

Antidepressants use is associated with overall survival improvement of patients with gastric cancer after surgery and adjuvant chemotherapy in Taiwan

A large population-based cohort study

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Abstract

To determine whether exposure to antidepressants (ATDs) results in improved overall survival (OS) of patients with gastric cancer (GC) after surgery, we conducted a large cohort study and considered confounding factors that might affect the research outcomes.

Patients who received a new diagnosis of GC and received surgery and chemotherapy between 1999 and 2008 were recruited and were classified into different groups based on the ATD level used. The association between the OS of patients with GC after surgery with different levels of ATD use, and the hazard ratio with comorbidities at different ATD use levels were compared.

According to Kaplan–Meier method, the more of an ATD was taken, the longer the OS and a dose-dependent relationship was discovered in the OS curve; the adjusted HRs were 0.76 (95% confidence interval [CI] = 0.68–0.84) and 0.48 (95% CI = 0.41–0.57) for ATD users taking a cumulative defined daily dose (cDDD) of 28–167 and ≥ 168 , respectively. Sensitivity analyzes were performed to investigate the effect of various comorbidities on OS with different degrees of ATD use and the results remained consistent among the varying models. Additionally, the effect of ATD use still exhibited a dose-dependent relationship in distinct stratifications for sex and age.

The OS for patients with GC after surgery and chemotherapy improved with ATD use, and a dose-dependent relationship was discovered in this study. Further studies on the association between OS of GC and ATD use are required.

Abbreviations: ATD = antidepressant, cDDD = cumulative defined daily dose, CI = confidence interval, CIRPD = catastrophic illness registry patient database, DDD = defined daily dose, GC = gastric cancer, HR = hazard ratio, NHIRD = National Health Insurance Research Database, OS = overall survival, SSRI = selective serotonin reuptake inhibitor.

Keywords: antidepressant, gastric cancer, overall survival, population-based cohort study

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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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1. Introduction

According to global cancer statistics from 2018, gastric cancer (GC) ranks as the fifth most commonly diagnosed cancer worldwide (fifth and eighth in incidence for men and women, respectively), causing more than 1,000,000 new cases yearly; there were 783,000 deaths from GC in 2018, and GC was the fourth and sixth leading cause of cancer death in men and women, respectively.^[1] The age-standardized 5-year overall survival rate is 20% to 40% globally; however, a considerable variation exists in this percentage in Asia, with survival rate being 69% in South Korea and 60% in Japan.^[2] The incidence of GC exhibits clear geographic differences; it is markedly high in Asia and generally low in Northern America, Northern Europe, and Africa.^[1] This regional variation partly reflects different ethics, dietary patterns, food storage methods, and prevalence of *Helicobacter pylori* infection.^[3] In 1994, the International Agency for Research on Cancer stated that *H. pylori* is a group I human carcinogen responsible for gastric adenocarcinoma.^[4]

Two types of classification system have been used for GC: the more widely used TNM system is based on the American Joint Committee on Cancer and Union for International Cancer Control classification, eighth edition; the other classification, which originated in Japan, classifies GC according to its anatomic location, especially lymph node stations. Locally restricted tumor (stages I to III) is generally curable; by contrast, patients with

advanced disease (stage IV) may be administered palliative treatment according to their functional status and symptoms. The survival rate in endoscopic resection versus surgical resection is similar.^[5] Complete tumor removal results in superior survival for patients with localized GC, especially when it is combined with adjuvant or perioperative chemotherapy.^[6,7]

GC is the fifth most commonly diagnosed cancer in Taiwan, and 3975 Taiwanese cases were diagnosed in 2012. The age-standardized incidence was 15.03 per 100,000 person-years; in addition, GC was reported to be the sixth greatest cause of cancer-related death in Taiwan, and the standardized mortality rate of patients diagnosed with GC was 6.4 per 100,000 person-years in 2012.^[8] According to the Taiwanese Cancer Registry Annual Report 2016, stages Ib, II, and III accounted for more than half of patients with GC, and most patients received surgery plus adjuvant chemotherapy.

