ECRONICON OPEN ACCESS

EC MICROBIOLOGY
Review Article

Prevalence of Re-bleeding after Initial Endoscopic Management in Peptic Ulcer: A Systematic Review and Meta-Analysis

Ashwaq Hamed Alsahafi[1]*, Waleed Eid Alraddadi[2], Ziyad Waleed Iskander[3], Abdulrahman Mossa Ghanem[4], Samah Butayhan Alatawi[5], Abdulaziz Khalid Maddah[2], Duaa Akram Rajh[6], Ahmed Abdullah Almulhim[7], Ali Ahmed Almutairi[8], Budur Obaidallah Alfaedi[5], Hassan Majed Sagga[9] and Safa MohammedSaeed Nassar[2]

[1]*Department of Internal Medicine, East Jeddah Hospital, Jeddah, Saudi Arabia*

[2]*Department of Internal Medicine, Al Noor Specialist Hospital, Mecca, Saudi Arabia*

[3]*Department of Internal Medicine, Al Laith General Hospital, Al Laith, Saudi Arabia*

[4]*College of Medicine, King Khalid University, Abha, Saudi Arabia*

[5]*College of Medicine, Jordan University of Science and Technology, Irbid, Jordan*

[6]*College of Medicine, Almaarefa University, Riyadh, Saudi Arabia*

[7]*College of Medicine, King Faisal University, Al Hofuf, Saudi Arabia*

[8]*College of Medicine, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia*

[9]*College of Medicine, University of Lublin, Lublin, Poland*

***Corresponding Author**: Ashwaq Hamed Alsahafi, Department of Internal Medicine, East Jeddah Hospital, Jeddah, Saudi Arabia.

Received: December 16, 2019; **Published:** December 31, 2019

Abstract

Peptic ulcer disease has been the most common source of bleeding diagnosed among patients admitted to a hospital for acute upper gastrointestinal bleeding. Patients presenting with a perforated peptic ulcer is another severe complication of peptic ulcer requiring hospitalization. For that, we performed an extensive literature search in 11 databases for all relevant original publications assessing the risk of re-bleeding following endoscopic hemostasis of bleeding peptic ulcer during the last ten years. There were no restrictions on study design, country or language. After extensive screening, three independent reviewers evaluated the risk of bias in included studies. For observational studies, methodological quality assessment was done using National Institutes of Health (NIH) quality assessment tool, while Cochran's tool was used for randomized controlled trials. R software version 3.6.1 was used to conduct the analyses. Six studies with 3043 patients were included in the analysis. The overall re-bleeding was 8.94% with 95% CI = 5.46 to 14.64; nevertheless, a significant heterogeneity among results I^2 = 92% and P-value < 0.001 was detected. On sensitivity analysis with removal, the heterogonous studies, the heterogeneity has disappeared (I^2 = 4% and P-value = 0.372) and the prevalence rate changed to be 6.84% with 95% CI = 5.97 to 7.85. The endoscopic management of bleeding peptic ulcers sounds to be a very effective method with low re-bleeding rates.

Keywords: *Peptic Ulcer; Re-Bleeding; Endoscopy; Hemostasis*

Introduction

A peptic ulcer usually defined as a mucosal break in the stomach or duodenum and has a diameter of more than 3 mm (some argue for a 5 mm) and a noticeable width [1]. Histologically, the concept of an ulcer is a breach through the mucosae muscularis [2]. If it splits only through the lamina propria mucosae, or if it is wider than 3-5 mm, it is considered erosion instead [2]. Peptic ulcer risks include leakage, perforation, entry (to another organ) and obstruction (from strictures) [3]. Bleeding from peptic ulcer occurs when an underlying vessel

is eroded by an ulcer [4]. A peptic ulcer's perforation or invasion means the entire stomach and duodenum wall is damaged [4]. Fibrotic strictures, complicated by an obstruction, would mainly affect the pyloric region; caused by chronic inflammation and ulceration [5].

Over recent years, the average prevalence of uncomplicated peptic ulcer has declined [6]. An annual incidence of 0.10 - 0.19 percent could be expected to decrease in the upcoming years [7]. A corresponding decline in the incidence of complicated peptic ulcer disease, as well as mortality, but these outcomes do not appear to be decreasing at the same rate [7]. There are contradictory results in publications on the incidence and mortality of complicated peptic ulcer diseases and there are significant variations among the various countries [8]. Bleeding is the most common complication in peptic ulcers, followed by perforation [9]. In a 2011 longitudinal study, the estimated annual peptic ulcer bleeding incidence rate in the general population ranged from 19 to 57 cases per 100,000 populations (0.02 to 0.06%) mainly based on European studies [10].

