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**9**  
**Prognosis value of heat-shock proteins in esophageal and esophagogastric cancer: A systematic review and meta-analysis**

Nakamura **E** *et al.* HSPs in esophageal and esophagogastric cancer

## **Abstract**

### **BACKGROUND**

Heat shock proteins (HSPs) are molecular chaperones that play an important role in cellular protection against stress events and have been reported to be overexpressed in many cancers. The prognostic significance of HSPs and their regulatory factors, such as heat shock factor 1 (HSF1) and CHIP, are poorly understood.

### **AIM**

To investigate the relationship between HSP expression and prognosis in esophageal and esophagogastric cancer.

### **METHODS**

A systematic review was conducted in accordance with PRISMA recommendations (PROSPERO: CRD42022370653), on Embase, PubMed, Cochrane, and LILACS. Cohorts, case-control, and cross-sectional studies of patients with esophagus or esophagogastric cancer were included. HSP-positive patients were compared with HSP-negative, and the endpoints analyzed were lymph node metastasis, tumor depth, distant metastasis, and overall survival (OS). HSPs were stratified according to the HSP family, and the summary risk difference (RD) was calculated using a random-effect model.

### **RESULTS**

Final selection comprised 27 studies, including esophageal squamous cell carcinoma (21), esophagogastric adenocarcinoma (5), and mixed neoplasms (1). The pooled sample size was 3465 patients. HSP40 and 60 were associated with a higher 3-year OS [HSP40: RD = 0.22; 95% confidence interval (CI): 0.09-0.35; HSP60: RD = 0.33; 95% CI: 0.17-0.50], while HSF1 was associated with a poor 3-year OS (RD = -0.22; 95% CI: -0.32 to -0.12). The other HSP families were not associated with long-term survival. HSF1 was associated with a higher probability of lymph nodal metastasis (RD = -0.16; 95% CI: -0.29 to -0.04). HSP40 was associated with a lower probability of lymph nodal dissemination

(RD = 0.18; 95%CI: 0.03-0.33). The expression of other HSP families was not significantly related to tumor depth and lymph node or distant metastasis.

## CONCLUSION

The expressions of certain families of HSP, such as HSP40 and 60 and HSF1, are associated with long-term survival and lymph nodal dissemination in patients with esophageal and esophagogastric cancer.

**Key Words:** Heat-shock proteins; Heat-shock response; Prognosis; Esophageal neoplasms; Meta-analysis

Nakamura E, Park A, Pereira MA, Kikawa D, Tustumi F. Prognosis value of heat-shock proteins in esophageal and esophagogastric cancer: A systematic review and meta-analysis. *World J Gastrointest Oncol* 2024; In press

**Core Tip:** Heat shock proteins (HSPs) and their regulatory factors, such as heat shock factor 1 (HSF1) and CHIP, play an important role in cellular protection against stress events, and are overexpressed in some types of cancer. But the prognostic significance of HSPs remains unclear. In the present study, we conducted a systematic review and meta-analysis to investigate the relationship between HSP expression and prognosis in esophageal and esophagogastric cancer that included 27 studies. Our findings demonstrated that some families of HSP expressions of, such as HSP40 and 60 and HSF1, are associated with long-term survival and lymph nodal dissemination in esophageal cancer.

## INTRODUCTION

Esophageal cancer (EC) stands as the sixth most incident cancer worldwide, with 600000 new cases reported annually, ranking as the eighth deadliest cancer<sup>[1]</sup>. Despite strides in therapeutics and screening methods, the prognosis remains grim, featuring a

5-year survival rate of approximately 15%-25%<sup>[2]</sup>. Conventional treatments like chemotherapy, radiation, and surgery often fall short in halting disease progression and recurrence, leaving patients with limited options<sup>[3]</sup>.

Regrettably, practical prognostic factors for EC, crucial for precise diagnosis and therapy, are underexplored<sup>[4]</sup>. This underscores the urgent need to develop novel prognostic markers for EC, enabling enhanced risk stratification and targeted therapy. While significant headway has been made in diagnosing EC, the pursuit of reliable prognostic indicators persists.

Numerous studies in cancer biology have unveiled a plethora of potential targets, with heat shock proteins (HSPs) emerging as crucial players in protein folding and apoptotic modulation, reported to be overexpressed in esophageal tumors<sup>[5]</sup>. Initially discovered as proteins robustly induced in response to heat shock and various stressors, HSPs are highly conserved in all mammalian cells<sup>[5]</sup>. They contribute to **protein quality control** by ensuring the **accurate folding of newly synthesized proteins** and the **refolding of denatured proteins under various intracellular and extracellular stressor conditions**.

