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Research article

Identification and validation of GIMAP family genes as immune-related prognostic biomarkers in lung adenocarcinoma

Yanyan Zhang [a,1], Shan Liu [b,1], Deyi Liu [c], Zhuxiang Zhao [a], Haifeng Song [d,**], Kunwei Peng [e,*]

[a] Department of Infectious Diseases, Guangzhou First People's Hospital, School of Medicine, South China University of Technology, Guangzhou, Guangdong, China
[b] Department of Cardiology, The Second Affiliated Hospital of Guangzhou Medical University, Guangzhou Institute of Cardiovascular Disease, Guangzhou, Guangdong, China
[c] Department of General Practice, The Second Affiliated Hospital of Guangzhou Medical University, Guangzhou, Guangdong, China
[d] Department of Oncology, Lianzhou People's Hospital, Lianzhou, Guangdong, China
[e] Guangzhou Key Laboratory for Research and Development of Nano-Biomedical Technology for Diagnosis and Therapy & Guangdong Provincial Education Department Key Laboratory of Nano-Immunoregulation Tumour Microenvironment, Department of Oncology, The Second Affiliated Hospital of Guangzhou Medical University, Guangzhou, Guangdong, China

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ABSTRACT

Background: The GIMAP family genes play a key role in immune function. Increasing evidence suggests that GIMAP genes were implicated in the tumorigenesis of lung adenocarcinoma (LUAD). This study aimed to investigate the clinical significance of GIMAP family genes in LUAD.

Methods: In this study, we explored the expression, mutation, prognostic value of GIMAP family genes and the correlation with immune microenvironment in LUAD. We further investigated the relationship between GIMAP family genes expression and immunotherapy response in GEO LUAD and melanoma cohorts.

Results: Among the GIMAP family genes, the expression levels of GIMAP1, GIMAP2, GIMAP4, GIMAP5, GIMAP6, GIMAP7, and GIMAP8 were significantly lower in LUAD tumor tissues than normal tissues. Most GIMAP genes were closely related to age, tumor grade and T stage, but not significantly related to sex, N stage and M stage. In the overall population, patients with high expression of GIMAP family genes had a significant longer overall survival (OS). GO and KEGG enrichment analysis showed that GIMAP family genes were highly enriched in immune-related biological process. The expression of GIMAP family genes was positively correlated with immune cell infiltration and immune checkpoint molecules. Furthermore, high expression of GIMAP family genes were correlated with therapeutic response to immunotherapy in LUAD and melanoma patients.

Conclusion: In this study, we identified that GIMAP family genes were significantly associated with immune cell infiltration and immune checkpoint molecules. They potentially play a critical role in anti-tumor immunity and serve as immunotherapy biomarkers.

* Corresponding author. No. 250 Changgang East Road, Guangzhou, 510260, China.
** Corresponding author. No. 5 Yangmei Road, Lianzhou, 513400, China.
E-mail addresses: 13926606793@163.com (H. Song), gypengkw@163.com, 2022682124@gzhmu.edu.cn (K. Peng).
[1] Contributed equally (Co-first authors).

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1. Introduction

The latest epidemiological studies have shown that lung cancer still remains the deadliest malignancy in the United States and China [1,2]. It is a molecular-heterogeneous disease, with more than 85 % cases classified as non-small cell lung cancer (NSCLC) [3]. The two main subtypes are lung adenocarcinoma (LUAD) and lung squamous cell carcinoma [4]. Twenty years ago, the treatment options for LUAD were largely confined to chemotherapy, radiotherapy and surgery. With the dramatic development in molecular biology research, great progress has been made in the treatment of LUAD with targeted drugs [5,6]. While epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitors have shown remarkable benefits for EGFR- and ALK-positive LUAD patients compared to conventional chemotherapy, the five-year survival rate remains low due to the emergence of primary and acquired resistance [7]. Immunotherapy, represented by anti-programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1) antibody has created a new prospect in LUAD treatment [8]. The biomarkers such as PD-L1 expression and tumor mutation burden (TMB) can be used to predict survival, but their predictive value were far from satisfactory due to the high heterogeneity of LUAD [9,10]. Consequently, the identification of novel immune-related biomarkers holds significant value in predicting the prognosis of LUAD.

Abbreviations

GIMAP	GTPase of the immunity-associated protein
LUAD	Lung adenocarcinoma
NSCLC	Non-small cell lung cancer
EGFR	Epidermal growth factor receptor
ALK	Anaplastic lymphoma kinase
PD-1	Programmed death-1
PD-L1	Programmed death-ligand 1
TCGA	The Cancer Genome Atlas
TIMER	Tumor Immune Estimation Resource
GEO	Gene Expression Omnibus
GEPIA	Gene Expression Profiling Interactive Analysis
PPI	Protein-protein interaction
GO	Gene Ontology
KEGG	Kyoto Encyclopedia of Genes and Genomes
TMB	Tumor mutation burden
OS	Overall survival
GSK3β	Glycogen synthase kinase 3β

The GTPase of immunity-associated protein (GIMAP) family genes reside on human chromosome 7, and include seven members: GIMAP1, GIMAP2, GIMAP4, GIMAP5, GIMAP6, GIMAP7, GIMAP8 [11–13]. The GIMAP genes encode proteins with structural features of GTP-binding protein motif and coiled-coil motif. Initially, the GIMAP genes were identified in plants mediating defense response to bacterial infection [14]. These genes are preferentially expressed in hematopoietic cells and lymphocytes, and there is also evidence that they are expressed in non-hematopoietic cells, particularly in the lung [15–17]. Despite limited research on individual GIMAP member functions, existing studies suggest their involvement in mediating pro-survival or pro-death signals in immune cells [18,19]. Previous animal studies have demonstrated interactions between GIMAP genes and apoptosis regulators, implicating them in differentiation, survival, and apoptosis of T cells and other cell types [20,21]. Significantly downregulated expression of GIMAP5 and GIMAP6 has been observed in tissues and plasma of patients with hepatocellular carcinoma, suggesting their potential application as diagnostic biomarkers [22]. Similarly, in the cervical cancer, GIMAP4 expression was strongly associated with immune cell infiltration, potentially signifying its role as a biomarker of immune state in tumour microenvironment [23]. These findings collectively suggest a potentially significant role for the GIMAP family genes in tumour microenvironment and anti-tumor immunity. However, the clinical significance of GIMAP family genes in LUAD remains unexplored.

