

Round-1

Reviewer #1

This is a manuscript describing primary NKF in accordance with the expertise of physicians. This paper is well written, and the topic of this paper is debatable even now. I have some concerns to be revised.

1. Background and study aim are not clearly noted.

1-1. The sentence of "...most endoscopists believe that a high level of experience is required in order to achieve a sufficiently high rate of successful cannulation and an acceptable rate of adverse events in patients with naïve papilla" is not suitable in this part. Is it concerned successful cannulation in all of patients with native papilla? I think that most physicians believe a high level experiences is required for successful cannulation with a use of primary NKF in patients with native papilla.

Reply: Thank you for your comment. It's a point of mistake of our process during English editing.

To clarify the meaning, we added "with a use of primary NKF" in that sentence.

1-2. Sentences of "The beginner endoscopist usually requires to perform more than 300 supervised procedures for achieving 80% of successful biliary cannulation using conventional methods. More experience may be necessary to achieve acceptable of success and adverse event with primary NFK." are unnecessary in this position, I think.

Reply: Thank you for your comment. We agree with your opinion, we delete that sentence.

1-3. The sentence of "Therefore, it is necessary to determine the effectiveness and safety of NKF for primary biliary cannulation performed by beginners compared to those of experts." cannot be understood. The context is not well constructed.

Reply: Thank you for your comment. To clarify the meaning, we changed the that sentences to the follows of "However, there are only few study about that the safety of primary NKF for achieving bile duct access in patients with naïve papilla.^[10] Furthermore, it is necessary to compare how many manageable adverse events occur between beginners and experts when performed NKF versus conventional cannulation for primary biliary cannulation in patients with naïve papilla."

1-4. The sentence of "We aimed to assess the effectiveness and safety of primary NKF in patients with naïve papilla undergoing bile duct cannulation and determine the role of the endoscopist's expertise level." could not be met. To assess the effectiveness and safety of primary NKF, patients underwent primary NKF should be compared with the patients underwent conventional cannulation method. In this manuscript, only comparison of expert vs. non-expert in each primary NKF group and conventional

cannulation method group were performed. In this situation, only "the role of expertise level for primary NKF", which is one of authors' aim, can be assessed.

Reply: Thank you for your comment. We edit that sentence as below according to your comment.

“We aimed to assess the effectiveness and safety of primary NKF according to expertise level of endoscopists in patients with naïve papilla undergoing bile duct cannulation.”

2. Methods

2-1. Statistical methods which were used for comparing variables and for univariate/multivariate analyses should be noted.

Reply: Thank you for your comment. We added associated sentence as below.

“Descriptive statistics are presented as frequencies and percentages for categorical variables and as means \pm standard deviations for continuous variables. Two-sample comparisons were performed using the χ^2 test or Fisher’s exact test. For proportions, Student’s t-tests were used for normally distributed variables. A two-sided P-value of <0.05 was used to indicate statistical significance in all analyses.”

2-2. In Figure 2, it is unclear which figures are of precut sphincterotomy or primary NKF. Figure legends should be revised in this point.

Reply: Thank you for your comment. We divided Figure 2 to Figure 2-1 & 2-2 as your comment.

3. Result

3-1. Table 1, 2. Ampulla configurations, including bulging, distorted, hook-nose shape, should be explained.

Reply: Thank you for your comment. We added figures that were shown ampulla configurations (bulging, distorted and hook-nose shape).

3-2. Table 3. In conventional cannulation group, cannulation success and cannulation time are almost same in expert and non-expert. PEP incidence is the only difference between the two endoscopists. It is doubtful whether this non-experienced endoscopist, in whom the cannulation success rate was 95% and mean cannulation time was 4.6 min (less than the experienced endoscopist), can be deemed as beginner or less-experienced endoscopist. Can this result be generalized? This endoscopist have had a sufficiently ability for ERCP already. What is the precise experienced cases of this endoscopist? Please describe,

not only >300.

Reply: Thank you for your comment. As your comment, high conventional cannulation rate is difficult for beginner endoscopist to achieve. However, our beginner observed and assisted expert's ERCP procedure including guidewire manipulation for one year. Although our beginner had shorter cannulation time and higher success rate compared to other beginner endoscopists, high complication rate, especially high rate of PEP, was shown as a limitation of beginner endoscopist. We redefined our beginner as "over 500 ERCP observations with an assistance such as guidewire manipulation and then over 300 ERCP procedures with supervision of an expert". It is thought that the observation and assistance of ERCP procedure could be a step to improve expertise. However, I think that their own ERCP procedure is more important to improve beginner's expertise.

3-3. Table 4, showing prognostic factor for PEP, should be revised. Usually, in such a situation describing factors associating the incidence, odds ratio and 95% CI should be noted in each variable. What kind of statistical method did authors use? I recommend authors to consult the expert of statistics.

Reply : Thank you for your comment. We added odds ratio and 95% CI in table 4.

4. Discussion.

4-1. In 2nd paragraph, authors mentions "In our study, the incidence rate of PEP was significantly higher in patients managed by the beginner than in those managed by the expert endoscopist, although there was no significant difference in the final rate of successful cannulation." Is that true? In this manuscript, incidence of PEP in entire cohort have not been noted; only incidence of PEP in each of conventional cannulation group and NKF group have been described.

Reply : Thank you for your comment. Before submission of article, some tables have been deleted to convey information concisely. That is a reason of discrepancy with the article content. So, we add table as supplementary that was associated with your comment (Add supplementary table 1.)

4-2. "However, PEP incidence was lower for primary NKF than for conventional cannulation with sphincterotomy even when the procedure was performed by the beginner." is also controversial. The comparison between conventional cannulation and NKF was not performed.

Reply: Thank you for your comment. We deleted this controversial discussion because this conclusion need another prospective study.

4-3. In last paragraph. The sentence of "Our findings suggest that primary NKF is associated with reduced PEP risk regardless of the endoscopist's expertise level," is overstatement, because if primary NKF can reduce the incidence of PEP rather than conventional cannulation has not been proved in this

manuscript. There are no direct comparison. And cannulation method was not included in variables of multivariate analysis for the estimate of the prognostic factor of PEP.

Reply: Thank you for your comment. We agree with your opinion of overstatement. So, we changed the sentence to the follow of “Our findings suggest that PEP risk is not associated with the endoscopist’s expertise level in cases of primary NKF.”

Round-2

Reviewer: Authors revised their manuscript according to reviewer's comment. Revised version is worth publishing. Congratulations! However, there is only one point requiring revision. Authors should describe statistical method for multivariate analysis in method section.

Reply : Thank you for your comment. we edited paragraph of statical analysis in method section as your comment.Univariate and multivariate analyses were conducted to identify the predictors of PEP. "In multivariable analysis, logistic regression analysis was used to identify factors predicting PEP. Factors with p values < 0.2 on univariate analysis were included in multivariate analysis, along with clinically meaningful variables." ,,,,Descriptive statistics are presented as frequencies and percentages for categorical variables and as means \pm standard deviations for continuous variables.....