Digestion

Review

Systematic Review of the Epidemiology of Complicated Peptic Ulcer Disease: Incidence, Recurrence, Risk Factors and Mortality

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Key Words

Peptic ulcer disease · Hemorrhage · Perforation · Mortality · Recurrence · Epidemiology

Abstract

Background/Aims: The incidence of uncomplicated peptic ulcer has decreased in recent years. It is unclear what the impact of this has been on the epidemiology of peptic ulcer complications. This systematic review aimed to determine the incidence, recurrence and mortality of complicated peptic ulcer and the risk factors associated with these events. ***Methods:*** Systematic PubMed searches. ***Results:*** Overall, 93 studies were identified. Annual incidence estimates of peptic ulcer hemorrhage and perforation were 19.4–57.0 and 3.8–14 per 100,000 individuals, respectively. The average 7-day recurrence of hemorrhage was 13.9% (95% CI: 8.4–19.4), and the average long-term recurrence of perforation was 12.2% (95% CI: 2.5–21.9). Risk factors for peptic ulcer complications and their recurrence included nonsteroidal anti-inflammatory drug and/or acetylsalicylic acid use, *Helicobacter pylori* infection and ulcer size ≥1 cm. Proton pump inhibitor use reduced the risk of peptic ulcer hemorrhage. Average 30-day mortality was 8.6% (95% CI: 5.8–11.4) after hemorrhage and 23.5% (95% CI: 15.5–31.0) after perforation. Older age, comorbidity, shock and delayed treatment were associated with increased mortality. ***Conclusions:*** Complicated peptic ulcer remains a substantial healthcare problem which places patients at a high risk of recurrent complications and death.

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Introduction

The incidence and prevalence of uncomplicated peptic ulcer have decreased in recent years, largely because of the availability of treatment to eradicate *Helicobacter pylori* and the decreasing prevalence of *H. pylori* infection [1–4]. However, the use of acetylsalicylic acid (ASA) and other nonsteroidal anti-inflammatory drugs (NSAIDs) that are associated with adverse gastrointestinal events [5] is becoming more widespread [6]. It is therefore possible that there may have been no corresponding decrease in peptic ulcer complications such as upper gastrointestinal hemorrhage or perforation.

These complications of peptic ulcer disease have a substantial economic impact. The total cost of peptic ulcer disease in the USA, incorporating both direct costs and loss of work productivity, has been estimated to be USD

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5.65 billion per year [7]. It is likely that disease-related complications contribute substantially to these costs. A study in the Netherlands calculated the per person costs of hemorrhage, perforation, or a combination of both to be EUR 12,000, EUR 19,000 and EUR 26,000, respectively [8].

The aim of this review is to determine the incidence and recurrence rate of complications associated with peptic ulcer disease in recent years, and to identify risk factors associated with these complications. We also set out to evaluate the mortality associated with these complications and the risk factors associated with this mortality.

Materials and Methods

The PubMed database was searched for articles that reported the incidence, mortality and associated risk factors for peptic ulcer complications (fig. 1). These searches were performed using the following search string: (peptic ulcer AND obstruction) OR gastric obstruction OR gastric outlet obstruction OR peptic ulcer hemorrhage OR peptic ulcer bleed OR peptic ulcer bleeding OR upper GI bleed OR peptic ulcer perforation AND (incidence OR cohort study OR mortality OR prognosis OR prevalence OR cross-sectional study OR occurrence). We limited our searches to studies in humans that were published in the English literature between 1997 and 2007. Citation list searches were also used to identify additional references.

Studies were reviewed manually first by title and abstract and then by full manuscript. Manuscripts were excluded if their study topic was irrelevant, or if they did not report any relevant information. Studies were also excluded if they described uncomplicated peptic ulcer, variceal bleeding or other causes of upper gastrointestinal complications. Studies with fewer than 50 patients were excluded for feasibility reasons. Studies in which data collection started before 1990 were also excluded from our analysis of incidence because we aimed to analyze only recent data.

The recurrence rate and 30-day mortality data were synthesized by calculating averages weighted by sample size. The studies varied in their use of odds ratio (OR) and relative risk (RR), and adjusted these measures by different factors; therefore, these have been reported as published rather than synthesized.

