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Are Complete Blood Count Parameters Associated with Climate and Environmental Factors? A Retrospective Study in the General Population of Fokis, Greece (Athens, 2023) †

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Abstract: The complete blood count (CBC), a cost-effective blood test, offers insights into the cell composition of blood, including white and red blood cells and platelets. Novel inflammatory biomarkers derived from combinations of CBC parameters include the neutrophil-to-lymphocyte ratio, reflect systemic and local inflammation. In this retrospective study, we successfully leveraged bioinformatics analysis to examine potential correlations between CBC biomarkers and climate and environmental factors, including temperature, humidity, and rainfall, in Fokis, Greece for a 4-year period (2019–2022). Our findings provide valuable insights into how these environmental factors might influence blood cell parameters in the general population.

Keywords: CBC biomarkers; neutrophil-to-lymphocyte ratio (NLR); inflammation; apparent temperature (AT)

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1. Introduction

Inflammation is an adaptive process to the noxious stimuli that the human body is constantly exposed to, including a wide range of physiological reactions varying from a local inflammatory response to a full-blown systemic inflammation [1]. The dysregulation of this complex sequence of events that consists of the inflammatory response is the common denominator in the pathophysiology of many diseases [2]. Associations between meteorological conditions and inflammation have been demonstrated in several studies from around the world [2,3], primarily in patients with cardiovascular diseases [4,5], but also in conditions involving arthritis and joint pain [6,7].

The complete blood count (CBC) is a fast, inexpensive and accessible blood test that provides information regarding the quantitative and qualitative characteristics of the blood cells' subpopulations (white blood cells, red blood cells, platelets) and is a valuable tool for the diagnostic approach of practically every disease. Recently, CBC-derived ratios, such as the NLR (neutrophil to lymphocyte ratio) and PLR (platelet-to-lymphocyte ratio) have been proposed as useful alternative inflammatory biomarkers which can be potentially used for the diagnostic and prognostic assessment of various medical conditions such as cardiovascular, neurological, autoimmune, neoplastic and psychiatric diseases [8–13]. The effects of meteorological parameters on human health is widely studied, but mostly with regard to specific pathological conditions, such as seasonal infections [14], cardiovascular diseases [15,16], autoimmune diseases [17,18], neurological diseases [19,20] and

mental disorders [21,22], allergies [23,24] and dermatitis [25,26]. There are quite a few studies which aim to determine the association between meteorological parameters and inflammation as the baseline of most pathologies [27,28]. This research work highlights the potential influence of weather changes on the exacerbation of various diseases based on inflammatory mechanisms. This study focuses on NLR, a novel inflammatory biomarker, and its association with meteorological changes.

Our purpose is to study the association between the novel inflammatory index NLR and meteorological parameters such as apparent temperature (AT), humidity, rain and wind speed.

2. Materials and Methods

Demographic (sex, age) and CBC data from 10,075 individuals (5359 men, average age 52.3 years; 4716 women, average age 53.6 years) residing in the area of Fokis, Greece were retrieved from the Laboratory Information System (LIS) database of the Medical Laboratory Department of General Hospital of Amfissa. These individuals underwent routine blood tests over a four-year period (2019–2022). The data were properly anonymized prior to being further processed. Corresponding daily meteorological data, including maximum, mean, and minimum temperatures (°C) and mean relative humidity (RH%), were sourced from the National Observatory of Athens' meteorological site, operational since June 2018, in Amfissa.

The neutrophil-to-lymphocyte ratio (NLR) was determined by dividing the absolute neutrophil count by the absolute lymphocyte count, the values of which were derived using the CBC [29]. The apparent temperature (AT) was calculated according to the methodology proposed by Niu, Gao et al. [30], whereas, in order to analyze the lag–exposure–response relationship between AT/humidity and NLR, we took into consideration the respective daily data and their weighted average over 3, 5 and 7 days. Analysis of Variance (ANOVA) in the R package was used to determine the main factors that determine NLR's variance. All results were crossmatched with ANOVA and Linear Regression from SPSS v20. Further analysis was implemented using the Random Forest package in R.

3. Results

The main factors that determine NLR's variance are shown in Table 1.

