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TIMING OF INFUSION AND IMMUNOTHERAPY EFFICACY IN METASTATIC NON-SMALL CELL LUNG CANCER: A META-ANALYSIS

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Summary *Circadian rhythms are endogenous biological cycles with a period of approximately 24 hours that regulate the functions of many bodily systems, including the immune system. They influence gene expression, immune cell activity, and tumor cell proliferation, suggesting a potential role in shaping responses to immunotherapy for malignant neoplasms. One of the emerging areas of oncological research is the impact of the time of infusion on the efficacy of immune checkpoint inhibitors (ICIs) in the treatment of metastatic non-small cell lung cancer (NSCLC).*

Purpose – *to assess the association between the time of infusion when ICI infusions are administered and overall survival (OS) in patients with metastatic NSCLC through a meta-analysis of published studies.*

Material and methods. *Seven studies that met the inclusion criteria were analyzed. The sample comprised 1,491 patients, of whom 813 received ICIs primarily in the morning, and 678 in the afternoon. Sources were identified through PubMed and proceedings from ESMO and ASCO conferences. A random-effects meta-analysis model was used to calculate effect sizes and standard errors. Heterogeneity was assessed, and a Galbraith plot was generated.*

Results. *All studies demonstrated an OS advantage for the "morning" group. The pooled effect size was 0.73 (95% CI: 0.521–0.938; p <0.001). Infusion time cut-off points ranged from 11:37 to 16:30. Six studies evaluated all treatment cycles, while one assessed only the first infusion. The I^2 statistic indicated high heterogeneity among studies (I^2 = 72.6%), suggesting substantial variability in effect sizes not attributable to chance (Q = 20.08; p = 0.0027). Effect sizes in individual studies ranged from 0.407 to 1.270, all favoring morning administration. No study contradicted the overall trend. The efficacy of immunotherapy in the morning group was approximately twice as high.*

Conclusions. *The time of ICI infusion is a statistically significant predictor of survival in patients with metastatic NSCLC. Morning infusions was associated with improved therapeutic efficacy and should be considered in treatment protocols.*

ЧАС ІНФУЗІЇ ТА ЕФЕКТИВНІСТЬ ІМУНОТЕРАПІЇ ПРИ МЕТАСТАТИЧНОМУ НЕДРІБНОКЛІТИННОМУ РАКУ ЛЕГЕНЬ: МЕТААНАЛІЗ

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Ключові слова: *імунотерапія, циркадні ритми, недрібноклітинний рак легень, PD-1, PD-L1, хронотерапія, загальна виживаність.*

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Анотація *Циркадні ритми – це ендогенні біологічні цикли з періодом близько 24 годин, які регулюють функції багатьох систем організму, зокрема імунної. Вони впливають на експресію генів, активність імунних клітин та проліферацію пухлинних клітин, що дозволяє припустити їхню роль у формуванні відповіді на імунотерапію злоякісних новоутворень. Одним із досліджуваних напрямків в онкології є вплив часу інфузії на ефективність інгібіторів імунних контрольних точок (ІІКТ) при лікуванні метастатичного недрібноклітинного раку легень (НДКРЛ).*

Мета роботи *– оцінити зв'язок між часом інфузії ІІКТ та загальною виживаністю (ЗВ) пацієнтів з метастатичним НДКРЛ на основі метааналізу опублікованих досліджень.*

Матеріал і методи. *Проаналізовано 7 досліджень, які відповідали критеріям включення. Вибірка включала 1491 пацієнта, із яких 813 отримували ІІКТ переважно вранці, а 678 – у другій половині дня. Джерела ідентифіковані через базу PubMed та огляди конференцій ESMO і ASCO.*

Використано рандомізовану модель метааналізу з розрахунком розміру ефекту та стандартної похибки. Оцінено гетерогенність даних та побудовано графік Гелбрейта.