Results

Search Results

Overall, 93 studies were identified that met the inclusion criteria of the review. Eleven studies reported the incidence of peptic ulcer complications (hemorrhage and perforation) in the general population, 18 reported risk factors for peptic ulcer complications, 30 reported recurrence rates of peptic ulcer complications, 20 reported risk
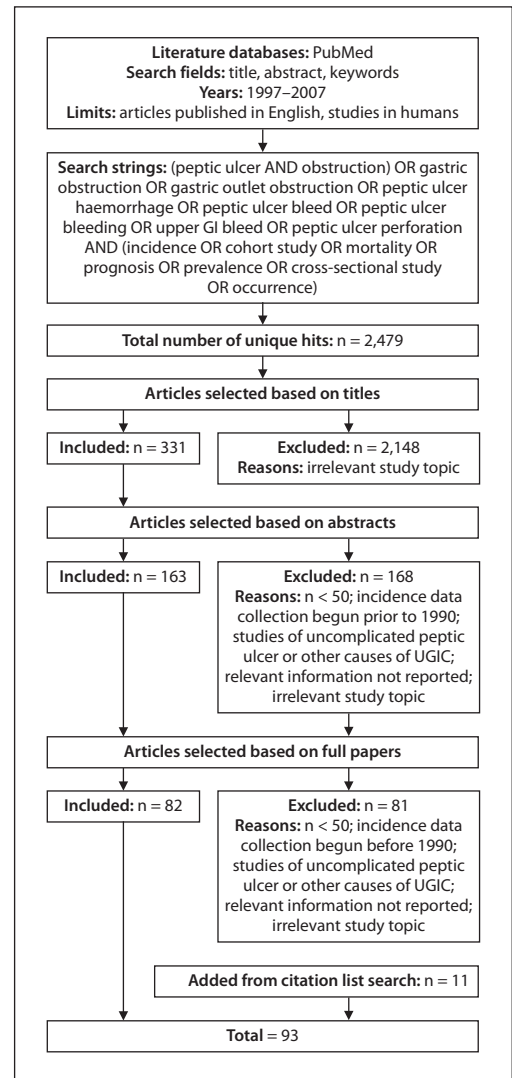

Fig. 1. Flow of prospective studies through the search and selection process. UGIC = Upper gastrointestinal complications.

factors for the recurrence of peptic ulcer complications, 51 reported mortality after peptic ulcer complications and 27 reported risk factors for mortality after peptic ulcer complications (a number of studies reported more than one of these factors).

Incidence of Peptic Ulcer Complications

Eleven studies, all of which were performed in Europe, reported the incidence of complications associated with peptic ulcer extrapolated to the general population (online suppl. table 1, for all online supplementary material see www.karger.com/doi/10.1159/000323958). Hemorrhage was much more common than perforation [3, 9–11]. The

reported annual incidence of hemorrhage in the general population ranged from 19.4 cases per 100,000 individuals [11] to 57.0 cases per 100,000 individuals [12]. A UK database study reported an annual incidence of 79 cases per 100,000 individuals [13]. However, this study was confined to individuals over 60 years of age, and thus cannot be extrapolated to the population as a whole.

Reported annual incidences of perforation ranged from 3.77 cases per 100,000 individuals [14] to 14 cases per 100,000 individuals [3].

No studies reporting the incidence of gastric obstruction met the inclusion criteria for this review.

Time Trends in Complicated Peptic Ulcer
The few studies that examined time trends in the incidence of peptic ulcer hemorrhage reported no significant change during the last decade. When comparing 1990–1994 with 1995–2000, Bardhan et al. [11] observed a decrease in the annual incidence of hemorrhage from 21.1 to 19.4 cases per 100,000 individuals in the UK. Van Leerdam et al. [15] reported a similar statistically nonsignificant decrease in the incidence of both gastric ulcer (GU) and duodenal ulcer (DU) hemorrhage between 1993 and 2000. However, Lassen et al. [3] reported a slight nonsignificant increase in the annual incidence of hemorrhage in Denmark from 55 cases per 100,000 in 1993 (95% CI: 49–62) to 57 cases per 100,000 in 2002 (95% CI: 51–64).

A study comparing the causes of upper gastrointestinal bleeding among patients admitted to a hospital in Greece between 1986 and 2001 found an increase in the rate of GU (12 vs. 19%; p = 0.005) and a concomitant decrease in the rate of DU (49 vs. 33%; p < 0.0001) [16].

