

# Clinical Significance of TRIM44 Expression in Patients with Gastric Cancer

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## Abstract

**Background:** Despite the tremendous efforts in finding a valuable markers for risk stratifying gastric cancer (GC) patients; still, management of this cancer faces multiple obstacles. Given this, we designed a study to explore the possible relationship between the tripartite motif-containing 44 (TRIM44) gene expression, and the outcome of the GC patients. **Methods:** The real-time quantitative PCR method was used to evaluate the mRNA expression level of TRIM44, and  $\beta$ -catenin in fresh primary tumor and adjacent normal tissues collected from 40 GC patients. The Pearson's correlation test, Kaplan–Meier method, and Cox proportional-hazards regression were performed to examine the association of TRIM44 expression with some clinicopathological data and the patients' overall survival (OS). **Results:** The expression level of both TRIM44 and  $\beta$ -catenin was remarkably higher in GC tissues than in normal tissues (Fold change=1.71,  $p=0.004$ ). In subgroup analysis based on the TRIM44 expression, patients with high TRIM44 expression level exhibited poorer overall survival (HR = 1.46, 95% CI: 1.07-1.98,  $p=0.016$ ). More strikingly, a positive correlation was also found between the expression of TRIM44 and  $\beta$ -catenin in GC, indicating that TRIM44 might exert its oncogenic activities probably through the  $\beta$ -catenin axis. **Conclusion:** This study highlighted the potent value of TRIM44 as an independent prognostic factor in gastric cancer and shed light on the probable interplay between this tripartite motif-containing protein and  $\beta$ -catenin. However, further investigations, especially with a larger sample size, are required to study the effect of TRIM44 in GC more precisely.

**Keywords:** Gastric cancer- TRIM44-  $\beta$ -catenin- overall survival- prognosis

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## Introduction

As the fourth prevalent cancer worldwide and the second dreadful cancer, considerable attention has been attracted to gastric cancer (GC) to manage this cancer better and decrease its mortality rate (Thrift and El-Serag, 2020). For many years, the main focus of studies on GC was centered on finding the probable drivers that lead to cancer development. Among the long list of factors, *H. pylori* infection seems to have a critical role in forming the malignant cells by aberrantly activating the inflammatory responses (Choi et al., 2020). However, it did not take long that other mediators such as genetic abnormalities and environmental factors have also been added to the list, and GC has been turned into a multi-factorial disease with heterogeneous characteristics (Rawla and Barsouk, 2019). Besides the high prevalence of cancer, which complicates the disease management, the induction of resistance against the conventional chemotherapeutic agents and the increased risk of metastasis are other factors that lead to a patient's loss of life (Sitarz et al., 2018). Given these, finding a way to

stratify patients according to their molecular profile could be valuable for managing the disease and customizing the therapeutic strategies according to the patient's characteristics (Venerito et al., 2018; Wang et al., 2019). This idea has opened a new gate in gastric cancer studies. Currently, many investigations are on the way to find a precise molecule for the classification of the patients. One of the molecules that has gained a reputation in the risk stratifying GC patients is HER2, also known as ERBB2 (Akiyama et al., 1986). Although numerous studies implied that HER2 expression in GC tissue is associated with aggressive phenotype of the disease and poor prognosis (Gravalos and Jimeno, 2008), in some cases, even with the absence of HER2, patients would experience shorter overall survival (Yoon et al., 2012). Therefore, it seems that further investigations are necessary to change the landscape of stratifying system of GC.

One of the molecules that seem to have a valuable prognostic potential in solid tumors is the tripartite motif-containing 44 (TRIM44). TRIM44 is a member of the tripartite motif-containing protein (TRIM) family that could be activated by interferons (Tan et al., 2017).

