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ORIGINAL RESEARCH

Association Between Complete Blood Cell Count (CBC)-Derived Inflammatory Markers and Natural Killer Cell Activity: A Cross-Sectional Study

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Introduction: This study investigated the association between natural killer cell activity (NKA) and five complete blood cell count (CBC)-derived inflammatory markers, including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), systemic immune-inflammation index (SII), and systemic inflammation response index (SIRI).

Methods: This cross-sectional study included a total of 10,329 individuals who underwent CBC and NKA tests at Chaum Life Center in Korea between January 2016 and May 2022. NKA was estimated by measuring the amount of interferon-gamma (IFN-γ) released by activated natural killer cells; low NKA was defined as IFN-γ level <500 pg/mL.

Results: The results showed a significant increase in the percentage of subjects with low NKA with increasing CBC-derived inflammatory markers. The odds ratios (ORs) for low NKA were 3.90 (3.45–4.41), 2.69 (2.38–3.05), 1.45 (1.29–1.63), 2.96 (2.62–3.35), and 4.80 (4.23–5.45) in the highest quartile of NLR, PLR, MLR, SIRI, and SII, respectively, compared to the lowest quartile. Moreover, NLR, SIRI, and SII showed higher discriminatory performance for low NKA compared with traditional inflammatory markers, such as C-reactive protein (CRP) and white blood cell (WBC) count.

Conclusion: These findings indicate that CBC-derived inflammatory markers are associated with low NKA in a large health-screening population, suggesting their potential relevance as indicators of immune–inflammatory status.

Keywords: natural killer cell activity, inflammatory marker, complete blood cell count, inflammation, innate immunity

Introduction

Natural killer (NK) cells are a key component of the innate immune system, responsible for identifying and destroying virus-infected and malignant cells without prior sensitization.[1] Natural killer cell activity (NKA) has emerged as a critical indicator of immune competence, influencing both immunity and disease progression. In clinical practice, NK cell dysfunction has been linked to a variety of conditions, including many types of cancers, autoimmune diseases, and chronic infections.[2–4] Given the role of NK cells in immune surveillance, understanding factors associated with variations in NKA may contribute to improved immune monitoring.

Conventional NKA measurement methods, such as flow cytometric assays or chromium-51 release assays, require isolation of peripheral blood mononuclear cells and involve substantial technical complexity, limiting their applicability in large-scale clinical studies.[5] A whole-blood–based assay that measures the amount of interferon-gamma (IFN-γ)

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released from activated NK cells has been available for over a decade and has been widely used in clinical practice for NKA assessment.[6] Previous studies have shown that decreased NKA measured using this assay is associated with the presence and prognosis of various cancers,[7,8] as well as systemic inflammatory markers including white blood cell (WBC) count and C-reactive protein (CRP).[9]

Complete blood cell count (CBC)-derived inflammatory markers, which are routinely measured in clinical settings, have recently gained attention as composite indices that integrate information from multiple immune cell populations and may reflect systemic inflammatory and immune status. Markers such as neutrophil-to-lymphocyte ratio (NLR), platelet-to -lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), systemic immune-inflammation index (SII), and systemic inflammation response index (SIRI) have been shown to correlate with inflammation in various pathological conditions, including many types of cancers,[10,11] cardiovascular diseases,[12–15] neurological diseases,[16] autoimmune disorders,[17,18] and overall mortality.[19,20] Since neutrophils, monocytes, lymphocytes, and platelets play distinct yet complementary roles in inflammatory and immune responses,[21,22] composite indices derived from their ratios or combinations are considered to provide a more integrated assessment of systemic inflammatory-immune status than single-cell parameters alone.[23,24]

To date, there has been limited research examining how these CBC-derived inflammatory markers are associated with innate immune function, particularly NK cell activity, in large population-based settings. Understanding the relationship between NKA and CBC-based inflammatory indices may provide insight into immune–inflammatory interactions at the population level. Accordingly, the present study investigated the association between NKA and multiple CBC-derived inflammatory markers and compared their performance in relation to NKA with that of traditional inflammatory markers, such as WBC count and CRP.

