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Research on Lumican (LUM) Expression Characteristics in Pancreatic Adenocarcinoma and Its Regulatory Function within the Tumor Immune Microenvironment

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Abstract

Pancreatic cancer remains a major clinical hurdle, largely because it is often detected late and shows strong resistance to existing therapies. This situation calls for new molecular biomarkers that could support early diagnosis and guide precision treatment. Using publicly available datasets from UCSC XENA and GTEx, the work reported here systematically assessed how the Lumican (LUM) gene behaves in pancreatic adenocarcinoma and whether its expression carries clinical relevance. Tumor tissues exhibited markedly higher LUM levels compared with normal samples, and this difference yielded excellent diagnostic accuracy (AUC = 0.964) for distinguishing malignant from benign tissues. On the other hand, no meaningful ties were seen between LUM expression and routine clinical variables such as age, sex, tumor stage, or race. Gene Set Enrichment Analysis (GSEA) pointed to a strong link between high LUM expression and immune-related pathways, including complement activation, humoral immune responses, and B-cell receptor signaling. Further immune infiltration analysis based on a single sample. GSEA (ssGSEA) showed that LUM expression correlated extensively with various immune cell subsets, with the most notable positive association involving central memory CD8+ T lymphocytes ($\rho = 0.759$; $P < 0.001$). This suggests LUM might play a part in shaping the pancreatic cancer immune microenvironment. Survival analyses did not support LUM as an independent prognostic factor, yet its potential role in immune microenvironment remodeling offers new angles for molecular stratification and the search for immunotherapeutic targets. Overall, this work builds a theoretical basis for understanding how LUM functions in the onset and progression of pancreatic cancer, thus aiding biomarker discovery and clinical

translation in this aggressive disease.

Keywords

Pancreatic Cancer, Lumican, Immune Microenvironment, Biomarker, Molecular Mechanism

1. Introduction

Pancreatic adenocarcinoma (PAAD) has become one of the most challenging malignancies in everyday clinical practice, as its incidence and mortality keep rising globally. Worldwide, around 12.5 new cases per 100,000 people are reported each year, and the numbers continue to climb. Unfortunately, fewer than 20% of cases are caught early; most patients are diagnosed at advanced stages, leading to a 5-year overall survival (OS) rate below 10%, with mortality nearly matching incidence [1] [2]. The lack of reliable screening tools and the absence of specific early symptoms often cause delayed diagnosis, which in turn lowers the chance of surgical resection and limits curative options. Even when standard treatments are given, patients face high risks of recurrence and distant spread, resulting in very poor survival [3] [4]. Over the past few years, progress has been made in molecular subtyping, genetic profiling, and tumor microenvironment studies of pancreatic cancer, and several biomarkers have been proposed as potentially useful. Still, advances in early diagnosis, risk prediction, and mechanism-guided personalized therapy remain slow. Only a handful of genes have been firmly linked to patient prognosis [5]-[8]. Therefore, digging deeper into the molecular drivers and biomarkers that underlie pancreatic cancer progression is a pressing scientific need, especially for improving early detection, refining risk stratification, and laying a theoretical foundation for precision diagnostics and therapies that work within the complex tumor microenvironment [9] [10]. Systematic exploration of these molecular mechanisms could open up new ideas and approaches for early intervention and personalized treatment [11] [12].

Lumican (LUM) was selected as the research candidate gene in advance rather than screened from genome-wide differential expression genes. Lumican (LUM) is a key member of the small leucine-rich proteoglycan (SLRP) family and is mainly found in the extracellular matrix (ECM), where it participates in collagen fibrillogenesis, cell migration, and tissue remodeling [13]. Although earlier studies have pointed to LUM's involvement in several cancers, its specific expression pattern and functional role within the pancreatic cancer immune microenvironment are still not well understood. In healthy tissues, Lumican helps maintain tissue structure and supports cell-cell communication by regulating collagen fiber assembly and stability [13]. In different cancers, LUM expression shows distinct patterns depending on the tumor type. It can influence cancer cell growth, movement, and invasion through ECM remodeling and by modulating signaling cas-

cades such as focal adhesion kinase (FAK), mitogen-activated protein kinase (MAPK), and matrix metalloproteinases (MMPs) [13] [14]. Within the tumor microenvironment, LUM has been linked to cancer-associated fibroblasts (CAFs), immunosuppressive factors, and immune escape mechanisms, thereby affecting immune infiltration, epithelial-mesenchymal transition (EMT), and the recruitment of tumor-associated immune cells [15] [16]. Interestingly, LUM seems to play context-dependent roles in cancer progression [17]. For example, in hepatocellular carcinoma, LUM influences tumor growth and metastatic potential by altering ECM composition [18]-[20]; in breast cancer, elevated LUM expression is tied to greater invasiveness and reprogramming of the immune microenvironment [21] [22], underscoring its multifunctional regulatory nature. Evidence from pancreatic cancer suggests that pancreatic stellate cells are the main source of Lumican production. LUM expression is controlled by the transforming growth factor-beta/SMAD family member 4 (TGF-β/SMAD4) pathway and affects stromal collagen dynamics, playing an important part in cancer cell adhesion, migration, and microenvironment remodeling [23]. Existing reports have uncovered complex regulatory mechanisms of LUM expression and its autophagic degradation under hypoxia, and some have noted associations with patient outcomes in pancreatic cancer. However, current knowledge often focuses on isolated cellular or molecular aspects, lacking a comprehensive view of LUM's integrated role in cancer initiation, progression, and immune microenvironment dynamics [24]. These observations provide good reasons to systematically investigate LUM function in pancreatic cancer and highlight the need to clarify its molecular regulation and interactions within the tumor microenvironment.