The endoscopic dual treatment with the infusion and epinephrine in conjunction with either a clip or a thermal system or an implant approach [11,12]. New methods exist, for instance, hemostatic dust, but further testing is required [13]. Second-view endoscopy is not advised after initial hemostasis unless the patient has clinical signs of re-bleeding [14]. Continuous proton pump inhibitors (PPIs) infusion will take 72 hours, both in the Forrest Class Ia-IIa and in the IIb ulcers that did not get treatment [15,16]. A second endoscopic attempt is advised if the patient re-bleeds again [17]. In this study, we provide a comprehensive overview of re-bleeding rates following endoscopic treatment of peptic ulcers.

Methods

Search strategy and study selection

We performed an extensive literature search in 11 databases including Popline, WHO health library (GHL), System for Information on Grey Literature in Europe (SIGLE), Scopus, Web of Science (ISI), PubMed, Virtual Health Library (VHL), The New York Academy of Medicine (NYAM), Medline, Cochrane, and EMBASE databases on 20 November 2019. Whenever supported, medical subject headings (MeSH) terms "peptic ulcer [MeSH Terms]" AND "bleeding [MeSH Terms]" AND "endoscopic hemostasis [MeSH Terms]". In databases where Mesh terms were not supported, combinations of different possible synonyms have been used. An additional manual search of references across relevant studies has been performed.

Three independent reviewers scanned the titles and abstracts against our inclusion and exclusion criteria to select potential articles. We included all relevant original publications assessing the risk of re-bleeding following endoscopic hemostasis of bleeding peptic ulcer, during the last ten years. There were no restrictions on study design, country or language. Papers were excluded if any of the following exclusion criteria were met: i) *in vitro* or animal studies; ii) data duplication, overlapping or unreliably extracted or incomplete data; iii) abstract only articles, reviews, thesis, books, conference papers or articles without available full texts (editorials, author response, letters, and comments) along with any previous systematic reviews, meta-analyses and literature reviews on our topic of interest. Full texts of initially eligible articles were then retrieved and reviewed for final inclusion. In both steps of the screening, a decision made by all three reviewers was considered conclusive. Controversies during the process were resolved by discussion and consensus. When necessary, disagreements and discrepancies were resolved by consensus with senior reviewers.

Data extraction

Based on a pilot review and extraction, a data extraction form was developed by two authors, using Microsoft Excel file. Three reviewers independently extracted data from included studies using the excel sheet. Whenever the re-bleeding rate was assessed at multiple points, the last and most complete data set was used. Data rechecking was carried out by at least two different authors and re-checked by a third reviewer for accuracy. All the disagreements and discrepancies were resolved by discussion and consensus. Papers published by the same research group were checked for potential duplicate data with reference to the year of patients' recruitment and the hospital where the patients were recruited.

Quality assessment

Three independent reviewers evaluated the risk of bias in included studies. For observational studies, methodological quality assessment was done using the National Institutes of Health (NIH) quality assessment tool [18]. Quality assessment of each study was obtained

through a scoring system including 14 questions. The criterion was judged as following; a score of 13 to 14 was good, 9 to 12 was fair, and studies scoring below 9 are considered of poor quality for cohort studies [19]. For randomized controlled trials (RCTs), methodological quality assessment was done using Cochran's tool for risk of bias [20].

Statistical analysis

R software version 3.6.1 was used to conduct the analyses [21]. To calculate the re-bleeding rate, a random-effects model was chosen due to the presence of heterogeneity between studies. Heterogeneity was evaluated using the Q statistic and I^2 test [22,23]. Publication bias testing, using Egger's regression test, was not performed because of the small number of studies per analysis (less than 10) [24,25].

Results

Search results

Database search yielded 1904 reports and no additional reports were found with the manual search of references. Following the removal of 832 duplicates via Endnote software, the total number passed to the title and abstract screening was 1,072; of which, 167 were relevant to our inclusion criteria. Following the extensive full-text screening, only six studies were included in the meta-analysis (Figure 1).

