Pediatric Surgery International (2018) 34:1073–1077
https://doi.org/10.1007/s00383-018-4316-3

ORIGINAL ARTICLE

Outcomes of Alagille syndrome following the Kasai operation: a systematic review and meta-analysis

Jun Fujishiro[1] · Kan Suzuki[1] · Miho Watanabe[1] · Chizue Uotani[1] · Toshiko Takezoe[1] · Naohiro Takamoto[1] · Kentaro Hayashi[1]

Accepted: 26 July 2018 / Published online: 2 August 2018

Abstract

Purpose Infants with Alagille syndrome (AGS) frequently develop neonatal cholestasis, and some AGS infants who suspected of biliary atresia subsequently undergo the Kasai operation with the diagnosis of biliary atresia. The aim of this study was to investigate the effect of the Kasai operation on liver and patient outcomes among AGS patients, using a meta-analysis.

Methods A systematic review and meta-analysis of studies describing the outcomes of AGS patients with/without the Kasai operation were conducted. The analyzed outcomes were liver transplantation, not living with the native liver, and mortality for any reason.

Results We identified 6 studies (394 AGS patients). All studies were retrospective cohort or case-control studies. The incidences of liver transplantation, not living with the native liver, and mortality were significantly higher in AGS patients who underwent the Kasai operation than in those who did not undergo the Kasai operation (odds ratio: 6.46, 95% CI 3.23–12.89, $p < 0.00001$; odds ratio: 25.88, 95% CI 2.83–236.84, $p < 0.004$; odds ratio: 15.05, 95% CI 2.70–83.93, $p = 0.002$, respectively).

Conclusion The Kasai operation was associated with poor outcomes in AGS patients. It remains unclear if the Kasai operation directly deteriorates liver and patient outcomes in AGS patients.

Keywords Alagille syndrome · Neonatal cholestasis · Biliary atresia · Kasai operation · Meta-analysis

Introduction

Alagille syndrome (AGS) is a complex autosomal dominant disorder that affects many parts of the body, such as the liver, heart, face, eyes, and skeleton [1]. The prevalence of AGS is reported as 1:70,000 [2], but this would be underestimated due to the variability and reduced penetrance of the condition [3]. The *JAGGED1* (JAG1) and *NOTCH2* genes in the Notch signaling pathway are known to be associated with AGS [4]. The majority of cases (~97%) are caused by haploinsufficiency of JAG1 gene [5, 6], and a small portion (< 1%) are caused by mutations in NOTCH2 gene [7]. AGS can be clinically diagnosed according to the classic criteria established by Alagille et al. [8]. A diagnosis is made if at least three of the following five major clinical features are noted: chronic cholestasis, cardiac disease, skeletal abnormalities, ocular abnormalities, and characteristic facial features.

In infants, the most common clinical features of AGS are cholestasis and conjugated hyperbilirubinemia [9]. Therefore, distinction between AGS and other diseases that cause neonatal cholestasis, such as biliary atresia, is necessary [10]. As prompt Kasai operation is the standard approach for the treatment of biliary atresia, some infants with AGS having suspicion of biliary atresia undergo intraoperative cholangiography and subsequent Kasai operation. Previous studies on the outcomes of AGS have shown a tendency of poor outcomes in AGS patients who have undergone the Kasai operation [10–13] and have suggested that the Kasai operation might be harmful in AGS patients [10]. However, the effect of the Kasai operation on the outcomes of AGS patients is not clear.

The aim of the present study was to investigate the effect of the Kasai operation on the outcomes of AGS patients by performing a systematic review and meta-analysis.

✉ Jun Fujishiro
jfujishi-tky@umin.ac.jp

[1] Department of Pediatric Surgery, Faculty of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan

Materials and methods

This systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A systematic search of the literature was conducted in the PubMed, Medline, and Cochrane Library electronic databases, using the keywords "Alagille syndrome" AND ("biliary atresia" OR "Kasai operation" OR "portoenterostomy"). A manual search of the references of selected articles was also performed. The titles, keywords, and abstracts of all retrieved publications were reviewed to select studies for full-text review. Full-text assessments were performed for selected articles. We intended to include all randomized controlled trials and observational studies that described outcomes of AGS with/without the Kasai operation. We used the following adverse outcomes in the study: liver transplantation, not living with the native liver (mortality or liver transplantation), and mortality for any reason. Thus, odds ratio more than 1 means that the Kasai operation was associated with adverse outcome in this study. Studies focusing on liver transplant patients were excluded because of the apparent bias for outcomes.

