Identification of ISCA1 as novel immunological and prognostic biomarker for bladder cancer

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Background: Iron-sulfur cluster assembly 1 (ISCA1) has a significant effect on respiratory complexes and energy metabolism. Although there is some evidence that ISCA1 gene expression impacts energy metabolism and consequently has a role in tumorigenesis and cancer metastasis in different types of malignancies, no systematic pan-cancer study of the ISCA1 has been conducted. As a result, we sought to investigate ISCA1's predictive value in 33 cancer types as well as its possible immunological function.

Methods: We included the pan-cancer expression profile dataset and clinical data from the public database. Firstly, the single-sample Gene Set Enrichment Analysis (ssGSEA) approach was employed for analyzing the immune link in pan-cancer, while the limma package was utilized for analyzing the differential expression in cancer species. Subsequently, ciberport, MCP-counter, TIMER2, quanTIseq, and xCELL were employed for analyzing bladder cancer (BLCA)'s immune infiltration. Least absolute shrinkage and selection operator (Lasso) were employed for choosing the best gene to develop the immune risk scoring model.

Results: ISCA1 gene expression was positively related to four immune signatures (chemokine, immunostimulator, MHC, and receptor) in BLCA. Samples of BLCA were sorted into two groups by the best cut-off of ISCA1 expression degree. The group with a high level of ISCA1 expression had a higher risk, suggesting that the ISCA1 gene was a risk factor in BLCA, and its high expression resulted in a poorer prognosis. Additionally, it was noted that ISCA1 was positively linked with these immune checkpoints. Moreover, there was a considerable positive link between ISCA1 and different immune properties in subgroups with different immune checkpoint inhibiting responses. Finally, an immune risk scoring model was made and it showed a better score in comparison to that of TIDE.

Conclusion: ISCA1 can be a prognostic marker for a variety of cancers, particularly BLCA. Its high level of expression has a deleterious impact on the
prognosis of BLCA patients. This strongly shows that ISCA1 is a significant prognostic factor for BLCA and that it could be used as a new prognostic detection target and treatment approach.

**KEYWORDS**
pan-cancer, ISCA1, BLCA, GSEA, immune microenvironment, prognostic analysis

**Introduction**

Cancer is the primary cause of mortality and a major setback to improving the quality of life all over the globe. There is no ultimate treatment for it as of the present day (1). Recently, cancer immunotherapy, particularly immune checkpoint blocking therapy has become a prominent cancer treatment approach (2). New immunotherapy targets can be found through pan-cancer expression analysis of genes and examination of their linkage with clinical prognosis and the associated signal pathways, thanks to the ongoing development and improvement of public databases like The Cancer Genome Atlas (TCGA) (3).

Mitochondria have become important pharmacological targets due to their essential role in cellular growth and apoptosis (4). Mitochondria in tumor tissues can transform metabolic phenotypes to cope with the high energy demand and macromolecule synthesis (5, 6). Additionally, mitochondria can interact with the tumor microenvironment, and signals from fibroblasts related to cancer have an impact on them (7). ISCA1 variant has been linked to mitochondrial malfunction (8), mainly because ISCA1 regulates the expression of essential proteins in the mitochondrial respiratory chain complex, having a significant impact on it as well as energy metabolism. ISCA1 is an evolutionarily conserved type A ISC protein involved in Fe-S synthesis. Knockdown investigations in HeLa cells of two type A proteins, ISCA1 and ISCA2, reveal that these two proteins may have a function in the increased synthesis of mitochondrial Fe4S4 in humans (9). Using recombinant human ISCA1 and ISCA2, recent in vitro biochemical experiments have confirmed cluster transfer and protein-protein interaction between human glutaredoxin GLRX5 and ISCA1 or ISCA2 (10).

Although, some research has been done on the role of ISCA1 in malignancies. Only relevant research has revealed that Integrin Subunit Beta 3 (ITGB3) affects energy metabolism through the expression of the ISCA1 gene, which has a role in breast cancer bone metastases (11). As a result, the possible role of ISCA1 in a range of malignancies has to be investigated in detail. The expression level of ISCA1 in different forms of cancer and its connection with prognosis were studied using two databases: TCGA and Gene Expression Omnibus (GEO). It also discussed the association between ISCA1 expression and immunity in 33 tumors. Following that, it was discovered that bladder cancer (BLCA) had the strongest link to immunity. The researchers next looked into the possible links between ISCA1 and mutation analysis, DNA methylation, tumor mutational burden (TMB), immunological infiltration, and clinical response. In addition, the biological function of ISCA1 in malignancies was investigated using protein-protein interaction (PPI) analyses between immune-linked differential genes and ISCA1. Finally, the immunological risk score (IRS) model was developed, and its result was superior to the TIDE result. Finally, our findings indicated that ISCA1 could be a predictive factor for bladder cancer (BLCA). ISCA1 may alter tumor-infiltrating immune cells, which could be majorly involved in tumor immunity. This research could help researchers better grasp ISCA1’s involvement in tumor immunotherapy.

