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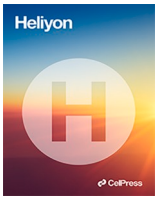

Research article

Identification of nomogram associated with durable clinical benefit gene for advanced non-small cell lung cancer with sensitivity to responsive to immunotherapy

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ABSTRACT

Background: Immunotherapy has become the standard treatment for advanced non-small cell lung cancer (NSCLC). However, a subset of the most advanced NSCLC patients fails to respond adequately to Immune checkpoint inhibitors (ICIs). Developing new nomograms and integrating prognostic factors are crucial for improving the clinical predictability of NSCLC patients undergoing ICIs.

Methods: Clinical information and genomic data of NSCLC patients undergoing ICIs were retrieved from cBioPortal. Gene alterations associated with durable clinical benefit (DCB) were compared to those linked to no durable benefit (NDB). The Kaplan-Meier plot method was employed for survival analysis, and a novel nomogram was formulated by selecting pertinent clinical variables.

Results: For the NSCLC patients receiving immunotherapy, three subgroups were identified based on the treatment regimen, including anti-PD-1 monotherapy, anti-PD-1 combination with anti–CTLA–4, and first-line treatment. The mutation status of TP53, PGR, PTPRT, RELN, MUC19, LRP1B, and FAT3 was found to be associated with progression-free survival (PFS). Using the clinicopathological parameters and genomic data of the patients, we developed three novel nomograms to predict the prognosis of ICI treatment in different subgroups.

Conclusion: Our study revealed that PGR, PTPRD, RELN, MUC19, LRP1B, and FAT3 mutation could serve as predictive biomarkers. Our systematic nomograms demonstrate significant potential in predicting the prognosis for NSCLC patients with sensitivity to different ICI treatment strategies.

1. Introduction

Nowadays, lung cancer is the second most incidence and the leading cause of death malignant tumor worldwide among various cancers [1]. About 85% of lung cancers are NSCLC [2]. Currently, immunotherapy has demonstrated compelling clinical benefits, markedly extending the survival of advanced NSCLC [3–6]. Several medical organizations, including the FDA and the National Medical Products Administration (NMPA), have recommended ICIs as first- or second-line treatments for patients with NSCLC. The NSCLC patients undergoing immunotherapy were broadly categorized into those receiving ICIs monotherapy or a combination of chemotherapy or anti-CTLA-4 inhibitors. However, some NSCLC patients do not respond to immunotherapy [7]. The development of

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Table 1
Advanced NSCLC patients with anti-PD-(L)1 monotherapy characteristics with NDB and DCB groups.

Clinical characteristics	NDB group	DCB group
Total cases	142	53
Gender		P = 0.6299
Female	71 (50.0%)	29 (54.7%)
Male	71 (50.0%)	24 (45.3%)
Age		P = 0.2027
<65	63 (44.4%)	29 (54.7%)
>=65	79 (55.6%)	24 (45.3%)
Smoking		P = 0.0609
Ever	111 (78.2%)	48 (90.6%)
Never	31 (21.8%)	5 (9.4%)
Line of treatment		P = 0.0725
First-line	17 (12.0%)	12 (22.6%)
Non-first line	125 (88.0%)	41 (77.4%)
PD-L1 expression		P = 0.4559
Negative	30 (21.1%)	7 (13.3%)
Weak	13 (9.2%)	5 (9.4%)
Strong	7 (5.0%)	5 (9.4%)
Unknown	92 (64.7%)	36 (67.9%)
TMB		P = 0.0103
High	64 (45.1%)	35 (66.0%)
Low	78 (54.9%)	18 (34.0%)

immunotherapy requires further identification of potential biomarkers to predict the effectiveness and prognosis of ICI treatment.

At present, some potential predictive biomarkers significantly related to NSCLC with ICIs have been found in many clinical trials, such as PD-L1 expression and TMB [8,9]. Most clinical trials have demonstrated elevated response rates and better prognoses in NSCLC expressing higher levels of PD-L1, but the enrichment of responses remains unclear [9,10]. Besides that, the expression of PD-L1 in tumors exhibits spatial and temporal heterogeneity, potentially varying between tumor sites such as primary and metastatic lesions. TMB also has been regarded as a predictive biomarker in NSCLC [11,12]. High TMB has been linked to enhanced survival, but there is currently no universally accepted definition for high TMB [13]. Therefore, various clinical variables and genomic data must be incorporated into prognosis nomograms for different NSCLC patients receiving immunotherapy.

In recent years, nomograms have gained increasing prominence in cancer research, providing a more interpretable and visually intuitive representation of predictive models. The heightened interest in nomograms stems from their ability to seamlessly incorporate a variety of predictive markers, thereby amplifying their significance as valuable graphical tools in the field of cancer researc [14–17]. The cBioPortal was used to download data from NSCLC patients treated with ICIs in this study [12,18,19]. Three novel nomograms were created based on clinicopathological and genome data to predict the prognosis for several types of advanced NSCLC with ICIs.

2. Materials and methods

2.1. Data download and processing

Two ICI cohorts of NSCLC were acquired from cBioPortal. The first cohort (MSK, J Clin Oncol 2018) consisted of NSCLC patients with anti-PD-(L)1 monotherapy or anti-CTLA-4 combination therapy [18]. Similarly, 75 patients with NSCLC treated with anti-PD-1 and anti–CTLA–4 were included in the second cohort (MSK, Cancer Cell 2018) [19]. Patients with NSCLC were treated with ICI monotherapy or in combination with anti-CTLA-4 and characterized using targeted NGS. The clinical information of ICI cohorts includes age, gender, treatment type, PD-L1 expression, TMB, and so on. DCB was characterized by complete response (CR), partial response (PR), or stable disease (SD) persisting for more than 6 months, and NDB was defined as progressive disease (PD) or SD that lasted 6 months or less [20].

