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The neutrophil-to-lymphocyte ratio in aging and immunosenescence

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Introduction

In recent years the number of publications reporting the use of the neutrophil/lymphocyte ratio (NLR) in disparate fields of human and veterinary medicine has swelled in the medical literature from less than 50/year in 2010 to 892 in 2019, and this figure has more than doubled up to 1,857 in 2024 [1].

The use of this index has gained recognition for several reasons, the main one being readily available at no extra cost, since it is easily determined from the white blood cell count, which is routinely performed in most clinical settings: in fact, NLR is simply the number of neutrophils divided by the number of lymphocytes (absolute numbers, generally per μL volume). NLR is assumed to be a biomarker that reflects the balance between systemic inflammation and immune response [2]. It has been studied across various conditions, demonstrating its prognostic and diagnostic utility.

Components of NLR

The first descriptions recognized that the two prominent features of a stress response, and in general of an inflammatory event, i.e., an increase of neutrophil numbers and a decrease of lymphocytes, could be combined in order to return a single number indicating their ratio, which offered a more accurate measure of stress or inflammatory response.

In one of the early studies of COVID-19 [3] significantly higher neutrophil counts accounted for the significant difference in total leucocyte count between mild/moderate and severe/critical cases at presentation; and this was found despite a significant decrease of lymphocyte counts in all patients (also in the moderate cases). No changes in other subsets, or other hematological parameters (hemoglobin, platelets) were recorded [3].

Neutrophils are major effectors of the innate immune response, and neutrophil extracellular traps (NETs)-related necroinflammation plays a central role in the development of the cytokine storm, sepsis and

multi-organ failure. Overproduction of NETs has been associated with COVID-19 severity [4]. The total number of circulating neutrophils is controlled by their bone marrow production from a progenitor common with the monocytic lineage, under the influence of a combination of cytokines (mainly colony stimulating factors), transcription factors, and environmental signals in the bone marrow. Other factors affecting neutrophil numbers are signals derived from infection and inflammation, mediated by cytokines, and stress, mainly mediated by cortisol. Apoptotic signals and spleen removal have a balancing effect on neutrophil number. Therefore, a complex regulation ensures neutrophil levels remain within a normal range, unless responding to physiological demands [5]. Lymphopoiesis is even more complex, due to the recognized vast heterogeneity of lymphoid cells and their subsets [6]. However, biological clocks regulate lymphocytes number and keep this within a normal range for age.

Normal values for NLR

There is no universally accepted normal value for NLR, however, the consensus is that in a healthy adult population, the normal NLR values range between 0.78 and 3.53 [2]. The study by Forget et al. [2] identified that the mean NLR in a healthy adult population is 1.65, with a standard deviation range of 0.78 to 3.53. Similarly, Lee et al. [7] reported a mean NLR of 1.65 in a large cohort of healthy adults in South Korea, further supporting this range. These values provide a reference for interpreting NLR in clinical practice. NLR varies with age in healthy individuals. Several studies have documented this variation, e.g., in young adults (18–75 years) the normal NLR range is approximately 0.74 to 4.94 in a large Danish population study and reflects the typical values seen in general practice [2, 7, 8]. In a study of 247 Sicilian subjects including supercentenarians, Accardi et al. [9] found NLR mean of 1.85 ± 0.64 in healthy adults aged 19.5–64.7 years. This was not significantly different in older subjects (aged 65 to 89) whose mean NLR was 1.98 ± 0.84 [9].

Older adults (above 75 years) tend to have a higher NLR, with a range of 0.89 to 8.80. In the study by Accardi et al. [9], NLR values increased to 2.47 ± 1.56 in the age group 75–105, and 2.97 ± 1.66 in 13 semi- and super- centenarians aged 105.4–111.8 years. These values were significantly different from those in younger age groups. This increase is attributed to age-related changes in the immune system, often referred to as immunosenescence [10], which includes higher levels of systemic inflammation and altered immune cell distribution.

Children and adolescents (0–17 years) generally have a lower NLR, with a range of 0.30 to 3.76. This lower range reflects the different baseline levels of neutrophils and lymphocytes in younger individuals compared to adults [2], with higher numbers of lymphocytes produced due to rapid post-natal maturation of the immune system and establishment of the immune repertoire.

