

## Six Transmembrane Epithelial Antigen 1 as a Prognostic Biomarker in Carcinomas: A Meta-Analysis

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#### Abstract

**Background**: Six transmembrane epithelial antigen 1 (STEAP1) is aberrantly expressed in cancers and could therefore be a potential biomarker. This study examined the connection between STEAP1 expression and clinical features/prognosis in cancer patients. **Methods**: Several databases were comprehensively searched for related published studies. The combination of hazard ratios (HRs), odd ratios (ORs), and 95% confidence intervals (95% CIs) was used to assess the role of STEAP1. The Cancer Genome Atlas (TCGA) dataset was used to estimate the prognostic value of STEAP1 in multiple cancer types, and several biological behaviors related to STEAP1 were evaluated by CancerSEA. **Results**: Searches of electronic databases revealed 7 relevant trials with 765 patients. A significant connection was found between high STEAP1 expression and worse overall survival amongst cancer patients (HR = 1.87, 95% CI: 1.49–2.34, p < 0.001). In addition, a strong correlation was found between high STEAP1 expression and the occurrence of lymph node metastases (OR = 3.19, 95% CI: 1.26–8.09, p < 0.001). Analysis of TCGA datasets verified that a higher level of STEAP1 expression is linked with reduced survival in many kinds of cancer. At the single cell level, STEAP1 expression was correlated with some tumor biological behaviors, such as angiogenesis, quiescence, and stemness. **Conclusions**: STEAP1 could regulate various biological functions in tumors and predict prognosis as a novel biomarker in a number of cancer types.

Keywords: STEAP1; cancer; biomarker; prognosis; meta-analysis

## 1. Introduction

The global occurrence of cancer has increased due to aging of the population and to a variety of nutritional and environmental factors in recent years. In the United States, there are estimated to be 609,820 cancer-related deaths and 1,958,310 new instances of cancer were reported in 2023 [1]. Despite the availability of treatments such as surgery, chemotherapy, targeted therapy and radiotherapy, the majority of cancer patients still have a bad prognosis. Hence, there is an urgent requirement to develop new methods for improving the accuracy of tumor diagnosis and patient prognosis. In recent years, a great deal of research effort has been directed at the discovery of novel biomarkers for improving diagnosis and for the development of novel targeted agents [2].

Six transmembrane epithelial antigen 1 (STEAP1) was the member of the STEAP family to be discovered. The STEAP1 protein is made up of six transmembrane domains, which are arranged with cytoplasmic C-terminal and N-terminal ends. These domains are interconnected by three extracellular and two intracellular loops [3,4]. This ion

channel and transporter protein make a difference in cell adhesion and also promotes tumor invasion and proliferation by adjusting the concentrations of Na<sup>+</sup>, K<sup>+</sup>, Ca<sup>2+</sup> and other small ions [5,6]. Although STEAP1 was initially researched as a possible biomarker for prostate cancer (PCa), it is known to be overexpressed in many different cancer types including bladder, colon and ovary [4,7,8]. Moreover, the low expression of STEAP1 in normal tissues renders it a promising target for cancer therapy [9]. A number of studies have reported that overexpression of STEAP1 could promote the invasion, migration, epithelial mesenchymal transition (EMT), and proliferation of cancer cells, while inhibiting their apoptosis and thereby favoring tumor growth [10-12].

This systematic review and meta-analysis were performed to assess the prognostic significance of STEAP1 expression in cancers. We also investigated The Cancer Genome Atlas (TCGA) datasets and single cell sequencing to further evaluate STEAP1 as a possible prognostic biomarker in a variety of cancer types and explore its biological behavior.



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## 2. Materials and Methods

### 2.1 Literature Search

An extensive literature search was conducted using the PubMed, Web of Science, Google Scholar, Cochrane Library, PMC, Wanfang, and China National Knowledge Infrastructure (CNKI) databases, with an April 1, 2023 cut-off date. The following phrases were searched in various combinations: ("STEAP1") and ("cancer" OR "carcinoma" OR "tumor" OR "neoplasm"). In addition, the reference list of relevant literature was examined to find studies in which STEAP1 was linked to clinical events.

#### 2.2 Inclusion and Exclusion Criteria

The inclusion criteria for this study were: (1) cancer patients, without restriction on the type of cancer; (2) an evaluation of correlations between STEAP1 expression and clinical features; (3) use of immunohistochemical techniques to evaluate STEAP1 expression; (4) classification of patients into two groups based on their STEAP1 expression level; (5) presentation of direct or indirect hazard ratios (HRs) for overall survival (OS), together with the associated 95% confidence intervals (95% CI).

