Overall mortality among patients surviving an episode of peptic ulcer bleeding

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Abstract

***Study objective*—The authors investigated whether patients who have survived an acute episode of peptic ulcer bleeding (PUB) have an excess long term all cause mortality compared with the general population free of PUB.**

***Design*—Follow up study of previously identified cohort of patients with a PUB episode and a general population cohort.**

***Setting*—The source population included all people aged 30 to 89 years, registered with general practitioners in the United Kingdom.**

***Patients*—All patients alive one month after the PUB episode constituted the cohort of PUB patients (n=978). A control group of 5000 people was randomly sampled from the source population. The same eligibility criteria as for patients with PUB were applied to the control series. Also, controls had to be free of PUB before start date.**

***Main results*—Relative risk of mortality among PUB patients was 2.1, 95%CI: 1.7, 2.6) compared with the general population. This increased mortality risk occurred mainly in the patients less than 60 years old. No difference was observed between men and women. The excess mortality was not only circumscribed to deaths attributable to recurrent gastrointestinal bleed, but also cardiovascular, cancer and other causes.**

***Conclusions*—People who have survived an acute episode of PUB have a reduced long term survival compared with the general population.This reduction was stronger among middle age patients than in the elderly.**

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Peptic ulcer disease is a major health problem and bleeding from peptic ulcer is a serious complication resulting most of the time in an admission to hospital with a case fatality rate of around 10%.[1–3] Several studies have reported factors predicting the short-term outcome of an upper gastrointestinal bleed (UGIB) such as age, comorbidity, ulcer site and size, most of which are not entirely independent of each other.[2 4 5] A few attempts have been made to study the long term survival experience after an acute episode of UGIB, although most of them are based on small series of cases.[4–7] Recently, a study with a larger series of elderly patients has been published.[8] Altogether these studies have suggested that patients with a peptic ulcer bleed have an excess long term mortality.

The main goal of this study was to estimate the overall mortality rate among patients who have survived an acute episode of peptic ulcer bleeding (PUB) and to compare their long term mortality with the one in the general population free of PUB. Also, we examined whether individual characteristics and clinical conditions predict long term survival.

Methods

DATA RESOURCE

The General Practice Research Database (GPRD) is a validated computerised health care data resource covering more than three million residents in the United Kingdom. Its characteristics and procedures have been described in detail in previous reports.[9–11] Briefly, it includes information on demographics, medical diagnoses, referrals to consultant and hospital, outpatient prescriptions, as well as laboratory results and a free comments section. The general practitioner records the clinical information of all patients under their care, and then sends the data anonymised to the Office of National Statistics (ONS).

STUDY POPULATION

The source population includes all people aged 30 to 89 years old registered with general practitioners who collaborate in the GPRD data resource. We used data from a previous epidemiological study that examined the short-term mortality from PUB.[12] There were 1020 patients identified as having been admitted to hospital and with a diagnosis of peptic ulcer bleeding involving the stomach and/or the duodenum (PUB) between 1 January 1991 and 31 March 1994. Patients presenting with haemorrhagic gastritis or duodenitis were not included. Patients with cancer, oesophageal varices, cirrhosis, Mallory-Weiss syndrome and intestinal vascular pathologies were excluded. All patients alive one month after the PUB episode constituted our cohort of PUB patients (n=978), and their study start date was 30 days after the PUB episode. A control group of 5000 people was randomly sampled from the source population. A random date within the study period was assigned to each of them to be used as start date and the same eligibility criteria as for patients with PUB were applied to the control series. Also, controls had to be free of PUB before start date. We then followed them up from start date until the earliest of death or end of the study period (31 December 1995).

All patients dying during the follow up were identified and their computerised patient

profiles were reviewed to ascertain the cause of death. We defined an upper gastrointestinal bleeding related death, as one occurring within 30 days of an UGIB episode subsequent to the study start date. Information on other factors related to survival was obtained from computerised files, and included age, sex, comorbidity, smoking status, body mass index (BMI), and units of alcohol consumed per week. This information was ascertained within a year of their start date, in a similar way for cases and controls. We categorised patients as abstainers or occasional drinkers, when they took less than two units per week, light drinkers from 2 to 15 units, and moderate to heavy drinkers when they took more than 16 units per week.[13] Comorbidity status before start date was obtained for the following diseases using the *International Classification of Disease*, ninth revision (ICD-9) codes: cardiovascular diseases (ICD-9 codes 410–417,428–429), cerebrovascular disease (ICD-9 codes 430–437), respiratory disease (ICD-9 codes 480–496), osteoarthritis (ICD-9 codes 715), rheumatoid arthritis (ICD-9 codes 711, 714), diabetes (ICD-9 code 250), and hypertension (ICD-9 codes 400–404).

