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Evaluating progression of liver disease from repeat liver biopsies in children with chronic hepatitis C- a retrospective study

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Abstract

Clinical and histologic progression of liver disease in untreated children with chronic hepatitis C virus (HCV) infection is poorly documented. The aim of this retrospective study was to characterize changes in liver histology over time in a cohort of HCV- infected children who had more than one liver biopsy separated by over one year. 44 untreated children without concurrent liver diseases, who had repeat liver biopsies at eight US based medical centers, were included. Biopsies were scored by a single pathologist for inflammation, fibrosis and steatosis and were correlated with demographic data including age at biopsy, time from infection to biopsies, and laboratory values such as serum alanine aminotransferase (ALT). Mode of transmission was vertical in 25 (57%) and from transfusions in 17 children (39%). Genotype 1 was present in 30/35 (84%) children. Mean age at first and final biopsy was 8.6 and 14.5 years respectively and the mean interval between biopsies, 5.8 ± 3.5 years. Duration of infection to biopsy was 7.7 and 13.5 years respectively. Laboratory values did not change significantly between the biopsies. Inflammation was minimal in about 50 % at both time points. Fibrosis was absent in 16% in both

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biopsies, limited to portal/periportal in 73% in the first biopsy and 64% in the final biopsy. Between the two biopsies, the proportion of patients with bridging fibrosis/cirrhosis increased from 11 to 20% (p =0.005).

Conclusion—Although in aggregate this cohort did not show significant histologic progression of liver disease over five years, 29.5 % (n= 13) of children showed an increase in severity of fibrosis. These findings may have long term implications for the timing of follow-up biopsies and treatment decisions.

Keywords

HCV Hepatitis C virus; ALT alanine aminotransferase; CHC chronic hepatitis C; liver biopsy grade and stage; fibrosis

Chronic hepatitis C (CHC) infection progresses insidiously over several decades. While the natural history of histologic progression in adults is well studied, until recently there have been only a few reports describing the histologic progression of CHC in children. Studies published from the Far East and Europe point to a relatively benign outcome [1–4], whereas a few reports from the United States suggest that fibrosis, cirrhosis and even hepatocellular carcinoma may occur in children with CHC [5–7]. In the past few years, several large treatment studies have been reported from Europe and USA which have highlighted a wide spectrum of histologic findings in CHC liver disease in children and adolescents [8,9,10,11]. Overall, these studies support that progression is much slower in children than in adults and rate of development of cirrhosis seems to be less than 10% before adulthood. Host and viral factors may account for the variability in the natural progression of the disease in different racial and ethnic groups.

CHC in children is characteristically a silent disease. Infected children have relatively few symptoms and morbidity. In adults and children with CHC, laboratory markers of hepatic inflammation such as serum aminotransferases may not correlate with the extent of histologic changes in the liver. Liver biopsy is still considered the gold standard in establishing the degree of liver involvement, which in turn influences the decision to treat adults with CHC[12]. Studies of repeated biopsies in infected adults have found that fibrosis tends to increase over time, and that, while there is great variability among individuals, adverse outcomes are most frequent in those with the most rapid fibrosis progression [13–20]. It is controversial whether histologic severity should affect treatment decisions in childhood [8,9,21]. In HCV infected children, liver biopsies are usually performed in the setting of clinical studies or treatment protocols and less often due to concerns regarding the severity of liver disease [11,21–23]. Reports of repeat liver biopsies as part of a HCV natural history study are therefore rare in children [6, 24–26].

The aim of this retrospective multicenter study was to characterize the progression of histologic liver disease over time in a group of treatment naïve children and adolescents with CHC, by reviewing their initial and repeat liver biopsies.