Odds ratios with 95% confidence intervals (CI) were computed according to the reported numbers of patients and events. The Mantel–Haenszel method with a random effects model was used for meta-analysis. All analyses were performed using Review Manager (RevMan) Version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). A p value < 0.05 was considered statistically significant.

Results

The initial search identified 180 articles (178 were identified from the databases and 2 were identified from cross-referencing). After removing duplications, 137 articles underwent initial screening (title, keywords, and abstract), and subsequently, 8 articles underwent full-text screening. Six articles (394 AGS patients) that met the inclusion criteria were finally selected for the meta-analysis (Fig. 1). Of the six studies, five were retrospective cohort studies and one was a case-control study in which an effort was made to adjust patient characteristics [9–14] (Table 1). There was no randomized controlled study.

Liver transplantation was described as an outcome in all six articles. In total, 34 of 54 AGS patients who underwent the Kasai operation and 78 of 340 patients who did not undergo the Kasai operation received liver transplantation. The incidence of liver transplantation was significantly higher in patients who underwent the Kasai operation than in those who did not undergo the Kasai operation (odds ratio: 6.46, 95% CI 3.23–12.89, $p < 0.00001$) (Fig. 2). Not living with the native liver (mortality or liver transplantation) was described as an outcome in two studies. In total, all 9 AGS patients who underwent the Kasai operation, and 9 of 32 patients who did not undergo the Kasai operation were not living with the native liver. The incidence of not living with the native liver was significantly higher in patients who underwent the Kasai operation than in those who did not undergo the Kasai operation (odds ratio: 25.88, 95% CI 2.83–236.84, $p < 0.004$) (Fig. 3). Mortality for any reason was described as an outcome in two studies. The incidence of mortality was significantly higher in patients who underwent the Kasai operation than in those who did not undergo the Kasai operation (odds ratio: 15.05, 95% CI 2.70–83.93, $p = 0.002$) (Fig. 4).

Discussion

This systematic review and meta-analysis revealed that the existing evidence for the effect of the Kasai operation on liver and patient outcomes in AGS patients is based on retrospective observational studies. The findings of this meta-analysis suggest that the Kasai operation is associated with poor liver and patient outcomes in AGS patients.

Timely Kasai operation is desirable for improving outcomes in patients with biliary atresia. However, there are problems in distinguishing AGS from other diseases associated with infantile cholestasis, including biliary atresia, in neonates and infants. It is known that the typical clinical features of AGS are not apparent in the neonatal or infantile period [15]. Dedic et al. reported that 5 of 72 patients with biliary atresia, who were evaluated for a *JAG1* mutation, showed a positive result. While these patients with *JAG1* mutation had only 1 or 2 major clinical features, including cholestasis, at the age of 2 months, all patients subsequently showed 3–5 major clinical features of AGS and were clinically diagnosed with AGS by the age of 3 years [15]. Paucity of the bile duct, which is a common pathological feature of AGS, is known to be less frequently observed in infants than in older patients with AGS, and its prevalence has been shown to increase with age [13, 15]. Moreover, bile duct proliferation, which is a common feature of biliary atresia, is frequently observed in liver biopsy samples from infants with AGS [12–14]. Thus, clinical and pathological features are not sufficient for differentiating AGS from other causes of neonatal cholestasis in the infantile period. Genetic testing for *JAG1* or *NOTCH2* mutation would help in the differential diagnosis of AGS in infants [15]. However, genetic testing for these genes has not been widely used in clinical settings for diagnosis in infantile cholestasis and it would

