REVIEW

Multifaceted roles and functions of SOX30 in human cancer

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Abstract

SRY-box transcription factor 30 (SOX30) participates in tumor cell apoptosis in lung cancer. The occurrence of somatic SOX30 mutations, the expression signature of SOX30 in normal and cancer tissues, the correlation of SOX30 with immune cells and immune-related genes, and the clinical significance of SOX30 in various cancers have stimulated interest in SOX30 as a potential cancer biomarker. SOX30 influences drug sensitivity and tumor immunity in specific cancer types. In this review, we have comprehensively summarized the latest research on the role of SOX30 in cancer by combining bioinformatics evidence and a literature review. We summarize recent research on SOX30 in cancer regarding somatic mutations, trials, transcriptome analysis, clinical information, and SOX30-mediated regulation of malignant phenotypes. Additionally, we report on the diagnostic value of SOX30 mRNA expression levels across different cancer types. This review on the role of SOX30 in cancer progression may provide insights into possible research directions for SOX30 in cancer and a theoretical basis for guiding future studies.

KEYWORDS
cancer progression, prognosis, SOX30

1 | INTRODUCTION

SRY-box transcription factor (SOX) family proteins are divided into eight groups, including the A, B (B1 and B2), and C–H groups, in accordance with the high-mobility group (HMG) structural sequence, protein structure, and evolutionary relationship [1–3]. Some studies have suggested that while different SOX family members demonstrate functional overlap, the specific substrates are unique to each SOX class. In some cases, each SOX protein is unique.

SOX30 is a SOXH group member that was first characterized in 1999, and its gene is located on human chromosome 2. The human SOX30 gene encodes three transcript variants (Figure 1). The three-dimensional structure of human SOX30 protein is available in the Protein Data Bank (ID: 7jjk.1). The crystal structure of SOX30 was resolved at a resolution of 1.40 Å, revealing a conserved HMG domain characterized by its DNA-binding capability. The N- and C-terminal regions contribute to overall protein folding and stability of the protein (Figure 1). SOX30 activates transcription from a synthetic promoter containing an ACAT motif and is expressed specifically in the testes [4].

In this review, we summarize the most recent knowledge of SOX30-mediated functions in cancer. We discuss SOX30 mRNA expression in normal and cancer tissues and the relationship between SOX30 and immune cells. We also review the current research findings on SOX30 somatic mutations, fusion proteins, the expression of SOX30 in nonsmall cell lung cancer (NSCLC), esophagogastric cancer and other tumor types, and SOX30 functions in regulating cancer progression. Moreover, we review the prognostic role of SOX30 in pan-cancer, its correlation with immune cells and immune genes, and its diagnostic value in pan-cancer.

2 | SOX30 SOMATIC MUTATIONS AND CANCER

Various mechanisms, including copy number variants and DNA methylation, play an important role in gene expression regulation [5, 6]. The SOX30 gene is altered in patients with cancer. Gene amplification and mutation is the main type of SOX30 alteration in patients with renal clear cell carcinoma and endometrial cancer, respectively. Deep deletion has been reported in melanoma, NSCLC, esophagogastric cancer, ovarian epithelial tumor, ocular melanoma, bladder cancer, colorectal cancer (CRC), pleural mesothelioma, breast cancer (BRCA), glioma, and head and neck cancer. We integrated recently published pan-cancer data from The Cancer Genome Atlas (TCGA) and the International Cancer Genome Consortium [7]. The SOX30 mutation signatures across cancer types were obtained from the cBioPortal (https://www.cbioportal.org/) database and are summarized in Figure 2 and Table 1 [8, 9].

Han et al. [10] showed that the SOX30 gene is hypermethylated in lung cancer and does not harbor mutations or deletions in lung cancer. Methylation is a key molecular marker for early diagnosis and prognosis evaluation of some tumors [11]. Hypermethylation of the SOX30 gene was shown to be involved in the development of lung cancer and has tumor heterogeneity.

3 | SOX30 EXPRESSION IN DIFFERENT CANCERS

SOX30 was identified as a target of microRNA-645 (miR-645) in CRC, suggesting that miR-645 regulates SOX30 expression [12]. In malignant lymphoma, miR-125b is negatively correlated with SOX30 [13].

SOX30 is expressed at low levels in prostate cancer cells [14], while it is upregulated in ovarian cancer (OV) [15]. We retrieved and normalized data from GTEx and TCGA data sets and evaluated pan-cancer SOX30 expression in cancer and paracancer tissues (Figure 3). SOX30 was upregulated in cervical cancer (CESC), cholangiocarcinoma (CHOL), colon adenocarcinoma, colon cancer (COAD), diffuse large B cell lymphoma (DLBC), esophageal cancer (ESCA), glioblastoma (GBM), head and neck squamous cell carcinoma (HNSC), acute myeloid leukemia (AML), low-grade glioma, lung adenocarcinoma (LUAD), LUSC, OV, pancreatic adenocarcinoma, pancreatic cancer (PAAD),
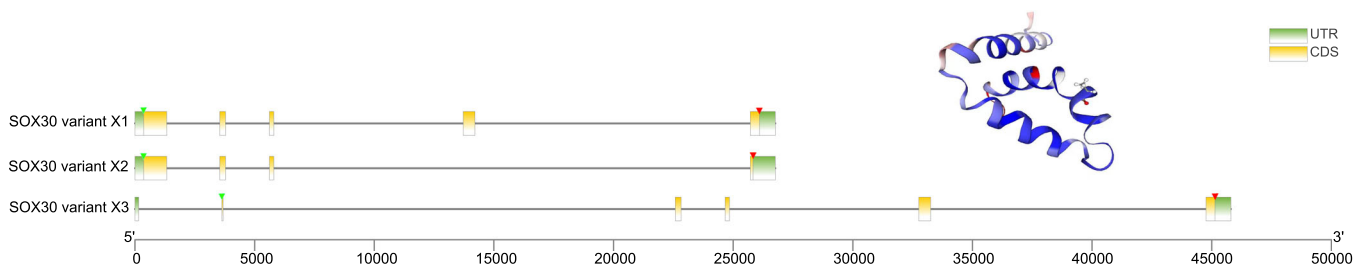

