

Letter to the Editor

Predictive value of LCP1 and ADPGK for immune-related adverse events across multiple cancer types in patients receiving immunotherapy-based regimens

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Dear Editor:

Immune checkpoint inhibitors (ICIs) targeting programmed cell death protein 1 (PD-1) and its ligand (PD-L1) have transformed oncology but are frequently compromised by immune-related adverse events (irAEs) [1]. irAEs can affect nearly any organ system, with the skin, gastrointestinal tract, endocrine glands, liver, and lungs being the most frequently involved. Although most events are moderate and can be controlled by corticosteroids and supportive care, 10% of individuals experience severe ($\geq$ grade 3) toxicities. Currently, no biomarker has been approved for clinical use in predicting irAEs [1]. Evidence from previous studies has identified LCP1 and ADP-dependent glucokinase (ADPGK) as potential irAE markers [2–4].

LCP1, an actin-binding protein, is essential for cytoskeletal reorganization underpinning T-cell receptor (TCR) signaling, immunological synapse stability, and cell motility. Several autoimmune diseases are linked to LCP1 dysregulation and increased T cell effector activity. Crucially, recent reports suggest that this heightened cytoskeletal plasticity in cancer cells is not merely structural but is functionally linked to the active modulation of the immune microenvironment, potentially through the enhanced secretion of immunomodulatory factors or extracellular vesicles [5,6].

ADPGK, a unique glucokinase, is essential for cellular metabolism, particularly in metabolically stressed tumor microenvironments. Upon activation, T cells undergo significant metabolic reprogramming and transition to aerobic glycolysis to support their rapid proliferation and effector functions. ADPGK ensures that activated T cells have the energy and biosynthetic precursors to

launch a strong immune response during this metabolic change [7]. Therefore, elevated ADPGK expression in tumor cells may serve as a surrogate marker for a metabolically stressed microenvironment that is susceptible to inflammatory dysregulation. Consequently, the concurrent high expression of tumoral LCP1 (reflecting cytoskeletal plasticity) and ADPGK (indicating metabolic adaptation) could delineate a distinct tumor profile associated with a heightened propensity for systemic immune overactivation following checkpoint blockade. This study aimed to validate the clinical predictive value of this dual-biomarker phenotype in a large multiple-cancer-type cohort.

A retrospective cohort study encompassing 253 patients receiving anti-PD1/PDL1 inhibitor-based regimens, including monotherapy, combination therapies, or bispecific antibodies, was conducted. The detailed clinical information of each patient is provided in [Supplementary Table S1](#). The study protocol was reviewed and approved by the Institutional Review Board and Ethics Committee of Shanxi Province Cancer Hospital (approval No. KY2023127). Comparison of baseline characteristics between patients who developed irAEs ($n = 69$) and those who did not ($n = 184$) showed no statistically significant differences in age ($P = 0.6225$), gender distribution ($P = 0.5975$), smoking history ($P = 0.3958$), disease stage ($P = 0.3883$), sampling site ($P = 0.4021$), sample type ($P = 0.3201$), or treatment plan ($P = 0.5361$). This indicated that the two groups matched well on key clinical and demographic factors, suggesting that the observed outcome differences were unlikely to be driven by these potential confounders. The cohort included diverse malignancies, predominantly lung, gastric, urinary tract,

and esophageal cancers. [Supplementary Figure S1](#) illustrates the irAE distribution across cancer types, ICI drugs, and grades. Among the 69 patients who experienced irAEs, 37 experienced $\geq$ grade 3 severe toxicity. The types of irAEs are listed in [Supplementary Table S2](#), with pneumonia being the most common event ($n = 18$), followed by hepatitis ($n = 14$), endocrine toxicity ($n = 11$), and rash ($n = 10$). The median time to onset of irAEs was 64 days after ICI administration, with median time to onset of pneumonia, hepatitis, endocrine toxicity, and rash being 54, 48, 183, and 24 days after ICI administration, respectively.

