Original Article

Major bleeding risk of endoscopic sphincterotomy versus endoscopic papillary balloon dilatation in hemodialysis patients

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Abstract

Background/Aims: Endoscopic sphincterotomy (EST) and endoscopic papillary balloon dilatation (EPBD) are used for therapeutic endoscopic retrograde cholangiopancreatography (ERCP). The postprocedure bleeding rate for EPBD is low in the normal population; however, this bleeding rate in a group of patients prone to bleeding, such as patients with end-stage renal disease, is not well-established. We therefore evaluated the post-EST and post-EPBD bleeding rate among hemodialysis (HD) patients based on data from Taiwan's National Health Insurance Research Database (NHIRD).

Patients and Methods: The NHIRD entries for a population of 2 million were screened for patients who had a catastrophic illness card for HD between 1st January 2004 and 31st December 2011 and these patients were enrolled as research subjects. The rates of major gastrointestinal tract bleeding events appearing within 14 days after EST or EPBD were compared between HD and non-HD patients.

Results: A total of 3561 patients, over 18 years of age and without liver cirrhosis or hematologic diseases, underwent 3826 EST and 280 EPBD procedures during the 8 calendar years selected for our analysis. The total post-ERCP major bleeding rate was much higher in HD than in non-HD patients (8.64% vs. 2.16%, $P < 0.0001$). The rate of postprocedure major bleeding events was lower for non-HD patients who underwent EPBD than those who underwent EST (0.75% vs. 2.26%; $P = 0.049$), whereas the postprocedure major bleeding event rates were similar in HD patients who underwent either EPBD or EST (8.70% vs. 8.33%; $P = 0.484$).

Conclusion: Post-ERCP, post-EST, and post-EPBD major bleeding rates were all higher in HD patients in this study. EPBD resulted in lower postprocedure major bleeding events than EST in the non-HD population,

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Access this article online	
Quick Response Code:	Website: www.saudijgastro.com
	DOI: 10.4103/sjg.SJG_246_18

How to cite this article: Tsai MC, Wang CC, Wang YT, Yang TW, Chen HY, Tseng MH, *et al*. Major bleeding risk of endoscopic sphincterotomy versus endoscopic papillary balloon dilatation in hemodialysis patients. Saudi J Gastroenterol 2019;25:106-12

but it failed to provide the reduction in bleeding events needed to perform endoscopic hemostasis in HD patients.

Keywords: Endoscopic papillary balloon dilatation, endoscopic sphincterotomy, hemodialysis, postprocedure bleeding

INTRODUCTION

Since its introduction in 1968,[1] endoscopic retrograde cholangiopancreatography (ERCP) had evolved as an advanced therapeutic procedure. The major indications for ERCP are choledocholithiasis, biliary or pancreatic neoplasms, and management of postoperative biliary complications.[2-4] Although improvements in endoscopic technology are now making more difficult procedures possible today, postprocedure complications remain troublesome issues. The major complications of therapeutic ERCP include post-ERCP pancreatitis,[5] hemorrhage,[6] and perforation.[5,7] Several important risk factors for post-ERCP bleeding are recognized, including coagulopathy, administration of an anticoagulant agent within 72 h, papillary stenosis, precut sphincterotomy, and inexperienced endoscopists.[5,8] A large multiple-center study also identified hemodialysis (HD) as an independent risk factor of post-endoscopic sphincterotomy (EST) bleeding.[9]

Endoscopic papillary balloon dilatation (EPBD) and EST have proven to be relatively safe and effective methods for the treatment of choledocholithiasis, and both procedures have few complications.[10] EPBD is regarded as an alternative method for common bile duct management and has a low postprocedure bleeding rate,[11] but some reports have indicated an even higher bleeding rate after EPDB than after EST in patients receiving anticoagulant agents.[12] However, little information is available regarding bleeding rates following EPBD in patients with bleeding tendencies, such as patients undergoing regular HD.[13] Therefore, obtaining an overview based on population-based research is worthwhile for establishing a better understanding of the occurrence of post-ERCP hemorrhage in subgroups of patients who have bleeding tendencies. The differences in post-ERCP bleeding rates in HD patients following EST and EPBD also require evaluation.