Although the 5-year survival rate of GC has been improving gradually, the occurrence of depression after cancer diagnosis has been increasing. Cancer is a common risk factor for emotional interference, especially depression.^[9] Considerable evidence has been obtained showing that depression is associated with poor outcome and decreased quality of life in patients with cancer.^[10] Hawkins et al reported that the incidence of taking medication for anxiety or depression was almost 2 times higher in the population of individuals who had survived cancer than the total population because of psychological suffering or physical burden caused by cancer.^[11] In a nationwide study, Hu et al found that there was a higher incidence (adjusted hazard ratio [HR] = 1.54, 95% confidence interval [CI] = 1.39–1.70, $P < .001$) of newly diagnosed depressive disorder after GC diagnosis in a GC cohort than in a matched cohort.^[12] Shoval et al reported that higher adherence to antidepressant drugs (ATDs) was associated with lower all-cause mortality in a large nationwide cohort of patients with cancer.^[13] The scope of this study is to determine whether the overall survival (OS) of patients with GC after surgery and adjuvant chemotherapy is superior after exposure to ATDs. In order to do that we employed a large cohort from the Taiwan National Health Insurance Research Database (NHIRD) and considered confounding factors that might affect outcomes.

2. Materials and methods

2.1. Source of study population

The population of this study was derived from the NHIRD, which covers almost the entire population of Taiwan of up to 23.7 million. Because of its strict secrecy guidelines, the NHIRD contains no identifiable personal information. This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital, Chiayi, Taiwan

2.2. Inclusion and exclusion criteria

Patients in the Catastrophic Illness Registry Patient Database (CIRPD) who received a new diagnosis of GC according to the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM code 151.xx) and received surgery and chemotherapy between 1999 and 2008 were enrolled as study patients. Patients with other cancer before the GC diagnosis, who did not undergo surgery or chemotherapy, who underwent surgery after neoadjuvant chemotherapy, who were aged less than 18 years, and with incomplete data were excluded.

2.3. Demographic data

Patients' demographic data, namely sex, age, level of urbanization, income level (New Taiwan Dollars per month), comorbidities, and chemotherapy regimen, were retrieved from the NHIRD. Comorbidities, namely diabetes mellitus, hypertension, alcoholism, smoking-related disorder, chronic renal failure, and liver cirrhosis, were analyzed. Chemotherapy regimens were classified into 4 groups:

1. epirubicin based,
2. mitomycin based,
3. taxanes, and
4. others (Table 1).

2.4. Antidepressant drug exposure

The source of exposure to ATD types and dosages were derived from the NHIRD, and in this study, ATDs were classified into 4 subtypes: selective serotonin reuptake inhibitor (SSRI), serotonin and norepinephrine reuptake inhibitor, tricyclic antidepressant, and others (combined serotonin antagonist and reuptake inhibitor, norepinephrine-dopamine reuptake inhibitor, and mirtazapine and monoamine oxidase inhibitor) The defined daily dose (DDD), defined by the World Health Organization, is the unit used for calculating a prescribed amount of a drug and is assumed the average maintenance dose of a drug consumed for its main indication per day. Using the following formula, we could compare different types of ATD on the basis of the same standard: (total amount of drug)/(amount of drug in DDD) = number of DDDs. The cumulative DDD (cDDD), which indicates the total exposure to an ATD, was calculated as the predictive sum of the dispensed DDD of any ATD and used to compare the drugs' positive effects on the survival of patients with GC after surgery.^[14]

To determine the dose-dependent relationship, cDDD was categorized into 3 gradients:

1. cDDD <28,
2. cDDD = 28–167, and
3. cDDD \geq 168. Patients who took a cDDD of less than 28 were defined as ATD nonusers.

2.5. Matched cohort

To understand the effect of ATDs on the OS of patients with GC after surgery, propensity scores were used to estimate the probabilities of assigning patients taking ATDs with the variables as sex, age, level of urbanization, income level, comorbidities, and chemotherapy regimen. ATD users and nonusers were matched with propensity scores in the ratio of 1:4. The baseline demographic data are presented in Table 1.