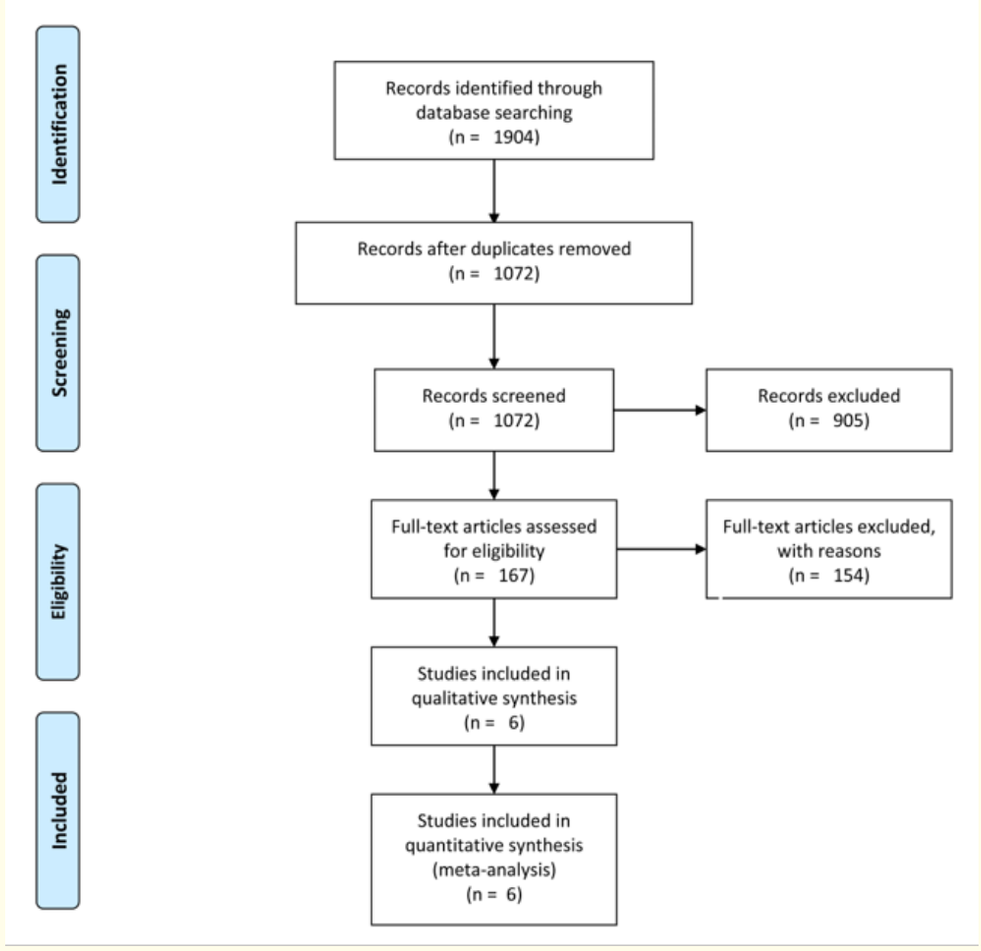

Figure 1: *Extensive full-text screening, six studies were included in the meta-analysis.*

Quality assessment and characteristics of included studies

Six studies with 248,517 total patients were included in this study with variable overall sample sizes ranging between 20 to 247,119. The total number of peptic ulcer patients assessed for re-bleeding risk was 3043. Moreover, the overall survival rate of FDPs ranged from

3.3% up to 30.6%. The mean age of the included patients was variable; ranging from 57.8 to 72.1 years old and male percentage ranged from 49% to 90% (Table 1).

Two studies have retrospectively screened patients' data and the other four were randomized controlled trials. The methodological quality of the included studies ranged from good to fair with moderate to low risk of biases (Table 1).