The aim of this study was therefore to provide an overview of post-EST and post-EPBD bleeding events among HD patients by conducting a cohort study using data from a nationwide database covering a period of more than 8 years.

PATIENTS AND METHODS

This study was approved by the Institutional Review Board (IRB) of Chung Shan Medical University Hospital, Taiwan. The IRB waved the need for informed consent for this study because of its retrospective nature based on an encrypted National Health Insurance Research Database (NHIRD).

Study design

The study was a population-based retrospective cohort study based on Taiwan's NHIRD, which now covers 99.9% of the entire population of Taiwan.[14] The NHIRD contains comprehensive data including date of birth, gender, diagnostic codes, prescriptions, procedures, surgeries and expenditures, in Taiwan. The study methods used to establish the NHIRD have been described in detail in previous studies.[15,16]

In our study, 2 million samples in eight calendar years were surveyed and organized into cohorts of chronic renal failure with HD (HD cohort) and non-chronic renal failure (non-HD cohort) and then further categorized as patients who underwent EST or EPBD procedures within each cohort. The last case was recruited on 27th December 2011 in the non-HD group. Patients who had underlying hematological disease and cirrhosis were excluded from further analysis because of other interfering factors that led to bleeding tendencies. Major gastrointestinal (GI) bleeding events among EST and EPBD patients in each group were compared to draw conclusions regarding the safety of EST and EPBD procedures. A flow chart of the study design is shown in Figure 1.

Hemodialysis cohort

Patients who receive regular HD in Taiwan receive a catastrophic illness card to reduce the economic burden of their medical expenses. We included patients who had catastrophic illness cards between 1st January 2004 and 31st December 2011 as our HD cohort. Patients younger than 18 years of age were excluded from further analysis because of the different etiology of cirrhosis. Others over 18 years of age but without catastrophic illness cards served as the non-HD control group. Among the 11,336 HD patients collected, after exclusion of patients with cirrhosis or other

hematologic problems, 63 patients underwent 69 EST procedures and another 11 patients underwent 12 EPBD procedures during the sampling period. The statistical data for complication events were then calculated for further analysis.

Nonhemodialysis cohort

In total, 1,950,457 patients were selected from the nationwide representative population of 2 million during 1st January 2004 and 31st December 2011 to serve as the non-HD group. Among these patients, 1,913,988 were included after exclusion of patients who had cirrhosis or other hematologic diseases. In this non-HD group, after exclusion of patients younger than 18 years old, 3757 EST procedures were performed in 3264 patients and 268 EPBD procedures were performed in 223 patients. Statistical data for major GI bleeding events were then calculated for further analysis [Figure 1].

Definition of endoscopic sphincterotomy or endoscopic papillary balloon dilatation patients

Patients who underwent EST (order code 56031B and 56033B) or EPBD procedures (order code 56032B) during the evaluation period were collected for further analysis. Patients who underwent both EST and EPBD procedures at the same hospital were regarded as undergoing EST in our analysis.

Definition of major postendoscopic sphincterotomy or post-endoscopic papillary balloon dilatation gastrointestinal bleeding events

Endoscopic hemostasis remained the first choice of treatment if post-ERCP bleeding occurred; therefore, endoscopic hemostasis (order code 47043B) events appearing within 14 days after ERCP were noted. Post-ERCP bleeding was evaluated by both endoscopic hemostasis procedures and discharge diagnoses. The severity of post-ERCP bleeding was defined based on the blood transfusion amount and the need for angiography or surgical intervention,[17,18] but we defined endoscopic hemostasis as a post-ERCP major bleeding event in our analysis. Repeated EST or EPBD procedures in different hospital courses were regarded as separate events in our analysis.

