TITLE PAGE

Title:

Biochemical evaluation of laparoscopic portoenterostomy for treating biliary atresia and redo for failed portoenterostomy.

Running Title:

Biochemical review: portoenterostomy/redo surgery.

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ABSTRACT

Background: Postoperative outcomes of portoenterostomy (PE) and redo-PE were evaluated using selected biochemical markers (SBM) and biochemical status categories (BSC).

Methods: Subjects were 70 consecutive PE performed for biliary atresia. SBM were aspartate aminotransferase (AST)/alanine aminotransferase (ALT), cholinesterase (ChE), and platelet count (PLT) assessed at 1, 2, 3, 6, and 12 months, thence annually for a maximum of 10 years. BSC were: all SBM normal (N-SBM), normal AST/ALT (N-SLT), normal ChE (N-ChE), normal PC (N-PLT), all abnormal (A-SBM), abnormal AST/ALT (A-SLT), abnormal ChE (A-ChE), abnormal PC (A-PLT). Subjects achieving jaundice clearance (JC) and surviving with native livers (SNL) also had gamma glutamyl transpeptidase (γGTP) assessed. Redo-PE indicated for failed PE were assessed postoperatively using the same SBM/BSC protocol.

Results: PE were laparoscopic (LPE; n=40) or open (OPE; n=30). Mean age/weight at PE and duration of follow-up were similar. For JC, LPE=34/40 (85.0%), OPE=22/30 (73.3%); p=0.23. For SNL, LPE=29/40 (72.5%), OPE=16/30 (53.3%); p=0.10. LPE and OPE were similar for SBM/BSC, except for a single significant increase in ALT in OPE at 6 months. Redo-PE was performed 17 to 180 days (mean 67.1 days) after primary PE. AST was significantly increased at the last pre-redo assessment 3 months after primary PE; $p<0.05$. After redo, AST decreased and SBM/BSC results were equivalent to non-redo subjects.

Conclusion: Postoperative biochemical data for all PE cases were comparable; redo-PE would appear to be viable for restoring SBM, and AST could be valuable as a single marker of deterioration in redo cases.

Keywords: Biliary atresia, Laparoscopy, Portoenterostomy, Redo surgery, Biochemistry

INTRODUCTION

Portoenterostomy (PE) improved the prognosis of biliary atresia (BA) immensely when it was first introduced [1] because BA requires surgical intervention, but cannot be cured by surgery. Laparoscopic PE (LPE), first reported by Esteves et al in 2002 [2] and developed to apply the advantages of minimally invasive surgery (MIS) to open PE (OPE) [3-7] was subsequently attempted by many pediatric surgeons worldwide [3,8] and despite high initial expectations, outcome of LPE was reported to be worse than OPE with concerns about safety and surgical stress [9-12] leading to the International Pediatric Endosurgery Group abandoning LPE as a recommended procedure in 2007 [13] because of high failure rates and poor outcomes. In 2011, similar results were reported by a prospective study in Europe conducted specifically to justify LPE as a valid treatment for BA [11] and LPE ceased to be performed in Europe thereafter.

Pediatric hepatobiliary surgeons face a dilemma because astute caregivers are aware of the benefits of MIS; less intraoperative blood loss, faster recovery times, smaller wounds, less requirement for postoperative analgesia, and technically, LPE interferes with liver hemodynamics less because intraoperative mobilization of the liver is not required, accuracy of anastomosis is similar to OPE because of magnification, and there are also reports of fewer adhesions [14] postoperatively that could facilitate surgical intervention should further surgery or liver transplantation (LTx) be required in the future [15]. In fact, more recent reports appear to favor LPE [5,7].

In 2016, the authors' colleagues published a report comparing postoperative changes in selected biochemical markers (SBM) after PE between LPE and OPE in an effort to improve understanding of the clinical impact of LPE. SBM used were AST and ALT as

indicators of liver cell damage [16], T-Bil, and platelet count (PLT) as an indicator of hypersplenism [17] secondary to the histopathologic progression of BA. Changes observed in SBM were similar for LPE and OPE [18]. Data were obtained prospectively from blood biochemistry assessed at the last outpatient clinic attendance made by each postoperative BA subject, so clinical status was assessed at a single point in time that varied between subjects.

The current study sought to improve on the earlier study by focusing on postoperative BA patients surviving with native livers (SNL) using more SBM (Cholinesterase (ChE) as an indicator of liver synthetic function [19] and gamma glutamyl transpeptidase (γGTP) as an indicator of liver cell and bile duct epithelial damage and cholestasis [20]), and making assessments at multiple predetermined times that were fixed and identical for all subjects to compare LPE and OPE more thoroughly and objectively.

Subject data were also analyzed using biochemical status categories (BSC) to further assess postoperative outcome from specific perspectives. While this approach was considered reasonable for comparing LPE and OPE, subjects who began to deteriorate requiring redo surgery, LTx, or at risk for death also require active intervention and an assessment of the biochemical status of redo-PE cases was included to demonstrate the value of SBM and BSC for assessing postoperative PE cases and the value of redo-PE for treating PE cases who fail to achieve jaundice clearance (JC). While the success of redo-PE has been reported [21,22], redo-PE cases have not been assessed previously using SBM and BSC.

The aim of this study was twofold; to use SBM and BSC for comparing LPE with OPE and to use SBM and BSC for comparing the outcome of redo-PE cases with non-redo cases.