MORTALITY ANALYSIS

We calculated estimates of mortality rate and 95% confidence intervals (CI) for the two study cohorts (PUB patients and general population). Patients alive at end of study period, those transferred to other practices or with their last practice visit before end of study were regarded as censored data at that date.

The Cox proportional hazards regression model was used to compute multivariate adjusted relative risk (RR) of mortality in the group of PUB patients compared with the general population. Included in the model were other risk factors such as age, sex, comorbidity, BMI, smoking and alcohol consumption. The appropriateness of proportionality assumption was examined graphically and statistically.[14] We evaluated whether the effect associated with PUB status was modified in various age strata, and between men and women. We examined the interaction by age of the association between PUB patients and mortality using as the reference group people from the general population, between 30 to 59 years of age.

Results

Table 1 presents the distribution of individual characteristics and other risk factors in the cohorts of PUB patients and general population. PUB patients were much older (mean age 64.4; SD =14.4) than the general population (mean age 52.7; SD=15.1). There was a greater proportion of men and patients with chronic diseases in the cohort of PUB patients than in the general population. When adjusting for age and sex, the association between most of the chronic diseases and PUB status decreased substantially. There were no major differences in the distribution of smoking habit among the two cohorts.

One hundred and fifty five deaths occurred in the PUB cohort during a mean follow up of 34 months (mortality rate 5.7 per 100 person years; 95% CI: 4.9, 6.7), and 193 deaths occurred in the general population cohort during the 39 months mean follow up period (mortality rate 1.2 per 100 person years; 95% CI: 1.1, 1.4), Crude relative risk associated with having a PUB episode was 4.7 (95% CI: 3.8, 5.9). Cardiovascular disease was the most frequent cause of death in both cohort groups (table 2). Fourteen of the deaths in the PUB cohort (9%) were related with an episode of UGIB, while only five (2.6%) were in the general population. The proportion of deaths related to UGIB in the PUB cohort was similar in both young and elderly patients. As shown in table 2, the greater excess relative risk of dying among PUB patients was not only circumscribed to UGIB related deaths, but also to cancer, and other causes.

PUB patients had a twofold increased risk of mortality (RR: 2.1, 95%CI: 1.7, 2.6) compared with the general population after adjusting for a number of risk factors (table 3). Age was the most powerful predictor of mortality during the four years of follow up. Cardiovascular, cerebrovascular disease and diabetes were also predictors of mortality. Among the life style variables, only smoking was associated with a significant increased risk of mortality. When we analysed the two cohorts separately, the effect of comorbidity and life style variables on

Table 1 Characteristics of cohorts of peptic ulcer bleeding (PUB) patients and general population

	PUB patients (n=978) (%)	*General population (n=5000) (%)*
Age		
30–59	326 (33.3)	3319 (66.4)
60–69	239 (24.4)	816 (16.3)
70–79	261 (26.7)	630 (12.6)
80–89	152 (15.5)	235 (4.7)
Sex		
Male	616 (63.0)	2380 (47.6)
Female	362 (37.0)	2620 (52.4)
Cardiovascular disease		
Yes	196 (20)	348 (7)
Cerebrovascular disease		
Yes	74 (7.6)	123 (2.5)
Diabetes		
Yes	53 (5.4)	135 (2.7)
Respiratory disease		
Yes	212 (21.7)	780 (15.6)
Hypertension		
Yes	222 (22.7)	606 (12.1)
Osteoarthritis		
Yes	263 (26.9)	685 (13.7)
Rheumatoid arthritis		
Yes	45 (4.6)	66 (1.3)
Body mass index (BMI)		
<25	300 (30.7)	1674 (33.5)
25–30	246 (25.2)	1306 (26.1)
>30	100 (10.2)	540 (10.8)
Unknown	332 (33.9)	1480 (26.6)
Smoking		
Non-smoker	465 (47.5)	2597 (51.9)
Smoker	238 (24.3)	1263 (25.3)
Ex-smoker	85 (8.7)	276 (5.5)
Unknown	190 (19.4)	864 (17.3)
Alcohol consumption		
None/occasional	241 (24.6)	1043 (20.9)
Light	140 (14.3)	702 (14.0)
Moderate/heavy	88 (9.0)	237 (4.7)
Unknown	509 (52.0)	3018 (60.4)
Censor status		
Death	155 (15.8)	193 (3.9)
Alive at end study	268 (27.4)	1956 (39.1)
Censored at last visit to GP	522 (53.4)	2718 (54.4)
Transferred out	33 (3.4)	133 (2.7)

