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Research article

Identification of GMFG as a novel biomarker in IgA nephropathy based on comprehensive bioinformatics analysis

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ABSTRACT

Background: IgA nephropathy (IgAN) stands as the most prevalent form of glomerulonephritis and ranks among the leading causes of end-stage renal disease worldwide. Regrettably, we continue to grapple with the absence of dependable diagnostic markers and specific therapeutic agents for IgAN. Therefore, this study endeavors to explore novel biomarkers and potential therapeutic targets in IgAN, while also considering their relevance in the context of tumors.

Methods: We gathered IgAN datasets from the Gene Expression Omnibus (GEO) database. Subsequently, leveraging these datasets, we conducted an array of analyses, encompassing differential gene expression, weighted gene co-expression network analysis (WGCNA), machine learning, receiver operator characteristic (ROC) curve analysis, gene expression validation, clinical correlations, and immune infiltration. Finally, we carried out pan-cancer analysis based on hub gene.

Results: We obtained 1391 differentially expressed genes (DEGs) in GSE93798 and 783 DGEs in GSE14795, respectively. identifying 69 common genes for further investigation. Subsequently, GMFG was identified the hub gene based on machine learning. In the verification set and the training set, the GMFG was higher in the IgAN group than in the healthy group and all of the GMFG area under the curve (AUC) was more 0.8. In addition, GMFG has a close relationship with the prognosis of malignancies and a range of immune cells.

Conclusions: Our study suggests that GMFG could serve as a promising novel biomarker and potential therapeutic target for both IgAN and certain types of tumors.

1. Introduction

IgAN stands as the most common form of glomerulonephritis globally and represents a significant contributor to the progression of end-stage renal disease (ESRD) [1,2]. Within 20–30 years post-diagnosis, 30–40% of individuals afflicted with IgA nephropathy will progress to ESRD, resulting in substantial financial burdens for families, society, and even entire nations [3]. The prevalence of IgA nephropathy varies by country, with the highest occurrence rate observed in Asian countries, accounting for 50% of primary glomerulonephritis cases [4]. The current diagnostic gold standard for IgAN, kidney puncture biopsy, is universally shunned by patients due to its invasive nature, potentially leading to an underestimation of IgAN prevalence. Hence, it is imperative to identify

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effective and reliable biological markers that can serve as non-invasive means of diagnosing IgAN. The recent surge in genome-wide association studies (GWAS) has unveiled links between diseases and susceptibility genes, offering fresh insights into the search for diagnostic markers in IgAN.

As specified in the glomerulonephritis medical practice recommendations that Kidney Disease Improving Global Outcomes (KDIGO) released in 2021 [5], systemic corticosteroid treatment and clinical trial enrollment are recommended for patients with high risk of progressing to ESRD. However, there remains ongoing debate regarding the efficacy of these interventions. Therefore, it is imperative that we explore novel therapeutic approaches. In the last ten years, more and more biologics have been employed in the treatment of immune-related conditions, such as infliximab for ulcerative colitis [6] and rituximab for membranous nephropathy [7]. Despite IgA nephropathy being an immune-related disease, there are currently no widely recognized biological agents specifically tailored for its treatment. In order to facilitate the development of biologics specifically designed to treat IgAN, it is imperative that we continue to explore therapeutic targets intimately linked to the disease's pathophysiology. The GEO database, which offers a wealth of sequencing data related to diseases, may serve as a valuable platform for uncovering potential therapeutic targets in IgAN.

Remarkably, several studies have uncovered a connection between glomerular disorders and a diverse range of cancers, with a particular emphasis on hematological and solid malignancies [8]. IgA nephropathy, as the most prevalent glomerular condition, has been linked to solid respiratory tract malignancies, cutaneous T-cell lymphoma, and kidney cell carcinoma [8]. Furthermore, an increasing amount of data suggests that individuals with IgAN have a higher susceptibility to developing cancer compared to their healthy counterparts [9].

In this study, datasets from the GEO, GTEx, and TCGA databases were acquired to delve into the intricate relationship between IgAN and various malignancies. Our approach involved a multi-faceted analysis. Initially, we employed differential gene expression analysis, machine learning, and WGCNA to identify key genes at the core of this relationship. Subsequently, we conducted ROC analysis, gene expression validation, clinical correlation assessments, and immune infiltration analysis to validate the significance of the core gene in IgAN. Finally, to underscore the pivotal role of the core gene in malignancies, a comprehensive pan-cancer analysis was carried. In summary, this study holds the potential to provide fresh insights into the intricate interplay between IgAN and cancer. Additionally, it may help identify a prospective biomarker and therapeutic target, not only in the context of IgAN but also across a

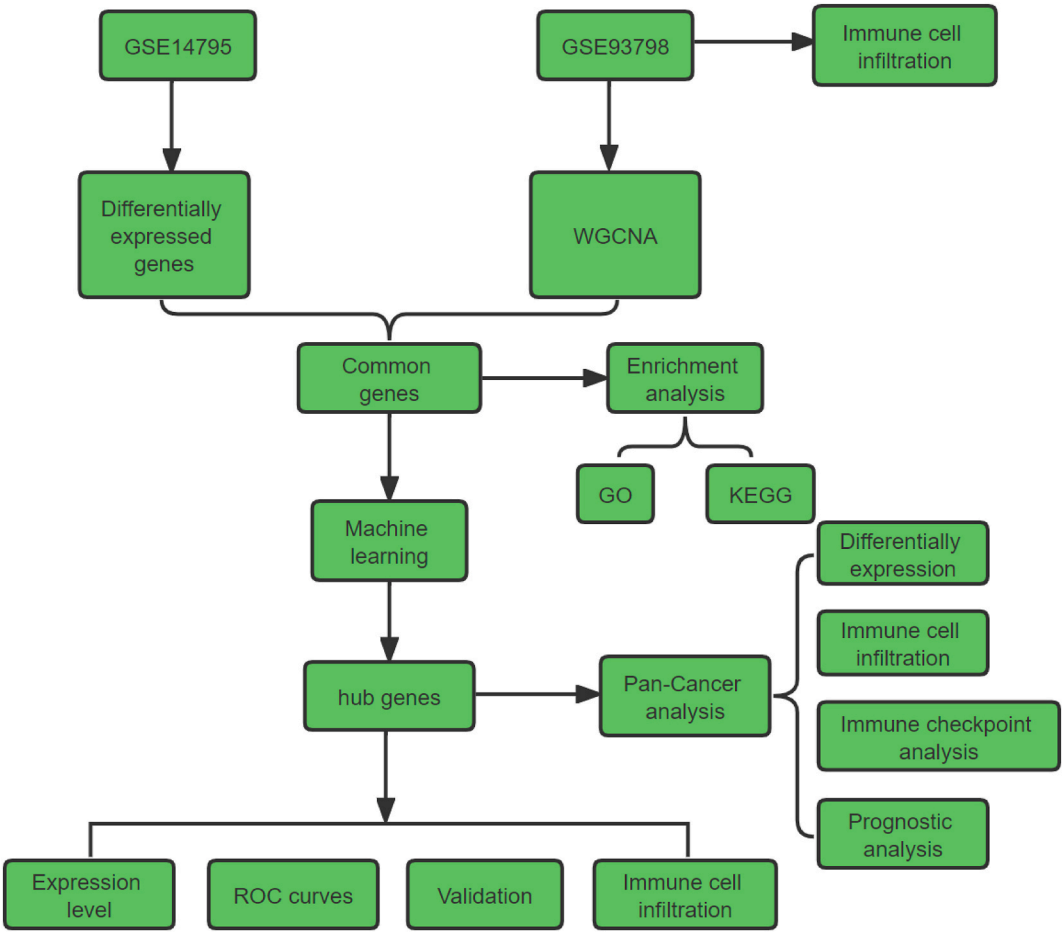

Fig. 1. The sketch of this study.

spectrum of malignancies. For a detailed depiction of the study's methodology, please refer to Fig. 1.