Building on this background, the present study used comprehensive public datasets of pancreatic cancer samples to systematically examine LUM expression patterns, their links with clinical variables, and their prognostic significance. Our goal was to better understand LUM's role in pancreatic cancer pathogenesis and its clinical relevance. We consolidated high-quality RNA-seq expression data, detailed clinical information from UCSC XENA and GTEx databases, applying rigorous preprocessing and sample quality filtering to ensure analytical robustness and cross-platform consistency. The research approach consisted of four main parts: 1) genome-wide differential expression analysis of LUM; 2) GSEA to explore functional pathway differences between high- and low-LUM expression states; 3) immune infiltration characterization using ssGSEA and the Tumor and Immune System Interactions Database (TISIDB), which allowed quantitative assessment of the relationships between LUM expression and 28 immune cell types; and 4) survival and prognostic evaluation using Kaplan-Meier analysis and multivariate Cox proportional hazards regression to assess the impact of LUM expression on OS, progression-free interval (PFI), and disease-specific survival (DSS), supplemented by receiver operating characteristic (ROC) curve analysis to evaluate diagnostic accuracy. In the statistical analysis phase, we used the Wilcoxon rank-sum test, Kruskal-Wallis test, and logistic regression to thoroughly assess associ-

ations between LUM expression and patient clinical parameters. With a particular focus on the LUM-immune microenvironment relationship, this study systematically examined these correlations across different clinical subgroups, thereby clarifying the previously ambiguous role of LUM in pancreatic cancer pathological mechanisms. The findings suggest that LUM holds considerable promise as a new biomarker for pancreatic cancer diagnosis, molecular subtype classification, and prognostic stratification, thus providing a theoretical foundation for future research into precision therapeutics.

2. Methods

2.1. Acquisition and Initial Processing of RNA Sequencing Data

All datasets used in this study are publicly available and were sourced mainly from the UCSC XENA database (https://xenabrowser.net/datapages/) and the Genotype-Tissue Expression (GTEx) project (https://gtexportal.org/). Specifically, whole-genome expression profiles in transcripts per million (TPM) format, complete clinical information from The Cancer Genome Atlas Pancreatic Adenocarcinoma (TCGA-PAAD) cohort, were retrieved directly from the UCSC XENA portal. The study cohort consisted of 183 TCGA-PAAD specimens (179 tumor samples and 4 adjacent non-malignant controls), supplemented by 167 normal tissue samples from the GTEx database. These samples were initially used to identify differentially expressed genes (DEGs) between tumor and control groups. Subsequently, normal control specimens and samples with incomplete survival data or missing clinical records were excluded from downstream analyses, leaving 178 tumor samples with complete clinical and molecular data for all subsequent investigations. All TPM expression matrices downloaded from TCGA-PAAD and GTEx databases were log2-transformed (log2(TPM + 1)) for uniform expression distribution. No batch correction algorithm (such as Combat) was applied to eliminate platform differences between the two independent datasets due to database access limitations. The cross-dataset comparison and subsequent ROC diagnostic analysis may be partially confounded by technical batch effects between TCGA and GTEx sequencing platforms, which is listed as one of the limitations of this bioinformatics research. This study strictly follows the data access policies and usage agreements of the respective databases and uses only publicly available, de-identified datasets; therefore, no additional institutional ethics approval was required.

2.2. Enrichment Analysis

We applied Gene Set Enrichment Analysis (GSEA) to determine whether predefined gene sets show statistically significant, coordinated expression differences across distinct biological states or phenotypes [25] [26]. For this analysis, expression data were split into high-LUM and low-LUM groups based on the median expression level. The R package clusterProfiler (version 3.14.3) was used to perform GSEA between these groups, with 1000 gene set permutations per analysis.

Statistical significance thresholds were set at a Normalized Enrichment Score (NES) ≥ |1.0| and a false discovery rate (FDR)-adjusted q-value < 0.25, following standard GSEA protocols [27] [28].

2.3. Immune Infiltration Analysis

To explore the immune landscape associated with LUM expression, we used Single Sample Gene Set Enrichment Analysis (ssGSEA) to quantify immune infiltration levels between the high- and low-LUM expression groups. ssGSEA extends conventional GSEA by calculating individual enrichment scores for each sample and gene set, with scores reflecting the degree of coordinated upregulation or downregulation of genes from specified sets within given samples [29]. Gene signatures for 28 immune cell types were obtained from the Tumor and Immune System Interactions Database (TISIDB) [30], covering: Activated CD8+ T cells, Central Memory CD8+ T cells, Effector Memory CD8+ T cells, Activated CD4+ T cells, Central Memory CD4+ T cells, Effector Memory CD4+ T cells, T follicular helper cells, Gamma delta ($\gamma\delta$) T cells, Type 1 helper T cells (Th1), Type 17 helper T cells (Th17), Type 2 helper T cells (Th2), Regulatory T cells (Tregs), Activated B cells, Immature B cells, Memory B cells, Natural killer (NK) cells, CD56bright NK cells, CD56dim NK cells, Myeloid-derived suppressor cells (MDSCs), Natural killer T (NKT) cells, Activated dendritic cells (DCs), Plasmacytoid DCs, Immature DCs, Macrophages, Eosinophils, Mast cells, Monocytes, and Neutrophils. The relative enrichment score for each immune cell subtype was quantified using gene expression profiles from individual tumor specimens [31]-[33]. Spearman's rank correlation coefficient was used to assess the association between LUM expression and infiltration levels of the 28 immune cell types.

