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CAUDAL TYPE HOMEOBOX 2 EXPRESSION AND PROGNOSTIC FACTORS IN PATIENTS WITH GASTRIC ADENOCARCINOMA

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Abstract

Background: *The prognosis of cancer is affected by factors such as lymph node involvement, the degree of tumor invasion, and markers like caudal type homeobox 2. This study investigates the immunohistochemical expression of caudal type homeobox 2 in gastric cancer adenocarcinoma biopsies concerning gastric cancer prognostic factors.*

Material and methods*: Tissue blocks from patients with gastric adenocarcinoma were used in this cross-sectional study. Demographic and clinicopathological data were extracted and recorded on a checklist from patients' pathology reports. The expression of caudal type homeobox 2 was subsequently examined using immunohistochemistry.*

Results*: In total, 80 patients with gastric adenocarcinoma were included, where 22 were female (27.5%). Caudal type homeobox 2 expression was reported as positive in 68 cases (85%) and negative in 12 cases (15%) of gastric adenocarcinoma biopsies. No significant correlation (p>0.05) was found between caudal type homeobox 2 expression and demographic and clinicopathological data, such as age, gender, and tumor grade (p>0.05).*

Conclusion: *This study concludes that age, gender, and tumor grade are unreliable prognostic factors for Iranian patients with gastric adenocarcinoma.*

Keywords: *gastrointestinal, stomach, caudal type homeobox 2, transcription factor, immunohistochemistry, prognosis.*

Introduction

Gastric cancer (GC) is the fifth most prevalent type of cancer and the fourth leading cause of death in 2020, with an estimated 800,000 deaths worldwide [*Rawla P, Barsouk 2019; Ilic M, Ilic I, 2022; Morgan E et al., 2022*]. Some direct and indirect factors, including tobacco use, age, genetics, H. pylori infection, dietary habits, and environmental conditions, can increase the risk of this cancer [*Shah D, Bentrem D, 2022*]. In the initial stage of gastric cancer, there are no diagnostic symptoms; however, symptoms such as heartburn, nausea, bloating, and indigestion. appear after the cancer has spread. In addition, the advanced stage is characterized by pain, ascites, swallowing difficulties, jaundice, weight loss, and blood in the stool [*Siegel R et al., 2023; Zhang Z et al., 2023*]. Preventing and screening at-risk individuals before the onset of symptoms can reduce the cost of curing and diagnosing this cancer before its terminal stages [*Sexton R et al., 2020*]. In recent years, invasive and non-invasive procedures for detecting gastric cancer have been developed, which

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may aid treatment planning. The most commonly used diagnostic procedures are radiology and upper endoscopy. This examination with biopsy is the gold standard in gastric cancer diagnosing [*Norwood D et al., 2022*]. Given the frequency and severity of this cancer, early diagnosis and prompt surgical removal of the tumor are of utmost importance [*Schwarz R, 2015*]. However, using non-invasive tests with high diagnostic accuracy may be important, and an accurate prognosis is necessary for a proper diagnosis [*Joshi S, Badgwell B, 2021*].

Therefore, an accurate prognosis is essential for diagnosing gastric cancer, particularly in its early stages, or even preventing its occurrence. The prognosis of cancer is affected by lymph node involvement, the degree of tumor invasion, and markers such as caudal type homeobox 2 (CDX-2) [*Wang X et al., 2012a*]. This protein is a member of the caudal homeobox gene family which is essential for normal fetal growth and differentiation and proliferation of the intestinal epithelium, and its adult expression is restricted to the intestinal epithelium [*Wu C et al., 2020*]. In addition, intestinal mucosa growth and maintenance are essential. The highest CDX2 mRNA expression of is in the gastric region, and clinical and pre-clinical studies indicate that an increase in CDX2 is associated with gastric adenocarcinoma [*Mizoshita T et al., 2003; Mutoh H et al., 2004; Saad R et al., 2011; Nakayama C et al., 2018; Kim K et al., 2021*]. According to research, the presence of CDX2 inhibits tumor proliferation in gastric cancer patients, resulting in a better prognosis [*Kim K et al., 2021; Ribeirinho-Soares S et al., 2021; Delhorme J et al., 2022*]. However, there is a few pieces of evidence link prognosis factors such as age, gender, and tumor grades with CDX2 expression in Iranian patients with gastric adenocarcinoma, and whether these factors play a role in prognosis is still debated [*Akbari F et al., 2019; Samadani A et al., 2019*]. As a result, this study aims to correlate CDX2 immunohistochemical (IHC) expression with prognostic factors in Iranian gastric cancer adenocarcinoma biopsy specimens.