2.6. Statistical analysis

Categorical variables were examined using the Chi-Squared test, and continuous variables were assessed using the *t*-test. To assess the association between the OS of patients with GC after surgery and the level of ATD use, the Kaplan–Meier method was used and the log-rank test employed to examine differences in survival

Table 1**Demographic characteristics of ATD users and ATD nonusers among GC patients after surgery and adjuvant chemotherapy in Taiwan during 1999~2008 in the matched cohort.**

	ATD user (N = 1007)		ATD nonuser (N = 4028)		P value
	n	%	n	%	
Sex					.7861
Female	426	42.3	1685	41.8	
Male	581	57.7	2343	58.2	
Age (year-old)					.3237
18–64	531	52.7	2054	51.0	
≥65	476	47.3	1974	49.0	
Mean (SD)	62.0 (12.9)		62.2 (13.5)		.6336
Urbanization			0.8017		
Very high	296	29.4	1125	27.9	
High	479	47.6	1954	48.5	
Moderate	170	16.9	707	17.6	
Low	62	6.2	242	6.0	
Income level (NTD [*] /month)					.8220
0	181	18.0	678	16.8	
1–15840	186	18.5	763	18.9	
15841–25000	458	45.5	1871	46.5	
≥25000	182	18.1	716	17.8	
Comorbidities					
Diabetes mellitus	227	22.5	901	22.4	.9058
Hypertension	456	45.3	1847	45.9	.7449
Alcoholism	23	2.3	97	2.4	.8173
Smoking-related disorder	110	10.9	416	10.3	.5803
Chronic renal failure	21	2.1	95	2.4	.6054
Liver cirrhosis	27	2.7	114	2.8	.7978
Chemotherapy regimen					.9205
Epirubicin-based	111	11.0	432	10.7	
Mitomycin-based	130	12.9	533	13.2	
Taxanes	16	1.6	54	1.3	
Others	750	74.5	3009	74.7	

ATD = antidepressant, GC = gastric cancer, NTD = New Taiwan Dollars.

^{*}1US \$ = 32.3 NTD in 2008.

among ATD users. Cox proportional hazard models were used to compare HRs with 95% CIs after adjusting for sex, age, level of urbanization, and income level. A *P* value of <.05 or 95% CI was considered statistically significant. All analyzes were performed using SAS statistical software (version 9.4; SAS Institute, Cary, NC, USA).

2.7. Sensitivity analysis

To compute the effects of different comorbidities on OS, cDDD was stratified into cDDD of 28–167 and cDDD ≥168. Subgroups were formed from baseline characteristics, such as sex and age, to verify the consistency between different levels of ATD use and OS.

3. Results

According to the CIRPD, 33,256 patients received a new diagnosis of GC between 1999 and 2008. Of these, 1331 were excluded due to cancer before GC diagnosis. Patients who underwent no surgery (N=12,067), no chemotherapy (N=8,786), or surgery after neoadjuvant chemotherapy (N=250) were also excluded. Another 205 patients were excluded because of age less than 18 years (N=2) and incomplete data (N=203).

The study cohort consisted of 10,617 patients—1007 ATD users and 9610 ATD nonusers. After propensity score matching in the ratio of 1:4, the number of ATD users and nonusers was 1007 and 4028, respectively (Fig. 1). No significant differences existed in baseline demographic characteristics between ATD users and nonusers (Table 1).

This study enrolled 5035 patients who were followed up for a total of 27,438.1 person-years. The mean follow-up duration was 5.1 years for ATD nonusers, 6.3 years for those taking ATDs at a cDDD of 28–167, and 7.5 years for those taking ATDs at a cDDD of ≥168. A total of 3314 deaths occurred during the 10-year follow-up period; of these, 2740 occurred in the ATD nonuser group. The incidence of death was 13,234.7 per 100,000 person-years in the ATD nonuser group and 9920.5, and 6216.7 per 100,000 person-years in the subgroups of cDDD of 28 to 167 and cDDD ≥168, respectively (Table 2). According to Kaplan–Meier method, the more of an ATD was taken, the longer the OS. The log-rank test revealed a significant difference in the survival curve (Fig. 2). Furthermore, a dose-dependent relationship was discovered in the OS curve; the adjusted HRs were 0.76 (95% CI = 0.68–0.84) and 0.48 (95% CI = 0.41–0.57) for ATD users taking a cDDD of 28 to 167 and ≥168, respectively. To investigate the effect of various comorbidities on OS with varying degrees of ATD use, sensitivity analyses were performed. The