Statistical analysis

Data obtained from the study were compared using Chi-square test or Fisher's exact test for categorical variables and Student's *t*-test for continuous variables. Fisher's exact test was preferred over Chi-square test

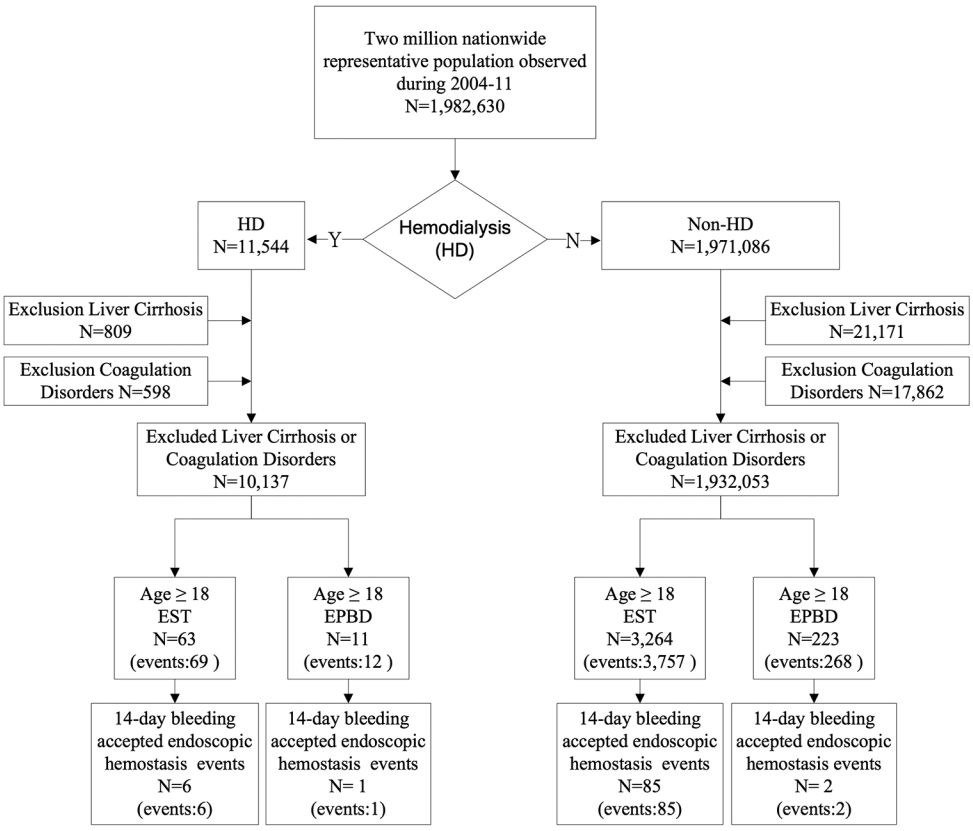

Figure 1: Flow chart of the study design. Hemodialysis patients were selected using catastrophic illness cards and following further exclusion of patients with cirrhosis or coagulation hematology. EST and EPBD groups were further separated for comparisons. HD: Hemodialysis; EST: Endoscopic sphincterotomy; EPBD: Endoscopic papillary balloon dilatation

given the small number of cases. A single-tailed *P* value of 0.05 was considered statistically significant in this study because EPBD procedures were reported to result in less post-ERCP hemorrhage in a previous study.[11]

Microsoft SQL Server 2008 R2 software (Microsoft Corporation, Redmond, WA, USA) was used to manage the study subjects using SQL programming language. Statistical analyses were conducted using SPSS version 19.0 software (SPSS, Inc., Chicago, IL, USA).

RESULTS

Hemodialysis versus nonhemodialysis

In total, 3561 patients older than 18 years of age and without cirrhosis or hematologic diseases underwent a total of 3826 EST and 280 EPBD procedures during the 8 calendar years selected in our analysis. The HD group included 74 patients who underwent 69 EST and 12 EPBD procedures, whereas the non-HD group included 3487 patients who underwent 3757 EST and 268 EPBD procedures. EST was adopted much more often than EPBD in both HD (69 vs. 12 events) and non-HD (3757 vs. 268 events) patients during the past decade in Taiwan. After the therapeutic ERCP, seven major GI bleeding events occurred in a total of 81 procedures, for a major GI bleeding event rate of 8.64% in the HD group, while the rate was 2.16% in the non-HD group (87 major GI bleeding events). The post-ERCP major GI bleeding rates were much higher in HD patients (8.64% vs. 2.16%, $P < 0.0001$).

