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Diabetes increases morbidity and mortality rates in peptic ulcer bleeding: An updated systematic review and meta-analysis

UPPER GI

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Original Article

ABSTRACT

Background/Aims: To elucidate the relationship between diabetes mellitus (DM) and the risk of peptic ulcer complications.

Materials and Methods: Fixed effects and random effects models were used for calculating pooled relative risks (RRs) and/or odds ratios (ORs). Subgroup and sensitivity analyses were also performed.

Results: Nineteen high-quality investigations were included in the present study. In an analysis of morbidity rates in primary peptic ulcer bleeding (PUB), we calculated a summary OR of 1.433 (95% CI=1.280–1.604) in the random effects model comparing incidence in diabetes patients and in those without diabetes. In addition, a meta-analysis using the fixed effects model indicated a higher 30-day mortality in PUB in DM patients (OR=1.442, 95% CI=1.245–1.671) than in patients without DM. Further subgroup analyses demonstrated that DM patients in prospective cohort studies had an increased risk of 30-day mortality in PUB (RR=1.407, 95% CI=1.177–1.681). A similar result was obtained in a retrospective cohort subgroup, in which DM significantly increased mortality rates in PUB (OR=1.521, 95% CI=1.171–1.976).

Conclusion: We provided convincing evidence by a meta-analysis that DM was associated with a 43.3% increase in morbidity rates in PUB and a 44.2% increase in the risk of 30-day mortality in PUB patients.

Keywords: Diabetes, peptic ulcer disease, complication, systematic review, meta-analysis

INTRODUCTION

Complications in patients with peptic ulcer diseases (including bleeding, perforations, obstruction, and tumors) are the most common causes of emergency admissions to hospital (1-3). The morbidity rate in peptic ulcer bleeding (PUB) ranges from 20 to 60 per 100,000 population per year in the adult population (4-7), and its ensuing mortality accounts for 1.3–17.6% of cases (3,8-11). It has been reported that comorbidities in PUB patients increase morbidity or mortality rates in PUB, e.g., cardiac disease, respiratory illness, hepatic disorders, renal illness, and malignancy (12-14). Treatment of PUB is costly, but an appropriate approach to the management of PUB and its comorbidities would dramatically reduce the burden of medical costs (4,15). Similarly, other complications (e.g., peptic ulcer perforations and tumors) remain a substantial healthcare problem and are common medical emergencies (3). Furthermore, the worldwide prevalence of diabetes mellitus (DM) has more than doubled in the past 30 years (16-18). It is well known that DM damages the heart, blood vessels, kidneys, eyes, and nerves of patients (16,19-21). Diabetes complications include diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, cardiac insufficiency, renal failure, and liver cirrhosis. The main purpose of the control of DM is the prevention of complications and the inhibition of disease progression.

Currently, the associations between DM and complications in patients with peptic ulcers remain ambiguous. There have been controversies over whether DM increases morbidity and mortality rates in PUB. As far

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as the correlation between DM and the incidence of PUB is concerned, some studies have reported that DM increases the morbidity rate in PUB patients (7,22-26), but other investigations have shown that there is no significant connection between them (27). In addition, Leontiadis et al. (4) demonstrated that DM increases mortality rates in PUB patients after reviewing four reported studies (3,28-30). However, this topic has been discussed in two more articles (10,11), which might affect the size or significance of the true association. Therefore, the topic on the relationship between DM and mortality rates in PUB remains a point for discussion. Given the controversial nature of published articles and the insufficient statistical power of primary studies, our purpose was to detect associations among DM and morbidity and mortality rates in peptic ulcer complications, which may help further etiological research and clinical management of DM and morbidity and mortality rates in peptic ulcer complications.

MATERIALS AND METHODS

Search strategy

We attempted to follow the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines in reporting the present meta-analysis (31). Two investigators (XL and JL) searched MEDLINE via PubMed, Ovid Online, ISI Web of Science, Scopus, and the Cochrane Controlled Trials Register, Wiley, Clinical Evidence, and Clinical Key databases from their inception to September 2014, independently. We used the combined terms: any fields related to ("diabetes" or "DM") and ("peptic ulcer" or "gastric ulcer" or "gastrohelcosis" or "gastrohelcoma" or "duodenal ulcer"), restricted to English. All studies chosen for this meta-analysis were approved by the Ethics Committee of the relevant institutions, as reported in the selected articles. Moreover, a manual search of the reference lists of retrieved papers and review articles was performed.