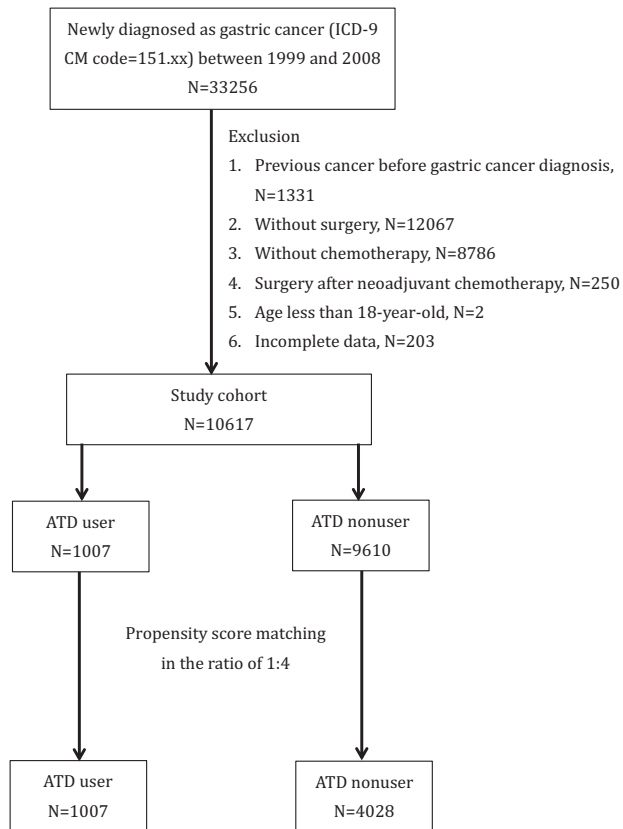


Figure 1. Flowchart of selection of subjects. ATD = antidepressant, GC = gastric cancer, ICD-9-CM = International Classification of Disease, Ninth Revision, Clinical Modification.

effects of different levels of ATD use on OS were found to remain consistent among the different models (Table 3). Additionally, the effect of ATD use still exhibited a dose-dependent relationship in distinct stratifications for sex and age.

4. Discussion

To our knowledge, this is the first study to explore whether an association exists between OS in early stage GC after surgery and ATD use by employing a large cohort database. The results revealed a dose-dependent association between ATD use and OS among patients with early stage GC after surgery. The findings persisted after controlling factors commonly related to GC. Hsieh et al concluded that no association existed between ATD exposure and risk of GC;^[15] moreover, in our study, an increase

in OS of GC after surgery among ATD users was confirmed, and a dose-dependent relationship was also discovered.

According to previous research, ATDs, namely SSRIs and TCAs, 2 of the most common subtypes, exhibit high apoptotic activity in human and murine neoplastic tissues and also strong effects on the cell cycle and signal transduction.^[16] Desipramine caused apoptotic cell death with suspension of cell cycle progression at either the G0/G1 phase or G2/M phase to inhibit tumor cell proliferation.^[17] Di Rosso et al reported that SSRI regulated immune function through the serotonin-dependent pathway and altered tumor cell viability.^[18] Grygier et al indicated that the inhibitory effect of fluoxetine on melanoma progression was related to elevated mitogen-induced T-cell proliferation, which partially participated in the mechanism underlying the antitumor effect of fluoxetine.^[19]

