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Analysis of pre-and intraprocedural risk factors for endoscopic pancreatitis

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RESEARCH

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ABSTRACT

Background

The most common complication of endoscopic retrograde cholangiopancreatography (ERCP) is acute pancreatitis (PEP), which occurs in 4per cent–5.1per cent of patients; however, depending on the prevalence of risk factors, the incidence may grow– to 7.8per cent–29.2per cent. It is therefore important to determine the pre-and intraprocedural risk factors and establish guidelines to proper assess the risks during ERCP.

Aims

Determine the pre-and intraprocedural risk factors and establish guidelines to assess the risks during ERCP.

Methods

The study group included 402 patients who underwent an endoscopic sphincterotomy. We evaluated 29 variables according to a three–stage assessment system: Stage I - during the qualification (seventeen variables), Stage II affecting the decision of two-stage access (eight variables), and Stage III – affecting the decision of two-stage procedure (four variables).

Results

The significant variables based on univariate and multivariate logistic regression analyses were as follows: during the first stage, age below 40 (OR = 6.9, p = 0.0004; OR = 5.2, p = 0.0032) and narrowed common bile duct (CBD)(OR 5.3, *p*=0.0007; OR = 4.4, *p*= 0.0037); at the second stage, non-prominent papillae (OR = 5.1, p = 0.0049; OR = 5.3, *p*= 0.0039) and difficult cannulation (OR = 3.2, p = 0.0298; OR= 3.4, *p*= 0.0227); and at the third stage, post-sphincterotomy bleeding (OR 3.6, *p*=0.0148; OR *p*=0.015).

Conclusion

The obtained results determined five PEP risk factors: age <40 years, a CBD diameter <9mm, non-prominent papillae, difficult cannulation and post sphincterotomy bleeding. Two of these risk factors, non-prominent papillae of Vater and post-sphincterotomy bleeding, were identified for the first time. The proposed three-stage PEP risk assessment system seems to be useful.

Key Words

Acute pancreatitis, pancreatic parenchyma, post sphincterotomy bleeding

What this study adds:

1. What is known about this subject?

Available studies evaluated 56 variables but only few confirm the significance of the same risk factors defined in the same way.

2. What new information is offered in this study?

Two risk factors (non-prominent papillae and post-sphincterotomy bleeding), were identified for the first time. The proposed three-stage PEP risk assessment system seems to be useful.

3. What are the implications for research, policy, or practice?

The knowledge about of all risk factors and creation guidelines for multi-stage risk assessment can help reduce the risk of PEP.

Background

The most common ERCP complication is post-endoscopic pancreatitis (PEP), which occurs in 4.1per cent–5.4per cent of patients. Depending on the prevalence of risk factors, it

may increase to between 0.4per cent–3.6per cent and 7.8per cent–29.2per cent with an odds ratio reaching 14.9. However, several coexisting variables may lead to acute pancreatitis occurring in 40per cent-43per cent of patients[1]. It is, therefore, understood that to reduce the occurrence of PEP, estimate the cumulative risk arising from the presence of several factors and the creation of rules to stage risk estimations during ERCP are necessary to decide the optimal patient-based course of treatment.

Previous studies evaluated 25 variables associated with the patient and 31 variables associated with the procedure. Many of these variables were identified as statistically significant for increased risk of PEP. Nevertheless, only a few studies duplicated most of the data and were defined in the same way[2-7]. Examples of this are the EAES guidelines[1] and the results of the three largest studies: a meta-analysis by Masci (10,000 patients)[5], retrospective studies by Cotton (11,000 patients)[2] and an analysis by Cheon (14,000 patients)/4/. In all these publications, only two risk factors are repeated, in three, female sex, and in two, pre-cut incision[1-4,8]. Therefore, it is likely that not all the significant risk factors have been identified, and the importance of those already identified has not been clearly specified. Therefore, there is still a need for further studies on this issue.

The second unresolved problem is that the risk factors occur not only prior to the treatment, but also during the procedure. An analysis of the cumulative risk of PEP development should therefore be conducted a few times during ERCP. However, the evaluation of this phenomenon was not fully possible due to the small number of patients who had two or more risk factors, so statistical analysis has a limited value. In addition, a general system of risk assessment with strict guidelines has yet to be adopted. The execution of this assessment seems to be justified prior to any maneuvers that could potentially reduce the risk of PEP. During the ERCP procedure, this type of situation exists in Stage I, the qualification stage; Stage II, before the implementation of the two-stage access (postpone subsequent access attempts by 4–7 days); and Stage III before the decision on the two-step procedure (completing the ERCP procedure after 4–12 weeks). The above assumption constituted the basis for the proposed three-stage PEP risk assessment system during ERCP, which was analysed in the present study.