Materials and Methods

Study Design and Population

This cross-sectional study analyzed health check-up data from Chaum Life Center, a single health-screening center in Seoul, Republic of Korea. The data were obtained from the electronic medical records, and were de-identified and extracted by the institution for analysis. The investigators did not have direct access to the full database, and no additional data cleaning or imputation procedures were performed. We screened subjects who underwent NKA assay from January 2016 to May 2022 (n = 11,251). Among the 11,251 eligible subjects, we excluded 29 subjects under 18 years of age. Then, we further excluded individuals with 1) a history of malignant disease or autoimmune disease, such as rheumatoid arthritis or inflammatory bowel disease (n = 563); 2) recent use of steroid, non-steroidal anti-inflammatory drugs (NSAIDs), or immuno-suppressants (n = 237); 3) missing data of CBC (n = 93). After these exclusions, a total of 10,329 subjects were included in the analysis. Missing data were handled using a complete-case analysis approach, and the study flow diagram is presented in Figure 1.

This study was approved by the Institutional Review Board of CHA Bundang Medical Center (CHAMC 2022–09-045). The study protocol conformed to the ethical guidelines of the 1964 Declaration of Helsinki and its subsequent amendments. Also, the study conductance and manuscript were drafted according to the REporting of studies Conducted using Observational Routinely-collected Data (RECORD) guidelines for cross-sectional studies.

Data Collection

Body weight (to the nearest 0.1 kg) and height (to the nearest 0.1 cm) were measured while the subjects wore lightweight clothing and no shoes. Body mass index (BMI) was calculated as the ratio of weight (kg) to height squared (m^2). Blood samples were collected from the antecubital vein in the morning after at least 8 hours of fasting. The complete blood cell count (CBC) was measured using XN-10 Hematology Analyzer (Sysmex, IL, USA), which count the number of blood cells (red blood cell, WBC, and platelet) and WBC differential counts (neutrophil, lymphocyte, and monocyte) in a given volume of blood. CRP was measured using the Hitachi 7600 Analyzer (Hitachi Co., Tokyo, Japan). Smoking status, drinking status, and exercise habits of the participants were obtained from a self-reported questionnaire. Smoking and drinking status were categorized into three groups, respectively: current smoker/drinker, former smoker/drinker, or never

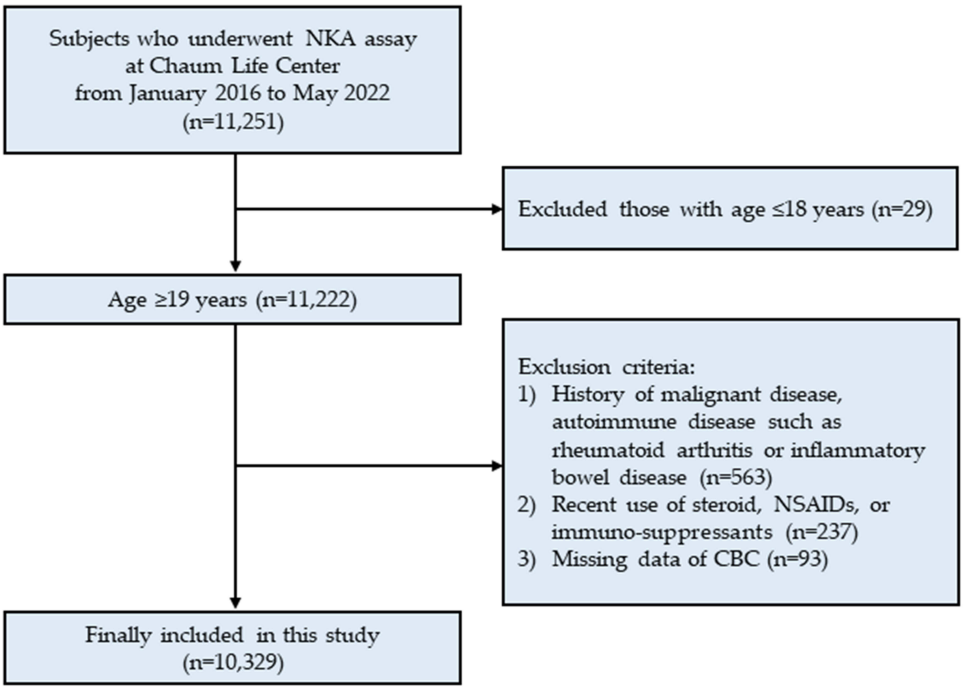

Figure 1 Flow chart of the selection of the study population.

smoker/drinker. We defined regular exercise as regularly exercising more than two days a month. Hypertension was defined as a systolic blood pressure of ≥140 mmHg, a diastolic blood pressure of ≥90 mmHg, or treatment with anti-hypertensive medication.[25] Diabetes mellitus was defined as follows: a fasting plasma glucose level of ≥126 mg/dL; glycosylated hemoglobin of ≥6.5%; or treatment with oral anti-diabetic medication or insulin therapy.[26]