FIGURE 1 The three-dimensional structure of human SRY-box transcription factor 30 (SOX30) protein and a structural diagram of human SOX30. Red and green arrows indicate the stop and start codon positions, respectively. Orange indicates the matching protein structures in each isoform. The data analyzed were obtained from the National Center for Biotechnology Information.
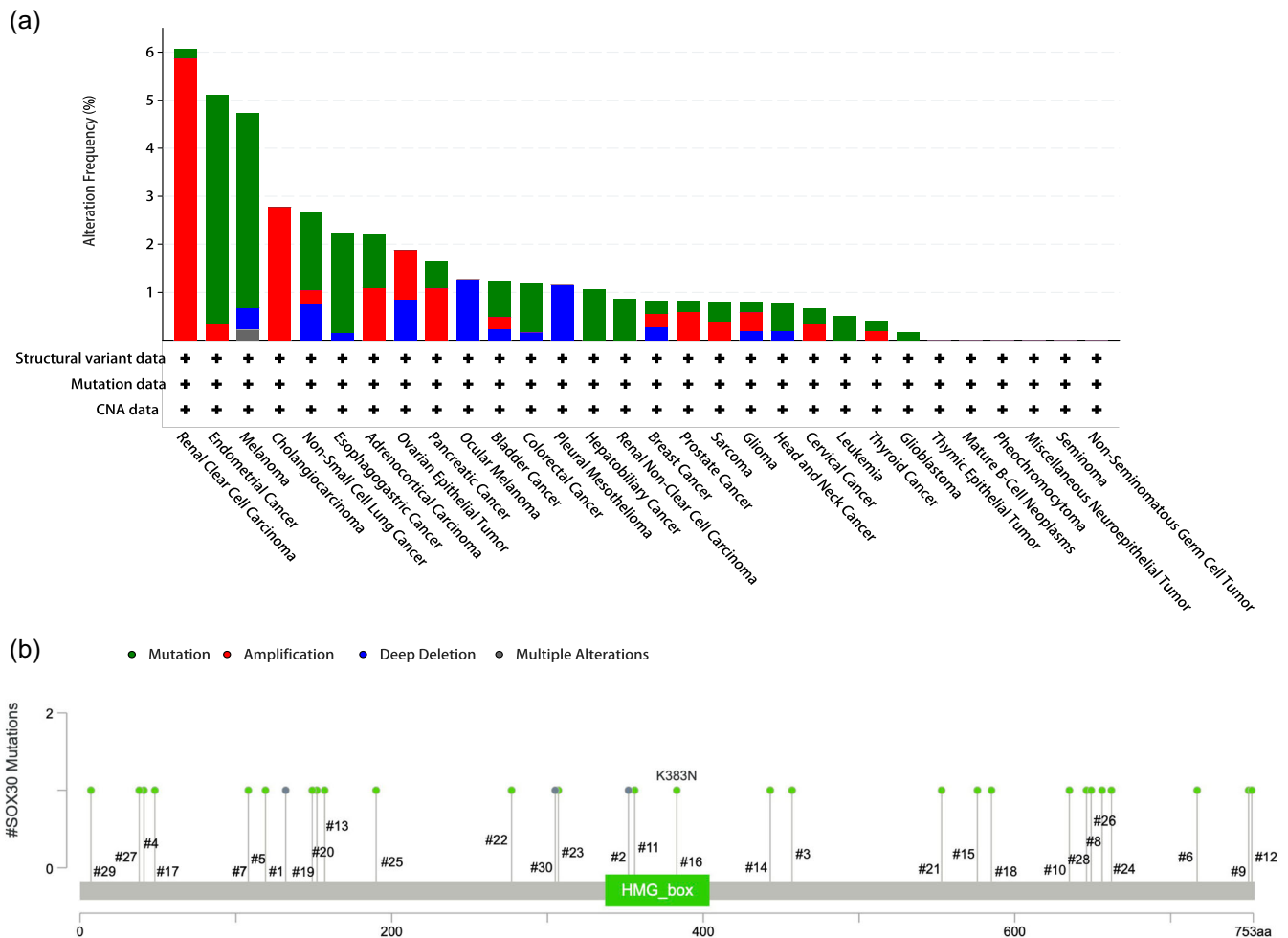
(a)

(b)

FIGURE 2 Mutational signature of SRY-box transcription factor 30 (*SOX30*) in different tumors. (a) Mutation type and frequency. (b) Pan-cancer study of the whole genome suggests the *SOX30* gene mutation type and location. Colors indicate the specific mutation type: light green indicates missense mutations (of unknown significance) while gray indicates truncating mutations (of unknown significance), including discontinuities, frame-shifting deletions, frame-shifting insertions, and splice points.

rectum adenocarcinoma (READ), skin cutaneous melanoma, stomach adenocarcinoma, stomach cancer (STAD), and thymoma (THYM). In contrast, SOX30 levels were low in bladder urothelial carcinoma (BLCA), kidney chromophobe (KICH), kidney renal clear cell carcinoma (KIRC), kidney papillary cell carcinoma (KIRP), prostate adenocarcinoma, prostate cancer (PRAD), testicular germ cell tumor (TGCT), thyroid cancer (THCA), and uterine corpus endometrial carcinoma (UCEC).

We also summarized SOX30 protein expression levels through the Human Protein Atlas (HPA) network (https://www.proteinatlas.org/). Quantitative analysis of immunohistochemistry (IHC) results demonstrated different degrees of SOX30 expression in BRCA, CESC, COAD, endometrial cancer (UCEC), liver hepatocellular carcinoma (LIHC), LUAD, lymphoma, OV, PAAD, prostate adenocarcinoma, PRAD, kidney cancer, SKCM, stomach adenocarcinoma, STAD, TGCT, THCA, and BLCA compared with healthy tissues (Supporting Information S1: Figure S1).

4 | SOX30 AND CLINICAL OUTCOMES

Numerous reports showed that SOX30 is closely related to the clinical outcomes of cancer patients. An association was found between SOX30 expression and clinical stage and histological type [16, 17]. SOX30 was identified as a prognostic factor for overall survival (OS) in patients with NSCLC, patients with high *SOX30* expression had a better prognosis. While SOX30 was an independent and favorable prognostic factor for patients with LUAD, no relationship was observed with prognosis in LUSC [16, 17]. SOX30 was associated with clinical stage, tissue grading, and lymph node positivity in LUAD patients [16]. One study showed that SOX30 regulates the expression of deglycosome genes and inhibits LUAD cell proliferation, invasion, and migration [18].

SOX30 is highly expressed in OV tissues and associated with OV clinical stage and metastasis.

TABLE 1 SOX30 mutations in pan-cancer.

Sample ID	Cancer type detailed	Protein change	Mutation type	Variant type	Copy number	Mutations in sample
#1	Uterine leiomyosarcoma	A132Gfs*25	Frame_Shift_Del	DEL		127
#2	Esophageal adenocarcinoma	R352*	Nonsense_Mutation	SNP		164
#3	Soft tissue myoepithelial carcinoma	P457L	Missense_Mutation	SNP		1726
#4	Soft tissue myoepithelial carcinoma	P41L	Missense_Mutation	SNP		1726
#5	Breast invasive ductal carcinoma	A119T	Missense_Mutation	SNP		1070
#6	Cutaneous melanoma	G717E	Missense_Mutation	SNP		1291
#7	Lung adenocarcinoma	R108L	Missense_Mutation	SNP		392
#8	Cutaneous melanoma	L649F	Missense_Mutation	SNP		1975
#9	Cutaneous melanoma	L750F	Missense_Mutation	SNP		837
#10	Cutaneous melanoma	P635L	Missense_Mutation	SNP		6485
#11	Melanoma of unknown primary	A356V	Missense_Mutation	SNP		580
#12	Cutaneous melanoma	D752N	Missense_Mutation	SNP		1691
#13	Melanoma	E157K	Missense_Mutation	SNP	ShallowDel	1893
#14	Diffuse-type stomach adenocarcinoma	R443H	Missense_Mutation	SNP	ShallowDel	222
#15	Colorectal adenocarcinoma	R576K	Missense_Mutation	SNP	Diploid	12,012
#16	Colorectal adenocarcinoma	K383N	Missense_Mutation	SNP	Diploid	12,012
#17	Glioblastoma	S48N	Missense_Mutation	SNP	Diploid	2510
#18	Melanoma	P585L	Missense_Mutation	SNP	Diploid	2106
#19	Pancreatic neuroendocrine tumor	S149L	Missense_Mutation	SNP	Diploid	19
#20	Pancreatic adenocarcinoma	P152S	Missense_Mutation	SNP	Diploid	248
#21	Renal clear cell carcinoma	A553D	Missense_Mutation	SNP	Gain	107
#22	Renal clear cell carcinoma	G277E	Missense_Mutation	SNP	Gain	107
#23	Mucinous adenocarcinoma of the colon and rectum	K307N	Missense_Mutation	SNP	Diploid	11,034
#24	Hepatocellular carcinoma	I662V	Missense_Mutation	SNP	Diploid	63
#25	Diffuse-type stomach adenocarcinoma	E190K	Missense_Mutation	SNP	ShallowDel	222
#26	Uterine endometrioid carcinoma	Y656H	Missense_Mutation	SNP	Diploid	1321
#27	Melanoma	P38Q	Missense_Mutation	SNP	Diploid	1261
#28	Melanoma	P646L	Missense_Mutation	SNP	ShallowDel	1893
#29	Lung squamous cell carcinoma	E7K	Missense_Mutation	SNP	Diploid	325
#30	Cholangiocarcinoma	S305Hfs*16	Frame_Shift_Del	DEL	Diploid	41

Abbreviation: SOX30, SRY-box transcription factor 30.

High SOX30 expression was not associated with OS in patients with early OV, but it predicted better OS in patients with advanced disease and may be an independent prognostic factor [15]. SOX30 was found to prevent OV metastasis by inhibiting epithelial-to-mesenchymal transition (EMT) [15].