2.2. Development of nomogram

The Kaplan-Meier plot method was employed for survival analysis, and a novel nomogram was formulated by selecting pertinent clinical variables. Utilizing the patient's data, nomograms can forecast the probability of various events, such as PFS, overall survival (OS), and recurrence. In this study, three novel nomograms based on the patient's data were built to predict the prognosis for different NSCLCs with ICIs. The "rms" package, an acronym for Regression Modeling Strategies, comprises a set of functions designed to streamline and enhance various aspects of regression modeling. The "rms" R package establishes scoring criteria by considering the magnitudes of the regression coefficients associated with all independent variables in the model. Consequently, each level of every independent variable is assigned a specific score. For each patient, a cumulative score is computed by summing the individual scores across all variables. Following this, a conversion function, which correlates the total score with the probability of the outcome, is applied to estimate the survival probability for each patient. The nomogram serves as a visual representation of the Cox regression equation. Utilizing the cph function from the "rms" package, a Cox regression model is crafted to scrutinize variables previously chosen

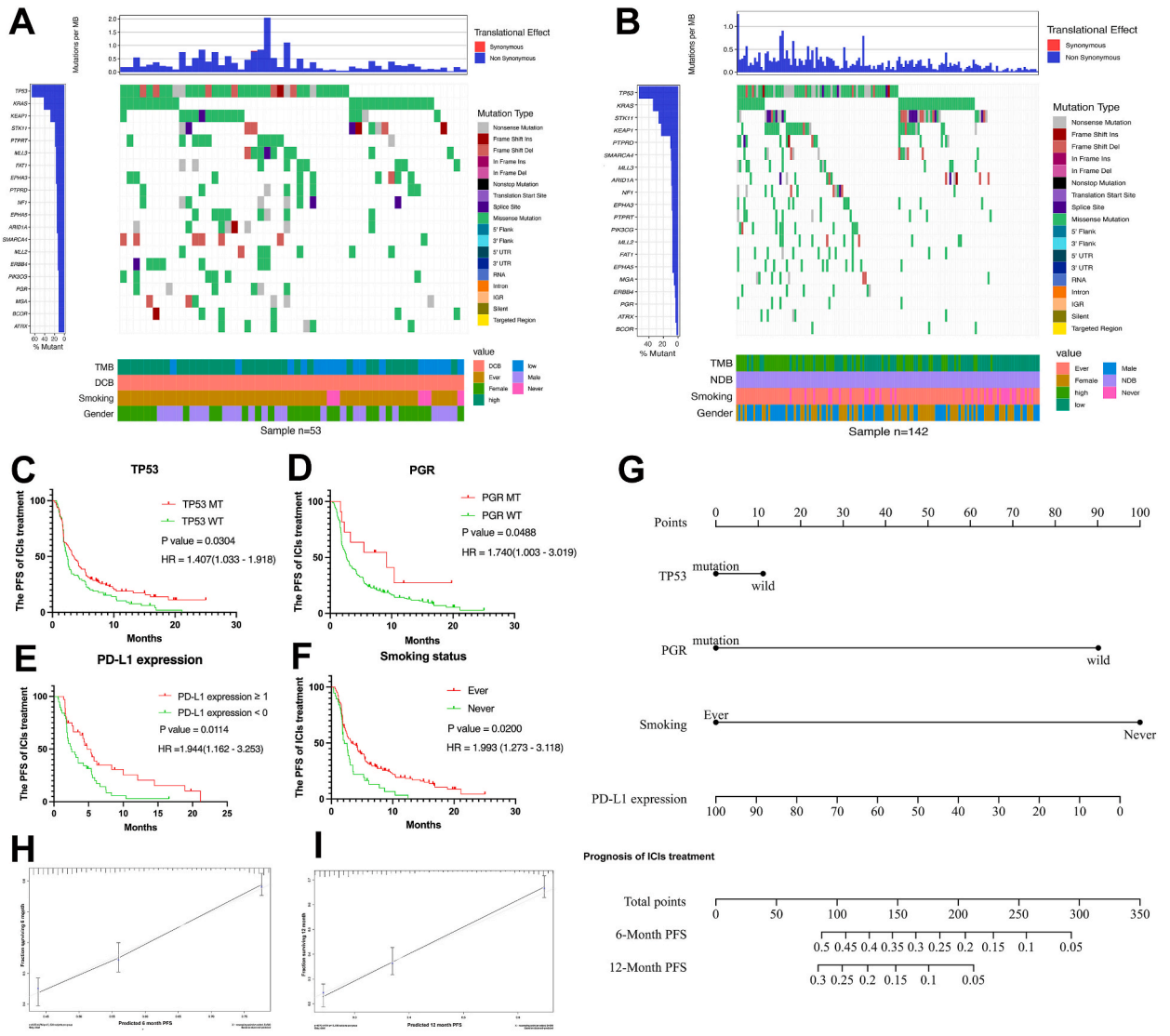

Fig. 1. Summary of genomic landscape and nomogram of anti-PD-(L)1 monotherapy. (A, B) Top 20 gene alterations in the DCB group and NDB group. The Kaplan-Meier plot of TP53 mutation(C), and PGR mutation(D). PD-L1 expression (E), and smoking status (F). (G) Nomogram (H, I) The calibration plot.

through Kaplan-Meier and log-rank tests. Subsequently, an additional Cox regression analysis is executed to pinpoint the variables with the utmost significance. The function also provides the corresponding scores or points for each variable. The concordance index (C-index) and calibration curve were employed as the main indicators to assess the predictive accuracy value of the nomogram.

2.3. Estimation of tumor immune infiltration

Gene mutations, gene expressions, and clinical information about NSCLC were collected from the TCGA database. By converting gene expression into the proportion of immune cells, the relative abundance of immune cells in NSCLC patients was determined. The R package *CIBERSORT* was used to estimate the status of immune and stromal cell infiltration in each NSCLC samples [21].

2.4. Verification of the prognostic value of gene

To externally validate the prognostic significance of the gene, another ICI cohort (MSKCC, Nat Genet 2019) was utilized. In this cohort, 1662 advanced cancer patients received anti-PD-(L)1 monotherapy or combined therapy with anti-CTLA- 4 [12].