HSPs, categorized into six families based on their relative molecular sizes (HSP 20, HSP 40, HSP 60, HSP 70, and HSP 90)<sup>[5,6]</sup>, are regulated by a complex interplay of factors. The swift induction of HSP expression in response to stressors constitutes **the heat shock response (HSR)**<sup>[7]</sup>, **regulated at the transcriptional level by heat shock factors (HSFs)**, crucial **upstream transcriptional regulators of HSPs**<sup>[8]</sup>. HSF1 is recognized as the primary regulator of HSR, activated by the denaturation of intracellular proteins due to proteotoxic exposures. States of hypoxia, acidosis, and inflammation, for instance, may trigger proteotoxic effects and HSF1 activation.

Several clinical conditions linked to different families of HSP, such as acute and chronic renal diseases<sup>[9]</sup>, psoriasis<sup>[10]</sup>, and neurodegenerative diseases<sup>[11]</sup>, disrupt normal cell functions. Abnormal expression levels of certain HSPs have been illuminated in various cancer types, including prostate, bladder, breast, ovarian, colorectal, and lung

cancers<sup>[12-14]</sup>. Some HSP families exhibit a significant correlation with the prognosis of different cancer types<sup>[15,16]</sup>.

The varying expression levels of HSPs during malignant transformation prompt the question of whether HSPs can serve as prognostic indicators in routine clinical settings for EC<sup>[17,18]</sup>. The objective of our study was to assess the prognostic value of HSPs and their regulatory factors in the context of esophageal and esophagogastric cancer through a comprehensive meta-analysis.

## **MATERIALS AND METHODS**

The systematic review and meta-analysis adhered to the PRISMA guidelines<sup>[19]</sup>. The research protocol underwent registration on PROSPERO<sup>[20]</sup> (International Prospective Register of Systematic Reviews) with the registration number CRD42022370653.

### ***Eligibility criteria***

This meta-analysis considered studies evaluating HSP in patients with esophageal squamous cell carcinoma (ESCC) or esophagogastric adenocarcinoma cancer. Inclusion criteria comprised cohort, case-control, and cross-sectional studies, while case reports, editorials, abstracts, and those without full-text availability were excluded

### ***Information sources and search strategy***

The search spanned PubMed, Embase, LILACS (BVS), Cochrane Library Central, and references from included articles, previous systematic reviews, and meta-analyses. A combination of MeSH terms and keywords, such as “Heat Shock Proteins”, “HSP”, “Heat Shock”, “Esophagus”, “Esophageal”, and others, formed the basis of the search. The period covered was from the inception of databases to March 2023.

### ***Study selection***

Conducted by two independent authors (Nakamura E and Park A), the systematic literature search followed predetermined eligibility criteria. Discrepancies in study

inclusion were resolved by a third reviewer. No language or publication date restrictions were imposed, and selection filters were not applied.

### ***Data extraction***

Reviewers (Nakamura E and Park A) manually retrieved baseline characteristics and outcomes, including author name, publication year, study design, sample size, histologic cancer type, treatment type, HSP family, age, sex, stage, and follow-up.

### ***Assessment of risk of bias***

The Newcastle-Ottawa Scale (NOS) facilitated bias risk assessment, executed by two authors (Nakamura E and Kikawa D), with adjudication by a third author (Tustumi F) in case of disagreements.

### ***Outcomes***

The analysis encompassed postoperative mortality, postoperative complications, grade of cellular differentiation, lymph node dissemination, tumor depth, metastasis, and survival.

### ***Statistical analysis and data synthesis***

Meta-analysis was performed using STATA 16.1 software (StataCorp LLC). Categorical variables were reported as risk differences (RD), and continuous variables as mean differences (MD), both with a 95% confidence interval (CI). The  $I^2$  test assessed statistical heterogeneity, and a random-effect model was employed to balance statistical and clinical heterogeneity. Forest plots were utilized for the meta-analysis compilation. Subgroup analysis was used to control histological cancer type as potential confounding variables. We assessed the subgroup of cohorts that evaluated exclusively ESCC.