In a study including 510 BRCA samples, high SOX30 expression was an independent factor for favorable
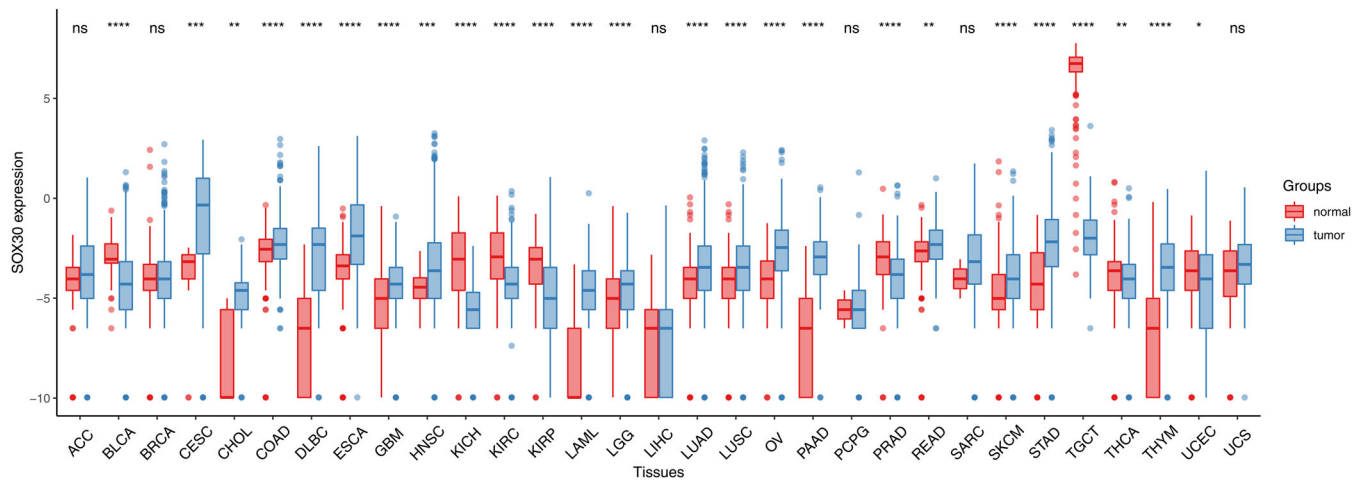
FIGURE 3 SRY-box transcription factor 30 (*SOX30*) expression level in a pan-cancer data set. *SOX30* expression levels are displayed in 31 types of cancer. The red column represents normal tissue, while the blue column represents tumor tissue. ns, no significance, *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

disease-free survival and OS [19]. Other studies revealed that CRC tumor tissue had significantly lower SOX30 protein and mRNA expression than paracancerous tissue. Higher SOX30 mRNA and protein expression were negatively correlated with tumor size, lymph node metastasis, T stage, N stage, and tumor-node-metastasis stages. However, SOX30 protein expression was positively correlated with OS while its mRNA expression was not. Multivariate Cox regression analysis demonstrated that high SOX30 expression was an independent factor for favorable OS [20]. Another study showed SOX30 expression had a predictive influence on the prognosis of clear cell carcinoma patients [21].

We analyzed TCGA data and found SOX30 resulted in poorer outcomes for esophageal adenocarcinoma, KIRC, KIRP, LIHC, LUSC, gastric adenocarcinoma, endometrial carcinoma, and pancreatic ductal carcinoma. Good patient outcomes were recorded between SOX30 and adenocarcinoma, rectal adenocarcinoma, sarcoma, and THCA, while SOX30 had no significant effect on breast, bladder, and OVs. The influence of SOX30 on the outcome of patients with some cancers, such as LUSC and OV, was inconsistent with previous reports; this may be from differences in case numbers and ethnicity and inconsistent detection platforms (Tables 2 and 3). SOX30 methylation was related to the disease progression of chronic myeloid leukemia and related to OS and leukemia-free survival in AML [22, 23].

Recent studies have implicated SOX30 in the development and progression of various cancers, including BRCA, PRAD, lung cancers, and CRC. In BRCA, SOX30 was shown to be upregulated in breast tumor tissues, and its upregulation contributes to the development of aggressive and treatment-resistant subtypes of the disease [19]. Studies also demonstrated that SOX30 promotes the

survival and proliferation of BRCA cells and functions in the regulation of cellular processes such as angiogenesis and EMT [19]. SOX30 was identified as a potential therapeutic target in PRAD; high levels of SOX30 expression were associated with aggressive prostate tumors and a poorer prognosis. In vitro studies showed that inhibiting SOX30 expression in prostate cancer cells leads to decreased cell viability and increased apoptosis [14]. SOX30 is upregulated in NSCLC and promotes cell proliferation and tumor growth [24]. In CRC, SOX30 was identified as a predictor of poor prognosis; it is involved in the regulation of cancer stem cell properties [25].

In conclusion, SOX30 is emerging as a promising therapeutic target in a wide variety of human cancers. Further studies are necessary to clarify the mechanisms underlying the role of SOX30 in cancer and to develop effective strategies for targeting SOX30 in the clinic.

5 | THE DIAGNOSTIC ROLE OF SOX30 IN CANCER

miR-125b is negatively correlated with SOX30 in malignant lymphoma and functions as a diagnostic and treatment marker for the disease [13]. Evaluation of diagnostic accuracy by receiver operating characteristic analysis [26] demonstrated that SOX30 had good predictive value in CHOL (area under the curve [AUC] = 89.2%, 95% confidence interval [CI] = 77.8%–100.0%, specificity = 88.9%, sensitivity = 80.6%), CESC (AUC = 88.6%, 95% CI = 75.3%–100.0%, specificity = 100.0%, sensitivity = 76.5%), ESCA (AUC = 81.7%, 95% CI = 70.7%–92.6%, specificity = 81.8%, sensitivity = 74.7%), KICH (AUC = 99.4%, 95% CI = 98.5%–100.0%, specificity = 100.0%, sensitivity = 95.4%), KIRC

TABLE 2 Correlation between SOX30 and OS of patients with cancer.

Symbol	Cancer type	Prognosis	Endpoint	*p* Value	Case	Data set	Method
SOX30	Bladder carcinoma	–	OS	0.2084	404	TCGA	RNA-seq
SOX30	Breast cancer	–	OS	0.0917	1089	TCGA	RNA-seq
SOX30	Cervical squamous cell carcinoma	–	OS	0.0762	304	TCGA	RNA-seq
SOX30	Esophageal adenocarcinoma	Poor	OS	0.0137	80	TCGA	RNA-seq
SOX30	Esophageal squamous cell carcinoma	–	OS	0.251	81	TCGA	RNA-seq
SOX30	Head-neck squamous cell carcinoma	–	OS	0.0823	499	TCGA	RNA-seq
SOX30	Kidney renal clear cell carcinoma	Poor	OS	0.0222	530	TCGA	RNA-seq
SOX30	Kidney renal papillary cell carcinoma	Poor	OS	0.0247	287	TCGA	RNA-seq
SOX30	Liver hepatocellular carcinoma	Poor	OS	0.0176	370	TCGA	RNA-seq
SOX30	Lung adenocarcinoma	–	OS	0.1759	504	TCGA	RNA-seq
SOX30	Lung squamous cell carcinoma	Poor	OS	0.0061	495	TCGA	RNA-seq
SOX30	Ovarian cancer	–	OS	0.0883	373	TCGA	RNA-seq
SOX30	Pancreatic ductal adenocarcinoma	Good	OS	0.0287	177	TCGA	RNA-seq
SOX30	Pheochromocytoma and paraganglioma	–	OS	0.2949	178	TCGA	RNA-seq
SOX30	Rectum adenocarcinoma	Good	OS	0.0064	165	TCGA	RNA-seq
SOX30	Sarcoma	Good	OS	0.034	259	TCGA	RNA-seq
SOX30	Stomach adenocarcinoma	Poor	OS	0.0431	371	TCGA	RNA-seq
SOX30	Testicular germ cell tumor	–	OS	0.1513	134	TCGA	RNA-seq
SOX30	Thymoma	–	OS	0.261	118	TCGA	RNA-seq
SOX30	Thyroid carcinoma	Good	OS	0.0112	502	TCGA	RNA-seq
SOX30	Uterine corpus endometrial carcinoma	Poor	OS	0.0008	542	TCGA	RNA-seq

Abbreviations: OS, overall survival; SOX30, SRY-box transcription factor 30; TCGA, The Cancer Genome Atlas.

