The Association between Early Changes in Neutrophil-Lymphocyte Ratio and Survival in Patients Treated with Immunotherapy

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Abstract: Dynamic changes in the blood-based biomarkers could be used as a prognostic biomarker in patients treated with immune checkpoint inhibitors (ICIs), although the data are limited. We evaluated the association between the neutrophil–lymphocyte ratio (NLR) and early NLR changes with survival in ICI-treated patients. We retrospectively evaluated the data of 231 patients with advanced-stage cancer. We recorded baseline clinical characteristics, baseline NLR and fourth-week NLR changes, and survival data. A compound prognostic score, the NLR2-CEL score, was developed with the following parameters: baseline NLR (<5 vs. ≥5), ECOG status (0 vs. ≥1), Charlson Comorbidity Index (CCI, <9 vs. ≥9), LDH (N vs. ≥ULN), and fourth-week NLR change (10% or over NLR increase). In the multivariable analyses, higher NLR (HR: 1.743, p = 0.002), 10% or over NLR increase in the fourth week of treatment (HR: 1.807, p = 0.001), higher ECOG performance score (HR: 1.552, p = 0.006), higher LDH levels (HR: 1.454, p = 0.017), and higher CCI (HR: 1.400, p = 0.041) were associated with decreased OS. Compared to patients with the lowest scores, patients in the highest score group had significantly lower OS (HR: 7.967, 95% CI: 3.531–17.979, p < 0.001) and PFS. The composite score had moderate success for survival prediction, with an AUC of 0.702 (95% CI: 0.626–0.779, p < 0.001). We observed significantly lower survival in patients with higher baseline NLR values and increased NLR values under treatment.

Keywords: biomarker; cancer; Charlson Comorbidity Index; immunotherapy; neutrophil–lymphocyte ratio; NLR2-CEL

1. Introduction

Immune checkpoint inhibitors (ICIs) added another dimension to cancer care with a unique mechanism of action and became the fifth pillar of oncologic treatments [1,2]. The ICIs demonstrated survival improvements in several tumors and entered treatment algorithms [3–6]. Long-term disease control and even a possible cure in the metastatic setting were reported in a significant portion of patients with relatively chemoresistant tumors, such as melanoma and renal cell carcinoma [7,8]. Furthermore, the use of ICI-based combination strategies improved the survival landmarks further, as evidenced by the unprecedented median overall survival of six years in metastatic melanoma [7] and a median survival of around four years in intermediate-high risk renal cell carcinoma [8] with nivolumab plus ipilimumab combination.
Although deep and durable responses are possible with ICIs, the response rates are lower than 40% in most tumors, especially in the later lines of treatment, and toxicities, including class-specific immune-related adverse events, could be debilitating [9–11]. Additionally, most countries have limited access to immunotherapy due to the significant financial burden of immunotherapy [12]. These issues denote the need for biomarkers to aid in better patient selection for ICI use.

Despite the stunning rate of ICI development and clinical trials, biomarker development has been relatively slow. Other than the tumor PD-L1 expression in the first-line ICI use in non-small cell lung cancer (NSCLC) and tumor agnostic use of tumor mutational burden (TMB) and microsatellite instability (MSI), no other biomarker has entered routine clinical use [13–15]. These biomarkers require a tissue section, and the TMB requires a complex platform [16]. Additionally, these biomarkers encompass a limited number of patients benefitting from ICIs [17]. Due to limitations with these biomarkers, there is a growing interest in blood-based biomarkers, which are readily available and could be serially evaluated in times of progression.

While measuring the TMB, PD-L1, and lymphocyte immune profile is possible via the blood samples, simple biomarkers retrieved from complete blood count, such as the neutrophil–lymphocyte ratio (NLR), could be valuable for prognosis prediction also [18–20]. The higher levels of NLR were consistently associated with decreased survival with ICIs, possibly due to increased inflammatory pressure leading to immune exhaustion; however, the cutoffs for NLR and patient cohorts were very variable [21–25]. Additionally, the dynamic changes in NLR could reflect the changes in the immune machinery in response to ICIs and could present a minimally invasive way to monitor the host earlier in the treatment course [26–28]. Considering the instrumental role of adaptive immune system as a driver of ICI efficacy, the exploitation of NLR as a prognostic biomarker has a strong biologic rationale [29]. However, the studies evaluating the prognostic role of baseline NLR and early NLR changes are limited in ICI-treated patients. Furthermore, baseline NLR levels were previously used in the compound scoring systems incorporating several baseline laboratory and clinical parameters with the aim of treatment tailoring and prognosis estimations; however, none of the previously available compound prognostic scores was included the changes in NLR-levels in follow-up to the equations [30–32]. Therefore, we evaluated the association between NLR and early NLR changes with survival in ICI-treated patients. Additionally, we created an NLR-based compound prognostic score (NLR2-CEL score) and tested the efficacy of this score in a cohort of two institutions.

2. Materials and Methods

2.1. Patient Population

We retrospectively evaluated the adult (≥18 years of age) patients with advanced cancer treated with any ICI between January 2014 and August 2021 in two centers. We included all patients in the prespecified dates other than patients meeting prespecified exclusion criteria: (i) patients treated within the expanded access programs and clinical trials, (ii) biomarker selected patients, (iii) patients with missing laboratory or clinical data, and (iv) patients who died in the first four weeks of ICI treatment (Figure 1). We recorded the following variables from the patient files and hospital registry system: patient age, sex, Eastern Cooperative Oncology Group (ECOG) performance score, baseline height and weight, baseline and the fourth-week NLR, Charlson Comorbidity Index (CCI), immunotherapy line, metastatic sites at the start of ICIs, the best response to ICIs, and progression-free (PFS) and overall survival (OS). We recorded the type of ICI, the start and cessation dates of ICI, and the number of ICIs from the automated hospital treatment order system.
Figure 1. Flow diagram of patient selection process.