## **RESULTS**

### *Characteristics of the included studies*

As illustrated in Figure 1, the search flow diagram delineates the identification process, initially yielding 266 primary studies. Following the removal of duplicates and exclusion of articles irrelevant to the meta-analysis, 110 candidate studies underwent full-text review. Subsequently, 27 studies aligning with inclusion criteria were deemed suitable for the study's objectives<sup>[21-47]</sup>. Within this subset, 21 studies focused on ESCC, five on esophagogastric adenocarcinoma, and one on a mixed neoplasm. The cumulative sample size encompassed 3465 patients, with an average age of 60.7 years (range: 46-69) and a predominant male representation (76.9%; range: 38%-91%). A comprehensive summary of the included studies is presented in Table 1.

### *Overall survival*

Elevated expression levels of HSP40 (RD = 0.22; 95%CI: 0.09-0.35) and HSP60 (RD = 0.33; 95%CI: 0.17-0.50) were associated with a heightened 3-year overall survival (OS). Conversely, the presence of HSF1 was linked to a poorer 3-year OS (RD = -0.22; 95%CI: -0.32 to -0.12). Refer to Figure 2. Similar findings were observed for ESCC cohorts (Table 2).

### *Grade of cellular differentiation*

No significant correlation was found between the expression of CHIP (RD = -0.03; 95%CI: -0.15 to 0.09), HSF1 (RD = 0.04; 95%CI: -0.09 to 0.17), HSP20 (RD = -0.09; 95%CI: -0.34 to 0.16), HSP40 (RD = 0.03; 95%CI: -0.10 to 0.16), HSP60 (RD = -0.21; 95%CI: -0.57 to 0.15), HSP70 (RD = -0.14; 95%CI: -0.33 to 0.04), and HSP90 (RD = -0.08; 95%CI: -0.18 to 0.02) with grade of cellular differentiation (Figure 3A).

### *Lymph node dissemination*

The results suggested that overexpression of HSF1 (RD = -0.16; 95%CI: -0.29 to -0.04) was significantly associated with positive lymph node metastasis. High HSP40 values were associated with less risk for lymph node dissemination (RD = 0.18; 95%CI: 0.03-



0.33). There was no significant difference observed on CHIP (RD = 0.00; 95%CI: 0.00-0.00), HSP20 (RD = 0.05; 95%CI: -0.15-0.24), HSP60 (RD = -0.14; 95%CI: -0.36 to 0.08), HSP70 (RD = -0.20; 95%CI: -0.48 to 0.07), HSP90 (RD = 0.26; 95%CI: -0.62 to 0.10). See Figure 3B. Similar findings were observed for ESCC cohorts (Table 2).

### *Tumor depth*

There was no significant association between tumor depth and HSF1 (RD = -0.22; 95%CI: -0.51 to 0.06), HSP20 (RD = -0.03; 95%CI: -0.01 to 0.16), HSP40 (RD = -0.04; 95%CI: -0.14 to 0.06), HSP60 (RD = 0.01; 95%CI: -0.17 to 0.18), HSP70 (RD = 0.00; 95%CI: -0.21 to 0.22), HSP90 (RD = -0.04; 95%CI: -0.19 to 0.12) (Figure 4A).

### *Distant metastasis*

There was no significant association between distant metastasis and HSF1 (RD = -0.01; 95%CI: -0.06 to 0.08), HSP20 (RD = 0.04; 95%CI: -0.09 to 0.17), HSP40 (RD = 0.03; 95%CI: -0.05 to 0.11), HSP60 (RD = 0.00; 95%CI: -0.12 to 0.13), HSP70 (RD = -0.14; 95%CI: -0.38 to 0.09), HSP90 (RD = -0.22; 95%CI: -0.55 to 0.10) (Figure 4B).

### *Risk of bias assessment*

All eligible studies underwent a risk of bias assessment with the NOS. Two independent reviewers assessed the quality and risk of bias. In the event of a tie, the decision was determined by a third reviewer after a group discussion in which all sides were taken into account. Points given to each study are shown in Table 3.

## **DISCUSSION**

The association between HSPs and cancer prognosis has generated significant interest, offering potential implications for clinical decision-making in cancer management. Prognostication, a pivotal aspect of cancer care, can be significantly enhanced through the exploration of HSPs in EC. This investigation holds promise for refining prognostic

predictions, tailoring treatment approaches, and ultimately improving patient outcomes<sup>[48]</sup>.