Study	Study Design	Case Group				Control Group				Overall Re-bleeding Rate (%)	Quality
		Definition	N	Age; Mean (SD/ range)	Male (%)	Definition	N	Age; Mean (SD/ range)	Male (%)		
Enestvedt/2010/ USA [26]	Observational (Retrospective)	All adult patients who underwent esophagogastroduodenoscopy (EGD) performed for peptic ulcer hemostasis	3,692	65.2	70%	All adult patients who underwent esophagogastroduodenoscopy (EGD) performed for any other cause	243,427	57.8	49%	7.3% of all patients, 12.2% in injection monotherapy, 6.1% in thermal monotherapy and 7.1% in combination thermal/ injection therapy	Fair (moderate risk of bias)
Kuipers/2011/ Canada [27]	Randomized controlled trial	Adults who had undergone successful hemostatic treatment of a bleeding peptic ulcer by endoscopy with intravenous esomeprazole followed by oral esomeprazole	375	62.1 (18-95)	68%	Adults who had undergone successful hemostatic treatment of a bleeding peptic ulcer by endoscopy with intravenous placebo followed by oral esomeprazole	389	60.2 (18-98)	69%	4.8% in the esomeprazole group and 7.7% in the placebo group	Good (low risk of bias)
Chen/2012/ Taiwan [28]	Randomized controlled trial	patients with active spurting (Forrest Ia), active oozing (Forrest Ib) ulcers or those with the non-bleeding visible vessel (NBVV, Forrest IIa) followed by **high-dose pantoprazole regimen**	100	65.5 (15.1)	79%	patients with active spurting (Forrest Ia), active oozing (Forrest Ib) ulcers or those with the non-bleeding visible vessel (NBVV, Forrest IIa) followed by standard-dose pantoprazole regimen	101	64.9 (12.2)	70%	7% in the high-dose group and 6.9 in the standard-dose group	Good (low risk of bias)

Kuo/2015/ Taiwan [29]	Observational (Retrospective)	Patients with peptic ulcer bleeding who underwent endoscopic interventions followed by prophylactic antibiotics	88	61.8 (15.2)	81%	Patients with peptic ulcer bleeding who underwent endoscopic interventions (Control Group)	147	62.5 (12.5)	75%	3.4% in antibiotic group and 30.6% in control group	Fair (moderate risk of bias)
Kwek/2017/ Singapore [30]	Randomized controlled trial	Patients having peptic ulcers with high-risk stigmata of recent hemorrhage (Forrest classes IA, IB, IIA, and IIB) with combined technique (CCT) of saline adrenaline injection with a mechanical clip or heater probe	10	72.1 (11.4)	70%	Patients having peptic ulcers with high-risk stigmata of recent hemorrhage (Forrest classes IA, IB, IIA, and IIB) with TC-325	10	67.9 (18.4)	90%	10% in the CCT group and 33.3% in TC-325 therapy	Fair (moderate risk of bias)
Toosi/2018/ Iran [31]	Randomized controlled trial	Patients older than 18 years with successful endoscopic therapy of high-risk ulcers followed by intravenous (IV) pantoprazole	88	60.3 (25-89)	56%	Patients older than 18 years with successful endoscopic therapy of high-risk ulcers followed by oral pantoprazole	90	58.4 (18-100)	70%	4.5% in the IV group and 3.3% in the oral group	Fair (moderate risk of bias)

Table 1: *Characteristics of the included studies.*
N: Number; SD: Standard Deviation.

Re-bleeding rate following endoscopic hemostasis

Six studies with 3043 patients were included in the analysis. The overall re-bleeding was 8.94% with 95% CI = 5.46 to 14.64. However, there was significant heterogeneity among results I^2 = 92% and P-value < 0.001 (Figure 2). Two studies [29,30] were the main sources of this heterogeneity for the highest rates; one [30] was a pilot RCT (33.3% re-bleeding rate) and the other [29] did not use any re-bleeding prevention medication in the control group (30.6% re-bleeding rate). A sensitivity analysis with removing those two studies has been performed. The heterogeneity has disappeared (I^2 = 4% and P-value = 0.372) and the prevalence rate changed to be 6.84% with 95% CI = 5.97 to 7.85 (Figure 3).

One study [26] has compared different endoscopy techniques where injection monotherapy has the highest re-bleeding rate (12.2%) followed by a combination of thermal/injection therapy (7.1%) and thermal monotherapy (6.1%), respectively. The studies that used proton pump inhibitors (PPIs) have reported the lowest re-bleeding rates with 3.3% [31] using the oral pantoprazole, 4.5% using the intravenous pantoprazole [31] and 4.8% using esomeprazole [27].