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In similarity with ubiquitin hydrolases, this molecule contains B-box, coiled-coil domains, and a zinc-finger domain that endow it with the ubiquitin E3 ligase-like property (Urano et al., 2009). In cancer cells, a compelling body of evidence declared that TRIM44 could tightly regulate most, if not all, intracellular processes, such as cell proliferation, cell migration, and invasions (Tan et al., 2017; Yamada et al., 2017; Yamada et al., 2020). Moreover, through bifurcating at many signaling pathways, including mammalian target of rapamycin (mTOR), the Phosphoinositide 3-kinases (PI3K)/Akt, and nuclear factor (NF)- $\kappa$ B signaling pathways (Luo et al., 2015; Wang et al., 2020), this tripartite motif-containing protein could confer drug-resistant phenotype in cancer cells. For example, in glioma cells, up-regulation of TRIM44 has been reported to be associated with uncontrolled cell proliferation through the Akt/p21 signaling pathway (Zhou et al., 2019). Or, the overexpression of TRIM44 claimed to be associated with doxorubicin resistance in hepatocarcinoma cells (Zhu et al., 2016). TRIM44 has also been considered to be the poor prognostic marker for breast cancer, as it could enhance TNF $\alpha$ -dependent phosphorylation of the p65 subunit of both NF- $\kappa$ B and IKK in breast cancer-derived cell lines (Kawabata et al., 2017). Although multiple lines of evidence have evaluated the prognostic value of TRIM44 in different human cancers, the function and mechanism of this molecule are still elusive in gastric cancer. Considering the importance of signaling pathways such as NF- $\kappa$ B and the PI3K/Akt axes in the pathogenesis of GC (Shen et al., 2019; Khorasani et al., 2021), we designed a study to explore the relationship between the expression of TRIM44 and the outcome of the GC patients and to propose a probable molecular mechanism through which this gene might participate in the progression of GC.

## Materials and Methods

### Patients Sample Collection

The gastric tissue samples, both cancerous and normal tissues, were collected from 40 gastric cancer patients attending in first affiliated hospital of Mashhad University of Medical Sciences, Mashhad, Iran, between November 2015 and February 2018. The total average age of patients was 65.73 $\pm$ 10.19 years. Around 77.5% of the participants were male, and 22.5% were female. All patients with GC relevant clinical symptoms such as dysphagia, dyspepsia, gastrointestinal bleeding, anemia, weight loss, anorexia, inappetence, nausea, reflux, and vomiting; and GC verification by pathology tests were enrolled in this study. Patients with history of any treatment including chemotherapy, radiotherapy, and surgery and those who received medications for stomach disorders were excluded from the study. Among the patients, 80% experienced weight loss, and 72.5% had nausea and vomiting. Other clinicopathologic features were anemia (67.5%), bleeding (37.5%), reflux (52.5%), and anorexia (37.5%). GC tissue specimens and cancer-adjacent normal tissues (>5 cm away from tumor sites) were collected using endoscopy. Specimens were kept in RNAlater for RNA preservation (Thermo Fisher Scientific, Waltham, MA, USA) at 4°C overnight and then stored at -80°C until

RNA extraction. The study protocol was in accordance with the Declaration of Helsinki and was approved by the ethics committee of Mashhad University of Medical Sciences (IR.MUMS.MEDICAL.REC.1398.606). All the participants signed a consent form before attending the study.

### Gene expression analysis using qRT-PCR

RNA was extracted from gastric cancer and normal tissue using Wizol™ Reagent (Wizbiosolutions Inc., Korea) according to the manufacturer's protocols. After ensuring the quality and the quantity of the extracted RNA by Nanodrop ND-1000 (Thermo Fisher Scientific, Waltham, MA, USA), 2 mg of extracted RNAs was used to synthesize cDNA using a cDNA synthesis kit (wizbiosolutions, Seongnam, Gyeonggi, Korea). The synthesized cDNA, along with the specific primers; (TRIM44, 5'-GTGGACATCCAAGAGGCAAT-3' (forward), 5'-AGCAAGCCTTCATGTGTCTCT-3' (reverse);  $\beta$ -actin, 5'-TCTGAGGACAAGCCACAAGATTACA-3' (forward) and 5'-TGGGCACCAATATCAAGTCCAA-3' (reverse) and  $\beta$ -actin, 5'-GCGCGGCTACAG

C T T C A - 3 ' ( f o r w a r d ) a n d 5'-CTTAATGTCACGCACGATTTC-3' (reverse)), were then subjected to SYBR green-based real-time quantitative polymerase chain reaction (qRT-PCR) (Rotor-Gene 6000, Qiagen, Germany). All tests were done in triplicate, and relative expression for each mRNA normalized to  $\beta$ -actin (fold changes) was calculated using the comparative CT method ( $2^{-\Delta\Delta CT}$ ).