2. Materials and methods

2.1. Collecting and processing data

The datasets (GSE14795, GSE93798, and GSE37460) were obtained from the GEO database (https://www.ncbi.nlm.nih.gov/geo/) [10]. A summary of the specifics can be found in Table 1. To identify differentially expressed genes (DEGs) in GSE14795, we employed the R package "limma" [11]. The criteria used for this analysis were $|\log FC| > 0.5$ and P-value <0.05. The modules in GSE93798 that exhibited the strongest association with IgAN were selected using the "WGCNA" method [11]. The validation dataset GSE37460 was utilized to validate the main genes expression and their diagnostic utility.

2.2. GO and KEGG pathway enrichment analyses

We utilized the "jvenn" tool (http://jvenn.toulouse.inra.fr/app/example.html) [12] to select interacting genes between GSE14795 and GSE93798. The enrichment analyses were conducted by using the Database for Annotation, Visualization, and Integrated Discovery (DAVID; https://david.ncifcrf.gov/tools.jsp) based on aforementioned genes [13].

2.3. Selecting and validation of diagnosis biomarkers in IgAN

Three machine learning algorithms, namely Random Forest (RF) [14], LASSO [15], and SVM-RFE [16], were employed to identify the primary IgAN biomarkers. For RF, we used the "randomForest" [17] and "caret" [18] R packages. The "glmnet" R package was used to perform LASSO [19]. The "e1071" R package was used to conduct SVM-RFE [20]. Genes were considered important if they were identified by all three techniques. ROC analysis was used to evaluate the diagnostic significance of these significant genes. Subsequently, GSE37460 was then employed as the validation dataset to validate the expression levels and diagnostic usefulness of these significant genes.

2.4. Clinical correlation analysis

The Nephroseq V5 database (https://v5.nephroseq.org) [21] contains clinical traits and gene expression data. To investigate the correlation among the important genes and clinical characteristics of IgAN, we integrated these genes into the database.

2.5. Immune infiltration analysis

We employed the "CIBERSORT" algorithm [22] to investigate the connection among immune infiltrated cells, IgAN, and the expression levels of key genes.

2.6. Pan-cancer analysis

Pan-cancer datasets were obtained from the University of California, Santa Cruz (UCSC) (https://xenabrowser.net/) [23]. Differential expression analyses of the main genes were conducted in various cancer types using R software (version 4.1.3) [24]. To explore the association between important genes expression and malignancies prognosis, cox regression analysis was constructed using the R package "survival" [25]. We discovered the association between crucial genes and immune infiltrated cells in malignancies using the TIMER [26], xCELL [27], and EPIC algorithms [28]. Finally, in order to ascertain the connection between significant genes and previously investigated immune checkpoint genes, we lastly ran Pearson's correlation analysis.

3. Results

3.1. Identification of the common genes in IgAN

We obtained two datasets, GSE14795 and GSE93798, for use as training sets in identifying crucial genes in IgAN. The analysis of differential gene expression in the GSE14795 dataset resulted in 783 DEGs. Fig. 2 (A, B) displays a heatmap and a corresponding volcano plot to visualize these findings. Meanwhile, WGCNA network was constructed using the GSE93798 dataset, leading to the

Table 1
Microarray datasets of IgA nephropathy.

Series	Platform	GeneChip	Samples
GSE14795	GPL96	[HG-U133A] Affymetrix Human Genome U133A Array	20
GSE93798	GPL22945	[HG-U133_Plus_2] Affymetrix Human Genome U133 Plus 2.0 Array	42
GSE37460	GPL14663	Affymetrix GeneChip Human Genome HG-U133A Custom CDF	35

retrieval of 1391 genes by selecting the brown and turquoise modules with the strongest association with IgAN (Fig. 3A–F). Ultimately, by examining the intersection of DGEs and module genes, we identified 69 common genes, as depicted in Fig. 4A.

3.2. GO and KEGG pathway enrichment analysis

Based on the common genes, we performed enrichment analysis for KEGG and GO analysis. The Molecular Function (MF), Cellular Component (CC), and Biological Process (BP) components were included in the GO results [29]. Fig. 4B illustrates the top five terms in each component. Among the BP terms, the positive regulation of cell migration and proliferation exhibited an abundance of these common genes. In the CC category, cytosol, nucleus, and cytoplasm were the top three terms. Regarding MF, the common genes were connected to protein and protein kinase binding. The JAK-STAT signaling pathway may be crucial in the development of IgAN, according to the findings of the KEGG pathway.

3.3. Identification of GMFG as the biomarker in IgAN and its clinical correlation analysis

We utilized three analysis techniques (Random Forest, SVM-RFE, and LASSO) to select the core gene in IgAN among genes displaying the same expression patterns in the training sets (Fig. 5A–G). Remarkably, the three algorithms produced one overlapping gene, GMFG (Fig. 5H), suggesting that GMFG may be the primary IgAN biomarker. Subsequently, we conducted a clinical correlation study of GMFG using the Nephroseq V5 database. The results revealed a positive association between GMFG and serum creatinine, and an inverse relationship with age and glomerular filtration rate (GFR) (Fig. 6A–C).

3.4. Validation of the expression level and assessment of the diagnostic value of GMFG

To validate the expression level and diagnostic utility of GMFG, we used GSE14795 and GSE93798 as training sets (Fig. 7A–D). The findings demonstrated a statistically significant increase of GMFG expression in IgAN group, with both AUC values exceeding 0.8, indicating a strong diagnostic potential for GMFG in IgAN. As a validation set, we employed GSE37460 to verify GMFG expression and diagnostic utility (Fig. 7E–F). Once again, the results indicated elevated GMFG expression in IgAN and an AUC exceeding 0.8.

3.5. Immune infiltration analysis in IgAN

Realizing that IgAN is an autoimmune illness and the most common primary glomerular disease, we conducted an immune infiltration analysis to assess the extent of immune cell invasion in IgAN and the relationship between GMFG and immune cells (Fig. 8A–E). The expression levels of neutrophils, resting memory CD4 T cells, activated NK cells, resting dendritic cells, macrophages M2, naive B cells, macrophages M1, CD8 T cells, and resting NK cells were different between IgAN and healthy ($P < 0.05$) (Fig. 8C). Notably, the expression of CD8 T cells, activated NK cells, macrophages M2, resting dendritic cells, and macrophages M1 increased, while others decreased in IgAN. Furthermore, the strongest associations were observed between GMFG and neutrophils and resting dendritic cells (Fig. 8E).