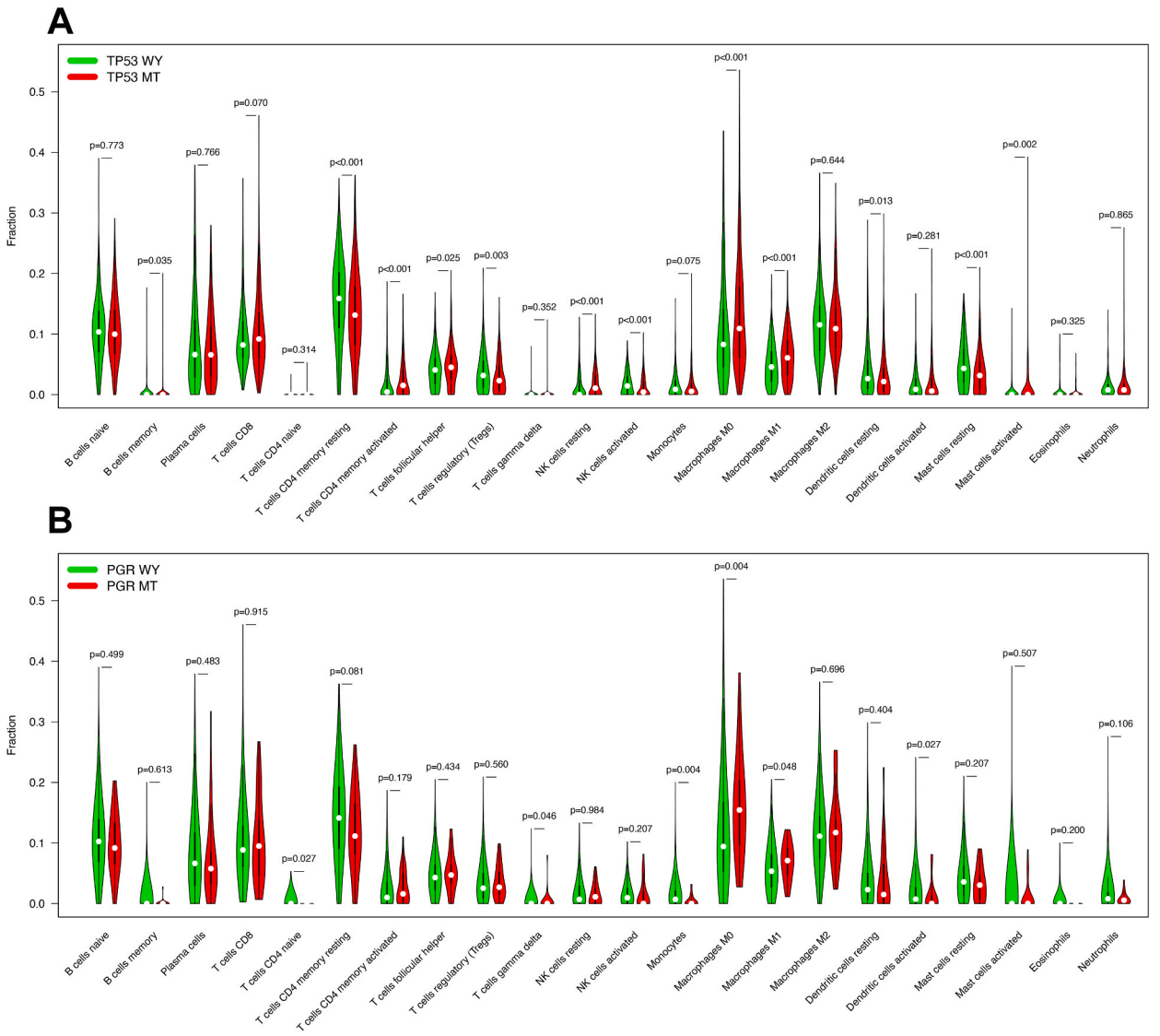

Fig. 2. The role of TP53 mutation and PGR mutation in TIICs. (A) The relationship between the mutation status of TP53 and immune cells in NSCLC. (B) The relationship between the mutation status of PGR and immune cells.

2.5. Statistical analyses

Statistical analyses were conducted using GraphPad Prism 9.0 and R 4.2.2. Survival analyses were performed employing the Kaplan-Meier plot method and compared using the log-rank test, where a $P < 0.05$ was deemed statistically significant.

3. Result

3.1. Construction of nomogram for anti-PD-(L)1 monotherapy

A total of 195 NSCLC patients were involved in the construction of the nomogram. And NSCLC patient's characteristics with anti-PD-(L)1 monotherapy are shown in Table 1. Top 20 gene alterations in DCB group were TP53, KRAS, KEAP1, STK11, PTPRT, MLL3, FAT1, EPHA3, PTPRD, NF1, EPHA5, ARID1A, SMARCA4, MLL2, ERBB4, PIK3CG, PGR, MGA, BCOR, and ATRX (Fig. 1A). We also investigated those gene alterations in NDB. (Fig. 1B). The mutation of TP53 ($P = 0.0304$) and PGR ($P = 0.0488$) were closely associated with the PFS of ICI monotherapy (Fig. 1C–D). Moreover, several clinicopathological variables were associated with the PFS of ICI monotherapy, including PD-L1 expression ($P = 0.0114$), and smoking status ($P = 0.0200$) (Fig. 1E–F). However, there was no significant difference in survival between TMB ($P = 0.0958$) and the treatment line ($P = 0.3807$) (**Extended Data** Fig. 1A–B). Utilizing these variables, we constructed a comprehensive nomogram to predict PFS for NSCLC undergoing ICI monotherapy (Fig. 1G). The C-

Table 2
Advanced NSCLC patients with anti-PD-(L)1 combination with anti–CTLA-4 characteristics with NDB and DCB groups.

Clinical characteristics	NDB group	DCB group
Total cases	38	37
Gender		P = 0.8187
Female	20 (52.6%)	18 (48.6%)
Male	18 (47.4%)	19 (51.4%)
Age		P = 0.8185
<65	19 (50.0%)	17 (45.9%)
>=65	19 (50.0%)	20 (54.1%)
Smoking		P = 0.5655
Ever	29 (76.3%)	31 (83.8%)
Never	9 (23.7%)	6 (16.2%)
PD-L1 expression		P = 0.5368
Negative	14 (36.9%)	11 (29.8%)
Weak	18 (47.3%)	17 (45.9%)
Strong	3 (7.9%)	7 (18.9%)
Unknown	3 (7.9%)	2 (5.4%)
TMB		P = 0.0055
High	13 (34.2%)	25 (67.6%)
Low	25 (65.8%)	12 (32.4%)

index of this nomogram was 0.632 (95% CI 0.554 to 0.709) (Fig. 1H–I).