### Statistical analysis

All continue data were presented as mean  $\pm$  standard deviation (SD). The paired-samples t-test was used to compare the mRNA expression levels of TRIM44, and  $\beta$ -catenin between cancerous and noncancerous tissues. According to the TRIM44 median expression level, patients were divided into two groups of high (tumor tissue expressed TRIM44 mRNA above the median value) and low (tumor tissue expressed TRIM44 mRNA below the median level) expression. Student's t-test, Chi-square, and/or Fisher's exact test were applied to assess the possible correlation between TRIM44 expression levels and clinicopathologic parameters in GC patients. Kaplan–Meier plot and Log Rank (Mantel-Cox) test were applied to compare overall survival between two groups. Univariate and multivariate Cox proportional hazards regression models were also used to evaluate the impact of TRIM44 expression and each clinicopathologic variable on overall survival of GC patients. All of the statistical analyses were performed by IBM SPSS Statistics 22 and P-value < 0.05 was considered as statistically significant.

## Results

### The differences between the expression of TRIM44 in gastric cancer and normal tissues

To evaluate whether the expression of TRIM44 is altered in cancerous tissue, we assessed the expression of this gene in both cancerous and normal tissues obtained from GC patients. The results of the qRT-PCR analysis

revealed the expression of TRIM44 was significantly higher in the tumor tissue compared to the normal tissue (Fold change=1.71, P=0.004) (Figure 1). More interestingly, according to TRIM44 expression, patients were categorized into two groups; patients with higher expression of TRIM44 (22 patients) and patients with the lower TRIM 44 expression (18 patients). Having established that TRIM44 is overexpressed in malignant tissue, it was of particular interest to evaluate whether there is a correlation between the expression of this gene and some clinicopathological features of the patients. No statistically meaningful association was found for the expression of TRIM44 and patient characteristics (Table 1).

#### *The correlation between TRIM44 expression and the overall survival of GC patients*

Next, to evaluate whether TRIM44 could act as a valuable factor to predict the overall survival (OS) of the GC patients, we did a Kaplan–Meier analysis. The results showed that the high expression of TRIM44 was associated with a more unfavorable OS (Figure 2). We found that while the median survival time of GC patients

with low TRIM44 was 41 month, the OS of patients with high TRIM44 expression was 36 month, indicating that the high TRIM44 expression is probably a poor prognosis factor for GC patients (log-rank test, P=0.007). To evaluate which interfering factor could impact the effect of TRIM44 on OS of patients, univariate and multivariate Cox analyses were also performed. The Univariate analysis results revealed that TRIM44 expression (HR = 1.21, 95% CI: 1.02-1.67, p=0.03, gender (P = 0.044), smoking (P = 0.013), anemia (P = 0.009), weight loss (P = 0.038), bleeding (P = 0.005), and stomachache (P = 0.014) were significantly associated with the overall survival in GC patients (Table 2). However, multivariate analysis showed that only the expression of TRIM44 was correlated with a high risk of mortality for GC patients (adjusted HR = 1.46, 95% CI: 1.07-1.98, p=0.016) (Table 2). This indicated the probable role of TRIM44 expression as an independent prognostic factor in GC patients.