MATERIALS AND METHODS

Subjects enrolled in this study were 70 consecutive BA patients treated by either LPE or OPE between 2009 and 2021. The type of procedure performed was indicated by clinical status and weight at the time of planning PE; choice of procedure was made by the operating surgical team. Surgical techniques for OPE and LPE may be found elsewhere [23]. All PE were performed by a team of surgeons who trained and worked together at Juntendo University School of Medicine and all patient management was strictly protocolized.

For comparing LPE and OPE biochemically, subjects were classified according to post-PE outcome into: group 1: all subjects who achieved JC (T-bil≤1.2mg/dL) at least once, surviving with native livers (SNL), irrespective of the type of PE (primary or redo) or technique (LPE, OPE, redo-LPE, redo-OPE); group 2: subjects who achieved JC initially but required redo-PE or liver transplantation (LTx); and group 3: subjects who did not achieve JC and required redo-PE, LTx, or died.

SBM (AST, ALT, γGTP, ChE, and PLT for group 1, and AST, ALT, ChE, and PLT for groups 2 and 3) were used to compare LPE with OPE and redo-PE cases with non-redo cases. Definitions of "normal" used in this study obtained from the Department of Clinical Laboratory Medicine at Juntendo University School of Medicine were: T-Bil≤1.2 mg/dL, AST≤37 IU/L, ALT≤43 IU/L, γGTP≤75 IU/L, ChE≥178 IU/L, and PLT≥153×10^9/L. All subjects were also classified into 8 biochemical status categories (BSC): all SBM normal (N-SBM), normal AST/ALT (N-SLT), normal ChE (N-ChE), normal PC (N-PLT), all SBM abnormal (A-SBM), abnormal AST/ALT (A-SLT), abnormal ChE (A-ChE), and abnormal PC (A-PLT).

All data were obtained retrospectively from outpatient clinic records. Commonly assessed demographic criteria (age/weight at PE, types of BA) were compared. SBM and BSC were assessed according to a standard protocol (1, 2, 3, 6, 12 months) in each group, thence annually for 10 years in group 1, until redo-PE or LTx in group 2, and until redo-PE, LTx, or death in group 3. Subjects who required redo-PE were assessed for SBM and BSC postoperatively, according to the standard protocol. Numbers of subjects at each scheduled assessment decreased over time because newer subjects had shorter duration of follow-up and subjects who had LTx or died were excluded. No subject was lost to follow-up. Other criteria associated with operative safety and outcome such as operative time, blood loss, and duration of hospitalization were considered beyond the scope of this study.

Statistical analysis

The Student's *t* test and chi-squared test were used for statistical analysis. A *p* value less than 0.05 was considered to be statistically significant.

Ethics

Informed consent for the PE procedure chosen to be performed by the senior operating surgeon was obtained from caregivers for each subject in this study after careful explanation of the procedure and risks by the senior operative surgeon. The institutional review board number for this study granted by the Ethics Committee at Juntendo University School of Medicine for complying with the Helsinki Declaration of 1975 (revised 1983) was 20-307.

RESULTS

PE (n=70) was LPE=40 and OPE=30. Types of BA were: LPE: type III: n=33, type II: n=5, type I: n=2; OPE: type III: n=24, type II: n=2, type I: n=4; *p*=0.37; according to being syndromic: LPE: non-syndromic: n=38, syndromic: n=2; OPE: non-syndromic: n=26, syndromic: n=4; *p*=0.22; according to being cystic: LPE: non-cystic: n=38, cystic: n=2; OPE: non-cystic: n=26, cystic: n=4; *p*=0.22.

Mean age at primary PE was 65.5 days (range: 21–123 days) for LPE and 72.6 days (range: 29–149 days) for OPE; *p*=0.31. Mean weight at primary PE was 4.3kg (range: 3.2–7.1kg) for LPE and 4.7kg (range: 2.5–7.0kg) for OPE; *p*=0.16. JC was achieved in 34/40 (85.0%) taking a mean of 54.8 days (range: 22-110 days) in LPE and 22/30 (73.3%) taking a mean of 45.0 days (range: 14-134 days) in OPE; *p*=0.23 and 0.21, respectively. SNL was 29/40 (72.5%) in LPE and 16/30 (53.3%) in OPE; *p*=0.10. See Table 1.

Table 1

The number of subjects in each group was: group 1 (n=45: LPE=29, OPE=16; redo-PE=6, non-redo=39), group 2 (n=10: LPE=4, OPE=6; redo-PE=2, non-redo=8), and group 3 (n=15: LPE=7, OPE=8; redo-PE=3, non-redo=12). Mean durations of postoperative follow-up were: group 1=5.6 years (range: 0.3-12.9 years), group 2=1.6 years (range: 0.3-4.9 years), and group 3=0.6 years (range: 0.1-0.8 years). Differences in mean duration of postoperative follow-up between groups were significant; *p*<0.0001, respectively. Mean durations of postoperative follow-up for LPE were 5.4 years (range: 0.1–12.3 years) and for OPE were 5.4 years (range: 0.8–12.9 years); *p*=0.94.