**Methods**

**Data source and pretreatment**

The RNA sequencing (RNA-seq) expression profile data, somatic mutation data, and survival data regarding pan-cancer (33 species) were taken from the database of UCSC Xena (https://xenabrowser.net/). The format of RNA-seq data was changed from Fragments Per Kilobase Million (FPKM) to the format of Transcripts per million (TPM), and then we did a log2 conversion. Among them, analysis and processing of the downloaded somatic mutation data were done by mutect. Finally, the copy number variations (CNV) data processed by the gistic algorithm was also provided by the UCSC Xena database (http://xena.ucsc.edu/), while the methylation data was taken from the LinkedOmics database (http://linkedomics.org).

The BLCA GEO queue was retrieved from the GEO database (https://www.ncbi.nlm.nih.gov/geo/), which has extensive survival data, such as GSE31684, GSE48075, GSE13507, GSE32894, GSE48277, and GSE69795. The BLCA samples were kept.
Afterward, we also downloaded three cohorts linked with immunotherapy, GSE78220 (melanoma), GSE135222 (NSCLC), and GSE91061 (melanoma). Following the knowledge sharing 3.0 License Agreement, the complete expression data and comprehensive clinical data of the IMvigor210 queue (BLCA immunotherapy-related queue) came from http://research-pub.Gene.com/imvigor210corebiologies/.

### Analysis of tumor immune microenvironment and immune infiltration

#### Single sample gene set enrichment analysis

Single sample gene set enrichment analysis (ssGSEA) (12) was proposed for the first time in 2009 and was made for a single sample that could not be utilized for GSEA. The R package GSVA can be used to implement it. At present, ssGSVA is frequently utilized for assessing the extent of tumor immune cell infiltration.

#### Estimate

Moreover, we utilized estimate (13) for evaluating the tumor immune microenvironment scores of samples, and then a comparison of their differential distribution in different subtypes was done. Following the expression data, estimate provided scholars with tumor purity scores, the stromal cells’ level, and the immune cell infiltration level in tumor tissue.

#### Ciberport

Deep learning algorithms such as convolution and deconvolution are commonly known. Each sample is treated as a mixture of numerous immune cells in this procedure. The link between the components and expression of each immune cell and the final combination is fit using linear regression. The expression properties of each immune cell were retrieved using a deconvolution technique. The method of calculating immune cell infiltration known as CIBERPORT (14) is widely utilized. For estimating the abundance of immune cells, it employs the technique of linear support vector regression to deconvolute the expression matrix of immune cell subtypes.

#### Tumor immune estimation resource

The Tumor Immune Estimation Resource (timer) is one of the procedures for deconvolution of cell mixtures following the expression characteristics (15). Timer2 is one of the most widely utilized approaches for immune infiltration analysis in bioinformatics. MCP-counter (Microenvironment Cell Populations-counter) (16) is an R tool that uses normalized transcriptome data to quantify the absolute abundance of eight immune cells and two stromal cells in diverse tissues. The score can be used to demonstrate the degree of infiltration in the immunological milieu, but the number of cells cannot be compared. ESTIMATE can’t assess particular immune cell infiltration; it can only assess immune cell purity, tumor cell abundance, and stromal cell abundance.

#### QuanTseq

The QuanTseq (17) was utilized for quantifying both the tumor immune status according to the human RNA-seq data as well as the proportion of ten distinct types of immune cells along with other non-characterized cells in the sample by deconvolution.

#### Xcell

Xcell (18) is an ssGSEA-based procedure with the ability to do cell type enrichment analysis according to gene expression data of 64 types of immune and stromal cells. Since the Xcell employs expression level ranking rather than the actual value, normalization has no effect, although the input data requires a normalization format. As a result, the immune infiltration of BLCA was analyzed using CIBERPORT, MCP-counter, TIMER2, quanTseq, and Xcell, and the connection between the expression of ISCA1 and their scores were measured.