(AUC = 91.2%, 95% CI = 88.1%–94.2%, specificity = 88.9%, sensitivity = 84.3%), KIRP (AUC = 92.1%, 95% CI = 88.8%–95.4%, specificity = 87.5%, sensitivity = 88.6%), and PRAD (AUC = 80.7%, 95% CI = 75.1%–86.3%, specificity = 78.8%, sensitivity = 73.1%). However, SOX30 showed no diagnostic significance for LIHC (AUC = 48.4%, 95% CI = 41.0%–55.8%, specificity = 80.0%, sensitivity = 28.3%) (Figure 4 and Table 4). SOX30 expression may be useful in diagnosing CHOL, CESC, ESCA, KICH, KIRC, KIRP, and PRAD. These results are preliminary and follow-up research is required.

6 | CORRELATION BETWEEN SOX30 AND IMMUNE INFILTRATION IN CANCER

Analysis of the CIBERSORT database demonstrated that SOX30 expression correlated with various immune cells in most cancers. In the European Prospective Investigation into Cancer and Nutrition database, SOX30 was significantly, negatively correlated with B cells, cancer-associated fibroblasts (CAFs), natural killer cells, and macrophages. SOX30 was significantly positively correlated with CD4+T cells. TIMER2.0 database analysis demonstrated different relationships between SOX30 and the same immune cell subtypes. For example, in the CD4+T cell subsets, SOX30 was significantly, negatively correlated with Th1 cells and significantly, positively correlated with CD4+ memory cells. Moreover, there was a significant negative correlation between SOX30 and T cells (Figure 5a,b). These findings demonstrated that SOX30 participates in immune infiltration to a certain extent and builds an important bridge between tumor and immunity. Notably, various tumors have different or even opposite trends regarding immune infiltration. Some studies have reported that CAFs can support tumor growth [27] and enable tumors to escape immune surveillance [28]. CAFs are associated with PAAD.

Metastasis [29], apoptosis, and drug resistance are significantly related to poor prognosis in lung cancer [30], ESCA [31], and colon cancer [32]. There is increasing evidence that tumor-infiltrating immune cells may play a

TABLE 3 Correlation between SOX30 and survival rate (RFS) of patients with cancer.

Symbol	Cancer type	Prognosis	Endpoint	*p* Value	Case	Data set	Method
SOX30	Bladder carcinoma	Poor	RFS	0.0241	187	TCGA	RNA-seq
SOX30	Breast cancer	Good	RFS	0.0079	947	TCGA	RNA-seq
SOX30	Cervical squamous cell carcinoma	Poor	RFS	0.0473	174	TCGA	RNA-seq
SOX30	Esophageal adenocarcinoma	Poor	RFS	0.0008	19	TCGA	RNA-seq
SOX30	Esophageal squamous cell carcinoma	–	RFS	0.115	54	TCGA	RNA-seq
SOX30	Head-neck squamous cell carcinoma	Poor	RFS	0.0135	134	TCGA	RNA-seq
SOX30	Kidney renal clear cell carcinoma	Poor	RFS	0.0229	117	TCGA	RNA-seq
SOX30	Kidney renal papillary cell carcinoma	Poor	RFS	0.0197	183	TCGA	RNA-seq
SOX30	Liver hepatocellular carcinoma	Good	RFS	0.0029	316	TCGA	RNA-seq
SOX30	Lung adenocarcinoma	Good	RFS	0.0453	300	TCGA	RNA-seq
SOX30	Lung squamous cell carcinoma	–	RFS	0.4276	300	TCGA	RNA-seq
SOX30	Ovarian cancer	Poor	RFS	0.0274	177	TCGA	RNA-seq
SOX30	Pancreatic ductal adenocarcinoma	–	RFS	0.2785	69	TCGA	RNA-seq
SOX30	Pheochromocytoma and paraganglioma	–	RFS	0.2005	159	TCGA	RNA-seq
SOX30	Rectum adenocarcinoma	Good	RFS	0.0051	47	TCGA	RNA-seq
SOX30	Sarcoma	–	RFS	0.1432	152	TCGA	RNA-seq
SOX30	Stomach adenocarcinoma	Poor	RFS	0.0077	215	TCGA	RNA-seq
SOX30	Testicular germ cell tumor	–	RFS	0.2579	105	TCGA	RNA-seq
SOX30	Thyroid carcinoma	Good	RFS	0.1331	353	TCGA	RNA-seq
SOX30	Uterine corpus endometrial carcinoma	Poor	RFS	0.0377	422	TCGA	RNA-seq

Abbreviations: SOX30, SRY-box transcription factor 30; TCGA, The Cancer Genome Atlas.

greater role in patient survival than previously thought [25]. Correlation analysis revealed that SOX30 was associated with genes-encoding factors involved in immune activation and immunosuppression, chemokines, and chemokine receptors (Figure 5c–f). SOX30 is co-expressed with most immune activation genes in various types of cancers, especially intrahepatic cholangiocarcinoma, GBM, and HNSC (Figure 5c,d). Additionally, SOX30 is strongly co-expressed with chemokine and chemokine receptor genes in pan-cancer (Figure 5e,f). SOX30 expression was positively correlated with most chemokine receptor and chemokine genes in BLCA, BRCA, CHOL, GBM, and HNSC, but was negatively correlated with those genes in adrenocortical carcinoma and CESC. While there is no published report on SOX30 in GBM, some studies demonstrated that SOX transcription factors play key roles in GBM, and almost all *SOX* genes are expressed in GBM and correlate with patient prognosis and survival rate [33]. Three genes (*SOX5*, *SOX6*, *SOX13*) of the SOXD group that share a common ancestor with *SOX30* are abnormally expressed in GBM [34–37].

Together, these results indicate that SOX30 may regulate the infiltration of immune cells into tumors and the biological function of immune-related genes within the tumor immune microenvironment.

7 | SOX30-RELATED GENES ENRICHMENT ANALYSIS

An enrichment analysis was conducted using the Kyoto Encyclopedia of Genes and Genomes to investigate the biological relevance of SOX30 (Figure 6). SOX30 was mainly associated with KIRP, READ, DLBC, OV, PAAD, KIRC, BLCA, LUAD, LIHC, BRCA, pheochromocytoma and paraganglioma, and other cancers in the adherens junction, ERBB signaling pathway, WNT signaling pathway, neurotrophin signaling pathway, PAAD, renal cell carcinoma, pathways in cancer, and regulation of actin cytoskeleton.

