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Relationship between HSP90 protein expression and overall survival and clinicopathological outcomes in gastric cancer patients

Wkład autorów:
A – Projekt badań
B – Zbieranie danych
C – Analiza statystyczna
D – Interpretacja danych
E – Przygotowanie manuskryptu
F – Analiza literatury
G – Zbieranie funduszy

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ABSTRACT:

Introduction: Gastric cancer is a highly prevalent public health problem with high morbidity and mortality. Its primary treatment is surgery. Recently, studies involving biological parameters and genetics in gastric cancer have been emerging but with many blind spots.

Aim: Our study aims to investigate the clinicopathological and prognostic significance of heat shock proteins (HSP90) expression in patients with resectable gastric cancer.

Methods: Single-center retrospective clinical study conducted at the General Surgery Department of the local training and research hospital. Our study involves 54 patients who had curative surgery for gastric cancer between 2011 and 2014.

Results: Pathological specimens fixed in formalin and paraffin were re-evaluated with HSP90 staining and expression of HSP90 was evaluated. It was found that only 39 (72.2%) patients showed HSP90 expression. Seventeen (31.5%) of those showed mild, 13 (24.1%) had moderate, and 9 (10.5%) severe expression. HSP90 expression did not have a significant effect on survival in patients who underwent curative resection for gastric cancer, although statistically close. The effect of expression and intensity on overall survival was not statistically significant either.

Conclusions: There are various reports in literature on HSP90 expression in gastric cancer – some find it to be a prognostic factor, some not. There is a number of limitations of our study as we did not include metastatic tumors, the number of patients was low, the study involved only our patients and a single pathologist. This is the first study carried out in our population on this subject. Further studies could be done to evaluate this particular relationship in an effort to possibly identify novel treatments in gastric cancer.

KEYWORDS: gastrectomy, gastric neoplasms, heat shock proteins, survival

ABBREVIATIONS

EDTA – Ethylenediaminetetraacetic acid
HSP – Heat Shock Protein
RDW – Red Cell Distribution Width
TNM – Tumor Node Metastasis

BACKGROUND

Gastric cancer ranks fourth for incidence among all cancers while it ranks second for mortality [1]. Gastric cancer exhibits a poor prognosis with generally low rates of long-term survival. The 5-year survival even after effective surgery is around 35%, which reaches up to 40% in some selected patient groups following adjuvant therapy. Chaperons or heat shock proteins (HSP), first described in 1962, are a group of proteins that are produced by cells in response to exposure to high temperature (42–46°C) [2]. Apart from the heat factor, many factors can also cause an increase in HSPs, such as ethanol, arsenic, infection, inflammation, toxin, hunger, hypoxia, dehydration and cancer. Therefore, these proteins are also called stress proteins and they are a component of the body's response to stress. Under normal physiological conditions, their task is to prevent proteins from collapsing, enable newly synthesized proteins to acquire tertiary structures, separate misfolded and collapsed proteins from each other, ensure correct folding and transfer them from the ribosome to their location [3]. There are many forms of HSPs, at different locations in cells each (Tab. I.). Heat shock proteins are over-expressed in cancer cells and play roles in tumor progression. These effects include suppression of anti-cancer mechanisms and acceleration of the expression of metastatic genes. Additionally, the increase in heat shock proteins causes resistance to treatment [4]. HSP90 is responsible for these effects in gastric cancer. Therefore, it has been a promising anticancer drug target in the treatment of gastric cancer. A recent therapeutic strategy in cancer treatment includes inhibition of HSPs achieved by targeting the ATPase domains of HSP90 [5]. Following the inhibition of HSP90 in malignant cells, proteins that are responsible for autonomous growth and involved in the protection of tumoral cells are destructed. Additionally, HSPs can also be used to create vaccines. The expression of HSP90 in patients with gastric cancer is not clearly known in our population. The objective of the study to investigate the clinicopathological and prognostic significance of HSP90 expression in patients with resectable gastric cancer. The objective of the study is to investigate the clinicopathological and prognostic significance of HSP90 expression in patients with resectable gastric cancer.

Tab. I. HSPs and their locations inside cell.

