Usefullness of Baseline Neutrophil to Lymphocyte Ratio (NLR) in Hematological Malignancies

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Abstract: Systemic inflammatory response was reported to be a poor prognostic factor in several malignancies. An inexpensive and readily available laboratory tool, neutrophil to lymphocyte ratio (NLR), can be easily obtained from differential blood counts. Current evidence suggests that a baseline NLR may predict the long-term survival results of patients with lymphoproliferative diseases (especially diffuse large B-cell lymphoma). The relationship between systemic inflammation and cancer, and the usefulness of NLR in hematological malignancies will be disscussed in this comprehensive review.

Keywords: Neutrophil to lymphocyte ratio, Inflammation, Cytokines, Cancer, Metastasis, Predictive, Prognosis.

INTRODUCTION

Neutrophil to lymphocyte ratio (NLR), calculated from complete blood count with differential, may reflect and clarify the immune response in systemic inflammatory states [1]. NLR has been reported as an independent prognostic marker in solid [2] and hematological malignancies [3]. However, the number of studies about the use of NLR on the long-term results of hematological malignancies are quite a few when compared to those carried out with solid tumors. In this review, the basic mechanisms of inflammation, cancer development, and their relationship between NLR will be discussed. Additionally, the clinical use of NLR in hematological malignancies including classical Hodgkin lymphoma (HL), diffuse large B cell lymphoma (DLBCL), multiple myeloma (MM), and finally peripheral T-cell lymphoma will be reported in the light of current medical literature.

CANCER AND INFLAMMATION

A high NLR is associated with adverse outcomes in non-malignant conditions such as chronic inflammation in ischemic heart diseases [4], hepatic cirrhosis [5], and ulcerative colitis [6]. From this perspective, some researchers have demonstrated a positive correlation with NLR and known markers of systemic inflammation (*i.e*. erythrocyte sedimentation rate, C-reactive protein (CRP), fibrinogen) [1].

Cancer-related systemic inflammatory response can up regulate cytokines, chemokines and other inflammatory mediators [7]. About 25% of cancers are associated with chronic inflammation [8, 9]. Although the exact mechanism between inflammation and cancer remains unclear, two main factors are suggested: "*extrinsic factors*" that cause an ongoing chronic inflammation, and "*intrinsic factors*" that alters the expression of inflammation-related pathways via oncogenes and/or tumor suppressor genes [8].

Tumor necrosis factor-alpha (TNF-α), interleukin (IL)-6 and IL-1 are the most commonly released inflammatory cytokines in the tumor microenvironment [7]. Plasma levels of TNF-α are elevated in patients with advanced cancer [10]. TNF-α produced either by host cells or malignant cells directly activate oncogens and DNA damage, which in turn may contribute to an increased propensity for metastasis activity. One of its receptor, TNF receptor 2, is generally found on the recruited leukocytes [11].

Suppressed T-cell activity by neutrophils or immature myeloid cells, called myeloid-derived supressor cells (MDSCs), was linked to immune deregulation in advanced cancer patients. The major cause of severe systemic T-cell supression was thought to be induced by a neutrophil-derived effector molecule, H_2O_2 [12]. IL-8 induces exocytosis of arginase-1 by neutrophils in non-small cell lung cancer cell lines which inhibits T-cell proliferation by degrading extracellular arginine [13]. Arginase production from CD11b+, CD14-, CD15+ cells with polymorphonuclear morphology in metastatic renal cell carcinoma patients have been shown to be a mechanism of tumor evasion [14]. Matrix metalloproteinase (MMP)- 9 predominantly expressed by bone marrow-derived CD-45 positive leukocytes contributes to the formation of a mature vasculature, resulting in angiogenesis and tumor progression in a murine neuroblastoma model [15].

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E-ISSN: 2408-9877/16

More recently, upregulated MMP-2 expression by ovarian cancer cells has been associated with the initial steps of metastasis [16]. CXCL1/macrophage inflammatory protein-2 (MIP-2) leads to accululation of murine neutrophils that, in turn, increase the production of vascular endothelial growth factor-A, resulting in angiogenesis *in vivo* [17].

Taken together, development of cancer still remains to be explained in terms of inflammation. However, there are growing evidence-based data supporting the critical role of cancer-related systemic inflammation on tumor cell survival and proliferation, angiogenesis, tumor invasion and progression.

WHY DO WE NEED A NOVEL PROGNOSTIC MARKER?