#### GSEA and annotation of differentially expressed genes

The analysis difference between subtypes was done using the limma package (19), and differentially expressed genes were chosen through the $|\log_2 \text{(Fold Change)}| > 1$ and False Discovery Rate (FDR) < 0.05. We enriched the differentially expressed genes among subtypes and then carried out an analysis using Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) through the WebGestaltR package (version 0.4.2) (20), and the chosen gene set was “c2.cp.kegg.v7.0.symbols.Gmt”, which had the KEGG channel. The GSEA input file consisted of the expression profile data. The threshold values of enriched pathways were $p < 0.05$ and FDR $< 0.25$. Likewise, the GO function enrichment analysis of differentially expressed genes was done using the R software package WebGestaltR (threshold value was set as $P < 0.05$).

#### Univariate and multivariate cox analysis

The R-package survminer (https://cran.r-project.org/package=survminer) was employed to get the best cutoff of genes from various datasets, and the samples were sorted into high and low expression groups following the best cutoff, and afterward, we drew the KM curve. We randomly collected the BLCA cancer samples from the TCGA dataset using the ratio
TIDE analysis of immunotherapy effect

Through a comprehensive study of hundreds of various tumor expression profiles, the Tumor Immune Dysfunction and Exclusion (TIDE) analysis can uncover biomarkers that predict the therapeutic response of immune checkpoint inhibitors/medicines. The TIDE score obtained from TIDE analysis can be used to determine the sensitivity of immunological checkpoints.

Tumor mutation burden

TMB is a quantifiable immune-response biomarker that reflects the number of mutations in tumor cells. TMB scores were calculated using a Perl script and corrected by dividing by the total length of exons.

ssGSEA

Base on genes from previous research and ssGSEA analysis was used to analyze these genes to define T cell inflamed score.

Statistical analysis

The difference in clinicopathological features among the three subtypes was investigated using the Chi-square test. The expression levels of three subtypes were determined using ANOVA. The difference in the two groups was investigated using the T-test. For correlation analysis, the Pearson correlation coefficient was used. R (version 4.0.2) was used for statistical analyses. Statistical significance was defined as a P-value of < 0.05.

Results

Immune correlation of ISCA1 gene in pan-cancer

We discovered four types of genes in the literature including MHC, chemokine, immune-stimulator, and receptor. The Spearman correlation between these genes and the ISCA1 was measured in pan-cancer. The link between these four gene types with ISCA1 was varied in various types of cancer. It was mostly positive in uveal melanoma (UVM), BLCA, kidney papillary cell carcinoma (KIRP), etc. while thyroid carcinoma (THCA), testicular germ cell tumors (TGCT), etc. were mostly linked negatively (Figure 1A). Moreover, the link between CTLA4, PDCD1, CD86, CD274, and ISCA1 in various cancer types was measured. The outcomes revealed that these four genes were substantially positively linked with ISCA1 in BLCA (Figures 1B–E). Furthermore, ssGSEA was employed for evaluating the scores of 28 immune cell scores in various cancer types, and then their link with ISCA1 was measured. The outcomes of this analysis suggested that there was a considerable positive link between the expression of ISCA1 and 20 immune scores in BLCA (Figure 1F).

Moreover, the ISCA1 gene expression in pan-cancer was observed (Figure 2). The outcomes indicated that: among the 24 tumors with para-cancerous samples, the expression of the ISCA1 gene in 15 cancer species was considerably varied in comparison to that in para-cancerous samples. Among them, the expression of the ISCA1 gene was lowered in tumor samples of 11 cancer species, including breast invasive carcinoma (BRCA), BLCA, cervical squamous cell carcinoma (CSCC), glioblastoma multiform (GBM), kidney chromophobe (KICH), endocervical adenocarcinoma (CESC), kidney renal clear cell carcinoma (KIRC), KIRP, THCA, endometrial carcinoma (UCEC), lung adenocarcinoma (LUAD), rectum adenocarcinoma (READ), etc. Moreover, the expression of cholangiocarcinoma (CHOL), head and neck squamous cell carcinoma (HNSC), liver cancer (LIHC), and stomach cancer (STAD) were enhanced in tumor samples of four cancer species.

