BMJ Open Epidemiology of adverse events attributed to airway management in paediatric anaesthesia: protocol for the prospective, multicentre, registry-based, cross-sectional Japan Pediatric Difficult Airway in Anesthesia study (J-PEDIA)

Taiki Kojima,1,2 Yusuke Yamauchi,1 Fumio Watanabe,1 Shogo Ichiyanagi,1 Yasuma Kobayashi,3 Yu Kaiho,4 Shugo Kasuya,5 Kevin Y Urayama,6 Norifumi Kuratani,7 Yasuyuki Suzuki5

ABSTRACT

Introduction Failure to secure an airway during general anaesthesia is a major cause of adverse events (AEs) in children. The safety of paediatric anaesthesia may be improved by identifying the incidence of AEs and their attributed risk factors. The aim of the current study is to obtain real-world data on the incidence of adverse peri-intubation events and assess their association with patient characteristics (including the prevalence of difficult airway features) and choice of anaesthesia management. These data can be used to develop a targeted education programme for anaesthesia providers towards quality improvement activities.

Methods and analysis This prospective, multicentre, registry-based, cross-sectional study will be conducted in four tertiary care hospitals in Japan from June 2022 to May 2025. Children <18 years of age undergoing surgical and/or diagnostic test procedures under general anaesthesia or sedation by anaesthesiologists will be enrolled in this study. Data on patient characteristics, discipline of anaesthesia providers and methodology of airway management will be collected through a standardised verification system. The exposure of interest is the presence of difficult airway features defined based on the craniofacial appearance. The primary and secondary endpoints are all AEs associated with airway management and reduced peripheral capillary oxygen saturation values. Potential confounders are related to the failure to secure the airway and variations in the anaesthesia providers’ levels, adjusted using hierarchical multivariable regression models with mixed effects. The sample size was calculated to be approximately 16 000 assuming a 99% probability of obtaining a 95% Wilson CI with±0.3% of the half-width for the 2.0% of the incidence of critical AEs.

Ethics and dissemination The study protocol was approved by the Institutional Review Board at Aichi Children's Health and Medical Center (2021051). The results will be reported in a peer-reviewed journal and a relevant academic conference.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study will be a large prospective, registry-based, multicentre, observational study; it will provide anaesthesiologists with important information regarding the incidence of critical adverse events and their associated risk factors while securing the airway during anaesthesia induction in children.
⇒ Investigating real-world data regarding patient characteristics (including the prevalence of difficult airway features) and characteristics of paediatric anaesthesia practice can provide anaesthesia providers with useful information to improve the safety and effectiveness of airway management.
⇒ A standardised data collection system that will be applied in this study allows our study to maintain the quality of the collected data and minimise potential information biases.
⇒ This registry-based study will collect the data based on a self-reporting manner by anaesthesia providers that can cause reporting bias.
⇒ Unmeasured confounders could remain unadjusted owing to the observational nature of the study.

INTRODUCTION

The incidence of perioperative life-threatening adverse events (AEs) in children is higher than that in adults due to their unique physiological and anatomical characteristics.1 These AEs are related to hypoxia in children commonly occur following failure to secure the airway since children are less tolerant to apnoea.2-4 Therefore, identifying the incidence of AEs and the risk factors in
securing the airway is desired for safe and strategic airway
management in paediatric anaesthesia.

Epidemiological data on AEs during general anaes-
thesia in children have been reported in previous large
prospective cohort studies. The APRICOT (Anaesthesia
PRactice In Children Observational Trial) study, which
was the largest multicentre prospective study conducted
in Europe, reported an incidence rate of 5.2% for severe
perioperative events in children.5 In addition, Subra-
manyam et al reported prediction models for periop-
erative respiratory AEs based on preoperative patient
comorbidities.6 However, the APRICOT study was not
designed to explore AEs specifically attributed to airway
management during general anaesthesia. Therefore, it
did not include detailed information regarding the diffi-
cult airway features of patients, anaesthesia methods,
device used for securing the airway and disciplines of
anaesthesia providers. The PeDI (The Pediatric Difficult
Intubation) registry study, a multicentre cohort study
conducted in children’s hospitals in the USA, reported
that the incidence rate of intraoperative AEs was high
in children with difficult airway features.2 However,
approximately 80% of the study cohort were patients with
difficult airway features; therefore, the results did not
represent the entire paediatric population. In addition,
these major studies did not adjust for the variability in the
techniques and skill level of anaesthesia providers (eg,
each anaesthesia provider could have a specific method-
ology for securing the airway and anaesthesia). A lack of
adjustment for this clustering effect at each anaesthesia
provider’s level could be a bias in reporting the incidence
of AEs in the previous large studies.