In this study, we downloaded data from The Cancer Genome Atlas (TCGA) and performed a comprehensive analysis of GIMAP family genes. We found that GIMAP family genes were significantly lower in LUAD tissues and closely related with longer survival. We identified that GIMAP family genes were significantly associated with immune cell infiltration in the tumor microenvironment. Furthermore, high expression of GIMAP family genes were correlated with therapeutic response to immunotherapy in LUAD and melanoma. In conclusion, these findings suggest that GIMAP family genes have the potential to serve as prognostic indicators and immunotherapy biomarkers in LUAD.

2. Method

2.1. TCGA database

TCGA is a publicly funded project that provides a comprehensive, multi-dimensional analysis of human cancer based on genome sequencing and survival data [24]. We downloaded mRNA expression data and clinicopathological parameters of LUAD patients from TCGA. Student's t-test was used to evaluate the expression of GIMAP genes in different subgroups. Pearson's correlation analysis was used to evaluate the correlation between GIMAP genes expression and immune score, stromal score and TMB. $p < 0.05$ was considered statistically significant difference.

2.2. TIMER analysis

Tumor Immune Estimation Resource (TIMER, https://cistrome.shinyapps.io/timer/) is an interactive web application for comprehensive analysis of tumor-immune interactions [25]. By using Gene module, the correlation coefficient between GIMAP genes expression and immune cell infiltration, immune checkpoint molecules expression was calculated. The survival module was used to describe the effect of GIMAP genes expression on survival. $p < 0.05$ was considered statistically significant difference.

2.3. Kaplan-meier plotter

The prognostic value of GIMAP family genes was analyzed by Kaplan-Meier plotter (http://kmplot.com/analysis/, K-M) [26]. Patients were divided into two groups based on gene expression level, and the OS was assessed by K-M survival. $p < 0.05$ was considered statistically significant difference.

2.4. GEO database

To test the predictive value of GIMAP genes in immunotherapy response, we downloaded gene expression data of LUAD (GEO126044) and melanoma (GEO78220) immunotherapy cohorts from the Gene Expression Omnibus (GEO) database [27]. Patients were divided into high and low expression group according to the median gene expression level.

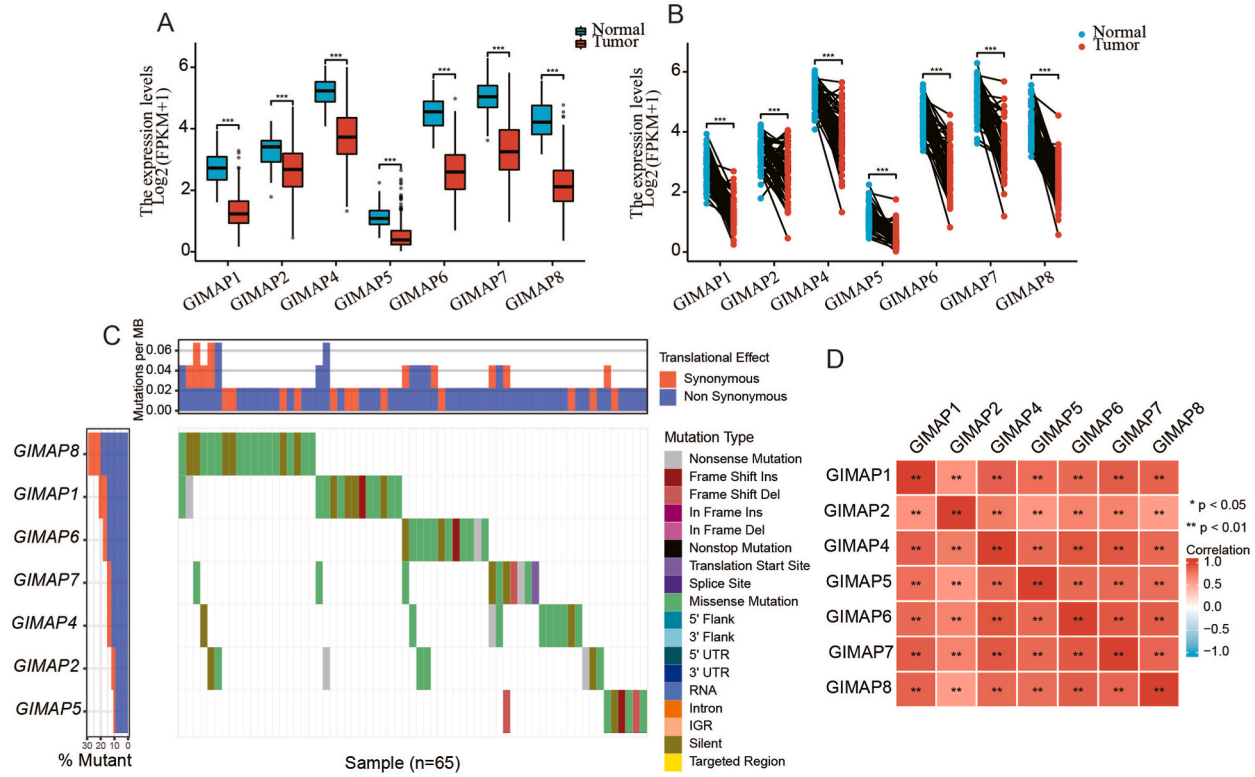

Fig. 1. The expression of GIMAP family genes in LUAD. A. Expression of GIMAP family genes in non-paired samples of LUAD. B. Expression of GIMAP family genes in paired samples of LUAD. C. Mutation analysis of GIMAP family genes in LUAD. D. Relationship between different GIMAP family genes in LUAD. (**: $p < 0.01$, ***: $p < 0.001$).