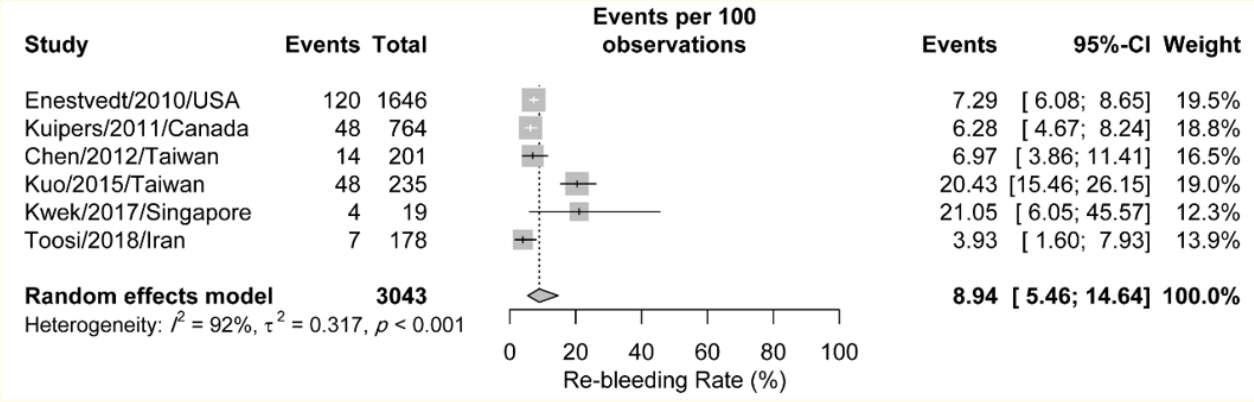

Figure 2: *Significant heterogeneity among results I2 = 92% and P-value < 0.001.*

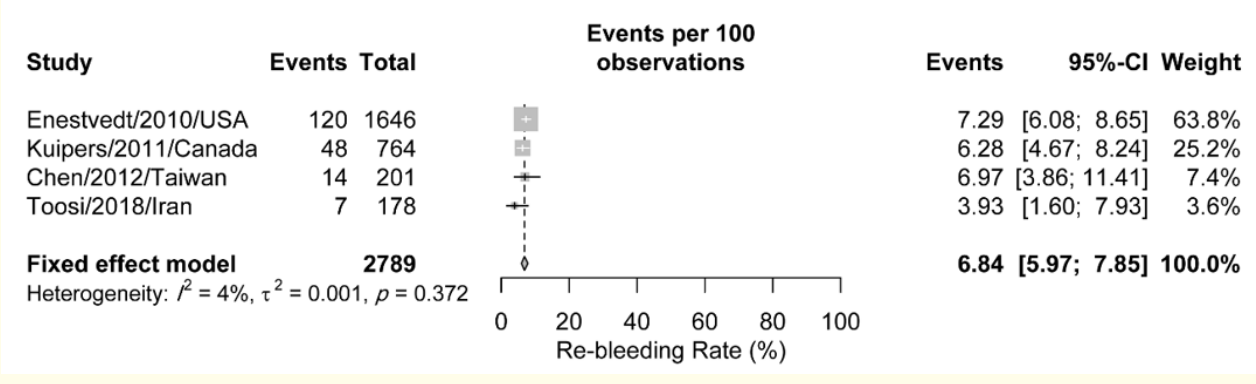

Figure 3: *Prevalence rate changed to be 6.84% with 95% CI = 5.97 to 7.85.*

Discussion

Peptic ulcer bleeding is the most common complication in peptic ulcer patients [10,32] with decreasing incidence [33-35]. The incidence of bleeding peptic ulcers varies from 19 per 100,000 in the UK [36] to 80 per 100,000 in Spain [32]. Bleeding peptic ulcers are usually categorized according to the Forrest classification with differences in re-bleeding and mortality rates [37]. The reported re-bleeding rates and mortality were based on older publications when patients did not receive endoscopic therapy [38]. Based on the Forrest classification, ulcers can nowadays be categorized based on their need for endoscopic therapy as major stigmata of ulcer bleeding (Forrest Ia-IIb), or minor stigmata of ulcer bleeding (Forrest IIc or III) [37].