Two studies noted a decrease in the annual incidence of perforation over time. In Denmark, Lassen et al. [3] reported a significant decrease from 14 cases per 100,000 individuals in 1993 (95% CI: 11–18) to 8 cases per 100,000 individuals in 2002 (95% CI: 6–11; p = 0.01). Bardhan et al. [11] found a decrease in annual incidence in the UK from 9.4 cases per 100,000 individuals during 1990–1994 to 7.9 cases per 100,000 individuals during 1995–2000. The significance of this was not tested.

A study of emergency admissions due to complications of peptic ulcer carried out in Poland between 1996 and 2001 found that the admissions due to hemorrhage and perforation remained relatively constant during this period [17]. There were 52 cases of hemorrhage in 1996, 31 in 1999 and 45 in 2001. There were 18 cases of perforation in 1996, 27 in 1997 and 18 in 2001.

Risk Factors for Complications in Peptic Ulcer Disease
Eighteen studies identified risk factors associated with the initial occurrence of peptic ulcer complications (online suppl. table 2). Most studies examined risk factors for hemorrhage, but two examined risk factors for perforation [18, 19], and one included patients with any complication [20]. Prior use of NSAIDs was the most commonly identified risk factor for peptic ulcer hemorrhage (10 studies) [21–30]. The largest increase in risk was found in a prospective study of 96 patients with hemorrhage and 106 control patients with a nonbleeding ulcer in Turkey, which found an OR associated with NSAID use of 33.9 (95% CI: 4.4–263.0) [26]. In a second prospective study of 227 patients with peptic ulcer hemorrhage in the Netherlands, the RR of bleeding associated with NSAID use was 8.4 (95% CI: 6.4–10.9) [22].

Lanas et al. [28] performed a case-control study using prospective case ascertainment and retrospective data collection to study 2,777 patients admitted to hospital in Spain because of peptic ulcer bleeding. NSAID use was associated with an increased risk of hemorrhage (RR: 5.3; 95% CI: 4.5–6.2). This increase in risk was dose-dependent; the RR was 6.8 (95% CI: 5.3–8.8) with high-dose and 4.0 (95% CI: 3.2–5.0) with medium- or low-dose NSAIDs. This study also found that current use of ASA increased the risk of hemorrhage (RR: 5.3; 95% CI: 4.5–6.3). This increase was also dose-dependent; the RR was 2.7 (95% CI: 2.0–3.6) with 100 mg/day and 7.5 (95% CI: 5.7–9.9) with 500 mg/day. With the concurrent use of ASA and NSAIDs, the risk was cumulative (RR: 12.7; 95% CI: 7.0–23.0).

A retrospective study of 176 patients in Spanish secondary care centers found NSAID use to be the only factor significantly associated with perforation (OR: 3.6; 95% CI: 1.3–10.0) [19].

Three further European studies examined the association between ASA use and peptic ulcer complications [21, 23, 31]. All three studies used a prospective case-control design, although two studies used patients with no peptic ulcer disease as controls [23, 31], while the third used individuals with uncomplicated peptic ulcer [21]. Labenz et al. [31] found that prior use of ASA (>100 mg/day) or NSAIDs increased the risk of hemorrhage from GU (OR: 8.1; 95% CI: 1.2–56.6; p = 0.034) but not from DU (OR: 1.3; 95% CI: 0.5–3.8). Santolaria et al. [23] found that use of high-dose ASA (>300 mg/day) was associated with an increased risk of both DU (OR: 8.0; 95% CI: 4.2–14.9) and GU (OR: 19.7; 95% CI: 8.6–45.4) bleeding. There was a significant association between low-dose ASA (<300 mg/day) use and hemorrhage from GU (OR: 3.1;

Lau/Sung/Hill/Henderson/Howden/Metz

95% CI: 1.4–6.6) but not with hemorrhage from DU (OR: 1.5; 95% CI: 0.6–3.9).

Three prospective studies reported an association between H. pylori infection and peptic ulcer bleeding [22, 23, 31]. The greatest increase in risk was found by Santolaria et al. [23], who reported a RR of 5.98 (95% CI: 2.9–12.3) in their study of 520 patients in secondary care in Spain. However, a fourth prospective study of 67 patients in Mexico found no association between H. pylori infection and hemorrhage [32].

Examination of the relationship between H. pylori infection, NSAID use and peptic ulcer complications revealed inconsistent results. In their prospective case-control study, Santolaria et al. [23] found that the combination of NSAID use and H. pylori infection was associated with a significantly reduced risk of GU hemorrhage (OR: 0.19; 95% CI: 0.04–0.88). A prospective study in Turkey found a similar reduction in the risk of bleeding peptic ulcer associated with NSAID use in H. pylori-infected individuals (OR: 0.09; 95% CI: 0.01–0.83) [26], but this study did not distinguish patients with GU and DU. By contrast, a prospective study in Singapore found that 79% of GU patients who were H. pylori-positive and using NSAIDs presented with bleeding, compared with 20% of those who were H. pylori-negative and not using NSAIDs [25].

