The prognostic significance of survivin expression in patients with HNSCC: a systematic review and meta-analysis

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Abstract

Background: Survivin has been recently identified as a promising novel therapeutic target and prognostic marker in different types of cancer. Here we conducted a comprehensive meta-analysis to better clarify the precise prognostic and diagnostic value of survivin in head and neck squamous cell carcinoma (HNSCC).

Methods: Database of PubMed (Medline), Embase, and Web of Science were systematically searched for related published literature up to September 2020. Pooled hazards ratios (HR) and related 95% confidence intervals (CI) were used to estimate the association of survivin expression and survival outcomes in HNSCC patients.

Results: Twenty-eight studies with 4891 patients were finally included in this meta-analysis, the pooled analysis indicated that the survivin expression was significantly correlated with poorer overall survival (OS) (HR, 2.02; 95% CI, 1.65–2.47, P < 0.001), and poorer disease-free survival (DFS)/disease-specific survival (DSS) (HR = 2.03, 95% CI: 1.64–2.52, P < 0.001; HR = 1.92, 95% CI: 1.41–2.60, P < 0.001, respectively). Similar results were observed in subgroup analysis stratified by different cancer types, such as laryngeal squamous cell carcinoma (LSCC) (HR = 1.35, 95% CI: 1.05–1.74, P < 0.001), oral squamous cell carcinomas (OSCC) (HR = 2.45, 95% CI: 1.89–3.17, P < 0.001), nasopharyngeal carcinoma (NPC) (HR = 2.53, 95% CI: 1.76–3.62, P < 0.001) and HNSCC (HR = 1.52, 95% CI: 1.25–1.86, P < 0.001). Furthermore, ethnicity-stratified analysis indicated that survivin was significantly associated with poorer OS among both Asian and Non-Asian HNSCC patients (HR = 2.16, 95% CI: 1.76–2.66; HR = 1.56, 95% CI: 1.33–1.82, respectively).

Conclusions: Our results suggested that survivin is predictors of worse prognosis in HNSCC patients. Hence, survivin is a potential therapeutic target for HNSCC.

Keywords: Survivin, Head and neck squamous cell carcinoma, Prognosis, Meta-analysis

Introduction

Head and neck squamous cell carcinoma (HNSCC) is ranking as the sixth most prevalent cancer worldwide [1], they develop from the squamous mucosa of the upper aerodigestive tract, including nasal cavity, nasopharynx, larynx, hypopharynx, oropharynx and so on. Squamous cell carcinoma (SCC) accounts for up to 90% of malignant tumor in the head and neck region. The group of malignancies have similar pathogenesis, staging system, therapeutic strategy, and prognosis despite they arise from different sites of head and neck region, hence, it is rational to classify them into one category, HNSCC [2]. There are several risk factors associated with HNSCC, such as environmental exposures, tobacco use, alcohol consumption and so on [3]. Although the diagnosis and multimodality treatments improved quickly, the 5-year survival rate still remains very low due to the complex anatomy of head and neck region [4]. Therefore, it...
is necessary to identify more reliable new prognostic biomarkers and therapeutic targets.

Survivin, an important member of the ‘inhibitor of apoptosis’ (IAP) family, is encoded by baculoviral inverted repeats (BIR) C5 gene [5]. The expression is minimal in normal tissues, however, strong survivin expression is largely observed in numerous cancers [6]. Survivin is an anti-apoptotic factor and regulate intrinsic and extrinsic apoptotic pathways by interacting with many factors. It also plays key roles in cellular stress response by interfering with autophagy. Different proteins of the autophagic machinery, such as Beclin 1, chemo-kine ligand 2 and light chain 3 interact with survivin [7, 8]. In addition, survivin expression is associate with the process of angiogenesis, it overcomes G2/M phase of the cell cycle and causes mitotic progression in most adults’ cancers [9].

Although numerous researches have revealed the association between survivin and the prognosis of HNSCC, the results still remain controversial due to the variance in the sample size, study design, test approach and cut-off value. Therefore, it is essential to clarify the diagnostic and prognostic value of survivin in HNSCC based on the findings from the independently small sample size publications. Here, we searched PubMed (Medline), Embase, and Web of Science databases for relevant publications and undertaken a comprehensive meta-analysis to systematically assess the diagnostic and prognostic role of survivin in HNSCC.