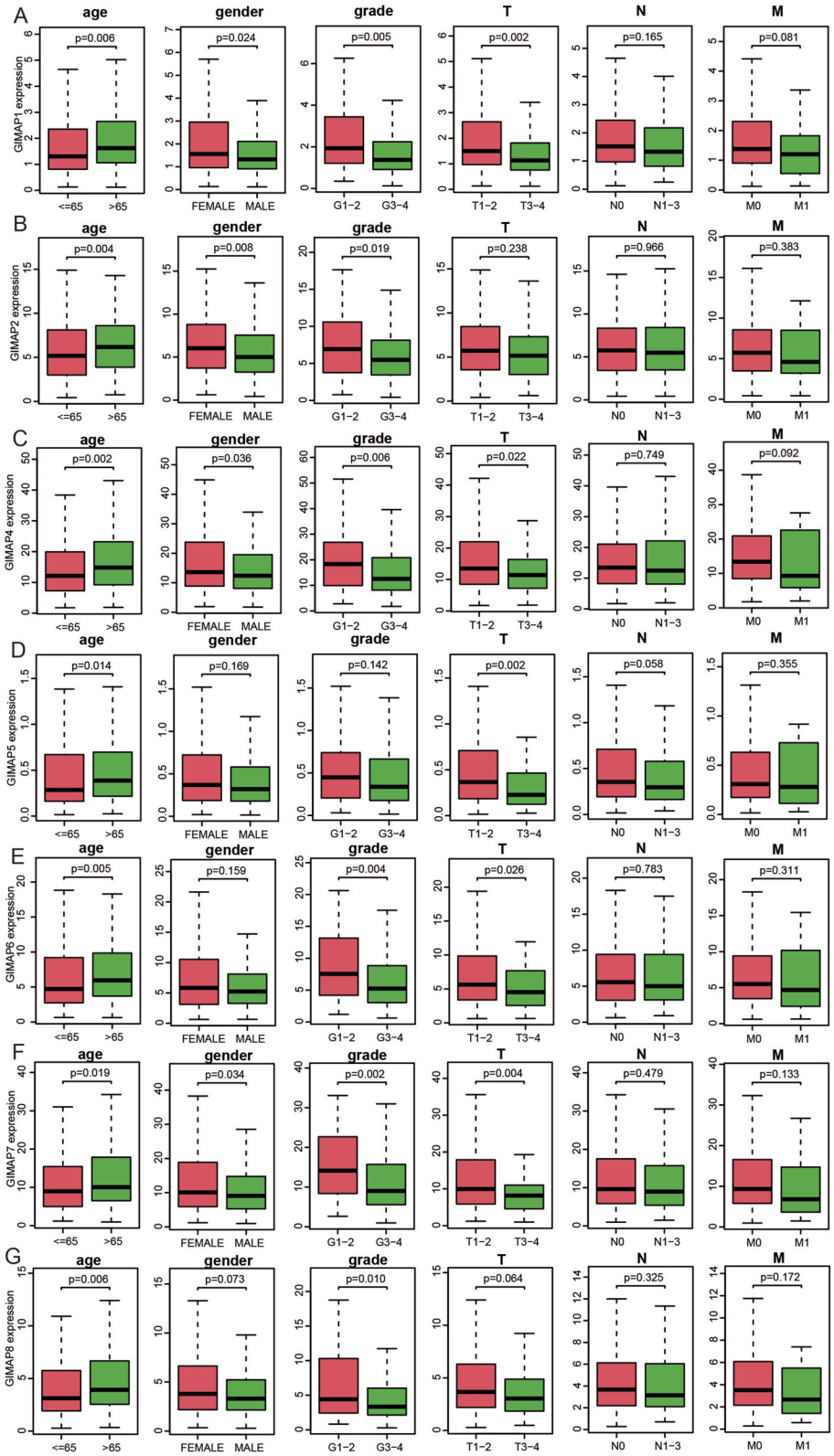

Fig. 2. Boxplot showing relative expression of GIMAP family genes in LUAD patients stratified by age, gender, grade, T stage, N stage and M stage.

2.5. GEPIA dataset

GEPIA (Gene Expression Profiling Interactive Analysis) is an interactive online platform [28]. The similar gene detection module was used to identify the top10 similar genes for each GIMAP family member. During this process, duplicate genes were removed to obtain a final set of similar genes.

2.6. Functional enrichment and protein-protein interaction (PPI) network of GIMAP

GIMAP similar genes were subjected to Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis using the R package of clusterProfiler, and a cut-off value of false discovery rate <0.05 was considered statistically significant. PPI network (STRING v11.0) analysis was conducted to integrate the potential interactions of GIMAP similar genes [29]. $p < 0.05$ was considered statistically significant difference.