Lanas et al. [33] also found H. pylori infection to be a risk factor for upper gastrointestinal bleeding in low-dose ASA users in Spain (OR: 4.69; 95% CI: 2.02–10.91). This increase in risk was found primarily in patients with DU (OR: 8.11; 95% CI: 2.02–26.93); however, there was also a trend towards an increased risk in patients with GU (OR: 2.74; 95% CI: 0.98–7.63).

In their prospective study of 119 patients with peptic ulcer in Taiwan, Hsu et al. [24] found patients with an ulcer size of ≥1 cm to be at greater risk of hemorrhage than patients with smaller ulcers (OR: 4.18; 95% CI: 1.62–10.81).

Prospective studies have found inconsistent results when examining a range of demographic and lifestyle factors. Only one Turkish study [26] found male sex to be a risk factor for hemorrhage (OR: 3.70; 95% CI: 1.65–8.29). In Singapore, Ng et al. [25] found that patients aged 65 years and older were at greater risk of peptic ulcer hemorrhage than younger patients (OR: 3.38; 95% CI: 1.93–5.92), while in Turkey, Okan et al. [26] found an association between older age and peptic ulcer hemorrhage in their univariate, but not in their multivariate, analysis. Hsu et al. [24] found no association between age and peptic ulcer hemorrhage in Taiwan.

A large population-based prospective cohort study in Denmark (n = 26,518) found that peptic ulcer hemorrhage was significantly associated with the consumption of 28–41 alcoholic drinks per week (RR: 2.8; 95% CI: 1.4–5.4) and the consumption of 42 or more alcoholic drinks per week (RR: 4.4; 95% CI: 2.3–8.3) [18]. However, two further prospective studies in Taiwan and Germany found no association between hemorrhage and alcohol consumption [21, 24]. Similar patterns were seen with tobacco use. The Danish study reported an association between smoking more than 15 g of tobacco per day (1 cigarette contains 1 g of tobacco on average) and the risk of perforated peptic ulcer [18], while the Taiwanese and German studies found no association between smoking and hemorrhage [21, 24].

A case-control study of 2,777 Spanish patients with peptic ulcer hemorrhage found that acid-suppressing drugs have a protective effect against hemorrhage [30]. This study reported that current use of proton pump inhibitors (PPIs; RR: 0.52; 95% CI: 0.38–0.70) or H_2-receptor antagonists (RR: 0.65; 95% CI: 0.50–0.85) was associated with a reduction in the risk of peptic ulcer hemorrhage. The indications for PPI or H_2-receptor antagonist use were not recorded. Current PPI use was associated with an even greater reduction in risk among users of ASA or NSAIDs (RR: 0.13; 95% CI: 0.04–0.19). This protective effect was apparent against both GU (RR: 0.21; 95% CI: 0.15–0.29) and DU (RR: 0.15; 95% CI: 0.10–0.21) hemorrhage. A second, smaller Spanish study (n = 89) also found a reduction in the risk of upper gastrointestinal hemorrhage to be associated with PPI use (OR: 0.02; 95% CI: 0.002–0.26) and, to a lesser extent, H_2-receptor antagonist use (OR: 0.16; 95% CI: 0.05–0.57) [33].

Recurrence of Peptic Ulcer Complications

Twenty-eight studies reported the recurrence of peptic ulcer hemorrhage (online suppl. table 3). Fourteen of these studies did not report the time frame over which this recurrence took place. Three studies reported a recurrence time of 7 days, four reported a recurrence time between 28 days and 1 month, and the remainder reported varying recurrence times of between 90 days and 76 months.

Hemorrhage recurrence rates ranged from 0% [34] to 31% [35]. In the USA, Gralnek et al. [35] observed rebleeding within 30 days in 31% of 155 patients surviving an initial peptic ulcer hemorrhage. Cheng et al. [36] found a 28-day recurrence rate of 37.5% in Taiwanese patients with one or more comorbidities, but only a 5% recurrence rate in patients without comorbidity. Vergara et al. [34] found no rebleeding in a median follow-up of 27 months

among 103 patients with bleeding DU in Spain who had undergone *H. pylori* eradication treatment. The average recurrence rate (28 studies) weighted by sample size was 10.0% (95% CI: 6.9–13.1). The average 7-day recurrence rate (3 studies) weighted by sample size was 13.9% (95% CI: 8.4–19.4), whereas the average 1-month recurrence rate (4 studies) weighted by sample size was 15.8% (95% CI: 11.0–20.5).

