

REPLY FOR

REVIEWER#1

This study analyzed the ages at diagnosis and operation of biliary atresia in Taiwan and found that the ages at diagnosis and operation in biliary atresia have decreased over time and Kasai operation performed at younger age reduces the need for liver transplantation. The results indicated the Kasai operation at younger age. However, there was no significant difference between those patients who received the Kasai operation within 60 days of age and those who received the operation over 60 days of age ($p = 0.133$). So, the conclusion should be more precisely.

Reply: Thanks for your appreciation. According to your comments, we have further calculated the survival rates. Though there was no significant difference between those patients who received the Kasai operation within or over 60 days of age (Chi-square test, $p = 0.133$, Table 2), the survival rates between these two groups still showed significant difference (log-rank test, $p = 0.014$, Table 2). We have revised the **Results, Tables and Conclusions** accordingly. The revised Conclusions are as below:

CONCLUSIONS

The incidence of BA in Taiwan has fluctuated, and has no overall increasing or decreasing trend. No seasonality of BA was found. The ages at diagnosis, Kasai operation and LT in BA cases have decreased over time. **The survival rates were much better in patients with Kasai operation within 60 days of age, which indicated the effectiveness of early Kasai operation.** The need for LT in BA cases may be reduced if patients receive the Kasai operation as early as possible.

REVIEWER#2

1. Nicely done

Reply: Thanks for your appreciation.

2. There are several errors that need correction. For example in the Introduction "The Kasai operation (hepatoportoenterostomy) as the primary surgical treatment for BA cases is recommended to be performed **as early as good** [1, 2, 5, 6], because increased age at the time of surgery may result in a deleterious effect on the outcomes of BA cases [2, 4, 7]." I assume you meant **as early as possible** not "as early as good." You should have someone familiar with English proofread your manuscript and revise it, so your meaning is correctly stated.

Reply: Thanks for your correction. We have revised this sentence as below:

Introduction:

The Kasai operation (hepatoportoenterostomy) as the primary surgical treatment for BA cases is recommended to be performed as early as ~~good~~ possible [1, 2, 5, 6], because increased age at the time of surgery may result in a deleterious effect on the outcomes of BA cases [2, 4, 7]."

This manuscript has already been reviewed and edited by *American Journal of Expert* before its submission. After revision, we have someone familiar with English proofread our manuscript again. We hope current writing can be satisfactory.

REVIEWER#3

Thank you for submitting a nice manuscript. It is a well-designed multi center, national cohort study that showed a very impressive finding.

Reply: Thanks for appreciation.

Major points:

- 1. Have you compared the overall survival rate among 3 groups?**
- 2. I suggest add percentages of healthy survivors without LT according to 3 phases, which could reveal the effectiveness of early Kasai operation.**

Reply: Because survival rate is a time-dependent function, we did not compare the survival rates among three time periods which had different follow-up duration. Instead, we compared the survival rates among three groups: (1) without Kasai; (2) with Kasai within 60 days of age; (3) with Kasai over 60 days of age. The survival rates were summarized in the **revised Table 2**, which really revealed the effectiveness of early Kasai operation. Please check the revised **Table 2, Results and Discussion** accordingly.

Minor points:

- 1. Kasai operation performed at younger age could have reduced the need for LT, but there was no statistical significance. I suggest modify your conclusion.**

Reply: According to your comments, we have further calculated the survival rates.

Though there was no significant difference between those patients who received the Kasai operation within or over 60 days of age (Chi-square test, $p = 0.133$, Table 2), the survival rates between these two groups still showed significant difference (log-rank test, $p = 0.014$, Table 2). Please check the revised **Results, Tables and Conclusions** accordingly.

CONCLUSIONS

The incidence of BA in Taiwan has fluctuated, and has no overall increasing or decreasing trend. No seasonality of BA was found. The ages at diagnosis, Kasai operation and LT in BA cases have decreased over time. **The survival rates were much better in patients with Kasai operation within 60 days of age, which indicated the effectiveness of early Kasai operation.** The need for LT in BA cases may be reduced if patients receive the Kasai operation as early as possible.

2. It would be better to add the limitation of your study at the end of the discussion.

Reply: We have added the **Limitation** at the end of Discussion as below:

Limitations

Some limitations of this study should be mentioned. First, this was a retrospective study to analyze the claims dataset which was lack of clinical and laboratory information. Therefore, it was unable to analyze some important information like the grade of portal fibrosis, type of graft in liver transplant (cadaveric or living-related). Such limitation is a common restriction of secondary data analysis. Second, the sample size may be too small to show a statistical significance and the percentages of patients receiving operation within or over 60 days of age were not significantly different. However, the survival rates still showed significant difference among the groups, which indicated the effectiveness of early Kasai operation.