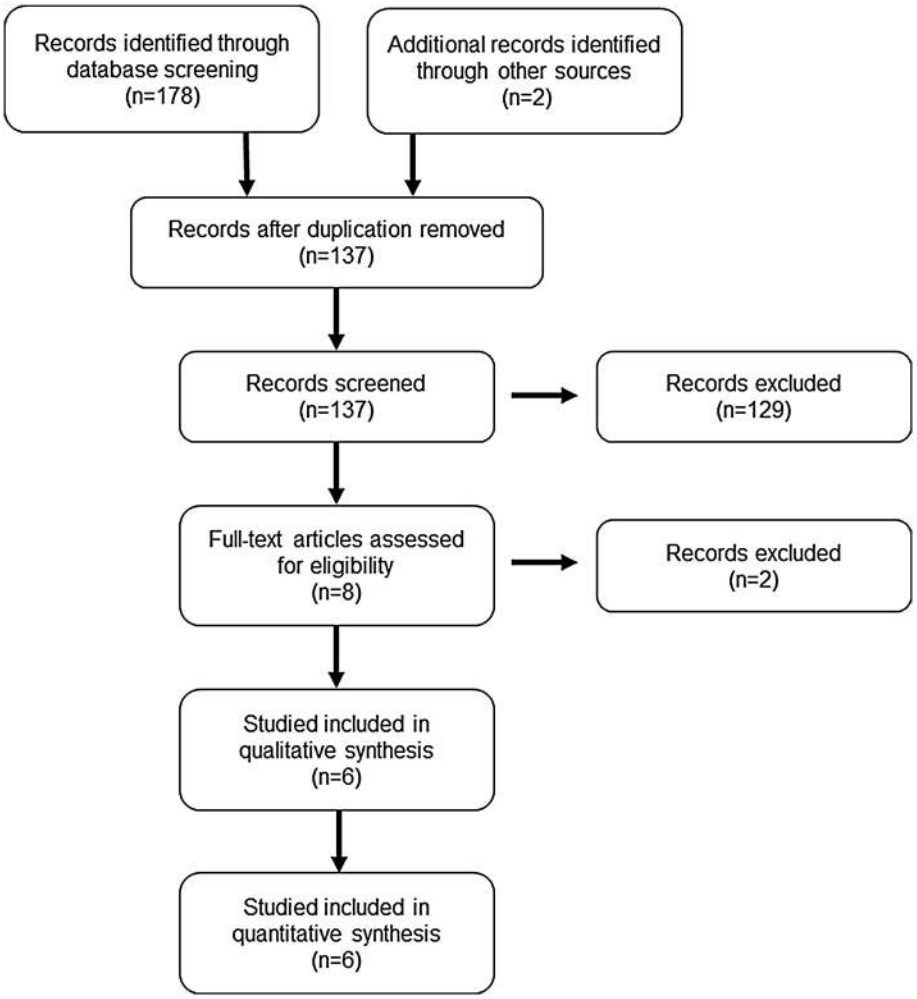

Fig. 1 Flow diagram for data extraction

Table 1 Characteristics of studies included in the meta-analysis

Author, year of publication	Study design	Study period	Observation period	Outcomes		
				LTX	Not LNL	Mortality
Hoffenberg [9], 1995	Cohort study	1983-	ND	+	+	
Emerick [6], 1999	Cohort study	1974–1997	ND	+		
Quiross-Tejeira [8], 1999	Cohort study	1976–1997	Outcome determined as of 1997	+		
Lykavieris [4], 2001	Cohort study	1960–2000	ND	+		
Kaye [5], 2010	Case-control study[a]	N.D	ND	+		+
Lee [7], 2015	Cohort study	1999–2014	Median: 528 days	+	+	+

ND not described, *LNL* living with native liver

[a]With adjusting patient characteristics

take approximately 1 month for the genetic testing. Thus, due to the availability and significant delay of the Kasai operation in BA infant, it is not realistic that all infants with cholestasis received the genetic testing before the intraoperative cholangiography or the Kasai operation.

