 doi:10.20944/preprints202209.0441.v1

Accumulation of postoperative unexpected events assessed by the Comprehensive Complication Index® are prognostic outcome parameters after Kasai procedure

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Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 28 September 2022 doi:10.20944/preprints202209.0441.v1

Abstract

Introduction Kasai procedure in children with biliary atresia (BA) is associated with several complications in the short-term. The Comprehensive Complication Index (CCI®) is a validated metric in adult surgery for the analysis of complication and morbidity in surgical patients. We aimed to analyze the CCI® for the first time in BA infants and to corelate its association with the outcome.

Material and Methods Retrospective review of medical records of infants with type III BA undergoing Kasai procedure between January 2011 and December 2021 at our institution. All unexpected events were ranked according to the Clavien-Dindo classification and the CCI® per patient was subsequently calculated. Clavien-Dindo grades, individual events, the CCI® and the total event number per patient were correlated with the one- and two-year outcome post Kasai.

Results 131 events were identified in 101 patients (range 0 – 11 per patient). Forty-four Grade I (33.6%), 67 Grade II (51.1%), 18 Grade III (13.7%) and two sentinel events [> Grade IV] (1.5%) were documented according to Clavien-Dindo, including one death in a cardiac-associated BA patient. None of the complications correlated significantly with a poor outcome. Sixty-three (62.4%) CCI® were calculated (range 0 – 100). The mean CCI® during the in-patient treatment post Kasai, was significantly higher in patients with a poorer outcome compared to patients with native liver survival at one- and two-year follow-up (22.7± 21.7 vs 13.2± 18.1; p=0.02).

Conclusion Not the severity of complications, but the accumulation of numerous events related to Kasai procedure are associated with a poorer outcome. Therefore, the CCI® is an excellent instrument for the postoperative morbidity assessment of BA patients.

Keywords: biliary atresia; complications; unexpected events; Clavien-Dindo; CCI

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Introduction

Kasai portoenterostomy (KPE) is a palliative surgical procedure in infants with biliary atresia, aiming to restore the biliary drainage and to prevent liver transplantation. While temporary jaundice-clearance is achieved in about 50% of the children, liver transplantation is necessary in about 70% of patients in the long-term.[1–4] A few prognostic parameters for the latter outcome are known at the time of KPE.[5,6] While disease-related complications are well-known catalysators for the Kasai outcome, data on the postoperative complications and morbidity after Kasai procedure are scarce. However, recent studies have shown that surgical and medical errors and events do not affect the survival with native liver in the short- and long-term.[7,8] Those studies mainly focused on the analysis of single events in individuals, without putting the adverse events in the context of the overall morbidity.[9]

The systematic assessment and documentation of postoperative complications in adult hepatobiliary surgery has been established early in 2004 with the introduction of the Clavien-Dindo classification.[10] This instrument focusses on the consequences of complications and grades events according to their severity.

Recently, the Comprehensive Complication Index (CCI®) has been introduced, giving a detailed view on the postoperative morbidity of patients based on adverse events.[11,12] This metric summarizes multiple complications in an individual, based on a prior ranking according to the Clavien-Dindo classification, and we recently reported on its accuracy in pediatric cohorts.[13] Studies in adult oncological cohorts have shown a correlation of the CCI® within the surgical treatment period and the long-term outcomes.[14–16] For pediatric hepatobiliary diseases, the predictive value of the CCI® has not yet been tested.

 doi:10.20944/preprints202209.0441.v1

The aims of this study were to evaluate the accuracy of the CCI® in the postoperative treatment of BA infants and to correlate its results with the short-term outcome.

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Material and Methods

Ethical approval was obtained from the local ethics committee (approval no 9557_BO_K_2021). Informed consent was obtained from the legal guardians on admission.

A retrospective chart review of patients undergoing Kasai portoenterostomy between January 2011 and December 2021 at the Hannover Medical School has been performed. For the analysis all patients with type III biliary atresia, according to the abbreviated Japanese Association of Pediatric Surgeons (JAPS) classification were included. Patients with syndromic BA, cytomegaly virus positive BA and other types of BA according to the JAPS classification were excluded from the analysis. The one-year follow-up was available for all (100%) and the two-year follow-up data for 86% of the patients through the Biliary Atresia and Related Diseases Registry (www.bard-online.com).[17] Fourteen patients (14%) did not reach the two-year follow-up at the time of the analysis.

