subjective Global Assessment; Hb, hemoglobin; WCC, white cell count; CRP, C reactive protein; GFR, glomerular filtration rate; CR-PWV, carotid-radial pulse wave velocity; CF-PWV, carotid-femoral pulse wave velocity.

Table 2. Correlation analysis between baseline variables and baseline NLR

Variables	r	p value
Age (years)	-0.13	0.85
MIS	0.05	0.55
SGA	-0.07	0.39
BMI (kg/m^2)	-0.05	0.48
Hb (g/dL)	0.004	0.96
WCC ($x10^9/L$)	0.51	<0.001
CRP (mg/l)	0.05	0.54
Neutrophil ($x10^9/L$)	0.70	<0.001
Lymphocyte ($x10^9/L$)	-0.53	<0.001
Albumin (g/l)	0.05	0.49
GFR ($ml/min/1.73m^2$)	-0.08	0.24
Total weekly Kt/V	0.01	0.85
CR-PWV	-0.02	0.82
CF-PWV	0.03	0.65

NLR, neutrophil to lymphocyte ratio; MIS, Malnutrition Inflammation Score; SGA, Subjective Global Assessment; BMI, body mass index; Hb, hemoglobin; WCC, white cell count; CRP, C reactive protein; GFR, glomerular filtration rate; CR-PWV, carotid-radial pulse wave velocity; CF-PWV, carotid-femoral pulse wave velocity

Table 3. Univariate and multivariate Cox regression analysis for all-cause mortality.

Variables	All-cause mortality			
	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P value	HR (95%CI)	P value
NLR (per one unit)	1.05 (1.00, 1.11)	0.05	1.08 (1.02, 1.15)	0.01
Age (per year)	1.07 (1.05, 1.09)	<0.02	1.07 (1.05, 1.10)	<0.001
DM	3.20 (2.18, 4.70)	<0.01	1.98 (1.24, 3.16)	0.004
Biocompatible solution	0.27 (0.15, 0.48)	<0.001	0.25 (0.13, 0.49)	<0.001
Albumin (per 1 g/l)	0.93 (0.90, 0.97)	0.001	0.95 (0.91, 0.99)	0.02
IHD	1.46 (1.01, 2.11)	0.05	-	-
CF-PWV (per m/s)	1.19 (1.12, 1.28)	<0.01	-	-

CI, confidence interval; NLR, neutrophil to lymphocyte ratio; DM, diabetes mellitus; IHD, ischemic heart disease; CF-PWV, carotid-femoral pulse wave velocity.

Table 4. Univariate and multivariate Cox regression analysis for all-cause mortality.

Variables	All-cause mortality			
	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P value	HR (95%CI)	P value
Persistently high NLR	1.73 (1.14, 2.63)	0.01	1.74 (1.09, 2.79)	0.02
Evolving NLR	1.38 (0.86, 2.21)	0.18	-	-
Persistently low NLR	1 (reference)	-	1 (reference)	-
Age (per year)	1.07 (1.05, 1.09)	<0.02	1.08 (1.05, 1.10)	<0.001
DM	3.20 (2.18, 4.70)	<0.01	2.05 (1.32, 3.20)	0.002
Biocompatible solution	0.27 (0.15, 0.48)	<0.001	0.26 (0.13, 0.51)	<0.001
Albumin (per 1 g/l)	0.93 (0.90, 0.97)	0.001	0.95 (0.91, 0.99)	0.02
IHD	1.46 (1.01, 2.11)	0.05	-	-
CF-PWV (per m/s)	1.19 (1.12, 1.28)	<0.01	-	-

CI, confidence interval; NLR, neutrophil to lymphocyte ratio; DM, diabetes mellitus; IHD, ischemic heart disease; CF-PWV, carotid-femoral pulse wave velocity.