The exclusion criteria for this study were: (1) studies lacking survival data; (2) not categorized by STEAP1 expression into 2 groups as low and high expression; (3) duplicate studies; (4) publications in the form of reviews, metaanalyses, case reports, fundamental studies, animal studies, letters, expert opinions, conference abstracts, and reviews.

#### 2.3 The Process of Extracting Data and Assessing its Quality

Papers that were potentially suitable were reviewed in their entirety. Data and information from eligible studies were independently extracted by two researchers, who then separately verified the extracted data. A third researcher arbitrated any inconsistent points that arose between the two researchers.

For each eligible study, the first author's name, detection method for STEAP1 expression, STEAP1 expression level, and clinicopathological factors including gender, age, TNM stage, distant metastasis, lymph node metastasis, tumor cell differentiation, and tumor size were recorded. When only Kaplan-Meier curves were presented in the article, Engauge Digitizer version 11.2 was used to calculate survival from the curves and to determine HRs and 95% CIs. If both univariate and multivariate analysis results were shown, the latter were used because of their superior precision.

Study quality was evaluated by the Newcastle-Ottawa Scale (NOS), which takes into account three primary categories: selection, comparability, and outcome. The spectrum of NOS scores ranges from the minimum of 0 stars to the maximum of 9 stars. A study was deemed to be highquality if it had an NOS score of at least 6.

#### 2.4 Survival Analysis

The Gene Expression Profiling Interactive Analysis 2 (GEPIA2.0, http://gepia2.cancer-pku.cn/#index) was used to obtain data on STEAP1 expression and prognostic value in cancer patients [13].

Cancer patients from the TCGA dataset were separated into two categories (high and low expression) using a 50% cut-off threshold, and HR was calculated according to the Cox proportional hazards model. The Kaplan-Meier plotter was utilised to analyse the survival of cancer patients, with differences between groups evaluated using the log-rank test [14].

## 2.5 Single Cell Sequencing

The CancerSEA (http://biocc.hrbmu.edu.cn/CancerS EA/) dedicated single cell sequencing database was used to obtain information on the functional status of cancer cells at the single cell level. The analysis was performed based on data obtained from single cell sequencing, and associations between STEAP1 expression and biological functions of tumors was examined. STEAP1 expression patterns of individual cells within the TCGA dataset were shown using T-SNE diagrams.

#### 2.6 Statistical Analysis

The statistical analysis was performed using Stata 16.0 (StataCorp LLC, 4905 Lakeway Drive College Station, TX, USA). HRs and 95% CIs assessed the associations between STEAP1 expression and OS, lymph node metastases, TNM stage, and tumor cell differentiation. Patient groups with bad prognosis were defined by an HR >1. Heterogeneity was assessed using a Q test based on the Chi-square and I<sup>2</sup> statistics. In cases where heterogeneity was employed. In contrast, a fixed-effects model was applied when there was substantial heterogeneity. A funnel plot was applied to evaluate potential publication bias. p < 0.05 was deemed statistically significant [15]. A sensitivity analysis was conducted to determine the consistency of the outcomes.

## 3. Results

#### 3.1 Eligible Publications

The search approach identified 386 articles in the different databases. Of these, 157 duplicate articles were eliminated, leaving 229 articles that underwent a second round of meticulous scrutiny of their title and abstract. After reading the entire text of 91 publications, 7 articles that satisfied the inclusion requirements were ultimately chosen for meta-analysis. Details regarding the selection procedure are shown as a flow chart in Fig. 1.

#### 3.2 Characteristics of Included Studies

Based on the search strategy and selection criteria, 7 papers from Germany, Brazil and China that included 1263



#### Fig. 1. Flow charts of study search and selection for meta-analysis.

patients in total were selected for further investigation (Table 1, Ref. [11,16–21]). The cancer types included osteosarcoma, gastric cancer, colorectal cancer, Ewing's sarcoma, PCa, ovarian cancer, and lung adenocarcinoma.

# 3.3 STEAP1 Expression and the Survival of Cancer Patients

Because of the lack of a statistically significant difference across trials, we used a fixed effects model ( $I^2 = 0.0\%$ ), high STEAP1 expression was found to be significantly correlation with declining OS (HR = 1.87, 95% CI: 1.49–2.34, p < 0.001) (Fig. 2).

