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Relationship of Neutrophil to Lymphocyte Ratio (NLR) With Bone Markers and Vascular Changes in Chronic Kidney Disease Patients

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Relationship of Neutrophil to Lymphocyte Ratio (NLR) with Bone Markers and Vascular Changes in Chronic Kidney Disease Patients

Ahmed Ahmed Elsawy Ahmed Mohamed Saad, Hani Ibrahim Hamed, Mohamed Fawzy Ibrahim Mosa, Ahmed Khalud Mohamed Khaled

Abstract

Background: The neutrophil/lymphocyte ratio (NLR), which increases during inflammation and may be linked to a worse prognosis in chronic kidney disease (CKD), has been the subject of several recent research.

Aim and objectives: The objective of the current study was to investigate how individuals with chronic renal disease’s NLR correlated with bone markers and vascular alterations.

Patients and methods: This was a prospective case control study which done at Nephrology Department, Ahmed Maher Teaching Hospital, Cairo, Egypt. The study was conducted over a 1-year duration, from October 2021 to October 2022.

Results: Serum vitamin D showed a significant decline in patients with CKD compared with controls, as it had mean values of 30.34, 20.43, and 20.56 ng/ml in the study groups, respectively (P < 0.001). On the other hand, serum parathyroid hormone (PTH) had increased levels in CKD groups compared with controls, as it had median values of 40, 101.8, and 391.5 pg/ml in the three study groups, respectively.

Conclusion: End stage renal disease (ESRD) is associated with a significant increased carotid internal medical therapy (IMT), reflecting atherosclerotic burden in such patients. CKD is not associated with significant changes in NLR. NLR is not significantly correlated with either bone or vascular changes in CKD patients. Therefore, it should not be used to monitor these changes in the CKD setting.

Keywords: Bone markers, Chronic kidney disease, Neutrophil to lymphocyte ratio (NLR), Vascular

1. Introduction

According to estimates, more than 9.1% of people worldwide suffer from chronic renal disease (697.5 million in 2017). Chronic kidney disease (CKD).

Only 2 million people globally, or 10% of those with CKD Stage 5 who require it to survive, are believed to get life-saving dialysis. The risk of cardiovascular mortality, undernutrition, and the complete spectrum of morbidities associated with maintenance hemodialysis are all primarily caused by chronic inflammation (MHD). The neutrophil to lymphocyte ratio determines the proportion of neutrophils to lymphocytes in peripheral blood (NLR). The outcome of a complete blood count led to it (CBC), a straightforward test that is frequently used to assess a variety of diseases, including anemia, inflammation, and infections. NLR is a commonly available and fairly priced indication for inflammation despite not being especially unique. NLR is less expensive than other indicators of inflammation like CRP, IL6, or ferritin since it has been used for prognostication in cancer more than other professions. It has lately gained attention once again as an intriguing marker connected to a variety of outcomes, including

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cardiovascular mortality and death from all causes. It has been shown that in these people, it predicts all-cause death more precisely than Total Leukocyte WBC Count (TLC).\(^5\)

However, other investigations have shown that NLR is substantially correlated with the development of CKD and is independently (of hsCRP) linked with endothelial dysfunction. In several studies, NLR has been analyzed as a substitute for High Sensitive CRP (hsCRP) in the population with CKD.\(^6\)

One of a number of mineral and bone diseases (CKD-MBD) that develop from CKD, including secondary hyperparathyroidism (SHPT), which has a high bone turnover rate, is renal osteodystrophy.\(^7\)

Given that the majority of hemodialysis patients have high levels of para thyroid hormone (PTH) and a high incidence of inflammation, it has been hypothesized that PTH and inflammation in this population are positively correlated. However, very few studies have examined the connection between PTH and inflammation in the dialysis population, and those that did change how they selected PTH-based subsets because they found a very weak correlation.\(^8\)

The objective of the current study was to investigate how individuals with chronic renal disease's NLR correlated with bone markers and vascular alterations.