The current study has shown a pooled re-bleeding rate of 8.94% with individual studies ranging between 3.93% to 21.05%, which is consistent with the previous literature. The re-bleeding rates of peptic ulcers by Forrest classification after successful endoscopic hemostasis but with no PPIs therapy were 23% in Ia ulcers, 5% in Ib, 11% in IIa, and 18% in IIb, respectively, suggesting that Ib ulcers after initial endoscopic management should not be categorized as major stigmata of hemorrhage [39]. In another study from the Netherlands during 2009 - 2012, the overall re-bleeding rate was quite high (19%) varying from 59% among Forrest Ia ulcers to 7% in Forrest III ulcers [40]. In that study, only 70 - 74% of patients were treated with dual therapy in endoscopy. Based on a systemic review of 28 studies, the recurrent rate of all bleeding ulcers after successful initial endoscopic hemostasis has varied from 0-38%, being on average at 10%

[10]. In a recently published study from Finland, 4.4% of bleeding peptic ulcer patients hospitalized during 2000 - 2015 needed a secondary procedure for bleeding, and 1.0% were admitted to prophylactic transcatheter arterial embolization [41].

The endoscopic therapy is recommended for ulcers with active bleeding or with a non-bleeding visible vessel or an adherent clot (Forrest Ia-IIb) for their risk of recurrent bleeding [42]. The removal of an adherent clot (IIb) in search of an artery is suggested in some studies, and only when it is present the endoscopic therapy should be given [43,44]. Among patients with haematin on ulcer base (IIc) or a clean base ulcer (III) endoscopic therapy is not needed. According to the international guidelines, dual therapy with epinephrine injection is recommended for reducing the risk of rebleeding, surgery and mortality [17,45]. The endoscopic treatment can be traditionally divided into injection, thermal and mechanical methods. Recently, novel endoscopic topical hemostatic powders have come onto market [44]. However, the proportion of patients receiving dual therapy for major stigmata of hemorrhages has been reported in some national audits to be as low as 34% in Canada, 35% in Italy and 38% in the UK [46-48].

The current study has some limitations; including the small number of studies included and heterogeneity of treatments used along with endoscopic treatment. Although the heterogeneity could be resolved with sensitivity analysis, it is a limitation to be considered. Studies have good methodological quality; nevertheless, two studies were retrospective with the associated flaws of this study design.

Conclusion

The endoscopic treatment of bleeding peptic ulcers has shown to be effective with low risk of re-bleeding. Adjuvant treatment with PPIs has shown to reduce the re-bleeding rates even more. Large scale studies are needed for a better assessment and more concrete conclusions.

Funding

None.

Conflicts of Interest

No conflicts related to this work.

Bibliography

1. Malik Talia F and Kevin Singh. "Peptic Ulcer Disease". Statpearls. Treasure Island (FL): StatPearls Publishing (2019).
2. Malfertheiner Peter., *et al*. "Peptic Ulcer Disease". *Lancet* 374.9699 (2009): 1449-1561.
3. Gossman William., *et al*. "Gastric Perforation". Statpearls. Treasure Island (FL): StatPearls (2019).
4. Palmer, Kelvin. "Acute Upper Gastrointestinal Haemorrhage". *British Medical Bulletin* 83.1 (2007): 307-324.
5. Me Lauret., *et al*. "Peptic Ulcer Disease". *Journal of Gastroenterology and Hepatobiliary Disorders* 1.1 (2015).
6. Groenen Marcel JM., *et al*. "Incidence of Duodenal Ulcers and Gastric Ulcers in a Western Population: Back to Where It Started". *Canadian Journal of Gastroenterology* 23.9 (2009): 604-608.
7. Sung JJ Y., *et al*. "Systematic Review: The Global Incidence and Prevalence of Peptic Ulcer Disease". *Alimentary Pharmacology and Therapeutics* 29.9 (2009): 938-946.
8. Sostres Carlos and Angel Lanas. "Epidemiology and Demographics of Upper Gastrointestinal Bleeding: Prevalence, Incidence, and Mortality". *Gastrointestinal Endoscopy Clinics of North America* 21.4 (2011): 567-581.
9. Milosavljevic Tomica., *et al*. "Complications of Peptic Ulcer Disease". *Digestive Diseases* 29.5 (2011): 491-493.
10. Lau James Y., *et al*. "Systematic Review of the Epidemiology of Complicated Peptic Ulcer Disease: Incidence, Recurrence, Risk Factors and Mortality". *Digestion* 84.2 (2011): 102-113.

11. Marmo Riccardo., *et al*. "Dual Therapy Versus Monotherapy in the Endoscopic Treatment of High-Risk Bleeding Ulcers: A Meta-Analysis of Controlled Trials". *The American Journal of Gastroenterology* 102.2 (2007): 279-469.