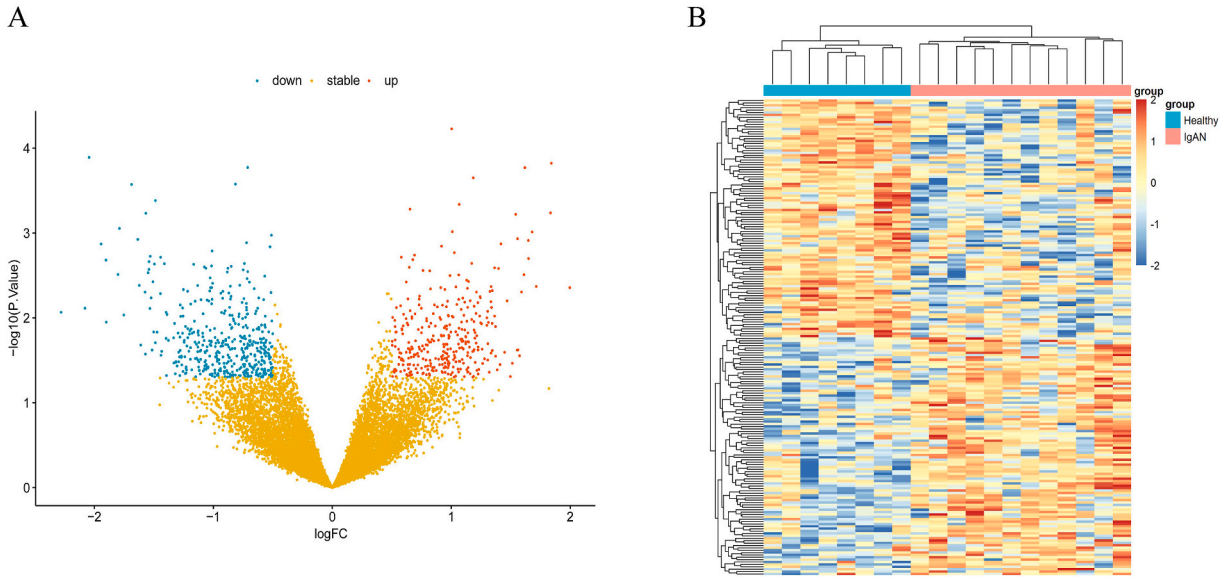

Fig. 2. The volcano plot (A) and heatmap graph (B) of GSE14795.

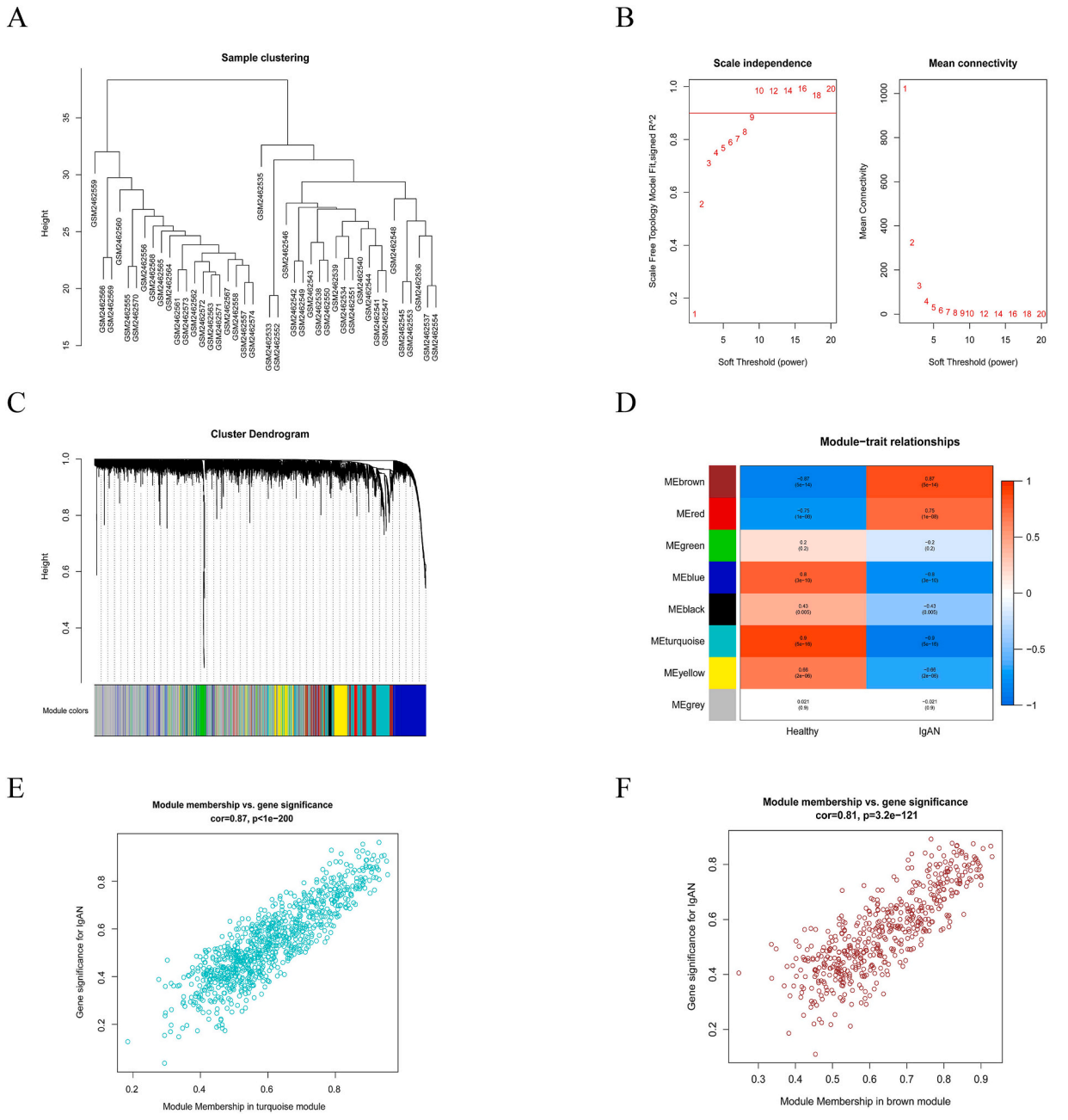

Fig. 3. The WGCNA network of GSE93798. (A) The sample clustering of GSE93798. All samples were divided into two clusters. (B) The identification of optimal soft threshold ($\beta = 9$). (C) The gene clustering dendrogram and corresponding module colors. (D) Module-trait relationships. (E–F) Module membership vs. gene signification scatter plot of IgAN in turquoise and blue modules.