Table 1. ANOVA results, indicating main factors of NLR variance in the full dataset and subsets.

	Anova with Full Dataset			**Age ≤ 73**			**Age > 73**		
	F value	Pr(>F)		F value	Pr(>F)		F value	Pr(>F)	
Gender	0.27	0.605		7.13	0.008	**	29.86	<0.001	***
Age	259.72	<0.001	***	15.89	<0.001	***	34.82	<0.001	***
Mean_Temp	21.77	<0.001	***	23.17	<0.001	***	3.53	0.061	.
Max_Humidity	1.12	0.291		0.00	0.983		1.34	0.248	
Min_Humidity	2.21	0.137		1.52	0.218		0.94	0.333	
RAIN	0.43	0.513		0.40	0.526		1.48	0.225	
AVG_Wind_Speed	6.49	0.011	*	5.12	0.024	*	1.54	0.215	
Max_Wind_Speed	0.56	0.454		0.10	0.757		0.08	0.777	
AT	1.52	0.217		0.25	0.62		1.50	0.22	
AT3daysLag	0.43	0.511		0.27	0.601		1.99	0.159	
AT5daysLag	3.77	0.052	.	1.78	0.182		1.56	0.212	
AT7daysLag	1.10	0.295		0.50	0.48		0.44	0.506	

Table 1. *Cont.*

	Anova with Full Dataset			Age ≤ 73			Age > 73	
Max_Humidity_3daysLag	0.35	0.552		0.78	0.376		0.18	0.675
Max_Humidity_5daysLag	4.06	0.044	*	4.83	0.028	*	0.30	0.585
Max_Humidity_7daysLag	4.01	0.045	*	4.55	0.033	*	0.38	0.54
TempCategory	0.40	0.526		0.25	0.62		1.16	0.281
RaiseCategory	<0.01	0.952		0.16	0.685		0.13	0.715

Significant codes: *** 0.001, ** 0.01, * 0.05, '.' 0.1, ' ' 1.

Age and mean daily temperature emerged as the main factors, whilst average wind speed (p = 0.0108), maximum humidity with 5 (p = 0.0438)- and 7 (p = 0.0438)-day lag also had statistically significant contributions. Also, the weighted average of AT for 5 days (p = 0.0523) had marginal statistical significance and in research at a larger scale, it could become significant. All results were crossmatched with ANOVA and Linear Regression from SPSS v20. With age established as the primary predictor for NLR, we employed decision trees for our analysis, utilizing the RPART package in the R programming language (Figure 1). Age at 73 years was revealed as a split factor for NLR, providing further evidence for aging and the ability to adapt to weather conditions.

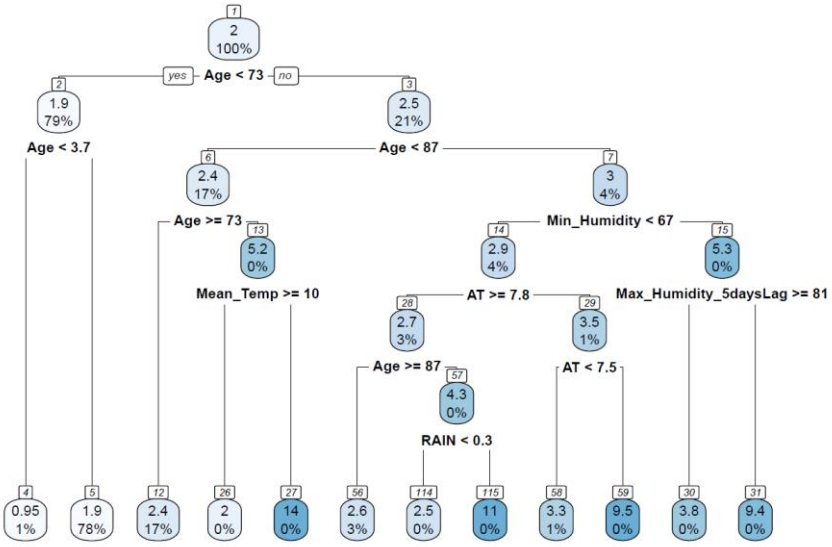

Figure 1. Classification results, indicating 4 main age groups for which different weather conditions affect NLR.