Before the administration of PD1/PD-L1, two pathologists initially assessed Formalin-Fixed Paraffin-Embedded (FFPE) tumor samples to corroborate the malignancy and subtype of solid cancers, as well as to confirm that more than 50% of the sample consisted of tumorous tissues and less than 20% of the sample was necrotic. The slides were stained with primary antibodies against LCP1 (1:500, LJ-

mAB-0002; Liangjue Technology, Beijing, China) and ADPGK (1:500, LJ-mAB-0001; Liangjue Technology) using standard immunohistochemistry protocols. The DAB development system and secondary antibody were acquired from Servicebio (G1212-200T and G1301-100ML, respectively; Beijing, China). Hematoxylin was used for counterstaining, and the entire specimen was scanned using a PANNORAMIC 1000 system (3DHISTECH, Budapest, Hungary). CaseViewer2.4 (3DHISTECH) was used for the image output. Images with a resolution of 600 dpi were quantified using the Aperio ImageScope software (v14.3) and the Positive Pixel Count v9 (PPCv9) algorithm, as previously described [3]. The final positivity of either LCP1 or ADPGK was determined by averaging at least seven regions for each sample. Representative immunohistochemical micrographs captured at 40 $\times$ magnification to visualize the architectural distribution and illustrate the differential expression profiles across diverse malignancies are presented in [Figure 1A](#).