Eligibility criteria and exclusion criteria

The eligibility criteria included all the following conditions: (a) evaluated the correlation between DM and the risk of peptic ulcers; (b) included patients without DM as controls; (c) complications resulted from peptic ulcer disease; (d) were of case-control, cross-sectional, or cohort design; and (e) the relative risk (RR) or odds ratio (OR) and their 95% confidence intervals (CIs) were reported in a cohort, case-control, or cross-sectional study (or data for calculating them). Studies were excluded if they included any of the following: (a) nonhuman populations, review articles, experimental studies, case reports, or studies that lacked controls; and (b), to avoid unusually high levels of blood sugar influencing the results of detection, we excluded studies regarding pancreatic diseases or pancreatic resection.

Data extraction

Data extraction was carried out in triplicate and independently by two authors (XL and FW). A third reviewer (XX) independently evaluated the study for consensus in the event of disagreement. We selected the most recent if there were multiple publications from the same study. A standard data collection form was used when we carried out data extraction. The following information was extracted from the included studies: journal title, author name, publication year, number of different genders, number of participants, mean age, study design (case-control, cross-sectional, or cohort), geographical region, time of follow-up, type of DM, diagnostic approaches to PUB, events (PUB morbidity rate, 30-day mortality in PUB, risk of peptic ulcer rebleeding, morbidity rate in peptic ulcer perforation, morbidity rate in upper gastrointestinal hemorrhage, and surgical risk of PUB), effects of diabetes (RR or OR and their 95% CI), and matched/adjusted factors. Most of the studies defined the primary endpoint of PUB as follows: the occurrence of an administrative record of PUB as the major diagnosis during hospitalization. Rebleeding was also diagnosed during hospitalization. Thirty-day mortality was defined as any death occurring within 30 days following the diagnosis of PUB. The primary endpoint was the 14-day rebleeding rate. Length of hospital stay, volume of blood transfusion, surgery, and mortality within 30 days were considered as secondary endpoints.

Statistical analysis

All statistical analyses were performed using STATA version 12.0 (StataCorp LP; College Station, Texas, USA). The combined values of OR/RR and their corresponding 95% CI were used to compare the association between the risk of PUB and DM. Because the risk of PUB in the general population is relatively low, the value of RR acquired from a prospective cohort study numerically approximates to that of OR. We evaluated heterogeneity using the Q and I^2 statistics. For the Q statistic, a value of p of less than 0.10 was considered statistically significant. A value of I^2>50% was considered a measure of severe heterogeneity. If heterogeneity was present, a random effects model (the DerSimonian–Laird method) would be used. Otherwise, a fixed effects model was adopted (the Mantel–Haenszel method). Publication bias was calculated by the Begg rank correlation test and Egger linear regression test. A two-tailed p value of less than 0.05 was assumed to indicate publication bias. Subgroup and sensitivity analyses were also performed to reveal the relationship between DM and the risk of PUB.

RESULTS

Study selection

The number of pooled search results found across the above-mentioned databases was 6,797 (Figure 1). We selected 19 high-quality studies, which consisted of 46,674 patients with diabetes and 159,630 patients without diabetes. Kawamura et al. reported that DM was more frequent in patients with peptic ulcers than in those without peptic ulcers (32). Seven investigations, which included 44,647 DM patients and 141,119 non-diabetic patients, concentrated on the relationship between the morbidity rate in PUB and DM. Six research studies, which focused on the correlation between DM and mortality rate in PUB, contained 1,468