Assessment of CBC-Derived Inflammatory Markers

We calculated five CBC-derived inflammatory markers as follows: NLR = neutrophil counts/lymphocyte counts, PLR = platelet counts/lymphocyte counts, MLR = monocyte counts/lymphocyte counts, SIRI = (neutrophil counts × monocyte counts)/lymphocyte counts, SII = (platelet counts × neutrophil counts)/lymphocyte counts.[23,24]

IFN-γ Measurement for NKA

Natural killer (NK) cell activity was assessed by quantifying interferon-gamma (IFN-γ) secretion using a commercially available blood test (NK Vue® Kit, NKMAX, Seongnam, Korea). For this assay, 1 mL of peripheral whole blood was collected directly into a specialized tube (Promoca®, NKMAX, Seongnam, Korea) containing a proprietary cytokine stimulant that selectively activates NK cells. The tube was gently mixed within 30 minutes of collection and then incubated at 37.0 °C for 20 to 24 hours. During incubation, the stimulant induces IFN-γ release primarily from NK cells, with minimal contribution from other immune cells.[6,27,28] After incubation, the supernatant was separated by centrifugation at 3000 × g for 3 minutes, and IFN-γ levels were measured in pg/mL using an enzyme-linked immunosorbent assay (ELISA). According to the manufacturer's validation data, the assay demonstrated acceptable precision, with inter-assay coefficients of variation below 10% across different sessions, operators, laboratories, days, and reagent lots.[29] Low NK cell activity was defined as an IFN-γ level below 500 pg/mL, based on previously published clinical studies using the same whole-blood assay and manufacturer-recommended thresholds, in which this cut-off has been associated with impaired immune function and adverse clinical outcomes.[7,9]

Statistical Analysis

All data were presented as means ± standard deviations for continuous variables and as numbers (percentages) for categorical variables. Differences in clinical characteristics between participants with normal and low NKA were

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analyzed using the independent *t*-test for continuous variables and the chi-square test for categorical variables. We categorized the participants into four groups according to quartiles of each CBC-derived inflammatory marker. The odds ratios (OR) and 95% confidence intervals (CI) for low NKA of Q2, Q3, and Q4 compared to Q1, as the reference, were calculated by using multiple logistic regression analysis after adjusting for potential confounding variables. Non-linear relationship between CBC-derived markers and NKA was assessed by comparing a linear model with a generalized additive model using penalized splines. P-values for non-linearity were obtained from a F-test comparing the two models. Furthermore, to compare the discriminatory performance of CBC-derived inflammatory markers with that of traditional inflammatory markers (WBC count and CRP) for low NKA, we calculated receiver operating characteristic (ROC) curves and compared the areas under the ROC curves (AUROC). Sensitivity analyses were also performed using alternative cut-off values for low NKA (IFN-γ level below 250 pg/mL and 100 pg/mL). All statistical analyses were conducted using SPSS statistical software (version 25.0, SPSS Inc., Chicago, IL, USA) and R (version 4.4.0; R Foundation for Statistical Computing, Vienna, Austria). A *p*-value of <0.05 was considered statistically significant.

Results

Clinical Characteristics of the Study Population

Table 1 represents the clinical characteristics of the study population. Participants with low NKA showed significantly higher age, CRP levels, WBC, neutrophil, monocyte, platelet counts, and five CBC-derived inflammatory markers, and higher proportions of current smokers and current drinkers. The mean lymphocyte count and proportion of regular exercise were significantly lower in subjects with low NKA. The mean BMI and proportions of male sex, hypertension, and diabetes mellitus showed no significant differences between subjects with normal and low NKA.