2.2. Statistical Analyses

We expressed the baseline characteristics with medians and interquartile ranges (IQR) for continuous variables and frequencies and percentages for categorical variables. We used five as the cutoff value for baseline NLR and an NLR increase of 10% or greater (from baseline) for the fourth week of NLR change. We compared baseline characteristics of the prognostic groups with Chi-square and Kruskal–Wallis H tests. The OS was defined as the period from treatment initiation to the last follow-up and/or death, and PFS was defined as the period between treatment initiation to disease progression and/or death. We conducted survival analyses with Kaplan–Meier analyses and compared survival times between prognostic subgroups by the log-rank test. We conducted the multivariable analyses by the Cox regression analyses and calculated hazard ratios with 95% confidence intervals (CIs). The predictive performance of the NLR-based composite score for OS was assessed as receiver operating characteristic (ROC) curves. Additionally, the performance of two previous compound scores, the Gustave Roussy Score (GRS) [30] and Royal Marsden Hospital Score (RMH) [31], were assessed by the ROC analyses. The statistical analyses were performed in SPSS, version 25.0 (IBM Inc., Armonk, NY, USA), and the ROC analyses were conducted with GraphPad Prism, version 8.0.0, for Windows (GraphPad Software, San Diego, CA, USA). A type-I error level of 5% (p < 0.05) was considered as the threshold limit for statistical significance.

2.3. Ethical Approval

All procedures performed in studies involving human participants were under the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the ethics committee of Istinye University.

3. Results

3.1. Baseline Characteristics

We included a total of 231 patients in the analyses (Figure 1). The median age of the cohort was 61 (IQR 51–67), and 67.1% of the patients were male. The most common diagnoses were RCC and melanoma. The 87% of the patients had 0 or 1 ECOG performance status. Most patients were treated in second or third lines (60.2%), and nivolumab was the most frequently used immunotherapy agent. The median CCI was 8, and the CCI high or low groups were defined according to this cutoff (Table 1). In the fourth-week evaluation,
97 patients (42%) had a 10% or higher increase in NLR levels compared to baseline values. The percentage of patients with 10% or higher increase in NLR levels was similar across different tumor types (melanoma, RCC, NSCLC, or other; \( p = 0.117 \)), type of ICI (\( p = 0.714 \)), or treatment line (\( p = 0.380 \)). We separated the study cohort into three categories according to baseline NLR and fourth-week NLR change. The baseline characteristics of the three groups were similar, other than the LDH levels (Table 2).

### Table 1. Baseline patient characteristics of study population.

| Clinical Feature | \( n \) (%) |
|------------------|------------|
| Median Age (IQR) | 61 (51–67) |
| Median CCI (IQR) | 8 (7–9)    |
| Sex              |            |
| Male             | 155 (67.1) |
| Female           | 76 (32.9)  |
| ECOG PS          |            |
| 0                | 132 (57.1) |
| 1                | 69 (29.9)  |
| 2                | 26 (11.3)  |
| 3                | 4 (1.7)    |
| Immunotherapy Agent |        |
| Nivolumab        | 169 (73.2) |
| Atezolizumab     | 28 (12.1)  |
| Pembrolizumab    | 20 (8.7)   |
| Ipilimumab       | 13 (5.6)   |
| Avelumab         | 1 (0.4)    |
| Primary Tumor    |            |
| RCC *            | 49 (21.2)  |
| Melanoma         | 49 (21.2)  |
| NSCLC *          | 34 (14.7)  |
| Other #          | 99 (42.9)  |
| Concomitant CT or TT + |       |
| Absent           | 176 (76.2) |
| Present          | 55 (23.8)  |
| Line of Treatment|            |
| 1                | 31 (13.4)  |
| 2                | 91 (39.4)  |
| 3                | 48 (20.8)  |
| 4 or later       | 61 (26.4)  |

* RCC, renal cell carcinoma; NSCLC, non-small cell lung cancer; # Head and neck: 17, urothelial: 14, Hodgkin’s lymphoma: 11, small cell lung cancer: 10, other: 47; + CT, chemotherapy; TT, targeted therapy.

### 3.2. Survival Analyses

During the 36.4 months of follow-up, 169 (73.2%) patients died, and 218 (92.2%) patients had any PFS event. The median OS and PFS of the cohort were 13.5 (95% CI = 10.10–16.90) and 4.98 (95% CI = 3.57–6.02), respectively. In univariate survival analyses, patients with higher NLR at baseline (<5 vs. \( \geq 5 \), \( p = 0.013 \)), 10% or over NLR increase in the fourth week of treatment (\( p = 0.002 \)), higher ECOG performance score (0 vs. \( \geq 1 \), \( p < 0.001 \)), higher LDH levels (N vs. \( \geq ULN \), \( p = 0.003 \)), and higher CCI (<9 vs. \( \geq 9 \), \( p = 0.002 \)) had decreased OS. In contrast, the association between the combined use of chemotherapy (CT) or targeted therapy (TT) (\( p = 0.998 \)) did not reach statistical significance. The PFS analyses were consistent with the OS analyses.
Table 2. The comparisons of baseline characteristics in the three groups according to baseline NLR and fourth-week NLR change.

| NLR < 5 and NLR < 10% Increase (n = 76) | NLR ≥ 5 or NLR ≥ 10% Increase (n = 138) | NLR ≥ 5 and NLR ≥ 10% Increase (n = 673) | p-Value |
|----------------------------------------|--------------------------------------|--------------------------------------|---------|
| Age (median, IQR) 61 (54–66) | 59 (50–67) | 64 (60–70) | 0.109 |
| CCI (median, IQR) 8 (7–9) | 8 (7–9) | 8 (8–9) | 0.290 |
| Metastatic Site (median, IQR) Melanoma 22 (28.9) | 24 (17.4) | 3 (17.6) | 0.375 |
| Primary Tumor RCC 15 (19.7) | 27 (19.6) | 7 (41.2) | 0.182 |
| NSCLC 9 (11.8) | 23 (16.7) | 2 (11.8) | 0.025 |
| Other 30 (39.5) | 64 (46.4) | 5 (29.4) | 0.025 |
| LDH Normal 52 (68.4) | 68 (49.3) | 9 (52.9) | 0.477 |
| Charlson Comorbidity Index <9 52 (68.4) | 91 (65.9) | 9 (52.9) | 0.072 |
| Concomitant CT or TT Absent 63 (82.9) | 100 (72.5) | 13 (76.5) | 0.230 |
| Present 13 (17.1) | 38 (27.5) | 4 (23.5) | 0.025 |
| Baseline Liver Metastasis Absent 50 (65.8) | 96 (69.6) | 12 (70.6) | 0.834 |
| Present 26 (34.2) | 42 (30.4) | 5 (29.4) | 0.834 |
| ECOG 0 46 (60.5) | 74 (53.6) | 12 (70.6) | 0.057 |
| ORR Absent 30 (42.3) | 37 (29.4) | 2 (14.3) | 0.057 |

