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SYSTEMATIC REVIEWS

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

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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. Cohort, 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

The 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 node metastasis (RD = -0.16; 95%CI: -0.29 to -0.04). HSP40 was associated with a lower probability of lymph node 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 expression levels of certain families of HSP, such as HSP40 and 60 and HSF1, are associated with long-term survival and lymph node dissemination in patients with esophageal and esophagogastric cancer.

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

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 or cancer. However, 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 the expression levels of some families of HSP, such as HSP40 and 60 and HSF1, are associated with long-term survival and lymph node dissemination in esophageal cancer.

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INTRODUCTION

Esophageal cancer (EC) is the sixth most common cancer worldwide, with 600000 new cases reported annually, and is the eighth deadliest cancer[1]. Despite strides in therapeutics and screening methods, the prognosis remains grim, with a 5-year survival rate of approximately 15%-25%[2]. Conventional treatments such as chemotherapy, radiation, and surgery often fall short in halting disease progression and recurrence, leaving patients with limited options[3].

Regrettably, practical prognostic factors for EC, crucial for precise diagnosis and therapy, are underexplored[4]. 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[5]. Initially discovered as proteins robustly induced in response to heat shock and various stressors, HSPs are highly conserved in all mammalian cells[5]. 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)[5,6], are regulated by a complex interplay of factors. The swift induction of HSP expression in response to stressors constitutes the heat shock response (HSR)[7], regulated at the transcriptional level by heat shock factors (HSFs), crucial upstream transcriptional regulators of HSPs[8]. HSF1 is recognized as the primary regulator of the 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[9], psoriasis[10], and neurodegenerative diseases[11], disrupt normal cell functions. Abnormal expression levels of certain HSPs have been revealed in various cancer types, including prostate, bladder, breast, ovarian, colorectal, and lung cancers[12-14]. Some HSP families exhibit a significant correlation with the prognosis of different cancer types[15,16].

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[17,18]. 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[19]. The research protocol underwent registration on PROSPERO[20] (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. 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 the databases to March 2023.

Study selection

Conducted by two independent authors (Nakamura ET 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 ET 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 ET and Kikawa D), with adjudication by a third author (Tustumi F) in the 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 the inclusion criteria were deemed suitable for the study's objectives[21-47]. 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) (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

Table 1 Characteristics of included studies

Ref.	Cancer type	*N*	HSP	Age (yr)	Male (%)	Upper third cancer location (%)	Stage III/IV (%)	Follow-up (months)
Akutsu *et al*[21], 2011	ESCC	78	HSP90	62	89	19	51	24
Berezowska *et al*[22], 2013	EA and G	347	HSP90	69	64	0	NI	NI
Berg *et al*[23], 2011	EA	87	HSP20	63	91	0	NI	NI
Doak *et al*[24], 2004	EA	4	HSP20	63	83	0	NI	NI
Faried *et al*[25], 2004	ESCC	123	HSP60, 90	61	86	14	38	NI
Huang *et al*[26], 2014	ESCC	81	HSP90	58	38	0	30	NI
Iqbal *et al*[27], 2016	ESCC	46	HSP20, 70, 90	58	65	0	16	NI
Kawanishi *et al*[28], 1999	ESCC	102	HSP20, 70	62	82	NI	36	25
Liao *et al*[29], 2015	ESCC	134	HSF1	61	81	NI	46	NI
Luz *et al*[30], 2017	ESCC	28	HSP20, 70	60	82	NI	NI	60
Lv *et al*[31], 2022	ESCC and EA	87	HSP60	NI	NI	NI	52	NI
Miyazaki *et al*[32], 2005	ESCC	61	HSP20, 70	65	87	21	49	23
Nakajima *et al*[33], 2002	ESCC	62	HSP20, 70	61	85	13	42	NI
Nakajima *et al*[34], 2009	EC	125	HSP70	62	86	14	38	NI
Noguchi *et al*[35], 2002	ESCC	71	HSP70	64	89	11	45	.
Ou *et al*[36], 2014	ESCC	328	HSP90	59	82	NI	NI	51
Söderström *et al*[37], 2019	EA	151	HSP20, 70	65	80	0	83	NI
Tsukao *et al*[38], 2017	ESCC	212	HSF1, HSP20, 70, 90	65	87	14	54	NI
Wang *et al*[39], 2007	G	60	HSP70, HSP90	46	53	0	NI	NI
Wang *et al*[40], 2010	ESCC	120	HSP70, 90	57	77	NI	NI	NI
Wen *et al*[41], 2013	ESCC	234	CHIP	58	83	10	NI	18
Xue *et al*[42], 2014	ESCC	112	HSP20	60	54	NI	NI	NI
Yu *et al*[43], 2015	ESCC	72	HSP40	65	82	NI	66	NI
Zhang *et al*[44], 2013	ESCC	120	HSP70	53	75	29	36	60
Zhang *et al*[45], 2017	ESCC	162	HSP20	63	67	NI	NI	NI
Zhang *et al*[46], 2020	ESCC	345	HSP20	NI	69	NI	NI	NI
Zhao *et al*[47], 2015	ESCC	113	HSP70	58	82	20	74	NI

HSP: Heat shock protein; ESCC: Esophageal squamous cell carcinoma; G: Gastric; EC: Esophageal cancer; EA: Esophageal adenocarcinoma; NI: Not informed; HSF: Heat shock factor.

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 for 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), and HSP90 (RD = 0.26; 95%CI: -0.62 to 0.10) (Figure 3B). Similar findings were observed for ESCC cohorts (Table 2).