In vivo long-term administration of fluoxetine was recently demonstrated to suppress tumor growth by increasing antitumor T-cell activity.^[18] Fluoxetine has been shown to be a highly effective chemosensitizer: in vitro, its cytotoxicity was 10 to 100-fold of the anticancer drugs provided; in vivo, 12-fold enhancement of doxorubicin accumulation in tumors was achieved without changing the pharmacokinetics.^[20] With the combination of fluoxetine and doxorubicin, almost 2- to 3-fold improvement was achieved in both response and survival.^[20] In related research, fluoxetine has been shown to activate receptors overexpressed in cancer stem cells, and this finding might explain why SSRIs can lower the risk of various types of cancer.^[21] Furthermore, fluoxetine inhibited multi-drug-resistance pumps, adding the effects of multiple chemotherapies.^[21] Because of the great potential of SSRIs in cancer therapy, ATDs should be more extensively used not just for cancer-related depression but also to increase the efficacy of standardized chemotherapy regimens.^[21]

The strengths of this study have several aspects as follows. First, the data used in this research came from the NHIRD, which covers almost whole population in Taiwan rather than a small sample, helping the study avoid selection bias. Second, all patients' diagnoses were confirmed by the CIRPD, which requires proof from tissue pathology, related images, or laboratory data and strict review by a formal committee consisting of members of the Bureau of National Health Insurance to ensure inclusion accuracy. Third, all surgical interventions, medical histories, and prescriptions were recorded in either outpatient records or hospitalization records in the NHIRD and could be analyzed and stratified to eliminate recall bias. Furthermore, propensity score matching was used in this research design to reduce numbers lost among ATD users/nonusers and heterogeneity among all patients.

This study has some limitations that may affect the results and interpretations of this study. First, the body mass index, which may affect the concentration of an ATD was not included in demographic data. Second, data in the CIRPD did not include

Table 2
Statistic of deaths in varying levels of ATD use.

ATD use	Death	Total follow-up (person-year)	Incidence rate ^a	95% CI	Mean follow-up (year)
<28cDDD	2740	20703.2	13234.7	12748.3	5.1
28-167cDDD	416	4193.3	9920.5	9011.6	6.3
≥168cDDD	158	2541.6	6216.7	5319.1	7.5

ATD = antidepressant, cDDD = cumulative defined daily dose, CI = confidence interval.

^a: per 100,000 person-years.