We conducted the multivariable survival analyses via a binary logistic regression model constructed by the statistically significant parameters in the univariate analyses. In multivariate analyses, a higher NLR at baseline (HR = 1.743, p = 0.002), 10% or over NLR increase in the fourth week of treatment (HR: 1.807, p = 0.001), higher CCI performance score (HR: 1.552, p = 0.006), higher LDH levels (HR: 1.454, p = 0.017), and higher CCI (HR: 1.400, p = 0.041) were associated with decreased OS (Table 3). While there was a negative trend for lower PFS for all five parameters, the association reached statistical significance in patients with higher ECOG status (HR: 1.401, p = 0.017) and patients with an increase of 10% or higher at the fourth-week follow-up (HR: 1.544, p = 0.004) (Table 3). Additional sensitivity analyses for patient age, sex, and tumor type yielded consistent results.

Table 3. Cox regression analysis of the NLR-based compound prognostic score and overall survival and disease-free survival.

| Progression-Free Survival | Overall Survival |
|----------------------------------------|--------------------------------------|--------------------------------------|---------|
| Hazard Ratio | 95% CI * | p-Value | Hazard Ratio | 95% CI * | p-Value |
| CCI (<9 vs. ≥9) 1.193 | 0.890–1.600 | 0.238 | 1.400 | 1.014–1.932 | 0.041 |
| Baseline NLR (<5 vs. ≥5) 1.354 | 0.997–1.839 | 0.053 | 1.743 | 1.227–2.476 | 0.002 |
| Fourth-week NLR increase (<10% vs. ≥10%) 1.544 | 1.152–2.068 | 0.004 | 1.807 | 1.294–2.524 | 0.001 |
| ECOG (0 vs. ≥1) 1.401 | 1.061–1.848 | 0.017 | 1.552 | 1.134–2.123 | 0.006 |
| LDH (N vs. ≥ULN) 1.219 | 0.926–1.605 | 0.158 | 1.454 | 1.069–1.976 | 0.017 |

* 95% CI: 95% confidence interval.
3.3. Construction of the Prognostic Model

We incorporated the parameters with a statistically significant association with OS in the multivariable analyses to the prognostic survival model. We coded NLR-based parameters as 0-1-2 (0 = baseline NLR < 5 and fourth-week NLR increase <10%, 1 = baseline NLR ≥ 5 or fourth-week NLR increase ≥10%, and 2 = baseline NLR ≥ 5 and fourth-week NLR increase ≥10%) and other prognostic factors as 0 or 1 and calculated the prognostic score with the sum of individual parameters due to similar OS HRs for individual model parameters. The total score spanned from 0 to 5. We used the NLR2-CEL name for the scoring system based on an acronym of included parameters (baseline and on-treatment NLR, CCI, ECOG, and LDH).

The higher scores were associated with decreased OS and PFS in the Kaplan–Meier survival analyses (Figure 2). Compared to patients with the lowest scores, patients in the highest score group had significantly lower OS (HR = 7.967, 95% CI = 3.531–17.979, p < 0.001) and PFS (HR = 2.971, 95% CI = 1.570–5.620, p = 0.001). The prognostic score had a linear negative association with survival outcomes with lower OS with increased scores (Figure 3). The composite score had moderate success for OS prediction with AUC of 0.702 (95% CI = 0.626–0.779, p < 0.001). A score of 2 or higher had 71.6% sensitivity and 61.3% specificity for survival prediction. The AUC of NLR-based composite score had numerically higher AUC values than GRS (0.621, 95% CI = 0.541–0.701, p = 0.005) and RMH scores (0.639, 95% CI = 0.560–0.719, p = 0.001) for survival prediction (Figure 4).

![Figure 2. Kaplan–Meier analyses of overall survival and progression–free survival according to NLR2–CEL prognostic score (0–1 vs. 2 or higher).](image)

![Figure 3. The association of the NLR2-CEL score with overall survival.](image)
with higher NLR levels in most studies; however, cutoff and population-related factors with different cutoffs (>ULN vs. >2 × ULN).

The predictive powers of these scoring systems were very variable in the reported studies. However, in contrast to our study, most of these scoring systems did not include the baseline LDH parameters into the scoring systems; however, dynamic changes in the laboratory parameters are absent in these scores [30,32,38,39]. The most thoroughly investigated of these scores are the GRS and RMH scores [31,40,41]. Both scores include the baseline LDH (normal vs. ≥ULN) and albumin levels (3.5 g/dL vs. <3.5 g/dL), while the baseline NLR levels and number of metastatic sites were used in the GRS [30] and RMH scores [31], respectively. The predictive powers of these scoring systems were very variable in the reported studies and generally spanned between 0.60 and 0.90 [30,31,42–44].

The LDH levels were considered as a surrogate of tumor burden and tissue destruction, as well as tumor metabolism [45–47]. The prognostic role of LDH is well-defined in melanoma patients treated with ICIs, and the LDH levels are being used as stratification criteria in melanoma clinical trials [31,48–50]. Similarly, a worse prognosis was observed in ICI-treated patients with other indications, such as NSCLC and RCC in the observational studies [31,51–54]. The LDH levels were included in some of the prognostic models, albeit with different cutoffs (>ULN vs. >2 × ULN) used for patient dichotomization [55]. We observed shorter OS and PFS in patients with higher LDH levels and used >ULN to define the higher LDH values due to relatively modest sample size and a small percentage of patients with LDH levels >2 × ULN.