2.4. Kaplan-Meier Survival Analysis

To examine relationships between LUM expression levels and patient prognosis in pancreatic adenocarcinoma, we built prognostic assessment models across various clinical subgroups [34]. Patients were first divided into high- and low-LUM expression cohorts based on the median LUM expression value. Both univariate and multivariate Cox proportional hazards regression analyses were then performed to evaluate the relationship between LUM expression and patient outcomes, including OS, PFI, and DSS. Covariates incorporated into univariate and multivariate Cox proportional hazards regression models included age (dichotomized by a median of 60 years), gender, race (White/non-White; Black, Asian, and other minority subgroups were merged into the non-White group due to small sample sizes), and tumor stage (stage I - II / stage III - IV). Samples with missing clinical stage or survival outcome information were directly excluded before regression analysis to avoid imputation bias. All subgroup survival stratification was performed based on the above unified grouping criteria to ensure statistical reliability of the negative prognostic results of LUM. Kaplan-Meier curves were generated with the Survminer R package (version 0.4.8) to compare survival outcomes between the high- and low-LUM expression groups. Finally, ROC curve

analysis was carried out to evaluate the diagnostic discriminatory power of LUM gene expression for distinguishing pancreatic cancer tissues from non-cancerous tissues. The ROC methodology graphically presents the relationship between sensitivity and specificity across diagnostic thresholds, with the Area Under the Curve (AUC) as the primary performance metric. AUC values were computed using the R package "pROC" (version 3.50.0), where values closer to 1.0 indicate better diagnostic accuracy [35] [36].

2.5. Statistical Analysis

All statistical analyses and data visualizations were done with R statistical software (version 4.1.2). The choice of statistical test depended on the distribution characteristics of the data, assessed via normality testing. For normally distributed variables, independent-samples t-tests were used to identify significant differences. For non-normally distributed data, the Wilcoxon rank-sum test and Kruskal-Wallis rank-sum test were applied to assess group differences. In addition, univariate logistic regression analysis was conducted to explore associations between clinical features and LUM expression levels. Correlations between two continuous variables were evaluated using Spearman's rank correlation coefficient. All hypothesis tests were two-tailed, and P-values < 0.05 were considered statistically significant. Where appropriate, multiple testing corrections were performed using the Benjamini-Hochberg false discovery rate (FDR) method.

3. Results

3.1. LUM Is Upregulated in Pancreatic Cancer Tissues

A comparison of LUM expression levels between pancreatic cancer tumor specimens and normal tissue controls revealed significantly higher expression in the tumor group (Wilcoxon rank-sum test, $P < 0.001$; **Figure 1(A)**). ROC curve analysis was performed to assess LUM's diagnostic performance for pancreatic cancer discrimination, yielding an AUC of 0.964 (95% CI: 0.944 - 0.984; **Figure 1(B)**). This result indicates that LUM has excellent diagnostic discriminatory capacity and could serve as a valuable biomarker for identifying pancreatic cancer and as a potential molecular target in pathogenesis.

3.2. Relationship between LUM Expression and Clinicopathological Features

To see whether LUM expression patterns differ across clinical subgroups, we performed stratified analyses using patient characteristics such as age and sex. No significant differences in LUM expression were observed among subgroups stratified by age or gender (**Figures 2(A)-(B)**). Fisher's exact test and independent-samples t-tests revealed that LUM expression levels (dichotomized as high/low based on the median) were not significantly associated with the distribution of clinical parameters, including age, sex, race, or tumor stage. Univariate logistic regression analysis further confirmed the absence of significant associations between LUM expression status and these clinical features.

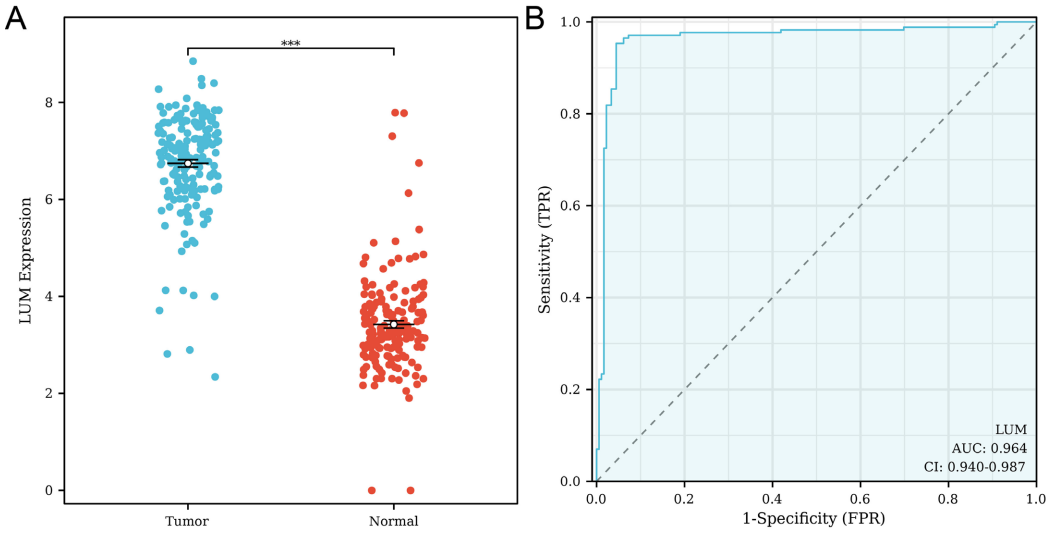

Figure 1. Correlation between LUM gene expression and pancreatic cancer tissue characteristics. (A) Box plot comparing LUM expression levels between pancreatic cancer specimens from TCGA patients and normal tissue samples from TCGA and GTEx databases, analyzed via the Wilcoxon rank-sum test. (B) Receiver operating characteristic (ROC) curve demonstrating the diagnostic utility of LUM in distinguishing tumor from non-tumor tissues, with the x-axis representing the false positive rate and the y-axis the true positive rate (AUC = 0.964).