In total, 85 major GI bleeding events were recorded in the non-HD group within 14 days after EST, whereas 6 major GI tract bleeding events occurred in the HD group. The incidence of post-EST major GI bleeding events was therefore notably higher in HD patients than in non-HD patients in our study (8.70% vs. 2.26%; $P < 0.0001$).

The choice of EPBD for papillary manipulation in therapeutic ERCP led to one major GI tract bleeding event after the procedure in a total of 12 EPBD procedures implemented in 11 HD patients, whereas only two major GI tract bleeding events occurred in 268 EPBD procedures implemented in 223 patients in the non-HD group. The incidence of post-EPBD major bleeding events was also much higher in the HD group than in the non-HD group (8.33% vs. 0.75%; $P = 0.006$), as shown in Figure 2.

Endoscopic sphincterotomy versus endoscopic papillary balloon dilatation

Table 1 shows the demographic characteristics of patients with regular HD schedules, including sex, age, reasons for the procedure, platelet transfusion, and fresh-frozen plasma transfusion during hospitalization. All patients were similar between EST and EPBD groups. The most frequent indication for therapeutic ERCP in Taiwan is choledocholithiasis in HD patients undergoing both EST and EPBD procedures. In a total of 69 procedures, only 6 post-EST major bleeding events occurred compared with 1 bleeding event in a total of 12 EPBD procedures in the HD group. Detailed information in EST patients were listed in Table 2. The incidence of major bleeding events were similar in the EST and EPBD groups of HD patients (8.70% vs. 8.33%; $P = 0.484$).

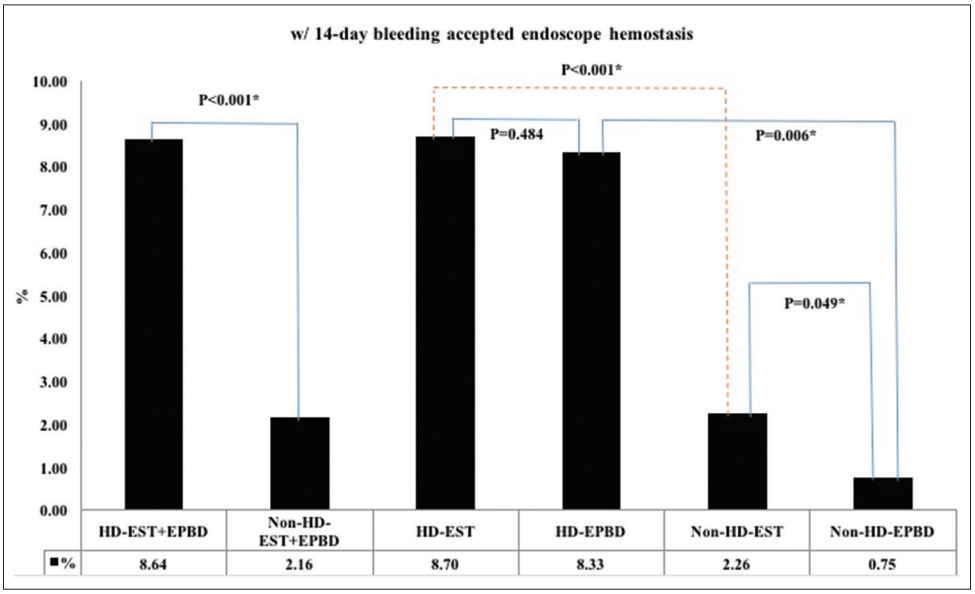

Figure 2: Bleeding event comparisons between EST and EPBD in HD patients vs the normal population. Post-ERCP, post-EST, and post-EPBD major bleeding rates were all higher in HD patients