This meta-analysis demonstrated that liver and patient outcomes were poorer in AGS patients who underwent the Kasai operation than in those who did not undergo the Kasai operation, and these findings are consistent with the results of previous studies [9, 10, 12]. However, delicate consideration is necessary for assessing the effect of the Kasai operation in AGS patients. Neonatal cholestasis itself has been reported as a prognostic factor for AGS. Lykavieris et al. showed that neonatal cholestatic jaundice

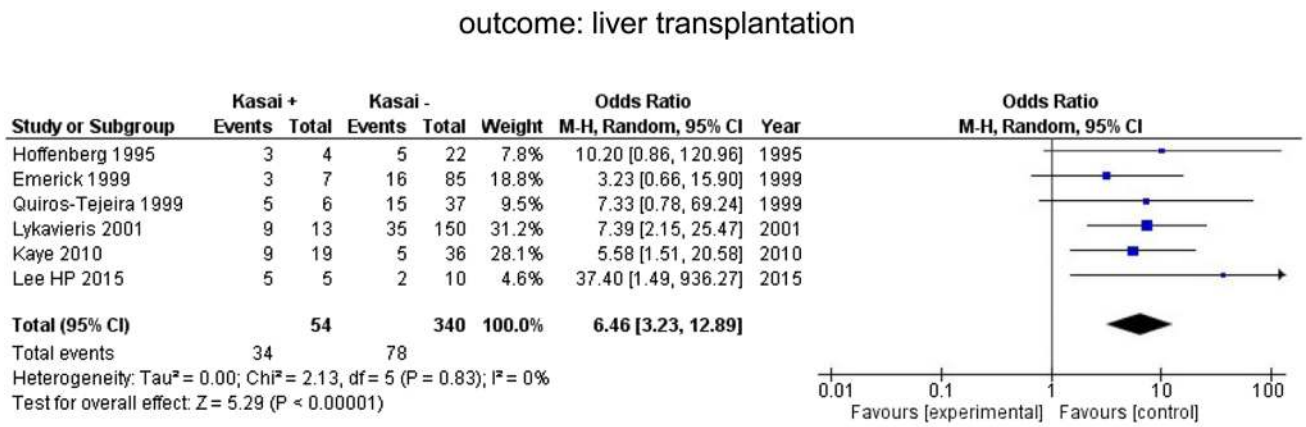

Fig. 2 Forest plot of liver transplantation in Alagille syndrome patients with/without the Kasai operation

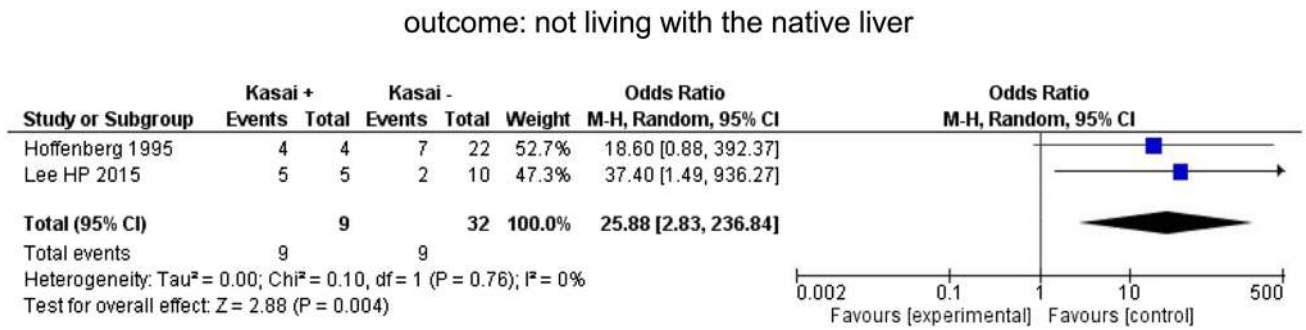

Fig. 3 Forest plot of not living with the native liver in Alagille syndrome patients with/without the Kasai operation

