Original Article

Factors Associated with Bleeding after Endoscopic Retrograde Cholangiopancreatography: A Cross-Sectional Study

Amirhossein Faraji[1], Mahshid Telloo[2*], Hossein Ajdarkosh[1], Mehdi Nikkhah[1], Zohre Dadvar[3], Mahmoodreza Khoonsari[1], Elham Sobh Rakhshankhah[1]

[1] Gastrointestinal and Liver Diseases Research Center, Iran University of Medical Sciences, Tehran, Iran

[2] Department of Internal Medicine, School of Medicine, Iran University of Medical Sciences, Tehran, Iran.

[3] Gastroenterology Department, Tehran University of Medical Sciences, Tehran, Iran

ABSTRACT

Background:
Bleeding after endoscopic retrograde cholangiopancreatography (ERCP) is a serious complication that requires identification of its underlying factors. We aimed to investigate the incidence and predictors of this complication in our center.

Materials and Methods:
We conducted a descriptive cross-sectional study on 500 patients who underwent ERCP for any indication at Firoozgar Hospital in 2020-2021. We collected data on demographic characteristics, medical history, medications, preoperative hemoglobin, and indication for ERCP from the hospital records. We also measured intraoperative bleeding, sphincterotomy, and hemoglobin levels at 6 hours and one week after ERCP. We used SPSS software for data analysis and considered $P< 0.05$ statistically significant.

Results:
The mean ± SD age of the patients was 60.37 ± 16.37 years, and 50.8% were male. The incidence of acute and delayed bleeding after ERCP was 4.2% and 0.6%, respectively, and the rate of acute and delayed moderate to severe hemoglobin drop was 7.8% and 13%, respectively. There was no difference in demographic information, medical history, and medications between patients with and without acute and delayed hemoglobin drop. However, patients with a history of diabetes mellitus had a higher rate of mild delayed bleeding, and patients with smoking and clopidogrel use had a higher rate of moderate to severe hemoglobin drop ($P< 0.05$). Sphincterotomy, precut, peri-ampullary anatomy, and common bile duct (CBD) size did not affect the incidence of acute and delayed bleeding and hemoglobin drop.

Conclusion:
Diabetes mellitus was the only risk factor for delayed bleeding, and smoking and clopidogrel were risk factors for moderate to severe hemoglobin drop. Due to the discrepancy between overt and laboratory bleeding in this study, we recommend regular hemoglobin monitoring as a more accurate indicator of bleeding after ERCP.

Keywords: Endoscopic retrograde cholangiopancreatography (ERCP), Bleeding, Risk factor

please cite this paper as:
Faraji AH, Telloo M, Ajdarkosh H, Nikkhah M, Dadvar Z, Khoonsari MR, Sobh Rakhshankhah E. Factors Associated with Bleeding after Endoscopic Retrograde Cholangiopancreatography: A Cross-Sectional Study. *Govaresh* 2024; 29:32-37

Corresponding author:
Mahshid Telloo, MD

Department of Internal Medicine, School of Medicine, Iran University of Medical Sciences, Tehran, Iran; Firoozgar Hospital, Beh-Afarin ST., Valiasr Ave., P.O.Box: 1593748711, Tehran, Iran.
Telefax : + 98 21 88941831
Email: mtelloo76@gmail.com

Received: 03 Sep. 2023
Revised: 02 Feb. 2024
Accepted: 03 Feb. 2024

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is an invasive procedure used to diagnose and treat various biliary and pancreatic disorders, such as bile duct stones, stenosis, masses, and sphincter of Oddi dysfunction (1,2). ERCP may also be indicated for some cases of pancreatitis associated with inflammatory cholangitis due to obstruction of the Wirsung duct by gallstones, papillary hyperplasia, or gallbladder reflux (3). However, ERCP carries a risk of serious complications, such as bleeding, pancreatitis, perforation, and infection (4-6).