2. Patients and methods

This was a prospective case control study which was conducted over one-year duration, from October 2021 to October 2022.

The study included 90 participants who were divided into three equal groups; Group 1 included 30 healthy controls. Group 2 included 30 patients with conservative treatment (stage 3 and 4). Group 3 included 30 patients with end stage renal disease (ESRD) and on regular haemodialysis. The stage of CKD was determined based on the KDIGO classification.\(^9\)

Inclusion criteria: Patient's age greater than 18 and less than 65 years old, patients in conservative treatment, patients on regular haemodialysis sessions greater than 6 months duration and healthy controls with serum creatinine less than 1.2 mg/dl.

Exclusion criteria: The exclusion criteria for healthy controls included limited mobility, extensive enteral medical procedure, short gut condition, malabsorption, glucocorticoid treatment, provocative problems (counting dynamic rheumatoid joint pain and fiery gut sickness requiring oral glucocorticoids), constant liver illness, flow therapy with teriparatide or strontium ranelate, and cooperation in a preliminary.

Ethical consideration: The Al-Azhar University faculty of medicine's regional ethical committee gave the study their blessing. All participants—patients and controls—felt free to voluntarily discontinue the research at any time. Personal privacy was maintained, and the data were only utilized for research purposes.

Patient consent: An informed written consent was obtained from all participants after complete explanation of the benefits of the study, and the possible complications of each intervention.

3. Patient evaluation

3.1. History taking

3.1.1. Clinical examination

Laboratory investigations: Complete blood count with its main parameters (hemoglobin, leucocytic count, and platelet). The differential leucocytic count was calculated as well (including neutrophils and lymphocytes). It was performed by Sysmex XS-500i, SYSMEX EUROPE GMBH, Germany.\(^10\)

Measurement of carotid internal medical therapy (IMT): An accomplished radiologist estimated the thickness of the carotid intima-media utilizing the carotid ultrasound contraption (Mindray Constant ultrasound scanner DC-6 with Doppler offices: transducer test recurrence of 7.5 MHz).

And controls, comparing carotid IMT between CKD patients and controls.

3.2. Statistical analysis

The factual program for sociologies (SPSS 22.0, IBM/SPSS Inc., Chicago, IL) and Pearson's relationship coefficient were utilized to survey the outcomes genuinely. \(\chi^2\) test (2) Constrasting one subjective variable between at least two groups was applied. At the point when the assumption that somewhere
around 80% of the anticipated frequencies are more prominent than five was broken, the Fisher's Careful Test was applied instead of the Chi-Square (2) test.

Test Kruskal-Wallis: It is a non-parametric option in contrast to ANOVA and is utilized to look at multiple gatherings of slanted information when ANOVA suppositions have been broken.

4. Results

Table 1.

The mean age of the included cases was 41.3, 54.03, and 59.07 years in Groups 1, 2, and 3, respectively, with a significant increase in the latter group ($P < 0.001$). Regarding gender distribution, men represented 56.7%, 36.7%, and 26.7% of patients in the three groups, respectively, while the remaining cases were women. The prevalence of male gender showed a significant increase in Group 3 ($P = 0.008$) Table 2.

The prevalence of diabetes was statistically comparable between the three study groups ($P = 0.093$), as it was present in 36.7%, 53.3%, 63.3% of cases in the three study groups, respectively. Nonetheless, the duration of hypertension showed a significant decline in Group 1 compared with the other two diseased groups ($P < 0.001$). It had mean values of 4.45, 11.56, and 11.47 years in the three groups, respectively Table 3.

Table 2.