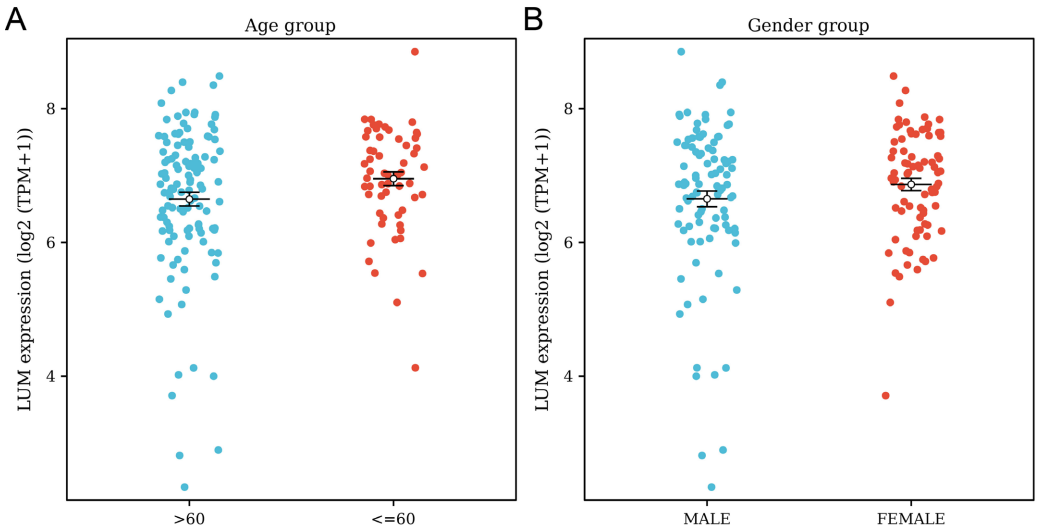

Figure 2. Correlation between LUM gene expression and clinicopathological parameters. (A) Box plot illustrating LUM expression differences across patient age groups (dichotomized at median age 60 years). (B) Box plot showing LUM expression differences between male and female patient subgroups. Statistical comparisons were performed using the Wilcoxon rank-sum test; $P > 0.05$ for both comparisons.

3.3. Prognostic Value of LUM Expression

Univariate Cox proportional hazards regression analysis indicated that tumor stage was significantly associated with overall survival (HR: 4.43; 95% CI: 2.32 - 8.48; $P < 0.05$), while LUM expression showed no significant independent prognostic value. Multivariate Cox regression analysis, after adjusting for clinicopathological covariates, confirmed that tumor stage remained independently associated with

overall survival (HR: 4.57; 95% CI: 2.38 - 8.78; P < 0.05), whereas LUM expression did not emerge as an independent prognostic factor.

3.4. Kaplan-Meier Survival Analyses

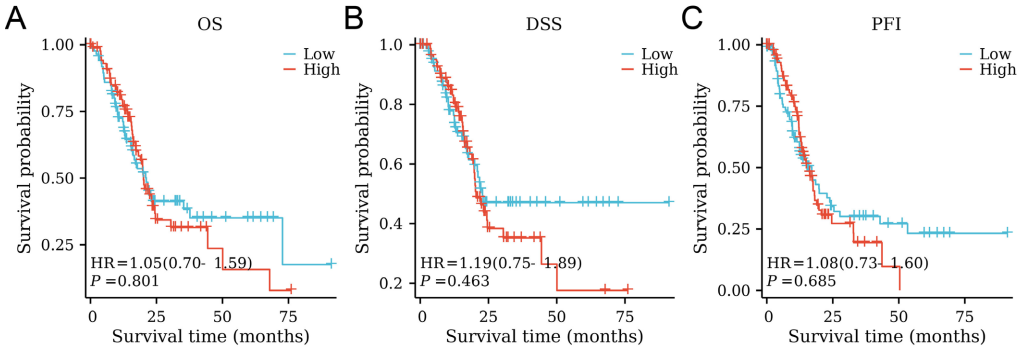

Figure 3. Kaplan-Meier survival curves comparing high versus low LUM expression groups in TCGA-PAAD patients. (A) Overall survival (OS) curves. (B) Disease-specific survival (DSS) curves. (C) Progression-free survival (PFS) curves. Log-rank tests were used for statistical comparison; P > 0.05 for all comparisons.