Method

The study was retrospective and carried out during ERCP procedures in a single centre over 21 months. In that period, 1,040 procedures were performed. The criterion for inclusion in the study was undergoing endoscopic sphincterotomy. The exclusion criterion was having acute pancreatitis before ERCP or operative procedures on the papillae of Vater. Acute pancreatitis was defined as the level of serum amylase three times above the norm with coexisting pancreatic pain 24 hours after the procedure. According to these criteria, 402 patients were enrolled in the study. The mean age was 66 years, with less than 8per cent of the participants under 40 years. Women accounted for 58.2per cent (234) of the participants. Coexisting systemic diseases were reported in 54.2per cent (218) of the patients. The indication for ERCP in 56.7per cent of the patients (228) was choledocholithiasis and in 41.2per cent (168) was biliary strictures causing obstructive jaundice, while in 24.4per cent (98), at the time of examination, the indication was not clearly defined, mainly due to lack of pathological confirmation. The biliary tree was narrowed at the level of the ampulla of Vater in 16.9per cent (68), the distal part in 13.2per cent (53), the middle part of the CBD in 4.2per cent (17), the level of the hepatic hilus in 5.5per cent (22) and in multiple locations in 1.9per cent of the patients (8). In the remaining 1.5per cent (6) of the patients, the procedure was performed because of postoperative biliary leakage. According to the Houriuchi classification,[11] the papillae of Vater was non-prominent /flat (Type I) in 42.5per cent (171), prominent (Type II) in 30.3per cent (122) and bulging (Type III) in 8.2per cent of the patients (33). The papillae located in the diverticulum or on its periphery were found in 19.4per cent (78) of the patients. The diameter of the CBD measured on the cholangiography image at 2 cm from the ampulla did not exceed 9 mm in 17.2per cent (69) of the patients, and the distal segment was narrower than 5 mm in 33.8per cent (136) of the patients. Post-endoscopic pancreatitis occurred in 4.47per cent (18) of the patients.

ERCP technique: All patients in the analysed group underwent sphincterotomy. Difficult cannulation was defined as unsuccessful access to the biliary tree during 5 minutes of the procedure, and this occurred in 46.02per cent (137) of the patients. Unintentional insertion of the guide-wire into the duct of Wirsung occurred in 10.7per cent (43) of the patients, and the duct was opacified in 8.2per cent (33) of the patients. The pre-cut incision was performed in 41.0per cent (165) of the patients, and a two-step procedure was implemented in 11per cent (44) of the patients. In 16.2per cent (65) of the patients, the CBD prosthesis that was employed had a diameter larger than 7Fr. Post-sphincterotomy bleeding occurred in 13.2per cent (53) of the patients, and endoscopic management was necessary in 10.9per cent (44) of the patients. Pathological examination from the ampulla of Vater was collected in 10.2per cent (41) of the patients. The prosthesis on the Wirsung's duct was introduced in 3per cent (12) of the

patients. Altogether, 29 variables were analyzed, including six that had not been previously assessed in the available published research, namely, the level of biliary strictures, the shape of the ampulla of Vater, post-sphincterotomy bleeding, bleeding treatment and sample collection for pathological examination. When using the three-stage risk assessment system, the following variables were analyzed. In the first stage, during the qualifying procedure, seventeen variables were assessed: young age, female gender, systemic diseases, level of biliary strictures, lack of CBD stones, normal bilirubin levels prior to ERCP, chronic pancreatitis, suspected dysfunction of the sphincter of Oddi and a narrow common bile duct. At the second stage, prior to the implementation of a two-stage access, eight other variables were assessed: the shape of the ampulla of Vater (according to the Houriuchi classification), difficult cannulation, unintentional insertion of the guide-wire, opacification of the duct of Wirsung and the performance of the pre-cut incision. During the third stage, before the decision on the two-step procedure (postponement of further part of ERCP by 4-12 weeks). The remaining four variables were measured: CBD prosthesis with a diameter greater than 7Fr, post-sphincterotomy bleeding, endoscopic injections and collection of samples for pathological examination.