Predictivity of NLR

NLR is considered one of the accurate haematologic markers of systemic inflammation associated with infections as well as chronic diseases. A systematic review and meta-analysis showed that an elevated NLR was significantly associated with poor clinical outcomes in patients with advanced cancer [11]. Another systematic review and meta-analysis found that an NLR greater than 4 is associated with a hazard ratio for overall survival of 1.81, indicating a significant adverse prognostic impact [12]. Additionally, a study involving over 28,000 participants from the NHANES dataset found a positive association between higher NLR and increased cancer risk (odds ratio = 1.20) [13].

Association with higher NLR has been reported for diabetes [14]. Elevated NLR is linked to chronic inflammation and poor prognosis in diabetes mellitus [15], NLR has prognostic value in cardiovascular diseases [16]. Elevated NLR is linked to higher mortality and adverse outcomes in patients with cardiovascular conditions [17]. A higher NLR is associated with increased risk of incident atrial fibrillation, particularly in younger adults [18].

In the Framingham Heart Study [19] individuals with higher NLR were found to be at a greater risk of subsequent dementia during a 5.9-year follow-up period. An association of higher NLR with Alzheimer's disease in particular was also reported [20]. Higher NLR values correlate with more severe cognitive decline in a meta analysis of 11 studies, with an odds ratio of 2.53, and diabetes moderated this association, but was also independently associated with higher NLR [21]. In Alzheimer's disease NLR correlated with severity of dementia [22]. We could not confirm this in the Mugello study of a cohort of nonagenarians [23] where higher lymphocyte counts were associated with any type dementia, resulting in lymphocyte/monocyte ratio to be associated with dementia, whereas NLR did not.

In patients with COVID-19, an NLR above 6.82 is associated with poor clinical outcomes [24]. Similarly, higher NLR values are indicative of bacterial infections and can help differentiate between bacterial and viral infections in febrile patients [25].

In conditions like interstitial lung disease (ILD), elevated NLR is associated with disease presence and poor prognosis, particularly in connective tissue disease-associated ILD [26], and in the general population, increased NLR is associated with overall mortality and specific causes of death, such as heart disease, chronic lower respiratory disease, and kidney disease [27].

Inflamm-aging and other inflammatory markers

The numbers of neutrophils and lymphocytes vary with age (the so-called inversion in infants and children), with a progressive increase of the NLR in the first years of life [2], and then tend to remain at similar levels in steady state condition during adult life [28]. A decline of total lymphocyte numbers (particularly severe for B cells [29]) is often observed in aging, with nearly preserved levels of neutrophils [9].

The term "Immunosenescence" indicates changes in the innate and the adaptive immune systems occurring with aging, and it is associated with a low-grade chronic pro-inflammatory status named inflammaging [10, 30]. Aging, likely via inflammaging, is associated with the emergence of chronic diseases including cardiovascular and neurodegenerative diseases, cancer, and diabetes. The origin of this inflammaging is not known with certainty, but several concurrent contributing factors have been suggested [31] including an imbalance between inflammatory and anti-inflammatory networks [32]. The relationship of immunosenescence with NLR, which reflects an imbalance of innate and adaptive immunity, leading to an inflammatory scenario, has been the object of many studies. Other parameters for inflammatory status have been studied in comparison with NLR, some in use before, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), and some of more recent introduction, as the systemic inflammation response index (SIRI) [33] derived by the formula NxM/L, and developed in conditions like pancreatic cancer, where NLR had poor prognostic value.

In young adults (18–75 years), NLR correlates with CRP and ESR, serving as a marker of systemic inflammation. Elevated NLR values are associated with higher CRP levels, indicating an inflammatory response. This correlation is evident in various conditions, including infections and cardiovascular diseases [8, 17].

In older adults (above 75 years), NLR values are also associated with increased CRP and ESR levels, reflecting chronic low-grade inflammation. This is consistent with findings from the Rotterdam Study, which showed that NLR, CRP, and ESR all increase with age and are higher in individuals with comorbidities such as diabetes and cardiovascular disease [34, 35]. NLR was strongly correlated with CRP and ESR also in Alzheimer's disease, showing an increase with the degree of cognitive impairment [36].

Elevated SIRI levels are independent risk factors for both in-hospital and 1-year mortality in patients with atrial fibrillation and type 2 diabetes mellitus [37]. SIRI is positively associated with fasting plasma glucose, fasting serum insulin, and insulin resistance, indicating its utility in assessing systemic inflammation in diabetes [38].