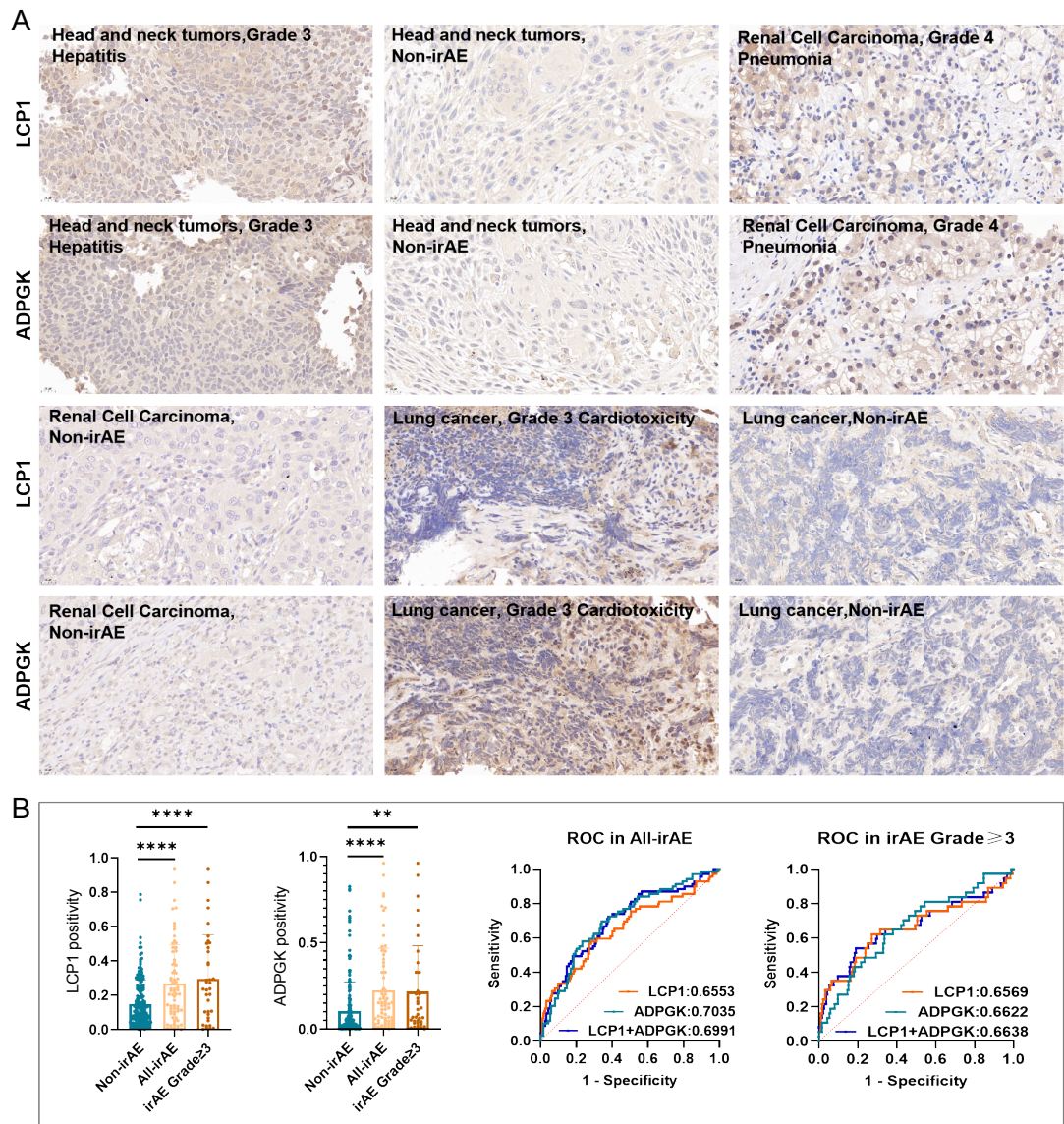


Figure 1. Immunohistochemistry and predictive value of LCP1 and ADPGK for irAE (A) IHC staining images of patients with and without irAEs. (B) Association between LCP1 and ADPGK expression levels and irAEs in cancer patients receiving immune checkpoint inhibitor therapy. LCP1 and ADPGK positivity rates across non-irAE, all-irAE, and grade ≥ 3 irAE groups, and receiver operating characteristic (ROC) curve analysis for LCP1 and ADPGK as predictors of irAE development. $**P < 0.01$, $****P < 0.0001$.

A striking dichotomy in protein abundance was evident between patients experiencing severe immune-related toxicities and those remaining adverse event-free. In cases complicated by high-grade irAEs, tumor tissues exhibited pronounced upregulation of both markers. [Figure 1A](#) shows several typical IHC images. LCP1 was observed in both tumor cells and a subset of infiltrating lymphocytes. Notably, in patients who developed immune-related adverse reactions, this protein is expressed in the nucleus and cytoplasm of tumor tissues. ADPGK, a glucokinase, is primarily localized to the cytoplasm. The tumor cells of affected individuals presented diffuse or granular brown staining. In stark contrast, the matched non-irAE specimens across all three tumor types showed negligible immunoreactivity, retaining only the pale blue hematoxylin counterstain, indicating that the overexpression of LCP1 and ADPGK is highly specific to the irAE-susceptible tumor microenvironment.

Both LCP1 and ADPGK expression levels were significantly higher in patients who developed irAEs (all-irAE and $\geq$ grade 3 subgroups, $P < 0.0001$). ROC analysis confirmed their predictive ability for any-grade irAEs: LCP1 (AUC = 0.6553, $P = 0.0001$) and ADPGK (AUC = 0.7035, $P < 0.0001$). The combined LCP1 + ADPGK model AUC was 0.6991 ($P < 0.0001$), and for irAEs $\geq$ grade 3: LCP1 (AUC = 0.6569, $P = 0.0026$) and ADPGK (AUC = 0.6622, $P = 0.0019$). The combined LCP1 + ADPGK model AUC was 0.6638 ($P = 0.0017$; [Figure 1B](#)).

Cancer-specific analyses revealed varying biomarker performance ([Figure 2A](#)). In non-small cell lung cancer/small cell lung cancer (NSCLC/SCLC) patients ($n = 64$), LCP1 (AUC = 0.6800, $P = 0.0407$) and ADPGK (AUC = 0.7271, $P = 0.0098$) demonstrated significant prediction for all-irAEs, as did their combined model (AUC = 0.7243, $P = 0.0108$). Similar robust performance was noted in gastric cancer (GC) patients ($n = 64$, LCP1 AUC = 0.7299, $P = 0.0365$; ADPGK AUC = 0.7969, $P = 0.0069$; combined AUC = 0.7567, $P = 0.0196$). However, for renal cell carcinoma/urothelial carcinoma (RCC/UC) ($n = 45$), esophageal carcinoma (EC) ($n = 31$), and cervical cancer (CC) ($n = 13$), these biomarkers showed limited predictive value.

Similar findings emerged from irAE subtype analyses ([Figure 2B](#)). For pneumonia, a severe irAE, LCP1 (AUC = 0.6720, $P = 0.0160$), ADPGK (AUC = 0.6993, $P = 0.0052$), and the combined model (AUC = 0.7402, $P = 0.0008$) all exhibited good predictive capacity. Endocrine toxicity was significantly predicted by individual markers (LCP1 AUC = 0.7261, $P = 0.0020$; ADPGK AUC = 0.7495, $P = 0.0007$). Conversely, cardiac toxicity prediction remained non-significant. For hepatitis and rash, only ADPGK showed significant individual predictive value (AUC = 0.6958, $P = 0.00231$ and AUC = 0.7125, $P = 0.0136$, respectively). Patients with enteritis, myositis, nephritis, and pancreatitis (≤ 5 cases each) were excluded from analysis.

