Research Article

Pancancer Analysis of Revealed TDO2 as a Biomarker of Prognosis and Immunotherapy

Jing Cui,1,2 Yongjie Tian,3 Tianhang Liu,3 Xueyan Lin,3 Lanyu Li,4 Zhonghui Li,5 and Liang Shen3

1Department of Oral and Maxillofacial Surgery, Jinan Stamotological Hospital, Jinan, 101 Jinglv Road, Shandong 250001, China
2Central Laboratory of Jinan Stamotological Hospital, Jinan Key Laboratory of Oral Tissue Regeneration, Jinan, 101 Jinglv Road, Shandong 250001, China
3Department of Gynecology, Shandong Provincial Hospital Affiliated to Shandong First Medical University, 324 Jingwu Weiqi Road, Jinan, Shandong 250021, China
4Department of Gynecology, Central Hospital Affiliated to Shandong First Medical University, 105. jiefang road, Jinan, Shandong 250013, China
5Department of Gynecology, Meihekou City Central Hospital, 2688 Kangmei Avenue, Meihekou city, Jilin 135000, China

Correspondence should be addressed to Liang Shen; shenlang007@163.com

Received 1 June 2022; Accepted 27 August 2022; Published 9 September 2022

Academic Editor: Drenka Trivanovic

Copyright © 2022 Jing Cui et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Background. Tryptophan 2,3-dioxygenase (TDO) encoded by TDO2, a rate-limiting enzyme in the kynurenine pathway, catabolizes tryptophan to kynurenine, evades immune surveillance, and promotes tumor growth. Although accumulating evidence suggests a crucial role of TDO2 during tumor formation and development, systematic evaluation of TDO2 across human cancers has rarely been reported.

Methods. To shed more light on the role of TDO2 in human cancer, we explored the expression profiles of TDO2 and identified its prognostic value in pancancer analysis through TCGA, CCLE, and GTEx databases. We further utilized TCGA data to evaluate the association between TDO2 and tumor immunological features, such as mismatch repair (MMR), tumor immune infiltration, immune checkpoint-related genes, tumor mutational burden (TMB), microsatellite instability (MSI), and DNA methyltransferase (DNMT).

Results. TDO2 exhibited different expression levels in various cancer cell lines. Frequently, TDO2 was detected to be highly expressed in the majority of cancers. In addition, high TDO2 expression level positively correlated with higher immune infiltration, especially dendritic cells. Additionally, there is a close relationship between TDO2 and immune checkpoint-related gene markers, such as LAIR1, CD276, NRPI, CD80, and CD86. Finally, correlation analysis has demonstrated a high-correlation between TDO2 and TMB, MSI, MMR, and DNMT of multiple cancer types.

Conclusion. Therefore, our results suggest that TDO2 can function as a potential prognostic biomarker due to its role in tumor immunity regulation.

1. Introduction

Globally, cancer remains an enormous health threat and the second most lethal cause of death [1]. Recently, immunotherapy, especially immune checkpoint inhibitor, has been becoming a hot research topic in field of cancer treatment [2]. With the rapid development of public databases, such as The Cancer Genome Atlas (TCGA) and The Genotype-Tissue Expression (GTEx), it is possible to explore novel immunotherapeutic target genes by searching for the relationship between expression and prognosis as well as various biological processes in pancancer [3, 4].

Tryptophan 2,3-dioxygenase (TDO) is encoded by the TDO2 gene and functions as an initial, rate-limiting enzyme in the catabolism of tryptophan (Trp) via the kynurenine (Kyn) pathway and plays an essential role in the balance of systemic Trp levels [5]. Kyn, the major metabolism of Trp degradation, could activate aryl hydrocarbon receptor
Kruskal-wallis test $p = 0$

(a)

Kruskal-wallis test $p = 9.9e-08$

(b)