Table 1 Clinical Characteristics of the Study Population

Characteristics	Normal NKA	Low NKA	*p*-value
Participants, n	6458	3871	
Age, years	47.3 ± 11.5	48.3 ± 11.5	<0.001
Male sex, %	3008 (46.6)	1769 (45.7)	0.386
BMI, kg/m^2	23.4 ± 3.7	23.4 ± 3.9	0.942
CRP, mg/dL	0.14 ± 0.29	0.18 ± 0.52	<0.001
WBC count, $10^3/\mu L$	5.27 ± 1.39	5.88 ± 1.81	<0.001
Neutrophil, $10^3/\mu L$	2.91 ± 1.05	3.57 ± 1.54	<0.001
Lymphocyte, $10^3/\mu L$	1.81 ± 0.51	1.75 ± 0.56	<0.001
Monocyte, $10^3/\mu L$	0.38 ± 0.13	0.39 ± 0.15	0.003
Platelet, $10^3/\mu L$	246.6 ± 53.1	265.7 ± 61.9	<0.001
CBC-derived indicators			
NLR	1.70 ± 0.74	2.24 ± 1.39	<0.001
PLR	145.4 ± 47.2	165.1 ± 62.6	<0.001
MLR	0.22 ± 0.08	0.23 ± 0.10	<0.001
SIRI, $10^3/\mu L$	0.67 ± 0.46	0.89 ± 0.77	<0.001
SII, $10^3/\mu L$	421.2 ± 214.6	597.4 ± 408.2	<0.001
Current smoker, n (%)	1072 (16.6)	730 (18.9)	0.012
Current drinker, n (%)	911 (14.1)	565 (14.6)	0.036
Regular exercise, n (%)	4205 (65.1)	2406 (62.2)	0.002
Hypertension, n (%)	855 (13.2)	514 (13.3)	0.955
Diabetes mellitus, n (%)	335 (5.4)	234 (6.3)	0.069

Notes: Data are presented as mean ± standard deviation or number (%). *p*-value was calculated using the *t*-test for continuous variables and the chi-square test for categorical variables.

Abbreviations: BMI, body mass index; CBC, complete blood cell count; CRP, C-reactive protein; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index; WBC, white blood cell.

Relationship Between CBC-Derived Inflammatory Markers and Low NKA

Figure 2 shows the proportion of subjects with low NKA according to quartiles of NLR, PLR, MLR, SIRI, and SII. The proportion of low NKA increased with higher CBC-derived inflammatory indices for all indices (p for trend <0.05 by the Cochran–Armitage test).

Table 2 presents the ORs (95% CIs) for low NKA according to the quartiles of each CBC-derived inflammatory marker. Compared to the lowest quartile, the multivariable-adjusted ORs (95% CIs) for low NKA were 3.90 (3.45–4.41) in the highest quartile of NLR, 2.69 (2.38–3.05) in the highest quartile of PLR, 1.45 (1.29–1.63) in the highest quartile of MLR, 2.96 (2.62–3.35) in the highest quartile of SIRI, and 4.80 (4.23–5.45) in the highest quartile of SII, respectively, after adjusting for age, sex, BMI, smoking status, drinking status, regular exercise, hypertension, and diabetes mellitus. Although these estimates should be interpreted cautiously given the cross-sectional design, the observed effect sizes indicate a meaningful gradient in the likelihood of low NKA across increasing levels of CBC-derived inflammatory markers. Sensitivity analyses using alternative cut-off values for low NKA yielded results consistent with the primary analysis (Supplementary Table S1).

When NKA was analyzed as a continuous variable using generalized additive models, significant non-linear associations were observed for NLR, PLR, SIRI, and SII (all p for non-linearity <0.0001), whereas no evidence of non-linearity was found for MLR (p for non-linearity >0.1) (Figure 3).

Comparison of the Discriminatory Performance of CBC-Derived Inflammatory Markers for Low NKA

Figure 4 and Table 3 present the comparative discriminatory performance of traditional inflammatory markers (CRP and WBC) and CBC-derived inflammatory markers for low NKA. The AUROCs of CRP, WBC, NLR, PLR, MLR, SIRI, and SII were 0.534, 0.601, 0.645, 0.595, 0.544, 0.616, and 0.667, respectively. Among the evaluated markers, SII exhibited the largest AUROC, followed by NLR and SIRI. Pairwise comparisons of AUROCs demonstrated statistically significant differences between SII and other CBC-derived inflammatory markers (Supplementary Table S2). Compared with CRP,