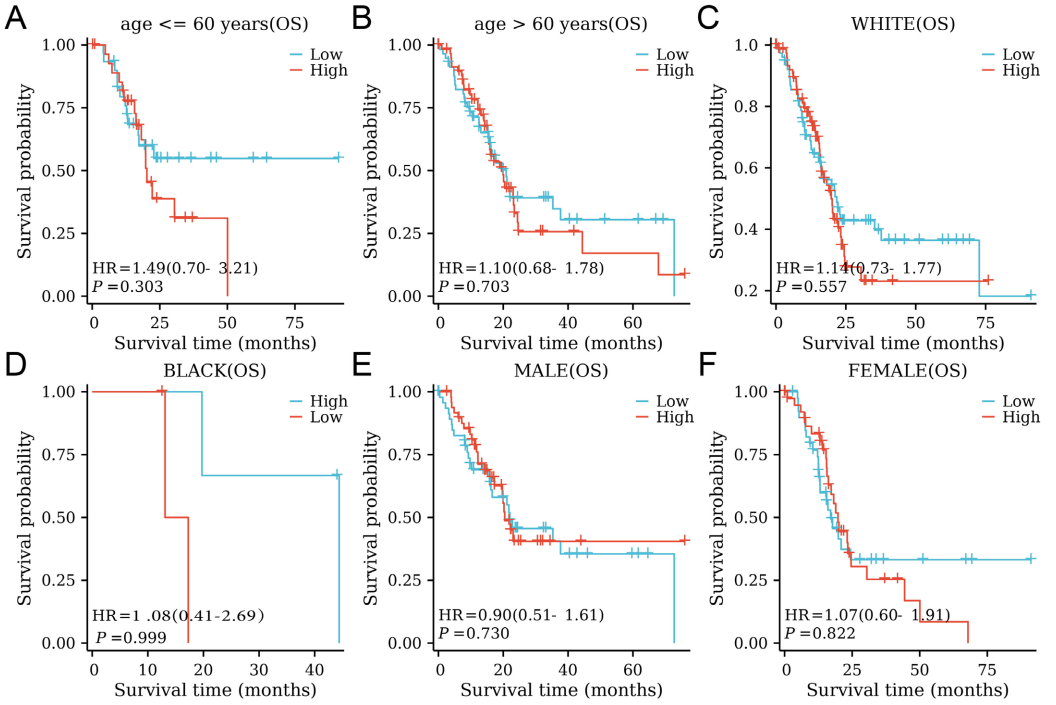

Figure 4. Subgroup Kaplan-Meier survival analyses stratified by clinicopathological characteristics in the TCGA-PAAD cohort. (A) - (B) OS stratified by age (<60 years vs. ≥60 years). (C) - (D) OS stratified by race (White vs. Black). (E) - (F) OS stratified by sex (Male vs. Female). No significant survival differences were observed between high and low LUM expression groups in any subgroup.

We used Kaplan-Meier analysis to compare survival outcomes between the high- and low-LUM expression groups across multiple survival endpoints (Figures 3(A)-(C)). No significant survival differences were observed between the two groups for: 1) OS (HR: 1.054; 95% CI: 0.700 - 1.586; P = 0.801), 2) PFI (HR: 1.189; 95%

CI: 0.749 - 1.886; P = 0.463), or 3) DSS (HR: 1.084; 95% CI: 0.733 - 1.605; P = 0.685). Subgroup survival analyses stratified by clinicopathological characteristics further revealed no significant LUM expression-associated survival differences across age groups (<60 years: P = 0.303; ≥60 years: P = 0.703), sex (male: P = 0.730; female: P = 0.822), or race (White: P = 0.557; Black: P = 0.999) (**Figures 4(A)-(F)**).