We also assessed the association between TP53 mutation, PGR mutation, and TIICs. In the TCGA-NSCLC cohort, B cell memory, memory CD4 T cells, T cells follicular helper, resting NK cells, Macrophages M0, and Macrophages M1 were more enriched in the TP53 mutant sample (Fig. 2A). And resting memory CD4 T cells, Treg, activated NK cells, resting dendritic cells, resting Mast cells were more enriched in the TP53 wild sample (Fig. 2A). Macrophages M0, Macrophages M1 were enriched in the PGR mutant (Fig. 2B). Besides that, naive CD4 T cells, T cells gamma delta, Monocytes, and activated dendritic cells were more enriched in the PGR wild sample (Fig. 2B). The mutation frequency of TP53 and PGR were 66% and 11% in the DCB group, respectively (Fig. 1A). Based on the findings, we reasonably deduced that the PGR mutation could serve as a potential biomarker for the sensitivity to ICI monotherapy.

3.2. Construction of nomogram for anti-PD-(L)1 combination with anti–CTLA-4

A total of 75 NSCLC patients were involved in the construction of the systematic nomogram. Advanced NSCLC patient's characteristics with anti-PD-(L)1 combination with anti–CTLA-4 are shown in Table 2. Top 20 gene alterations in DCB group were TP53, TTN, RYR2, USH2A, MUC16, PRIM2, OBSCN, ZFHX4, FAT3, KMT2C, CSMD1, Y_RNA, TENM3, SYNE1, SSPO, RELN, PDE4DIP, MUC19, LRP1B, and CNTNAP2 (Fig. 3A). We next examined those gene alterations in NDB group (Fig. 3B). The mutation of RELN (P = 0.0235), MUC19 (P = 0.0016), LRP1B (P = 0.0430) and FAT3 (P = 0.0164) were closely related to the PFS of ICIs combination (Fig. 3C–F). Besides that, Only TMB (P = 0.0004) exhibited a significant association with the PFS of ICI (Fig. 3G). No significant differences in survival were observed between PD-L1 expression (P = 0.6300) and smoking status (P = 0.2870) (**Extended Data** Fig. 1C–D). Utilizing these variables, we constructed a comprehensive nomogram to predict PFS for NSCLC undergoing anti-PD-(L)1 combination with anti–CTLA–4 (Fig. 3H). The C-index of this nomogram was 0.646 (95% CI 0.566 to 0.726)(Fig. 3I–J).

We also evaluated the relationship between RELN, MUC19, LRP1B, FAT3, and TIICs in NSCLC. Plasma cells, activated T cells CD4 memory, and Macrophages M1 were more enriched in the RELN mutant (Fig. 4A). Monocytes, resting dendritic cells, and Neutrophils were more enriched in the RELN wild sample (Fig. 4A). Besides that, activated T cells CD4 memory, Macrophages M1 were more enriched in the LRP1B mutant sample (Fig. 4B). Resting T cells CD4 memory and resting mast cells were more enriched in the LRP1B wild sample (Fig. 4B). Moreover, activated T cells CD4 memory, T cells follicular helper, resting NK cells, and Macrophages M1 were more enriched in the FAT3 mutant sample (Fig. 4C). Activated NK cells, Monocytes, resting dendritic cells, activated dendritic cells, and resting mast cells were more enriched in the FAT3 wild sample (Fig. 4C). In addition, the mutation frequency of RELN, MUC19, LRP1B, and FAT3 were 35%, 35%, 38%, and 41% in the DCB group, respectively (Fig. 3A). However, the mutation frequency of RELN, MUC19, LRP1B, and FAT3 were only 18%, 13%, 26% and 24% in NDB group, respectively (Fig. 3B).

3.3. Construction of nomogram for first-line treatment

A total of 47 NSCLC patients were involved in the construction of the systematic nomogram. Advanced NSCLC patient's characteristics with first-line treatment are shown in Table 3. Top 20 gene alterations in DCB group were TP53, KRAS, FAT1, PTPRT, KEAP1, EPHA5, MLL3, STK11, SMARCA4, SETD2, PTPRD, PIK3CG, PAK7, NF1, MGA, MET, LATS1, INHBA, FLT4, and ERBB4 (Fig. 5A). We also examined ttop 20 gene alterations in NDB group (Fig. 5B). The mutation of PTPRT (P = 0.0324) was closely related to the PFS of ICIs first-line treatment (Fig. 5C). In addition, treatment type (P = 0.0135), TMB (P = 0.0301) and PD-L1 expression (P = 0.0312) were also significantly related to the PFS (Fig. 5D–F). No significant difference between smoking status and PFS (P = 0.3487) (Extended Data Fig. 1E). Utilizing these variables, we constructed a comprehensive nomogram to predict PFS for advanced NSCLC with ICIs first-line treatment (Fig. 5G). The C-index of this nomogram was 0.699 (95% CI 0.580 to 0.818) (Fig. 5H–I).