#### *The correlation between TRIM44 expression and $\beta$ -catenin in GC patients*

The results of the previous studies declared that TRIM44 could provide a platform for the survival and

Table 1. The Relationship between TRIM44 Expression and Clinicopathological Features in GC Patients

Variables	TRIM44 Expression		P-value	
	Low (n=18)	High (n=22)		
Age (mean $\pm$ sd)*	67.11 $\pm$ 9.18	64.59 $\pm$ 11.04	0.444	
Age Composition**	$\leq$ 65	9 (50.0)	12 (54.5)	0.775
	>65	9 (50.0)	10 (45.5)	
Gender***	Male (%)	14 (77.8)	17 (77.3)	0.636
	Female (%)	4 (22.2)	5 (22.7)	
Anemia**	+	12 (66.7)	15 (68.2)	0.592
	-	6 (33.3)	7 (31.8)	
Weight loss***	+	15 (83.35)	17 (77.3)	0.709
	-	3 (16.7)	5 (22.7)	
Bleeding	Yes	8 (44.4)	7 (31.8)	0.412
	No	10 (55.6)	15 (68.2)	
Dysphagia***	No	1 (5.6)	2 (9.1)	0.692
	Rarely	5 (27.8)	4 (18.2)	
	Yes	12 (66.6)	16 (72.7)	
Tumor location***	Proximal	8 (44.4)	10 (45.5)	0.964
	Body	7 (38.9)	9 (40.9)	
	Distal	3 (16.7)	3 (13.6)	
Smoking**	Yes	9 (50.0)	9 (40.9)	0.565
	No	9 (50.0)	13 (59.1)	
Stomachache***	Yes	14 (77.8)	15 (68.2)	0.499
	No	4 (22.2)	7 (31.8)	
Nausea**	Yes	13 (72.2)	15 (68.2)	0.781
	No	5 (27.8)	7 (31.8)	
Reflux**	Yes	8 (44.4)	13 (59.1)	0.356
	No	10 (55.6)	9 (40.9)	
Anorexia**	Yes	9 (50.0)	6 (27.3)	0.14
	No	9 (50.0)	16 (72.7)	

T-test (\*), Chi-square test (\*\*), and Fisher's exact test (\*\*\*) were used to compare two groups.

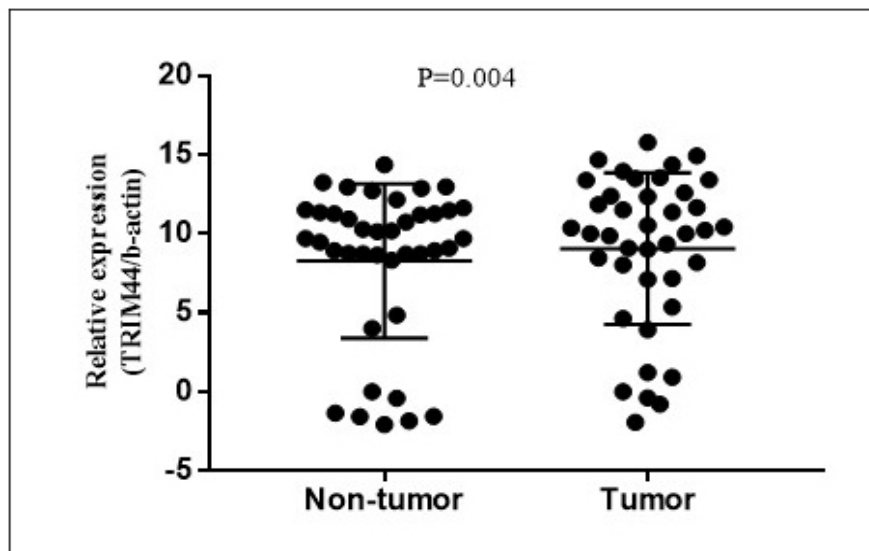


Figure 1. The Expression of TRIM44 in GC Tissues and Their Adjacent Noncancerous Controls. The results of the qRT-PCR analysis revealed that the expression of TRIM44 in gastric cancer tissue is higher than the normal tissue, ( $p = 0.004$ ).

