Neutrophil-to-lymphocyte ratio as a novel and valuable marker for assessing disease severity in Ulcerative colitis, Multiple sclerosis, and Kawasaki disease: A review

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Abstract

Ulcerative colitis (UC), multiple sclerosis (MS), and Kawasaki disease (KD) are three autoimmune diseases that involve the colon mucosa, myelin of the central nervous system neurons, and vascular epithelium. All these diseases need invasive, expensive, and complex modalities or criteria in order to monitor the disease severity. Recently, the neutrophil-to-lymphocyte ratio (NLR) has been proposed as a valuable, cheap, and easy marker of systemic inflammation. As all the above-mentioned diseases involve neutrophils and lymphocytes as the two major cell lines, it may be applicable to assess their severity according to the NLR. Here, we review the available literature with this regard.

Keywords: Neutrophil to lymphocyte ratio, Ulcerative colitis, Multiple sclerosis, Kawasaki disease

Introduction

Autoimmune diseases (ADs) are a vast category of disorders characterized by self-destructive action of the immune system (1). These diseases comprise several pathologies including at least 80 different disorders. They have affected more than 20 million people in the USA (2). Although the cornerstone of the pathophysiology of ADs is common, they usually affect different organs and present themselves with various features (1). Besides the challenging diagnosis of ADs, the assessment of their severity and activity is not easy. Ulcerative colitis (3), multiple sclerosis (4), and Kawasaki disease (5) are three different ADs that have different system involvement. Patients with ulcerative colitis (UC) should undergo regular colonoscopies to assess their response to the treatment, which is an invasive and expensive method (6). Another marker of severity and activity for UC patients is the Truelove–Witts severity index, which consists of several clinical and laboratory findings (7, 8). Furthermore, the severity of coronary artery lesions in Kawasaki disease, which is a pediatric disease, is usually assessed by ultrasonography (9). Besides, predicting which patients are resistant to intravenous immunoglobulin therapy (IVIg) is not easy and needs a predictive marker (10). Expanded Disability Status Scale (EDSS) is a clinical scale of MS severity and activity

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that is assessed by a neurological examination (11).

Most of the criteria and diagnostic modalities that are used for assessing ulcerative colitis, MS, and Kawasaki disease are complex, expensive, and invasive. Therefore, identifying a cheap and easy method to evaluate the disease severity in these patients is very useful. Recently, the neutrophil-to-lymphocyte ratio (NLR) has been reported as a marker of inflammation in these three diseases (12-14).

Ulcerative colitis

It is hypothesized that the N/L ratio changes can be a marker for an active ulcerative colitis (UC) (15). A study conducted by Celikbilek et al. assessed the relation between UC and NLR comparing 26 UC patients with 28 control cases. NLR was also compared between active and inactive phases of the disease. They reported the clinical activity of the disease according to the modified Truelove–Witts severity index (MTWSI). Also, based on colonoscopic findings, they classified the cases into mild, moderate, and severe. The Montreal classification was used for the disease extension assessment. They reported the NLR as 1.77 ± 0.68, 2.40 ± 1.05, and 3.18 ± 1.76 in the control, inactive UC, and active UC cases, respectively, and the difference was statistically significant. A ROC curve analysis proposed a cut-off value of 2.47 with a sensitivity of 53.9% (33.4–73.4), specificity of 63.2% (38.4–83.7), and overall accuracy of 57.8%. They believed that neutrophils can play a role in UC pathophysiology and related inflammatory processes. They found no statistically significant difference regarding the levels of NLR in disease extension and endoscopic disease activity (15). A study conducted in 2015 compared a group of 71 patients with a control group of 140 healthy people. They excluded the patients with inflammatory or infectious diseases and used the MTWSI for the UC activity measurement. Their study showed that the NLR was significantly higher in active UC patients compared with inactive cases and the control group. They reported a sensitivity of 48.6% and specificity of 77.5% at the cut-off of 2.39 for NLR. However, a multivariate logistic regression model, after adjustment for white blood cell count (WBC), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP), showed that the NLR cannot discriminate between the active and inactive phases of the disease. The only marker that can differentiate between the active and inactive forms of the disease was CRP. Moreover, they found no significant correlation between the NLR and the active phase of the disease. An important limitation of this study is that it was conducted in the community of only one inpatient hospital in Turkey (16).