SOX30 was previously shown to inhibit WNT signaling to improve the prognosis of patients with LUAD [17, 38] and SOX30 inhibits prostate cancer cell proliferation and invasion [14]. Hao et al. [18] showed that SOX30 inhibits Wnt and REK signaling in a desmosomal gene-dependent manner. The antitumor effect of SOX30 in cancer may be mediated through the
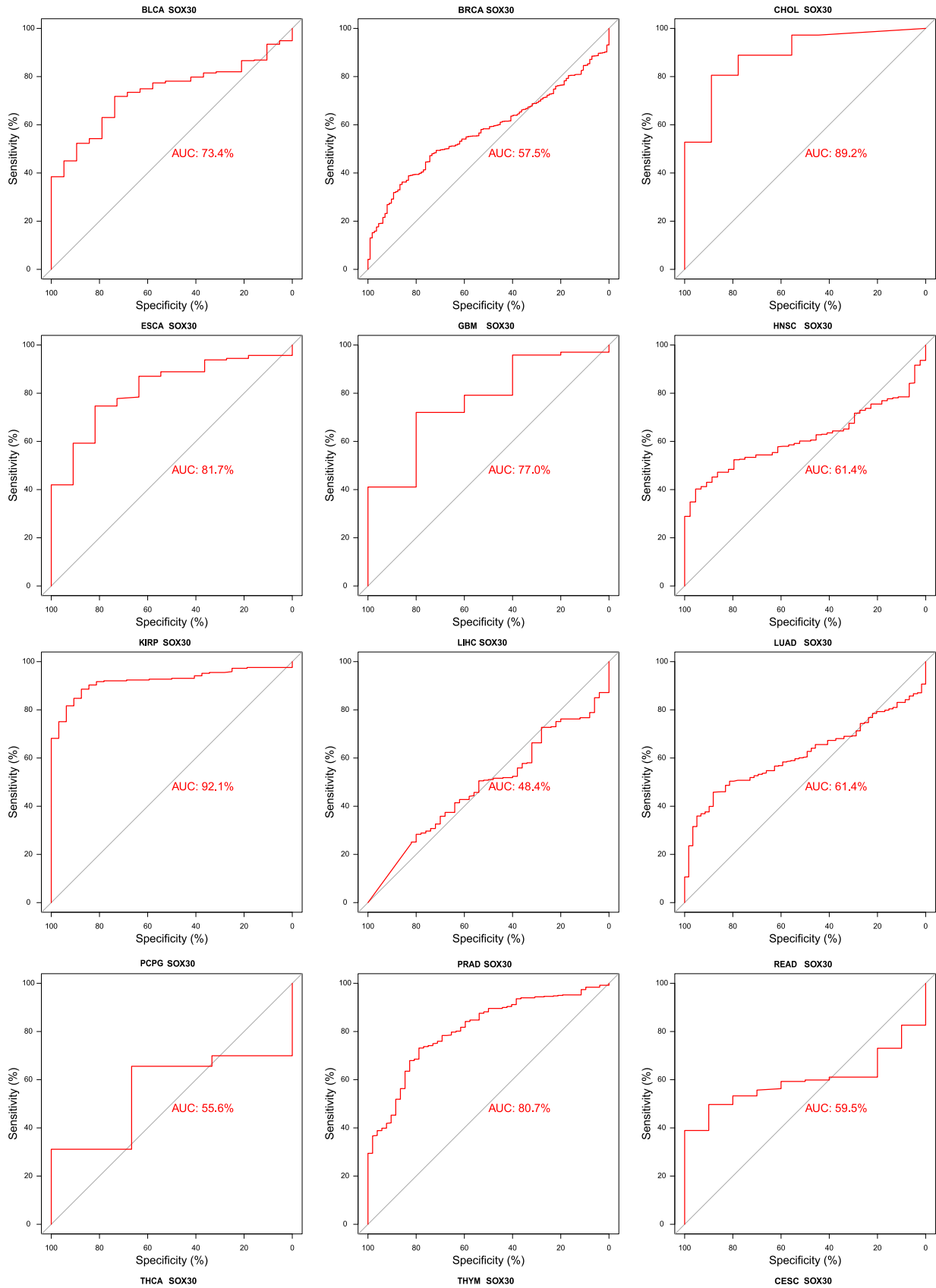
FIGURE 4 Receiver operating characteristic curve analysis of SRY-box transcription factor 30 in pan-cancer. AUC, area under the curve.
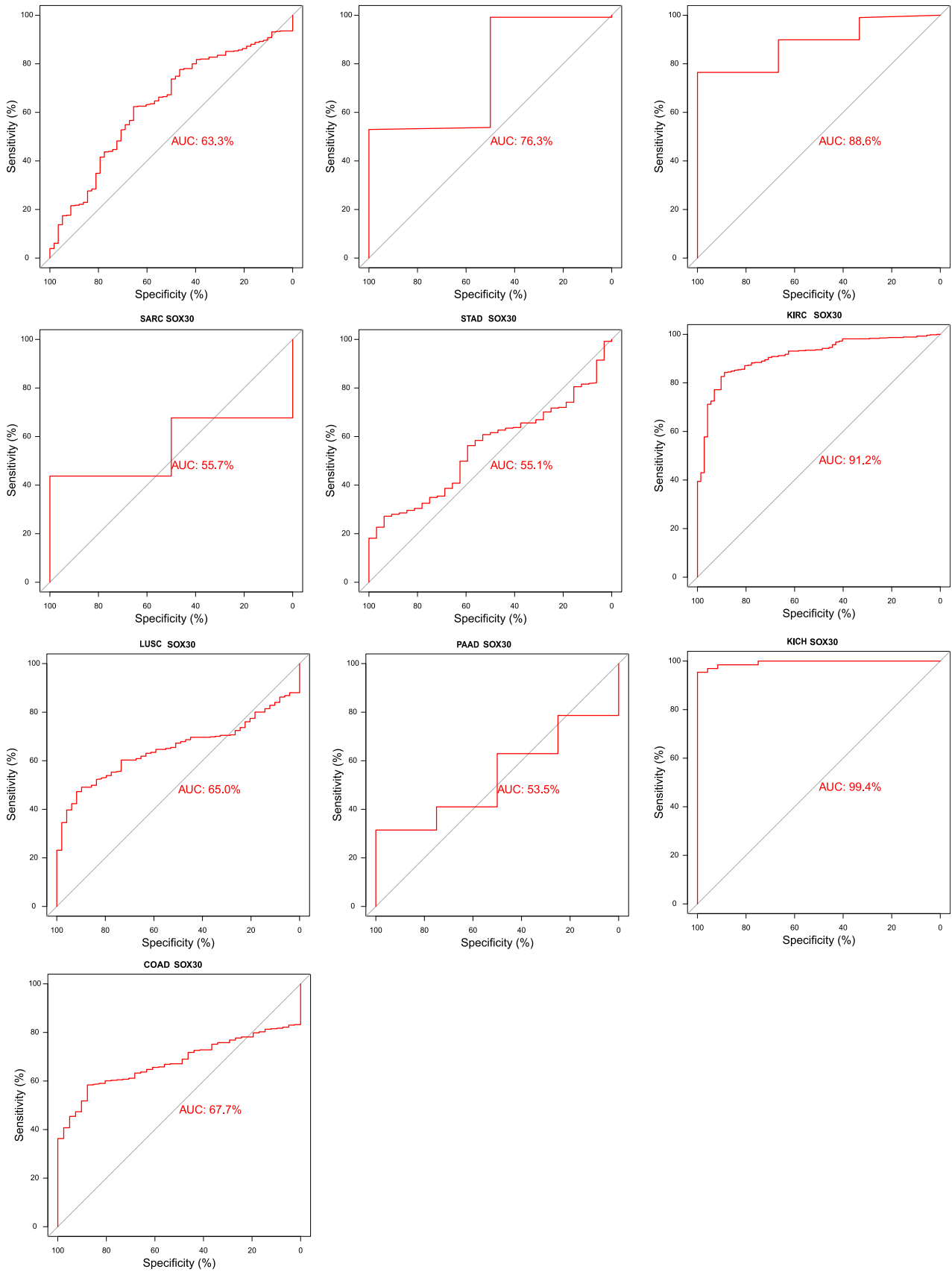
FIGURE 4 (Continued)

TABLE 4 ROC curve analysis of SOX30 in pan-cancer.

SOX30	AUC(%)	95% CI of AUC(%)	Cutoff value	Specificity(%)	Sensitivity(%)
BLCA	73.4	65.6–81.2	0.1	73.7	71.8
BRCA	57.5	53.2–61.8	0.1	85.8	36.2
CHOL	89.2	77.8–100.0	0.0	88.9	80.6
COAD	67.7	62.6–72.8	0.5	87.8	58.4
CESC	88.6	75.3–100.0	0.2	100.0	76.5
ESCA	81.7	70.7–92.6	0.1	81.8	74.7
GBM	77.0	56.7–97.4	0.1	80.0	72.0
HNSC	61.4	55.9–66.9	0.5	95.5	40.2
KICH	99.4	98.5–100.0	0.1	100.0	95.4
KIRC	91.2	88.1–94.2	0.2	88.9	84.3
KIRP	92.1	88.8–95.4	0.2	87.5	88.6
LIHC	48.4	41.0–55.8	0.0	80.0	28.3
LUAD	61.4	56.0–66.8	0.1	88.1	45.85
LUSC	65.0	59.8–70.2	0.1	91.8	47.3
PAAD	53.5	31.9–75.1	0.1	100.0	31.5
PCPG	55.6	30.8–80.3	0.0	66.7	65.6
PRAD	80.7	75.1–86.3	0.2	78.8	73.1
READ	59.5	49.6–69.3	0.4	90.0	49.7
SARC	55.7	31.7–79.8	0.2	100.0	43.7
STAD	55.1	46.8–63.5	0.6	93.8	27.2
THCA	63.3	56.0–70.6	0.1	65.5	62.4
THYM	76.3	31.1–100.0	0.2	100.0	52.9
UCEC	65.0	57.6–72.5	0.1	94.3	10.9