Результати. *У всіх дослідженнях спостерігалася перевага «ранкової» групи за показником ЗВ. Узагальнене значення розміру ефекту становило 0,73 (95% ДІ: 0,521–0,938; p < 0,001). Граничні значення часу інфузії варіювали від 11:37 до 16:30. У шести дослідженнях враховувались усі цикли терапії, в одному – лише перша інфузія. Тест I^2 показав високу гетерогенність досліджень (I^2 = 72,6%), що свідчило про суттєву варіабельність ефектів, яка не пояснювалася випадковістю (Q = 20,08; p = 0,0027). Розмір ефекту в окремих дослідженнях варіював від 0,407 до 1,270, у всіх випадках на користь ранкового введення. Жодне дослідження не суперечило загальній тенденції. Ефективність імунотерапії у пацієнтів «ранкової» групи була вдвічі вищою.*

Висновки. *Час інфузії ІІКТ має статистично значущий вплив на виживаність пацієнтів із метастатичним НДКРЛ. Ранкові інфузії асоційовані з кращими результатами лікування і повинні враховуватися в протоколах лікування.*

Introduction. Circadian rhythms are endogenous biological oscillations with a periodicity of approximately 24 hours that coordinate the functions of nearly all organs and systems, including the immune system. These rhythms lead to changes at the cellular and systemic levels, clinically manifesting as rhythmic patterns in physiological, biochemical, and behavioral responses in humans. Cell division, gene expression, and DNA repair are also closely linked to circadian rhythms, suggesting their potential involvement in carcinogenesis [1]. An increasing body of evidence indicates a direct influence of the molecular clock on the course of malignant diseases, particularly non-small cell lung cancer (NSCLC).

The effectiveness of NSCLC treatment is influenced by a multitude of factors. One of the most intriguing potential predictors of treatment response is the time of infusion. In oncology, the impact of chronotherapy on clinical outcomes in patients receiving chemotherapy [2], radiotherapy [3] and immunotherapy, especially immune checkpoint inhibitors (ICIs) [4; 5] has been actively explored.

Circadian rhythms are generated at the cellular level by the molecular clock, composed of 15 specific genes. Disruptions in circadian rhythms are associated with reduced treatment efficacy, accelerated carcinogenesis, and metastasis. These effects are largely attributed to immune evasion through the creation of an immunosuppressive tumor microenvironment [6].

The human immune system – including T-cell activity, PD-1/PD-L1 expression, and cytokine production – exhibits circadian variability. Specifically, the BMAL1, PER1/2, and CLOCK genes, which regulate the circadian clock, influence T-lymphocyte proliferation and the expression of molecules essential for antitumor responses [7]. Consequently, the tumor microenvironment also undergoes circadian changes. One study demonstrated that $CD8^+$ T-cell infiltration into tumor tissue was higher during certain phases of the daily cycle, highlighting the potential of chronobiological approaches in immunotherapy planning [8].

Neglecting chronobiology in oncological practice may lead to suboptimal timing of treatment and reduced efficacy. Conversely, integrating circadian data into treatment planning may facilitate a more personalized approach to managing NSCLC, potentially improving both survival and quality of life [9]. Further research will contribute to the development of clinical protocols that consider patients' individual circadian profiles to maximize response to ICIs.

The purpose of this study was to assess the association between the time of infusion when ICI infusions are administered and overall survival (OS) in patients with metastatic NSCLC through a meta-analysis of published studies.

Material and methods

The primary endpoint of this meta-analysis of published data was to assess the effect of infusion timing of ICIs on overall survival (OS) in patients with metastatic NSCLC. A literature search was conducted using the PubMed database and manual screening of conference proceedings from the European Society for Medical Oncology and the American Society of Clinical Oncology. Filters were applied to select publications from 2015 to 2025. Search terms included: "immunotherapy, programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1)", "infusion timing, circadian rhythms, chronotherapy", and "pembrolizumab, nivolumab, atezolizumab, immune checkpoint inhibitors", "non-small cell lung cancer". For each included study, the following data were extracted: authors and publication year, time cut-off for ICI infusion, type of ICI, total number of patients, number of patients in the "morning group" and "evening group," and median OS. Only studies involving metastatic NSCLC were included.

The study was conducted using the Cochrane method for meta-analysis. Calculations and graph generation were performed using the Stata software environment (version 19.5, USA). Sample heterogeneity was assessed using the I^2 statistic and the t^2 test, where $p < 0.05$ indicated the presence of heterogeneity. A Galbraith plot was created to visually represent inter-study heterogeneity. Due to the high level of heterogeneity among studies, a random-effects model (REML) was employed to calculate the pooled relative risk. For each study, the effect size was

calculated as the natural logarithm of the ratio of median survival times in the morning versus evening groups (log_median_ratio). After calculating the log_median_ratio and its standard error (SE), a meta-analysis was conducted. The results of the meta-analysis are presented as effect sizes with 95% confidence intervals (CI). Statistical significance was defined as $p < 0.05$. Graphical representation of the results was performed using the meta forestplot function.