Patients and methods

Children and adolescents who had at least two standard-of-care liver biopsies more than one year apart were identified through eight of the participating centers in the PEDS-C study, a U.S. based multi-center, placebo controlled study designed to assess the effect of therapy with pegylated interferon and ribavirin in children with CHC[11]. Inclusion criteria for the PEDS-C study specified a liver biopsy within 36 months prior to enrollment, which meant that some children underwent a second liver biopsy if they had a previous biopsy more than 36 weeks prior to enrollment [22,23]. Nine children enrolled in the PEDS C trial who had repeat liver biopsies were included in our study as were 36 treatment naïve children with CHC followed by PEDS C investigators but not included in the clinical trial. The latter cohort was not included in the PEDS-C study due to several factors such as geographical location, age, unwillingness to participate and inability to locate. Many of these patients underwent treatment subsequently and the data are not reported here; results of the PEDS-C trial are reported elsewhere (PEDS-C)[11]. Repeat biopsies in this latter group were performed for deteriorating clinical status, re-evaluation for treatment decision or, at the time of surgery for concurrent indications such as a cholecystectomy. Exclusion criteria for this study were known other causes of liver disease such as hepatitis B, Wilson's disease, autoimmune hepatitis or, past or current treatment for HCV infection. The study was conducted with Institutional Review Board approval from each participating center.

General demographic data included gender, ethnicity, age at infection, duration of infection to biopsy, source of infection (vertical, transfusion, and unknown), and BMI Z scores. The putative date of infection was defined as the date of birth in those who acquired HCV vertically, or, the date of transfusion or any surgery, presumed exposure to contaminated needles during hospitalization; if none of the above was known, this data was excluded from the calculation of duration of infection to biopsy.

Laboratory values within 3 months of the initial and follow-up biopsies including complete blood count, serum alanine aminotransferase (ALT), total and direct bilirubin, prothrombin time, albumin, and HCV RNA quantification by polymerase chain reaction (PCR) were retrieved from retrospective chart review. Viral genotype was included when available. All biopsies were scored for inflammation, fibrosis and steatosis by a single pathologist to guarantee uniformity of interpretation. They were coded in a uniform manner and the pathologist was blinded to clinical data, the sequence of the biopsies and the histologic scoring originally performed [22]. Liver biopsies were evaluated for necroinflammation (grade) with the modified Histology Activity Index (HAI) and fibrosis (stage) by Ishak classification [22]. Demographic data and laboratory values were correlated with histologic grading (grade of inflammation 0–18) and staging (stage of fibrosis 0–6) from the initial and repeat biopsies to assess if there were significant histologic changes between the biopsies and to identify any factors that predicted progression of liver disease in these children and adolescents.

Statistical methods

If there were more than two biopsies performed on the same patient, the first and last biopsies were used for statistical analysis. For comparative purposes, necroinflammatory

scores were collapsed to none/minimal (HAI: 0–3), mild (4–6), moderate (7–9) and marked ≥ 10. Fibrosis scores were collapsed to none (stage 0), portal/periportal (stages 1–2), bridging fibrosis and cirrhosis (stages 3–6). Data were organized to enable determination of changes from the first to the last liver biopsy. Percentages, means, and standard deviations were calculated in the usual way. For categorical/binary variables, contingency table analysis was used to assess the relationship between two variables with reference to the likelihood ratio chi-square for the p-value. The likelihood ratio chi-square was used because it is robust with small sample sizes and small cell sizes. For continuous variables, a standard t-test was used for comparison of means between two groups (adjusting for heterogeneity of variance as appropriate) and a standard ANOVA for comparison of means among three or more groups. No adjustment was made for multiple comparisons. For highly skewed variables, a Wilcoxon rank sum statistic (a nonparametric analog to the t-test) was used to confirm statistical significance/non-significance. Z-scores for height, weight, and BMI were calculated using the CDC growth tables, implemented using the gc-calculate-BIV. SAS program from CDC. All analyses were performed using SAS Version 9.3.

Results

We identified 44 treatment naïve children with chronic HCV infection and no concurrent liver diseases with at least two liver biopsies more than one year apart from the eight participating centers. Their demographics are given in Table 1. The mode of transmission was vertical in 25 (57%) of children, via transfusions in 17 (39%) and unknown in 2 (4%) adopted children. Viral genotype was known in 35 children and was 1 (*a* / *b*) in 30 (84%) children. Mean age at the first and last liver biopsy was 8.6 and 14.5 years, respectively. The mean interval between biopsies was 5.8 ± 3.5 years, range 1–17 years. The duration of infection to the two biopsies was 7.7 and 13.5 years, respectively. Laboratory values including complete blood count, prothrombin time, bilirubin and albumin did not differ significantly between the two sets of biopsies.