Another analysis was carried out on the prevalence of PEP in the case of the coexistence of several risk factors. For this purpose, we created a risk model in which we calculated the risk of PEP according to the number of risk factors that were statistically significant.

Statistical analysis: Logistic regression univariate and multivariate models were used for statistical analyses. For each independent variable, the regression coefficient, standard error of the regression coefficient, quotient of the opportunities and 95per cent statistically significant range were determined. In the multifactor regression for the introduction of data, Enter and Forward techniques were used. We also assessed prediction values with a Hosmer and Lemeshow test, the percent correctly classified observations, and an analysis of the ROC specifying the area under the curve (AUC). For the calculations, we used Windows Statistics for Biomedical Research. Version 12.4.

Results

At the stage of qualifications for ERCP (Stage I), 17 variables subjected to univariate regression analysis proved to be statistically significant. All three criteria relating to young age were shown to be significant: under 30 (OR=6.6, *p*=0.0025), under 40 (OR=6.9 *p*=0.0004) and under 50 (OR=3.3, *p*=0.0234). The two parameters related to biliary strictures were significant: narrower than 9 mm (OR=5.3, p=0.0007) or narrower than 5 mm (OR=3.3, *p*=0.0171). Multivariate regression analysis performed at this stage confirmed that the greatest risk factors for PEP were age under 40 (OR=5.4, p=0.008) and a CBD diameter less than 9 mm (OR=3.0, *p*=0.0409). At Stage II, before a decision about potentially delaying the access for 4–7 days, a statistically significant odds ratio in the univariate analysis was found for two parameters: non-prominent/flat papillae (OR=5.1, *p*=0.0049) and difficult cannulation (OR=3.2, *p*=0.0298). In the multivariate regression analysis, statistically significant values were found for a non-prominent/flat papilla of Vater (OR=6.2, *p*=0.0029) and difficult cannulation (OR=8.1, *p*=0.0014). During the third stage, preceding the possible decision of two-stage procedure, in the univariate logistic regression analysis, a statistically significant effect on the PEP risk was found for post-sphincterotomy bleeding (OR=3.6, *p*=0.0148). The significance of this variable was also confirmed in the multiple regression analysis (OR=3.6, *p*=0.015). Summarized results of all logistic regression analyses are presented in Graph I.

In the second part of the analysis, we assessed the impact of coexisting risk factors. The highest risk for developing PEP was observed for the coexistence of the following pairs of variables: age under 40 and difficult cannulation (38.4per cent), age under 40 and CBD diameter of less than 9 mm (29.48per cent), CBD diameter of less than 9 mm and post-sphincterotomy bleeding (24.5per cent), age under 40 and post-sphincterotomy bleeding (23.4per cent) and age under 40 and non-prominent/flat papilla of Vater (21.6per cent). The results for PEP risk with the coexistence of pairs of variables are presented in Graph II and cumulative risk in the case of coexistence of all statistically significant variables is presented in Graph III.

Discussion

The risk of developing acute pancreatitis occurring after ERCP is influenced by the presence of risk factors, which are connected to both the patient and the technique of the procedure itself. As a result, the risk is also modified during the endoscopic procedure. Therefore, knowledge concerning the prognostic value of each endoscopic maneuver is important for the selection of the best strategy for each patient. However, to be able to achieve this, three conditions must be met. The first condition involves identification of all known risk factors and specifying the importance of each. The second condition involves the creation of a system for evaluating the probability of PEP development, which allows assessment of the risk both during the qualification stage and during the procedure. The third condition involves the determination of risk resulting from the co-existence of several variables in one patient.