3.6. The results of pan-cancer analysis

Our study investigated GMFG expression across various malignancies using tumor-related datasets from TCGA and GTEx databases (Fig. 9A–B). Elevated GMFG expression levels were observed in several tumors, including KIPAN, STES, GBM, ESCA, HNSC, STAD, KIRC, and CHOL, across 26 distinct tumor expression datasets. Combining datasets from 34 cancers confirmed increased GMFG expression levels in GBM, OV, LIHC, STES, CHOL, STAD, HNSC, KIRC, LGG, SKCM, GBMLGG, PAAD, TGCT, and KIPAN, suggesting its potential oncogenic role in these cancers. Prognostic analysis using UCSC database showed high GMFG expression negatively correlated with OS in tumors such as LGG, KIPAN, LAML, GBMLGG, and UVM, while positively associated with OS in tumors like BRCA, CESC, and LUAD (Fig. 10A–C). Furthermore, analysis using TIMER database revealed associations between GMFG expression

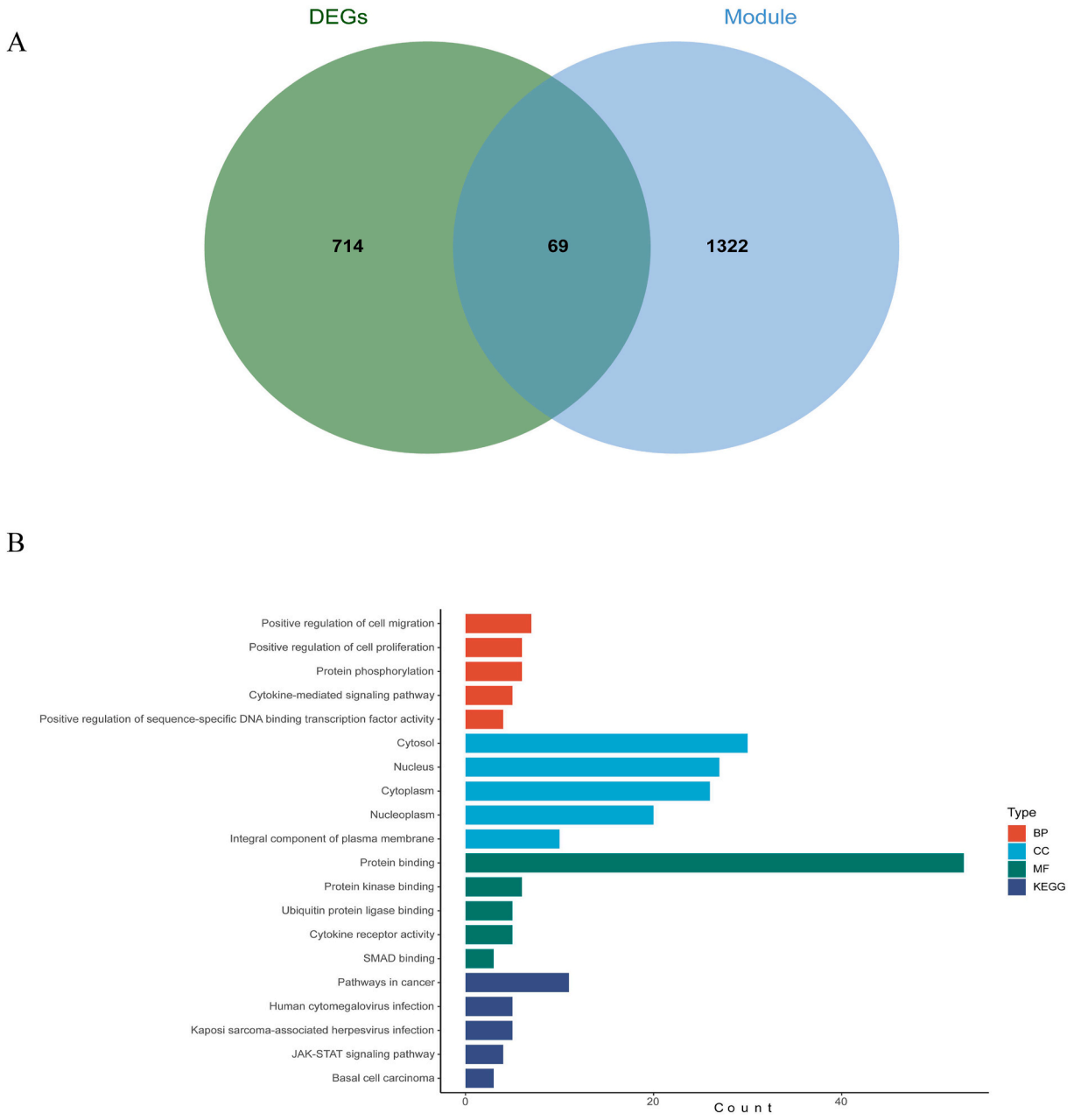

Fig. 4. (A) The identification of 69 overlapped genes between selected modules and DEGs. (B) The top 5 terms in GO and KEGG pathway enrichment analysis.

and immune cell infiltration levels across various malignancies, with significant links observed in LGG, COAD, SKCM-M, and others (Fig. 11A–C). Evaluation of common immunological checkpoints also showed close correlation with GMFG expression in tumors (Fig. 11D).

4. Discussion

IgAN stands as the most prevalent form of glomerulonephritis globally, and it shares characteristics with autoimmune disorders, often leading to a challenging prognosis [30]. The cornerstone of IgAN diagnosis remains kidney biopsy. However, IgAN can manifest with a spectrum of symptoms, ranging from asymptomatic microscopic hematuria to a rapid decline in renal function accompanied by persistent proteinuria [31]. Due to the invasive nature of kidney biopsy, many patients with mild symptoms tend to defer the procedure, resulting in delayed diagnosis, often leading to the presence of stage 3 or stage 4 chronic kidney disease (CKD) by the time of