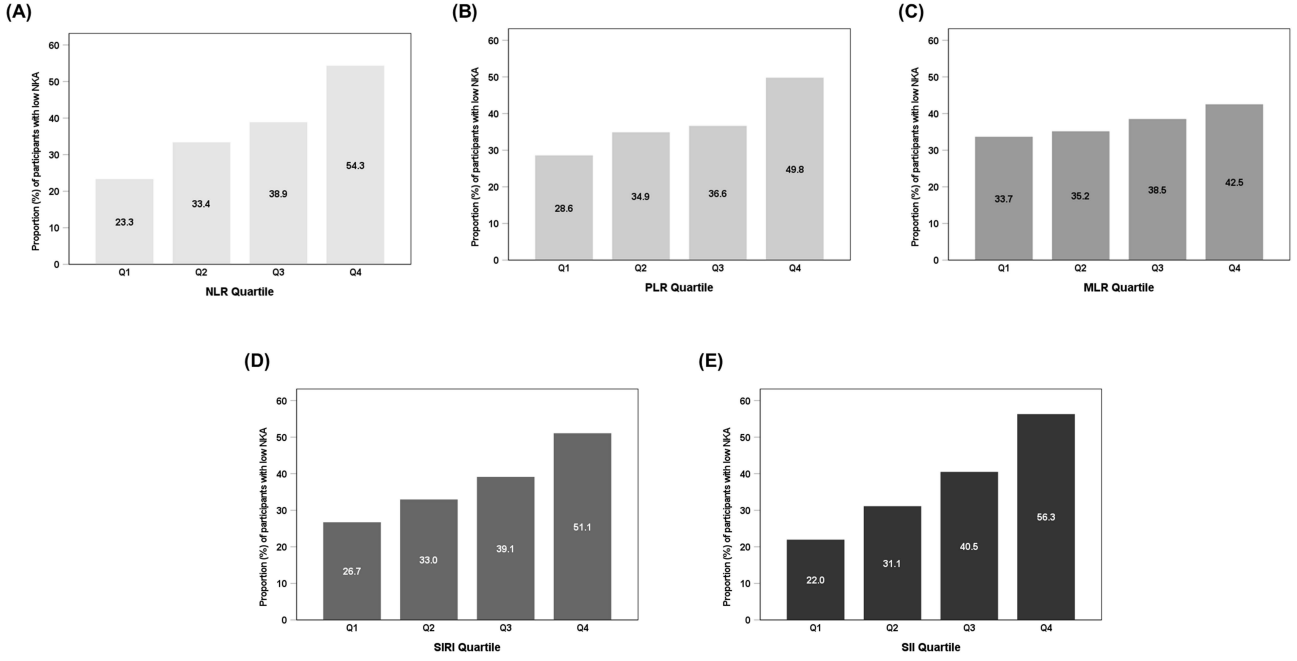

Figure 2 The proportion of subjects with low NKA according to each quartile of CBC-derived inflammatory markers. (**A**) NLR; (**B**) PLR; (**C**) MLR; (**D**) SIRI; (**E**) SII.

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Table 2 Odds Ratios for Low NKA According to Quartiles of Complete Blood Cell Count (CBC)-Derived Inflammatory Markers

		Quartiles of CBC-Derived Inflammatory Markers Levels				Overall *p*
		Q1	Q2	Q3	Q4	
NLR	Range	<1.30	1.30–1.67	1.67–2.20	>2.20	
	Unadjusted	1 (Ref.)	1.65 (1.461.86)	2.09 (1.86–2.36)	3.91 (3.47–4.41)	<0.001
	Adjusted	1 (Ref.)	1.64 (1.45–1.86)	2.08 (1.84–2.36)	3.90 (3.45–4.41)	<0.001
PLR	Range	<116.1	116.1–144.2	144.2–178.9	>178.9	
	Unadjusted	1 (Ref.)	1.34 (1.19–1.51)	1.45 (1.29–1.62)	2.48 (2.21–2.78)	<0.001
	Adjusted	1 (Ref.)	1.38 (1.22–1.56)	1.55 (1.37–1.75)	2.69 (2.38–3.05)	<0.001
MLR	Range	<0.17	0.17–0.21	0.21–0.26	>0.26	
	Unadjusted	1 (Ref.)	1.07 (0.95–1.20)	1.23 (1.10–1.38)	1.46 (1.30–1.63)	<0.001
	Adjusted	1 (Ref.)	1.06 (0.94–1.20)	1.23 (1.09–1.38)	1.45 (1.29–1.63)	<0.001
SIRI	Range	<0.43	0.43–0.61	0.61–0.89	>0.89	
	Unadjusted	1 (Ref.)	1.35 (1.20–1.52)	1.76 (1.57–1.98)	2.86 (2.55–3.22)	<0.001
	Adjusted	1 (Ref.)	1.36 (1.20–1.54)	1.81 (1.60–2.04)	2.96 (2.62–3.35)	<0.001
SII	Range	<304.8	304.8–417.3	417.3–574.9	>574.9	
	Unadjusted	1 (Ref.)	1.61 (1.42–1.82)	2.42 (2.14–2.73)	4.58 (4.06–5.17)	<0.001
	Adjusted	1 (Ref.)	1.64 (1.44–1.86)	2.44 (2.16–2.77)	4.80 (4.23–5.45)	<0.001