Table 2 Subgroup analysis, the impact of heat shock protein on 3-year overall survival, grade of cellular differentiation, and tumor-node-metastasis stage in esophageal squamous cell carcinoma

HSP		Overall survivall	Grade of cellular differentiation	T	N	M
CHIP	RD (95%CI)	0.03 (-0.09 to 0.15)	-	-	0.00 (0.00-0.00)	-
	Studies	1	-	-	1	-
HSF1	RD (95%CI)	-0.22 (-0.32 to -0.12)[1]	0.04 (-0.09 to 0.17)	-0.22 (-0.51 to 0.06)	-0.16 (-0.29 to -0.04)[1]	0.01 (-0.06 to 0.08)
	Studies	2	2	1	2	1
HSP20	RD (95%CI)	0.16 (-0.12 to 0.45)	0.03 (-0.05 to 0.11)	0.01 (-0.13 to 0.16)	-0.04 (-0.22 to 0.14)	0.00 (0.15 to -0.15)
	Studies	6	7	6	7	4
HSP40	RD (95%CI)	0.22 (0.09-0.35)[1]	0.03 (-0.10 to 0.16)	-0.04 (-0.14 to 0.06)	0.18 (0.03-0.33)[1]	0.03 (-0.05 to 0.11)
	Studies	1	1	1	1	1
HSP60	RD (95%CI)	0.33 (0.17-0.50)[1]	-0.03 (-0.20 to 0.13)	0.09 (-0.09 to 0.26)	-0.04 (-0.21 to 0.14)	0.07 (-0.06 to 0.20)
	Studies	1	1	1	1	1
HSP70	RD (95%CI)	0.07 (-0.18 to 0.31)	-0.08 (-0.17 to 0.00)	-0.07 (-0.25 to 0.11)	-0.17 (-0.45 to 0.12)	-0.10 (-0.33 to 0.12)
	Studies	8	8	6	8	5
HSP90	RD (95%CI)	0.03 (-0.23 to 0.29)	-0.02 (-0.06 to 0.03)	-0.10 (-0.20 to 0.01)	-0.24 (-0.74 to 0.26)	0.18 (-0.18 to 0.54)
	Studies	3	2	4	3	3

[1]Significant values.
RD: Risk difference; CI: Confidence interval; HSP: Heat shock protein; HSF: Heat shock factor.

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), and 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), and 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[48].

The tumor microenvironment, characterized by conditions such as low glucose, pH, and oxygen levels, induces the expression of HSPs[15]. These molecular chaperones, crucial in apoptosis regulation[49], 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[50]. 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[5]. For instance, HSP70 exhibits differential expression following thermal injury to the esophageal epithelium, with reduced levels post-injury and subsequent recovery-induced upregulation[51]. This finding highlights the distinct roles of certain HSPs in the context of esophageal injury and recovery in gastroesophageal reflux, known risk factors for Barrett's esophagus and esophagogastric adenocarcinoma[52]. This nuanced understanding of HSP behavior contributes to the heterogeneous differentiation[53,54] observed within HSPs, with some members associated with aggressive cancer phenotypes and others playing a protective role in cancer development[55].

Table 3 Risk of bias assessment scores based on the Newcastle-Ottawa Scale of studies

Ref.	Selection of cohorts				Comparability of cohorts	Outcome		
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow up long enough for outcomes to occur	Adequacy of follow up of cohorts
Akutsu *et al* [21], 2011	☆	☆	☆	☆	☆☆	☆	☆	
Berezowska *et al*[22], 2013	☆	☆	☆	☆	☆☆	☆	☆	
Berg *et al* [23], 2011	☆	☆	☆	☆	☆☆	☆	☆	
Doak *et al* [24], 2004	☆	☆	☆	☆	☆☆	☆	☆	
Faried *et al* [25], 2004	☆	☆	☆	☆	☆	☆		
Huang *et al* [26], 2014	☆	☆	☆	☆	☆☆	☆	☆	☆
Iqbal *et al* [27], 2016	☆	☆	☆	☆	☆☆	☆		
Kawanishi *et al*[28], 1999	☆	☆	☆	☆	☆☆	☆	☆	☆
Liao *et al* [29], 2015	☆	☆	☆	☆	☆☆	☆	☆	☆
Luz *et al* [30], 2017	☆	☆	☆	☆	☆☆	☆		
Lv *et al*[31], 2022	☆	☆	☆	☆	☆☆	☆	☆	☆
Miyazaki *et al*[32], 2005	☆	☆	☆	☆	☆☆	☆	☆	☆
Nakajima *et al*[33], 2002	☆	☆	☆	☆	☆☆	☆	☆	☆
Nakajima *et al*[34], 2009	☆	☆	☆	☆	☆☆	☆	☆	☆
Noguchi *et al*[35], 2002	☆	☆	☆	☆	☆☆	☆	☆	☆
Ou *et al* [36], 2014	☆	☆	☆	☆	☆☆	☆	☆	☆
Söderström *et al*[37], 2019	☆	☆	☆	☆	☆☆	☆	☆	☆
Tsukao *et al* [38], 2017	☆	☆	☆	☆	☆☆	☆	☆	☆
Wang *et al* [39], 2007	☆	☆	☆	☆	☆☆	☆		
Wang *et al* [40], 2010	☆	☆	☆	☆	☆☆	☆		
Wen *et al* [41], 2013	☆	☆	☆	☆	☆☆	☆	☆	☆
Xue *et al* [42], 2014	☆	☆	☆	☆	☆☆	☆	☆	☆
Yu *et al*[43],	☆	☆	☆	☆	☆☆	☆	☆	☆

2015								
Zhang *et al* [44], 2013	☆	☆	☆	☆	☆☆	☆	☆	☆
Zhang *et al* [45], 2017	☆	☆	☆	☆	☆☆	☆		
Zhang *et al* [46], 2020	☆	☆	☆	☆	☆☆	☆		
Zhao *et al* [47], 2015	☆	☆	☆	☆	☆☆	☆	☆	☆