3. Results

3.1. GIMAP family genes expression in LUAD

We first investigated the expression of GIMAP family genes in LUAD using TCGA data. The results showed that GIMAP1, GIMAP2,

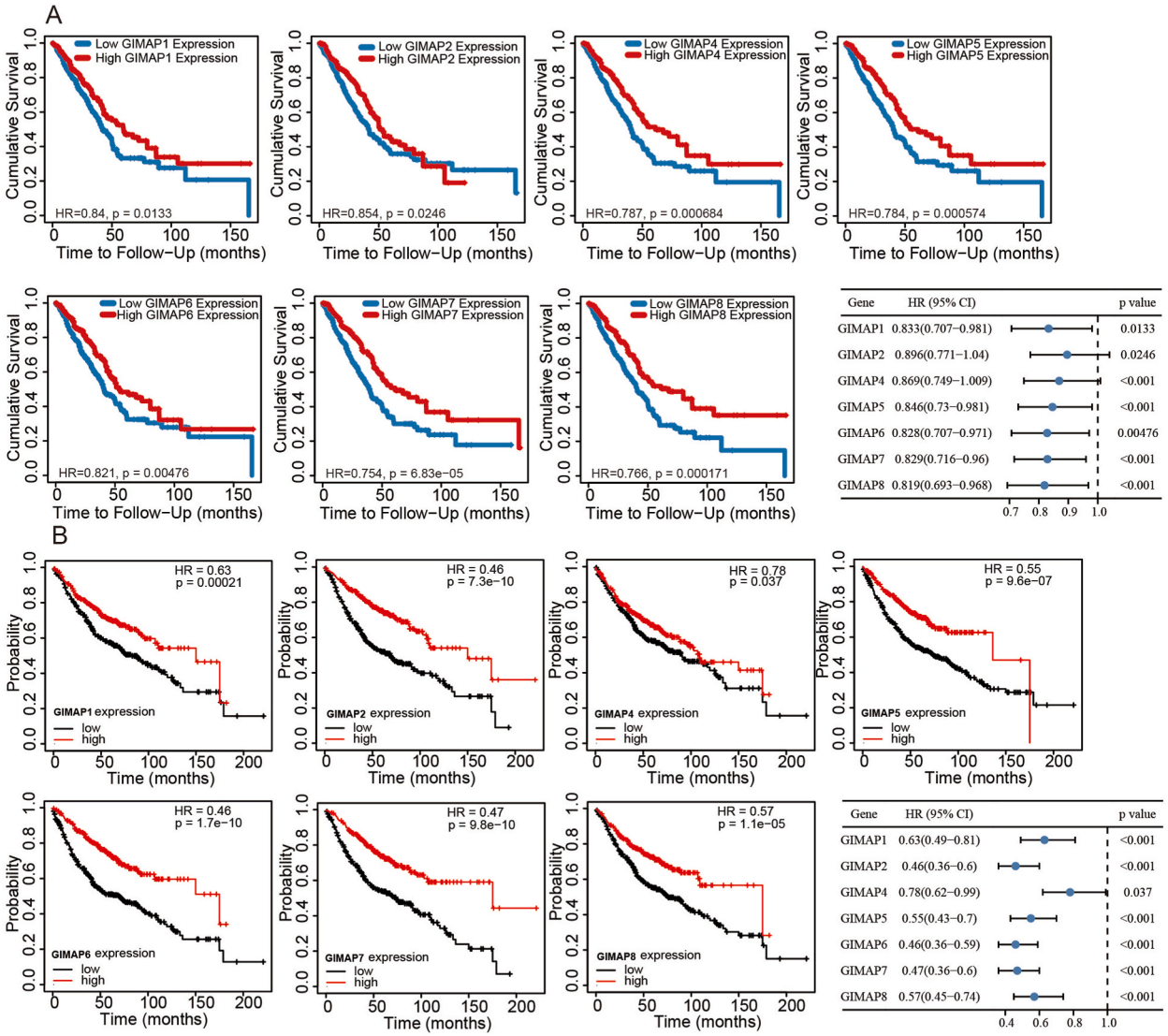

Fig. 3. The prognostic value of GIMAP family genes in LUAD patients. (A: TIMER; B: Kaplan-Meier Plotter).

