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Risk of suicide among operated and non-operated patients hospitalized for peptic ulcers

Short title: Suicide risk among peptic ulcer patients

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Abbreviations:

CI, confidence interval; *H. pylori*, *Helicobacter pylori*; NRN, national registration number; RR, relative risk; SMR, standardized mortality ratio;

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Abstract

Background: Some small studies reported high risk of suicide after surgical treatment for peptic ulcer. Our aim was to explore the risk of suicide in hospitalized gastric ulcer and duodenal ulcer patients separately among operated and unoperated cohorts.

Methods: Retrospective cohorts of 163,579 unoperated patients with gastric ulcer or duodenal ulcer and 28,112 patients with surgical treatment for ulcer, recorded in the Swedish Inpatient Register since 1965, were followed from the first hospitalization, or operation for the surgery cohort, until death, any cancer, emigration, or December 31, 2003. Standardized mortality ratios (SMRs) were calculated using rates from the age, sex and calendar period-matched Swedish population. Poisson regression produced adjusted relative risk estimates among operated and unoperated patients.

Results: Unoperated patients hospitalized for peptic ulcer showed a 70% excess risk of suicide (SMR=1.7, 95% CI 1.6-1.9) and those who underwent operation had a 60% increased risk (SMR=1.6, 95% CI 1.4-1.8). The risk of suicide was very high during the first year after hospitalization (SMR=4.0, 95% CI 3.4-4.7) and more marked among women, patients younger than 70 and patient who were hospitalized without complications of ulcer. Both gastric ulcer and duodenal ulcer patients had high risk of suicide completion.

Conclusion: Hospitalized patients with gastric ulcer or duodenal ulcer have an increased risk of suicide disregard of surgical treatment. These patients, especially women, are at very high risk during the first year after first hospitalization/operation. The evaluation and management of suicidal thoughts in patients in medical settings should be considered.

What this paper adds
<p>What is already known on this subject?</p> <p>Various somatic disorders have been associated with an increased risk of suicide. For peptic ulcer, affecting 6-15% of the western populations, an excess risk of suicide after operation has been reported. However, the studies are small and encumbered with methodological problems.</p>
<p>What does this study add?</p> <p>Hospitalized patients with gastric ulcer or duodenal ulcer have an increased risk of suicide disregard of surgical treatment. These patients, especially women, are at very high risk during the first year after first hospitalization/operation. The evaluation and management of suicidal thoughts in patients in medical settings should be considered.</p>

Introduction

Suicide mortality varies considerably internationally. Based on latest available suicide mortality statistics from the WHO mortality database, suicide rates in males ranged from below 5 per 100,000 in some Southern European countries to rates around 50-80 per 100,000 in Northern and Eastern European countries.[1] The annual number of suicide deaths in Sweden exceeds the number of lethal traffic accidents nearly threefold [1] and this number is increasing among young individuals.[2]

Even though suicidal behaviour has a multifactorial ethiology, including biological, social, psychological and cultural influences, the majority of suicides are committed by people who suffer from some kind of mental illness.[3] With regard to somatic illnesses, an excess risk of

suicide has been found for neurological and neurodegenerative disorders [4] and cancer.[5, 6] There are some reports of an excess mortality from suicide among patients with peptic ulcer both medically [7] and surgically treated.[8-17] However, few studies have explored the risk of suicide in gastric ulcer and duodenal ulcer patients separately comparing before and after partial gastric resection or vagotomy. In a study in Copenhagen on ulcer patients after attempted or committed suicide, no difference were found in frequency between operated and non-operated patients.[18]

We conducted a retrospective cohort study to investigate the risk of mortality from suicide among patients hospitalized for peptic ulcer from 1965 to 2003 in Sweden. We studied the risk of suicide among operated and unoperated patients separately. The definition “peptic ulcer” used throughout this paper means all types of ulcers i.e. gastric ulcer, duodenal ulcer patients and ulcer with an unspecified site unless otherwise mentioned.

Material and Methods

Study cohorts

The Swedish National Board of Health and Welfare has collected data of individual hospitalizations in the Swedish Inpatient Register since 1964. All the records are identifiable by the National Registration Number (NRN), a unique personal identification number assigned to all Swedish residents from birth or immigration. All patients in the Inpatient Register who were discharged between 1965 and 2003 with a diagnosis of duodenal ulcer (ICD-7 code 541, ICD-8 and ICD-9 code 532, and ICD-10 code K26), gastric ulcer (ICD-7 code 540, ICD-8 and ICD-9 code 531, and ICD-10 code K25) or peptic ulcer with an unspecified site (ICD-8 and ICD-9 code 533, and ICD-10 code K27) were considered for inclusion in the study cohorts. For each potential subject, we identified the first recorded

hospitalization for the ulcer as the index episode. All the individuals who underwent surgical treatment were included in the cohort of operated patients.