Figure 1: Continued.
**Figure 1:** TDO2 expression levels in different normal tissues and tumors. (a) TDO2 expression in 31 normal tissues from GTEx database. (b) TDO2 expression in 21 cancer cell lines from CCLE database. (c) Different expression of TDO2 between tumor and peritumor samples from TCGA database. (d) Different expression of TDO2 between normal and tumor samples from TCGA and GTEx databases. Statistical analyses were performed using Kruskal–Wallis test. *P < 0.05, **P < 0.01, ***P < 0.001.
| Disease | HR (95% CI) | P value |
|---------|-------------|---------|
| ACC     | 1.02 (0.99 - 1.03) | 1.2e-01 |
| BLCA    | 1.03 (0.98 - 1.01) | 6.2e-01 |
| BRCA    | 1.01 (0.99 - 1.03) | 2.5e-01 |
| CESC    | 1.03 (0.97 - 1.08) | 7.5e-01 |
| CHOL    | 1 (1 - 1.01) | 9.8e-02 |
| COAD    | 1.01 (0.99 - 1.01) | 6.7e-01 |
| DLBC    | 1.05 (0.95 - 1.16) | 3.6e-01 |
| ESCA    | 1.02 (0.95 - 1.11) | 5.4e-01 |
| GBM     | 1.02 (0.99 - 1.03) | 2.3e-01 |
| HNSC    | 1 (0.98 - 1.01) | 9.3e-01 |
| KIRP    | 1.02 (1 - 1.03) | 1.8e-02 |
| KIRC    | 1.02 (1 - 1.03) | 6.7e-02 |
| KIRP    | 2.01 (1.15 - 3.88) | 2.1e-06 |
| LAML    | 1.29 (0.81 - 2.04) | 2.8e-01 |
| LGG     | 1.28 (1.12 - 1.46) | 2.0e-04 |
| LIHC    | 1 (1 - 1) | 9.8e-01 |
| LUAD    | 0.99 (0.97 - 1.02) | 7.3e-01 |
| LUSC    | 1 (0.97 - 1.02) | 7.5e-01 |
| MESO    | 1.01 (1 - 1.03) | 7.1e-02 |
| ov      | 0.99 (0.97 - 1.01) | 3.4e-01 |
| PAAD    | 1.01 (0.93 - 1.09) | 8.8e-01 |
| PCPG    | 1.02 (0.71 - 1.47) | 9.2e-01 |
| PRAD    | 0.98 (0.93 - 1.04) | 5.6e-01 |
| READ    | 1.02 (1 - 1.03) | 3.3e-02 |
| SARC    | 1 (1 - 1.01) | 9.0e-01 |
| SKCM    | 1 (1 - 1) | 4.3e-01 |
| STAD    | 1.05 (0.98 - 1.11) | 1.8e-01 |
| TGCT    | 1.42 (1.04 - 1.94) | 2.7e-02 |
| THCA    | 0.67 (0.28 - 1.59) | 3.6e-01 |
| THYM    | 1.03 (0.94 - 1.14) | 4.8e-01 |
| UCEC    | 1.01 (1 - 1.01) | 1.7e-01 |
| UCS    | 1.03 (0.98 - 1.08) | 3.0e-01 |
| UVM    | 14.15 (2.17 - 92.36) | 5.6e-03 |

**Figure 2: Continued.**
(AhR), inhibit antitumor immune, and accelerate the survival of cancer cells [6]. TDO2 is found predominantly in the liver under physiological conditions [7]. Recently, increasing evidence has confirmed that TDO2 is also involved in the occurrence and development of many cancers, such as colorectal, breast, esophagus, and bladder cancer [8–10]. Studies

![Graph](image)

**Figure 2:** The correlation between TDO2 expression and OS in pancreatic cancer. (a) Forest plot of OS associations in different cancer types of TCGA. (b) Kaplan–Meier analysis of the association between TDO2 expression and OS in KIRP. (c) Kaplan–Meier analysis of the association between TDO2 expression and OS in LGG. (d) Kaplan–Meier analysis of the association between TDO2 expression and OS in TGCT. (e) Kaplan–Meier analysis of the association between TDO2 expression and OS in UVM. P < 0.05 was considered significant, dash lines for 95% CI.
Table 1: Disease Markers