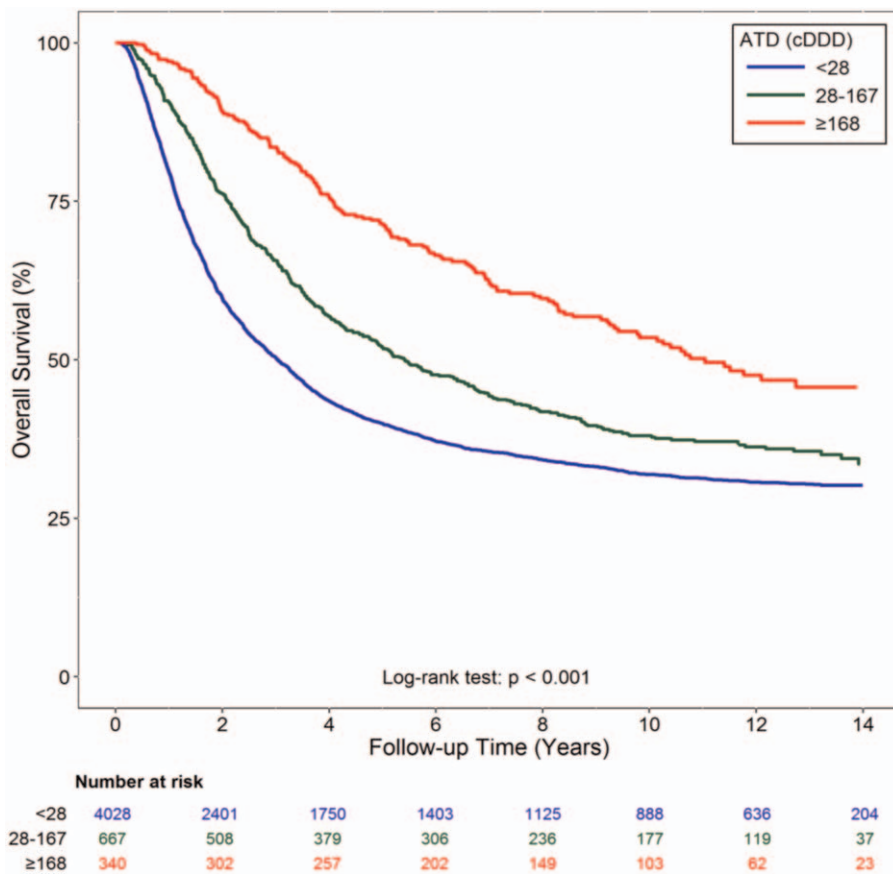


Figure 2. Kaplan–Meier curves for the OS of GC patients taken with different cDDD of ATD. ATD = antidepressant, cDDD = cumulative defined daily dose, GC = gastric cancer, OS = overall survival.

Table 3

Adjusted HR of OS associated with different comorbidities on cDDD levels.

Variables	28-167 cDDD			≥168 cDDD				
	HR	95% CI	P value	HR	95% CI	P value		
Main model ^a	0.76	0.68	0.84	<.0001	0.48	0.41	0.57	<.0001
Additional covariates ^b								
Main model+ diabetes mellitus	0.75	0.68	0.84	<.0001	0.48	0.41	0.56	<.0001
Main model+ hypertension	0.76	0.68	0.84	<.0001	0.48	0.41	0.56	<.0001
Main model+ alcoholism	0.76	0.68	0.84	<.0001	0.48	0.41	0.57	<.0001
Main model+ smoking-related disorder	0.76	0.68	0.84	<.0001	0.48	0.41	0.56	<.0001
Main model+ chronic renal failure	0.76	0.68	0.84	<.0001	0.48	0.41	0.57	<.0001
Main model+ liver cirrhosis	0.76	0.68	0.84	<.0001	0.48	0.41	0.57	<.0001
Main model+ chemotherapy regimen	0.75	0.68	0.83	<.0001	0.48	0.41	0.57	<.0001
Subgroup effects								
Sex								
Male	0.78	0.68	0.89	.0002	0.51	0.41	0.62	<.0001
Female	0.73	0.61	0.86	.0002	0.45	0.35	0.58	<.0001
Age at surgery								
18~64 -year-old	0.81	0.70	0.94	.0057	0.47	0.37	0.59	<.0001
> 65-year-old	0.71	0.62	0.82	<.0001	0.50	0.40	0.62	<.0001

cDDD = cumulative defined daily dose, CI = confidence interval, HR = hazard ratio, MAOI = monoamine oxidase inhibitor, NDRI = norepinephrine-dopamine reuptake inhibitor, OS = overall survival, SARI = serotonin antagonist and reuptake inhibitor.

*a: Adjusted for all covariates (all kinds of ATD, sex age, urbanization, income).

*b: Other: combined SARI, NDRI, Mirtazapine, MAOI.

cancer staging data; therefore, the results of this research could not be applied to all patients with GC. However, by screening according to the type of medical intervention received—that is, surgery or not and with or without a chemotherapy regimen—we could select patients ranged between stage Ib to III GC. In this study, we excluded those who did not receive surgery (stage IV) because palliative treatment was usually performed instead of curative treatment; those who did not receive chemotherapy (very early stage, such as stages 0 and Ia) because their 5-year survival rate is higher than 90%; and those who received neoadjuvant chemotherapy (debulking for primary tumor invading through the submucosa, T2 or higher). Our patients were in early stage as Ib, II, or III, which corresponded to the statistics of GC stage in Taiwan. Third, employing prescription records as data of ATD exposure may have resulted in overestimation of the cDDD level due to uncertain medical compliance, and other self-paid over-the-counter medications were not detailed in prescription records. In addition, nutritional status, which substantially influences the survival of patients with cancer, was also not noted in medical records and could not be systematically analyzed and compared.

5. Conclusion

The OS of patients with early stage GC improved with ATD use, and a dose-dependent relationship was discovered in this study. Additional studies regarding the association between the OS of GC and ATD use are required.

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