Table 2 Distribution of causes of death in the cohort of PUB patients and general population and cause specific relative risk of mortality

	PUB patients (n=155) (%)	*General population (n=193) (%)*	*Relative risk* (95% CI)*
UGIB related†	14 (9.0)	5 (2.6)	9.6 (3.2,28.6)
Cardiovascular disease	47 (30.3)	72 (37.3)	1.7 (1.2,2.5)
Cerebrovascular disease	10 (6.5)	22 (11.4)	1.0 (0.5,2.2)
Respiratory disease	27 (17.4)	37 (19.2)	1.6 (1.0,2.7)
Cancer	20 (12.9)	19 (9.8)	3.3 (1.7,6.2)
Other causes‡	37 (23.9)	38 (19.7)	2.8 (1.7,4.5)

*RR associated with PUB status. Estimates are ajusted by age, sex, cardiovascular, cerebrovascular, diabetes and respiratory comorbidity, smoking, BMI and alcohol consumption. †Death within 30 days of an episode of upper gastrointestinal bleed. ‡Information on cause of death was not available in 20 (13%) of PUB cases and 26 (14%) persons in the general population cohort.

Table 3 Adjusted relative risk of death from all causes associated with PUB status and other variables

	Deaths (n=348)	*RR (95% CI)**
PUB status		
General population cohort	193	1
PUB patients cohort	155	2.1 (1.7,2.6)
Age at start date		
30–59	30	1
60–69	66	5.5 (3.6,8.6)
70–79	138	11.4 (7.5,17.2)
80–89	114	18.8 (12.1,29.1)
Sex		
Male	180	1
Female	168	0.8 (0.6,1.0)
Cardiovascular disease		
No	218	1
Yes	130	2.4 (1.9,3.1)
Cerebrovascular disease		
No	292	1
Yes	56	2.2 (1.6,2.9)
Diabetes		
No	309	1
Yes	39	2.2 (1.6,2.9)
Respiratory disease		
No	247	1
Yes	101	1.4 (1.1,1.7)
Smoking†		
Non-smoker	143	1
Smoker	65	1.4 (1.1,2.0)
Ex-smoker	20	0.9 (0.6,1.5)
Body mass index (BMI)†		
<25	79	1
25–30	62	0.9 (0.6,1.3)
>30	24	0.9 (0.6,1.5)
Alcohol consumption†		
None/occasional	91	1
Light	24	0.6 (0.4,1.0)
Moderate/heavy	10	0.7 (0.4,1.3)

*RR estimates are adjusted by all the variables present in the table using Cox regression models. †Numbers may not add up to the total (n=348) because of missing information, which was assigned to a separate category for the analysis.

Table 4 Adjusted relative risk of death among PUB patients compared with the general population stratified by age groups

Age	*RR (95% CI)**
30–59	7.0 (3.1, 15.9)
60–69	2.7 (1.6, 4.6)
70–79	1.8 (1.2, 2.5)
80–89	1.6 (1.1, 2.4)

*Adjusted by sex, cardiovascular, cerebrovascular, diabetes, respiratory diseases, smoking status, BMI and alcohol consumption.

mortality was of the same magnitude in the PUB and general population cohorts.

The increased mortality risk found among the PUB patients occurred mainly in the youngest age groups. As table 4 shows, the adjusted relative risk of dying among PUB patients aged 30 to 59 years was 7.0 (95%CI: 3.1, 15.9) compared with the general population, while in the oldest age group (80+) the RR was only 1.6 (95%CI: 1.1, 2.4).

In the general population cohort, the relative mortality risk in elderly (60+ years) was 15 times greater than in younger people of 30 to 59 years old (table 5). In the PUB cohort, the difference in mortality risk among the two age groups was smaller, approximately a threefold to fourfold increase. Indeed, young PUB patients were associated with a RR close to nine compared with the group of young general population, and elderly PUB patients presented a RR just over 30. No effect modification of mortality risk by sex was observed (data not shown).