Material and methods

Study Design: In this retrospective cross-sectional study, samples of gastric adenocarcinoma biopsy were collected from the archives of the pathology department of Imam Khomeini Hospital in Ahvaz, Iran, during 2020-2021. This study was approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (Code: *IR.AJUMS.HGOLESTAN.REC.1400.046*).

Sample collection was performed, and the sample size was determined based on the census. The inclusion criteria were the completeness of the patient's records, sufficient tissue, and the absence of necrosis or bleeding. Demographic and clinical characteristics of each sample, including age and gender of patients and tumor grade of tumor were extracted and recorded from the patient's file.

Immunohistochemical (IHC) staining assay: Staining is assessed with hematoxylin and eosin for histological analysis, and IHC is evaluated for CDX2 expression. For five minutes, the 5 μm paraffin sections were immersed in a solution of water alcohol. Slides have been placed for 30 minutes in the microwave oven at 60°C. Deparaffinization of the slides took place by soaking in xylene (Merck, Germany) and alcohol from 100 to 75% concentration for 5 to 10 minutes. Sections were rinsed with 10% phosphate-buffered saline (Yekta Tajhiz Azma, Iran), followed by H2O2/ methanol (1:9) and 10% phosphate-buffered saline for 10 minutes which the slides were heated in a microwave oven with ethylenediaminetetraacetic acid (EDTA; Yekta Tajhiz Azma, Iran). Once the room's temperature has been reached, the samples will be rinsed with phosphate-buffered saline. Anti-CDX2 antibodies were then added to the sections and incubated at 4C. The antibody against CDX2 was then applied to the sections and kept in a humid chamber at 4C during the night. Afterward, tissue sections were incubated with a horseradish peroxidase-conjugated secondary antibody for 30 minutes and subsequently visualized using a diaminobenzidine substrate at room temperature. Counterstaining was performed using hematoxylin in space for 2 minutes, and a placebo antibody was used as a harmful control. Immunohistochemical staining in tumor cell nuclei was scored using the following scale: negative, 0; weak, 1; moderate, 2; and strong, 3. The proportion of stained cells was scored via the following scale: 0, 1% to 5%; 1, 6% to 25%; 2, 26% to 50%; 3, 51% to 75%; and 4, 76% to 100% (Figure). Overall severity plus extent scores were calculated, which were considered 0-1 negative and 2-12 positive [*Dixon M et al., 1996*].

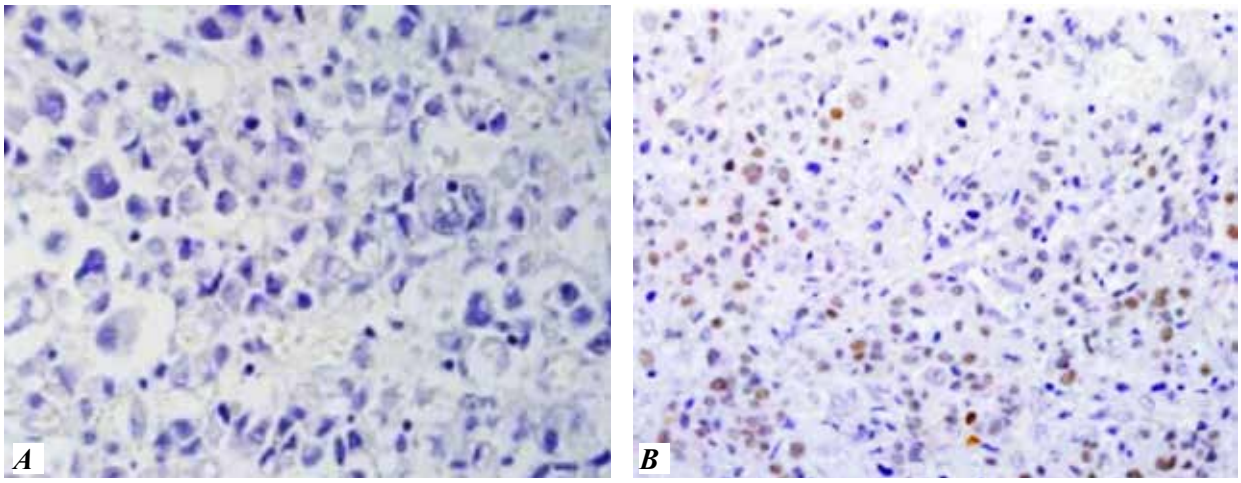

Figure 1. *Immunohistochemical expression of CDX2 in gastric adenocarcinoma. IHC staining for CDX2 was evaluated in terms of nuclear staining. From top left: (A) Gastric adenocarcinoma tissue with negative expression of CDX2 (B) Gastric adenocarcinoma tissue with positive CDX2 expression.*

Statistical Analysis: The data analysis was conducted using IBM SPSS Statistics, version 22. The normal distribution of quantitative data was assessed using the Kolmogorov-Smirnov test. The relationship between qualitative variables was evaluated using Chi-Square and Fisher's exact tests, with statistical significance defined at a p-value less than 0.05.