The histologic features in the 44 children at the time of initial and final biopsies are shown in Table 2. Biopsy sizes were excellent (containing over 11 portal tracts) in 40 biopsies, adequate (between 6–11 portal tracts) in 43 and modest (between 3–5 tracts) in 14. There were two wedge and two surgical resection specimens. Thirty seven patients had 2 biopsies each and 7 patients had more than two biopsies (five patients had 3 biopsies, two patients had 4 each). The total biopsies reviewed were 97. Necroinflammatory activity was minimal in 55 % and 50% of the patients on the first and the final biopsy respectively. Fibrosis was absent in 16% at both biopsies and limited to portal/periportal in73% of children at the first biopsy and 64% at the final biopsy. Bridging fibrosis/cirrhosis was present in 5 patients (11%) at the first biopsy and 9 patients (20%) at the final biopsy (p =0.0046). Thirteen patients showed progression in fibrosis at varying stages between the two sets of biopsies. The changes of progression and regression of fibrosis between biopsies in 24 patients are discussed below. Steatosis was minimal or moderate in 23 % and 27% of the biopsies and showed no progression or regression. “Chicken wire” fibrosis was found in three, giant cell transformation in two and iron overload in two biopsies.

Histologic changes in the initial biopsy

The demographic features such as age at biopsy, duration of infection, BMI, laboratory values such as ALT and viral load, and histologic changes of inflammation and steatosis on the initial liver biopsy were analyzed for correlation with the stage of fibrosis to identify any characteristics which had a predictive value for the severity of fibrosis (Table 3). Necroinflammatory changes (p = <0.0001) and male gender (p = 0.03) positively correlated with increasing stage of fibrosis. None of the other parameters such as age and duration of infection to biopsy, mode of transmission, BMI or serum ALT had any significant association with the severity of fibrosis.

Histologic changes between the first and final biopsies

We examined the differences in the clinical, biochemical and histologic characteristics between the first and the final biopsies. Of the 44 patients, 20 (45.5%) did not show any progression in fibrosis between the two biopsies. Thirteen (29.5%) had an increase in fibrosis stage as shown in Fig 1. Eleven patients (25%) showed a regression of fibrosis on the second biopsy (Fig 2). Serum ALT did not have any predictive value in indicating progression or regression. Necroinflammatory changes, which had a positive correlation with higher stages of fibrosis on the initial biopsies, also did not have any predictive value in differentiating those who showed fibrosis progression on the final biopsy. Although genotype 1 seemed to have a positive correlation with progression of fibrosis, the disproportionately low numbers of non-genotype 1 (15%) may not support that assertion.

We evaluated the pattern and rate of progression of fibrosis in the 13 patients who showed worsening of fibrosis between the first and final biopsies (Figure 1). Four patients progressed from no fibrosis to portal/periportal fibrosis over an interval ranging from 4 to 17 years. Another four progressed from portal/periportal fibrosis to bridging fibrosis at intervals from 2 to 8 years, two from portal/periportal fibrosis to cirrhosis at 8 and 11 years and one patient from bridging fibrosis to cirrhosis in 4 years. Two patients showed progression from stage 1 to 2 at intervals of 9 and 10 years, respectively. In aggregate, 5 patients demonstrated bridging fibrosis or cirrhosis (stage 3–6) on the first biopsy and 9 on the final biopsy. The details of the regression of fibrosis in 11 patients are shown in figure 2. Most of the changes involved regression within portal/periportal fibrosis (stage 2 to 1) and from portal/periportal to none. Two patients, at intervals of 10 and 12 years, showed a regression of fibrosis from early bridging fibrosis (stage 3) to periportal fibrosis (fig 2).

Discussion

We present a retrospective study involving a group of treatment naïve children and adolescents with CHC with the aim to characterize the progression of histologic liver disease over time using repeat liver biopsies. These patients had no other coexisting diseases or complications such as viral infections, malignancy, autoimmune disease or chronic medications that may have affected liver histology. The clinical and histological characteristics of the patients who participated in the PEDS-C study have been detailed previously [11, 22, 23]. Majority of patients had only mild histologic liver disease during the first two decades of life and in aggregate most of the children did not show significant

progression in fibrosis at an interval of about five years. Significant fibrosis was noted in 5 children at the initial biopsy at a mean duration of 8 years of infection. Worsening of fibrosis was noted in 13 children in whom there was no correlation with the mode of acquisition of HCV infection, demographic, clinical or laboratory variables such as ALT or presence of autoimmune antibodies. To our knowledge, this is the largest series of treatment naïve pediatric patients who have been evaluated for histologic progression of CHC liver disease based on repeat liver biopsies. This study provides a unique opportunity to explore the natural history of pediatric HCV infection in an untreated pediatric population in a longitudinal manner.

