

Prognosis of Otitis Media with Effusion in Pediatric Patients with Cleft Palate During Language-acquisition Period Treated by Simultaneous Tympanostomy Tube Placement with Palatoplasty

Maho Iemura-Kashiwagi^{a,b}, Takayuki Okano^a, Noriko Iwai^{a,c}, Mirei Taniguchi^a, Koichi Omori^a

^aDepartment of Otolaryngology-Head and Neck Surgery, Graduate School of Medicine, Kyoto University, Kyoto, Japan

^bDepartment of Otolaryngology-Head and Neck Surgery, Uji-Tokushukai Medical Center, Kyoto, Japan

^cIwai Clinic, Hirakata, Japan

Conflict of interest: The authors have no conflicts of interest to report.

Corresponding Author: Takayuki Okano

Department of Otolaryngology-Head and Neck Surgery

Graduate School of Medicine, Kyoto University

54 Shogoin Kawaharacho, Sakyo, Kyoto 606-8507, Japan

Tel: +81-75-751-3346, Fax: +81-75-751-7225

Email: tokano@ent.kuhp.kyoto-u.ac.jp

Keywords: cleft palate, otitis media with effusion, tympanostomy tube insertion, palatoplasty

Abstract

Objective: Cleft palate (CP) in children is frequently complicated by otitis media with effusion (OME) due to Eustachian tube dysfunction. Although tympanostomy tube (TT) placement can be beneficial in the treatment of OME to prevent short-term hearing loss, there is no consensus regarding the indications for and timing of TT insertion. The present study was performed to define the safety and effectiveness of simultaneous TT placement with palatoplasty during the language-acquisition period.

Methods: We retrospectively reviewed the medical charts of pediatric patients who underwent palatoplasty for CP in a tertiary medical center, Kyoto University Hospital, from June 2010 to October 2018. The TT retention time was estimated using the Kaplan-Meier method. The incidence of OME recurrence was compared among four Veau classification groups based on the patients' sex, type of CP, median TT retention time, and type of fluid.

Results: Seventy-six subjects (150 ears) were enrolled in the study. The median follow-up duration was 48.7 months (range, 18.2-108.0 months) after the first TT placement. A first TT retention time of <20.1 months was a significant risk factor for OME recurrence. Subjects with maxillofacial anomaly complex and subjects with cleft lip and palate and an alveolar cleft showed a significantly higher OME recurrence rate than subjects with clefts only in the hard and/or soft palate. There was no significant difference in the occurrence of sequelae between subjects with only a single TT placement and subjects with more than one TT placement.

Conclusions: Based on the findings of the present study, it is reasonable to perform TT insertion at the same time as palatoplasty on patients who meet the indications. This technique may reduce the number of times the patient requires general anesthesia and maintain good middle ear condition during the period of language acquisition between 1 and 3 years of age.

1. Introduction

Cleft palate (CP) in children is frequently complicated by otitis media with effusion (OME) due to Eustachian tube dysfunction with an incidence of around 90%¹⁻³. Such children often develop hearing difficulties and recurrent acute otitis media^{3,4}. The sequelae of OME also include perforation, adhesion, and retraction of the tympanic membrane as well as other chronic changes such as myringosclerosis or tympanosclerosis, which can lead to moderate to severe hearing impairment later in life. Treating OME by tympanostomy tube (TT) insertion is one of the most common procedures to prevent adverse effects of hearing loss on speech and language development. Several previous reports have emphasized the importance of early placement of a TT because hearing plays a significant role in articulation training after palatoplasty by helping the patient to hear others' voices and pronounce words correctly by hearing their own voice during a critical period of growth and development^{5,6}. Conductive hearing loss has been thought to have a significant impact on children's language and psychosocial development. Although this philosophy has gained some support, a more conservative approach is favored by others because of the risk of morbidity associated with repeated TT insertion, including persistent perforations and myringosclerosis. Although TT placement can be beneficial in the treatment of OME to prevent short-term hearing loss⁴, there is no consensus regarding the indication criteria or timing of TT insertion. A better understanding of the incidence of sequelae following TT insertion would help to determine the indication criteria for TT insertion. In the present study, no prophylactic TT insertion was performed; TTs were prescribed only for patients with persistent OME diagnosed by one otolaryngologist. The purpose of this study was to define the safety and effectiveness of simultaneous TT placement with palatoplasty during the language-acquisition period.

2. Materials and methods

2.1. Study design

A retrospective chart review was performed among pediatric patients who underwent palatoplasty for CP in a tertiary medical center, Kyoto University Hospital, from June 2010 to October 2018, highlighting those whose CP was complicated by OME and who underwent TT placement concomitantly with palatoplasty. All patients underwent palatoplasty in the Department of Plastic and Reconstructive Surgery, Kyoto University Hospital and received otologic care in the Department of Otolaryngology-Head and Neck Surgery. The study complied with the Declaration of Helsinki and its amendment or comparable ethical standards and was approved by the Ethics Committee of Kyoto University (R2817).

2.2. Classification of CP

The subjects were categorized into four groups based on the Veau classification of cleft lip/palate: Group 1 (Veau I), Group 2 (Veau II), Group 3 (Veau III), and Group 4 (Veau IV and maxillofacial anomaly complex) ⁷ (Table 1).

2.3. Surgical procedure for CP

Two-stage surgery was performed for the patients with cleft lip/palate in the Department of Plastic and Reconstructive Surgery of our hospital. The primary surgery was performed for cleft lip, if present, at the age of 3 to 6 months, and the secondary surgery was performed for closure of the soft and hard palate at the age of 1.0 to 1.5 years. Patients with CP and no cleft lip were treated by a single operation for closure of the soft and hard palate at the age of 1.0 to 1.5 years. The Furlow or pushback procedure was conducted for the secondary surgery (palatoplasty) and was focused on constructing a levator veli palatini muscle sling. Simultaneous TT insertion was performed concomitantly with surgical treatment of the CP.