| Gene   | HR (95% CI)          | P value |
|--------|----------------------|---------|
| AOC    | 1.02 (0.99 – 1.05)   | 1.1e-01 |
| BLCA   | 1.01 (0.98 – 1.05)   | 6.3e-01 |
| BRCA   | 1.02 (0.99 – 1.05)   | 2.3e-01 |
| CESC   | 0.99 (0.94 – 1.05)   | 8.3e-01 |
| CHOL   | 1 (1 – 1.01)         | 8.7e-02 |
| COAD   | 0.99 (0.97 – 1.02)   | 6.5e-01 |
| DLBC   | 1 (0.85 – 1.19)      | 9.6e-01 |
| ESCA   | 1.01 (0.92 – 1.11)   | 8.3e-01 |
| GBM    | 1.02 (0.99 – 1.05)   | 2.2e-01 |
| HNSC   | 1.01 (0.99 – 1.04)   | 3.4e-01 |
| KICH   | 1.22 (1.02 – 1.45)   | 2.6e-02 |
| KIRC   | 1.02 (1 – 1.96)      | 3.6e-02 |
| KIRP   | 2.32 (1.73 – 3.09)   | 1.3e-08 |
| LAML   | NA (NA – NA)         |         |
| LGG    | 1.27 (1.11 – 1.46)   | 6.5e-04 |
| LIHC   | 1 (1 – 1)            | 8.5e-01 |
| LUAD   | 0.99 (0.95 – 1.03)   | 6.1e-01 |
| LSIC   | 1 (0.94 – 1.04)      | 8.2e-01 |
| MESO   | 1.01 (1 – 1.03)      | 1.1e-01 |
| OV     | 0.99 (0.97 – 1.01)   | 2.0e-01 |
| PAAD   | 1.02 (0.94 – 1.1)    | 6.6e-01 |
| PCPG   | 1.05 (0.73 – 1.52)   | 7.9e-01 |
| PRAD   | 0.99 (0.95 – 1.04)   | 7.9e-01 |
| READ   | 1.03 (1.01 – 1.05)   | 7.5e-03 |
| SARC   | 1 (1 – 1)            | 6.4e-01 |
| SKCM   | 1 (1 – 1)            | 6.8e-01 |
| STAD   | 0.98 (0.88 – 1.09)   | 6.6e-01 |
| TGCT   | 1.35 (0.94 – 1.93)   | 1.0e-01 |
| THCA   | 0.58 (0.33 – 0.98)   | 6.6e-01 |
| THYM   | 1.05 (0.85 – 1.30)   | 6.1e-01 |
| UCEC   | 1.01 (1 – 1.02)      | 7.7e-02 |
| UCS    | 1.04 (0.89 – 1.17)   | 8.3e-01 |
| UVM    | 11.53 (5.33 – 24.62) | 1.8e-02 |

Figure 3: Continued.
Figure 3: Continued.
**Figure 3: Continued.**

Survival probability

- **High TDO2 in KIRP Exp**
- **Low TDO2 in KIRP Exp**

**Survival probability**

- HR = 2.32, 95% CI (1.73, 3.09)
- p < 0.0001

**Time**

- 0 1000 2000 3000 4000 5000 6000

- **High**
  - 78  23  8  1  0  0  0

- **Low**
  - 205  82  34  11  4  1  0

**Legend**

- Red: High
- Blue: Low
Figure 3: Continued.

- **TDO2 in LGG Exp**
  - High
  - Low

- Survival probability: $p = 0.0056$
- HR = 1.27, 95% CI (1.11, 1.46)

![Graph showing survival probability over time with categories High and Low for TDO2 in LGG Exp.](image)
have found that liver metastasis of colon cancer could be accelerated by activating the TDO2-Kyn-AhR pathway [11]. However, most research on TDO2 in cancer is limited to a given cancer type. To date, there are rare reports regarding a systematic pancancer analysis of TDO2.

Pancancer analysis aims to examine the commonalities and differences among the genomic and cellular alterations found across different tumor types and can help us explore the mechanisms and predict treatment outcomes from one tumor type to another tumor type. In this study, we utilized a variety of databases, including TCGA, CCLE, and GTEx to explore TDO2 expression levels and their survival on pancancer data. Subsequently, we employed coexpression analysis of TDO2 with immune cells infiltration, immune checkpoint-related genes MMR, DNMT, TMB, and MSI to elucidate the biological functions of TDO2 across 33 types of cancers.

2. Materials and Methods

2.1. Data Collection and Progression. GTEx program provided expression data for 31 normal tissues, which could be downloaded through the GTEx portal. Based on the CCLE database, data were obtained for TDO2 expression in 21 cancer cell lines. Using the GTEx and TCGA data, we examined the differences between TDO2 expression levels in normal tissues and cancer. The level 3 RNA sequencing data and corresponding follow-up information were collected from the TCGA database. The values were performed to remove duplicates, then transformed using log2(TPM + 1) using the robust multichip average (RMA) method [12].

2.2. Cox Regression and Prognosis Analysis. Cox regression analysis was adopted to explore correlations between TDO2 and major clinical outcome endpoints, such as overall survival (OS), disease-specific survival (DSS), and disease-free interval (DFI). Using the Kaplan–Meier method with R package survival, the survival curves were constructed for patients of each cancer type after classifying them into groups based on their TDO2 expression in the best way. The time-dependent receive operating characteristic (ROC) curves were determined with the R packages survival ROC and survival [13]. A P value of less than 0.05 indicated significance.