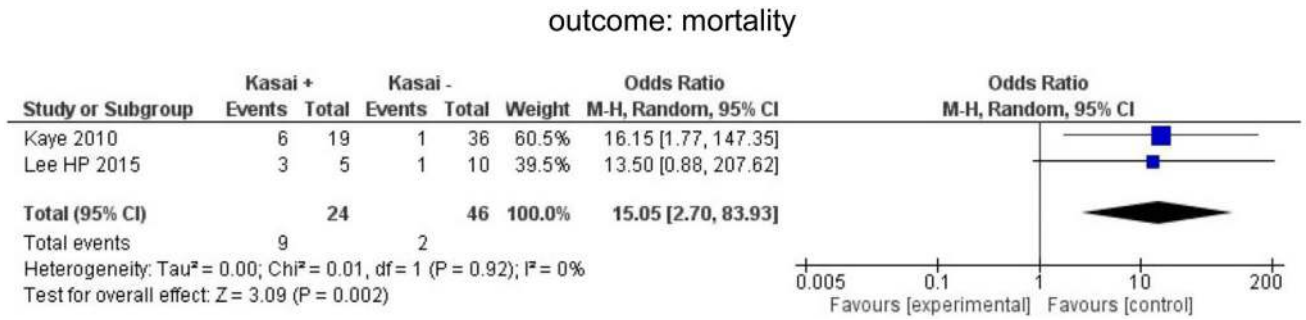

Fig. 4 Forest plot of mortality in Alagille syndrome patients with/without the Kasai operation

was the only independent risk factor for 10-year survival with the native liver and that the Kasai operation was not a significant factor [9]. Hoffenberg et al. showed that AGS with cholestasis onset in infancy was associated with a 50% probability of long-term survival without liver transplantation, which was worse than the findings in other studies on AGS [14]. This poor outcome in AGS patients with neonatal cholestasis could be associated with severe liver damage or comorbidities, such as complex heart disease [12]. Another factor is the possible co-existence of AGS and biliary atresia. It is presumed that intraoperative cholangiography in AGS patients who have undergone the Kasai operation would show findings consistent with biliary atresia, such as occlusion of the extrahepatic bile duct [11]. Therefore, while previous studies described that the Kasai operation for patients who were subsequently diagnosed with AGS was

associated with misdiagnosis [10, 12, 16], these cases might have had co-existence of AGS and biliary atresia or biliary atresia due to AGS. It is yet to be investigated whether the Kasai operation itself can directly worsen the outcomes of AGS patients. Kaye et al. mentioned that the Kasai operation does not benefit children with AGS and actually appears to worsen the outcomes [10]. They speculated that exposure to intestinal content and/or ascending cholangitis following the Kasai operation would result in worsening of an already abnormal bile duct in AGS patients [10]. Emerick et al. reported that there was no increased mortality rate for AGS patients who underwent the Kasai operation and that none of these patients developed cholangitis after the operation [11]. They also mentioned that it remains unclear whether AGS patients undergoing the Kasai operation belong to a subpopulation with more severe liver disease resulting in liver transplantation or whether the need for liver transplantation develops secondary to the Kasai operation itself. Nevertheless, the present study and previous studies suggest that the Kasai operation does not have a positive effect on outcomes in AGS patients.

The present study has some limitations. All articles included in the meta-analysis involved retrospective cohort/case-control studies. Different patient backgrounds between the studies and between groups (with/without the Kasai operation) and different study periods would affect the results. Another limitation is regarding the statistical method in this study. The outcomes in the study such as receiving liver transplantation or mortality is time-dependent event. Therefore time-to-event analysis such as Kaplan–Meier analysis or Cox regression analysis would be more suitable. However, none of the studies used described sufficient data for these analyses. From a scientific point of view, a prospective study is ideal for clarifying the effect of the Kasai operation on outcomes in AGS patients suspected with biliary atresia. However, such a study would not be realistic in a clinical setting.

In conclusion, this meta-analysis showed that the Kasai operation was associated with poor liver and patient outcomes among AGS patients. However, it remains unclear if the Kasai operation directly deteriorates liver and patient outcomes in AGS patients. Under the existing circumstances, careful diagnosis and decision-making with high suspicion of AGS is necessary in the treatment of infants suspected of having biliary atresia with some clinical features of AGS. Genetic testing for *JAG1* or *NOTCH2* mutation would be helpful in such a situation in the future.

Compliance with ethical standards

Conflict of interest The authors report no conflicts of interest.