Bleeding is one of the most common and severe complications of ERCP, especially after sphincterotomy. The reported incidence of bleeding during sphincterotomy ranges from 0.5% to 2% in otherwise healthy individuals (5,7). Other possible causes of bleeding include splenic, hepatic, or vascular injury and pseudoaneurysm formation (8). Bleeding can be acute or delayed, depending on whether it occurs during or after the procedure, respectively. Acute bleeding is usually detected by the endoscopist, while delayed bleeding may manifest as melena, hematochezia, or hematoma within a few hours to weeks after ERCP. Several risk factors for bleeding after ERCP have been identified, such as underlying coagulopathy, cholangitis, anticoagulant therapy, liver cirrhosis, dilated common bile duct (CBD), CBD stones, inexperienced endoscopist, and periampullary diverticulum (9,10).

The effect of using cautery for sphincterotomy on bleeding rate is unclear. Various endoscopic methods have been used to control bleeding after sphincterotomy, such as injection of diluted epinephrine, clipping of arteries, bipolar coagulation, and tamponade (11,12). Recently, self-expanding metal stents have also been employed for this purpose (13,14). If endoscopic hemostasis fails and the patient becomes hemodynamically unstable, mesenteric artery embolization or laparotomy may be required (15,16). Routine laboratory tests before ERCP include evaluating hemoglobin (Hb), platelet (PLT), prothrombin time (PT), partial thromboplastin time (PTT), INR (international normalized ratio), and potassium serum levels, regardless of the underlying disease (17). In this study, we aimed to determine the incidence and predictors of bleeding after ERCP in our center.

MATERIALS AND METHODS

This was a descriptive cross-sectional study that included patients who were referred to Firoozgar Hospital, affiliated to Iran University of Medical Sciences, Tehran, Iran, to undergo ERCP for any reason during 2020-2021. The inclusion criterion was undergoing ERCP for any reason. The exclusion criteria were patient dissatisfaction with participating in the study, non-subsequent referral to the clinic, or death. The patient's hospital records provided demographic information, history of previous diseases, medications, preoperative hemoglobin, and the cause of ERCP. Intraoperative bleeding was defined as any bleeding from the ampulla observed during endoscopy. The timeout bleeding was considered a week after ERCP.

The patients' documents were assessed for sphincterotomy or the occurrence of intraoperative bleeding. Hb was checked 6 hours after ERCP. Patients were discharged and revisited one week later. Hb level was also checked at the one-week visit. Data were extracted using the hospital registry system for laboratory findings and a researcher-made questionnaire for demographic data and medical history. Anemia was classified based on the National Cancer Institute as follows: Mild Hb drop: 10.0 g/dL or lower than normal; Moderate Hb drop: 8.0 to 10.0 g/dL; and Severe Hb drop: 6.5 to 7.9 g/dL (1).

Statistical analyses

The qualitative variables were reported as numbers and percentages, and the quantitative variables as means and standard deviations. T test, one-way ANOVA, repeated measures ANOVA, Chi-square, and Fisher's exact testwere used to investigate the association between qualitative and quantitative variables where applicable. Kolmogorov–Smirnov was used to assess data normality. In case of non-normal distribution, equivalent non-parametric tests were used. P values below 0.05 were considered statistically significant. SPSS software version 25 (SPSS Inc. Chicago, IL, USA) was used for statistical analysis.

Ethical consideration

The researchers adhered to the Helsinki Convention at all stages of the research. The information of the participants was used without revealing their identities. Moreover, written informed consent was obtained from all patients. They had the right to withdraw from the study whenever they wished without affecting their medical care. The study protocol was approved by the ethics committee of the Iran University of Medical Sciences (code: IR.IUMS.FMD.REC.1399.513).