**Methods**

**Search strategy**

We searched for articles published between 2000 and 2020. Electronic searches for relevant retrieve studies were performed throughout databases, including PubMed (Medline), Web of Science and EMBASE databases in accordance with Dickersin et al. in September 2020 [10]. The retrieval strategy included: (survivin) and (prognosis OR outcome OR mortality OR survival OR progression OR recurrence) and (head and neck or laryngeal or tonsil or oropharyngeal or oral or oropharynx or nasopharyngeal) and (squamous cell cancer or carcinoma). Furthermore, the reference lists of retrieved articles for additional articles were also manually searched. If several studies reported the same patient populations, we enrolled the most complete one to avoid duplication.

**Selection criteria**

This meta-analysis was limited to studies about the association between HNSCC and survivin. The inclusion criteria of the meta-analysis were as follows: (1) all patients should be diagnosed with HNSCC; (2) survivin was evaluated in both samples of the HNSCC and normal controls; (3) studies revealed the association between survivin and survival of HNSCC; (4) sufficient statistical analysis was required, including hazard ratios (HR) and their related 95% confidence interval (95% CI)) for survival outcomes, if not we could calculate them by p values and Kaplan–Meier curves [11] (5) the language of publications was limited to English. The exclusion criteria were: (1) studies without sufficient data for meta-analysis; (2) abstracts, case reports, reviews, letters, expert opinions, etc.; (3) studies about cell lines, in vivo/vitro studies, and human xenografts. If the same cohort was reported by several studies, the most recent one was included in our study.

**Statistical analysis**

The HR and the related 95% CI of survival outcomes were obtained directly from the primary publications or estimated by p values and other published data following Parmer’s methods [15]. Statistical heterogeneity among the studies was evaluated using the χ²-based Q test and the I² statistics [16]. The fixed-effects model was employed for analysis without obvious statistical
heterogeneity between studies ($P > 0.10$, $I^2 < 50\%$). Otherwise, the random-effects model was applied. Moreover, we performed subgroup analysis to explore the potential source of heterogeneity. Sensitivity analysis was conducted to investigate the influence of each individual study on the overall pooled results. We used the Begg’s and Egger’s tests to assess the potential publication bias. We conducted all statistical analyses by STATA statistical software version 15.0 (StataCorp Lp).

Results
Selection and characteristics of included studies
A total of 778 potential records were initially identified by searching the electronic databases (Fig. 1). Following exclusion of the duplicates ($n = 431$), reviews, abstracts and letters ($n = 25$) and the studies of irrelevant topics ($n = 244$), 78 studies were remained for further assessment by reading their full-text articles. A total of 50 studies did not provide specific data regarding HNSCC or survivin and therefore were excluded. Finally, a total 4891 HNSCC patients in 28 studies with publication years ranging from 2002 to 2019 were enrolled in the present meta-analysis.

The characteristics of the eligible studies were summarized in Table 1. The participants were from China, Tunisia, Turkey, Germany, Italy, Australia, Canada, South Korea, Sweden and Slovenia. Immunohistochemistry (IHC) and/or reverse-transcription polymerase chain reaction (RT-PCR) were used to analysis the survivin protein and/or mRNA expression in the including studies. The characters of antibodies in different studies are summarized in Table S1. They have different clones, dilutions, sources and positive signals. Different PCR instruments were also used in different studies. Our meta-analysis including eight studies for laryngeal squamous cell carcinoma (LSCC), ten studies for oral squamous cell carcinomas (OSCC), five studies for head and neck squamous cell carcinoma (HNSCC) and five studies for nasopharyngeal carcinoma (NPC). Fifteen publications included > 100 patients and 13 publications enrolled < 100 patients, twenty one studies including a total of 3036 patients reported overall survival (OS), nine studies including a total of 925 patients reported disease-free survival (DFS) and three studies including a total of 1485 patients reported disease-specific survival (DSS). The HR and 95% CI were directly reported in fifteen publications and were estimated in thirteen studies in the original literature. All of the publications’ NOS scores were above 6 and the REMARK scores were between 11 and 15.