Table 2. Univariate and Multivariate Analyses for Variables Associated with the Overall Survival of GC Patients

Variables	Univariate analysis		Multivariate analysis	
	HR (95 % CI)	P-value	HR (95 % CI)	P-value
TRIM44	1.21 (1.02-1.67)	0.03	1.46 (1.07-1.98)	0.016
Age	1.04 (0.99-1.08)	0.06		
Gender	0.29 (0.09-0.97)	0.044	2.90 (0.38-22.45)	0.307
Tumor location	1.54 (0.85-2.79)	0.154		
Anemia	0.012 (0.00-0.33)	0.009	0.001 (0.00-2.84)	0.92
Weight loss	0.02 (0.001-0.81)	0.038	0.001 (0.00-1.39)	0.944
Bleeding	0.31 (0.14-0.71)	0.005	0.74 (0.29-1.89)	0.532
Dysphagia	0.88 (0.66-1.16)	0.355		
Stomachache	0.22 (0.06-0.74)	0.014	0.37 (0.08-1.78)	0.212
Smoking	0.34 (0.15-0.797)	0.013	0.74 (0.29-1.89)	0.532
Nausea and Vomiting	0.42 (0.16-1.14)	0.089		
Reflux	1.15 (0.52-2.54)	0.726		
Anorexia	0.55 (0.25-1.22)	0.14		

the proliferation of cancer cells through integrating with the Wnt signaling pathway (Zhou et al., 2017). Given this, it was of particular interest to evaluate whether there is a correlation between the expression of TRIM44 and  $\beta$ -catenin, one of the essential components of the Wnt axis, in GC patients. As presented in Fig. 3A, the results of the qRT-PCR analysis indicated the overexpression of  $\beta$ -catenin in cancer tissues as compared to the normal tissues ( $P = 0.001$ ). More interestingly, the potent correlation between the expression of TRIM44 and  $\beta$ -catenin in GC patients was identified ( $r=0.89$ ,  $P<0.01$ ); suggesting that the oncogenic effects of TRIM44 on GC cells are mediated, at least in part, through  $\beta$ -catenin and the WNT signaling axis (Figure 3B).

## Discussion

Signaling pathways recently are the main focus of

many cancer research, as harnessing them could add a new wave in the treatment strategies and the successful management of cancer (Koury et al., 2017). Although numerous small molecule inhibitors have been developed thus far to shut these pathways down, it seems that these axes could be compensatorily stimulated (Krishnamurty and Maly, 2010). The ubiquitination system also post-translationally modifies the expression of several mediators to alter fundamental cellular processes to endow the cancer cells with the survival advantage (Di Fiore et al., 2003). Among several intracellular molecules, the tripartite motif-containing 44 (TRIM44), a well-known member of the tripartite motif-containing protein (TRIM) family (Tan et al., 2017), seems to have a hand in both mentioned mechanisms. It could compensatorily trigger the PI3K/Akt and mTOR signaling pathways within malignant cells and regulate the ubiquitination system (Urano et al., 2009; Li et al., 2019; Zhou et al., 2019).



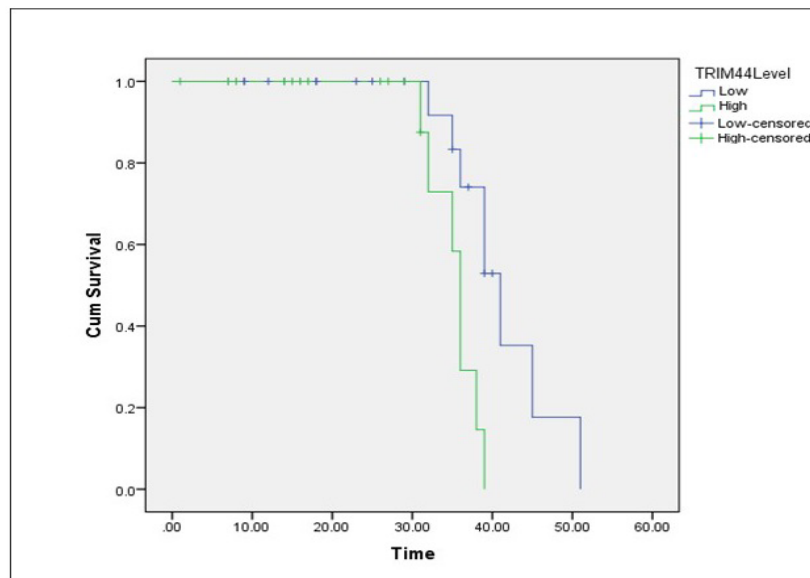


Figure 2. The Correlation between TRIM44 Expression and the Overall Survival (OS) of the Patients. The results of the Kaplan-Meier analysis revealed that patients with higher TRIM44 expression had a shorter OS as compared to those patients with low TRIM44 ( $P = 0.007$ ).