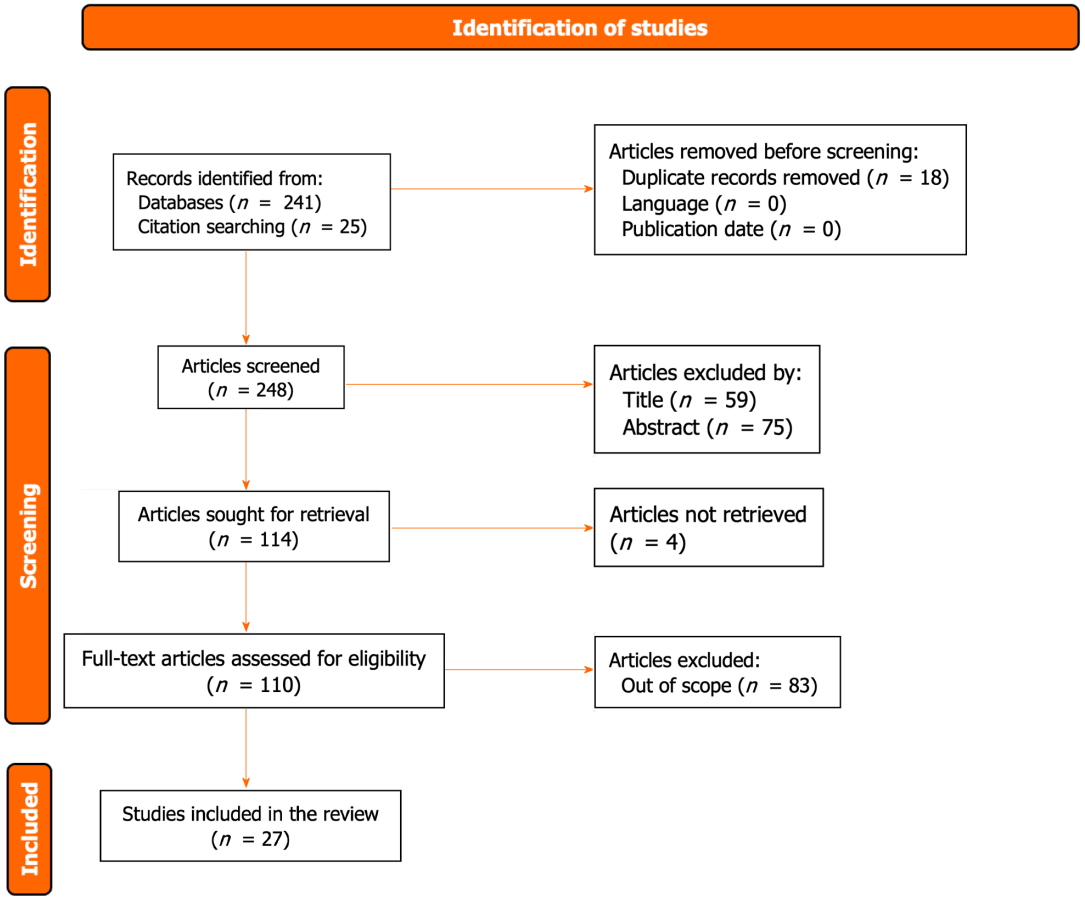


Figure 1 PRISMA flowchart of study inclusions and exclusions.

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[56-62].

DNAJ, a HSP40 family member[63], plays a crucial role in cellular functions, including stimulating ATPase activity and performing chaperone functions such as protein folding, unfolding, translation, translocation, and degradation[64]. The research conducted by Yu *et al*[43] 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[43]. 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 node metastasis, suggesting a potential association with host immunity and immune-promoting functions[25,33,35].

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[65]. The significance of this family is highlighted by the observation that HSP60 inactivation in mice results in embryonic lethality[66]. Xanthoudakis *et al*[67] 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[68,69].