Association between survivin and survival outcomes of HNSCC patients
A total of twenty one studies in the present analysis examined the association between survivin and the OS of in HNSCC patients. The heterogeneity among the publications in our study was significant for Q test ($P < 0.1$). Hence, the random-effects model was adopted and subgroup analysis was used to seek for the potential causes of heterogeneity. The results of these studies indicated expression of survivin were associated with poorer OS (HR, 2.02; 95% CI, 1.65–2.47, $P < 0.001$). Medium heterogeneity was noted ($I^2 = 50.3\%$, $P_{\text{heterogeneity}} = 0.005$) (Fig. 2). Nine studies examined the association between

![Fig. 1 Flow diagram of the selection of relevant studies included in the meta-analysis](image-url)
Table 1 Characteristics of the studies examined in the meta-analysis

| Author       | Year | Country | Ethnicity | Cancer type | Sample size | Age        | Follow-up (month) | Survival analysis | Method                | Cut-off value | HR   | NOS/REMARK score |
|--------------|------|---------|-----------|-------------|-------------|------------|------------------|-------------------|---------------------|---------------|-------|------------------|
| Elhadj       | 2019 | Tunisia | Non-Asian | LSCC        | 70          | 63 (45–88) | NR               | OS, DFS           | IHC                 | 5%            | Reported 7/12 |
| Erpolat      | 2012 | Turkey  | Non-Asian | HNSCC       | 58          | 56.7 (35–80) | 56.5 (38.7–112.5)| OS               | IHC                 | 5%            | Reported 7/11 |
| Fiedler      | 2018 | Germany | Non-Asian | HNSCC       | 139         | 60.5 (43.4–83.6) | 17.4 (0–120.9) | OS,DSS            | IHC                 | median value | Reported 6/14 |
| Jin          | 2019 | China   | Asian     | NPC         | 164         | 450 (24–70) | 49.2 (6–60)     | OS,DMFS, LRFS, DFS| IHC, RT-PCR       | 0%            | Reported 6/13 |
| Li           | 2008 | China   | Asian     | NPC         | 280         | 46 (14–86) | NR               | OS               | IHC                 | 5%            | Reported 7/11 |
| Li           | 2011 | China   | Asian     | LSCC        | 86          | 51 (37–84) | NR               | OS               | IHC                 | 0%            | Reported 7/12 |
| Lin          | 2005 | China   | Asian     | OSCC        | 96          | NR          | NR               | OS               | IHC                 | 25%           | Reported 6/12 |
| Muzio        | 2005 | Italy   | Non-Asian | OSCC        | 78          | 665 (18–87) | 72               | DFS              | IHC                 | 5%            | Reported 7/11 |
| Preuss       | 2008 | Australia | Non-Asian | OSCC        | 106         | 57 (34–82) | 20.3 (0.33–79.8)| DFS              | IHC                 | 5%            | Reported 7/13 |
| Tastekin     | 2017 | Turkey  | Non-Asian | OSCC        | 46          | 5948 (31–91) | NR               | OS               | IHC                 | 13.00%        | Reported 6/11 |
| Wang         | 2011 | China   | Asian     | NPC         | 1268        | 46 (15–90) | 69 (1–20)       | DSS              | IHC                 | median value | Reported 7/13 |
| Xiang        | 2006 | China   | Asian     | NPC         | 80          | NR          | 60               | OS, DFS           | IHC                 | 25%           | Reported 7/13 |
| Yip          | 2006 | Canada  | Non-Asian | NPC         | 198         | NR          | 1368            | OS               | IHC                 | 5%            | Reported 8/15 |
| Zhao         | 2008 | China   | Asian     | LSCC        | 146         | 546 (42–76) | 41.4 (36–72)    | DFS              | IHC                 | 5%            | Reported 7/14 |
| Dong         | 2002 | Japan   | Asian     | LSCC        | 102         | 6349 (38–89)| NR               | OS, DFS           | IHC                 | 5%            | Reported 7/13 |
| Kim          | 2005 | South Korea | Asian     | OSCC        | 113         | 58 (18–78) | NR               | OS               | RT-PCR             | 50%           | Estimated 6/12 |
| Zhang        | 2013 | China   | Asian     | OSCC        | 110         | 58 (37–78) | > 60             | OS               | IHC                 | median value | Estimated 7/13 |
| Farnebo      | 2013 | Sweden  | Non-Asian | HNSCC       | 40          | 68          | 30               | OS               | IHC                 | 0%            | Estimated 6/11 |
| Freier       | 2007 | Germany | Non-Asian | OSCC        | 296         | 60 (16–92) | 34 (0–147)      | OS               | IHC                 | 10%           | Estimated 7/13 |
| Hansson      | 2017 | Sweden  | Non-Asian | LSCC        | 149         | NR          | 67 (9–163)      | DFS              | IHC                 | 10%           | Estimated 7/11 |
| Munschier    | 2019 | Germany | Non-Asian | HNSCC       | 452         | NR          | 41.3 (1–306)    | OS,DFS            | IHC                 | 50%           | Estimated 7/11 |
| Pickhard     | 2014 | Germany | Non-Asian | HNSCC       | 180         | 53 (35–72) | 60–162          | OS               | IHC                 | 10%           | Estimated 6/11 |
| Su           | 2010 | China   | Asian     | OSCC        | 78          | NR          | NR               | OS               | IHCRT-PCR          | median value | Estimated 6/11 |
| Troiano      | 2018 | Italy   | Non-Asian | OSCC        | 342         | NR          | NR               | OS               | IHC                 | 60%           | Estimated 7/11 |
| Pizem        | 2004 | Slovenia | Non-Asian | LSCC        | 68          | 592 (37–78) | NR               | OS               | IHC                 | 50%           | Estimated 6/12 |
| Marioni      | 2013 | Italy   | Non-Asian | LSCC        | 33          | NR          | 43               | DFS              | IHC                 | 10.00%        | Estimated 6/11 |
| Marioni      | 2017 | Italy   | Non-Asian | LSCC        | 75          | 636         | 67.3             | DFS              | IHC                 | 6%            | Estimated 7/13 |
| Kim          | 2010 | South Korea | Asian     | OSCC        | 38          | 585 (40–75)| NR               | OS               | IHC                 | 20%           | Estimated 6/11 |
Fig. 2 Forest plot indicating the association between survivin expression and OS in HNSCC