SNV, CNV, and methylation analysis in BLCA

Based on the above analysis of pan-cancer, the ISCA1 gene had a considerable positive link with four types of genes in BLCA: immune-stimulator, MHC, chemokine, and receptor. In BLCA, the ISCA1 gene was positively linked with CTLA4, PDCD1, CD86, CD274, and immune score. Using the difference analysis, it was discovered that the expression of the
**ISCA1** gene in BLCA tumor samples was decreased in comparison to that in adjacent samples. Furthermore, the survival analysis highlighted that samples were divided into the high **ISCA1** expression group and low **ISCA1** expression group, so we were focused on the role of **ISCA1** in BLCA.

In herein, we used the surv_cutpoint function of the SurvMiner package to find the best cutoff for grouping. BLCA samples were categorized into two groups (Figure 3A) as per the best cutoff of **ISCA1** expression value. The group with high **ISCA1** expression showed a poor prognosis, suggesting that **ISCA1** is a risk factor in BLCA. Afterward, we mapped 10 genes with the highest mutation frequencies in the high and low expression groups. The outcomes revealed that TTN, synb1, TP53, RB1, kmt2d, arid1a, and other genes in the low expression group had lower mutation frequencies (Figure 3B). However, no major variation was observed in the TMB of high and low expression groups of **ISCA1** (Figure 3C). We observed that there was a major difference in the expression of **ISCA1** with CNV amplification and deletion and the normal copy number, and the expression of **ISCA1** with CNV amplification was greatly enhanced, while that with CNV deletion was greatly reduced (p < 0.0001, Figure 3D). Meanwhile, no major link was seen between the methylation degree and the expression of **ISCA1** (Figure 3E). Also, using limma analysis, 1672 genes, included 1505 upregulated genes and 167 downregulated genes, were screened between high **ISCA1** group and low **ISCA1** group (Figure S1A). KEGG pathways enrichments analysis showed that 1505 genes were enriched in 10 KEGG pathways, such as, PI3K-Akt signaling pathway, cell cycle (Figure S1B), while 167 genes were not enriched into the KEGG pathway.

**Comparative analysis of the immune status of **ISCA1** groups in BLCA**

In the **ISCA1** expression group, the differential expression of chemokine, immune-stimulator, MHC, and receptor genes was investigated (Figures 4A–E). The expression was higher in the
The ISCA1 high expression group had a high immune score, and the distribution differences of 28 immune cell scores in the ISCA1 group were examined, revealing that 21 had major variations (Figure 5A). The immune infiltration of BLCA was next investigated, and a link was observed between ISCA1 expression and immune infiltration score. The marker genes of high expression group, and most of the four different types of genes had substantial variations.

The ISCA1 high expression group had a high immune score, and the distribution differences of 28 immune cell scores in the

FIGURE 3
SNV, CNV, and methylation analysis in BLCA. (A): In BLCA, the KM curve showed that patients in high ISCA1 group had worse survival outcome compared to low ISCA1 group, both of which were borderline significant. (B): The mutation distribution of the top 10 genes with the highest frequency of mutations in the high ISCA1 expression group and low ISCA1 expression group. (C): The distribution of TMB in high ISCA1 expression groups and low ISCA1 expression group was compared. (D): The gene expression difference of ISCA1 in ISCA1 gene amplification group. (E): Correlation analysis between gene ISCA1 expression and methylation (** represents p<0.0001, ns represents p > 0.05).
Five cell types were studied: CD8 T cells, dendritic cells, macrophages, NK cells, and Th1 cells. In the ISCA1 high expression group, the majority of the genes were highly expressed (Figure 5B). The link between ISCA1 and immunological checkpoints was also measured. Based on the outcomes, ISCA1 and these immunological checkpoints had a substantial positive link (Figure 5C).

**ISCA1 prediction of clinical response and excessive progression of immune checkpoint blockade in BLCA**

The link between ISCA1 expression value and pan-cancer T cell inflamed score was measured, and the outcomes indicated a major positive link (Figure 6A). Moreover, the link between ISCA1 and different immune properties (immune checkpoin,t expression of immunomodulator and TIIC effector genes, and characteristics linked with immunotherapy) in subgroups with varied immune checkpoint blockade (ICB) responses were analyzed (Figure 6B). The outcomes suggested that ISCA1 had a major positive link with them.