The number of subjects at each assessment for 10 years in group 1 (n=45) was: 1 month (n=45), 2 months (n=45), 3 months (n=45), 6 months (n=43), 12 months (n=37), 2 years (n=34), 3 years (n=31), 4 years (n=28), 5 years (n=27), 6 years (n=27), 7 years (n=19), 8 years (n=12), 9 years (n=9), and 10 years (n=6). The number of subjects at each

assessment until redo-PE or LTx in group 2 (n=10) was: 1 month (n=10), 2 months (n=10), 3 months (n=10), 6 months (n=8), 12 months (n=5), and 2 years (n=3). The 3-year assessment could not be performed in group 2. The number of subjects at each assessment until redo-PE, LTx, or death in group 3 (n=15) was: 1 month (n=15), 2 months (n=14), 3 months (n=12), and 6 months (n=9). The 12 months assessment could not be performed in group 3.

Figure 1 shows differences in SBM data according to PE technique. AST, ALT and γ-GTP results were higher and ChE and PLT results were lower for LPE but differences were not significant throughout the entire study in group 1; there was a significant improvement in ALT 6 months postoperatively in OPE that was transient ($p<0.05$). The range in differences between LPE and OPE data decreased with longer follow-up but all differences were not significant (data not shown).

Figure 1

For BSC, there were no significant differences between LPE and OPE in group 1 (range in *p* for completed protocol assessments was 0.20-0.88), group 2 (range in *p* for completed protocol assessments was 0.20-0.75), and group 3 (range in *p* for completed protocol assessments was 0.35-0.95). For group 1, only BSC data for 1 month, 3 months, 6 months, 12 months, 2 years, 4 years, 6 years, 8 years, and 10 years are presented in Figure 2 results for other assessments were similar. BSC distributions for LPE and OPE completed in group 2 (n=10) from 1 month (n=10) to 2 years (n=3) and completed in group 3 (n=15) from 1 month (n=15) to 6 months (n=9) were similar (ranges in *p* for completed protocol assessments were 0.20-0.75 and 0.35-0.95, respectively). Mid- to long-term changes in N-SBM in group 1 for LPE were: 5 years (n=3), 6 years (n=4; +1 for a new N-SBM case), 7 years (n=3; -1 for abnormal results), 8 years (n=3: unchanged), 9 years (n=2; -1 for abnormal results), and 10 years (n=1; -1 for abnormal results); and for OPE were: 5 years (n=3), 6

Figure 2

years (n=3; unchanged), 7 years (n=1; -2 for abnormal results), 8 years (n=1; unchanged), 9 years (n=1; unchanged), and 10 years (n=0; -1 for abnormal results). See Figures 2-4.

Figures 2-4

During the study period, 11 redo-PE (5 by LPE and 6 by OPE) were performed. Specifically, 5 failed LPE had redo-LPE and 3 failed LPE and 3 failed OPE had redo-OPE. Mean age at redo-PE was 127.8 days (range: 90-256 days). Redo-PE was performed 17 to 180 days (mean: 67.1 days) after primary PE; mean age at primary PE was 54.1 days (range: 30-76 days) for redo cases and 69.5 days (range; 21-146 days) for non-redo cases; p=0.08. Mean weight at redo-PE was 4.8kg (range: 2.6-6.5kg); mean weight at primary PE was 3.9kg (range: 2.6-5.0kg) for redo cases and 4.5kg (range: 2.5-7.1kg) for non-redo cases; p=0.10. JC was achieved in 6/11 redo-PE cases; SNL was achieved in 6/11 redo-PE cases. Redo-PE data were included in the overall analysis of LPE versus OPE according to the type of redo performed; 3/8 LPE subjects who had redo OPE were included in OPE. SBM assessments of subjects requiring redo before redo was indicated tended to have higher AST/ALT and γGTP and lower ChE, but differences were only significant for AST at the last scheduled assessment (3 months) before redo; p<0.05. After redo, AST decreased and there were no differences in SBM and BSC for redo-PE and non-redo cases. In other words, outcomes according to SBM and BSC for redo-PE were the same as non-redo cases. See Figure 5.

Figure 5

DISCUSSION

Historically, LPE has come to be considered as an inferior procedure with worse outcome. While this study is limited somewhat by its retrospective design, impact of LPE on BA patients was the same as for OPE; in other words, by choosing SBM that assess post-

PE liver status specifically, outcome of LPE was no worse than OPE, at least biochemically. Although the SBM used in this study have been reported previously, they have not been validated categorically as specific markers of success or failure of PE although they assess clinical status using criteria that are relevant to BA. Of note, there are few reports that include ChE and PC as SBM although Davenport et al. [24] reported that high PLT and low AST levels may be prognostic. Thus, ChE was added as an indicator of liver synthetic function and PLT to reflect hypersplenism associated with the natural progression of BA. ChE was relatively preserved in many cases, but an upward trend was observed in the first few months after initial PE, along with decreased T-Bil, AST, ALT, and γGTP, suggesting that ChE may be useful as a postoperative indicator. γGTP is known to be raised in BA patients but was considered to be potentially useful for following liver cell and bile duct epithelial damage and cholestasis because of its sensitivity [20,25]. In this study, it continued to remain high postoperatively irrespective of operative technique and took more than 5 years to reach normal levels. For all SBM investigated in group 1, results for OPE seemed better, but statistically, there was only a significant difference in ALT at 6 months ($p<0.05$), and no significant differences in SBM results according to operative technique (Figure 1). As there were no differences between LPE and OPE identified in this study using SBM results, LPE could be reappraised as a valid option for treating BA rather than being bypassed for historical reasons. In fact, LPE could be associated with other advantages typical of MIS such as superior cosmesis because of smaller scars and less reported adhesions [14] that could influence the incidence of postoperative intestinal obstruction and the success of any future surgery.