Two studies (performed in the USA and Hong Kong) that reported the rebleeding rate at both 7 and 30 days found that approximately 90% of recurrent bleeds occurred in the first 7 days [37, 38].

Five studies reported the recurrence of peptic ulcer perforation (online suppl. table 3). Only one study reported postoperative reperforation [39]. This Swedish study found an incidence of 0.4% among 237 patients who had surgical management of ulcer perforation. The remaining studies reported long-term recurrence of up to 20 years. The highest recurrence rate was 24.6% over 5 years in 130 individuals from Japan who were over 70 years of age [40]. The average long-term recurrence rate (4 studies) weighted by sample size was 12.1% (95% CI: 6.3–17.8).

Risk Factors for the Recurrence of Peptic Ulcer Disease Complications

Twenty studies identified risk factors for the development of further complications in patients with a history of peptic ulcer complications (online suppl. table 4). However, only one retrospective study looked specifically at risk factors for recurrent perforation [41]. One prospective study examined risk factors for the occurrence of any further complication after perforation [42]. The remaining studies assessed risk factors for rebleeding.

Three prospective studies (performed in the USA and the UK) reported that NSAID use increased the risk of rebleeding [43–45]. However, a fourth prospective study set in Sweden found that admission due to ASA or NSAID-associated ulcer bleeding was associated with a significantly lower risk of rebleeding (OR: 0.53; 95% CI: 0.28–0.95) [46], perhaps because ASA or NSAIDs were discontinued after the initial bleed.

Large ulcer size has also been identified as a risk factor for rebleeding. One study in Hong Kong reported an almost fivefold increase in risk associated with ulcers larger than 1 cm in diameter (OR: 4.69; 95% CI: 1.6–13.8) [47]. Two further prospective studies, in Korea and Italy, also found an association between ulcer size and rebleeding [48, 49].

Examination of the relationship between age and rebleeding has produced inconsistent results. In a pro-

spective study of 1,744 patients treated for peptic ulcer bleeding in China, patients over 80 years of age were found to have a significantly increased risk of rebleeding compared with patients younger than 80 years [50]. A second study in the USA found the age of 60 years or older to be associated with a significant increase in the risk of rebleeding (OR: 8.0; 95% CI: 2.8–22.8) [37]. However, four subsequent studies in Europe and Asia found no association between age and the risk of rebleeding [46, 49, 51, 52].

It is possible that there is a genetic component to peptic ulcer complications. In Korea, Kim et al. [53] observed a potential association between the 4G/4G genotype of the plasminogen activator inhibitor type 1 and the recurrence of peptic ulcer rebleeding. Other reported risk factors for rebleeding included anticoagulant use [37, 52], shock [46] and low blood pressure [48, 51].

A history of PPI use, however, appears to reduce the risk of rebleeding. A study using the UK General Practice Research Database found that current long-term use of omeprazole was associated with a reduction in the risk of recurrent bleeding (RR: 0.2; 95% CI: 0.02–1.0) [52]. This reduction in risk was also apparent when the analysis was restricted to those patients who were also taking NSAIDs (RR: 0.0; 95% CI: 0.0–1.0). Two other studies in Sweden and Taiwan also found that omeprazole use reduced the risk of rebleeding. Hasselgren et al. [46] found omeprazole use to be associated with a 64% decrease in the risk of rebleeding, while Lin et al. [54] found omeprazole use to be an independent factor for preventing rebleeding (OR: 7.68; 95% CI: 1.64–35.98).

Only one retrospective study in Australia (n = 147) examined risk factors for recurrent perforation [41]. This study found that the presence of malignancy (RR: 4.2; 95% CI: 1.4–13.0), use of immunosuppressants (RR: 6.3; 95% CI: 2.1–19.4), use of corticosteroids (RR: 4.4; 95% CI: 1.5–13.1), presence of shock (RR: 3.4; 95% CI: 1.1–10.6) and admission to intensive care (RR: 4.7; 95% CI: 1.6–14.4) were all associated with an increased risk of recurrent perforation.