Total leucoycotic count had mean values of 6.14, 7.7, and 6.73 $\times 10^3$/ml in the three study groups, with a significant difference on the statistical analysis ($P = 0.009$). However, both neutrophil and lymphocytic counts showed no significant difference between the three study groups ($P = 0.344$ and 0.829, respectively. The former had median values of 4.5, 4.3, and 4.34 $\times 10^3$/ml, while the latter had median values of 1.63, 1.57, and 1.55 $\times 10^3$/ml in the three study groups, respectively. NLR had median values of 2.55, 2.63, and 2.55 in the same three
groups, respectively, which was nonsignificant on statistical analysis ($P = 0.796$) Table 4.

Serum vitamin D showed a significant decline in patients with CKD compared with controls, as it had mean values of 30.34, 20.43, and 20.56 ng/ml in the study groups respectively ($P < 0.001$). On the other hand, serum PTH had increased levels in CKD groups compared with controls, as it had median cut-off value of 2.92 was used Fig. 2. Carotid IMT had mean values of 0.65, 0.63, and 0.69 mm in the three study groups, respectively, with a significant difference between the three groups ($P = 0.044$). Although group 3 had a comparable IMT with group 1 (controls), it had a significantly higher value compared with group 2 ($P = 0.036$) Fig. 1.

NLR had sensitivity and specificity of 43.3% and 63.3%, respectively, with a diagnostic accuracy of 55.3% to differentiate group 2 from controls, when a cut-off value of 2.92 was used Fig. 2.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control group ($n = 30$)</th>
<th>CKD stage 3–4 ($n = 30$)</th>
<th>ESRD ($n = 30$)</th>
<th>significance test</th>
<th>Intergroup Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (gm/dl) [Mean ± SD]</td>
<td>12.98 ± 1.21</td>
<td>10.76 ± 1.48</td>
<td>10.06 ± 1.12</td>
<td>F = 42.332</td>
<td>$P_1 &lt; 0.001^*$</td>
</tr>
<tr>
<td>WBCs (10^3/ml) [Mean ± SD]</td>
<td>6.14 ± 1.64</td>
<td>7.70 ± 2.10</td>
<td>6.73 ± 2.02</td>
<td>F = 4.987</td>
<td>$P = 0.009^*$</td>
</tr>
<tr>
<td>Neutrophil (10^3/ml) [Median (range)]</td>
<td>4.5 (2.33–66)</td>
<td>4.3 (2.03–66)</td>
<td>4.34 (2.43–11.1)</td>
<td>KW = 0.340</td>
<td>$P_1 = 0.998$</td>
</tr>
<tr>
<td>Lymphocytes (10^3/ml) [Median (range)]</td>
<td>1.63 (0.33–3.61)</td>
<td>1.57 (0.44–3.61)</td>
<td>1.55 (0.30–3.24)</td>
<td>KW = 0.375</td>
<td>$P_1 = 0.947$</td>
</tr>
<tr>
<td>NLR [Median (range)]</td>
<td>2.55 (1.10–40.47)</td>
<td>2.63 (1.10–40.47)</td>
<td>2.55 (1.38–23)</td>
<td>KW = 0.456</td>
<td>$P_1 = 0.909$</td>
</tr>
</tbody>
</table>

**Table 3. Comparison of the complete blood count (CBC) in the study groups.**

KW, Kruskal–Wallis test; F, One-way ANOVA; PTH, para thyroid hormone; ESRD, end stage renal disease.