The NRNs were first checked in the nationwide registers of Total Population, Emigration and Causes of Death and those that could not be located in any of these registers were regarded invalid and were excluded. Totally 6,643 records were excluded for this and other inconsistencies revealed during data editing and record linkages. We further excluded all patients with a diagnosis of any cancer before or at time of the index episode (22,946), and data of 12,323 individuals who died during the index hospitalization. Finally, our cohorts encompassed 181,053 individuals.

Follow-up

We linked the NRNs to the nationwide registers of Migration and Causes of Death and the national Swedish Cancer Register to obtain censoring information. We used ICD-7 code 970-979, ICD-8 and ICD-9 code 950-959, and ICD-10 code X60-X84 to identify the suicide cases. The patients in the cohort were followed from the date of discharge from their first recorded in-hospital episode with peptic ulcer until the date of emigration, death, a diagnosis of any cancer, partial/total gastrectomy, vagotomy, or until December 31, 2003, whichever occurred first.

Patients who underwent gastric resection or vagotomy for peptic ulcer were also followed from the time of surgery until the date of emigration, death, a diagnosis of any cancer, or until December 31, 2003, whichever occurred first.

Statistical analysis

The standardized mortality ratio (SMR) — the ratio of the observed to the expected number of deaths — was used as a measure of relative risk of suicide among non-operated and operated peptic ulcer patients. The expected number of fatal suicides was calculated on the basis of person-time experienced in the cohorts, divided into strata of sex, age (in five-year age groups) and calendar year of observation (in 5-year intervals). The stratum-specific numbers of accumulated person-years were multiplied by the rates of specific causes of death in the corresponding strata, observed in the entire Swedish population. The 95 % confidence intervals (CIs) for the SMRs were calculated assuming that the observed events followed a Poisson distribution. We performed stratified analyses by follow-up duration, sex, presence of complications (bleeding or perforation) at index hospitalization, calendar period of index hospitalization (before vs. after 1980), and age at entry (<30, 30-49, 50-69, 70-).

Additional analyses were done using Poisson regression to estimate relative risks between strata of follow-up duration, sex, presence of complications at index hospitalization, calendar period of index hospitalization, and age at entry. Test of homogeneity was performed using Poisson regression. All the mentioned variables were included in the model. To study the association of suicide with gastric ulcer and duodenal ulcer separately, we performed further analyses using information from patients who had a record of only gastric ulcer or duodenal ulcer in their files.

All statistical analyses were performed with SAS, release 9.1 (SAS Institute, Cary, NC). Proc Genmod was used for Poisson regression and the logarithm of the expected number of cases was used as offset variable. All statistical tests were two-sided with alpha equal to 0.05.

Results

The final cohort included 163,579 unoperated patients with a diagnosis of peptic ulcer, among which 61,548 patients had duodenal ulcer, 81,379 patients had gastric ulcer, and 20,652 patient had peptic ulcer with an unspecified site or reports of both gastric and duodenal ulcers (table 1). There were 28,112 patients with surgical treatment. Surgically treated patients were younger than the un-operated group and had a longer follow-up time. About half of the peptic ulcer patients were hospitalized due to bleeding and some 9 percent due to perforation.

Table 1. **Some characteristics of patients with peptic ulcer in Sweden, 1965-2003**

Characteristics	Non-operated Peptic ulcer	Only gastric ulcer	Only duodenal ulcer	Operated patients
Number of patients	163,579	81,379	61,548	28,112
Male/female ratio	1.40	1.11	1.82	1.84
Age at index hospitalization (%)				
<30 yr	3.2	2.1	4.7	5.8
30-49 yr	15.7	12.6	19.3	33.8
50-69 yr	35.6	34.7	36.0	46.3
>=70 yr	45.5	50.6	40.1	14.2
Mean, years	64.6	66.7	62.1	53.2
Total person-year of follow-up	1,272,710	576,458	524,960	473,082
Average follow-up time, years	8.3	7.2	9.1	16.3
Mean age at suicide, years	59.0	61.0	58.0	56.0

Nonoperated peptic ulcers

After an average eight years of follow-up 609 deaths occurred due to suicide among hospitalized unoperated patients with peptic ulcer (SMR=1.7, 95% CI 1.6-1.9) (Table 2). Stratified analyses revealed that the risk of suicide has a decreasing trend by follow-up time and is highest during the first year after hospitalization of ulcer (SMR=4.0, 95% CI 3.4-4.7) (Figure 1).