Based on the conditions above, five factors were identified that increase the risk of post-endoscopic pancreatitis. Two of these occurred at the first stage of the assessment, two at the second stage and one at the third stage. In Stage I, during the qualification stage for the procedure, an increased risk of PEP development was found in patients younger than 40 years old and those with a CBD smaller than 9 mm. A decrease risk of PEP, together with age, is most likely a consequence of progressive degradation of the pancreatic parenchyma, which results in a smaller response of this organ to irritations caused by an endoscopic procedure. This was confirmed by the fact that 57per cent of all severe forms of acute pancreatitis affected young people. However, data pertaining to this issue are not consistent when age limits from 20 years to over 70 years were adopted. The importance of young age was confirmed in 19 publications with OR values ranging from 0.8 to 3.5, while contrary conclusions were drawn by Rabenstein, Cotton and Testoni. Analyses aimed at defining mutual relations between aging and the risk of PEP showed that the OR decreased by 0.75 for each 20 years[15] or by 1.09 for each 5 years of the patient's life.[17] In percentage values, the frequency of PEP occurrence below 30 years of age was 6.2per cent-8per cent; in the 30-49 age group, 4.7per cent-36per cent; in the 50-69 age group, 4.4per cent-33per cent, and in patients over 70 years of age, 2.9per cent-22per cent.[3,15] In the presented study to determine the optimal age value for the groups under analysis, the OR single-factor regression values were first calculated for the 30 year, 40 year and 50 year age limits. The greatest additional risk, which was over six times higher, occurred in patients less than 40 years of age with a 15.5per cent difference in the frequency of occurrence compared to the group of older people. Therefore, the limit of 40 years of age was included in the calculations of the multi-factor regression. For the model including Stage I variables, for patients less than 40 years of age, the OR value was 5.6, and it was 5.4 for the model containing statistically significant variables in a single-factor regression. In the available studies, the same age limit (40 years of age) was assessed only in one study, in which the obtained OR value was 1.53[13]. In the ESGE recommendations, in contrast, age was defined only as a probable risk factor with OR values provided by numerous studies ranging from 1.09 to 6.68[1]. Compared to the data above, the results of the present analysis for the single-factor regression were outside the scope of values reported by other centers. This may result from a relatively low age limit adopted for the analysis (< 40 years), demographic differences of the analyzed groups of patients[13]. and techniques of the procedure[3,6,7,17-19] .

A narrow common bile duct with a diameter 2 cm away from the ampulla of Vater of less than 9 mm was another statistically significant factor. Based on the obtained results, it was found that this variable caused an increase in PEP development from three times (multivariate regression) to over five times (univariate regression). A potential explanation for this phenomenon is the fact that cannulation of the bile duct, in which a higher pressure does not occur, is more difficult, which results in a larger number of ineffective catheterizations. Co-existence of sphincter of Oddi dysfunction (SOD) is another probable reason. A comparison of this study's results with the results of studies from other centers is difficult, as there is no commonly adopted definition of a narrow common bile duct. In criteria used in available publications, its diameter ranged from 5 mm to 10mm[3,15,19]. Three authors used criteria like the present study, and the conclusions presented in these studies were contradictory. Masci showed a nearly two-fold increase in the risk (OR=1.8),[5] while no increase in the risk of developing PEP due to a narrow CBD was found in studies by Friedland[15] and Wang[6]. Using other criteria, the influence of a narrow bile duct on increased risk for PEP was documented in few studies with OR values ranging from 0.8 to 2.6[7,19,20]. No such relationship was confirmed in other subsequent studies[9,13,19]. Additionally, in ESGE recommenda -tions from the year 2014, this parameter was only defined as a probable risk factor.[1] Other studies assessed a decrease in the frequency of acute pancreatitis together with an increase in the diameter of the CBD. The results obtained on this basis showed that the PEP frequency in patients with a duct narrower than 5 mm was 19.6per cent, within the range from 6mm to 7mm was 10.3per cent, from 8mm to 9mm was 6.2per cent, from 10mm to 11mm was 2.1per cent, from 12mm to 13mm was 4–6per cent and above 14mm was 2.0per cent[1,20]. The data above imply that the importance of this variable has not been precisely established yet, and it requires further analyses based on uniform criteria[1,3,6,9,19,21].

At Stage II, before a decision was made about delaying the access for 4–7 days, another eight variables were analysed. Among these, statistically significant OR values were found for patients with a non-prominent/flat papilla of Vater and for those with difficult cannulation, both in single-factor and multi-factor regressions. The first of these variables resulted in a nearly five-fold increase in the risk of the development of acute pancreatitis, and a potential explanation of its influence involves the proximity of the bile duct opening and the pancreatic duct. This results in an increase in the probability of mechanical (failed attempts at catheterization) or thermal (during sphincterotomy) damage to the pancreatic duct with consequent outflow impairment and secondary development of post-endoscopic

pancreatitis. Therefore, the results obtained are justified from a logical point of view; however, they certainly need to be confirmed in further studies. In available publications, the shape of the ampulla of Vater was the object of only two studies, in which Masci[13] did not confirm its importance, while Cheng assessed only the location of the ampulla in the diverticulum and showed that such an anatomical variation decreased the probability of PEP.[19] In contrast to these data, it was not confirmed in the material collected for the purposes of this study that the ampulla in a diverticulum had a statistically significant protective influence on the development of acute pancreatitis, despite the fact that the calculated OR value was below one (OR=0.2345; *p*=0.1619), which might imply that such a relationship might occur in a study including a larger group of patients.