Mortality after Peptic Ulcer Complications

Twenty-six studies reported the mortality associated with peptic ulcer hemorrhage (online suppl. table 5). The 30-day mortality after peptic ulcer hemorrhage ranged from 1.7% in Scotland [55] to 10.7% in Denmark [56] (fig. 2a), giving a sample size-weighted average (6 studies) mortality of 8.6% (95% CI: 5.8–11.4). Twenty-seven studies reported the mortality associated with peptic ulcer perforation (online suppl. table 6). The 30-day mortality

Fig. 2. Thirty-day mortality after peptic ulcer: hemorrhage (**a**) [37, 38, 46, 55, 56, 97] and perforation (**b**) [39, 57, 58, 113].
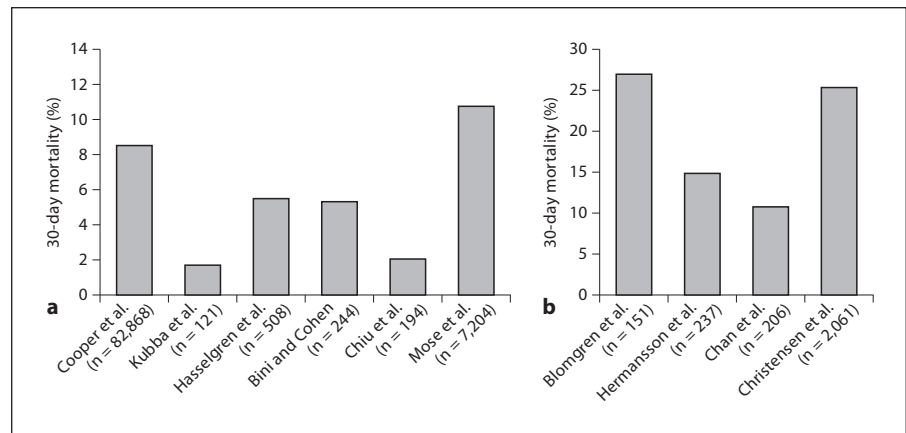
after peptic ulcer perforation ranged from 10.7% in Singapore [57] to 27.0% in Sweden [58] (fig. 2b), giving a sample size-weighted average (4 studies) mortality of 23.5% (95% CI: 15.5–31.0).

Risk Factors for Mortality in Peptic Ulcer Disease
The most widely reported risk factor for mortality was increasing age, reported by 14 studies (online suppl. tables 5 and 6) [12, 15, 39, 46, 51, 59–67]. In most cases, this increase in mortality was associated with age over 60 years. A UK database study (n = 1,020) examined the association between age and mortality in peptic ulcer patients in more detail [67]. Compared with patients aged 30–59 years, there was a trend towards an increased mortality risk in patients aged 60–69 years (OR: 2.8; 95% CI: 0.9–9.1). This association reached significance in patients aged 70–79 years (OR: 4.2; 95% CI: 1.4–12.7) and increased still further in patients aged 80–89 years (OR: 6.2; 95% CI: 2.0–19.1). A prospective secondary care-based study in the Netherlands (n = 379) found an increased risk of mortality in patients aged 58–71 years (OR: 2.47; 95% CI: 1.11–5.53) and patients aged 72–79 years (OR: 2.10; 95% CI: 1.02–3.97) when compared with patients aged 7–57 years [15]. However, this study found no significant increase in risk in patients aged 80–99 years (OR: 0.91; 95% CI: 0.52–1.57).

Increased age has also been shown to be associated with increased mortality after perforation [39, 59, 60, 64]. In a prospective study of 102 patients who underwent surgery for perforated peptic ulcer in Germany, patients aged over 65 years had a significantly worse prognosis than younger patients (p < 0.05) [59]. A retrospective Swedish study of 246 patients with perforation found that mortality after perforation was 0% in patients aged under

50 years, 6% in patients aged 50–70 years and 30% in patients aged over 70 years (p < 0.0001) [39].

The presence of comorbidity is also associated with an increase in mortality after hemorrhage and perforation. In their prospective study in Estonia, Soplepmann et al. [12] found that mortality was significantly increased in patients with peptic ulcer hemorrhage who also had major cardiac disease (p = 0.0001). A retrospective study in Denmark also found that, after ulcer bleeding, patients with diabetes had a higher 30-day mortality than patients without diabetes (mortality rate ratio: 1.40; 95% CI: 1.15–1.70); this was also apparent after ulcer perforation (mortality rate ratio: 1.51; 95% CI: 1.15–1.98) [68]. Other prospective studies in Europe [15, 69] and retrospective studies in Asia [57, 70] have also reported a link between unspecified comorbidities and increased mortality after peptic ulcer hemorrhage or perforation.