In addition to LDH, NLR levels were among the most frequently investigated peripheral blood parameters in ICI-treated patients, and decreased OS was reported in patients with higher NLR levels in most studies; however, cutoff and population-related factors could affect the results [31,56–58]. In our analyses, the NLR values remained significant in the multivariable analyses and were included in the prognostic model. We used baseline NLR values as a prognostic parameter similar to previously published compound prognostic scores, such as the GRS and RMH score [30,31]. While the pretreatment values of these parameters are related to survival, changes in these markers could also aid in survival prediction [29,59]. However, in contrast to our study, most of these scoring systems did not...
include the dynamic changes in the peripheral blood cells in the equations [60,61]. Recent observational studies suggested that early changes of the peripheral blood markers could aid in prognosis prediction in ICI treated patients with reflecting host–tumor interactions and host immune activation [62,63]. The response rates were better in patients with lymphocyte or eosinophil expansion under ICIs [31,64–66]. In contrast, a lower benefit with ICIs would be expected in patients with neutrophilic expansion due to protumorigenic and immunosuppressive properties of neutrophils secondary to the secretion of increased progranulopoietic cytokines and blunting of T-cell antitumor responses [67,68]. Considering this biological rationale, the changes in NLR values under treatment could benefit survival prediction. Li et al. reported better OS in patients with baseline and on treatment NLR of less than five in a large cohort of ICI-treated patients (n = 509) [29]. The median OS of patients with a moderate NLR decrease was 27.8 months, while the patients with a significant increase in NLR levels had a median OS of 5 months. We selected the percentage of NLR changes within the fourth week of treatment due to the receipt of two cycles of ICIs at that timeframe and data availability at this period. Additionally, we aimed to select a timeframe before the first radiological response evaluation. We observed lower OS and PFS in patients with a 10% increase from baseline at the fourth week of treatment in multivariable analyses and included this parameter in our prognostic score. We think that our observation supported the notion of adding early changes in peripheral blood markers to compound prognostic scores as a surrogate of changes in host immune status.

The ECOG performance status is a consistent predictor of survival in patients treated with chemotherapy or surgery and is a part of clinical oncology practice as a robust denominator of the patient’s general status and symptom burden [69,70]. While a significantly lower OS and PFS was observed in patients with an ECOG performance status of 2 compared to 0–1 [71,72], recent single-arm observational ICI studies reported significantly better survival in patients with 0 compared to patients with an ECOG performance status of 1 [73]. Additionally, ICI clinical trials primarily enrolled patients with ECOG status 0 to 1 only, and the ECOG status (0 vs. 1) was used as a stratification criterion in most clinical trials [74]. Based on the experience from clinical trials and a relatively low number of patients with an ECOG status of two or higher, we dichotomized patients as ECOG 0 vs. >0 in our model. We observed significantly lower OS in patients with an ECOG status of 1 or higher compared to ECOG 0 patients.

In addition, different from the other models, we added CCI to a compound ICI-prognostic model. The CCI was developed and used to precisely quantify the comorbidity burden [75]. Additionally, CCI could be used as an indirect denominator of frailty in retrospective cohorts [76]. A large body of data demonstrated decreased survival and increased toxicity in patients with higher CCI treated with chemotherapy [77,78]. However, the role of CCI in the clinical management of ICI-treated patients is relatively unknown. In a recent publication from National Cancer Database, patients with higher comorbidity index had significantly decreased ICI use (HR, 0.85; 95% CI, 0.77–0.93) [79]. Another recent small study (n = 66) in non-small cell lung cancer patients treated with anti-PD1 treatment demonstrated decreased PFS and disease control rates in patients with CCI 7 or higher [80]. We used a different cutoff (CCI 9 or higher) for dichotomization and observed significantly lower OS in patients with higher CCI, while the PFS difference did not reach statistical significance. Based on our observations, we think that data CCI could be an adjunct to ECOG performance status for prognosis prediction and could be incorporated into the compound prognostic scores in ICI-treated patients.

The present study is subject to several limitations. First, the retrospective design and a heterogeneous patient group with a modest patient number in subgroups prevented us from conducting additional subgroup analyses; however, the sensitivity analyses according to tumor type yielded consistent results. Most of our patients were treated in the later lines and as ICI monotherapy, and that limited the generability of our results to patients treated in the countries with access to immunotherapy in the earlier lines and patients treated with
ICI-based combinations. However, despite these limitations, we demonstrated the promise of an NLR-based compound score (NLR2-CEL) as a possible biomarker for prognosis prediction.

5. Conclusions

In conclusion, we observed a significantly lower OS in patients with poorer ECOG status, higher LDH levels, higher CCI, higher baseline NLR values, and increased NLR values under treatment. Our proposed prognostic score, NLR2-CEL, which encompassed these parameters, had a moderate predictive power for OS. If it could be validated in prospective cohorts, this compound prognostic scoring system could be used for prognosis prediction in ICI-treated patients.

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References

1. Darvin, P.; Toor, S.M.; Sasidharan Nair, V.; Elkord, E. Immune checkpoint inhibitors: Recent progress and potential biomarkers. *Exp. Mol. Med.* 2018, 50, 1–11. [CrossRef]

2. Esfahani, K.; Roudaia, L.; Buhlaiga, N.; Del Rincon, S.V.; Papneja, N.; Miller, W.H., Jr. A review of cancer immunotherapy: From the past, to the present, to the future. *Curr. Oncol.* 2020, 27, 587–597. [CrossRef]

3. Rangachari, D.; Costa, D.B. From Hope to Reality: Durable Overall Survival With Immune Checkpoint Inhibitors for Advanced Lung Cancer. *J. Clin. Oncol.* 2019, 37, 2511–2513. [CrossRef]

4. Sangro, B.; Sarobe, P.; Hervás-Stubs, S.; Melero, I. Advances in immunotherapy for hepatocellular carcinoma. *Nat. Rev. Gastroenterol. Hepatol.* 2021, 18, 525–543. [CrossRef] [PubMed]

5. Hue, J.J.; Bingmer, K.; Sugumar, K.; Markt, S.C.; Rothermel, L.D.; Hardacre, J.M.; Ammori, J.B.; Winter, J.M.; Ocuin, L.M. Immunotherapy Is Associated with a Survival Benefit in Patients Receiving Chemotherapy for Metastatic Pancreatic Cancer. *J. Pancreat. Cancer* 2021, 7, 31–38. [CrossRef] [PubMed]

6. Maiorano, B.A.; Maiorano, M.F.P.; Lorusso, D.; Maiello, E. Ovarian Cancer in the Era of Immune Checkpoint Inhibitors: State of the Art and Future Perspectives. *Cancers* 2021, 13, 4438. [CrossRef]