3.5. Gene Set Enrichment Analysis of LUM-Associated Signaling Pathways

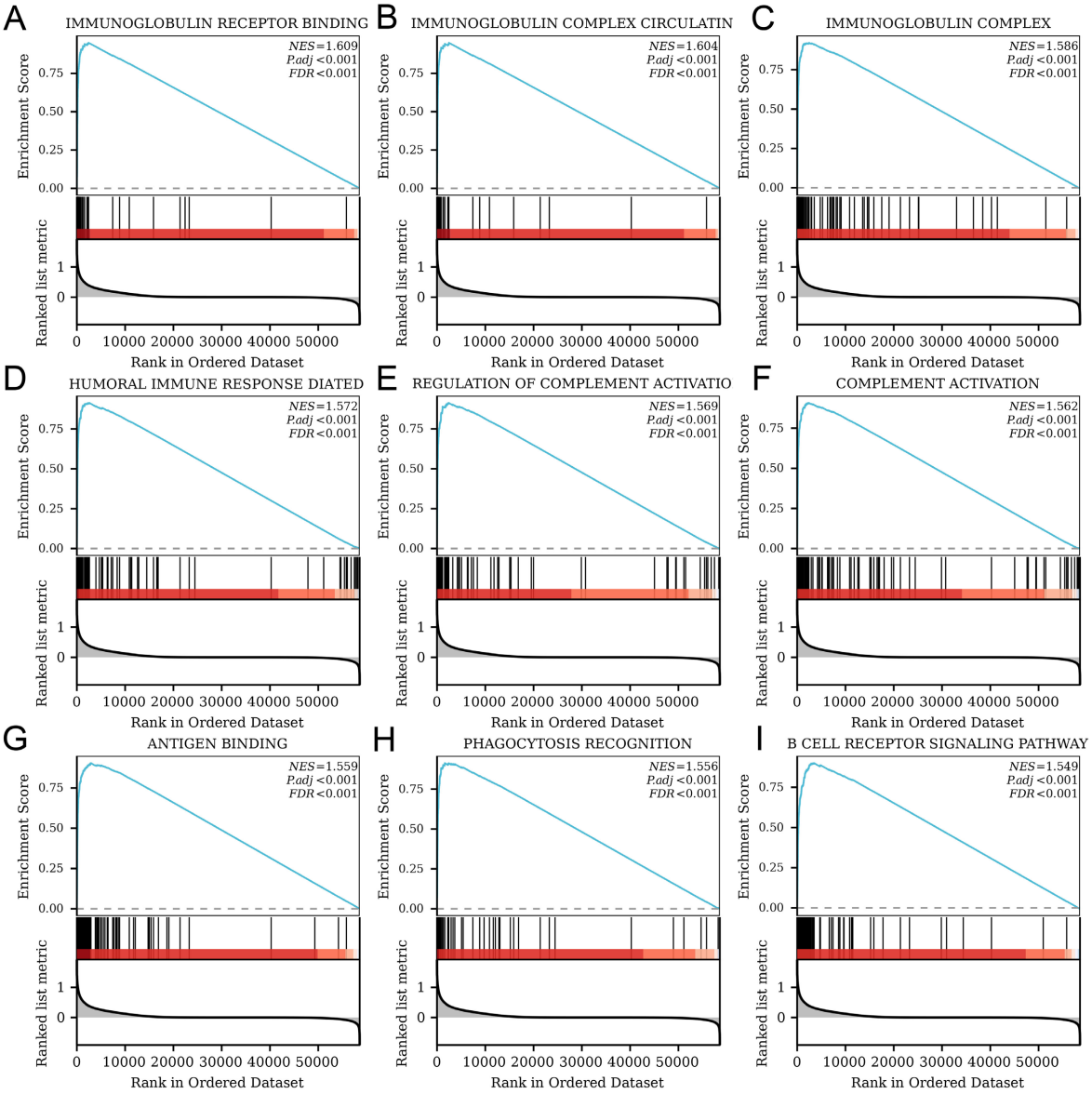

Figure 5. GSEA enrichment plots for the high LUM expression phenotype. (A) - (I) Enrichment plots for significantly enriched pathways in high LUM samples, including Immunoglobulin Receptor Binding, Circulating Immunoglobulin Complex, Immunoglobulin Complex, Humoral Immune Response Mediated by Circulating Immunoglobulin, Regulation of Complement Activation, Complement Activation, Antigen Binding, Phagocytosis Recognition, and B Cell Receptor Signaling Pathway. NES = Normalized Enrichment Score; FDR = False Discovery Rate.

To better understand the biological mechanisms behind LUM-driven pancreatic cancer progression, we conducted GSEA comparing tumor specimens with high versus low LUM expression (Figure 5). GSEA identified significant enrichment of multiple immune-related pathways and functional modules in the high LUM expression group, including: Immunoglobulin Receptor Binding, Circulating Immunoglobulin Complex, Immunoglobulin Complex, Humoral Immune Response Mediated by Circulating Immunoglobulin, Regulation of Complement Activation, Complement Activation, Antigen Binding, Phagocytosis Recognition, and B Cell Receptor Signaling Pathway (NES ≥ 1.0; FDR q-value < 0.25; random seed: 4298). These findings suggest that elevated LUM expression contributes to pancreatic cancer pathogenesis by modulating these immunerelated biological processes.