12. Vergara Mercedes., *et al*. "Epinephrine Injection Versus Epinephrine Injection and a Second Endoscopic Method in High-Risk Bleeding Ulcers". *The Cochrane Database of Systematic Reviews* 10 (2014): CD005584.

13. Haddara Sami., *et al*. "A Novel Hemostatic Powder for Upper Gastrointestinal Bleeding: A Multicenter Study (the "Graphe" Registry)". *Endoscopy* 48.12 (2016): 1084-1095.

14. Chi Philip Wai Yan., *et al*. "High-Dose Omeprazole Infusion Compared with Scheduled Second-Look Endoscopy for Prevention of Peptic Ulcer Rebleeding: A Randomized Controlled Trial". *Endoscopy* 48.8 (2016): 717-722.

15. Rácz István., *et al*. "Management of Peptic Ulcer Bleeding in Different Case Volume Workplaces: Results of a Nationwide Inquiry in Hungary". *Gastroenterology Research and Practice* (2012): 956434-95634.

16. Cheng Hsiu-Chi., *et al*. "Risk Factors Determining the Need for Second-Look Endoscopy for Peptic Ulcer Bleeding after Endoscopic Hemostasis and Proton Pump Inhibitor Infusion". *Endoscopy International Open* 4.3 (2016): E255-E262.

17. Gralnek Ian M., *et al*. "Diagnosis and Management of Nonvariceal Upper Gastrointestinal Hemorrhage: European Society of Gastrointestinal Endoscopy (Esge) Guideline". *Endoscopy* 47.10 (2015): a1-a46.

18. Health National Institutes of. "Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies". National Heart, Lung, and Blood Institute.

19. Leung Amy., *et al*. "A Systematic Review of Patient-Related Risk Factors for Catheter-Related Thrombosis". *Journal of Thrombosis and Thrombolysis* 40.3 (2015): 363-373.

20. Higgins JPT., *et al*. "Chapter 8: Assessing Risk of Bias in a Randomized Trial". In: Higgins Jpt, Thomas J, Chandler J Cumpston M., *et al*. Cochrane Handbook for Systematic Reviews of Interventions. Cochrane (2019).

21. Team R and Core R. "A Language and Environment for Statistical Computing". Vers. R Foundation for Statistical Computing (2017).

22. DerSimonian R and N Laird. "Meta-Analysis in Clinical Trials". *Controlled Clinical Trials* 7.3 (1986): 177-188.

23. Higgins Julian PT., *et al*. "Measuring Inconsistency in Meta-Analyses". *BMJ (Clinical Research Edition)* 327.7414 (2003): 557-560.

24. Peters Jaime L., *et al*. "Comparison of Two Methods to Detect Publication Bias in Meta-Analysis". *JAMA* 295.6 (2006): 676-680.

25. Egger M., *et al*. "Bias in Meta-Analysis Detected by a Simple, Graphical Test". *BMJ* 315.7109 (1997): 629-634.

26. Enestvedt Brintha K., *et al*. "Endoscopic Therapy for Peptic Ulcer Hemorrhage: Practice Variations in a Multi-Center U.S. Consortium". *Digestive Diseases and Sciences* 55.9 (2010): 2568-2576.

27. Kuipers Ernst J., *et al*. "Safety and Tolerability of High-Dose Intravenous Esomeprazole for Prevention of Peptic Ulcer Rebleeding". *Advances in Therapy* 28.2 (2011): 150-159.

28. Chen CC., *et al*. "Randomised Clinical Trial: High-Dose Vs. Standard-Dose Proton Pump Inhibitors for the Prevention of Recurrent Haemorrhage after Combined Endoscopic Haemostasis of Bleeding Peptic Ulcers". *Alimentary Pharmacology and Therapeutics* 35.8 (2012): 894-903.

29. Kuo Ming-Te., *et al*. "Predicting Risk Factors for Rebleeding, Infections, Mortality Following Peptic Ulcer Bleeding in Patients with Cirrhosis and the Impact of Antibiotics Prophylaxis at Different Clinical Stages of the Disease". *BMC Gastroenterology* 15 (2015): 61-61.

30. Kwek Boon Eu Andrew., *et al*. "Tc-325 Versus the Conventional Combined Technique for Endoscopic Treatment of Peptic Ulcers with High-Risk Bleeding Stigmata: A Randomized Pilot Study". *Journal of Digestive Diseases* 18.6 (2017): 323-329.