References

1. Vajro P, Ferrante L, Paolella G (2012) Alagille syndrome: an overview. Clin Res Hepatol Gastroenterol 36:275–277
2. Danks DM, Campbell PE, Jack I, Rogers J, Smith AL (1977) Studies of the aetiology of neonatal hepatitis and biliary atresia. Arch Dis Child 52:360–367
3. Turnpenny PD, Ellard S (2012) Alagille syndrome: pathogenesis, diagnosis and management. Eur J Hum Genet EJHG 20:251–257. https://doi.org/10.1038/ejhg.2011.181
4. Kamath BM, Bauer RC, Loomes KM, Chao G, Gerfen J, Hutchinson A, Hardikar W, Hirschfield G, Jara P, Krantz ID, Lapunzina P, Leonard L, Ling S, Ng VL, Hoang PL, Piccoli DA, Spinner NB (2012) NOTCH2 mutations in Alagille syndrome. J Med Genet 49:138–144
5. Li L, Krantz ID, Deng Y, Genin A, Banta AB, Collins CC, Qi M, Trask BJ, Kuo WL, Cochran J, Costa T, Pierpont ME, Rand EB, Piccoli DA, Hood L, Spinner NB (1997) Alagille syndrome is caused by mutations in human Jagged1, which encodes a ligand for Notch1. Nat Genet 16:243–251. https://doi.org/10.1038/ng0797-243
6. Oda T, Elkahloun AG, Pike BL, Okajima K, Krantz ID, Genin A, Piccoli DA, Meltzer PS, Spinner NB, Collins FS, Chandrasekharappa SC (1997) Mutations in the human Jagged1 gene are responsible for Alagille syndrome. Nat Genet 16:235–242. https://doi.org/10.1038/ng0797-235
7. McDaniell R, Warthen DM, Sanchez-Lara PA, Pai A, Krantz ID, Piccoli DA, Spinner NB (2006) NOTCH2 mutations cause Alagille syndrome, a heterogeneous disorder of the notch signaling pathway. Am J Hum Genet 79:169–173. https://doi.org/10.1086/505332
8. Alagille D, Estrada A, Hadchouel M, Gautier M, Odievre M, Dommergues JP (1987) Syndromic paucity of interlobular bile ducts (Alagille syndrome or arteriohepatic dysplasia): review of 80 cases. J Pediatr 110:195–200
9. Lykavieris P, Hadchouel M, Chardot C, Bernard O (2001) Outcome of liver disease in children with Alagille syndrome: a study of 163 patients. Gut 49:431–435
10. Kaye AJ, Rand EB, Munoz PS, Spinner NB, Flake AW, Kamath BM (2010) Effect of Kasai procedure on hepatic outcome in Alagille syndrome. J Pediatr Gastroenterol Nutr 51:319–321
11. Emerick KM, Rand EB, Goldmuntz E, Krantz ID, Spinner NB, Piccoli DA (1999) Features of Alagille syndrome in 92 patients: frequency and relation to prognosis. Hepatology 29:822–829
12. Lee HP, Kang B, Choi SY, Lee S, Lee SK, Choe YH (2015) Outcome of alagille syndrome patients who had previously received kasai operation during infancy: a single center study. Pediatr Gastroenterol Hepatol Nutr 18:175–179
13. Quiros-Tejeira RE, Ament ME, Heyman MB, Martin MG, Rosenthal P, Hall TR, McDiarmid SV, Vargas JH (1999) Variable morbidity in alagille syndrome: a review of 43 cases. J Pediatr Gastroenterol Nutr 29:431–437
14. Hoffenberg EJ, Narkewicz MR, Sondheimer JM, Smith DJ, Silverman A, Sokol RJ (1995) Outcome of syndromic paucity of interlobular bile ducts (Alagille syndrome) with onset of cholestasis in infancy. J Pediatr 127:220–224
15. Dedic T, Jirsa M, Keil R, Rygl M, Snajdauf J, Kotalova R (2015) Alagille syndrome mimicking biliary atresia in early infancy. PLoS One 10:e0143939
16. Subramaniam P, Knisely A, Portmann B, Qureshi SA, Aclimandos WA, Karani JB, Baker AJ (2011) Diagnosis of alagille syndrome-25 years of experience at King's College Hospital. J Pediatr Gastroenterol Nutr 52:84–89