By comparing the scores of BLCA tumors and immunerelated pathways, it was discovered that there were major variations in related immune pathways in the high ISCA1 group and the low ISCA1 group of BLCA tumors, the correlation between ISCA1 expression and Neuroendocrine differentiation pathway is positive in low ISCA1 group (Figure 6C). For example, the Neuroendocrine_ differentiation pathway score was higher in the high ISCA1 group, whereas the score was lower in the low ISCA1 group. ARID1A, RB1, ERBB2, FANCC, and other genes that could be linked to radiotherapy and chemotherapy were compared. It was observed that the mutation frequencies in the high and low ISCA1 groups were different (Figure 6D). ARID1A, RB1, ERBB2, ERCC2, and FANCC mutation frequencies were greater in high ISCA1 groups, for instance, missense mutation of ERCC2 was 5% in the high ISCA1 group and 4% in the low ISCA1 group. In high and low ISCA1 expression groups, the differences in three categories (EGFR network, immune inhibit oncogenic pathways, and radiotherapy predicted pathways) were compared (Figure 6E). The high ISCA1 group was mostly positively correlated in the EGFR network in the EGFR_ligands pathway, while the low ISCA1 group was mostly negatively linked.
Identification of immune-related differential genes and PPI analysis

A total of 575 up-regulated genes and 100 down-regulated genes were obtained by grouping the up-regulated and down-regulated genes of the BLCA sample species ISCA1, StromalScore, and ImmuneScore, respectively (Figures 7A, B). The GO and KEGG function enrichment of differential genes was then analyzed using WebGestaltR. Genes were discovered to be closely linked to cancer and immune pathways such as myeloid leukocyte migration, leukocyte migration, angiogenesis, Th1 and Th2 cell differentiation, and so on (Figures 7C–F).

Using the string website, PPI found and analyzed a total of 675 differential genes. Following that, Cytoscape was used to visualize the data and the MCODE plug-in was utilized to identify significant clusters. There were three gene clusters with more than ten genes each (Mcode1, Mcode2, and Mcode3 respectively). The genes MRC1, CXCL11, CCL3, CCL4, CSF1, and FN1 were all found in Mcode1 (Figure 8A). Then, to determine their functions, WebGestaltR was utilized to do a GO and KEGG function enrichment analysis (Figures 8B–E). The findings revealed that the Mcode1 module was linked to immunological pathways such as the Toll-like receptor signaling pathway and the interaction between cytokine and cytokine receptors.

Construction of BLCA cancer immune risk score model

After the above analysis, 675 we identified the differential genes linked with immunity, and then 172 genes linked with prognosis were provided by univariate analysis (p < 0.05).
Afterward, Lasso was employed for selecting the most suited gene for developing the IRS model. Based on the minimum lambda = 0.04090851, we obtained 21 genes (Figure 9A). These genes were used for the multivariate analysis. To further decrease gene number, the stepAIC approach was employed. Finally, we got 11 genes (Figure 9B), and the risk coefficients of linked genes were obtained. The risk scores of each sample in the training and validation datasets were measured, and the best cutoff score was used to categorize them into high and low-risk groups, with their KM curves and ROC curves demonstrated separately. In the training set, the AUC value for the 1-year survival rate was 0.81, the AUC value for the 3-year survival rate was 0.75, and the AUC value for the 5-year survival rate was 0.77, whereas in the test set, the AUC value for the 1-year survival rate was 0.75, the AUC value for the 3-year survival rate was 0.72, and the AUC value for the 5-year survival rate was 0.64. (Figures 9C, D). A greater survival rate (p < 0.0001) was observed in the low-risk group in both the training and validation sets. In addition, all TCGA datasets, GSE13507 datasets, and GSE32894 datasets were used to validate our IRS model (Figure 9E–G).
The immunotherapy datasets IMvigor210, GSE91061, GSE78220, and GSE135222 were chosen to predict, evaluate, and compare the efficacy scores of immunotherapy. Our approach was used to calculate IRS in these data, and TIDE was utilized to evaluate the effect of immunotherapy, after which the predictive effect of IRS and TIDE on treatment response was evaluated. The immunotherapy samples were separated into high and low-scoring groups following the best IRS and TIDE cut-off scores. Our IRS score was higher than the TIDE score, according to the results (Figure 10).

