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## FRONTIER

- 2921 Fecal microbiota transplantation for irritable bowel syndrome: An intervention for the 21<sup>st</sup> century  
*El-Salhy M, Patcharatrakul T, Gonlachanvit S*

## REVIEW

- 2944 Interplay between nuclear factor erythroid 2-related factor 2 and inflammatory mediators in COVID-19-related liver injury  
*Zhu DD, Tan XM, Lu LQ, Yu SJ, Jian RL, Liang XF, Liao YX, Fan W, Barbier-Torres L, Yang A, Yang HP, Liu T*
- 2963 Mucosal lesions of the upper gastrointestinal tract in patients with ulcerative colitis: A review  
*Sun Y, Zhang Z, Zheng CQ, Sang LX*
- 2979 Application of artificial intelligence-driven endoscopic screening and diagnosis of gastric cancer  
*Hsiao YJ, Wen YC, Lai WY, Lin YY, Yang YP, Chien Y, Yarmishyn AA, Hwang DK, Lin TC, Chang YC, Lin TY, Chang KJ, Chiou SH, Jheng YC*
- 2994 Hepatocellular carcinoma in viral and autoimmune liver diseases: Role of CD4<sup>+</sup> CD25<sup>+</sup> Foxp3<sup>+</sup> regulatory T cells in the immune microenvironment  
*Granito A, Muratori L, Lalanne C, Quarneti C, Ferri S, Guidi M, Lenzi M, Muratori P*

## MINIREVIEWS

- 3010 Role of bile acids in liver diseases mediated by the gut microbiome  
*Shao JW, Ge TT, Chen SZ, Wang G, Yang Q, Huang CH, Xu LC, Chen Z*
- 3022 Liver injury in COVID-19: Detection, pathogenesis, and treatment  
*Cai Y, Ye LP, Song YQ, Mao XL, Wang L, Jiang YZ, Que WT, Li SW*
- 3037 Role of imaging in evaluating the response after neoadjuvant treatment for pancreatic ductal adenocarcinoma  
*Zhang Y, Huang ZX, Song B*
- 3050 Current approach to treatment of minimal hepatic encephalopathy in patients with liver cirrhosis  
*Moran S, López-Sánchez M, Milke-García MDP, Rodríguez-Leal G*
- 3064 COVID-19 and pediatric fatty liver disease: Is there interplay?  
*Di Sessa A, Lanzaro F, Zarrilli S, Picone V, Guarino S, Miraglia del Giudice E, Marzuillo P*

**ORIGINAL ARTICLE****Basic Study**

- 3073 Enhancer of zeste homolog 2 contributes to apoptosis by inactivating janus kinase 2/ signal transducer and activator of transcription signaling in inflammatory bowel disease

*Zhou J, Yang Y, Wang YL, Zhao Y, Ye WJ, Deng SY, Lang JY, Lu S*

**Retrospective Study**

- 3085 Quinone oxidoreductase 1 is overexpressed in gastric cancer and associated with outcome of adjuvant chemotherapy and survival

*Jiang ZN, Ahmed SMU, Wang QC, Shi HF, Tang XW*

- 3097 Idiopathic mesenteric phlebosclerosis associated with long-term oral intake of geniposide

*Wen Y, Chen YW, Meng AH, Zhao M, Fang SH, Ma YQ*

- 3109 Early serum albumin changes in patients with ulcerative colitis treated with tacrolimus will predict clinical outcome

*Ishida N, Miyazu T, Tamura S, Tani S, Yamade M, Iwaizumi M, Hamaya Y, Osawa S, Furuta T, Sugimoto K*

**Observational Study**

- 3121 Preservation of superior rectal artery in laparoscopically assisted subtotal colectomy with ileorectal anastomosis for slow transit constipation

*Wu CW, Pu TW, Kang JC, Hsiao CW, Chen CY, Hu JM, Lin KH, Lin TC*

**Prospective Study**

- 3130 High fecal calprotectin levels are associated with SARS-CoV-2 intestinal shedding in COVID-19 patients: A proof-of-concept study

*Zerbato V, Di Bella S, Giuffrè M, Jaracz AW, Gobbo Y, Luppino D, Macor P, Segat L, Koncan R, D'Agaro P, Valentini M, Crocé LS, Ruscio M, Luzzati R*

**CORRECTION**

- 3138 *Helicobacter pylori* promotes invasion and metastasis of gastric cancer by enhancing heparanase expression

*Liu LP, Sheng XP, Shuai TK, Zhao YX, Li B, Li YM*

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## Retrospective Study

**Quinone oxidoreductase 1 is overexpressed in gastric cancer and associated with outcome of adjuvant chemotherapy and survival**

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**Abstract****BACKGROUND**

Quinine oxidoreductase 1 (NQO1) plays a vital role in protecting normal cells against oxidative damage and electrophilic attack. It is highly expressed in many solid tumors, suggesting a role in cancer development and progression. However, the role of NQO1 in gastric cancer and its effect on cancer development and prognosis have not been fully investigated.