Abbreviations: AUC, area under the curve; BLCA, bladder urothelial carcinoma; BRCA, breast cancer; CESC, cervical cancer; CI, confidence interval; COAD, colon adenocarcinoma, colon cancer; ESCA, esophageal cancer; GBM, glioblastoma; HNSC, head and neck squamous cell carcinoma; KICH, kidney chromophore; KIRC, kidney renal clear cell carcinoma; KIRP, kidney papillary cell carcinoma; LIHC, liver hepatocellular carcinoma; LUAD, lung adenocarcinoma; PAAD, pancreatic adenocarcinoma, pancreatic cancer; PCPG, pheochromocytoma and paraganglioma; PRAD, prostate adenocarcinoma, prostate cancer; READ, rectum adenocarcinoma; ROC, receiver operating characteristic; SOX30, SRY-box transcription factor 30; STAD, stomach adenocarcinoma, stomach cancer; THCA, thyroid cancer; THYM, thymoma; UCEC, uterine corpus endometrial carcinoma.

p53 pathway. Han et al. [10] found that SOX30 is mainly involved in the mediation of genes that control cell proliferation and apoptosis. Apoptosis-promoting genes including the p53 gene and its downstream target genes were also upregulated upon SOX30 overexpression.

SOX30 is also associated with pathways such as the B and T cell signaling pathway and chemokine signaling pathway. The association of SOX30 with these signaling pathways may influence the function, differentiation, and activation status of immune cells. For example, the positive correlation between SOX30 and CD4+T cells suggests its role in regulating T cell helper functions and memory responses. Conversely, the negative correlation with Th1 cells implies a potential role of SOX30 in immune inflammation regulation. The chemokine signaling pathway plays a crucial role in regulating the migration and localization of immune cells. The correlation of SOX30 with this pathway suggests its involvement in the regulation of tumor-related immune cell migration and infiltration processes, which is important in tumor immunotherapy and immune checkpoint inhibitor therapy.

The association of SOX30 with B/T cell signaling pathways and the chemokine signaling pathway provides insights into its potential role in tumor biology and immune responses. Further studies should delve deeper into the mechanisms by which SOX30 regulates immune cell function and tumor-related immune responses. These findings may reveal new targets and strategies for the development of novel immunotherapeutic approaches.
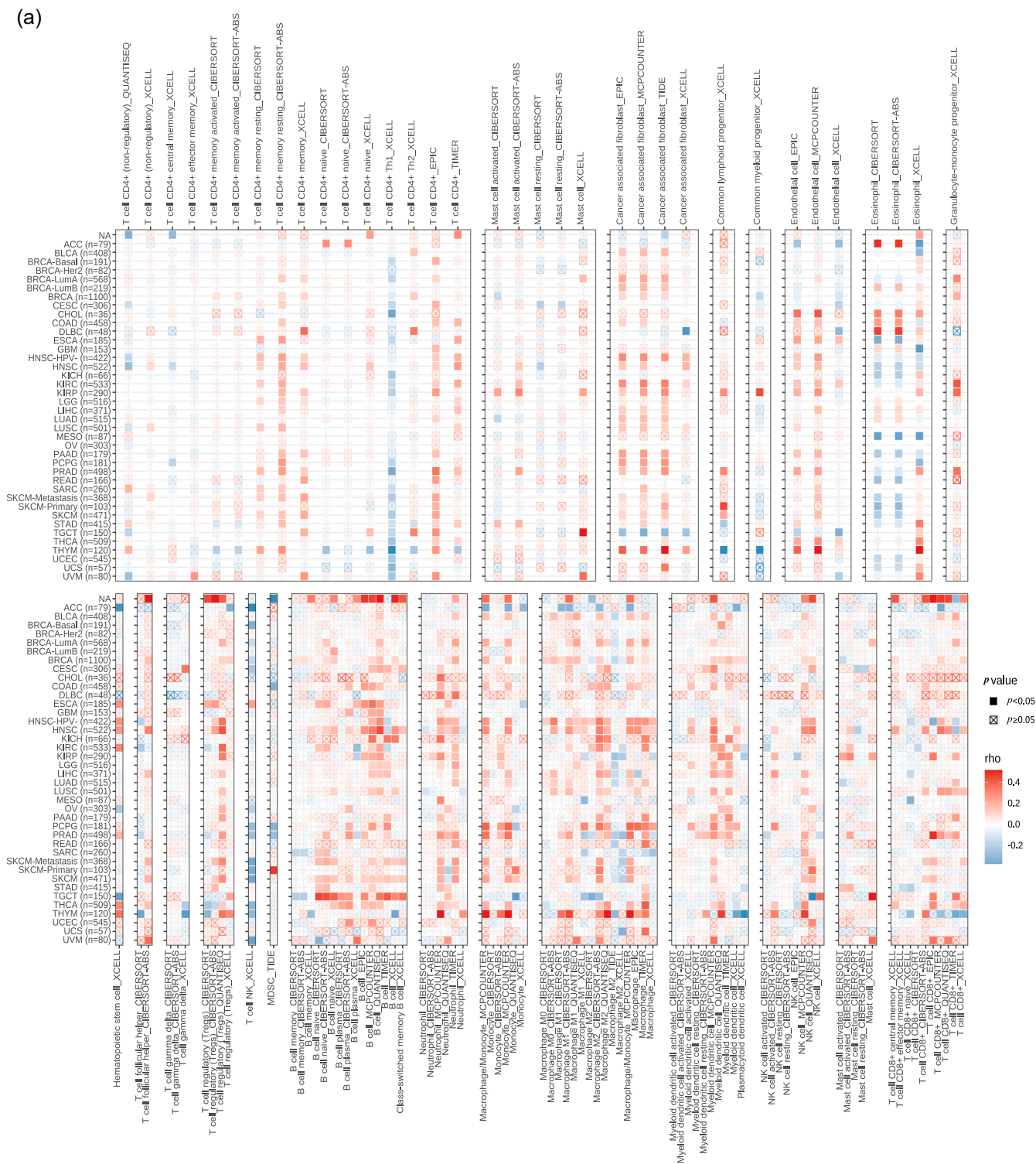
FIGURE 5 Correlation between SRY-box transcription factor 30 (*SOX30*) expression and tumor immunity. (a and b) Heatmaps depicting the potential correlation of SOX30 expression levels with immune cells in different types of cancers under different algorithms. (c–f) Heatmaps depicting the correlations of immune-related genes in SOX30 pan-cancer. (c) Chemokine receptors. (d) Chemokines. (e) Immune-activating genes. (f) Immunosuppressive genes. *$p < 0.05$, **$p < 0.01$.
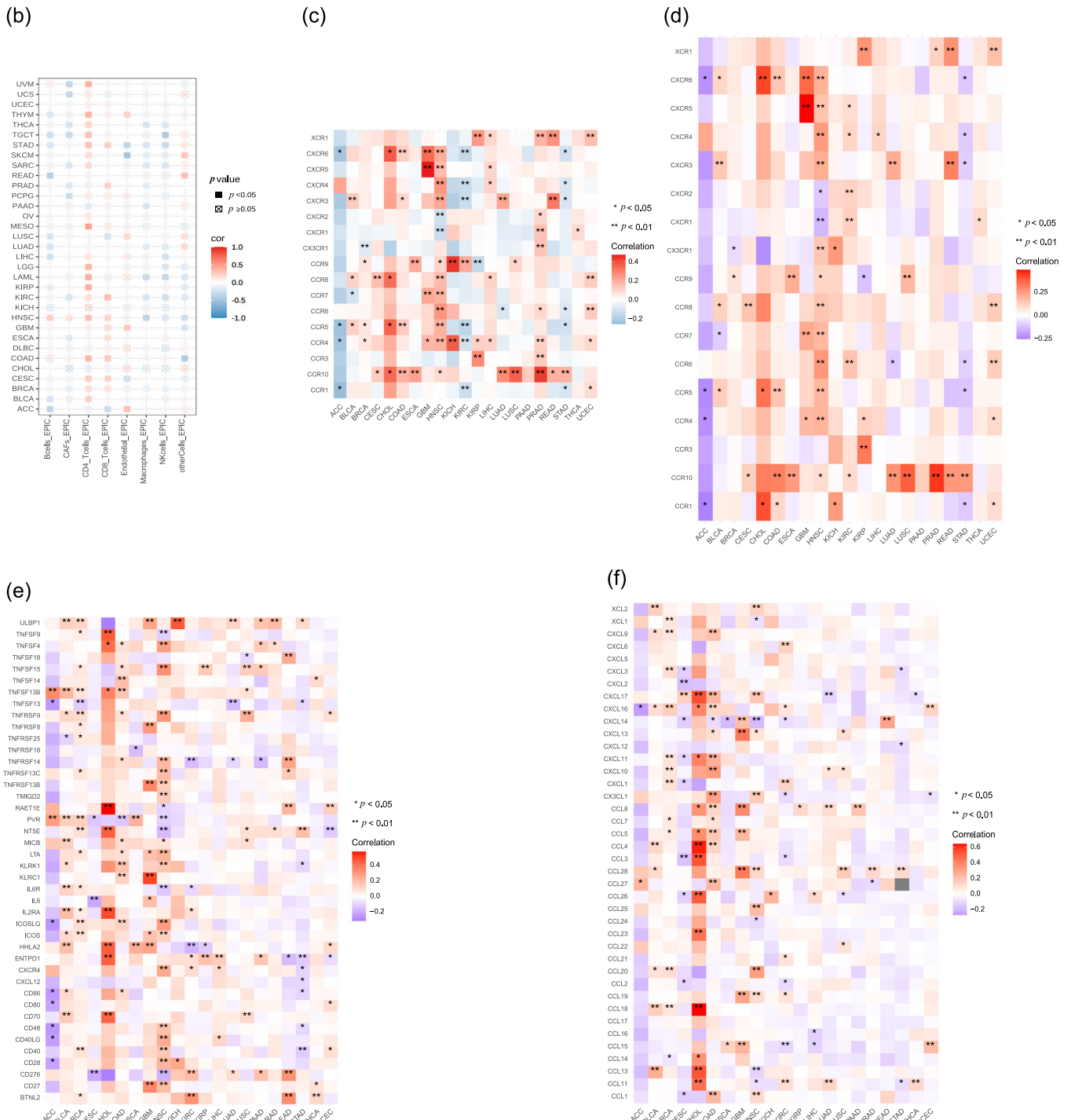
FIGURE 5 (Continued)