2.4. Diagnosis and treatment of OME

The presence of OME was defined as unilateral or bilateral effusion lasting more than 3 months behind the tympanic membranes diagnosed with a microscope by otolaryngologists. TT insertion was indicated

when at least one of the following three conditions was present: (1) hearing loss of >45 decibels hearing level (dB HL), (2) type B tympanogram, or (3) soft tissue density indicating middle ear fluid on temporal bone computed tomography imaging.

Hearing examination (visual reinforcement audiometry) was conducted in a sound-proof room by an audiologist using a Rion AA-76 audiometer (until March 2016) or a Rion AA-78 audiometer (from April 2016) (Rion Co., Ltd., Tokyo, Japan). Hearing thresholds at octave frequencies from 0.25 to 4 kHz were measured. Hearing loss was defined as the average of a hearing threshold of >45 dB HL at four frequencies (0.5, 1, 2, and 4 kHz)^{8,9}. Tympanometry was conducted at 226 Hz by an audiologist using a Rion RS-21 audiometer (until March 2016) or a Rion RS-H1 audiometer (from April 2016) (Rion Co., Ltd.). The tympanogram was interpreted as type B when a poorly defined sharp peak was present with little or no variation in impedance over a wide range. A computed tomography scan was performed with a slice thickness of 0.5 mm and was reconstructed for the temporal bones. It contributes to the accurate evaluation of OME status and differential diagnosis of conductive hearing loss. Three-dimensional reconstructions of the maxillary and palatal bones were also made and used for the diagnosis and surgical planning of CP.

A short-term tympanostomy ventilation tube (TympoVent Star Tube; Atos Medical Inc., Malmö, Sweden) was placed at the anterior inferior quadrant of the tympanic membrane and maintained until the tube spontaneously fell out. If the patient had unilateral effusion, we placed a TT only on the affected side. The patients visited board-certified otolaryngologists every 3 months after TT placement until they reached at least 3 years of age without recurrence of OME. The TTs were removed from the tympanic membrane before spontaneous extrusion only when there was granulation tissue with repeated otorrhea around the TT that was resistant to conservative treatment. When recurrence of OME was diagnosed after spontaneous extrusion of the TTs, we placed the TTs again. Recurrence of OME after TT expulsion was defined by the same criteria described above. The TT retention time was defined as the time between TT placement and TT extrusion observed at the revisit.

2.5. Statistical analysis

The TT retention time was estimated using the Kaplan-Meier method. The incidence of OME recurrence was estimated using the Kaplan-Meier method and compared using a Cox proportional hazards model. A p value of <0.05 was considered statistically significant. Variables with a p value of <0.1 were particularly included in the multivariate analysis. The incidence of OME recurrence was compared between two groups divided by the median TT retention time; a group with a first TT retention time of less than 20.1 months and a group with more than 20.1 months, using the chi-square test. The incidence of retraction and adhesion and/or atelectasis of the tympanic membrane and persistent perforation of the tympanic membrane was compared between subjects who underwent a single TT placement and those who required repeated TT placement using Fisher's test. All statistical analyses were performed using JMP® 15 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Subject characteristics

Among 221 patients who underwent palatoplasty, 94 (42.5%) underwent simultaneous TT placement. Eighteen patients who did not complete follow-up before the age of 3 years were excluded. Seventy-six subjects (150 ears) were enrolled in the study (Table 2). The subjects' median age at the first TT placement was 13.7 months (range, 9.4-32.1 months). Group 1 (Veau I) comprised 38 ears, Group 2 (Veau II) comprised 10 ears, Group 3 (Veau III) comprised 62 ears, and Group 4 (Veau IV and maxillofacial anomaly complex) comprised 40 ears. The 76 subjects included two cases of Pierre Robin sequence, a case suspected of having Pierre Robin sequence with PGAP3 mutation, and a case of Pallister-Killian syndrome. A case with combined partial trisomy of chromosome 7 and partial monosomy of chromosome 9 was also included. All of the subjects with syndromic cleft palate had maxillofacial anomaly complex so that these subjects were all categorized as Group 4. There was also a case of Coffin-Siris syndrome

which lacked maxillofacial anomaly and was categorized as Group 2. The 127 cases without simultaneous TT placement included cases of Pierre Robin sequence, Treacher Collins syndrome, Stickler syndrome, Cornelia de-Lange syndrome, trisomy of chromosome 21. Seventy-four subjects underwent bilateral TT placement, whereas one subject with congenital auditory canal atresia and one subject with unilateral OME underwent unilateral TT placement. Details of inclusion/ exclusion criteria in the study group are shown in Figure 1. The median follow-up duration was 48.7 months (range, 18.2-108.0 months) after the first TT placement. The subjects' mean age at the last ENT outpatient clinic visit was 61.6 months (range, 36.6-128.7 months). During the observation period, the average hearing level among all subjects was maintained at <40 dB HL at four frequencies measured by pure tone audiometry.

3.2. TT retention time and TT replacement

The median TT retention time was 20.1 months (range, 1.2-57.3 months) (Figure 2). Nine subjects (12 ears) had a retained TT at the last visit. Eighteen subjects (32 [21%] ears) developed recurrence of OME and required second or subsequent TT placement. In the univariate analyses, the subjects in Groups 3 and 4 showed a significantly higher recurrence rate of OME than the subjects in Groups 1 and 2 (hazard ratio [HR] = 11.7 [2.27-60.6], $p < 0.01$ and HR = 7.18 [1.69-30.4], $p < 0.01$, respectively) (Table 3 and Figure 3). Notably, one subject with Veau III CP (Group 3) and one subject with Veau IV CP (Group 4) required TT placement seven and eight times, respectively. The subjects' sex was related to recurrence of OME with borderline significance (HR = 2.05 [0.93-5.15], $p = 0.09$). Neither the type of fluid in the middle ear nor the subjects' age at first TT placement was significantly associated with recurrence of OME (HR = 1.37 [0.66-3.03], $p = 0.42$). In the multivariate analysis, only the CP type (Group 3 or 4) was significantly associated with recurrence of OME (HR = 7.05 [2.09-44.0], $p < 0.05$). After the first TT placement, a first TT retention time of <20.1 months was a significant risk factor for recurrence of OME (chi-square test, $p = 0.03$). In the 127 cases who underwent CP surgery without simultaneous TT placement, 33 cases were

followed at ENT outpatient clinic for check-up of hearing status and 10 of them had required TT placements after CP surgery.