Results

Biopsy samples from 80 gastric adenocarcinoma patients, which the mean age of patients was 70.41 ± 13.82 years. Among of patients 22 (27.5%) cases were female. Regarding age distribution, most cases in patient 27 (33.8%) were in the 81-94-year age group, and the fewest cases in patient 13 (16.3%) were in the 71-80-year age group. Grade II was highest with 30 (37.5%) cases, followed by grade I with the frequency of 26 (32.5%) cases, and lowest associated with grade III with the frequency of 24 (30%) cases. Patient demographic and pathologic information is presented in table 1.

In 68 cases (85%) and 12 cases (15%) of gastric adenocarcinoma biopsy specimens, CDX2 expression was reported as positive and negative, respectively. 51 (87.9%) males were positive CDX2 expression, while in females 17 cases (77.3%) were positive and 5 cases (22.7%) were negative. There was no significant association between gender and CDX2 expression (p=0.295) (Table 2). Caudal type homeobox 2 expression was observed in 21 cases (80%), 28 cases (93.3%), and 19 cases (79.2%) of grade I, II, and III specimens,

Table 1.

Patient demographic and clinicopathological information

Variables		Patients (n=80)
Gender, n (%)	Male	58 (72.5)
	Female	22 (27.5)
Tumor grade, n (%)	I	26 (32.5)
	II	30 (37.5)
	III	24 (30)
Age, n (%)	≤ 60	16 (20)
	61-70	24 (30)
	71-80	13 (16.3)
	81-94	27 (33.7)

Table 2

Correlation between CDX2 expression and patient demographic and pathological information

Variables		CDX2 expression		p-value
		Negative	Positive	
Gender, n (%)	Male	7 (12.1)	51 (87.9)	0.295
	Female	5 (22.7)	17 (77.3)	
	Total	12 (15)	68 (85)	
Tumor grade, n (%)	I	5 (19.2)	21 (80.8)	0.267
	II	2 (6.7)	28 (93.3)	
	III	5 (20.8)	19 (79.2)	
	Total	12 (85)	68 (15)	
Age, n (%)	≤ 60	4 (15)	12 (75)	0.590
	61-70	3 (12.5)	21 (87.5)	
	71-80	1 (7.7)	12 (92.3)	
	81-94	4 (14.8)	23 (85.2)	
	Total	12 (85)	68 (85)	

respectively. Although the number of cases of positive CDX2 expression was higher in grade II specimens; however, there was not statistically significant (p=0.267). Regarding age distribution, the highest and lowest number of positive CDX2 expressions was related to the age groups 81-94 and ≤ 60 and 80-71 years, respectively (Table 2).

DISCUSSION

Regarding tissue and biological properties, gastric cancer is a heterogeneous disease, particularly in its advanced stages [*Machlowska J et al., 2020*]. Some clinical studies have demonstrated that this cancer's biological behavior and prognosis may vary significantly between patients at the same stage and with the same histological types or degrees of differentiation [*Hultman B et al., 2014; Raja U et al., 2017; Zhao S et al., 2021*]. This study assessed the level of CDX2 gene expression and the prognosis of patients with gastric cancer. No statistically significant correlation was found between increased CDX2 gene expression age, gender, tumor progression, or tumor grade.

Using biomarkers to reveal biological characteristics and predict the outcome of gastric cancer patients appears crucial [*Jiang T et al., 2022*]. Caudal type homeobox 2 is a transcription factor that stimulates the transcription of target genes associated with intestinal epithelial differentiation which regulates several essential cellular functions, including differentiation, growth, and cell death, in normal tissue cells are used, particularly intestinal epithelial cells [*Guo R et al., 2010; Zhao H et al., 2022*]. Constitutively and functionally, increased expression of CDX2 in tumors and normal mucosa indicates that CDX2 may contribute to the development of bowel metaplasia in adults [*Seno H et al., 2002*]. Moreover, CDX2 has been demonstrated to play a crucial role in gastric intestinal metaplasia [*Yuan T et al., 2019*]. Recent studies have demonstrated aberrant expression of CDX2 in adenocarcinomas of the stomach, colon, thyroid, ovary, endometrium, bladder, and prostate [*Kaimaktchiev V et al., 2004; Antonio D'Antonio, 2011; Agarwal K et al., 2023*]. This marker is widely employed in intestinal adenocarcinoma diagnosis [*Saad R et al., 2011*]. Caudal type homeobox 2 is highly expressed in all types of gastrointestinal metaplasia, but its expression decreases in types I, II, and III [*Liu Q et al., 2007*].