Table 2. Standardized mortality ratios (SMRs) and their 95% confidence intervals (CIs) for suicide among hospitalized non-operated and operated patients with peptic ulcer, by follow-up duration, sex, presence of complications, and calendar year of index hospitalization

	Non-operated peptic ulcer N=163,579		Surgery N=28,112	
	No. cases	SMR (95%CI)	No. cases	SMR (95%CI)
Overall	609	1.7 (1.6-1.9)	214	1.6 (1.4-1.8)
Follow-up duration, years				
<1	163	4.0 (3.4-4.7)	20	2.3 (1.4-3.5)
1-4	250	2.1 (1.8-2.3)	57	1.8 (1.3-2.3)
5-9	113	1.2 (1.0-1.5)	67	2.0 (1.6-2.6)
≥10	83	0.8 (0.7-1.0)	70	1.1 (0.9-1.4)
P for trend		< 0.001		0.021
Sex				
Men	435	1.5 (1.4-1.7)	154	1.4 (1.2-1.6)
Women	174	2.6 (2.2-3.0)	60	2.5 (1.9-3.2)
P value		< 0.001		< 0.001
Complication*				
Yes	330	1.4 (1.3-1.6)	96	1.4 (1.2-1.7)
No	279	2.3 (2.0-2.5)	118	1.7 (1.4-2.0)
P value		<0.001		0.527
Calendar year of index hospitalization				
1965-1979	286	2.0 (1.8-2.2)	156	1.5 (1.3-1.8)
1980-2003	323	1.6 (1.4-1.7)	58	1.6 (1.2-2.1)
P value		< 0.001		0.722
Age at hospitalization				
<30	10	2.4 (1.2-4.4)	3	1.7 (0.4-5.1)
30-49	102	3.5 (2.9-4.3)	37	2.2 (1.5-3.0)
50-69	140	2.8 (2.4-3.3)	66	2.2 (1.7-2.9)
≥70	357	1.3 (1.2-1.5)	108	1.2 (1.0-1.5)
P for trend		< 0.001		<0.001

* Including bleeding and perforation.

Figure legend: Standardized Mortality Ratio for Suicide in Patients with Peptic Ulcer,
According to the Year of Follow-up.

Increased SMRs were seen in virtually all investigated substrata, but were more marked among women and patients who were hospitalized without complications of ulcer. The relative excess mortality tended to be higher among patients entering the cohort in the early part of the study period, and also among the middle aged and older patients (Table 3).

Table 3. Relative risk (RR) and their 95% confidence intervals (CIs) for suicide among hospitalized non-operated and operated patients with peptic ulcer estimated in a multivariate Poisson regression model

	Non-operated peptic ulcer		Surgery		Homogeneity test
	No. cases	RR (95%CI)	No. cases	RR (95%CI)	P value
Follow-up duration, years					<0.001
<1	163	4.9 (3.7-6.4)	20	1.7 (1.0-2.8)	
1-4	250	2.5 (2.0-3.3)	57	1.3 (0.9-1.9)	
5-9	113	1.5 (1.1-2.0)	67	1.6 (1.1-2.2)	
≥10	83	Reference	70	Reference	
P for trend		< 0.001		0.021	
Sex					0.454
Men	435	Reference	154	Reference	
Women	174	1.7 (1.4-2.0)	60	1.7 (1.3-2.4)	
P value		< 0.001		< 0.001	
Complication*					0.089
Yes	330	0.7 (0.6-0.8)	96	0.8 (0.6-1.4)	
No	279	Reference	118	Reference	
P value		<0.001		0.527	
Calendar year of index hospitalization					0.051
1965-1979	286	1.6 (1.3-1.9)	156	1.1 (0.8-1.4)	
1980-2003	323	Reference	58	Reference	
P value		< 0.001		0.722	
Age at hospitalization					0.022
<30	10	1.5 (0.8-2.8)	3	1.6 (0.5-5.1)	

30-49	102	2.6 (2.0-3.2)	37	1.9 (1.3-2.9)
50-69	140	2.1 (1.7-2.6)	66	1.9 (1.4-2.6)
≥70	357	Reference	108	Reference
P for trend		< 0.001		<0.001
Ulcer type				0.891
Only duodenal ulcer	228	Reference	91	Reference
Only gastric ulcer	299	1.3 (1.1-1.5)	77	1.9 (1.4-2.7)
Peptic ulcer [†]	82	1.2 (0.9-1.5)	46	1.9 (1.3-2.8)
P value		0.067		0.329

* Including bleeding and perforation.