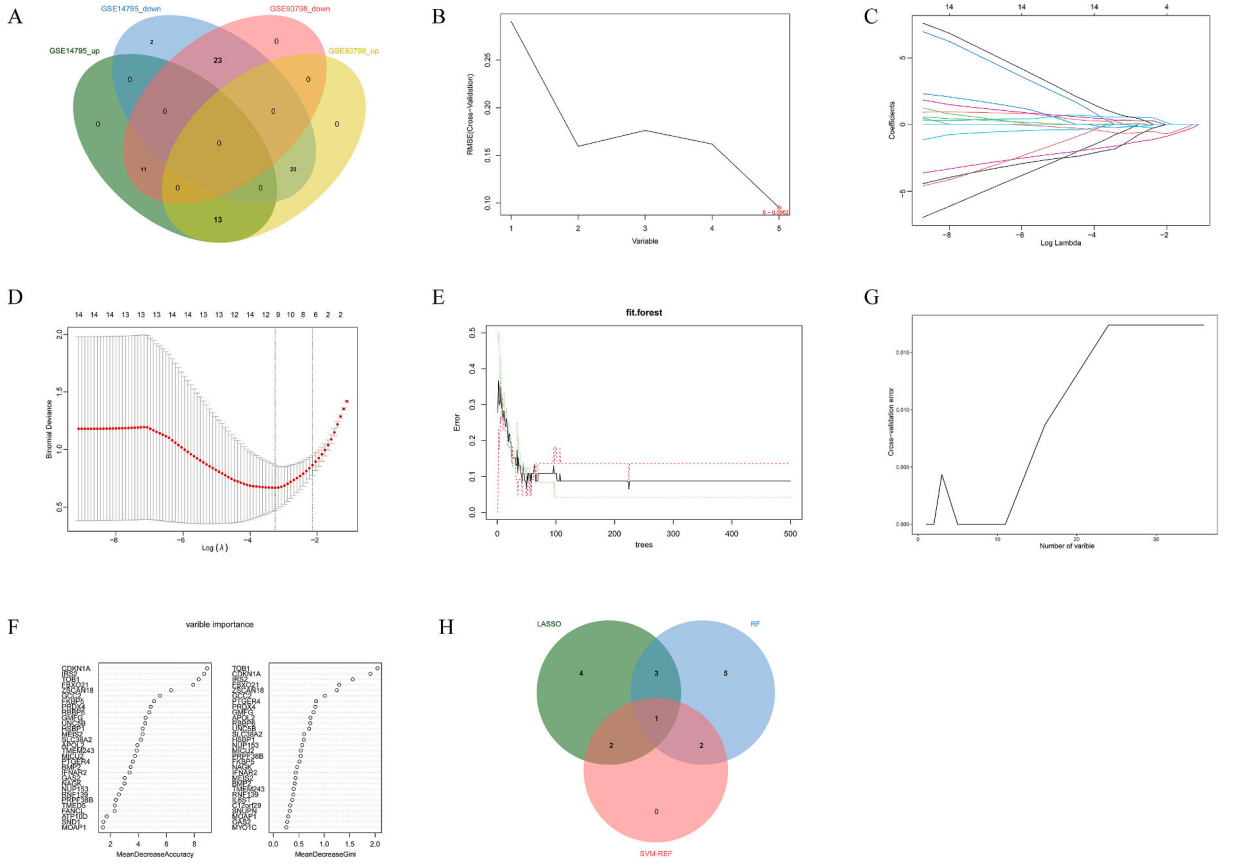

Fig. 5. The selection of special genes. (A) The confirmation of common expression pattern genes in GSE14795 and GSE93798. (B) The biomarkers selection by the support vector machine-recursive feature elimination (SVM-RFE) technique. (C–D) The feature genes identification by using the least absolute shrinkage and selection operator (LASSO) model. (E–G) The selection of significant genes by Random Forest. (H) The Venn graph of three machine learning results.

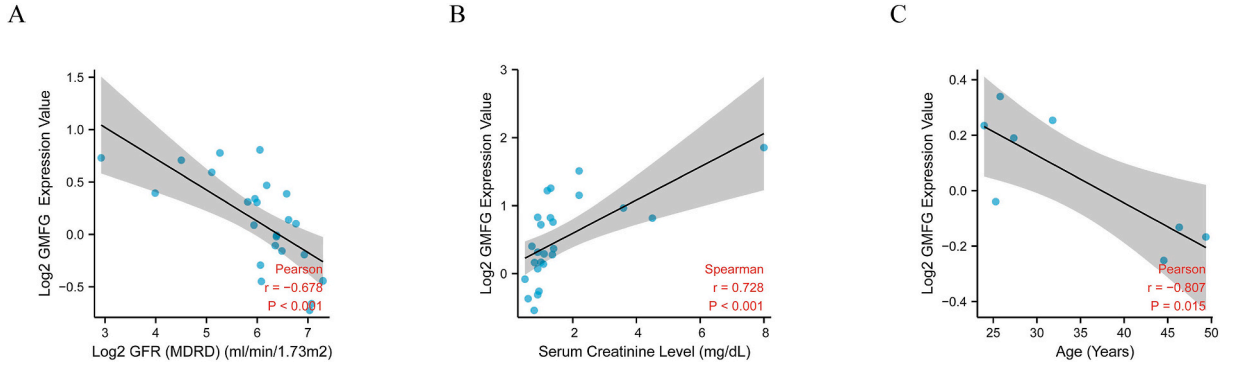

Fig. 6. The clinical correlation analysis of GMFG. (A) The expression of GMFG is negatively connected with GFR. (B) The expression of GMFG is positively correlated with serum creatine level. (C) The expression of GMFG is negatively connected with age.

biopsy [32]. Additionally, owing to the absence of specific drugs, the primary treatment for IgAN is currently optimal supportive care, which, regrettably, does not prevent the progression of IgAN to end-stage renal disease [33]. As a result, targeted therapy has emerged as a modern approach for treating immune-related disorders. Although targeted treatment plans for IgA nephropathy are still under development, the search for novel biomarker genes for early IgAN diagnosis and targeted therapy is of paramount importance.

The field of molecular research has undeniably witnessed explosive growth over the past decade, with genome-wide analyses playing a prominent role in uncovering novel insights into disease pathophysiology and laying the groundwork for more accurate early disease detection and management [34]. In this context, the GEO database stands as a freely accessible repository, housing a wealth of