**Table 4. Comparison of the kidney functions and serum electrolytes in the study groups.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control group ($n = 30$)</th>
<th>CKD stage 3–4 ($n = 30$)</th>
<th>ESRD ($n = 30$)</th>
<th>significance test</th>
<th>Intergroup Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR (ml/min/1.73m^2) [Median (range)]</td>
<td>132 (74–190)</td>
<td>27 (15.5–56.6)</td>
<td>13 (5–15)</td>
<td>KW = 79.204</td>
<td>$P_1 &lt; 0.001^*$</td>
</tr>
<tr>
<td>Serum Urea (mg/dl) [Median (range)]</td>
<td>30 (20–50)</td>
<td>70 (39–192)</td>
<td>131 (109–167)</td>
<td>KW = 71.878</td>
<td>$P_1 &lt; 0.001^*$</td>
</tr>
<tr>
<td>Serum Creatinine (mg/dl) [Mean ± SD]</td>
<td>0.93 ± 0.16</td>
<td>2.27 ± 0.54</td>
<td>9.33 ± 2.96</td>
<td>F = 201.655</td>
<td>$P_1 &lt; 0.001^*$</td>
</tr>
<tr>
<td>Total Serum calcium (mg/dl) [Mean ± SD]</td>
<td>9.54 ± 0.73</td>
<td>8.76 ± 0.97</td>
<td>8.33 ± 0.51</td>
<td>F = 19.729</td>
<td>$P_1 &lt; 0.001^*$</td>
</tr>
<tr>
<td>Serum phosphorous (mg/dl) [Mean ± SD]</td>
<td>3.92 ± 0.52</td>
<td>4.31 ± 0.71</td>
<td>4.75 ± 0.99</td>
<td>F = 8.808</td>
<td>$P_1 &lt; 0.001^*$</td>
</tr>
<tr>
<td>25-(OH-Vit D) (ng/ml) [Mean ± SD]</td>
<td>30.34 ± 5.92</td>
<td>20.43 ± 5.15</td>
<td>20.56 ± 3.42</td>
<td>F = 39.709</td>
<td>$P_1 &lt; 0.001^*$</td>
</tr>
<tr>
<td>PTH (pg/ml) [Median (range)]</td>
<td>40 (23–63)</td>
<td>101.8 (28.7–436.7)</td>
<td>391.5 (5.5–2000)</td>
<td>KW = 46.411</td>
<td>$P_1 &lt; 0.001^*$</td>
</tr>
</tbody>
</table>

KW, Kruskal–Wallis test; F, One-way ANOVA; PTH, para thyroid hormone; ESRD, end stage renal disease.
Using a cut-off value of 2.46, NLR has sensitivity and specificity of 56.7% and 47.7%, respectively, with an accuracy of 53.3% to differentiate between Group 2 and 3.

5. Discussion

NLR is elevated during inflammation and may be linked to a worse prognosis in CKD, according to a number of recent studies Kocyigit and colleagues.14 Recent studies have stressed that NLR could be used as a marker for inflammation because inflammation causes an increase in neutrophil numbers while a decrease in lymphocyte counts Yilmaz and colleagues.15

NLR are particularly useful as indicators of inflammation since they can be assessed by a straightforward blood count. Therefore, we conducted the current study at Ahmed Maher Teaching Hospital with the goal of examining the link between bone markers and vascular alterations in CKD patients and NLR. The mean age of the cases included in the current investigation was 41.3 years for Groups 1, 2, and 3, and 59.07 years for group 3, with the latter group showing a significant increase (p 0.001). According to Tonyali and colleagues, 16 CKD patients were significantly older than the control group (64.1 vs. 56.1, respectively d P 0.001), which is consistent with our findings. However, Behairy and colleagues 20 found that the ages of CKD patients and controls were comparable (64.23 and 61.53 years, respectively d P ¼ 0.123).

Men made up 56.7, 36.7, and 26.7% of the patients in the current study’s three patient groups, respectively, with women accounting for the remaining instances. In group 3, there was a discernible rise in the proportion of men (P ¼ 0.008).

Another recent study reported no significant difference between CKD patients and controls regarding gender (P = 0.084). Men represented 71.7 and 53.3% of patients in the CKD and control groups, respectively, while the remaining portion was occupied by women Behairy and colleagues.17 The previous study agrees with our findings regarding the increased prevalence of male sex in association with CKD.

Table 5. Comparison of the intimal thickness in the study groups.