**AIM**

To investigate the clinical relevance of NQO1 protein expression in gastric cancer and to explore the potential of NQO1 to serve as a prognostic biomarker and therapeutic target.

**METHODS**

In this retrospective study, gastric cancer specimens of 175 patients who were treated between 1995 and 2011 were subjected to immunohistochemistry analyses for NQO1. The correlation of NQO1 expression with gastric cancer prognosis and

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clinical and pathological parameters was investigated.

## RESULTS

NQO1 protein was overexpressed in 59.43% (104/175) of the analyzed samples. Overexpression of NQO1 was associated with a significantly inferior prognosis. In addition, multivariate analysis suggested that NQO1 overexpression, along with tumor stage and patient age, are prominent prognostic biomarkers for gastric cancer. Moreover, NQO1 overexpression was correlated to a better response to 5-fluorouracil (5-FU)-based adjuvant chemotherapy.

## CONCLUSION

NQO1 overexpression is associated with a significantly poor prognosis and better response to 5-FU in patients with gastric cancer. These findings are relevant for improving therapeutic approaches for gastric cancer patients.

**Key Words:** Gastric cancer; Quinone oxidoreductase 1; Prognosis; Immunohistochemistry; Kaplan-Meier curves; Biomarker

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**Core Tip:** Quinone oxidoreductase 1 may be used as a useful prognostic biomarker and therapeutic target for the efficient management of patients with gastric cancer.

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## INTRODUCTION

Gastric cancer (GC) is now the fourth most common cancer and the third most common cause of cancer-related deaths worldwide. It is estimated that 951600 new GC cases and 723100 deaths occurred in 2012. East Asia, including China, is among the areas with the highest incidence of GC, accounting for > 40% of all new cases[1,2]. Presently, the prevalence rates of GC are declining in most parts of the world owing to the establishment of mass screening and advanced treatment techniques. Despite this decline, the clinical outcomes of GC patients remain disappointing. Moreover, the prognosis of GC strongly depends on the TNM stage, biological factors, and clinical pathological factors[3,4]. Therefore, finding a new biomarker for the diagnosis and treatment of GC is of great value.

Quinine oxidoreductase 1 (NQO1) is a cytoplasmic flavoenzyme located on chromosome 16q22. It is also known as DT-diaphorase, menadione reductase, or quinone reductase 1. NQO1 directly reduces quinines to hydroquinones using reduced form of nicotinamide-adenine dinucleotide (NADH) or nicotinamide adenine dinucleotide phosphate (NADPH) as an electron donor[5,6]. Numerous functions of NQO1 have been reported, such as xenobiotic detoxification, superoxide scavenging, and maintenance of endogenous antioxidant vitamins[7]. It is likely that NQO1 plays an important role in protecting normal cells against oxidative damage and electrophilic attack. Paradoxically, despite the suggestion that it exerts a protective action and plays an antioxidant role, disruption of an NQO1 genetic polymorphism increases the risk of xenobiotic-induced toxicity and cancer[8,9]. High levels of NQO1 expression have been found in many human tumors, including breast cancer, melanoma, lung cancer, cholangiocarcinoma, and pancreatic cancer[10-13]. Garate *et al*[10] reported that NQO1 protein expression induces cell cycle progression and proliferation in melanoma cells. In a study by Lin *et al*[14], NQO1 expression in GC patients, non-cancer patients, and normal controls was quantified by immunohistochemistry (IHC). They reported that NQO1 played an important role in the progression of GC, and might be a potential prognostic biomarker and therapeutic target for GC. However,

the role of NQO1 in cancer progression remains controversial, and data on its expression in GC are scarce. In this study, we analyzed the expression of NQO1 and its potential association with survival and pathological parameters in primary GC. We aimed to investigate the associations between NQO1 protein expression status and responses to 5-fluorouracil (5-FU)-based adjuvant chemotherapy in patients with GC and thereby determine the potential of NQO1 to serve as a prognostic biomarker and therapeutic target.