To our knowledge, there is a lack of well-designed
paediatric prospective studies using registry-based, real-
world data in the Asian region regarding the incidence
of AEs and the risk factors attributed to airway manage-
ment. Differences in craniofacial and oropharyngeal anatomy
and the sensitivity to anaesthetics between Asians and
Caucasians have been reported.7–14 These anatomical
and pharmacodynamic differences may provide different
epidemiological data on critical AEs during airway

This study aims to investigate the incidence of AEs
attributed to airway management during general anaes-
thesia in children and to identify their risk factors.

**METHODS AND ANALYSIS**

**Study design and setting**

This is a prospective, registry-based, real-world, multi-
centre, cross-sectional study that will initiate data registra-
tion from 1 June 2022 to 31 May 2025 in five tertiary care
hospitals in Japan: Aichi Children’s Health and Medical Center (Aichi), National Center for Child Health and Development (Tokyo), Saitama Prefectural Children’s Medical Center (Saitama), Tohoku University Hospital (Sendai) and Hokkaido University Hospital (Sapporo).

**Target population**

Advanced airway management is defined as the following procedures.

► Tracheal intubation (oral, nasal and via tracheostomy).
► Placement of supraglottic airway devices.
► Surgical airway secure including cricothyroidotomy, tracheostomy, securing the airway with a ridged bronchoscope.

However, blow-by oxygen administration, mask ventilation providing positive pressure and insertion of oral/nasal airway are not included as advanced airway management.

**Inclusion criteria:** We will enrol cases that meet all of the following criteria.

► Children <18 years of age undergoing general anaesthesia or sedation for both scheduled and emergency surgery and/or test procedures conducted by anaesthesiologists or anaesthesia providers under the supervision of anaesthesiologists.

► The cases that receive advanced airway management at least once during general anaesthesia or sedation (eg, a tracheal intubation performed during general anaesthesia with mask ventilation will be included).

► General anaesthesia or sedation is performed in operating suites, catheterisation laboratory rooms, rooms for radiological imaging and procedures (eg, CT, MRI, radiation therapy) or general ward.

**Exclusion criteria:** We will exclude cases that meet at least one of the following criteria.

► Emergency cases outside operating suites where anaesthesiologists are consulted for airway management for resuscitation.

► Cases where airway management is performed in the emergency department and intensive care unit.

► Duplicate cases during the study period.

► Patients or their families who refuse to provide their medical information for the current study through the opt-out procedure.

**Data collection**

This registry-based cross-sectional study will prospectively collect data regarding the characteristics of patients and surgery, disciplines of anaesthesia providers, practice of airway management, occurrence of AEs and treatments for AEs (tables 1–3).

In addition, the specific number assigned for each anaesthesia provider is reported for each attempt to secure the airway (table 3).

The practice of airway management includes reasons to start the airway management, medication administered during the airway management, results of securing the airway, types of devices to secure the airway, presence of cricoid pressure/external laryngeal manipulation and percentage of glottic opening score (table 3).

AEs include cardiac arrest (survival or death), laryngospasm, upper airway obstruction, severe cough, bronchial intubation, oesophageal intubation, vomiting, hypotension, hypertension, tooth injury, pneumothorax, mediastinal emphysema, bronchospasm, atelectasis, pulmonary oedema, stridor, airway trauma, arrhythmia, agitation and dislodgement of airway securing devices (table 3).