2.3. Correlation of TDO2 expression with Tumor Immune Microenvironment. The Tumor Immune Estimation
Figure 4: Continued.
Resource (TIMER) is a web-based, free database designed for comprehensive analysis of immune infiltrates in various types of cancer. It identifies immune cell types found in malignancies, such as dendritic cells, neutrophils, CD8+ T cells, CD4+ T cells, macrophages, and B cells. TIMER has already calculated immune cell infiltration scores from the TCGA data and published the results online. A correlation analysis was conducted between the infiltration data and the expression of TDO2 here. Subsequently, a Spearman’s correlation heat map analysis was performed to determine the association between immune checkpoint-related genes and TDO2 gene expression in multiple cancers. TMB refers to the sum of all DNA mutations in tumor cells [14, 15]. The phenomenon of MSI is characterized by the addition or deletion of nucleotides in repeating DNA fragments [16]. Spearman’s correlation analysis was conducted to evaluate the strength of correlation between TDO2 expression and TMB or MSI. In addition, MMR can reduce chromosomal rearrangements, thereby preventing tumor genesis [17]. MutS homolog 6 (MSH6), MutS homolog 2 (MSH2), MutL homolog 1 (MLH1), epithelial cell adhesion molecule (EPCAM), and postmeiotic segregation increased 2 (PMS2) are five critical MMR genes [18]. The correlation of TDO2 with MMR and DNMTs (DNMT1, DNMT2, DNMT3A, and DNMT3B) was investigated.

2.4. Statistics. Spearman’s correlation tests were utilized by using R function correlation to determine the association between TDO2 and a variety of immune-related targets, including immune cell infiltration, immune checkpoint-related genes, TMB, MSI, MMR, and DNMTs. Student’s t-test was performed to determine differences in the TDO2 expression levels between tumors and normal tissues using t-test function in R package. Graphs were generated by the R package ggplot2 and forest plot [19]. A P value of less than 0.05 indicated significance.

3. Results

3.1. Differential Expression of TDO2 in Normal Tissues and Cancer. Based on data from the GTEx, TDO2 expression was deficient across all normal tissues, with the apparent exception of the liver and pituitary (Figure 1(a)). The TDO2 expression level was elevated in various cancer cell lines (Figure 1(b)). Based only on TCGA data, the difference in expression level was statistically significant in 15 of 20
cancer types (KICH, KIRP, LGG, PAAD, and PRAD were five exceptions) (Figure 1(c)). Because the TCGA database contains a small number of normal specimens, we combined it with normal data from GTEx to analyze TDO2 expression differences. The result showed significant differences in TDO2 expression across 24 cancers, with higher TDO2 expression in 20 cancer types (BLCA, BRCA, CESC, COAD, ESCA, GBM, HNSC, KIRC, LUAD, LUSC, OV, PAAD, PRAD, READ, SKCM, STAD, TGCT, THCA, UCEC, and UCS) and with lower TDO2 expression in four cancer types (ACC, CHOL, LAML, and LIHC) as compared with the normal tissues (Figure 1(d)).

3.2. Prognosis Values Analysis of TDO2. We first analyzed the TCGA data to evaluate correlations between TDO2 expression levels and overall survival using univariate Cox regression. The HRs for TDO2 achieved significance in KICH, KIRP, LGG, READ, UVM, and TGCT, among which the highest risk effect was observed in UVM (Figure 2(a)). When Kaplan–Meier analysis was performed on these cancer types, the differences in OS were statistically significant and patients with high TDO2 expression had a poor outcome in KIRP, LGG, TGCT, and UVM (Figures 2(b)–2(e)). Considering nononcological mortality throughout the follow-up, we subsequently examined the associations between TDO2 and DSS in 33 cancer types. There was a significant HR only in READ, LGG, KIRP, KIRC, KICH, and UVM (Figure 3(a)). According to the survival analyses of the six cancer types, patients with lower TDO2 expression have a significantly better prognosis (Figures 3(b)–3(f)). Furthermore, we investigated their relationship and DFI across 33 cancer types. HR was found to be significant in the KIRP, PAAD, and SARC (Figure 4(a)). The survival curve showed that tumors recurred or metastasized sooner in KIRP and PAAD patients with high TDO2 expression (Figures 4(b)–4(c)).

3.3. TDO2 Expression and Immune Cell Infiltration Analyses. Our results suggest that TDO2 could serve as a prognostic biomarker for several cancers. In the immune microenvironment,
immune cells play essential roles and may affect tumor prognosis through tumor immunity [20]. This warrants further study to investigate the relationship between immune infiltration levels and TDO2 expression. Our results show that TDO2 expression correlated significantly with tumor purity in multiple cancer types. The BRCA, CESC, and COAD cancer were the top-ranking cancers. Dendritic cells were the most significant of six cell types in those three cancers (Figure 5).