Note: Adjusted for age, sex, BMI, smoking status, drinking status, regular exercise, hypertension, and diabetes mellitus.
Abbreviations: MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index.

the AUROCs of NLR, PLR, SIRI, and SII were significantly higher, whereas no significant difference was observed between MLR and CRP. In addition, the AUROCs of NLR, MLR, SIRI, and SII were significantly higher than that of WBC, while no significant difference was observed between PLR and WBC.

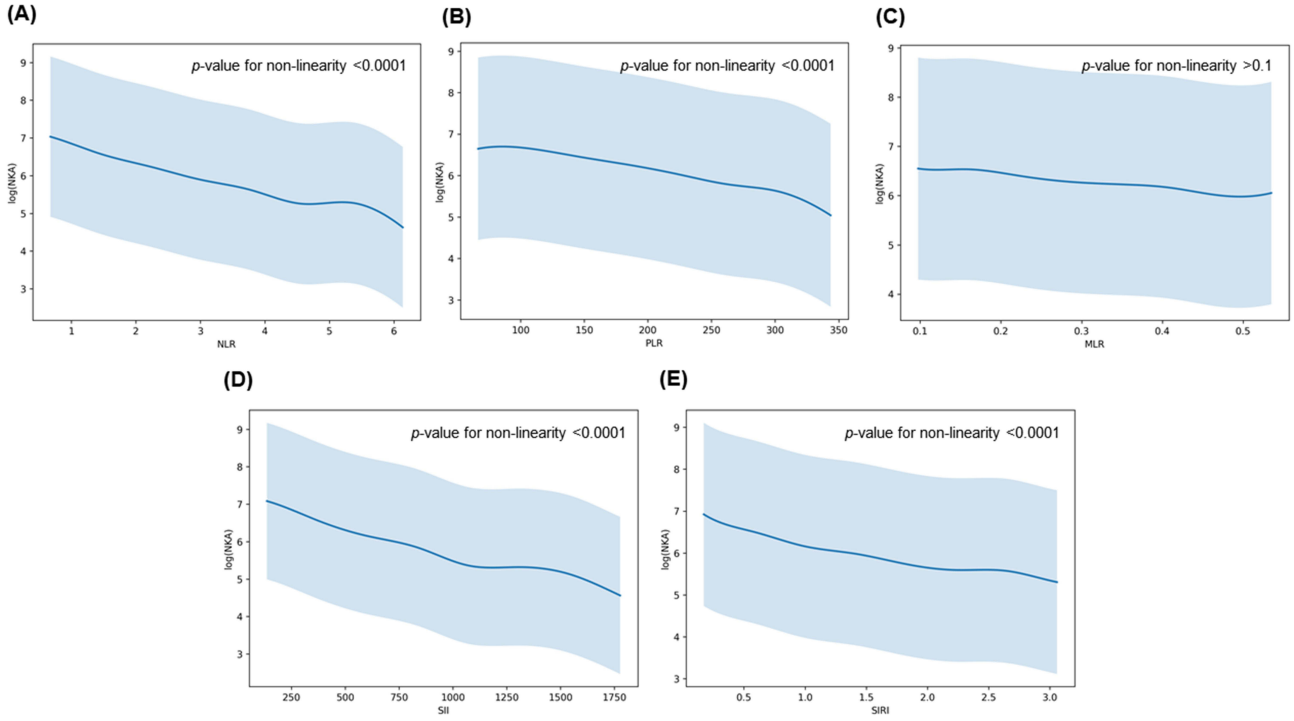

Figure 3 Spline curves between CBC-derived inflammatory markers and continuous NKA. Generalized additive models with penalized splines were used to examine potential non-linear associations between CBC-derived inflammatory markers and continuous NKA. Solid lines represent fitted spline curves, and shaded areas indicate 95% confidence intervals. (**A**) NLR; (**B**) PLR; (**C**) MLR; (**D**) SIRI; (**E**) SII.