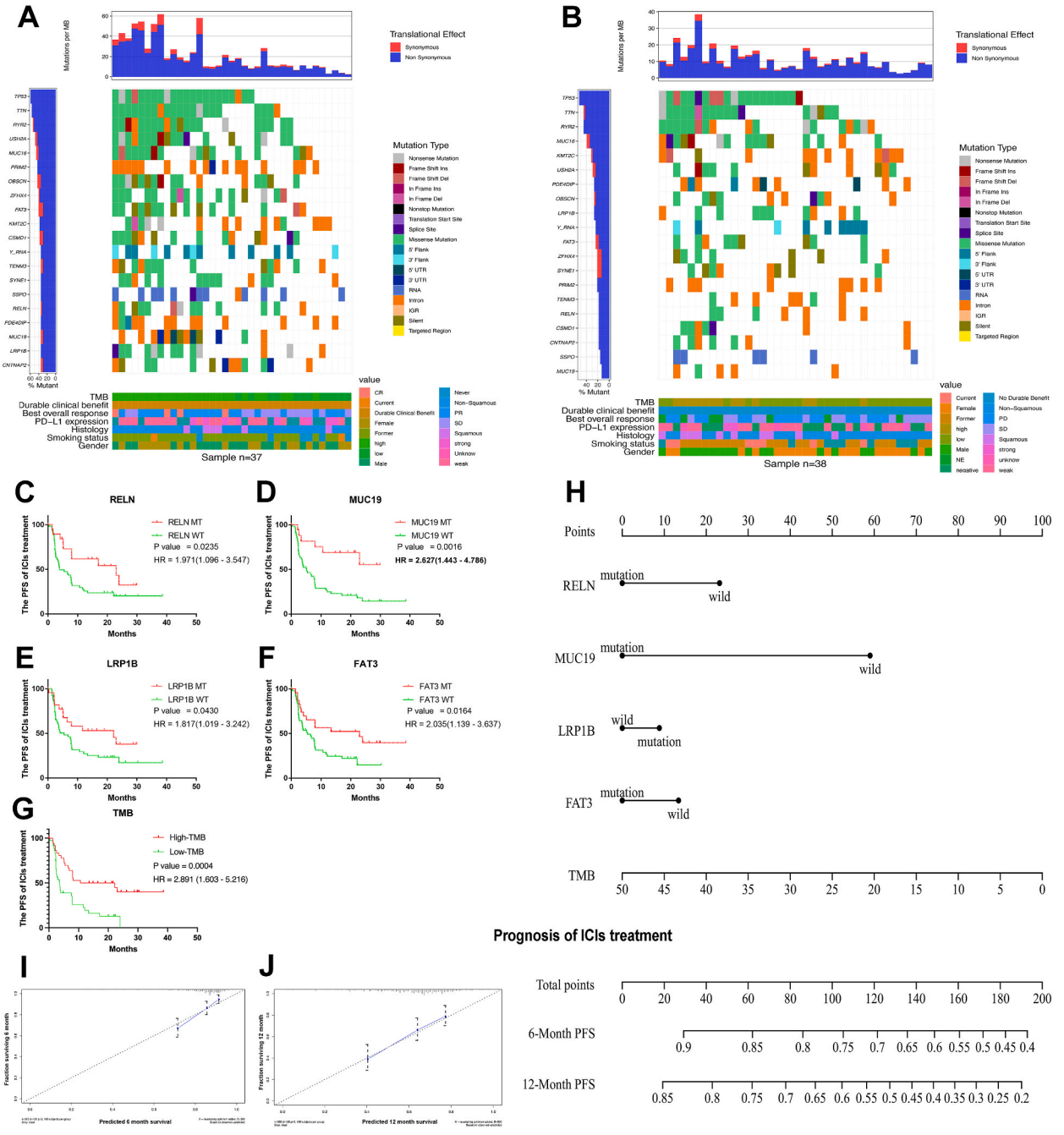

Fig. 3. Summary of genomic landscape and nomogram of anti-PD-(L)1 plus anti–CTLA-4. (A, B) Top 20 gene alterations in the DCB group and NDB group. The Kaplan-Meier plot of RELN mutation (C), MUC19 mutation (D), LRP1B mutation (E), FAT3 mutation (F), and TMB (G). (H) Nomogram. (I, J) The calibration plot.