3.3. Sequelae

The major sequelae of TT placement were persistent perforation of the tympanic membrane and adhesion and/or retraction of the tympanic membrane. In this study, persistent perforation of the tympanic membrane occurred in 8 (5.3%) ears, and adhesion and/or retraction of the tympanic membrane occurred in 26 (17.3%) ears. There was no significant difference in the occurrence of persistent perforation of the tympanic membrane or adhesion and/or retraction of the tympanic membrane between subjects with only a single TT placement and those with more than one TT placement ($p = 0.13$ and $p = 0.21$, respectively) (Table 4).

4. Discussion

The three major findings of this retrospective chart review focusing on children with CP who underwent simultaneous TT placement with palatoplasty are as follows. (1) In total, 81% of the subjects treated with TT placement concomitant with CP surgery had uncomplicated postoperative courses with a single TT placement and no recurrence of OME during their first 3 years. (2) The type of CP was a significant risk factor for recurrence of OME. (3) There were no significant differences in the occurrence of sequelae such as persistent perforation or adhesion and/or retraction of the tympanic membrane between subjects who required a single TT placement and those who required repeated TT placements.

4.1. Intervention for OME and indication for TT insertion

In general, about 50% of infants will develop OME during their first year of life, and this proportion increases to about 60% by the age of 2 years. In most cases, OME spontaneously resolves within 3 months, and only 5% to 10% of cases of OME last ≥ 1 year¹⁰. In contrast, despite the fact that most newborns with

CP pass the newborn hearing screening ¹¹, infants with CP frequently develop OME within 6 months of age ¹; the incidence of OME increases to approximately 90% during the first year ¹² and to 97% by the age of 2 years ¹³. Eustachian tube dysfunction is a significant cause of OME in children with CP, and palatoplasty is thought to result in recovery of Eustachian tube function. However, compensation of Eustachian tube function takes an average of 6.0 years (range, 1.0-10.3 years) ¹⁴.

One study showed a significant negative association between a history of OME in early childhood and receptive and expressive language in preschoolers without CP ¹⁵, whereas Majerus et al. ¹⁶ found no significant association between a history of repeated OME before the age of 3 years and verbal short-term memory and new word learning abilities at the age of 8 years in children without CP. Although tube placement can improve early hearing loss¹⁷, there is no consensus on the indications or appropriate duration of TT placement in patients with CP. Kobayashi et al.¹⁸ reported that tube placement for CP patients with OME is effective because there was no significant difference in language development at the age of 5 years between CP patients with or without OME when CP patients with OME underwent TT placement. In our hospital, speech therapists provide CP patients with postoperative articulation trainings and assessments for articulation and psychological development. Although it is uncertain whether the recurrence of OME affects language development, we believe that early detection and treatment of the recurrence of OME could prevent subjects' language development from being affected. Some researchers suggest watchful waiting for OME in children with CP. Muntz ¹⁹ indicated that more than 50% of children with CP who develop OME naturally recover from OME after 3 years of age. During the observation period, patients may wear hearing aids to attain the same hearing threshold of children with TTs. In contrast to conservative management, some researchers recommended systematic TT placement in all children with CP because the TT might optimize air flow in the middle ear and thus reduce further complications. In a study by Skuladottir et al.²⁰, patients with CP were prophylactically treated in both ears at the time of palatal closure in the most affected ear or both ears and followed up until the age of 15 years; the authors reported significant improvement in hearing levels from childhood to adolescence in

these patients. However, because TT insertion can cause serious sequelae, the risks of prophylactic TT insertion are currently considered to outweigh its benefits. Ponduri et al.¹² reported that there was insufficient evidence for a benefit of routine early tube insertion in children with CP on hearing and speech and language development. However, Phua et al.²¹ compared patients who underwent routine TT insertion and patients who underwent conservative management favoring a selective approach to TT insertion, and better otologic outcomes and fewer tube insertions were noted in the latter group. The authors therefore recommended the use of TTs in children with CP only when they have symptomatic middle ear infection or significant hearing loss.²¹ This idea can be supported in light of the fact that relief of effusions in the middle ears improves the accuracy of hearing level diagnosis and detection of underlying non-fluid-related, less reversible conductive hearing loss.

In addition, Maheshwar et al.²² proposed that the use of TTs should be limited to only patients who have poor compliance with the use of hearing aids or who develop recurrent OME. Our findings regarding TT insertion in patients with CP are consistent with those of recent studies demonstrating that selective approaches are reasonable for OME in children with CP according to the type of CP or condition of the middle ear. Felton et al.²³ proposed that early TT placement (before palatoplasty) resulted in speech and audiology outcomes similar to those of children without CP and better than those of children with CP who underwent later TT placement (at or after palatoplasty). In addition, early TT placement is suggested to play a role in the development of the mastoid air cell system in children with CP^{18,24}. However, when the first TT placement was performed before palatoplasty, the recurrence rate of OME is higher than in cases with first TT placement performed simultaneously with or after palatoplasty²⁵. Boston et al.²⁶ also concluded that children without CP aged <18 months at the time of first TT placement are 65% more likely to require subsequent TT placement than children aged >18 months. Our data regarding the OME recurrence rate of <20% suggest the usefulness of simultaneous TT placement with palatoplasty at the age of 1.0 to 1.5 years. It is difficult to assess language development of CP patients accurately. In addition, cultural differences; linguistic differences; community customs like medical insurance and compliance

with medical recommendations all affect the outcomes in patients. Therefore, development of consensus guidelines for the management of OME in children with CP may remain "community specific". Nevertheless, we consider that simultaneous TT placement with palatoplasty is reasonable if the patients meet the criteria because the cost and burden to perform TT placement under general anesthesia in pediatric patients are high.