Hasselgren et al. [46] found that Swedish patients with a history of peptic ulcer disease had a lower mortality risk after hemorrhage than patients with no previous peptic ulcer disease (OR: 0.26; 95% CI: 0.09–0.74). García Rodríguez et al. [67] found similar results in the UK, in that patients with no previously recorded peptic ulcer disease had a higher mortality risk after hemorrhage than patients with previously recorded peptic ulcer disease (RR: 3.0; 95% CI: 1.2–7.1).

Shock is another major risk factor for increased mortality after both hemorrhage and perforation. In Portugal, Noguiera et al. [69] found that shock was associated with a sevenfold increase in mortality in patients with peptic ulcer hemorrhage (OR: 7.26; 95% CI: 1.53–34.52). Five further studies in Europe, Asia and Africa also reported increased mortality associated with shock in patients with hemorrhage [12] or perforation [57, 60–62, 71].

Table 1. Factors associated with the occurrence and recurrence of peptic ulcer complications and with mortality after peptic ulcer complications

Risk factor	Occurrence	Recurrence	Mortality
Male sex	✓		
Increasing age	✓	✓	✓
Serious comorbidity	✓	✓	✓
PAI-1 4G/4G genotype		✓	
Tertiary education	✓		
High alcohol use	✓		
Smoking	✓		
NSAID use	✓	✓	
ASA use	✓	✓	
High-dose	✓		
Low-dose	✓		
Anticoagulant use		✓	
Immunosuppressant use		✓	
Corticosteroid use		✓	✓
Shock		✓	✓
Low hemoglobin levels at initial presentation		✓	✓
Low blood pressure		✓	✓
Treatment delay			✓
H. pylori infection	✓	✓	
History of peptic ulcer	✓		
No history of peptic ulcer			✓
Large ulcer size (>1 cm)	✓	✓	
Forrest class I–II		✓	✓
Recurrence of complication			✓

However, three studies (performed in Sweden, Estonia and Taiwan) found no association between shock and mortality [64, 66, 70]. One retrospective study in Saudi Arabia found an increase in mortality after hemorrhage in patients with low systolic blood pressure (OR: 7.44; 95% CI: 1.01–54.55) [51].

Delayed treatment is also associated with an increase in the risk of mortality in patients with peptic ulcer perforation. In their prospective study in India, Rajesh et al. [60] found an increased risk of death if surgery for perforation was delayed for more than 24 h [RR: 1.75; p = 0.004 (this study did not report a confidence interval)]. In a retrospective study in Taiwan, Chou et al. [70] also reported an increased risk of death in patients whose surgery for perforation was delayed.

In a study of the UK General Practice Research Database, García Rodríguez et al. [67] found that current NSAID use was associated with a nonsignificant increase in mortality in patients with peptic ulcer hemorrhage (RR: 2.0; 95% CI: 1.0–3.8). Three further studies in Estonia, Portugal and Taiwan found no association between NSAID use and mortality in patients with peptic ulcer hemorrhage [12] or perforation [69, 70]. In Denmark, Mose et al. [56] found that individuals with peptic ulcer bleeding who were current users of low-dose ASA had an adjusted mortality ratio of 0.83 (95% CI: 0.68–1.01) when compared with those individuals who had never used low-dose ASA.

Discussion

The prevalence of peptic ulcer has fallen in recent years [1, 2, 72]. Despite this and recent advances in ulcer treatment, complications remain a substantial healthcare problem. This may be due to an increase in the use of ASA and NSAIDs and to the increasing number of elderly people in many countries.

Our review of recently published studies found annual incidences of ulcer hemorrhage and perforation of 19.4–57.0 and 3.8–14 cases per 100,000 individuals, respectively. These complications are more common with

increasing age [13, 73]. Several risk factors for peptic ulcer complications are also associated with an increase in recurrence and mortality (table 1). The widespread use of ASA and NSAIDs probably contributes substantially to the burden of complicated peptic ulcer [6]. Use of ASA (even at low doses) or NSAIDs was the most commonly reported risk factor for DU and GU hemorrhage in the studies that we identified [23, 28].