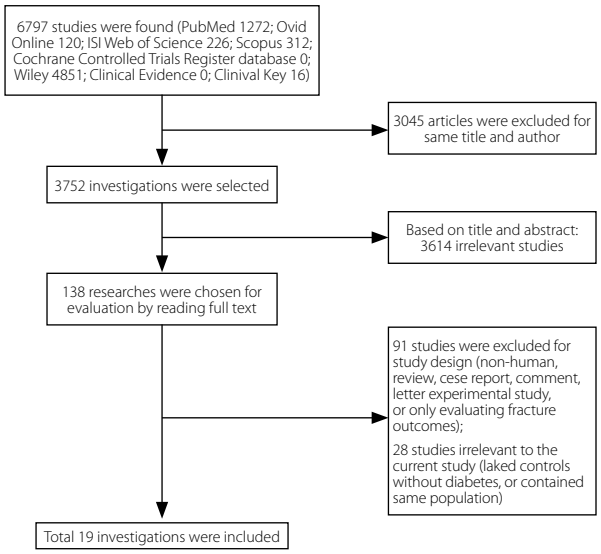

Figure 1. Selection process for inclusion of studies

diabetic patients and 13,838 controls without DM. A relationship between DM and rebleeding in PUB was reported in two articles (3,27). Three articles mentioned that perforated peptic ulcer was associated with DM (3,33,34). Three other related investigations were involved in the present study (6,35,36).

Characteristics of studies and patients

All the above articles included precise definitions of study populations, clarified diagnostic criteria for diabetes, explicit controls for DM, consecutive selection of cases, and identification of important confounders. Age- and gender-matching were performed in case-control and cohort studies, and patients without diabetes were randomly selected as a control group. Table 1 shows the characteristics of the study population and the effects of DM on the risk of PUB. The factors of study, location (country), type of diabetes, study design, time of follow-up, events (morbidity rate in PUB, 30-day mortality in PUB, morbidity rate in peptic ulcer rebleeding, morbidity rate in peptic ulcer perforation, length of hospital stay regarding peptic ulcer perforation, 30-day mortality in peptic ulcer perforation, morbidity rate in upper gastrointestinal hemorrhage, mortality rate in upper gastrointestinal hemorrhage, and surgical risk of PUB), matched or adjusted factors, and effects of diabetes (pooled OR/RR and 95% CI) are presented. Most of the above-mentioned studies adjusted for factors such as age, gender, dyspepsia in the past year, heart failure, cardiac insufficiency, renal failure, and liver cirrhosis, etc. (Table 1).

Evaluation of subgroup analyses of PUB morbidity rate in DM patients and publication bias

In analyses of morbidity rates in primary PUB in seven studies (7,22-27), we calculated that the summary OR was 1.433 (95% CI=1.280–1.604) in the random effects model, which compared the incidence in patients with diabetes and without diabetes. There was slightly significant heterogeneity among the studies

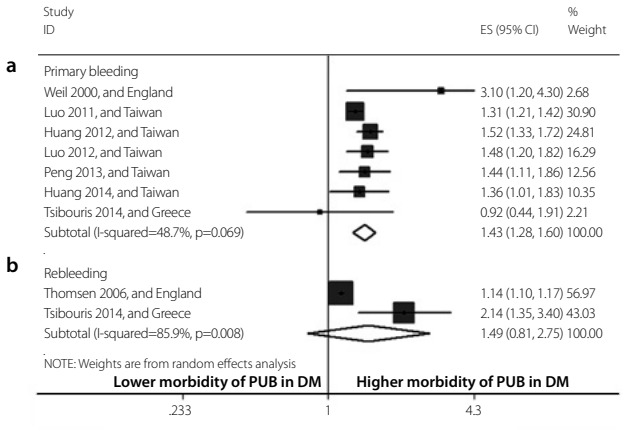

Figure 2. a, b. Forest plot of the association between DM and morbidity rate in PUB. Primary bleeding (a), rebleeding (b)

(Q=11.69, p=0.069, I^2=48.7%; Figure 2a). The Begg rank correlation test (p=1.000) and Egger linear regression test (p=0.351) did not suggest any publication bias. Moreover, we found a combined OR of 1.495 (95% CI=0.811–2.754; test for heterogeneity Q=7.11, p=0.008, I^2=85.9%; Figure 2b) in calculating the prevalence of rebleeding in PUB, which suggests that DM would result in a 49.5% increase in the risk of rebleeding in PUB; nevertheless, the combined effect was only borderline.