## MATERIALS AND METHODS

### Western blot analysis

Unless otherwise stated, all chemicals were procured from Sigma-Aldrich Co. (Shanghai, China). Antibodies against rabbit NQO1 were used as described previously [15,16]. The human gastric cancer cell line AGS was obtained from the American Type Culture Collection (Manassas, VA, United States). Cells were maintained in RPMI-1640 growth medium (Shenggong, Shanghai, China) supplemented with 10% fetal bovine serum and antibiotics in a humidified atmosphere of 5% CO<sub>2</sub> and 95% air at 37 °C [17]. Cell extracts were prepared for sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE), and NQO1 immunoblotting was performed using a standard protocol with anti-NQO1 antibodies (dilution at 1:2000) [17,18].

### Patients

A total of 175 samples of GC were used in this study. All patients were enrolled and treated between 1995 and 2011 at the Department of Surgical Oncology, Affiliated Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, China. All patients received surgical treatment and were periodically followed for the determination of their survival status.

### Immunohistochemistry

Tumor samples were assembled as multiple tissue arrays, as described in our previous study [19]. IHC staining for NQO1 in paraffin-embedded tumor sections was performed using standard procedures. In brief, to eliminate endogenous peroxidase activity, the slides were deparaffinized in xylene, rehydrated through a graded series of ethanol solutions, and incubated with 3% H<sub>2</sub>O<sub>2</sub> in methanol for 15 min at room temperature. Antigen retrieval was performed by placing the slides in 0.01 M sodium citrate buffer (pH 6.0) at 121 °C for 15 min. Next, the slides were incubated with the NQO1 antibodies (1:5000) overnight at 4 °C. The immunoreactions were visualized with an ImmPRESS detection kit (Vector Laboratories), which uses a second antibody conjugated with horseradish peroxidase and a diaminobenzidine-based stain. Finally, the sections were counterstained with Mayer's hematoxylin, dehydrated, and mounted.

Cytoplasmic NQO1 staining was considered as positive for NQO1 expression. NQO1 expression was semiquantitatively assessed by two experienced pathologists who were blinded to the clinical parameters. Analyses of NQO1 expression were based on both the staining intensity and proportion of positive cells. The staining intensity was scored from 0 to 3+ as follows: 0 for no staining, 1+ for weak staining, 2+ for moderate staining, and 3+ for strong staining [20]. The proportion of NQO1-positive cells was expressed as a percentage and divided into four grades: grade 0, 0% positive; grade 1, 1%-30% positive; grade 2, 31%-60% positive; and grade 3, > 60% positive cells. The total score was obtained by multiplying these two parameters (range 0-9); for statistical purposes, the samples were divided into two groups: Low expression level (0-4) and high expression level or overexpression (> 4) groups. As the median score of NQO1 expression in the GC samples was 4.5, a cut-off value of 4 was selected [20].

### Data analysis

The correlation between the expression of NQO1 and clinical and pathological parameters was determined by statistical analysis using SPSS 16.0 for Windows (SPSS, incorporated, Chicago, IL, United States). The  $\chi^2$  or Fisher's exact test, Kaplan-Meier survival analysis, and Cox regression analysis were used as appropriate. *P* values < 0.05 were considered significant.

## RESULTS

### ***NQO1 antibody is specific and sensitive for IHC staining***

Protein extracts from AGS human GC cells were separated by SDS-PAGE, and the proteins were detected by Western blot analysis. The results showed that NQO1 can be readily detected, and no other protein cross-reacted with the NQO1 antibodies (Figure 1). Therefore, these antibodies are sensitive and specific for IHC staining to detect NQO1 expression in paraffin-embedded tumor sections.

### ***Patient characteristics***

A total of 175 patients were enrolled in this study. The baseline characteristics are described in detail and summarized in Table 1. The patients ranged from 26 to 84 years of age. The study population consisted of 124 men and 51 women. The clinical and pathological parameters consisted of age, gender, tumor size, tumor location, tumor stage, tumor depth, lymph node metastasis, histological differentiation, and survival data. The number of patients with a tumor size < 5 cm and ≥ 5 cm was 63 and 99, respectively. The stage of GC was determined at the time of analysis, according to the American Joint Commission on Cancer system AJCC TNM 8<sup>th</sup> edition. Of the 175 samples, 69 cases were stage I-II and 102 were stage III-IV GC. Among all patients, 67 underwent total gastrectomy, 83 received distal subtotal gastrectomy, 1 received partial resection, and 14 received proximal subtotal gastrectomy. The information of the remaining 10 patients was missing. None of the patients received chemotherapy prior to surgery. A total of 84 patients were treated with 5-FU + platinum-based adjuvant chemotherapy. The patients were followed until the last follow-up date or death. Among the 175 patients, there were 75 death events and 65 recurrence events in total. The follow-up period ranged from 0.5-182 mo, and the median follow-up time was 22.4 mo.