4.2. Risk factors for recurrence of OME

Our data demonstrated a significant correlation between the CP type and OME recurrence. Frequent complications of OME in pediatric patients with CP are thought to be caused by Eustachian tube dysfunction, which is the result of aberrations of the levator veli palatini muscle and tensor veli palatini muscle (the muscles primarily responsible for Eustachian tube opening) ²⁷. Whereas palatoplasty in the present study focused on constructing a paratubal muscle sling, the risk of recurrence of OME after palatoplasty remained higher in Groups 3 and 4 (subjects with cleft lip and palate) than in Groups 1 and 2 (subjects with soft and hard CP). These results are considered reasonable because it takes an average of 6.0 years (range, 1.0-10.3 years) to recover Eustachian tube function after palatoplasty ¹⁴. Even when palatoplasty is performed, a more severe CP type may be associated with less mature Eustachian tube function. Another significant risk factor for OME recurrence in this study was the first TT retention time. The shorter first TT retention time raises the risk for OME recurrence. Ahn et al. ²⁸ reported that complete CP (Veau II and greater) contributed to OME recurrence in patients with CP and that a significant difference was present between the single- and repeated-TT groups in the indwelling period of the first TT (12.7 ± 9.6 and 10.5 ± 6.5 months for the single- and repeated-TT groups, respectively). The authors also reported that there were significantly more male patients in the repeated-TT group than in the single-TT group ²⁸. In contrast, our data did not show that sex was a risk factor for recurrence of OME (HR = 1.54 [0.70-3.89], $p = 0.31$). Considering that CP occurs more frequently in male than female patients ²⁹, further

analyses are needed to elucidate the correlation between sex and the risk of recurrence of OME in children with CP.

4.3. Risk factors for sequelae after TT insertion

OME causes atelectasis and retraction of the tympanic membrane as well as other chronic changes such as myringosclerosis or tympanosclerosis, which might lead to moderate to severe hearing impairment in children with CP ^{8, 9}. Up to 90% to 96% of children with CP develop conductive hearing loss ^{30, 31}. In comparison, children without CP have an approximately 12.9% prevalence of OME ³². Furthermore, OME causes primary acquired cholesteatoma in 0.9% to 5.9% of patients with CP. This rate represents a 100- to 200-fold higher probability of developing cholesteatoma in patients without CP. One of the reasons for simultaneous TT placement in children with CP should be prevention of sequelae affecting the tympanic membrane later in life, such as acquired cholesteatoma or adhesive otitis media.

TT placement for OME in patients with CP is sometimes controversial. While there is a possibility of sequelae due to untreated OME, as mentioned above, TT placement might cause pathologic changes in the tympanic membrane such as calcification, persistent perforation (1.3%-19.0%), and adhesion and/or retraction (7.7%-36.8%) ^{24, 30}. Moreover, one study showed that TT placement caused secondary acquired cholesteatoma in 1 (3.8%) of 26 patients ²². Dominguez and Harker ³³ also reported that the risk of cholesteatoma in children with CP after myringotomy and/or TT placement was 2.6% (3 of 113 patients). In contrast, Gordon et al. ³⁴ reported that the incidence of cholesteatoma was comparable between the TT insertion and non-TT insertion groups. In our study, there were no significant differences in the occurrence of major sequelae such as persistent perforation or adhesion and/or retraction of the tympanic membrane between the single-TT and repeated-TT groups during the observation period. These findings suggest that repeated TT placement is not a risk factor for major sequelae, further indicating that TT replacement can be recommended as an effective and safe treatment option if OME recurs. Even if the patient had a high risk of recurrence with a severe CP type and/or a short retention period of initial TT placement, no

predictable factors have been reported whether OME will recur after subsequent TT placement. Therefore, repeated short-term TT insertions are recommended in order to keep the risk of sequelae low.

4.4. Limitations

This study has two main limitations. First, this was a small, single-center, single-arm retrospective chart review without a control group. Second, the risk of recurrence of OME remains high until about 6 years of age, but the subjects in this study were followed until only just beyond 3 years of age (mean, 61.6 months; range, 36.6-128.7 months). If we had followed the subjects until 6 years of age or beyond, the recurrence rate of OME might have been higher.

5. Conclusions

More than 80% of subjects had an uncomplicated clinical course until the final examination with only single TT insertion. It is reasonable to perform TT insertion at the same time as palatoplasty in patients who meet the indications; this technique may reduce the number of episodes of general anesthesia and maintain a good middle ear condition during the period of language acquisition between 1 and 3 years of age.

Acknowledgment

We would like to thank Dr. Motonori Katsube, Department of Plastic and Reconstructive Surgery, Graduate School of Medicine, Kyoto University, Kyoto, Japan, for providing useful comments upon drafting the manuscript. We also thank Angela Morben, DVM, ELS, from Edanz (<https://jp.edanz.com/ac>), for editing a draft of this manuscript.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

1. T. Flynn, C. Moller, R. Jonsson, A. Lohmander, The high prevalence of otitis media with effusion in children with cleft lip and palate as compared to children without clefts, *Int J Pediatr Otorhinolaryngol.* 73 (2009) 10 1441-1446. <https://www.ncbi.nlm.nih.gov/pubmed/19709760>.
2. H.R. Grant, R.E. Quiney, D.M. Mercer, S. Lodge, Cleft palate and glue ear, *Arch Dis Child.* 63 (1988) 2 176-179. <https://www.ncbi.nlm.nih.gov/pubmed/3348665>.
3. P. Sheahan, I. Miller, J.N. Sheahan, M.J. Earley, A.W. Blayney, Incidence and outcome of middle ear disease in cleft lip and/or cleft palate, *Int J Pediatr Otorhinolaryngol.* 67 (2003) 7 785-793. <https://www.ncbi.nlm.nih.gov/pubmed/12791455>.
4. T.J. Fria, J.L. Paradise, D.L. Sabo, B.A. Elster, Conductive hearing loss in infants and young children with cleft palate, *J Pediatr.* 111 (1987) 1 84-87. <https://www.ncbi.nlm.nih.gov/pubmed/3598793>.
5. I. Hocevar-Boltezar, A. Jarc, V. Kozelj, Ear, nose and voice problems in children with orofacial clefts, *J Laryngol Otol.* 120 (2006) 4 276-281. <https://www.ncbi.nlm.nih.gov/pubmed/16623971>.
6. A.G. Schilder, A.F. Snik, H. Straatman, P. van den Broek, The effect of otitis media with effusion at preschool age on some aspects of auditory perception at school age, *Ear Hear.* 15 (1994) 3 224-231. <https://www.ncbi.nlm.nih.gov/pubmed/8076720>.