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**Table 2** Details of the data collection forms regarding anaesthetic management

<table>
<thead>
<tr>
<th>Anaesthetic management</th>
<th>Contents for reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Status of nil per os</td>
<td>Yes/no</td>
</tr>
<tr>
<td>Full-stomach pathophysiology</td>
<td>Yes/no</td>
</tr>
<tr>
<td>Drainage of gastric contents before airway management</td>
<td>Yes/no</td>
</tr>
<tr>
<td>Premedication</td>
<td>None, midazolam, diazepam, others</td>
</tr>
<tr>
<td>Syndrome assuming difficult airway</td>
<td>Yes/no</td>
</tr>
<tr>
<td>Preoperative difficult airway evaluation</td>
<td>None, preoperative recognition of possible difficult airway, history of difficult airway, limited cervical range of motion, width of mouth opening ≤2 patient’s fingers, hyomental distance ≤2 patient’s fingers, upper airway obstruction, midface hypoplasia, macroglossia, micrognacia, macrocephaly.</td>
</tr>
<tr>
<td>Difficult mask ventilation</td>
<td>Yes/no</td>
</tr>
<tr>
<td>Types of anaesthesia induction</td>
<td>Inhalational with or without maintaining spontaneous breathing, intravenous with or without maintaining spontaneous breathing, rapid sequence induction with or without positive pressure ventilation, awake induction with only topical local anaesthetics, others.</td>
</tr>
</tbody>
</table>
### Table 3  Details of the data collection forms regarding airway management

<table>
<thead>
<tr>
<th>Items</th>
<th>Contents for reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Value of SpO₂ at the initiation of airway management</td>
<td>%</td>
</tr>
<tr>
<td>Lowest value of SpO₂ during airway management</td>
<td>%</td>
</tr>
<tr>
<td>Times of attempts to secure the airway per one airway securing procedure</td>
<td>Number of times</td>
</tr>
<tr>
<td>Reasons to start securing the airway</td>
<td>Scheduled procedure, airway concerns after extubation, desaturation, apnoea, dislodgement of airway devices, obstruction of airway devices, avoiding airway stimulation by airway devices, inadequate ventilation with excessive air-leakage, prevention of aspiration, laryngeal oedema, laryngospasm, bronchospasm, airway trauma, atelectasis formation, pulmonary oedema, pulmonary secretion removal, pneumothorax/pneumomediastinum, unstable haemodynamics, others.</td>
</tr>
<tr>
<td>Medications administered during airway management</td>
<td>Sevoflurane, desflurane, nitrous oxide, fentanyl, morphine, remifentanil, rocuronium, vecuronium, suxamethonium, sugammadex, midazolam, propofol, thiopental, remimazolam, ketamine, dexmedetomidine atropine, epinephrine, lidocaine (intratracheal, intravenous).</td>
</tr>
<tr>
<td>Provider's assigned number</td>
<td>Number</td>
</tr>
<tr>
<td>Success of securing airway</td>
<td>Success, failure (inadequate exposure of glottic view, unstable haemodynamics, upper airway obstruction/oxygenation failure, unable to insert airway device (proximal or distal site of the vocal cords), excessive air-leakage, oversized airway device, others).</td>
</tr>
<tr>
<td>Provider's training level</td>
<td>Residents (junior or senior), fellow (anaesthesia or other), board-certified anaesthesiologists (percentage of paediatric cases among the whole experienced cases over the last 1 year; &gt;80%, 50–80%, &lt;50%, other board-certified physicians (emergency medicine, intensive care medicine, others), others (eg, nurse anaesthetists).</td>
</tr>
<tr>
<td>Postgraduate year of provider</td>
<td>1, 2, 3, 4, 5, 6–9, ≥10 years</td>
</tr>
</tbody>
</table>