Fig. 3 Forest plot examining the association between survivin expression and DFS/DSS in HNSCC
survivin and the DFS and three studies examined the association between survivin and the DSS in HNSCC patients. Figure 3 summarized HR for DFS (HR = 2.03, 95%CI: 1.64–2.52) and DSS (HR = 1.92, 95%CI: 1.41–2.60), and there was no significant heterogeneity noted between survivin expression and DFS (I^2 = 0.0%, P_{heterogeneity} = 0.875), low heterogeneity was noted between survivin expression and DSS (I^2 = 40.2%, P_{heterogeneity} = 0.188).

Subgroup analysis for OS was also performed and was stratified according to different cancer types or geographic populations
Cancer-stratified analysis showed that the summarized HR for LSCC was 1.35 (95% CI, 1.05–1.74, P < 0.001) with low heterogeneity (I^2 = 42.3%, P_{heterogeneity} = 0.158); for HNSCC was 1.52 (95% CI, 1.25–1.86, P < 0.001) with medium heterogeneity (I^2 = 55.3%, P_{heterogeneity} = 0.062); for NPC was 2.53 (95% CI, 1.76–3.62, P < 0.001) with no significant heterogeneity (I^2 = 0.0%, P_{heterogeneity} = 0.540) and for OSCC was 2.45 (95% CI, 1.89–3.17, P < 0.001) with no significant heterogeneity (I^2 = 7.7%, P_{heterogeneity} = 0.370) (Fig. 4).

Ethnicity-stratified analysis demonstrated that the summarized HR for Non-Asian HNSCC patients was 1.56 (95% CI, 1.33–1.82, P < 0.001) with medium heterogeneity (I^2 = 68.4%, P_{heterogeneity} = 0.001); for Asian patients was 2.16 (95% CI, 1.76–2.66, P < 0.001) with no heterogeneity (I^2 = 0.0%, P_{heterogeneity} = 0.844) (Fig. 5).

Sensitivity analysis. The sensitivity analysis was applied to detect the effects of each single study on the overall effect. The analysis did not detect a study that could alter significantly the combined results (Fig. 6). The results of the sensitivity analysis indicated that the pooled effect size of the meta-analysis results was stable and reliable.

Publication bias
The publication bias was assessed by the Begg’s funnel plots and the Egger’s test in the present study. The results indicated the publication bias existed among the studies (p = 0.018). Therefore, “trim and fill” analysis was further utilized, and the pooled HR of 1.569 (95% CI, 1.276–1.930) remained statistically significant (Fig. 7),
**Fig. 5** Forest plot of OS in association with survivin in different types of geographic populations

**Fig. 6** The sensitivity analyses were conducted to evaluate the effects of each single study on the overall effect
Fig. 7 Publication bias and trim and fill analysis of the enrolled analysis. a The Begg’s funnel plots; b The Egger’s test. c Trim and fill analysis
therefore, the results of the present studies were robust in spite of the significant publication bias.