The data collection included patient characteristics, the age at KPE, liver function tests prior to the KPE, the Ishak (semiquantitative fibrosis scoring) interpretation of liver biopsies taken during the KPE according to a standardized protocol, all unexpected events including surgical and medical interventions (within the first three months following KPE) and the Kasai outcome (jaundice-free survival with native liver [Bilirubin < 20μmol/l], survival with native liver, liver transplantation, death) at the one- and two-year follow-up.

Postoperative Kasai management protocol

The standardized treatment protocol included the pre- and postoperative administration of ursodeoxycholic acid and fat-soluble vitamins, as well as a 2-week

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course of intravenous antibiotics (3rd generation cephalosporins or penicillin + beta-lactamase inhibitor) followed by oral prophylaxis for 6 months. The antibiotic drugs were discussed with the department of microbiology and were changed based on their recommendations. On the fifth postoperative day, adjuvant treatment with rectal budesonide (2mg per day) was started and continued for three months.[18]

Definition of unexpected events

According to our previously published protocols, unexpected events were defined as any subsequent deviations from the planned perioperative course and changes in the management with any delay in treatment or recovery.[13,19,20] Therefore, we included data on surgical events (re-do surgery due to anastomotic leaks, severe bleeding etc.) and medical interventions not included in our standardized protocol of perioperative care (electrolytes, specific analgetics, albumin substitution, diuretics, transfusions etc.), taking into consideration that those events are liver disease-related.

Assessment of unexpected events

According to our previously published protocol, the documentation of all unexpected events of the previous 24 hours was performed by a designated team of surgeons during the daily routine team conferences.[13] Data of the patients included demographics, diagnosis, management/ treatment of the unexpected events, classification according to the Clavien-Dindo classification. The designated team members stored the data in a password-encrypted database, only accessible to the core team.

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Classification of unexpected events

All events were classified according to the Clavien-Dindo system. This severity grading instrument includes five grades, based on the consequences of unexpected events and their severity.[10] Briefly, the classification differentiates between:

Deviations from the postoperative course without the need for pharmacological treatment or other interventions, with defined allowed therapeutic regimens (Grade I); Requiring pharmacological treatment with drugs other than such allowed for Grade I complications (Grade II); Interventions not under general anesthesia (Grade IIIa); Interventions under general anesthesia (Grade IIIb); Single organ dysfunction (Grade IVa); Multiorgan dysfunction (Grade IVb); Death of a patient (Grade V).

We then assessed the CCI® score for all patients, a metric that is based on a prior ranking according to the Clavien-Dindo classification, as an instrument for the postoperative morbidity on a scale of zero (no complication) to 100 (death). For the calculation of the CCI® score the template available at http://www.cci.assessurgery.com was used. In this calculation, all events within the follow-up period of 90 days following Kasai procedure were included.

Statistical analysis

Statistical analysis was performed using GraphPad Prism (v8.0; GraphPad Software, San Diego, California, USA). Spearman´s correlation coefficient was used (r) to compare complications and their consequences with the latter outcome.; $r > 0.8$ was defined as strong, and $r > 0.9$ as very strong. Data are presented as mean (s.d.). Statistical significance was set at $P < 0.050$.

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Results

Patient characteristics

Between the study period of January 2011 and December 2021, 155 infants underwent Kasai procedure at the Hannover Medical School, of whom 101 patients (65.2%) matched the inclusion criteria.

The mean age at KPE in the cohort of patients with type III BA was 61 days (± 21). The mean liver function tests pre KPE were 244 U/l (± 190) AST, 163 U/L (± 118) ALT, 537 U/l (± 355) Gamma-GT and 141 (± 45) μmol/l for the conjugated bilirubin.

The native liver survival of patients at the one-year follow-up was 65.3% (66/101), of whom 44 (67.0%) were jaundice free; and at the two-year follow-up 54.0% (47/87), with 44 out of 47 (93.6%) being jaundice-free.

Analysis of unexpected events

A total of 131 events according to the Clavien-Dindo classification in 101 patients were identified (Table 1).

Stratified according to the severity, 44 Grade I (44/131; 33.6%) interventions were documented, the majority being administration of diuretics (n=39; 88.6%) due to postoperative edema and ascites with an insufficient urine output less than 1.0 cc/kg/h. In three children (6.8%) electrolyte substitutions were necessary (sodium & potassium) and in two children (4.5%) analgetic treatment had to be reintroduced or increased.