### Table 3  Continued

<table>
<thead>
<tr>
<th>Airway management</th>
<th>Ora, nasal, tracheostomy, others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route of securing the airway</td>
<td>Laryngoscope, supraglottic airway devices, video laryngoscope (with or without guide), stylet, non-directed laryngoscope without video monitor, gum elastic bougie/tube exchanger, flex bronchoscope, tracheostomy tube, surgical airway secure, tracheal intubation via supraglottic airway devices.</td>
</tr>
<tr>
<td>Device to secure the airway</td>
<td>Normal, armoured, RAE, double-lumen, others</td>
</tr>
<tr>
<td>Cuffed tracheal tube</td>
<td>Yes/no</td>
</tr>
<tr>
<td>Performing cricoid pressure</td>
<td>Yes/no</td>
</tr>
<tr>
<td>Performing external laryngeal manipulation</td>
<td>Yes/no</td>
</tr>
<tr>
<td>Performing apnoeic oxygenation</td>
<td>Yes/no</td>
</tr>
<tr>
<td>POGO score</td>
<td>%</td>
</tr>
<tr>
<td>Complications during securing airway</td>
<td>None, cardiac arrest (survive, death), laryngospasm, upper airway obstruction, severe cough, endobronchial intubation, oesophageal intubation, vomiting, hypotension, hypertention, tooth injury, pneumothorax, mediastinal emphysema, bronchospasm, atelectasis, pulmonary oedema, stridor, airway trauma, arrhythmia, agitation, dislodgement of airway securing devices, others.</td>
</tr>
<tr>
<td>Treatment for complications during securing airway</td>
<td>None, sedatives, muscle relaxants, ventilatory support with tracheal tube, bronchodilator, intratracheal suctioning, inhalational epinephrine, intravenous epinephrine, intravenous steroid, atropine, surgical airway secure, cardioversion/defibrillation, inotropes/vasopressors, bolus infusion, anti-arrhythmic medications, cardiopulmonary resuscitation, extracorporeal membrane oxygenation, reversal medications, diuretics, admission to intensive care unit, others.</td>
</tr>
<tr>
<td>POGO, percentage of glottic opening</td>
<td>RAE, right angle endotracheal tubes; SpO₂, peripheral capillary oxygenation saturation.</td>
</tr>
</tbody>
</table>

POGO, percentage of glottic opening; RAE, right angle endotracheal tubes; SpO₂, peripheral capillary oxygenation saturation.
Data quality control
This study applies site-specific research leaders’ data verification system to minimise reporting and selection biases. Site-specific research leaders for this study were preassigned to each institutional research group before initiating data collection.

Initially, all data described in tables 1–3 are reported by anaesthesia providers with paper-based data collection forms. Each site-specific research leader reviews and verifies the collected initial paper-form-based data. This verification process is standardised among the five recruited institutions. The site-specific research leaders daily check missing information in the reported forms and unreported cases to be included in this study. In the case of missing cases or information, the site-specific research leader collects the necessary information by asking the case-assigned anaesthesiologists about airway management and reviewing the anaesthesia and medical charts. Before initiating the data collection, the goal of the capture rate was ≥95% of whole cases that should be included in this study at each institution. To standardise the definitions of the terms for data collection, they are predetermined and described in the operational research manual created by the primary investigator (TK). The research operational committee will be convened regularly to confirm the definitions of the terms used in the data collection process. Site-specific research leaders instructed the anaesthesia providers by distributing the operational research manual to increase the accuracy of the collected data at each recruited institution, aiming to minimise misclassification bias (figure 1). The research collaborators can confirm uncertainty regarding data collection (eg, definitions of the terms for data collection) and share the information with each other using communication software (Slack, Slack Technologies, San Francisco, California, USA).

Data storage and processing
The initially collected paper-form-based data will include information that can identify the study participants (ie, medical record number and name initials). Thus, only anonymous information will be registered in the Research Electronic Data Capture (REDCap, Tokyo, Japan) system hosted by the National Center for Child Health and Development. Site-specific research leaders will use a standardised participant’s correspondence file, which will include the participant’s initials, medical record number and REDCap registration number for a potential review (figure 1).