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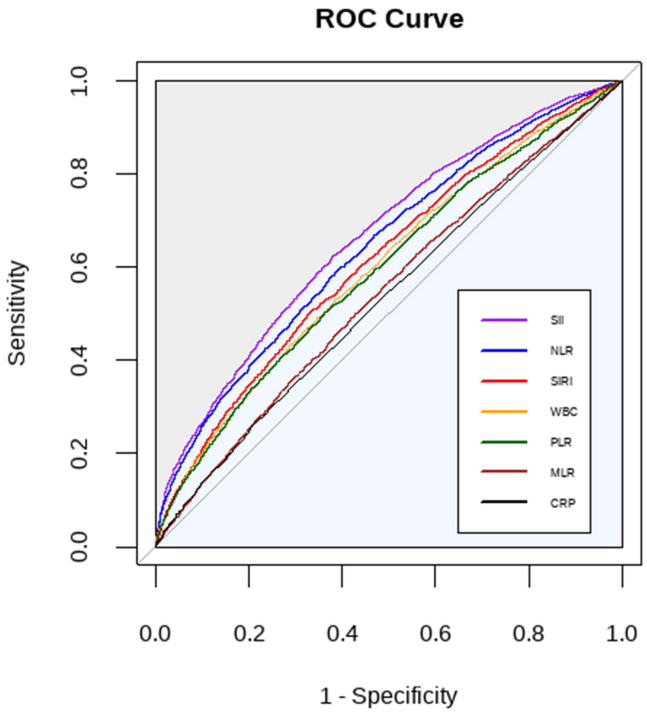

Figure 4 Comparison of the discriminatory performance of CBC-derived inflammatory markers and traditional inflammatory markers (CRP and WBC) for low NKA. Key CBC-derived inflammatory markers (SII, NLR, and SIRI) are highlighted in the legend; other indices are shown for reference.

Discussion

This study explored the relationship between CBC-derived inflammatory markers and NKA in a large cohort of healthy individuals. The findings suggest that higher levels of certain inflammatory markers, such as SII, NLR, and SIRI, were significantly associated with reduced NKA. These findings are consistent with an association between systemic inflammatory status and immune dysfunction, particularly in relation to lower NK cell activity, an important component of immune surveillance and host defense.

Many studies have already shown that elevated levels of CBC-derived inflammatory markers (SII, NLR, and SIRI) are associated with a higher risk of cancer development and poor prognosis. Several studies have shown that higher SII scores are correlated with poor prognosis in cancers such as gastric cancer,[30] cervical cancer,[31] and Hodgkin lymphoma,[32] where they are linked to increased tumor progression and metastasis. Similarly, NLR, a simple and cost-effective marker, has been associated with poor cancer outcomes by reflecting the balance between neutrophils and

Table 3 Comparison of AUROCs of CBC-Derived Inflammatory Markers and Traditional Inflammatory Markers (CRP and WBC) for Low NKA

	AUROC (95% CI)	*p* for Comparison With CRP	*p* for Comparison With WBC
CRP	0.534 (0.521–0.546)	Ref.	Ref.
WBC	0.601 (0.590–0.613)	<0.0001	Ref.
NLR	0.645 (0.634–0.656)	<0.0001	<0.0001
PLR	0.595 (0.583–0.606)	<0.0001	0.4903
MLR	0.544 (0.533–0.556)	0.1897	<0.0001
SIRI	0.616 (0.604–0.627)	<0.0001	0.0029
SII	0.667 (0.656–0.677)	<0.0001	<0.0001

Note: *p*-values were obtained using the DeLong test for correlated ROC curves.
Abbreviations: CRP, C-reactive protein; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index; WBC, white blood cell.

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lymphocytes. Higher NLR ratios have been linked to adverse outcomes in non-small cell lung cancer,[33] cholangiocarcinoma,[34] and colorectal cancer.[35] Elevated SIRI has been found to reflect immune dysfunction and has been identified as a valuable marker for evaluating immune suppression, particularly in cancers like pancreatic cancer,[24] colorectal cancer,[36] and breast cancer.[37] From all these previous studies, inflammation is believed to be linked to immunosuppression, which in turn is related to cancer occurrence. The results of this study indicate that higher inflammatory marker levels are associated with lower NKA, a functional measure of innate immune activity.