Higher SIRI values correlate with worse outcomes in Alzheimer's disease [22], although the predictive value of NLR is stronger. Elevated SIRI scores are linked to increased phenotypic and biological age, highlighting its role in assessing aging and related health outcomes [39]. Overall, NLR correlates positively with other inflammatory markers like CRP and ESR across all age groups, and shows comparable predictive value to more complex leucocyte-derived markers.

Our experience

We recently applied NLR to the analysis of several aspects of aging, using data from three established cohort studies, the first one being the already mentioned Mugello study [23], exploring dementia risk factors.

The second cohort was from the InCHIANTI study which enrolled representative samples from the registry list of two towns in Tuscany, Italy, with a follow-up of 20 years [40]. In our analysis, NLR resulted to be the only significant marker associated with aging, despite showing gender dimorphism, due to lower neutrophil counts in females, and decrease of lymphocyte counts in both sexes. However, NLR showed no statistically significant first and second-order effect for neoplastic diseases, diabetes, and stroke. In females only, congestive heart failure was directly associated with the NLR, and with creatinine clearance, an indicator of kidney disease. The decrease of lymphoid cells and an increase of myeloid cells (monocytes, dendritic cells) with age has been confirmed by single cell RNA-sequencing and validated by flow cytometry [41] in a study which revealed compositional changes of myeloid and lymphocytic compartments and sex differences in several subsets, together with unique transcriptional profiles of centenarians. Sex differences have been reported for NLR [42, 43] as well as monocyte-to-lymphocyte ratio (MLR) [44]. An analysis of data of the National Health and Nutrition Examination Survey found racial differences in NLR, and associations with diabetes, cardiovascular disease, and smoking [41]. In particular, non-Hispanic White males generally have higher NLR values compared to females. The average NLR for non-Hispanic Whites is 2.24 [41] compared to non-Hispanic Blacks who have lower NLR values, with an average NLR of 1.76, with females having lower NLR values [41]. The average NLR in Hispanics is 2.08, which is lower than that of non-Hispanic Whites but higher than non-Hispanic Blacks [41]. The values for Chinese Han show lower NLR, with a mean of 1.59 for males and 1.62 for females, with females having higher NLR at ages 30–49 and males having higher NLR at ages 60–69 [45]. In the general population MLR values are generally higher in males than females, particularly in the 16–45 years age group, where immune differences due to sex hormones are likely greatest [46]. No particular differences have been reported for South Koreans [7].

In a subsequent study, we demonstrated that the longitudinal NLR (and the MLR) variations predict longitudinal changes in fat area and in muscle components (muscle area, muscle density, and strength) independently of age, sex, body composition, comorbidities score, and markers of inflammation [47].

As a conclusive report on the association of NLR with aging, we analysed the data from the InCHIANTI study with regard to the pathway leading from robust status shifts to pre-frailty and frailty, and finally to death [48], and found that subjects with the highest NLR values were more likely to experience a transition from robust to pre-frail, and to overt frailty status. Moreover, NLR (and MLR) were both predictors of mortality. All this was independent of inflammatory or other markers of aging (Figure 1).

In that study, women were more likely to progress to frailty, and subjects with NLR and MLR above the 90th percentile (> 3.53 and > 0.30, respectively) had higher incidence rate for the increase of the number of frailty criteria, thus transitioning from robust to pre-frail and then to frail, and also for all cause mortality, as shown in the Figure 1, which also represents some of the other causes for the outcome, including genetics, multimorbidity, inflammation, environment, infections and chronological age. The upper limits for transition from pre-frail to frail are also indicated (2.44 and 0.38). Robust subjects in the first decile showed values of NLR < 1.19 and MLR < 0.12 [48].

It is noteworthy that in a search for good prognostic factors of aging and age-associated diseases, Li et al. [49] excluded neutrophil counts, but retained lymphocytes and monocytes, precluding the possibility to derive NLR as risk factor, and then resorting to a composite 17-item index for their analysis of three datasets, two of which we have also studied.