Endpoints
The primary and secondary endpoints are any AEs attributed to securing the airway and decreased values of peripheral capillary oxygen saturation (SpO₂) from the time of initiation to completion of securing the airway. The criteria for AEs were predetermined (ie, cardiac arrest (status of dead or alive at 24 hours after the critical event happened), laryngospasm, upper airway obstruction, severe cough, bronchial intubation, oesophageal intubation, vomiting, hypotension, hypertension, tooth injury, pneumothorax, mediastinal emphysema, bronchospasm, atelectasis, pulmonary oedema, stridor, airway trauma, arrhythmia, agitation, dislodgement of airway securing devices) based on the National Emergency Airway Registry for children (NEAR4KIDS), which is a national registry database to evaluate AEs during emergency tracheal intubation in paediatric intensive care units mostly located in North America.16 Severe AEs have been classified as severe and non-severe before data collection. Severe AEs include cardiac arrest, oesophageal intubation with a ≥5% decrease in SpO₂, vomiting with aspiration, hypotension requiring treatments, laryngospasm, pneumothorax, mediastinal emphysema, bronchospasm, pulmonary oedema and direct airway trauma. Non-severe AEs include bronchial intubation, oesophageal intubation with a <5% decrease in SpO₂, vomiting without aspiration, hypertension requiring treatments, upper airway obstruction, severe cough, tooth injury, atelectasis, stridor, arrhythmia and dislodgement of airway securing devices.

Exposures and potential confounders
Exposure is defined as the presence of any of the difficult airway features (ie, preoperative recognition of difficult airway by anaesthesiologists, history of difficult airway, restricted cervical flexion, restricted mouth opening ≤2 patient’s fingers, narrow thyromental distance ≤2 patient’s fingers, upper airway obstruction, or anatomical barrier to visualise glottic opening, midfacial hypoplasia, large tongue, micrognathia and large head circumference) that were predetermined based on previous nationwide registry-based studies in North America (NEAR4KIDS).16 17 This current registry-based study depends on self-reports by anaesthesia providers. Therefore, board-certified anaesthesiologists report the difficult airway features based on previous diagnosis and clinical judgement if these features do not have standards of objective measurement.

Potential confounders were selected before the initiation of data collection based on a review of previous literature and clinical experience of experienced anaesthesiologists among the research team members. The
selected potential confounders were age, sex, prematurity, obesity (weight-for-age ≥95 percentile), preoperative comorbidities, families smoking status, provider discipline, location, institution, fiscal year, Cormack-Lehan grade, method of anaesthesia induction, status of nothing per os and a full stomach, type of device for securing the airway and application of external laryngeal manipulation or cricoid pressure. These potential confounders are included in the data collection form (tables 1–3). However, the Cormack-Lehane grade is not commonly applied to evaluate the glottic view by a video-laryngoscope. Thus, the percentage of glottic opening score will be reported as surrogate data.

Sample size estimation
The reported incidence rate of critical events occurring during general anaesthesia induction in children was 5.2%, including an incidence of 1.9% for cardiovascular instability in the general paediatric population who received general anaesthesia. Therefore, we estimated the sample size with the assumption of the lowest incidence of critical AEs during general anaesthesia in children as 2.0%. The estimated sample size was approximately 16 000 assuming a 99% probability of obtaining a 95% Wilson CI with ±0.3% of the half-width for the incidence of critical AEs.

Statistical analysis
For summary statistics, categorical variables will be described as numbers and percentages, whereas normally and non-normally distributed continuous variables will be described as means and SDs or medians and IQRs. Univariable and multivariable analyses will be performed to evaluate risk factors associated with the primary outcome. Baseline differences between subjects with and without difficult airway features will be evaluated using the Student’s t-test for normally distributed continuous variables, Wilcoxon rank-sum test for continuous variables with skewed distributions and $\chi^2$ test or Fisher’s exact test for categorical variables. Hierarchical multivariable regression models with mixed effects analysis will be conducted to adjust for the potential confounders and the clustering effects of individual anaesthesia providers and institutions as different levels. Ten variables were selected for fixed effects and two variables for random effects a priori to be adjusted in hierarchical multivariable regression models with mixed effects analysis based on previous studies and clinical experience. Ten variables as fixed effects include age, sex, preoperative comorbidity (ie, oxygenation failure, haemodynamic instability, chromosomal abnormality, congenital cardiac diseases, active or recent history of upper respiratory symptoms), provider’s discipline, devices for airway management (ie, video laryngoscope, flexible bronchoscope). The two variables as random effects are individual anaesthesia providers (level 2) and institution (level 3). Interaction terms will be incorporated into the Hierarchical multivariable regression models to evaluate the presence of interaction among the predictors and covariates. The variance inflation factor of <5 was determined as a threshold to evaluate the multicollinearity.