Table 1: Demographic characteristics of hemodialysis patients

Variable	HD with EST (*n*=63)		HD with EPBD (*n*=11)		*P*
	Number	Column%	Number	Column%	
Sex					0.619
Male	26	41.3	6	54.5	
Female	37	58.7	5	45.5	
Age, mean (range)	67 (33-86)		66 (40-80)		0.643
Indication for ERCP					
Choledocholithiasis	55	87.3	9	81.8	0.919
Acute pancreatitis	5	7.9	0	0.0	0.873
Malignancy					
HCC	4	6.3	1	9.1	>0.999
Cholangiocarcinoma/Gallbladder cancer	3	4.8	0	0.0	>0.999
Pancreatic cancer	2	3.2	0	0.0	>0.999
Blood transfusion					
PLT transfusion	5	7.9	0	0.0	0.873
FFP transfusion	13	20.6	4	36.4	0.437
α=0.05* α=0.01**					

HD: Hemodialysis; EST: Endoscopic sphincterotomy; ERCP: Endoscopic retrograde cholangiopancreatography; HCC: Hepatocellular carcinoma; PLT: Platelet, FFP: Fresh frozen plasma

Table 2: Comparison of events in hemodialysis patients undergoing EST

Variable	HD-EST with major bleeding events (*n*=6)		HD-EST without major bleeding events (*n*=57)		*P*
	Number	Column%	Number	Column%	
Sex					>0.999
Male	2	33.3	24	42.1	
Female	4	66.7	33	57.9	
Age, mean (range)	65 (56-77)		67 (33-86)		0.407
Indication for ERCP					
Choledocholithiasis	5	83.3	50	87.7	>0.999
Acute pancreatitis	1	16.7	4	7.0	0.809
Malignancy					
HCC	0	0.0	4	7.0	>0.999
Cholangiocarcinoma/Gallbladder cancer	1	16.7	2	3.5	0.526
Pancreatic cancer	0	0.0	2	3.5	>0.999
Blood transfusion					
PLT transfusion	0	0.0	5	8.8	>0.999
FFP transfusion	3	50	10	17.5	0.193
α=0.05* α=0.01**					

HD: Hemodialysis; EST: Endoscopic sphincterotomy; ERCP: Endoscopic retrograde cholangiopancreatography; HCC: Hepatocellular carcinoma; PLT: Platelet; FFP: Fresh frozen plasma

In the non-HD group, 85 post-EST major bleeding events were recorded in a total of 3757 EST procedures, for an incidence of 2.26%, whereas post-EPBD bleeding events happened in 0.75% of patients ($P = 0.049$). The postprocedure major bleeding rate was significantly lower following the EPBD procedure than following the EST procedure, in non-HD patients in our analysis. The comparison of instances of post-EST or post-EPBD major bleeding events in the HD and non-HD patients are shown in Figure 2.

DISCUSSION

Previous studies have shown variations in post-ERCP bleeding rates ranging from 0.3% to 1.3%.[18,19] Some rare intraductal bleeding and hematomas had been reported,[20-22] but most ERCP-associated hemorrhage is intraluminal. Previous studies also showed that the postprocedure hemorrhage rate was lower for EPBD than for EST in a normal population[11] and that EPBD significantly reduced the risk of post-ERCP bleeding when compared with EST application in patients with advanced cirrhosis and coagulopathy.[23] Endoscopic hemostasis is currently the first choice of treatment for post-ERCP bleeding, whereas angiography or surgery can serve as alternative rescue management if endoscopic hemostasis fails to stop the hemorrhage.[24] Therefore, we chose the recording of a of post-ERCP endoscopic hemostasis procedure in the NHIRD as a surrogate marker for post-EST or post-EPBD major bleeding events.

The use of Taiwan's NHIR database in this study allowed evaluation of real-world data of therapeutic ERCP and determination of the true post-ERCP bleeding rate. Our results showed that patients who undergo regular HD are at higher risk for post-ERCP bleeding than patients

in the general population, regardless of whether EST or EPBD is chosen for biliary management. Both the EST and EPBD groups showed statistically significant differences, as more major postprocedure bleeding events occurred in HD patients. The post-EST bleeding rates were higher (2.26%) than the post-EPBD bleeding rates (0.75%) and this difference was statistically significant ($P = 0.049$). In contrast, the post-EST bleeding rate was similar to the post-EPBD bleeding rate in regular HD patients. Thus, EPBD failed to reduce the postprocedure hemorrhage rate in the HD group in our cohort study.