3.4. Correlation of TDO2 with TMB, MSI, and Immune Checkpoint-Related Genes MMR and DNMT. TMB and MSI function as essential regulators on the occurrence and progression of tumors [21]. There was a significant relationship between TDO2 and TMB in 10 of the 32 cancer types (BRCA, COAD, HNSC, LGG, LUAD, OV, TGCT, and TYUM). TYUM obtained the highest correlation coefficient, while TGCT obtained the lowest (Figure 6(a)). Furthermore, there was a significant relationship between TDO2 and MSI in 9 out of 32 cancer types (CESC, COAD, DLBC, HNSC, KIRP, LIHC, LUAD, LUSC, SKCM, and STAD). The highest coefficients were obtained for COAD and the lowest coefficient was obtained for DLBC (Figure 6(b)). Further studies were carried out to determine the connection between TDO2 and 47 immune checkpoint genes (Figure 7). TDO2 expression was highly correlated with 37 genes in UVM, 36 genes in PAAD, 33 genes in LGG, and 32 genes in TGCT. Moreover, TDO2 expression was associated with some specific immune checkpoint genes, including LAIR1, CD276, NRPI, CD80, and CD86. Mismatch repair (MMR), part of the DNA repair system, plays a crucial role in keeping genomes stable [22]. Our findings revealed that TDO2 expression highly correlates with the MMR genes expression in different cancer types (KIRP, LGG, PAAD, and PRAD) (Figure 8(a)). Several recent studies have demonstrated that DNA methylation plays an essential regulatory function in tumorigenesis [23]. As shown in Figure 8(b), we identified the relationship between TDO2 and four DNMTs. Many tumors express TDO2 associated with four DNMTs, particularly PAAD, MESO, LGG, KIRP, KICH, GMB, and UVM. Mutation and DNA methylation in tumor cells may play a role in TDO2’s involvement in tumor development.

4. Discussion

In the present study, we identified that TDO2 is highly expressed in 20 types of cancer, including BLCA, BRCA, CESC, COAD, ESCA, GBM, HNSC, KIRP, LUAD, LUSC, OV, PAAD, PRAD, READ, SKCM, STAD, TGCT, THCA, UCEC, and UCS, which are in line with previous findings [8–10, 24–28]. However, Wu et al. found that TDO2 was overexpressed in HCC, and their overexpression was correlated with tumor progression and poor prognosis [29, 30], which contradicts our current results. On the other hand, Yu et al. investigated the expression of TDO2 in HCC tissues compared with paired adjacent normal tissues and found that there was downregulation of TDO2 expression in HCC, which agrees with our results [31]. This discrepancy may be due to the complex mechanisms of TDO2 in HCC distinct from other tumors because under normal conditions, TDO2 is predominantly highly expressed in the liver where it is the major metabolic location of Trp.

We found that high TDO2 expression functions as a poor prognostic factor in multiple cancer types, such as KIRP, LGG, TGCT, and UVM. The previous study has proven that TDO2 expression was highly elevated in colorectal cancer, and knockdown of TDO2 significantly inhibited...
the proliferation, migration, and invasion of colorectal cancer cells [32]. In addition, TDO2 was shown to overexpress in liver metastases from UVM and may be related to metastatic potential [33]. TDO2 expression was upregulated in renal cell carcinoma and was associated with worse outcomes [34]. These results imply that aberrant TDO2 expression plays a vital role in the development of cancer.

Our finding suggests that TDO2 expression level is associated with the infiltration distribution of immune cells in various tumors. TDO2 has been reported to suppress proliferation of T cells and induce T cell apoptosis, and in turn can alter the immune response [35]. Studies have proven that an overexpression of TDO2 could activate AhR of immune cells and achieve immune escape [36]. It has been confirmed that TDO2 is involved in mediating tumoral immune resistance, which raised considerable interest of targeting TDO2 for cancer immunotherapy [37]. The treatment with a TDO2 inhibitor could promote the function of dendritic cell and improve T cell mediated immune response, thereby diminishing tumor metastasis in mice [27]. The strong correlation between TDO2 expression and some specific immune checkpoint gene expressions may be consequential to immune cell differentiation activated by AhR pathway.

TMB and MSI could serve as an emerging immunotherapy biomarker predictive of response to immune checkpoint inhibitors of tumors and guide personalized immunotherapy in the precision medicine era [38]. There are studies indicating that TMB has been proposed as an emerging, independent, and important predictive biomarker for cancer especially in non-small-cell lung carcinoma [39]. Multiple studies have found that MSI-H individuals have an improved overall prognosis and a favorable independent predictor. Our results showed that TDO2 expression is associated with TMB in 10 different types of cancer and with MSI in 9 different types of cancer. This may suggest that

![Figure 7: Correlation between TDO2 expression levels and immune checkpoint related expression in multiple tumors. *P < 0.05, **P < 0.01, ***P < 0.001.](image-url)
TD02 expression level will influence the TMB and MSI of cancer, thereby impacting the patient's response to immune checkpoint inhibitors. This might supply some reference to explore the therapeutic effect of TDO2 in immunotherapy.