Sensitivity and subgroup analyses of incident primary bleeding in peptic ulcer in DM patients

In research into incident primary bleeding in peptic ulcer, we took into account the same authors and potential repetitions of different investigations (22-25). We deleted studies with a shorter duration of follow-up via sensitivity analyses. Exclusion of the investigation by Luo et al. (23) or that by Huang et al. (25) in the random effects model made little difference to the overall pooled effect size (OR=1.429, 95% CI=1.248–1.637 and OR=1.447, 95% CI=1.271–1.646, respectively). When we removed both of the above two studies simultaneously (23,25), the overall OR for the effect of DM on the incidence of PUB was 1.447 (95% CI=1.232–1.700) in the random effects model.

Furthermore, in stratified analyses according to the factor of location in the fixed effects model, we demonstrated that DM patients in other countries, with the exception of England (7,22-25,27), had an increased risk of morbidity rate in PUB compared with patients without diabetes (OR=1.375, 95% CI=1.294–1.462; test for heterogeneity p=0.356, I^2=9.3%; Figure 3a). A pooled effect measure for the England subgroup could not be calculated because only one study (26) was involved in this category (Figure 3a). Therefore, the sources of heterogeneity came from different countries. Although both subgroups showed a higher incidence of PUB in DM patients compared with patients without diabetes, patients in England exhibited a more pronounced effect than in other countries. In further subgroup analyses on the basis of study design in the random effects model, we found that there was an evident correla-

Table 1. Characteristics of the study populations and the effects of covariates on peptic ulcer diseases in DM patients

Study and country	Type of diabetes	Study design	Time of follow-up (year.month)	Number of participants		Events	on PUB OR/RR (95% CI)	Effects of DM Matched/adjusted factors
				Patients with DM	Patients without DM			
Weil et al. (26) England	Type I or II	Retrospective case-control	1986.04–1991.01	96	2014	PUB morbidity	OR=3.1 (1.2–4.3)	Age, gender, oral corticosteroids, use of warfarin, previous peptic ulcer, dyspepsia in past year, heart failure, and current smoking
Luo et al. (23) Taiwan	Type I or II	Retrospective cohort	1995–2006	22711	49797	PUB morbidity	OR=1.31 (1.21–1.42)	Age, sex, hypertension, diabetes, coronary artery disease, heart failure, cirrhosis, and drug use
Huang et al. (22) Taiwan	Type I or II	Retrospective cohort	1996–2007	8493	54383	PUB morbidity	RR=1.52 (1.33–1.72)	Age, gender, presence of comorbidities, history of peptic ulcer disease, and use of ulcerogenic medication
Luo et al. (24) Taiwan	Type I or II	Retrospective case-control	1995–2002	4122	15697	PUB morbidity	OR=1.48 (1.20–1.82)	Age, gender, presence of comorbidities, history of peptic ulcer disease, economic status, area inhabited, and drug use
Peng et al. (7) Taiwan	Type II	Retrospective cohort	1995–2002	5699	11226	PUB morbidity	OR=1.44 (1.11–1.86)	Age, sex, presence of comorbidities, and use of ulcerogenic medication
Huang et al. (25) Taiwan	Type I or II	Retrospective cohort	1996–2006	3503	7905	PUB morbidity	OR=1.36 (1.01–1.83)	Age, gender, presence of comorbidities, and use of ulcerogenic medication
Tsibouris et al. (27) Greece	Type I or II	Prospective case-control	2008.01–2009.12	23	97	PUB morbidity Morbidity of peptic ulcer rebleeding	RR=0.917 (0.439–1.913) RR=2.14 (1.35–3.40)	Age, gender, smoking, and alcohol consumption
Branicki et al. (28) Hong Kong	Type I or II	Prospective cohort	1985.09–1987.11	53	782	30-day mortality in PUB	RR=1.403 (0.824–2.389)	Age, gender, dates of hospital stay, preexisting medical illness, surgical history, malignant disease, past history of onset of dyspepsia, recent drug ingestion, previous antiulcer therapy, smoking, and drinking habits
Hasselgren et al. (29) Sweden	Type I or II	Retrospective cohort	1989.01–1993.12	48	628	30-day mortality in PUB	OR=1.06 (0.34–3.38)	Age, gender, Forrest class, presence of shock on admission, heart disease, drug use, previous history of ulcer, and site of ulcer
Nousbaum et al. (30) France	Type I or II	Prospective cohort	1996 (length >6 months)	68	725	30-day mortality in PUB	RR=1.52 (0.72–3.19)	Age, gender, presence of comorbidities, history of peptic ulcer disease, and drug use
de la Fuente et al. (11) U.S.	Type I or II	Retrospective cohort	1991.01–2001.12	134	773	30-day mortality in PUB	OR=1.443 (1.071–1.924)	Age, resection procedure, American Society of Anesthesiologists class, and presence of comorbidities
Thomsen et al. (3) England	Type I or II	Prospective cohort	1991–2003	731	6501	30-day mortality in PUB Morbidity of peptic ulcer rebleeding 30-day mortality in peptic ulcer perforation	RR=1.40 (1.15–1.70) RR=1.14 (1.10–1.17) RR=1.51 (1.15–1.98)	Age, gender, Charlson index score, previous uncomplicated peptic ulcer disease, use of antiulcer drugs, and drug use
Murata et al. (10) Japan	Type I or II	Retrospective cohort	2008.04–2008.12	434	4429	30-day mortality in PUB	OR=2.285 (1.161–4.497)	Age, gender, causes of PUB, chronic comorbid conditions, hospital type, ambulance transportation, drug use, and previous antiulcer therapy
Kim et al. (33) Korea	Type I or II	Retrospective cohort	2005.01–2010.10	14	128	Morbidity in peptic ulcer perforation	OR=2.6 (0.94–7.69)	Age, gender, American Society of Anesthesiologists score, preoperative shock, surgical approach method, operating time, pulmonary disease, and hypertension