### ***Overexpression of NQO1 protein is associated with GC prognosis***

IHC staining showed that the NQO1 protein was mainly localized in the cytoplasm of GC cells (Figure 2). The level of NQO1 protein expression was high in 49.43% of the samples, with an overall score of > 4, while 71 (40.57%) samples showed low NQO1 expression levels, with an overall score of ≤ 4. To evaluate the role of the NQO1 protein in GC progression, we analyzed the correlation between its expression and the clinical and pathological parameters (Table 2). The number of patients with high levels of NQO1 expression and lymph node metastasis was higher than that of patients with low NQO1 expression, but this difference was not significant ( $P = 0.06$ ; Table 2). In addition, there were no significant correlations between NQO1 and other clinical parameters (Table 2). However, the follow-up results showed that the mean survival time for patients with low levels of NQO1 expression was 34 mo, while for those with NQO1 overexpression, it was 22 mo. Kaplan-Meier survival analysis revealed that patients with NQO1 overexpression had significantly poorer survival rates than those with low levels of NQO1 expression ( $P = 0.02$ ; Figure 3).

We further used the Cox proportional hazard regression method to examine the correlations between various clinical indexes and survival (Table 3). Univariate analysis revealed significant associations of tumor size ( $P < 0.001$ ), tumor stage ( $P < 0.001$ ), and NQO1 expression ( $P = 0.01$ ) with overall survival, whereas the other factors showed no significant association. However, multivariate analysis of these factors, including NQO1 expression, indicated that age, tumor stage, and NQO1 were independent prognostic factors for the overall survival of GC patients [hazard ratio (HR) = 1.90,  $P = 0.01$ ; HR = 2.64,  $P < 0.001$ ; and HR = 1.56,  $P = 0.05$ , respectively].

### ***NQO1 overexpression predicts a favorable response to chemotherapy in GC patients***

We also performed the survival analysis of patients from the various treatment subgroups based on the NQO1 expression. Among 84 patients treated with 5-FU-based chemotherapy, 52 (61.09%) had high levels of NQO1 expression and 32 (38.10%) had low levels of NQO1 expression. Similarly, high and low levels of NQO1 expression were found in 60% and 40% of patients who did not receive treatment, respectively. Patients with low levels of NQO1 expression showed poor response to adjuvant chemotherapy and similar survival, compared to those that underwent surgery alone (log rank  $P = 0.82$ ) (Figure 4A). However, high levels of NQO1 expression indicated good response to adjuvant chemotherapy and longer overall survival compared with those in patients that underwent surgery alone (log rank  $P = 0.03$ ) (Figure 4B). In addition, in the Kaplan-Meier analysis, we stratified NQO1

**Table 1** Clinical characteristic of the gastric cancer patients

Clinical parameter	Number of cases (n)	(%)
Age group	Range (26-84, mean = 58.9)	
< 60 yr	83	47.43
≥ 60 yr	92	52.57
Sex		
Male	124	70.86
Female	51	29.14
Tumor size (cm)		
< 5	63	36.00
≥ 5	99	56.57
Unknown	13	7.43
Tumor location		
Fundus	40	22.86
Body	44	25.14
Antral	82	46.68
Whole	4	2.29
Unknown	5	2.85
TNM stage		
I II	69	39.43
III IV	102	58.29
Unknown	4	2.28
Tumor depth		
T1/T2	33	18.86
T3/T4	139	79.43
Unknown	3	1.71
Lymph node metastasis		
Yes	43	24.57
No	123	70.29
Unknown	9	5.14
Vascular invasion		
Yes	19	10.86
No	156	89.14
Histological Differentiation		
Poor	20	11.43
Moderate	44	25.14
Well	111	63.43
Surgical type		
Complete resection	67	38.29
Distal resection	83	47.43
Proximal resection	14	8.00
Partial resection	1	0.57
Unknown	10	5.71

Chemotherapy		
Adjuvant chemotherapy	84	48.00
Without chemotherapy	80	45.71
Unknown	11	6.29

**Table 2 Association of quinone oxidoreductase 1 expression with clinical and pathological features of gastric patients**