TYPE	LOCATION	FUNCTION
HSP27	Cystoplasma	Inhibition of protein aggregation, cell growth, differentiation.
HSP60	Cystoplasma	Inhibition of mitochondria protein aggregation, protein folding.
HSP70	Cystoplasma	Inhibition of protein aggregation, protein folding.
HSP75	Mitochondria	Unknown.
HSP94	Endoplasmic reticulum	Protein quality control.
HSP90	Cystoplasma	Inhibition of protein aggregation, protein stabilization and transfer.

MATERIAL AND METHODS

This study was carried out at the General Surgery Department of our hospital with institutional ethical committee approval number 622/2015 on 27 October 2015. Our study included a total of 54 patients who underwent curative surgery for gastric cancer between 2011–2014. Patients' clinical records, pathology and surgery reports were analyzed retrospectively. Patients diagnosed with primary gastric cancer undergoing curative surgery were included in the study. Patients with Stage 4 cancer, patients with unresectable tumors, patients receiving neoadjuvant therapy, patients operated on under emergency conditions (perforation, bleeding, etc.) and patients with metastases were excluded from the study. After patient selection, the tumor samples embedded in paraffin blocks in the archives of the Pathology Department were obtained. After tissue sections were selected immunohistochemical staining was performed.

Immunohistochemical staining

Immunohistochemical staining was performed on the Leica Bond device (New Castle, United Kingdom) by taking 3-micron-thick sections from selected paraffin blocks. Sections were boiled in an ethylenediaminetetraacetic acid-based solution ("Bond Epitope Retrieval Solution 2, New Castle, United Kingdom) for 20 minutes following deparaffinization. Peroxidase blocking (10 minutes) was performed using the 'Bond Polymer Refine Detection kit'. The samples were incubated with HSP90 antibody (HSP90, mouse polyclonal antibody, Ab13492, clone: AC88 Abcam, Cambridge, United Kingdom) for 20 minutes at 1:100 dilution. Incubation was performed for 10 minutes in post primer, 10 minutes in polymer, 10 minutes in diaminobenzidine-chromogen, and 5 minutes in hematoxylin for staining. Slides were washed after each stage. After drying with alcohol, they were kept in xylene for 2 minutes and then covered with Entellan. Testicular tissue was used as a positive control. Specimens were considered positive for HSPs when more than 5% of the tumor cells were stained. This criterion was used to determine the presence of HSP90 expression. Additionally, the intensity of HSP90 expression was also divided into 3 scales. The intensity was classified as (+) mild, (++) moderate, and (+++) severe [6] (Fig. 1.). All immunohistochemically stained sections were examined by a single pathologist.

Statistical analysis

IBM SPSS 11.5 (SPSS Inc., Chicago, IL, United States) software was used for data analysis. Mean ± standard deviation and median

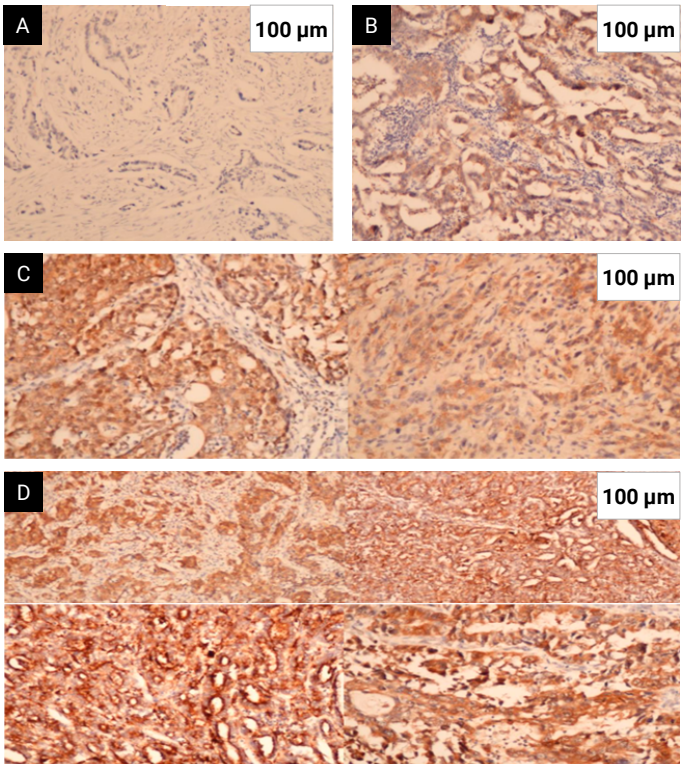

Fig. 1. Staining gastric specimens with hematoxylin-eosin (A) Tumor cells without HSP90 expression at x100 magnification (B) Tumor cells with mild HSP90 expression at x100 magnification (C) Tumor cells with moderate HSP90 expression at x100 magnification (D) Tumor cells with severe HSP90 expression at x100 magnification.