The tumor microenvironment, characterized by conditions such as low glucose, pH, and oxygen levels, induces the expression of HSPs<sup>[15]</sup>. These molecular chaperones, crucial in apoptosis regulation<sup>[49]</sup>, respond to stressors during carcinogenesis, triggered by the emergence of oncoproteins. However, the diverse functions of HSPs within tumors are influenced by the complex genetic and epigenetic alterations characterizing carcinogenesis<sup>[50]</sup>. HSPs may play a protective role in the early stages of cancer initiation, such as in chronic esophagitis, yet exhibit different patterns as cancer progresses<sup>[5]</sup>. For instance, HSP70 exhibits differential expression following thermal injury to the esophageal epithelium, with reduced levels post-injury and subsequent recovery-induced upregulation<sup>[51]</sup>. This finding highlights the distinct roles of certain HSPs in the context of esophageal injury and recovery in gastroesophageal reflux, known risk factor for Barrett's esophagus and esophagogastric adenocarcinoma<sup>[52]</sup>. This nuanced understanding of HSP behavior contributes to the heterogeneous differentiation<sup>[53,54]</sup> observed within HSPs, with some members associated with aggressive cancer phenotypes and others playing a protective role in cancer development<sup>[55]</sup>.

The present study highlights the overexpression of HSP40 and HSP60, which correlates with higher 3-year OS in EC. Moreover, these HSP families are found overexpressed in various human cancer types beyond EC, including cervical cancer, glioma, skin cancer, lung cancer, colorectal cancer, kidney cancer, and gastric cancer<sup>[56-62]</sup>.

DNAJ, HSP40 family member<sup>[63]</sup>, plays a crucial role in cellular functions, including stimulating ATPase activity and performing chaperone functions like protein folding, unfolding, translation, translocation, and degradation<sup>[64]</sup>. The research conducted by Yu *et al*<sup>[43]</sup> on DNAJB6, a nuclear-localized member of the HSP40 family, establishes its independence as a factor associated with better OS in ESCC. Elevated DNAJB6 levels were linked to down regulated AKT signaling and decreased sensitivity to AKT

inhibition, providing insights for molecular targeted therapy focusing on oncogene addiction<sup>[43]</sup>. The prognosis related to HSP40 is, in part, explained by its connection to lymphatic dissemination, as HSP40 overexpression is linked to a lower probability of lymph nodal metastasis, suggesting a potential association with host immunity and immune-promoting functions<sup>[25,33,35]</sup>.

The HSP60 family serves as an antigen for both B and T-lymphocytes, acting as a ligand for toll-like receptors and playing a pivotal role in immunity<sup>[65]</sup>. The significance of this family is highlighted by the observation that HSP60 inactivation in mice results in embryonic lethality<sup>[66]</sup>. Xanthoudakis *et al*<sup>[67]</sup> demonstrated that HSP60 facilitates pro-caspase-3 maturation, initiating apoptosis through a Fas-independent pathway. Additionally, HSP60 regulates mitochondrial permeability transition, establishing a cytoprotective network that counters CypD-associated cell death in tumor contexts, where CypD is a component of the mitochondrial permeability transition pore. Furthermore, HSP60 plays a crucial role in protein import and quality control machinery<sup>[68,69]</sup>.

The HSP60 family holds potential as a novel prognostic biomarker in esophageal and esophagogastric cancer<sup>[25,31]</sup>. The consequences of HSP60 knockdown are substantial, compromising the integrity of respiratory complex I and inducing an excessive production of reactive oxygen species (ROS). This surplus ROS production fuels tumor progression by activating AMP-activated protein kinase, facilitating the acquisition of the Warburg phenotype in HSP60 knockdown cells. Elevated ROS levels may lead to the fragmentation of iron-sulfur clusters, consequently upregulating the expression of ADHFe1. This, in turn, triggers an increase in the production of 2-hydroxyglutarate, impacting DNA methylation and influencing the tumor's epigenetic landscape<sup>[50]</sup>.

The investigation delves into HSF1 expression and its correlation with lymph nodal metastasis and diminished 3-year OS in EC. HSF1, a participant in the HSR, plays a multifaceted role in orchestrating molecular changes contributing to malignancy progression<sup>[70]</sup>. Its activation transforms the tumor microenvironment, promoting processes such as angiogenesis, extracellular matrix (ECM) organization, adhesion, and