Distributions of the 8 BSC chosen specifically to assess liver status from different perspectives without functional overlap were not different between LPE and OPE, although transient significant differences were observed. Koga et al. [26] reported that AST can continue to be high even after successful PE, suggesting that hepatocyte deterioration is progressive in BA; AST would appear to be a correlated significantly with risk for LTx as early as 1 month post-PE. Thus, all post-PE cases with high levels of AST should be considered as LTx candidates, especially if postoperative clinical improvement is poor. In fact, the simplest approach to outpatient postoperative monitoring may be observing AST/ALT closely during the first few months after PE. The most common BSC for both LPE and OPE in this study was A-SLT (only AST/ALT abnormal). In group 1, AST/ALT gradually improved over time, with some subjects achieving normal results after 2 years.

While performing BSC analysis, the BSC category, N-SBM (all SBM normal) was of particular interest because no similar data could be found in the literature. Mid-term follow-up (5-7 years after PE) identified N-SBM in 6/70 subjects (3 LPE and 3 OPE) which fell to 3/70 (1 LPE and no OPE) on long-term follow-up (10 years after PE) indicating that N-SBM after PE using the SBM in this study is uncommon and unrelated to PE technique. Despite good results reported for JC and SNL, data for N-SBM is surprisingly limited in the literature and other centers are encouraged to report data for their postoperative PE cases who are SNL with normal data to create a database for this important category of BA patient.

There are several reports in the literature about postoperative SBM and prognosis [16,19,24-27]. One assessed SNL subjects after OPE with SBM and another compared LPE with OPE using SBM, but both are less intensive than the current study; in the SNL paper only OPE subjects were reviewed for a few months after surgery with no comparison with

LPE [16] and in the paper comparing LPE and OPE with SBM, SNL subjects were not investigated specifically and the study period was for only 6 months after PE [28]. This is the first time for post-PE patients to be compared at multiple predetermined points in time according to surgical technique (LPE or OPE) using SBM (AST, ALT, ChE, and PLT for all subjects and with the addition of γGTP for group 1 subjects).

Redo-PE is performed more often in Japan because of limited access to LTx; in other words, patients indicated for redo-PE in Japan would probably have LTx at centers overseas. [14,29,30] Redo-PE was performed using redo-OPE until 2018 when redo-LPE was introduced. More than half of the 11 redo-PE cases achieved JC in this study and post-redo SBM and BSC results were equivalent to non-redo subjects. The postoperative clinical status of redo-PE cases was similar to non-redo subjects according to SBM and BSC analysis, suggesting that redo-PE has the capacity to improve deteriorating clinical status even in the LTx era. Unfortunately, follow-up after redo-PE in this study is inadequate for making a concrete recommendation about redo-PE, but it would appear from this study and a report about redo-LPE performed elsewhere with promising results [14], that redo-PE has potential for improving the postoperative status of deteriorating BA patients. Although technique would not appear to be an issue from the current study, further follow-up will clarify the effect of technique on prognosis of redo-PE cases.

In terms of SBM/BSC biochemical analysis used in this study, LPE did not underperform and results were not nearly as bad as previously reported. In fact, LPE was so similar to OPE that they could even be considered equivalent. Increasing the number of subjects and extending follow-up will focus further attention on the potential of LPE and redo-PE for treating BA.

Declaration of competing financial interest

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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Aires: 6–9

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FIGURE LEGENDS

Figure 1: Trends in AST, ALT, γ-GTP, ChE, and platelet count in group 1 expressed according to surgical technique (LPE/OPE).

Note: OPE subjects appear to do better; there was a transient statistically significant difference for ALT at 6 months ($p<0.05$); otherwise there were no significant differences in SBM between LPE and OPE (ranges in p for completed protocol assessments were 0.06-0.99).

Figure 2: Biochemical status categories for group 1.

Subjects in group 1 completed the full assessment protocol.

BSC distributions followed similar patterns; A-SLT was the most common BSC in both LPE and OPE and there were no significant differences between LPE and OPE (ranges in p for completed protocol assessments were 0.20-0.88).

Figure 3: Biochemical status categories for group 2.

Subjects in group 2 were only assessed for 2 years because of redo-PE, LTx, or death.

BSC distributions followed similar patterns with no significant differences between LPE and OPE (ranges in p for completed protocol assessments were 0.20-0.75).

Figure 4: Biochemical status categories for group 3.

Subjects in group 3 were only assessed for 6 months because of redo-PE, LTx, or death.

BSC distributions followed similar patterns with no significant differences between LPE and OPE (ranges in p for completed protocol assessments were 0.35-0.95).

Figure 5: Selected biochemical markers and biochemical status categories for redo-PE cases.

There were significant differences in SBM for AST at 3 months, the last assessment before redo-PE in redo-PE cases; (p<0.05). After redo-PE, AST decreased and there were no differences between redo-PE cases and non-redo cases for SBM and BSC.