(minimum-maximum) were used for quantitative variables while number of patients (percent) was used for qualitative variables. The Student's t-test was used to compare quantitative variables with two qualitative categories where normal distribution assumptions were met, and the Mann-Whitney U test was used if not met. The Chi-square and Fisher's exact tests were used to compare two qualitative variables. Survival analysis was performed using the Kaplan-Meier method for qualitative variables and the log-rank test was used to determine significant differences between the groups. A P-value less than 0.05 was considered as statistically significant.

RESULTS

Gastrectomy and D2 dissection were performed for 54 patients with gastric cancer. Average follow-up time was 40.8 months.

Tab. II. Descriptive variables of patients.

VARIABLE		
Age	Mean ± SD	61.80 ± 11.54
	Median (Min.–Max.)	61.00 (33.00–89.00)
Tumor size (cm)	Mean ± SD	7.24 ± 4.26
	Median (Min.–Max.)	6.00 (2.00–25.00)
Total lymph nodes	Mean ± SD	25.36 ± 14.68
	Median (Min.–Max.)	25.00 (2.00–68.00)
Lymph node size (cm)	Mean ± SD	1.57 ± 0.72
	Median (Min.–Max.)	1.50 (0.60–4.50)
Survival time (month)	Mean ± SD	30.64 ± 21.94
	Median (Min.–Max.)	23.00 (3.00–90.00)
Gender	Male	29 (53.7)
	Female	25 (46.3)
Lymphovascular invasion	Yes	36 (66.7)
	No	17 (31.5)
T stage	1	6 (11.1)
	2	4 (7.4)
	3	44 (81.5)
N stage	0	15 (27.7)
	1	15 (27.7)
	2	6 (11.1)
	3	18 (33.5)
Stage	1	7 (13.0)
	2	11 (20.4)
	3	36 (66.6)
HSP expression	No	15 (27.8)
	Yes	39 (72.2)
Recurrence	Yes	3 (5.6)
	No	51 (94.4)
Metastasis	Yes	17 (31.5)
	No	37 (68.5)
HSP expression intensity	Mild	17 (43.5)
	Moderate	13 (33.3)
	Severe	9 (23.2)

SD – standard deviation; Max. – maximum; Min. – minimum

Tab. III. The relationship between HSP and qualitative variables.

VARIABLES		HSP				P-VALUE
		NO		YES		
		N	%	N	%	
Gender	Male	7	46.7	22	56.4	0.758[a]
	Female	8	53.3	17	43.6	
Lymphovascular Invasion	Yes	14	93.3	22	57.8	0.845[b]
	No	1	6.7	16	42.2	
T	1	2	15.4	4	9.7	0.402[b]
	2	0	0.0	4	9.7	
	3	11	84.6	33	80.6	
N	0	5	33.3	10	25.6	0.715[b]
	1	3	20.0	12	30.7	
	2	1	6.7	5	12.8	
	3	6	40.0	12	30.9	
Stage	1	2	13.3	5	12.9	0.832[b]
	2	2	13.3	9	23.0	
	3	11	73.4	25	64.1	
Recurrence	Yes	2	13.3	1	2.6	0.986[b]
	No	13	86.7	38	97.4	
Metastasis	Yes	6	40.0	11	28.3	0.90[a]
	No	9	60.0	28	71.7	
RDW	≤13.4	5	33.3	9	23.1	0.522[b]
	>13.4	10	66.7	30	76.9	
Albumin	Normal	11	78.6	27	67.5	0.736[b]
	Low	3	21.4	13	32.5	
CEA	Normal	11	73.3	30	76.9	0.724[b]
	High	4	26.7	9	23.1	
CA 19-9	Normal	10	66.7	34	87.1	0.108[b]
	High	5	33.3	5	12.9	
Metastatic Lymph Node	Absent	5	33.3	8	21.6	0.497[b]
	Present	10	66.7	31	79.4	