The main dataset was split in two sub-datasets, one with the records with ages of over 73 years, and the other with the records with ages of 73 years and below. RPART and ANOVA were used in these two sub-datasets, providing the following results. For the subset of below-73-year-old individuals, individuals with an age up to 15 years seem to be affected by the5-day weighted average of AT and the weighted average of humidity for 5 and 7 days (Figure 2). From ages 15 to 73, daily average temperature, AT and maximum wind speed contribute in NLR prediction (Figure 2).

For the individuals over 73 years old, minimum humidity at high values, AT and weighted AT over 7 days seem to determine NLR values (Figure 3).ANOVA in the subset of individuals below 73 years old confirmed the results of RPART, having as the main factors age (p < 0.001), average daily temperature (p < 0.001), gender (p = 0.008), daily average wind speed (p = 0.02), and the weighted average of 5 (p = 0.03)- and 7 (p = 0.03)-day maximum humidity. In the subset of individuals over 73 years old, analysis of variance (ANOVA) reaffirmed the results from the recursive partitioning analysis (RPART). Age (p < 0.001) and gender (p < 0.001) were identified as the primary contributors to the variance

in NLR. Interestingly, average daily temperature ($p < 0.06$) might also play a role, although its level of significance is marginal. This suggests that while age and gender are the key factors influencing NLR, daily temperature could potentially have a subtle influence as well, though more research is needed to confirm this finding.

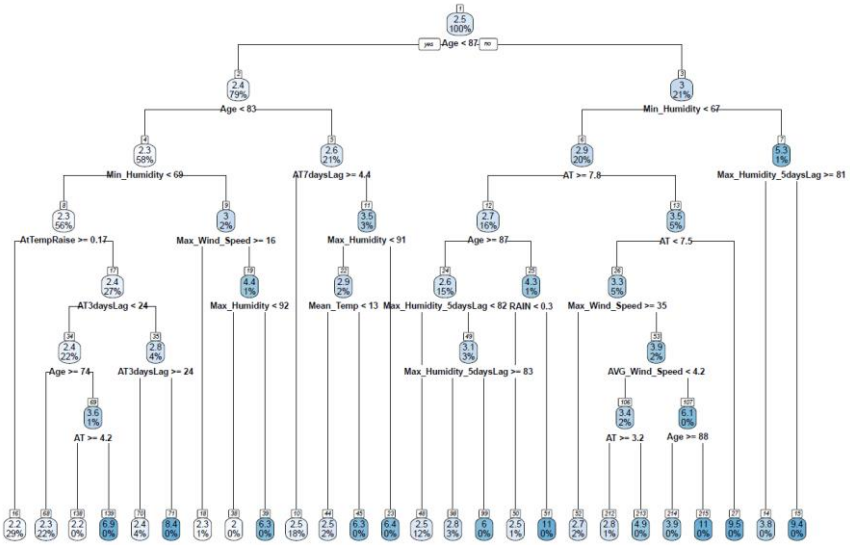

Figure 2. Classification results for under-73-years-old subgroup indicating subgroups and factors contributing to segmentation.

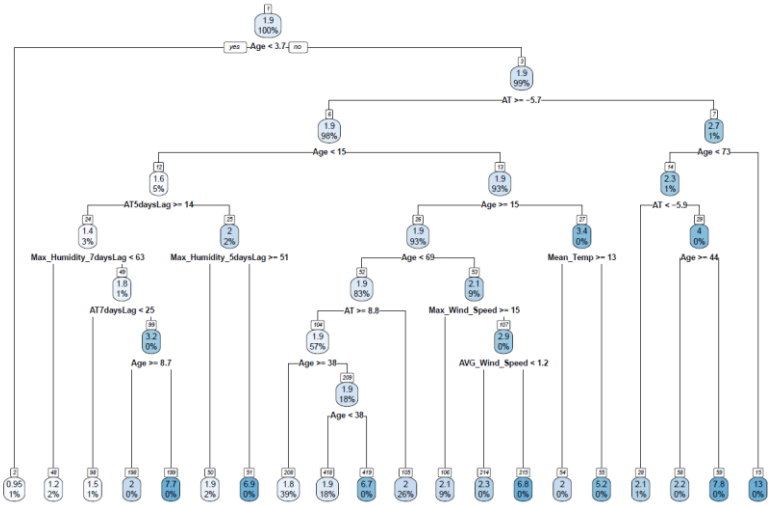

Figure 3. Classification results for the over-73-years-old subgroup indicating subgroups and factors contributing to segmentation.