There are only a few reports involving repeat liver biopsies in untreated children with CHC [6,24–26]. The prognostic factors in predicting liver disease progression have been variable in these studies; in some of the adult series serum ALT, duration of infection, viral load and steatosis have been associated with fibrosis progression [13–20]. In one of the pediatric studies involving repeat biopsies, Guido et al identified 13 children who had paired liver biopsies from a retrospective multi-center study comprising of 112 children with chronic CHC [24]. The main finding from this study was that age at biopsy and the duration of infection correlated with the stage of fibrosis [24]. In a study spanning 35 years involving 31 adults who were infected with HCV from mini-transfusions in infancy, Cashiraghi et al reported 5 patients who had a repeat liver biopsy after 5 years; only one patient showed an increase in fibrosis by one stage [2].

Key pediatric studies involving single liver biopsies in the evaluation of the natural history of untreated CHC have also shown conflicting results[1–7, 25]. In a retrospective study of 40 children with CHC, Badizadegan et al found varying degrees of portal fibrosis in 78 % of pediatric patients including cirrhosis in 8 % at a mean age of 11 years [5]. In contrast, large long term follow up studies of transfusion acquired HCV infection early in life indicate a relatively benign course over a 20–35 year interval with fibrosis progression in only a few subjects[1,2]. Perinatal transmission has been implicated as a factor leading to a more aggressive course for CHC related liver disease including hepatocellular carcinoma in case reports and a few series [6,7,26]. Our data showed that mode of transmission was not a predictive factor for progression.

One of the limitations of this study is the sampling variability inevitable in a retrospective study and the relatively small number of subjects. Liver biopsy sizes were excellent with 11 portal tracts only in 40/97 biopsies [22]. They were adequate, although possibly suboptimal, containing 6 portal tracts in 43/97 biopsies. Therefore any apparent improvement or even worsening of fibrosis could have been in part due to sampling error of less than optimal specimens available for review [12,13,22,28,29]. Moreover the distribution of fibrosis is reported to be patchy in CHC and small needle biopsies may not reliably estimate the extent of the overall fibrosis which may also explain the finding of regression in a few of our patients [12,13,27–29]. It is well recognized that the staging system often demonstrates a non-linear progression of fibrosis[12,13]. Prospective randomized controlled studies in untreated children to address the adequacy and heterogeneity in biopsy sizes are challenging because of the decreasing number of HCV infected patients, the benign clinical course during the first two decades of life and the risks involved in liver biopsy. This clearly highlights the

need for noninvasive markers of fibrosis which should be specifically validated for use in infants and children. Until they are available, liver biopsy will remain the gold standard for assessment of disease severity [12,13,28].

In this era of expanding treatment options for children and adolescents with CHC, the role of an initial or repeat liver biopsy for treatment decisions needs to be examined. In the past, many treatment trials mandated a liver biopsy; this approach is now being questioned since children tolerate treatment well and the outcome of treatment is excellent, especially in non genotype1patients [8–11]. The current NASPGHAN guidelines for management of pediatric patients with chronic HCV recommend a liver biopsy if the result influences medical decision making, such as initiation of treatment in genotype 1, or in the event of sudden hepatic decompensation in a previously stable patient [21]. These guidelines have been supported by other investigators who advocate for a liver biopsy in the presence of autoimmune markers, obesity, or suspected cirrhosis, and recognize that markers such as ALT or viral load may not be predictive of severity or treatment outcomes [8,9,30]. It may be argued that treatment of a slowly progressing disease in an asymptomatic child may be deferred given the side effects and limitations of the currently available therapy. On the other hand, some might favor early treatment of a population with very little co- morbidity, facing many decades with the potential unpredictability of the course of CHC liver disease[8–11]. Liver biopsy finding is one of the critical factors which may influence decisions regarding therapy [21,31].