Results

A total of 157 studies were identified through the literature search. Following a detailed screening process, articles reporting the effect of time of day on immunotherapy for malignancies other than NSCLC were excluded (n=101). In addition, preprints (n=10), duplicate studies (n=7), and studies combining PD-1/PD-L1 inhibitors with cytotoxic T-lymphocyte-associated protein (CTLA-4) inhibitors (n=31), chemotherapy and chemoradiotherapy (n=2) were also excluded. Ultimately, seven studies were included in which the authors compared OS in patients with metastatic NSCLC depending on the time of day ICIs were administered [10–16].

Each study was examined for how the cut-off time separating the “morning” and “evening” groups was defined. Most authors used a pragmatic approach, based on the average time of day each patient received their ICI infusions. According to this parameter, the discrepancy between some studies reached up to 5 hours (ranging from 11:37 to 16:30). In six studies, the effect of all immunotherapy cycles was evaluated, while in one study only the timing of the first infusion was considered.

In three studies, the cutoff times were classified as "early" (11:37, 12:00, and 12:55), whereas in four studies they were "late" (14:30, 16:00, and 16:30). In all studies, patients were assigned to the "morning group" if they received more than 80% of their ICI infusions before the designated cutoff time. Conversely, patients who received more than 20% of their ICI infusions after the cutoff time were included in the "evening group."

A total of 1,491 patients were included in the meta-analysis, of whom 813 (54.5%) were assigned to the morning group and 678 (45.5%) to the evening group. The results of the publication analysis included in the meta-analysis are presented in Table 1.

A total of seven studies investigating the association between the timing of ICI infusion and OS in patients with advanced NSCLC were included in the meta-analysis. The primary outcome was the log-transformed ratio of median OS between the morning and evening infusion groups (log_median_ratio). In all seven studies, log_median_ratio was more than 0, indicating greater median survival in the morning groups.

The random-effects meta-analysis revealed a pooled effect size of 0.729 (95% CI: 0.521 to 0.938; $p < 0.001$), indicating that, on average, patients who received ICI therapy in the morning had significantly longer median overall survival compared to those treated in the evening. This corresponds to an exponentiated effect size of approximately 2.07, suggesting that morning infusion was associated with more than twice the median OS compared to evening infusion (Fig. 1).

Heterogeneity across studies was substantial, with an I^2 value of 72.6%, indicating considerable variability in effect sizes beyond chance ($Q = 20.08$, $p = 0.0027$). Individual study effect sizes ranged from 0.407 to 1.270, all favoring morning administration.To assess heterogeneity among the included studies, a Galbraith plot was generated. None of the calculated effect sizes exceeded the 95% confidence intervals, indicating consistency across studies (Fig. 2). These results consistently support the hypothesis that circadian timing of ICI administration influences treatment efficacy, with morning infusion associated with superior survival outcomes in patients with advanced NSCL.

Discussion. We performed a meta-analysis of seven studies that reported the impact of ICI infusion timing on OS in patients with metastatic NSCLC. A statistically significant improvement in OS was observed in patients who received the majority of their ICI infusions in the morning. The effectiveness of immunotherapy in the "morning group" was nearly twice as high.