Mutations and deficiency of MMR genes can result in genetic errors, contributing to tumorigenesis by causing genomic or microsatellite instability [40]. There is evidence that the MMR gene mutation is well positioned to be a predictor of tumorigenesis. Our results indicated that TDO2 expression in human pancancer was closely associated with mutation rates of five MMR genes from pancancer analysis. The alteration of DNA methylation levels has been associated with tumorigenesis and immune evasion in cancer. According to our results, DNMTs and TDO2 expression were specifically correlated in numerous types of cancer, indicating DNA methylation is likely to function in modulating TDO2.

To summarize, our pancancer analysis shows that TDO2 expression was elevated in a variety of tumor types. Our findings demonstrate that TDO2 could exert an oncogenic role and serve as a powerful cancer prognosticator of many
immune functions of TDO2. These checkpoint-related genes, TMB, MSI, MMRs, and DNMTs. This will help us enhance the understanding of immune functions of TDO2 in occurrence and development of various cancers and provide a new perspective on precise immunotherapy.

**Abbreviations**

AhR: Aryl hydrocarbon receptor  
ACC: Adrenal cortical carcinoma  
BLCA: Bladder urothelial carcinoma  
BRCA: Breast invasive carcinoma  
CCLE: Cancer Cell Line Encyclopedia  
CHOL: Cholangiocarcinoma  
COAD: Colon adenocarcinoma  
DFI: Disease-free interval  
DLBC: Lymphoid neoplasm diffuses large B-cell lymphoma  
DSS: Disease-specific survival  
DNMT: DNA methyltransferase  
ESCA: Esophageal carcinoma  
EPCAM: Epithelial cell adhesion molecule  
GBM: Glioblastoma multiforme  
GTEx: The Genotype-Tissue Expression  
KIRC: Kidney renal clear cell carcinoma  
KIRP: Kidney renal papillary cell carcinoma  
Kyn: Kynurenine  
LAML: Acute myeloid leukemia  
LGG: Brain lower grade glioma  
LIHC: Liver hepatocellular carcinoma  
LUAD: Lung adenocarcinoma  
LUSC: Lung squamous cell carcinoma  
MESO: Mesothelioma  
MLH1: Mutl. homolog 1  
MMR: Mismatch repair  
MSI: Microsatellite instability  
MSH2: MutS homolog 2  
MSH6: MutS homolog 6  
OS: Overall survival  
OV: Ovarian serous cystadenocarcinoma  
PAAD: Pancreatic adenocarcinoma  
PCPG: Pheochromocytoma and paraganglioma  
PD-1: Programmed cell death protein 1s  
PMS2: Postmeiotic segregation increased 2  
PRAD: Prostate adenocarcinoma  
READ: Rectum adenocarcinoma  
SARC: Sarcoma  
SKCM: Skin cutaneous melanoma  
STAD: Stomach adenocarcinoma  
TCGA: The Cancer Genome Atlas  
TDO: Tryptophan 2,3-dioxygenase  
TGCT: Testicular germ cell tumor  
THYM: Thymoma  
TIMER: Tumor Immune Estimation Resource  
TMB: Tumor mutation burden  
Trp: Tryptophan  
UCEC: Uterine corpus endometrial carcinoma  
UVM: Uveal melanoma.

**Data Availability**

All data are present in table and figures in this article; it can be available from the journal website.

**Conflicts of Interest**

The authors have declared that no competing interests exist.

**Acknowledgments**

This work was supported by the Shandong First Medical University Teaching Reform Project Funds (Grant No. 2021XY096).

**References**

[1] S. Maleki, J. Jabalee, and C. Garnis, “The role of extracellular vesicles in mediating resistance to anticancer therapies,” *International Journal of Molecular Sciences*, vol. 22, no. 8, p. 4166, 2021.

[2] K. E. Mayer, S. Mall, N. Yusuf et al., “T-cell functionality testing is highly relevant to developing novel immuno-tracers monitoring T cells in the context of immunotherapies and revealed CD7 as an attractive target,” *Theranostics*, vol. 8, no. 21, pp. 6070–6087, 2018.

[3] C. Zhang, X. Ren, J. He, W. Wang, C. Tu, and Z. Li, “The prognostic value of long noncoding RNA SNHG16 on clinical outcomes in human cancers: a systematic review and meta-analysis,” *Cancer Cell International*, vol. 19, no. 1, p. 261, 2019.

[4] A. Mock, S. Murphy, J. Morris, F. Marass, N. Rosenfeld, and C. Massie, “CVE: an R package for interactive variant prioritization in precision oncology,” *BMC Medical Genomics*, vol. 10, no. 1, p. 37, 2017.