A previous large-scale study[9] also demonstrated that risk factors for post-EST bleeding included HD, visible bleeding during the procedure, higher serum bilirubin level, cirrhosis,[25,26] and the use of a pre-cut method for sphincterotomy.[5]

Our study has some advantages. First, our database comprised a nationwide representative population of 2 million persons treated from 2004 to 2011, randomly selected from the NHIR database that covered 99% of 23 million Taiwanese persons; hence, our study has low selection bias. Second, our data covered all the therapeutic ERCP procedures conducted in the selected period and therefore most likely represents the real-world situation in Taiwan.

Nevertheless, our study has some limitations. First, although this is a large-scale population-based cohort study that included almost 2 million people, only 69 EST and 12 EPBD procedures were recorded in the HD group because of the low incidence of HD and these two procedures in the general population. Second, because our analysis is based on NHIRD data, factors such as blood examinations, coagulopathy status, pre-cut attempts, pancreatic duct cannulations, the duration or method of cannulation, operator experience, and the condition of visible bleeding during the procedure could not be evaluated, thus detailed reasons for other complications cannot be discussed. However, because of the difficulty of conducting a randomized study given the low incidence of this therapeutic procedure, and especially in a population with a rare bleeding tendency, our retrograde database cohort study provides valuable information. Further larger scaled prospective randomized studies are needed.

CONCLUSION

The post-ERCP, post-EST, and post-EPBD major bleeding rates were all higher in HD patients than in non-HD patients in this study. EPBD resulted in fewer postprocedure major bleeding events in the non-HD population, but EPBD did not reduce the occurrence of bleeding events that necessitated endoscopic hemostasis in HD patients. Both EST and EPBD resulted in similar postprocedure bleeding rates in HD patients in our study.

Financial support and sponsorship

This study was funded by Chung Shan Medical University Hospital, Taichung, Taiwan (CSH- 2013-C-032).

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. McCune WS, Shorb PE, Moscovitz H. Endoscopic cannulation of the ampulla of vater: A preliminary report. Ann Surg 1968;167:752-6.
2. ASGE Standards of Practice Committee, Maple JT, Ben-Menachem T, Anderson MA, Appalaneni V, Banerjee S, *et al.* The role of endoscopy in the evaluation of suspected choledocholithiasis. Gastrointest Endosc 2010;71:1-9.
3. Baron TH, Mallery JS, Hirota WK, Goldstein JL, Jacobson BC, Leighton JA, *et al.* The role of endoscopy in the evaluation and treatment of patients with pancreaticobiliary malignancy. Gastrointest Endosc 2003;58:643-9.
4. Costamagna G, Shah SK, Tringali A. Current management of postoperative complications and benign biliary strictures. Gastrointest Endosc Clin N Am 2003;13:635-48, ix.
5. Masci E, Toti G, Mariani A, Curioni S, Lomazzi A, Dinelli M, *et al.* Complications of diagnostic and therapeutic ERCP: A prospective multicenter study. Am J Gastroenterol 2001;96:417-23.
6. Halme L, Doepel M, von Numers H, Edgren J, Ahonen J. Complications of diagnostic and therapeutic ERCP. Ann Chir Gynaecol 1999;88:127-31.
7. Howard TJ, Tan T, Lehman GA, Sherman S, Madura JA, Fogel E, *et al.* Classification and management of perforations complicating endoscopic sphincterotomy. Surgery 1999;126:658-63.
8. Freeman ML, Nelson DB, Sherman S, Haber GB, Herman ME, Dorsher PJ, *et al.* Complications of endoscopic biliary sphincterotomy. N Engl J Med 1996;335:909-18.
9. Williams EJ, Taylor S, Fairclough P, Hamlyn A, Logan RF, Martin D, *et al.* Risk factors for complication following ERCP; results of a large-scale, prospective multicenter study. Endoscopy 2007;39:793-801.
10. Yao LQ, Zhang YQ, Zhou PH, Gao WD, He GJ, Xu MD, *et al.* Endoscopic sphincterotomy or papillary balloon dilatation for choledocholithiasis. Hepatobiliary Pancreat Dis Int 2002;1:101-5.
11. Zhao HC, He L, Zhou DC, Geng XP, Pan FM. Meta-analysis comparison of endoscopic papillary balloon dilatation and endoscopic sphincteropapillotomy. World J Gastroenterol 2013;19:3883-91.
12. Hamada T, Yasunaga H, Nakai Y, Isayama H, Matsui H, Horiguchi H, *et al.* Bleeding after endoscopic sphincterotomy or papillary balloon dilation among users of antithrombotic agents. Endoscopy 2015;47:997-1004.
13. Takahara N, Isayama H, Sasaki T, Tsujino T, Toda N, Sasahira N, *et al.* Endoscopic papillary balloon dilation for bile duct stones in patients on hemodialysis. J Gastroenterol 2012;47:918-23.
14. Cheng TM. Taiwan's new national health insurance program: Genesis and experience so far. Health Aff (Millwood) 2003;22:61-76.
15. Wu CY, Kuo KN, Wu MS, Chen YJ, Wang CB, Lin JT, *et al.* Early *Helicobacter pylori* eradication decreases risk of gastric cancer in patients with peptic ulcer disease. Gastroenterology 2009;137:1641-80.
16. Wu CY, Chan FK, Wu MS, Kuo KN, Wang CB, Tsao CR, *et al.* Histamine2-receptor antagonists are an alternative to proton pump inhibitor in patients receiving clopidogrel. Gastroenterology