Prognostic models for hematologic malignancies that are inexpensive, readily available, easy to perform and interpret are needed in clinical practice, especially in resource-poor countries. Besides the solid tumors, there is a growing interest about the use of NLR in an attempt to predict the long-term results of hematological malignancies. The core studies about this recent issue are listed in Table **1**.

CLASSICAL HODGKIN LYMPHOMA

It has long been known that the baseline lymphocyte count has a prognostic role in classic Hodgkin lymphoma (cHL). Lymphopenia (<600 cells/μL or <8% of the white blood cell count) is related to adverse survival outcome [18], as well as tumor-infiltrating lymphocytes and tumor-infiltrating macrophages that constitute tumor microenvironment [19, 20].

The accumulation of neutrophils is thought to be related with increased cytokin levels, especially IL-8 [21]. By combined isotopic in situ hybridization and advanced immunohistologic studies, IL-8 expression is

Table 1: Core Clinical Studies About the Use of Neutrophil-to-Lymphocyte Ratio in Several Hematological Malignancies for Predicting Long-Term Results

References	Disease	n	NLR	Cut off NLR	Median Follow-Up	Clinical Value
Porrata *et al*. [3]	DLBCL	255	NS	3.5	59.1 months	Patients with a NLR ≥3.5 at diagnosis experienced inferior 5-year OS and PFS compared with patients with a NLR <3.5. A higher NLR at diagnosis was also associated with higher IPI scores, B-symptoms and LDH levels.
Troppan *et al*. [27]	DLBCL	290	NS	4	33.5 months	NLR ≥4 was associated with worse OS.
"	"	"	"	1.8	"	NLR ≥1.8 was associated with shorter DFS.
Keam *et al*. [28]	DLBCL	447	2.54 (0.03-94.0)	3	59.0 months	A pre-NLR ≥ 3 was independently related with poor OS and PFS in newly-diagnosed DLBCL patients treated with R-CHOP. Among patients who had an initially pre-NLR ≥3, those whose NLR decreased to <3 after R-CHOP had significantly better OS and PFS than patients whose NLR remained high after R-CHOP.
Ho *et al*. [30]	DLBCL	148	4.25 ± 3.63	4.35	53.28 months	NLR was found to be a prognostic tool of 5-year OS and 5-year PFS.
Melchardt *et al*. [31]	DLBCL	515	NA	5.54	53 months	NLR did not correlate with survival.
Koh YW *et al*. [23]	cHL	312	3.8 (0.09-29.67)	4.3	64 months	Patients with a NLR ≥4.3 at diagnosis experienced inferior 5-year OS compared with patients with a NLR <4.3, but did not differ in terms of EFS.
Kelkitli *et al*. [37]	MM	151	2.79 ± 1.82	2	41 months	Patients with a NLR ≥2 at diagnosis experienced inferior 5-year OS and EFS compared with patients with a NLR <2.
Romano *et al*. [38]	MM	309	1.9 (0.4-15.9)	2	NS	In the era of novel anti-myeloma agents, patients with a NLR ≥2 at diagnosis experienced inferior 5-year OS and PFS compared with patients with a NLR <2.
Beltran *et al*. [39]	PTCL-U	83	2.5 (0.3-99)	4	NS	NLR ≥4 was associated with worse OS.

Abbreviations: NLR: Neutrophil to lymphocyte ratio; n: Number of patients; DLBCL: Diffuse large B-cell lymphoma; cHL: Classical Hodgkin lymphoma; MM: Multiple myeloma; PTCL-U: Peripheral T-cell lymphoma unspecified; OS: Overall survival; DFS: Disease-free survival; PFS: Progression-free survival; EFS: Event-free survival; IPI: International prognostic index; LDH: Lactate dehydrogenase; R-CHOP: Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; NS: Not stated, NA: Not available.

largely confined to reactive infiltrate cells and less frequently to Hodgkin and Reed-Stenberg cells, particularly in the nodular sclerosing subtype [22].

We could find only one study in the medical literature about the use of NLR in cHL [23]. In this retrospective analysis, 312 patients with cHL were enrolled and the median follow-up after diagnosis and NLR value were, 64 months and 3.8, respectively. Patients with NLR ≥4.3 at diagnosis were found to be more likely to present with anemia, lymphopenia, hypoalbuminemia, abnormal lactate dehydrogenase (LDH), presence of B symptoms, and advanced disease stage. In contrast, NLR did not corralete with age, treatment modality, chemoteraphy regimen or the presence of Epstein-Barr virus. The patients with NLR ≥4.3 had significantly lower 5-year estimated overall survival (OS) than those patients with NLR <4 (80.3% vs. 91.9%, p= < .001), but the groups did not differ in terms of event-free survival (EFS). The OS advantage was detected in only advanced-stage (stage IV) subgroups. In multivariate analyses NLR ≥4 was detected as an independent prognostic factor.

