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Letters to Editor

Time-Adjusted Immune Indices: A Circadian Perspective on Neutrophil-to-Lymphocyte Ratio in Immunotherapy

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ABSTRACT

Immune indices such as the neutrophil-to-lymphocyte ratio (NLR) are widely used to monitor patients on immune checkpoint inhibitors, yet their interpretation rarely consider time-of-day biology. This perspective proposes a circadian framework in which sampling time and treatment timing shape baseline values, short-term fluctuations, and prognostic thresholds. Drawing on clinical observations across lungs, renal, and other tumors, I outline how morning versus afternoon therapy and corticosteroid administration may differentially modulate NLR trajectories and toxicity and introduce practical steps for time-adjusted reporting: record clock time, analyze intra-patient trends, and compare like-for-like time windows. Integrating chronobiology into routine hematologic

To the Editor,

Circadian regulation is increasingly recognized as an important modulator of immune function1. However, in daily oncology practice, immune-related adverse events (irAEs) continue to be challenging to anticipate, and current tools are often limited in their precision. Traditional hematologic markers, such as the neutrophil-to-lymphocyte ratio (NLR) and the systemic immune-inflammation index (SII), provide significant prognostic insights, yet they do not account for temporal dynamics. This omission signifies a limitation of current indices, which are typically measured as single time-point values without considering circadian context.

From our institutional observations (n=23 patients; median age 66 years, range 49–81; 14 males, 9 females; observation period 2019–2024), treatment timing appeared to influence immune indices. Patients receiving immune checkpoint inhibitors in the morning (n=15) demonstrated stable or declining pre-infusion NLR values, coinciding with sustained clinical benefit. In contrast, those treated predominantly in the afternoon (n=8) more frequently exhibited transient elevations in NLR or SII, occasionally preceding immune-related toxicities. A summary of these exploratory findings is provided in Table 1. Importantly, NLR seems particularly sensitive to circadian variation, reflecting both neutrophil mobilization and lymphocyte redistribution across day [2].

Table 1: Baseline characteristics and circadian-related immune trends in 23 patients receiving immune checkpoint inhibitors.

Variable	Morning group (n=15)	Afternoon group (n=8)
Median age (range), years	65 (49–80)	68 (52–81)
Sex, M/F	9/6	5/3
Predominant tumor type (NSCLC, %)	67%	62%
Median baseline NLR	3.2	3.4
NLR trend during therapy	Stable/declining	Frequent transient ↑
Median baseline SII	540	560
SII trend during therapy	Mostly stable	Occasional transient ↑
irAEs (any grade)	3 (20%)	4 (50%)
Clinical benefit (SD/PR/CR, %)	80%	50%

Morning-treated patients (n=15) demonstrated more stable or declining neutrophil-to-lymphocyte ratio (NLR) and systemic immune-inflammation index (SII) values, with fewer immune-related adverse events (irAEs) and higher rates of clinical benefit compared to the afternoon group (n=8), where transient increases in NLR/SII and higher irAE incidence were more frequently observed.

These exploratory findings suggest that conventional indices, while useful, may overlook a key dimension: the circadian context. We therefore propose a time-adjusted approach to immune indices. As a working hypothesis, a composite parameter—the „Circadian Immune Index“ (CII)—could be defined as the relative fluctuation of immune markers across circadian windows. Conceptually, one might express CII as the ratio between morning and afternoon NLR values, normalized to individual baseline variation. This framework could also be extended to other circadian-sensitive markers, such as SII, platelet-to-lymphocyte ratio (PLR), or cytokine levels, to capture temporal immune dynamics otherwise missed by single time-point measures.

This perspective does not aim to replace established predictors, but rather to stimulate discussion about whether circadian adjustment adds incremental value to risk stratification. Recent analyses, including a study-level meta-analysis, support the hypothesis that the time of immunotherapy infusion may correlate with overall survival in advanced cancers [3]. We encourage future observational and prospective studies to test the feasibility of circadian-adjusted indices, ideally in multicenter cohorts. Ultimately, even simple temporal adjustments to commonly used markers like NLR could represent a practical step toward chrono-immunological personalization of cancer therapy.

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Data Availability:

This letter is based on summarized observational insights, and no additional datasets were generated or analyzed. Further information supporting the observations discussed is available from the author upon reasonable request.

Conflict of Interest

Authors declare no conflict of interest.

The author meets the ICMJE criteria for authorship and are accountable for all aspects of the work.

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