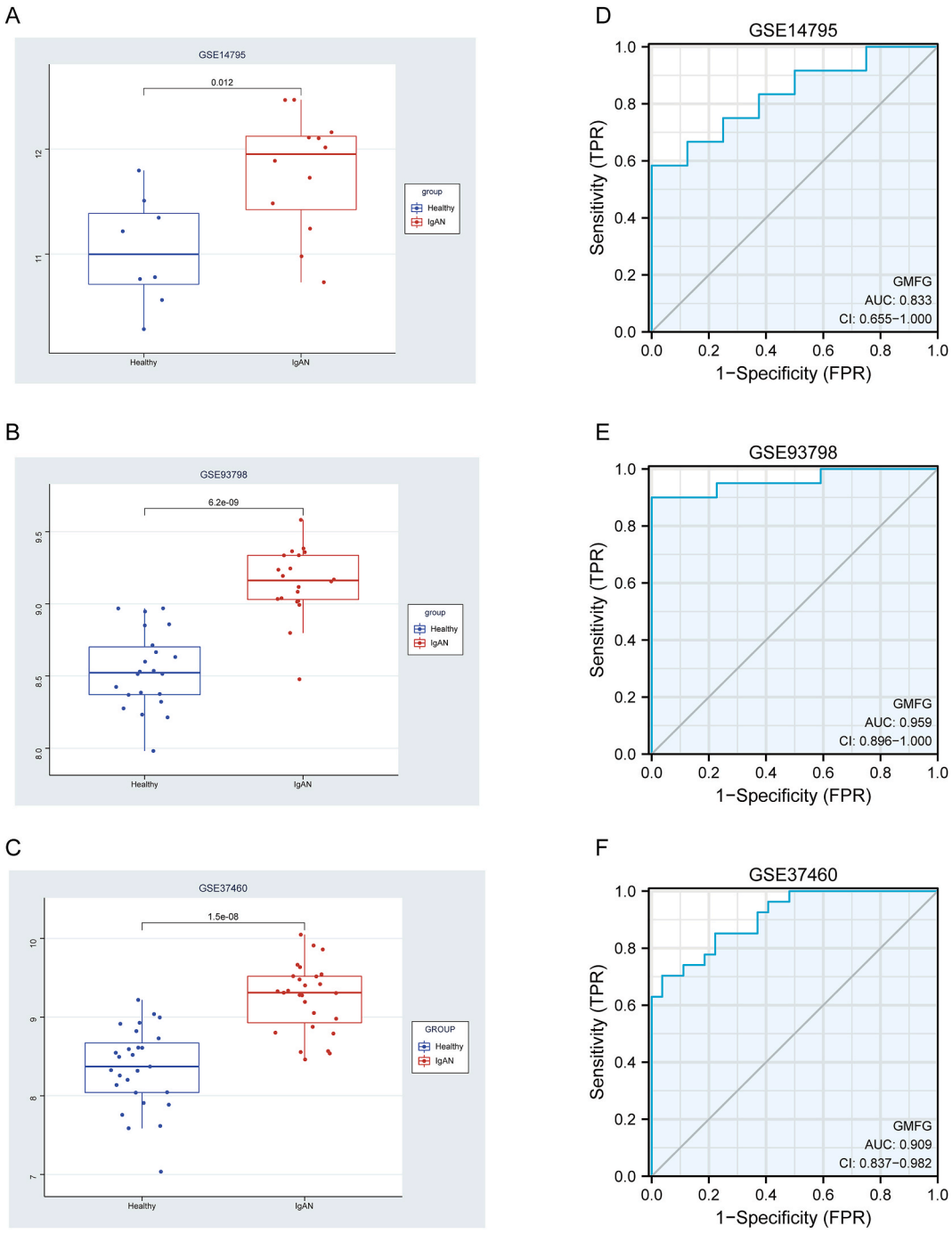

Fig. 7. The expression validation and ROC analysis of GMFG in GSE93798, GSE14795, and GSE37460. A–C: The expression level of GMFG is up-regulated among the three datasets. D–F: The AUCs of GMFG are more than 0.8 among the three datasets.

high-throughput microarray genomic datasets and second-generation sequence datasets. It serves as a pivotal platform for delving into the molecular underpinnings of disease development [35]. The utility of the GEO database is evident in the multitude of studies that have harnessed its potential to explore target genes and the underlying mechanisms of various diseases, including conditions like rheumatoid arthritis [36], inflammatory bowel disease [37], and different types of tumors [38]. In our pursuit of potential target genes for the early diagnosis and management of IgAN, we have adopted a comprehensive approach in this study. We amalgamated WGCNA, machine learning techniques, and immune infiltration methodologies to conduct a thorough and in-depth examination of IgAN-related datasets within the GEO database.

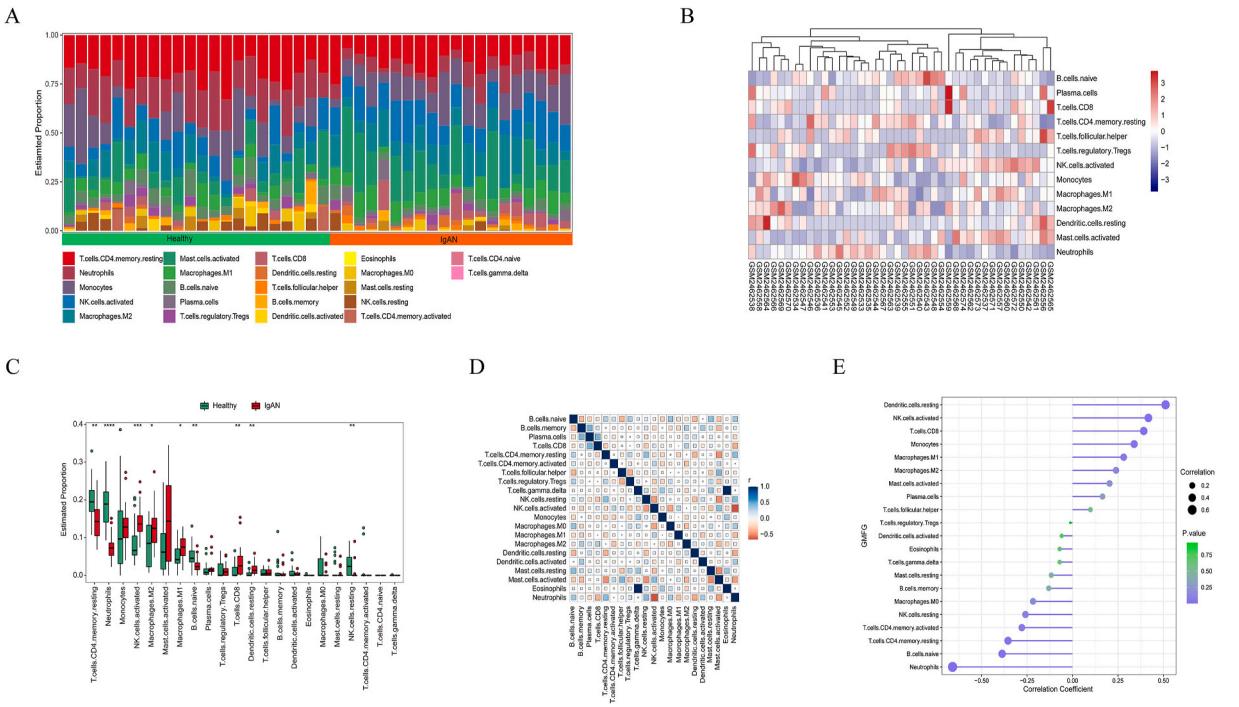

Fig. 8. The immune infiltration analysis. (A) The stacked chart of 22 immune cell subpopulations comparing IgAN and healthy samples. (B) The heatmap of 22 immune cell subpopulations in samples of GSE93798. (C) The bar graph indicates the different expression levels of 22 immune cells in IgAN versus healthy samples. (D) The heatmap performed the relationship between 22 immune cells in IgAN and healthy samples. (E) The correlation between immune cells and GMFG.

In our study, we conducted an intersection analysis between the 1391 module genes from the GSE93798 dataset and the 783 DGEs from the GSE14795 dataset, identifying 69 common genes for further investigation. Subsequently, we carried GO and KEGG pathway enrichment analyses. The KEGG results were enriched in the Janus kinase-signal transducer and activator of transcription (JAK-STAT) signaling pathway, pathways associated with cancer, Kaposi sarcoma-associated herpesvirus infection, and human cytomegalovirus infection. Notably, the GO analysis indicated that all of the identified genes were correlated with processes related to the positive regulation of cell proliferation and migration, cell components such as the cytosol and nucleus, and functions involving the binding of proteins and protein kinases. The JAK-STAT signaling pathway is a critical intracellular route that responds to extracellular signals, such as chemokines and cytokines [39]. Several studies have suggested that the JAK-STAT pathway is active in IgAN and may contribute to the development of galactose-deficient IgA1, a key component in the pathogenesis of IgAN [39]. As such, these shared genes may indeed play a pivotal role in the pathogenesis of IgAN, particularly through their involvement in the JAK-STAT pathway.

We employed three machine-learning methods to pinpoint the hub gene, and the results consistently pointed to GMFG as the key gene. To validate the significance of GMFG as a potential biomarker in IgAN, non-rank sum tests and ROC analysis were performed on both the training and validation datasets. These analyses aimed to confirm GMFG's expression level and its diagnostic utility in IgAN. The findings from both datasets consistently demonstrated that IgAN exhibited higher levels of GMFG expression compared to control groups. Notably, the AUC values in the ROC analysis exceeded 0.8, underscoring the strong potential of GMFG as a biomarker for early diagnosis and treatment of IgAN. Furthermore, we conducted clinical correlation analyses on GMFG, which unveiled valuable insights. GMFG expression levels exhibited a negative correlation with age and GFR but a positive correlation with serum creatinine. These results suggest that GMFG expression levels are closely associated with the severity of IgAN. Consequently, GMFG emerges as a candidate diagnostic marker and a valuable prognostic indicator in the context of IgAN.