RESULTS

We examined 500 patients. The mean±SD age of the patients was 60.43±16.37 years (range: 11 to 95 years). Regarding medical history, 12.2% (61 patients) had type 2 diabetes mellitus (DM). Table 1 presents the baseline characteristics of the study population. The most common causes of ERCP in our study were gallstones (55.8%, 279 patients), bile sludge (13.6%, 68 patients), pancreatic mass (7.6%, 38 patients), and CBD stenosis (4 patients). In 27 patients (5.4%), we also observed signs and symptoms of

cholangitis.

Table 1. Baseline characteristics of the study population

Variable		Number	Percentage
Sex	Male	254	50.8%
	Female	246	49.2%
	Diabetes mellitus	61	12.2%
	Hypertension	18	3.6%
	Cardiovascular disease	76	15.2%
	Chronic kidney disease	3	0.6%
	Hematological disease	3	0.6%
Smoking		18	3.6%
Drug history	Clopidogrel	13	2.6%
	Rivaroxaban	8	1.6%
	Warfarin	9	1.8%
	NSAIDs	14	2.8%
	Aspirin	71	14.2%

In 73.4% (367 patients) of the patients, the anatomy of the ampulla was normal. In 1.4% (n = 7), a pre-ampullary lesion, in 3% (n=15), bulging, in 2% (n=10) infiltration in or near the ampulla, and in 2.5% (n=26) diverticulum near or inside the ampulla were reported. We performed ERCP in 11.6% (n=58) of the patients without sphincterotomy. However, in 17.2% (n=86), incomplete sphincterotomy and in 71.2% (n=356), a complete sphincterotomy were performed. We also performed precut and balloon dilation in 42 (8.2%) and 27 patients (5.4%), respectively.

Of the 500 patients included in this study, 21 (4.2%) had bleeding during ERCP. We performed epinephrine injections in 20 patients to stop bleeding. Due to the failure of this method, we used vascular clipping in one patient. In another patient, we used vasoconstriction to control bleeding from the beginning. The prevalence of overt bleeding 24 hours after ERCP was 0.6% (n=3). The mean±SD of Hb level before, 24 hours, and 1 week after ERCP were 12.6±1.90, 12.15±1.97, and 12.06±1.96 mg/dL, respectively. Acute bleeding during ERCP did not have any statistical association with age, sex, history of DM, chronic hypertension, cardiovascular diseases, renal diseases, hematological diseases, smoking, or clopidogrel, rivaroxaban, warfarin, NSAIDs, and aspirin use. However, regarding delayed bleeding, there was a statistically significant association with DM history (P=0.036).

Moreover, there was no association between laboratory data, including WBC (white blood cell), PLT (platelet), PT, PTT, INR, serum potassium, and serum creatinine, before ERCP with acute or chronic bleeding. Furthermore, there was no association between acute or chronic bleeding and the indication of ERCP. There was no association between acute or chronic bleeding and the ampulla anatomy, performing precut, balloon dilatation, pancreatic and biliary stent insertion, or the stent type. There was also no association between CBD size and acute or chronic bleeding.

In addition, 24 hours after ERCP, 54% (n = 270) of the patients had a mild Hb drop, and 7.8% (n=39) had a moderate to severe drop. These values were 45.6% (n=228) and 13% (n=65) during the first week after ERCP. In patients with moderate to severe hemoglobin drop after 24 hours, the mean age was significantly lower (P=0.029), and smoking prevalence was higher (P=0.008). Moreover, in patients with moderate to severe hemoglobin drop after a week, clopidogrel consumption was significantly more common (P=0.03). However, in patients with periampullary diverticulum, moderate to severe hemoglobin drop during the first 24 hours of ERCP was significantly higher than in those with normal ampulla anatomy (P<0.001). Table 2 shows the association between some study variables and hemoglobin drop during the first 24 hours.