The second risk factor that was statistically significant in Stage II was difficult cannulation causing an increase in PEP risk from three to eight times in various models of logistic regression. In the literature, this parameter was examined on numerous occasions, and the OR values ranged from 1.76 to 14.9 with a percentage difference of occurrence ranging from 1.4per cent to 14.9per cent[2,3,6,21]. The discrepancies resulted from the use of various definitions of difficult cannulation that pertained to the time (from 5 min to 30 min) from the beginning of the procedure, or different number of failed attempts at catheterization of the bile ducts (from 3 to 20), the number of unplanned catheterizations of the pancreatic duct (from 2 to 5) [1,19,22]. Additionally, not all operators used a guide that lowered the risk of PEP from 8,6per cent to 16.6per cent, which, as shown by Artifon[23] and Lella. was associated with a lower frequency of unintended contrasting of the Wirsung duct and intraduodenal-wall contrast injection.[1] Another attempt at defining the risk involved an assessment of the relationship between the numbers of attempts at catheterization and the frequency of PEP. Two studies showed that for less than three attempts at catheterization, the risk of acute pancreatitis was 3.0per cent, for more than three attempts, the risk was 5per cent–3.3per cent, from 4 to 10 attempts, the risk was 6.5per cent, from 5 to 20 attempts, the risk was 9per cent, and for more than 20 attempts, the risk was 14.9per cent[3]. In analyses using logistic regression, the OR value was 4.4 for 10–15 attempts at catheterization and 9.4 for more than 15 attempts, and each attempt at cannulation increased the risk of PEP development by the OR value - 1.39. The results of the current research are reflected in ESGE guidelines from 2016, which defined difficult cannulation as presence: more than 5 contacts with the papilla; more than 5 minutes spent attempting to cannulate; more than one unintended pancreatic duct cannulation or opacification. At the same time, the mentioned guidelines suggest: the use of a guide, needle sphincterotomy as the preferred technique of pre-cut incision, in the case of a small wart the use of transpancreatic biliary sphincterotomy[1]. Unfortunately, these recommendations have only moderate or low quality of evidence, that is why they are not widely used. Therefore, it seems necessary to perform further prospective studies on groups of patients in whom an identical procedure and the same definition of difficult cannulation were used[1-3,6,21,22,25,27]. At Stage III, another four variables were assessed. Statistically significant OR values were found in a group of patients in whom bleeding occurred after sphincterotomy. This parameter has not been analysed so far in any available published studies. The obtained results show that its presence increased the probability of developing acute pancreatitis 3.5 times after an ERCP procedure with a difference of occurrence of 7.88per cent. It seems that specific anatomy can be a potential explanation for this relationship where, perhaps, the openings of the pancreatic and bile ducts were situated in direct vicinity, resulting in the pancreatic duct being more susceptible to mechanical and thermal damage during cannulation attempts and sphincterotomy. Another potential mechanism could result from the fact that bleeding is only a consequence of a technical error involving an incision in the wrong direction (too far toward the opening at 1 o'clock), which might result in a possible reaction on the part of the pancreas. However, an analysis of the relationship revealed a perplexing fact that no influence on the PEP risk was found in patients in whom bleeding was so intense that it required endoscopic injection. From a logical point of view, the formation of a mucous bubble is a factor that may additionally impair the outflow of pancreatic juice; however, such a relationship was not observed in the present study. It seems that this phenomenon can be explained by the fact that when haemostatic solution is injected around the bleeding point, a prosthesis to the Wirsung duct was simultaneously introduced. Such a strategy ensured proper outflow of pancreatic juice, despite edema in the adjacent tissues caused by hemostasis[22].