[†] Individuals with a report of peptic ulcer with an unspecified site or both gastric ulcer and duodenal ulcer in their file

Surgical Treatment

Among the 28,112 peptic ulcer patients who underwent partial gastric resection or were vagotomized, 214 patients died due to suicide during an average of 16.3 years follow-up (SMR=1.6, 95% CI 1.4-1.8) (Table 2). In stratified analyses the excess risk was limited to the first decade of follow-up and more marked among women than men. Individuals who were 30 to 70 years of age at the time of surgical intervention had the highest risk (SMR=2.2). In multivariate Poisson regression models the relative risks for suicide among un-operated and operated patients with peptic ulcer was investigated. The suicide risk was higher the closer to time of first hospitalization in un-operated patients, while there was no such apparent trend for the operated patients (homogeneity test $p < 0.001$) (Table 3). Women had a higher suicide risk than men regardless of procedure. For un-operated patients with complications the suicide risk was significantly lower than for those without complications (RR=0.7, 95% CI=0.6-0.8), and the same tendency was observed for operated patients, although the risk estimate did not reach statistical significance (RR=0.8, 95% CI=0.6-1.4). Younger patients had a higher risk of suicide than older patients, for un-operated as well as for operated patients, but to some higher

extent for the un-operated ($p=0.022$). Hospitalized patients with gastric ulcer had a significantly increased risk of suicide compared to patients with duodenal ulcer, with no significant difference between un-operated and operated patients ($p=0.891$). In a separate multivariate model with adjustment for follow-up duration, sex, presence of complications at index hospitalization, calendar period of index hospitalization, ulcer type and age at hospitalization, we investigated the overall association of surgical treatment with suicide and found a relative risk of 0.8 (95% CI 0.7-1.0) (data not shown).

Duodenal ulcers and Gastric ulcer

In the analyses restricted to hospitalized un-operated patients with duodenal ulcer (61,548) or gastric ulcer (81,379), a higher than expected number of deaths due to suicide were found among both groups (SMR=1.5; 95% CI 1.3-1.7 for duodenal ulcer and SMR=2.0; 95% CI 1.8-2.2 for gastric ulcer). The pattern of risks were almost the same in stratified analyses of both ulcer groups i.e. higher relative risk among women and during the first five years of follow-up after diagnosis which were more marked in the first year with a fourfold risk (data not shown).

Discussion

In this retrospective cohort study with essentially complete and long-term follow-up we found a statistically significant 70 and 60% excess risk of death due to suicide among hospitalized unoperated patients with peptic ulcer and among those who underwent surgical treatment, respectively, compared to the sex, age and calendar-period matched general Swedish population. Women had a statistically significant 70% increase risk of death due to suicide compared to men. Moreover, the present analysis revealed that the high risk occurred among both duodenal ulcer and gastric ulcer patients. A 4-fold risk of suicide was found during the first year after diagnosis of ulcer.

Strengths of our study include the cohort design with almost complete and unbiased follow-up. To our knowledge, this is the largest study to date with 1,272,710 person year contribution of cohort members. The validity of information in Swedish inpatient registry about both diagnosis and procedure is convincing [19] therefore it was possible to compare operated patients with un-operated to elucidate the effect of surgery, while taking into account the effects of the underlying disease. Another point worth to highlight is that our cohort members were only hospitalized peptic ulcer patients so we had more precise disease classification compared to outpatient basis. Furthermore, we were able to restrict the analysis to “clean” cases of duodenal and gastric ulcer to find precise relative risk of suicide in each group. Another strength of the present study is that we excluded all the cancer cases from the analyses. It is well established that the incidence of some malignancies is extremely high, especially during the first year of follow-up, such as gastric cancer [20] and cancer cases have increased risk of suicide.[21, 22]

This study has also some limitations. Similar to all other register based studies, we did not have information about a number of possible confounding factors such as smoking,

socioeconomic status or other psychosocial factors known to influence suicide risk and may be more frequent among ulcer patients such as alcohol addiction, substance abuse or psychiatric disorder. It could be argued that surgical treatment has become less frequent in the last decades on behalf of pharmacological treatment. Less is known if early effective pharmacological intervention affects the suicide rate. However, our results indicate that the risk of suicide do not seem to be attributed to surgery. Finally, as peptic ulcer is a common disease in the general population, if the association exists also among non-hospitalized peptic ulcer patients the relative risks might have been biased to some extent towards the null, since our comparison group was the general Swedish population.