The majority of events in our cohort were Grade II interventions according to the Clavien-Dindo classification, with 67 in total (67/131; 51.1%). In 30 patients (30/67; 44.8%) an early cholangitis was diagnosed and treated with intravenous antibiotic treatment, 10 children (14/67; 14.9%) received parenteral nutrition within the hospitalization and 10 children (14/67; 14.9%) received a transfusion (independent

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from Kasai procedure). Nine patients (9/67; 13.4%) underwent intravenous antibiotic treatment for central line and wound infections, one (1/67; 1.5%) received antimycotics based on an intraabdominal swap with signs of a fungal infection and peritonitis and in 8 cases (8/67; 11.9%) albumin substitutions for generalized edema were necessary.

Two ascites drains (2/131; 1.5%) were placed without general anesthesia (Grade IIIa according to Clavien-Dindo).

Sixteen procedures (16/131; 12.2%) were performed under general anesthesia (Grade IIIb according to Clavien-Dindo). Five anastomotic leaks (5/16; 31.3%) were documented, one at the portoenterostomy and four at the jejuno-jejunostomy, of which two occurred in the same dystrophic patient. Two re-laparotomies (2/16; 12.5%) were performed due to postoperative intestinal hemorrhage, of which one patient went into cardiopulmonary arrest and resuscitation (Grade IVb) and received a postoperative MRI under general anesthesia (1/16; 6.3%) to rule out cerebral ischemia. Two wound (2/16; 12.5%) and one revision (1/16; 6.3%) of the fascia were performed, and three patients (3/16; 18.8%) received a biloma and another two (2/16; 12.5%) an ascites drain under general anesthesia.

One Grade V event (death), occurred in a patient with CABA (Cardiac-associated biliary atresia) with postoperative cardiac arrest.

Analysis of unexpected events and the Kasai outcome

In the group of 66 patients with native liver survival (SNL) at the one-year follow-up, a mean of 1.1 events (± 1.9) occurred within the first three months following KPE, compared to 1.7 (± 1.7) in the group of 35 patients with rapid liver deterioration and early liver transplantation (LTx) (p= 0.11). Stratified according to the Clavien-Dindo classification, a statistical trend was observed for a higher number of Grade I events

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in the LTx group (0.6 vs 0.4; p= 0.08), with no statistical difference for the additional Clavien-Dindo Grades at the one- and two-year follow-up (> p= 0.1).

Comprehensive Complication Index in our BA cohort

We cumulated multiple events in an individual (within the first three months after KPE) in one CCI®. Thirty-eight children (38/101; 37.6%) had no events and therefore a CCI® of 0. For 63 BA infants (63/101; 62.4%) a CCI between 8.7 and 100 (death) was calculated. The average CCI® in the cohort was 16.5 (± 19.8) with a median of 8.7. A significant difference was detected comparing the SNL group, with a mean CCI® of 13.2 (± 18.1), with a median of 8.7, and the LTx/ death group with a mean CCI® of 22.7 (± 21.7) and a median of 20.9 (p=0.02). A significant correlation for the CCI® and the outcome at the one-year (p=0.001) and the two-year follow-up (0.02) was observed. The CCI® additionally correlated inversely with the time to transplantation (r=-0.5; p=0.003). Furthermore, the CCI® significantly correlated (> r=0.8; p= 0.001) with the length of hospital stay (in days) following Kasai procedure.

In contrast, no significant correlation was detected for the total complication number per patient (range 0 – 11) with the outcome, without using the severity grading and formula of the CCI® (> p=0.1).

Multivariate analysis

In the multiple stepwise regression, all complications and their consequences were analyzed for their association with the outcome at one- and two-year follow up. A significant association with the latter outcome for early postoperative cholangitis (p=0.05) and electrolyte fluctuations and substitutions (p=0.02) was detectable, while a trend was observed for postoperative ascites drains (p=0.1). For re-laparotomies

 doi:10.20944/preprints202209.0441.v1

(p=0.4), transfusions (p=0.3), parenteral nutrition (p=0.5), albumin substitutions (p=0.9) and antibiotics for other causes of sepsis (p=0.5) no association with the outcome were present.