Table 2. The association between the study variables and hemoglobin drop during the first 24 hours

		Hb drop		P value
		Mild (< normal range to 10.0 g/dL)	Moderate to severe (< 10.0 g/dL)	
Age, year		60.00±16.64	15.89±54.51	0.029
Sex	Male	126 (84.6%)	23 (15.4%)	0.150
	Female	144 (90%)	16 (10%)	
Diabetes mellitus	No	230 (87.8%)	32 (12.2%)	0.535
	Yes	26 (83.9%)	5 (16.1%)	

Hypertension	No	248 (87.3%)	36 (12.7%)	0.889
	Yes	8 (88.9%)	1 (11.1%)	
Cardiovascular disease	No	208 (87.8%)	29 (12.2%)	0.678
	Yes	48 (85.7%)	8 (14.8%)	
Chronic kidney disease	No	254 (87.3%)	37 (12.7%)	1.00
	Yes	2 (100%)	0	
Hematological disease	No	255 (87.3%)	37 (12.7%)	1.00
	Yes	1 (100%)	0	
Smoking	No	250 (88.3%)	33 (11.7%)	0.008
	Yes	6 (60%)	4 (40%)	
Clopidogrel use	No	246 (87.2%)	36 (12.8%)	0.719
	Yes	10 (90.9%)	1 (9.1%)	
Rivaroxaban use	No	253 (87.2%)	37 (12.8%)	1.00
	Yes	3 (100%)	0	
Warfarin use	No	247 (87%)	37 (13%)	0.247
	Yes	9 (100%)	0	
NSAIDs use	No	246 (87.5%)	35 (12.5%)	0.667
	Yes	10 (83.3%)	2 (16.7%)	
Aspirin use	No	221 (88%)	30 (12%)	0.465
	Yes	37 (84.1%)	7 (15.9%)	

DISCUSSION

ERCP indication is primarily therapeutic; however, the overall incidence of post-ERCP complications is higher than before but varies in different studies. Pancreatitis and bleeding have remained as two main complications (2). A systematic review of 21 prospective studies between 1977 and 2006 involving 16,885 patients reported an overall complication rate of 6.85%, with a mortality of 0.33% (3). In contrast, another retrospective study involving only therapeutic ERCP procedures (including 2,715 patients) by a single endoscopist reported a 4.9% complication rate (4).

Bleeding after ERCP occurs in up to 2% of patients (severe bleeding in 0.1 to 0.5%) and is specifically related to sphincterotomy (5). In contrast, sphincterotomy was not associated with a higher prevalence of bleeding in our study. In our study, the rates of immediate and delayed bleeding after ERCP were 4.2% and 0.6%, respectively. Different studies have reported diverse rates of bleeding after ERCP. For example, in a study by Su Baeh and others performed on 3,650 patients over 7 years, bleeding was reported in 9.8% of cases after ERCP, which is higher than our study (6).

We can classify risk factors for ERCP-related bleeding into patient-related, technique-related, and operator-related factors. In our study, the patient's age and sex did not affect the incidence of immediate bleeding. Moreover, the presence of medical comorbidities or smoking did not increase the risk of bleeding. We recommended our patients to stop using anticoagulants, including clopidogrel, rivaroxaban, and warfarin, three days prior to ERCP. Although the risk of bleeding associated with the use of thienopyridines (ticlopidine, clopidogrel, and prasugrel) has not been well studied, we recommend stopping them at least 5 to 7 days before high-risk endoscopic procedures (such as ERCP with sphincterotomy) (7-9). Current guidelines suggest that we should terminate antiplatelet agents (APAs) (not acetylsalicylic acid (ASAs)) before ERCP. The risk of post-ERCP bleeding increases in patients who start taking anticoagulants within 3 days after ERCP due to any coagulation disorder. ASAs or NSAIDs are safe before the procedure and do not increase the risk of bleeding after ERCP. Current guidelines indicate that we can safely continue low doses of aspirin or NSAIDs during the pre-endoscopic period (10), which is consistent with the results of our study.