7. A.C. Allori, J.B. Mulliken, J.G. Meara, S. Shusterman, J.R. Marcus, Classification of Cleft Lip/Palate: Then and Now, *Cleft Palate Craniofac J.* 54 (2017) 2 175-188. <https://www.ncbi.nlm.nih.gov/pubmed/26339868>.
8. A.H.C. Chow, T. Cai, B. McPherson, F. Yang, Otitis media with effusion in children: Cross-frequency correlation in pure tone audiometry, *PLoS One.* 14 (2019) 8 e0221405. <https://www.ncbi.nlm.nih.gov/pubmed/31437206>.
9. J.S. Gravel, I.F. Wallace, Effects of otitis media with effusion on hearing in the first 3 years of life, *J Speech Lang Hear Res.* 43 (2000) 3 631-644. <https://www.ncbi.nlm.nih.gov/pubmed/10877434>.
10. R.M. Rosenfeld, L. Culpepper, K.J. Doyle, et al., Clinical practice guideline: Otitis media with effusion, *Otolaryngol Head Neck Surg.* 130 (2004) 5 Suppl S95-118. <https://www.ncbi.nlm.nih.gov/pubmed/15138413>.
11. C. Szabo, K. Langevin, S. Schoem, K. Mabry, Treatment of persistent middle ear effusion in cleft palate patients, *Int J Pediatr Otorhinolaryngol.* 74 (2010) 8 874-877. <https://www.ncbi.nlm.nih.gov/pubmed/20537733>.
12. S. Ponduri, R. Bradley, P.E. Ellis, S.T. Brookes, J.R. Sandy, A.R. Ness, The management of otitis media with early routine insertion of grommets in children with cleft palate -- a systematic review, *Cleft Palate Craniofac J.* 46 (2009) 1 30-38. <https://www.ncbi.nlm.nih.gov/pubmed/19115800>.
13. R.S. Dhillon, The middle ear in cleft palate children pre and post palatal closure, *J R Soc Med.* 81 (1988) 12 710-713. <https://www.ncbi.nlm.nih.gov/pubmed/3065499>.

14. T.L. Smith, D.C. DiRuggiero, K.R. Jones, Recovery of eustachian tube function and hearing outcome in patients with cleft palate, *Otolaryngol Head Neck Surg.* 111 (1994) 423-429. <https://www.ncbi.nlm.nih.gov/pubmed/7936674>.
15. J.E. Roberts, R.M. Rosenfeld, S.A. Zeisel, Otitis media and speech and language: a meta-analysis of prospective studies, *Pediatrics.* 113 (2004) 3 Pt 1 e238-248. <https://www.ncbi.nlm.nih.gov/pubmed/14993583>.
16. S. Majerus, P. Amand, V. Boniver, J.P. Demanez, L. Demanez, M. Van der Linden, A quantitative and qualitative assessment of verbal short-term memory and phonological processing in 8-year-olds with a history of repetitive otitis media, *J Commun Disord.* 38 (2005) 6 473-498. <https://www.ncbi.nlm.nih.gov/pubmed/15950984>.
17. J. Lous, M.J. Burton, J.U. Felding, T. Ovesen, M.M. Rovers, I. Williamson, Grommets (ventilation tubes) for hearing loss associated with otitis media with effusion in children, *Cochrane Database Syst Rev.* (2005) 1 CD001801. <https://www.ncbi.nlm.nih.gov/pubmed/15674886>.
18. H. Kobayashi, T. Sakuma, N. Yamada, H. Suzaki, Clinical outcomes of ventilation tube placement in children with cleft palate, *Int J Pediatr Otorhinolaryngol.* 76 (2012) 5 718-721. <https://www.ncbi.nlm.nih.gov/pubmed/22386274>.
19. H.R. Muntz, An overview of middle ear disease in cleft palate children, *Facial Plast Surg.* 9 (1993) 3 177-180. <https://www.ncbi.nlm.nih.gov/pubmed/8270210>.
20. H. Skuladottir, A. Sivertsen, J. Assmus, A.R. Remme, M. Dahlen, H. Vindenes, Hearing outcomes in patients with cleft lip/palate, *Cleft Palate Craniofac J.* 52 (2015) 2 e23-31. <https://www.ncbi.nlm.nih.gov/pubmed/24805872>.

21. Y.S. Phua, L.J. Salkeld, T.M. de Chalain, Middle ear disease in children with cleft palate: protocols for management, *Int J Pediatr Otorhinolaryngol.* 73 (2009) 2 307-313. <https://www.ncbi.nlm.nih.gov/pubmed/19091429>.
22. A.A. Maheshwar, M.A. Milling, M. Kumar, M.I. Clayton, A. Thomas, Use of hearing aids in the management of children with cleft palate, *Int J Pediatr Otorhinolaryngol.* 66 (2002) 1 55-62. <https://www.ncbi.nlm.nih.gov/pubmed/12363423>.
23. M. Felton, J.W. Lee, D.D. Balumuka, J.S. Arneja, N.K. Chadha, Early Placement of Ventilation Tubes in Infants with Cleft Lip and Palate: A Systematic Review, *Otolaryngol Head Neck Surg.* 158 (2018) 3 459-464. <https://www.ncbi.nlm.nih.gov/pubmed/29161200>.
24. H. Valtonen, A. Dietz, Y. Qvarnberg, Long-term clinical, audiologic, and radiologic outcomes in palate cleft children treated with early tympanostomy for otitis media with effusion: a controlled prospective study, *Laryngoscope.* 115 (2005) 8 1512-1516. <https://www.ncbi.nlm.nih.gov/pubmed/16094135>.
25. M.S. Brgoch, K.M. Dodson, T.C. Kim, D.M. Kim, R.Trivelpiece, J.L. Rhodes, Timing of Tympanostomy Tube Placement and Efficacy of Palatoplasty Technique on the Resolution of Chronic Otitis Media: A Cross-sectional Analysis, *Eplasty.* 15 (2015) e32. <https://www.ncbi.nlm.nih.gov/pubmed/26240670>.
26. M. Boston, J. McCook, B. Burke, C. Derkay, Incidence of and risk factors for additional tympanostomy tube insertion in children, *Arch Otolaryngol Head Neck Surg.* 129 (2003) 3 293-296. <https://www.ncbi.nlm.nih.gov/pubmed/12622537>.