In this study, CDX2 was detected in 68 (85%) of 68 biopsies. Some studies reported a range of positive expressions for gastric cancer patients (4.54-100%) [*Almeida R et al., 2003; Liu G et al., 2006; Ge J et al., 2008; Zhang X et al. 2009; Oz Puyan F et al., 2011; Qin R et al., 2012; Halder A et al., 2018; Akbari F et al., 2019; Sardar A et al., 2022b*]. These results suggest that gender, age, and geographic location may influence CDX2 expression in gastric patients based on their genetic type. Regarding this study, other Iranian researchers found identical outcomes (70, and 78%) with significantly increased positive expression [*Akbari F et al., 2019; Samadani A et al., 2019*].

A meta-analysis of 13 studies (1513 patients) revealed that the positive expression of CDX2 in males was statistically significantly higher than in females [*Wang X et al., 2012b*]. In addition, several studies have highlighted the findings of these studies [*Yuasa Y et al., 2005; Qin R et al., 2012; Zhang Y et al., 2016; Sardar A et al., 2022b*]. Similarly, positive CDX2 expression was reported in 51 (87.9%) males and 17 cases (77.3%) in females. Like other Iranian studies, the positive expression of CDX2 was higher in males, yet no statistically significant association between the sexes was observed [*Akbari F et al., 2019*]. Nonetheless, *Ge et al. 2008* demonstrated a statistical significance (p=0.02) between positive CDX2 and male patients [*Yuasa Y et al., 2005*]. The higher incidence of positive CDX2 expression in males than females may be attributable to the more prevalent type of gastric cancer in males and the gender mismatch of subjects included in different studies study participants.

Although in the present study, the mean age of samples with positive CDX2 expression was older than that of samples with negative CDX2 expression, and most samples with positive CDX2 expression were in the age groups 61-70 and 81-94 years, there was no correlation between age and CDX2 expression. The results of this study and a review of the relevant literature indicate that the age factor is unrelated to the expression of the CDX2 marker, which may be one of the causes of the age mismatch in these studies [*Zhang X et al., 2009; Qin R et al., 2012; Xiao Z et al., 2012; Akbari F et al., 2019*]. Although *Sardar AA et al. 2022* and other researchers demonstrated a statisti-

cally significant relationship between positive CDX2 and age (p=0.02) [*Ha Kim G et al., 2006; Schildberg C et al., 2014; Sardar A et al., 2022a; b*], they indicated that expression of this factor may be lower in younger individuals.

In a 2016 Chinese study by *Zhang et al.,* grade II CDX2 expression was reported in most cases (28/30) but it was not statistically significant (p=0.173). Nonetheless, in the study by *Qin et al. (2012),* the highest positive expression of CDX2 was in grades I and II in 29/44 (65.9%) cases. In contrast, in grade III, only 12 of 41 cases (29.3%) had positive CDX2 expression, which was statistically significant (P = 0.0001) compared to the present study. While the highest number of CDX2 expression was found in grade II (28/30), and grade I (21/26) cases, the lowest number of cases of CDX2 expression cases was found in grade III (19/24). Nevertheless, neither CDX2 expression nor tumor grade was statistically significant (p=0.264). In addition, several studies have demonstrated that CDX2 decreases the rate of cell proliferation, and CDX2 positive IHC expression decreases with the progression of the gastric cancer stage [*Srivastava A et al., 2010; Wang X et al., 2012a; Sardar A et al., 2022a; b*]. CDX2 expression, on the other hand, is regarded as an independent prognostic indicator for gastric carcinoma. A meta-analysis association revealed a correlation between CDX2 positivity and a lower clinical stage [*Wang X et al., 2012b*].

Conclusion

This study concludes that age, gender, and tumor grade are unreliable prognostic factors in Iranian patients with gastric adenocarcinoma, possibly due to sample size limitations. Cohort studies can demonstrate this correlation, allowing health policymakers to develop regional guidelines for preventing this disease.

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