2010;139:1165-71.
17. Cotton PB. Therapeutic endoscopy in the 1990s: Objectivity, teaching, and service. Gastrointest Endosc 1991;37:202-5.
18. Cotton PB, Garrow DA, Gallagher J, Romagnuolo J. Risk factors for complications after ERCP: A multivariate analysis of 11,497 procedures over 12 years. Gastrointest Endosc 2009;70:80-8.
19. Andriulli A, Loperfido S, Napolitano G, Niro G, Valvano MR, Spirito F, *et al*. Incidence rates of post-ERCP complications: A systematic survey of prospective studies. Am J Gastroenterol 2007;102:1781-8.
20. Costa Macedo T, Maldonado R, Valente A, Palma R, Raimundo M, Liberato M, *et al*. Hemobilia in hereditary hemorrhagic telangiectasia: An unusual complication of endoscopic retrograde cholangiopancreatography. Endoscopy 2003;35:531-3.
21. Shinjo K, Matsubayashi H, Matsui T, Kawata N, Uemura S, Yamamoto Y, *et al*. Biliary hemostasis using an endoscopic plastic stent placement for uncontrolled hemobilia caused by transpapillary forceps biopsy (with video). Clin J Gastroenterol 2016;9:86-8.
22. McArthur KS, Mills PR. Subcapsular hepatic hematoma after ERCP. Gastrointest Endosc 2008;67:379-80.
23. Park DH, Kim MH, Lee SK, Lee SS, Choi JS, Song MH, *et al*. Endoscopic sphincterotomy vs. endoscopic papillary balloon dilation for choledocholithiasis in patients with liver cirrhosis and coagulopathy. Gastrointest Endosc 2004;60:180-5.
24. Lee MH, Tsou YK, Lin CH, Lee CS, Liu NJ, Sung KF, *et al*. Predictors of re-bleeding after endoscopic hemostasis for delayed post-endoscopic sphincterotomy bleeding. World J Gastroenterol 2016;22:3196-201.
25. Prat F, Tennenbaum R, Ponsot P, Altman C, Pelletier G, Fritsch J, *et al*. Endoscopic sphincterotomy in patients with liver cirrhosis. Gastrointest Endosc 1996;43:127-31.
26. Adler DG, Haseeb A, Francis G, Kistler CA, Kaplan J, Ghumman SS, *et al*. Efficacy and safety of therapeutic ERCP in patients with cirrhosis: A large multicenter study. Gastrointest Endosc 2016;83:353-9.