Given these and based on the critical roles of TRIM44 in the pathogenesis of a wide range of cancers such as prostate cancer (Tan et al., 2017), hepatocarcinoma (HCC) (Zhu et al., 2016), lung cancer (Luo et al., 2015; Xing et al., 2016), and esophageal carcinoma (Ong et al., 2014; Kawaguchi et al., 2017), in the present study, we aimed to study the association of this gene with the development of gastric cancer (GC). Our results showed that the expression of TRIM44 was remarkably higher in gastric tumor tissues than in normal tissues. Moreover, according to TRIM44 expression, GC patients could be categorized into two groups at which those with the higher expression of TRIM44 had lower overall survival (OS). Since we failed to find any correlation between the expression of TRIM44 and the clinicopathological features of the patients, we suggested that the lower expression of

TRIM44 could act as an independent prognostic factor for GC patients. In consistent with our results, Xiong et al. who indicated that the high expression of TRIM44 in esophageal cancer is indicative of the poor prognosis (Xiong et al., 2018). In gastric cancer, it has been indicated that TRIM44 overexpression could increase the risk of macroscopic lesion and lymphatic invasion (Kashimoto et al., 2012). It has been proposed that patients with higher expression of TRIM44 are more at risk of disease relapse as compared to those with lower expression of TRIM44 (Kashimoto et al., 2012).

A compelling body of evidence declared that TRIM44 is a main regulator of several signaling pathways. In lung cancer, it has been indicated that TRIM44 could enhance the metastatic potential of the cancer cells through integrating with the mTOR signaling axis (Xing et al.,

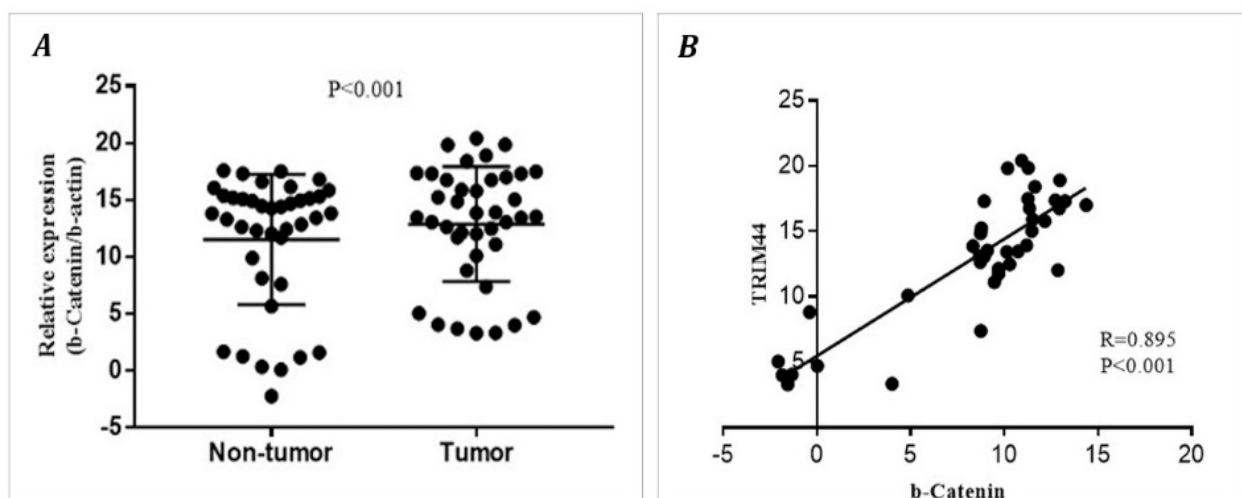


Figure 3. The Correlation between TRIM44 Expression and  $\beta$ -catenin in GC Patients. A) The results of the qRT-PCR analysis showed that as compared to the normal tissue, there is an elevation in the expression of  $\beta$ -catenin in malignant tissue ( $p < 0.001$ ). B) Pearson's correlation analysis indicated that the expression of TRIM44 in GC patients had a tight correlation with the expression of  $\beta$ -catenin ( $r=0.895$ ;  $p < 0.001$ ).