[5] L. Wang, Z. Pi, S. Liu, Z. Liu, and F. Song, “Targeted metabolome profiling by dual-probe microdialysis sampling and treatment using *Gardenia jasminoides* for rats with type 2 diabetes,” *Scientific Reports*, vol. 7, no. 1, p. 10105, 2017.

[6] M. Wyatt and K. L. Greathouse, “Targeting dietary and microbial tryptophan-indole metabolism as therapeutic approaches to colon cancer,” *Nutrients*, vol. 13, no. 4, p. 1189, 2021.

[7] S. Sari, P. Tomek, E. Leung, and J. Reynisson, “Discovery and characterisation of dual inhibitors of tryptophan 2,3-dioxygenase (TDO2) and indoleamine 2,3-dioxygenase 1 (IDO1) using virtual screening,” *Molecules*, vol. 24, no. 23, p. 4346, 2019.

[8] Q. Liu, J. Zhai, X. Kong et al., “Comprehensive analysis of the expression and prognosis for TDO2 in breast cancer,” *Molecular Therapy-Oncolytics*, vol. 17, pp. 153–168, 2020.

[9] I. C. Chen, K. H. Lee, Y. H. Hsu, W. R. Wang, C. M. Chen, and Y. W. Cheng, “Expression pattern and clinicopathological relevance of the indoleamine 2,3-dioxygenase 1/tryptophan 2,3-dioxygenase protein in colorectal cancer,” *Disease Markers*, vol. 2016, Article ID 8169724, 9 pages, 2016.

[10] Q. T. Pham, D. Taniyama, S. Akabane et al., “TDO2 overexpression correlates with poor prognosis, cancer stemness, and resistance to cetuximab in bladder cancer,” *Cancer Reports*, vol. 4, no. 6, article e1417, 2021.
T. Miyazaki, S. Chung, H. Sakai et al., “Stemness and immune evasion conferred by the TDO2-ARH pathway are associated with liver metastasis of colon cancer,” Cancer Science, vol. 113, no. 1, pp. 170–181, 2022.

P. Eriksson, N. A. Marzouka, G. Sjodahl, C. Bernardo, F. Liedberg, and M. Hoglund, “A comparison of rule-based and centroid single-sample multiclass predictors for transcriptional classification,” Bioinformatics, vol. 38, no. 4, pp. 1022–1029, 2022.

S. Yang, T. Liu, Y. Cheng, Y. Bai, and G. Liang, “Immune cell infiltration as a biomarker for the diagnosis and prognosis of digestive system cancer,” Cancer Science, vol. 110, no. 12, pp. 3639–3649, 2019.

B. Zhou and S. Gao, “Pan-cancer analysis of FURIN as a potential prognostic and immunological biomarker,” Frontiers in Molecular Biosciences, vol. 8, article 648402, 2021.

F. Chen, J. Song, Z. Ye et al., “Integrated analysis of cell cycle-related and immunity-related biomarker signatures to improve the prognosis prediction of lung adenocarcinoma,” Frontiers in Oncology, vol. 11, article 666826, 2021.

K. H. Huang, M. H. Chen, W. L. Fang et al., “The clinicopathological characteristics and genetic alterations of signet-ring cell carcinoma in gastric cancer,” Cancers (Basel), vol. 12, no. 8, 2020.

T. F. Hansen, S. Kjaer-Frifeldt, A. C. Eriksen et al., “Prognostic impact of CDX2 in stage II colon cancer: results from two nationwide cohorts,” British Journal of Cancer, vol. 119, no. 11, pp. 1367–1373, 2018.

S. M. Son, C. G. Woo, D. H. Kim et al., “Distinct tumor immune microenvironments in primary and metastatic lesions in gastric cancer patients,” Scientific Reports, vol. 10, no. 1, p. 14293, 2020.

D. Xiong, Y. Wang, and M. You, “Tumor intrinsic immunity related proteins may be novel tumor suppressors in some types of cancer,” Scientific Reports, vol. 9, no. 1, p. 10918, 2019.

J. Wang, X. Bo, C. Wang et al., “Low immune index correlates with favorable prognosis but with reduced benefit from chemotheraphy in gallbladder cancer,” Cancer Science, vol. 111, no. 1, pp. 219–228, 2020.

R. Park, L. L. Da Silva, and A. Saeed, “Immunotheapy predictive molecular markers in advanced gastroesophageal cancer: MSI and beyond,” Cancers (Basel), vol. 13, no. 7, 2021.

Y. Wang, Z. Zhao, J. Zhuang et al., “Prognostic value of autophagy, microsatellite instability, and KRASMutations in colorectal cancer,” Journal of Cancer, vol. 12, no. 12, pp. 3515–3528, 2021.