Based on the data from this retrospective study we conclude that, in the absence of specific non-invasive predictive tools and more robust mathematical models of fibrosis estimation, a follow-up biopsy after more than five years may be justified to evaluate CHC liver disease severity and progression for treatment decisions, particularly in genotype 1 patients.

Abbreviations

HCV	Hepatitis C Virus
ALT	alanine aminotransferase
CHC	chronic hepatitis C
HCV RNA	hepatitis C virus ribonucleic acid
PCR	polymerase chain reaction
HAI	histologic activity index
BMI	body mass index
NASPGHN	North American Society of Pediatric Gastroenterology, Hepatology and Nutrition

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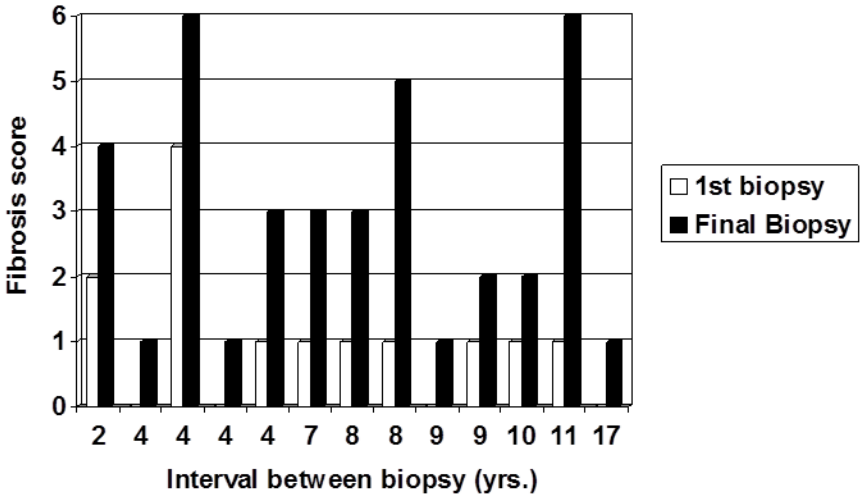

Figure 1. Pattern and rate of progression in 13 patients with worsening fibrosis between first and final biopsies

Four patients progressed from no fibrosis to portal/periportal fibrosis (from stage 0 to 1), and four progressed from portal/periportal fibrosis to bridging fibrosis. Two patients progressed from stage 1 to 2 within portal/periportal fibrosis and another two from portal/periportal to bridging fibrosis/ cirrhosis (stage 1 to 5–6). There was worsening from bridging fibrosis to cirrhosis (stage 4 to 6) in one patient. Each set of bars represents one patient.