International Prognostic Score (IPS) is also an independent predictor and is used for risk stratification in HL [18]. Therefore, Koh *et al*. have combined NLR and IPS, "*IPS-NLR*". In low-risk IPS patients (IPS <4), the patients with NLR ≥4 presented with worse OS than those with NLR <4. This difference was not noted in high IPS risk patients (IPS= 4). Nodular sclerosing was found to be the most common (56.7%) subtype in the aforementioned cohort. When the statistical analyses were reanalysed in noduler sclerosing subgroup alone, the predictive impact of a NLR value of ≥ 4 were ongoing in terms of OS (but not for EFS) [23].

DIFFUSE LARGE B CELL LYMPHOMA

NLR is most frequently investigated in patients with diffuse large B-cell leymphoma (DLBCL). Besides direct apoptosis against lymphoma cells and antibody-dependent cell cytotoxicity, another possible mechanism of action of rituximab is to target the inflammatory component of the tumor by causing neutropenia [24] and direct inhibition of signal transducer and activator of transcription-3 [25] and nuclear factor kappa-B [26].

Firstly, Porrata *et al*. have investigated the possible predictive effect of NLR on survival rates of 255 DLBCL patients. With a median follow-up of 4 years, DLBCL patients with a NLR < 3.5 at diagnosis experienced a superior OS (87% vs. 56%, respectively) and progression-free survival (PFS, 72% vs. 45%, respectively) compared to those patients with a NLR ≥ 3.5 at diagnosis. Multivariate analysis showed NLR to be an independent prognostic factor for OS and PFS. Extranodal disease, number of cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone (R-CHOP), post-chemotherapy radiation therapy, and the reasons for post-chemotherapy radiation therapy was similar in both groups. A higher NLR was also associated with higher IPI scores and B-symptoms. The authors have also identified a positive correlation between NLR at diagnosis and LDH levels. NLR at diagnosis was an independent predictive factor besides stage for LDH production [3].

Afterwards, Troppan *et al*. have demonstrated that a high derived NLR at diagnosis of DLBCL significantly associated with poor outcome in terms of OS and disease-free survival (DFS) [27]. Similarly, a pre-NLR ≥ 3 was independently related with poor OS and PFS in newly-diagnosed DLBCL patients treated with R-CHOP. In patients with high pre-NLR, reduction of the post-NLR < 3 after R-CHOP treatment was correlated with improved survival. When adding pre-NLR to the IPI score, survival prediction and risk stratification were improved. Moreover, low pre-NLR (< 3) was associated with a higher number of peripheral $CD19^+$ lymphocytes and natural killer cells [28]. Although, these two studies [27, 28] were retrospective, they have had large number of DLBCL patients (290 and 447, respectively).

Chang *et al*. [29] have compared peripheral blood samples of 77 patients with DLBCL and 30 healthy controls. The patients with DLBCL had significantly higher percentages of neutrophils, and lower percentages of lymphocytes compared to control patients. In univariate analysis, high neutrophil counts (≥6,000/μL) were found to be a poor prognostic factor for survival in addition to high IPI scores. And finally, in a retrospective analysis including 148 newly-diagnosed DLBCL patients, the NLR was found to be a prognostic tool of 5-year OS and 5-year PFS by univariate analyses [30].

In contrast to these hopeful results, in a very recent retrospective analysis including 515 patients with DLBCL, NLR did not correlate with survival [31], as well as high gamma-glutamyl transferase levels, and platelet to lymphocyte ratio. In multivariate analyses, anemia, high C-reactive protein and high bilirubin levels had an independent prognostic value for survival in

addition to the National Comprehensive Cancer Network-International Prognostic Index (NCCN-IPI) score.

MULTIPLE MYELOMA

MM is a clonal disorder characterized by the proliferation of plasma cells and their accumulation within the bone marrow. Age, performance status, serum β_2-microglobulin level, the hemoglobin level, the presence of circulating plasma cells, plasmablastic morphology, the plasma cell proliferation status (detected either by plasma cell labeling index or flow cytometry) are well-known prognostic factors in MM. Additionally, in some reports, a low platelet count, hypercalcemia, and a low serum albumin level have associated with poor prognosis [32]. Given the disease heterogenity and the dynamic process of the disorder, it is sometimes not possible to predict the prognosis of patients exactly.