migration. Elevated HSF1 expression in both tumor and stromal cells significantly correlates with worse disease-free survival and OS in ESCC. Conversely, lower levels of HSF1 activation indicate a more favorable outcome, suggesting its potential as a biomarker for ESCC patient prognosis. *In vivo* experiments demonstrate that the absence of HSF1 reduces tumor formation, further supporting its role in malignant growth<sup>[71]</sup>. This transformation occurs through the upregulation of genes promoting the malignant phenotype and the downregulation of genes that might trigger an anticancer immune response<sup>[50]</sup>. Moreover, HSF1 activation drives specific beneficial pathways within the malignant elements, fostering processes such as angiogenesis, ECM organization, adhesion, and migration<sup>[72]</sup>. It is plausible that HSF1 is involved in the ESCC microenvironment through the same molecular mechanism. Additionally, stress-damaged proteins, when accumulated in the cytoplasm, recruit HSP70 and HSP90, which bind to HSF1, impeding its activation. Upon activation, HSF1 translocates to the nucleus, binding to the heat shock element sequence in the promoter regions of HSP genes, thereby inducing the expression of inducible HSPs like HSP27, HSP60, HSP70, HSP90, and multidrug resistance 1<sup>[73]</sup>. Furthermore, HSF1 activation plays a pivotal role in the tumor stroma, especially within cancer-associated fibroblasts. In this context, HSF1 triggers the activation of genes associated with processes such as angiogenesis, ECM remodeling, cellular adhesion, and migration. These molecular alterations collectively contribute to the promotion of malignant growth<sup>[74]</sup>. *In vivo* experiments have substantiated this, demonstrating that the absence of HSF1 reduces tumor formation in a mouse model lacking p53<sup>[71]</sup>. This multifaceted role underscores the potential significance of HSF1 in orchestrating molecular changes contributing to the progression of malignancy, particularly within the context of ESCC. Liao *et al*<sup>[29]</sup> demonstrated that the high level of HSF1 expression in both tumor cells and stromal cells was significantly associated with worse disease-free survival and OS of ESCC patients. It was also demonstrated that lower levels of HSF1 activation in both stromal and tumor cells are indicative of a more favorable outcome for patients with ESCC, suggesting the potential of HSF1 activation as a biomarker for ESCC patient

prognosis<sup>[29]</sup>. These findings align with prior research indicating heightened levels of HSF1 expression across diverse cancer types. In a study involving over 1800 participants, nuclear HSF1 levels were elevated in 80% of *in situ* invasive breast carcinomas<sup>[75]</sup>.

Aligned to the current finding in ESCC, HSF1 has been linked to poor prognosis in various cancer types. Engerud *et al*<sup>[76]</sup> established an association between HSF1 overexpression and poor survival after analyzing 823 lesions from endometrial cancer. Ishiwata *et al*<sup>[77]</sup> similarly demonstrated an association between HSF1 expression and lower OS in oral squamous cell carcinoma. Santagata *et al*<sup>[75]</sup> revealed that high HSF1 expression was associated with lymph node invasion in breast cancer patients. Evidence related to cytoskeleton suggests that HSF1 regulates cell motility in esophagogastric adenocarcinoma by binding to the ArgBP2 promoter with the sequence nGAAn<sup>[78]</sup>. The interaction of HSF1 with MORC2 further mediates invasion and migration in esophagogastric cancer cells by inhibiting ArgBP2, a crucial regulator of cytoskeleton and cellular motility<sup>[78]</sup>. These findings indicate that HSF1 presence influences cell motility, thereby impacting invasion and migration in esophagogastric cancer cells.

The biomarker profile of HSPs holds the potential to enhance prognostic stratification accuracy in EC, offering a pathway for personalized medicine and precision therapy-essential components of modern oncology<sup>[79]</sup>. Targeted therapy, linked to extended OS and reduced treatment costs<sup>[80-82]</sup>, can be optimized by understanding the role of HSPs in cancer development and progression. Breakthroughs in HSP inhibitors and HSP cancer vaccines have been proposed, with studies suggesting their capacity to induce therapeutic resistance against radiotherapy and chemotherapy. HSPs may emerge as crucial targeting molecules for cancer therapy, particularly in esophageal oncology<sup>[5]</sup>. HSP inhibitors, by targeting key pathways regulated by HSP, have the potential to revolutionize the treatment landscape, inhibiting pro-survival pathways and altering HSP receptor expression<sup>[83]</sup>, thereby reducing malignant transformation and tumor growth<sup>[84,85]</sup>. Strategies such as genetic removal, stress pathway inhibitors, RNA aptamer insertion, and gene silencing with short hairpin RNA (shRNA) exhibit

promising results in inhibiting HSF1 and impeding cancer progression<sup>[86,87]</sup>. Another practical possibility is the silencing of the HSF1 gene with a shRNA, as shown by Nakamura *et al*<sup>[88]</sup>, with promising results regarding cancer cell proliferation and activation of apoptotic pathways.