Table 1. Characteristics of the study populations and the effects of covariates on peptic ulcer diseases in DM patients *(continued)*

Study and country	Type of diabetes	Study design	Time of follow-up (year.month)	Number of participants: Patients with DM	Number of participants: Patients without DM	Events	Effects of DM on PUB OR/RR (95% CI)	Matched/adjusted factors
Taiwan	Type I or II	Retrospective cohort	1995.01–2006.12	17	178	Length of hospital stay regarding peptic ulcer perforation	OR=5.883 (5.114–6.653)	——
Kawamura et al. (32) Japan	Type I or II	Retrospective cohort	2010.01–2010.12	41	185	Morbidity in peptic ulcer	OR=3.793 (1.239–11.612)	——
Faigel et al. (36) U.S.	Type I or II	Retrospective cohort	1992.01–1994.06	193	91	Morbidity in upper gastrointestinal hemorrhage	OR=0.30 (0.07–1.32)	——
Rockall et al. (6) England	Type I or II	Retrospective cohort	1993 (length= 4 months)	277	3908	Mortality in upper gastrointestinal hemorrhage	OR=5.07 (3.53–7.28)	——
Parreira et al. (35) Portugal	Type I or II	Retrospective cohort	1998–2001	17	183	Surgical risk of PUB	OR=4.618 (1.794–11.887)	Age, gender, causes of PUB, and drug use

PUB: peptic ulcer bleeding; DM: diabetes mellitus; OR: odds ratio; RR: relative risk; 95% CI: 95% confidence interval