3.6. Correlation between LUM Expression and Immune Cell Infiltration

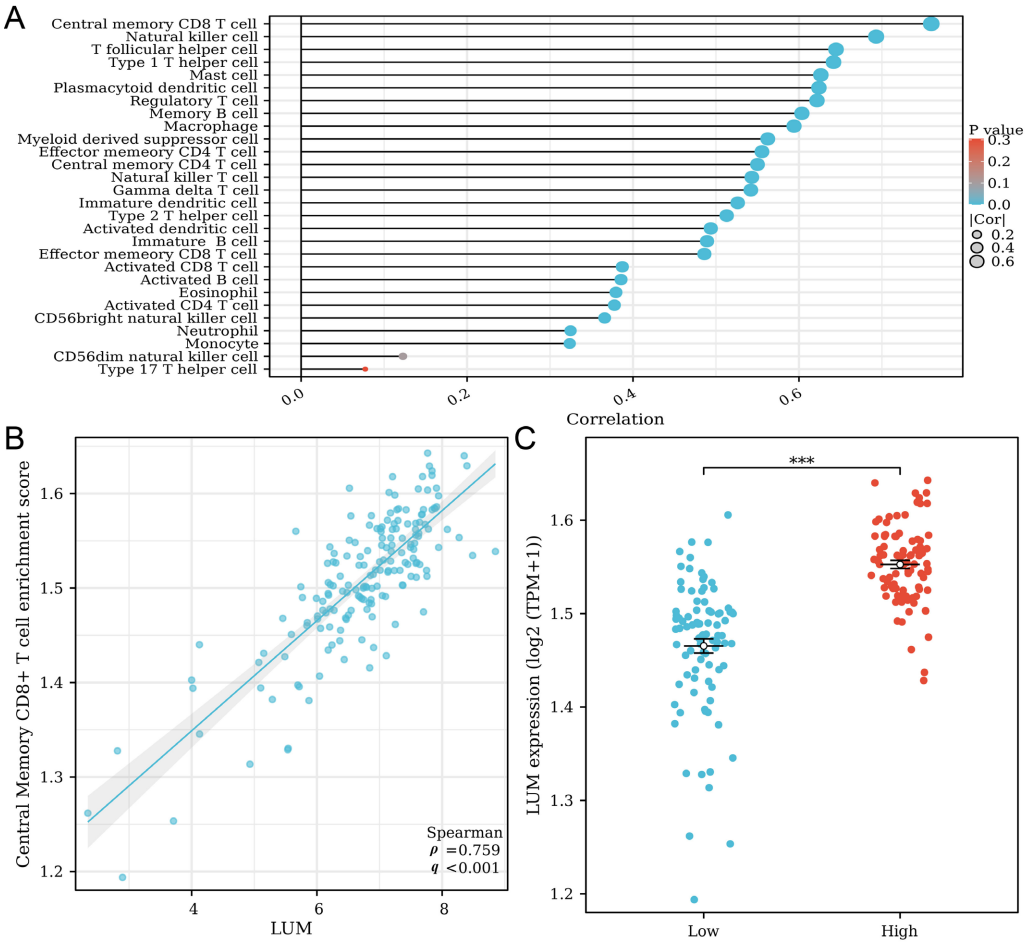

Figure 6. Correlation between LUM expression and tumor immune microenvironment composition. (A) Heatmap illustrating Spearman correlation coefficients between LUM expression and 28 immune cell types. (B) Scatter plot demonstrating the strong positive correlation between LUM and Central Memory CD8+ T cells (Spearman $\rho = 0.759$, significant after FDR correction). (C) Box plot comparing Central Memory CD8+ T cell enrichment scores between high and low LUM expression groups (Wilcoxon rank-sum test, $P < 0.001$).

We performed ssGSEA-based immune infiltration analysis to systematically evaluate the relationships between LUM expression and tumor microenvironment composition. Spearman correlation analysis revealed that after multiple testing correction, LUM expression showed significant positive correlations (adjusted q < 0.05) with the infiltration abundance of 24 immune cell subtypes, including Activated B cells, Activated CD4+ T cells, Activated CD8+ T cells, Activated Dendritic Cells, CD56bright Natural Killer cells, Central Memory CD4+ T cells, Central Memory CD8+ T cells, Effector Memory CD4+ T cells, Effector Memory CD8+ T cells, Eosinophils, Gamma Delta T cells, Immature B cells, Immature Dendritic Cells, Macrophages, Mast cells, Memory B cells, Monocytes, Myeloid-derived Suppressor Cells, Natural Killer cells, Natural Killer T cells, Neutrophils, Plasmacytoid Dendritic Cells, Regulatory T cells, T Follicular Helper cells, Type 1 Helper T cells, and Type 2 Helper T cells (**Figure 6(A)**). Among them, Central Memory CD8+ T cells exhibited the strongest correlation with LUM expression (Spearman $\rho = 0.759$, adjusted q < 0.001; **Figure 6(B)**). Consistently, the enrichment score of Central Memory CD8+ T cells was significantly higher in the high-LUM group than the low-LUM group (Wilcoxon rank-sum test, P < 0.001; **Figure 6(C)**).

4. Discussion

Through systematic bioinformatic analysis of transcriptomic and clinical data from public repositories (UCSC XENA and GTEx), this investigation comprehensively characterized LUM expression in pancreatic cancer and yielded several key findings. First, LUM was markedly upregulated in pancreatic cancer tissues compared with normal specimens, and it showed excellent diagnostic discrimination (AUC = 0.964), pointing to its potential as a diagnostic biomarker. Second, LUM expression levels did not depend on major clinicopathological variables such as age, sex, ethnicity, or tumor stage, suggesting that traditional clinical factors do not confound LUM expression. Third, GSEA revealed that high LUM expression was significantly enriched in multiple immune-related pathways, especially those involving complement activation, humoral immune responses, and B-cell receptor signaling, implicating LUM in immune modulation. Fourth, ssGSEA-based immune infiltration analysis showed that LUM expression significantly correlated with infiltration of various immune cell subsets, with the strongest association observed for central memory CD8+ T cells. Taken together, these findings offer new mechanistic insights into LUM's potential role in immune microenvironment remodeling and provide a biological rationale for exploring LUM as a molecular target and biomarker in pancreatic cancer.

LUM is generally highly expressed across many tumor types and has been widely implicated in immunosuppression, tumor progression, and poor clinical outcomes. Numerous large-scale cohort studies and functional experiments have confirmed its role in promoting malignant phenotypes and establishing immunosuppressive microenvironments [15] [37]. For example, in solid tumors such as

gastric and bladder cancers, LUM expression is enriched in pathways related to ECM remodeling and EMT, which facilitate tumor cell invasion and immune evasion through interactions with stromal cells, fibroblasts, and immunomodulatory cells [38] [39]. In breast cancer, elevated LUM expression is strongly associated with faster tumor cell proliferation, greater metastatic capacity, and activation of CAFs; moreover, LUM can enhance immunosuppression by regulating TGF-β signaling pathways [15]. However, in contrast to findings in some malignancies where high LUM expression correlates with significantly worse survival, our study observed that LUM expression did not stand out as an independent prognostic factor for overall survival in pancreatic adenocarcinoma. This discrepancy may indicate that LUM's role in pancreatic cancer is more focused on tumor initiation and microenvironmental modulation rather than directly dictating survival outcomes. Overall, our work confirms high LUM expression in pancreatic cancer and its robust link to immune pathway activation from multiple analytical angles, thereby enriching our cross-tumor understanding of LUM's multifaceted roles in immune microenvironment regulation and tumor biology.