Moreover, in our patients with a history of diabetes mellitus, the incidence of chronic bleeding was significantly higher. A meta-analysis and retrospective studies had confirmed cirrhosis, kidney disease, and dialysis for end-stage renal disease (especially one-year hemodialysis) as risk factors for ERCP-related bleeding (11-13). However, no study has suggested the role of diabetes mellitus as a risk factor for bleeding after ERCP, which is novel in our investigation.

We can attribute the higher risk of delayed bleeding in diabetes mellitus to two factors. First, medications such as

aspirin or anticoagulants might have a role in patients at risk for cardiovascular disease or atherosclerosis. However, the results of our study showed that if we stopped anticoagulants in time before ERCP, the risk of bleeding was not increased. In another study, DM was associated with bleeding after polypectomy with a 2.5 ratio, but this effect disappeared after adjusting the confounders for the use of anticoagulants (14). The second factor is the role of DM in the development of coagulation and hematological disorders, which can increase the susceptibility to bleeding. In some other studies, the role of DM has been reported as an independent factor influencing the incidence of bleeding in percutaneous nephrolithotomy (15), intracerebral hemorrhage in elderly patients with ITP (16), transcatheter aortic valve implant surgery (17), and Roux-en-Y gastric bypass surgery (18).

Freeman introduced three categories to anticipate the risk of bleeding after ERCP: definite, probable, and non-risk factors. Patients with underlying coagulopathy cholangitis and those receiving anticoagulant therapy less than 3 days after sphincterotomy are at increased risk of bleeding during and after the procedure. Other potentially dangerous risk factors for bleeding include liver cirrhosis, dilated CBD, common bile duct stones, and periampullary diverticulum (19). However, in our study, CBD size did not show a difference in patients with and without acute and delayed bleeding. The presence of pre-ampullary diverticulum in our patients was associated with a higher incidence of acute and chronic bleeding, but this higher incidence of bleeding was not statistically significant. In our patients with pre-ampullary diverticulum, the prevalence of chronic bleeding was 11 times higher than in those with normal ampulla anatomy, but this difference was not statistically significant. Moreover, the rate of drop in Hb was significantly higher in patients with pre-ampullary diverticulum. As a result, based on our study data, the presence of a diverticulum appears to be a risk factor for bleeding after ERCP, especially non-clinical and occult bleeding.

The role of precut in post-ERCP bleeding is controversial. Two meta-analyses showed that primary precut incision sphincterotomy in difficult biliary access did not increase the rate of bleeding after ERCP compared with continuous cannulation efforts (19,20). However, in contrast to these meta-analyses, precut sphincterotomy has been associated with an increased incidence of bleeding in previous multicenter studies (5,21). In contrast in our study, none of the indicators related to ERCP technique, including precut, balloon dilatation, pancreatic and biliary stent implantation, and biliary stent material, had an effect on increasing the incidence of bleeding, both acute and delayed.

We performed epinephrine injections in 20 patients to stop bleeding. Due to the failure of this method, we used vascular clipping in one patient. The most widely used and generally effective endoscopic intervention is the injection of diluted epinephrine therapy (1: 10000) through a sclerotherapy needle in and around the sphincterotomy site (22).

We define clinically significant bleeding as the presence of hematomas and/or melena, a drop in hemoglobin of more than 2 gr/dL, or the need for interventions such as blood transfusions or endoscopy and its prevalence is estimated to be between 0.1% and 2% (23,24). In our study, the prevalence of moderate to severe Hb drop (within the first24 hours after ERCP) was 7.8%, and the prevalence of moderate to severe chronic hemoglobin drop (up to one week after ERCP) was 13%, which are relatively higher compared with previous investigations. Among underlying factors affecting acute Hb decline, smoking was associated with moderate to severe Hb drop. In a study examining the effects of active smoking on antithrombotic therapy in patients with atrial fibrillation, patients with AF who smoked actively did not have a higher risk of thromboembolic events, but the risk of massive bleeding was significantly higher, especially in patients treated with vitamin K analogues. The authors suggested that the reason for the increased risk of bleeding in smokers might be INR instability, which leads to an increased risk of bleeding (25).