7. Wolchok, J.D.; Chiarion-Sileni, V.; Gonzalez, R.; Grob, J.-J.; Rutkowskisi, P.; Lao, C.D.; Cowey, C.L.; Schadendorf, D.; Wagstaff, J.; Dummer, R.; et al. Long-Term Outcomes With Nivolumab Plus Ipilimumab or Nivolumab Alone Versus Ipilimumab in Patients With Advanced Melanoma. *J. Clin. Oncol.* 2021, 40, 127–137. [CrossRef]

8. Albiges, L.; Tannir, N.M.; Burotto, M.; McDermott, D.; Plimack, E.R.; Barthélémy, P.; Porta, C.; Powles, T.; Donskov, F.; George, S.; et al. Nivolumab plus ipilimumab versus sunitinib for first-line treatment of advanced renal cell carcinoma: Extended 4-year follow-up of the phase III CheckMate 214 trial. *ESMO Open* 2020, 5, e001079. [CrossRef]

9. Bellmunt, J.; de Wit, R.; Vaughn, D.J.; Fadet, Y.; Lee, J.L.; Fong, L.; Vogelzang, N.J.; Climent, M.A.; Petrylak, D.P.; Choueiri, T.K.; et al. Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. *N. Engl. J. Med.* 2017, 376, 1015–1026. [CrossRef]

10. Hellmann, M.D.; Paz-Ares, L.; Bernabe Caro, R.; Zurawski, B.; Kim, S.-W.; Carcereny Costa, E.; Park, K.; Alexandru, A.; Lupinacci, L.; de la Mora Jimenez, E.; et al. Nivolumab plus Ipilimumab in Advanced Non–Small-Cell Lung Cancer. *N. Engl. J. Med.* 2019, 381, 2020–2031. [CrossRef] [PubMed]
11. Spigel, D.R.; Vicente, D.; Ciuleanu, T.E.; Gettinger, S.; Peters, S.; Horn, L.; Audigier-Valette, C.; Pardo Aranda, N.; Juan-Vidal, O.; Cheng, Y.; et al. Second-line nivolumab in relapsed small-cell lung cancer: CheckMate 331(abstract). *Ann. Oncol.* 2021, 32, 631–641. [CrossRef] [PubMed]

12. Verma, V.; Sprave, T.; Haque, W.; Simone, C.B.; Chang, J.Y.; Welsh, J.W.; Thomas, C.R. A systematic review of the cost and cost-effectiveness studies of immune checkpoint inhibitors. *J. Immunother. Cancer* 2018, 6, 128. [CrossRef] [PubMed]

13. Schroek, A.B.; Ouyang, C.; Sandhu, J.; Sokol, E.; Jin, D.; Ross, J.S.; Miller, V.A.; Lim, D.; Amanam, I.; Chao, J.; et al. Tumor mutational burden is predictive of response to immune checkpoint inhibitors in MSI-high metastatic colorectal cancer. *Ann. Oncol.* 2019, 30, 1096–1103. [CrossRef] [PubMed]

14. Andrè, T.; Shiu, K.-K.; Kim, T.W.; Jensen, B.V.; Jensen, L.H.; Punt, C.; Smith, D.; Garcia-Carbonero, R.; Benavides, M.; Gibbs, P.; et al. Pembrolizumab in Microsatellite-Instability–High Advanced Colorectal Cancer. *N. Engl. J. Med.* 2020, 383, 2207–2218. [CrossRef]

15. Herbst, R.S.; Giaccone, G.; de Marinis, F.; Reinmuth, N.; Vergnenegre, A.; Barrios, C.H.; Morise, M.; Felip, E.; Andric, Z.; Geater, S.; et al. Atezolizumab for First-Line Treatment of PD-L1–Selected Patients with NSCLC. *N. Engl. J. Med.* 2020, 383, 1328–1339. [CrossRef]

16. Büttner, R.; Longshore, J.W.; López-Rios, F.; Merkelbach-Bruse, S.; Normanno, N.; Rouleau, E.; Penault-Llorca, F. Implementing TMB measurement in clinical practice: Considerations on assay requirements. *ESMO Open* 2019, 4, e000442. [CrossRef] [PubMed]

17. Guven, D.C.; Sahin, T.K.; Dizdar, O.; Kilickap, S. Predictive biomarkers for immunotherapy efficacy in non-small-cell lung cancer: Current status and future perspectives. *Biomark. Med.* 2020, 14, 1383–1392. [CrossRef]

18. Cai, L.-L.; Wang, J. Liquid biopsy for lung cancer immunotherapy. *Oncol. Lett.* 2019, 17, 4751–4760. [CrossRef]

19. Cupp, M.A.; Mairouli, M.; Tzoulaki, I.; Aune, D.; Evangelou, E.; Berlanga-Taylor, A.J. Neutrophil to lymphocyte ratio and cancer prognosis: An umbrella review of systematic reviews and meta-analyses of observational studies. *BMC Med.* 2020, 18, 360. [CrossRef]

20. Bilen, M.A.; Rini, B.I.; Voss, M.H.; Larkin, J.; Haanen, J.; Albige, L.; Pagliaro, L.C.; Voog, E.G.; Lam, E.T.; Kislov, N.; et al. Association of Neutrophil-to-Lymphocyte Ratio with Efficacy of First-Line Avelumab plus Axitinib vs. Sunitinib in Patients with Advanced Renal Cell Carcinoma Enrolled in the Phase 3 JAVELIN Renal 101 Trial. *Clin. Cancer Res.* 2022, 28, 738–747. [CrossRef]

21. Vano, Y.-A.; Oudard, S.; By, M.-A.; Tuzi, P.; Elaidi, R. Optimal cut-off for neutrophil-to-lymphocyte ratio: Fact or Fantasy? A prospective cohort study in metastatic cancer patients. *PLoS ONE* 2018, 13, e0195042. [CrossRef]

22. Howard, R.; Kanetsky, P.A.; Egan, K.M. Exploring the prognostic value of the neutrophil-to-lymphocyte ratio in cancer. *Sci. Rep.* 2019, 9, 19673. [CrossRef] [PubMed]