A second analysed problem is the possibility of assessing the probability of PEP for a patient with several risk factors. The development of PEP is nearly twice as high in young patients compared to older persons. In addition, performance of the procedure in a patient with suspected sphincter of Oddi dysfunction increases these chances nearly five times. The coexistence of these two factors translates into a 10-fold increase in the risk, regardless of difficulties during cannulation[9]. Data pertaining to this phenomenon in

published studies showed that the size of groups of patients with several risk factors is relatively small even in large studies. Additionally, attempts at comparing results of studies from various centers have related to the problem of various endoscopic techniques, definitions and compositions of analysed models in terms of risk factors. All these elements may lead to different conclusions. Therefore, knowledge presented in available publications is incomplete. In addition, an assessment of the mutual influences of risk factors based on an analysis of logistic regression has limited value with insufficiently sized groups compared to the occurrence of the end (i.e., PEP). Therefore, in the present study, we decided to analyse the frequency of PEP in patients with the coexistence only of 2-3 variables. Based on this analysis, it was found that the highest risk appears in patients less than 40 years of age in whom cannulation was difficult (38.4per cent) or the common bile duct was narrow (29.5per cent) and when a narrow CBD was present with bleeding after sphincterotomy (24.5per cent). Additionally, we calculated the probability of PEP developing with the coexistence of risk factors, which proved to be statistically significant in the logistic regression in our study. Based on our model, it was found that PEP could develop in 2per cent of patients under 40 years of age. If the diameter of the CBD was less than 9 mm, this risk increased to 6per cent; additionally, if the ampulla of Vater was non-prominent/flat, it increased to 19per cent; if cannulation was difficult, the risk of PEP increased to 48per cent; and in patients in whom bleeding occurred, it reached the value of 71per cent (Graphe III). Unfortunately, the calculations above also have limited value in groups of patients in whom the presence of the aforementioned risk factors was small. Therefore, they can be treated only as suggestions, requiring verification in further studies involving larger groups of patients. However, the results obtained were confirmed in a multi-center study by Freeman, in which 1,963 patients took part, which showed that risk factors accumulated. For this reason, in women with elevated bilirubin levels and easy access to the CBD, the risk of PEP was 5per cent; if cannulation was difficult, it increased to 16per cent; and if no gallstones were found in the bile ducts, SOD was suspected and episodes of acute pancreatitis occurred in the past, the risk reached 42.1per cent.[3,30,31] Tarnasky, showed that the risk of developing PEP in patients with a CBD diameter <5mm was three times higher (relative risk, RR=3.1), while in patients with an overactive sphincter, the RR was 10.3, and with co-occurrence of these characteristics, the risk was 18.1 with a frequency of 57per cent[32]. Mehta found that in patients under 59 years of age without gallstones in the common bile duct in whom sphincterotomy was performed, the risk was 27per cent, and in the case of co-occurrence with a narrow CBD (the diameter distally <5mm) with sphincter of Oddi dysfunction, 37per cent has a mortality rate at a level of 1.7per cent. It was shown in further studies with suspected sphincter of Oddi dysfunction, difficult cannulation and normal bilirubin levels that acute pancreatitis may occur in 31per cent–46.3per cent of patients with an OR value of 16.8[3,9]. Therefore, from a practical point of view, care must be taken in patients with co-existence of the aforementioned factors[3].

Three-stage risk assessment tactic proposal: To fulfil the third main target of this study, it should be concluded that the risk of developing acute pancreatitis is modified during the ERCP procedure. In addition, because of the coexistence of several factors, the overall risk for an individual patient is cumulative. Therefore, this risk should be assessed not only during the qualification stage but also during the procedure. For this purpose, the moments during the ERCP, should be specified on which the PEP risk assessment should be carried out. From a logical point of view, it seems that these assessments are justified before the maneuvers are performed, which can reduce the risk of PEP development. This seems to by exist during ERCP at the qualification stage, before deciding about delaying the next cannulation attempts for 4–7 days (two-step access) and before the decision on the two-step procedure (postponement of further part of ERCP by 4–12 weeks).

At Stage I, a comparison of potential advantages resulting from the procedure with existing risk factors results in ERCP being performed only in patients in whom the balance is unambiguously positive.[18] In the group of patients with an elevated risk, the introduction of additional preventive treatment should be considered, e.g., administration of an indomethacin suppository and intensive fluid therapy as its protective action has been documented in the largest number of studies[1,3]. The next maneuver that might lower PEP risk is delaying the next cannulation attempts for 4–7 days if, after a pre-cut incision, access to the bile ducts is still impossible. This is aimed at avoiding further traumatization of the ampulla of Vater when numerous ineffective attempts at obtaining access to the bile ducts and a pre-cut incision cause edema of tissues in the ampulla of Vater. This phenomenon also causes a change in anatomical conditions, which results in greater difficulty in obtaining access to the CBD with a probability of creating a false route on the one hand and deterioration of the outflow of pancreatic juice on the other hand. In addition, at this stage should be considered early introduction of protective methods as early precut or prosthesis to Wirsung 's duct.[1,3,6,19,21,27,38] Postponement of the procedure until the time when edema of the tissues subsides, the anatomy of