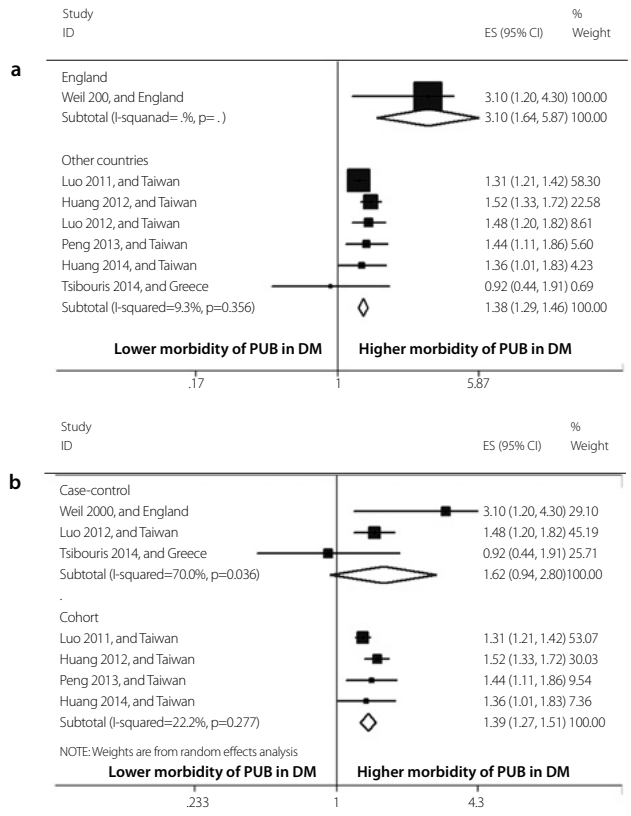

Figure 3. a, b. Subgroup analyses of DM and morbidity rate in primary bleeding in patients with peptic ulcers. Location (a), study design (b)

tion in the subgroup of cohort studies (7,22,24,25) (OR=1.386, 95% CI=1.275–1.507; test for heterogeneity Q=3.86, p=0.277, I^2=22.2%; Figure 3b), but the effect of DM on the subgroup of case-control studies (23,26,27) was only on the borderline of statistical significance (OR=1.623, 95% CI=0.941–2.799; test for heterogeneity Q=6.66, p=0.036, I^2=70.0%; Figure 3b).

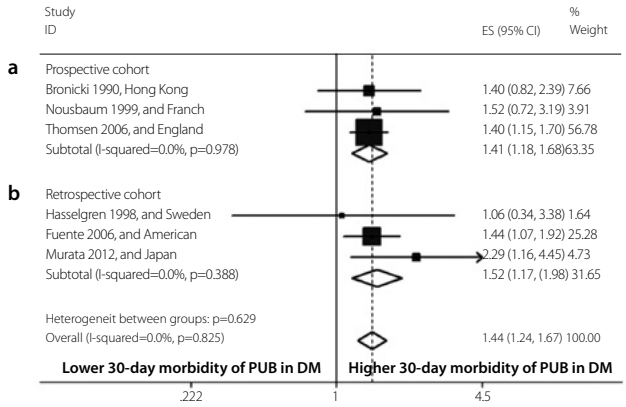

Figure 4. a, b. Combined and subgroup analyses of the effect of DM on 30-day mortality in PUB. Prospective cohort studies (a), retrospective cohort studies (b)

Assessment of effect of DM on 30-day mortality in PUB and publication bias

Six articles focused on the connection between DM and mortality rate in PUB (3,10,11,28-30). Summary analyses in the fixed effects model demonstrated that the rate of 30-day mortality in PUB in DM patients was higher (OR=1.442, 95% CI=1.245–1.671) than in controls without diabetes, with no significant heterogeneity between studies (Q=2.17, p=0.825, I^2=0%; Figure 4). We found no publication bias in this meta-analysis from the Begg rank correlation test (p=1.000) and Egger linear regression test (p=0.580). When we performed stratified analyses by the factor of study design, we found that DM patients in the subgroup of prospective cohort studies (3,28,30) had an increased risk of 30-day mortality in PUB compared with patients without diabetes (RR=1.407, 95% CI=1.177–1.681; test for heterogeneity p=0.978, I^2=0%; Figure 4a). A similar result was ob-

tained in the retrospective cohort subgroup (10,11,29), in which DM significantly increased 30-day mortality in PUB (OR=1.521, 95% CI=1.171–1.976; test for heterogeneity p=0.388, I^2=0%; Figure 4b).

Review of the association between DM and perforated peptic ulcer

Kim et al. (33) reported that the OR of incident perforated peptic ulcer for an increase in DM was 2.6 (95% CI=0.94–7.69). Moreover, DM was associated with a greater length of hospital stay in patients who survived surgery for perforated peptic ulcer (OR=5.883, 95% CI=5.114–6.653) (34). Furthermore, results from a prospective cohort study indicated that the RR for 30-day mortality among diabetic patients compared with that for patients without DM was 1.40 (95% CI=1.15–1.70) (3).