23. Ferrucci, P.F.; Ascierto, P.A.; Pigozzo, J.; Del Vecchio, M.; Maio, M.; Antonini Cappellini, G.C.; Guidoboni, M.; Queirolo, P.; Savoia, P.; Mandalà, M.; et al. Baseline neutrophils and derived neutrophil-to-lymphocyte ratio: Prognostic relevance in metastatic melanoma patients receiving ipilimumab. *Ann. Oncol.* 2016, 27, 732–738. [CrossRef] [PubMed]

24. Capone, M.; Giannarelli, D.; Mallardo, D.; Madonna, G.; Festino, L.; Grimaldi, A.M.; Vanella, V.; Simeone, E.; Paone, M.; Palmieri, G.; et al. Baseline neutrophil-to-lymphocyte ratio (NLR) and derived NLR could predict overall survival in patients with advanced melanoma treated with nivolumab. *J. Immunother. Cancer* 2018, 6, 74. [CrossRef] [PubMed]

25. Guida, M.; Bartolomeo, N.; Quaresmini, D.; Quaglino, P.; Madonna, G.; Pigozzo, J.; Di Giacomo, A.M.; Minisini, A.M.; Tucci, M.; Spagnolo, F.; et al. Basal and one-month differed neutrophil, lymphocyte and platelet values and their ratios strongly predict the efficacy of checkpoint inhibitors immunotherapy in patients with advanced BRAF wild-type melanoma. *J. Transl. Med.* 2020, 18, 2021. [CrossRef]

26. Li, Y.; Zhang, Z.; Hu, Y.; Yan, X.; Song, Q.; Wang, G.; Chen, R.; Jiao, S.; Wang, J. Pretreatment Neutrophil-to-Lymphocyte Ratio (NLR) May Predict the Outcomes of Advanced Non-small-cell Lung Cancer (NSCLC) Patients Treated With Immune Checkpoint Inhibitors (ICls). *Front. Oncol.* 2020, 10, 654. [CrossRef]

27. Hsiang, C.W.; Huang, W.Y.; Yang, J.F.; Shen, P.C.; Dai, Y.H.; Wang, Y.F.; Lin, C.S.; Chang, W.C.; Lo, C.F. Dynamic Changes in Neutrophil-to-Lymphocyte Ratio are Associated with Survival and Liver Toxicity Following Stereotactic Body Radiotherapy for Hepatocellular Carcinoma. *J. Hepatol. Cancer.* 2021, 8, 1299–1309. [CrossRef]

28. Lalani, A.A.; Xie, W.; Martini, D.J.; Steinhardt, J.A.; Norton, C.K.; Krajewski, K.M.; Duquette, A.; Bossé, D.; Bellmunt, J.; Van Allen, E.M.; et al. Change in Neutrophil-to-lymphocyte ratio (NLR) in response to immune checkpoint blockade for metastatic renal cell carcinoma. *J. Immunother. Cancer* 2018, 6, 5. [CrossRef]

29. Li, M.; Spakowicz, D.; Burkart, J.; Patel, S.; Husain, M.; He, K.; Bertino, E.M.; Shields, P.G.; Carbone, D.P.; Verschraegen, C.F.; et al. Change in neutrophil to lymphocyte ratio during immunotherapy treatment is a non-linear predictor of patient outcomes in advanced cancers. *J. Cancer Res. Clin. Oncol.* 2019, 145, 2541–2546. [CrossRef]

30. Bigot, F.; Castanon, E.; Baldini, C.; Hollebecque, A.; Carmona, A.; Postel-Vinay, S.; Angevin, E.; Armand, J.-P.; Ribrag, V.; Aspeslagh, S.; et al. Prospective validation of a prognostic score for patients in immunotherapy phase I trials: The Gustave Roussy Immune Score (GRIm-Score). *Eur. J. Cancer* 2017, 84, 212–218. [CrossRef]

31. Arkenau, H.T.; Olmos, D.; Ang, J.E.; de Bono, J.; Judson, I.; Kaye, S. Clinical outcome and prognostic factors for patients treated within the context of a phase I study: The Royal Marsden Hospital experience. *Br. J. Cancer* 2008, 98, 1029–1033. [CrossRef]
32. Sen, S.; Hess, K.; Hong, D.S.; Naing, A.; Piha-Paul, S.; Janku, F.; Fu, S.; Subbiah, I.M.; Liu, H.; Khanji, R.; et al. Development of a prognostic scoring system for patients with advanced cancer enrolled in immune checkpoint inhibitor phase 1 clinical trials. *Br. J. Cancer* 2018, 118, 763–769. [CrossRef] [PubMed]

33. Havel, J.J.; Chowell, D.; Chan, T.A. The evolving landscape of biomarkers for checkpoint inhibitor immunotherapy. *Nat. Rev. Cancer* 2019, 19, 133–150. [CrossRef] [PubMed]

34. Oloomi, M.; Moazzezy, N.; Bouzari, S. Comparing blood versus tissue-based biomarkers expression in breast cancer patients. *Heligyon* 2020, 6, e03728. [CrossRef] [PubMed]

35. Seo, M.K.; Cairns, J. How are we evaluating the cost-effectiveness of companion biomarkers for targeted cancer therapies? A systematic review. *BMC Cancer* 2021, 21, 980. [CrossRef]

36. Kazandjian, D.; Gong, Y.; Keegan, P.; Pazdur, R.; Blumenthal, G.M. Prognostic Value of the Lung Immune Prognostic Index for Patients Treated for Metastatic Non-Small Cell Lung Cancer. *JAMA Oncol.* 2019, 5, 1481–1485. [CrossRef]

37. Brown, J.T.; Liu, Y.; Shabto, J.M.; Martini, D.; Ravindranathan, D.; Hitron, E.E.; Russler, G.A.; Caulfield, S.; Yantorni, L.; Joshi, S.S.; et al. Modified Glasgow Prognostic Score associated with survival in metastatic renal cell carcinoma treated with immune checkpoint inhibitors. *J. Immunother. Cancer* 2021, 9, e002851. [CrossRef]

38. Guven, D.C.; Sahin, T.K.; Erul, E.; Kilickap, S.; Gambichler, T.; Aksoy, S. The Association between the Pan-Immune-Inflammation Value and Cancer Prognosis: A Systematic Review and Meta-Analysis. *Cancers* 2022, 14, 2675. [CrossRef]