the ampulla of Vater returns to normal and a trace amount of bile appears at the opening of the bile ducts (which is made easier by its location) reduces the risk of PEP. In the analyzed group, this type of procedure was implemented in 10.9per cent (44/402) of patients, while at other centers, it was implemented in 13per cent to 44.8per cent of patients (11per cent – Bruins, 13per cent – Shakoor, 33per cent – Tweedle, 35per cent – Leung, 37per cent – Katuscak, Huigbertse, 44per cent – Dowsett). While assessing these results, it should be noted that such significant differences might result from the lack of uniform rules for this part of the ERCP procedure. This could result in the need for postponing further attempts at cannulation at various stages of the endoscopic procedure. Based on published results and the author's own experience (over 10,000 ERCP procedures), the adoption of this stage as the second point of the risk analysis seems justified. Of course, such a position may give rise to controversy, especially because many authors have documented that a pre-cut incision is a risk factor for PEP development[3,6]. However, there are research results that did not show any influence from a pre-cut incision on the risk of PEP development[2,19,]. In the present study (OR=0.22, p=0.018), a protective character of this maneuver on the risk of post-endoscopic pancreatitis was observed.[1,3] Such discrepancies support the thesis that an increase in the risk of acute pancreatitis after the pre-cut incision may mostly depend on mechanical damage to the ampulla resulting from numerous failed attempts at cannulation and not on the incision itself.[39] A potential explanation for the protective influence is the fact that sphincterotomy changes the gradient of pressures between the sphincter and the lumen of the duct of Wirsung and facilitates the outflow of pancreatic juice. The data show that a pre-cut incision performed at an early stage of the procedure in a technically correct manner does not increase the probability of PEP development. Such arguments were the basis for adopting as the second stage of the assessment the moment at which the decision about postponing a further procedure is made after the pre-cut incision. Another important aspect of using such a strategy is qualification for the procedure, which resulted in performing ERCP procedures only for therapeutic reasons. Therefore, as opposed to other analyses, there existed a clear justification for the pre-cut incision in all patients. On this basis, it seems justified that the second risk assessment should be made before the potential postponement of a further attempts of cannulation by 4-7 days[3,5,6,21].

The third step on which the cumulative risk during ERCP should be assessed is the moment in which access to the bile tree was obtained. If the added risk is high, then you should consider two-stage procedure. (completing the ERCP procedure after 4–12 weeks). Thanks to such tactics the potential risk of further maneuvers that could cause mechanical damage to the papilla (for example, by attempt to remove of big stones, lithotripsy or cannulation attempts during bleeding after a sphincterotomy) with subsequent edema is reduced. Simultaneously during stage II and III, depending on the cumulative risk of PEP should by consider the need for protective stenting of Wirsung duct. This maneuver, ensures proper outflow of pancreatic juice despite the appearance of contraction of the sphincter of Oddi and edema of tissues around the opening. Shakhor, Vandervoort, Guerland and Sherman showed that it had importance in patients with an elevated risk for sphincter of Oddi dysfunction (SOD), difficult cannulation, pre-cut incision or unplanned opacification of the pancreatic duct. In this group, introduction of a prosthesis into the pancreatic duct reduces the probability of PEP from 34per cent to 2per cent with an OR of 0.3[35] Additionally, Madacsy and Singh showed that a combination of early sphincterotomy with early preventive prosthetics of the duct of Wirsung in patients with a high risk reduces the frequency of PEP occurrence from 42per cent to 0per cent[21]. It seems that these differences may result from a different frequency of using this technique, which is a consequence of fear of failure, as even an experienced endoscopist has problems with getting access to the lumen of the pancreatic duct in 10per cent of patients, and after a failed attempt at prosthetics, the risk of acute pancreatitis increases dramatically, up to the OR value of 16.1 with a frequency of 65per cent.[1,41] Therefore, this maneuver should be performed by an experienced operator.[1,3] However, the level of failure may still reach 3.2per cent to 10per cent[10,41]. At the same time ESGE guidelines from 2016 recommends attempting prophylactic pancreatic stent in all patients with PGW-assisted attempts at biliary cannulation. Based on the provided information, the use of preventive prosthetics of the duct of Wirsung, despite the existing doubts pertaining to the tactics of performing this procedure, has an established position as a method of preventing PEP development. Therefore, depending on the cumulative risk should be considered at each stage of ERCP[1,3,10,14,19,21,22]. The proposed three-stage scheme of conduct based on risk analysis are presented in Table II.