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To assess clinical relevance, fixed-effects subgroup analyses were conducted based on sample size, number of follow-up months, and data extraction methods (Fig. 3). High STEAP1 expression was associated with falling OS in cancer patients from China (HR = 1.88; 95% CI: 1.48– 2.39; p < 0.001) (Fig. 3a). Sample size did not affect the observed predictive value of STEAP1 expression (Fig. 3b). Moreover, the prognostic significance of STEAP1 expression for OS remained consistent in each of the cancer types studied, regardless of the length of follow-up or the method of data extraction (Fig. 3c,d).

Sample Clinical Follow-up Detected Data extraction Author Year Country Tumor type Cutoff value Survival analysis Outcome NOS Ref. size stage (months) method method IRS  $\geq 3$ [16] Zhang D. et al. 2022 China 160 I–IV 120 IHC Univariate/Multivariate OS 8 Osteosarcoma Indirect Zhang Z. et al. 2020 China 212 I–IV IHC IRS  $\geq 6$ OS 8 [17] GC 100 Univariate/Multivariate Indirect Lee C.H. et al. 165 OS 8 [18] 2016 China CRC I–IV 156 IHC Immunostaining score >100 Univariate/Multivariate Direct 9 Grunewald T.G.P. et al. ES 114 I–IV 210.12 IHC Immunoreactivity grade  $\geq 2$ Univariate/Multivariate OS [19] 2012 Germany Direct  $IRS \geq \! 3$ IHC 8 [20] Ihlaseh-Catalano S.M. et al. 2013 Brazil PCa 198 I–IV 150 Univariate/Multivariate BCR-FS Direct Jiao Z. et al. 2020 China OC 384 I–IV IHC IRS  $\geq 2$ Univariate/Multivariate PFS 8 [11] 120 Direct [21] 30 I–IV 30 OS 7 Li P. et al. 2023 China LUAD IHC Staining score values >8Univariate/Multivariate Indirect

Abbreviations: ES, Ewing's sarcoma; PCa, Prostate carcinoma; CRC, colorectal cancer; GC, gastric cancer; LUAD, lung adenocarcinoma; OC, ovarian Cancer; IHC, immunohistochemistry; IRS, immunoreactivity score; PFS, progression free survival; OS, overall survival; BCR-FS, Biochemical recurrence-free survival; NOS, Newcastle–Ottawa Scale.

Table 1. Main characteristics of all studies included in the meta-analysis.



Fig. 2. Forest plot examining the relationship between six transmembrane epithelial antigen 1 (STEAP1) expression and overall survival.

#### 3.4 Interactions between STEAP1 Expression and the Clinical Characteristics of Cancer Patients

A meta-analysis of the correlations between STEAP1 expression and various clinicopathological features was conducted using data from 7 studies involving 765 tumor specimens. As shown in Fig. 4, no significant correlations were found between high STEAP1 expression and TNM stage (OR = 1.67, 95% CI: 0.67–4.16, p < 0.001, Fig. 4a), tumor cell differentiation (OR = 3.09, 95% CI: 0.85–11.24, p < 0.001, Fig. 4b), or gender (OR = 1.37, 95% CI: 0.77–2.43, p < 0.001, Fig. 4c). However, high STEAP1 expression in tumor tissue was significantly associated with the presence of lymph node metastasis (OR = 3.19, 95% CI: 1.26–8.09, p < 0.001, Fig. 4d).

#### 3.5 Analysis of Sensitivity and Publication Bias

We completed a sensitivity analysis to assess the stability of the meta-analysis for the expression of STEAP1 and OS. The pooled HR was not substantially altered by excluding individual studies, thus demonstrating the consistency of the findings (Fig. 5a).

The funnel plot and Begg's bias test were applied to assess the potential for publication bias. A nearly symmetrical form was observed (Fig. 5b). Moreover, the Begg's test (p = 0.806) and the Egger test (p = 0.37) of OS in the included studies indicated there was no appreciable publication bias.