27. D.S. Heidsieck, B.J. Smarius, K.P. Oomen, C.C. Breugem, The role of the tensor veli palatini muscle in the development of cleft palate-associated middle ear problems, *Clin Oral Investig.* 20 (2016) 7 1389-1401. <https://www.ncbi.nlm.nih.gov/pubmed/27153847>.
28. J.H. Ahn, W.S. Kang, J.H. Kim, K.S. Koh, T.H. Yoon, Clinical manifestation and risk factors of children with cleft palate receiving repeated ventilating tube insertions for treatment of recurrent otitis media with effusion, *Acta Otolaryngol.* 132 (2012) 7 702-707. <https://www.ncbi.nlm.nih.gov/pubmed/22668076>.
29. F. Blanco-Davila, Incidence of cleft lip and palate in the northeast of Mexico: a 10-year study, *J Craniofac Surg.* 14 (2003) 4 533-537. <https://www.ncbi.nlm.nih.gov/pubmed/12867870>.
30. C.L. Kuo, C.F. Lien, C.H. Chu, A.S. Shiao, Otitis media with effusion in children with cleft lip and palate: a narrative review, *Int J Pediatr Otorhinolaryngol.* 77 (2013) 9 1403-1409. <https://www.ncbi.nlm.nih.gov/pubmed/23931986>.
31. R. Reiter, S. Brosch, H. Wefel, G. Schlomer, S. Haase, The submucous cleft palate: diagnosis and therapy, *Int J Pediatr Otorhinolaryngol.* 75 (2011) 1 85-88. <https://www.ncbi.nlm.nih.gov/pubmed/21112097>.
32. F. Martines, D. Bentivegna, F. Di Piazza, G. Martinciglio, V. Sciacca, E. Martines, The point prevalence of otitis media with effusion among primary school children in Western Sicily, *Eur Arch Otorhinolaryngol.* 267 (2010) 5 709-714. <https://www.ncbi.nlm.nih.gov/pubmed/19859723>.
33. S. Dominguez, L.A. Harker, Incidence of cholesteatoma with cleft palate, *Ann Otol Rhinol Laryngol.* 97 (1988) 6 Pt 1 659-660. <https://www.ncbi.nlm.nih.gov/pubmed/3202568>.

34. A.S. Gordon, F. Jean-Louis, R.P. Morton, Late ear sequelae in cleft palate patients,
Int J Pediatr Otorhinolaryngol. 15 (1988) 2 149-156.
<https://www.ncbi.nlm.nih.gov/pubmed/3397234>.

Table 1. Classification of patients with cleft palate

Cleft palate type	
Group 1	Veau I (soft palate only)
Group2	Veau II (hard and soft palate)
Group 3	Veau III (unilateral cleft lip and palate)
Group 4	Veau IV (bilateral cleft lip and palate) and maxillofacial anomaly complex

Table 2. Characteristics of the study population

		Number of patients (ears)	Frequency per 150 ears
Total population = 76 (150)			
Sex			
Male		47 (92)	61.3%
Female		29 (58)	38.7%
Cleft palate type			
Group 1 (Veau I)		19 (38)	25.3%
Group2 (Veau II)		5 (10)	6.7%
Group 3 (Veau III)		31 (62)	41.3%
Group 4	Veau IV	16 (31)	20.7%
	Maxillofacial anomaly complex	5 (9)	6.0%
TT placement			
Bilateral		74 (148)	98.7%