Reviewer#4

The authors aimed to describe the ages at diagnosis and operation of biliary atresia (BA) and its incidence over a 15-year period in Taiwan. They found that the age at diagnosis and Kasai was significantly reduced, and attributed this decrease for better awareness, stool color screening programs and better improvement in medical care services in addition to availability of transplant grafts. Though it is purely descriptive, yet the findings are interesting, but still need better analysis.

Reply: Thanks for your appreciation.

Major comments:

1- Present the age by median and range in all groups

Reply: Because the purpose of this paper was to check the trend of ages over time, we thought it would be more appropriate to use mean (SD) to present the ages at each period. However, for your comment, we added the median (Q1-Q3)

in the **Table 1**. We did not use median (range) in order to avoid the extreme effect of outliers.

2- Describe the outcome of Kasai in patients operated before 60 and after 60 days

Reply: Following your suggestion, we have calculated the outcomes of patients with Kasai operation within/over 60 days of age and summarized them in the **revised Table 2 and Results**.

RESULTS

Liver transplant and survival rates

There were a total of 189 (35%) BA patients had undergone LT during the study period. Fifty-six BA patients who did not receive the Kasai operation ultimately needed LT (Table 2). The rates of LT were 25.2% among those patients who received the Kasai operation within 60 days of age and 32.9% among those who received the operation over 60 days of age (Chi-square test, $p = 0.133$, Table 2).

The survival rates from one to five years were summarized in Table 2, which were significantly different among three above-mentioned groups (log-rank test, $p < 0.001$, Table 2) as well as between two groups receiving operation within/over 60 days of age (log-rank test, $p = 0.014$, Table 2).

- 3- **Present the preoperative data of such patients to justify the later need for liver transplant. (The issue is not always the age at diagnosis, other factors may intervene such as grade of portal fibrosis)**

Reply: We agree with Reviewer's comment that some factors may can affect the later need for liver transplant in BA patients, in addition to the age at diagnosis. Unfortunately, we did not have such preoperative clinical and laboratory information in this claims dataset. This is a common inherent limitation of secondary data analysis. We have addressed it in the **Limitations**.

Limitations

Some limitations of this study should be mentioned. First, this was a retrospective study to analyze the claims dataset which was lack of clinical and laboratory information. Therefore, it was unable to analyze some important information like the grade of portal fibrosis, type of graft in liver transplant (cadaveric or living-related). Such limitation is a common restriction of secondary data analysis. Second, the sample size may be too small to show a statistical significance and the percentages of patients receiving operation within or over 60 days of age were not significantly different. However, the survival rates still showed significant difference among the groups, which indicated the effectiveness of early Kasai operation.

- 4- **The different findings by Tiao and Lin are not explained by the annual incidence in this study. It is matching with their finding and NOT an explanation. The authors need to postulate another explanation.**

Reply: We have discussed the findings between our study and the studies of Tiao & Lin at in **DISCUSSION**. One goal of this study was to check the incidence trend of BA in Taiwan. It was confusing with the opposite conclusions by Tiao and Lin, possibly due to using different dataset from different periods. Our study took the advantage of a longer period (1997-2011), including both Tiao (1996-2003) and Lin's (2004-2009) periods, so our results could not only match their individual finding, but also provide a more comprehensive picture of the incidence trend. Therefore, the conclusion of the incidence trend of BA in Taiwan would be more reliable.

- 5- **In figure 1, it is better to indicate the birth rate/year, which may be related to the increased or decreased cases of BA. It may be just a percent of increased or decreased total.**

Reply: The incidence in **Figure 1** is the **case number per 10,000 live births**, which has already considered the birth rate per year.

6- Type of graft in liver transplant (cadaveric or living-related) may be related to the change of age of transplant. Please present these data and then analyze.

Reply: We agree with Reviewer's comment that the graft of liver transplant may be related to the age of transplant. **The 5th paragraph of Discussion** has discussed it. Unfortunately, we did not have such information in the analyzed dataset. We have addressed it in the **Limitations**.

Limitations

Some limitations of this study should be mentioned. First, this was a retrospective study to analyze the claims dataset which was lack of clinical and laboratory information. Therefore, it was unable to analyze some important information like the grade of portal fibrosis, type of graft in liver transplant (cadaveric or living-related). Such limitation is a common restriction of secondary data analysis. Second, the sample size may be too small to show a statistical significance and the percentages of patients receiving operation within or over 60 days of age were not significantly different. However, the survival rates still showed significant difference among the groups, which indicated the effectiveness of early Kasai operation.

Minor comments

7- English language needs careful revision

Reply: This manuscript has already been reviewed and edited by *American Journal of Expert* before its submission. After revision, we have someone familiar with English proofread our manuscript again. We hope current writing can be satisfactory.

8- Abbreviations must be spelled out at first appearance

Reply: We have carefully checked and spelled out all abbreviations at their first appearance.