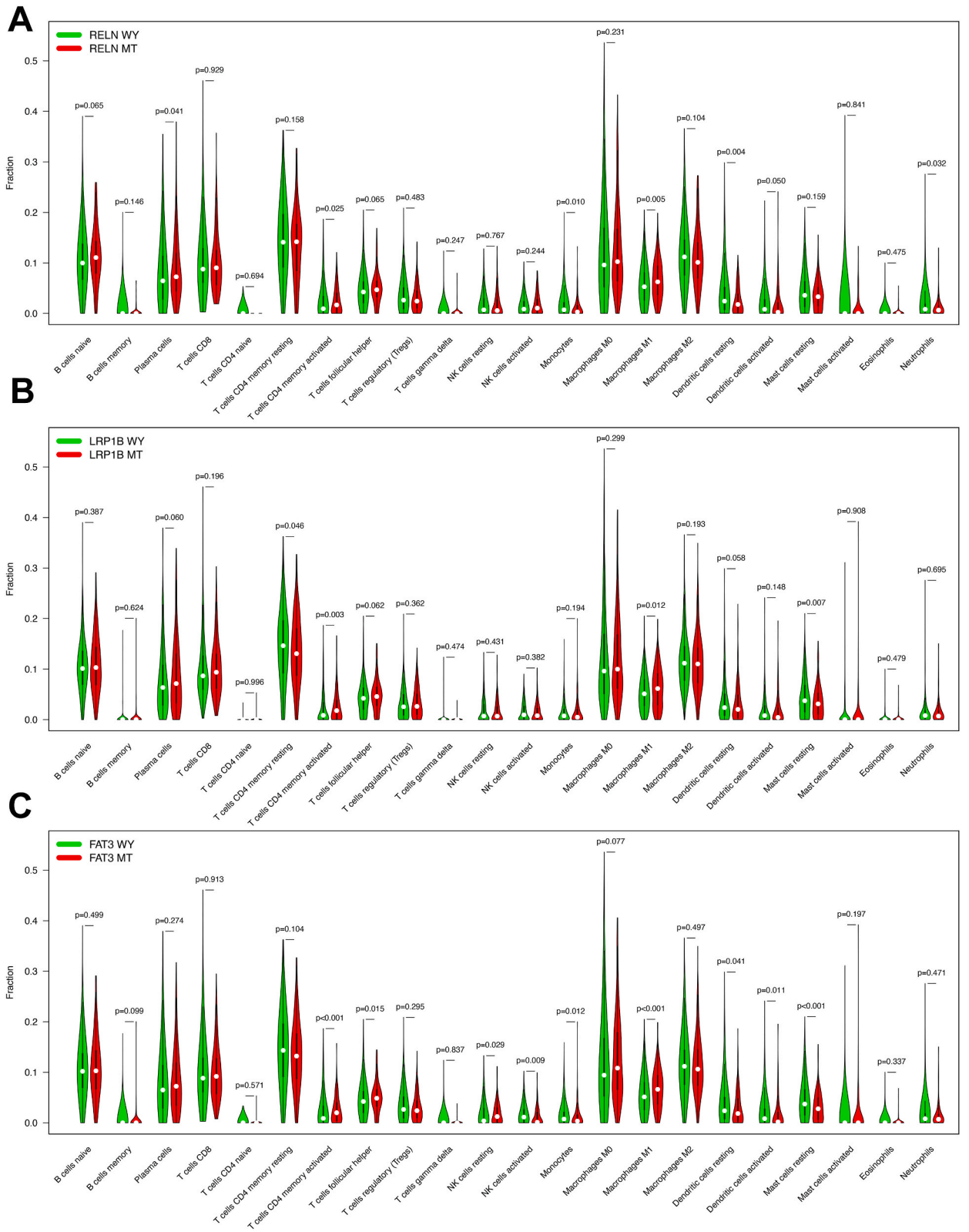

Fig. 4. The role of RELN mutation, LRP1B mutation, and FAT3 mutation in TIICs. (A) The relationship between the mutation status of RELN and immune cells. (B) The relationship between the mutation status of LRP1B and immune cells. (B) The relationship between the mutation status of FAT3 and immune cells.

Table 3
Advanced NSCLC patients with ICIs first-line treatment characteristics with NDB and DCB groups.

Clinical characteristics	NDB group	DCB group
Total cases	23	24
Gender		P = 0.7702
Female	10 (43.5%)	9 (37.5%)
Male	13 (56.5%)	15 (62.5%)
Age		P = 0.9999
<65	13 (56.5%)	13 (54.2%)
>=65	10 (43.5%)	11 (45.8%)
Smoking		P = 0.4614
Ever	18 (78.3%)	21 (87.5%)
Never	5 (21.7%)	3 (12.5%)
Treatment type		P = 0.1351
Monotherapy	17 (73.9%)	12 (50.0%)
Combination	6 (26.1%)	12 (50.0%)
PD-L1 expression		P = 0.3312
Negative	7 (30.4%)	4 (16.7%)
Weak	6 (26.1%)	4 (16.7%)
Strong	2 (8.7%)	6 (25.0%)
Unknown	8 (35.8%)	10 (41.6%)
TMB		P = 0.2476
High	10 (43.5%)	15 (62.5%)
Low	13 (56.5%)	9 (37.5%)

Moreover, resting dendritic cells were more enriched in the PTPRT wild sample (Fig. 6A). The mutation frequency of PTPRT was 29% in the DCB group (Fig. 5A). However, the mutation frequency of PTPRT was only 4% in the NDB group (Fig. 5B). These results indicate that PTPRT mutation could serve as potential biomarkers for the prognosis of NSCLC with first-line treatment.

3.4. Verification of the prognostic value of TP53, PGR, and PTPRT

We further explored the predictive value of TP53, PGR, and PTPRT mutation in another ICI cohort (MSKCC, Nat Genet 2019) as an independent external validation. The mutation frequency of TP53, PGR, and PTPRD were 45%, 5%, and 11%, respectively (Fig. 7A). The same, the mutation of TP53 ($P < 0.001$), PGR ($P = 0.0425$) and PTPRD ($P < 0.001$) were closely related to the prognosis of ICIs in pan-cancer (Fig. 7B–D).

4. Discussion

The clinical trials of ICIs have shown a clear benefit in NSCLC patients [6,22–25]. Pembrolizumab monotherapy has obtained FDA approval as the primary treatment for NSCLC with PD-L1 expression of 50% or higher [25]. The FDA has approved Nivolumab Plus Ipilimumab as a first-line treatment for NSCLC patients with PD-L1 expression of 1% or higher [23]. Apart from PD-L1 expression and TMB, gene mutations such as EGFR, EPHA, STK11, and NOTCH are associated with the efficacy of ICIs. These mutations regulate the tumor microenvironment and may serve as potential biomarkers to predict the clinical benefits [26–29]. Hence, it is crucial to integrate prognostic biomarkers to formulate a nomogram, enhancing the clinical prediction ability for diverse NSCLC patients undergoing ICI treatment.

In this study, based on treatment type and line of treatment of NSCLC, The top 20 gene alterations in DCB were subsequently compared with those in NDB. We found that the mutation of TP53, PGR, PTPRD, RELN, MUC19, LRP1B, and FAT3 were related to the prognosis of ICIs. The mutation frequency of PGR, PTPRD, RELN, MUC19, LRP1B, and FAT3 in the DCB group was significantly higher in the NDB group. To explain why TP53, PGR, PTPRD, RELN, MUC19, LRP1B, and FAT3 mutations were associated with favorable ICI prognosis, we evaluated the role of that gene mutation in immune infiltration. However, these mutated genes are still in the early stages of exploration. Wang et al. reported a potential association between PTPRD mutation and immunotherapy in NSCLC, but the underlying mechanism remains unclear [30]. And some studies have preliminarily reported an association between mutations in RELN, MUC19, LRP1B, and FAT3 and immunotherapy in lung cancer [31–34]. The mutation of TP53, PGR, PTPRD, RELN, MUC19, LRP1B, and FAT3 may influence immune cell infiltration, fostering the development of a “hot” tumor microenvironment (TME) with enhanced anti-tumor immunity.

Presently, a multitude of nomograms focusing on immunotherapy for NSCLC have been published. However, there is a critical need for a more comprehensive analysis of immunotherapy. The spectrum of immunotherapy encompasses single-agent immunotherapy, combination therapy with chemotherapy, and regimens involving PD-1 and CTLA-4. Moreover, patients undergo both first-line and second-line treatments. Consequently, there is an urgent demand for a more detailed subdivision and in-depth analysis of nomograms tailored specifically to immunotherapy. There remain some limitations in our work. First, some specific information and clinicopathological data of NSCLC were unclear or not available. Second, the clinical sample size in this study remains relatively small, necessitating further investigations into the role of PGR, PTPRD, RELN, MUC19, LRP1B, and FAT3 in NSCLC with immunotherapy. Besides that, given the lack of pertinent studies in public databases, our three nomograms have not undergone external validation to