31. Valizadeh Toosi Seyed Mohammad., *et al*. "Comparison of Oral Versus Intravenous Proton Pump Inhibitors in Preventing Re-Bleeding from Peptic Ulcer after Successful Endoscopic Therapy". *Middle East Journal of Digestive Diseases* 10.4 (2018): 236-241.

32. Pérez-Aisa M. A., *et al*. "Clinical Trends in Ulcer Diagnosis in a Population with High Prevalence of Helicobacter Pylori Infection". *Alimentary Pharmacology and Therapeutics* 21.1 (2005): 65-72.

33. Wang Y., *et al*. "Trends and Outcomes of Hospitalizations for Peptic Ulcer Disease in the United States, 1993 to 2006". *Annals of Surgery* 251.1 (2010): 51-58.

34. Åhsberg K., *et al*. "Mortality from Peptic Ulcer Bleeding: The Impact of Comorbidity and the Use of Drugs That Promote Bleeding". *Alimentary Pharmacology and Therapeutics* 32.6 (2010): 801-810.

35. Lanas A., *et al*. "The Changing Face of Hospitalisation Due to Gastrointestinal Bleeding and Perforation". *Alimentary Pharmacology and Therapeutics* 33.5 (2011): 585-591.

36. Bardhan KD., *et al*. "Admission Rates for Peptic Ulcer in the Trent Region, Uk, 1972--2000. Changing Pattern, a Changing Disease?" *Digestive and Liver Disease* 36.9 (2004): 577-588.

37. Forrest JA., *et al*. "Endoscopy in Gastrointestinal Bleeding". *Lancet* 2.7877 (1974): 394-397.

38. Laine L and WL. Peterson. "Bleeding Peptic Ulcer". *The New England Journal of Medicine* 331.11 (1994): 717-727.

39. Jensen Dennis M., *et al*. "Reassessment of Rebleeding Risk of Forrest Ib (Oozing) Peptic Ulcer Bleeding in a Large International Randomized Trial". *The American Journal of Gastroenterology* 112.3 (2017): 441-446.

40. de Groot Nicolette L., *et al*. "Reassessment of the Predictive Value of the Forrest Classification for Peptic Ulcer Rebleeding and Mortality: Can Classification Be Simplified?" *Endoscopy* 46.1 (2014): 46-52.

41. Nykänen Taina., *et al*. "Bleeding Gastric and Duodenal Ulcers: Case-Control Study Comparing Angioembolization and Surgery". *Scandinavian Journal of Gastroenterology* 52.5 (2017): 523-530.

42. Kim Joon Sung., *et al*. "Endoscopic Management of Peptic Ulcer Bleeding". *Clinical Endoscopy* 48.2 (2015): 106-111.

43. Lau James YW., *et al*. "Challenges in the Management of Acute Peptic Ulcer Bleeding". *Lancet* 381.9882 (2013): 2033-2043.

44. Lu Yidan., *et al*. "Endoscopic Management of Acute Peptic Ulcer Bleeding". *Gastroenterology Clinics of North America* 43.4 (2014): 677-705.

45. Barkun, Alan N., *et al*. "International Consensus Recommendations on the Management of Patients with Nonvariceal Upper Gastrointestinal Bleeding". *Annals of Internal Medicine* 152.2 (2010): 101-113.

46. Barkun Alan., *et al*. "The Canadian Registry on Nonvariceal Upper Gastrointestinal Bleeding and Endoscopy (Rugbe): Endoscopic Hemostasis and Proton Pump Inhibition Are Associated with Improved Outcomes in a Real-Life Setting". *The American Journal of Gastroenterology* 99.7 (2004): 1238-1246.

47. Hearnshaw Sarah A., *et al*. "Use of Endoscopy for Management of Acute Upper Gastrointestinal Bleeding in the Uk: Results of a Nationwide Audit". *Gut* 59.8 (2010): 1022-1029.

48. Marmo Riccardo., *et al*. "Predicting Mortality in Non-Variceal Upper Gastrointestinal Bleeders: Validation of the Italian Pned Score and Prospective Comparison with the Rockall Score". *The American Journal of Gastroenterology* 105.6 (2010): 1284-1291.

Volume 16 Issue 1 January 2020