The effects have been inconsistent when the relationship between *H. pylori* infection, NSAID use and peptic ulcer complications have been assessed. Two studies found a reduced risk of GU complications among *H. pylori*-infected patients taking ASA or NSAIDs [23, 26]. This could be because *H. pylori* induces an increase in gastric mucosal prostaglandin E_2 levels that may partially reverse the mucosal toxicity of ASA or NSAIDs [74–76]. *H. pylori* infection may suppress gastric acid secretion in some individuals [77]. However, other studies have reported an increase in the risk of rebleeding when both *H. pylori* infection and ASA/NSAID use were present [25, 33]. A meta-analysis looking specifically at this issue found an additive effect between *H. pylori* infection and NSAID use [78]. When *H. pylori* infection and NSAID use were present together, the risk of bleeding was higher than when the risk factors were present on their own.

Risk factors for complicated peptic ulcer may be different in Asian and Western countries. Increasing age and large ulcer size were associated with a significant increase in the risk of complicated peptic ulcer only in Asia, and serious comorbidity was associated with a significant increase in risk only in Western countries. However, not all studies examined these risk factors, so this may simply reflect differences in study methodology.

Up to 31% of patients with peptic ulcer hemorrhage experience rebleeding within 30 days. Mortality is high among patients with complicated peptic ulcer, especially after perforation. Mortality increases with age, which probably reflects an increased prevalence of comorbidities [79].

Patients with no previous diagnosis of peptic ulcer may have a higher risk of dying than patients with a known history of ulcer disease [46, 67]. This may be because preventative measures are more likely to have been taken in patients with a known history of ulcer (e.g. *H. pylori* eradication, PPI therapy, avoidance of ASA and NSAIDs). Furthermore, these patients are perhaps more likely to seek treatment earlier.

Despite the fact that ASA and/or NSAID use are risk factors for recurrent bleeding and recurrent bleeding is a risk factor for death, mortality after peptic ulcer complications appears to be the same whether or not patients take ASA or NSAIDs. Again, this suggests that a large proportion of the deaths that occur after hemorrhage or perforation is due to comorbid disease rather than the event itself.

Patients with prior complicated ulcers should have their risk factors eliminated wherever possible. This includes the eradication of *H. pylori* and cessation of ASA or NSAID treatment whenever appropriate. Patients with *H. pylori*-negative idiopathic ulcers and those who require continuation of ASA or NSAID treatment should receive maintenance PPI therapy. Prompt management of perforated peptic ulcer should decrease mortality.

This is the first systematic review of the epidemiology of complicated peptic ulcer disease. A key strength of the review is the wide range of studies with varying methodologies that were identified, analysis of which is likely to give an accurate picture of clinical practice. However, one limitation was the lack of detail reported in some studies. Many of the studies failed to distinguish between GU and DU. This made it difficult to analyze any potential differences between the two in terms of risk factors and recurrence. We excluded studies that were published before 1997 and, from our examination of incidence, those that began data collection before 1990. This may have led to the underestimation of some results. However, it does ensure that we have focused on the most current picture possible. Most data on risk factors come from case-control studies in which the risk estimate is highly dependent on the group of individuals chosen for comparison. Incidence is based on extrapolating data from secondary care to the general population as a whole. This process could cause some cases to be missed, and individuals who died before they could be admitted to hospital would perhaps not be counted. This could again lead to underestimation of the results.

Another limitation is the lack of incidence data from outside Europe. In this respect, our findings may therefore not be fully representative of the situation in the rest of the world. However, the data on recurrence and mortality do come from a wide variety of locations in Asia and Africa as well as Western countries, which provides support for the validity of our results.

Our analysis suggests that there may be different risk factors for GU and DU complications. It would be interesting to carry out more studies to clarify this. It would also be useful to perform studies examining temporal trends in the incidence and prevalence of complicated peptic ulcer in order to gain a fuller understanding of the

epidemiology of this disease, and to help plan for future healthcare needs.

In conclusion, peptic ulcer complications remain a substantial healthcare problem, which is likely to be due to the widespread use of ASA and NSAIDs. This widespread use of NSAIDs may also increase the risk of recurrent complications. Mortality after peptic ulcer complications increases with age, which is probably caused by an age-related increase in comorbidity. However, mortality does not appear to be affected by the use of ASA or NSAIDs. Swift diagnosis and treatment of complicated peptic ulcer is likely to decrease mortality. Use of a PPI may help to reduce the risk of peptic ulcer complications, and may also reduce the risk of rebleeding in patients with a history of peptic ulcer hemorrhage.

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