The markedly elevated LUM expression in pancreatic cancer tissues and its excellent diagnostic performance in ROC analysis (AUC reaching 0.964) provide strong molecular evidence for potential clinical use in early disease detection and differential diagnosis [40] [41]. Current evidence suggests that multi-biomarker panels, including LUM, can effectively identify pancreatic cancer at various stages and help with molecular subtype stratification [40]. Our investigation further shows that LUM expression does not correlate significantly with routine clinical variables (e.g., age, gender, tumor stage), indicating that LUM expression is largely independent of traditional clinicopathological stratification factors. This independence minimizes potential confounding and enhances its practical utility for risk stratification and molecular subtype identification [42]. Although survival analysis did not establish LUM as an independent prognostic factor, both the existing literature and our findings suggest that LUM retains substantial value for facilitating molecular subtype classification and mechanistic elucidation, particularly in shedding light on processes such as tumor cell proliferation, migration, drug resistance, and immune regulation [41] [43] [44]. Therefore, LUM shows considerable promise as a biomarker for clinical translation in pancreatic cancer early diagnosis, molecular classification, and mechanistic investigation.

Furthermore, the ssGSEA-based immune characterization revealed that LUM expression is prominently associated with the infiltration intensity of multiple immune cell populations, and notably, it shows a remarkably strong positive correlation with central memory CD8+ T cell enrichment. This observation carries substantial scientific and clinical significance [45]. Traditionally, LUM research has emphasized its ECM component function in regulating tumor cell behaviors [13] [46]; however, our study uncovered a close relationship between LUM and immune cell populations, suggesting that LUM is significantly correlated with the infiltration abundance of multiple immune cell subsets and immune-related sig-

naling pathways, suggesting its potential regulatory association with the pancreatic tumor immune microenvironment. Currently, the clinical efficacy of immunotherapy in pancreatic cancer remains suboptimal, partly because of the highly complex and immunosuppressive regulation of the tumor immune microenvironment [47] [48]. Thus, these findings offer new perspectives and a theoretical foundation for understanding the immune characteristics of pancreatic cancer and identifying immunotherapeutic targets. Future fundamental and translational investigations focused on clarifying the interaction mechanisms between LUM and immune cells are expected to advance our understanding of the molecular pathways that mediate immune evasion and progressive tumor development in pancreatic cancer, while also creating new therapeutic avenues that target the tumor immune microenvironment [49]. Notably, as an extracellular matrix gene quantified via bulk RNA-seq, elevated LUM expression may mirror stromal abundance rather than solely representing intrinsic tumor biological features, which acts as a confounding factor for the correlation between LUM and immune infiltration.

By integrating the GSEA and immune infiltration analysis results, LUM may facilitate immune microenvironment remodeling and intercellular signaling through the regulation of multiple immune response pathways, including immunoglobulin receptor binding, complement activation, antigen recognition, and B-cell receptor signaling cascades [50]. The strong correlation between LUM and diverse immune cell subsets, particularly central memory CD8+ T cells, further suggests that LUM could be involved in orchestrating tumor immune dynamics and modulating the infiltration and activation status of these immune populations [51]. The proposed mechanistic models await further validation through targeted in vitro and in vivo functional assays to rigorously establish LUM's precise roles in pancreatic cancer initiation and progression, as well as to clarify its utility as a molecular therapeutic target.

5. Limitations

This study relies on publicly available transcriptomic databases (UCSC XENA and GTEx) and has not verified the biological functions of LUM through in vitro or in vivo experimental approaches. In addition, the combination of TCGA and GTEx datasets without batch correction may introduce platform-specific technical bias, which may overestimate the diagnostic AUC value of LUM; the diagnostic performance of LUM needs further verification in unified single-center sequencing cohorts. The limited sample sizes in these databases, together with missing data at some clinical and molecular levels, may affect statistical robustness and the generalizability of the conclusions. Moreover, the available data are primarily transcriptomic, lacking protein-level validation and functional experimental evidence; consequently, the clinical applicability of these findings is substantially constrained by data availability and current analytical methods. Future investigations should integrate large-scale, multi-institutional clinical datasets with experimental validation to strengthen the research framework and enhance the translational

relevance of these molecular insights.

6. Conclusion

This systematic investigation demonstrates that the LUM gene is significantly upregulated in pancreatic adenocarcinoma and shows excellent diagnostic discrimination (AUC = 0.964), yet it does not exhibit a significant independent association with patient survival outcomes. Notably, elevated LUM expression is prominently enriched in immune-related biological pathways and shows a strong positive correlation with infiltration of multiple immune cell types, especially central memory CD8+ T cells ($\rho = 0.759$; $P < 0.001$). These findings suggest that LUM may contribute to pancreatic cancer pathogenesis through immunomodulation involving complement activation, humoral immune responses, and B-cell receptor signaling. Although LUM does not function as an independent prognostic factor, its substantial role in molecular subtyping and immune microenvironment regulation underscores its potential value as both a diagnostic biomarker and an immunomodulatory target. Future efforts should prioritize rigorous experimental validation and multicenter clinical investigations to translate these findings into clinical diagnostic and therapeutic applications, thereby advancing precision medicine approaches for pancreatic cancer management.

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Data Availability

All data supporting the findings are included within the manuscript and supplementary materials. Transcriptomic and clinical datasets analyzed in this work were retrieved from UCSC XENA (TCGA-PAAD) and GTEx public databases (https://xenabrowser.net/, https://gtexportal.org/). Additional raw data are available from the corresponding author upon reasonable request.

Author Contributions

Chen and Li conceived and designed the study. Li performed data curation, formal analysis, methodology, and software. Chen conducted an investigation, visualization, and wrote the original draft. All authors participated in validation, project administration, resource provision, and critical review and editing of the manuscript. All authors reviewed the manuscript.

Conflicts of Interest

The authors declare that they have no competing interests.

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