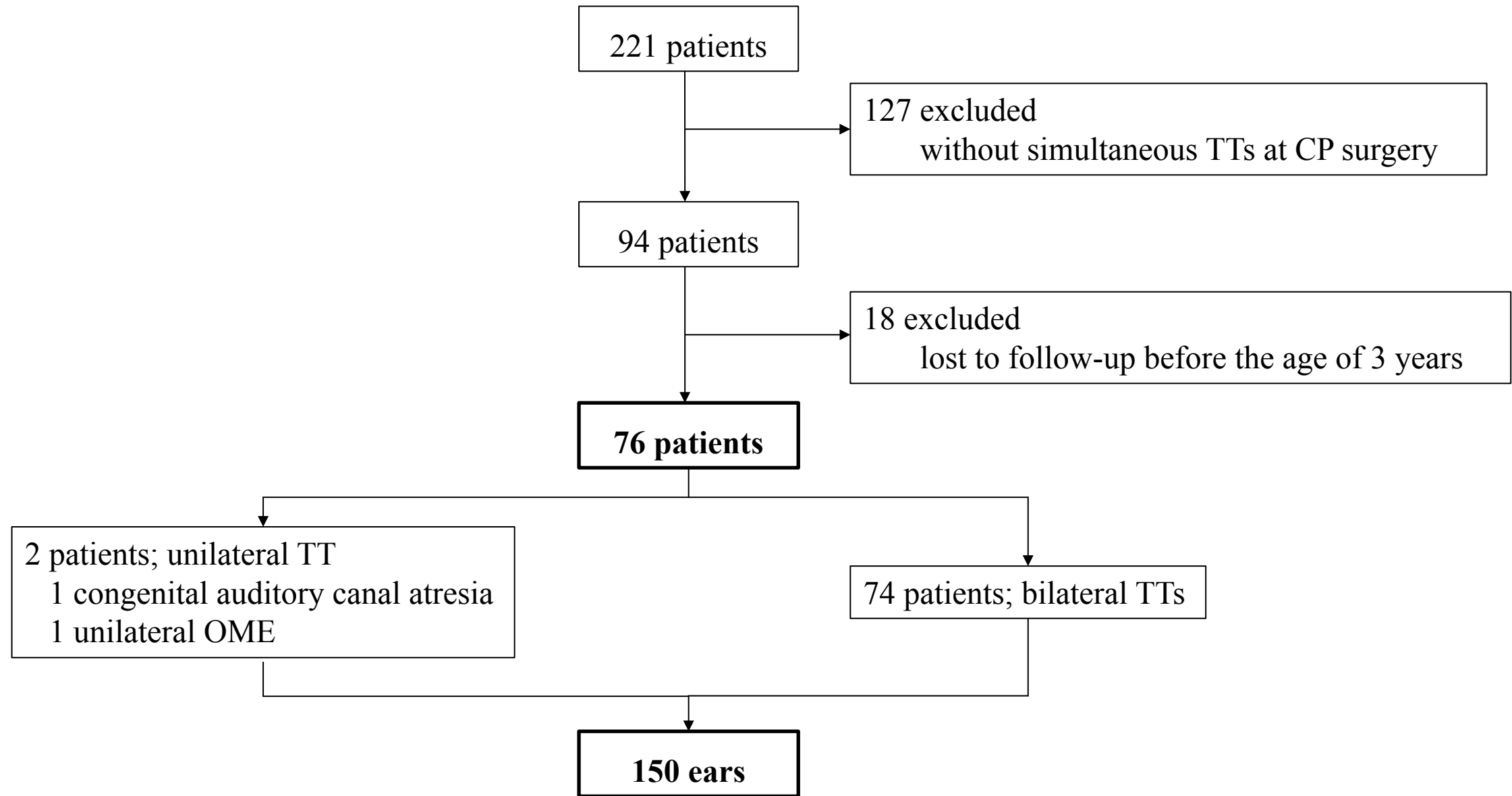
Unilateral	2 (2)	1.3%
Type of fluid in the middle ear at first TT placement		
viscous	84 ears	56%
serous	51 ears	34%
no data	15 ears	10%
Median age at first TT placement	13.7 months (range, 9.4–32.1)	
Median follow-up period	48.7 months (range, 18.2–108.0)	
Median TT retention time	20.1 months (range, 1.2–57.3)	

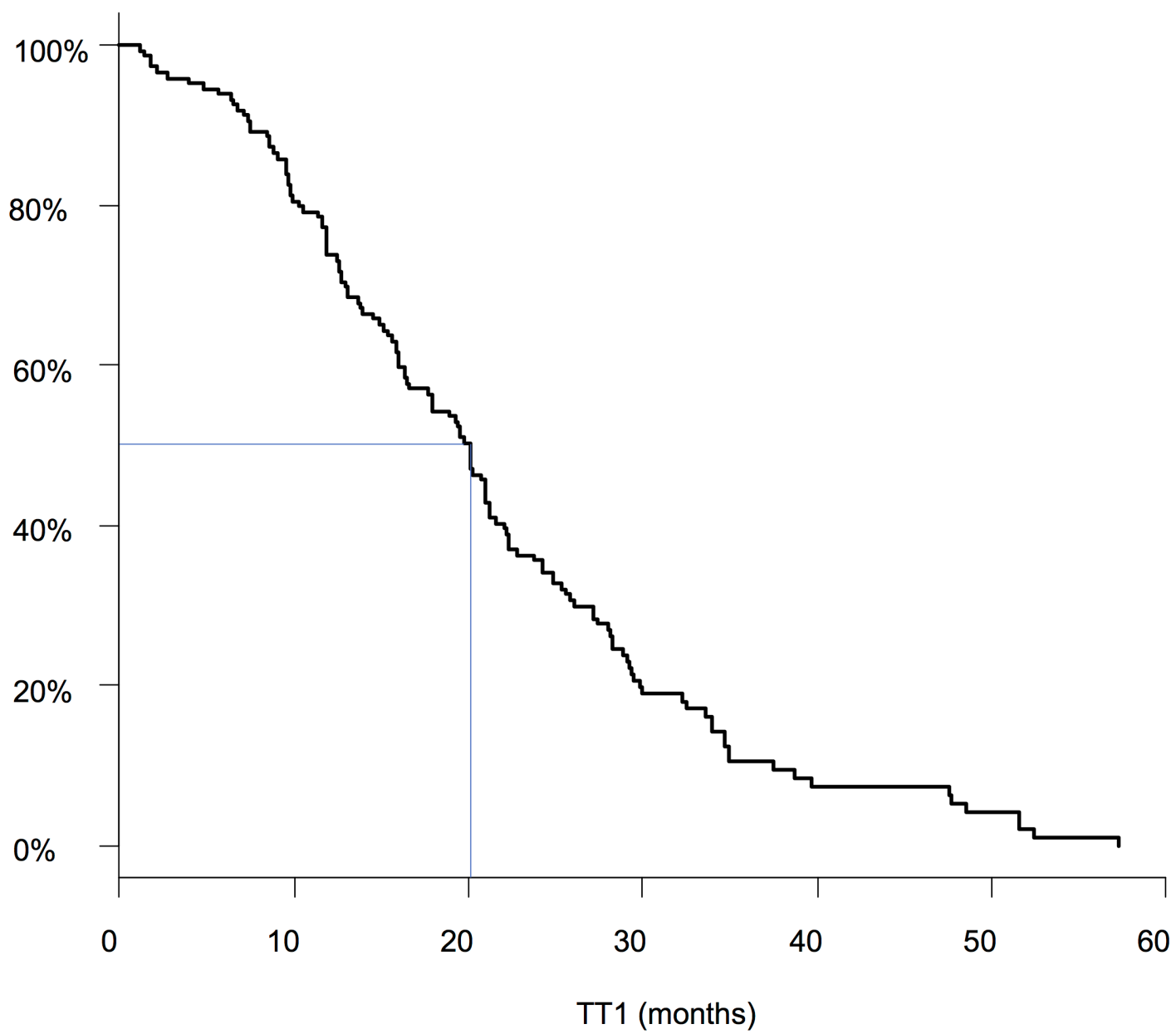
Table 3. Variables affecting recurrence of otitis media with effusion