39. Tian, S.; Cao, Y.; Duan, Y.; Liu, Q.; Peng, P. Gustave Roussy Immune Score as a Novel Prognostic Scoring System for Colorectal Cancer Patients: A Propensity Score Matching Analysis. *Front. Oncol.* 2021, 11, 737283. [CrossRef] [PubMed]

40. Castanon Alvarez, E.; Resano, L.; Chaves, I.; Eresú, S.; González, J.; Sánchez, J.; Díez, M.; Garcia, H.; et al. The Prognostic Value of the Lung Immune Prognostic Index for Patients with Advanced Non-Small-Cell Lung Cancer (NSCLC): Topic: IT Biomarkers. *J. Thorac. Oncol.* 2018, 13, 133–150. [CrossRef] [PubMed]

41. Naik, S.G.; Rathnasabapathy, C.; Chenthil, H.; Sangal, A.; Dumlao, T.; Kodali, S.; He, Z.; Kalavar, M. LDH in solid tumors as a surrogate marker for tumor burden and response to treatment. *J. Clin. Oncol.* 2020, 38, e14094. [CrossRef]

42. Al Darazi, G.; Martin, E.; Delord, J.P.; Korakis, I.; Betrian, S.; Estrabaut, M.; Poublanc, M.; Gomez-Roca, C.; Filleron, T. Improving patient selection for immuno-oncology phase 1 trials: External validation of six prognostic scores in a French Cancer Center. *Int. J. Cancer* 2021, 148, 2502–2511. [CrossRef]

43. Nencleares, P.; Gunn, L.; Soliman, H.; Bover, M.; Trinh, A.; Leslie, I.; Wong, K.H.; Newbold, K.; Nutting, C.M.; et al. On-treatment immune prognostic score for patients with relapsed and/or metastatic head and neck squamous cell carcinoma treated with immunotherapy. *J. Immunother. Cancer* 2021, 9, e002718. [CrossRef]

44. Naik, S.G.; Rathnasabapathy, C.; Chenthil, H.; Sangal, A.; Dumlao, T.; Kodali, S.; He, Z.; Kalavar, M. LDH in solid tumors as a surrogate marker for tumor burden and response to treatment. *J. Clin. Oncol.* 2020, 38, e14094. [CrossRef] [PubMed]

45. Mishra, D.; Banerjee, D. Lactate Dehydrogenases as Metabolic Links between Tumor and Stroma in the Tumor Microenvironment. *Cancers* 2019, 11, 750. [CrossRef]

46. Forskaisiewicz, A.; Dorociak, M.; Stach, K.; Szelałowski, P.; Tabola, R.; Augoff, K. The usefulness of lactate dehydrogenase measurements in current oncological practice. *Cell. Mol. Biol. Lett.* 2020, 25, 35. [CrossRef]

47. Ascierto, P.A.; Robert, C.; Lewis, K.; Gutzmer, R.; Stroyakovskiy, D.; Gogas, H.J.; Prosenko, S.; Pereira, R.P.; Eigentler, T.; Rutkowski, P.; et al. 1102P Clinical benefit in melanoma patients with elevated LDH treated with nivolumab for advanced melanoma: Confirmatory analyses from the IMspire150 study. *Clin. Cancer Res.* 2021, 27, 3841–3849. [CrossRef]

48. Wang, Y.; Li, G.; Wan, F.; Dai, B.; Ye, D. Prognostic value of D-lactate dehydrogenase in patients with clear cell renal cell carcinoma. *Oncl. Lett.* 2018, 16, 866–874. [CrossRef] [PubMed]

49. Shirotake, S.; Takamatsu, K.; Mizuno, R.; Kaneko, G.O.; Nishimoto, K.; Oya, M.; Oyama, M. Serum Lactate Dehydrogenase as a Surrogate Biomarker to Checkpoint-Inhibitors for Patient with Elevated LDH status: Exploratory analyses from the IMspire150 study. *Clin. Cancer Res.* 2021, 27, 763–769. [CrossRef] [PubMed]

50. De Castro, A.M.; Navarro, A.; Perez, S.C.; Martinez, A.; Pardo, N.; Hernandez, A.; Ortiz, C.; Amair, F.; Biosca, M.; Aguilar-Company; J.; et al. P3.02c-063 Lactate Dehydrogenase (LDH) as a Surrogate Biomarker to Checkpoint-Inhibitors for Patient with Elevated LDH status: Exploratory analyses from the IMspire150 study. *Clin. Cancer Res.* 2021, 27, 7372–7383. [CrossRef] [PubMed]

51. De Castro, A.M.; Navarro, A.; Perez, S.C.; Martinez, A.; Pardo, N.; Hernandez, A.; Ortiz, C.; Amair, F.; Biosca, M.; Aguilar-Company; J.; et al. Outcome of melanoma patients with elevated LDH treated with first-line targeted therapy or PD-1-based immune checkpoint inhibition. *Eur. J. Cancer* 2018, 81, 61–75. [CrossRef]

52. Mehnert, J.M.; Mitchell, T.C.; Huang, A.C.; Aleman, T.S.; Kim, B.J.; Schuchter, L.M.; Linette, G.P.; Karakousis, G.C.; Mitnick, S.; Giles, L.; et al. BAMA (BRAF Autoptography and MEK Inhibition in Melanoma): A Phase I/II Trial of Dabrafenib, Trametinib, and Hydroxychloroquine in Advanced BRAFV600-mutant Melanoma. *Clin. Cancer Res.* 2022, 28, 1098–1106. [CrossRef] [PubMed]

53. De Castro, A.M.; Navarro, A.; Perez, S.C.; Martinez, A.; Pardo, N.; Hernandez, A.; Ortiz, C.; Amair, F.; Biosca, M.; Aguilar-Company; J.; et al. P3.02c-063 Lactate Dehydrogenase (LDH) as a Surrogate Biomarker to Checkpoint-Inhibitors for Patient with Advanced Non-Small-Cell Lung Cancer (NSCLC): Topic: IT Biomarkers. *J. Thorac. Oncol.* 2017, 12, S1313. [CrossRef]

54. Wang, Y.; Li, G.; Wan, F.; Dai, B.; Ye, D. Prognostic value of D-lactate dehydrogenase in patients with clear cell renal cell carcinoma. *Oncl. Lett.* 2018, 16, 866–874. [CrossRef] [PubMed]