Beyond cancer, elevated NLR, SIRI, and SII have also been widely recognized as markers associated with cardiovascular and metabolic diseases. Elevated SII, NLR and SIRI have been linked to increased cardiovascular mortality and adverse outcomes, particularly in conditions like acute coronary syndrome, as they reflect systemic inflammation and immune dysregulation.[38,39] Similarly, SIRI has shown prognostic value in predicting cardiovascular mortality.[40] In metabolic diseases, a higher NLR has been associated with diabetic mortality,[41] SII and SIRI related to complications such as diabetic retinopathy[42] highlighting their role in chronic inflammation-driven pathologies. Obesity and metabolic syndrome is also positively associated with SII and SIRI in adults[43] and NLR, SII, SIRI with children.[44]

Although studies directly linking CBC-derived inflammatory markers to NKA are limited, it was previously demonstrated that reduced NKA levels correlate with elevated inflammatory markers, including neutrophil counts and NLR,[9] as well as with a higher resting heart rate, a physiological indicator of increased sympathetic activity and stress.[45] These observations suggest that reduced NKA may be associated with heightened systemic inflammation. From a biological perspective, chronic inflammatory environments have been shown to impair NK cell function through cytokine-mediated mechanisms, including suppression of activating receptors and reduced IFN-γ production.[1,46] Sustained inflammatory signaling may also promote functional exhaustion of NK cells, characterized by diminished effector capacity and altered immune regulation.[47] These mechanisms provide biological plausibility for the observed association between elevated inflammatory markers and lower NKA, without implying a causal relationship. In the present study, a larger sample size was incorporated and a broader range of inflammatory markers, including MLR, PLR, SIRI, and SII, was simultaneously evaluated. In addition, the comparative assessment of these CBC-derived inflammatory markers in relation to NKA demonstrated that SII showed relatively stronger discriminatory performance than other indices, although the overall predictive ability remained modest.

While CRP and WBC count are commonly used to assess systemic inflammation, their utility as sole indicators of NKA remains controversial. One study indicated that while the NLR was significant, CRP levels did not significantly correlate with NKA, suggesting that CRP may not be a reliable marker for assessing NKA.[48] In this context, CBC-derived inflammatory markers (NLR, SII, and SIRI) showed greater discriminatory ability for low NKA than traditional inflammatory markers such as CRP and WBC count, with SII demonstrating the highest AUROC among the evaluated indices. This finding aligns with previous studies demonstrating that SII, which integrates neutrophil, lymphocyte, and platelet counts, provides a comprehensive assessment of the inflammatory-immune balance and has shown superior predictive value in various inflammatory-related conditions.[23,49,50] While CRP and WBC are widely used to assess inflammation, CBC-derived inflammatory markers are derived from standard hematologic parameters and therefore may be conveniently assessed in routine laboratory data, particularly in observational or population-based studies.

Despite the significance of our findings, several limitations should be acknowledged. First, this study was conducted at a single health-screening center, which may limit the representativeness and generalisability of the results. Second, NKA was assessed using an IFN-γ–based assay without direct measurement of NK cell counts; however, this assay offers practical advantages for large-scale studies. Third, residual confounding cannot be fully excluded, as information on acute illness or transient medical conditions at the time of examination was unavailable. In addition, although this study was supported by institutional funding and employed a commercially available assay, neither the funder nor the manufacturer had any role in the study design, analysis, interpretation, or manuscript preparation; nonetheless, the possibility of residual bias cannot be entirely ruled out. Finally, the cross-sectional design precludes causal inference, and future longitudinal and mechanistic studies are needed to clarify temporal and biological relationships between inflammatory markers and NK cell activity.

Conclusions

In conclusion, this study demonstrates that CBC-derived inflammatory markers, particularly NLR, SIRI, and SII, are associated with lower NKA in a health check-up population. These indices may serve as simple and accessible indicators reflecting immune–inflammatory status in observational and research settings. The present findings highlight an association rather than establishing clinical applicability or predictive utility. While CBC-derived inflammatory markers, especially SII, show potential usefulness for identifying individuals with low NKA, further longitudinal and mechanistic studies are required before these markers can inform screening strategies or personalized clinical decision-making.

Data Sharing Statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics Approval and Informed Consent

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Institutional Review Board of CHA Bundang Medical Center (CHAMC 2022-09-045). Informed consent was obtained from all individual participants included in the study.

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Author Contributions

A-RC: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. HO: Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. ES: Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. J-HJ: Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. JM: Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. BC: Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Funding acquisition, Conceptualization. Y-KL: Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Funding acquisition, Conceptualization.

All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

A-Ra Cho and Hyoju Oh contributed equally to this work and share first authorship. Baek Hwan Cho and Yun-Kyong Lee are co-corresponding authors.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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