Clinical parameter	NQO1 expression		P value
	High (%)	Low (%)	
Age (yr)			0.92
< 60	34 (40.96)	49 (59.04)	
≥ 60	37 (40.22)	55 (59.78)	
Gender			
Male	48 (38.71)	76 (61.29)	
Female	23 (45.10)	28 (54.90)	
Tumor size (cm)			0.81
< 5	23 (36.51)	40 (63.49)	
≥ 5	38 (38.38)	61 (61.62)	
Tumor location			0.19
Fundus	18 (40.91)	26 (59.09)	
Body	11 (27.50)	29 (72.50)	
Antral	34 (41.46)	48 (58.54)	
Whole	3 (75.00)	1(25.00)	
Tumor staging			0.06
I/II	22 (31.88)	47 (68.12)	
III/IV	47 (46.08)	55 (53.92)	
Tumor depth			0.37
T1 T2	11 (33.33)	22 (66.67)	
T3 T4	58 (41.73)	81 (58.27)	
Lymph node metastasis			
Yes	12 (27.91)	31 (72.09)	
No	54 (43.90)	69 (56.10)	
Vascular invasion			0.72
Yes	7 (36.84)	12 (63.16)	
No	64 (41.03)	92 (58.97)	
Histological differentiation			0.57
Poor	8 (40.00)	12 (60.00)	
Moderate	15 (34.10)	29 (65.90)	
Well	48 (43.24)	63 (56.76)	

According to Table 1, the total case number is 162 based on tumor size, 170 based on tumor location, 171 based on tumor stage, and 172 based on tumor depth.

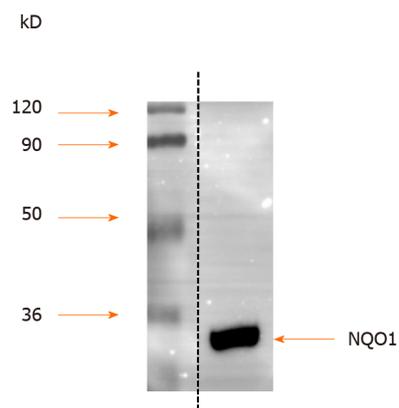
expression based on chemotherapy. Interestingly, the results showed that in patients who underwent surgery only, significant difference in overall survival was observed (log rank  $P = 0.003$ ), whereas in patients who underwent surgery plus chemotherapy,

**Table 3 Univariate and multivariate analyses of prognostic factors in gastric cancer patient**

Clinical factor	Univariate			Multivariate		
	P value	HR	95%CI	P value	HR	95%CI
Interval						
Age (< 60/≥ 60)	-	-	-	0.01	1.90	1.20-3.02
Gender (male/female)	-	-	-	0.96	1.03	0.62-1.66
Tumor size (< 5/≥ 5 cm)	< 0.001	1.75	1.10-2.87	0.40	1.00	0.76-2.25
Tumor location						
Proximal		1 (Reference)			1 (Reference)	
Body	0.67	1.13	0.65-1.94	0.82	1.06	0.59-1.95
Distal	0.09	0.7	0.43-1.15	0.11	0.69	0.41-1.19
Whole <sup>2</sup>	-	-	-	-	-	-
Tumor stage (III, IV/I, II)	< 0.001	3.11	1.96-5.09	< 0.001	2.64	1.56-4.61
Histological differentiation						
Well		1 (Reference)			1 (Reference)	
Moderate	0.3	1.58	0.68-4.30	0.62	1.26	0.53-3.48
Poor	0.07	2.03	0.96-5.23	0.15	1.79	0.83-4.67
NQO1 (high/low)	0.01	1.73	1.16-2.58	0.05	1.56	1.01-2.40