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Discussion

Kasai portoenterostomy, in the vast majority of infants with biliary atresia, is the first-line treatment, achieving biliary drainage in more than 50% of the patients.[21] Despite the jaundice clearance, sequelae of portal hypertension are the main drivers for liver deterioration in the short- and long-term follow-up.[22] Multimodal treatment strategies, including Kasai procedure and liver transplantation, eventually necessary in 70-80% of all BA patients, continuously increased the overall survival in BA infants over the last decades.[23] However, up to 10% of the children do not survive the transplant waiting lists.[24,25] Therefore, pediatric surgeons and hepatologists tried to decipher the successful Kasai procedure and few prognostic markers were identified. The logic of those markers remains cryptic and by far not every BA infant undergoing Kasai procedure less than 60 days of age will survive with its native liver.

Whether or not postoperative complications following Kasai procedure result in rapid liver deterioration and early transplantation was recently discussed by Calinescu et al.[7] The systematic analysis of postoperative events, according to the Clavien-Dindo classification, did not detect a correlation with the latter overall outcome. In adult surgery, recent developments of morbidity scores have resulted in applicable prognostic markers for oncological outcomes after surgical interventions. The Comprehensive Complication Index (CCI®), a metric from 0 to 100 [death] that includes numerous complications and events in an individual during the in-patient management, is an indicator for the postoperative morbidity and recently a correlation with the oncological outcomes for colorectal, gastric and hepatic cancers have been reported.[14,26,27]

We therefore translated those concepts into the perioperative Kasai management and included all unexpected events, including disease related interventions (diuretics,

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electrolytes, albumin etc.) not part of our standardized protocol, and calculated the CCI® for the first time in Kasai surgery.

Within the study period a total of 131 surgical, non-surgical and medical interventions were documented, of which two (Clavien-Dindo > Grade IV) are considered sentinel events. One death during the in-patient stay, in a child with CABA (cardiac-associated biliary atresia)[28], was identified and the patient was excluded from the further analysis. For the standardization of our heterogenous cohort, we only included type III BA infants.

The number of events in our cohort is much a higher compared to other surgical BA collectives in the literature.[7,9] This can be attributed to our definition of unexpected events, including any deviation of the planned postoperative course, that results in a delay in treatment and recovery. Therefore, the analysis is focused on the postoperative morbidity, including KPE-associated events and also liver-disease related sequelae. We did not identify any correlation between the events and the age at Kasai, the degree of liver fibrosis and cirrhosis at Kasai and the bilirubin and gamma-GT levels at Kasai procedure.

As the CCI® is based on a prior ranking of events according to the Clavien-Dindo classification, we first ranked all events according to the Clavien-Dindo instrument and then individually correlated those gradings with the outcome. While none of the Clavien-Dindo events (Grade I – IV) were significantly associated with a worse outcome at the one- and two-year follow-up, detailed analysis revealed a significant association of electrolyte substitutions (Grade I) for hyponatremia, and early postoperative cholangitis (Grade II) with transplantation and death. Hyponatremia is a well-known sequelae of pediatric liver diseases, mainly associated with portal hypertension, systemic vasodilatation and hypovolemia.[29] Low sodium levels are

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considered a negative predictor for mortality in pediatric liver transplant candidates and more recently an association with poor outcome in biliary atresia children with cirrhosis has been reported.[29,30] All children with electrolyte substitution had already moderate to severe signs of liver cirrhosis in liver biopsies at KPE.

The entity of postoperative cholangitis in children with biliary atresia is largely unknown, but an ascending bacterial infection from the roux-loop is the main suspect resulting in long-term antibiotic treatment and prophylaxis.[31,32] A cholangitis incidence between 40% and 93% has been reported in BA infants and recurrent cholangitis episodes are blamed for a poorer Kasai outcome.[33] In our cohort the cholangitis incidence was not related to the age at Kasai and the degree of fibrosis and cirrhosis in the liver biopsy.