[a]Chi-square test; [b]Fisher's exact test
HSP – heat shock proteins; RDW – Red Cell Distribution Width; CEA Carcinoembryonic antigen; Ca 19-9 – Cancer antigen

Twenty-nine (53.7%) of the patients were male and 25 (46.3%) were female. The mean ± standard deviation and median (minimum-maximum) of the patients' age were 60.8 ± 11.38 and 60.00 (33.00–89.00) respectively. Mean survival time was 30.64 ± 21.94 (3–90) months. Seven (13%) patients were Stage 1, 11 (20.3%) were Stage 2, 36 (66.7%) were Stage 3. Of the tumors, 14 were located in the cardia, 17 were in the corpus and 26 were in the antrum of the pylorus. None of the patients received preoperative neoadjuvant therapy. All participating patients were diagnosed with adenocarcinoma. While 36 patients had lymphovascular invasion, 17 did not. The status of lymphovascular invasion was not specified in 1 patient. While 14 (25.9%) of the specimens had no lymph node metastasis, 40 (74.1%) had metastatic lymph nodes.

With respect to the T stage, 6 (11.1%) patients were T1, 4 (7.4%) were T2, and 44 (81.5%) were T3. None of the patients had distant metastases. The evaluation of surgery type demonstrated that 22 (40.7%) patients underwent total gastrectomy while 32 (59.3%) underwent subtotal gastrectomy. In the postoperative follow-up, recurrence occurred in 3 (5.6%) of the patients while 51 (94.4%) did not develop recurrence. Likewise, 17 (31.5%) developed metastases in the follow-up period while 37 (68.5%) did not develop metastasis. In the postoperative follow-up, 23 patients died and 31 were still alive. Descriptive variables of our patient cohort are given in Tab. II.

Out of 54 patients, 39 (72.2%) exhibited HSP90 expression while 15 (27.8%) did not. The classification of HSP90 expression by intensity revealed that out of 39 patients 17 (31.5%) had mild, 13 (24.1%) had moderate, and 9 (10.5%) had severe expressions. The examination of the association between patients' demographic, histopathological and clinicopathological characteristics and HSP90

Tab. IV. The relationship between HSP and qualitative variables.

VARIABLES	HSP				P-VALUE
	NO		YES		
	MEAN ± SD	MEDIAN (MIN.–MAX.)	MEAN ± SD	MEDIAN (MIN.–MAX.)	
Tumor size (cm)	6.07 ± 2.31	5.00 (3.50–10.00)	7.64 ± 4.71	6.25 (2.00–25.00)	0.383[b]
Total lymph node	19.07 ± 11.25	15.00 (5.00–35.00)	27.56 ± 15.21	26.00 (2.00–68.00)	0.053[a]
Lymph node size (cm)	1.60 ± 0.68	1.50 (0.60–3.20)	1.55 ± 0.74	1.50 (0.70–4.50)	0.638[b]
Survival time (month)	39.60 ± 24.33	32.00 (3.00–82.00)	27.59 ± 20.47	21.50 (5.00–90.00)	0.052[b]

[a]Studet-s t-test; [b]Mann-Whitney U test

HSP – heat shock proteins; SD – standard deviation; Max. – maximum; Min. – minimum

Tab. V. Relationship between survival and HSP90 expression/expression intensity.

		MORTALITY				P-VALUE
		DEATH		SURVIVAL		
		N	%	N	%	
HSP90 expression	Positive	14	60.8	25	80.6	0.098
	Negative	9	39.2	6	19.4	
HSP90 expression intensity	Mild	7	50.0	10	40.0	0.095
	Moderate	2	14.2	11	44.0	
	Severe	5	35.8	4	16.0	

HSP – heat shock proteins

expression did not reveal any statistically significant correlation between HSP90 expression and intensity, gender, tumor location, lymphovascular invasion, T stage, tumor size, lymph node status, stage, recurrence at follow-up and metastasis at follow-up (P > 0.05). RDW was investigated as it increases with inflammation and malignancy, however, no significant relationship was found with HSP90 expression (P = 0.522). The association between hypoalbuminemia and HSP was examined since it is a marker of poor prognosis and nutrition, but no significant relationship was found (P = 0.736). Again, there was no statistically significant association between tumor markers, which are indicative of poor prognosis, and HSP (P = 0.724/0.108). The survival time was 39.60 ± 24.33 months in those without HSP expression while those with HSP had 27.59 ± 20.47 months, meaning that patients with HSP expression had shorter survival time but the statistical significance was obtained with a P-value of 0.052. (Tab. III., IV.).