International Staging System (ISS) is a worldwide-accepted classification system based on serum albumin and β_2-microglobulin levels [33]. The patients should be divided into 3 subgroups according to the ISS, with median survival varying from 62 months (stage I) to 29 months (stage III). Although ISS is inexpensive and readily available, it does not take into account the cytogenetic profile of the patients and the role of bone marrow microenvironment. Additionally it was validated retrospectively on patients treated prior to the advent of novel anti-myeloma agents including proteasome inhibitors (bortezomib, carfilzomib), immunomodulators (lenalidomide, pomalidomide), or their combinations. Therefore, the investigators have tried to enhance the performance of the ISS by adding other soluble markers or genetic risk features [34-36].

In a retrospective analysis including 151 patients with MM [37], mean NLR was significantly higher in patients with MM than age- and gender- matched healthy controls (2.79 ± 1.82 vs. 1.9 ± 0.61). Patients with NLR ≥2 had significantly higher serum CRP levels, more frequent renal impairment, and more advanced ISS stage. In addition, NLR is independently associated with long-term results of MM patients. After a 41 months follow-up, 5-year estimated OS and event-free survival (EFS) rates were significantly lower in patients with a NLR ≥2 (42.4% vs. 87.5%) compared to those with a NLR <2 (41.8% vs. 88.4%). On the other hand, mean lymphocyte counts, bone marrow infiltration ratio by plasma cells, treatment regimens, and autologous stem cell transplantation rates were found to be similar between the groups in terms of NLR. A major limitation of this retrospective analysis was that the limited use of initial cytogenetic analysis which is a prognostic parameter that affects long-term survival rates of MM patients [34-36]. Cytogenetic data were available for only 34.4% of the cases. Among these patients 44.2% of them had cytogenetic abnormalities and the most frequent (30.7%) adverse chromosomal abnormality was reported as del(13q) [37].

More recently, Romano *et al*. [38] have investigated the predictive value of initial NLR in 309 newly diagnosed MM patients whom treated upfront with novel agents in a retrospective fashion. 37% of their cohort received high-dose therapy followed by autologous stem cell transplantation (ASCT) as consolidation. A NLR ≥2 was correlated with inferior estimated PFS and OS rates among non-elderly (<65 years) MM patients in all ISS stages and those patients underwent ASCT. In contrast, NLR values did not add any significant impact on long-term survival parameters for elderly MM patients. Despite the upfront administration of novel and more efficient therapies, the results were found to be less promising. Romano *et al*. have reported their 5-year estimated PFS and OS rates, respectively, 18.2% and 36.4% for MM patients with NLR ≥2 versus 25.5% and 66.6% for patients with NLR <2.

The authors have also provided a new model including both NLR and ISS staging, "*ISS-NLR*", and they have limited the deeper analyses for non-elderly MM patients. They have reported that NLR-ISS was able to predict PFS and OS rates in very-low, standard, and very-high risk subgroups, while ISS only was unable. This new model may provide a cost-effective and sustainable prognostic parameter in newly diagnosed MM patients especially in countries where cytogenetic analyses are not available in daily clinical practice. Additionally, a higher NLR did not correlate with the type of induction regimen (based on proteasome inhibitors, immunomodulator agents, or combined) or an adverse karyotype. The authors have also stated that initial cytogenetic analyses were available for 54% of patients and adverse chromosomal abnormalities were observed in 17% of the cases (detailed data not presented) [38].

As a result, novel and available predictors of long-term survival in newly diagnosed MM patients are encouraged in order to better evaluate the risk profile of these patients in the era of novel anti-myeloma agents.

PERIPHERAL T-CELL LYMPHOMA

Recently, Beltran *et al*. retrospectively evaluated 83 peripheral T-cell lymphoma unspecified (PTCL-U) patients in terms of NLR [39]. In multivariate analyses, a NLR ≥4 was independently associated with worse OS after adjustment for the IPI score and the Prognostic Index for PTCLU (PIT) score.

CONCLUSION

NLR, seems to be a promising prosnostic tool for predicting long-term results in lymphoproliferative hematologic malignancies. Further and comprehensive prospective studies are needed in order to better understand and interpret the exact role of NLR in these complex disorders. These efforts will also provide further therapeutic insights for clinicians.

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Received on 17-12-2015 Accepted on 08-01-2016 Published on 20-01-2016

http://dx.doi.org/10.15379/2408-9877.2016.03.01.03