Nishida et al. assessed the predictive value of NLR for the response to infliximab therapy. They enrolled patients with moderate to severe forms of UC with histological confirmation who had received the first dose therapy of infliximab and experienced some improvement. Their findings suggested that the high NLR is independently and strongly related to the high level of loss of response to infliximab therapy. They also proposed that corticosteroid therapy, despite affecting the neutrophils count, does not affect the NLR (17).

Two other studies assessed the predictive value of NLR in determining disease activity and severity. One of the studies found that NLR can be used as a marker of disease severity. They found the NLR very sensitive and specific which was far superior to the absolute count of leukocytes, neutrophils, lymphocytes, ESR, and CRP. They also found the NLR independent from the WBC count (18). The other study found higher levels of NLR in active cases of UC compared to inactive patients. The cut-off

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value for detecting active UC patients with NLR was found to be ≥ 2.3 with a sensitivity of 61.2% and specificity of 66.7%. They also found WBC, CRP, and platelets counts to be significantly higher in the active group. They found no significant difference in the level of lymphocytes and ESR (19).

Multiple sclerosis

We found only few studies that assessed the clinical significance of the NLR in multiple sclerosis (MS). Demirci et al. enrolled 102 patients with relapsing-remitting MS (RRMS) based on the McDonald classification and Lublin and Reingold criteria, who were compared with 56 control cases to find the clinical significance of the NLR. Out of these 102 patients, 31 were in the relapse phase and 71 were in remission, at the time of the study. They excluded patients with any kind of inflammatory or neurologic disease. The findings of the study proposed the NLR as a predictor of MS presence with a sensitivity of 81% and specificity of 62.5% at the cut-off of 2.04. Besides, the NLR can be used as a predictor of MS severity. NLR has a specificity of 97% and sensitivity of 67% for detecting the activity of the disease at the cut-off of 3.90. Furthermore, they showed that the NLR was significantly higher in patients in the relapse phase than those in the remission.

Another similar study on the NLR value in detecting MS activity was done on 88 patients in remission and/or exacerbation phases who were compared with 89 healthy subjects. Patients with an MS attack had a significantly higher NLR than controls, but the difference between the patients in remission and normal controls was not statistically significant.

Kawasaki disease

Nakada Toshimasa conducted a study on 163 Kawasaki patients from a pediatric centre who were diagnosed based on the Fifth Edition of the Japanese Criteria. The patients were classified into IVIG resistants and IVIG responders based on the presence or recurrence of fever in the first 24 hours after IVIG treatment. In addition, the resistant group was divided into a rescue group that received rescue therapies and a non-rescue group who did not receive any rescue therapy. The median value in the resistant group was significantly higher than in the responders, and it was also statistically higher in the rescue group when compared with the non-rescue patients. The highest value of NLR was found in a child with a coronary artery lesion as a complication of the disease. In overall, the author found the NLR useful for the risk stratification of Kawasaki disease (KD), but the study was limited to children (20). Similarly, another study was conducted on 196 KD patients who were grouped into responder and resistant cases to IVIG therapy. The IVIG resistant patients had higher values of NLR compared to responders. However, they did not find the NLR useful for the prediction of coronary artery abnormalities. However, they had a low number of significant coronary artery aneurysm cases (21).

A retrospective study on 437 KD patients showed that a combination of the NLR ≥ 3.83 and platelet-to-lymphocyte ratio (PLR) ≥ 150 can be used as a scoring system for intravenous immunoglobulin (IVIG) resistance with a sensitivity of 0.72 and specificity of 0.67 which are higher than the Kobayashi, Egami, and Sano scoring systems. They found the scoring system based on the NLR and PLR more convenient and cost-effective than the other systems with several items (10). In a similar study, Kawamura et al. proposed a cut-off value of NLR ≥ 3.83 and PLR ≥ 150 with an area under the curve (AUC) of 0.75 and 0.73 respectively. They also proposed the cut-off values of NLR ≥ 1.27 and PLR ≥ 201 after IVIG with an AUC of 0.86 and 0.53

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respectively. They found the combined NLR and PLR indices significantly higher in the IVIG resistant group than in the responders (12). A Chinese article proposed the NLR and PLR as independent factors for predicting the IVIG sensitivity with the best cut-off of 4.36 and 162 before the IVIG therapy, and 1.45 and 196 after the IVIG therapy respectively (22).