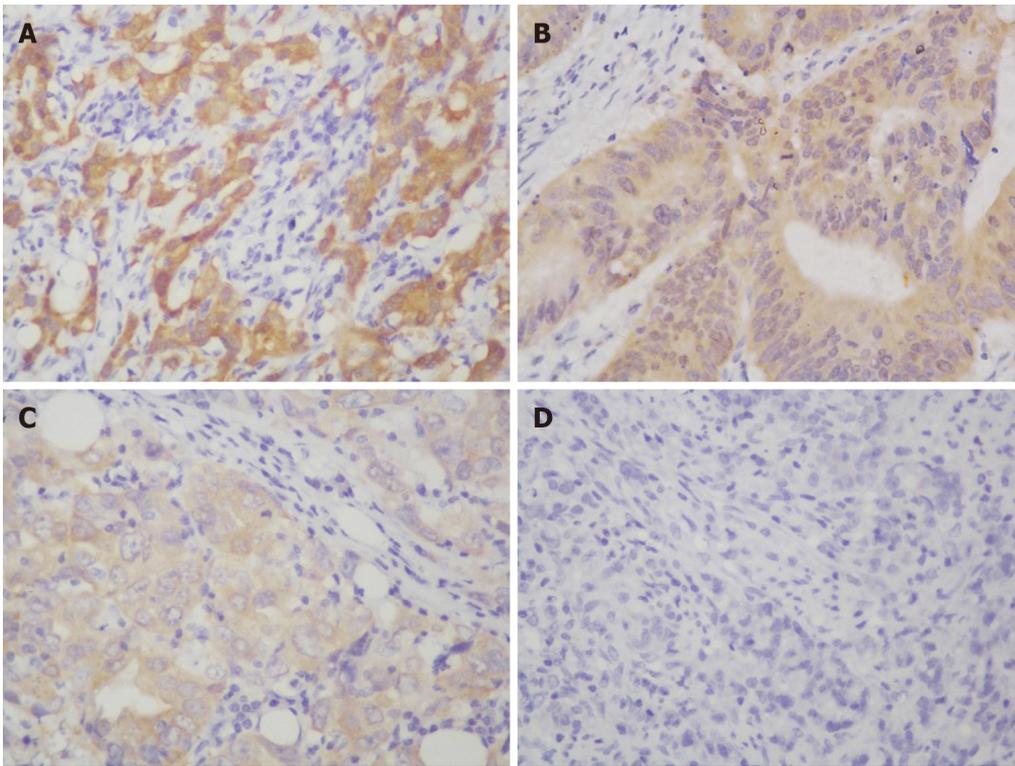
<sup>1</sup>Adjusted for age and gender.

<sup>2</sup>Patients in whole were not included due to too few cases (n = 4). NQO1: Quinine oxidoreductase 1; CI: Confidence interval; HR: Hazard ratio.

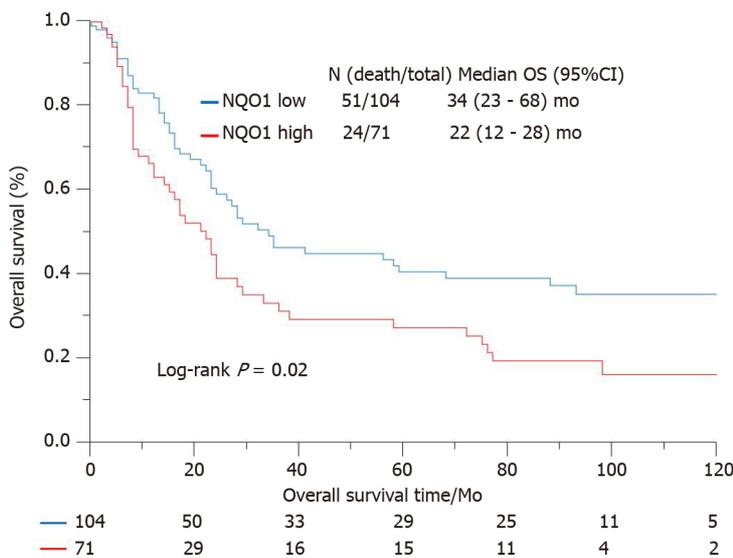


**Figure 1 Western blot analysis of quinine oxidoreductase 1 expression in gastric carcinoma cell line AGS.** Protein extracts from AGS human gastric cancer cells were separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis, and the proteins were detected by Western blot using anti-quinine oxidoreductase 1 antibodies. Molecular masses in kDa are indicated to the left. NQO1: Quinine oxidoreductase 1.

no difference was found (log rank  $P = 0.61$ ) (Figure 4C and D). These findings indicated that GC patients with NQO1 overexpression may be suitable for adjuvant chemotherapy.