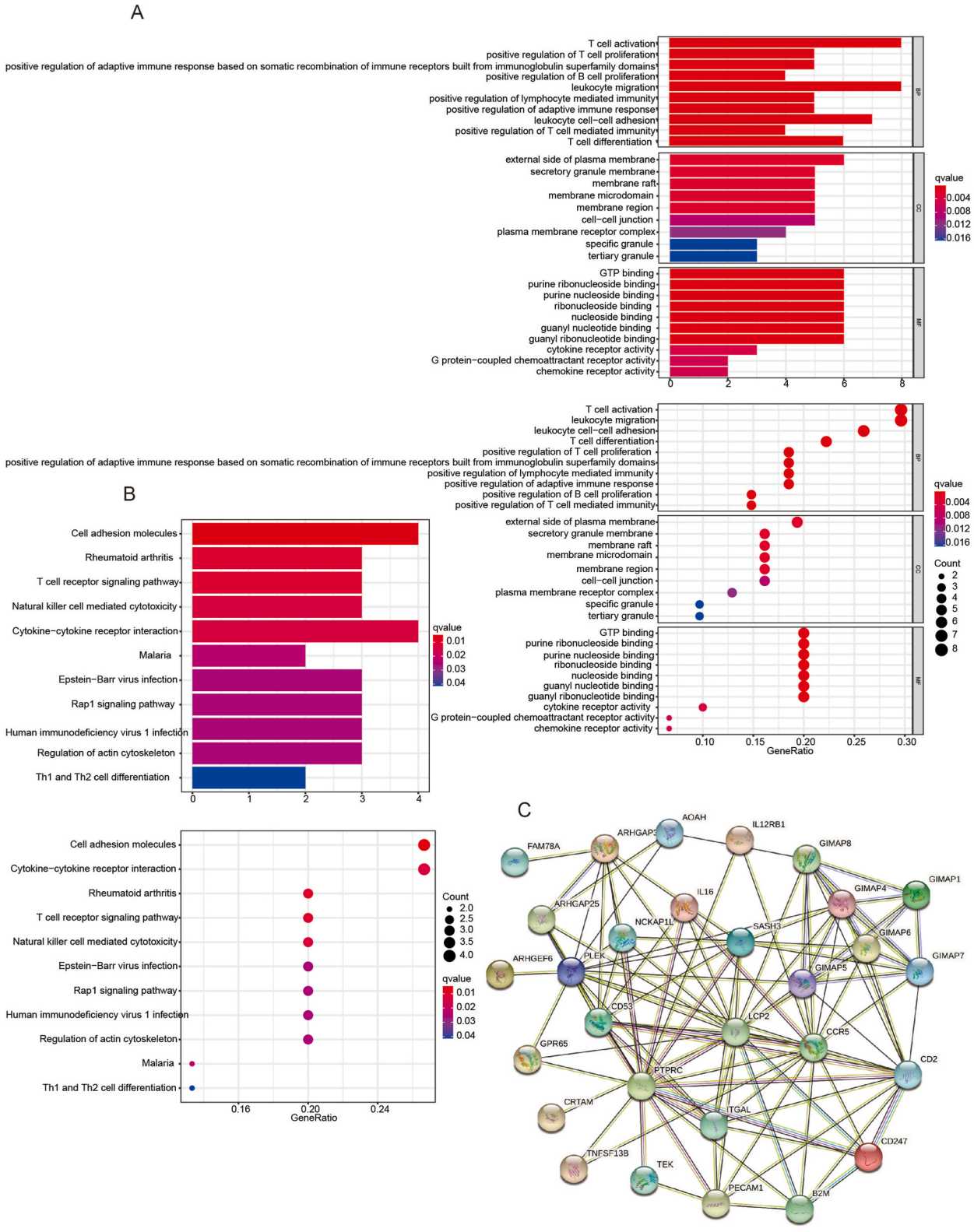

Fig. 4. Predicted functions and pathways of GIMAP family genes in LUAD. A–B: GO and KEGG enrichment analysis of 34 similar genes of GIMAP family. C: The PPI network of 34 similar genes of GIMAP family.

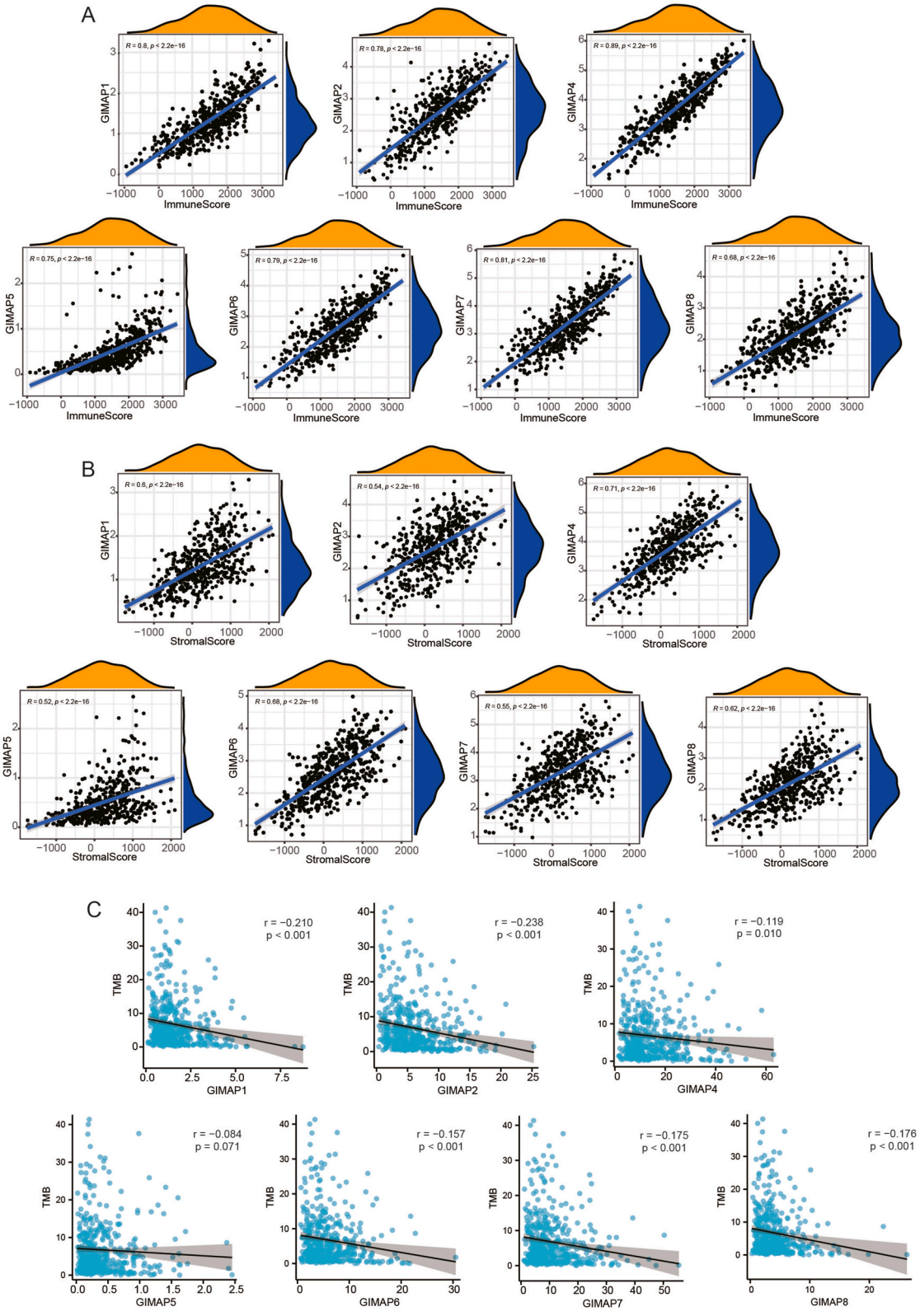

Fig. 5. Relationship between GIMAP family genes and tumor immune microenvironment in LUAD. A–B: Correlation of immune score and stromal score with GIMAP family genes. C: Relationships between GIMAP family genes and the tumor mutation burden.