Bispecific antibody therapy was administered to 25 patients, with the majority ($n = 21$) receiving cadonilimab. Among the cadonilimab recipients, 14 had urological tumors, 6 had cervical cancer, and 1 had lung cancer. Forty-eight percent of patients experienced irAEs of varying severity, including one irAE-related death. ADPGK (AUC = 0.8364, $P = 0.0092$) and the combined LCP1 + ADPGK model (AUC = 0.8000, $P = 0.0201$) demonstrated excellent predictive performance for irAEs, whereas LCP1 alone did not show a statistically significant association with irAE occurrence ($P > 0.05$; [Figure 3](#)).

Grouped analysis by sample type (biopsy vs. surgical specimens) consistently showed higher LCP1 and ADPGK expression in the irAE group, with both single-marker and combined models exhibiting significant predictive capabilities ([Supplementary Figure S2](#)).

Analysis by treatment regimen revealed that in PD-1/PD-L1 monotherapy, the combined model (AUC = 0.6892, $P = 0.03$) and LCP1 alone (AUC = 0.6976, $P = 0.0234$) were significant. In contrast, for the combined modalities, all models demonstrated significant predictive values ([Supplementary Figure S3](#)).

We observed that the combined LCP1 + ADPGK model did not improve predictive efficacy in some subgroups. We analyzed the correlation between LCP1 and ADPGK in the overall cohort ($n = 253$). Analysis in the subgroup showed that the individual LCP1 or ADPGK models and the combined LCP1 + ADPGK model effectively predicted irAEs ([Supplementary Figure S4](#)). The results showed that in the overall cohort and most subgroups, the strong correlation indicates that LCP1 and ADPGK likely reflect overlapping biological processes in these patients. Statistically, this collinearity means that LCP1 and ADPGK provide redundant information to each other. Therefore, the combined model may not enhance predictive power and, in some cases, slightly reduces the AUC due to model complexity penalties.

As previously reported [2–4], our study confirms tumoral LCP1 and ADPGK as novel predictive biomarkers for irAEs but critically demonstrates that their utility is highly dependent on the clinical context. Although higher expressions of these proteins are strongly associated with irAE risk in the overall patient population and provide better predictive power for patients with lung or gastric cancer and for the development of pneumonitis, their value diminishes in other malignancies, such as urologic and esophageal cancers, and they fail to predict rare toxicities like cardiotoxicity. For esophageal and cervical cancers, factors such as distinctive tumor antigens, local cytokine milieu, and immune evasion mechanisms might promote irAEs through pathways less dependent on the LCP1/ADPGK axis, thereby diminishing its predictive power [8,9]. The inability to predict lethal cardiotoxicity is also informative: Myocarditis is rare and is driven by a highly specific, clonally expanded T-cell response to shared antigens. A general biomarker (LCP1/ADPGK) is unlikely to capture this antigen-driven specificity, suggesting the necessity for focused biomarkers such as TCR clonotypes or circulating autoantibodies [10]. A particularly novel aspect of our cohort is the inclusion of patients receiving cadonilimab, a bispecific antibody that targets both PD-1 and CTLA-4. As such dual-targeting agents emerge—representing a clear advance in immuno-oncology—they introduce greater complexity in managing toxicities. By design, these agents induce more robust T-cell activation than monotherapies, which logically elevates the risk of irAEs. This concern is substantiated in our cohort, where forty-eight percent of the patients experienced irAEs, underscoring the urgent need for predictive biomarkers in this advanced therapeutic setting. Within the cadonilimab-treated group, ADPGK emerged as a powerful predictor but LCP1 failed to show statistical significance. This result may be attributable to the small sample size ($n = 21$), or it may reflect that the potent, concurrent blockade of PD-1 and CTLA-4 fundamentally alters the critical determinants of T-cell hyperactivation. Currently, research on predictive biomarkers for irAEs induced by bispecific antibodies remains in its early stages; our findings could pave the way for biomarker-guided strategies, enabling safer deployment of these potent therapies. This study has several strengths, including its relatively large, real-world cohort, the use of quantified immunohistochemistry for biomarker assessment, and the detailed subgroup analyses. However, several limitations must be acknowledged. First, its retrospective design is