## 3.6 The Association between STEAP1 Expression and OS in Patients from TCGA Database

To confirm and validate our findings, GEPIA2.0 (Peking University, Beijing, China) was employed to examine STEAP1 expression levels in different cancer types. Kaplan-Meier analysis indicated a substantial correlation between elevated STEAP1 expression and decreased OS in all cancer types (Fig. 6a). High STEAP1 expression was strongly associated with bad prognosis in lung adenocarcinoma (LUAD), adrenocortical carcinoma (ACC), pancreatic adenocarcinoma (PAAD), brain low grade glioma (LGG), and kidney renal clear cell carcinoma (KIRC) (Fig. 6b–f). Overall, these results support the conclusion that increased STEAP1 expression is associated with worse OS in several different tumor types. Hence, STEAP1 expression could potentially serve as a prognostic indicator in several types of cancer.

### 3.7 STEAP1 Expression at the Single Cell Level

Sequencing the transcriptome of a single cell is a valuable method for analysing the potential roles of molecules at level of the single cell [22,23]. The CancerSEA website was applied here to investigate the relationship between the change of STEAP1 expression and other biological functions at the single cell level (Fig. 7a). STEAP1 expression was favorable correlation with angiogenesis in lung adenocarcinoma (LUAD). Moreover, a negative correlation was reported between STEAP1 expression and apopto-



**Fig. 3.** Stratified analyses to determine the relationship of STEAP1 expression and overall survival (OS). (a) Subgroup study of hazard ratios (HRs) of OS based on country. (b) Subgroup study of HRs of OS based on sample size. (c) Subgroup study of HRs of OS based on follow-up time. (d) Subgroup study of HRs of OS based on the method of data extraction.

sis in acute myelocytic leukemia (AML) patients (Fig. 7a), whereas a positive correlation was observed with the cell cycle, DNA repair, invasion, proliferation, and stemness, suggesting a possible mechanism of action in this cancer type. Based on the analysis of Fig. 7a, stemness was positively correlated with STEAP1 expression in AML, uveal melanoma (UM), and head and neck squamous cell carcinoma (HNSCC), while a negative correlation was observed between quiescence and STEAP1 expression in AML and UM, both of which are statistically significant. STEAP1 expression profiles at the single cell level in UM are shown by t-SNE plots in Fig. 7b. DNA repair, DNA damage, apoptosis, and metastasis were inversely correlated with STEAP1 expression in UM (Fig. 7c).

## 4. Discussion

Although earlier studies demonstrated that elevated STEAP1 expression was an adverse prognostic factor in various cancer types, STEAP1 was originally mostly used in the diagnosis and prognostic analysis of PCa [9,17,24]. In the current study, we investigated the relation between its expression and clinical features in a wide range of tumors, which extended the breadth of its application. We

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performed a meta-analysis of 7 studies to first put forward the prognostic value of STEAP1, as well as its potential as a cancer biomarker.

Our results revealed a statistically significant correlation between elevated STEAP1 expression levels and decreased OS in cancer patients. A study not included in our meta-analysis reported that cancer patients with high STEAP1 expression had an elevated risk of biochemical recurrence (BCR) (HR = 4.23, 95% CI: 1.68-10.61) [20], while another study reported that STEAP1 overexpression correlated with worse progression free survival (PFS) (HR = 1.2, 95% CI: 1.06–1.37) [11]. The present analysis revealed a correlation between elevated STEAP1 expression and the occurrence of adverse prognostic events. Moreover, when doing subgroup analysis, a strong association was seen between heightened STEAP1 expression and unfavorable OS, specifically among Chinese cancer patients. This finding suggests that more aggressive treatments could be used in patients who has elevated STEAP1 expression.

The upregulation of STEAP1 was revealed to be significantly correlated with unfavorable clinical characteristics, such as the presence of lymph node metastases. However, we did not find significant associations with clinical stage, differentiation, and gender, possibly because of the



**Fig. 4.** Forest plot for the relationship between STEAP1 expression with clinical characteristics. Forest plot for the relationship between STEAP1 expression with (a) TNM stage, (b) tumor cell differentiation, (c) gender, and (d) lymph node metastasis.



Fig. 5. Sensitivity analysis and publication bias for STEAP1 expression and OS. (a) Sensitivity analysis, and (b) funnel plot of publication bias for OS.

limited quantity of studies. The reliability of our study was confirmed by sensitivity analysis and by the low publication bias, providing further evidence that STEAP1 could be a potential biomarker for cancer prognosis. We also analyzed the TCGA database using GEPIA 2.0 and confirmed that increased STEAP1 expression was associated with decreased OS in various tumor types.