We investigated the effects of patients' demographic, histopathological and clinicopathological characteristics on survival. The univariate analysis did not reveal statistically significant relationship between age, gender, T stage, tumor location, lymphovascular invasion, degree of differentiation, tumor size and survival of the stage (P > 0.05). HSP was not associated with metastasis at follow-up, recurrence at follow-up, and the N stage, however, these variables were found to be significantly correlated with survival, the P-values of which were as follows: 0.004/0.005/0.042, respectively. The multivariate analysis revealed that metastasis was statistically significant as a prognostic factor at follow-up (P < 0.05).

HSP90 expression did not have a significant effect on survival in patients who underwent curative resection for gastric cancer, although statistically close (P = 0.052). The effect of expression and intensity on overall survival was not statistically significant either. (P = 0.098/0.095) (Tab. V., Fig. 2.).

DISCUSSION

There are many factors affecting the prognosis of gastric cancer. These factors depend on the patient, tumor and treatment. Factors depending on the patient include gender, age, alcohol, smoking and obesity while factors depending on tumor include location, type, degree of invasion, grade, differentiation, size and lymphovascular invasion [7]. The following factors also affect prognosis: surgery performed curatively or not, adequate lymph node dissection, preoperative neoadjuvant or postoperative adjuvant treatment. Recently, the association between tumors and different biological parameters and genetics, apart from the mentioned factors, has been examined. But there are still many aspects that have not been clarified regarding these two factors which require further research. It is obvious that once these aspects have been clarified we will be able to obtain information that can support or change our approach towards gastric cancer as well as treatment regimens.

HSP90 exhibits high expression in germ and embryonic cells and low expression in aging cells. Protein synthesis increases during cell proliferation, where a large amount of HSP is required for this activity [8]. In malignant cells, HSP90 expression plays an important role in protein homeostasis in hypoxic and acidotic environments. In addition, HSPs enable tumor cells to tolerate fatal genetic mutations. HSP90 expression increases in many solid tumors and hematological malignancies. Although some publications have demonstrated its increase, particularly in stomach [6, 9–12], pancreas [13], lung [14], breast [15], hepatocellular [16], over-endometrium [17], prostate [18], colorectal [19] and gastrointestinal stromal tumors [20], there is still controversy whether HSP90 expression is associated with prognosis in patients with gastric cancer [9, 21].

Available studies have highlighted HSP90 in the last 20–30 years reporting that it may be a potential therapeutic target. It is thought that the inhibition of HSP90 expression can be quite effective for preventing tumor progression, on the other hand, fails to arrest apoptosis. The aim of our study was to investigate the association of HSP90 expression and intensity with demographic, clinicopathological features and survival of patients who underwent curative resection due to gastric cancer, and the factors affecting survival in these patients.

The results of our study did not show a statistically significant association between patients' demographic, clinicopathological features and survival characteristics and HSP90 expression and intensity. The univariate analysis showed that the N stage, metastasis and recurrence in the follow-up period were prognostic factors while the multivariate analysis only revealed metastasis to be a prognostic factor in gastric cancer. In our study, 18 of those under the age of 60 were positive for HSP90 whereas 21 of those aged 60 and above were positive for HSP90. Consistent with the literature, no significant correlation was found between age and HSP90 expression in our study [6, 9, 22]. While available studies had a male/female ratio of 2:1, the different ratio in our study resulted from the inclusion of patients who only underwent curative resection. Similar to previous studies, no significant correlation was found between gender and HSP90 expression in our study [6, 23].