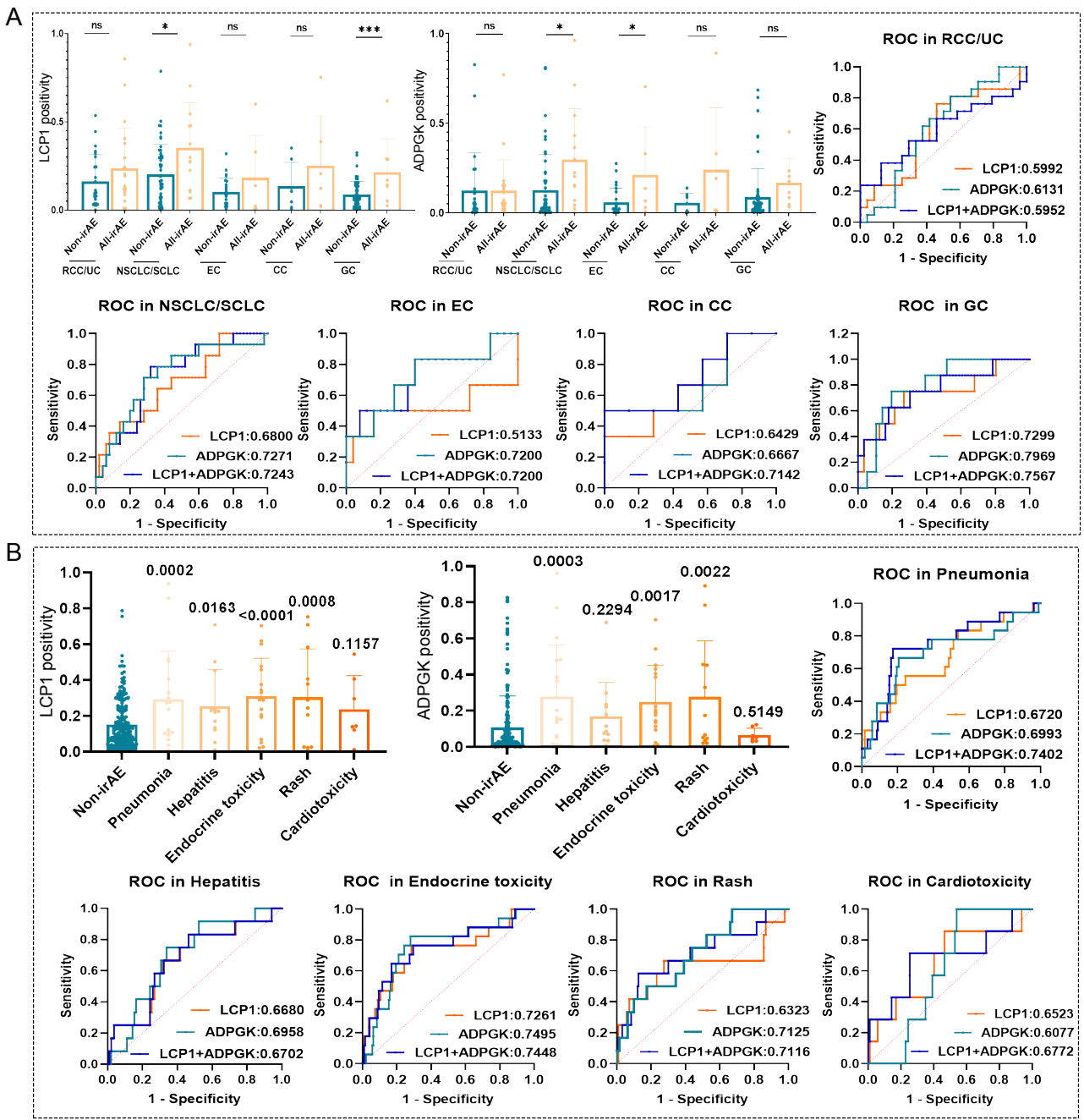


Figure 2. Predictive performance of LCP1 and ADPGK for irAEs across cancer types and irAE types (A) Comparison of the positive rates of LCP1 and ADPGK between the non-irAE and irAE groups in RCC/UC, NSCLC/SCLC, EC, CC, and GC, along with the ROC curves of LCP1, ADPGK, and the combined LCP1 + ADPGK model for predicting irAEs in these cancer types. (B) Comparison of LCP1 and ADPGK positivity rates among patients without irAEs and those with specific irAEs (including pneumonitis, hepatitis, endocrine toxicities, skin rash, and cardiotoxicity), along with the predictive performance of LCP1, ADPGK, and their combination for these irAE types as evaluated by ROC curves. * $P < 0.05$, *** $P < 0.001$. ns, not significant.