The registration system using REDCap in this study does not allow the registration process to proceed if missing data exist. In addition, each site-specific research leader review missing data daily. Thus, we assume that the number of cases with missing data is minimal. Cases missing values will be removed from the analysis (ie, complete case analysis). As sensitivity analysis, multiple imputation analysis will be conducted if the missing data can be considered as missing at random.

Data will be analysed using Stata V.17.0 (StataCorp, College Station, Texas, USA), with a two-sided $p$ value of <0.05, serving as the criterion for assessing the null hypothesis for each analysis.

Harms
No harmful events will occur during data collection because of the nature of an observational study without interventions.

Patient and public involvement
None.

Ethics and dissemination
This study will be conducted in accordance with the Declaration of Helsinki. The study protocol was reviewed and approved by the Institutional Review Board at Aichi Children’s Health and Medical Center (approval number 2021051, 29 September 2021) and local ethical approval will be obtained from each recruited institution before initiating data collection. The Institutional Review Board considered that written consent could be waived by performing the opt-out procedure in the current clinical study. The results of this study will be reported in a peer-reviewed journal and a relevant academic conference.

DISCUSSION
This is a prospective, registry-based, multicentre, cross-sectional study that aims to describe real-world data on the incidence of AEs and the risk factors attributed to securing the airway in children under general anaesthesia. Investigating real-world data regarding patient characteristics (including the prevalence of difficult airway features) and characteristics of paediatric anaesthesia practice can provide anaesthesia providers with useful information to improve the safety and effectiveness of airway management.

This study has several important limitations owing to the observational nature of the study. First, unmeasured confounders could remain unadjusted owing to the observational nature of the study. Second, there might be a selection bias due to the sampling method. Third, reporting bias (ie, misclassification bias) can occur due to incorrect reports during data collection. To address these potential limitations, we carefully designed this
study to collect detailed information regarding the exposure (presence of difficult airway features), potential confounders and institutions based on previous literature and meetings with experienced board-certified anaesthesiologists during the development of the study protocol. In addition, anaesthesia providers can tend to avoid reporting AEs in their cases, while the occurrence of both of these reporting biases can cause over-reporting and under-reporting. Therefore, we structured a standardised system to confirm the data collected by local research leaders among the recruited institutions. The local research leaders daily check the occurrence of AEs in each institution. This standard data confirmation system has been used in NEAR4KIDS, which achieved a data capture rate of ≥95%.16 Our standardised data collection system allows our study to maintain the quality of the collected data and minimise potential information biases (eg, misclassification). In addition, the REDCap data registration system does not allow data registration to proceed if there are missing data. We will use this system for data registration to minimise missing data for future analysis. Fourth, there might be Hawthorn effect during the data collection. The anaesthesia providers’ behaviour might be affected when they are aware of being observed. Therefore, this behavioural bias must be taken into consideration when interpreting the final results. Finally, the absence of normative ranges for blood pressure in small children could cause under-reporting of the occurrence of haemodynamic instability. This study defines haemodynamic instability as needing some interventions to treat hypotension, such as infusion, inotropes, vasopressors, extracorporeal membrane oxygenation, cardioversion and cardiopulmonary resuscitation. Therefore, careful interpretation is needed to evaluate the association between the haemodynamic AEs and their risk factors in this study due to the lack of data regarding non-severe haemodynamic instability.

Previous registry-based prospective studies (ie, APRICOT study, PeDI registry study) were performed mainly in Europe and North America.2,3 The evidence regarding the incidence of AEs related to securing the airway is insufficient in Asian settings. The incidence and risks of AEs attributed to airway management in the Japanese paediatric population might be different from those in Europe and North America owing to the differences in the characteristics of the patient population and anaesthesia practices.

This prospective, registry-based, real-world cross-sectional study in Japan can be a stepping stone for further research to identify the specific risk factors for AEs attributed to failure to secure the airway in the Asia region. Furthermore, the data regarding the risks of AEs can be used to develop targeted educational programmes for anaesthesia providers towards quality improvement activities, to reduce AEs during airway management in children.


22 Austin PC. A tutorial on multilevel survival analysis: methods, models and applications. *Int Stat Rev* 2017;85:185–203.