Discussion

Research has suggested that the ISCA1 gene is downregulated in 11 types of cancer and upregulated in 4 cancer types. Specifically, the expression of ISCA1 in BLCA was positively linked with the immune score. Therefore, BLCA is the major type of cancer for follow-up analysis and research. BLCA is a highly malignant tumor in the urinary tract. In 2018, there were nearly 549000 new cases and 200000 deaths, ranking the 10th (1). Non-muscle invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC) are the two main subtypes of heterogeneous carcinoma (MIBC). The main component of BLCA in NMIBC. It is prone to recur, despite the fact that it is not lethal (26). To prevent recurrence and progression, chemotherapeutic medicines and the BCG vaccine are administered intrathecally (27). Tumor immunology has been the subject of increasing research recently. Many immune checkpoint inhibitors that have been discovered and demonstrated to produce strong and long-lasting responses in cancer patients (28–30). This is consistent with the findings of this study, demonstrating its validity. CTLA4, PDCD1, CD86, and CD274 had strong positive correlations with ISCA1 in BLCA.

Based on the clinical trials of immune checkpoint inhibitors, the in situ infiltration of TME immune cells is now considered important for the prognosis prediction of different cancer types and observation of how they react to immunotherapy (31, 32). As a result, the overall status of TME immune cell infiltration was thoroughly examined by evaluating the distribution difference of 28 immune cell scores in BLCA in the ISCA1 group. The results revealed that the ISCA1 group had significantly distinct immune cells, with the group with high ISCA1 expression having a higher immunological score.
Furthermore, because macrophages are immunosuppressive cells, most of their hallmark genes were significantly expressed in the *ISCA1* high expression group. The CD8+T and natural killer cells’ activation was suppressed by these immunosuppressive cells (33). Immunosuppressive cells respond to changes in other immune cells and play a key role in the tumor immunological microenvironment. Therefore, we concluded that the poor prognosis of high expression of *ISCA1* can be linked to this tumor immunosuppressive microenvironment. Moreover, CTLA-4, PD-1/PD-L1, and
other immune checkpoints also functioned as rheostats in regulating the immune response by preventing the initiation and immune monitoring of protective immune cells (34, 35). We observed that the expression of immune checkpoints was greatly enhanced in the high expression group of \textit{ISCA1}, which suggests that \textit{ISCA1} might be helpful in predicting the effect of immune checkpoint inhibitor therapy.

\textit{ISCA1} was found to be useful in immunotherapy response prediction in the TCGA-BLCA cohort using the IRS model and TIDE algorithm. All of this suggested that \textit{ISCA1} was a useful biomarker for the immunotherapy response prediction.

However, even if the data from various databases were studied and integrated, the current report still has certain limitations. First, while bioinformatics analysis supplied us with some useful information on \textit{ISCA1}'s role in cancer, we still needed \textit{in vitro} or \textit{in vivo} biology experiments to confirm our findings and boost therapeutic use. More research on the mechanism of \textit{ISCA1}'s function at the molecular and cellular levels would be beneficial.

Second, although post-translational modification was important in controlling intracellular signal transduction and regulatory factor activity, no post-translational modification information for \textit{ISCA1} was found in these databases. Furthermore, whereas \textit{ISCA1} expression was linked to both immunological and clinical survival in human cancer, it was unclear whether \textit{ISCA1} affected clinical survival via the immune pathway.

Finally, the first pan-cancer investigation of \textit{ISCA1} indicated that the factor was differently expressed between tumor and normal tissues, as well as a link between \textit{ISCA1} expression and BLCA clinical outcome. Our outcomes show that the level of \textit{ISCA1} expression influences prognosis. Further research into the
involvement of ISCA1 in each cancer is required. ISCA1 expression in BLCA is also linked to the invasion of different immune cells. These outcomes may help in clarifying the role of ISCA1 in tumorigenesis and development, particularly in BLCA, and give a reference for more accurate and tailored immunotherapy in the future.

Conclusion

Overall, our outcomes indicated that ISCA1 is involved in the progression of pan-cancer, particularly in BLCA. In BLCA, the high expression of ISCA1 predicted a worse prognosis, and the immune scores of some immune cells indicated a major positive link with them. Finally, an IRS model was developed, and the ISCA1-related low-risk group had a higher survival rate. In conclusion, the possibility of ISCA1 as a biomarker for predicting pan-cancer was evaluated comprehensively, and its value in BLCA was determined, which expanded our vision in immunotherapy and can provide a useful evaluation system for clinical application.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Author contribution

All authors contributed to this present work: RLZ designed the study, NXP acquired the data. WL drafted the manuscript and revised the manuscript. All authors read and approved the manuscript.
Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2022.975503/full#supplementary-material

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