<table>
<thead>
<tr>
<th>Parameter*</th>
<th>Control group (n = 30)</th>
<th>CKD stage 3–4 (n = 30)</th>
<th>ESRD (n = 30)</th>
<th>significance test</th>
<th>Intergroup Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intimal thickness (mm)</td>
<td>0.65 ± 0.09</td>
<td>0.63 ± 0.10</td>
<td>0.69 ± 0.11</td>
<td>F = 3.235</td>
<td>P1 = 0.627</td>
</tr>
<tr>
<td>[Mean ± SD]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P2 = 0.255</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P3 = 0.036*</td>
</tr>
</tbody>
</table>

KW, Kruskal–Wallis test; ESRD, end stage renal disease.
One more review revealed tantamount orientation dissemination between CKD patients and controls, as men addressed 43.3, 53.3, 70, and 51.4% of patients in charge, predialysis, hemodialysis, and peritoneal dialysis bunches separately (P = 0.17) Okyay and colleagues.18 Our discoveries showed the critical expansion in the commonness of hypertension in Gatherings 2 and 3 contrasted with Gathering 1 (P = 0.001). That comorbidity was available in 33.3, 80, and 60% of patients in the three review bunches separately. A past report led by Shakeri and colleagues19 likewise detailed a critical expansion in the commonness of hypertension in CKD patients contrasted with controls (29.2% vs. 0% separately — P < 0.001), which concurs with our discoveries.

Then again, Lahoti and colleagues20 revealed that the commonness of hypertension was genuinely equivalent between the two gatherings (62% and 55.33% in CKD and control bunches separately—P = 0.29).

In the ongoing review, the commonness of diabetes was genuinely equivalent between the three review gatherings (P = 0.093), as it was available in 36.7%, 53.3%, 63.3% of cases in the three review bunches separately.

In accordance with our discoveries, another review detailed that the predominance of diabetes didn't essentially vary among CKD and control gatherings (36.67% vs. 33.33% separately—P = 0.62) Lahoti and colleagues.20

In our review, Hemoglobin showed a critical drop in Gathering 3 contrasted with the other two gatherings (P < 0.001). It had mean upsides of 12.98, 10.76, and 10.06 gm/dl in the three review bunches separately.

The diminished erythropoietin creation is the principal factor for hemoglobin drop in such cases Agarwal and colleagues.21 Different reasons for draining incorporate breaking down platelets, iron deficiency, folate and vitamin B12 lack, uremia (which causes RBC disfigurement that causes hemolysis), and every so often, blood misfortune after hemodialysis Agarwal and colleagues.21

In our review, complete leucocytic count had mean upsides of 6.14, 7.7, and 6.73 × 103/ml in the three review gatherings, with a tremendous contrast on the measurable examination (P = 0.009). It showed a critical expansion in CKD patients.

In a similar setting, Arai and colleagues22 detailed that raised WBC count is a notable indicator of CKD progression. They credited that ascent to the constant incendiary state related with CKD.

Oppositely, another new review noticed no huge distinction between CKD patients and controls in regards to WBCs (P = 0.276). It had mean upsides of 7.18 and 7.72 × 103/mm in CKD and control bunches, respectively Behairy and colleagues.17

Our discoveries showed that neutrophil count had middle upsides of 4.5, 4.3, and 4.34 × 103/ml in the three review bunches separately, with no huge contrast on measurable examination.

Solak and colleagues23 likewise noticed equivalent neutrophil counts between various CKD stages (P = 0.84), which had mean upsides of 4.95, 5.12, and 5 × 103/mm3 in patients with CKD stages 3, 4, and 5 separately. This concurs with our discoveries.

In the ongoing review, lymphocytic count had middle upsides of 1.63, 1.57, and 1.55 × 103/ml in the three review bunches separately, which was tantamount on factual examination.

Similar discoveries were additionally revealed by Solak and colleagues23 who announced that a similar boundary had mean upsides of 1.72, 1.73, and 1.53 × 103/mm2 in patients with CKD stages 3, 4, and 5 separately with no huge contrast on factual examination (P = 0.07).