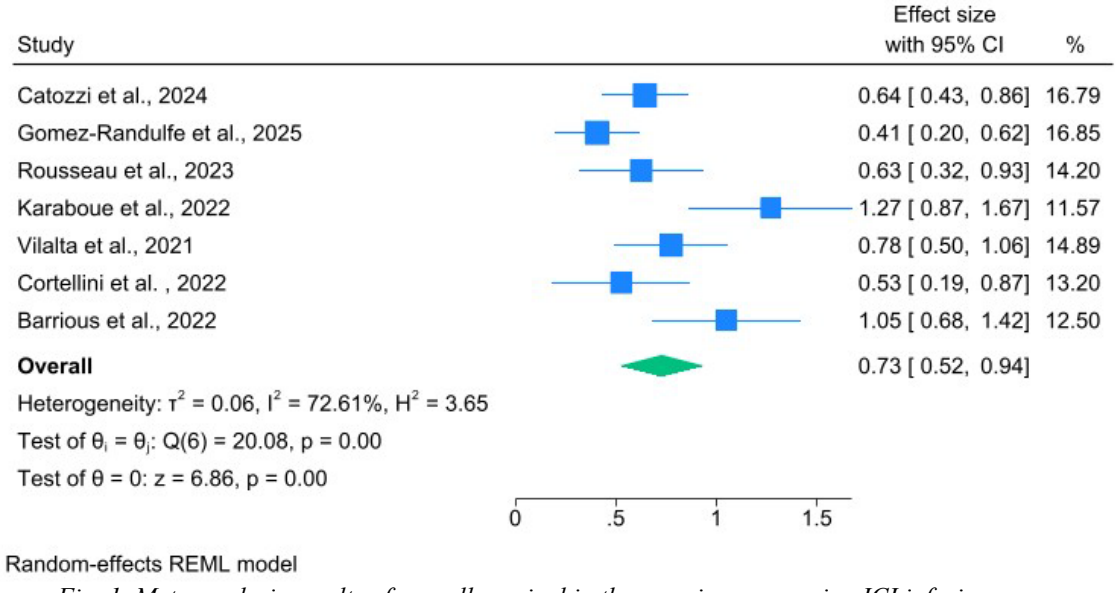

Fig. 1. Meta-analysis results of overall survival in the morning vs. evening ICI infusion groups

Table 1

Characteristics of studies included in the meta-analysis

Authors and year of publication	Country	Type of ICI	Cut-off value	Number of patients (morning group / evening group)
Gomez-Randulfe et al., 2025	UK	PD-1/PD-L1	14:30	349 (188/161)
Catozzi et al., 2024	France	PD-1/PD-L1	11:37	361 (136/225)
Rousseau et al., 2023	France	PD-1/PD-L1	16:30	180 (115/65)
Karaboue et al., 2022	France	PD-1	12:55	95 (48/47)
Cortellini et al., 2022	Spain	PD-1/PD-L1	16:30	180 (136/44)
Barrious et al., 2022	Brazil	PD-1/PD-L1	16:00	129 (86/43)
Vilalta et al., 2021	Spain	PD-1/PD-L1	12:00	197 (104/93)

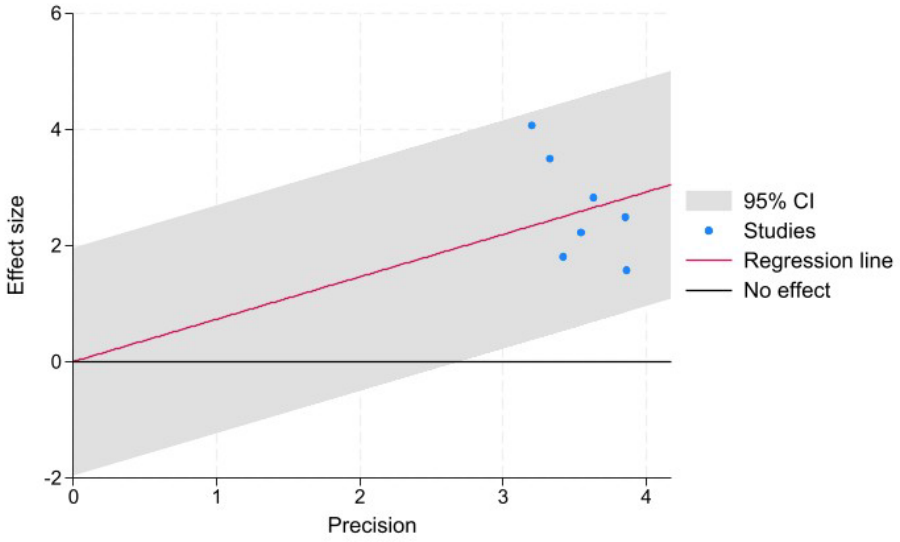

Fig. 2. Heterogeneity assessment – Galbraith plot summary for the meta-analysis

Our findings are consistent with those of Landre et al. [17], who investigated the effect of time of day on the efficacy of immunotherapy in metastatic solid tumors. Of the 16 studies included in their meta-analysis, five focused specifically on metastatic NSCLC. The authors concluded that early ICI infusions were associated with better progression-free and overall survival (Hazard Ratio 0.53, 95% CI: 0.34–0.80).