Several studies have been conducted to assess the predictive value of NLR for coronary artery lesions in Kawasaki. Demir et al. compared 49 patients with coronary artery lesions (CAL) with 26 patients without CAL. CAL was defined as a diameter of two standard deviations above the normal value adjusted for the body surface area, named as ectasia or aneurysm. They calculated the cut-off value of the NLR for the prediction of coronary artery lesions as 1.32, with a specificity of 38.8% and a sensitivity of 92.3%. However, they did not find any significant difference between the Kawasaki patients and healthy controls regarding the NLR value. Unlike the previous study, a poster presentation proposed that the NLR cannot predict CAL in Kawasaki patients (23).

A retrospective cohort study on 587 patients assessed the effectiveness of the NLR in predicting IVIG resistance and coronary artery abnormalities (CAAs). The resistant group had a significantly higher NLR than responders. However, they reported that this significant difference lasted only 3 to 4 weeks after the cessation of fever. The best cut-off value for predicting IVIG resistance was reported to be 5.49 with a specificity of 86% and sensitivity of 39% in the febrile phase of the disease. There was no significant difference in terms of NLR between the patients with CAAs and those without CAAs in the febrile phase. The statistically significant difference was only found when the CAA-negative patients were compared with those with only aneurysm in the febrile phase. Furthermore, they proposed that NLR could not predict dilatation. The best NLR cut-off for predicting coronary aneurysm in Kawasaki disease was calculated to be 4.86 with a sensitivity of 60% and specificity of 72% (24).

Discussion

The basis of auto-inflammatory disorders is inflammation. This inflammation can happen in the mucosal lining in UC patients (25-27), myelin of the central nervous system neurons (28-30), or even in the coronary arteries in KD (31-33). The basic inflammatory processes that are responsible for the autoimmune diseases usually involve neutrophils and lymphocytes as the two main cellular components of the immune system (34).

Neutrophils are the most abundant cells in the bloodstream and usually one of the first cells that are involved in the immunologic response (35, 36). In fact, the neutrophil count is a marker of inflammation, and severely ill patients, such as those with sepsis or shock, usually have neutrophilia and also lymphopenia. These two cell lines are the predictors of inflammation severity (37).

The basic pathogenesis of UC can be interpreted by the neutrophils' invasion into the mucosal lining of the colon. It is suggested that the compromised integrity of the mucosal lining lets the bacteria infiltrate the colon epithelium; subsequently, neutrophils are recruited into the affected part of the intestine (38, 39). The accumulation of the neutrophils in the crypt epithelium leads to abscess formation, which is evident in pathologic sections (40). Moreover, the malfunction of the lymphocytes is evident in the mucosal site and peripheral bloodstream, and the absolute lymphocyte count is a marker of treatment responsiveness in UC patients (41).

The underlying demyelination in MS is also another process that involves lymphocytes

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and neutrophils. Local activation of inflammatory cytokines and chemokines leads to the destruction of the blood brain barrier and allows the autoreactive T-cells to enter the central nervous system (42). It is then the activation of these T-cells by macrophages or microglial cells that cause demyelination (41, 43). Both $CD4^+$ and $CD8^+$ T-cells are responsible for the demyelination process in MS (43, 44). Moreover, neutrophils show abnormal phenotypes and elevated expression in patients with relapsing remitting MS (45, 46).

The process of inflammation in the vascular endothelium is also mediated with neutrophils. The neutrophils in KD usually release higher levels of cytokines, such as myeloperoxidase, neutrophil elastase, and reactive oxygen species, which leads to endothelial damage (47). Subsequently, the mononuclear cells infiltrate to the sub-endothelium and cause a chronic state of inflammation. Pathology sections of the affected vessels have shown infiltration of macrophages, neutrophils, and lymphocytes (48).

As the two above-mentioned cell lines (i.e., neutrophils and lymphocytes) are both involved in the pathogenesis and severity assessment of the three mentioned autoimmune diseases (UC, MS, and KD), the NLR can be used as a ratio that considers both cell lines. In fact, the NLR is a systemic marker of inflammation that is a ratio of two complementary immune pathways (49, 50). Moreover, this marker is less affected by factors such as exercise and dehydration (49).

Conclusion

The neutrophil-to-lymphocyte ratio (NLR) is a worthwhile marker of inflammation that combines two main immune system cells. This ratio can be used as a marker of inflammation in patients with UC, MS, and KD; however, further investigations through meta-analyses should still be conducted. Furthermore, a unified cut-off value should be proposed for each of the reviewed diseases in order to assess their activity.

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Conflicts of interest

The authors declare that they have no conflict of interest.

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