Table 5 Adjusted relative risk of death associated with age and PUB status using a common reference group

	*RR (95% CI)**
General population cohort	
30–59 years†	1
60+ years	15.1 (8.9,25.4)
PUB patients cohort	
30–59 years	8.8 (4.3,18.1)
60+ years	30.7 (18.1,52.0)

*Adjusted by sex, cardiovascular, cerebrovascular, diabetes, respiratory diseases, smoking status, BMI and alcohol consumption. †Common reference group.

Discussion

People who have survived an acute episode of PUB have a reduced long term survival compared with the general population. Our study is the first one to compare survival experience between a large general population cohort and PUB patients. Our results show that patients after an episode of PUB carry a twofold greater risk of death compared with the general population. The increased long term excess mortality in PUB patients is noticeably higher at younger ages than at older ages. The impact of PUB on life expectancy is similar in men and women.

Previous studies on long term outcome of peptic ulcer haemorrage have generally included small series of patients,[4 5 7] however none evaluated a general population cohort, hampering a direct comparison with this study. The mortality risk reported by Hudson *et al* in a recent study among elderly after an hospital discharge for PUB was similar to the one observed in our study.[8] The authors reported a 50% survival probability at five year follow up among the PUB cases resulting in a RR of 1.7 (95%CI: 1.5, 2.1) compared with expected death rates in England and Wales. When we restricted our cohort of PUB patients to subjects 60 years of age or older, the survival at four years was 68% and the adjusted RR of mortality compared with general population was 1.9 (95%CI: 1.5, 2.4). Another study on late outcome of bleeding gastric ulcer patients also reported a significantly reduced survival rate (close to 60% at five years) compared with the one derived from national statistics.[5] An Australian study on survival after a perforated peptic ulcer reported survival rate at 1, 5, and 10 years to be 78%, 60% and 46% respectively. These figures were barely lower than the expected ones in the general population based on national life tables statistics.[6]

The cause of the reduced long term survival among patients who had suffered an episode of PUB compared with the general population remains unclear. PUB could be a marker of a general deterioration in health. Some studies have related this excess mortality to smoking and an excesive alcohol consumption among other factors.[5 8] Our results were adjusted for BMI, alcohol use and smoking. Several other studies have attributed the increased mortality observed among patients with a peptic ulcer

disease to comorbid conditions,[4 8 15] and especially in elderly. In our study, we recorded history for the following chronic diseases: cardiovascular diseases, cerebrovascular disease, chronic respiratory disease, diabetes, osteoarthritis, rheumatoid arthritis, and hypertension. All but the three later ones were associated with an increased all cause mortality. As well as for alcohol use, smoking and BMI, our estimate of mortality risk among PUB patients was adjusted for all comorbidities.

The excess mortality observed among PUB patients during the study period was not only circumscribed to deaths from a new episode of gastrointestinal bleeding, but also from cancer, and other causes. This has also been documented by other authors.[4–7] The twofold increased mortality risk in PUB patients compared with general population remained unchanged when we excluded the 19 deaths related to UGIB from the survival analysis. Of the 155 deaths among the PUB patients, only 14 occurred within 30 days of a new bleed episode. A recent study also reported few deaths resulting from recurrent ulcer complication.[8] There has been a decrease in recurrent ulcer complication rates (including rebleed, perforation and death) compared with earlier studies in the 1980s. Hudson *et al* suggest that this reduction in recurrent complications of PUB in recent years may be because of the introduction of acid suppressing drugs in the treatment and prophylaxis of ulcer disease. However, agreement is not complete regarding a causal explanation for this mentioned association.[16] We could not test this hypothesis and further research is needed to clarify this issue.

The group with the greatest mortality were elderly patients with PUB, although the long term prognostic importance of having had a PUB decreased substantially with age. Patients under the age of 60 years old carried a sevenfold increased risk of long term mortality compared with the general population with the same age and sex distribution. In persons older than 70 years, the mortality risk was less than twice greater than in the general population of same age and sex distribution. Competing risks could be a partial explanation for the observed decreased risk with increasing age. Indeed, older patients have more competing risk factors for death (presence of other comorbidity, treatment related complications, impaired activity and functions, etc) than younger persons.[17] Therefore, the effect of a new risk factor (in this case having had a PUB episode) on survival would be expected to be smaller among elderly patients than in younger populations.

KEY POINTS

- Long term survival experience after an episode of upper gastrointestinal bleed has not been well studied.
- Patients after a peptic ulcer bleed have a reduced long term survival compared with the general population, especially middle aged patients.

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