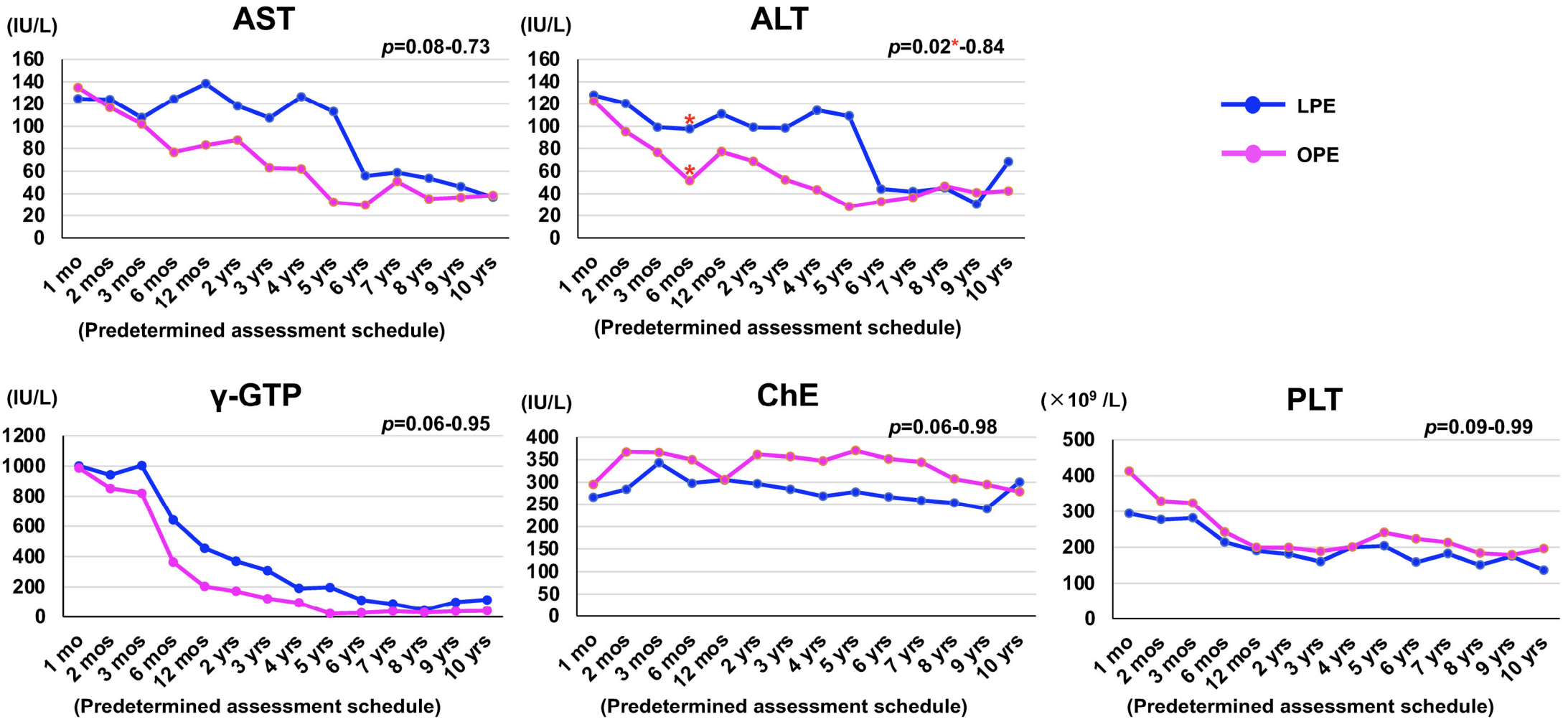
Table 1: Summary of data according to types of portoenterostomy (PE)

	LPE (n=40)	OPE (n=30)	*p*
Types of biliary atresia (n=70)			0.37
I (n=6)	2	4	
II (n=7)	5	2	
III (n=57)	33	24	
Isolated (n=64)	38	26	0.22
Cystic biliary atresia (n=6)	2	4	0.22
Mean age at primary PE; days (range)	65.5 (21-123)	72.6 (29-149)	0.31
Mean weight at primary PE; kg (range)	4.3 (3.2-7.1)	4.7 (2.5-7.0)	0.16
Jaundice clearance* ratio; (n)	85.0% (34/40)	73.3% (22/30)	0.23
Time for jaundice clearance*; days (range)	54.8 (22-110)	45.0 (14-134)	0.21
Survival with native liver ratio; (n)	72.5% (29/40)	53.3% (16/30)	0.10
Mean follow-up after primary PE; years (range)	5.4 (0.1-12.3)	5.4 (0.8-12.9)	0.94

LPE: laparoscopic portoenterostomy, OPE: open portoenterostomy

kg: kilograms, *postoperative T-Bil≤1.2mg/dL, n: number of cases,

Figure 1: Trends in AST, ALT, γ-GTP, ChE, and platelet count in group 1 expressed according to surgical technique (LPE/OPE)



LPE: laparoscopic portoenterostomy, OPE: open portoenterostomy, AST: aspartate aminotransferase, ALT: alanine aminotransferase, γ-GTP: glutamyl transpeptidase, ChE: cholinesterase, PLT: platelet count, mo: month, mos: months, yr: year, yrs: years

Figure 2: Biochemical status categories for group 1.