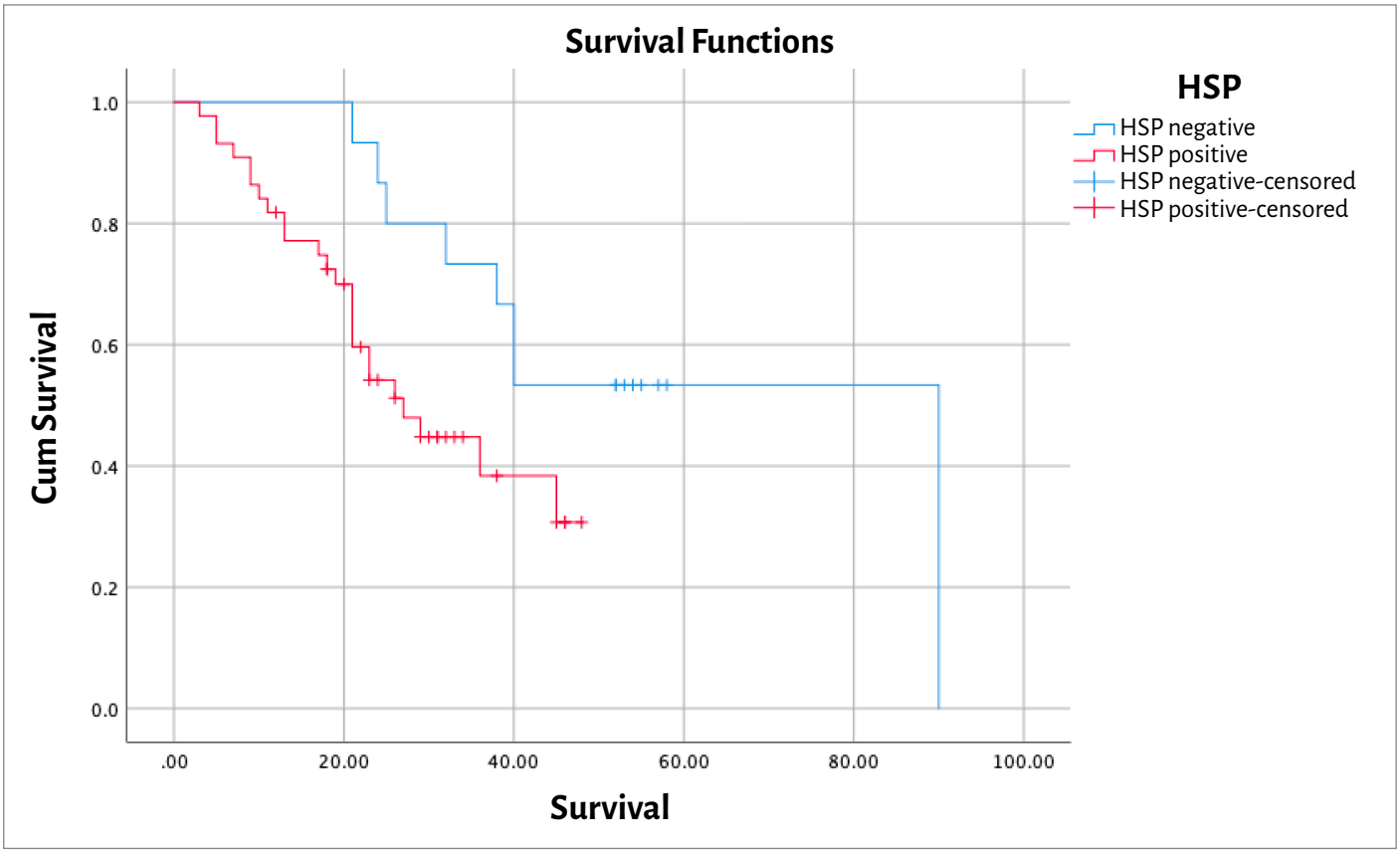

Fig. 2. Kaplan-Meier analysis.

Wang et al. [11] conducted a study in which they mentioned a statistically significant correlation between increased HSP90 expression and tumor size (> 5 cm), tumor location, T3–T4 tumors, lymph node metastasis, and Stage 3–4. No significant correlation was observed between age, gender and differentiation. Our study demonstrated similar results in terms of age and gender. The same study revealed a significant relationship between HSP90 and invasion and metastatic gastric cancer. On the other hand, prognosis was poorer in patients with HSP90 expression so it was argued that HSP90 was a significant prognostic factor for gastric cancer. In our study, HSP expression was not found to play a role in prognosis, however, patients with HSP expression had shorter survival times and bigger tumor size, although not statistically significant. Moreover, HSP expression was higher in patients with advanced Tumor Node Metastasis (TNM) stages, although not statistically significant.