Discussion
Numerous studies have focused on the identification of new prognostic biomarkers that can be used for cancer monitoring and detection. An association between survivin expression and survival outcomes has been shown in HNSCC patients. The study by Fiedler et al. found that high survivin expression was significantly correlated to unfavorable DSS in HNSCC patients [19]. Kim et al. demonstrated that survivin overexpression had a significant negative effect on survival outcomes of OSCC patients [44]. However, contradictory results were reported by Hansson et al. that patients with strong nuclear survivin expression had better 5-year DFS compared with those with weak nuclear survivin expression [36]. Furthermore, Kim et al. found that Asian patients diagnosed with non-nasopharyngeal head and neck cancer tended to exhibit better OS than non-Asian patients [45]. The present study is the first meta-analysis including 28 published studies with 4891 patients to provide useful information for clinical decision-making in HNSCC. Survivin was significantly associated with poorer OS in HNSCC patients, with HR values of 2.02, similar results were found in subgroup analysis stratified by cancer type, such as LSCC, OSCC, NPC, etc. Significant correlation between survivin and shorter DFS/ DSS (HR 2.03/HR 1.92, respectively) was also observed. Moreover, ethnicity-stratified analysis showed that survivin was significantly associated with poorer OS among both Asian and Non-Asian HNSCC patients (HR 2.16/HR 1.56, respectively). These findings confirmed that survivin could be widely applied as diagnostic markers and therapeutic targets in HNSCC patients.

The prognostic value of survivin was investigated in HNSCC and gathering evidences suggested that survivin was an independent prognostic marker in HNSCC [46, 47]. Epigenetic modifications play roles in HNSCC by regulating survivin expression [48]. The hypomethylation of BIRC5 is an important step in OSCC tumorigenesis due to its GC-rich region [49]. p53 also participates in the survivin upregulation in OSCCs, positive correlation was found between survivin expression and p53 in both HNSCC and premalignant lesions by Khan et al. [50]. The survivin gene locus encodes for multiple alternative splice variants with several different functions and heterodimerization possibilities [51]. Twenty three HNSCC cell lines at different differentiation levels showed higher survivin expressed levels compared to a human cell line of epidermal keratinocyte [52]. Targeted therapies have produced striking benefits for patients with cancers. Survivin is preferable targets of therapeutic modalities, namely antisense nucleotides, small-molecule inhibitors, antitumor immunotherapy and RNA interference [53, 54]. According to our results, the survivin inhibitors could be the therapeutics against the HNSCC. The expression of survivin in HNSCC patients represents an important factor that predicts poor prognosis and resistance to chemo- and radiotherapy. The clinical application of survivin as a molecular target in HNSCC therapy significantly benefits HNSCC patients.

However, the present meta-analysis also had several limitations. First, we found that different paper qualities and sample sizes across the studies might cause bias in the meta-analysis. Second, the approaches used to evaluate the survivin expression were different, such as antibodies characters in IHC and instruments used in RT-PCR. Third, the cut-off value defining positive survivin expression varied among eligible studies (Table 1). Forth, our analysis might overestimate the prognostic significance of survivin to some degree due to the positive results reported in most of the including publications. Fifth, partial survival data of some including papers were extracted from Kaplan–Meier curves and may not as accurate as that obtained from original paper directly.

In conclusion, we searched the electronic databases and a total of 4891 patients in 28 studies were enrolled for meta-analysis, the results demonstrating that patients with survivin expression are more likely to have worse prognosis. Taken together, our meta-analysis results suggest that survivin gains a prognostic and diagnostic value for the HNSCC patients. However, more larger sample size studies are required to acquire a more representative and precise result.

Supplementary Information
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Authors’ contributions
YH and LZ collected and analyzed the data, wrote the paper. LZ, YH and HX analyzed the data and wrote the paper. LZ and HX conceived and designed this study, analyzed the data, wrote the paper. All authors read and approved the final manuscript.

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Availability of data and materials
All data generated or analysed during this study are included in this published article [and its supplementary information files]. The data that support the findings of this study are available from the corresponding author upon reasonable request.
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