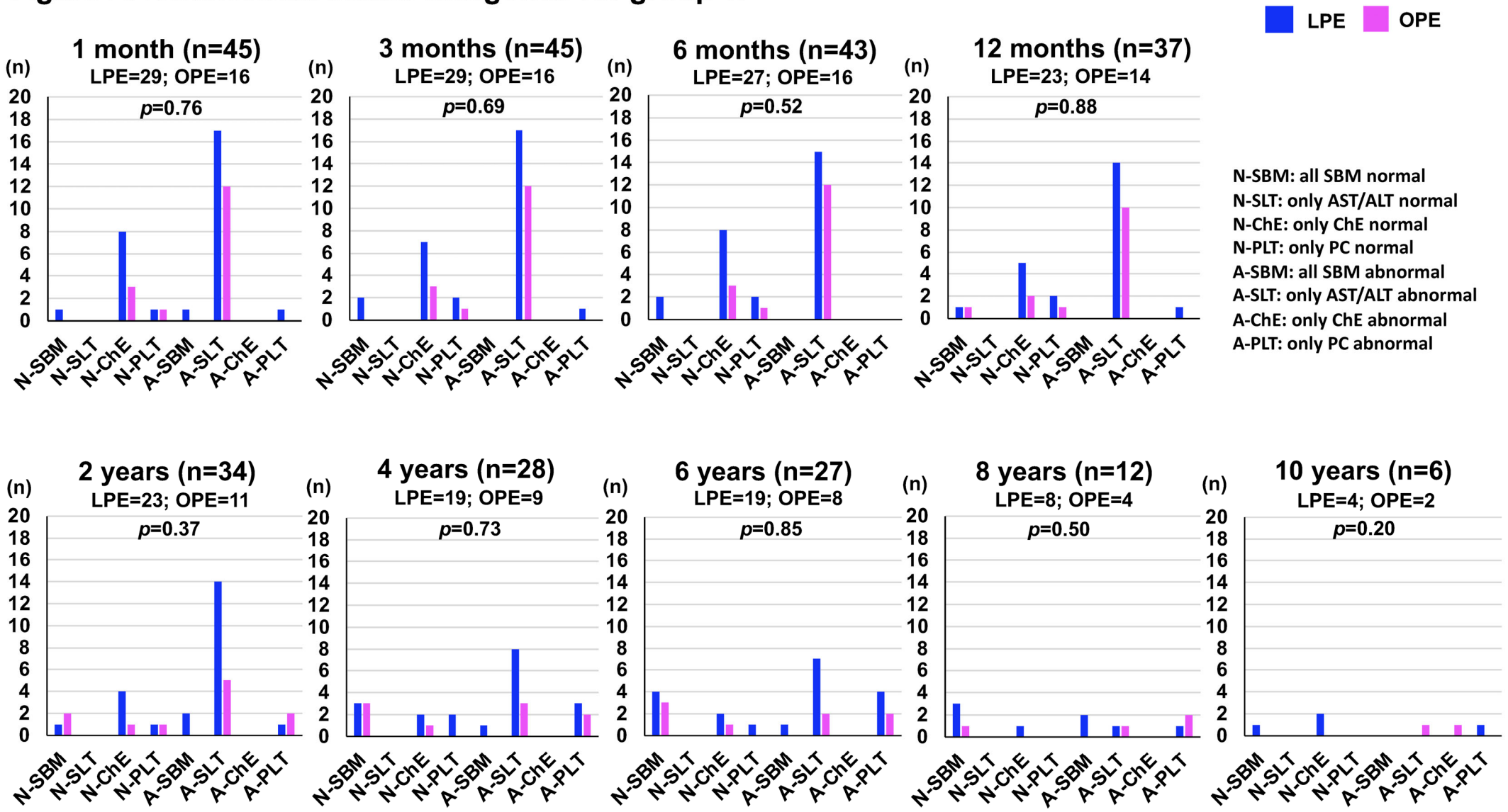
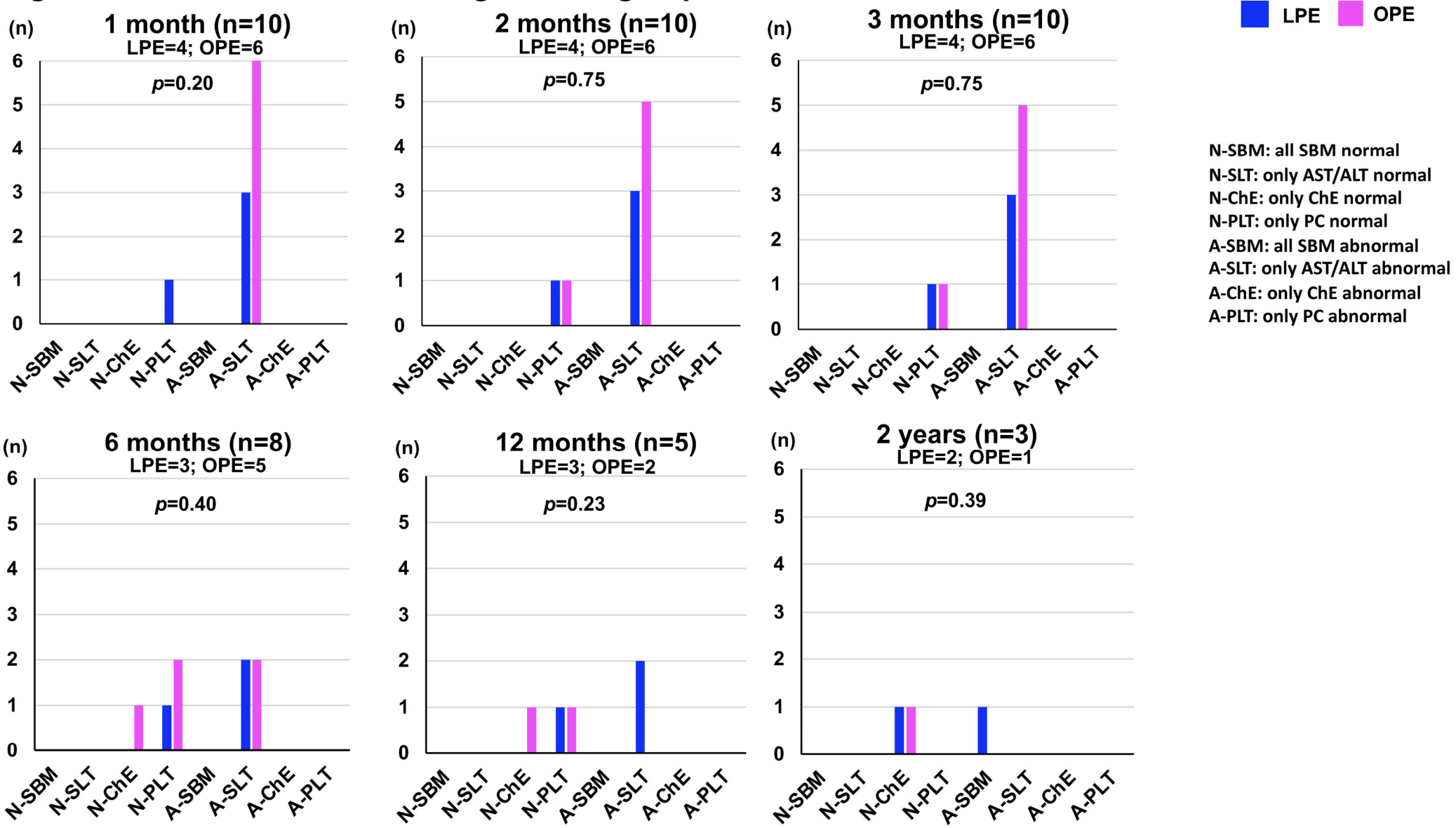