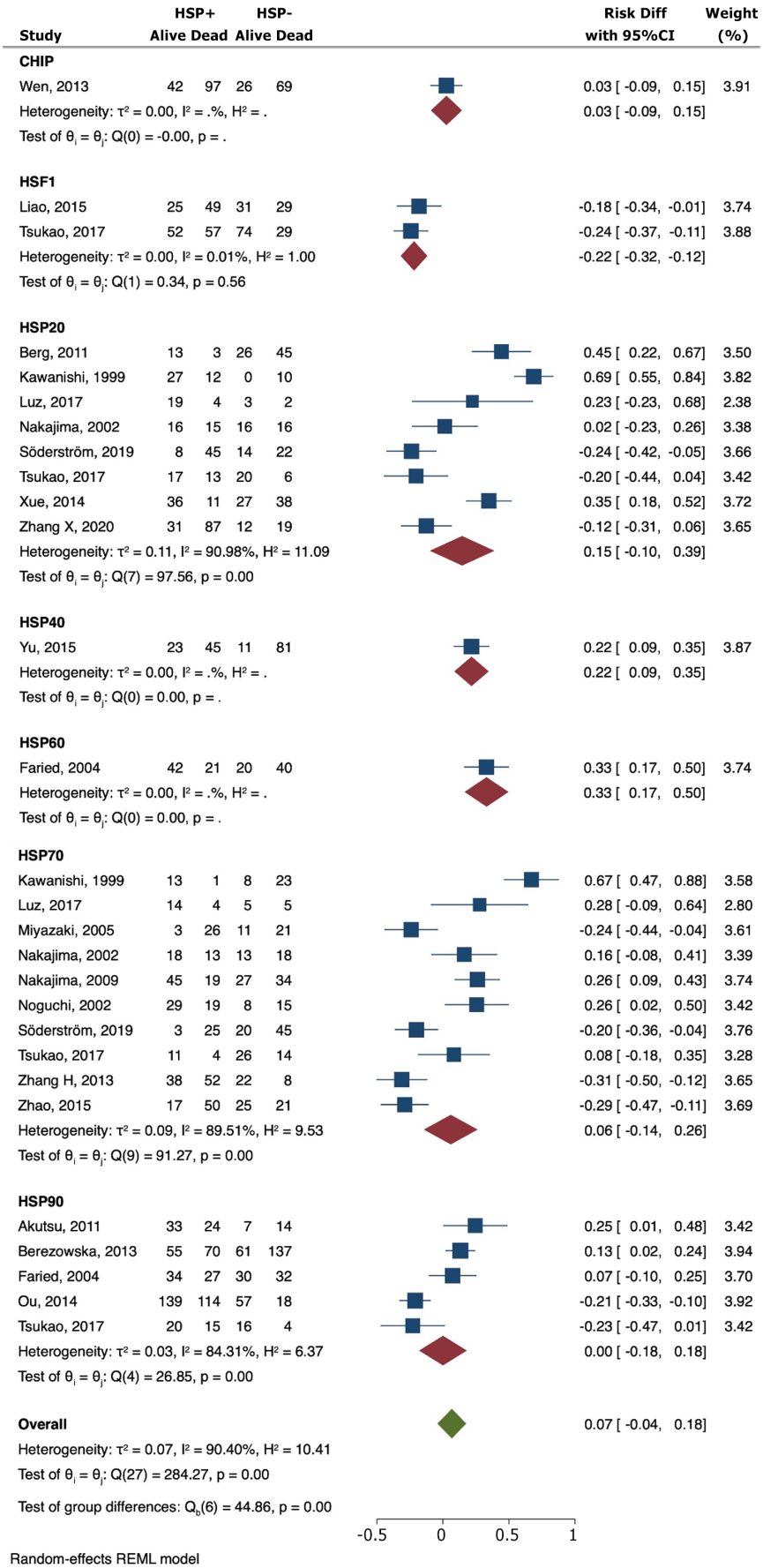
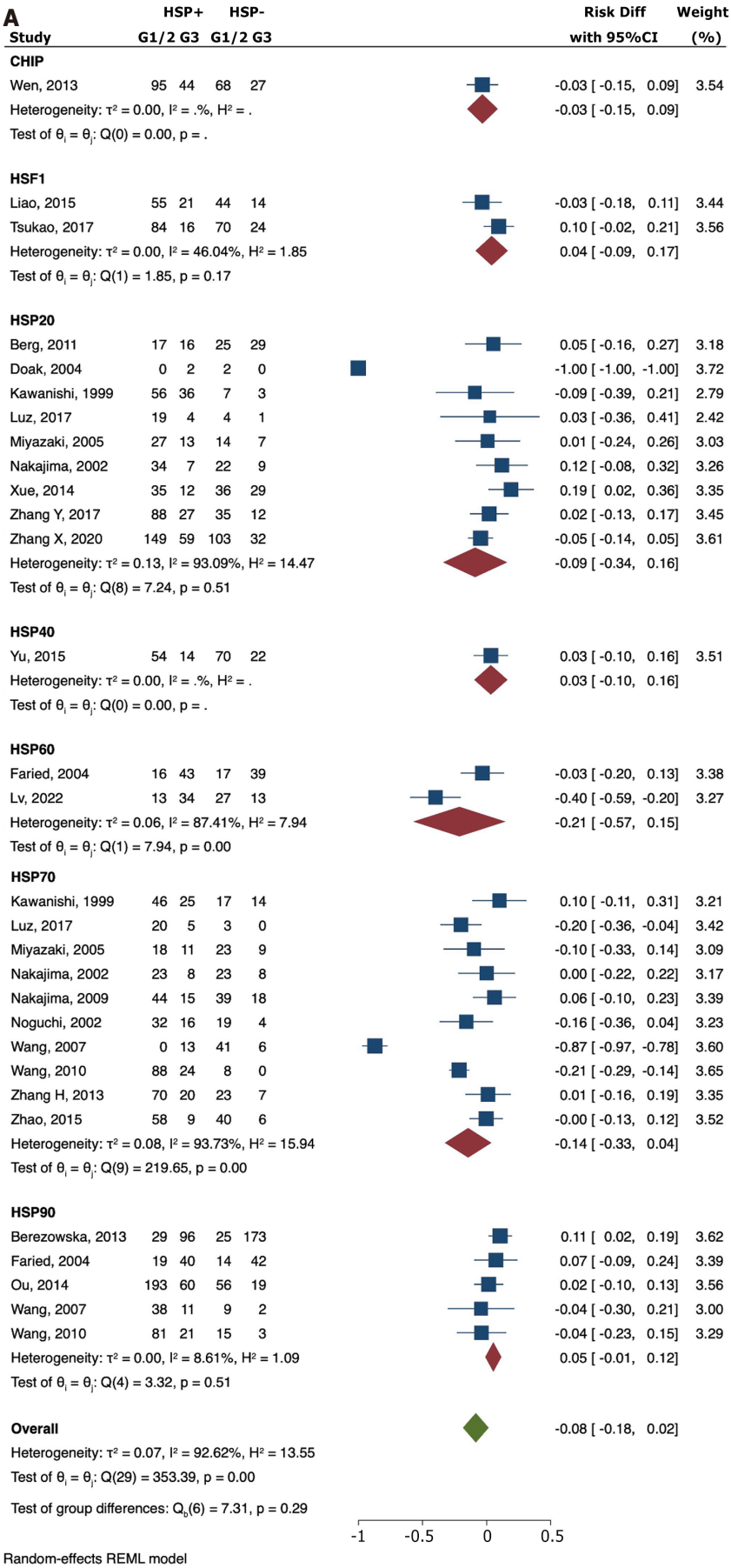


Figure 2 Forest plot of the eligible studies assessing the relationship between heat shock protein expression and overall survival. HSP: Heat shock protein; CI: Confidence interval.