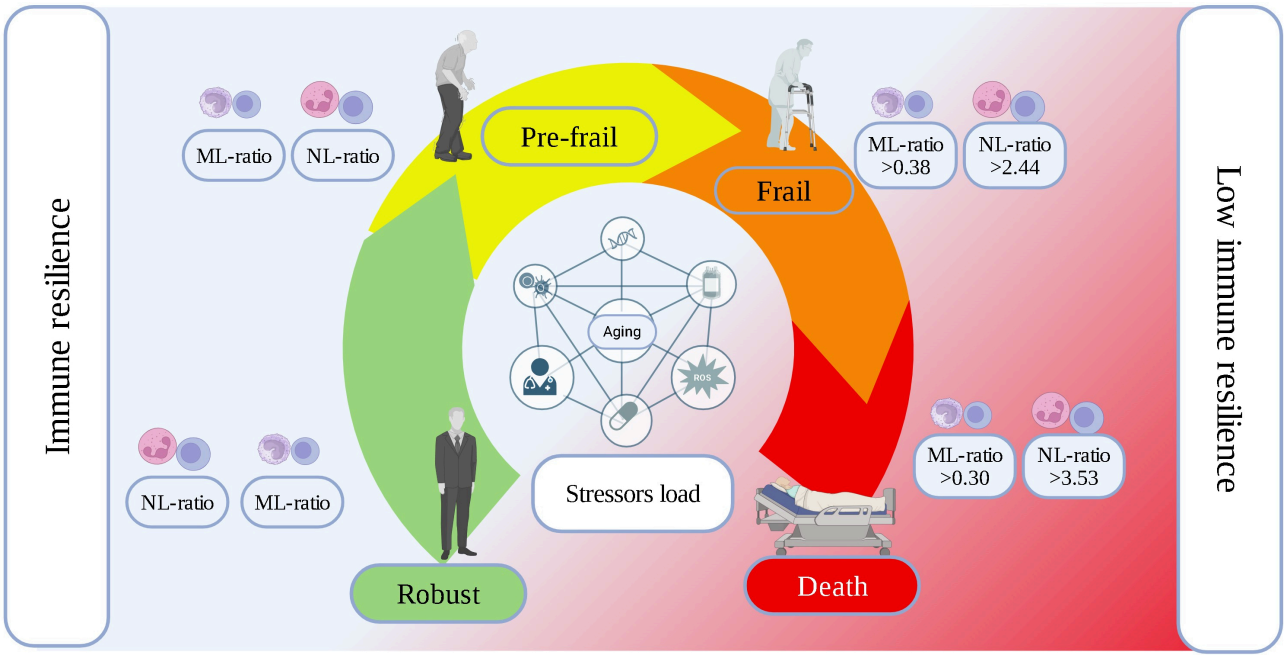

Figure 1. NLR and ML-ratio as markers of immune resilience, frailty progression, and mortality. Data from [48]. NLR: neutrophil/lymphocyte ratio. Created in BioRender. Di iorio, A. (2025) https://BioRender.com/uugd84v

The third study was the Baltimore Longitudinal Study on Aging, where we examined the longitudinal association of absolute counts of both neutrophils and lymphocytes, and their ratio, with longitudinal risk for multimorbidity and mortality [50]. The NLR increased with age and was associated with a higher mortality, while a lower NLR was inversely correlated with multimorbidity. Neutrophil number increased with aging and was predictive of mortality.

Conclusions

Taking into account the numerous factors governing the number of circulating leucocytes, and their different life span and routes, it is surprising how the NLR can persist at constant levels in general, being affected by genetic factors, gender and disease. The main result of our studies is that NLR represents a useful marker of aging, as well as an indicator of immune resilience, frailty and multimorbidity leading to death. It should be taken into account in studies of immunosenescence and age-associated diseases, and owing to the absence of universal agreement on normal reference values for age, race and sex, healthy controls should be included in all studies of NLR as well as other composite indexes.

Abbreviations

CRP: C-reactive protein

ESR: erythrocyte sedimentation rate

MLR: monocyte-to-lymphocyte ratio

NLR: neutrophil/lymphocyte ratio

SIRI: systemic inflammation response index

Declarations

Author contributions

RP and ADI: Conceptualization, Writing—original draft, Writing—review & editing. Both authors read and approved the submitted version.

Conflicts of interest

Roberto Paganelli who is the Editorial Board Member and Guest Editor of *Exploration of Immunology* had no involvement in the decision-making or the review process of this manuscript. The other author declares that there are no conflicts of interest.

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