Although a statistical trend was observed for Grade I events (p=0.1) and the Kasai outcome, analysis of the CCI® revealed that the cumulation of events mirrors the overall morbidity and is the superior parameter. The mean CCI® in the LTX group was significantly higher compared to the SNL group (22.7 vs 13.2; p=0.02). Translating the CCI® numbers into the events per patient showed that children in the SNL in average suffered one to two Grade I events (Grade I = CCI® equivalent 8.7) , while in the LTx group one and more Grade II events (Grade II = CCI® equivalent 20.9) occurred. The combination of events within those groups were inconsistent and the multivariate analysis did not identify individual events to be significantly associated with the outcome. Furthermore, the CCI® data confirmed the results of previous publication on surgical (interventional) complications and events (> Grade IIIa = CCI® equivalent > 26.2), that did not present an association with the native liver survival.[7]

While in adult oncological surgery the Grade IIIa events and higher are the significant drivers for the overall postoperative outcome using the CCI®,[15,26] our study confirms

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that in BA patients postoperative symptoms and conditions requiring alterations in the postoperative pharmacological treatment (Clavien-Dindo Grade I & II) are important predictors for the outcome of Kasai procedure.

In addition to our previous report on the feasibility of the CCI® in a general pediatric surgical cohort, more recently the authors in Fuchs et al. reported on the utilization of the CCI® in pediatric liver surgery.[13,34] Not only did the authors report on the advantages of the CCI® for the standardization of outcome measures, but they also emphasized its advantages in establishing standardized measures of quality in pediatric surgery. Experiences in adult surgery already show that the CCI® can be evaluated for the comparison between surgical techniques and for the perioperative morbidity and mortality comparison between institutions. Therefore, the CCI® should be considered a potential indicator for the surgical quality in pediatric surgery.

Although further validation of the CCI® in Kasai procedure is necessary, we recommend its assessment for future studies in BA surgery.

Limitations

Several limitations of our study need to be addressed. The medical records were analyzed retrospectively, which might have led to missing values in our cohort. Furthermore, the events were ranked retrospectively according to the Clavien-Dindo classification and the CCI® and a plausibility validation of the historical data was not possible in all cases. At last, the indication for pharmacological treatment underwent protocol changes during the study period, which might have led to a lower threshold for the cholangitis and diuretic treatment in the some patients.

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Figure 1 Boxplot with information on the median CCI® (standard deviations, maximum scores) after Kasai procedure, in the group of children with native liver survival (SNL) and liver transplantation or death (LTx/ Death) at the 12 months follow-up

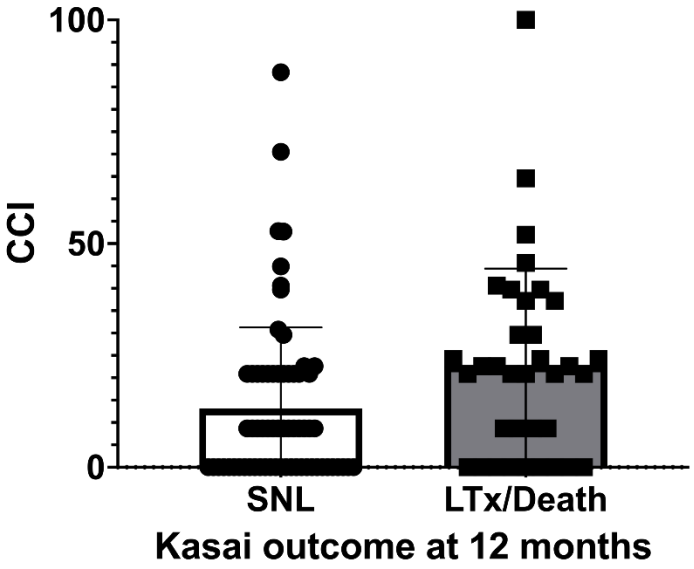

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Table 1 Information on all unexpected events in the postoperative management of biliary atresia following Kasai procedure and the grading according to the Clavien-Dindo classification

Clavien-Dindo Grade	Type	n=	Total (n)
I	Diuretics	39	**44**
	Analgetics	2	
	Electrolytes	3	
II	Parenteral nutrition	10	**67**
	Transfusion	10	
	Antibiotics for wound infection	1	
	Antibiotics for sepsis	8	
	Antimycotics for intraabdominal fungal infection	1	
	Antibiotics for cholangitis	30	
	Albumin substitution	6	
	Vitamin K iv substitution	1	
IIIa	Ascites drain	2	**2**
IIIb	Wound revision	2	**16**
	Re-laparotomy for bleeding	2	
	Ascites drain	2	
	Biloma drain	3	
	Fascia dehiscence	1	
	Anastomotic leak	5	
	MRI to rule out cerebral ischemia	1	
IVa	/	0	**0**
IVb	Cardiopulmonary resuscitation	1	**1**
V	Cardiac arrest	1	**1**

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