M. Moradi Sarabi, R. Mohammadrezaei Khorraramabadi, Z. Zare, and E. Eftekhar, “Polyunsaturated fatty acids and DNA methylation in colorectal cancer,” World Journal of Clinical Cases, vol. 7, no. 24, pp. 4172–4185, 2019.

Q. T. Pham, N. Oue, Y. Sekino et al., “TDO2 overexpression is associated with cancer stem cells and poor prognosis in esophageal squamous cell carcinoma,” Oncology, vol. 95, no. 5, pp. 297–308, 2018.

M. K. Halle, A. C. Munk, B. Engesaeter et al., “A gene signature identifying CIN3 regression and cervical cancer survival,” Cancers (Basel), vol. 13, no. 22, 2021.

Y. Zhao, F. Tao, J. Jiang et al., “Tryptophan 2, 3-dioxygenase promotes proliferation, migration and invasion of ovarian cancer cells,” Molecular Medicine Reports, vol. 23, no. 6, 2021.

C. Riess, B. Schneider, H. Kehnscherper et al., “Activation of the kynurenine pathway in human malignancies can be suppressed by the cyclin-dependent kinase inhibitor dinaciclib,” Frontiers in Immunology, vol. 11, p. 55, 2020.

F. Li, Z. Zhao, Z. Zhang, Y. Zhang, and W. Guan, “Tryptophan metabolism induced by TDO2 promotes prostatic cancer chemotherapy resistance in a AhR/c-Myc dependent manner,” BMC Cancer, vol. 21, no. 1, p. 1112, 2021.

Z. Wu, L. Yan, J. Lin, K. Ke, and W. Yang, “Constitutive TDO2 expression promotes liver cancer progression by an autocrine IL-6 signaling pathway,” Cancer Cell International, vol. 21, no. 1, p. 538, 2021.

H. Liu, Y. Xiang, Q. B. Zong et al., “TDO2 modulates liver cancer cell migration and invasion via the Wnt5a pathway,” International Journal of Oncology, vol. 60, no. 6, 2022.

C. Yu, D. Rao, H. Zhu et al., “TDO2 was downregulated in hepatocellular carcinoma and inhibited cell proliferation by upregulating the expression of p21 and p27,” BioMed Research International, vol. 2021, Article ID 4708439, 10 pages, 2021.

L. Zhao, B. Wang, C. Yang et al., “TDO2 knockdown inhibits colorectal cancer progression via TDO2-KNYU-Ahr pathway,” Gene, vol. 792, article 145736, 2021.

M. Terai, E. Londin, A. Rochani et al., “Expression of tryptophan 2,3-dioxygenase in metastatic uterine melanoma,” Cancers, vol. 12, no. 2, p. 405, 2020.

Q. T. Pham, D. Taniyama, Y. Sekino et al., “Clinicopathologic features of TDO2 overexpression in renal cell carcinoma,” BMC Cancer, vol. 21, no. 1, p. 737, 2021.

C. P. Yu, Y. L. Song, Z. M. Zhu, B. Huang, Y. Q. Xiao, and D. Y. Luo, “Targeting TDO in cancer immunotherapy,” Medical Oncology, vol. 34, no. 5, p. 73, 2017.

D. L. Dewi, S. R. Mohapatra, S. Blanco Cabanes et al., “Suppression of indoleamine-2,3-dioxygenase 1 expression by promoter hypermethylation in ER-positive breast cancer,” Oncoimmunology, vol. 6, no. 2, article e127477, 2017.

F. Chen, G. Xu, W. Tian, and S. Gou, “Breakdown of chemo-immune resistance by a TDO2-targeted Pt(IV) prodruk via attenuating endogenous Kyn-Ahr-AQP4 metabolic circuitry and TLS-promoted genomic instability,” Biochemical Pharmacology, vol. 193, article 114785, 2021.

J. Zhu, T. Zhang, J. Li et al., “Association between tumor mutation burden (TMB) and outcomes of cancer patients treated with PD-1/PD-L1 inhibitions: a meta-analysis,” Frontiers in Pharmacology, vol. 10, p. 673, 2019.

J. N. Bodor, Y. Boumber, and H. Borghaei, “Biomarkers for immune checkpoint inhibition in non-small cell lung cancer (NSCLC),” Cancer, vol. 126, no. 2, pp. 260–270, 2020.

H. Zhao, B. Thienpont, B. T. Yesilyurt et al., “Mismatch repair deficiency endows tumors with a unique mutation signature and sensitivity to DNA double-strand breaks,” eLife, vol. 3, article e02725, 2014.