Other related effects of DM on peptic ulcer disease

Investigations indicated that DM increased the surgical risk of PUB by a factor of 4.618 (95% CI=1.794–11.887) (35). Faigel et al. (36) found that there was a trend toward less new-onset diabetes in the group with upper gastrointestinal hemorrhage (p<0.08), but PUB patients had a longer duration of diabetes (p<0.02). Further research showed that DM increased morbidity rate in upper gastrointestinal hemorrhage significantly (OR=3.793, 95% CI=1.239–11.612) (6).

DISCUSSION

Our research provided insights into the reported association between DM and peptic ulcer complications. The results of the meta-analysis confirmed that in general, patients with DM had a morbidity rate in PUB that was approximately 1.433 times higher compared with patients without diabetes. Subgroup and sensitivity analyses further verified these presumptions. When we performed stratified analyses by location, DM patients in countries other than England had a 1.375-fold increase in the incidence of PUB than controls without DM. Furthermore, increases in the prevalence of PUB in diabetic patients in case-control studies accounted for 62.3% and DM patients in the subgroup of cohort investigations amounted to 38.6% of the increase in the prevalence of PUB. Moreover, there was a 1.442-fold increase in 30-day mortality in PUB in DM patients compared with patients without diabetes. In summary, we provided robust evidence that DM increased morbidity and mortality rates in PUB.

The current study has its own strengths. Firstly, our meta-analysis of the associations between DM and the risk of PUB contained only multivariate adjusted/matched OR and RR. The magnitude of the correlation greatly increased when studies were adjusted/matched for potential confounding factors, e.g., age, gender, dates of hospital stay, preexisting medical illness, surgical history, malignant disease, past history and age of onset of dyspepsia, recent drug ingestion, previous antiulcer therapy, smoking, and drinking habits, etc. Secondly, to the best of our knowledge this systematic review and meta-analysis is the first and the most comprehensive to estimate the association between DM and the incidence of PUB. Thirdly, a strength of the present study was its all-inclusive scope with a wide range of populations, which tended to be less susceptible to selection bias.

Although our study is the largest systematic effort to quantitatively synthesize data concerning peptic ulcer complications in DM patients, this meta-analysis is undermined somewhat by the inherent shortcomings of observational studies. First, there were insufficient data regarding the association between DM and peptic ulcer complications other than PUB. Moreover, most of the included studies adjusted for a large range of potential confounders; in the present study, however, there could still be some unmeasured confounding factors, which might mask the true association. Furthermore, most studies could not distinguish between type I and type II DM and could not discern the specific site of peptic ulcers. Finally, because the study design of most investigations was retrospective, more prospective and randomized studies are needed to further confirm our findings.

The etiology of the effect of DM on peptic ulcer complications remains mysterious. We tried to review the plausible causes of the effect of DM on the risk of PUB. Several studies indicated that in-hospital blood glucose levels are in proportion to hemorrhage from peptic lesions (36-40), which hinted that glycemic control helps counteract the increased risk of PUB caused by DM. Further studies have shown that diabetic angiopathy could damage mucosal integrity and lead to more severe ulcers, which made it more difficult to halt hemorrhage in patients with peptic ulcers (24,26). Moreover, some studies have demonstrated that DM affects the associations between *Helicobacter pylori* infection and peptic lesions (41-44). Furthermore, animal studies have shown that diabetes increases the release of pro-inflammatory cytokines and attenuates angiogenesis, which results in impaired ulcer healing (45-47). Therefore, more well-designed, long-term studies regarding this topic are needed to further confirm our findings.

In conclusion, the present study provided convincing evidence by meta-analysis that DM was associated with a 43.3% increase in the incidence of PUB and a 44.2% increase in the risk of 30-day mortality in PUB patients. Additional research with prospective and randomized cohort studies is needed to be able to detect whether glycemic control in DM patients could reverse the risk of peptic ulcer complications.

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Informed Consent: N/A.

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Author contributions: Concept - F.W., X.L.; Design - X.L.; Supervision - X.L.; Resource - F.W., X.L.; Materials - F.W., X.L.; Data Collection and/

or Processing - F.W., X.L.; Analysis and/or Interpretation - F.W., X.L.; Literature Search - F.W., X.L.; Writing - F.W., X.L.; Critical Reviews - F.W., X.L. *FW and XL contributed equally to this paper.

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