Glia maturation factor (GMFG), primarily synthesized in inflammatory cells, is now recognized as a novel member of the actin depolymerization factor/cofilin superfamily of proteins [40]. Research indicates that GMFG plays a pivotal role in regulating the chemotaxis of neutrophils, lymphocytes, and monocytes, making it an integral component of the body's inflammatory response [41]. IgA nephropathy (IgAN) is well-documented to typically develop in the wake of pathogenic invasions of the mucosa, and the inflammatory response holds a central position throughout the course of the disease [42]. When pathogens infiltrate the mucosal barrier, GMFG might act as a chemoattractant, guiding neutrophils and T cells to the site of infection. Subsequently, these immune cells release various inflammatory factors, initiating a cascade of inflammatory reactions. Moreover, our study has demonstrated a high expression of GMFG in IgAN. Based on these findings, it is reasonable to hypothesize that GMFG may substantially contribute to the onset of IgAN by triggering robust inflammatory responses. This points to the potential importance of GMFG in the pathogenesis of IgAN, particularly in the context of orchestrating heightened inflammatory reactions.

IgAN stands as the most prevalent form of primary glomerulopathy, and it also presents characteristics of an autoimmune condition

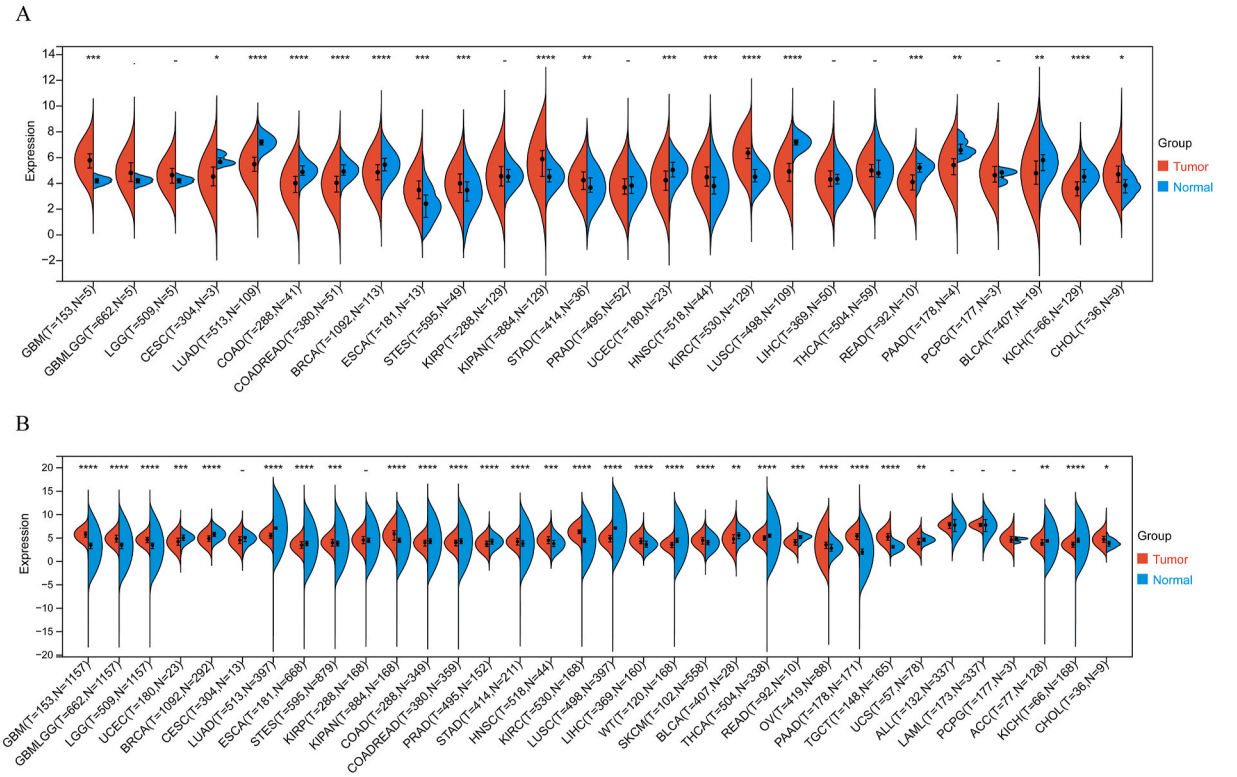

Fig. 9. The expression levels of GMFG in cancers. (A) GMFG expression levels across cancer types in the TCGA dataset. (B) GMFG expression levels across cancer types in the TCGA and GTEx datasets.

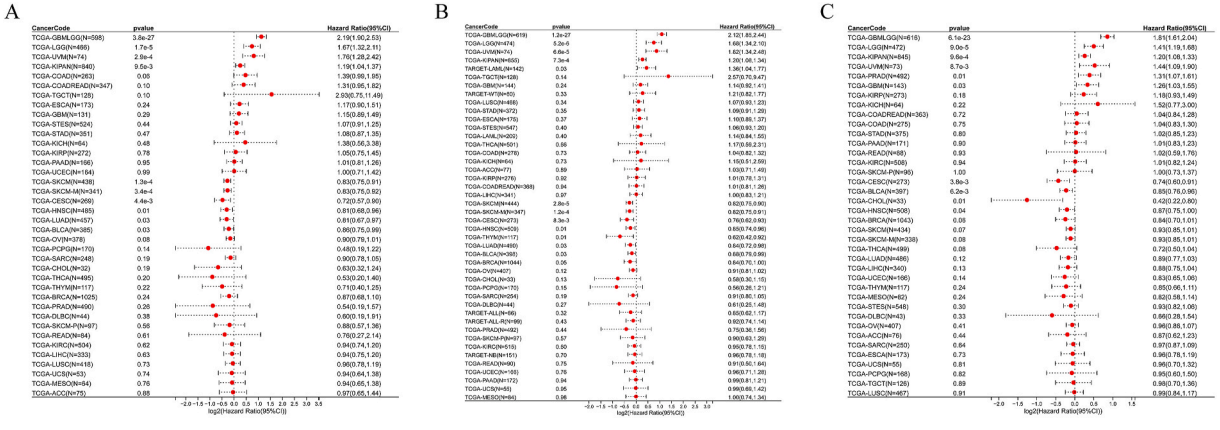

Fig. 10. The relationship between CYFIP2 and pan-cancer prognosis. (A)The correlation between GMFG expression and DSS in tumors. (B) The correlation between GMFG expression and OS in tumors. (C) The correlation between GMFG expression and PFI in tumors.