55. Shirotake, S.; Takamatsu, K.; Mizuno, R.; Kaneko, G.O.; Nishimoto, K.; Oya, M.; Oyama, M. Serum Lactate Dehydrogenase Before Nivolumab Treatment to Be a Therapeutic Prognostic Biomarker for Patients With Metastatic Clear Cell Renal Cell Carcinoma. *Anticancer. Res.* 2019, 39, 4371–4377. [CrossRef]

56. Daher, S.; Lawrence, Y.R.; Dudnik, E.; Hanovich, E.; Urban, D.; Peled, N.; Navon, R.; Leibowitz, R.; Hammerman, A.; Battat, R.; et al. Nivolumab in Non-Small Cell Lung Cancer: Real World Long-Term Survival Results and Blood-Based Efficacy Biomarkers. *Front. Oncol.* 2021, 11, 2792. [CrossRef]
55. Zhang, Z.; Li, Y.; Yan, X.; Song, Q.; Wang, G.; Hu, Y.; Jiao, S.; Wang, J. Pretreatment lactate dehydrogenase may predict outcome of advanced non-small cell lung cancer patients treated with immune checkpoint inhibitors: A meta-analysis. *Cancer Med.* 2019, 8, 1467–1473. [CrossRef] [PubMed]

56. Dusselier, M.; Deluche, E.; Delacourt, N.; Ballouhey, J.; Egenod, T.; Mellon, B.; Vergnenègre, C.; Veillon, R.; Vergnenègre, A. Neutrophil-to-lymphocyte ratio evolution is an independent predictor of early progression of second-line nivolumab-treated patients with advanced non-small-cell lung cancers. *PLoS ONE* 2019, 14, e0219060. [CrossRef] [PubMed]

57. Petrova, M.P.; Eneva, M.I.; Arabadjiev, J.I.; Conev, N.V.; Dimitrova, E.G.; Koynev, K.D.; Karanikolova, T.S.; Valev, S.S.; Gencheva, R.B.; Zhanbantov, G.A.; et al. Neutrophil to lymphocyte ratio as a potential predictive marker for treatment with pembrolizumab as a second line treatment in patients with non-small cell lung cancer. *Biosci. Trends* 2020, 14, 48–55. [CrossRef] [PubMed]

58. Möller, M.; Turzer, S.; Schütte, W.; Seliger, B.; Riemann, D. Blood Immune Cell Biomarkers in Patients With Lung Cancer Undergoing Treatment With Checkpoint Blockade. *J. Immunother.* 2020, 43, 57–66. [CrossRef]

59. Bartlett, E.K.; Flynn, J.R.; Panageas, K.S.; Ferraro, R.A.; Sta Cruz, J.M.; Postow, M.A.; Coit, D.G.; Ariyan, C.H. Effective neutrophil-to-lymphocyte ratio (NLR) is associated with treatment failure and death in patients who have melanoma treated with PD-1 inhibitor monotherapy. *Cancer* 2020, 126, 76–85. [CrossRef]

60. Hirahara, T.; Arigami, T.; Yanagita, S.; Matsushita, D.; Uchikado, Y.; Kita, Y.; Mori, S.; Sasaki, K.; Omoto, I.; Kurahara, H.; et al. Combined neutrophil-lymphocyte ratio and platelet-lymphocyte ratio predicts chemotherapy response and prognosis in patients with advanced gastric cancer. *BMC Cancer* 2019, 19, 672. [CrossRef]

61. Satakornnukul, J.; Chanvimalueng, W.; Patumanond, J.; Thephamongkhol, K. Cutoff point of neutrophil-to-lymphocyte ratio for predicting survival in nasopharyngeal carcinoma. *Medicine* 2021, 100, e27095. [CrossRef]

62. Lim, J.U.; Kang, H.S.; Yeo, C.D.; Kim, J.S.; Park, C.K.; Kim, J.W.; Kim, S.J.; Lee, S.H. Predictability of early changes in derived neutrophil-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio in patients with advanced non-small cell lung cancer treated with immune checkpoint inhibitors. *J. Thorac. Dis.* 2021, 13, 2824–2832. [CrossRef]

63. Thomas, J.; Riaz, I.B.; Freeman, D.; Adib, E.; Nuzzo, P.V.; Zarii, T.E.; Davidsohn, M.; McClure, H.; Curran, C.; Ravi, P.; et al. Early changes in peripheral blood neutrophil-lymphocyte ratio (NLR) to predict outcomes with immune checkpoint inhibitors (ICIs) for metastatic urothelial carcinoma (mUC). *J. Clin. Oncol.* 2022, 40, 449. [CrossRef]

64. Krishnan, T.; Tomita, Y.; Roberts-Thomson, R. A retrospective analysis of eosinophilia as a predictive marker of response and toxicity to cancer immunotherapy. *Future Sci. OA* 2020, 6, FSO68. [CrossRef]

65. Ghebeh, H.; Elshenawy, M.A.; AlSayed, A.D.; Al-Tweigeri, T. Peripheral blood eosinophil count is associated with response to treatment in patients with non-small cell lung cancer. *BMC Pulm. Med.* 2017, 17, 112. [CrossRef] [PubMed]
78. Stromberger, C.; Yedikat, B.; Coordes, A.; Tinhofer, I.; Kalinauskaite, G.; Budach, V.; Zschaech, S.; Raguse, J.-D.; Kofla, G.; Heiland, M.; et al. Prognostic Factors Predict Oncological Outcome in Older Patients With Head and Neck Cancer Undergoing Chemoradiation Treatment. Front. Oncol. 2021, 10, 566318. [CrossRef]

79. Zhang, D.; Tailor, T.D.; Kim, C.; Atkins, M.B.; Braithwaite, D.; Akinyemiju, T. Immunotherapy Utilization Among Patients With Metastatic NSCLC: Impact of Comorbidities. J. Immunother. 2021, 44, 198–203. [CrossRef]

80. Zeng, X.; Zhu, S.; Xu, C.; Wang, Z.; Su, X.; Zeng, D.; Long, H.; Zhu, B. Effect of Comorbidity on Outcomes of Patients with Advanced Non-Small Cell Lung Cancer Undergoing Anti-PD1 Immunotherapy. Med. Sci. Monit. 2020, 26, e922576. [CrossRef]