Giaginis et al. [6] investigated HSP90 expression and intensity and classified the intensity of expression as mild, moderate and severe. No statistically significant association was observed between HSP90 expression and clinicopathological characteristics. The intensity of expression was shown to be associated with tumor size alone, but a statistically significant relationship was observed between HSP90 expression and survival considering it as a prognostic factor. However, our study also revealed that the intensity of HSP90 expression is not a prognostic factor. High expression of HSP90 was associated with long survival time in node-negative gastric cancers, likewise HSP90 expression was associated with long overall survival in well-differentiated tumors and in cases without organ metastasis. This alone indicates that HSP90 is still a matter of great controversy.

Berezowska et al. [9] reported a statistically significant relationship between each parameter and grade in the TNM staging and HSP90 expression but found no statistically significant relationship between prognosis and HSP90 expression and intensity, similar to our study.

On the other hand, Zuo et al. [22] compared gastric cancers and gastritis in terms of HSP90 expression, reporting statistically higher HSP90 expression in gastric cancer cases compared to gastritis. Additionally, lymph node metastasis was shown to have a statistically significant association with HSP90 expression in patients with gastric cancer. The study did not include any statement with respect to prognosis. Isomoto et al. [24] and Maehara et al. [25] conducted studies and found no significant association between gastric cancer and HSP expression.

In our study, HSP90 expression and intensity were not statistically significant in terms of clinicopathological characteristics and prognosis in patients with gastric cancer. The inconsistent results stem from the fact that, as opposed to the literature, the patients included in our study underwent curative resection while other studies also included patients with metastatic cancers. Accordingly, perhaps HSP90 expression increases in much later stages of the tumor. Another reason may be genetic differences. The association between gastric cancer and HSP90 expression has not been investigated in our population before, therefore only available publications were foreign studies. HSP90 expression may be based on different factors in our population, and therefore the relationship between HSP90 and the population should be further investigated and supported by new studies. Another reason may be the different types of signals produced by the tumor microenvironment and the different histological types of each tumor cell. These outcomes

may have resulted from technical differences. Examination of the tissues by a single pathologist and technical differences in tissue staining may have altered the results of HSP90 expression and intensity in our study when compared with the literature.

Limited number of patients, retrospective design, single center and no randomized control were among the limiting factors of our study. It is necessary to investigate the effects of HSP90 expression in our population with larger numbers of patients. In addition, there are not many publications in the literature showing the relationship between gastric cancer and HSP90 expression, and available data are rather limited. Contradicting articles in the literature have failed to reveal the association between HSP90 expression and gastric cancer clearly. Therefore, we believe that more studies should be conducted on this issue, especially in countries where gastric cancer is more prevalent.

All these studies aim to find out how to utilize HSP90 expression in the treatment of gastric cancer. There are relevant studies in the literature investigating the role of HSP90 inhibition in cancer treatment [26, 27]. HSP90 inhibition is one of the major issues that scientists have recently focused on. The use of it alone or in addition to other treatment methods is being investigated for the therapy of gastric cancer. To date, there is still no approved HSP90 inhibitor for cancer treatment [28]. Especially in recent studies, it has been shown that inhibition of HSP90 may be effective in the treatment of cancer and drug resistance [29–32]. Treatment strategies can be established once the association between HSP90 expression and cancer is understood more clearly.

In conclusion, we do not have clear evidence that HSP90 expression is a prognostic factor in patients with non-metastatic gastric cancer in our population. Our study is the first study demonstrating the association between gastric cancer and HSP90 expression in our population. With current findings, we think it is too early to introduce HSP90 inhibitors in the treatment of gastric cancer in our population. Further study may help uncover the unknown aspects of HSP90 expression in our population. This might demonstrate that HSP90 plays an important role in tumor development, invasion, metastasis and prognosis, thus enabling us to target HSP90 and achieve more successful, satisfying results in the treatment of gastric cancer.

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