Of course, it should be noted that a drawback of the proposed system, apart from the doubts discussed above, also involves a lack of assessment of the probability of occurrence of other complications, such as bleeding or perforation. However, their occurrence is most often connected with technical error involving an incision that is too long or has the wrong direction. Therefore, as opposed

to PEP, these complications do not require a several-stage assessment.

Conclusion

1. The obtained results determined five PEP risk factors: age under 40 years, a CBD diameter narrower than 9 mm, non-prominent/flat papillae of Vater, difficult cannulation and post sphincterotomy bleeding. Two of these risk factors, non-prominent/flat papillae of Vater and post-sphincterotomy bleeding, were identified for the first time.
2. The likelihood of post-endoscopic pancreatitis is particularly high in the group of patients who were of young age and had difficult cannulation or a narrow CBD.
3. The proposed three-stage PEP risk assessment system seems to be useful; however, it requires further evaluation in larger groups of patients.

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Figure 1: Summarized results of all logistic regression analyses

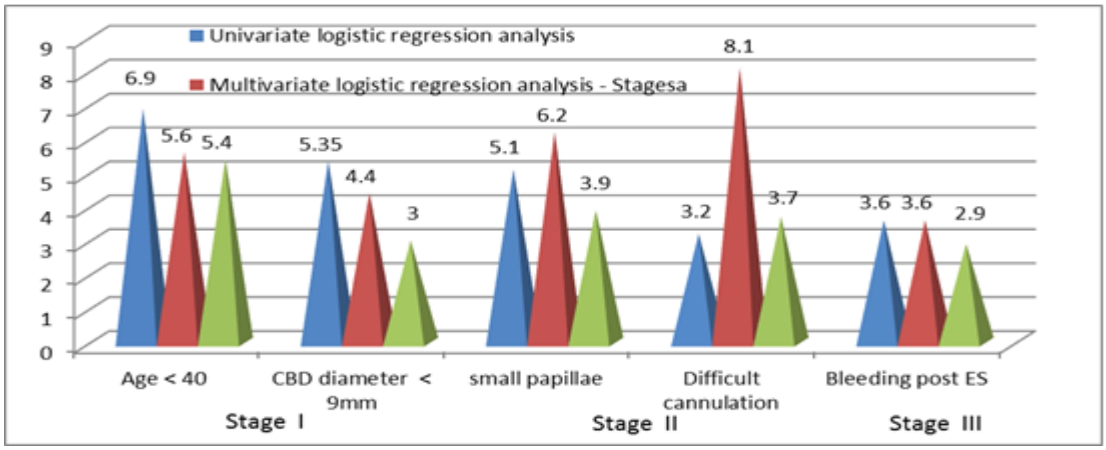
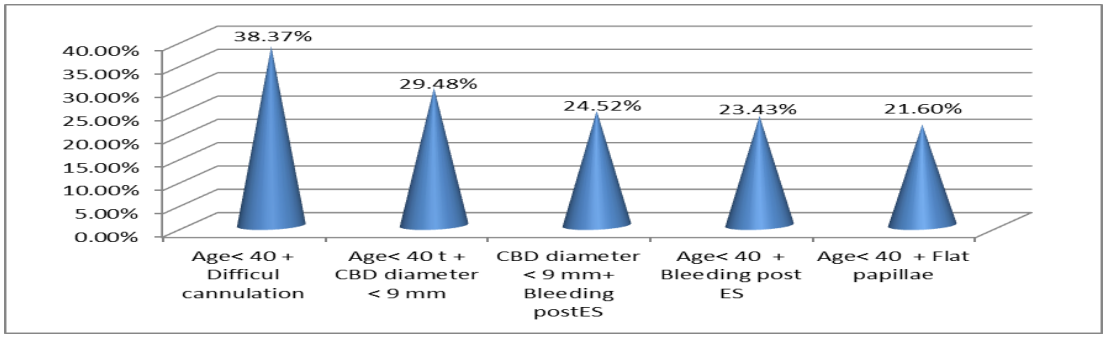


Figure 2: Results of calculated PEP risk for coexistence of pairs of variables



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