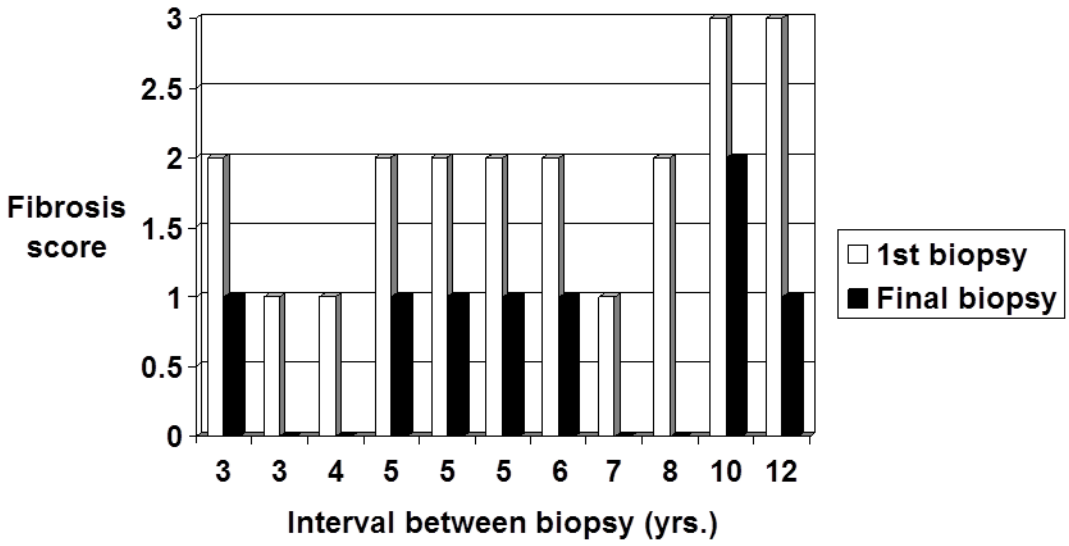

Figure 2. Fibrosis regression in 11 patients between first and final biopsies

The figure represents 11 patients who showed a regression of fibrosis between the two biopsies. Most of the changes involved regression within (stage 2–1) and from portal/periportal fibrosis to none. Two patients, at intervals of 10 and 12 years, showed a regression of fibrosis from early bridging fibrosis to periportal fibrosis. Each set of bars represents one patient.

Table 1

Patient Characteristics

Patient Characteristics	**N**	**%**
Gender	44	
Female	20	45%
Male	24	55%
Genotype	35	
1a*	20	56%
1b	10	28%
2	3	9%
3	2	6%
Race/Ethnicity	44	
White	32	73%
Black	6	14%
Asian	1	2%
Mixed	5	11%
Ethnicity	44	
Hispanic	5	11%
Mode of Transmission	44	
Vertical	25	57%
Transfusion	17	39%
Unknown	2	4%
	1st Biopsy Mean (SD)	2nd Biopsy Mean (SD)
Age (Yrs)	8.6 (4.1)	14.5 (4.0)
Duration (Yrs)	7.7 (4.3)	13.5 (4.4)
Viral Load ($\times 10^6$) IU/ml	0.85 (1.24)	1.84 (2.39)
ALT (U/L)	90 (73)	70 (53)

*includes 3 patients with Genotype 1 (not otherwise specified)

Table 2

Histology Findings in Patients at First and Final Biopsy

	First Biopsy		Second Biopsy		
Histologic changes	**N**	**Percentage**	**N**	**Percentage**	***p*-Value**
Steatosis					
None	34	77%	32	73%	0.62
Mild/Moderate (<33% tissue)	10	23%	12	27%	
Grade					
None/Minimal (0–3)	24	55%	22	50%	
Mild (4–6)	8	18%	11	25%	0.89
Moderate (7–9)	9	20%	8	18%	
Marked (≥10)	3	7%	3	7%	
Stage					
None (Stage 0)	7	16%	7	16%	**0.0046**
Portal/Peri-Portal (Stage 1–2)	32	73%	28	64%	
Bridging/Cirrhosis (Stage 3–6)	5	11%	9	20%	

Table 3

Comparison of Patient Characteristics and histology by Stage of Fibrosis at First Biopsy

Characteristic at First Biopsy	**Stage of Fibrosis at First Biopsy**			***p*-Value**
	None (N=7)	**Portal/Peri-Portal (N=32)**	**Bridging/Cirrhosis (N=5)**	
Age (Yrs) *	9.9 (3.9)	8.0 (4.1)	11.0 (3.7)	0.22
Duration (Yrs) *	9.3 (4.2)	7.0 (4.0)	10.0 (5.6)	0.19
HCV RNA × 10^6 *(IU/ml)	1.6 (2.1)	0.6 (0.8)	--	0.11
ALT (U/L) *	56 (29)	94 (81)	118 (56)	0.34
BMI Z-Score *	0.97 (0.94)	0.12 (1.50)	0.72 (0.39)	0.28
Gender (Male) % (n)	43% (3)	50% (16)	0% (0)	**0.03**
Transmission (Vertical) % (n)	43% (3)	59% (19)	60% (3)	0.68
Genotype - % (n)				
1	100% (7)	88% (22)	50% (1)	0.11
2	0% (0)	6% (2)	50% (1)	
3	0% (0)	6% (2)	0% (0)	
Steatosis % (n)				
None	71% (5)	78% (25)	80% (4)	0.15
Mild/Moderate	29% (2)	22% (7)	20% (1)	
Grade % (n)				**<0.0001**
None/Minimal	100% (7)	53% (17)	0% (0)	
Mild	0% (0)	25% (8)	0% (0)	
Moderate	0% (0)	22% (7)	40% (2)	
Marked	0% (0)	0% (0)	60% (3)	

*Mean (± S.D.)