A
Study
HSP+ G1/2 G3
HSP- G1/2 G3
Risk Diff with 95%CI
Weight (%)
CHIP
Wen, 2013 95 44 68 27 -0.03 [-0.15, 0.09] 3.54
Heterogeneity: τ² = 0.00, I² = .%, H² = . -0.03 [-0.15, 0.09]
Test of θi = θj: Q(0) = 0.00, p = .
HSF1
Liao, 2015 55 21 44 14 -0.03 [-0.18, 0.11] 3.44
Tsukao, 2017 84 16 70 24 0.10 [-0.02, 0.21] 3.56
Heterogeneity: τ² = 0.00, I² = 46.04%, H² = 1.85 0.04 [-0.09, 0.17]
Test of θi = θj: Q(1) = 1.85, p = 0.17
HSP20
Berg, 2011 17 16 25 29 0.05 [-0.16, 0.27] 3.18
Doak, 2004 0 2 2 0 -1.00 [-1.00, -1.00] 3.72
Kawanishi, 1999 56 36 7 3 -0.09 [-0.39, 0.21] 2.79
Luz, 2017 19 4 4 1 0.03 [-0.36, 0.41] 2.42
Miyazaki, 2005 27 13 14 7 0.01 [-0.24, 0.26] 3.03
Nakajima, 2002 34 7 22 9 0.12 [-0.08, 0.32] 3.26
Xue, 2014 35 12 36 29 0.19 [0.02, 0.36] 3.35
Zhang Y, 2017 88 27 35 12 0.02 [-0.13, 0.17] 3.45
Zhang X, 2020 149 59 103 32 -0.05 [-0.14, 0.05] 3.61
Heterogeneity: τ² = 0.13, I² = 93.09%, H² = 14.47 -0.09 [-0.34, 0.16]
Test of θi = θj: Q(8) = 7.24, p = 0.51
HSP40
Yu, 2015 54 14 70 22 0.03 [-0.10, 0.16] 3.51
Heterogeneity: τ² = 0.00, I² = .%, H² = . 0.03 [-0.10, 0.16]
Test of θi = θj: Q(0) = 0.00, p = .
HSP60
Faried, 2004 16 43 17 39 -0.03 [-0.20, 0.13] 3.38
Lv, 2022 13 34 27 13 -0.40 [-0.59, -0.20] 3.27
Heterogeneity: τ² = 0.06, I² = 87.41%, H² = 7.94 -0.21 [-0.57, 0.15]
Test of θi = θj: Q(1) = 7.94, p = 0.00
HSP70
Kawanishi, 1999 46 25 17 14 0.10 [-0.11, 0.31] 3.21
Luz, 2017 20 5 3 0 -0.20 [-0.36, -0.04] 3.42
Miyazaki, 2005 18 11 23 9 -0.10 [-0.33, 0.14] 3.09
Nakajima, 2002 23 8 23 8 0.00 [-0.22, 0.22] 3.17
Nakajima, 2009 44 15 39 18 0.06 [-0.10, 0.23] 3.39
Noguchi, 2002 32 16 19 4 -0.16 [-0.36, 0.04] 3.23
Wang, 2007 0 13 41 6 -0.87 [-0.97, -0.78] 3.60
Wang, 2010 88 24 8 0 -0.21 [-0.29, -0.14] 3.65
Zhang H, 2013 70 20 23 7 0.01 [-0.16, 0.19] 3.35
Zhao, 2015 58 9 40 6 -0.00 [-0.13, 0.12] 3.52
Heterogeneity: τ² = 0.08, I² = 93.73%, H² = 15.94 -0.14 [-0.33, 0.04]
Test of θi = θj: Q(9) = 219.65, p = 0.00
HSP90
Berezowska, 2013 29 96 25 173 0.11 [0.02, 0.19] 3.62
Faried, 2004 19 40 14 42 0.07 [-0.09, 0.24] 3.39
Ou, 2014 193 60 56 19 0.02 [-0.10, 0.13] 3.56
Wang, 2007 38 11 9 2 -0.04 [-0.30, 0.21] 3.00
Wang, 2010 81 21 15 3 -0.04 [-0.23, 0.15] 3.29
Heterogeneity: τ² = 0.00, I² = 8.61%, H² = 1.09 0.05 [-0.01, 0.12]
Test of θi = θj: Q(4) = 3.32, p = 0.51
Overall -0.08 [-0.18, 0.02]
Heterogeneity: τ² = 0.07, I² = 92.62%, H² = 13.55
Test of θi = θj: Q(29) = 353.39, p = 0.00
Test of group differences: Qb(6) = 7.31, p = 0.29
-1
-0.5
0
0.5
Random-effects REML model