Figure 3: Biochemical status categories for group 2.



N-SBM: all SBM normal
N-SLT: only AST/ALT normal
N-ChE: only ChE normal
N-PLT: only PC normal
A-SBM: all SBM abnormal
A-SLT: only AST/ALT abnormal
A-ChE: only ChE abnormal
A-PLT: only PC abnormal

Figure 4: Biochemical status categories for group 3.

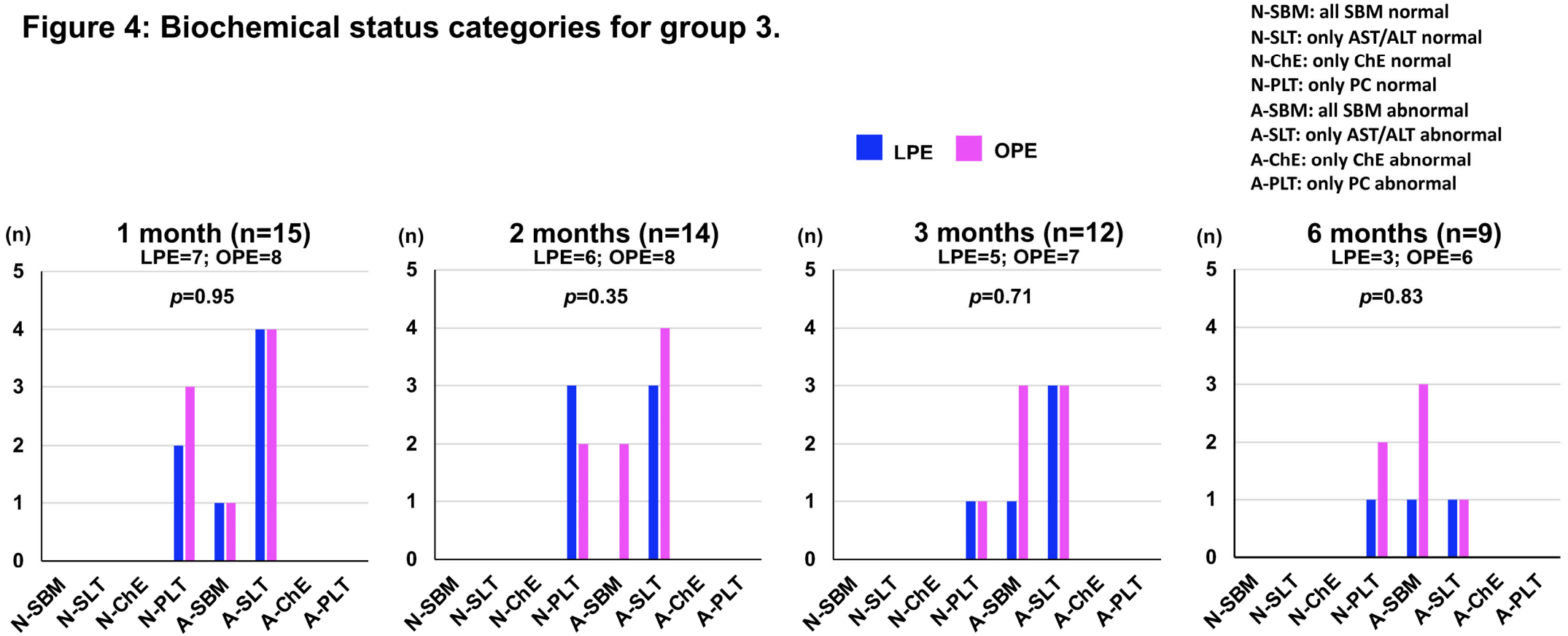
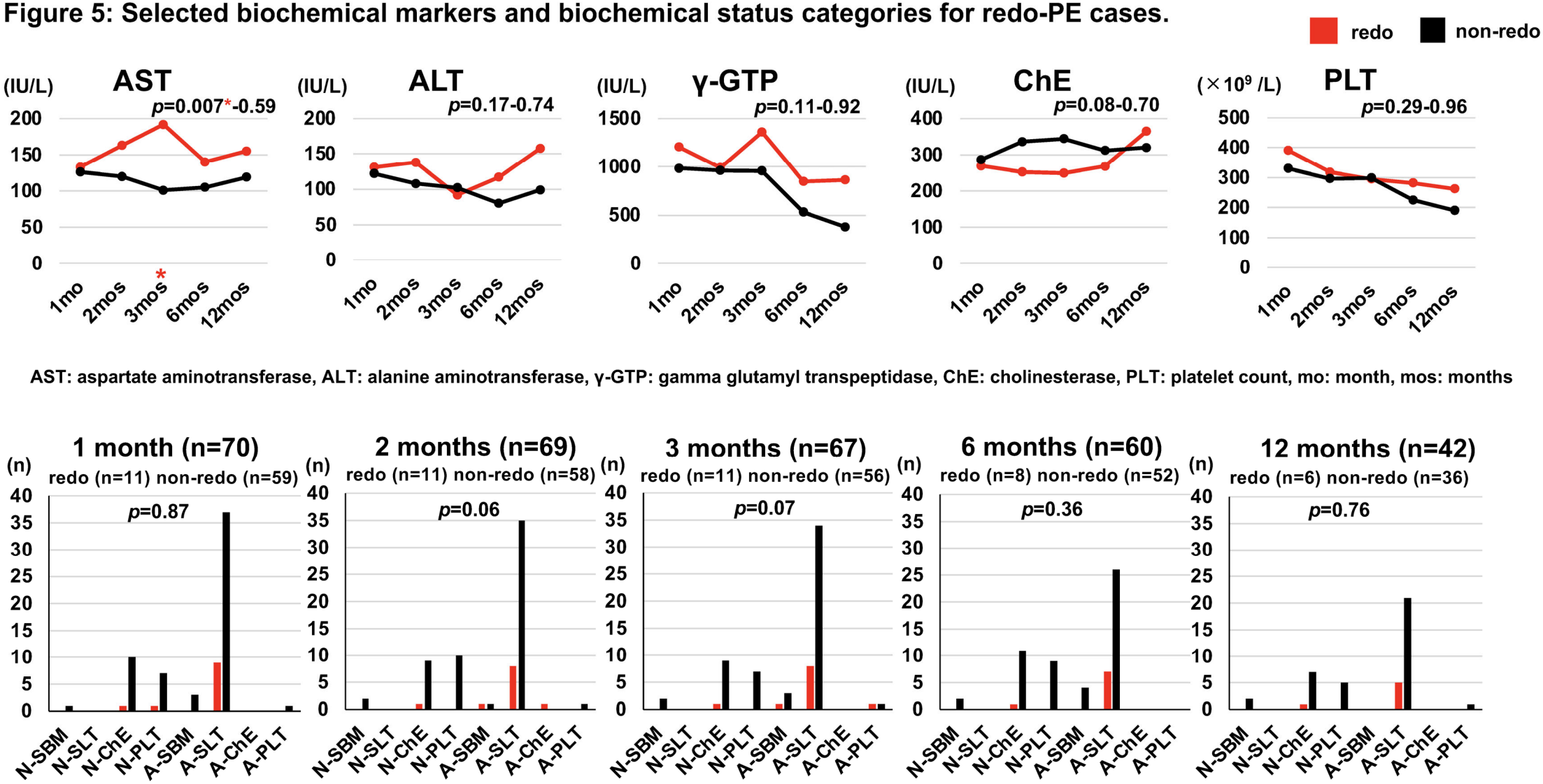


Figure 5: Selected biochemical markers and biochemical status categories for redo-PE cases.



AST: aspartate aminotransferase, ALT: alanine aminotransferase, γ-GTP: gamma glutamyl transpeptidase, ChE: cholinesterase, PLT: platelet count, mo: month, mos: months

N-SBM: all SBM normal, N-SLT: only AST/ALT normal, N-ChE: only ChE normal, N-PLT: only PC normal, A-SBM: all SBM abnormal, A-SLT: only AST/ALT abnormal, A-ChE: only ChE abnormal, A-PLT: only PC abnormal