GIMAP4, GIMAP5, GIMAP6, GIMAP7 and GIMAP8 expression in tumor tissues was significantly lower than normal tissues in both paired and unpaired samples ($p < 0.01$) (Fig. 1A–B). To further explore the genetic alternation of GIMAP genes, we analyzed their mutation patterns. Mutations in GIMAP genes were found in 65 patients, with a mutation rate of 12.3 %, GIMAP8 had the highest mutation rate (Fig. 1C). We also evaluated the correlation of different GIMAP genes, and the results showed that there was a significant positive correlation among GIMAP family members (Fig. 1D).

3.2. Relationship between GIMAP family genes expression and clinical parameters in LUAD

The clinical data of LUAD were analyzed to explore the correlation between the GIMAP family genes expression and clinical features. Subgroup analysis basis on age showed that GIMAP family genes expression was significantly higher in patients older than 65 years (Fig. 2A–G, $p < 0.05$). The expression of GIMAP1, GIMAP2, GIMAP4 and GIMAP7 was higher in female group (Fig. 2A, B, C, F, $p < 0.05$), while GIMAP5, GIMAP6 and GIMAP8 expression showed no significant difference (Fig. 2D, E, G, $p > 0.05$). GIAMP genes expression had no significant relationship with N stage and M stage (Fig. 2A–G, $p < 0.05$). However, GIMAP1, GIMAP4, GIMAP5, GIMAP6, and GIMAP7 expression decreased significantly with tumor grade (G) and T stage (Fig. 2A–C, D, E, F, $p < 0.05$).

3.3. Prognostic value of GIMAP family genes in LUAD

The effects of GIMAP family genes on survival in LUAD patients were analyzed using the TIMER and KaplanMeier databases (Fig. 3A–B). As shown in Fig. 3A, we used TIMER database to visualize the relationship between GIMAP family genes expression and prognosis. Patients with higher expression of GIMAP family genes exhibited longer OS (all $p < 0.05$) (Fig. 3A). In addition, we further validated the predictive value of GIMAP family genes using KM database and reached consistent conclusions (Fig. 3B). These results showed that GIMAP genes were prognostic factors in LUAD patients.

3.4. Functional enrichment analysis of GIMAP family genes in LUAD

To explore the biological role of GIMAP family genes, we obtained 34 similar genes of GIMAP family from GEPIA dataset. GO enrichment analysis showed that the GIMAP family genes were mainly related to the immune functions, especially T-cell activation and leukocyte migration (Fig. 4A). KEGG analysis results also revealed a link to immune-related biological processes, such as cell adhesion molecules and cytokine-cytokine receptor interactions (Fig. 4B). Subsequently, we searched the STRING database (https://string-db.org/) for possible potential interactions between the 34 similar genes of GIMAP family, and constructed a protein interaction network (Fig. 4C). Taken together, these findings demonstrate that GIMAP family genes were associated with immune-related pathways.

3.5. Relationships between GIMAP family genes and immune microenvironment in LUAD

In this study, we used TCGA and TIMER databases to investigate the relationships between GIMAP family genes and tumour immune microenvironment. The results showed that the immune scores and stromal scores were increased with the expression of GIMAP genes (Fig. 5A–B). Conversely, TMB was attenuated with GIMAP genes expression (Fig. 5C). Furthermore, we analyzed the relationship between GIMAP genes and immune microenvironment through using TIMER database. As shown in Table 1, all GIMAP family geness were positively associated with 14 important immune checkpoint molecules (CD274, CTLA4, HAV, IDO1, PDCD1, CD8A, CXCL10, CXCL9, GZMA, GZMB, IFNG, PRF1, TBX2, TNF). Notably, GIMAP4 exhibited the strongest positive correlation with CD274 expression (partial correlation = 0.601, $p < 0.0001$), while GIMAP5 exhibited the strongest positive correlation with PDCD1 expression (partial correlation = 0.521, $p < 0.001$). Moreover, we found that GIMAP family genes were correlated with the infiltration

Table 1
Association between GIMAP family genes and immune checkpoint molecules (TIMER database).

Immune relevant genes	GIMAP1 cor	p	GIMAP2 cor	p	GIMAP4 cor	p	GIMAP5 cor	p	GIMAP6 cor	p	GIMAP7 cor	p	GIMAP8 cor	p
CD274	0.544	***	0.505	***	0.601	***	0.574	***	0.537	***	0.481	***	0.477	***
CTLA4	0.618	***	0.542	***	0.667	***	0.697	***	0.548	***	0.63	***	0.512	***
HAVCR2	0.673	***	0.684	***	0.803	***	0.732	***	0.721	***	0.636	***	0.597	***
IDO1	0.41	***	0.51	***	0.517	***	0.521	***	0.415	***	0.464	***	0.334	***
LAG3	0.577	***	0.41	***	0.583	***	0.637	***	0.459	***	0.528	***	0.425	***
PDCD1	0.673	***	0.524	***	0.651	***	0.71	***	0.549	***	0.61	***	0.478	***
CD8A	0.597	***	0.583	***	0.717	***	0.757	***	0.63	***	0.694	***	0.526	***
CXCL10	0.458	***	0.544	***	0.65	***	0.654	***	0.538	***	0.526	***	0.383	***
CXCL9	0.557	***	0.519	***	0.682	***	0.715	***	0.576	***	0.609	***	0.472	***
GZMA	0.549	***	0.604	***	0.696	***	0.744	***	0.599	***	0.669	***	0.463	***
GZMB	0.423	***	0.383	***	0.535	***	0.601	***	0.438	***	0.464	***	0.352	***
IFNG	0.446	***	0.46	***	0.576	***	0.622	***	0.471	***	0.53	***	0.364	***
PRF1	0.619	***	0.534	***	0.642	***	0.685	***	0.586	***	0.602	***	0.521	***
TBX2	0.445	***	0.119	0.0068	0.286	***	0.274	***	0.38	***	0.366	***	0.5	***
TNF	0.453	***	0.418	***	0.463	***	0.425	***	0.436	***	0.448	***	0.37	***