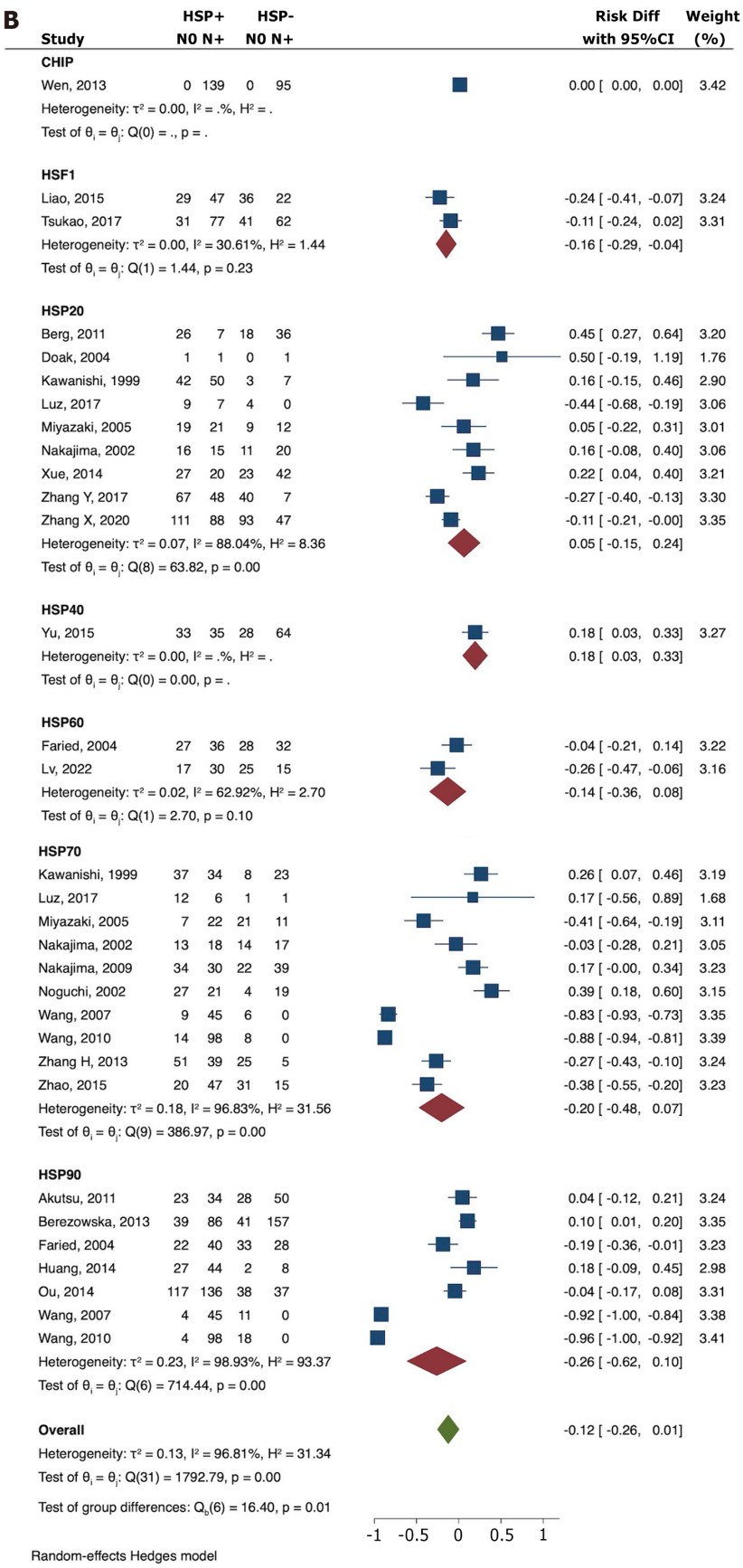


Figure 3 Forest plot of the eligible studies evaluating the association of the heat shock proteins with the grade of cellular differentiation and lymph node dissemination. A: Forest plot of the eligible studies evaluating the association of the heat shock proteins with the grade of cellular differentiation; B: Forest plot of the eligible studies evaluating the association of the heat shock protein s with lymph node dissemination. HSP: Heat shock protein; CI: Confidence interval.

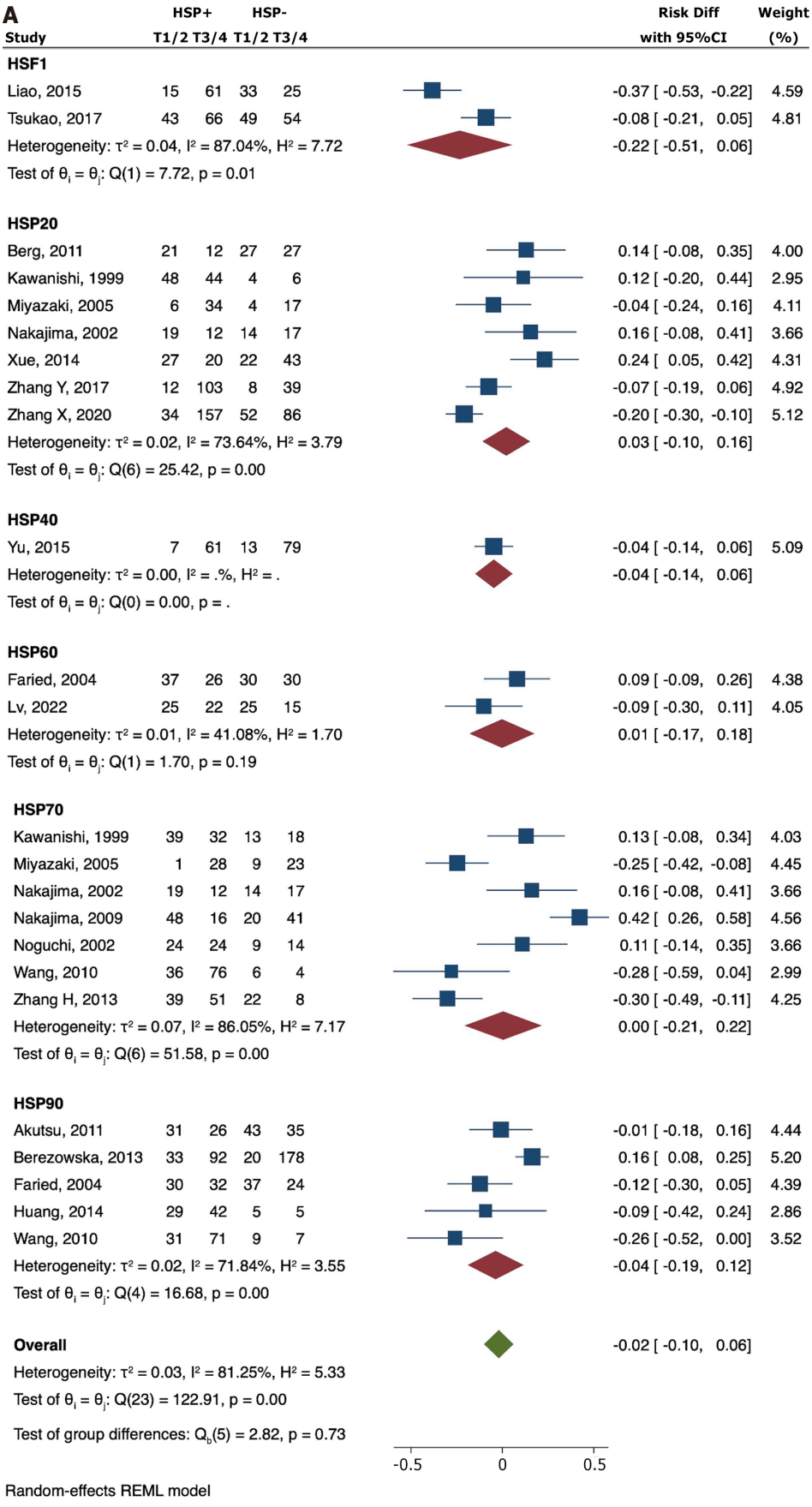
The HSP60 family holds potential as a novel prognostic biomarker in esophageal and esophagogastric cancer[25,31]. The consequences of HSP60 knockdown are substantial, compromising the integrity of respiratory complex I and inducing an excessive production of reactive oxygen species (ROS). This surplus 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[50].