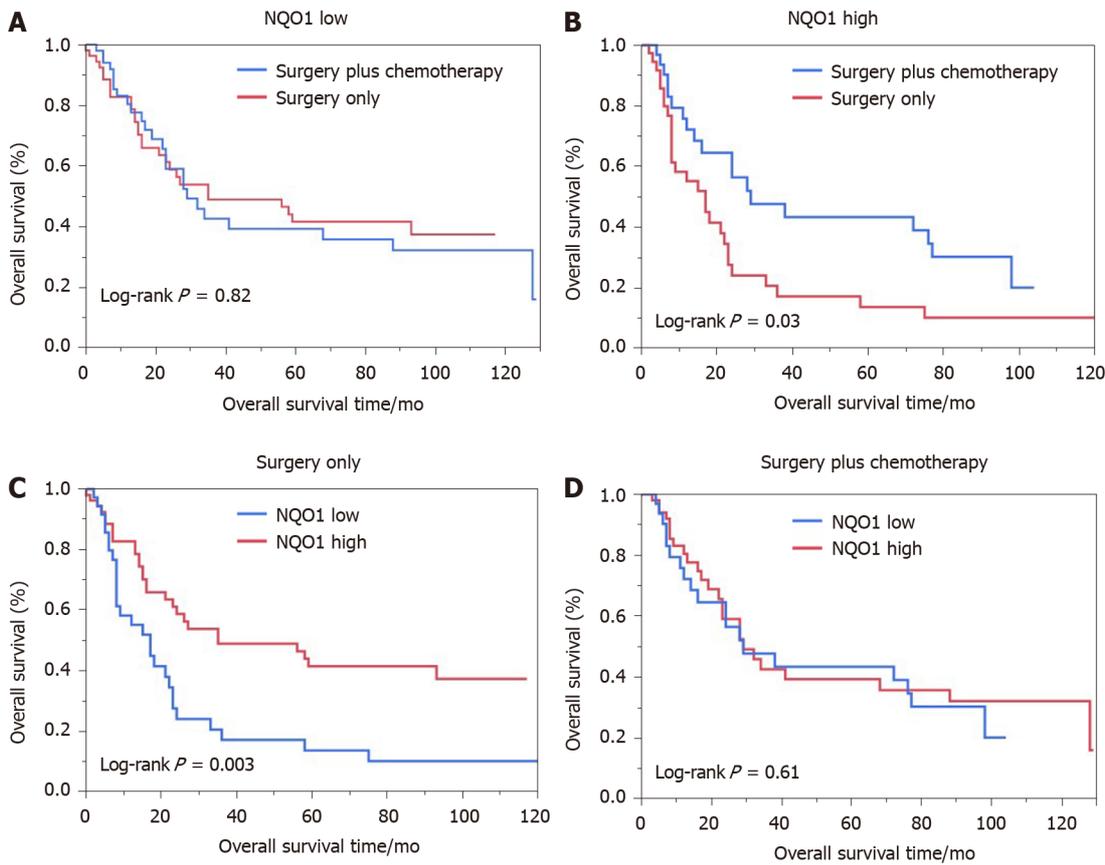
**Figure 2** Representative images of immunohistochemical staining for quinone oxidoreductase 1 in gastric cancer samples. A: Strong (+++); B: Moderate (++); C: Weak (+); D: Negative staining (original magnification × 400).



**Figure 3** Kaplan-Meier survival curves of postoperative outcomes of gastric cancer patients according to quinone oxidoreductase 1 expression status. The correlation of high and low quinone oxidoreductase 1 expression with the overall survival rate was statistically significant ( $P = 0.02$ ). NQO1: Quinone oxidoreductase 1; OS: Overall survival; CI: Confidence interval.

## DISCUSSION

The catalytic properties of NQO1 were first reported by Ernster and Navazio[21] in 1958. NQO1 is a homodimeric flavoprotein that reduces quinines to hydroquinones in an obligatory two-electron reduction step[6]. After years of research, cumulative data have shown that NQO1 protects cells from exogenous substances, oxidants, and ultraviolet and ionizing radiation by inducing a series of protective reactions[10]. Consistent with this finding, recent research by Nagata *et al*[22] and Malik *et al*[23] showed that the C609T polymorphism in the NQO1 gene might be linked to the risk of



**Figure 4 Kaplan-Meier analysis of overall survival rates in patients with gastric cancer.** A: Low oxidoreductase 1 expression; B: High quinine oxidoreductase 1 expression; C: Surgery only; D: With adjuvant chemotherapy. NQO1: Quinine oxidoreductase 1.

cancer-associated death. In addition, an *NQO1* polymorphism that causes inactivation of the enzyme predicts a poor outcome in breast cancer[24]. Moreover, *NQO1* plays a prominent role in regulating the stability of p53 by inhibiting its degradation and that of other labile proteins, such as ornithine decarboxylase[25,26]. Based on this evidence, *NQO1* plays an important role in cancer progression.

Recent studies have reported that *NQO1* protein expression is significantly elevated in the cytoplasm and nucleus in many human solid tumors[27]. For instance, Yang *et al* [28] showed that *NQO1* is highly expressed in breast cancer tissues and may be associated with breast cancer progression. Cheng *et al*[29] demonstrated strong *NQO1* expression in primary melanomas compared with that in dysplastic nevi, and that *NQO1* may be involved in the initiation of melanoma development. Similarly, the expression of *NQO1* in the cervical epithelium indicated that it might be responsible for cervical carcinogenesis[30]. Malkinson *et al*[31] reported elevated *NQO1* expression in human lung cancer tissues. Li *et al*[32] showed that *NQO1* is upregulated in non-small cell lung cancer and identified it as a biomarker of poor prognosis. In addition, the gene encoding *NQO1* is thought to participate in the pathogenesis of lung cancer [33,34]. Consistently, Ji *et al*[35], Awadallah *et al*[13], and Lyn-Cook *et al*[36] demonstrated that elevated *NQO1* expression is associated with pancreatic ductal adenocarcinoma and may be a potential prognostic biomarker for pancreatic cancer.