8 | THE TUMOR-SUPPRESSIVE ROLE OF SOX30

Recent research has highlighted the tumor-suppressive role of SOX30 in various cancer types. The SOX30 transcription factor directly binds to the p53 promoter, leading to the activation of p53 gene transcription. This activation initiates apoptosis and suppresses tumor formation [6, 10].

The methylation status of the SOX30 promoter region has been associated with changes in SOX30 expression patterns, suggesting that hypermethylation negatively affects SOX30 expression. In AML, SOX30 is down-regulated because of hypermethylation of its promoter region. Overexpression of SOX30 in AML leads to the inhibition of β-catenin expression, resulting in inactivation of the Wnt/β-catenin signaling pathway. These findings
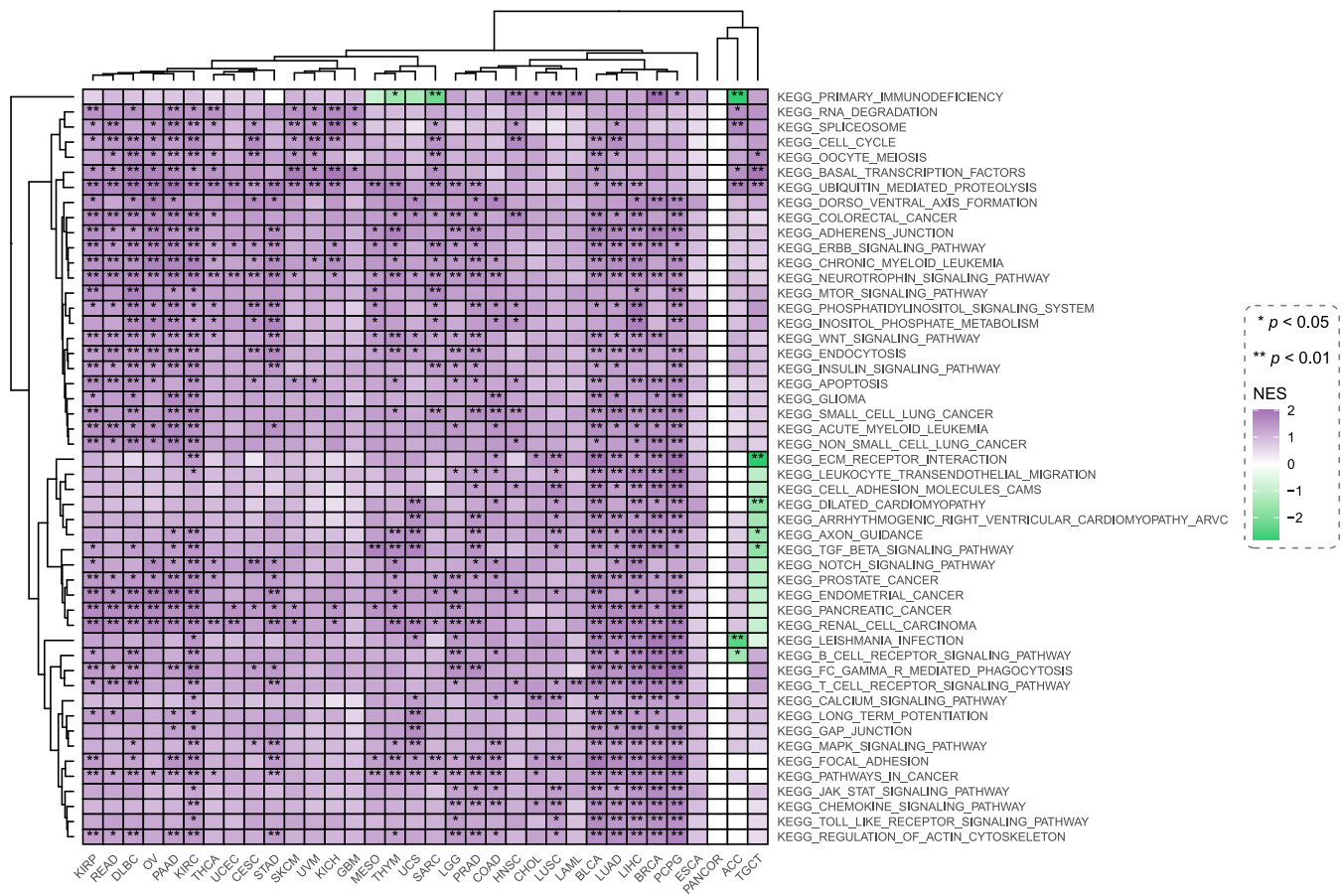
FIGURE 6 Kyoto Encyclopedia of Genes and Genomes annotation of *SRY-box transcription factor 30* in pan-cancer. A total of 6096 gene sets were generated from the RNA sequencing data set (https://www.gpsadb.com). The gene sets were further categorized into two groups: the high-expression gene set and the low-expression gene set, which were used for subsequent enrichment analysis. *$p < 0.05$, **$p < 0.01$.

suggest that SOX30 may play a crucial role in AML progression [23, 39].