The investigation delved into HSF1 expression and its correlation with lymph node 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[70]. 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[71]. This transformation occurs through the upregulation of genes promoting the malignant phenotype and the downregulation of genes that might trigger an anticancer immune response[50]. Moreover, HSF1 activation drives specific beneficial pathways within the malignant elements, fostering processes such as angiogenesis, ECM organization, adhesion, and migration[72]. 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[73]. 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[74]. *In vivo* experiments have substantiated this, demonstrating that the absence of HSF1 reduces tumor formation in a mouse model lacking p53[71]. 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*[29] 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[29]. 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[75].

Aligned to the current finding in ESCC, HSF1 has been linked to poor prognosis in various cancer types. Engerud *et al* [76] established an association between HSF1 overexpression and poor survival after analyzing 823 endometrial cancer lesions. Ishiwata *et al*[77] similarly demonstrated an association between HSF1 expression and lower OS in oral squamous cell carcinoma. Santagata *et al*[75] 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[78]. 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[78]. These findings indicate that the presence of HSF1 influences cell motility, thereby impacting invasion and migration in esophagogastric cancer cells.

The biomarker profile of HSPs has the potential to enhance prognostic stratification accuracy in EC, offering a pathway for personalized medicine and precision therapy-essential components of modern oncology[79]. Targeted therapy, linked to extended OS and reduced treatment costs[80-82], 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[5]. 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[83], thereby reducing malignant transformation and tumor growth[84,85]. 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[86,87]. Another practical possibility is the silencing of the HSF1 gene with a shRNA, as shown by Nakamura *et al*[88], 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[89]. The proinflammatory response elicited by HSP60 in macrophages triggers an adaptive cellular immune reaction, suggesting its potential in enhancing immunotherapy for cancer[72]. 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[48]. 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.


A
Study
HSP+ T1/2 T3/4
HSP- T1/2 T3/4
Risk Diff with 95%CI
Weight (%)
HSF1
Liao, 2015 15 61 33 25 -0.37 [-0.53, -0.22] 4.59
Tsukao, 2017 43 66 49 54 -0.08 [-0.21, 0.05] 4.81
Heterogeneity: τ² = 0.04, I² = 87.04%, H² = 7.72 -0.22 [-0.51, 0.06]
Test of θi = θj: Q(1) = 7.72, p = 0.01
HSP20
Berg, 2011 21 12 27 27 0.14 [-0.08, 0.35] 4.00
Kawanishi, 1999 48 44 4 6 0.12 [-0.20, 0.44] 2.95
Miyazaki, 2005 6 34 4 17 -0.04 [-0.24, 0.16] 4.11
Nakajima, 2002 19 12 14 17 0.16 [-0.08, 0.41] 3.66
Xue, 2014 27 20 22 43 0.24 [0.05, 0.42] 4.31
Zhang Y, 2017 12 103 8 39 -0.07 [-0.19, 0.06] 4.92
Zhang X, 2020 34 157 52 86 -0.20 [-0.30, -0.10] 5.12
Heterogeneity: τ² = 0.02, I² = 73.64%, H² = 3.79 0.03 [-0.10, 0.16]
Test of θi = θj: Q(6) = 25.42, p = 0.00
HSP40
Yu, 2015 7 61 13 79 -0.04 [-0.14, 0.06] 5.09
Heterogeneity: τ² = 0.00, I² = .%, H² = . -0.04 [-0.14, 0.06]
Test of θi = θj: Q(0) = 0.00, p = .
HSP60
Faried, 2004 37 26 30 30 0.09 [-0.09, 0.26] 4.38
Lv, 2022 25 22 25 15 -0.09 [-0.30, 0.11] 4.05
Heterogeneity: τ² = 0.01, I² = 41.08%, H² = 1.70 0.01 [-0.17, 0.18]
Test of θi = θj: Q(1) = 1.70, p = 0.19
HSP70
Kawanishi, 1999 39 32 13 18 0.13 [-0.08, 0.34] 4.03
Miyazaki, 2005 1 28 9 23 -0.25 [-0.42, -0.08] 4.45
Nakajima, 2002 19 12 14 17 0.16 [-0.08, 0.41] 3.66
Nakajima, 2009 48 16 20 41 0.42 [0.26, 0.58] 4.56
Noguchi, 2002 24 24 9 14 0.11 [-0.14, 0.35] 3.66
Wang, 2010 36 76 6 4 -0.28 [-0.59, 0.04] 2.99
Zhang H, 2013 39 51 22 8 -0.30 [-0.49, -0.11] 4.25
Heterogeneity: τ² = 0.07, I² = 86.05%, H² = 7.17 0.00 [-0.21, 0.22]
Test of θi = θj: Q(6) = 51.58, p = 0.00
HSP90
Akutsu, 2011 31 26 43 35 -0.01 [-0.18, 0.16] 4.44
Berezowska, 2013 33 92 20 178 0.16 [0.08, 0.25] 5.20
Faried, 2004 30 32 37 24 -0.12 [-0.30, 0.05] 4.39
Huang, 2014 29 42 5 5 -0.09 [-0.42, 0.24] 2.86
Wang, 2010 31 71 9 7 -0.26 [-0.52, 0.00] 3.52
Heterogeneity: τ² = 0.02, I² = 71.84%, H² = 3.55 -0.04 [-0.19, 0.12]
Test of θi = θj: Q(4) = 16.68, p = 0.00
Overall -0.02 [-0.10, 0.06]
Heterogeneity: τ² = 0.03, I² = 81.25%, H² = 5.33
Test of θi = θj: Q(23) = 122.91, p = 0.00
Test of group differences: Qb(5) = 2.82, p = 0.73
-0.5
0
0.5
Random-effects REML model