[43]. To gain insights into the extent of immune cell infiltration in IgAN, we conducted an immune infiltration study using the dataset GSE93798. The expression of several immune cell types, such as resting memory CD4 T cells, neutrophils, activated NK cells, resting dendritic cells, macrophages M2, CD8 T cells, macrophages M1, naive B cells, and resting NK cells, was found to differ statistically significantly between the IgAN and control groups. The "multi-hit" hypothesis [44], posits that when B cells are activated by pathogens, they may produce significant quantities of Gd-IgA1, a key factor in the development of IgAN, which is associated with a decline in naive B cells [45]. Studies have also suggested that NK cells may contribute to the pathophysiology of IgAN by promoting an inflammatory environment [46], which could explain their elevated presence in IgAN. Furthermore, previous research on IgAN has pointed to the involvement of various immune cell types in the disease process, such as T cells and dendritic cells stimulating Gd-IgA1 production [47,48], and macrophage polarization leading to kidney fibrosis in IgAN [49]. In line with these findings, our research has

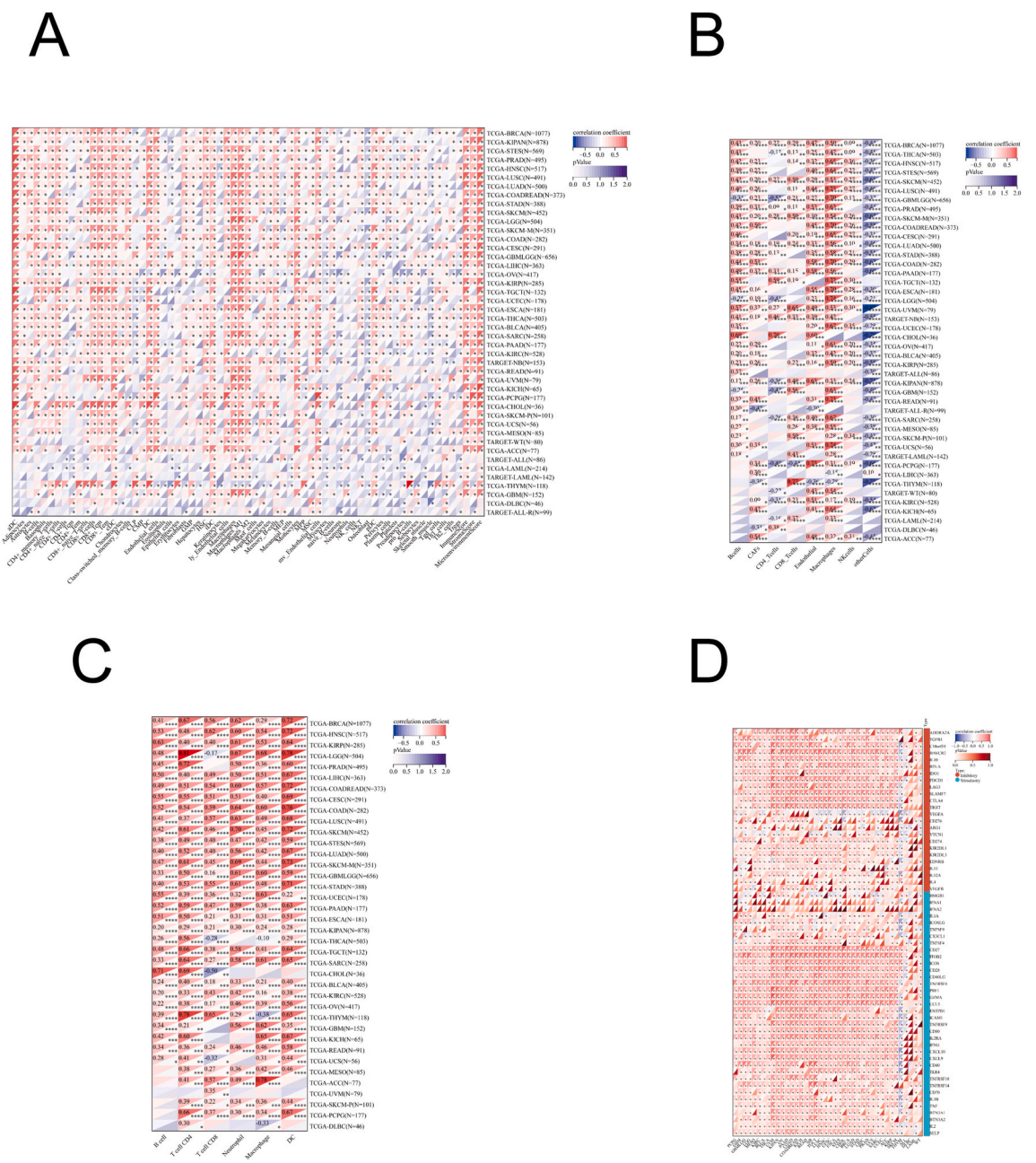

Fig. 11. The role of GMFG in cancer immune response. (A) xCELL immune score. (B) EPIC immune score. (C) TIMER immune score. (D) The correlation of GMFG with immune checkpoint genes. *p < 0.05, **p < 0.01, ***p < 0.001.

revealed strong correlations between GMFG and active NK cells, resting dendritic cells, neutrophils, and naive B cells, further bolstering the case for GMFG's potential as a biomarker in IgAN. These correlations suggest that GMFG may play a role in immune cell regulation in IgAN and could be a valuable indicator of disease activity and progression.

In a comprehensive pan-cancer investigation, these findings illustrate that GMFG plays diverse roles in various malignancies. Several studies have contributed to our understanding of GMFG's role in cancer. For instance, it has been shown to inhibit the growth of lung cancer by activating the p53 signaling pathway [50]. In the case of LGG, which exhibit higher levels of GMFG expression, it has been associated with worse overall survival [40]. Furthermore, GMFG has been found to play a critical role in the metastasis of epithelial ovarian cancer and colorectal cancer [51,52]. Analysis also revealed significant correlations between GMFG and various immune cell types, aligning with findings in IgAN. Additionally, GMFG showed strong associations with existing immunological checkpoint genes in tumors, suggesting its potential as a new immune checkpoint for cancer treatment.

While our study has extensively explored diagnostic biomarkers in IgAN and expanded its findings to pan-cancer analyses, it is

important to acknowledge certain limitations in our work. Firstly, despite our efforts to validate the biomarker in various datasets, it is crucial to conduct in vivo or in vitro experiments to further confirm the robustness and functional significance of GMFG as a potential biomarker. Secondly, as there has been no previous report on GMFG in the context of IgAN, more in-depth research is needed to investigate the underlying mechanisms through which GMFG may be involved in the pathophysiology of IgAN. This could illuminate its specific role in the disease. Thirdly, while the prognostic analysis of GMFG in IgAN shows promise, it is based on available data and requires further validation through additional clinical investigations to strengthen its reliability and applicability as a prognostic indicator. Addressing these limitations will be crucial for developing a more comprehensive understanding of GMFG's role in IgAN and its potential as a diagnostic and prognostic marker in both IgAN and cancer.

5. Conclusion

In summary, our study has identified GMFG as a significant diagnostic and prognostic marker not only in IgAN but also across various cancer types. This suggests that GMFG holds promise as a valuable diagnostic tool and a potential therapeutic target for IgAN and malignancies.

Ethics approval and consent to participate

Not applicable.

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Data availability statement

The datasets generated during the current study are available in the NCBI GEO (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi) and the University of California, Santa Cruz (UCSC, https://xenabrowser.net/).

CRediT authorship contribution statement

Xiaoqi Deng: Conceptualization. **Yu Luo:** Formal analysis. **Meiqi Lu:** Formal analysis. **Yun Li:** Formal analysis. **Li Ma:** 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.

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