Variables		Univariate		Multivariate	
		HR (95%CI)	<i>p</i>	HR (95%CI)	<i>p</i>
Age at operation	16 months or over to less than 16 months	1.30(0.54-2.79)	0.52		
Sex	Male to female	2.05(0.93-5.15)	0.09	1.54 (0.70-3.89)	0.31
A fluid type at first TT placement	Viscous to serous	1.37(0.66-3.03)	0.42		
CP type (Group)	Group 3 or 4 to Group 1 or 2	7.73(2.32-47.90)	<0.01 *	7.05 (2.09-44.0)	<0.01 *

Table 4. Sequelae following tympanostomy tube placement

(ears)	total (N=150)	cases with single tympanostomy tube placement (N=118)	cases repeated tympanostomy tube placement (N=32)	p
perforation of the tympanic membrane	8 (5.3%)	8 (5.3%)	0 (0.0%)	p=0.13
adhesion or retraction of the tympanic membrane	26 (17.3%)	18 (15.2%)	8 (25.0%)	p=0.21





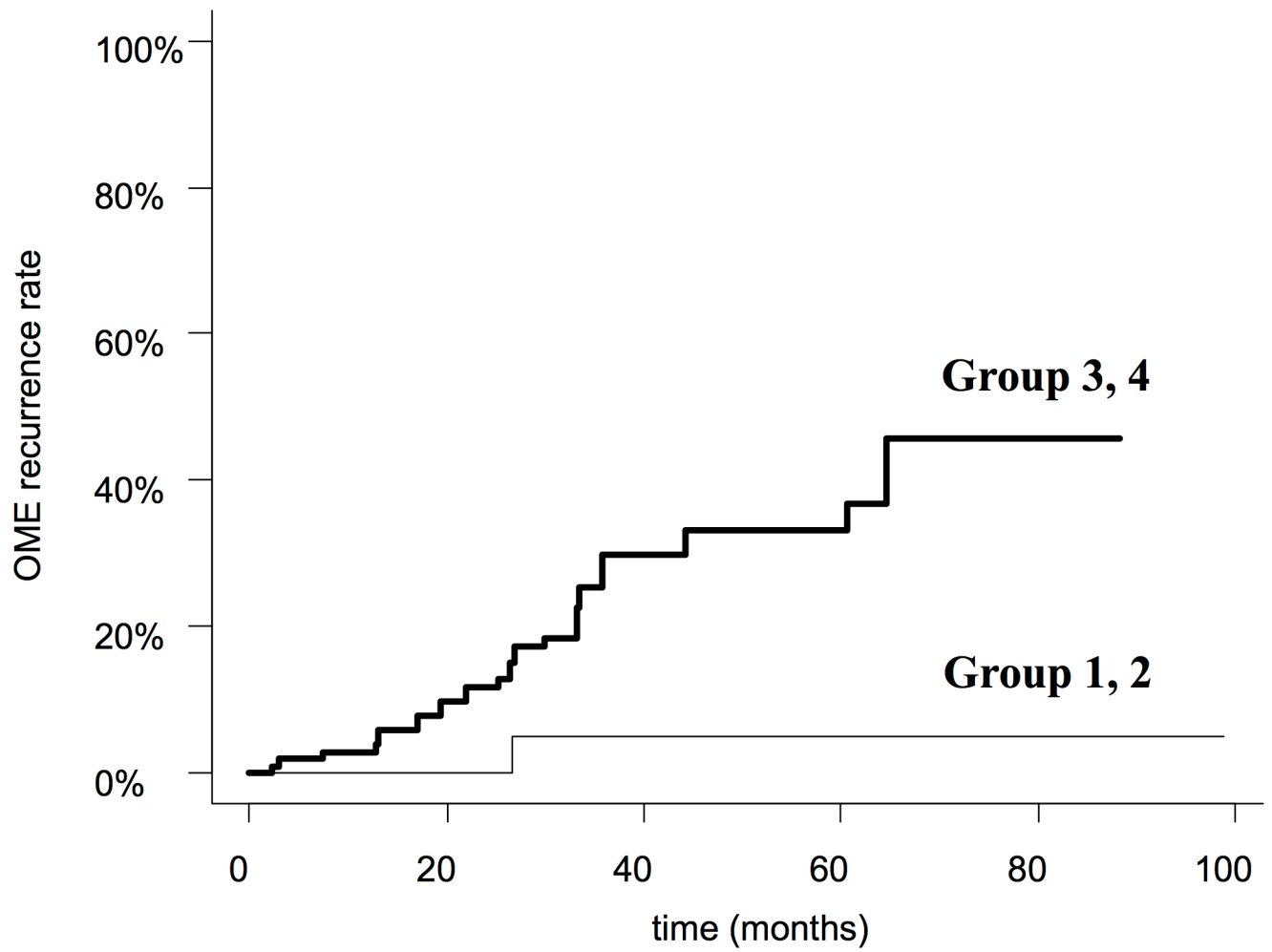


Figure Legends

Figure 1. Chart of participants in the study group (pediatric patients with cleft palate who underwent surgery for cleft palate). TT: tympanostomy tube. CP: cleft palate. OME: otitis media with effusion.

Figure 2. First tympanostomy tube retention time. The first tympanostomy tube retention time (TT1) is demonstrated using a Kaplan–Meier curve considering the first expulsion of the tympanostomy tube as the event of interest.

Figure 3. Impact of the type of the cleft palate on the otitis media with effusion (OME) recurrence rate. The OME recurrence rate was compared between the patients in Group 1 (Veau I) and Group 2 (Veau II) and between the patients in Group 3 (Veau III) and Group 4 (Veau IV and maxillofacial anomaly complex).