In prostate cancer, bladder cancer, and colon cancer, SOX30 acts as a tumor suppressor, inhibiting cell proliferation and invasion [14, 20, 40]. The SOX30 promoter region was found to be highly methylated in lung tumors compared with normal lung tissue. SOX30 is frequently silenced or downregulated in lung cancer cell lines and samples, but expressed at detectable levels in normal lung tissue. The upregulation of p53 and its downstream targets by SOX30 suggests its tumor-suppressive role in lung carcinogenesis [10]. Studies have shown that SOX30 expression levels can serve as independent prognostic markers in LUAD, correlating with histological type and clinical stage. SOX30 acts as a tumor suppressor in LUAD by suppressing the Wnt/β-catenin signaling pathway. However, its role in LUSC remains unclear [17, 38]. Furthermore, SOX30 has been implicated in the regulation of intercellular junction molecules, such as desmosomes, which play a crucial role in inhibiting tumor growth and metastasis [18]. The

interaction of SOX30 with desmosomal genes may contribute to the development of lung tumors.

In summary, SOX30 shows promise as a potential biomarker and therapeutic target in various cancer types. Its tumor-suppressive effects, involvement in key signaling pathways, and regulation of intercellular junctions highlight its importance in cancer tumorigenesis and progression. The current literature indicates that SOX30 exhibits a certain degree of expression heterogeneity among tumors, which may imply distinct functional roles in various tumor types or different subtypes within tumors. This possibility is particularly relevant when considering subtypes such as the triple-negative subtype of BRCA. Further investigation is warranted to understand the precise impact of SOX30 in these specific contexts, and this remains an area of ongoing scientific inquiry. Additional studies are needed to fully understand the molecular mechanisms underlying SOX30 functions and its potential clinical applications in cancer management. The main biological effects associated with SOX30 in different cancer types are summarized in Table 5.

TABLE 5 Biological effects of SOX30 in different cancer types.

Cancer type	Proliferation	Metastasis	Drug resistance
CRC	↓;[12] [20]	↓;[20]	
AML	↓;[38] [39]		
OV		↓;[15]	oxaliplatin ↓; gemcitabine ↑;[15]
LUAD	↓;[16–18] [37]	↓;[16] [17] [37]	
NSCLC	↓;[42]		
PRAD	↓;[14]		
ML	↓;[13]		
BLCA	↓;[40]	↓;[40]	
LIHC	↓;[43]		
BRCA	↓;[19]	↓;[19]	

Note: ↑: increase. ↓: decrease.

Abbreviations: AML, acute myeloid leukemia; BLCA, bladder urothelial carcinoma; BRCA, breast cancer; CRC, colorectal cancer; LIHC, liver hepatocellular carcinoma; LUAD, lung adenocarcinoma; ML, myeloid leukemia; NSCLC, nonsmall cell lung cancer; OV, ovarian cancer; PRAD, prostate adenocarcinoma, prostate cancer; SOX30, SRY-box transcription factor 30.

9 | DRUG SENSITIVITY ANALYSIS

Cancer research has historically focused on understanding the drug sensitivity of tumors, as this plays a crucial role in determining the effectiveness of treatments and overall patient prognosis. The use of drugs that are effective in a particular cancer type has been shown to enhance treatment efficacy and significantly improve patient outcomes. Administering drugs to a cancer type that is insensitive to those particular drugs can result in rapid disease progression during treatment, leading to poor clinical outcomes.

In a previous study, researchers investigated the relationship between SOX30 gene expression and drug sensitivity in patients with advanced OV. The authors found that patients with high SOX30 expression levels had significantly better outcomes when treated with platinum + paclitaxel compared with gemcitabine [15]. This highlights the importance of considering individual genetic factors, such as SOX30 expression, when determining the most appropriate treatment approach for patients with OV.

To further explore the role of SOX30 in chemotherapy or targeted therapy, we conducted an integrated analysis of drug sensitivity and SOX30 gene expression data using CellMiner™, which provided insights into the correlation between SOX30 expression and sensitivity to various drugs. Our analysis revealed several interesting findings. SOX30 expression was positively correlated with drug sensitivity to teglarinad, fludarabine, and cladribine, while it was significantly, negatively associated with drug sensitivity to bortezomib, ABT-737, and vandetanib

(Table 6). Furthermore, we observed a positive correlation between SOX30 expression and gemcitabine sensitivity. Additional studies focusing on specific cancer types are needed to validate these findings. Nonetheless, this analysis sheds light on the potential clinical implications of considering SOX30 drug sensitivity when selecting appropriate treatments. It also indicates that SOX30 may have a dual role in potentially influencing both drug sensitivity and drug resistance mechanisms in cancer cells.

These findings highlight the importance of understanding drug sensitivity in cancer research. The integration of gene expression data, such as SOX30, with drug sensitivity analysis can provide valuable insights into personalized treatment approaches and potentially improve patient outcomes. Further research is needed to fully understand the role of SOX30 in chemotherapy and targeted therapy and its impact on drug resistance mechanisms.

10 | SUMMARY AND PERSPECTIVES

SOX30 expression and immune cell infiltration in cancer are correlated, and SOX30 expression may serve as a biomarker for various cancer types. SOX30 function in CHOL, ECSC, ECSA, KICH, KIRC, KIRP, PRAD, and GBM should be investigated in future studies. SOX30 has a good diagnostic effect in the above cancers, and it is mainly related to immune cell infiltration and involved in immune-related pathways. The differential expression of SOX30 at the RNA level in specific cancer types is

TABLE 6 Correlation between SOX30 and drugs.

Drug name	Pearson	p Value
Teglarinad	0.357927391	0.004987393
Fludarabine	0.338624236	0.008133464
Cladribine	0.333322557	0.009255266
Gemcitabine	0.286119892	0.026677115
Pyrazoloacridine	0.281827265	0.029144091
Benzimate	0.271384311	0.035953549
Clofarabine	0.270235547	0.036777337
Bisacodyl, active ingredient of Viraplex	0.267323987	0.038935588
5-Fluoro deoxy uridine 10mer	0.265522206	0.04032292
Acetalax	0.261984582	0.043165634
timazid	0.258508487	0.046117543
METHOTREXATE	0.255001324	0.049261593
Idelalisib	−0.257447418	0.047050893
JNJ-28312141	−0.260835521	0.044123712
AZD-5363	−0.273101124	0.034751011
Sonolisib	−0.279553484	0.030526486
O-6-Benzylguanine	−0.285445413	0.027052689
Copanlisib	−0.288927336	0.025160602
6-(4-pyrimidinyl)-1H-indazole derivative	−0.297210945	0.02110295
Saracatinib	−0.303788528	0.01828971
Vandetanib	−0.305324394	0.017680958
ABT-737	−0.306049482	0.017399626
Bortezomib	−0.343199346	0.00726259

Note: We performed Pearson correlation analysis using the cor.test() function in R software (version 4.2.0). This function calculates the Pearson correlation coefficient and associated *p* value to assess the strength and significance of the linear relationship between variables.

Abbreviation: SOX30, SRY-box transcription factor 30.

further evidence for the necessity of mechanistic studies into factors affecting transcriptional activity. The prognostic findings in several types of cancer are inconsistent, suggesting more research is needed to clarify the impact of SOX30 on prognosis. SOX30 may have tumor heterogeneity. We believe that the cellular functions of SOX30 have not been completely understood. The above results provided a theoretical basis for explaining the key role of SOX30 in pan-cancer and immune function and add to the information on the role of SOX30 in tumorigenesis and progression. We described the most recent insights into personalized cancer immunotherapy.

Together, these research findings may help aid in the development of immunotherapy methods targeting SOX30 in tumors.

While much remains to be learned about SOX30 and its biological roles, research suggests that it is an important regulator of development, pluripotency, and disease. Continued exploration of these areas may yield valuable insights into human health and pave the way for new treatments and therapies.

AUTHOR CONTRIBUTIONS

Na Sun: Formal analysis (equal); software (equal); writing—original draft (equal). **Cheng Wang**: Formal analysis (equal); software (equal); writing—original draft (equal). **Pingping Gao**: Formal analysis (equal); funding acquisition (equal). **Rui Wang**: Formal analysis (equal); writing—original draft (equal). **Yi Zhang**: Software (equal); writing—review and editing (equal). **Xiaowei Qi**: Funding acquisition (equal); writing—review and editing (equal).

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CONFLICT OF INTEREST STATEMENT
The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT
The study used three publicly available data sets.

ETHICS STATEMENT
Not applicable.

INFORMED CONSENT
Not applicable.

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