Age is the trait that has the highest importance in group prediction (mean decrease in accuracy) and highest contribution to the node homogeneity (mean decrease in Gini Index) (Figure 4). Gender and an AT rise over a 3-dayperiod appear to only contribute to node homogeneity. AT either daily or with a 3- or 7-day delay seems to contribute to group prediction, while humidity (either daily, or with a 3-, 5- or 7-day delay) seems to contribute to both group prediction and node homogeneity. Wind speed and rain are also considered factors in model accuracy and homogeneity. This suggests that while age is the predominant factor in predicting group membership, environmental factors such as temperature, humidity, wind speed, and rainfall also have some influence. These findings contribute to our understanding of the complex interplay between environmental factors and health, potentially providing new insights for future research and health policy.

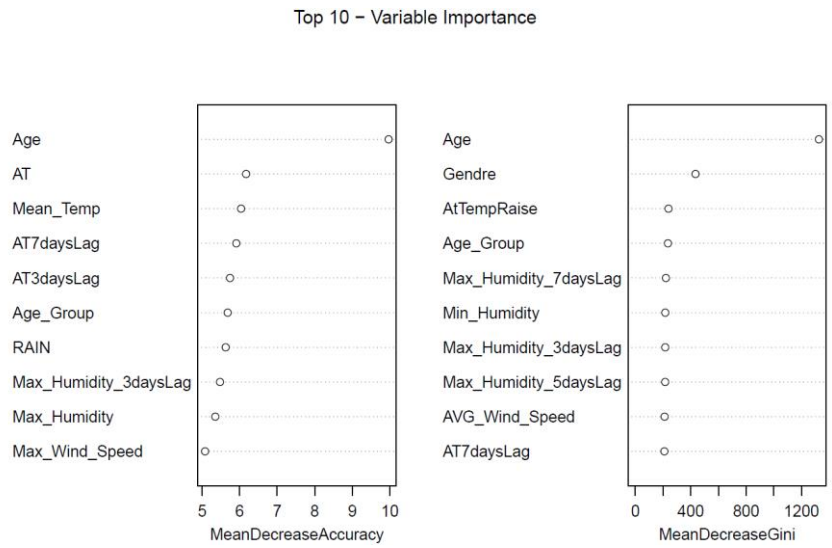

Figure 4. Random Forest (ntrees = 500) Gini Index results (mean decrease in accuracy and mean decrease in Gini Index).

4. Discussion

A significant positive effect between meteorological parameters and NLR levels was found in this study. Gender, age and mean daily temperature have emerged as major factors contributing to the shaping of NLR's variation in the general population, whereas humidity, average wind speed and rain also affect NLR's levels. These conclusions are strongly supported by the results of the statistical analysis performed on our study population. According to our findings, age has the most powerful effect in NLR's variation, revealing the age of 73 years as a distinct boundary between two subgroups. In individuals under 73 years of age, apart from gender, mean daily temperature ($p < 0.001$) is a potent contributor to NLR's variation, whereas average wind speed and maximum humidity on the 5th and 7th lag day also a play a role, albeit a less important one ($p < 0.05$). On the other hand, in individuals over 73 years of age, gender and age are the predominant modulators of NLR's variation. Our findings are consistent with the results of Lin, Hottenga et al. [31], who successfully determined the factors which affect variation of NLR and PLR in a twin study. In summary, the association between meteorological changes and NLR can help us to better understand not only the clinical course of several conditions and the way the observed exacerbations reflect the influence of weather conditions on them, but also the value of NLR as an inflammatory biomarker with the potential to be further utilized for the evaluation, monitoring and prognosis of diseases with an inflammatory background.

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