HSPs may also serve as adjuvants for vaccines, as evidenced in experimental models where HSP60-containing exosomes induce a substantial antitumor CD8(+) T cell response<sup>[89]</sup>. The proinflammatory response elicited by HSP60 in macrophages triggers an adaptive cellular immune reaction, suggesting its potential in enhancing immunotherapy for cancer<sup>[72]</sup>. Furthermore, HSPs could assist in indicating specific palliative, adjuvant, or neoadjuvant chemotherapy or radiotherapy regimens. Profiling HSPs has the potential to improve precision in EC management, enabling the categorization of patients based on their likelihood of responding to chemotherapy<sup>[48]</sup>. This knowledge could spare some patients from unnecessary treatment and enhance OS. However, it is crucial to acknowledge that most studies involving HSP inhibitors are limited to preclinical analysis and early-stage trials, and only future research will provide robust evidence for the efficacy of HSP therapies in clinical practice.

Despite these insights, the meta-analysis is subject to limitations. The number of studies conducted for HSP40, HSP60, and HSF1 was relatively small, potentially impacting the overall robustness of the findings. Besides, most of the studies included only ESCC, and few studies assessed the impact of HSP on esophageal adenocarcinoma and esophagogastric junction neoplasms. Although we performed subgroup analysis for ESCC, the same subgroup analysis was not possible for adenocarcinoma due to the small number of articles. Consequently, future studies should investigate the potential value of HSP in cancer prognostication and therapy.

## **CONCLUSION**

Our systematic review and meta-analysis highlight a significant correlation between the overexpression of HSP40 and 60, and low HSF1 expression, and favorable outcomes, including prolonged survival and diminished lymph nodal dissemination in



individuals with esophageal and esophagogastric cancer. These results underscore the noteworthy prognostic implications of HSPs within the realm of cancer research, suggesting potential avenues for therapeutic interventions. The ongoing exploration of this field offers the prospect of furthering precision medicine and developing targeted strategies for the management of esophageal and esophagogastric cancer.

## **ARTICLE HIGHLIGHTS**

### ***Research background***

The association between heat shock proteins (HSPs) and cancer prognosis has generated significant interest, offering potential implications for clinical decision-making in cancer management. HSPs and their regulatory factors, such as heat shock factor (HSF)1 and CHIP, play an important role in cellular protection against stress events, and are overexpressed in some types of cancer.

### ***Research motivation***

The prognostic significance of HSPs and their regulatory factors, such as HSF1 and CHIP, are poorly understood in esophageal and esophagogastric cancer.

### ***Research objectives***

We conducted a systematic review and meta-analysis to investigate the relationship between HSP expression and prognosis in esophageal and esophagogastric cancer.

### ***Research methods***

A systematic review was conducted in accordance with PRISMA recommendations, on Embase, PubMed, Cochrane, and LILACS. Cohorts, case-control, and cross-sectional studies of patients with esophagus or esophagogastric cancer were included. HSP-positive patients were compared with HSP-negative, and the endpoints analyzed were lymph node metastasis, tumor depth, distant metastasis, and overall survival (OS).

HSPs were stratified according to the HSP family, and the summary risk difference (RD) was calculated using a random-effect model.

### ***Research results***

Final selection comprised 27 studies, including esophageal squamous cell carcinoma (21), esophagogastric adenocarcinoma (5), and mixed neoplasms (1). The pooled sample size was 3465 patients. HSP40 and 60 were associated with a higher 3-year OS, while HSF1 was associated with a poor 3-year OS. The other HSP families were not associated with long-term survival. HSF1 was associated with a higher probability of lymph nodal metastasis. HSP40 was associated with a lower probability of lymph nodal dissemination. The expression of other HSP families was not significantly related to tumor depth and lymph node or distant metastasis.

### ***Research conclusions***

Our findings demonstrated that some families of HSP<sup>2</sup> expressions, such as HSP40 and 60 and HSF1, are associated with long-term survival and lymph nodal dissemination in esophageal and esophagogastric cancer.

### ***Research perspectives***

The results of study underscore the noteworthy prognostic implications of HSPs within the realm of cancer research, suggesting potential avenues for therapeutic interventions. The ongoing exploration of this field offers the prospect of furthering precision medicine and developing targeted strategies for the management of esophageal and esophagogastric cancer.



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