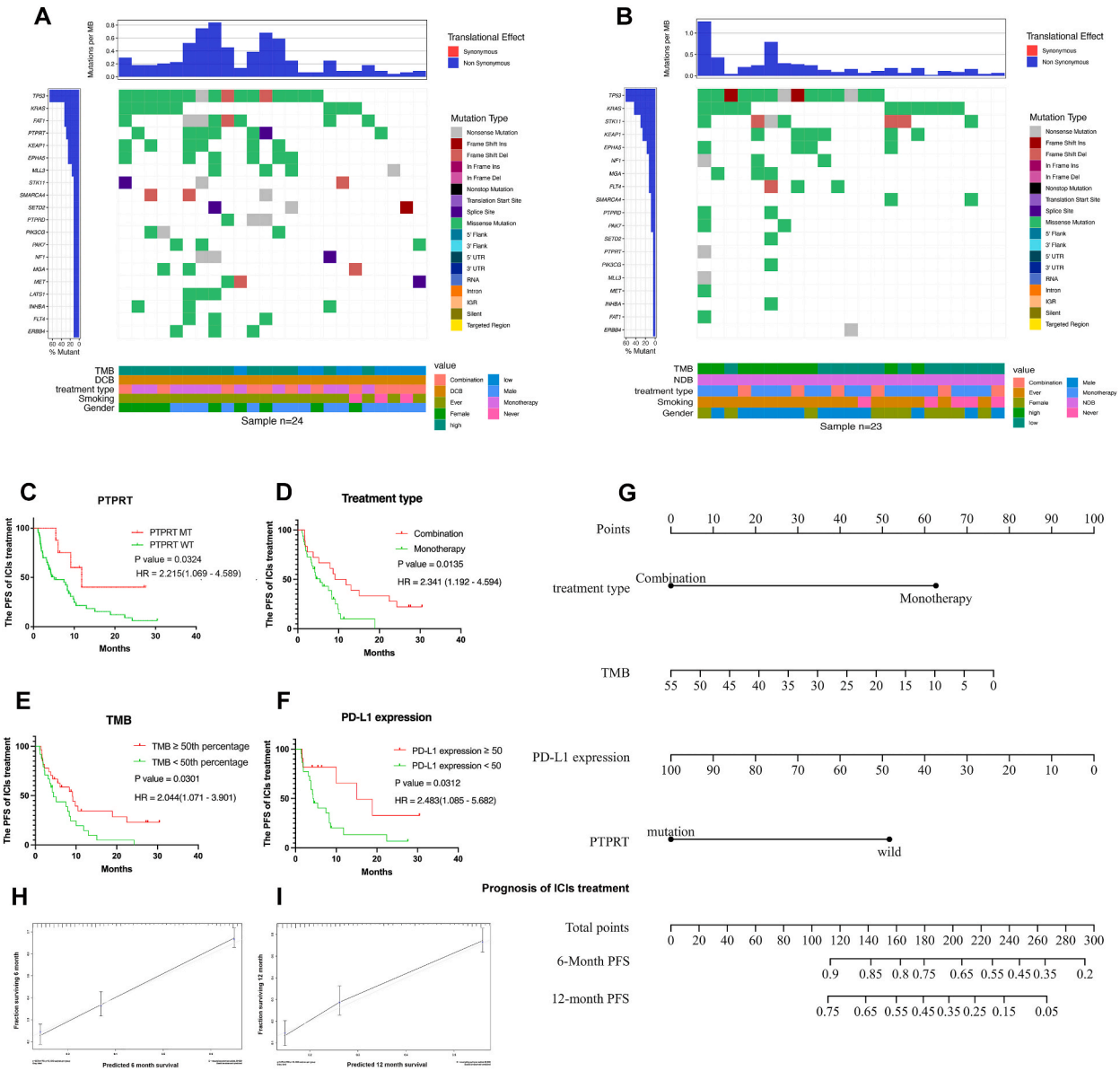

Fig. 5. Summary of genomic landscape and nomogram with ICIs first-line treatment (A, B) Top 20 gene alterations in the DCB group and NDB group. The Kaplan-Meier plot of PTPRT mutation (C), treatment type (D), TMB (E), and PD-L1 expression (F). (G) Nomogram. (H, I) The calibration plot.

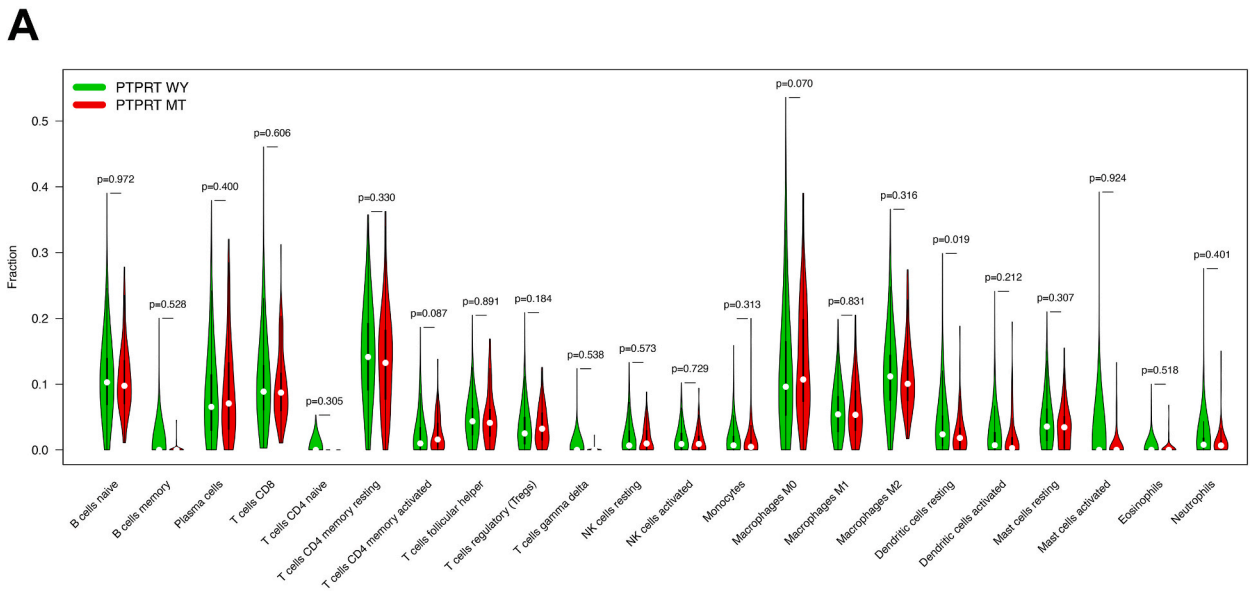

Fig. 6. The role of PTPRT mutation in TIICs. (A) The relationship between the mutation status of PTPRT and immune cells.

date. To fortify the credibility of our findings, we intend to pursue additional external datasets in future research to verify the robustness and practicality of our models. This validation process is crucial for affirming the reliability of our study and bolstering the credibility of our models. Finally, the molecular mechanism underlying these correlations still needs to be validated in vivo and in vitro experiments.