of B cells, $CD8^+$ T cells, $CD4^+$ T cells, macrophages, neutrophils, and dendritic cells (Table 2). The GIMAP4 expression was most positively correlated with the infiltration of $CD8^+$ T cells (partial correlation = 0.59, $p < 0.0001$) and dendritic cells (partial correlation = 0.735, $p < 0.0001$). The results suggested that GIMAP family genes play a role in shaping the tumor immune microenvironment.

3.6. Association between GIMAP genes expression and immunotherapy response

The relationship between GIMAP family genes and immunotherapy response were validated by analysing the data from the immunotherapy cohorts of LUAD (GEO126044) and melanoma (GEO 78220). In LUAD cohort, patients with high GIMAP family genes expression showed therapeutic response to immunotherapy, while patients with low GIMAP gene expression showed non-response (Fig. 6A). Similarly, melanoma patients with high GIMAP genes expression had a higher response rate (Fig. 6B). The above results suggested that GIMAP family genes were associated with immunotherapy response and could serve as immunotherapy biomarkers.

4. Discussion

As tumor suppressor genes, GIMAP genes have been confirmed to affect tumor apoptosis [30,31], and their expression were at a low level in various cancer tissues and cell lines [32–34]. Some studies showed that GIMAP genes were highly expressed in human T-cell acute lymphoblastic leukemia, and the aberrant activation of GIMAP genes enhancer made a contribution to the development of T-cell leukemia [35]. However, the clinical significance of GIMAP family genes in LUAD remain unclear. In our study, we explored the expression, mutation, prognostic value of GIMAP family genes and the relationship with immune microenvironment in LUAD.

In this study, GIMAP family genes were found significantly low expressed in LUAD tissues, which were negatively correlated with T stage, suggesting a potential link between GIMAP expression and tumor stage. Consistent with these results, a pilot microarray analysis of 6 cases of NSCLC revealed that GIMAP family genes expression in tumor tissues were lower than in adjacent non-tumor tissues [36]. A recent study showed that GIMAP1, GIMAP5, GIMAP6, GIMAP7 and GIMAP8 expression were significantly lower in breast tumor tissues [37]. Our findings corroborated these observations, showing downregulation of GIMAP1, GIMAP2, GIMAP4, GIMAP5, GIMAP6, GIMAP7 and GIMAP8 in tumor tissues. Furthermore, we explored the prognostic value of GIMAP family genes in LUAD patients, which showed that high espression of GIMAP genes were associated with longer survival.

The components and hospitable properties of tumor microenvironment significantly influence tumor progression, especially immune components [38]. GIMAP genes were highly expressed in immune cells and closely correlated with the immune-related biological process such as T cell differentiation, peripheral lymphocytes apoptosis, and thymocyte development [39–42]. Studies have shown that GIMAP5 was essential for the inactivation of glycogen synthase kinase 3β (GSK3β) after T cell activation. In the absence of GIMAP5, constitutive GSK3β activity limited c-Myc induction, thereby limiting the proliferation of productive $CD4^+$ T cells [43]. In our study, we also found that GIMAP family genes significantly correlated with immune cell infiltration (B cells, $CD8^+$ T cells, $CD4^+$ T cells, macrophages, neutrophils, and dendritic cells) and immune checkpoint molecules (CD274, CTLA4, HAV, IDO1, PDCD1, CD8A, CXCL10, CXCL9, GZMA, GZMB, IFNG, PRF1, TBX2, TNF). Notably, GIMAP4 exhibited the strongest positive correlation with CD274 expression, while GIMAP5 exhibited the strongest positive correlation with PDCD1 expression. Immune cell infiltration and immune checkpoint molecules expression were important components of tumor microenvironment and form the foundation for tumor immunotherapy [44–46]. Together, these results suggested that the GIMAP genes may have a positive effect on immunotherapy. In the immunotherapy cohort of LUAD and melanoma, we found that GIMAP genes expression level were closely related to immunotherapy response. In conclusion, this study demonstrates that GIMAP genes contribute to predicting the clinical outcomes and immunotherapy response. The excellent performance and applicability of GIMAP family genes highlighted its advantages and reliability as a clinical evaluation tool.

5. Limitation

There are some limitations in our study. Firstly, all data analyzed in this study were obtained from online databases. Although the current online database has powerful biological analysis capabilities, the results may be biased due to different databases. Secondly, further basic experimental studies are needed to validate our findings and explore the potential mechanisms.

Table 2
Association between GIMAP family genes and immune cell infiltration. (TIMER database).