Reasons for the elevated risk of suicide in patients suffering from a somatic illness, such as peptic ulcer, include the psychosocial dimensions of the disease. Although the majority of peptic ulcers are due to *H. pylori* infection and/or NSAIDs use, there is some evidence supporting the association of this disease with stressful life events and anxiety [23-25] and most likely these etiological factors have an additive effect with stress. Moreover, in the non-*H. pylori* non-NSAIDs ulcers stress might be a key factor [26]. Psychological factors might play a significant role for the insight of symptoms and reporting the illness by patients with peptic ulcer.[27-29] It is reported that patients with functional dyspepsia who do not seek medical consultation differ from those who ask for medical intervention regarding their perceptual style, coping behaviours, and psychological symptoms.[30] Although the incidence of peptic ulcer disease in Western countries has decreased during past decades, about 6-15 percent of these populations are still affected.[31, 32] Moreover, despite decline in the number of patients with peptic ulcer undergo surgical treatment, there will still be a substantial proportion of the elderly population that previously underwent partial gastric resection [33-36] and the long-term outcome of these patients is important.

It is conceivable to assume that hospitalized ulcer patients have more complications, more comorbidity and in general have unhealthier lifestyle, compared to patients seen only in outpatient care. Thus, a higher risk of suicide in this group is not beyond expectations. A higher risk of suicide is reported among alcoholic patients with peptic ulcer comparing to alcoholics without peptic ulcer.[37] We believe the observed association between peptic ulcer disease and suicide is most likely explained by stress, other psychological problems, a comorbid psychiatric disorder and/or alcohol abuse. We observed that the shorter the duration after the diagnosis the higher the suicide rate which is consistent with this speculation. However, the lower risk of suicide after 1980, when H2-receptor antagonists and proton pump inhibitors were widely used, seeks an interpretation. This might be due to higher standards of health care system especially for patients with psychiatric disorders.

Most of previous studies investigated the risk of suicide among peptic ulcer patients after surgical treatment and generally found an excess risk.[8-17] Essentially, the results of the present study confirmed the excess risk of suicide among operated patients with peptic ulcer. However, an excess risk in both patients who underwent operation and those who were treated medically in hospital demonstrates that the increase in suicide risk is not attributed to surgery *per se*. Our finding on the difference in suicide risk between operated and non operated patients with peptic ulcer is in line with the study in Copenhagen,[18] the only study in which operated and unoperated peptic ulcer patients were compared and no significant difference was found in the risk of suicide.

Although incidence of suicide is higher among men than among women, we observed a higher risk of suicide among women who were hospitalized for peptic ulcer compared with men. However, it has been reported that the association between some disorders such as alcohol use disorders [38] and suicide was more pronounced in women than in men. We

revealed a statistically significant higher risk of suicide among hospitalized peptic ulcer patients essentially in all age strata. Quan et al [22] in a well designed case-control study investigated the association of some physical illnesses with suicide and found a not statistically significant odds ratio of 1.35 for suicide in elderly patient with peptic ulcer (95% CI 0.80-2.29). However, despite of large number of suicide cases they had too few cases and controls with peptic ulcer disease – 55 and 35 respectively – which might prohibit them to get a statistically significant result. Furthermore, their control group was individuals who died due to motor vehicle accident which may not be a good representative of general population.

In conclusion, hospitalized patients with peptic ulcer have an increased risk of death due to suicide which is more marked among women and during the first year after hospitalization. Both medically treated and those who underwent surgical treatment for peptic ulcer are at a higher risk of suicide. Even if there have been major changes in treatment regime for peptic ulcer and surgery is indicated only if complications develop or if the ulcer is unresponsive to medications, our findings urge special attention in caring for persons with ulcer diseases. The evaluation and management of depression and suicidal thoughts in patients with peptic ulcer in medical settings should be considered.

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