5. Conclusion

Our study demonstrated that PGR, PTPRD, RELN, MUC19, LRP1B, and FAT3 mutation could serve as a prognostic biomarker in NSCLC patients with ICI treatment. Additionally, our systematic nomograms demonstrated promising potential for clinical application in predicting the prognosis of NSCLC patients undergoing different ICI treatment strategies. These findings contribute to identifying biomarkers that can assist in personalized treatment decision-making, enhancing patient outcomes in the era of immunotherapy for advanced NSCLC. Further validation and clinical implementation of these biomarkers and nomograms are warranted to enhance the precision and efficacy of ICI treatment in NSCLC patients.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Data availability

All data included in this study are available including cBioPortal of Cancer Genomics ([MSK, J Clin Oncol 2018], [MSK, Cancer Cell 2018]) and [MSK, Nat Genet 2019].

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CRediT authorship contribution statement

Li Wang: Writing – review & editing, Writing – original draft, Validation, Software, Methodology, Investigation, Formal analysis,

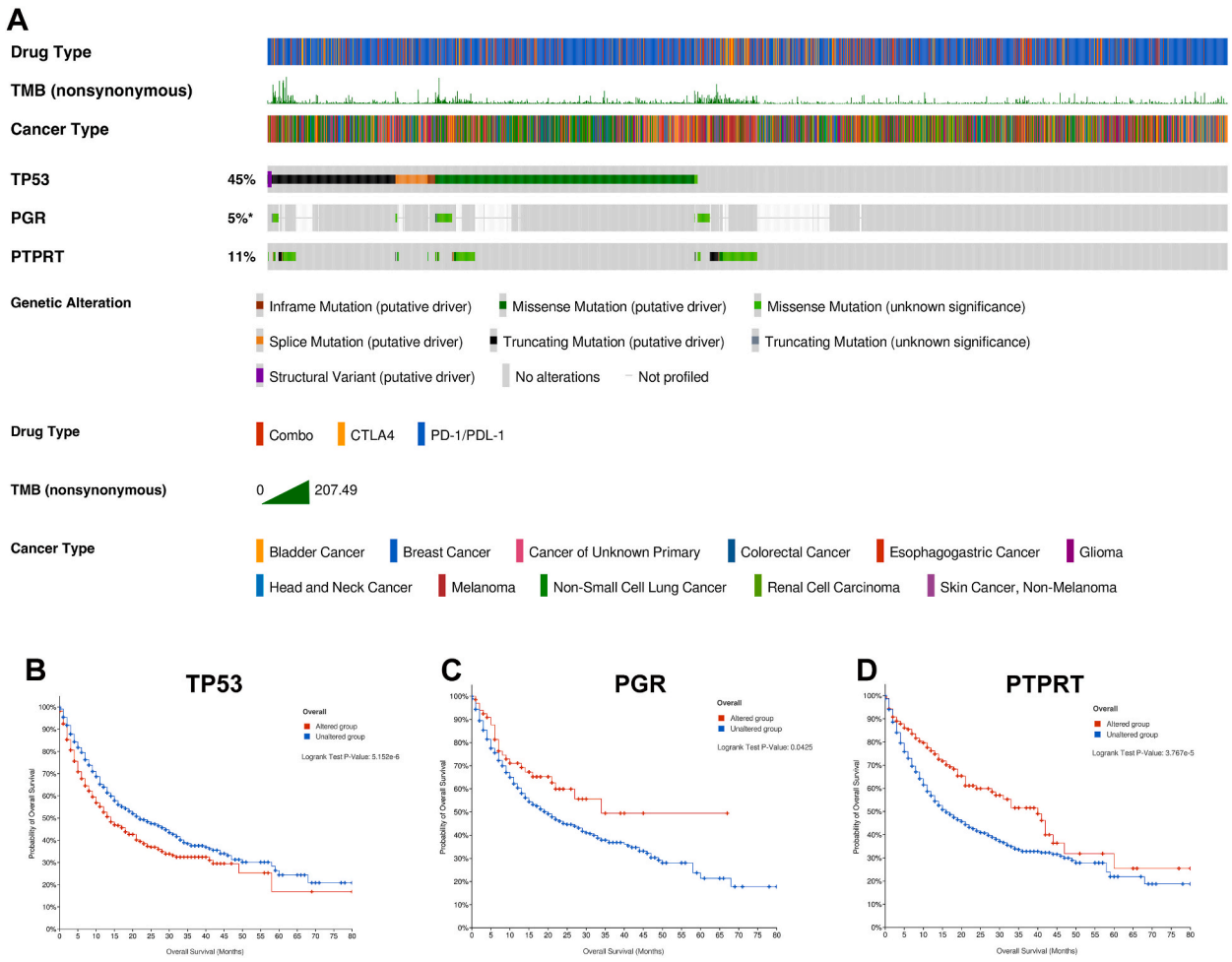

Fig. 7. Verification of the prognostic value of TP53, PGR, and PTPRT mutation. (A) Genomic landscape and clinical feature of TP53, PGR, and PTPRT mutations. (B) The mutation of TP53 was closely related to the prognosis of ICIs in pan-cancer. (C) The mutation of PGR was closely related to the prognosis of ICIs in pan-cancer. (D) The mutation of PTPRT was closely related to the prognosis of ICIs in pan-cancer.

Data curation. **Xiangling Chu:** Writing – review & editing, Writing – original draft, Software, Resources, Methodology, Investigation, Formal analysis. **Xin Yu:** Writing – review & editing, Visualization, Software, Investigation. **Chunxia Su:** Writing – review & editing, Visualization, Supervision, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

Not applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e27801.

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