Fey et al. [18] also explored how the timing of ICI administration affects treatment outcomes, including in NSCLC. The authors emphasized that morning ICI administration may enhance treatment efficacy, based on the understanding that circadian rhythms influence immune system activity and that aligning treatment with these rhythms may optimize therapeutic outcomes. Of the 29 studies they reviewed, nine focused exclusively on NSCLC. While most studies supported improved outcomes with morning administration, some did not report significant differences, indicating variability depending on patient-specific factors and study design. In conclusion, the authors advocated for more personalized treatment approaches that take into account the patient's biological rhythms.

ICIs, particularly anti-PD-1/PD-L1 agents, have revolutionized the treatment of NSCLC. However, their effectiveness depends heavily on individual patient factors. Our findings confirm that circadian rhythms may significantly influence ICI efficacy.

One explanation proposed in the literature is socioeconomic: patients with greater access to healthcare resources are more likely to receive treatment earlier in the day, and consequently have better outcomes [19]. However, this factor alone is unlikely to explain the differences in OS.

A more plausible explanation is biological. The effectiveness of ICIs is largely dependent on $CD8^+$ cytotoxic T-cells, which are also key mediators of vaccine-induced immunity [20]. Similar to immunotherapy, vaccine efficacy is greater in the morning. Hazan et al. [21] studied 1,515,754 patients aged 12 and older who received COVID-19 vaccination and analyzed complication rates and effectiveness based on the time of day. Morning and daytime vaccinations were associated with fewer complications and hospitalizations, attributed to higher production of antibodies, TNF-α, IFN-γ, IL-1β, and memory B-cells – factors essential for both short- and long-term immunity. In addition, stronger activation of T-cells, B-cells, dendritic cells, and monocytes was observed [22].

Experimental studies also suggest that immune cells are sensitive to circadian modulation. Time of day influences dendritic cell activity, which in turn enhances their ability to interact with T-cells. PD-1 receptors are not only found on T-cells but also on tumor-associated macrophages – the most abundant immune cells in the tumor microenvironment. Mouse models have shown that the number of PD-1-expressing tumor-associated

macrophages varies significantly throughout the day [23].

Circadian rhythms affect the immune system by regulating T-cell activity, immune checkpoint expression, and cytokine secretion. For example, $CD8^+$ T-cell activity – central to the antitumor effect of ICIs – fluctuates during the day, potentially influencing treatment response. Studies have shown that PD-L1 expression on tumor cells and PD-1 expression on T-cells undergo circadian variation, affecting ICI sensitivity [24]. Lifestyle factors such as sleep patterns, physical activity, diet, and light exposure may modulate circadian rhythms and thus the immune response. Some authors suggest that regular exercise and adherence to a Mediterranean diet positively influence the circadian clock and may enhance ICI effectiveness [25].

Druzd et al. [26] demonstrated that lymphocyte migration is tightly regulated by circadian rhythms. During rest periods (nighttime), a significant number of circulating lymphocytes move into the tumor and lymph nodes. As a result, morning ICI infusions may coincide with heightened lymphocyte availability, enhancing therapeutic outcomes. The effect of circadian variation on ICI pharmacokinetics remains unclear. Some authors argue that ICIs have half-lives of 2 to 3 weeks, making circadian influence negligible. Other patient-related factors, such as sex, hormonal status, and clinical-pathological features, may have greater impact on treatment outcomes [19].

Glucocorticoids – which have broad immunomodulatory effects – are closely linked to both circadian rhythms and ICI effectiveness. Although they are known to suppress cellular immunity and cytokine expression, Shimba et al. [27] showed that endogenous circadian-induced glucocorticoids enhance immune responses by promoting survival and redistribution of B- and T-cells. Their synthesis peaks in the morning, potentially contributing to the higher efficacy of morning ICI infusions.

This study has certain limitations. First, only seven scientific publications were included in the meta-analysis, which may be considered a relatively small sample size. Second, differences in sex, PD-L1 expression levels, patient age groups, and smoking status may have influenced the outcomes.

Conclusions. The timing of treatment administration is one of the simplest and most accessible strategies for improving the effectiveness of ICIs in patients with metastatic NSCLC. Patients receiving a higher proportion of morning infusions derive the most benefit from immunotherapy. Future research should focus on developing personalized treatment strategies that account for individual circadian rhythms.

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Conflict of interest. The authors declare no conflict of interest.

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