In addition, in patients taking clopidogrel, the rate of moderate and severe hemoglobin drops was significantly higher. The reason could be due to the anticoagulant properties of this drug, which increase the rate of bleeding. However, the results showed that in patients taking clopidogrel, the rate of clinically overt bleeding was not different. As a result, a drop in hemoglobin can be caused by latent and delayed bleeding that has not been reported during ERCP. Another cause of hemoglobin drop in these patients may be due to the side effects of clopidogrel consumption, including neutropenia, thrombocytopenia, acquired hemophilia, and in rare cases, hemolytic uremic syndrome (HUS) syndrome with thrombotic thrombocytopenia purpura (TTP) (26). We had some limitations. First, the cross-sectional design might have some biases, such as incomplete information derived from documents. Moreover, due to several factors that might affect the risk of post-ERCP bleeding, analyses could have been biased. We suggest performing large and multi-centric investigations to assess more underlying factors. Well-designed meta-analyses are also highly recommended.

CONCLUSION

The prevalences of acute and delayed clinical bleeding after ERCP were 4.2% and 0.6%, respectively, and the rates of moderate to severe and delayed Hb drop were 7.8% and 13%, respectively. The only risk factor for chronic bleeding was a history of DM. In contrast, sphincterotomy, dilated CBD, periampullary diverticulum, and precut incision did

not increase the incidence of bleeding after ERCP. Smoking and clopidogrel were risk factors for moderate to severe hemoglobin loss in our study. We recommend checking Hb levels at regular intervals as a more accurate indicator for monitoring bleeding after ERCP.

ACKNOWLEDGEMENT

We would like to thank the staff of the endoscopy ward of Firoozgar Hospital, who kindly helped us perform the procedures.

Funding and support

None

Disclosure

None

REFRENCES:

1. Badireddy M, Baradhi KM, Wilhite Hughes A. Chronic Anemia (Nursing). 2021.
2. Vandervoort J, Soetikno RM, Tham TC, Wong RC, Ferrari Jr AP, Montes H, et al. Risk factors for complications after performance of ERCP. Gastrointestinal *Endosc*. 2002;56(5):652-6.
3. 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 Aug;102(8):1781-8.
4. Katsinelos P, Lazaraki G, Chatzimavroudis G, Gkagkalis S, Vasiliadis I, Papaeuthimiou A, et al. Risk factors for therapeutic ERCP-related complications: an analysis of 2,715 cases performed by a single endoscopist. *Ann Gastroenterol*. 2014;27(1):65-72.
5. Loperfido S, Angelini G, Benedetti G, Chilovi F, Costan F, De Berardinis F, et al. Major early complications from diagnostic and therapeutic ERCP: a prospective multicenter study. *Gastrointest Endosc*. 1998;48(1):1-10.
6. Bae SS, Lee DW, Han J, Kim HG. Risk factor of bleeding after endoscopic sphincterotomy in average risk patients. *Surg Endosc*. 2019;33(10):3334-3340.
7. Chandrasekhara V, Khashab MA, Muthusamy VR, Acosta RD, Agrawal D, Bruining DH, et al. Adverse events associated with ERCP. *Gastrointest Endosc*. 2017;85(1):32-47.
8. Freeman ML, Nelson DB, Sherman S, Haber GB, Herman ME, Dorsher PJ, et al. Complications of endoscopic biliary sphincterotomy. *New England Journal of Medicine.* 1996;335(13):909-19.
9. Acosta RD, Abraham NS, Chandrasekhara V, Chathadi KV, Early DS, Eloubeidi MA, et. *Endosc*. 2016;83(1):3-16.
10. Yildirim AE. ERCP-related bleeding. *J Exper Clin Med*. 2021;38(2s):44-52.
11. Mashiana HS, Dhaliwal AS, Sayles H, Dhindsa B, Yoo JW, Wu Q, et al. Endoscopic retrograde cholangiopancreatography in cirrhosis-a systematic review and meta-analysis focused on adverse events. *World J Gastrointest Endosc*. 2018;10(11):354.
12. Nakaji S, Hirata N, Matsui H, Shiratori T, Kobayashi M, Yoshimura S, et al. Hemodialysis is a strong risk factor for post-endoscopic sphincterotomy bleeding in patients with choledocholithiasis. *Endosc Int Open*. 2018;6(5):E568-E574
13. Leal C, Prado V, Colan J, Chavez-Rivera K, Sendino O, Blasi A, et al. Adverse events and acute chronic liver failure in patients with cirrhosis undergoing endoscopic retrograde cholangiopancreatography: a multicenter matched-cohort study. *Am J Gastroenterol*. 2019;114(1):89-97.
14. Sawhney MS, Salfiti N, Nelson DB, Lederle FA, Bond JH. Risk factors for severe delayed postpolypectomy bleeding. *Endoscopy*. 2008;40(02):115-9..
15. Amri M, Naouar S, Khalifa B, Hmidi N, Braiek S, ElKamel R. Predictive factors of bleeding and fever after percutaneous nephrolithotomy. *Tunis Med*. 2019;97(5):667-674.
16. Kapoor R, Pati HP, Mahapatra M, Monga A. Presence of essential hypertension or diabetes mellitus is a predictor of intracranial bleeding in elderly patients: a study of 108 patients with isolated thrombocytopenia from a single reference center. *Turk J Hematol*. 2015;32(2):158-62.
17. Pilgrim T, Stortecky S, Luterbacher F, Windecker S, Wenaweser P. Transcatheter aortic valve implantation and bleeding: incidence, predictors and prognosis. *J Thromb Thrombolysis*. 2013;35(4):456-62.
18. Rabl C, Peeva S, Prado K, James AW, Rogers SJ, Posselt A, et al. Early and late abdominal bleeding after Roux-en-Y gastric bypass: sources and tailored therapeutic strategies. *Obes Surg*. 2011;21(4):413-20.
19. Balmadrid B, Kozarek R. Prevention and management of adverse events of endoscopic retrograde cholangiopancreatography. *Gastrointest Endosc Clin*. 2013;23(2):385-403.
20. Tang Z, Yang Y, Yang Z, Meng W, Li X. Early precut sphincterotomy does not increase the risk of adverse events for patients with difficult biliary access: A systematic review of randomized clinical trials with meta-analysis and trial sequential analysis. *Medicine*. 2018;97(36):e12213.
21. 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(2):417-23.
22. Boujaoude J, Pelletier G, Fritsch J, Choury A, Lefebvre JF, Roche A, et al. Management of clinically relevant bleeding following endoscopic sphincterotomy. *Endoscopy*. 1994 b;26(02):217-21.
23. Wilcox CM, Canakis J, Mönkemüller KE, Bondora AW, Geels W. Patterns of bleeding after endoscopic sphincterotomy, the subsequent risk of bleeding, and the role of epinephrine injection. *Am J Gastroenterol*. 2004 Feb;99(2):244-8.
24. Ferreira LE, Fatima J, Baron TH. Clinically significant delayed postsphincterotomy bleeding: a twelve year single center experience. *Minerva Gastroenterol Dietol*. 2007;53(3):215-23.
25. Angoulvant D, Villejoubert O, Bejan-Angoulvant T, Ivanes F, Saint Etienne C, Lip GY, et al. Effect of active smoking on comparative efficacy of antithrombotic therapy in patients with atrial fibrillation: the Loire Valley Atrial Fibrillation Project. Chest. 2015 1;148(2):491-8.
26. Balamuthusamy S, Arora R. Hematologic adverse effects of clopidogrel. *Am J Ther*. 2007;14(1):106-12.