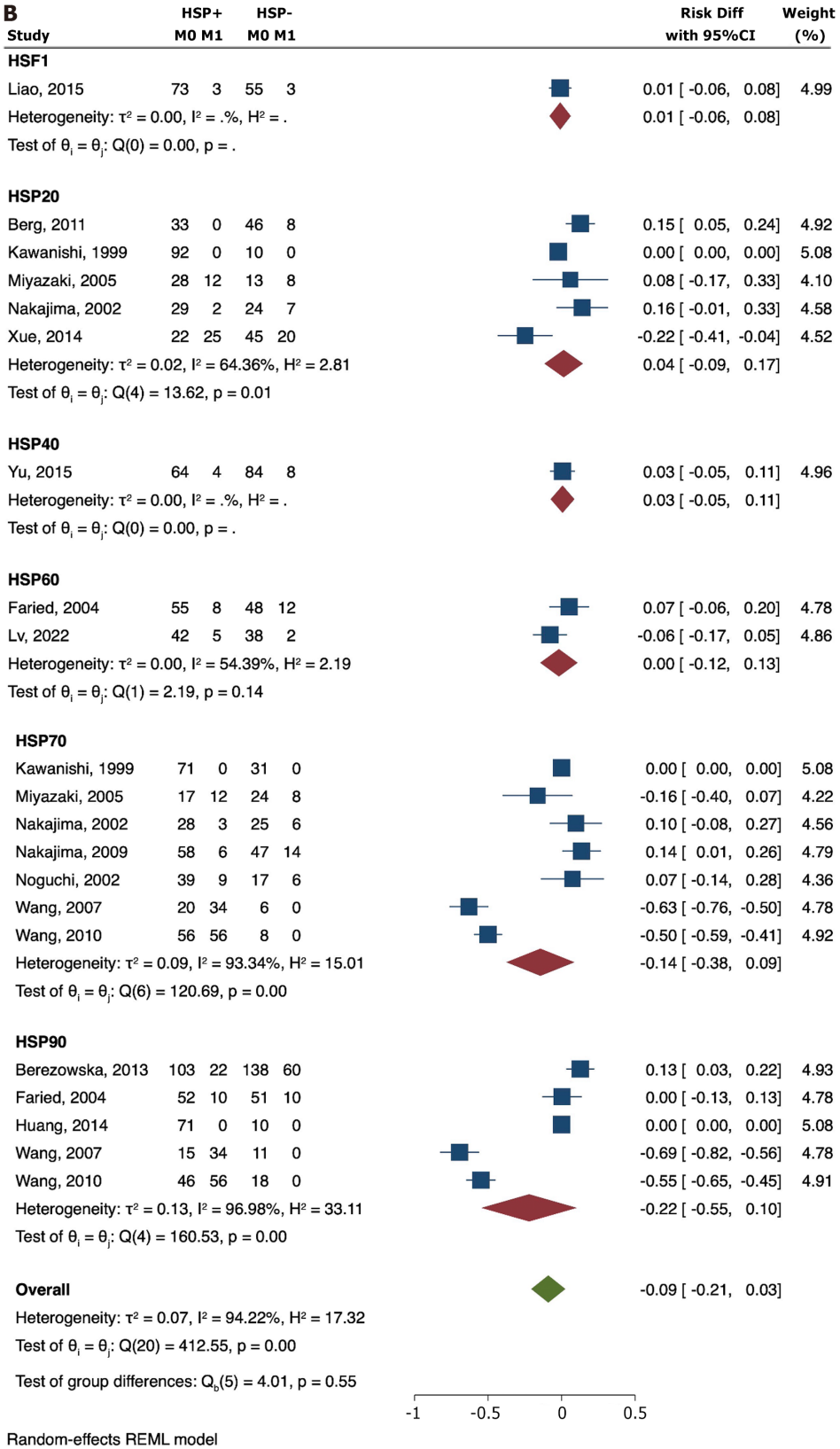


Figure 4 Forest plot of the eligible studies evaluating the association of heat shock proteins with tumor depth and distant metastasis. A: Forest plot of the eligible studies evaluating the association of heat shock proteins with tumor depth; B: Forest plot of the eligible studies evaluating the association of heat shock proteins with distant metastasis. HSP: Heat shock protein; CI: Confidence interval.

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 node 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. Cohort, 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

The 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 node metastasis. HSP40 was associated with a lower probability of lymph node 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 the expression levels of some families of HSP, such as HSP40 and 60 and HSF1, are associated with long-term survival and lymph node dissemination in esophageal and esophagogastric cancer.

Research perspectives

The results of this 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.

FOOTNOTES

Author contributions: Tustumi F designed the research, analyzed the data; Nakamura ET, Park A, and Tustumi F wrote the paper; Nakamura ET and Park A performed the research; Pereira MA and Kikawa D assisted in the research and reviewed the final manuscript.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

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P-Editor: Zhang XD

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