susceptible to inherent biases, although the well-matched baseline characteristics between our groups help to lessen these biases. Second, the sample sizes for some subgroups were limited, which may have reduced our statistical power to detect more modest associations and led to some of the negative findings. Third, our analysis focused on the expression of these proteins within tumor cells, but their expression within the tumor-infiltrating immune cells may be an even more direct and relevant measure of the immune system. Future studies using multiplex IHC or spatial

transcriptomics could dissect these contributions by cell type. Finally, this is the only institution discovery study that lacks an independent validation cohort.

Regarding LCP1, its ectopic expression in epithelial malignancies has been well documented to drive cytoskeletal remodeling, particularly through the formation of actin-rich invasive structures [11]. Recent studies about tumor biology have indicated that cytoskeletal dynamics are integral to the biogenesis and secretion of tumor-derived extracellular vesicles (EVs) [6]. The literature

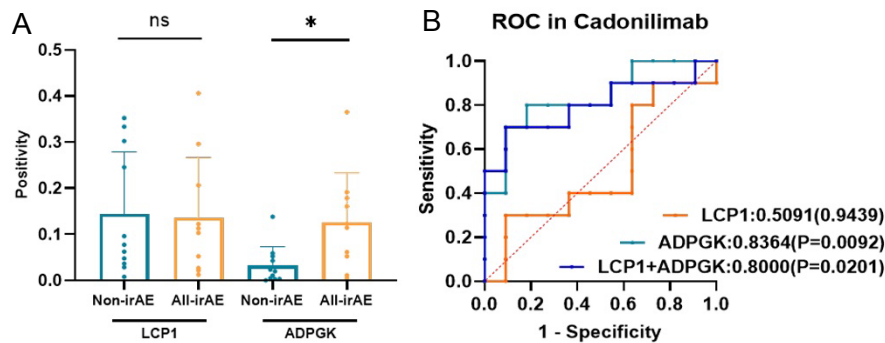


Figure 3. Association between LCP1 and ADPGK expression levels and irAEs in cancer patients receiving cadonilimab (A) LCP1 and ADPGK positivity rates between non-irAE and all-irAE. Bar plots with overlaid scatter points showing individual data distribution. (B) ROC curve analysis for alone LCP1, ADPGK and LCP1 + ADPGK as predictor of irAE development in patients receiving cadonilimab. * $P < 0.05$. ns, not significant.

demonstrates that these tumor-derived vesicles act as mediators of systemic immune crosstalk and are capable of traveling to distant sites and priming myeloid cells to release pro-inflammatory cytokines [5]. Although this study did not involve direct mechanistic investigation, the above theory and the correlation between high tumoral LCP1 and irAEs observed here may offer a valuable direction for further investigating the role of LCP1 in systemic immune regulation. Regarding ADPGK, its elevated expression in tumor cells likely reflects a metabolic adaptation to microenvironmental stress, such as hypoxia or nutrient deprivation. It has been documented that tumor cells under metabolic stress can switch to alternative glycolytic pathways to sustain survival [7]. Although the precise intercellular signaling remains to be fully elucidated, recent studies suggest that aberrant tumor glycolysis and the associated accumulation of metabolic byproducts can function as paracrine signals, potentially conditioning the surrounding immune infiltrate toward a state of heightened alertness or fragility [12]. Currently, there is a lack of causal evidence regarding the prediction of irAEs by LCP1 and ADPGK. Therefore, this study proposes a working hypothesis that a potential causal relationship exists between them, which awaits further experimental validation. The path forward in irAE prediction will likely require moving beyond single markers and toward integrated, multi-modal biomarker panels. Our study serves as a crucial step in this process by mapping the specific clinical scenarios for LCP1 and ADPGK.

Supplementary Data

Supplementary data are available at *Acta Biochimica et Biophysica Sinica* online.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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