In the ongoing review, NLR had middle upsides of 2.55, 2.63, and 2.55 in similar three gatherings separately, which was nonsignificant on factual examination (P = 0.796).

One more review concurred with our discoveries, as higher NLR was not related with CKD in ordinary weight people in a grown-up wellbeing assessment dataset. In any case, that relationship was available in overweight/stout population Lin and colleagues.24

Okyay and colleagues,18 likewise concurred with the past discoveries, as NLR had middle upsides of 1.75, 2.54, 2.42, and 3.15 in the control, predialysis, hemodialysis, and peritoneal dialysis bunches separately, with a huge contrast between the review gatherings (P < 0.001).

In the ongoing review, NLR had responsiveness and explicitness of 43.3% and 63.3% separately, with a demonstrative exactness of 55.3% to separate Gathering 2 from controls, when a cut-off worth of 2.92 was utilized.

In the past review directed by Tonyali and colleagues,16 the end an incentive for NLR related with CKD (Glomerular Filtrations Rate, GFR<60 ml/min/1.73 m2) was 3.18, with 39% awareness and 81% explicitness (P = 0.11). One could see the low awareness of NLR in the discovery of such cases.

In the ongoing review, eGFR had middle upsides of 132, 27, and 13 ml/min/m2 in the three review bunches separately, with a critical decrease in Gather-erings 2 and 3 contrasted with controls (P < 0.001). Likewise, Gathering 3 showed a huge decay of a similar boundary contrasted with Gathering 2.

Another review concurs with our discoveries, as GFR showed a critical decrease in relationship with
CKD (34.7 vs. 108.3 ml/min/1.73 m² separately—P < 0.001) Yilmaz and colleagues.\textsuperscript{15}

Furthermore, Solak and colleagues,\textsuperscript{23} noticed an ever-evolving decline of GFR with the expanded CKD stage (P < 0.001). eGFR had middle upsides of 44, 28, and 11 ml/min/1.73 m² in patients with stage 3, 4, and 5 separately. The past investigations agree with our outcomes.

In our review, serum creatinine had middle upsides of 0.93, 2.27, and 9.33 mg/dl in the three review bunches separately, with a huge expansion in CKD patients. A byproduct of solid movement found in the blood is creatinine. The kidneys usually dispense the blood is creatinine. The kidneys usually dispense it from the blood, yet when kidney capability declines, the creatinine level increases Wong Vega and colleagues.\textsuperscript{25} this makes sense of our discoveries.

Our findings showed that serum phosphorus had median values of 3.92, 4.31, and 4.75 mg/dl in the three study groups, respectively, with a significant rise in CKD patients (P < 0.001). Behairy and his colleagues reported that serum phosphorus showed a significant rise in patients with CKD compared with controls (4.44 vs. 3.64 mg/dl, respectively—P < 0.001) Behairy and colleagues.\textsuperscript{17}

In our study, blood serum PTH had magnified levels in CKD teams compared with controls, because it had median values of 40, 101.8, and 391.5 pg/ml within the 3 study teams severally. A previous Egyptian study conjointly rumored a big increase in blood serum PTH in CKD cases compared with controls (169.5 vs. 27.83 pg/ml severally—P < 0.001) 20, that coincides with our findings. Our discoveries showed that blood serum cholecalciferol showed a vital decrease in patients with CKD contrasted with controls, because it had mean upsides of 30.34, 20.43, and 20.56 ng/ml within the review bunches one by one. As indicated by data-based exploration, cholecalciferol inadequacy demolishes over the long haul, advancing from stage three to rearrange five-dimensional. 28 what is more, Guesseous and colleagues uncovered in an ever-evolving decline of GFR with the expanded noncommunicable diseases. Kidney Int. 2011;80:1258–1270.