In the present study, elevated *NQO1* expression was observed in cancer tissues. In addition, a higher rate of *NQO1* protein overexpression in patients with lymph node metastasis than in those without metastasis was observed. This is partly consistent with the findings of Lin *et al*[14], which suggested that *NQO1* upregulation contributes to tumorigenesis and progression of GC.

With regard to survival, we found that GC patients with overexpression of *NQO1* protein had a significantly lower overall survival than those with low *NQO1* expression. Buranrat *et al*[12] showed a significant correlation between overexpression of *NQO1* protein and short overall survival in cholangiocarcinoma patients, enhancing the possibility of using *NQO1* as a tumor biomarker. Univariate survival analysis revealed that tumor size, tumor location, tumor stage, histological differentiation, and *NQO1* expression status were significantly associated with the overall survival of GC

patients. Likewise, multivariate survival analysis revealed that NQO1 was an independent prognostic biomarker, along with the tumor stage and patient age. Interestingly, it was also notable that patients with elevated NQO1 expression may be more sensitive to 5-FU-based chemotherapy than those with low NQO1 expression. Although the mechanism underlying this phenomenon remains unclear, the results indicated that NQO1 may serve as a biomarker for the early diagnosis and prognosis of GC, and as a potential molecular target for GC therapy. However, the role of NQO1 in GC has not been fully elucidated. Further manipulation of *NQO1* gene expression in different gastric cancer cell lines and investigation of the characteristics and mechanism of its effects on gastric cancer are needed in additional studies.

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## CONCLUSION

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NQO1 is involved in the initiation and progression of GC. High NQO1 expression levels indicates a worse overall survival and better response to 5-FU therapy. NQO1 could be a useful prognostic biomarker and therapeutic target for the appropriate management of patients with GC.

## ARTICLE HIGHLIGHTS

### **Research background**

Quinone oxidoreductase 1 (NQO1) plays a cytoprotective role in normal tissues. It is overexpressed in many solid tumors, suggesting a role in cancer development and progression. However, the expression of NQO1 in gastric cancer and its influence on cancer development and prognosis have not been fully addressed.

### **Research motivation**

Identifying molecular markers that can be used as an independent prognostic factor for gastric cancer is of great significance for the early diagnosis and targeted therapy of gastric cancer. The expression of NQO1 in gastric cancer and its influence on clinicopathological characteristics and prognosis have not previously been extensively determined.

### **Research objectives**

The objective of this study was to discover novel effective biomarkers to classify patients with low or high survival. This would provide a guide to clinicians to design personalized therapeutic approaches for gastric cancer patients. In this study, we investigated NQO1 protein, which may determine patient management strategies.

### **Research methods**

We used IHC to detect the expression of NQO1 in gastric cancer and adjacent tissues. Western blot analysis was performed to detect the expression of NQO1 in gastric cancer cell line. According to IHC scores, the patients were divided into NQO1 high expression group and NQO1 low expression group, and the relationship between the expression level and clinicopathological data was analyzed.

### **Research results**

We found no significant correlations between NQO1 and clinical parameters. However, the follow-up results showed that patients with NQO1 overexpression had a significantly poorer survival rates than those with low levels of NQO1.

Patients with low levels of NQO1 expression showed a poor response to adjuvant chemotherapy and similar survival, compared to those who underwent surgery alone. However, high levels of NQO1 expression indicated a good response to adjuvant chemotherapy and longer overall survival compared with those in patients who underwent surgery alone. In addition, in the Kaplan-Meier analysis, we stratified NQO1 expression based on chemotherapy. The results showed that in patients who underwent surgery only, a significant difference in overall survival was observed, whereas in patients who underwent surgery plus chemotherapy, no difference was found.

### Research conclusions

This study found that high expression of NQO1 is closely related to a poor prognosis and better response to 5-fluorouracil in patients with gastric cancer.

### Research perspectives

Our study found prognostic value of NQO1 protein expression in patients with gastric cancer. However, our results need to be validated by independent groups or cohorts in a prospective study.

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