2016). This molecule has also been accused of being the main regulator of melanoma pathogenesis, as it stabilizes TRIL4 expression in melanoma cells by activating the PI3K/Akt signaling pathway (Wei et al., 2019). Another signaling pathway that has been reported to be associated with TRIM44 is the MAPK axis. Peng et al. have reported that TRIM44 plays a critical role in inducing metastasis in cholangiocarcinoma through stimulating MAPK signaling axis (Peng et al., 2018). What has convergent between all these signaling pathways is their ability to stimulate the Wnt axis. This pathway is notorious for its role in transforming epithelial cells to mesenchymal cells (EMT) (Wong et al., 2010; Shorning et al., 2020). EMT is the main step in developing cancer metastasis, as it allows cancer cells to penetrate into the bloodstream and migrate throughout the body (Brabletz et al., 2018).

In the present study, we found that the expression of  $\beta$ -catenin, a critical component of the Wnt signaling axis, was higher in GC tissue than the normal tissue, suggesting that the Wnt signaling axis is probably stimulated in this type of cancer. The more striking results were obtained when we found a positive correlation between the expression of  $\beta$ -catenin and TRIM44 in GC patients. It is well-established that  $\beta$ -catenin is a well-known poor prognostic factor in multiple human cancers, including colorectal cancer (Elzagheid et al., 2008), breast cancer (Pang et al., 2013), ovarian cancer (Bodnar et al., 2014), and lung adenocarcinoma (Kim et al., 2013). It has been indicated that  $\beta$ -catenin not only could increase the risk of metastasis in cancer cells by increasing the expression of matrix metalloproteinases (40) and could exacerbate the proliferative capacity of cancer cells by increasing the expression of c-Myc (Zhang et al., 2012).

Moreover, some reports have been declared that TRIM44 might have a hand in the regulation of cell metastasis. In a study conducted by Luo et al., it has been indicated that through stimulating the nuclear factor (NF)- $\kappa$ B signaling pathway, TRIM44 could enhance the migration of lung cancer cells to the lymph nodes (Luo et al., 2015). Although there is evidence in thyroid carcinoma that knockdown of TRIM44 could reduce the expression of  $\beta$ -catenin, c-Myc, and Cyclin-D1 (Zhou et al., 2017), as far as we know, no study has indicated a possible correlation between these two genes in GC, and our study proposed for the first time that probably the oncogenic action of TRIM44 in GC cells might be mediated through  $\beta$ -catenin. Taking advantages of these and based on the positive correlation between TRIM44 and  $\beta$ -catenin in the present study, it is reasonable to assume that perhaps the overexpression of these genes could provide a platform for tumor cells to spread and by this approach reduce the survival rate of the patients. Our two previous study were also confirmed the genetic interaction between some TRIM family genes and  $\beta$ -catenin expression in GC patients (Afshar et al., 2021; Farhadi et al., 2021).

In conclusion, overall, the results of this study highlighted the potent value of TRIM44 as an independent prognostic factor in gastric cancer and shed light on the probable mechanism of action of this tripartite motif-containing protein in the pathogenesis of cancer. Furthermore, we proposed for the first time that TRIM44

overexpression could decrease the overall survival of the patients, at least in part, through making a partnership with  $\beta$ -catenin. However, further investigations, especially with a larger sample size, are required to study the effect of TRIM44 in GC more precisely.

## Author Contribution Statement

Study concept and design: Mehrad-Majd H, Acquisition of data: Afshar J, Goshayeshi L, Statistical analysis: Mehrad-Majd H, Drafting of the manuscript: Mehrad-Majd H, Afshar J, Goshayeshi L, Study supervision: Mehrad-Majd H

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