Finally, single cell sequencing results suggest that STEAP1 could regulate several tumor biological functions, such as angiogenesis, stemness and quiescence. The overgrowth of blood vessels promotes infiltration and distant metastasis of solid tumors, thus explaining the association between high STEAP1 expression and poor prognosis. Studies indicated that cancer cells possessing a greater degree of stemness tend to exhibit heightened proliferation and metastatic potential [25,26]. The upregulation of STEAP1 could enhance the stemness of tumor cells, thereby leading to an escalation in malignancy. Study have indicated that cancer metastasis can be prevented using maintenance of tumor cell quiescent [27,28]. This is con-



**Fig. 6. Prognostic value of STEAP1 expression in various cancer types.** GEPIA2.0 was utilized to examine the relationship between STEAP1 expression and OS in all cancer types (a), Lung adenocarcinoma (LUAD) (b), pancreatic adenocarcinoma (PAAD) (c), adrenocortical carcinoma (ACC) (d), brain low grade glioma (LGG) (e), kidney renal clear cell carcinoma (KIRC) (f).

sistent with our finding that quiescent and high STEAP1 expression are negatively correlated. We hypothesize that higher STEAP1 expression may lead to tumor invasion and metastasis via cancer stem cells and quiescence. However, there are few studies about the mechanism of STEAP1, and additional research is required.

Several studies have investigated the potential molecular mechanisms that underlie the oncogenic effects of STEAP1. This protein has been found to promote cancer progression via multiple pathways. In vitro and in vivo investigations have reported on the function of STEAP1 in the tumor microenvironment. STEAP1 expression is associated with elevated levels of reactive oxygen species and oxidative stress, which could further regulate redox- aggressive and sensitive genes [29]. Another study found that immunogenic peptides derived from STEAP1, together with mobilized dendritic cells, favor identification by cytotoxic T lymphocytes, thus indicating their potential use in the creation of anticancer vaccines [30]. An ongoing PCa clinical trial is testing an antibody-drug conjunction (DSTP3086S) of a humanized monoclonal antibody (mAb 120.545) that targets the STEAP1 protein [31]. A radiolabeled form of this antibody (89Zr-DFO-MSTP2109A) is also being used for PET imaging [32]. The safety and significant antitumor activity of DSTP3086S was demonstrated in a phase I trial of 77 patients with metastatic, castration-resistant PCa. In this trial, 18% of patients showed a >50% decrease in prostate-specific antigen [31]. Analysis of the TCGA and Genotype-Tissue Expression databases revealed that STEAP1 expression has prognostic significance in many types of tumor and is also a potential biomarker for chemosensitivity, the tumor microenvironment, microsatellite instability (MSI), and tumor mutational burden (TMB) [33].

In summary, the above findings indicate that STEAP1 is a feasible prognostic biomarker, and may also serve as a specific target for anti-tumor vaccines and targeted therapeutic drugs in cancer patients. Several limitations exist in the meta-analysis. Firstly, all of the included studies were retrospective. Secondly, some studies lacked original data and it was therefore necessary to compute HRs using Kaplan-Meier survival curves, which inevitably results in errors. Finally, all of the included studies were from China or Germany, and hence the findings may not be applicable to other populations.

## 5. Conclusions

In general, the findings of this meta-analysis indicate that the expression of STEAP1 has the potential function as a prognostic indicator for unfavorable OS, and also correlates with the occurrence of lymph node metastases. The potential application of STEAP1 for predicting the clinical



Fig. 7. STEAP1 expression correlates with tumor biological behavior at the single cell level. (a) The CancerSEA tool was applied to explore the relationship between STEAP1 expression and different biological functions in tumors. \* p < 0.05; \*\* p < 0.01; \*\*\* p < 0.001. (b) STEAP1 expression in single cells of uveal melanoma (UM) as shown by t-SNE plots. (c) Correlation of STEAP1 expression with tumor biological behavior in UM.

outcome of different cancer types should be further confirmed by conducting extensive, forward-looking, multisite, and rigorous investigations.

## Availability of Data and Materials

The data and material used in this study are available from the corresponding author on reasonable request.

## **Author Contributions**

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by JY, SZ, HC, YZ, QW, XL, NY, and LY. The figures were drawn by SZ, HC, and QW. The first draft of the manuscript was written by SZ, HC, and YZ. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

## **Ethics Approval and Consent to Participate**

Not applicable.



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## **Conflict of Interest**

The authors declare no conflict of interest.

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