Immune cell	GIMAP1 cor	p	GIMAP2 cor	p	GIMAP4 cor	p	GIMAP5 cor	p	GIMAP6 cor	p	GIMAP7 cor	p	GIMAP8 cor	p
B cell	0.544	***	0.406	***	0.454	***	0.469	***	0.401	***	0.502	***	0.37	***
$CD8^+$T cell	0.309	***	0.495	***	0.59	***	0.548	***	0.559	***	0.541	***	0.425	***
$CD4^+$T cell	0.718	***	0.398	***	0.537	***	0.511	***	0.439	***	0.539	***	0.521	***
Macrophage	0.446	***	0.402	***	0.537	***	0.452	***	0.549	***	0.392	***	0.501	***
Neutrophil	0.57	***	0.576	***	0.714	***	0.617	***	0.636	***	0.552	***	0.564	***
Dendritic cell	0.651	***	0.619	***	0.735	***	0.609	***	0.629	***	0.556	***	0.544	***

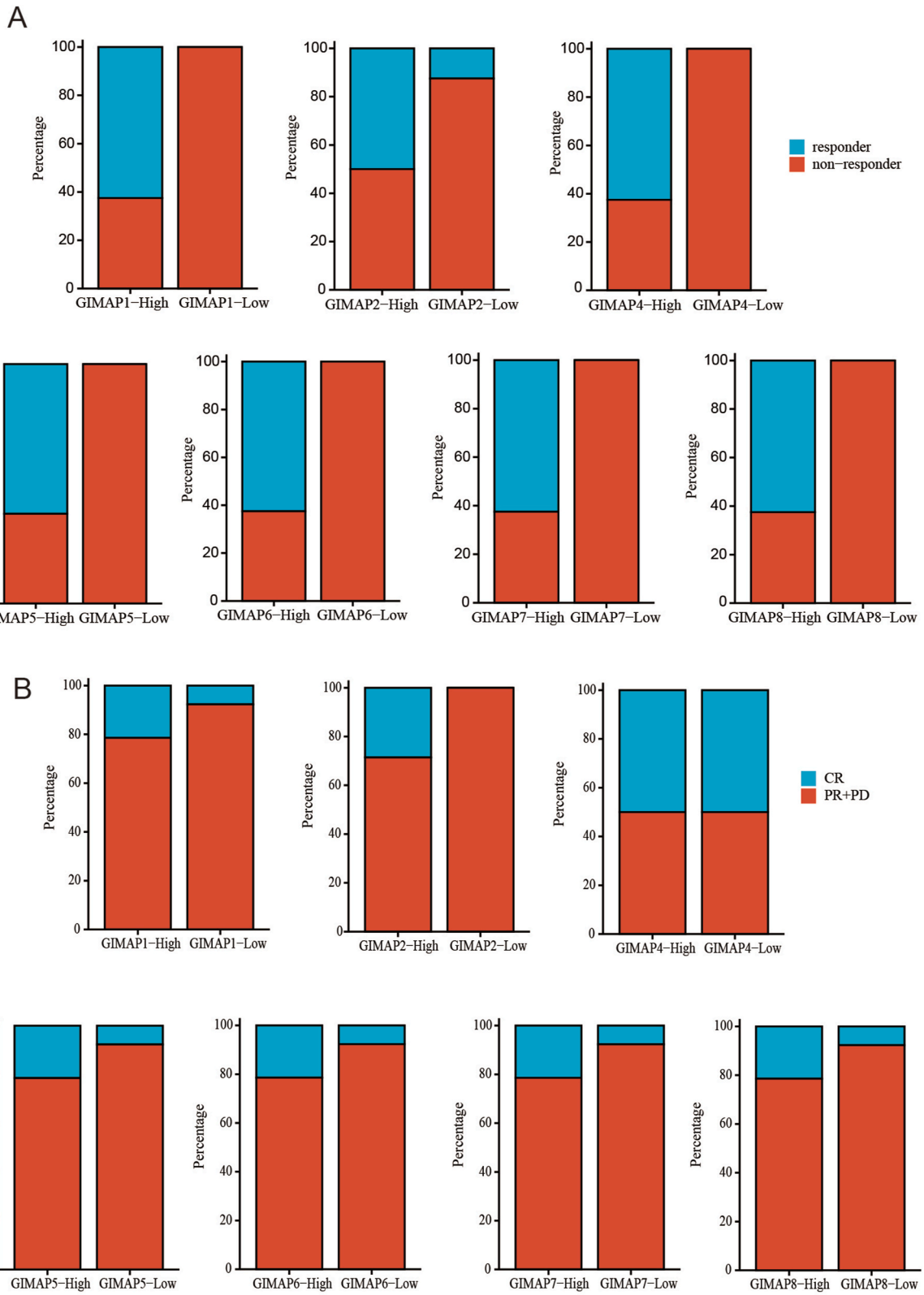

Fig. 6. Association between GIMAP genes expression and immunotherapy response. **A:** Association between GIMAP genes expression and immunotherapy response in LUAD patients (GEO126044).
B: Association between GIMAP genes expression and immunotherapy response in melanoma patients (GEO 78220).

6. Conclusion

In conclusion, we found that GIMAP family genes were low in LUAD tissues. Most GIMAP genes were closely related to age, tumor grade and T stage. Patients with high GIMAP family genes expression had a significant longer OS. In addition, GIMAP family genes were highly enriched in immune-related biological processes and positively correlated with immune cell infiltration and immune checkpoint molecules. Furthermore, GIMAP family genes high expression showed therapeutic responses to immunotherapy in LUAD and melanoma. Collectively, these findings suggest that GIMAP family genes may play a critical role in anti-tumor immunity. However, further investigation is warranted to elucidate the precise mechanisms by which these genes regulate immune responses.

Ethical approval

This study was approved by the institutional review board and ethics committee of The Second Affiliated Hospital of Guangzhou Medical University. It was determined to be a retrospective analysis of publicly available data, and written informed consent was waived.

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Data availability statement

All data examined in this study were obtained from the TCGA and GEO database. The data supporting the results of this study are available from the corresponding author on reasonable request.

CRediT authorship contribution statement

Yanyan Zhang: Writing – original draft, Conceptualization. **Shan Liu:** Visualization, Formal analysis, Data curation. **Deyi Liu:** Visualization, Formal analysis, Data curation. **Zhuxiang Zhao:** Writing – review & editing, Funding acquisition. **Haifeng Song:** Writing – review & editing, Project administration. **Kunwei Peng:** Writing – review & editing, Project administration, Funding acquisition.

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.

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N/A.

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